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TH-OR001

Role of PAD4 and NETs in Ischemia Reperfusion Injury in the Kidney William Brian Reeves,[1] Wesley M. Raup-Konsavage,[1] Weiwei Wang,[1] Jinquan Sun,[2] Yanming Wang.[2] *[1]Div of Nephrology, Penn State College of Medicine, Hershey, PA; [2]Biochemistry and Molecular Biology, Penn State Univ, Univ Park, PA.*

Background: Ischemia-reperfusion injury (IRI) is a common cause of AKI. Neutrophils contribute to renal IRI though the mechanism by which they cause injury is uncertain. The formation of neutrophil extracellular traps (NETs) is a defense against infection but may also contribute to tissue injury. The role of NETs in ischemic AKI is unknown. Peptidyl arginine deiminase 4 (PAD4) is essential for NET formation and regulates gene expression through the citrullination of histones.

Methods: Wild type (WT) and PAD4 KO mice were subjected to renal ischemia. Renal function, histology and circulating cell-free DNA were measured.

Results: PAD4 KO mice were markedly resistant to ischemic injury as measured by serum BUN (WT 136±14 vs KO 49±9 mg/dl, P<0.0001) and creatinine (WT 1.54±.13 vs KO 0.43±.13 mg/dl, P<0.0001) levels. We assessed NET formation by measuring serum DNA levels. Serum DNA levels increased after IRI but were lower in KO than WT mice (1310±16 vs 1678±157 ng/ml,P<0.01). Additionally, we observed less citrullinated histone H3 in tissue from PAD4 KO vs WT mice. Kidney expression of TNF and IL-6 were lower, while IL-10 was higher, in KO vs WT mice. DNase I has been used to reduce NET formation in vivo. Therefore, we treated WT mice with DNaseI just prior to ischemia and again 8 hrs after reperfusion. DNaseI treatment resulted in better preservation of kidney function (BUN: veh. 130±6 vs DNase 86.6±12 mg/dl and creatinine: veh. 1.48±.24 vs DNase 0.84±.06 mg/dl, P<0.05). To determine if neutrophils were the major site of action for PAD4 in IRI, we transferred WT or PAD4 KO neutrophils into PAD4 KO mice prior to IRI. PAD4 KO mice which received WT neutrophils developed much greater injury than mice which received PAD4 KO neutrophils (BUN 136±9 vs 63±10 mg/dl, P<0.001). In contrast, neutrophils lacking TNFR1 did not increase injury (BUN 73±6 mg/dl).

Conclusions: Our findings suggest that formation of NETs mediates IRI and that inhibition of PAD4 or degradation of NETs may reduce the severity of ischemic AKI. Moreover, neutrophils are targets of TNF in IRI, perhaps leading to NET formation.

Funding: NIDDK Support

TH-OR002

Inhibition of Signal Transducer and Activator of Transcription 3 (STAT3) Protects against Renal Ischemia-Reperfusion Injury Jae Wook Lee,[1] Sun Moon Kim,[2] Seung Hee Yang,[3] Yon Su Kim.[3] *[1]National Cancer Center, Korea; [2]Chungbuk National Univ Hospital, Korea; [3]Seoul National Univ, Korea.*

Background: STAT3 promotes survival of naïve T cells and differentiation of T helper 17 (Th17) cells. Cln three requiring 9 (Ctr9), a subunit of RNA polymerase II-associated factor complex, functions as a negative regulator of Th17 cells by repressing IL-17 transcription. On the other hand, STAT3 in tubular epithelial cells (TECs) is activated by ischemia-reperfusion (IR) injury and compromises adaptation to hypoxia. Here, we investigated the role of STAT3 and Ctr9 in renal IR injury.

Methods: IR injury was induced in wild-type mice, wild-type mice pre-treated with CADPE (a STAT3 inhibitor), and mice with T cell-selective STAT3 deletion (*Stat3*$^{\Delta/\Delta}$). Renal injury was assessed by serum creatinine and immunohistochemistry at 48 h. Activation of intrarenal Th17 cells was determined by intrarenal IL-17 concentrations and flow cytometry for CD4$^+$ T cells. Changes in the proportions of Th17 cells following RNA interference of Ctr9 (Ctr9-siRNA) were analyzed using flow cytometry. Primary human TECs were grown under hypoxia (1% O_2 for 6 h) with or without CADPE. Cytokine production was quantified using real-time PCR and ELISA.

Results: Renal injury was significantly reduced in mice pre-treated with CADPE and *Stat3*$^{\Delta/\Delta}$ mice, both of which exhibited a significant reduction in intrarenal Th17 cells. Ctr9-siRNA treatment on intrarenal T cells further enhanced differentiation of Th17 cells, consistent with the inhibitory role of Ctr9 in Th17 differentiation. In cultured TECs, hypoxia upregulated STAT3, IL-17 receptor, and other markers of cell injury (e.g. IL-18). CADPE treatment significantly reduced STAT3 activation and the markers of cell injury. Interestingly, Ctr9 expression was also observed in TECs of normal kidneys and repressed with IR injury. Ctr9-siRNA treatment reduced the expression of STAT3 and Th17-related transcripts in TECs under hypoxia.

Conclusions: Inhibition of STAT3 protects against renal IR injury by reducing activation of Th17 cells and production of pro-inflammatory cytokines from TECs. Ctr9 is a negative correlate of STAT3 activity and functions as a negative regulator of IR-induced inflammation in both cell types.

TH-OR003

Vagus Nerve Stimulation-Conditioned CD11b+F4/80+ Cells Protect from Kidney Ischemia-Reperfusion Injury Tsuyoshi Inoue,[1] Chikara Abe,[2] Liping Huang,[1] Hong Ye,[1] Diane L. Rosin,[1,2] Patrice G. Guyenet,[2] Mark D. Okusa.[1] *[1]Div of Nephrology and Center for Immunity, Inflammation and Regenerative Medicine, Univ of Virginia, Charlottesville, VA; [2]Dept of Pharmacology, Univ of Virginia, Charlottesville, VA.*

Background: We recently showed that prior vagus nerve stimulation (VNS) protects the kidney from ischemia-reperfusion injury (IRI) through the cholinergic anti-inflammatory pathway. The phenotypic change of macrophages (VNS induces M2 phenotype) in the kidney was observed by flow cytometry, however the causal role of these conditioned macrophages in vivo was not established.

Methods: CD11b+ splenocytes (MACS-enriched; 85% CD11b+) or peritoneal macrophages (70% CD11b and F4/80 double positive) were isolated from wild type mice and alpha 7 nicotinic acetylcholine receptor (α7nAChR) knock out (α7KO) mice 24 hr after electrical VNS (5 Hz, 50 μA for 10 min), then CD11b+ splenocytes or C11b+F4/80+ peritoneal macrophages were transferred into the recipient mice. Kidney IRI was performed 1 hr after the adoptive transfer and kidney injury was evaluated 24 hr later using plasma creatinine (PCr), kidney Kim-1 mRNA expression and histology (H&E).

Results: Adoptive transfer of CD11b+ splenocytes (1x10^5 cells) from VNS-treated mice to recipient mice subjected to IRI provided greater protection than CD11b+ splenocytes from mice who received sham VNS stimulation (PCr: 0.14 and 1.01 mg/dl (P<0.001) for VNS- and sham VNS-treated CD11b+ splenocytes from spleen, respectively, n=6). When peritoneal macrophages (1x10^5 cells) from donor mice were transferred, a similar protective effect was observed (PCr: 0.62 and 1.57 mg/dl (P=0.001) for VNS- and sham VNS-treated peritoneal macrophages, respectively, n=7). In addition, α7KO mice were used to evaluate the role of α7nAChR+ macrophages. The protective effect in recipient mice was much smaller if they received peritoneal macrophages from VNS-treated α7KO mice than from VNS-treated WT mice.

Conclusions: These data demonstrate that activation of CD11b+F4/80+ cells through α7nAChR is important for the protective effect of VNS in AKI and extend our findings on the role of neuroimmune regulation of kidney injury through the inflammatory reflex pathway.

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

TH-OR004

Iron-Retaining Splenic Myeloid Cells Are Central for Hepcidin-Induced Protection in Renal Ischemia-Reperfusion Injury Yogesh M. Scindia,[1] Ewa U. Mandziak,[1] Liping Huang,[1] Mark D. Okusa,[1] Diane L. Rosin,[2] Sundararaman Swaminathan.[1] *[1]Medicine, Univ of Virginia, Charlottesville, VA; [2]Pharmacology, Univ of Virginia, Charlottesville, VA.*

Background: We showed previously that pretreatment with hepcidin mitigates kidney ischemia-reperfusion injury (IRI) by increasing the splenic iron content. We have further demonstrated that transfer of hepcidin-treated splenocytes into naïve recipients protects against renal IRI. In this study we have explored the role of different splenic immune cells responsible for this protective effect. In addition, we evaluated the therapeutic potential of hepcidin after the onset of IRI.

Methods: C57BL/6 (WT) and *Rag1*$^{-/-}$ mice were injected with saline or 50mg hepcidin, and 24 hours later subjected to bilateral renal IRI (24-27min). Some Rag1$^{-/-}$ mice were treated with a Thy1.2 depleting antibody to deplete nature killer (NK) and innate lymphoid cells (ILC). In some experiments WT mice were injected with hepcidin after 2 h of reperfusion. Outcomes (renal function, injury markers, histopathology and inflammation) were examined after 1-30 d of reperfusion.

Results: Hepcidin significantly reduced kidney injury in Rag1$^{-/-}$ mice as measured by plasma creatinine (Rag1$^{-/-}$ P_{Cr}: IRI; 2.6±0.13 vs hepcidin + IRI; 0.26±0.01 mg/dl, $p < 0.005$), NGAL, acute tubular necrosis and immune cell infiltration. Rag1$^{-/-}$ mice depleted of Thy1.2$^+$ cells were also protected by hepcidin pretreatment. In a separate experiment, WT mice injected with hepcidin 2 h after the onset of AKI had significantly lower plasma creatinine than saline-treated animals, after 3 days of reperfusion (WT P_{Cr}: IRI; 1.2±0.38 vs hepcidin + IRI; 0.47±0.06 mg/dl, $p < 0.05$). The kidneys of hepcidin-treated mice had more M2 macrophages and fewer inflammatory cells and survived for up to 30 d after reperfusion. In contrast, the majority of saline-treated mice died after 3 d of reperfusion.

Conclusions: Our results demonstrate that hepcidin-mediated protection against renal IRI is critically dependent on iron retention in myeloid cells and is independent of Tregs, lymphocytes, NK cells and ILC. The ability of hepcidin to protect when administered after the onset of IRI highlights its therapeutic potential.

Funding: NIDDK Support

TH-OR005

Tamm-Horsfall Protein (Uromodulin) Regulates the Number and Function of Macrophages in the Kidney Radmila Micanovic, Shehnaz Khan, Pierre C. Dagher, Takashi Hato, Tarek M. El-Achkar. *Medicine Nephrology, Indiana Univ and Indianapolis VA Medical Center, Indianapolis, IN.*

Background: Tamm-Horsfall protein (THP also known as Uromodulin) is a kidney specific protein produced by cells of the thick ascending limbs (TAL). While predominantly secreted apically towards the urinary lumen, THP is also released basolaterally by TAL cells, towards the interstitium and the systemic circulation. We previously showed that THP mediates an anti-inflammatory tubular cross-talk between TAL and S3 proximal tubules. It has been proposed that THP also functions as an immuno-modulator, but the exact role of THP in regulating the function of renal macrophages is still unclear.

Methods: Various methodologies described below.

Results: Using THP-/- and THP+/+ mice, we show that THP deficiency is associated with partial macrophage depletion which is limited to the kidney and not other organs such as the liver or spleen. This depletion occurs mostly in the inner stripe of the outer medulla, the site of maximum THP abundance. After ischemia-reperfusion injury (IRI), THP-/- mice exhibit an impaired macrophage response and chemokine profile, and are more susceptible to renal neutrophil infiltration and acute kidney injury (AKI). Treatment of THP-/- mice with purified THP restores the number of kidney macrophages. In addition, treatment of THP-/- mice 24 hours after IRI mitigates subsequent worsening of AKI. Intravital 2-photon microscopy in CXCR3GFP+ mice shows that, intravenously injected, fluorescently-labeled THP is taken up by resident renal macrophages. In vitro, THP stimulates the proliferation of SC human macrophage cells in a concentration dependent manner. This effect, which was not due to inhibition of apoptosis, was explained by specific activation of AKT but not ERK or NFkB. Finally, THP-/- renal macrophages show resistance to the depleting effect of liposomal clodronate in vivo, suggesting impaired phagocytosis with THP deficiency.

Conclusions: Taken together, our data support that THP positively regulates macrophage proliferation and phagocytic activity. In addition to its effect on the epithelium, this emergent immuno-modulatory role could explain the protection conferred by THP in the setting of AKI.

Funding: VA Support

TH-OR006

Macrophage Extracellular Traps Induced by Mac-1 (CD11b/CD18) Dependent Platelet-Macrophage Interactions Promotes Acute Kidney Injury in Rhabdomyolysis Koshu Okubo, Matsuhiko Hayashi, Junichi Hirahashi. *Apheresis and Dialysis Center, Keio Univ, School of Medicine, Tokyo, Japan.*

Background: Rhabdomyolysis-induced acute kidney injury (AKI) is a critical complication after breakdown of skeletal muscles. Crush syndrome, an emergency condition caused by traumatic rhabdomyolysis, occurs commonly in natural disasters such as earthquakes and man-made disasters such as wars or terrorism. Recently, macrophages were implicated in disease pathogenesis, however, the detailed molecular mechanism remains unclear. Leukocytes release extracellular traps (ETs) composed of chromatin fibers and granule proteins to eliminate invading pathogens. However, ETs may also cause tissue damage.

Methods: We show that macrophages released ETs in a mouse model of rhabdomyolysis, and contributed to the pathogenesis of rhabdomyolysis-induced AKI.

Results: Administration of ET inhibitors, depletion of platelets, and genetic ablation of Mac-1 (leukocyte specific β2 integrin expressed on macrophages) ameliorated rhabdomyolysis-induced AKI. Heme-activated platelets enhanced macrophage extracellular traps (METs) production, involving intracellular ROS generation and histone citrullination. These results revealed an unanticipated role for platelets in rhabdomyolysis-induced AKI, and suggested that an interaction between platelets and Mac-1 contributed to disease pathogenesis.

Conclusions: Our findings provide a novel mechanism in rhabdomyolysis-induced AKI that Mac-1 may potentially be targeted for treatment of the disease.

Funding: Government Support - Non-U.S.

TH-OR007

FTY720 Regulates Mitochondria Biogenesis in Dendritic Cells to Prevent Acute Kidney Injury Elvira Kurmaeva, Kyle J. Alexander, Liping Huang, Amandeep Bajwa. *Medicine, Univ of VA, Charlottesville, VA.*

Background: FTY720, a S1PR agonist has been shown to protect kidneys from IRI. However, systemic use is limited due to adverse side effects. Dendritic cells (DCs) have the ability of regulate innate and adaptive responses in AKI. In current study we tested if FTY720 could induce mitochondria biogenesis to induce tolerogenic DCs to use as cellular therapy to limit the off-target effects associated with systemic drug admiration in kidney IRI.

Methods: Renal injury was assessed by plasma creatinine (PCr; mg/dl). 8-wk old C57BL/6 WT mice were used for generating highly pure DCs from bone marrow precursors. Cells were treated with cocktail of GM-CSF±FTY720. On day 7 DCs were treated with 100ng/ml LPS or Veh to induce activation. All four groups (Veh/Veh, Veh/LPS, FTY/Veh and FTY/LPS) were analyzed using real-time PCR for cytokines and mitochondria: nuclear DNA ratio, facs (for activation (MHCII) and co-stimulation (CD40/80/86) markers, and mitochondrial function (mass (MitoTrackerGreen), potential (CMXRos), oxidation (MitoSOX))and Seahorse flux analyzer for MitoStress. For in vivo studies, Veh/LPS and FTY/LPS-DCs ($0.5X10^6$, i.v.) were transferred 24hrs prior to or 4hrs after IRI.

Results: FTY720-DCs have higher oxygen consumption rate (38.18 vs 107.16; $p<0.01$), ATP production (45.29 vs 101.12; $p<0.01$) and spare respiratory capacity (163.67 vs 314.82) compared to vehicle DCs. FTY/LPS-DCs have significantly lower expression of MHCII and CD40/80/86 compared to Veh/LPS-DCs. FTY/LPS-DCs also have higher mtDNA/ncDNA ratio, significantly higher MitoSox (MFI, 800±50.1 vs 152±10.3; $p<0.001$) and MitoTracker Green (515±25.1 vs 1000±16.1; $p<0.001$) signal compared to Veh/LPS-DCs. FTY/LPS-DCs have higher gene expression for IL10, S1Pr1 and PGC1α compared to Veh/LPS-DC. Furthermore, transfer of FTY/LPS-DCs to WT mice 24hrs prior (PCr, 0.17±0.02 vs 1.5±0.17, $p<0.001$) or 4hrs after IRI (PCr, 0.53±0.08 vs 1.3±0.12, $p<0.01$) significantly protects the kidneys from IRI compared to Veh/LPS-DCs treated mice.

Conclusions: FTY720 induces tolerogenic phenotype in DCs by modulating mitochondrial biogenesis and adoptive transfer of FTY720-DCs either prior to or after established ischemic injury protects kidneys from IRI.

Funding: NIDDK Support

TH-OR008

Cardiorenal Syndrome: A Novel Mouse Model Assessed Using Near-Infrared Transcutaneous Fluorescence Michael Hutchens,[1] Rumie Wakasaki,[1] Mizuko Ikeda,[1] Hak Soo Choi,[3] Sharon Anderson.[2] *[1]Anesthesiology & Perioperative Medicine, Oregon Health & Science Univ, Portland, OR; [2]Internal Medicine, Oregon Health & Science Univ, Portland, OR; [3]Radiology, Massachusetts General Hospital/Harvard Univ, Boston, MA.*

Background: Cardiorenal syndrome type 1 causes acute kidney injury (AKI). Animal models and diagnostic aids are lacking. Near-infrared fluorophores are resistant to biologic interference and thus favorable in injury models. We developed a mouse model of cardiorenal syndrome and tested a near-infrared fluorophore, ZW800-1, to assess cardiac and renal function.

Methods: ZW800-1 (MW943D)was synthesized, and mouse CA/CPR conducted, as described. Cardiac function was measured by transthoracic echocardiography, 2- and 24h after CA/CPR. GFR was assessed by inulin clearance. Tubular cell death was quantified by unbiased stereology, creatinine (sCr) by creatine aminohydrolase assay, and transcutaneous fluorescence of ZW800-1 with a whole-animal imager at 800nm emission, simultaneously with GFR. ZW800-1 fluorescence distribution was measured at 7 ROIs every 1 s for 5m and decay every 5m for 120m, after injection . Clearance was calculated from fluorescence by standard curve, modeled with delayed (55m) single-phase kinetics. Correlation and Bland-Altman analysis were performed.

Results: CA/CPR causes biventricular failure at 2h compared to sham (LV FS 8±13% vs 16±25%/RV:PA systolic notch index 0.97±0.2 vs 0±0 n=12, $p<0.05$) which resolved by 24h. CA/CPR caused severe AKI,correlating with LV>RV dysfunction (GFR sham 87±32 CA/CPR 3±3 μL/m sCr sham 0.2 CA/CPR 1.2 mg/dL n=16, $p<0.01$ 2h LVFS:24h sCr r=-0.71, n=12,$p<0.001$). ZW800-1 was not cleared in 4 mice with bilateral nephrectomy. ZW800-1 decay half time and clearance correlated with GFR (r=0.92, bias 5‡24μL/m, 95% agreement-41-52μL/m, n=32, $p<0.0001$) ZW800-1 fluorescence was lower in CA/CPR than sham animals 8-10s after injection ($p<0.01$) correlating with 2h LV function (r=0.74, $p<0.01$).

Conclusions: CA/CPR is a model of cardiorenal syndrome type 1. ZW800-1, a small near-infrared fluorophore being developed for clinical intraoperative imaging is favorable for evaluating cardiac and renal function noninvasively.

Funding: NIDDK Support, Private Foundation Support

TH-OR009

Early DNA Hypometlylation, HIF-1 α Reduction and Increased Oxidative Stress Promotes Acute Kidney Injury (AKI) to Chronic Kidney Disease (CKD) Transition Andrea Sanchez-Navarro,[1,2] Norma Gonzalez Rubio,[1,2] Rosalba Pérez-Villalva,[1,2] Norma Bobadilla.[1,2] *[1]Molecular Physiology Unit, Inst de Investigaciones Biomédicas, UNAM, Mexico City, Mexico; [2]Dept of Nephrology, Inst Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.*

Background: AKI is now recognized as an independent risk factor for CKD development. The mechanisms involved in the AKI to CKD transition are poorly understood and even less is known about the temporality of renal alterations along the transition. The aim was to analyze the time course response of inflammation, oxidative stress, hypoxia, and fibrosis, as well as, epigenetic modifications in the AKI to CKD transition.

Methods: Fifty-two male Wistar rats were divided in: sham operated (S), right nephrectomy (UNx) and nephrectomy plus left renal ischemia (45 min, UNx+IR) groups. The animals were sacrificed and studied at 1, 2, 3 or 4 months. At the end of each period, mean arterial pressure, creatinine clearance, and renal blood flow were determined. Proteinuria and oxidative stress was evaluated monthly. In the kidney, the mRNA levels of inflammation, hypoxia and fibrosis markers, as well as, the global DNA methylation were assessed since 1 to 4 months. Renal histopathological alterations were also examined.

Results: After 4 months, the UNx+IR group developed CKD characterized by progressive proteinuria, renal dysfunction, glomerular hypertrophy, tubular dilation and tubulointerstitial fibrosis. These alterations were not seen in S and UNx groups. Since 1-month after AKI, there was a significant increase in oxidative stress by 2-fold and a reduction in the global DNA methylation by 15% that remained along the study. HIF-1α and VEGF were completely depressed by 99% in the 1st and 2nd month, and then recovered in the UNx+IR group compared to control group. Whereas TGF-β and IL-6 were up-regulated lately and occurred when the renal fibrosis was detected.

Conclusions: The HIF-1α/VEGF reduction could be responsible of inducing vascular rarefaction and chronic renal hypoxia. Our results suggest that reduced HIF-1α signaling, increased oxidative stress and DNA hypomethylation play a crucial role in the early phase of AKI to CKD transition.

Funding: Government Support - Non-U.S.

TH-OR010

The Gli1+ Kidney MSC Population Is Not Fixed but Dynamically Acquires Gli1 Expression after AKI Flavia G. Machado,[1] Gizely C.S. Moreira,[1,2] Eoghainín O Hainmhire,[1] Benjamin D. Humphreys.[1] *[1]Div of Nephrology, Washington Univ in St. Louis, St. Louis, MO; [2]Renal Div, Univ of Sao Paulo, Sao Paulo, SP, Brazil.*

Background: We have shown that Gli+ expression in kidney defines a population of MSC-like pericytes that are the major myofibroblast progenitor population in kidney fibrosis. It is unclear whether this population is fixed, or if interstitial cells can dynamically gain Gli1 expression and myofibroblast differentiation capacity after injury.

Methods: We performed bilateral ischemia reperfusion injury (biIRI) in Gli1-nLacZ reporter mice and evaluated the distribution and density of Gli1+ cells, over a 14 day time course. We investigated whether the Gli1+ population proliferated or if Gli1 expression occurred in a previously Gli1- population. In vitro, we cultured fibroblasts from normal rat kidney (NRK-49F) with TGFβ and evaluated Gli1 expression.

Results: Using a moderate, reversible biIRI model (24 hr BUN, 121 + 20, avg. + SD), Gli1 mRNA was progressively upregulated during days 1, 3, 7 and 14 days after IRI reaching a maximal level of 14-fold over control mice on day 14. Quantitation of nLacZ expression by automated image analysis revealed a doubling of Gli1+ cells by day 14 in the cortex, from 0.31±0.01 cells/mm² in control *vs.* 0.57±0.08 cells/mm² in d14 biIRI. Gli1+ cell numbers were higher in the outer medulla, the site of maximal injury. There, Gli1+ cells rose from 0.50±0.05 cells/mm² at baseline to 1.64±0.15 cells/mm² by d14 biIRI. As expected, all Gli1 cells were PDGFRβ+. Gli1 cells differentiated into myofibroblasts during AKI repair as well, reflected by acquisition of αSMA expression by double immunofluorescent staining. Despite the overall increase in Gli1 cell number, there was no more than 0.5% of Gli1/Ki67 co-positive cells in cortex, and no more than 4% co-positive cells in medulla at all time points.

Conclusions: During AKI repair, stromal cells can acquire Gli1 expression de novo. Since Gli1 expression defines a myofibroblast progenitor population, these results indicate that myofibroblast progenitors are recruited from a Gli1-negative stromal cell pool, rather than the proliferation of a fixed Gli1-positive population.

Funding: NIDDK Support

TH-OR011

Novel Biomarkers Predict Progressive Nephropathy in Patients with Type 2 Diabetes after Acute Coronary Syndrome: The EXAMINE Trial

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Background: Novel biomarkers may improve identification of individuals at risk of progressive nephropathy in type 2 diabetes (DM2), but prior studies are limited in size.

Methods: Filtration (Cystatin C) and urine tubular injury markers (neutrophil gelatinase-associated lipocalin [NGAL], kidney injury molecule-1, [KIM1]) were collected in >90% and urine protein/Cr ratio(PCR) in >58% of 5,380 patients with DM2 and recent acute coronary syndrome enrolled in the EXAMINE trial. eGFR was estimated with the CKD-EPI equation. End-stage renal disease was defined as a requirement for dialysis or eGFR <15 mL/min/1.73m^2.

Results: Median follow-up was 18 mo and 71% had eGFR ≥60 mL/min/1.73m^2. Increasing quartiles of Cystatin C, KIM1, NGAL, and PCR strongly associated with combined ESRD or 50% decline in eGFR and mean change in eGFR (P_{trend}≤0.03 for all comparisons).

Biomarker	Q1	Q2	Q3	Q4	P Trend
Cystatin C	(N=1272)	(N=1313)	(N=1337)	(N=1291)	
ESRD or 50% decline in eGFR	0.16%	0.23%	0.90%	6.05%	<0.001
Change in eGFR (mL/min/1.73m^2)	0.02 ± 10.6	0.06 ± 11.6	-0.9 ± 13.4	-0.7 ± 12.4	0.03
KIM-1/Cr	**(N=1199)**	**(N=1235)**	**(N=1217)**	**(N=1224)**	
ESRD or 50% decline in eGFR	0.58%	1.38%	1.48%	3.68%	<0.001
Change in eGFR (mL/min/1.73m^2)	0.7 ± 11.7	-0.2 ± 11.7	0.4 ± 12.1	-1.4 ± 2.6	<0.001
NGAL/Cr	**(N=1250)**	**(N=1237)**	**(N=1237)**	**(N=1238)**	
ESRD or 50% decline in eGFR	0.56%	0.89%	1.38%	4.37%	<0.001
Change in eGFR (mL/min/1.73m^2)	0.6 ± 11.2	0.2 ± 11.6	-0.7 ± 12.2	-1.5 ± 12.9	<0.001
PCR	**(N=910)**	**(N=1162)**	**(N=977)**	**(N=1000)**	
ESRD or 50% decline in eGFR	0.66%	0.52%	0.41%	6.81%	<0.001
Change in eGFR (mL/min/1.73m^2)	1.4 ± 11.1	0.1 ± 11.8	-0.8 ± 12.4	-2.9 ± 12.8	<0.001

Conclusions: This is the largest study to date of novel and traditional biomarkers and suggests they allow early identification of DM2 patients at risk for worsening kidney function.

Funding: Pharmaceutical Company Support - Takeda

TH-OR012

Plasma Biomarkers and Progressive GFR Decline in Early and Established Diabetic Kidney Disease: Analyses from ACCORD and VA NEPHRON-D

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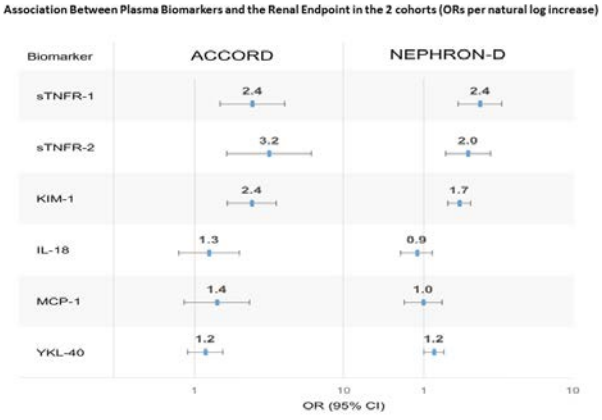
Background: Current measures for predicting renal function decline in persons with type 2 diabetes (T2DM) are unsatisfactory. We examined inflammation, injury and repair biomarkers for risk-stratification for progressive diabetic kidney disease (DKD).

Methods: We measured 6 biomarkers: sTNFR-1 and 2, KIM-1, IL-18, MCP-1 and YKL-40 in banked baseline plasma samples from participants of two randomized, controlled trials (ACCORD, VA NEPRHON-D) in T2DM. In ACCORD, we employed a nested case-control design (n=190 cases of sustained eGFR decline≥40% and 190 controls with eGFR decline<10% over 5 years, matched on baseline eGFR, albuminuria, and BP). In the VA NEPHRON-D trial, we used the entire cohort with banked plasma (n=1156). The renal outcome in VA NEPHRON-D was 50% decline in eGFR if baseline eGFR<60 ml/min/1.73m^2 or decline of 30 ml/min if baseline eGFR>60 ml/min/1.73m^2.

Results: Median biomarker concentrations were roughly two-fold higher in NEPHRON-D vs. ACCORD. After adjusting for baseline covariates, including albuminuria and eGFR, 3 of the 6 plasma biomarkers were significantly associated with the renal outcome in both cohorts. In ACCORD, the adjusted odds ratios (ORs) for sustained eGFR decline ranged from 2.4-3.2 per log increase in sTNFR1, sTNFR2, and KIM-1.



Similarly, in VA NEPHRON-D, the adjusted ORs for sustained eGFR decline ranged from 1.7-2.4 per log increase in sTNFR1, sTNFR2, and KIM-1. The other 3 biomarkers were not significantly associated with the renal outcome in either cohort.

Conclusions: Although the absolute concentrations differed, 3 plasma biomarkers (sTNFR 1 and 2, and KIM-1) were independently associated with higher risk of eGFR decline in T2DM persons with both early (ACCORD) and established DKD (VA NEPHRON-D).

TH-OR013

Urinary Epidermal Growth Factor Is Inversely Associated with Impaired Kidney Function in a Population-Based Lupus Cohort

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Background: Over 30% of systemic lupus erythematosus (SLE) patients have kidney impairment. Urinary epidermal growth factor (uEGF), a marker representing tubular cell regenerative potential, adds prognostic value to estimated glomerular filtration rate (eGFR) and proteinuria in chronic kidney disease (CKD) patients. However, uEGF as a non-invasive biomarker for kidney function and CKD incidence in SLE has not been studied.

Methods: uEGF was measured in the MI Lupus Epidemiology & Surveillance (MILES) Cohort (394 SLE; 170 control) at baseline by ELISA. Statistical analyses included ANOVA, Pearson's correlation, and ROC curves. uEGF concentration in lupus nephritis (LN) cases (n=47) from the independent Clinical Phenotyping & Resource Biobank (C-PROBE) cohort, was used to validate our cross-sectional findings and further determine its association with *longitudinal* kidney function decline.

Results: In MILES SLE cases, uEGF was inversely correlated with baseline eGFR (r=-0.62 ,p< 0.001) and its level distinguished CKD (AUC=0.80 by uEGF vs 0.62 by proteinuria). Further, uEGF distinguished ESRD in cases and controls (AUC=0.88). In C-PROBE, the inverse correlation of uEGF with eGFR was validated in LN cases (r=0.83, p<0.001), and over 3.5 years, uEGF correlated with change in eGFR (r=0.56, p <0.001).

Conclusions: We validate significant correlation between uEGF and eGFR in SLE. For the first time, in a high CKD risk population, we show that uEGF is superior to proteinuria in distinguishing SLE cases with impaired kidney function. Whether uEGF can be used as an early biomarker that can *predict* CKD incidence in SLE requires further longitudinal follow-up.

Funding: NIDDK Support, Other NIH Support - CSTA UL1TR000433; CDC; NIH/NIEHS, Other U.S. Government Support

TH-OR014

Cigarette Smoking Partially Negates the Kidney Protective Effect of ACE Inhibition in Stage 2, Non-Diabetic, Hypertension-Associated CKD

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Background: Cigarette smoking appears to exacerbate nephropathy progression but by unknown mechanisms.

Methods: We recruited 108 smoking and 108 non-smoking, non-diabetic adults with CKD due to hypertension-associated nephropathy, stage 2 eGFR (60-89 ml/min/1.73 m^2), and urine albumin (mg)-to-creatinine (g) ratio (alb/cr) >200. Smokers received substance abuse counseling, nicotine patch, and oral bupropion to encourage quitting by pre-specified reduction of urine cotinine. Non-smokers (n = 108), continued smokers (n = 83), and quitters (n = 25) were followed 5 years after starting ACE inhibition with yearly eGFR (CKD-EPI), alb/cr, and urine (µg)-to-creatinine (g) isoprostane 8-isoprostaglandin $F_{2\alpha}$(8-iso/cr), a measure of oxidative stress.

Results: There was no difference in entry eGFR (p=0.53), alb/cr (p=0.30), or systolic and diastolic blood pressure (p=0.06 and 0.38, respectively) and no difference in either blood pressure at 5 years (p=0.45 and 0.25). Entry 8-iso/cr was higher (p<0.01) in continued smokers (4.3 ug/cr) and quitters (4.1 ug/cr) than non-smokers (1.6 ug/g). At 1 year, non-smokers had lower than entry alb/cr (395±143 vs 420±148, p<0.01), consistent with ACE-related reduced kidney injury. By contrast, at 1 year continued smokers had higher alb/cr (453±152 vs 426±138, p<0.01), consistent with increased kidney injury despite ACE. One-year alb/cr in quitters (356±178 vs 367±160, p=0.15) was not different from entry. One year urine 8-iso/cr was higher in continued smokers (3.6±0.8) than non-smokers (1.6±0.3, p<0.01) and quitters (1.6±0.3, p<0.01). At 5 years, eGFR was lower (p<0.01) in continued smokers (54.9±5.6 ml/min) than non-smokers (66.8±5.8 ml/min) and quitters (64.1±5.6 ml/min).

Conclusions: Continued cigarette smoking in CKD partially negates kidney protection associated with ACEI, possibly by inducing oxidative stress, an effect which appears to be ameliorated by smoking cessation.

Funding: Pharmaceutical Company Support - Texas Tech University

TH-OR015

Risk and Protective Metabolomic Signatures Associated with Albuminuria in Type 1 Diabetes (T1D): A Joslin Kidney Study

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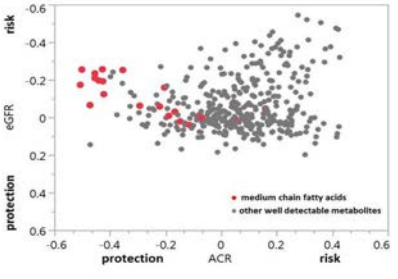
Background: Albuminuria and renal function impairment are intermediate phenotypes of diabetic nephropathy. We aimed to investigate whether these two phenotypic features would be associated with distinct metabolomic signatures in a large study of subjects with T1D of a long duration.

Methods: Plasma metabolites were analyzed via mass spectrometry-based global platform in a cross-sectional study of 419 subjects (T1D duration: median, 25th, 75th percentile: 24, 18-31 years). We examined the associations of metabolites with albumin:creatinine ratio (ACR) and renal function (eGFR) in the following study groups with normal renal function: normoalbuminuria (Resistors, n=92), microalbuminuria (n=44) and proteinuria (n=189)) and in subjects with proteinuria and CKD stage 3 (n=94).

Results: Of the 580 detected metabolites, 383 metabolites were measured at ≥ 80% frequency in the study subjects. With Bonferroni correction, 55 metabolites were significantly associated with ACR (26↓, 29↑). Among the 26 metabolites that levels were higher in the Resistors than in subjects with microalbuminuria and proteinuria; 13 metabolites (50%) belonged to the lipid class. Top protective lipid metabolites included monocarboxylic (e.g. undecanoate) and dicarboxylic (e.g. decanedioate) medium chain fatty acids. 28 metabolites were significantly elevated in the presence of an impaired eGFR. There were 12 metabolites that were associated with both, albuminuria and eGFR.

		ACR ↑		eGFR ↓		ACR ↑ and eGFR ↓
	n [80%]	protection	risk	protection	risk	risk
Amino Acid	121	6	14	0	17	6
Carbohydrate	24	2	1	0	3	1
Lipid	167	13	10	0	1	0
Nucleotide	16	2	1	0	1	3
Other	55	3	3	0	6	2
Total	383	26	29	0	28	12



Conclusions: Metabolomic signatures associated with albuminuria and renal function impairment in diabetic kidney disease are uncoupled to a major degree. Our study suggests that medium chain fatty acids may play a protective role against albuminuria in T1D subjects.

Funding: NIDDK Support, VA Support, Private Foundation Support, Clinical Revenue Support

TH-OR016

Association between Soluble Klotho and Change in Kidney Function: The Health ABC Study

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Background: Chronic kidney disease (CKD) is a condition of soluble klotho deficiency. Despite associations between low soluble klotho and higher degrees of oxidative stress and fibrosis, conditions that promote kidney damage, the longitudinal association between soluble klotho levels and change in kidney function has not been well studied.

Methods: Serum soluble α-klotho was assayed in 2,496 participants within the Health Aging and Body Composition Study, a cohort of well-functioning older adults. Kidney function was determined by cystatin C at baseline and years 3 and 10. Associations between baseline soluble klotho levels and rapid decline in kidney function (defined as either estimated glomerular filtration rate (eGFR) decline of greater than 30% or decline in eGFR greater than 3 ml/min/year) and incident CKD (incident eGFR < 60 ml/min/1.73 m^2 and at least 1 ml/min/year decline) were evaluated. Models were adjusted for demographics, baseline eGFR, UACR, comorbidity, and measures of mineral metabolism including FGF-23.

Results: Mean (SD) age was 75 years (3), with 52% female, and 38% African American. Median klotho level was 630 pg/ml (25^{th} – 75^{th} = 477 – 817 pg/ml). In fully adjusted continuous models, each two fold higher klotho had significant associations with lower odds of rapid decline in kidney function (30% decline: OR = 0.78 [0.66, 0.93] and > 3 ml/min/year decline: OR = 0.85 [0.73, 0.98]) but was not significantly associated with incident CKD (IRR = 0.90 [0.78, 1.04]).

Table 1. Association of the doubling of Klotho with kidney function outcomes in the Health ABC Study

Kidney Function Outcomes	Total N	N with outcome	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
> 30% decline in eGFR	2496	405	0.82 (0.69, 0.97)	0.81 (0.68, 0.97)	0.78 (0.65, 0.93)	0.78 (0.66, 0.93)
>3 ml/min/yr decline in eGFR	2496	702	0.92 (0.80, 1.07)	0.87 (0.75, 1.01)	0.84 (0.72, 0.97)	0.85 (0.73, 0.98)
Incident CKD	1914	536	0.90 (0.79, 1.02)	0.89 (0.77, 1.01)	0.89 (0.77, 1.02)	0.90 (0.78, 1.04)

Incident CKD = incident eGFR < 60 ml/min/1.73m^2 and at least 1 ml/min/year decline. Incident CKD group excludes those with eGFR < 60 ml/min/1.73m^2 at baseline

Model 1 = unadjusted analysis.
Model 2 = adjusted for demographics and baseline eGFR.
Model 3 = M2 + diabetes, cardiovascular disease, hypertension, and UACR.
Model 4 = M3 + calcium, phosphorus, PTH, and FGF-23.

Conclusions: Higher soluble klotho concentrations are independently associated with a lower risk of decline in kidney function. Future studies should replicate these results in those with advanced CKD and evaluate the mechanism underlying these findings.

Funding: Other NIH Support - NIA

TH-OR017

Lung Function and Incident Kidney Disease: The Atherosclerosis Risk in Communities (ARIC) Study

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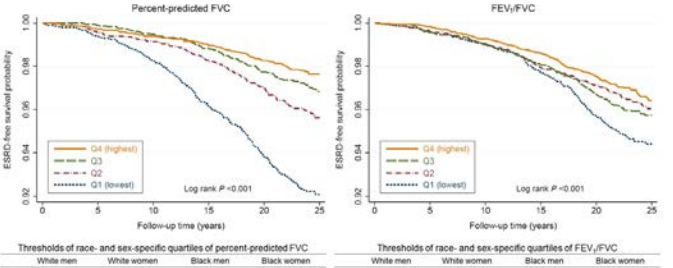
Background: Reduced lung function is associated with various clinical outcomes like cardiovascular disease. Little is known about its association with incident ESRD and CKD.

Methods: In 14,946 ARIC participants aged 45-64 years at baseline (1987-89), we examined the associations of race- and sex-specific quartiles of percent-predicted forced vital capacity (FVC) and the proportion of forced expiratory volume in 1 second in FVC (FEV_1/FVC) with subsequent risk of ESRD (initiation of dialysis therapy, transplantation, or death due to CKD) and CKD (ESRD, ≥25% decline in eGFR reaching <60 mL/min/1.73 m^2, or CKD-related hospitalizations) through 2012, using Kaplan-Meier method and Cox proportional hazards models with adjustment for potential confounders.

Results: During 25 years of follow-up, 526 and 3,704 cases developed ESRD and CKD, respectively. The incidence of ESRD was higher in those with lower percent-predicted FVC and FEV_1/FVC (Figure). The adjusted hazard ratio (HR) [95% CI] of incident ESRD for the lowest (vs. highest) quartile was 1.72 [1.31-2.26] for percent-predicted FVC and 1.33 [1.03-1.73] for FEV_1/FVC. Compared with normal lung function pattern, mixed pattern (3.4% of participants with percent-predicted FVC <80% and FEV_1/FVC <70%) demonstrated the highest adjusted HR of ESRD (1.97 [95% CI, 1.36-2.85]), followed by restrictive (1.77 [1.35-2.31] in 4.8% with percent-predicted FVC <80%) and then obstructive (1.28 [1.01-1.62] in 18.9% with FEV_1/FVC <70%). Similar associations were seen with incident CKD.



Thresholds of race- and sex-specific quartiles of percent-predicted FVC

	White men	White women	Black men	Black women
Q4	≥108.0	≥114.4	≥103.8	≥110.1
Q3	98.9 to <108.0	105.0 to <114.4	94.9 to <103.8	99.5 to <110.1
Q2	90.1 to <98.9	95.1 to <105.0	85.3 to <94.9	89.1 to <99.5
Q1	<90.1	<95.1	<85.3	<89.1

Thresholds of race- and sex-specific quartiles of FEV_1/FVC

	White men	White women	Black men	Black women
Q4	≥78.2	≥79.3	≥80.7	≥82.0
Q3	74.0 to <78.2	75.7 to <79.3	76.5 to <80.7	78.5 to <82.0
Q2	68.6 to <74.0	71.5 to <75.7	70.9 to <76.5	73.8 to <78.5
Q1	<68.6	<71.5	<70.9	<73.8

Conclusions: Reduced lung function, particularly lower percent-predicted FVC, is independently associated with CKD progression.

Funding: Other NIH Support - NHLBI

TH-OR018

A Peptide Transporter 2 (PEPT2) Gene Variant Predicts the Severity of Porphyria-Associated Chronic Kidney Disease Nicolas Pallet,[1] Alexandre Karras,[1] Eric Thervet,[1] Hervé Puy.[2] *[1]Hôpital Européen Georges Pompidou; [2]Centre Français des Porphyries.*

Background: CKD occurs in the majority of patients with AIP (Acute Intermittent Porphyria). During AIP, d-aminolevulinc acid (ALA) is excreted in urine, where it promotes apoptosis of proximal tubular cells, leading to tubulointerstitial damage. The peptide transporter 2 (PEPT2, also known as SLC15A2) is expressed by renal proximal tubular cells and mediates the reabsorption of ALA. A functional single nucleotide variant is associated with a lower affinity of the transporter for ALA.

Methods: To test if *PEPT2* variants impact the severity of AIP induced CKD, we follow-up a cohort of 122 patients with AIP for 10 years. *PEPT2* has been genotyped for the T/C substitution at the position 1048 in exon 13, and the T/C substitution at position 1225 (exon 15) (total linkage disequilibrium). The allelic frequency of the variants was 0.53, and the distribution was in accordance with the Hardy Weinberg equilibrium.

Results: Carriers of the *PEPT2*1*1* genotype experienced significantly worse renal function compared to **2* carriers (54.4±1, 66.6±2. and 78.1±3.8 ml/min/1.73m^2, p=0.0004). eGFR loss was -11 ml/min/1.73m^2 over the follow-up period for *PEPT2*1/*1* carriers, compared to -2.4 ml/min/1.73m^2 for the *PEPT2*1*2* genotype *and* +3.4 ml/min/1.73 m^2 for *PEPT*2*2* patients (p=0.0016). During the follwo-up, incident renal dysfunction (defined by eGFR<60 ml/min/1.73m^2) was diagnosed in up to 20% *PEPT2*1*1* patients, 14% of the *PEPT2*1*2* and 0% of the *PEPT2 *2*2* (p=0.007). At the end of the follow-up, 68% of the *PEPT2*1*1* had eGFR<60 ml/min/1.73m^2 compared with 37 % of the *PEPT2*1*2,* and 15% of the *PEPT2*2*2* (p=0.0002). In multiple regression models, *PEPT2*1*1* genotype remained significantly associated with eGFR<60 ml/min/1.73m2, with an odds ratio of 10.7. Losartan, a specific inhibitor of PEPT2, reduces ALA intracellular accumulation and inhibits ALA-induced apoptosis in proximal tubular cells in culture.

Conclusions: PEPT2 is critical the severity of AIP-induced CKD and is a potential therapeutic target. Since PEPT2 transports peptide-like molecules such as antiviral nucleoside prodrugs, it may represent a susceptibility factors for the nephrotoxicity of these drugs.

TH-OR019

Glycoprotein A (GlycA), a Pro-Inflammatory Marker of Protein Glycosilation, Is Associated to Albuminuria Independently of Cardiovascular Risk Factors and C-Reactive Protein: Results from ELSA-Brasil Silvia M. Titan,[1] Roberto Pecoits-Filho,[2] Isabela M. Bensenor,[3] Paulo Lotufo.[3] *[1]Nephrology Div, Faculty of Medicine, Sao Paulo Univ, Sao Paulo, Brazil; [2]School of Medicine, Pontifícia Univ Católica do Paraná, Curitiba, Paraná, Brazil; [3]Epidemiological and Clinical Research Center, Univ Hospital, Sao Paulo Univ, Sao Paulo, Brazil.*

Background: Systemic inflammation has been implicated in several chronic diseases. GlycA is a new nuclear mass ressonance (NMR) spectroscopy-derived biomarker of systemic inflammation that reflects protein glycosilation. We evaluated the role of GlycA in CKD, using albuminuria as a surrogate marker.

Methods: The association between GlycA, measured by NMR, LabCorp, (Raleigh, NC) and overnight 12h-albuminuria was evaluated among 5050 participants from the Sao Paulo site of the Brazilian Longitudinal Study of Adult Health (ElSA-Brasil).

Results: GlycA was higher among older, women, smokers, alcohol abstemious, obese and in those with diabetes, hypertension or dyslipidemia. In addition, albuminuria was positively associated with GlycA. In linear regression, glycA was significantly associated to log albuminuria (B 0.0008; 95%CI 0.0007–0.0009, P<0.0001), remaining significant after adjustment for age, sex, diabetes, SBP, smoking, alcohol and lipids. Importantly, the association between GlycA and albuminuria remained significant after hsCRP was added to the model. In logistic regression, GlycA was positively related to the risk of being micro or macroalbuminuric (versus normoalbuminuric), even after adjustments including hsCRP (OR 1,008, 95%CI 1,005–1,010, p<0,0001). By repeating this model with a stepwise procedure, GlycA was left in the model, while hsCRP was not. In the ROC curve, GlycA had a higher AUC in comparison to hsCRP (p=0,06, for association to micro or macroalbuminuria).

Conclusions: In conclusion, the present study demonstrates that GlycA is associated with albuminuria, independently of other major risk factors for CKD progression, including (and with a stronger association than) hsCRP. Our results suggest that GlycA may be an interesting novel marker of CKD progression, through its protein glycosylation-induced inflammation properties.

Funding: Government Support - Non-U.S.

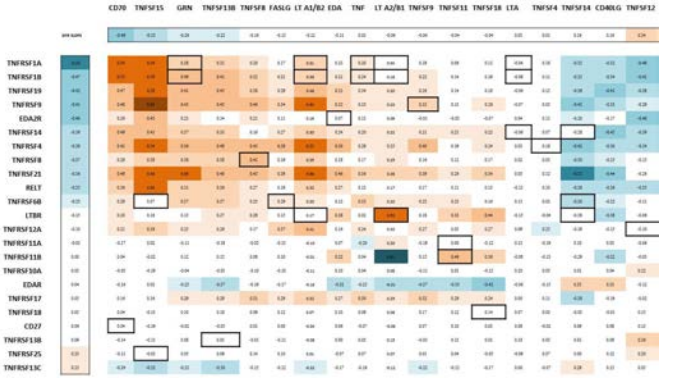
TH-OR020

Multiple Proteins of TNF Superfamily Contribute to Progression to ESRD in Diabetes in a Global Profiling Study Monika A. Niewczas,[1] John J. Tsay,[1] Adam Smiles,[1] Melissa Major,[1] Joseph V. Bonventre,[2] Andrzej S. Krolewski.[1] *[1]Genetics and Epidemiology, Joslin Diabetes Center, Harvard Medical School, Boston, MA; [2]Renal Div, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.*

Background: We previously showed, using a targeted approach, that Tumor Necrosis Factor Receptors 1 & 2 (TNFRs) are robust predictors of renal function decline in diabetes. Here, we aimed to determine a comprehensive inflammatory signature associated with risk of ESRD using global profiling.

Methods: Our study group included 219 Joslin Kidney Study participants with T1D, proteinuria and CKD Stage 3 that were followed up to 12 years. Non-Progressors (eGFR decline ≤ 2.5 ml/min.1.73m^2 /yr) accounted for 34% of the cohort (n=76), whereas Rapid Progressors to ESRD (eGFR decline > 5 ml/min/1.73m^2 /yr) comprised 38% (n=84). Proteomic profiling of inflammatory proteins (n=210) was performed on an aptamer-based platform (Somascan).

Results: In the multivariate analysis 38 proteins differed between Progressors and Non-Progressors (Bonferroni corrected p value <0.05). A roster of significant proteins was enriched with TNF family members that included receptors: TNFR1 and TNFR2, TAJ, DR6, and ligands TWEAK or TNFSF15. TNFα and β were not associated with the outcome. Correlations among TNF superfamily members (figure: orange to blue) did not correspond to their known ligand-receptor interactions (figure: black open squares).



Conclusions: Our global proteomic profiling study confirmed associations of TNFRs as robust predictors of renal function decline in T1D. Further, it revealed that TNF superfamily members accounted for a major part of the inflammatory signature contributing to the progression of diabetic nephropathy. Mechanisms regulating circulating levels of this family and their contributions to the disease progression urgently need to be determined.

Funding: NIDDK Support, Private Foundation Support

TH-OR021

Akt Is a Multifaceted Protein in Albumin Endocytosis Elif Erkan, Cory S. Newland. *Pediatric Nephrology, Cincinnati Children's Hospital, Cincinnati, OH.*

Background: Proteins involved in endocytosis can elicit cell signaling events. Albumin in the glomerular filtrate is retrieved by receptor mediated endocytosis (RME) in proximal tubule epithelial cells. We reported a link between albumin endocytosis and cell signaling protein, protein kinase B (Akt). Akt1 and Akt2 both mediate albumin endocytosis in proximal tubule epithelial cells in cell culture. We propose that Akt mediates albumin endocytosis through its interaction with clathrin associated sorting proteins.

Methods: Inhibition of Akt1 and Akt2 in proximal tubule epithelial cells is accomplished by generation of Akt1/2 lox/lox SGLT2 cre mouse. Urinary albumin and creatinine excretion is measured with 24-hour urine collection. Renal expression of megalin, cubilin and clathrin HC is evaluated by western blotting and immunofluorescence. Protein-protein interactions are assessed by coimmunoprecipitation experiments.

Results: Global knock-out (KO) of Akt1 or Akt2 causes down regulation of megalin and cubilin expression in the proximal tubule epithelial cells associated with increased urinary albumin excretion and low molecular proteinuria. In order to eliminate systemic effects of global inhibition Akt1 and Akt2, we generated a mouse with targeted deletion of Akt1 and Akt2 (Akt1/2lox/lox SGLT2 cre) in proximal tubule epithelial cells. Akt1/2lox/lox SGLT2 cre mice displayed decreased expression of clathrin-heavy chain (clathrin-HC), megalin and cubilin in association with significant albuminuria. Coimmunoprecipitation experiments revealed an interaction between clathrin-HC, μ2 subunit of adaptor protein2 (AP2) and Akt. Furthermore KO of Akt1 and Akt2 in human proximal tubule epithelial cells resulted in a decrease in clathrin coated pits.

Conclusions: We conclude that Akt links cell signaling events to albumin endocytosis in proximal tubule epithelial cells. We propose that Akt orchestrates albumin endocytosis by recruiting clathrin to the plasma membrane and inducing formation of clathrin-coated pits. Potentially phosphorylation of clathrin HC by Akt can initiate this event. We postulate that perturbed expression of pro-survival protein Akt to limit endocytosis has implications in induction of tubulointerstitial injury in proteinuric states.

TH-OR022

Mixed Lineage Kinase Domain-Like (MLKL) Mediates Necroptosis in Humans Nina Himmerkus,[1] Hannes Olauson,[2] Ina Maria Schiessl,[3] Jan U. Becker,[4] Karl Kunzelmann,[3] Markus Bleich,[1] Joel M. Weinberg,[5] Andreas Linkermann.[6] *[1]Inst of Physiology, Christian-Albrechts-Univ, Kiel, Germany; [2]Div of Renal Medicine, CLINTEC, Karolinska Inst, Stockholm, Sweden; [3]Inst for Physiology, Univ of Regensburg, Regensburg, Germany; [4]Inst of Pathology, Univ Hospital of Cologne, Cologne, Germany; [5]Dept of Internal Medicine, VA Ann Arbor Healthcare System, Univ of Michigan, Ann Arbor, MI; [6]Clinic for Nephrology and Hypertension, Christian-Albrechts-Univ, Kiel, Germany.*

Background: Necrosis is a pathophysiological hallmark of diseases including myocardial infarction, stroke, sepsis, acute tubular necrosis, autoimmunity and cancer. Necroptosis is a form of regulated necrosis mediated by receptor-interacting protein kinase 3 (RIPK3). The pseudokinase mixed-lineage kinase domain like (MLKL), a RIPK3 target, is required for necroptosis execution *in vitro*, but the role of MLKL *in vivo* has not been investigated in preclinical disease conditions or humans.

Methods: *In vivo* mouse models, *ex vivo* investigation of freshly isolated nephron segments, human kidney transplant biopsies.

Results: We demonstrate that MLKL-deficient mice are protected from all necroptosis-related *in vivo* models such as TNFa-mediated severe inflammatory response syndrome (SIRS) and renal ischemia-reperfusion injury (IRI). Freshly isolated perfused proximal tubules of MLKL-deficient mice showed reduced single cell death events and a delayed onset in synchronized tubular necrosis. Moreover, intravital microscopy revealed a strongly elevated peritubular capillary blood flow in MLKL-deficient mice in comparison to wild type littermates. In matched human kidney transplant biopsies, the activated form of MLKL (pMLKL) was detected in endothelial cells within two hours after transplantation and in parenchymal cells within four days.

Conclusions: In summary, MLKL deficiency protects mice from renal damage by i) the prevention of parenchymal necroptosis and ii) an increase in capillary blood flow. In addition, this is the first detection of activation of the necroptosis pathway in humans.

TH-OR023

Pik3c3 Mediates Nephron Loss-Induced Compensatory Nephron Hypertrophy Ting Liu,[1] Jinxian Xu,[1] Benjamin D. Humphreys,[2] Caihong Dai,[1] Jian-Kang Chen.[1] *[1]Cellular Biology & Anatomy and Medicine, Medical College of Georgia at Augusta Univ, Augusta, GA; [2]Renal Div, Dept of Medicine, Washington Univ School of Medicine, St. Louis, MO.*

Background: Nephron loss stimulates the residual nephrons to undergo compensatory nephron hypertrophy (CNH), which is implicated in progressive nephron damage. Activation of the mechanistic (formerly mammalian) target of rapamycin complex 1 (mTORC1) mediates uninephrectomy (UNX)-induced CNH. We recently observed class 3 phosphatidylinositol 3-kinase (Pik3c3) activation in the remaining kidney after UNX. However, whether Pik3c3 activation is essential for mTORC1 activation and CNH remains undefined.

Methods: We created a *Pik3c3*-floxed mouse and crossed it to *SLC34a1.CreER^{T2}* mice to generate tamoxifen-inducible proximal tubule-specific *Pik3c3* knockout (*KO*) mice, which have a genotype of *Pik3c3$^{flox/flox}$;SLC34a1.CreER^{T2}*(+). Gender-matched *Pik3c3$^{flox/flox}$;CreER^{T2}*(-) littermates were used as controls (*Ctrl*) mice.

Results: Upon induction with tamoxifen (120 mg/kg by I.P. at 6 weeks of age), *KO* mice but not *Ctrl* mice showed Pik3c3 deletion only in the proximal tubules (mainly in the S1 and S2 segments). The *KO* mice did not exhibit any apparent phenotype, with a mean body weight and kidney-to-body weight ratio similar to those of *Ctrl* littermates. It is known that in response to UNX, all components of the nephron may hypertrophy to a certain degree but the proximal tubule undergoes the most prominent hypertrophy. Interestingly, when subjected to UNX, *KO* mice developed significantly less renal hypertrophy compared to *Ctrl* mice, revealed by UNX-induced increases in kidney-to-body weight ratio (*Ctrl*: 33.15±1.97 vs. *KO*: 15.81±2.82%; $p<0.001$, $n=7$) and protein-to-DNA ratio (*Ctrl*: 25.00±4.01 vs. *KO*: 9.78±2.88%; $p<0.05$, $n=7$). Signaling studies with immunoblotting and immunostaining indicated that Pik3c3 knockout inhibited UNX-induced mTORC1 activation in the proximal tubules, particularly in the S1 and S2 segments.

Conclusions: This study provides the first genetic evidence of Pik3c3 activation as a major mechanism mediating nephron loss-induced residual nephron hypertrophy upstream of mTORC1 activation.

Funding: NIDDK Support

TH-OR024

NADPH Oxidase 4 Deficiency Increases Acute Renal Injury and Tubular Apoptosis during Ischemic Reperfusion Injury Romain Dissard, Stellor Nlandu Khodo, Pierre-Yves F. Martin, Sophie M. De Seigneux. *Dept of Medicine Specialties, Service of Nephrology, Univ Hospital of Geneva, Geneva, Switzerland.*

Background: NADPH oxidase 4 (NOX4) is highly expressed in kidney proximal tubular cells. NOX4 constitutively produces hydrogen peroxide, which may regulate important pro-survival and anti-oxidant pathways, or play a deleterious role. Renal ischemia reperfusion injury (IRI) is a classical model mimicking human ischemic acute tubular necrosis. We hypothesized that endogenous NOX4 may play a protective role in kidney IRI.

Methods: Wild type (WT) and NOX4 Knock-out (KO) animals were subjected to sham or 22 minutes bilateral renal artery ligation and sacrificed 24 hours after reperfusion. Stable renal tubular cells lines with transient NOX4 silencing and mouse embryonic fibroblasts issued form WT and NOX4KO mice were used for in vitro experiments.

Results: In WT animals subjected to IRI, NOX4 protein expression increased after 24 hours. Compared to WT, NOX4 KO mice displayed worst renal function, more severe tubular apoptosis, decreased Bcl-2 expression and higher histological damage scores. Activation of the NRF2 pathway was decreased in NOX4 KO mice in response to IRI. This was related to decreased baseline KEAP1 oxidation leading to decreased NRF2 stabilization. This also resulted in decreased glutathione levels at baseline. *In vitro* silencing of NOX4 in cultured tubular cells and cells derived from NOX4 KO mice showed an enhanced propensity to apoptosis, with reduced expression of NRF2, glutathione content, decreased mitochondrial membrane potential and Bcl-2 expression. Overexpression of a constitutively active form of NRF2 (caNRF2) in NOX4 depleted cells rescued most of this phenotype in cultured cells, implying that NRF2 regulation by ROS issued from NOX4 may play an important role in its anti-apoptotic property in kidney tubular cells.

Conclusions: NOX4 protein displays anti-apoptotic properties in renal tubular cells subjected to injury. NOX4 deletion aggravates IRI lesions and renal function in mice. Baseline NRF2 regulation by NOX4 may play an important role in this phenotype, whereas other pathways are not excluded. NOX4 inhibition may aggravate tubular injury in stress conditions.

Funding: Government Support - Non-U.S.

TH-OR025

Bone Marrow Is Central to the Severity of Gadolinium-Associated Systemic Fibrosis Brent Wagner,[1,2] Chunyan Tan,[2] Viktor Drel,[2] Jeffrey L. Barnes,[2] Yves C. Gorin,[2] Doug Yoon Lee.[2] *[1]Medical Service, South Texas Veterans Health Care System, San Antonio, TX; [2]Medicine (Nephrology), Univ of Texas Health Science Center at San Antonio, San Antonio, TX.*

Background: Gadolinium-based magnetic resonance imaging contrast induces systemic fibrosis in humans and rodents. Cumulative doses correlate with severity. Bone marrow–derived fibrocytes accumulate in the dermis. Whether target organs liberate chemokines to recruit these cells or if they are stimulated to home to the affected tissue is unknown.

Methods: Transgenic (tagged) donor rats were treated with gadolinium–based contrast. Bone marrow was obtained from the treated animals and age–matched controls. Rats with subtotal nephrectomies were lethally–irradiated followed by salvage transplant with either the contrast–naïve or contrast–exposed bone marrow. Bone marrow recipients were randomized into control or contrast treatment.

Results: Dermal fibrosis was induced by contrast. This was exacerbated in recipients of contrast–exposed marrow. Fibronectin, the C-C chemokine receptors 2 and 7, and oxidative stress were all increased in skin from the contrast–treated animals—all parameters more severe in recipients of contrast–treated animals. The respective ligands, monocyte chemoattractant protein and C-C motif ligand 19, were both elevated in the skin from contrast–treated animals. When a C-C chemokine receptor inhibitor was co-administered with contrast, the severity of skin disease (including dermal cellularity) was reduced. Neutralizing antibody to monocyte chemoattractant protein 1 suppressed myeloid infiltration (using an *in situ* skin punch biopsy/labeled bone marrow co-culture assay).

Conclusions: These data demonstrate that the dermal liberation of specific chemokines recruits circulating myeloid cells. The systemic fibrosis is augmented by bone marrow exposure to contrast. This explains why multiple exposures correlate with severity. Furthermore, bone marrow has a memory of gadolinium exposure; these findings have serious clinical ramifications.

Funding: NIDDK Support, VA Support

TH-OR026

A Podocyte-Specific Knockout of the DNA Repair Rene Ercc1 Resembles Podocyte Aging and Leads to Proteinuria and Focal Segmental Glomerulosclerosis Fabian Braun,[1] Roman Aaron Akbar,[1] Björn Schumacher,[2] Bernhard Schermer,[1,2,3] Wilhelm Bloch,[4] Thomas Benzing,[1,2,3] Christine E. Kurschat.[1,2] *[1]Dept II of Internal Medicine and Center for Molecular Medicine Cologne, Univ of Cologne, Cologne, Germany; [2]Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, Univ of Cologne, Cologne, Germany; [3]Systems Biology of Ageing Cologne, SyBaCol, Univ of Cologne, Cologne, Germany; [4]Dept of Molecular and Cellular Sport Medicine, German Sport Univ Cologne, Cologne, Germany.*

Background: Chronic kidney disease is common among elderly patients. Yet, models investigating this functional decline are lacking. In a previous study, we identified a progeria mouse model of Ercc1-deficiency to exhibit expression profiles similar to those of glomerular aging in wild type mice. Ercc1 facilitates the 5' incision around interstrand cross links and other bulky DNA lesions in the nucleotide excision repair pathway. Thus, a podocyte-specific knockout of Ercc1 may help us gain new insights into glomerular and podocyte aging processes.

Methods: Ercc1$^{flox/flox}$ mice were bred with mice expressing Cre recombinase under the podocin promoter. At 7, 9, 11 and 13 weeks of age weight, urine and serum were analyzed. Kidneys were fixed in paraformaldehyde and embedded in paraffin, fresh-frozen in OCT, or prepared for electron microscopy.

Results: Ercc1^{pko} show no developmental abnormalities but die prematurely at week 13-18. 7 week old kidneys show no morphological changes in light or electron microscopy.

At 9 weeks of age foot process effacement and focal segmental glomerular sclerosis occur. This phenotype is aggravated by week 11. End-stage kidneys reveal sclerosed glomeruli, interstitial fibrosis with tubular atrophy and tubular protein casts. Cultured podocytes subjected to DNA damage exhibited an increase of mTOR phosphorylation and mTOR-Complex1 activation. This phenotype was rescued by rapamycin and was observed in both Ercc1^{pko} and 96 week old wild type glomeruli.

Conclusions: Our study underlines the critical role of podocyte DNA maintenance. Furthermore the podocyte specific knockout of Ercc1 depicts accelerated features of the podocyte aging process and will prove a crucial tool to investigate kidney aging.

Funding: Government Support - Non-U.S.

TH-OR027

KIM-1 Mediates the Uptake of Exosomes and Transfer of MHC II

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Background: Urinary exosomes (EXO) are lipid membrane bound structures that mediate intercellular signaling through the transfer of proteins, miRNA and other factors. Kidney injury molecule 1 (KIM-1) acts as a phosphatidylserine (PS) receptor, inducing the uptake of apoptotic cells and necrotic debris. We hypothesize that KIM-1 acts as an endocytosis receptor, taking up EXO containing PS and mediating the intercellular exchange of signaling molecules, such as MHC II.

Methods: LLC-PK1 cells expressing KIM-1 (PK1-KIM1) and cells expressing empty vector (PK1-pcDNA) were incubated with liposomes composed of PS and fluorescently labeled phosphatidylcholine (PC) or EXO isolated from LLC-PK1 cells, mouse dendritic cells (DC) or human urine by ultracentrifugation. EXO were fluorescently labeled with CytoTracker dye or MHC II-GFP. Uptake was quantified by measuring fluorescence intensity and flow cytometry. EXO were characterized by western blot and electron microscopy. MHC-II levels in urinary EXO from healthy subjects and CKD patients were determined by western blot.

Results: PK1-KIM-1 took up significantly more liposomes than PK1-pcDNA. EXO derived from LLC-PK1 cells, DCs and urine were positive for EXO markers HSP70, Flot-1 and TSG101. The diameter of EXO were between 30-150 nm. KIM-1 expressing cells took up significantly more EXO than empty vector expressing cells independent of the source of EXO. Urinary EXO from CKD patients were found to carry MHC II while EXO from healthy subjects were MHC II negative. We found the transfer of MHC II to primary PTCs to be greater in cells expressing KIM-1 after incubation with DC-derived EXO.

Conclusions: KIM-1 is a PTC receptor for EXO. Urinary EXO from CKD patients carried MHC-II, while urinary EXO in healthy subjects did not. MHC-II on EXO can be transferred to and presented by KIM-1 positive cells, suggesting EXO may serve to link DC activation to PTC MHC II expression and antigen presentation cells in inflammatory settings.

Funding: NIDDK Support

TH-OR028

RTN1A Is a Key Mediator for Progression of Acute Kidney Injury to Chronic Kidney Disease through Increased Endoplasic Reticulum Stress

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Background: A large body of evidence suggests that severe acute kidney injury (AKI) could progress to chronic kidney disease (CKD). ER stress has been considered as a key pathological process leading to tubular cell injury in AKI. However, it remains unclear whether sustained and maladaptive ER stress contributes to the progression from AKI to CKD. Recently, we reported that RTN1A expression is highly associated with the progression of human kidney disease and increased RTN1A expression in renal tubular epithelial cells (RTECs) induces apoptosis and renal fibrosis in the UUO mice through induction of ER stress. Based on these findings, we hypothesized that RTN1A mediated the progression of AKI to CKD through induction of maladaptive ER stress in RTECs.

Methods: To test this, we generated doxycycline-inducible RTN1A RTEC-specific knockdown and over expression mice. Meanwhile, we studied the expression of RTN1A and other ER Stress markers in kidney biopsies of 50 AKI (ATN and AIN) patients at various disease stages.

Results: We found that induction of RTN1A knockdown in RTECs had reduced ER stress and apoptosis of RTECs at the AKI stage and minimal renal fibrosis at the late stage in mice with folic acid nephropathy (FAN) or aristolochic acid nephropathy (AAN). In contrast, induction of RTN1A overexpression in RTECs at the AKI stage resulted more ER stress and apoptosis of RTECs at the AKI stage and more renal fibrosis at the late stage in these mice with FAN or AAN. Then, we validated that in patients with AKI there was also a significant association between renal expressions of RTN1A and ER stress markers (Phosphor-PERK and CHOP). Interestingly, we found in 10 patients with progression of AKI to CKD, RTN1A and CHOP expressions were significantly higher than those without progression to CKD.

Conclusions: In conclusion, our data suggest that RTN1A is a key molecule mediating the progression of AKI to CKD through induction of sustained and maladaptive ER stress in renal tubular epithelial cells.

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

TH-OR029

Proximal Tubule Deletion of Dynamin Related Protein 1 Protects against Renal Ischemia-Reperfusion Injury

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Background: Mitochondrial dysfunction plays a crucial role in the pathogenesis of kidney disease. A key mediator of mitochondrial function is the GTPase, dynamin related protein 1 (DRP1). Pharmacological inhibition of DRP1 in mice has shown to protect against ischemic mediated AKI. Yet, the specific cellular target of DRP1 inhibition in AKI has not been determined. Proximal tubule cells are highly dependent on mitochondrial function. Thus, we hypothesize that the genetic deletion of DRP1 in proximal tubules (PT) protects against renal ischemia-reperfusion injury (IRI) in mice.

Methods: *PepckCre+ Drp1$^{f/f}$* (PT-Drp1 KO, n = 9) and littermate control *PepckCre- Drp1$^{f/f}$* (n = 8) mice were subjected to 26' of bilateral renal ischemia or sham operation. After 24hr of reperfusion, plasma was collected to quantify PCr as a measure of kidney function and kidneys were prepared for assessment of acute tubular necrosis (ATN) by H&E staining, TUNEL and Ki67 positivity by immunofluorescence, quantification of mRNA transcripts by RT-qPCR and neutrophils (CD45$^+$CD11b$^+$Ly6G$^+$) by flow cytometry.

Results: PT-Drp1 KO mice had attenuated IRI-induced PCr levels compared to control mice (1.44 vs. 0.35 mg/dl respectively, $p < 0.001$). Consistent with preserved kidney function, PT-drp1 KO mice had attenuated renal injury indicated by reduced ATN and transcript levels of tubule injury markers *Kim1* and *Ngal* compared to controls. Lastly, PT-Drp1 KO mice had reduced renal inflammation characterized by fewer neutrophils and transcript levels of *Il6* and *Ccl2* compared to control mice. Mechanistically, kidneys from PT-Drp1 KO mice had fewer TUNEL+ and increased Ki67+ epithelial cells.

Conclusions: Loss of PT DRP1 directs epithelial cells from IRI induced cell death pathways to proliferation, enhancing renal recovery. Recovered tubules prevent tubular damage and subsequent necroinflammation. Targeting DRP1 and mitochondrial function may be a therapeutic strategy to divert PT cells from cell death to recovery pathways, mitigating AKI.

Funding: NIDDK Support

TH-OR030

An Intracellular Matrix Metalloproteinase-2 Isoform Induces Tubular Regulated Necrosis: Implications for Acute Kidney Injury in the Elderly

David H. Lovett, Carla Speroni Ceron, Sunil Kumar Joshi, Shaynah Wanga, Joy Walker, Sang Heon Song. *Univ of California San Francisco.*

Background: Acute kidney injury (AKI) causes severe morbidity and mortality and chronic kidney disease (CKD). Mortality is particularly marked in the elderly and with pre-existing CKD. To date, therapeutic targets based models of AKI have failed to translate into preventative or therapeutic treatments. Oxidative stress is a common theme in models of AKI induced by ischemia/reperfusion injury (I/R/I) or sepsis. We recently characterized an intracellular isoform of matrix metalloproteinase-2 (MMP-2) induced by oxidative stress-mediated activation of an alternate promoter in the first intron of the MMP-2 gene. This generates an **N**-**t**erminal **t**runcated MMP-2 isoform (NTT-MMP-2) that is retained intracellularly and is localized to the mitochondria. Significantly, the NTT-MMP-2 isoform is expressed in the proximal tubules of older mice (14 months) and in models of CKD. We recently determined that NTT-MMP-2 is induced in human renal transplants with delayed graft function and that NTT-MMP-2 expression correlates with tubular epithelial cell injury, validating NTT-MMP-2 as a potential target.

Methods: To determine mechanism(s) of action, we generated proximal tubule cell-specific NTT-MMP-2 transgenic mice.

Results: While morphologically normal at the light microscopic level at 4 months, there was evidence for increased mitochondrial oxidative stress. Ultrastructure studies revealed foci of epithelial cell necrosis, loss of the mitochondrial permeability transition and mitophagy. To determine if NTT-MMP-2 expression enhances sensitivity to I/R injury, we performed limited unilateral I/R/I sufficient to induce mild tubular injury in wild type mice. In contrast, expression of the NTT-MMP-2 isoform resulted in a dramatic increase in tubular cell necrosis, inflammation and fibrosis. NTT-MMP-2 mice had enhanced expression of innate immunity genes and prolonged release of danger associated molecular pattern (DAMP) molecules.

Conclusions: We conclude that NTT-MMP-2 "primes" the kidney to enhanced susceptibility to I/R injury via induction of mitochondrial dysfunction. NTT-MMP-2 may be a novel AKI preventative or treatment target.

Funding: NIDDK Support, VA Support

TH-OR031

Treatment of Myeloma Cast Nephropathy: A Randomized Trial Comparing Intensive Hemodialysis with High Cutoff or Standard High-Flux Dialyzers (The MYRE Study) Frank Bridoux,[1] Pierre-Louis Carron,[2] Eric Alamartine,[3] Marie-Noelle Peraldi,[4] Alexandre Karras,[5] Cecile M. Vigneau,[6] Alain Wynckel,[7] Nolwenn Rabot,[8] Christian Combe,[9] Sylvie Chevret,[10] Jean-Paul Fermand.[11] *[1]Nephrology, CHU Poitiers; [2]CHU Grenoble; [3]CHU Saint Etienne; [4]Hopital Saint Louis, Paris; [5]HEGP, Paris; [6]CHU Rennes; [7]CHU Reims; [8]CHU Tours; [9]CHU Bordeaux; [10]Biostatistics, Hopital Saint Louis, Paris; [11]Immunology, Hopital Saint Louis, Paris, France.*

Background: Multiple myeloma (MM) is often revealed by acute kidney injury (AKI) usually related to cast nephropathy (CN). Recovery of renal function is a key prognostic factor. With novel anti-myeloma agents, hemodialysis (HD) independence occurs in about 30% of patients (pts) with severe AKI, advocating for the use of additional strategies to rapidly remove serum monoclonal free light chains (FLC).

Methods: We designed a prospective randomized phase III trial to compare the HD independence rate in pts with inaugural severe AKI secondary to biopsy–proven CN, treated with intensive HD (8 sessions of 5 hours over the first 10 days, then thrice a week) using either high cutoff (HCO) or conventional high-flux dialyser. In both groups, pts received 21 day-courses of bortezomib and dexamethasone (BD) reinforced by cyclophosphamide after 3 cycles in the absence of hematological response.

Results: Between 2011 and 2015, 98 pts were randomized. One pt withdrew consent and 3 had main exclusion criteria. Baseline characteristics in the control arm (n=48) and HCO arm (n=46) were close, including similar high FLC levels (median 6,015 mg/L). HD independence was achieved in 33% and 43% (P=0.31) at 3 months, and in 37.5% and 60% (P=0.03) at 6 months in control and HCO arms, respectively. Rate of hematologic very good partial response or above at 3 months, based on FLC, was 48% in control and 59% in HCO arm (p=0.29). Tolerance of HD schedule and chemotherapy was acceptable in both arms. At 12 months, 10 and 8 pts had died, respectively.

Conclusions: This randomized trial demonstrates that in MM pts with CN and severe AKI treated with bortezomib-based chemotherapy, intensive HCO HD increases renal response rate at 6 months, compared to similar HD dose with conventional high-flux dialyzers.

Funding: Pharmaceutical Company Support - Janssen; Baxter, Government Support - Non-U.S.

TH-OR032

European Trial of Free Light Chain Removal by Extended Haemodialysis in Cast Nephropathy (EuLITE); Survival and Renal Outcomes Colin A. Hutchison,[2] Paul Cockwell,[1] Nils Heyne,[3] Katja C. Weisel,[3] Lesley B. Fifer,[1] Julian D. Gillmore,[4] Arthur R. Bradwell,[5] Mark Cook.[1] *[1]Queen Elizabeth Hospital, Birmingham, United Kingdom; [2]Hawke's Bay District Health Board, Hawke's Bay, New Zealand; [3]Univ of Tuebingen, Tuebingen, Germany; [4]National Amyloidosis Centre, Univ College London, London, United Kingdom; [5]Univ of Birmingham, Birmingham, United Kingdom.*

Background: Myeloma cast nephropathy (MCN) is caused by a pathogenic immunoglobulin serum free light chain (sFLC). High cut-off haemodialysis (HCO-HD) can remove large quantities of sFLC and retrospective uncontrolled clinical trials report better outcomes; however it is uncertain if these were associated with HCO-HD or novel chemotherapy regimens.

Methods: We carried out a prospective multi-centre RCT in patients with newly diagnosed MM and associated MCN who required acute dialysis, comparing HCO-HD to standard high flux (HF)-HD, and using bortezomib based chemotherapy. 90 patients were randomised and followed for 2-years. Results are reported as intention to treat (ITT).

Results: The groups were similar for demographics, myeloma type (light chain only vs intact Ig), and sFLC isotype. At 3 weeks sFLC levels were similar between groups. 24/43 patients (55.8%) in the HCO-HD group and 24/47 (51.6%) in the HF-HD group recovered renal function by 3 months (not significant, NS). There were more lung infections in the first 3-months in the HCO-HD group (12 vs 3, P=0.014). Overall recovery of renal function was 62%; 58.1% in the HCO-HD group, 66% in the HF-HD group (NS). Overall survival at 2-years was 24 (55.8%) in the HCO-HD group and 36 (76.6%) in the HF-HD group. 82.1% who became independent of dialysis were alive at 2 years compared to 41.2% who remained dialysis dependent (P<0.001). Following renal recovery there was no subsequent difference in eGFR between groups; overall median eGFR (range) at 2-years was 34 ml/min/1.73m^2 (13-90).

Conclusions: In this RCT, HCO-HD compared to HF-HD did not improve outcomes in patients requiring acute dialysis for MCN.

Funding: Pharmaceutical Company Support - Baxter Gambro, Janssen, The Binding Site, Government Support - Non-U.S.

TH-OR033

Effects of Intensive SBP Lowering on Incident Chronic Kidney Disease (CKD) and Cardiovascular (CV) Outcomes in Non-CKD Subgroup in Systolic Blood Pressure Intervention Trial (SPRINT) Srini Beddhu, Michael V. Rocco, Robert D. Toto, Timothy Craven, Tom Greene, Alfred K. Cheung, Paul L. Kimmel, Paul K. Whelton. *For SPRINT Research Group.*

Background: The public health significance of the reported higher incidence of CKD with intensive SBP lowering in high-risk hypertensive adults without CKD in SPRINT is unclear.

Methods: In 6662 SPRINT participants without CKD (eGFR ≥ 60 ml/min/1.73 m^2) at baseline, the effects of intensive SBP control (goal <120 vs. standard <140 mm Hg) on incident CKD and the composite of CV outcome or all-cause death were examined. Incident CKD was defined as a >30% decrease in eGFR to a value <60 ml/min/1.73m^2. CV outcome was defined as the first occurrence of MI, ACS, stroke, heart failure, or CV death.

Results: Mean age was 66 ± 9 yrs, 34% were women and 34% were Black. Mean eGFR was 81 ±16 mL/min/1.73 m^2. The SBP difference between the two arms after 6 months of follow-up was 15±0.2 mm Hg. The slopes of eGFR were -5.42±0.50 (intensive) vs. 0.23±0.50 (standard) mL/min/1.73m^2 in the first 6 months (p<0.001). After 6 months, eGFR slopes were similar (-0.79±0.13 vs. -0.68±0.13; p=0.51). Numbers needed to treat for harm (NNTH) for incident CKD and the numbers needed to treat for benefit (NNTB) for CV event/death over the 3.26 yrs of median follow-up are summarized in Table.

Outcome	Intensive arm incidence*	Standard arm incidence*	Hazard ratio [95% CI]	% Absolute risk reduction (increase) [95% CI]	NNTB (NNTH) [95%CI]
Incident CKD	1.32 (140/10583)[$]	0.37 (40/10750)[$]	3.55[2.52, 5.11]	(3.01) [(3.78), (2.26)]	(34) [(45), (26)]
CV event or all-cause death	1.80 (192/10674)[$]	2.51(266/10604)[$]	0.72[0.60, 0.87]	2.17 [1.03, 3.69]	47 [27,97]
* events per 100 person years of follow-up, [$] (N events/ total years of follow-up)					

For each CV event/ death prevented, there were 1.4 incident CKD events (3.01/2.17). None in either arm reached ESRD.

Conclusions: As asymptomatic incident CKD is much more benign than CV event/ death, the risk of incident CKD appears to be outweighed by CV benefits. When the SPRINT intervention is adopted in routine clinical practice, the incidence and consequent prevalence of CKD will need to be determined over the long-term.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIA, NINDS

TH-OR034

Folic Acid Therapy Delays the Progression of Chronic Kidney Disease: The Renal Substudy of the China Stroke Primary Prevention Trial (CSPPT) Xin Xu,[1] Xianhui Qin,[1] Youbao Li,[1] Yong Huo,[2] Fan Fan Hou.[1] *[1]Renal Div, Nanfang Hospital, Southern Medical Univ; National Clinical Research Center for Kidney Disease; [2]Dept of Cardiology, Peking Univ First Hospital.*

Background: The efficacy of folic acid therapy on renal outcomes has not been previously investigated in populations without folic acid fortification. This study was to test whether treatment with enalapril and folic acid is more effective in slowing renal function decline than enalapril alone among Chinese adults with hypertension.

Methods: A randomized, double-blinded clinical trial was conducted in 20 communities in Jiangsu province in China, enrolling 15104 eligible CSPPT participants with an eGFR≥30 ml/min/1.73m^2, including 1671 patients with CKD. Participants were randomized to receive a single tablet daily containing 10mg enalapril and 0.8mg folic acid (n=7545) or 10mg enalapril alone (n=7559). The primary outcome was progression of CKD, defined as a decrease in eGFR of ≥30% and to a level of <60 ml/min/1.73m^2 if the baseline eGFR was ≥60 ml/min/1.73m^2, or a decrease in eGFR of ≥50% if the baseline eGFR was <60 ml/min/1.73m^2; or ESRD. Secondary outcomes included a composite of the primary outcome and all-cause death, rapid decline in renal function, and rate of eGFR decline.

Results: Median followup was 4.4 years. There were 164 and 132 primary events in the enalapril group and the enalapril-folic acid group, respectively. Compared with the enalapril group, enalapril-folic acid group had a 21% reduction in the odds of the primary event (OR,0.79; 95%CI,0.62-1.00), and a slower rate of eGFR decline (1.28% vs 1.42% per year, P=0.02). Among the participants with CKD at baseline, folic acid therapy resulted in a significant reduction in the risks for the primary event (OR,0.44; 95%CI,0.26-0.75), rapid decline in renal function (0.67;0.47-0.96) and the composite event (0.62;0.43-0.90), and a 44% slower decline in renal function (0.96% vs 1.72% per year, P=0.0002). Among those without CKD at baseline, there was no between-group difference in the primary endpoint.

Conclusions: Enalapril-folic acid therapy, compared with enalapril alone, can significantly delay the progression of CKD among patients with mild to moderate CKD.

Funding: Government Support - Non-U.S.

TH-OR035

Effect of Folic Acid Supplementation on the New-Onset Proteinuria: New Insight from a Randomized Controlled Trial Youbao Li,[1] Xianhui Qin,[1] Binyan Wang,[1] Yong Huo,[2] Fan Fan Hou,[1] Xin Xu.[1] *[1]Nanfang Hospital, Southern Medical Univ; National Clinical Research Center for Kidney Disease; [2]Peking Univ First Hospital.*

Background: The efficacy of folic acid supplementation for the preventing the new-onset proteinuria was still inconclusive. We aimed to test the hypothesis that treatment with enalapril and folic acid is more effective in preventing the new-onset proteinuria than enalapril alone among Chinese adults with hypertension.

Methods: This report was a sub-study of the China Stroke Primary Trial (CSPPT).A total of 14538 eligible CSPPT patients without overt proteinuria, including 1866 patients with diabete, were randomized to receive a single tablet daily containing 10mg enalapril and 0.8mg folic acid (n=7212) or 10mg enalapril alone (n=7326) in 20 communities in Jiangsu province in China. The primary outcome was the new-onset proteinuria, defined as a urine dipstick reading ≥1+ at exit visit.

Results: Median followup was 4.4 years. The primary event occurred in 260 (4.4%) and 242 (4.1%) participants, respectively, in the enalapril group and the enalapril-folic acid group. Compared with the enalapril group, the enalapril-folic acid group had no significant effect on the primary event (OR, 0.93; 95% CI, 0.77, 1.11). Among the participants with diabetes at baseline, folic acid therapy resulted in a significant reduction in the risks for the primary event (8.5% in the enalapril group vs. 5.6% in the enalapril-folic acid group; OR, 0.63; 95%CI, 0.42-0.94). Among those without diabetes at baseline, there was no between-group difference in the primary endpoint.

New-onset proteinuria	No. of event (%)		Odds ratios (95% CI)		P	P for interaction
	Enalapril	Enalapril-Folic acid	Unadjusted	Adjusted		
Total	260 (4.4)	242 (4.1)	0.93 (0.78, 1.11)	0.93 (0.77, 1.11)	0.405	
Non-diabetes	194 (3.7)	200 (3.8)	1.03 (0.84, 1.26)	1.02 (0.84, 1.25)	0.828	ref
Diabetes	66 (8.5)	42 (5.6)	0.64 (0.43, 0.95)	0.63 (0.42, 0.94)	0.024	0.035

Conclusions: Enalapril-folic acid therapy, compared with enalapril alone, can significantly preventing the new-onset proteinuria in hypertensive patients with diabetes.

Funding: Government Support - Non-U.S.

TH-OR036

Correction of Metabolic Acidosis Improves Insulin Resistance in Chronic Kidney Disease Antonio Bellasi,[1] Lucia Di Micco,[2] Luca Di Lullo,[3] Mario Cozzolino,[4] Biagio Raffaele Di Iorio.[2] *[1]ASST-Lariana; [2]PO Landolfi; [3]Ospedale Parodi Delfino; [4]Univ of Milan.*

Background: Correction of metabolic acidosis (MA) with nutritional therapy or bicarbonate administration is widely used in chronic kidney disease (CKD) patients. However, it is unknown whether these interventions reduce insulin resistance (IR) in diabetic patients with CKD. We sought to evaluate the effect of MA correction on endogenous insulin action in diabetic type 2 (DM2) CKD patients.

Methods: Sub-study evaluation of the first 145 CKD subjects (83 men e 62 women) with DM2 treated with oral antidiabetic drugs recruited in the ongoing BIC study (NCT01640119) who completed 12 months followup. All patients were randomly assigned 1:1 to either open-label (A) oral bicarbonate to achieve serum bicarbonate levels of 24-28 mmol/L (treatment group) or (B) no treatment (control group). The Homeostatic model assessment (HOMA) index was used to evaluate IR at study inception and conclusion. Parametric and non-parametric tests as well as linear regression were used.

Results: At baseline no differences in demographic and clinical characteristics between the 2 groups was observed. Average dose of bicarbonate in the treatment group was 0.7±0.2 mmol/kg. Treated patients showed a better metabolic control as confirmed by lower insulin levels (13.4+5.2 vs 19.9+6.3; for treated and control subjects respectively; p<0.001), Homa-IR (5.9[5.0-7.0] vs 6.3[5.3-8.2]; p=0.01) and need for oral antidiabetic drugs. The serum bicarbonate and HOMA-IR relationship was non-linear and the largest HOMA-IR reduction was noted for serum bicarbonate levels between 24-28 mmol/l. Adjustment for confounders, suggests that serum bicarbonate rather than treatment drives the effect on HOMA-IR.

Conclusions: Serum bicarbonate is related to IR and the largest HOMA-IR reduction is noted for serum bicarbonate between 24-28 mmol/l. Treatment with bicarbonate influences IR. However, changes in serum bicarbonate explains the effect of treatment on HOMA index. Future efforts are required to validate these results in diabetic and non-diabetic CKD patients.

Funding: Government Support - Non-U.S.

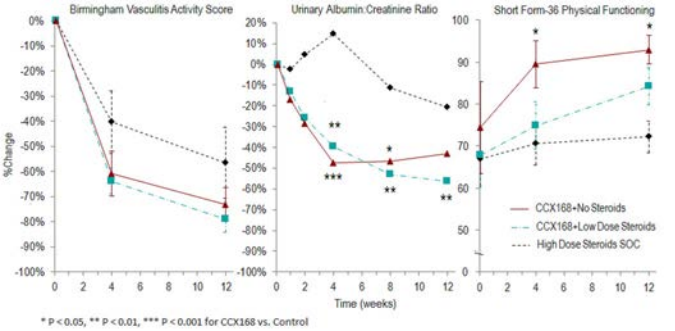
TH-OR037

Rapid Onset of Action of Orally Administered C5aR Inhibitor CCX168 in Randomized Clinical Trial in ANCA-Associated Vasculitis (CLEAR) Vladimir Tesar,[9] David R.W. Jayne,[1] Annette Bruchfeld,[2] Lorraine Harper,[3] Matthias Schaier,[4] Patrick Hamilton,[5] Volker Rolf Burst,[6] Franziska Grundmann,[6] Michel Y. Jadoul,[7] Istvan Szombati,[8] Antonia Potarca,[10] Thomas J. Schall,[10] Pirow Bekker.[10] *[1]Univ of Cambridge, United Kingdom; [2]Karolinska Inst, Sweden; [3]Univ of Birmingham, United Kingdom; [4]Univ Hosp Heidelberg, Germany; [5]Manchester Univ, United Kingdom; [6]Univ of Cologne, Germany; [7]Cliniques Saint-Luc, Belgium; [8]Budai Irgalmasrendi Korhaz, Hungary; [9]Charles Univ, Czech Republic; [10]ChemoCentryx, Inc.*

Background: CCX168 is being developed for anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV).

Methods: This was a randomized, placebo-controlled trial in AAV. The aim was to reduce or replace steroid treatment with CCX168 without compromising efficacy. There were 3 treatment groups: (1) High dose (60 mg) prednisone standard of care control, (2) CCX168 30 mg b.i.d.+low dose (20 mg) prednisone, and (3) CCX168 30 mg b.i.d.+no prednisone. All patients received CYC, 15 mg/kg IV q2 to 4 wks, or RTX, 375 mg/m^2 IV weekly for 4 wks. Primary endpoint: treatment response at wk 12, based on Birmingham Vasculitis Activity Score (BVAS) decrease from baseline of ≥50% and no worsening in any body system.

Results: 67 patients were enrolled. Mean age was 57-59 yrs, BVAS 13 to 14. The primary endpoint was met: BVAS response at wk 12 was higher and statistically non-inferior to SOC control (P = 0.002 and P = 0.01 for each CCX168 group vs. control), with a rapid onset of action (see figure).



The incidence of events likely associated with steroids, e.g., diabetes, psychiatric disorders, weight gain, fracture, and cataract was lower in patients on CCX168 (34%) vs. control (65%), P = 0.02. CCX168 was generally well tolerated.

Conclusions: CCX168 successfully replaced glucocorticoid treatment, with a more rapid onset of action based on BVAS, UACR, and HRQOL, and a lower incidence of steroid-related adverse effects.

Funding: Pharmaceutical Company Support - ChemoCentryx, Inc.

TH-OR038

Exercise Training in Hypertensive Patients with Chronic Kidney Disease: A Randomized Controlled Trial Franklin Correa Barcellos,[1,2] Annelise Reges,[2] Maristela Bohlke.[2] *[1]Medicine Faculty, Univ Federal of Pelotas, Pelotas, Brazil; [2]Medicine School, Univ Catholic of Pelotas, Brazil.*

Background: Chronic kidney disease (CKD) is a progressive illness that leads to end-stage renal disease and renal replacement therapy. These patients are at increased risk for cardiovascular events and progression to kidney failure. Observational studies have found that higher physical activity is associated with slower rates of glomerular filtration rate (GFR) decline. However, there is no definitive evidence on exercise-structured programs. The purpose study was evaluated the effects of exercise in cardiovascular risk factors and progression of kidney disease in hypertensive patients with CKD non-dialysis.

Methods: Randomized controlled trial. **Participants:** Non-diabetic patients with high blood pressure and renal disfunction. Among 935 eligible individuals, 150 individuals were randomized into the intervention or control group. **Intervention:** Exercise training of the resistance and aerobic exercises, three times per week for 16 weeks. **Outcomes:** Glomerular filtration rate estimated, blood pressure, weight, fasting glucose, lipid profile, high-sensitivity C-reactive protein, hemoglobin levels and health-related quality of life. Data were examined using linear mixed-effects models for repeated measures over time.

Results: 76 participants were allocated to the intervention and 74 to the control group. The decrease in GFR was faster in the control group than in intervention group (-2.6 against -1.9 mL/minute/1.73m^2), but the between-groups difference was not significant (+0.7; -4.0 to +5.4 mL/minute/1.73m^2) considering time and intervention interaction. C-reactive protein, mean body weight and fasting glucose levels had a significant reduction (p< 0.01) throughout the study in the intervention, but not the control group. Blood pressure decreased in both groups, physical fitness increased in the intervention group and there were no changes in quality of life.

Conclusions: Sixteen weeks of physical training exercise reduced C-reactive protein, body weight and fasting glucose levels in this high-risk population. However,have no impact on eGFRs decline in non-diabetic hypertensive patients with renal disfunction.

TH-OR039

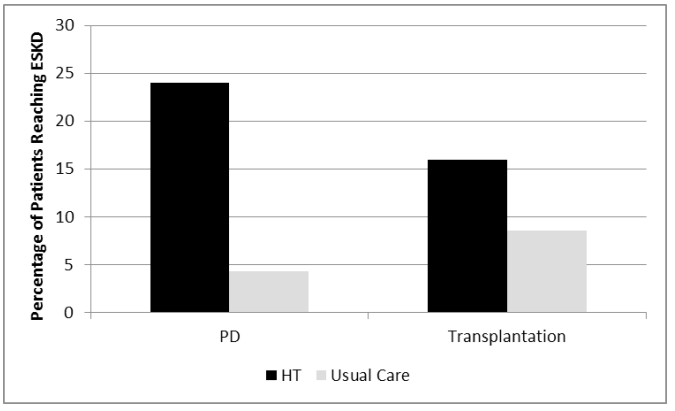
A Randomized Controlled Trial of Care Management in Late Stage CKD – Preparation for ESKD Candice Halinski,[1] Sofia Agoritsas,[1] Vipulbhai Sakhiya,[1] Leah Balsam,[2] Steven Fishbane.[1] *[1]Div of Nephrology, Hofstra Northwell School of Medicine, Great Neck, NY; [2]Div of Nephrology, Nassau Univ Medical Center, East Meadow, NY.*

Background: Healthy Transitions (HT) is a care management and informatics program to improve late stage CKD care (stages 4/5). Nurses partner with nephrologists guided by a clinical informatics system. A primary goal is improved education / preparation for ESKD. In the current analysis, the program impact on ESKD initiation was evaluated.

Methods: Patients with stage 4/5 CKD were randomized to the HT intervention or usual care (UC) at four clinical sites. The only exclusions were for dementia, metastatic cancer or no consent. All patients were followed for up to 18 months. The primary outcome of this analysis was the proportion of patients reaching ESKD who initiated treatment with home dialysis or kidney transplantation with secondary outcomes including initiating hemodialysis (HD) without hospitalization and access type for HD.

Results: 65 patients were randomized to each group. There were no significant differences in baseline characteristics. The mean eGFR at baseline was 18.5±6.4 ml/min and 19.9±6.7 ml/min (HT/UC). 25 HT patients and 23 UC patients initiated RRT. The primary outcome was achieved in 10 of 25 (40%) HT (6 PD and 4 transplantation), 3 of 23 (13.0%) UC (1 PD and 2 transplantation) (P=0.05). Of patients who initiated HD, a non-hospital outpatient start occurred in 8/15 (53.3%) HT and 3/20 (15%) UC (P=0.03). For HD, a catheter was the sole access in 3/15 (20%) HT and 8/20 (40%) UC (p=0.28). A working AVF or AVG was in place in 8/15 (52.3%) HT 6/20 (30%) UC (p=0.18).

Conclusions: The HT intervention significantly increased utilization of home dialysis and kidney transplantation and outpatient, nonhospital starts compared to UC. Further studies will help evaluate the cost effectiveness and scalability of the HT approach.



Funding: Clinical Revenue Support

TH-OR040

Impact of a Primary Care Registry on Chronic Kidney Disease Management in a Safety-Net Setting Delphine S. Tuot, Charles E. McCulloch, Alexandra Velasquez, Dean Schillinger, Chi-Yuan Hsu, Neil R. Powe. *Univ of California, San Francisco, San Francisco, CA.*

Background: Early stage CKD is asymptomatic; detection by primary care providers (PCPs) is critical to prevent disease progression via blood pressure (BP) control, minimization of albuminuria and prescription of angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB). In a randomized control trial (KARE, NCT01530958), we examined the impact of implementing a primary care CKD registry on delivery of guideline-concordant care in a racially/ethnically diverse low-income patient population. At point of care, the registry identified patients with CKD, those with uncontrolled BP (>140/90 mmHg), those were not on ACEi/ARBs, and those whose albuminuria had not been quantified in the past year. Quarterly feedback pertinent to these metrics was also provided to PCPs/health care teams.

Methods: PCPs were randomized to receive the registry or usual care for one year. Mixed models and generalized estimating equations adjusted for age, gender, race/ethnicity and clinic, were used to account for PCP and patient clustering and repeated measures, to assess the impact of the registry, time, and their interaction on change in systolic BP and change in proportion of patients with BP control, prescription of ACEi/ARB and quantification of albuminuria in the prior year.

Results: Patients whose providers were randomized to the registry (n=22 PCPs, 263 patients) had no significant change in systolic BP or change in proportion of patients with BP control compared to those randomized to usual care (n=61 PCPs, 551 patients). Randomization to the registry was associated with greater prescription of ACEi/ARB over time ($p_{time\ x\ registry}$=0.01) with a post-intervention average of 82% for patients with registry vs 72% without registry, p=0.04 and increased albuminuria quantification over time ($p_{time\ x\ registry}$ =0.009), with a change from 7% to 43% with registry vs. 10 to 34% without registry, p=0.04.

Conclusions: A primary care CKD registry can improve processes of care (ACEi/ARB use and albuminuria quantification) for safety-net patients with CKD.

Funding: NIDDK Support

TH-OR041

Cognitive Function and Kidney Disease: Baseline Data from the SPRINT Trial Daniel E. Weiner,[1] S. Gaussoin,[8] John W. Nord,[2] Alexander P. Auchus,[10] G. Chelune,[2] Michel Chonchol,[3] Laura H. Coker,[8] William E. Haley,[4] Anthony Alexander Killeen,[5] Paul L. Kimmel,[6] Alan J. Lerner,[11] Mohammad G. Saklayen,[7] Yelena Slinin,[5] Clinton Wright,[8] Manjula Kurella Tamura.[9] *[1]Tufts; [2]Utah; [3]Colorado; [4]Mayo; [5]Minnesota; [6]NIH; [7]Dayton VA; [8]Wake Forest; [9]Stanford; [10]Mississippi; [11]Case Western.*

Background: People with kidney disease are at high risk of cognitive impairment. The nature of this relationship remains uncertain.

Methods: To explore the relationship among kidney disease, cognitive function, and cerebrovascular disease, we evaluated baseline data from the Systolic Blood Pressure INTervention (SPRINT) cognition substudy, SPRINT-MIND. Five cognitive domains were defined based on 11 cognitive tests using z-scores, and the associations of both urine albumin to creatinine ratio (ACR) and estimated GFR with cognitive performance and and brain abnormal white matter volume quantified by MRI were evaluated using linear and quantile regression, respectively.

Results: Among 9361 SPRINT-MIND participants, 2800 were administered an expanded cognitive battery at baseline and 2707 had complete data; 637 had brain imaging. Mean age was 69 years, 37% were women, 30% were black, and 20% had known CVD. Mean eGFR was 71±21 ml/min/1.73 m^2 and median urine ACR was 9.7 (IQR 5.7, 22.5) mg/g. In analyses adjusted for demographic and clinical characteristics, higher ACR was associated with worse performance on tests of global cognitive function, executive function, memory and attention, such that each doubling of urine ACR explained similar declines in cognitive performance as with 7 months, 10 months, 6 months, and 14 months of increasing age, respectively per domain. Lower eGFR was independently associated with worse performance on tests of global cognitive function and memory. In adjusted models, higher ACR (p=0.001) but not lower eGFR (p=0.38) was associated with larger abnormal white matter volume; the association was present at low ACR levels (30 mg/g).

Conclusions: In older adults, higher urine ACR and lower eGFR have additive effects on global cognitive performance with different patterns of affected domains. Albuminuria, even at low levels, identifies a higher burden of abnormal brain white matter disease, suggesting that vascular disease may mediate these relationships.

Funding: Other NIH Support - HHSN268200900040C, HHSN268200900046C, HHSN268200900047C, HHSN268200900048C, HHSN268200900049C, and Inter-Agency Agreement Number A-HL-13-002-001, VA Support

TH-OR042

Serum Bicarbonate Level and Cognitive Dysfunction in Hypertensive Adults with and without CKD Mirela A. Dobre,[1] S. Gaussoin,[2] Jeffrey T. Bates,[3] Michel Chonchol,[4] Debbie L. Cohen,[5] Thomas H. Hostetter,[1] Kalani L. Raphael,[6] Addison A. Taylor,[3] Alan J. Lerner,[1] Jackson T. Wright,[1] Mahboob Rahman.[1] *[1]Case Western Reserve Univ; [2]Wake Forest School of Medicine; [3]Baylor College of Medicine; [4]Univ of Colorado; [5]Univ of Pennsylvania; [6]Univ of Utah.*

Background: Acid base balance is intimately involved in cerebral autoregulation, and hydrogen ions are important signals for neuronal function. We evaluated the association between serum bicarbonate and cognitive dysfunction in hypertensive adults with and without CKD.

Methods: A total of 2853 participants in the Systolic Blood Pressure Intervention Trial (SPRINT) were included in the study. Five cognitive summary scores were created: Global Cognitive Function, Executive Function, Memory, Attention/Concentration and Language. Multivariable linear regression models adjusted for demographics, clinical center network, education level, comorbidities, systolic blood pressure, diuretics, anti-acidosis medications, eGFR and albuminuria were built to evaluate the association between bicarbonate level and above cognitive scores. For those who underwent brain MRI (N=681), the models were also adjusted for structural and functional cerebral measurements, including white matter hyperintensity volume, vascular reactivity and cerebral blood flow.

Results: The mean age (SD) was 68.3 (8.5) years. Participants with bicarbonate ≤24mEq/L were more likely to smoke, have CKD and high albuminuria. Global Cognitive Function and Executive Function summary scores were significantly associated with serum bicarbonate (Estimate (SE): 0.014(0.006), p=0.01, and 0.018(0.006), p=0.003, respectively). The positive association with Global Cognitive Function persisted after adjustment for MRI measurements (Estimate (SE):0.03 (0.01), p=0.01). There was no association between serum bicarbonate level and Memory, Attention/Concentration and Language summary scores.

Conclusions: In a large cohort of hypertensive adults with and without CKD, we found a positive linear association between serum bicarbonate level and global cognitive and executive functions, suggesting that a low bicarbonate level may be detrimental to neuronal function.

Funding: Other NIH Support - Contract 268200900049C-0-0-1

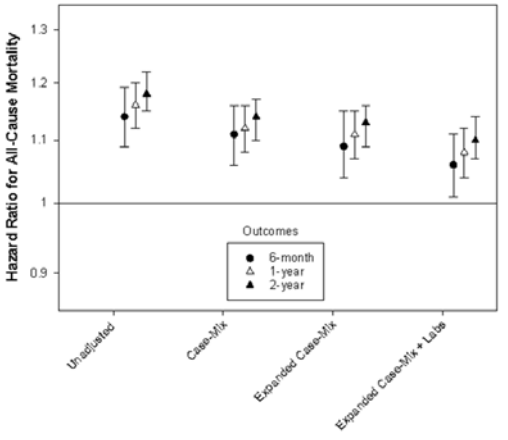
TH-OR043

Association of Pre-ESRD Depression with Post-ESRD Mortality: A Transition of Care in CKD Study Vanessa A. Ravel,[1] Melissa Soohoo,[1] Connie Rhee,[1] Elani Streja,[1] Miklos Zsolt Molnar,[2] Danh V. Nguyen,[1] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Univ of Tenn.*

Background: Depression in CKD patients is often undiagnosed, empirically overlooked, and often associated with worse outcomes including higher mortality; however, prior studies have been limited to either pre- or post-ESRD diagnoses of depression separately. We sought to examine the association of pre-ESRD depression with post-ESRD mortality in patients who transition to dialysis.

Methods: From a nation-wide cohort of 46,877 US veterans who transitioned to dialysis between 10/2007-09/2011, we identified 13,565 patients with a pre-dialysis depression diagnosis (from ICD9 codes) during the prelude (pre-dialysis) period and modeled it as a predictor of all-cause mortality within the first 6 months, 1 and 2 years upon maintenance dialysis therapy initiation using Cox hazards models adjusting for case-mix covariates, residential region, initial dialysis modality, BMI, and averaged laboratory values including eGFR.

Results: Patients were 72±11years old (mean±SD) and included 5% females, 45% diabetics, and 23% African Americans. 29% of the cohort had be previously diagnosed with depression prior to transition to ESRD. Compared to those not reporting depression, depressed patients had a 16% higher 1-yr mortality risk in the unadjusted model [HR (95% CI): 1.16 (1.12, 1.20)]. Upon further adjustment for demographic characteristics and labratory measures, this risk was attenuated to 8% [1.08 (1.04, 1.12)].



Conclusions: Pre-ESRD depression is associated with increased risk of post-ESRD mortality in veterans transitioning to dialysis. Intervention studies are warranted to examine whether management of pre-ESRD depression can improve ESRD outcomes.

Funding: NIDDK Support

TH-OR044

Cognitive Impairment (CI) in Patients with ESRD and Family Psychoeducation for Reducing Readmissions: Preliminary Results from a Randomized Clinical Trial Matthew James Jasinski,[1] Mark A. Lumley,[1] Sandeep S. Soman,[2] Jerry Yee,[2] Mark W. Ketterer.[2] *[1]Wayne State Univ; [2]Henry Ford Health System.*

Background: CMS has mandated reducing early hospital readmissions as a pathway to improving patient care while lowering costs. Patients with End-Stage Renal Disease (ESRD) have the highest 30-day hospital readmission rates of any medical condition. Studies have found that CI and health illiteracy predict readmissions. In patients with ESRD, interventions targeting these factors as a means for improving patient adherence and health post-discharge, and reducing early readmissions, have not been tested.

Methods: 120 patients (*M* Age= 57.5 years, *SD* = 14.4 years; 86% Black, 12% White; 60/60 women/men) were recruited from an inpatient nephrology unit in Detroit. All patients were assessed for CI and social support at baseline, and then randomized into a family meeting intervention (FMI) group or treatment-as-usual (TAU) control. Family meetings (~8 minutes) were conducted either via phone or at bedside. Meetings involved educating family members about patients' cognitive deficits and compensatory patient care at home. 30-day readmission rates were retrieved from charts. Chi-square tests and logistic regressions were used to identify predictors of readmissions.

Results: FMI patients had less early readmissions than TAU (χ = 2.13, 1-tailed p = .072). Including emergency department (ED) visits, patients in the FMI group had fewer ED visits or admissions within 30-days post-discharge compared to those in the control group (χ = 3.48, 1-tailed p = .031). Readmission and ED visits were 30% for the FMI vs 47% for TAU. However, this effect was of borderline significance when controlling for patient substance abuse history (OR = 0.545; 95% CI, 0.25-0.97, 1-tailed p = .061).

Conclusions: Results are the first to demonstrate that a brief psychosocial intervention can decrease readmissions in patients with ESRD, and the effect size of the reduction appears to be greater than other interventions that have been attempted. Implementing interventions such as this would help decrease health care expenditures while improving patient outcomes. Larger, more integrated replications of this intervention need to be studied.

Funding: Private Foundation Support

TH-OR045

Medicare Payments for Parts A and B Claims in Home Hemodialysis, In-Center Hemodialysis, and Peritoneal Dialysis Patients Eric D. Weinhandl,[1,2] Allan J. Collins.[2] *[1]NxStage Medical, Inc., Lawrence, MA; [2]Univ of Minnesota, Minneapolis, MN.*

Background: The United States Renal Data System (USRDS) annually publishes Medicare costs per person per year (PPPY) for hemodialysis (HD) and peritoneal dialysis (PD) patients, but does not publish costs for home HD (HHD) and in-center HD (IHD). Such costs are relevant to the Comprehensive ESRD Care Model. We assessed Medicare Parts A and B payments for HHD, IHD, and PD during 2012.

Methods: We analyzed USRDS data. We identified all patient-days in 2012 that were marked by HHD, IHD, or PD treatment and coincided with Medicare as primary payer (MPP). HHD patient-days were identified from NxStage records, which were linked to the USRDS registry, whereas IHD and PD patient-days were identified from USRDS data. Payments were ascertained from Medicare Parts A and B claims.

Results: Cumulative MPP patient-years for HHD, IHD, and PD were 2,659; 273,848; and 24,007, respectively. Medicare payments PPPY are shown in the table. Compared to IHD, HHD was associated with lower inpatient/post-acute and physician/supplier payments, but higher outpatient dialysis payments. Compared to PD, HHD was associated with similar inpatient/post-acute payments and higher payments for other cost centers. Excluding outpatient dialysis payments, HHD was roughly $10,000 PPPY less than IHD and $5,000 PPPY more than PD.

	HHD	IHD	PD	HHD - IHD	HHD - PD
Inpatient/post-acute	$26,533	$33,301	$26,550	($6,768)	($17)
Outpatient dialysis	$39,974	$28,294	$29,076	$11,679	$10,897
Other institutional	$5,329	$5,392	$3,073	($63)	$2,256
Physician/supplier	$10,914	$14,991	$8,363	($4,077)	$2,551
Parts A/B	$82,750	$81,979	$67,063	$771	$15,687
Parts A/B, minus outpatient dialysis	$42,776	$53,685	$37,987	($10,098)	$4,789

Conclusions: Medicare payments for HHD, IHD, and PD are heterogeneous. Home dialysis modalities are associated with lower inpatient/post-acute and physician/supplier costs, whereas HHD is associated with higher outpatient dialysis costs, likely due to payment for extra HD sessions. Additional analyses are needed to characterize geographic variability of between-modality cost differentials, as well as Medicare Part D payments with each dialytic modality.

TH-OR046

Gender Disparities in CKD Progression: Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study Ana C. Ricardo, Wei Yang, Lawrence J. Appel, Esteban A. Cedillo-Couvert, Jing Chen, Marie Krousel-Wood, Mahboob Rahman, Sylvia E. Rosas, Milda Renne Saunders, Daohang Sha, Kumar Sharma, Susan P. Steigerwalt, Jackson T. Wright, Martha L. Daviglus, James P. Lash. *CRIC Study Group.*

Background: In the US, men have 1.5 times higher incidence of end-stage renal disease (ESRD), despite having lower prevalence of chronic kidney disease (CKD) compared with women. Prior studies suggest that men have more rapid CKD progression, but this finding has not been consistent. We evaluated gender differences in CKD progression.

Methods: In this prospective, longitudinal study of 1778 women and 2161 men enrolled in the CRIC Study, we used Cox-proportional hazards models to investigate the association of gender (women vs. men) with incident ESRD (dialysis or transplantation), and linear mixed effects models to evaluate gender differences in estimated glomerular filtration rate (eGFR) slope.

Results: Mean age was 58 years, 42% were non-Hispanic black and 13% Hispanic. At entry, women were significantly more likely to have never smoked (53 vs 39%), be physically inactive (33 vs 28%), have higher body mass index (33 vs 31 kg/m^2), lower eGFR (44 vs 46 ml/min/1.73m^2), and lower proteinuria (113 vs 268 mg/24h). Over median follow up of 6.9 years, 844 participants developed ESRD. In fully-adjusted mixed effects models, the difference in eGFR slope in women vs. men was -0.17 ml/min/1.73m^2/year (p=0.05). The table summarizes failure-time analyses.

Outcome	HR (95% CI) Women vs. Men	P interaction Gender*Age
ESRD model		
1[a]	0.80 (0.69-0.93)	
2[b]	0.81 (0.69-0.96)	
3[c]	0.92 (0.78-1.09)	0.03
Adjusted[c] HR (95% CI) stratified by age		
21-45 y	1.36 (0.96-1.93)	
46-60 y	0.87 (0.68-1.12)	
61-74 y	0.79 (0.61-1.03)	

[a]Adjusted for clinical site, demographics, nephrology care and health insurance.
[b]Model 1+systolic BP, diabetes, history of CVD, LDL, ACEi/ARB, aspirin, statin, serum FGF23, calcium, phosphorus, baseline eGFR and proteinuria.
[c]Model 2+ lifestyle factors (smoking, physical activity and BMI)

Conclusions: In this large and diverse CKD cohort, the lower risk of ESRD in women relative to men was explained by differences in lifestyle factors, and this association was modified by age.

Funding: NIDDK Support

TH-OR047

Food Environment and Risk of Kidney Function Decline among Urban African Americans: The Achieving Blood Pressure Control Together (ACT) Study Deidra C. Crews,[1] Patti Ephraim,[1] Yang Liu,[1] Raquel C. Greer,[1] Jessica Ameling,[2] Kathryn A. Carson,[1] Lapricia Lewis Boyer,[2] Lisa A. Cooper,[2] L. Ebony Boulware.[3] *[1]Johns Hopkins U, MD; [2]U Michigan, MI; [3]Duke U, NC.*

Background: Studies suggest that dietary factors influence risk of kidney function decline. Barriers may hinder urban African Americans' (AAs) abilities to follow healthful diets that could mitigate their increased risk of kidney function decline, yet these barriers have not been well-examined.

Methods: In a randomized trial of urban AAs with uncontrolled hypertension, we assessed, at enrollment, food environment factors including healthy food access [Healthy Food Availability Index (HFAI) of stores near participants' homes; higher=better] and participants' dietary patterns [food insecurity (i.e. skipping meals due to lack of money), directly assessed presence of fresh or frozen fruits/vegetables in participants' homes; and Block fruit/vegetable screener (measure of dietary intake; higher=better)]. We used logistic regression to quantify the association of each factor with eGFR decline >4 ml/min/1.73m^2 (ml) over 1 yr, adjusting for age, sex, diabetes, albuminuria, and study arm.

Results: A majority (120 out of 159 participants) had eGFR>15ml at baseline and completed follow up labs. Mean age was 58, 74% were female, 41% had diabetes. Many lacked fresh/frozen fruits (40%) or vegetables (22%) in their homes. Median baseline eGFR was 85ml (IQR 67-104) and 16% had eGFR<60ml. Median eGFR decline over 1 year was 4ml and 46% declined >4ml.

Food Measure at Enrollment	Median score or % for measure	Adjusted Odds Ratio (95% CI) for eGFR decline >4ml over 1yr
HFAI (highest v. lowest tertile)	8.1 (out of possible 28.5)	0.38 (0.14-1.01); p=0.05
Food insecurity (yes v. no)	45%	1.13 (0.53-2.41); p=0.7
Fruit/vegetable screener (highest v. lowest tertile)	13 (out of possible 33)	0.45 (0.16-1.21); p=0.1

Conclusions: Among urban AAs, greater availability of healthful foods in neighborhood stores and healthful dietary intake patterns were associated with a trend towards lower risk of eGFR decline. The impact of the food environment on kidney function in vulnerable populations warrants further study.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-OR048

Emergency Department Use among Patients with Chronic Kidney Disease: A Population-Based Analysis Paul E. Ronksley, Robert G. Weaver, Chandra Mary Thomas, Jennifer M. MacRae. *Univ of Calgary, Calgary, AB, Canada.*

Background: While prior studies have observed high resource use among patients with chronic kidney disease (CKD), there is limited exploration of emergency department (ED) use in this population and the proportion of encounters related to CKD care.

Methods: We identified all adults (≥18 years) with eGFR<60 mL/min/1.73m^2 (including dialysis-dependent patients) in Alberta, Canada between Apr 1, 2010 and Mar 31, 2011. Patients with CKD were linked to administrative data to capture clinical characteristics and frequency of ED visits, and followed until death or end of study (Mar 31, 2013). Within each CKD category we calculated adjusted rates of overall ED use, as well as rates of potentially preventable ED encounters (defined by 4 CKD-specific ambulatory care sensitive conditions (ACSCs); heart failure, hyperkalemia, volume overload, malignant hypertension).

Results: During mean follow-up of 2.4 years, 111087 patients had 294113 ED encounters; 64.2% of patients had category 3A CKD and 1.6% were dialysis dependent. Adjusted rates of overall ED use increased linearly by CKD category, with dialysis patients having 1798 (95% CI: 1686-1911) visits/1000 p-yrs. 5.8% of all ED encounters were for CKD-specific ACSCs with approximately one-third resulting in hospital admission. Heart failure accounted for over 80% of all potentially preventable ED events among patients in categories 3A, 3B, and 4 CKD, while hyperkalemia accounted for almost half (48%) of all ACSCs among dialysis patients. Adjusted rates of ED events for heart failure showed a U-shaped relationship with rates peaking among category 4 CKD patients (61 (95% CI: 56-66) visits/1000 p-yrs. In contrast, rates of ED use for hyperkalemia increased in parallel with CKD category; rates were highest among category 5 patients who were dialysis-dependent (22 (95% CI: 17-28) and those not receiving dialysis therapy (23 (95% CI: 17-29) visits/1000 p-yrs.

Conclusions: ED use is high among patients with CKD, although only a small proportion of these encounters are for potentially preventable CKD-related care. These findings suggest that strategies to reduce ED use among CKD patients will need to target other conditions besides CKD-specific ACSCs.

TH-OR049

Trajectories of Multidimensional Quality of Life among Patients Receiving Chronic Dialysis: Fluctuation, Gradation, and Improvement over Time Mi-Kyung Song,[1] Sudeshna Paul,[1] Sandra E. Ward,[2] Constance A. Gilet,[3] Gerald A. Hladik.[3] *[1]School of Nursing, Emory Univ, GA; [2]School of Nursing, Univ of Wisconsin-Madison, WI; [3]UNC Kidney Center, Univ of North Carolina at Chapel Hill.*

Background: Other than dialysis patients, no population must receive an invasive treatment every day or every other day to sustain life, yet inadequate attention has been paid to patient-reported multidimensional QOL over time in these patients.

Methods: 227 patients on chronic dialysis recruited from 12 clinics completed hour-long monthly measures of physical functioning, physical and emotional symptoms, cognitive functioning, and spiritual wellbeing for 12 months. Sessions were conducted by phone on a non-dialysis day if patients were on hemodialysis (n=216, 95.2%). Mean patient age was 59 years (SD=12.6) and they had been on dialysis for M=4.3 years (SD=5.3). 74% (n=168) were African Americans. Baseline Charlson Comorbidity Index (CCI) score was M=7.3 (SD=2.1). Linear mixed models were used in analysis.

Results: Patient-reported physical functioning, symptoms, cognitive functioning, and spiritual wellbeing fluctuated severely from month to month. Activities of Daily Living (ADL) gradually worsened over time (p=.035) while Instrumental ADL was unchanged. Moderate to severe pain remained unchanged (n=129, 56.8%) while fatigue slightly improved over time (p<.001). Anxiety symptoms (STAI) improved gradually (p<.001) whereas depressive symptoms (CESD-10) were stable. Baseline CCI predicted these physical functioning and symptom scores (all p<.01) while months on dialysis did not. Self-reported cognitive functioning and spiritual wellbeing (FACT-Sp) slightly improved over time (all p<.001). White race was associated with higher fatigue and lower spiritual wellbeing, and older age was associated with lower anxiety and depression and higher spiritual wellbeing.

Conclusions: While physical functioning worsened over time, older and African American patients reported improved emotional and spiritual wellbeing, possibly reflecting adaptation to their situation. Further analysis is needed to glean hypotheses regarding ways to direct clinical management.

Funding: Other NIH Support - NIH, R01NR013359

TH-OR050

A Comparison Study on Clinical Features and CKD Related Quality of Life between CKD G3a and CKD G3b Patients in China Zhangzhe Peng,[1] Qiongjing Yuan,[1] Jinwei Wang,[2] Luxia Zhang,[2] Qiaoling Zhou.[1] *[1]Renal Div, Dept of Medicine, Xiangya Hospital, Central South Univ, Changsha, Hunan, China; [2]Renal Div, Dept of Medicine, Peking Univ First Hospital, Beijing, China.*

Background: A new classification of chronic kidney disease (CKD) was proposed by the Kidney Disease: Improving Global Outcomes (KDIGO) in 2012. The major point of revision of this classification was the previous CKD stage 3 was subdivided into two stages (G3a and G3b). Furthermore, a two-dimensional staging of the CKD according to the level of albuminuria in addition to the GFR level was introducted.We compared the clinical features and CKD related quality of life between CKDG3a and CKDG3b patients in China to validate the neccesity of the new classfication.

Methods: Data of patients with CKD3 collected at baseline of the Chinese Cohort of Chronic Kidney Disease (C-STRIDE) which was performed in 3 000 pre-dialysis CKD patients aged between 18 and 74 years from 2011.09 to 2015.02.

Results: A population of 1277 patients with CKD3 was recruited for the study. 499(39.08%) patients were classified as CKD G3a group, 778(60.92%) patients were classified as CKD G3b group. We compared the clinical characteristics, laboratory parameters and overall rating of quality of life between CKD G3a and G3b patients. We found that serum PTH, uric acid, hemoglobin, serum HDL cholesterol and systolic blood pressure were significantly elevated in the G3b group compared with G3a group (P<0.05). Serum bicarbonate, serum total cholesterol were significantly decreased in the G3b group compared with G3a group (P<0.05). The proportions of subjects with hyperuricemia, anemia were significantly higher in the G3b group than in the G3a group (61.41% vs.52.03%, 26.35% vs.17.85 %, P<0.05). Most importantly, the overall rating of quality of life was significantly decreased in the G3b group compared with G3a group (P<0.05). Subsequently, we classified patients with CKD G3a and G3b according to the levels of ACR. We found that hyperuricemia, anemia were significantly more common in the later stages of both the eGFR and albuminuria (P < 0.01) .

Conclusions: There are differences in the clinical features and quality of life between CKDG3a and CKDG3b patients in China.

Funding: Government Support - Non-U.S.

TH-OR051

Results from the ATLAS Trial: A Phase 2 Study to Evaluate Efficacy and Safety of BIIB023 in Subjects with Lupus Nephritis Brad H. Rovin,[1] David Wofsy,[2] David R.W. Jayne,[3] Eduardo Mysler,[4] Karen V. Smirnakis,[5] Jeremy Stuart Duffield,[5] Nathalie Franchimont,[5] Fei Shih.[5] *[1]Nephrology, The Ohio State Univ Wexner Medical Center, Columbus, OH; [2]Rheumatology, Univ of California San Francisco, San Francisco, CA; [3]Vasculitis and Lupus Service, Addenbrooke's Hospital, Cambridge, United Kingdom; [4]Organizacion Medica de Investigacion, Buenos Aires, Argentina; [5]Biogen, Cambridge, MA.*

Background: BIIB023 is a humanized monoclonal antibody against TNF-related weak inducer of apoptosis (TWEAK). TWEAK has been linked to inflammation, mesangial proliferation, tubular cell death and fibrosis in lupus nephritis (LN). TWEAK acts through its receptor, Fn14. Fn14 is upregulated in LN kidney, but not expressed on T or B cells. Blocking TWEAK/FN14 pathway may attenuate inflammation and enhance the renal response (RR) to standard-of-care (SOC) therapy without adding to immunosuppression.

Methods: ATLAS was a phase II, placebo controlled, double blind, RCT to determine whether addition of BIIB023 (3 mg/kg or 20 mg/kg q4wk) to MMF+steroids improved complete or partial RR at 1yr. Patients had biopsy proven (centralized) proliferative LN, UPCR >1 and were treated with SOC for 12 wks. Only patients with a UPCR >0.5 after 12 wks of SOC were randomized.

Results: ATLAS enrolled 188 subjects. 145 finished BIIB023/placebo infusions through wk 44 before the trial was terminated for lack of efficacy. This group was designated the modified-ITT group, with 48 patients on placebo, 49 patients on 3 mg/kg and 48 patients on 20 mg/kg. At wk 52, complete and partial RR were seen in 25% (95% CI 15-35) of placebo patients, 16% (8-25) of the 3 mg/kg group and 31% (20-42) of the 20 mg/kg group. There was no difference in RR between placebo or BIIB023-treated patients nor in the time to RR. BIIB023 decreased serum and urine TWEAK dose-dependently. Serious adverse events were reported in 11% and 17% of placebo and BIIB023-treated patients, respectively.

Conclusions: The addition of BIIB023 to SOC LN therapy did not improve 1yr RR in proliferative LN. This was a unique trial design which excluded patients who responded rapidly to SOC therapy and this may have been a particularly resistant LN population.

Funding: Pharmaceutical Company Support - Biogen

TH-OR052

Circulating Lymphocyte Subsets and Disease Relapse in Lupus Nephritis Desmond Y.H. Yap, Paul Lee, Susan Yung, Daniel Tak Mao Chan. *Dept of Medicine, The Univ of Hong Kong, Hong Kong, Hong Kong.*

Background: Repeated renal flares herald adverse long-term outcomes in lupus nephritis (LN) but the mechanisms pertaining to relapse remain poorly understood. Lymphocyte subset abnormalities have been implicated in the pathogenesis of LN, but their relationship to LN relapse has not been investigated.

Methods: We compared circulating lymphocyte subsets and serum cytokine profiles during disease quiescence between patients with Class III/IV±V LN who are multiple relapsers (MR, defined as >=3 relapses within 36 months unrelated to non-compliance) and non-relapsers (NR, defined as no relapse after the presenting episode).

Results: 37 patients were included (MR n=24; NR n=13). MR showed lower percentage of circulating naïve B and memory B cells compared with NR (0.48%, IQR 0.24%-3.15% vs. 4.52%, IQR 3.18%-8.25%; and 0.51%, IQR 0.26%-0.67% vs. 0.96%, IQR 0.86%-1.91%; p=0.014 and 0.014 respectively), while the two groups had similar percentage of circulating plasma cells (0.61%, IQR 0.31%-0.77% vs. 0.38%, IQR 0.33%-0.79%, p=0.883). The plasma cell-to-naïve B cell ratio was higher in MR (1.52±2.19 vs.0.21±0.33, p=0.011). MR and NR did not differ in the percentage of circulating Th1, Th2, Th17 and Treg cells, nor the level of IL-6, IL-18, IL-21, IL-23, BAFF, IFN-α, IFN-γ or IP-10 (p>0.05 for all).

Conclusions: Our results suggest that altered prevalence of distinct circulating B cell subsets might be related to the pathogenesis of disease flares in LN patients.

TH-OR053

Urine Exosome Micro-RNA Profiling in Lupus Nephritis Xiaolan Zhang, Huijuan Song, Samir Parikh, John P. Shapiro, Brad H. Rovin. *Nephrology, Ohio State Univ, Columbus, OH.*

Background: Micro-RNA (miRNA) has emerged as a potentially important class of disease biomarkers as they play a key role in posttranscriptional regulation of gene expression. miRNA profiling has been done in the plasma, PBMC and kidey tissue of lupus nephritis (LN) patients, but thus far not in urine exosomes. The feasibility of measuring miRNA in urine exosomes was tested.

Methods: Urine exosome miRNA from 6 healthy control, and 12 biopsy-proven LN ISN/RPS class IV patients was screened for 800 miRNAs using the Nanostring nCounter® miRNA expression technique. Differentially-expressed miRNAs were confirmed by TaqMan gene expression real-timeRT-PCR. miRNA expression was normalized to a spiked-in miRNA control and urine creatinine, and analyzed by ANOVA followed by nonparametric Wilcoxon ranked-sum testing and multiple linear regression.

Results: The number of urine exosomes and their RNA content were significantly higher in LN than controls (p=0.006 and 0.008, respectively). The number of exosomes correlated with urine protein concentration (r^2=0.36, p=0.0040). miRNA profiling showed that 19 miRNAs were significantly increased in LN compared to control. These included some miRNAs previously identified in LN, such as miR-155-5p and miR-451a, and other miRNAs not previously described in LN, such as miRNA-21-5p and miRNA-1285. RT-PCR confirmed the Nanostring findings. For example, miRNA-451 was 30-fold higher in LN (p=0.0098). miRNA-21-5p and miRNA-1285-5p were over 200-fold higher in LN than control (p=0.0072 for both). miRNA-21-5p and miRNA-1285-5p were correlated with r^2=0.77 and p<0.0001. miRNA-451 showed a significant correlation with urine protein (r^2=0.31, p=0.008).

Conclusions: Urine exosome miRNA profiling was carried out in proliferative LN patients and healthy controls. Several differentially-expressed miRNAs were identified in LN exosomes and verified by RT-PCR. These data demonstrate the feasibility of developing urine exosomes as non-invasive biomarkers of LN activity.

Funding: NIDDK Support

TH-OR054

Molecular Imaging of Glomeruli from Serial Kidney Biopsies in Lupus Nephritis Samir Parikh,[1] Ana Malvar,[2] Huijuan Song,[1] John P. Shapiro,[1] Valeria Gabriela Alberton,[2] Jianying Zhang,[1] Michael T. Eadon,[3] Brad H. Rovin.[1] *[1]Nephrology, The Ohio State Univ Medical Center, Columbus, OH; [2]Nephrology, Hospital Fernandez, Buenos Aires, Argentina; [3]Nephrology, Indiana Univ, Indianapolis, IN.*

Background: Proliferative lupus nephritis (LN) is managed using only clinical and histologic data. We postulated that molecular profiling of kidney biopsies could provide novel information to improve management strategies. Here we present results of glomerular profiling.

Methods: A kidney biopsy was done at flare (Bx1) and after induction therapy (Bx2) in 5 patients with proliferative LN. Biopsies of living donor kidney transplants were controls (n=2). Glomeruli were isolated using laser capture microdissection, and glomerular RNA was extracted. The expression of 569 immune-response genes was profiled using Nanostring technology. Clinical response after induction was assessed by proteinuria and serum creatinine (SCr), and all patients achieved complete or partial remission.

Results: At Bx1 34 transcripts were differentially-expressed in LN glomeruli compared to control glomeruli. The top upregulated transcripts included *CCL2* (25-fold>control, P=0.0005), *IL21R* (11.2-fold, P=0.0002), *IL18RAP* (10.6-fold, P=0.009), *IL18R1* (4.1-fold, P=0.018), *IL7R* (9.5-fold, P=0.004), *ICAM1* (9.4-fold, P=0.0001), and *ITGAL* (5.3-fold, P=0.008). After treatment these levels fell but did not return to control levels. Comparing Bx2 to Bx1, TNF-related genes became upregulated during treatment, including *TRAF5* (3-fold>Bx1, P=0.015) *TNFSF12* (3.5-Fold, P=0.017), and *TNFRSF1B* (3.7-Fold, P=0.019).

Conclusions: LN glomeruli at flare express a dominant inflammatory molecular signature. This signature is attenuated but not eliminated with standard induction treatment, despite improvements in proteinuria and SCr. Unexpectedly, after treatment, a TNF-signature emerged in glomeruli. These data suggest that induction therapy may be improved by focusing efforts on abrogating inflammation. Furthermore, after a LN flare is initiated the TNF pathway may play an immunomodulatory as opposed to pro-inflammatory role. Because several cytokines have dual roles, the timing of anti-cytokine therapies in LN may be critical for therapeutic efficacy.

Funding: NIDDK Support, Other NIH Support - Strategic Pharma-Academic Research Consortium (SPARC) CCTS grant

TH-OR055

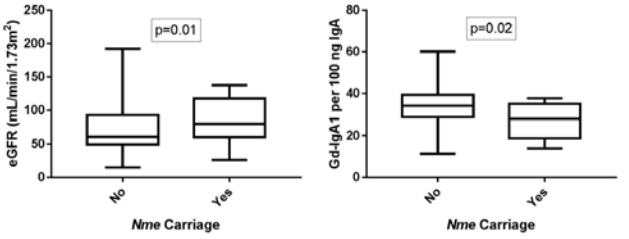
Microbiota Profile in IgAN Is Associated with Differences in Immunologic Function and Disease Severity Heather N. Reich,[1] David Guttman,[1] Bryan Coburn,[1] Jan Novak,[3] Ping Lam,[1] Scott Gray-Owen,[1] Christoph Licht,[2] Stuart Yang,[1] Michelle A. Hladunewich,[1] Sean Barbour,[3] Daniel C. Cattran,[1] Rulan S. Parekh,[2] Krzysztof Kiryluk,[5] Pauline Wang,[1] Rupert Kaul,[1] Kenneth Croitoru,[1] Jennifer Gommerman.[1] *[1]Univ of Toronto, Univ Health Network; [2]Hospital for Sick Children; [3]UBC; [4]Univ of Alabama; [5]Columbia Univ.*

Background: There is a reciprocal relationship between host commensal microbiota and the immune system, suggesting that study of microbiota can reveal functional differences in immune responses that underlie susceptibility to IgA nephropathy (IgAN) and disease progression. To better understand the immunopathogenesis of IgAN, we characterized the tonsil microbiota of patients with IgAN and healthy control subjects. We characterized the immune and clinical phenotype associated with microbiota profile.

Methods: The cohort included 120 adults with IgAN and 60 healthy controls (primarily household-matched). Tonsil microbiota were characterized using V4 16s rRNA gene sequencing and qPCR. Galactose-deficient (Gd) IgA1 was quantified using ELISA.

Results: Overall abundance of *Neisseria* genus is significantly increased in tonsils of IgAN patients (p<0.01) however *N.Meningitidis* (*Nme*) is underrepresented in IgAN (0.23 vs.0.17 p=6.5x10^{-5}). *Nme* carriage is associated with a milder clinical phenotype as characterized higher eGFR, and by lower levels of Gd-IgA1(Fig1).

Conclusions: IgAN is associated with differential tonsil colonization by *Neisseria* and *Nme*. The association of *Nme* carriage with milder clinical phenotype and decreased Gd-IgA1 is compelling and merits further exploration. Non-pathogenic (non-*Nme*) *Neisseria* may contribute directly to pathogenesis of IgAN and/or *Nme* carriage may be a biomarker of a milder immunologic phenotype. Current work to investigate mechanisms explaining these associations includes evaluating complement and cytokine profiles in relation to *Neisseria* status.



Funding: Private Foundation Support

TH-OR056

Systematic Analysis of IgA1 Glycosylation in IgA Nephropathy, Membranous Nephropathy and Healthy Subjects and the Effects of Ethnicity Karen Molyneux,[1] David Harry John Wimbury,[1] Daniel P. Gale,[2] Patricia Higgins,[1] Peiran Yin,[3] Xueqing Yu,[3] Jonathan Barratt.[1] *[1]Infection, Immunity & Inflammation, Univ of Leicester, Leicester, United Kingdom; [2]UCL Centre for Nephrology, Univ College, London, United Kingdom; [3]Inst of Nephrology, SunYat-Sen Univ, Guangzhou, China.*

Background: IgA nephropathy (IgAN) is characterised by the deposition of galactose deficient IgA1 (Gd-IgA)-containing immune complexes in the mesangium. IgAN is especially common in East Asia, and while the diagnostic criteria are the same worldwide, there are marked regional differences in gender distribution and clinical outcomes, suggesting that the biology of the condition is not uniform. The aim of this study was to compare levels of Gd-IgA in serum from Caucasian and Chinese patient and control cohorts.

Methods: An ELISA-based method was used to measure binding of the lectin Helix aspersa agglutinin to IgA captured from serum from: 1091 UK IgAN patients, 998 Chinese IgAN patients, 360 UK membranous nephropathy (MN) patients, 193 UK controls and 80 Chinese controls.

Results: UK IgAN patients exhibited higher Gd-IgA levels than UK controls with levels highest in patients with progressive renal damage ($p<0.05$ compared with non-progressors). Gd-IgA was lower in UK MN patients compared to both IgAN patients ($p<0.0001$) and the healthy subjects ($p<0.0001$) from the UK. Among Chinese individuals, Gd-IgA levels were higher in IgAN patients compared to healthy controls ($p<0.05$), but levels were lower in the Chinese compared to the UK cohort, in both IgAN patients ($p<0.0001$) and controls ($p<0.0001$).

Conclusions: Gd-IgA1 levels are associated with IgAN in Caucasian and Chinese patients but the difference in prevalence of IgAN cannot be attributed to differences in Gd-IgA levels between these populations. Results also presented at this meeting show that a C1GALT1 haplotype, common in Caucasians but rare in Chinese people, is strongly associated with elevated Gd-IgA1 levels and the reduced Gd-IgA in the Chinese population is consistent with reduced frequency of this haplotype. These data support the hypothesis that the causes of IgAN vary across the world.

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

TH-OR057

The MEST Kidney Biopsy Score Predicts Renal Outcome in STOP-IgAN Trial Patients - A Post-Hoc Study Jürgen Floege,[1] Thomas Rauen,[1] Judith Isabel Schimpf,[1] Christina Fitzner,[2] Frank Eitner,[3] Hermann-Josef Groene,[4] Ralf-Dieter Hilgers.[2] *[1]Nephrology, RWTH Aachen, Aachen, Germany; [2]Medical Statistics, RWTH Aachen, Aachen, Germany; [3]Bayer AG, Wuppertal, Germany; [4]German Cancer Research Center, Heidelberg, Germany.*

Background: Since the Oxford-MEST classification of IgA nephropathy (IgAN) was introduced, still there is limited information on its predictive power in randomized clinical trials.

Methods: We retrospectively re-analyzed renal biopsies from STOP IgAN trial participants (Rauen *et al*, NEJM 2015) using the MEST criteria (available biopsies in 70/162 patients) . The analyses were performed by researchers blinded to the clinical outcome of patients. Biopsies had been obtained at a median of 9.4 months prior to randomization. MEST scores were correlated with trial endpoints. Analyses were done by *Welch,* ANCOVA and *Fisher 's exact* tests.

Results: Mesangial hypercellularity (M1 score) significantly correlated with the subsequent annual eGFR loss during the 3 year trial and showed a weak association with full clinical remission and an eGFR-loss≥15 ml/min. T1/2 scores were significantly associated with ESRD onset in the group with additional immunosuppression, but not in the group with supportive-care only. Baseline eGFR was significantly lower when tubulointerstitial fibrosis (T1/2) was present (45.2±15.7 vs. 74.6±28.2 ml/min; $p<0.0001$), whereas initial proteinuria did not differ between the histological groups. Endocapillary hypercellularity (E) or glomerular segmental sclerosis (S) had no influence on any clinical outcome parameter.

	M0 (events/ total)	M1 (events/ total)	p-value	T0 (events/ total)	T1/2 (events/ total)	p-value
Full clinical remission	8/48 (17%)	0/17 (0%)	0.099	6/39 (15%)	2/26 (8%)	0.460
GFR-loss≥15 ml/min	14/51 (27%)	9/18 (50%)	0.092	11/40 (28%)	12/29 (41%)	0.302
ESRD	7/51 (14%)	1/18 (6%)	0.671	1/40 (3%)	7/29 (24%)	0.008
Absolute annual GFR change - ml/ min/1.73m² (mean±SD)	-0.79±4.50	-5.06±5.17	0.002	-2.05±5.40	-2.01±4.54	0.362

Conclusions: This post-hoc analysis of STOP IgAN biopsies indicates that the presence of a M1-score is associated with a worse eGFR course whereas a T1/2 score predicts ESRD.

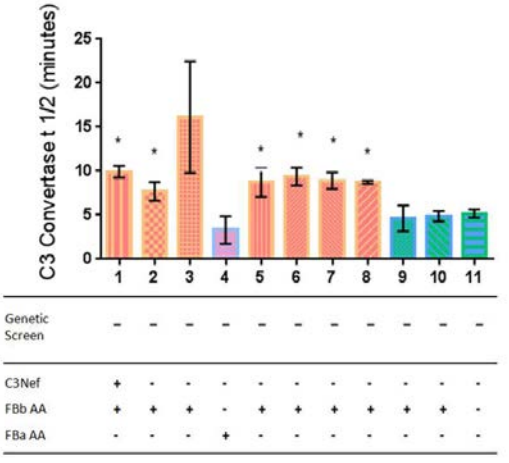
TH-OR058

C3 Glomerulopathy Associated Complement Factor B Autoantibodies Stabilize the C3 Convertase Alexandria Isabeau Clarissa Leonhardt,[1] Yuzhou Zhang,[1] Dingwu Shao,[1] Richard J. Smith,[2] Carla M. Nester.[2] *[1]Molecular Otolaryngology and Renal Research Laboratory, Univ of Iowa, Iowa City, IA; [2]Dept of Internal Medicine and Pediatrics, Univ of Iowa, Iowa City, IA.*

Background: C3 Glomerulopathy (C3G) can be a devastating glomerular disease for which targeted therapeutics are not available. The underlying disease mechanism is dysregulation of the alternative pathway of complement (AP), driven by either genetic factors or acquired autoantibodies. The most common of the latter are C3 nephritic factors, which stabilize the C3 convertase and are identified in the majority of patients. We hypothesized that antibodies to other complement proteins may also be associated with C3G. Their identification has treatment implications.

Methods: Comprehensive complement and genetic studies were completed on 87 patients with a biopsy diagnosis of C3G and 300 controls. FB autoantibodies (FBAA) were subtyped (ELISA) and evaluated by surface plasmon resonance (SPR) on a CM5 chip. After the formation of C3bBb, test IgG (x3) was flowed across the chip (dilutions, 25-400ug/ml). Interactions were analyzed with BIAcore software.

Results: FBAA were found in 9 of 87 patients and 4 of controls; 8 patients had sufficient sera for further testing. 7 of 8 patients had FBbAA (1 patient had FBaAAs). FBbAA increased convertase half-life (native convertase t ½ = 5.1 min; FBbAA stabilized, t ½ = 7.69 – 10.55 min, p = <0.05). With control IgG, FBbAA from control (subjects 9 and 10), and FBaAA from C3G patient 4, convertase t ½ was not increased. C3G patients with functionally significant FBAAs had AP biomarker abnormalities; no controls with FBAA had biomarker abnormalities.



Conclusions: FBbAA from C3G patients stabilize convertase. Nonstabilizing FBAAs can be identified in normal controls. Our data implicate FBAA as drivers of C3G.

Funding: NIDDK Support

TH-OR059

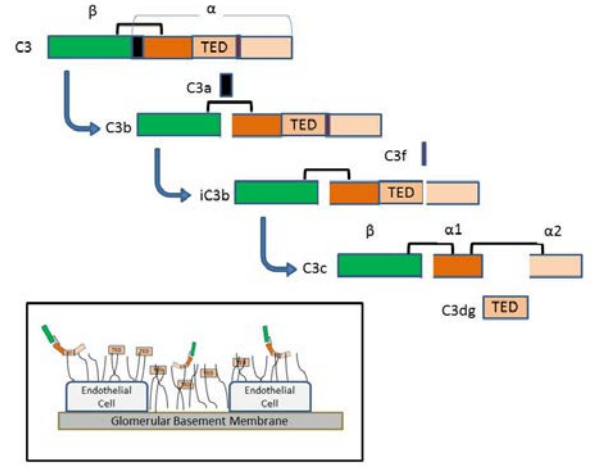
Characterization of C3 in C3 Glomerulopathy Sanjeev Sethi,[1] Fernando C. Fervenza,[1] Julie A. Vrana,[1] Richard J. Smith.[2] *[1]Mayo Clinic, Rochester, MN; [2]Carver College of Medicine, Iowa City, IA.*

Background: C3 glomerulopathy (C3G) is caused by over activity of the alternative pathway of complement that results in bright glomerular C3 and minimal/no Ig staining. Laser microdissection/mass spectrometry (MS) of the 2 subtypes, C3 glomerulonephritis (C3GN) and dense deposit disease (DDD), have identified C3 as the predominant glomerular complement protein. C3 plays a central role in complement activity, with its proteolytic cleavage first generating C3a and C3b, followed by inactivation of C3b generating iC3b (which includes C3α and C3β), and further breakdown yielding C3c and terminal breakdown product C3dg. The composition of C3 breakdown products in C3G is not known.

Methods: We chose 6 cases each of C3GN and DDD to analyze the composition of glomerular C3 deposits. We analyzed the amino acid sequence of C3 spectra detected by MS to determine the percentage coverage and relative abundance of C3 products. Thus, we were able to determine the amino acid sequences mapping to the various C3 products including C3dg, C3α (C3-α1 and 2) and C3-β.

Results: C3dg is the predominant cleavage product detected with the highest amino acid coverage. The amino acid coverage of C3dg ranged from 15.4% to 50% (avg 30.7%). The remaining amino acids were present in much lesser abundance and mapped to C3-α1 (avg 6.5 %), C3-α2 (avg 6.5 %) and C3-β (avg 7.3 %). Amino acids mapping to C3a and C3f were absent. Taken together, the C3α and C3-β amino acids represent iC3b prior to or C3c after cleavage of C3dg. The C3 spectra for C3GN and DDD were surprisingly similar.

Conclusions: The finding of large amounts of C3dg suggests that C3b deposition is an active process triggered by thioester binding of C3b to the glycocalyx over the endothelial cells and GBM. Regulatory protein-mediated inactivation of C3b results in the generation of iC3b. After additional cleavages and release of C3c, mostly C3dg remains.



TH-OR060

Eculizumab in Secondary Atypical Hemolytic Uremic Syndrome
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[1]Nephrology, Hospital Univ 12 de Octubre, Madrid, Spain; [2]Centro de Investigaciones Biológicas, Consejo Superior de Investigaciones Científicas, Madrid, Spain.

Background: Complement hyperactivity can be observed in thrombotic microangiopathies (TMA) other than atypical hemolytic uremic syndrome (aHUS), which may explain why some patients with aHUS associated with secondary TMA (secondary aHUS), have been successfully treated with eculizumab.

Methods: We present a series of 29 secondary aHUS patients treated with eculizumab: 15 drug-induced, 8 associated with systemic diseases (lupus erythematosus 3, systemic scleroderma 2, ANCA vasculitis 2, antiphospholipid syndrome 1), 2 associated with post-partum, 2 cancer-related, 1 associated with acute humoral rejection and 1 with intestinal lymphangiectasia. Prior to eculizumab treatment all patients showed severe anemia, thrombocytopenia and renal function impairment (14 requiring dialysis) and 11 presented severe extrarenal manifestations. Unsuccessful plasmapheresis was performed in 24 patients (83%). A positive outcome (TMA response) to the eculizumab treatment was defined by a normalization of hemoglobin and platelet counts and a renal function recovery with a ≥25% reduction in serum creatinine.

Results: A remarkable TMA response was observed in 20 patients (68%), with only 4 requiring dialysis and 15 (51%) showing a ≥50% serum creatinine reduction at the last follow-up. Patients with systemic diseases presented the worst outcomes with only 2 patients (one ANCA vasculitis, one antiphospholipid syndrome) showing a TMA response. Comprehensive genetic and molecular studies in 22 patients identified complement pathogenic variants in only 2 patients. With these two exceptions, eculizumab treatment was discontinued after a median of 8 weeks without the occurrence of TMA relapses.

Conclusions: Eculizumab may be an effective treatment in most patients with secondary aHUS.

TH-OR061

BMI Trajectory with Decline in Kidney Function: Results from the CRIC Study
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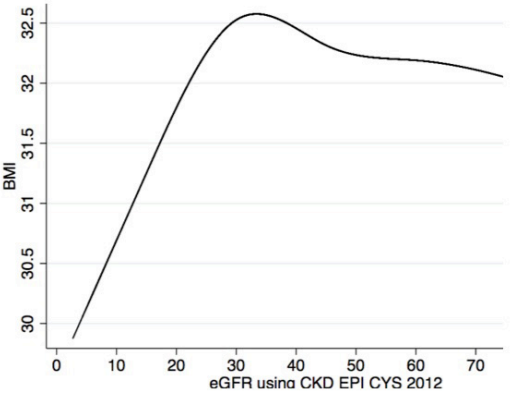
Background: Protein-energy wasting is associated with poor prognosis for CKD and ESRD patients. However, few studies have rigorously described the relationship between CKD progression and weight changes. We compared longitudinal weight trajectory, assessed by changes in body mass index [BMI] in the Chronic Renal Insufficiency Cohort (CRIC) participants, with decline in renal function.

Methods: We included 3933 participants with CKD in CRIC for longitudinal analysis. Weight, height, and cystatin C were measured annually. We used segmented, mixed effects regression for modeling the repeated measures of BMI as a function of estimated GFR (using 2012 CKD-EPI cystatin C equation). We then examined the association between weight loss and risk factors including age, race, sex, diabetes, and heart failure.

Results: During mean longitudinal follow-up over 7.6 years, BMI increased by 0.15 kg/m^2 (95% CI 0.11-0.18) with every 10 mL/min/1.73 m^2 decline in renal function until eGFR of approximately 30 mL/min/1.73m^2. When eGFR dropped below 30 mL/min/1.73 m^2, a 0.9 kg/m^2 (95% CI 0.88-1.1) decline in BMI was noted with every 10 mL/min/1.73 m^2 decline in eGFR. (An 0.9 point decline in BMI is ~3 kg loss in a 5'10" adult.) The associations between eGFR and BMI before and after an eGFR of 30 mL/min/1.73 m^2 were statistically significantly different (p<0.001).



Of the risk factors assessed, only black race and diabetes were risk factors that were statistically significantly associated with greater weight loss (p<0.001).

Conclusions: In adults with CKD, weight loss mostly occurs when eGFR is ≤30 mL/min/1.73 m^2. Further research is needed to determine whether interventions to prevent weight loss during advanced stages of CKD may improve outcomes.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-OR062

Associations of Sarcopenia and Its Individual Criteria with Mortality among Patients on Hemodialysis
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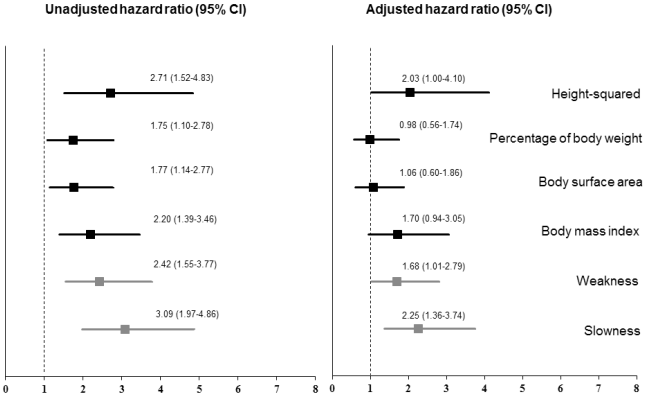
Background: Sarcopenia is defined as low muscle mass combined with reduced strength or physical performance. The relative importance of sarcopenia and its individual components as independent predictors of mortality in dialysis population have not been determined.

Methods: ACTIVE/ADIPOSE enrolled prevalent HD patients from San Francisco and Atlanta from 2009 to 2011. We estimated whole-body muscle mass using bioimpedance spectroscopy (n=645;age 56.7±14.5 years). We defined low muscle mass as>2SD below sex-specific means for young adults from NHANES and indexed to height^2, body weight, BSA, or BMI. We evaluated the association of sarcopenia, low muscle mass by four indexing methods, weak grip strength, and slow gait speed with mortality outcome.

Results: Seventy-eight deaths (12.1%) were observed during a mean follow-up of 1.9 years. Sarcopenia was not associated with mortality after adjusting for covariates. No muscle mass criteria were associated with death, regardless of indexing metrics. In contrast, having weak grip strength or slow gait speed was associated with mortality in adjusted model.



Only slowness improved the predictive accuracy for death with an increase in C-statistic from 0.63 to 0.68, p=0.004. However, both slowness and weakness significantly improved the continuous net reclassification index (cNRI) compared to the adjusted models without performance measures (overall cNRI of 50.5% for slowness and 33.7% for weakness) but models with muscle size did not.

Conclusions: Sarcopenia was not a better predictor of mortality than functional limitations alone in HD patients. Low muscle mass was not associated with mortality regardless of indexing method. In contrast, physical performance measures (slow gait speed and weak grip strength) were associated with mortality even after adjustment for confounders.

Funding: NIDDK Support

TH-OR063

Healthy Eating Patterns, Mortality, and End-Stage Kidney Disease: A Meta-Analysis of Cohort Studies Suetonia Palmer,[1] Jaimon T. Kelly,[2] Shu Ning Wai,[2] Marinella Ruospo,[3,4] Juan Jesus Carrero,[5] Giovanni F.M. Strippoli,[3,6,7] Katrina L. Campbell.[2,8] *[1]Univ of Otago Christchurch; [2]Bond Univ; [3]Diaverum Medical Scientific Office; [4]Amedeo Avogadro Univ of Eastern Piedmont; [5]Karolinska Inst; [6]Univ of Sydney; [7]Univ of Bari; [8]Univ of Queensland.*

Background: Patients with CKD are advised to follow dietary recommendations that restrict individual nutrients. Emerging evidence suggests that whole dietary patterns may be more important than single nutrients in influencing clinical outcomes. RCTs in the general population showed that adherence to a Mediterranean diet lowers mortality in people at high risk of cardiovascular disease. This meta-analysis aimed to evaluate the association between dietary patterns and risks of mortality and end-stage kidney disease (ESKD) among patients with CKD.

Methods: A systematic review and meta-analysis of cohort studies of dietary patterns in adults with CKD was conducted. Electronic databases (Medline, Embase, Cochrane) were searched without language restriction in November 2015 by two independent authors. Risk ratios were summarized using random effects meta-analysis. Primary outcomes were all-cause mortality and ESKD.

Results: Seven studies (n=15,285 patients) were included. Healthy eating patterns were higher in fruit and vegetables, fish, legumes, cereals, whole grains, and fiber, and lower in red meat, salt, and refined sugars. Health eating patterns were consistently associated with lower mortality (relative risk 0.73, CI 0.63-0.83; absolute risk 46 fewer deaths (CI 29-63) per 1000 patients over 5 years). There was no evidence of a significant association between healthy eating patterns and risks of ESKD (RR 1.04, CI 0.68-1.40).

Conclusions: Healthy eating patterns are associated with clinically-important reductions in mortality for people with CKD. Dietary advice on whole food approaches encouraging increased fruit and vegetable, fish, legume, whole grains, and fiber intake, and reduced red meat, sodium, and refined sugar consumption could be an effective strategy to lower mortality in CKD. A randomized trial of interventions to support healthy eating would be of clinical relevance in the CKD population.

TH-OR064

Protein Intake and Long-Term Change in eGFR in the Jackson Heart Study Rakesh Malhotra,[1] Loren Lipworth,[1] Kerri L. Cavanaugh,[1] Bessie A. Young,[2] Adolfo Correa,[3] Talat Alp Ikizler,[1] Edmond Kato Kabagambe.[1] *[1]VUMC; [2]UW; [3]UMMC.*

Background: Dietary protein intake could have deleterious renal effects in populations at risk for chronic kidney disease such as those with diabetes. Here, we examined whether higher protein intake($\geq 80^{th}$vs.$<20^{th}$ percentile of energy from protein) is associated with decline in kidney function and whether this decline varied by diabetes status.

Methods: Participants were African Americans(n=5301) who enrolled in the Jackson Heart Study between 2000 and 2004. Dietary intake was assessed using a validated FFQ at baseline and sCR was measured at baseline(visit1) and 8 years later(visit3). Estimated glomerular filtration rates(eGFRs) at baseline and follow-up were computed using the CKD-EPI equation. Participants with an eGFR<60 mL/min/1.73 m^2 at baseline or missing dietary data or sCR at visit 1 or visit 3 were excluded from the analyses. The change in eGFR was computed by subtracting eGFR at visit 1 from that at visit 3. ANOVA was used to determine whether long-term change in eGFR significantly varies by protein intake.

Results: Of 3,165 subjects,64% were women,57% hypertensive and19% diabetic. The median percent energy intake from protein was 14.3(12.4,16.4). During a median follow-up of 8.0(7.4,8.3) years, eGFR declined by 10.5% from a mean(SD) of 97.4(17.5) to 86.9(21.3) mL/min/1.73 m^2. Consumption of protein was positively associated with decline in eGFR, particularly among those with diabetes at baseline. In the fully adjusted model, protein(P=0.03) and diabetes(P <0.0001) main effects and their interaction term(P=0.01) were statistically significant.

Figure 1. Adjusted mean decline in eGFR by diabetes status and quintiles of percent energy from protein intake in the JHS

		Quintiles of energy from protein intake				
		1(n=633)	2(n=633)	3(n=633)	4(n=633)	5(n=633)
Protein intake, %*		10.7	12.7	14.3	16.0	18.7
Model 1†	Diabetic	-15.8 ± 2.7	-16.1 ± 2.3	-10.3 ± 1.6	-17.3 ± 1.8	-17.8 ± 1.6
	Non-diabetic	-10.6 ± 0.6	-8.8 ± 0.5	-9.6 ± 0.6	-8.8 ± 0.6	-8.2 ± 0.7
Model 2‡	Diabetic	-15.9 ± 2.8	-16.7 ± 2.3	-12.0 ± 1.6	-19.1 ± 1.8	-20.0 ± 1.7
	Non-diabetic	-11.1 ± 0.8	-10.0 ± 0.7	-11.4 ± 0.7	-10.8 ± 0.8	-11.3 ± 1.0

*Median protein intake in a given quintile. Other values are means ± s.e.m and are adjusted for the variables in the model.
† Model 1 includes age, diabetes(yes, no), energy from protein intake and diabetes*protein interaction term.
‡ Model 2 includes model 1 plus sex, smoking, BMI, alcohol use, SBP, DBP, years between creatinine measurements, total energy intake and percent energy from saturated fat, polyunsaturated fat, trans fat, and carbohydrate.

Conclusions: Our results show that among African Americans with diabetes at baseline, protein intake is positively associated with greater decline in eGFR after accounting for risk factors for kidney disease. Further studies are warranted to corroborate these findings and to elucidate the underlying mechanism.

Funding: Other NIH Support - National Heart,Lung, and Blood Institute; National Institite of Minority Health and Health Disparities

TH-OR065

Sarcopenia, Obesity, and Mortality in U.S. Adults with and without Chronic Kidney Disease Matthew K. Abramowitz,[1] Lagu A. Androga,[1] Afolarin Ayomide Amodu,[2] Deep Sharma.[1] *[1]Albert Einstein College of Medicine/ Montefiore Medical Center, Bronx, NY; [2]Seton Hall Univ School of Health and Medical Sciences, St. Francis Medical Center, Trenton, NJ.*

Background: In pre-dialysis chronic kidney disease (CKD), the association of muscle mass with mortality is poorly defined, and no study has examined outcomes related to the co-occurrence of low muscle mass and excess adiposity (sarcopenic-obesity). We hypothesized that associations of sarcopenia and sarcopenic-obesity with death would be stronger in persons with CKD than in those without, as CKD-induced muscle wasting is likely a poor prognostic factor.

Methods: We examined abnormalities of muscle and fat mass using dual-energy x-ray absorptiometry measurements in adult participants of the National Health and Nutrition Examination Survey 1999-2004 to define sarcopenia, obesity, and sarcopenic-obesity. Cox proportional hazard models were created to determine whether associations of body composition with all-cause mortality differed between participants with CKD compared to those without.

Results: CKD modified the association of body composition with mortality (p=0.01 for interaction). In participants without CKD, both sarcopenia and sarcopenic obesity were independently associated with increased mortality compared with normal body composition (hazard ratio (HR) 1.44 (95%CI 1.07-1.93) and 1.64 (95%CI 1.26-2.13), respectively). These associations were not present among participants with CKD (HR 1.24 (95%CI 0.89-1.71) and 1.05 (95%CI 0.75-1.46) for sarcopenia and sarcopenic-obesity, respectively; p-value for interaction by CKD status: sarcopenia, p=0.22; sarcopenic-obesity, p=0.003). Conversely, obese persons had the lowest adjusted risk of death among persons with CKD, with an increased risk among those with sarcopenia (HR 1.43 (95%CI 1.05-1.95)) but not sarcopenic-obesity (HR 1.21 (95%CI 0.89-1.65)), compared with obesity.

Conclusions: In conclusion, sarcopenia associates with increased mortality regardless of eGFR, but excess adiposity modifies this association among people with CKD. Future studies of prognosis and weight loss and exercise interventions in CKD patients should consider muscle mass and adiposity together rather than in isolation.

Funding: NIDDK Support

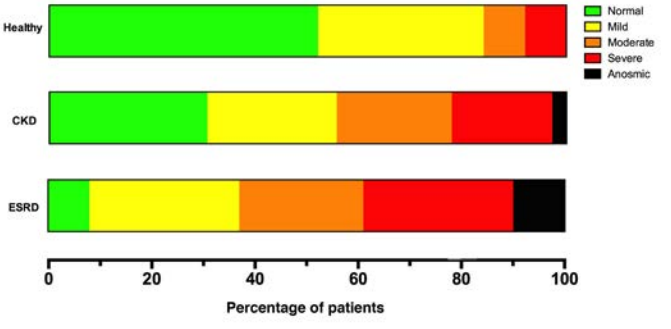
TH-OR066

Olfactory and Nutritional Impairment in Patients with Kidney Disease: Assessment and Intervention Teodor G. Paunescu, Jeremy Weiser, Joshua Wibecan, Sahir Kalim, Dihua Xu, Kristin M. Corapi, Nwamaka Denise Eneanya, Dennis Brown, Ravi I. Thadhani, Sagar U. Nigwekar. *Mass. General Hospital, Boston, MA.*

Background: Malnutrition is common in chronic kidney disease (CKD) and especially end-stage renal disease (ESRD) patients and may be partially mediated by olfactory defects. We characterized these defects in renal patients and tested a novel intervention to improve olfaction.

Methods: We quantified olfaction in CKD (n=36) and ESRD patients (n=100) and healthy volunteers (HV, n=25) using the validated Univ. of Penn. Smell Identification Test (UPSIT, through which subjects were categorized as normosmic; mildly, moderately or severely microsmic; or anosmic) and the Smell Threshold Test for 2-phenylethanol detection (Sensonics, Inc.). We then performed a pilot study to test the effect of nasal theophylline on olfactory impairment.

Results: Most HVs were normosmic or mildly microsmic. CKD patients were equally distributed among normal and mild, moderate and severe microsmic categories, and 1 patient was anosmic. Strikingly, only 8% of ESRD patients were normosmic and 10% were anosmic.



Odor threshold was not affected in CKD, but was impaired in ESRD patients (p=0.015 vs. CKD). Nutritional markers (total cholesterol, LDL, albumin and transferrin) showed a modest but statistically significant association with UPSIT categories (R^2 range: 0.10-0.16; p range: <0.001-0.006). We next enrolled 6 ESRD patients in a 6-week pilot clinical trial for nasal theophylline (CT.gov:NCT02479451). Compared to baseline, the mean UPSIT score increased in 5 patients by 2-10% during treatment. Patients reached maximum scores of 12±3% above baseline; 3 patients improved by 1 UPSIT category.

Conclusions: CKD and ESRD patients have olfactory defects that may correlate with malnutrition. Nasal theophylline should be further tested to determine if this novel intervention improves olfactory defects and potentially nutritional status.

TH-OR067

Intradialytic Protein Supplementation Increases Protein Intake in Older, but Not Younger, Hemodialysis Patients and Is Associated with Improved Hip Bone Mineral Density Annabel Biruete,[1] Peter J. Fitschen,[1] Jin Hee Jeong,[1] Pei-Tzu Wu,[2] Emily Tomayko,[3] Ken Wilund.[1] *[1]Univ of Illinois, Urbana, IL; [2]Univ of California, Los Angeles, CA; [3]Oregon State Univ, Corvallis, OR.*

Background: Hemodialysis (HD) patients have elevated risk of bone fractures, partly due to impaired bone metabolism and protein-energy wasting. Protein supplementation has shown to improve bone health in older adults, but this effect has not been explored in HD patients.

Methods: We performed a post-hoc analysis of the IHOPE trial. In short, HD patients (n=138; <60y: 48±9y, 54% male, 88% African American; ≥60y: 67±7y, 63% male, 80% African American) were randomized for 12 months to: placebo (CON), protein supplementation (PRO) or protein + exercise training (PRO+EX). Patients in PRO and PRO+EX received 30 grams of whey protein every HD session, while the PRO+EX group also cycled at moderate intensity for 30-45 minutes during HD. Patients where then divided into <60y (n=88) and ≥60y (n=50). Dietary intake and bone and body composition by DEXA were assessed at 0, 6 and 12 months. No differences were observed between PRO and PRO+EX in the variables measured, so the groups were collapsed for analysis.

Results: In patients ≥60y, PRO had higher total protein intake on dialysis days compared to CON at 6 and 12 months (≥60y CON: 0.58±0.33, 0.51±0.25 and 0.59±0.35 vs. PRO: 0.73±0.26, 0.98±0.32 and 1.07±0.34 g/kg/day for 0, 6 and 12 months, respectively, p interaction=0.009) with no effect in <60y (p=0.48) Furthermore, the ≥60y PRO maintained hip bone mineral density (h-BMD), while there was a decrease in CON (CON 0.87±0.13 and 0.84±0.13 vs. PRO 0.87±0.16 and 0.86±0.16 g/cm^2 at 0 and 12 months, respectively; interaction p=0.02) with a similar trend in the femoral neck BMD (p=0.07); this effect was not seen in <60y (p=0.826). Finally, there was no effect of PRO on body composition or blood markers of bone metabolism (calcium, phosphorus and parathyroid hormone) in either age group (p>0.05).

Conclusions: Intradialytic PRO supplementation improved protein intake and attenuated the decrease in h-BMD, a predictor of fractures, in older HD patients. Future studies should aim to explore the effect of whey protein on fracture rates in older HD patients.

Funding: NIDDK Support

TH-OR068

An Open Label Randomized Clinical Study to Evaluate Impact of Soy-Protein Powder in Malnourished Dialysis Patients (IMPROVES STUDY) Anita Saxena,[1] J. Kothari,[2] M. Gokulnath,[3] Amit Gupta,[1] Juan Jesus Carrero,[4] Chandra M. Pandey.[1] *[1]Nephrology, Sanjay Gandhi Post Graduate Inst of Medical Sciences, Lucknow, Uttar Pradesh, India; [2]Nephrology, Hinduja Hospital, Mumbai, Maharashtra, India; [3]Nephrology, St. John's Medical College, Bangalore, Karnatak, India; [4]Renal Medicine, Karolinska Inst, Karolinska Inst, Stockholm, Sweden.*

Background: Protein energy wasting (PEW) affects survival in patients on maintenance dialysis. Objective to evaluate effect of oral nutritional supplement on hypoalbuminemic dialysis patients.

Methods: Multicenter randomized intervention on maintenance dialysis (MD) patients with serum albumin <3.8g/dL. 180 patients were randomly assigned to 1:1 standard treatment (1.2 g/kg/d and 35 kcal/kg/d control) or standard treatment plus an oral nutritional supplement (ONS) for 6 months. The supplemented group received in addition 30 g/d of a renal-specific ONS (Proseventy©) containing 70% soya protein. At month 0, 3 and 6 routine biochemistry, subjective global assessment (SGA), dietary recalls, and skinfold thickness (SFT) were done.

Results: At inclusion, no difference was found in age, sex,dietary intake, SGA, CRP and biochemistry. Control group had significantly higher serum albumin (3.2±0.41 and 3.37±0.36 p 0.013) and subscapular SFT (14±6.0, 12.1±5.0 p 0.032) than supplemented group. At month 3, the supplemented group significantly increased their albumin (3.3 ±0.48 vs 3.4 ±0.43) and illiacSFT (15.5 ±8.5 and 18.1 ± 8.6 0.043). Protein intake was significantly higher in supplemented group compared to controls at 3 and 6 months (64± 21.5 54. ±1 16.3 p 0.004 and 69 ±28.4 and 53.5 ±15.1 p 0.000) respectively. In supplemented group subscapularSFT (16 ±5 12±5.1 p 0.000) was significantly high and albumin increased to 3.4± 0.049 versus 3.3 ±0.51 in controls at 6 months but difference in albumin was not significant. Serum phosphorus and lipid were not altered.

Conclusions: Addition of protein-rich renal specific ONS to standard nutritional counseling raised serum albumin and increased SFT in PEW patients undergoing dialysis. However, despite supplementation the serum albumin did not rise to ≥3.8 g/dL (ISRNM criteria). To correct PEW, ONS has to be given for longer period.

TH-OR069

Intramuscular Myostatin Gene Expression following Aerobic and Combined Exercise in Chronic Kidney Disease Douglas W. Gould,[1] Emma L. Watson,[1] Thomas James Wilkinson,[1] Soteris Xenophontos,[1] Alice C. Smith,[1,2] Joao L. Viana.[2] *[1]Leicester Kidney Exercise Team, Univ of Leicester, United Kingdom; [2]Univ Inst of Maia.*

Background: Muscle wasting is common in chronic kidney disease (CKD) and is associated with poor physical function and mortality. Myostatin (MSTN) is a potent negative regulator of muscle mass. It acts through the Activin 2B Receptor (AC2BR), eliciting both increased protein catabolism and reduced protein synthesis. The differential effects of aerobic exercise (AE) and resistance exercise (RE) on catabolic and anabolic pathways in CKD are poorly understood. Therefore we investigated the effects of AE or combined aerobic and resistance exercise (CE) on MSTN and AC2BR expression, and muscle hypertrophy in CKD.

Methods: 20 CKD patients (eGFR 25 ml/min/1.73m^2 [range 9-41]; age 59.6yrs [range 27-80]) were randomised to AE (3x/week for 12 weeks, n=9) or CE (AE + RE 3x/week for 12 weeks; n=11). Rectus femoris cross-sectional area (RF-CSA) was measured by ultrasound at baseline and 12-weeks. In 12 patients (AE n=5, CE n=7) muscle biopsies were obtained from the vastus lateralis at baseline (B1) and at 24h after the first (B2) and final (B3) exercise sessions. MSTN and AC2BR expression was analysed by RT-PCR and reported as % change from B1.

Results: RF-CSA was unchanged by AE (baseline 8.76±2.62cm^2, 12wks 9.21±2.44cm^2; p=.121) but significantly increased after CE (baseline 8.15±2.96cm^2, 12wks 9.25±3.15cm^2 p<.001). AE downregulated MSTN by 72% at B2 (p=.046) and 58% at B3 (p=.008). After CE, MSTN expression was downregulated by 69% (p=.005) at B2, but was non-significantly upregulated by 73% (p=.435) at B3. AC2BR expression mirrored this pattern but no significant interactions were seen between timepoints (AE; F=2.298, p=.163 & CE; F=1.099, p=.155).

Conclusions: These data suggest that AE can suppress MSTN expression in non-dialysis CKD, thereby potentially attenuating muscle catabolism. However, hypertrophy was only observed following CE, demonstrating that suppression of MSTN alone is insufficient to increase muscle size, and that an additional anabolic stimulus (RE) is required to achieve hypertrophy. These findings indicate the importance of RE in CKD and will inform guidelines for effective exercise in this underinvestigated population.

TH-OR070

Impact of L-Carnitine Pretreatment on Intravenous Iron Administration-Induced Oxidative Stress and Inflammatory Response in Patients with CKD Zaher Armaly,[1] Kamal Hassan,[2] Nayef Mohamed Habbashe,[3] Rawi Ramadan,[4] Gattas Naser,[5] Raymond Farah,[6] Zaid Abassi.[7] *[1]Nephrology, EMMS, Nazareth, Nazareth, Israel; [2]Nephrology, Western Galilee Hospital-Nahariya, Nahariya, Israel; [3]Nephrology, HaEmeq Medical Center, Afula, Israel; [4]Nephrology, Rambam Health Campus, Haifa, Israel; [5]Internal Medicine, Western Galilee Hospital-Nahariya, Nahariya, Israel; [6]Internal Medicine, Ziv Medical Center, Safed, Israel; [7]Physiology, Faculty of Medicine, Technion, IIT, Haifa, Israel.*

Background: Anemia is a common in CKD patients. It is attributed to decreased erythropoietin (EPO) production, low iron stores, and chronic inflammationy. Therefore, therapy includes not only recombinant EPO, but also iron replenishment. However, the latter induces oxidative stress/inflammation. L-carnitine supplementation might have positive effects on the response to EPO in HD patients. However, there is no evidence whether this approach is also beneficial in earlier-stage CKD patients. Thus, the present study examined whether long term L-carnitine therapy prevents IVIR-induced oxidative stress and whether it improves response to EPO.

Methods: This study included 32 anemic CKD patients (stages 2-4) that were divided into 2 subgroups: Group 1: 16 patients were given a weekly IVIR (Sodium ferric gluconate, [125 mg/100 ml]) for 12 weeks. Group 2: 16 patients received the same IVIR regimen but also carnitine (20 mg/kg, IV) was administered weekly prior to IVIR administration through the whole study. Weekly blood samples were drawn before and after each IVIR for C-reactive protein (CRP), advanced oxidative protein products (AOPP), TBARS, fibrinogen, NGAL, in addition to routine complete blood count and biochemical analyses.

Results: Combined administration of IVIR and carnitine increased Hb more profoundly (+8%) than those treated with IVIR alone (+13%). While IVIR alone induced oxidative and inflammatory responses, patients who received carnitine did not exhibit these adverse effects, as was evident by abolishing IVIR-induced elevation in CRP, NGAL, AOPP, TBARS and Fibronectin.

Conclusions: Our findings demonstrate that co-administration of carnitine with IVIR preferentially attenuates the adverse consequences of IVIR in CKD patients, suggests a role for carnitine therapy in these subjects.

TH-OR071

A CRISP(e)R View on Kidney Organoids Cecilia Borestrom, Anna Jonebring, Marcello Maresca, Barbara Valastro, Anna Collén. *Innovative Medicines & Early Development, AstraZeneca, Mölndal, Sweden.*

Background: Development of physiologically relevant cellular models, with strong translatability to human pathophysiology, is critical for identification and validation of novel therapeutic targets. Induced pluripotent stem cells (iPSCs) are an invaluable resource for modeling complex tissues, and tools to optimize differentiation protocols are crucial for progression of this promising field.

Methods: Utilizing CRISPR/Cas9 in hiPSCs we have established a model system, in which kidney commitment, glomerular maturation and podocyte health can be monitored in living cells using fluorescently tagged kidney lineage markers. Evaluation of differentiation and maturation has been confirmed using qPCR, flow cytometry, confocal microscopy, immunohistochemistry and electron microscopy.

Results: The presented work focuses on two kidney lineage markers; SIX2 and NPHS1, for tracing early nephron commitment and glomerular maturation in the same cell. Utilizing this dual reporter cell line, we have optimized progenitor formation and confirmed 3D culturing as a critical component in maturation of podocyte-containing kidney organoids. These organoids show expression of key markers of kidney biology, as well as renal cortical structures with microvilli, tight junctions and podocyte foot processes visualized by electron microscopy.

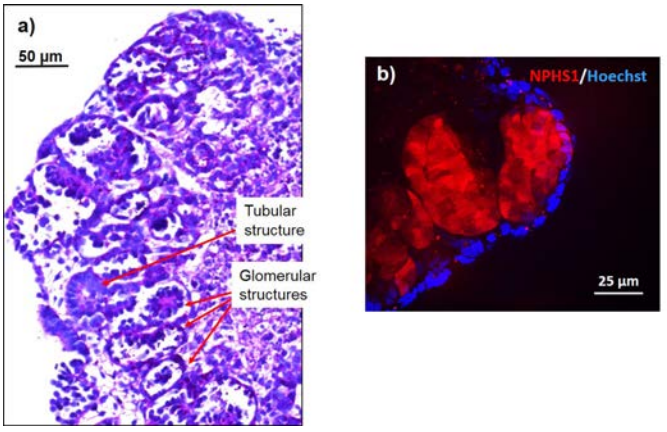


Figure a) PAS-stained section of organoid showing glomerular and tubular structures b) live image of organoid showing glomerular structures visualized by expression of NPHS1-reporter.

Conclusions: This work builds on the published kidney organoid work from the Small and Bonventre labs and extends it to build a system for live imaging in 3D, where we are able to assess longer term glomerular maturation and health. Furthermore, development of human nephron-like structures in vitro fills a major gap in assessing effectiveness of CKD-treatments and also in the possibility of clinical translations.

Funding: Pharmaceutical Company Support - AstraZeneca

TH-OR072

Monitoring and Improving Kidney Organiod Development through the Generation of Human Pluripotent Stem Cell Reporter Lines

Sara E. Howden,[1,2] Jessica May Vanslambrouck,[1] Andrew G. Elefanty,[1,2] Ed G. Stanley,[1,2] Melissa H. Little.[1,2] *[1]Murdoch Childrens Research Inst, Parkville, Vic, Australia; [2]Dept of Peadiatrics, Univ of Melbourne, Parkville, Vic, Australia.*

Background: We have recently established a robust protocol for the generation of kidney organoids from human pluripotent stem cells (Takasato et al, 2015). While such organoids appear to accurately model early human kidney, containing evidence of nephrons, vasculature and surrounding interstitium, further characterization of individual component cell types is required to both investigate and optimize their identity and function. One approach is the use of specific reporter lines to facilitate isolation and visualization of renal sub-compartments within kidney organoids.

Methods: We report the generation of reporters to characterise two key subcompartments; cap mesenchyme (CM), which represents the nephron progenitor population, and vasculature.To mark CM, the mCherry reporter gene (linked by a T2A sequence) was fused to the 3' end of human CITED1 using a previously described protocol (Howden et al, 2015) that enables reprogramming and gene targeting to be performed simultaneously in human fibroblasts. To mark vasculature we used an established (HES3) reporter line that carries mCherry targeted to the Sox17 locus (SOX17:mCherry).

Results: Seven CITED1-mCherry iPSC clones were correctly targeted according to PCR analysis of genomic DNA using primers flanking the recombination junction. During differentiation, mCherry expression could be detected several days after the initiation of differentiation and peaked around day 7 but declined as nephron differentiation proceeded. A SOX17:mCherry endothelial network was also visible early in organoid development, with vasculature increasing as the organoids matured.

Conclusions: We have demonstrated the utility of the CRISPR/Cas9 system for tagging key genes involved in kidney organogenesis. These reporter lines represent important tools for optimizing culture conditions for CM maintenance / self renewal and optimal vascularization within organoids.

Funding: NIDDK Support

TH-OR073

Kidney Organoids Generated from Human Pluripotent Stem Cells under Defined Conditions Become Vascularized upon Transplantation In Vivo

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Background: Human embryonic and induced pluripotent stem cells have the unique ability to differentiate into all lineages offering innovative approaches for regenerative medicine, such as the generation of transplantable organs. We aimed to derive kidney organoids from pluripotent stem cells (PSCs) under defined conditions. Recent studies have shown the ability to differentiate these cells into nephron progenitor populations; however these methods were based on PSC cultures on mouse embryonic fibroblasts.

Methods: We maintain PSCs on defined substrates in culture medium Essential 8 (E8). Adaptation of PSCs from passaging in clumps to single cells offered higher differentiation reproducibility due to more precise seeding of cell numbers. We generated kidney organoids by applying the temporospatial mechanisms that regulate the induction of renal structures during development. The 3-dimensional structures are formed by re-aggregation and contain structures derived from both ureteric epithelium and metanephric mesenchyme progenitor populations.

Results: The self-organizing organoids are positive for markers of the glomerulus, proximal and distal tubule, and collecting duct. In addition to this, we identified endothelial cell networks in the organoids. Scanning electron microscope analysis demonstrated the presence of glomerular-like structures containing podocytes with foot processes. However, we did not detect vascularization inside the glomerular structures. To further explore the possibility of vascularization of the organoids, we transplanted them under the renal capsule. Preliminary analysis showed the integration of mouse endothelial cells into the PSC-derived organoid, possibly promoting further maturation of the glomerular-like structures.

Conclusions: We demonstrated the generation of kidney organoids and their vascularization upon transplantation. These mini-kidneys are an important step forward for future applications in the development of a bioengineered kidney.

TH-OR074

Kidney Organoids Derived from Human Pluripotent Stem Cells Contain Multiple Kidney Compartments and Model Polycystic Kidney Disease

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Background: We generated nephron progenitor cells (NPCs) from human pluripotent stem cells (hPSCs) with 80~90% purity. These NPCs subsequently formed segmented nephron structures containing podocytes, proximal tubules, loops of Henle, and distal tubules juxtaposed to interstitial cells. To utilize this novel platform for studies of human kidney diseases, we further characterized kidney organoids and demonstrated the feasibility of modeling polycystic kidney disease.

Methods: Kidney organoids were evaluated by qRT-PCR and immunostaining for solute transporters and region specific proteins to evaluate the existence and functionality of multiple kidney compartments. We developed modified differentiation protocols for hiPSCs derived from patients with autosomal recessive polycystic kidney disease (ARPKD). Kidney organoids were generated from hESCs H9, hiPSCs HDF, and three lines of ARPKD hiPSCs.

Results: Kidney organoids highly expressed erythropoietin, 1-α-hydroxylase, ciliary proteins (PKD1, PKD2, PKHD1), and proximal tubule (AQP1, SGLT2, MDR1), distal tubule (SLC12A3), and collecting duct (AQP2) transporters. Immunostaining revealed CDH1+AQP2+ tubular cells, Endomucin+ or PDGFRβ+ vascular structures, and α-SMA+ or ICAM1+ interstitial cells, indicating the presence of collecting duct cells, endothelia, pericytes, myofibroblasts, and fibroblasts. More than 80% of organoids derived from ARPKD hiPSCs exhibited cyst formation in response to forskolin within 4 weeks of differentiation while control lines formed cysts rarely. Cysts were formed from CDH1+ tubules and were negative for LTL and KIM-1, indicating distal nephron derivation.

Conclusions: Kidney organoids derived from hPSCs contained nephron glomerular and tubular structures with many transporters present in the adult human nephron. In addition the organoids contained collecting duct and interstitial cells with multiple functional proteins. ARPKD patient-derived hiPSCs exhibited cystic phenotypes at high enough frequency serve as models of ARPKD.

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TH-OR075

Directed Differentiation to Kidney Organoids Represents a Reproducible and Developmentally Accurate Model of Human Kidney Development

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Background: We recently reported the generation of kidney organoids comprised of nephrons, collecting duct, vasculature and surrounding interstitium; bringing closer the prospect of personalised drug testing, disease modelling and regenerative medicine. The directed differentiation protocol relies upon replication of stepwise differentiation from pluripotency to kidney seen in embryogenesis. The utility of the protocol for these applications will rely implicitly on the reproducibility of the directed differentiation, the transferability between iPSC lines and the authenticity of the human cell types generated.

Methods: Here we report extensive RNA-seq based transcriptional analyses across the differentiation timecourse from pluripotent iPSC to kidney organoid. We also examined transcriptional variation between individual organoids, distinct differentiation experiments and between iPSC lines.

Results: Gene ontology interrogation of unsupervised clusters of synexpression, as well as pairwise temporal changes in gene expression, show a clear transition through appropriate intermediate developmental patterning events, including primitive streak, intermediate mesoderm, metanephric commitment and nephrogenesis. This confirms the high correlation between human and mouse metanephrogenesis, and provides a framework for quality control. A transcriptional correlation of >95% was observed between organoids and >90% between distinct differentiation experiments. Distinct iPSC clones also conformed to a matching transcriptional program. An examination of the most variable genes shows that these represent genes characteristic of nephron patterning, suggesting differential organoid maturation as the major source of both inter-experimental and intra-clonal variation.

Conclusions: This data provides a framework for removing sources of unwanted experimental variation in the analysis of expression data, thereby increasing the utility of this approach for personalised medicine and functional genomics.

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TH-OR076

Isolation and Maturation of Glomeruli in Human Induced Pluripotent Stem Cell-Derived Kidney Organoids Lorna J. Hale, Peter Farlie, Pei Xuan Er, Jessica May Vanslambrouck, Ed G. Stanley, Andrew G. Elefanty, Minoru Takasato, Thomas A. Forbes, Irene Ghobrial, Melissa H. Little. *Murdoch Childrens Research Inst, Melbourne, Victoria, Australia.*

Background: An essential function of the glomerular filtration barrier (GFB) is to limit the permeability of proteins from the blood to the urinary space. The GFB is composed of two highly specialised cell populations, the glomerular endothelial cells and podocytes, both of which contribute to the formation of the basement membrane, completing this three-layer structure. Defects in this barrier are a common feature of glomerulopathies, including Alport syndrome and nephrotic syndrome, however the cellular and structural complexity makes modelling of glomerulopathies *in vitro* challenging. We have generated kidney organoids from human iPSC that contain developing nephrons. These segment into distal tubules, proximal tubules and glomeruli with a primitive Bowman's capsule and podocytes with forming primary and secondary foot processes.

Methods: Glomeruli were isolated from human iPSC kidney organoids using mechanical disruption and sieving, followed by *in vitro* culture. The kidney organoids contain a network of endothelial cells, however there is only limited vascularisation of the glomeruli. To investigate whether we can overcome this issue, kidney organoids were transplanted onto the chorioallantoic membrane (CAM) of chicken embryos *in ovo*.

Results: When placed into culture, podocyte outgrowth from glomeruli was comparable to that seen from glomeruli isolated from postnatal human or mouse kidney. These podocytes form confluent monolayers with accurate polarity and podocyte-specific markers including CD2AP, Podocin, Synaptopodin and WT1. Organoids transplanted onto CAMs showed vascular ingrowth from the host embryo within 24-36hr, with organoid vascularisation increasing over time. The capacity for this exogenous blood supply to form glomerular capillaries and facilitate podocyte and GBM maturation was then investigated.

Conclusions: In conclusion, we have developed an *in vitro* method for the vascularisation of iPSC-derived kidney organoids. This will facilitate the modelling of human glomerular disease using patient-derived iPSC.

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TH-OR077

Human Pluripotent Stem Cell Derived Kidney Model for Toxicity and ADME Studies Piyush Bajaj, Claire Steppan, David Rodrigues, Thomas Schroeter. *PDM-NCE, Pfizer Inc, Groton, CT.*

Background: In vitro models of kidney function have been challenging to develop. Both primary and immortalized kidney cells quickly lose the apicobasal transporters and key proteins when grown in conventional culture systems. Therefore, a need exists to develop more physiologically relevant in vitro human cell models which could be used to support efficacy, safety and ADME testing.

Methods: Pluripotent stem cells were differentiated into podocytes and proximal tubule cells (PTCs) by mimicking elements of renal developmental biology and prior literature. The stem-cell derived cells were characterized in terms of gene expression, immunocytochemistry, and functionality. Presence of several key renal transporters was confirmed by gene expression. Finally, the in vitro model was subjected to 10 compounds and expression of renal biomarkers such as KIM-1 and HO-1 was monitored at different doses.

Results: Human embryonic stem cells (H9) were differentiated in a 6-step process over 24-days to yield both podocytes and PTCs by mimicking in vivo nephrogenesis. PTCs showed megalin-dependent cubilin-mediated endocytosis of fluorescently labeled dextran and active gamma-glutamyl transpeptidase enzyme. Several key renal transporters such as OATP4C1, PEPT1/2, MRP4, MATE1, P-gp, OCTN1/2, SLC34A1/3, etc. were present at physiological levels in the differentiated cells. Most current in vitro models only express a much smaller set of these transporters. Uptake studies using small molecules confirmed the functionality of a subset of these transporters. The in vitro cell model was also subjected to 7 nephrotoxic compounds and 3 benign compounds. The system correctly predicted 9 of the 10 compounds by showing dose-dependent changes of KIM-1 and HO-1.

Conclusions: By mimicking in vivo nephrogenesis, stem-cell derived podocytes and PTCs were generated and characterized. The model system showed physiological expression of several key renal transporters making it a useful platform for ADME studies. The model could also distinguish nephrotoxic compounds from benign compounds by monitoring key renal biomarkers showing its applicability for safety studies as well.

Funding: Pharmaceutical Company Support - Pfizer Inc

TH-OR078

PiggyBac Transposon-Mediated Direct Transcriptional Reprogramming to Nephron Progenitors Jessica May Vanslambrouck,[1] Lauren Elizabeth Woodard,[2] Norseha Suhaimi,[1,3] Matthew H. Wilson,[2] Melissa H. Little.[1] *[1]Murdoch Childrens Research Inst, Royal Children's Hospital, Melbourne, Australia; [2]Dept of Veterans Affairs and Dept of Medicine, Div of Nephrology and Hypertension, Vanderbilt Univ School of Medicine; [3]School of Biomedical Sciences, The Univ of Queensland, Brisbane, Australia.*

Background: Reprogramming holds great promise for the development of desperately needed novel treatments for chronic kidney disease (CKD). All nephrons in the kidney arise from embryonic nephron progenitors (NPs). However, this population is depleted near birth rendering the mature kidney unable to form new nephrons regardless of damage or disease. Recreation of NPs may allow regeneration of entire nephrons, making them an ideal target for reprogramming approaches to generate alternate CKD treatments. Using a lentivirus-mediated screen, we previously identified 6 transcription factors (*SIX1, SIX2, HOXA11, OSR1, EYA1* and *SNAI2)* sufficient to re-impose a NP-like state when co-expressed in adult human kidney epithelial cells (Hendry *et al.*, JASN, 2013). To improve reprogramming and transferability to *in vivo* models, we have developed a multicistronic transposon construct.

Methods: The transposon was generated by engineering reprogramming factors into a *piggyBac* construct with intervening 2A sequences, a tetracycline response element for doxycycline inducibility and a fluorescent reporter (mCherry) for enrichment. To assess functionality, the transposon was co-transfected with tetracycline-activator and *piggyBac* transposase constructs. Reprogramming was induced with doxycycline exposure in combination with brief valproic acid treatment.

Results: Transfected adult kidney cells showed tightly regulated, inducible mCherry expression. When exposed to the NP reprogramming protocol, these cells displayed key markers of NPs and epithelial-to-mesenchymal-transition, as well as morphological and functional characteristics of endogenous NP cells.

Conclusions: These results not only demonstrate the feasibility of transposon-based direct reprogramming, but also bring us closer to realizing patient-specific reprogramming to NPs for cellular therapies, bioengineering applications and nephrotoxicity screening.

Funding: Government Support - Non-U.S.

TH-OR079

Convoluted Proximal Tubule Modeling Enabled by Microfluidics and Bioprinting Kimberly Homan,[1] David Kolesky,[1] Jessica E. Herrmann,[1] Annie Moisan,[2] Jennifer A. Lewis.[1] *[1]The Wyss Inst, Harvard Univ, Cambridge, MA; [2]Roche Pharma Research and Early Development, Roche Innovation Center Basel, Basal, Switzerland.*

Background: Three-dimensional models of kidney tissue that recapitulate human responses are needed for drug screening, disease modeling, and, ultimately, kidney organ engineering.

Methods: We present a bioprinting method for creating functional 3D human renal proximal tubules in vitro that are fully embedded within an extracellular matrix and housed in perfusable tissue chips, allowing them to be maintained for greater than four months. Their convoluted tubular architecture is circumscribed by proximal tubule epithelial cells and actively perfused through the open lumen at physiological shear stresses.

Results: These engineered 3D proximal tubules exhibit significantly enhanced epithelial morphology and functional properties relative to the same cells grown on 2D surfaces with or without perfusion. The proximal tubule cells in 3D printed and perfused conditions deposit their own basement membrane over time and develop a brush border. Additionally, epithelial cells in curved regions of the convoluted tubule uptake albumin more than nearby straight regions. Lastly, upon introducing the nephrotoxin, Cyclosporine A, the epithelial barrier is disrupted in a quantifiable, dose-dependent manner.

Conclusions: In addition to the enhancement in morphology and function of tubule cells observed in our chips, the bioprinted platform is versatile can be customized to incorporate perfusable vasculature and multiple cell types in predefined locations, enabling both drug screening and drug toxicity mechanistic studies at user-defined levels of complexity.

Funding: Pharmaceutical Company Support - Roche, Private Foundation Support

TH-OR080

Rapid Iterative Development of Blood Conduits for Artificial Kidney Eliminates Thrombosis Rachel C. Forbes,[1] Clark David Kensinger,[1] Joseph J. Groszek,[2] Daniel Colvin,[3] Shuvo Roy,[4] William Henry Fissell.[2] *[1]Surgery, Vanderbilt Univ, Nashville, TN; [2]Nephrology and Hypertension, Vanderbilt Univ, Nashville, TN; [3]Inst for Imaging Sciences, Vanderbilt Univ, Nashville, TN; [4]Bioengineering and Therapeutic Sciences, Univ of California San Francisco, San Francisco, CA.*

Background: Implanted blood contacting devices, particularly dialyzers, tend to require pharmacologic anticoagulation of the patient to avoid local thrombosis and distant thromboembolism. Macrovascular encapsulation of islet cells utilizing a U-shaped device as a bioartifical pancreas was largely abandoned due to complications such as thrombosis. Improved design and manufacturing of devices might avoid the risks and costs of chronic anticoagulation and allow for the successful development of an artificial organ. Computational modeling and in vitro imaging facilitated rapid iterative development of a low-thrombosis blood conduit.

Methods: Following 3-90 day sustained preclinical implantation trials of hemofilter cartridges, correlations between low shear rates in silicon and areas of clot nucleation in vivo

led to modifications of outflow tract geometry. Computational fluid dynamics simulations of unsteady flow in design variations were followed by flow field imaging in vitro. The design with least recirculation and stasis was machined from medical grade polycarbonate and implanted in a Class A dog for 30 days without warfarin or heparin. Serial Doppler ultrasound examinations verified patency of the blood conduits. At postoperative day 30, the device was harvested and examined for thrombosis.

Results: Optimized designs had increased curvature radius and decreased taper in the outflow tract. The animal suffered no complications of surgery. No hemolysis or distal embolization was noted. The optically transparent cartridge had no visible thrombosis.

Conclusions: Meticulous attention to the flow fields in a blood contacting device, such as a bioartificial kidney, can reduce thrombosis and eliminate the need for systemic anticoagulation.

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TH-OR081

Women Have Higher Urine pH Than Men due to Increased Gastrointestinal (GI) Alkali Absorption

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Background: Calcium phosphate stones form at higher urine pH (UpH) and are more common in women (W) than in men (M). If UpH is higher in W, it may explain this disparity. In a General Clinical Research Center, we investigated whether W have higher UpH than M when eating identical diets and if so, what components of acid-base metabolism are responsible for the difference.

Methods: We measured UpH and determinants of acid-base regulation in 14 normal subjects (7 M). We collected 15 urines and 20 blood samples over a 15 hour day; diet was fixed. GI anion excretion (GIAE) = [(Na+K+Ca+Mg) - (Cl+P)] in urine (mEq/hr).

Results: UpH of W exceeded that of M; UpH rose with meals in W but not M (Table). Serum ultrafilterable (UF) CO_2 and GIAE rose with meals in W, not M; urine CO_2 excretion and GIAE exceeded M. Lower UpH in M was accompanied by higher net acid excretion (NAE), urine titratable acid (TA) and NH_4. Urine citrate (cit) and fractional excretion (FE) of cit was higher in W even adjusted for filtered load (FL) of cit, indicating reduced renal reabsorption of cit in W vs M.

	WOMEN		MEN	
	FAST	FED	FAST	FED
UpH	6.3±0.1	6.7±0.1*	5.8±0.1#	6.1±0.1#
UF CO_2	22±1	23±1*	22±1	22±1
U CO_2	0.6±0.2	1.4±0.1*	0.6±0.3	0.6±0.1#
U TA	0.36±0.08	0.35±0.04	0.46±0.08	0.65±0.04*#
U NH_4	0.9±0.1	0.9±0.1	1.1±0.1	1.2±0.1#
U NAE	0.7±0.4	-0.1±0.2*	1.0±0.4	1.3±0.2#
FL Cit	1.5±0.1	1.7±0.1	1.5±0.1	2.0±0.1*
U Cit	0.17±0.02	0.21±0.01*	0.12±0.02	0.15±0.01#
FE Cit	0.07±0.04	0.09±0.04	0.03±0.04#	0.03±0.03#
Adj U Cit	0.13±0.05	0.16±0.05	0.08±0.04#	0.08±0.04#
GIAE	2.5±0.5	3.9±0.3*	1.9±0.5	1.8±0.3#

Mean±SE, adjusted for age and weight; Adj U Cit also adjusted for FL cit. Excretions and FL are mmol/hr/BSA; UF CO_2 is mmol/L.*p<0.05 vs FAST same sex; #p<0.05 vs W same food period.

Conclusions: W have higher GI alkali absorption and GIAE than M which translates into increased urine CO_2 and higher UpH. The sex difference in UpH is not due to diet, but is related to ingestion of food.

Funding: NIDDK Support

TH-OR082

Comparison of Furosemide/Fludrocortisone with Ammonium Chloride Test in the Diagnosis of Incomplete dRTA in Recurrent Stone Formers: A Prospective Study

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Background: Incomplete dRTA (idRTA) is a frequently encountered entity in recurrent stone formers (SF). IdRTA cannot be discerned by conventional clinical criteria but requires unmasking by a provocative urinary acidification test. Since the original description by Wrong and Davies in 1959, the short ammonium chloride (NH4Cl) loading test is considered the gold standard for the diagnosis of idRTA. The furosemide/fludrocortisone (F/F) test has recently been proposed as a test with improved tolerability. Due to the lack of comparative prospective studies, however, the validity of the different provocative tests employed is currently unknown. In addition, it remains currently unclear which group of recurrent SF should undergo testing for idRTA.

Methods: We performed a prospective study in an unselected group of recurrent SF referred to our stone clinic to assess the reliability of the F/F test in the diagnosis of idRTA. All patients underwent metabolic work up for stone disease and sequential F/F and NH4Cl testing, at least 1 week apart.

Results: 142 recurrent SF were recruited for the study over a period of 3 years. Mean age was 45.7 ± 13.4 years, 73.2% of participants were men. Prevalence of idRTA was 22.6% with the F/F test and 9.2% with the NH4Cl test. Assuming failure to lower urinary pH <5.3 during the NH4Cl test as gold standard for diagnosis, the F/F test had a positive predictive value of 37% and a negative predictive value of 97 % for the diagnosis of idRTA. Furthermore, comparison of fasting urinary pH and urinary acidification capacity during F/F and NH4Cl tests indicates that only a morning fasting urinary pH of <5.3 reliably excludes idRTA.

Conclusions: Thus, the F/F test is an excellent screening test for idRTA diagnosis in recurrent SF with a high negative predictive value. Due the low positive predictive value, however, patients with a pathological F/F test need confirmation by the NH4Cl test for idRTA diagnosis. In the absence of provocative testing, a diagnosis of idRTA can only be ruled out confidently with a morning fasting urinary pH <5.3.

TH-OR083

Hydroxyproline Metabolism and Oxalate Synthesis in Primary Hyperoxaluria

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Background: The primary hyperoxalurias (PH) are severe inherited diseases of glyoxylate metabolism characterized by increased endogenous production of oxalate. A major source of glyoxylate in humans is hydroxyproline (Hyp), a collagen breakdown product. To quantify the contribution of Hyp turnover to oxalate synthesis, we infused labeled Hyp in fasting PH patients and healthy subjects.

Methods: Patients with PH type 1 (n: 7), 2 (n: 4), 3 (n: 8), and normal subjects (n: 9) were infused with ^{15}N-$^{13}C_5$-Hyp (750 nmol/kg/h) for 6 h continuously. Urine and plasma were collected hourly for analysis of ^{15}N-$^{13}C_5$-Hyp by GC/MS, total Hyp by HPLC, ^{12}C- and ^{13}C-oxalate and glycolate by IC/MS.

Results: Basal plasma Hyp concentrations and fluxes were lower in PH patients compared to controls [figure1A,B]. The contribution of Hyp metabolism to urinary oxalate excretion was 45% in PH2 patients compared to PH1 patients (16%) and controls (11%) [figure1C]. The contribution of Hyp to urinary glycolate was significantly decreased in PH2 and PH3 and marginally decreased in PH1 [figure1D].

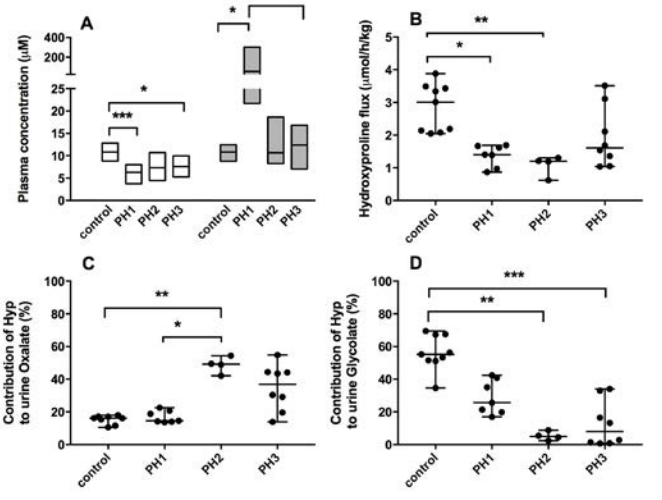

*Fig (1A) Plasma concentration of Hyp (white) and glycolate (grey) before infusion; (1B) Hyp flux; (1C) contribution of Hyp to urinary oxalate and (1D) glycolate. Results (median, range); */**/*** p<0.05/0.01/0.001 with Kruskall-Wallis test.*

Conclusions: Hydroxyproline contributes to glycolate and oxalate metabolism in humans confirming its potential as a therapeutic target in PH and the potential usefulness of dietary restrictions in PH2. The heterogeneity seen between PH3 patients highlights the complexity of oxalate synthesis in PH3. These data suggest other yet to be determined pathways are important to the increased synthesis of oxalate in PH.

Funding: NIDDK Support

TH-OR084

Enhanced Gastrointestinal Passive Paracellular Permeability Contributes to Hyperoxaluria in Obese Mice

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Background: Most kidney stones (KS) are composed of calcium oxalate, and small increases in urine oxalate affect the stone risk. Obesity is a risk factor for KS and obese stone formers often have mild hyperoxaluria. A positive correlation between increased body size and elevated urinary oxalate excretion was reported. To define the underlying mechanisms, we previously found the obese *ob/ob* mice to have hyperoxaluria (>2.9-fold) and increased paracellular jejunal (>46%) and ileal (>30%) oxalate absorption *ex vivo*.

Methods: *In vivo* intestinal oxalate absorption was assessed by giving the *ob* mice and their controls ^{13}C-oxalate by oral gavage, followed by 6 h urine collection. Gastrointestinal paracellular permeability was assessed *in vivo* by giving the *ob* mice and their controls a solution containing sucrose, mannitol, lactulose, and sucralose by oral gavage, followed by 24 h urine collection to determine the fractional urinary recovery of these sugar probes.

Results: *ob* mice have significantly higher (>5-fold) urine ^{13}C-oxalate compared to controls, indicating increased intestinal oxalate absorption *in vivo*. Observing a greater oxalate absorption *in vivo* compared to *ex vivo* suggest the possibility of increased paracellular permeability along the entire gut. *ob* mice have significantly higher urinary excretion of sucrose (>1.7-fold) and sucralose (>2.2-fold), reflecting increased proximal gut (including the stomach) and colonic paracellular permeability, respectively. *ob* mice also have significantly higher urinary excretion of lactulose (>4.4-fold), mannitol (>3-fold), and lactulose:mannitol (>1.52-fold), reflecting enhanced small intestinal paracellular permeability. Using qpcr, significantly reduced mRNA expression of the tight junction proteins occludin (37-90%) and ZO-1 (28-62%) is observed in the stomach, duodenum, jejunum, ileum, cecum, and distal colon of *ob* mice.

Conclusions: We conclude that obese mice have significantly higher paracellular permeability along the entire gut, which would likely contribute to the observed hyperoxaluria, since there is a favorable transepithelial oxalate concentration gradient.

Funding: NIDDK Support

TH-OR085

A Dose Finding Study with ALLN-177 in a Porcine Model of Mild Hyperoxaluria (20HO) Induced by a Human-Like Western Diet

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Background: Secondary hyperoxaluria is a known risk factor for recurrent urolitihiasis and progressive chronic kidney disease. Dietary modifications have limited effectiveness and no pharmacological therapies are available to reduce dietary hyper-absorption of oxalate. ALLN-177 is an oral, crystalline oxalate-degrading enzyme therapy (Rx) that specifically degrades dietary oxalate in the GI with the potential of reducing stone episodes.ALLN-177 was tested in a porcine dietary model of 2^{0}HO induced with a Western like diet (WLD) with average oxalate and calcium levels. Pigs were chosen due to their physiological similarities to humans in GI and renal functions.

Methods: To induce mild hyperoxaluria 24 pigs were fed the WLD for an initial pre-treatment period of 7 days and then randomized based on daily urinary oxalate (Uox) in a parallel 7d study to one of three treatment arms: ALLN 22,500 units/day (high dose, HD, n=8), 11,250 units/day (low dose, LD, n=8), or no treatment (n=6).The primary endpoint was the within-pig mean difference in 24h Uox (mg/g cr/24h) calculated from days 3,5,and 7 collected during the pre-treatment and treatment periods. A control group of 6 pigs was fed a regular pig feed (RF) to assess the impact of Rx on Uox vs RF alone and to establish normal Uox excretion.

Results: Twice daily oral Rx with ALLN-177 significantly reduced mean Uox by 15mg (17%) and 11mg (12%) with HD and LD respectively, when compared to WLD alone (HD: 85.08±15.0 to 70.60±10.1; LD 87.94±15.0 to 77.23±10.1 mg/gCr/d, p<0.001) whereas the mean Uox did not change in the WLD control group. Importantly, with the HD Rx, Uox excretion decreased to the normal range recorded on RF diet (66.2 ± 9.1mg gCr/d). Therapy was well tolerated without adverse symptoms.

Conclusions: Orally administered ALLN-177 with meals was well tolerated and normalized Uox with the 22,500 units/d. This porcine model that mimics 2^{0}HO in patients, and the positive efficacy results with ALLN-177, provided proof of concept for subsequent human studies that are underway.

TH-OR086

Claudin-2 Knockout Mice Spontaneously Develop Calcium Phosphate Deposition within the Renal Papilla

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Background: The proximal tubule (PT) is where the majority of calcium reabsorption in the kidney occurs by an unknown mechanism. Physiologic studies have shown this reabsorption to be predominantly passive. The tight junction proteins called claudins are important determinants of paracellular permeability and passive reabsorption in the kidney. In the PT, the highest claudin expression is that of claudin-2, which forms cation-selective pores in *in vitro* studies. Previous studies have shown that claudin-2 KO mice have an increase in urine calcium. We hypothesize that claudin-2 loss leads to defective PT calcium reabsorption and nephrocalcinosis.

Methods: Renal calcification was quantified by micro-CT (Scanco). Mineral composition of renal stones was determined by micro-Fourier Transform infrared spectroscopy. Transmission electron microscope was performed on 2% glutaraldehyde fixed papillary sections.

Results: We found that Cldn2-KO mice develop nephrocalcinosis concentrated within the renal papilla that is absent from wild type littermates. Using micro-FTIR analysis, these deposits were determined to be composed primarily of hydroxyapatite (calcium phosphate). Localization of these deposits was determined to be intraluminal by immunohistochemistry and transmission electron microscopy.

Conclusions: Randall's plaques are hydroxyapatite plaques which develop within the renal papilla in human kidney stone formers. Cldn2$^{-/y}$ mice may develop nephrocalcinosis in a similar manner. Physiologic analyses will help us further determine whether the observed increase in urine calcium is due to a defect in PT calcium reabsorption in Cldn2$^{-/y}$ mice.

Funding: NIDDK Support

TH-OR087

Insulin Resistance and the Risk of Calcium Kidney Stone

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Background: Insulin resistance is associated with a higher risk of uric acid kidney stone. But its role in calcium kidney stone formation is not clear.

Methods: We performed a cross-sectional study of 43 non-diabetic calcium kidney stone formers, and examined the associations between insulin resistance and 24-hour urine stone risk parameters. The homeostatic model assessment (HOMA)-IR and HOMA-B were used to quantify insulin resistance and pancreatic beta-cell function respectively. Both HOMA-IR and HOMA-B were log transformed and were modeled using univariate and multiple linear regression methods.

Results: All study participants had confirmed calcium kidney stones. Among them, 61% were male, 86% were Caucasian, 33% had prevalent hypertension and 12% had prevalent dyslipidemia. The median age was 53 years (range 21-76), and the average body mass index (BMI) was 29 (Standard Deviation, ±5). The mean serum 25-OH-vitamin D level was 25 ng/ml, the median HOMA-IR was 5.25 (range 1.4-68.4), and the median HOMA-B was 176.9 (range 52.25-2421). Both HOMA-IR and HOMA-B associated significantly with BMI, even after adjusting for hypertension, dyslipidemia and 25-OH-vitamin D (P<0.02). HOMA-IR associated significantly with urine calcium (P=0.011), urine uric acid (P=0.001) and urine ammonium (P=0.033) in univariate linear models. After adjusting for age, gender, race and BMI, only urine uric acid associated significantly with HOMA-IR (P=0.009). HOMA-B associated significantly with urine calcium (P=0.039) and urine uric acid (P=0.017) in univariate linear models. After adjusting for age, gender, race and BMI, the associations were no longer significant. Neither HOMA-IR nor HOMA-B had significant associations with urine pH, sodium, phosphorus, oxalate, and citrate in univariate analysis (P>0.05).

Conclusions: Neither HOMA-IR nor HOMA-B appeared to be associated with an increased risk of calcium kidney stone formation. The significance of the association between HOMA-IR and urine uric acid among calcium stone formers is not clear.

Funding: Clinical Revenue Support

TH-OR088

The Live Donor Champion Program: A Novel Approach to Identifying Live Kidney Donors

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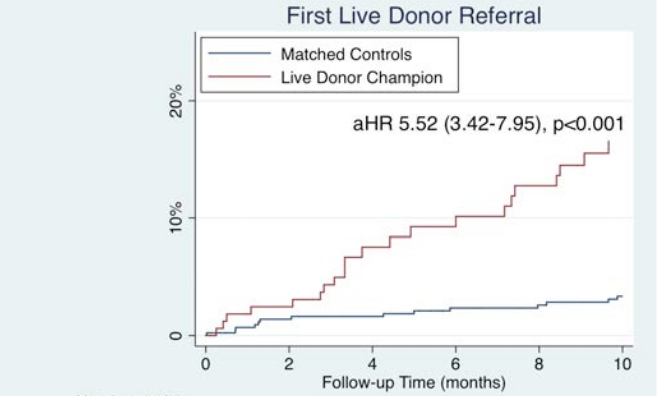
Background: The Live Donor Champion (LDC) program is a clinical program offered to kidney waitlist candidates at our transplant center. The five-month program provides education and advocacy training for candidates and a friend or family member chosen to serve as an advocate, or "Live Donor Champion", on each candidate's behalf. The goal of the program is to increase awareness of live donation and to identify potential live donors.

Methods: We studied 163 adult kidney transplant candidates that have participated in the LDC program at Johns Hopkins Comprehensive Transplant Center between October 2013 and May 2016. Paired t-tests were used to estimate the difference in knowledge about live donation and comfort approaching others about live donation before and after participation in the LDC program. We compared time to first live donor referral for candidates that participated in the program with matched controls from our waiting list using a cox proportional hazard model. We used 1:3 iterative expansion radius matching to choose controls based on age at listing, time on waitlist without a live donor, sex, race, and ABO blood type.

Results: Participation in the LDC program was associated with a statistically significant increase in knowledge of live donation among candidates participating alone, candidates participating with a LDC, and LDCs (all p- values <0.001). Comfort approaching others about live donation also increased significantly among all three groups (all p-values <0.001). Among LDC participants, there were a total of 81 live donor referrals. Participation in the LDC program was associated with 5.5-fold increase in having at least one donor referral compared to matched controls (aHR 5.52, 95% CI 3.42-7.95, p<0.001).



Conclusions: The LDC program is associated with increased knowledge of live donation, comfort approaching others about live donation, and live donor referrals.

Funding: Private Foundation Support

TH-OR089

The Live Kidney Donor Aotearoa (LDKA) Program: A Health Services Initiative to Increase Kidney Transplantation in New Zealand (NZ) Disadvantaged Populations Mark R. Marshall,[1,2] Denise Ann Beechey,[1] Caran Barratt-Boyes,[1] Nora Van der Schrieck,[3] Lisa Frances Hoyle,[1] Catherine Anne Tracy,[1] Hari Manoharlal Talreja.[1] *[1]Dept of Renal Medicine, Counties Manukau District Health Board, Auckland, New Zealand; [2]School of Medicine, Univ of Auckland, Auckland, New Zealand; [3]Kidney Society Auckland, Auckland, New Zealand.*

Background: Kidney transplantation (KT) is associated with the best outcomes for ESKD patients. NZ has a low rate of KT, especially in Māori and Pacific People (PP). We evaluate LDKA, a NZ government-funded 3-year demonstration program involving Counties Manukau District Health Board (CMDHB) - NZ's largest nephrology service - and Kidney Society Auckland - a patient support group. The LDKA aims to increase LDKT and thereby overall KT, particularly in disadvantaged NZ ethnic groups.

Methods: The LDKA program was initiated in April-2013 and consists of 6 projects (1) Culturally-sensitive and health literacy-appropriate educational resources on LDKT (www.ldka.org.nz) (2) A "Home & Kidney first" policy as part of CMDHB predialysis education to focus on transplantation (followed by home dialysis) as treatment of choice (3) Home-based LDKT education of family / social networks using culture-specific educators to build health literacy skills and understanding (4) Development of an engagement framework for targeted communities and their leaders (5) Educational programs for primary care providers (6) Peer-to-peer support for potential LDKT recipients and donors. We perform time series analysis using autoregressive Poisson regression to estimate the effect (IRR, 95% CI) of the LDKA program on KT and LDKT.

Results: Using the 5 years prior to the LKDA as baseline, there were 11 LDKTs from CMDHB in this period, 4 of which were in Māori or PP. In 2015 alone, there were 7 LDKTs, 4 of which were in Māori or PP. Accounting for underlying prior 5-year trends in KT or LDKT, the LDKA program is associated with an increase in KT by 1.84 (1.21-2.79) fold, and in LDKT by 3.60 (1.73-7.49) fold.

Conclusions: A whole-systems approach with a multi-faceted health service delivery improvement program is an effective way of increasing LDKT, particularly in disadvantaged populations.

Funding: Government Support - Non-U.S.

TH-OR090

Pre-Transplant Recipient Transcriptomic Profile May Predict Delayed Graft Function (DGF) in Kidney Transplantation Paola Pontrelli,[1] F. Rascio,[2] Francesco Pesce,[1] Matteo Accetturo,[1] Giuseppe Castellano,[1] Gianluigi Zaza,[3] Marco Fiorentino,[1] Loreto Gesualdo,[1] G. Stallone,[2] Giuseppe Grandaliano.[2] *[1]Univ of Bari; [2]Univ of Foggia; [3]Univ of Verona.*

Background: DGF is associated with a reduced long-term graft survival. Ischemia-reperfusion damage and donors' features have been always considered as key pathogenic factors in this setting. The aim of our study was to evaluate the role of recipients' characteristics in the development of DGF.

Methods: We prospectively enrolled 538 kidney graft recipients, 176 of whom experienced DGF. We selected 10 couples of DGF/early graft function (EGF) recipients for high throughput analysis. Peripheral blood mononuclear cells (PBMC) were harvested before transplantation. Transcriptomic profile was investigated by HG-U133A microarray (Affymetrix). The results were evaluated by statistical (Genespring software) and functional pathway analysis (Ingenuity Pathway Analysis).The transcriptomic data were validated by qPCR in an independent group (DGF n=10; EGF n=10).

Results: In 38 cases both recipients from the same donor presented with DGF (C group), whereas in 138 cases only one recipient/donor experienced DGF (D group), suggesting a key role of recipients features in the pathogenesis of this condition. We did not observe any difference in donors' features between C and D group, further supporting our working hypothesis. In the D group, DGF was independently associated (logistic regression) only with number of mismatches (OR 1.867, p=0.01) and dialysis vintage (months, OR 1.009, p=0.03). The transcriptomic profile demonstrated that, considering a fold change>2, 273 genes were differentially expressed between the 2 groups. The main biological functions were inflammatory disease (p range=9.8E-05-1.4E-14, 65 genes) and inflammatory response (p range=3.6E-04-3.2E-14, 80 genes), featuring the immunological profile of dialysis patients. Interestingly, the two main upstream regulators identified were TNF-alpha (p=4.6E-19) and TGF-β (p=4.0E-17), two key inflammatory mediators modulated by dialysis.

Conclusions: Our results suggest that recipients' immunological features, modulated by dialysis, are significantly associated with the development of DGF independently of donors' features.

Funding: Government Support - Non-U.S.

TH-OR091

Crossing the Valley of Death: A Validation Study of Noninvasive Diagnosis of Acute Cellular Rejection by a Composite Signature of 3-mRNAs and 4 Metabolites in Urine Mohamad M. Alkadi, Catherine Snopkowski, Carol Y. Li, Liana S. Perry, Matthew Magruder, Karan Jatwani, John R. Lee, Steven Salvatore, Darshana Dadhania, Surya V. Seshan, Hua Yang, Adhirai Muthukumar, Karsten Suhre, Manikkam Suthanthiran. *Weill Cornell Medicine.*

Background: Most biomarkers fail to be validated in an independent cohort- the valley of death encountered also during transitions from Phase I safety to Phase III efficacy trials. We investigated whether our 3-gene urinary cell RNA signature and the metabolite signatures for the noninvasive diagnosis of acute cellular rejection (ACR) are validatable in an independent cohort of kidney graft recipients.

Methods: We collected 118 biopsy-matched urine specimens from 95 kidney recipients (22 from 22 recipients with ACR; 96 from 73 recipients with no rejection). We isolated RNA from the urine cell pellets and quantified the absolute abundance of CD3ε mRNA, CXCL10 mRNA and 18S rRNA using qPCR assays. We measured the metabolites 3-silalyllactose, xanthosine, quinolinate and X-16397 in the corresponding cell-free urine supernatants using comprehensive GC/MS and LC/MS/MS platforms.

Results: Urinary cell 3-gene signature discriminated patients with ACR from no rejection (AUC: 0.81). The ratio of 3-silalyllactose/xanthosine (AUC: 0.65) and quinolinate/X-16397 (AUC: 0.74) discriminated ACR from no rejection. The combined mRNA and metabolite signature also discriminated patients with ACR from those with no rejection (AUC: 0.86).

Signature	Area Under the Curve (AUC)	
	Discovery Study	Validation Study
Urinary cell 3-gene mRNA signature: [−6.1487+0.8534 log(CD3ε/18S)+0.6376 log(IP-10/18S) +1.6464 log(18S)] *(Suthanthiran et al. NEJM 2013: 369:20-31)*	0.85	0.81
Metabolite signature: [log 3-sialyllactose/xanthosine] *(Suhre et al. JASN 2016: 27:626-36)*	0.75	0.65
Metabolite signature: [log quinolinate/X-16397] *(Suhre et al. JASN 2016: 27:626-36)*	0.71	0.74
Combined signature: [mRNA signature+1.1164* log(3-sialyllactose/xanthosine)+0.6937* log(quinolinate/X-16397)] *(Suhre et al. JASN 2016: 27:626-36)*	0.93	0.86

None of the AUCs differed significantly from the AUCs in our original biomarker studies (P>0.05, DeLong test).

Conclusions: To our knowledge, this is first-in-kind validation of urine-based biomarkers diagnostic of ACR using: (i) an independent cohort of kidney recipients, and (ii) a locked prediction model, i.e., using the same discovery study equation in the validation study. Our observations support consideration of these biomarkers in the clinical management.

TH-OR092

Urine Fibrosis Markers and Risk of Cardiovascular Events and Death in Kidney Transplant Recipients: The FAVORIT Trial Meyeon Park,[1] Ronit Katz,[2] Michael Shlipak,[1] Daniel E. Weiner,[3] Vasantha Jotwani,[1] Jan M. Hughes-Austin,[4] Francis B. Gabbai,[4] Chi-Yuan Hsu,[1] Nisha Bansal,[2] Andrew Bostom,[5] Orlando M. Gutierrez,[4] Mark J. Sarnak,[3] Andrew S. Levey,[3] Joachim H. Ix.[4] *[1]UCSF; [2]U. Washington; [3]Tufts; [4]UCSD; [5]Rhode Island Hospital.*

Background: Cardiovascular disease (CVD) risk is high in kidney transplant recipients (KTR) despite improvement in eGFR after transplant. Urine markers of kidney fibrosis may help to reveal mechanisms of this risk.

Methods: In a case-cohort study among stable KTR who participated in the FAVORIT trial, we measured 4 urine proteins known to correlate with kidney biopsy tubulo-interstitial fibrosis (alpha 1 microglobulin [α1m], monocyte chemoattractant protein-1 [MCP-1], procollagen type I [PINP] and type III [PIIINP] N-terminal amino peptide). We used spot urine specimens collected at baseline in a randomly selected subcohort (N=488) and in cases with CVD events [composite of CV death, myocardial infarction, resuscitated sudden death, and stroke] (N=282) and death (N=359) during 3.46 mean years of follow-up. We used weighted Cox proportional hazards regression.

Results: Urine α1m, MCP-1, and PINP were strongly associated with CVD events and death, after adjusting for demographics, CVD/CKD risk factors, eGFR, and ACR (Table 1). Relative to the lowest quartile, the highest quartile of urine α1m [HR 2.83 (1.43, 5.57)] and PINP [HR 2.88 (1.61, 5.16)] were associated with CVD events. All 3 markers were also associated with death in adjusted models: HR Q4 v. Q1 α1m 3.89 (2.05, 7.23), MCP-1 1.95 (1.02, 3.75), PINP 2.27 (1.35, 3.79). After adjustment, urine PIIINP was not associated with CVD events [HR Q4 v. Q1 0.97 (0.52, 1.82)] or death [1.63 (0.92, 2.90)] in either continuous or quartile analyses.

Adjusted associations of urine biomarker with outcomes (per log2 increase) [HR (95% CI)]		
	CV events	Death
α1m	1.43 (1.21, 1.69)	1.59 (1.36, 1.85)
MCP-1	1.26 (1.07, 1.47)	1.40 (1.20, 1.64)
PINP	1.23 (1.09, 1.39)	1.15 (1.03, 1.27)
PIIINP	1.04 (0.91, 1.18)	1.13 (0.99, 1.28)

Conclusions: Higher concentrations of urine α1m, MCP-1, and PINP identify KTR at risk for CVD events and death. Fibrotic processes in the transplanted kidney may reflect systemic fibrosis and CVD risk in KTR.

Funding: NIDDK Support

TH-OR093

Emerging Safety and Tolerability with Obinutuzumab, a Type 2 Anti-CD20 Monoclonal Antibody for the Desensitization of Renal Transplant Candidates

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Background: Allosensitization in end-stage renal disease (ESRD) patients (pts) may restrict the deceased donor pool, resulting in long waiting times, or prevent living donor kidney transplantation. B-cell depletion with rituximab (RTX) appears to be effective in desensitizing pts and enabling transplantation; however, B-cell depletion is incomplete in lymphoid organs despite complete peripheral depletion, and high antibody titers are only moderately reduced. Greater B-cell depletion in tissue may be more effective in alloantibody reduction. Obinutuzumab (Obi) is a glycoengineered anti-CD20 monoclonal antibody that binds CD20 differently from RTX and displays increased antibody-dependent cellular cytotoxicity and enhanced direct cell death compared with RTX, resulting in increased in vitro and in vivo B-cell depletion.

Methods: The open-label, phase 1b THEORY study assessed the safety, pharmacokinetics, and pharmacodynamics of Obi in hypersensitized ESRD pts awaiting renal transplantation. The first cohort of patients (n=5) received 1,000 mg Obi on day 1 and high-dose IVIG on days 22 and 43. Safety and tolerability were reviewed when the last enrolled patient had 4 weeks of follow-up.

Results: Most (4/5) pts were women, aged 34-54 years, who had been waitlisted for 2-11 years and had calculated panel reactive antibody values of 74%-100%. Obi resulted in depletion of peripheral B cells by FACS (5/5) and to less than or equal to the lower limit of quantification of high-sensitivity flow cytometry (3/5). Obi appeared well tolerated and safe. Main adverse events (AEs) were grades 1 and 2 infusion-related reactions in 3 pts that were manageable and did not prevent complete Obi administration. A serious AE of community-acquired pneumonia resolved on treatment with IV antibiotics.

Conclusions: Emerging experience with Obi indicates acceptable tolerability in ESRD patients requiring desensitization.

Funding: Pharmaceutical Company Support - Genentech, Inc.

TH-OR094

Efficacy and Safety of 3 Different Treatment Regimen in De Novo Renal Transplant Patients: 5 Year Follow-Up Data of the HERAKLES Trial on Everolimus-Based Immunosuppression

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Background: To compare safety and efficacy of 3 different immunosuppressive regimen at month (Mo) 60 after kidney transplantation (KTx) with or without everolimus (EVR).

Methods: 802 patients (pts) were included in this 1 year, prospective, open-label, randomized, controlled multi-center study with observational follow-up (FU) to Mo60 post KTx. After induction all pts received cyclosporine A (CsA), enteric-coated mycophenolate sodium (EC-MPS) and steroids. 3Mo post KTx, 499 pts were 1:1:1 randomized to either a) continue standard CsA(100-180ng/mL)+ EC-MPS (n=166) (STD) or convert b) to an EVR-based (5-10ng/mL) calcineurin inhibitor (CNI)-free regimen + EC-MPS (n=171) or c) to a CNI-reduced regimen (CsA 50-75ng/mL) with EVR (3-8ng/mL) (n=162); (steroids according to center praxis). In total 81% of pts completed the Mo60 FU visit.

Results: Efficacy events during FU to Mo60: BPAR reported in 8% STD, 8% CNI-free and in 7% CNI-reduced pts (p=ns). 7 deaths (4%) occurred in STD, 4 (2%) in CNI-free and 9 (6%) in the CNI-reduced group; 7 (4%) graft losses in the STD, 7 (4%) in the CNI-free and 3 (2%) in the CNI-reduced group. Composite failure occurred in 38(23%) STD, 35(20%) CNI-free and in 36(22%) CNI-reduced treated pts. GFR (Nankivell) was significantly improved by +6.7mL/min in favor of the CNI-free regimen at Mo60 (ITT, p<0.001). Safety profile did not differ between groups.

Overview on efficacy events during follow-up (ITT population)

Frequencies, n (%)	Standard (N=165)	CNI free (N=171)	CNI reduced (N=161)
Events starting after Month 12			
Biopsy-proven acute rejection (BPAR)	13 (7.88)	13 (7.60)	12 (7.45)
Graft loss	7 (4.24)	7 (4.09)	3 (1.86)
Death	7 (4.24)	4 (2.34)	9 (5.59)
Lost to follow-up	17 (10.30)	15 (8.77)	13 (8.07)
Toxicity	10 (6.06)	8 (4.68)	4 (2.48)
Therapy failure (composite endpoint)*	38 (23.03)	35 (20.47)	36 (22.36)
p-value (Fisher's exact Test): no significant differences found			

*Treatment failure as composite endpoint is defined as occurrence of at least one of the events: biopsy proven acute rejection, graft loss, death, lost to follow-up, discontinuation due to toxicity.

Overview on adverse and other safety relevant events during follow-up (Safety population)

Event	Standard N=165 n (%)	CNI-free N=171 n (%)	CNI-reduced N=161 n (%)
Death, n (%)	7 (4.2)	4 (2.3)	9 (5.6)
Hospitalization, n (%)	99 (60.0)	102 (59.6)	107 (66.5)
Discontinuation due to AE [a], n (%)	10 (6.1)	8 (4.7)	4 (2.5)
Infection, n (%)	83 (50.3)	85 (49.7)	81 (50.3)
Severe Infection, n (%)	19 (11.5)	21 (12.3)	19 (11.8)
Infection leading to hospitalization, n (%)	50 (30.3)	50 (29.2)	54 (33.5)
Of these the most common:			
Urinary tract infection, (%)	10.9%	9.4%	10.6%
Pneumonia, (%)	6.1%	9.9%	4.3%
Urosepsis, (%)	6.1%	4.7%	5.0%
CMV, (%)	3.0%	2.9%	3.1%
Gastroenteritis	3.0%	1.8%	4.3%

[a] documented as primary reason for prematurely discontinuation of follow-up period (reported at any follow-up visit); Footnote: The CRF and the clinical data base do only include serious adverse events for the follow-up period. Nevertheless, AEs were reported to Novartis drug safety but are not included in this analysis.

Conclusions: HERAKLES 5 year data show that immunosuppressive regimen using EVR with reduced-dose or without CNI reflect an efficacious and safe therapeutic approach offering the opportunity for an individualized immunosuppression to minimize CNI-exposure.

TH-OR095

Timing of Eculizumab Treatment and the Need for Dialysis in Patients with aHUS Who Receive a Kidney Transplant

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Background: Patients (pts) with atypical hemolytic uremic syndrome (aHUS) are at risk of thrombotic microangiopathy (TMA) and graft loss following transplantation. Eculizumab (Ecu), a complement C5a inhibitor, is effective in preventing and treating TMA and is increasingly used post-kidney transplant (KTx) in pts with aHUS. We report data on the timing of Ecu initiation and subsequent dialysis and TMA in aHUS patients undergoing KTx.

Methods: Our analyses utilized data from a Global aHUS registry (NCT01522183) with 1122 pts enrolled as of March 2016, of whom 252 (24%) had at least one KTx. Overall, 94/252 pts had a KTx between December 1, 2011 and December 1, 2014) and received Ecu. Pts were grouped by use of Ecu (prior to or at time of transplant [pre-transplant; n=57] vs started post-KTx [n=36]). Pts were monitored for up to 12 months post-KTx.

Results: Pts starting Ecu post-KTx were older, less likely to have a family history of aHUS, and had undergone fewer prior transplants (Table). Fewer pts treated pre-KTx with Ecu required any dialysis (4% vs 33%) and the median time to any dialysis was longer (15.3 vs 1.6 months) than in pts receiving Ecu post-KTx. Those pts starting Ecu post-KTx had a higher rate of TMA (61% vs 4%) and TMA occurred earlier (after a median of 3.0 vs 11.4 months), compared with those starting Ecu pre-KTx.

Table. Characteristics of pts with their last transplant between 01 December 2011 and 01 December 2014

	Ecu initiated at or prior to transplant (N=57)	Ecu initiated post-transplant (N=36)
Median age at diagnosis, years (IQR)	27.6 (5.4–35.4)	34.4 (24.6–45.7)
Family history, n (%)	18 (32)	3 (8)
Prior transplant, n (%)	19 (33)	3 (8)
Any dialysis post-transplant, n (%)*	2 (4)	12 (33)
Median time to dialysis, months (IQR)	15.3 (12.8–17.9)	1.6 (0.1–15.0)
Deaths, n (%)	1 (2)	0 (0)
TMA post-transplant, n (%)	4 (7)	22 (61)
Median time to TMA, months (IQR)	11.4 (4.3–21.5)	3.0 (0.2–8.7)

*Any dialysis includes patients who received either acute or chronic dialysis. Ecu, eculizumab; IQR, interquartile range; TMA, thrombotic microangiopathy

Conclusions: This retrospective analysis shows that fewer pts with aHUS who received Ecu prior to KTx compared with after KTx required dialysis or had TMA. This suggests initiating Ecu pre-transplant may be associated with better renal outcomes after KTx.

Acknowledgments: We wish to thank the patients and registry investigators.

Funding: Pharmaceutical Company Support - Alexion Pharmaceuticals, Inc.

TH-OR096

Effect of Denosumab on Peripheral Compartmental Bone Density, Microarchitecture and Estimated Bone Strength in De Novo Kidney Transplant Recipients: The POSTOP-HRpQCT Bone Microarchitecture Ancillary Study Rudolf P. Wuthrich,[1] Ursina Meyer,[2] Diana P. Frey,[3] Nicole Graf,[4] Heike A. Bischoff-Ferrari,[2] Marco Bonani.[1] *[1]Div of Nephrology, Univ Hospital, Zurich, Switzerland; [2]Dept of Geriatrics and Aging Research, Univ Hospital, Zurich, Switzerland; [3]Div of Rheumatology, Univ Hospital, Zurich, Switzerland; [4]Graf Biostatistics, Winterthur, Switzerland.*

Background: In a randomized controlled clinical trial in kidney transplant recipients (NCT01377467) we have recently shown that RANKL inhibition with denosumab significantly improved areal bone mineral density (aBMD) when given during the first year after transplantation. The effect of denosumab on skeletal microstructure and bone strength in kidney transplant recipients is not known.

Methods: The purpose of the present analysis was to investigate high-resolution peripheral quantitative computed tomography (HRpQCT) data from the distal tibia and distal radius in 24 study patients that had been randomized to receive either two injections of denosumab 60 mg at baseline and after 6 months (n=10) or no treatment (n=14).

Results: Denosumab reduced biomarkers of bone turnover, and significantly increased aBMD at the lumbar spine (median difference of 4.7%; 95% CI 2.6 – 7.8; p<0.001). Bone quality as assessed by total and cortical volumetric bone mineral density (Tot.vBMD, Ct.vBMD) and cortical thickness (Ct.Th) increased significantly at the tibia, while changes at the radius were less pronounced. The trabecular volumetric BMD (Tb.vBMD), thickness (Tb.Th), separation (Tb.Sp) and number (Tb.N) and the cortical porosity (Ct.Po) at the tibia and the radius did not significantly change in both treatment groups. Micro-finite element analysis (mFEA) showed that bone stiffness increased significantly at the tibia (median difference 5.6%; 95% CI 1.8% – 9.2%; p=0.002) but not at the radius (median difference 2.9%, 95% CI -3.7% – 9.1%; p=0.369). Likewise, failure load increased significantly at the tibia (median difference 5.1%; 95% CI 2.1% – 8.1%; p=0.002) but not at the radius (median difference 2.4%, 95% CI -3.2% – 8.5%; p=0.336).

Conclusions: Denosumab improves bone density and bone quality in first-year kidney transplant recipients at risk to develop osteoporosis.

Funding: Clinical Revenue Support

TH-OR097

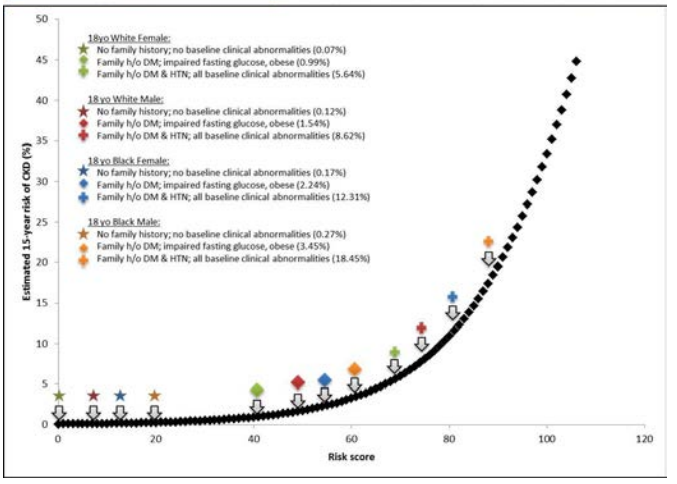
Kidney Failure Risk Projection for the Young Living Kidney Donor Candidate Jayme E. Locke,[1] Rhiannon D. Reed,[1] Deirdre L. Sawinski,[2] Paul A. Maclennan,[1] Vineeta Kumar,[1] Shikha Mehta,[1] John Jeffrey Carr,[3] James Gregory Terry,[3] Allan Massie,[4] Meredith Kilgore,[1] Robert S. Gaston,[1] Roslyn B. Mannon,[1] Dorry L. Segev,[4] Cora E. Lewis.[1] *[1]Univ of Alabama at Birmingham; [2]Univ of Pennsylvania; [3]Vanderbilt Univ; [4]Johns Hopkins Univ.*

Background: Living kidney donor selection practices aim to identify risk for chronic kidney disease (CKD). Assessment has evolved from examination of individual risk factors to a risk calculator that incorporates multiple candidate characteristics. Due to limited long-term data, current risk tools lack precision with regard to young living kidney donor candidates (LKDC).

Methods: We identified a cohort of potentially acceptable, young (18-30yo) LKDCs with no absolute contraindications to kidney donation (diabetes, hypertension, malignancy, heart disease, kidney problems, or pregnancy at year 0 exam) from the longitudinal cohort study CARDIA. Risk associations for CKD were identified and assigned weighted points, resulting in calculation of a risk score (c-statistic: 0.74).

Results: 3,554 LKDCs were identified; mean age 24.8yrs; 48.8% black; median follow-up of 24.9yrs (IQR: 24.5-25.2). For an 18yo LKDC 15-yr projection of the risk of CKD varied according to race and sex even in the absence of baseline clinical abnormalities; risk was 0.07% for white women, 0.12% for white men, 0.17% for black women, 0.27% for black men. Risk projections were higher among LKDCs with baseline clinical abnormalities - eGFR<100cc/min, obesity, impaired fasting blood sugar, family history of hypertension and/or diabetes.

Table. Risk calculator	aHR	95% CI	p-value	ß	Risk points
Age (per 1-year increase)	1.07	0.99-1.15	0.10	0.06279	1 per year > 18
Male sex	1.59	0.94-2.66	0.08	0.46031	7
Black race	2.26	1.28-4.02	0.005	0.81690	13
Impaired Fasting Glucose (FBG 100-125)	3.14	0.97-10.20	0.06	1.14312	18
Family history of DM	2.18	1.23-3.86	0.001	0.77817	12
Family history of HTN	1.94	1.09-3.47	0.02	0.66492	11
Obese (BMI ≥ 30 kg/m²)	1.99	1.04-3.82	0.04	0.69017	11
eGFR 90-99 mL/min at baseline	2.84	1.19-6.79	0.02	1.04277	17



Median time to CKD was 20.7yrs (IQR: 15.1-25.0).

Conclusions: Baseline health characteristics may be used to develop a risk prediction tool for projecting the long-term risk of CKD among young LKDCs. Risk tools may improve informed consent and LKDC autonomy in medical decision making.

Funding: NIDDK Support, Private Foundation Support

TH-OR098

Cultural Competency of a Mobile, Customized Patient Education Tool for Improving Potential Kidney Transplant Recipients' Knowledge and Decision-Making Crystal Anderson,[1] David A. Axelrod,[2,3] David Wojciechowski,[3] Marie Jacobs,[3] Krista L. Lentine,[4] Mark Schnitzler,[4] John Devin Peipert,[1] Amy D. Waterman.[1] *[1]David Geffen School of Medicine, Univ of California, Los Angeles, Los Angeles, CA; [2]Xyn Management Inc., Boerne, TX; [3]Dept of Medicine, Massachusetts General Hospital, Boston, MA; [4]Dept of Internal Medicine, St. Louis Univ, St. Louis, MO.*

Background: After Kidney Allocation System (KAS) reforms, patients have to decide between deceased donor kidney transplant (DDKT), living donor kidney transplant (LDKT) and dialysis. My Transplant Coach (MTC) is a mobile, iOS based tablet education tool that presents didactic animated videos and individualized charts derived from multivariate models of pre-transplant mortality rate, median waiting time to transplant, and post-transplant survival based on kidney donor profile index (KPDI) and transplant type. We assessed whether patients found the application helpful and culturally sensitive; whether transplant knowledge and informed decision-making improved; and how patients' race and comfort with technology were associated with changes.

Methods: In two US transplant centers, 81 patients (White: 27%, African American: 25%, Hispanic: 15%, Asian: 25%) varying in their experience with technology (51% were comfortable using internet) viewed the animated content and their own graphs and completed pre- and post- intervention knowledge assessments (0-20 scale) and usability questionnaires.

Results: 86% reported MTC helped them understand their options, 85% would recommend the app, and 78% felt more comfortable talking to their doctor about their treatment options. High proportions of patients said the app was suitable for people of their race/ethnic group (67%-85%, P=0.79). After reviewing MTC, patients reported having a greater ability to make informed DDKT (27%-52%, P<.0001) and LDKT decisions (40%-72%, P<.001). Knowledge increased (9.1 to 13.8 questions correct, P<.0001), with similar increases for patients of all races and levels of comfort with technology levels.

Conclusions: MTC was helpful for a diverse group of transplant candidates and resulted in increased transplant knowledge and informed decision-making.

Funding: Private Foundation Support

TH-OR099

Impact of Patient Navigators and Enhanced Personal Health Records on Health Literacy in Those with CKD Stacey Jolly,[1] Sankar D. Navaneethan,[2] Jesse D. Schold,[1] Susana Arrigain,[1] Georges Nakhoul,[1] Victoria Konig,[1] Jennifer Hyland,[1] Yvette K. Burrucker,[1] Priscilla Davis Dann,[1] Barbara H. Tucky,[1] Joseph V. Nally.[1] *[1]Cleveland Clinic; [2]Baylor College of Medicine.*

Background: The recognition of and education for patients with CKD is a public health need as patients with limited health literacy may have difficulty processing medical information and traversing an increasingly complex health system. There is a lack of

translational research in CKD that incorporates educational tools. We developed a CKD Patient Navigator program and an enhanced online personal health record (PHR) with links to publicly available NKDEP and NKF education materials. We report CKD health literacy survey results from our randomized-controlled clinical (RCT) trial.

Methods: 209 patients with CKD from 6 outpatient clinics were randomized in a 2x2 factorial design to CKD Patient Navigator or enhanced PHR, their combination, or usual care. Baseline survey was done at time of enrollment in person. An exit phone survey was done at the end of the 2-year follow-up. Survey included literacy, computer skills, and detailed CKD knowledge items.

Results: Mean age was 66.7 years with 75% whites and 22% blacks. Majority were CKD Stage 3b n=156 (76%) at enrollment. 194 completed exit survey (deceased = 11; declined/no response/unable to reach =4). Some pre-/post-survey results are shown in Table 1.

Pre	Navigator (n=53)	ePHR (n=50)	Both (n=49)	Control (n=57)
need help with medical forms	11(21%)	10(20%)	12(24%)	8(14%)
difficulty understanding when doctor talks about CKD	21(40%)	18(36%)	20(41%)	20(34%)
know your eGFR (yes)	9(17%)	10(20%)	9(18%)	9(16%)
Post	Navigator (n=50)	ePHR (n=47)	Both (n=45)	Control (n=52)
need help with medical forms	3(6%)	4(8%)	5(11%)	3(6%)
difficulty understanding when doctor talks about CKD	2(4%)	7(15%)	3(6%)	3(6%)
know your eGFR (yes)	12(24%)	6(12%)	9(20%)	4(7%)

Conclusions: We successfully conducted a RCT trial using educational tools. Health literacy improved in all groups. Future analyses are needed to evaluate the tools, such as which CKD educational links were most utilized, CKD Patient Navigators role in addressing barriers, and patient satisfaction with the intervention.

Funding: NIDDK Support

TH-OR100

Pediatric Nephrology Training Worldwide in 2016: Quantum Educatus?

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Background: Perceived adequacy of the pediatric nephrology (PN) workforce varies considerably worldwide. Likewise, training for qualification as a pediatric nephrologist varies from country to country. No compendium of these requirements exist. In the United States (US), PN workforce concerns have generated a discussion of whether a 2 year option, as opposed to 3 years, is advisable in order to increase the number of trainees. The purpose of our study is to synthesize and compare PN training requirements worldwide, and describe the opinions of pediatric nephrologists on the value of a 2 versus 3 year fellowship.

Methods: In the spring of 2013, survey invitations were sent to members of the American Society of Pediatric Nephrology (ASPN) and American Academy of Pediatrics (AAP) section on Pediatric Nephrology. In the Fall of 2015, survey invitations were sent to members of International Pediatric Nephrology Association (IPNA). E-mail messages were sent to pediatric nephrologists in countries with ≥ 25 contacts listed in the online IPNA member directory. Qualitative and quantitative analyses were performed, and data cross-referenced when possible.

Results: The AAP survey was sent to 766 pediatric nephrologists and had a 66% response rate. Forty nine percent of respondents favored a 2 year option for PN fellowship training and 34% were opposed to a change in training duration. Prominent themes in support of a 2 year fellowship were a perceived need for more clinicians in the PN workforce and a desire to limit the financial and time burdens of the third year of training. The IPNA survey was sent to 2304 valid e-mail addresses and had a 15% response rate. In some countries the duration and intensity of training varies with the PN responsibilities that the graduates are anticipated to assume.

Conclusions: We summarize the requirements for PN training in most areas of the world as of the beginning of 2016. Three years is the most common duration of PN fellowship and recently has become the new minimal recommendation in Europe, Australia, and New Zealand. Due to concerns of a potentially inadequate workforce, many U.S. pediatric nephrologists wonder if a 2 year clinical track should be considered.

TH-OR101

The Impact of Health Literacy in Transition Readiness

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Background: With medical and technological advances, the prevalence of youth with chronic diseases surviving into adulthood has become an important public health issue. This is especially true in the field of transplantation, in which transition has been identified as a vulnerable period for adolescents. Transition of care has been defined as a process that involves purposeful, planned efforts to prepare the pediatric patient to move from caregiver-directed care to disease self-management in the adult unit. Different approaches are currently being implemented to improve this process mainly centered on improved coordination and facilitation of the transition. Health literacy (HL) is known to be associated with poor clinical outcomes in adults and yet little is known about the relationship in the pediatric population and its contribution to difficulties during transition. Specifically, research is needed to determine if HL may be a factor in poor self-management acquisition in order to inform targeted interventions to improve transition.

Methods: Participants (N=75)are patients above 13 years of age with a diagnosis for at least 6 months of Chronic Kidney Disease (CKD), Hypertension (HTN) or kidney transplantation followed at Mount Sinai Medical Center. HL and self-management were measured with three screening tools, the S-TOFHLA (shortened version of The Test of Functional Health Literacy Assessment), Single Item Literacy Screen and the Developmentally Based Skills Checklist. Transition readiness was assessed using a center-specific checklist used for patients age 15 or older and medical record review for clinical outcomes.

Results: Based on the S-TOFHLA, HL was adequate (mean=33.31, SD=4.20). S-TOFHLA score was significantly correlated with team-rated transition readiness, r=.51, p=.01. When measured by the SILS, more patients displayed poor HL; 35% "sometimes" or more often have trouble reading medical instructions.

Conclusions: Preliminary findings suggest that HL is highly correlated with transition readiness. Therefore, pediatric preparation for transition should include assessment of and efforts to bolster HL.

TH-OR102

Macrophage: An Online Adaptive Learning Platform for Renal Physiology

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Background: Many educators now use online learning tools (videos, interactive modules, etc.) in place of traditional lectures to deliver content to medical students. Relative to lectures, online learning tools have the potential to be more interactive and adaptive (delivering content specially tailored to each individual, based on their empiric performance). We sought to study student satisfaction with an interactive, adaptive, online learning tool relative to traditional lectures.

Methods: We created "Macrophage" (https://macrophage-app.herokuapp.com/), an online platform for medical education that serves as a scaffold for courses consisting of short videos and questions. For each individual user, a learning algorithm models the probability of each individual user getting questions correct, such that it can deliver content in an individualized fashion. We created a renal physiology course for Macrophage, consisting of 60 videos with an average length of 3 minutes and 238 questions, which was used by the Columbia University first-year class as a supplemental resource during the traditional renal course. Afterwards, students were surveyed on the efficacy of Macrophage and lecture for their learning of renal physiology, using a 5-point Likert scale ("very effective", "somewhat effective", "undecided", "not very effective", "not at all effective"). Data were analyzed with the Wilcoxon signed-rank and Fisher exact tests.

Results: Out of 160 students, 84 (52.5%) used both Macrophage and lecture, and rated Macrophage as more effective than lecture (p = 0.0013, Wilcoxon signed-rank test). Students were also more likely to rate Macrophage "very effective", "somewhat effective", or "undecided", with an odds ration of 5 (p-0.00079 Fisher exact test) compared to lecture. Among the 84 students who used macrophage, 69.2% rated it as "very effective" or "somewhat effective", while 7.4% rated it as "not very effective" or "not at all effective."

Conclusions: Macrophage allowed medical students to learn more effectively as compared to lecture. Online learning tools represent a promising method to teach renal physiology to medical students.

Funding: Private Foundation Support

TH-OR103

An Integrated Pathology and Ultrasonography-Based Simulation Is an Effective Educational Tool for the Performance of a Kidney Biopsy

Juan Carlos Q. Velez,[1] Vandana Niyyar,[2] Kevin D. Phelan,[3] Nithin Karakala,[3] Manisha Singh,[3] Kelly W. Bulloch,[3] John M. Arthur,[3] Shree G. Sharma.[4] *[1]Div of Nephrology, Medical Univ of South Carolina, Charleston, SC; [2]Renal Div, Emory Univ, Atlanta, GA; [3]Div of Nephrology, Univ of Arkansas Medical Sciences, Little Rock, AR; [4]Arkana Laboratories, Little Rock, AR.*

Background: Proficiency in performance of percutaneous kidney biopsy (PKB) is required for accreditation in nephrology. Medical practice trends and limitations in trainees' duty hours have diminished the interest and exposure of nephrology fellows to PKBs. We hypothesized that a novel integrated nephrology-pathology-led simulation may be an effective educational tool.

Methods: A 4-hour PKB simulation workshop (KBSW) was led by 2 ultrasonography (US)-trained nephrologists and 1 pathologist and consisted of 6 stations: diagnostic kidney US with live patients, kidney pathology with embedded torso cross sections, US-based PKB simulation with mannequin (Blue Phantom™), kidney pathology with dissected cadavers, US-based PKB simulation in lightly-embalmed cadavers and tissue retrieval adequacy examination by microscope. A 10-question survey [6 multiple-choice questions assessing knowledge acquisition, 4 five-scale questions assessing procedural confidence gain] was administered pre and post KBSW.

Results: Twenty-one participants (4 nephrologists, 17 trainees) attended the KBSW and completed the surveys. The percentage of correct answers increased numerically in 5 of 6 knowledge questions, reaching statistical significance in 3 of them (p=0.0003–0.04). The overall percentage of correct answers increased from 55 to 83% (p=0.016). The number of Extremely Confident answers increased from 0-5% to 19-28% in all 4 questions (p=0.02–0.04), and the number of Not At All Confident answers significantly decreased from 14-62% to 0-5% in 3 out of 4 questions (p=0.0001–0.03).

Conclusions: A KBSW utilizing US-based training on patients, mannequins and cadavers, along with simultaneous pathology instruction, is an effective educational tool to gain proficiency in PKB performance. This novel approach could regain interest among trainees in performing PKBs.

TH-OR104

A Novel Quality Improvement Collaborative to Reduce Acute Kidney Injury Incidence and Progression in a Large Teaching Hospital in England

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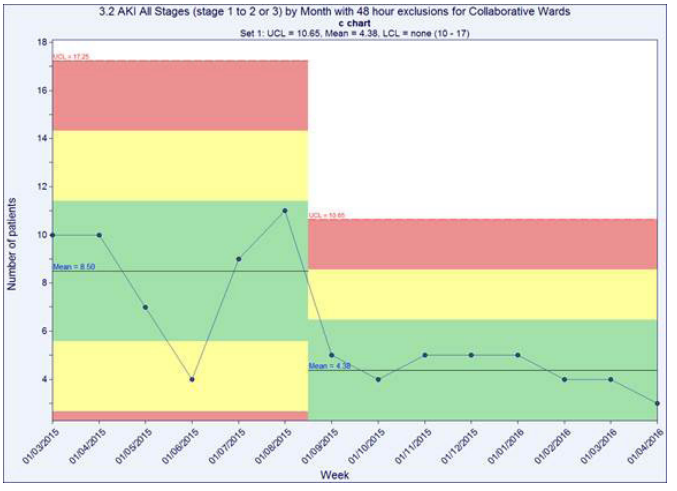
Background: Acute kidney injury (AKI) is a common condition which is associated with significant mortality and cost according to the NCEPOD report of 2009. The Quality Improvement Collaborative was established to review and improve both the recognition and management of AKI.

Methods: We designed a program of education and learning events to reduce all cause AKIs by 10%, reduce hospital acquired AKIs by 25% and reduce progression of AKI 1 to either AKI 2 or 3 by 50%. A driver diagram was developed for this improvement program based on the Institute for Healthcare Improvement's Breakthrough Series Collaborative Model. An information banner was inserted into the electronic patient records, modifications made to the admission document, post take ward round and discharge summary forms, and an AKI review template introduced. A team of selected doctors, nurse champions, pharmacists and quality improvement staff implemented an AKI bundle, based on the acronym 'SALFORD', to the collaborative wards.

Results: Whilst there was an increase overall in AKI seen, especially AKI 1, over the study (November 2015 to May 2016), there were several statistically significant results following the interventions made by the collaborative. A 15.56% reduction in overall hospital acquired AKI, with a 22.32% reduction on collaborative wards. Although there was normal variation shown for the overall hospital rates of progression of AKI 1 to AKI 2/3 there was a 48.47% reduction in AKI progression on the collaborative wards.



Conclusions: This is the first quality improvement project of its kind focussing on AKI. It has achieved statistically significant reductions of hospital acquired AKI and AKI progression particularly on the collaborative wards and is a testament to an effective quality improvement programme that is universally applicable and a step towards tackling AKI.

Funding: Other NIH Support - National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care (NIHR CLAHRC)

TH-OR105

Estimating Sodium Intake in Hemodialysis Patients to Help Assist Dietary Habits

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Background: Sodium restriction is encouraged in almost all patients on hemodialysis due to its easy and effective preventative therapy, which facilitates control of thirst, water overload, inter-dialytic weight (IDW) gains, hypertension, and cardiac failure. However this strategy is often neglected by patients. Our primary aim was to validate salt intake estimating equation in ESRD patients on dialysis and making these patients aware and our secondary aim was to evaluate changes in sodium intake after being counseled on their sodium restriction diet to 2g/day.

Methods: In this pilot study, data regarding sodium intake of 13 patients on hemodialysis was gathered during 3 consecutive months (January 2016 to March 2016). Each patient was counseled regarding sodium restriction in the first month and the subsequent two months were recorded to evaluate response to counseling. Sodium intake was estimated using the following formula: Sodium intake = $V \times ([Na]_{pre} - [Na]_{post}) + (\Delta W \times [Na]_{pre})$ where V= total body water and ΔW = interdialytic weight gain.

Results: Referring to table 1 you will see that the mean sodium intake was 3.7 ± 1.3 g in January, 4.1 ± 1.2 g in February, and 4.2 ± 1.3 g in March.

Variable	N	Mean	Standard Deviation	Median	Lower 95% CI	Upper 95% CI
January	13	3678.08	1271.44	3435	2909.75	4446.40
February	13	4104.31	1175.73	4322	3393.82	4814.80
March	13	4200.85	1270.48	4193	3433.10	4968.59

There was tremendous variability in salt intake and a single counselling session over 3 month period was not associated with adherence to salt restriction ($p = 0.54$) or IDW gains.

Conclusions: Further solutions to improve sodium intake need to be considered such as motivational behavioral therapy and provide access to low salt foods. We have assumed that the participants were anephric and had insignificant amount of GI and insensible fluid loss.

TH-OR106

Therapeutic Game-Based Exercise during Hemodialysis to Improve Balance: A Pilot Randomized Controlled Trial

Abdullah Hamad,[1] Fadwa S. Al-Ali,[1] He Zhou,[2] Talal Talal,[3] Sergio Nicolas Sardon Melo,[3] Mohamed Amin Elesnawi,[1] Rania Abdelaziz Ibrahim,[1] Bijan Najafi.[2] *[1]Nephrology, Hamad Medical Corporation, Doha, Qatar; [2]Baylor College of Medicine, Houston, TX; [3]Podiatry, Hamad Medical Corporation, Doha, Qatar.*

Background: Balance, mobility and falls are serious problems for older patients with end stage renal disease on hemodialysis (HD) especially with diabetic neuropathy. HD visit time provides an optimal opportunity for exercise intervention to improve balance and mobility and decrease falls.

Methods: Eleven HD subjects (age: 65±6 years) with confirmed diabetic peripheral neuropathy were consented and recruited. They were randomized to intervention (IG: n=7) and control group (CG: n=4). Both groups underwent a 4 weeks' ankle and knee exercise program, twice per week for duration of 30 minutes during HD. The IG received exercise via the Exergame platform developed by our team, which integrates data from wearable sensors attached to subject's feet and legs into a human-computer interface designed for game-based motor adaptation training. The CG received same exercises without technology. The feasibility, acceptability, perception of benefit, and enhancement in balance in different conditions were examined.

Results: One subject in IG was dropped out due to travelling. The rest finished all exercise sessions during HD sessions indicating its feasibility. The participants gave on average score of 3.7 out of 4 for entertainment and ease of usage of the Exergame platform. All participants in IG felt more energetic at home and perceived the balance program effective. Balance improved in IG compared to baseline almost in all tested balance conditions with highest effect size (improved by 57%, d=1.20) observed for hip stability during semi-tandem eyes closed test. The improvement in tested balance conditions in IG was on average 32% higher than CG with the highest effect size difference observed for semi-tandem eyes-closed (d=1.26).

Conclusions: Our pilot trial provide proof of concept for the feasibility and benefits of an interactive ankle and knee exercise program based on wearable technology. The program was perceived to be beneficial, easy and enjoyable to perform during hemodialysis sessions by target subjects.

Funding: Government Support - Non-U.S.

TH-OR107

"Home Run" Results of a Chronic Kidney Disease Telemedicine Patient Education Study

Andrea K. Easom, Manisha Singh, John M. Arthur. *U of AR for Medical Sciences, Mabelvale, AR.*

Background: Comprehensive pre-dialysis patient education (CPE) facilitates the choice of renal replacement therapy modalities and can slow progression of disease but it is not clear if education via telemedicine is comparable to face-to-face education (FTF). We present the two year results of a pilot randomized controlled study evaluating the effectiveness of CPE through telemedicine TM to FTF in patients with stage 4-5 CKD.

Methods: An 82 page CKD Workbook was created with corresponding slides and used to provide education to 82 patients in the FTF group and 58 patients in the TM group over three, 2-3 hour visits. Patient choice of dialysis modality is the primary endpoint of the study. Three assessment tools were utilized to compare groups: CKD Knowledge Questionnaire (based on the workbook and completed pre on visit 1 and post on all visits), S-TOFHLA on visit 1 and KDQoL on visits 1 and 3. All groups have quarterly phone follow-up. There are 7 telemedicine sites across the state.

Results: Of the 170 patients enrolled, 25 (15%) were initial drop outs. These results include data from 118 patients. Most patients were interested in transplant initially (90% FTF, 92% TM). This decreased slightly by visit 3 (86% FTF, 90% TM). Initially, about half felt they did not have enough information to choose a modality (46% FTF, 50% TM) but this decreased significantly by visit 3 (3% FTF, 15% TM). Home modalities choices increased from 16 to 25% home hemodialysis (HHD) and 14 to 46% peritoneal dialysis (PD) in the FTF group and from 11 to 20% HHD and 6 to 35 % PD in the TM group, resulting in home modalities chosen by 71% of the FTF group and 55% of the TM. Of the 26 patients completing at least one visit and needing to start therapy, 58% either started on home dialysis or received a pre-emptive transplant (HHD 12%, PD 42%, TXP 4%).

Conclusions: By the end of their 3rd visit, 97% of the FTF group and 85% of the TM group were able to choose a modality. Home modalities were chosen by 71% of the FTF group and 55% of the TM group, 58% of the patients that started therapy were either transplanted or started a home modality. The results show that TM can be an effective educational tool for CPE.

Funding: Pharmaceutical Company Support - Baxter Health Corp

TH-OR108

CD44 Is Required for the Pathogenesis of Experimental Crescentic Glomerulonephritis and Collapsing Focal Segmental Glomerulosclerosis
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Background: Activation, migration and proliferation of parietal epithelial cells (PECs) is a key feature of glomerular diseases such as crescentic glomerulonephritis and focal segmental glomerulosclerosis. CD44-positive activated PECs have been identified in proliferative cellular lesions in glomerular disease. However, it remains unknown whether CD44-positive PECs contribute to the pathogenesis of scarring glomerular diseases.

Methods: Here, we evaluated experimental crescentic glomerulonephritis and the transgenic anti-*Thy1.1* model for collapsing focal segmental glomerulosclerosis in CD44-deficient (*cd44-/-*) and wild type (WT) mice.

Results: For both models albuminuria was significantly lower in *cd44-/-* mice compared to WT mice. The number of glomerular Ki67-positive proliferating cells was significantly reduced in *cd44-/-* mice compared to WT mice, which was associated with a reduced number of glomerular lesions in crescentic glomerulonephritis. In collapsing FSGS, the extracapillary proliferative cellular lesions were smaller in *cd44-/-* mice, but the number of glomerular lesions was not different compared to WT mice. For crescentic glomerulonephritis the glomerular influx of granulocytes and macrophages was similar. *In vitro*, human CD24, CD133, CD44-positive PECs displayed haptotactic responses towards collagen I in a CD44 dependent manner.

Conclusions: In conclusion, CD44-positive proliferating glomerular cells, most likely PECs, are essential in the pathogenesis of scarring glomerular disease.

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

TH-OR109

Compound Effects of Aging and Experimental FSGS on Glomerular Parietal Epithelial Cells and Podocytes in Mouse Kidneys
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Background: Impaired kidney function is more common in the elderly, and occurs disproportionately in people >65yrs. Glomerular parietal epithelial cells (PECs) and podocytes (podo) undergo substantial changes with advanced age. This study tested the hypothesis that advanced aged adversely impacted PEC and podo responses in mice with FSGS.

Methods: Experimental FSGS was induced in young adult (Y-FSGS)(2-3m) and aged (A-FSGS)(24m) mice with a cytotoxic anti-podo antibody. Young (Y-BL) and aged (A-BL) mice without FSGS served as respective baselines. Podo density was measured by unbiased stereology on p57/PAS stained kidney sections; Desmin marked podo injury. Fibrosis was quantified using Collagen IV staining. Activated PECs ($Pax8^+CD44^+$) were examined for their localization along Bowman's Capsule (BC) and migration onto the glomerular tuft. PEC epithelial to mesenchymal transition (EMT) was measured by staining for a-smooth muscle actin and vimentin.

Results: As expected, podo density was lower in A-BL mice ($P<0.01$ vs. Y-BL). Upon induction, podo density decreased by >40% in both Y-FSGS and A-FSGS mice ($P>0.05$). However, Desmin expression increased further in podo in A-FSGS mice. Although the density of activated PECs along BC was higher in A-BL mice ($P<0.05$ vs. Y-BL), PEC increase along BC was 4 fold higher in A-FSGS mice ($P<0.01$ vs. Y-FSGS). The number of activated PECs on the tuft was also higher in A-FSGS mice. Notably, although Collagen IV staining was elevated in PECs in A-BL mice compared to Y-BL mice, staining in PECs increased in A-FSGS mice ($P<0.001$ vs. Y-FSGS). Despite A-BL mice having fewer PECs ($PAX8^+$ cells), the percentage of glomeruli with PECs expressing EMT markers was greatest in A-FSGS mice.

Conclusions: These data support the notion that, compared to young mice, aged mice are prone to more extensive glomerular damage in an experimental model of FSGS. Although the magnitude of podo depletion was similar between Y-FSGS and A-FSGS mice from their respective baselines, PECs were disproportionally more injured in A-FSGS mice, manifested by the extent of their activation, migration to the glomerular tuft, EMT and fibrosis.

Funding: NIDDK Support

TH-OR110

Glomerulosclerosis, Imploding Glomerulopathy and Podocytes
Christopher Lund O'Connor, Jian Shi, Jeffrey B. Hodgin, Roger C. Wiggins, Markus Bitzer, Rakhi Modak. *Univ of Michigan.*

Background: We have recently shown that podocyte density decreases with age in humans and identified imploding glomeruli (shrunken glomerular tuft, proteinaceous meterial and and detached podocytes in the Bowman's space) in human kidney tissue (Hodgin et al. JASN 2015). Very little is known about the etiology and relevance of this phenotype.

Methods: We performed quantitative morphometric and transcriptomic analysis of 47 kidney tissue samples from patients undergoing radical nephrectomy. 16 glomerular and tubule-interstitial parameters were assessed through routine and immunohistochemical stains and quantitative image analysis in FFPE sections. All glomeruli present in each sample were assessed (mean=199, stdev=98). mRNA (Affymetrix human ST 2.1) and small RNA expression (Illumina tru-seq) were assessed in micro-dissected glomeruli (approx. 30 from each sample) and tubule-interstitium and associated with morphometric parameters.

Results: We confirmed the age-associated decline in podocyte density ($p<0.01$) and increase in globally sclerosed glomeruli ($p<0.01$) in this cohort. The number of imploding glomeruli was positively associated with the number of global glomerulosclerosis ($p<0.0001$), mesangial index ($p<0.001$), interstitial fibrosis (Sirius red, Trichrome) ($p<0.01$) and eGFR ($p<0.001$), and negatively associated with podocytes/glomerulus ($p<0.01$) and podocyte density ($p<0.001$). Transcriptomic analysis of glomeruli identified 260 genes whose expression was highly significantly associated with the number of imploding glomeruli (FDR<0.001; Pearson correlation analysis). This transcriptomic signature was highly similar to those detected in diabetic nephropathy, focal segmental glomerulosclerosis, and IGA nephropathy (FDR<0.001) (www.nephroseq.org) and with podocyte damage but not endothelial cell injury (Ingenuity Pathway Analysis; Genomatix).

Conclusions: The frequency of imploding glomeruli is strongly correlated with phenotypes of glomerular damage and decreased eGFR. The morphometric and transcriptomic findings suggest high similarity to other glomerular diseases linked to podocyte stress and loss. Therefore we speculate that imploding glomerulopathy is a phenotype of accelerated podocyte damage in disease and aging.

Funding: NIDDK Support

TH-OR111

Sonic Hedgehog Links Podocyte Injury to Mesangial Cell Activation in Glomerular Disease
Dong Zhou, Haiyan Fu, Youhua Liu. *Dept of Pathology, Univ of Pittsburgh School of Medicine, Pittsburgh, PA.*

Background: Glomerular disease is often characterized by podocyte injury-triggered proteinuria, followed by glomerulosclerosis caused by mesangial activation and matrix over-production. However, how podocyte injury is linked to mesangial cell activation remains largely unknown. In this study, we have identified sonic hedgehog (Shh) as a novel factor that mediates podocyte-mesangial communication (PMC), which plays a crucial role in the pathogenesis of glomerulosclerosis after initial podocyte injury.

Methods: See results section.

Results: Shh was specifically induced in podocytes in animal models of glomerular diseases induced by adriamycin (ADR) and anti-GBM antibody, and in kidney biopsy specimens from patients with glomerular diseases. Using $Gli1^{LacZ}$ knock-in mice, we identified mesangial cells as the major Shh-responding cells in diseased glomeruli. Incubation of mesangial cells with Shh activated canonical Shh/Gli1 signaling pathway and promoted cell proliferation and extracellular matrix (ECM) accumulation in a time- and dose-dependent manner, as assessed by cell counting, MTT and BrdU incorporation assay, and induced numerous proliferation- and fibrosis-related genes. Furthermore, Shh promoted mesangial cells activation and ECM deposition in cultured glomeruli. However, Shh had little effects on podocyte proliferation. We further generated mice with podocyte-specific deletion of Shh, and found that conditional ablation of Shh had little effect on proteinuria in 1 and 5 weeks after ADR injection. However, loss of Shh in podocyte markedly ameliorated glomerulosclerosis. Consistently, blockade of Shh signaling by cyclopamine, an inhibitor of Smoothened, inhibited mesangial cells proliferation, reduced ECM accumulation and attenuated glomerulosclerosis after ADR injection at 5 weeks.

Conclusions: These studies demonstrate that podocyte-derived Shh acts as a previously unrecognized mediator to activate and promote mesangial cell expansion and matrix production, leading to glomerulosclerosis. Our studies uncover a novel pathway by which podocyte injury leads to glomerulosclerosis, and should have significant implication in designing future therapy for glomerular diseases.

Funding: NIDDK Support

TH-OR112

Single Kidney Cell Transcriptomics Applying Microfluidic Droplet Generation Technology (Drop-Seq)
Edgar A. Otto, Rajasree Menon, Celine C. Berthier, Matthias Kretzler. *Internal Medicine - Nephrology, Univ of Michigan, Ann Arbor, MI.*

Background: Microfluidic droplet-based technology (Drop-Seq) allows to uniquely barcode mRNA transcripts of thousands of individual cells derived from a complex tissue for downstream RNA-Seq expression analyses. The technique is based on combining single-cells with barcoded beads in separate nanoliter-sized droplets in the course of flowing oil, beads, and cells through a droplet-generator device via three syringe pumps[1].

Methods: Healthy adult kidney tissue derived from tumor nephrectomies was enzymatically and mechanically dissociated into single cell suspensions. Cells were processed according to the DropSeq workflow described by the McCarroll lab[1]. Individual cells were identified by barcodes, and all transcripts were tagged with Unique Molecular Identifiers (UMIs) in order to determine absolute transcript abundance. Paired-end RNA-Seq was performed on a HiSeq2500 platform. Bioinformatics analysis o was done using the tools embedded in Picard tools developed by the Broad Institute and unsupervised clustering algorithms were executed using the R package toolkit "Seurat" from the Satija lab.

Results: Single cell transcriptome analyses of 3,000 cells enabled the distinction of various cell types which correspond to specific nephron segments according to the of the "RNA-seq Analysis of Microdissected Rat Kidney Tubule Segment" database. Principal component analysis revealed cells showing high expression of *ALDOB* and *GBX3* corresponding most likely to segment S1 of the proximal convoluted tubules, *SLC12A3* and *WNK1* indicates distal convoluted tubule (DCT) and *UMOD* and *EGF* indicates cTAL nephron segment cell origin. About 10% of the cells expressed hemoglobin indicating the presence of red blood cells in the preparation.

Conclusions: We have implemented the DropSeq technique to establish transcriptome profiles on the single-cell level of human adult kidney tissue. Single cell transcriptomics may help to better define nephron cell type composition, identify cell type specific biomarkers for diagnostics, renal disease progression, and for potential therapeutic interference. [1]Macosky et al., 2015 *Cell 161,*1202-14.

Funding: Clinical Revenue Support

TH-OR113

Degradomic Analysis Dissects Intracellular Protease Signaling in Podocytes Markus M. Rinschen,[1] Pitter F. Huesgen,[2] Thomas Benzing.[1] *[1]Internal Medicine, Univ Hospital Cologne, Germany; [2]Forschungszentrum Juelich, Germany.*

Background: Proteases are successful therapeutic targets in many human diseases. Proteases are also crucial for maintenance of a physiological podocyte function. Based on previous system-wide analyses, threonine proteases are expressed at very high levels in podocytes both on the proteome and transcriptome levels. However, the intracellular protease targets are not completely characterized. The aim this study was to delineate posttranslational protease networks in podocytes.

Methods: Terminal Amine Isotope Labeling of Substrates (TAILS) is an innovative technology that allows identification and quantification of cleavage and native protein N-termini in various conditions using high-accuracy tandem mass spectrometry. We applied this technology to native glomeruli perfused with protease inhibitor to demonstrate the physiological presence of novel proteoforms originating from posttranslational proteolytic processing. Second, we performed a quantitative degradomic analysis of cultured podocytes under normal and stressed (PAN injury) conditions.

Results: In renal glomeruli, we discovered thousands of termini by TAILS proteomic analysis. Among these, we found a novel podocin proteoform lacking its N-terminal 60 amino acids. Novel proteoforms were also discovered for Nephrin, Synaptopodin and Actinin-4. Degradomic analysis of stressed podocytes demonstrated a distinct perturbation of protease signaling. Differentially regulated protease substrates were mainly cytoskeletal proteins, including ACTN4, further actin-associated and intermediary filament proteins. The data also determined preferential protease motifs during this damage and indicated that specific protease classes are activated during PAN injury. Novel proteoforms were also confirmed by differential migrational behavior on SDS PAGE gels.

Conclusions: The technology utilized here is crucial to identify protease classes and their intracellular targets involved in renal and podocyte disease. We demonstrate that a tightly regulated protease network strongly affects cytoskeletal and slit diaphragm proteins in podocytes.

Funding: Government Support - Non-U.S.

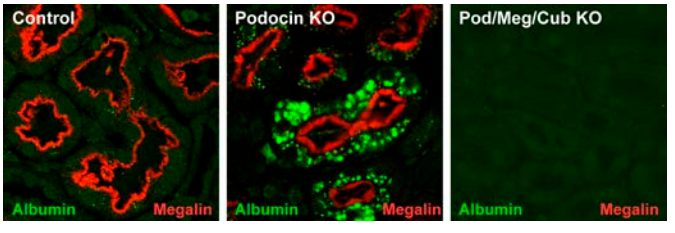
TH-OR114

Albumin Handling in Mice with Genetic Knockout of Megalin/Cubilin and Nephrotic-Range Proteinuria Kathrin Weyer,[1] Henrik Birn,[1] Geraldine Mollet,[2] Corinne Antignac,[2] Rikke Nielsen,[1] Erik I. Christensen.[1] *[1]Biomedicine, Aarhus Univ, Aarhus, Denmark; [2]INSERM U1163, Univ Paris Descartes, Inst Imagine, Hôpital Necker Enfants Malades, Paris, France.*

Background: It has been proposed that a high-capacity pathway for transtubular transport of albumin exists for recovery of large amounts of albumin in normal kidneys, with impact for plasma albumin levels. The megalin/cubilin receptor complex is essential for tubular uptake and degradation of filtered albumin. To determine whether a high capacity retrieval pathway exists, we investigated if knockout of the receptors under normal and nephrotic states is reflected in plasma albumin levels.

Methods: Inducible podocin knockout (KO), megalin/cubilin KO, megalin/cubilin/podocin KO mice, and controls, were followed for five weeks where urine, plasma, liver, and kidney tissue were collected. Albumin levels were determined in urine and plasma samples by ELISA. Liver albumin mRNA was quantified by qRT-PCR. Kidney albumin uptake was evaluated by immunostaining.

Results: Immunostaining of kidney slices from megalin/cubilin/podocin KO mice demonstrated an efficient blockade of albumin uptake in proximal tubule cells, whereas podocin KO mice displayed excessive albumin uptake compared to controls. Megalin/cubilin/podocin KO mice had increased urinary albumin excretion compared to podocin KO mice (albumin/creatinine: 31.1±5.1 vs. 19.6±6.1 mg/mg). Albumin plasma levels were similarly reduced in megalin/cubilin/podocin and podocin KO mice (11.0±0.9 vs. 9.1±1.0 g/L), compared to controls (24.8±1.0 g/L) and megalin/cubilin KO (22.4±2.4 g/L). Liver albumin mRNA was similarly increased in megalin/cubilin/podocin and podocin KO mice, compared to controls and megalin/cubilin KO.



Conclusions: Blockade of proximal tubular albumin reabsorption causes no changes in plasma albumin levels under normal and nephrotic states, and we thus find no evidence of a major renal retrieval pathway for albumin.

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

TH-OR115

Endothelial SIRT1 Inactivation Enhances Capillary Rarefaction and Fibrosis following Kidney Injury through Notch Activation Yujiro Kida,[1] Joseph A. Zullo,[1,3] Michael S. Goligorsky.[1,2,3] *[1]Medicine, New York Medical College, Valhalla, NY; [2]Pharmacology, New York Medical College, Valhalla, NY; [3]Physiology, New York Medical College, Valhalla, NY.*

Background: Peritubular capillary (PTC) rarefaction, along with tissue fibrosis, is a hallmark of progression of chronic kidney diseases (CKD). Although previous studies have demonstrated that functional loss of endothelial sirtuin 1 (SIRT1) aggravates renal fibrosis, mechanisms that afford renal protection are not completely elucidated. Recently, SIRT1 was found to deacetylate Notch intracellular domain-1 (NICD1, active form of Notch1) and accelerate its degradation. In this study, we hypothesized that impaired endothelial SIRT1 function induces Notch activation, which enhances kidney injury.

Methods: We created mice with deleted SIRT1 catalytic domain in endothelial cells (Sirt1 mutant mice). Both wild-type (WT) control and Sirt1 mutant mice were subjected to unilateral ureteral obstruction (UUO). For in vitro studies, we isolated microvascular endothelial cells (MVECs) from WT and Sirt1 mutant kidneys.

Results: In Sirt1 mutant mice, kidney injury enhanced apoptosis and senescence of PTC endothelial cells with impaired endothelial proliferation and expanded myofibroblast population and collagen deposition. Compared to WT kidneys, Sirt1 mutant kidneys showed increased expression of DLL4 (a potent Notch ligand), Hey1 (Notch target gene), and NICD1 in PTC endothelial cells post-injury. Sirt1 mutant primary MVECs reduced motility and enhanced senescence compared to WT MVECs. This phenotypical difference was negated with Notch inhibition. DLL4 and TGF-β1 synergistically increased transdifferentiation of primary kidney pericytes into myofibroblast.

Conclusions: Functional loss of endothelial SIRT1 aggravates PTC rarefaction via excessive Notch activation and tissue fibrosis through increased expression of endothelial DLL4. Endothelial SIRT1-Notch1 axis could be a novel therapeutic target to prevent progression of CKD.

Funding: NIDDK Support, Private Foundation Support

TH-OR116

Osteopontin Deficiency Reduces Alport Pathology Wen Ding, Keyvan Yousefi, Jayanti Singh, Stefania Goncalves, Bradley J. Goldstein, Lina Shehadeh. *Univ of Miami.*

Background: Alport Syndrome is characterized by progressive renal failure, hypertension, proteinuria, hearing loss, and cardiovascular dysfunction. The COL4A3$^{-/-}$ mouse phenocopies these symptoms, making it an ideal Alport model. Osteopontin (OPN), a secreted phosphoproprotein, has never been studied in Alport Syndrome. We elected to investigate the role of OPN in Alport pathology.

Methods: OPN protein expression from wild type (WT) and Alport mice (n=3-6) was analyzed by western blot. We generated Alport mice with hetero-or homo-zygous OPN deletion and evaluated effect on life span. At 8-9 weeks of age, WT, OPN$^{-/-}$, COL4A3$^{-/-}$, COL4A3$^{-/-}$OPN$^{-/-}$ and COL4A3$^{-/-}$OPN$^{+/-}$ mice (n=7-22/group) were studied. Urine from all groups was analyzed by Albumin and Creatinine Elisas, blood was analyzed for mean corpuscular hemoglobin concentration (MCHC), plasma was analyzed by Gelactin-3 Elisa, kidney injury molecule-1 (KIM-1) protein expression was analyzed by immunofluorescence, blood pressure was recorded by a tail cuff system, and hearing thresholds were determined by auditory brainstem responses to pure tone (4-16 kHz) or click stimuli. Heart function was assessed by echocardiography. Basement membrane morphology in kidneys and cochleas was analyzed by electron microscopy.

Results: OPN was increased in plasma (FC=1.4, p=.03) and kidneys (FC=2.1, p=.003) of Alport versus WT mice. COL4A3$^{-/-}$OPN$^{-/-}$ and COL4A3$^{-/-}$ OPN$^{+/-}$ mice significantly outlived the Alport mice (16 versus 10 weeks), with increase in body weight (FC=1.2, p=.02), MCHC (FC=1.3, p=.001) and endocardial stroke volume (FC=1.4, p=.003), while decrease in Albumin/Creatinine ratio (FC=.5, p=.01), Gelactin-3 (FC=.62, p=.01), renal Kim-1 (FC=.1, p=10^{-6}), and blood pressure (systolic FC=.81, p=.0002; diastolic FC=.78, p=.0001). COL4A3$^{-/-}$OPN$^{+/-}$ mice showed significantly improved hearing in response to 16 kHz stimuli. COL4A3$^{-/-}$OPN$^{-/-}$ mice had reduced thickness of glomerulus- and stria vascularis capillary- basement membrane.

Conclusions: This is the first study reporting that reduction of OPN can improve lifespan, proteinuria, hypertension, renal and cochlear histology, cardiac function and hearing ability in Alport mice. Our data suggest OPN as a therapeutic target for Alport Syndrome.

Funding: Private Foundation Support

TH-OR117

Role of Macula Densa Cells in Tissue Remodeling in Renovascular Hypertension Toshiki Doi, Anne Riquier-Brison, Janos Peti-Peterdi. *Physiology and Biophysics, Univ of Southern California, Los Angeles, CA.*

Background: Renovascular disease (RVD) accounts for an important proportion of secondary hypertension and is associated with progressive renal dysfunction. There is no specific cure for RVD and the resulting progressive, chronic kidney disease. Since robust alterations in tissue composition and renin are established features in RVD, this study tested the hypothesis that cells of the juxtaglomerular apparatus (JGA) play an important role in vascular and glomerular remodeling in RVD.

Methods: Genetic cell fate tracking using in vivo serial multiphoton microscopy (MPM) of the same glomeruli, and histology in tamoxifen-induced NG2CreERT2-Tomato mice and Ren1dCre-Confetti mice was performed to evaluate mesenchymal progenitor cell-

mediated tissue remodeling. Mice underwent either sham operation or renal artery cuffing (two-kidney, one-clip, 2K1C model of RVD) and were treated with specific inhibitors of macula densa (MD) cell-specific nitric oxide synthase (NOS1, 7-Nitroindazole (7-NI), 20 mg/kg/day ip), and cyclooxygenase (COX-2, 6 mg/L SC58236 in drinking water), or control (vehicle) groups, and sacrificed 3 weeks later.

Results: 2K1C mice showed high blood pressure, a significant decrease in the weight of the clipped kidney, and a significant increase in the weight of the non-clipped kidney compared with sham group. The number of NG2-derived cells, Ki-67 or renin positive cells increased more than 2-fold in the JGA in the clipped kidney. Some NG2-derived cells were co-labeled for Ki-67 or renin. On the other hand, 7-NI and COX-2 inhibitor attenuated these alterations. At baseline, Ren1d-Confetti cells existed at glomerular vascular pole, mesangium, Bowman's capsule, and in the proximal tubule. Serial MPM showed the migration of Ren1d-Confetti cells from vascular pole into glomerulus.

Conclusions: Our results suggest that mesenchyme-derived cells, including cells of the renin lineage have important roles in vascular and glomerular remodeling in RVD. Also, MD-derived (from COX-2 and nNOS) paracrine factors promote the migration of these cells to the JGA and glomerulus. In conclusion, MD cells may be important regulators of vascular and glomerular remodeling in RVD.

Funding: NIDDK Support

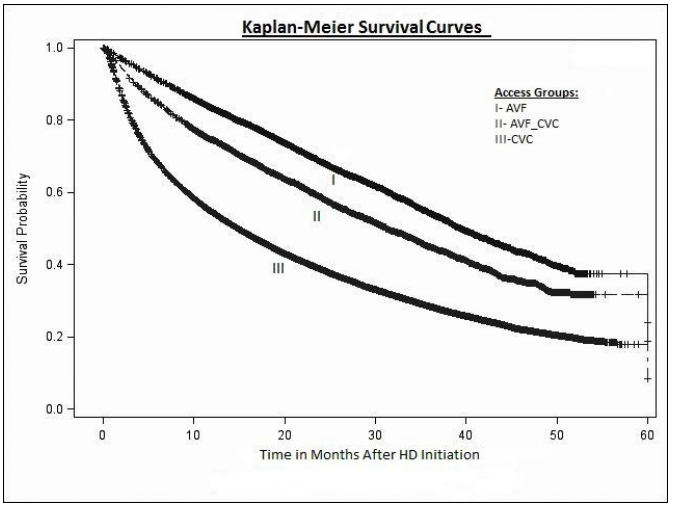
TH-OR118

'Patient First': The Survival Benefit of 'Fistula First, Catheter Last' in Hemodialysis Is Primarily due to Patient Selection Robert S. Brown,[1] Bhanu K. Patibandla,[2] Alexander S. Goldfarb-Rumyantzev.[1] *[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]Oregon Health & Science Univ, Portland, OR.*

Background: Patients needing hemodialysis (HD) are advised to have an arteriovenous fistula (AVF) rather than a catheter because of significantly lower mortality rates. However, disparities in AVF placement raise a question of the role patient selection plays in this apparent mortality benefit.

Methods: A cohort of 115,425 incident HD patients ≥67 years was derived from the United States Renal Data System with linked Medicare claims to identify the first predialysis vascular access placed. We compared mortality outcomes in patients initiating HD with a fistula placed first, a catheter after a fistula had been placed first, or a catheter placed first.

Results: Of 21,436 patients with an AVF placed first, 9,794 initiated HD with that AVF (AVF group) and 8,230 with a catheter rather than their AVF (AVF-CVC group). 90,517 patients initiating HD with a catheter (CVC group) served as the reference group. Those in the AVF group had the lowest mortality over the 58 month study period [HR 0.50, CI 0.48-0.52, p<0.0001] with mortality at 6, 12 and 24 months of 8.7%, 16.7% and 31.4%, respectively, compared to 31.6%, 45.6% and 62.3% in the CVC group. Surprisingly, those initiating HD with a catheter after AVF placement also had significantly lower mortality rates [HR 0.66, CI 0.64-0.68, p<0.0001] than the catheter group with 15.1%, 25.4% and 41.6% dying at 6, 12 and 24 months. Furthermore, analyzing the data in the AVF-CVC group by age, race, sex, comorbidities or whose 'failed' AVF was placed <4 or >2, 4, 6, or 9 months predialysis all showed similar mortality benefit compared to the CVC group.



Conclusions: Patient selection factors affecting fistula placement even when hemodialyzed with a catheter may explain at least two-thirds of the lesser mortality rates seen in those with a fistula compared to a catheter.

TH-OR119

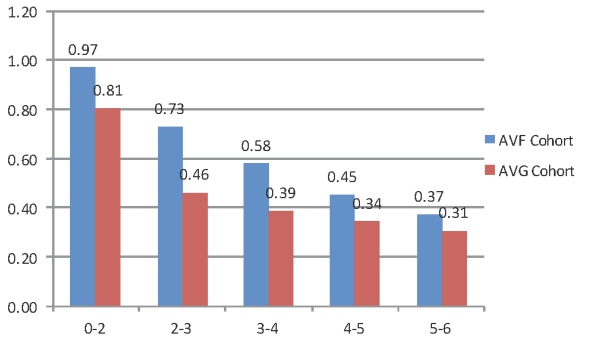
Choice of Vascular Access (VA) and Clinical Outcomes among Elderly Hemodialysis Patients Timmy C. Lee,[1] Mae Thamer,[2] Qian Zhang,[2] Michael Allon,[1] Yi Zhang.[2] *[1]Univ of Alabama at Birmingham; [2]Medical Technology and Practice Patterns Inst.*

Background: Current guidelines recommend placing an AVF rather than an AVG in HD patients. Our observational study compared VA and patient outcomes among elderly patients who initiated HD with a dialysis catheter (CVC), and subsequently had an AVF or AVG placed.

Methods: Using an observational equivalent of an intention-to-treat design, we identified ESRD patients from the USRDS age ≥67 who initiated HD from 7/1/2010-6/30/2011 with a CVC and no secondary VA, and who received an AVF (n=7,016) or AVG (n=2,228) within the ensuing 6 months. We evaluated CVC dependence during the 6 months after VA placement and used propensity score (PS)-weighted Cox proportional hazard models to evaluate the association of AVF vs AVG use with patient survival.

Results: Patients receiving an AVG were more likely to be female, black, and have high comorbidities. Those receiving an AVG had lower CVC use in the first 6 months after VA surgery (figure1).

Figure 1. Percentages of CVC dependence in AVF and AVG cohorts by months after surgery



In the PS-adjusted analysis of the entire cohort, patients with an AVF had a lower risk of death versus those with an AVG (OR 0.79, 95% CI 0.74-0.83). The survival difference between AVF and AVG persisted when patients were stratified by age and race (table 1).

Table 1. Adjusted Kaplan-Meier survival curve results based on VA type: AVF vs. AVG (ref)

Cohort	*Hazard Ratio (HR) 95% CI*
Whites 67 – 80 yrs	0.77 (0.70-0.85)
Whites >80 yrs	0.81 (0.73-0.91)
Blacks 67 – 80 yrs	0.71 (0.60-0.85)
Blacks >80 yrs	0.66 (0.53-0.83)

Conclusions: AVG placement in patients initiating HD with CVC is associated with significantly shorter duration of CVC dependence. Patient survival was significantly better in patients receiving an AVF despite longer CVC dependence, suggesting the survival advantage of patients with AVFs may be due to unmeasured clinical characteristics of these patients, rather than to presence of CVC.

Funding: NIDDK Support, Private Foundation Support

TH-OR120

Cost Comparisons of Hemodialysis Access Modalities among Patients Starting with Tunneled Catheters Jason Kane Wagner, Larry Fish, Theodore H. Yuo. *Vascular Surgery, Univ of Pittsburgh, Pittsburgh, PA.*

Background: Arteriovenous fistula (AVF) is the ideal hemodialysis (HD) access, but most patients start with tunneled dialysis catheter (TDC). AVF and arteriovenous graft (AVG) surgery may reduce TDC use and also increase procedural expenses. We compared Medicare costs associated with AVF, AVG, and TDC.

Methods: Using the US Renal Data System (USRDS), we identified incident HD patients in 2008 who started with TDC, survived at least 90 days, and had adequate Medicare records for analysis. We followed them until death or end of 2011; access modality was based on billing evidence of AVF or AVG creation. We assumed patients without such records remained with TDC. We generated multivariate linear regression models predicting Medicare expenditures, censoring costs when patients died; we included all payments to physicians and institutions. We also created algorithms to identify access-related costs.

Results: There were 113,505 patients in the USRDS who started HD in 2008, of whom 51,002 Medicare patients met inclusion criteria. Of that group, 41,532 (81%) began with TDC; 27,064 patients were in the final analysis file. In the first 90 days after HD initiation, 6,100 (22.5%) received AVF, 1,813 (6.7%) AVG, and 19,151 (70.8%) stayed with TDC. Annualized access costs by modality were: TDC $13,625 (95% CI $13,426-13,285); AVF $16,864 (95% CI $16,533-17,194); and AVG $20,961 (95% CI $20,967-21,654) (P<.001). Multivariate linear regression demonstrated that staying with TDC had lowest access-related costs, AVF was intermediate, and those who underwent AVG surgery were highest (P<.021). Access type was not significantly associated with total costs. Additional AVF and AVG

creation ($3,525 and $3,804 per access per year, respectively) and open and endovascular access-related interventions ($3,102 and $3,569 per procedure per year, respectively) (all P<.001) were important predictors of increased cost.

Conclusions: Among patients starting HD with TDC, continued TDC use is associated with lowest access-related cost. Both endovascular and open interventions are associated with significant additional costs. Further investigation is warranted to develop efficient patient-centered strategies for HD access.

Funding: Other NIH Support - KL2-TR000146, T32-HL098036, Clinical Revenue Support

TH-OR121

Access Blood Flow Surveillance in Native Arteriovenous Fistula: Reduction in Thrombosis Rate and Improvement in Assisted and Secondary Patency. A Randomized Clinical Trial Ines Aragoncillo,[1] Soraya Abad,[1] Silvia Caldés,[2] Antonio Cirugeda,[2] Almudena Vega,[1] Cristina Fernandez,[4] Cristina Moratilla,[3] Nicolás Macías,[1] Juan Manuel Lopez Gomez,[1] Fernando De Alvaro Moreno.[2] *[1]Nephrology, H Gregorio Marañon, Madrid, Spain; [2]Nephrology, H Infanta Sofia, Madrid, Spain; [3]Nephrology, Clinica Fuensanta, Madrid, Spain; [4]Nephrology, H Clinico, Madrid, Spain.*

Background: Stenosis is the main cause of arteriovenous fistula (AVF) failure. It is still unclear if surveillance based on Vascular Access Blood Flow (Q_A) enhances AVF function and longevity.

Methods: 3-year follow up randomized, controlled, multicentric, open-label trial, comparing Q_A surveillance (pre-emptive repair of subclinical stenoses with angioplasty and/or open surgery) with standard monitoring/surveillance (intervention based on classic criteria) in mature autologous AVFs. AVFs were randomized to either control group (surveillance based on venous pressure, recirculation, dialysis dose…; n=104) or to Q_A group [Q_A was measured quarterly using doppler ultrasound (*M-Turbo®*)and ultrasound dilution method (Transonic®)n=103]. The criteria for intervention in Q_A group were 25% reduction in Q_A, Q_A <500 ml/min or significant stenosis with >50% reducción in vessel lumen and haemodinamic repercussion [Peak Sistolic Velocity (PSV) >400ml/min or PSV stenosis/PSV pre-stenosis > 3).

Results: Significant reduction in thrombosis rate (0,025 thrombosis/patient/year in the Q_A group compared with 0,086 thrombosis/patient/year in control group. p= 0,007) Significant improvement in assisted primary patency rate and secondary patency rate in Q_A group (HR 0,30 CI 0,11-0,82. P=0,011 / HR 0,49 CI 0,26-0,93. p=0,030) No differences in non-assisted primary patency rate between groups (HR 0,98 CI 0,57-1,61. p=0,935). Higher needs of central venous catether and hospitalizations related with VA in control group (p<0,001 / p=0,003). - Higher total VA related costs in control group (217.845 € vs 124.186 €. p=0,029).

Conclusions: QA based surveillance combining doppler ultrasound and ultrasound dilution method prevents thrombosis, increases assisted and secondary patency rate in AVF and it is cost effective.

TH-OR122

Comparison of Postoperative Ultrasound Criteria to Predict Unassisted Clinical Arteriovenous Fistula (AVF) Maturation Timmy C. Lee,[1] Michelle L. Robbin,[1] Steven K. Burke,[2] Andrew T. Blair,[2] Missy Magill,[2] Michael Allon.[1] *[1]Univ of Alabama at Birmingham; [2]Proteon Therapeutics.*

Background: AVF maturation failure is a major clinical problem. A postoperative ultrasound (US) may provide objective measures to predict unassisted clinical AVF maturation and guide interventions to salvage nonmaturing AVFs. We compared predictive values of the NKF K/DOQI and University of Alabama (UAB) maturation criteria for unassisted clinical AVF maturation from data in a multicenter, randomized-clinical trial.

Methods: We analyzed prospective data from "A Study of PRT-201 Administered After Arteriovenous Fistula Creation in Patients with Chronic Kidney Disease.", which enrolled 151 subjects. We excluded 14 subjects with a missing 6-12 week postoperative US and 32 subjects with indeterminate clinical AVF maturation. The remaining 105 subjects were analyzed. Two US criteria were assessed:(1) NKF:AVF diameter ≥6 mm and blood flow ≥600 mL/min) and (2) UAB:AVF diameter ≥4mm and blood flow ≥500mL/min. Unassisted clinical AVF maturation was defined as successful cannulation for ≥90 days without requiring prior surgical or percutaneous interventions. Sensitivity and specificity were calculated for both criteria.

Results: 44% of AVFs were radiocephalic (RCF) and 56% brachiocephalic.

Table 1	Sensitivity	Specificity
All AVF (N=105)		
UAB Criteria	0.83	0.48
NKF Criteria	0.60	0.74
Radiocephalic AVF (N=46)		
UAB Criteria	0.82	0.85
NKF Criteria	0.39	0.92

Table 1 summarizes the sensitivity and specificity of both US criteria for unassisted clinical AVF maturation. Collectively, the UAB criteria had higher sensitivity and lower specificity for unassisted AVF maturation, as compared to the NKF criteria. For patients with a RCF AVF, the UAB criteria had higher sensitivity and similar specificity to the NKF criteria.

Conclusions: In the total population, the UAB criteria would minimize unnecessary early interventions in AVFs likely to clinically mature without an intervention, but delay interventions that may be indicated in AVFs that are unlikely to be clinically mature. However, for RCF AVFs, using the UAB criteria would reduce unnecessary early interventions without delaying necessary interventions.

TH-OR123

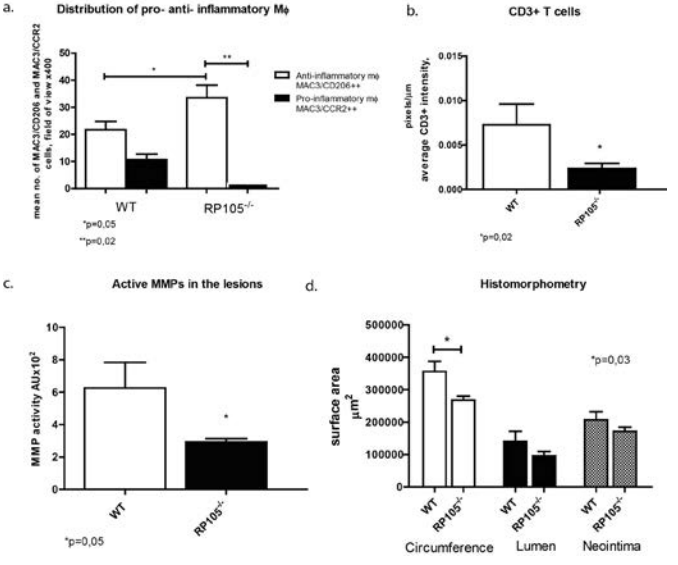
Deficiency of TLR4 Homologue RP105 Aggravates Outward Remodelling in a Murine Model of Arteriovenous Fistula Failure Taisiya Bezhaeva, ChunYu Wong, Margreet R. De Vries, Eric P. van der Veer, Carla van Alem, Joris I. Rotmans, Paul Quax. *Nephrology and Vascular Surgery, Leiden Univ Medical Centre, Netherlands.*

Background: The pathophysiology of arteriovenous fistula (AVF) maturation failure is unknown but impaired outward remodeling and intimal hyperplasia are both considered to contribute. RP105 is an important regulator of inflammatory TLR4 signalling, expressed on numerous cell types. In the present study, we defined cell specific effects of RP105$^{-/-}$ on vascular smooth muscle cells (VSMCs) and macrophages (mΦ) *in vitro* and *in vivo* effects of RP105$^{-/-}$ on AVF maturation in a murine model of AVF failure.

Methods: All *in vitro* experiments were performed on primary cells isolated from RP105$^{-/-}$ and wild type (WT) mice. AVFs were created in an end-to-side manner between *v.jugularis* and *carotid a.* in RP105$^{-/-}$ (n=13) and WT (n=11) mice. AVFs were harvested at day 14 and processed for morphometric analysis and immunohistochemistry. MMPSense probe was used to measure *in vivo* MMPs activity.

Results: *In vitro*, anti-inflammatory (M2) mΦ of RP105$^{-/-}$mice showed increased IL10 (ELISA) compared to WT. Venous VSMCs from WT mice exhibited increased mRNA of RP105 and TLR4 compared to arterial VSMCs, whereas proliferation rate of venous VSMCs was 50% lower in RP105-/- cells. *In vivo,* a shift towards M2 mΦ and a 70% reduction in CD3+ T cells was observed in RP105$^{-/-}$ mice(fig.a,b). MMP-activity was reduced by 50% in RP105$^{-/-}$(fig.c). Amount of SMA/Ki67^{++} VSMCs was decreased by 31%. Overall, RP105-/- mice showed 26% smaller circumference of the external jugular vein (fig.d).

fig.1



Conclusions: Deletion of RP105 results in a marked decrease in venous outward remodeling in AVF. The latter might relate to a shift towards M2 mΦ, reduction in MMP activity and decreased VSMCs proliferation in the venous outflow tract of AVF, illustrating the complex interactions between inflammation and VSMC biology in AVF maturation.

Funding: Government Support - Non-U.S.

TH-OR124

Loss of GSTA4 Enhances CKD-Induced Arteriovenous Fistula Failure Ming Liang, William E. Mitch, Jizhong Cheng. *Medicine/Nephrology, Baylor College of Medicine, Houston, TX.*

Background: A functioning arteriovenous fistula (AVF) is the "dialysis lifeline" but progressive neointima formation reduces AVF functions leading to AVF failure.We have found that chronic kidney disease (CKD) accelerates AVF failure. CKD induces oxidative stress leads to accumulation of the uremic toxin, 4-hydroxynonenal (4-HNE). This process is linked to CKD-suppressed expression of α-glutathione transferases (GSTs).

Methods: we created CKD and AVFs in GSTA4 KO mice and mice overexpressing GSTA4, we studied how GSTA4 can suppress CKD-induced AVF failure. In cultured VSMCs, we examined how 4-HNE induces VSMC proliferation and whether GSTA4 modulates these responses.

Results: GSTA4 expression measured as mRNA or protein was decreased and 4-HNE level was increased in AVFs in CKD mice. In GSTA4 (GSTA4 KO) mice, CKD increased both 4-HNE and pc-JUN levels in VSMCs, and stimulated VSMC proliferation and neointima formation in AVFs. Using a combined Tet-On/Cre induction system, a transgenic mice was generated to transiently overexpress GSTA4 in VSMCs. The overexpression of

GSTA4 resulted in lower levels of 4-HNE and decreased MAPK activation. There were reduced accumulation of SMA-α^+ VSMCs and PCNA positive cells in neointima in AVFs created in GSTA4 transgenic mice. The outcome was a reduction in the CKD-induced neointima formation and improved AVF maturation. In ex-vivo experiments, the loss of GSTA4 expression is accompanied with increased VSMC migration and outgrowth. In cultured VSMCs, treatment with 4-HNE was found to exclude $p27^{kip1}$ from the nuclei to promote VSMC proliferation. 4-HNE also upregulated MAPK activation (pERK1/2 and pJNK). Both responses were amplified when GSTA4 was knocked down, but were blocked when GSTA4 was overexpressed.

Conclusions: CKD complications decrease GSTA4 expression resulting in 4-HNE accumulation in AVFs. This increase in 4-HNE stimulates the proliferation of VSMC to stimulate the MAPK signaling pathway. When GSTA4 were specifically overexpressed in VSMCs, there was suppression of CKD-induced 4-HNE accumulation and VSMC proliferation. These results demonstrate that increased expression of GSTA4 can suppress CKD-induced neointima formation and AVF failure.

Funding: NIDDK Support

TH-OR125

Usability of the Endovascular Arteriovenous Fistula: 6m Results of the Novel Endovascular Access Trial (Neat) Charmaine E. Lok, Dheeraj K. Rajan. *On Behalf of NEAT Investigators, Univ Health Network, Toronto, Canada.*

Background: Recent high arteriovenous fistula (AVF) failure rates (20-60%) may be associated with vessel trauma incurred at the time of surgery. Vessel trauma may be mitigated by a novel approach to AVF creation endovascularly (endoAVF) using magnet-based catheter technology and radiofrequency energy (RFE). NEAT aimed to evaluate the safety and efficacy of this new technology in a prospective, multi-center study. We report key 6 mo outcomes.

Methods: 80 CKD V patients (60 study cohort;20 roll-in) from sites in Canada, Australia and New Zealand were enrolled. EndoAVFs were created using two magnetic catheters to create a channel between a vein and artery using RFE. Key inclusion criteria included: ineligibility for a distal forearm AVF, target vein and artery diameters > 2.0mm, no central vein stenosis. Primary endpoint was percentage of endoAVF physiologically mature (brachial artery flow >500 ml/min, vein diameter > 4mm) or 2 needle cannulation within 3 months. Patient satisfaction was evaluated via a validated survey (SF-VAQ). Only study cohort patients (n=60) were evaluated and reported.

Results: 65% of patients were men, mean age 60 yrs, mean BMI 28, 65% had diabetes and 57% were predialysis at the time of procedure. An endoAVF was successfully created in 98% (59/60) of patients; 5 (8.3%) patients had a serious device or procedure-related adverse event. Physiological maturation was 91% (52/57) of endoAVFs within 3 months. Mean brachial artery flow rate was 918ml/min at 3 months and sustained to 6 months. Cephalic, basilic, and median cubital vein diameters (mm) increased to 5.4, 5.8 and 6.1 at 6 months, respectively. 2-needle cannulation of endoAVF occurredin 90% (9/10) of predialysis patients who required dialysis and 73% (16/22) of patients who were already on dialysis at baseline. 6mo primary and secondary patency rates were 79% and 90%, respectively. 83% of patients were satisfied with their endoAVF at 6 months.

Conclusions: The NEAT reveals that endoAVF results in high physiological maturation success and ability to cannulate with 2 needles for dialysis. Patients were satisfied with their endoAVF. Ongoing follow-up will reveal the long-term durability of the endoAVF.

Funding: Pharmaceutical Company Support - TVA Medical

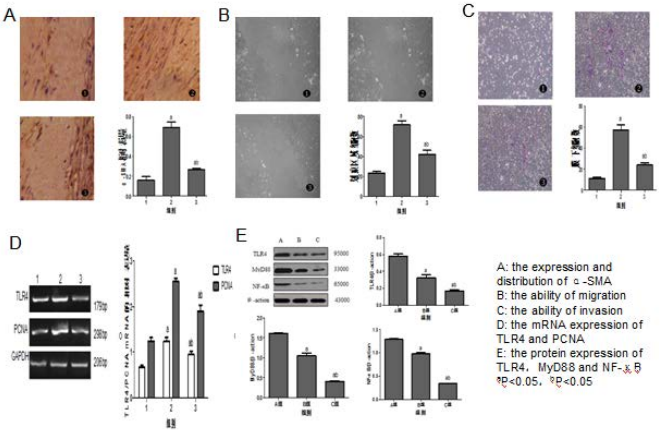
TH-OR126

The Effect and Mechanism of Chitosan Inhibiting Vascular Smooth Muscle Cells Hyperplasia of Uremia Patients Yan Yan. *Nephrology, The First Affiliated Hospital of Nanchang Univ, NanChang, JiangXi, China.*

Background: The most common complication of arteriovenous fistula(AVF) is stenosis. The pathological characteristic of stenosis is intimal hyperplasia.Our previous studies have found that chitosan can inhibit the internal jugular fistula intimal hyperplasia of rabbit.Our aim was to investigate the effect and mechanism about chitosan have on cultured vascular smooth muscle cells(VSMCs) of uremia patients with AVF.

Methods: Adopting the the second generation VSMCs of uremia patients with AVF and normal person which cultured with improved adherent method of tissue explants, VSMCs from normal person cultured with 20%FBS was blank control group, VSMCs from uremia patients cultured with 20%FBS and 100 ug/ml chitosan respectively were control group and experimental group. α-SMA were detected by immunohistochemistry method. The migration and invasion's ability of VSMCs were detected by scratches and transwell method, The mRNA expressions of TLR4 and PCNA were measured by Real-time PCR. VSMCs of uremia patients with AVF were intervened with different doses of chitosan(10, 100, 500ug/ml), the protein expressions TLR4, MyD88 and NF-κB were detected by Western blotting.

Results:



α-SMA was staining compared to blank control group. Compared experimental group with control group, the level of α-SMA was significantly decreased. The ability of migration and invasion of VSMCs after the intervention of chitosan were decreased significantly ($P < 0.05$), The mRNA expressions of TLR4 and PCNA decreased($P < 0.05$).TLR4, MyD88 and NF-κB protein expression were reduced by chitosan in the certain concentration range.

Conclusions: Chitosan not only decreases the ability of migration and invasion but also inhibits the proliferation of VSMCs of uremia patients with AVF, the mechanism may be concerned in the decreased expression of TLR4,MyD88 and NF-κB.

Funding: Government Support - Non-U.S.

TH-OR127

Taurolidine/Urokinase Based Locking Regimen Significantly Reduces Catheter-Related Blood Stream Infections and Dysfunction of Tunneled Haemodialysis Catheters when Compared to 4% Citrate Wolfgang Winnicki, Gurkan Sengoelge. *Dept of Medicine III, Div of Nephrology and Dialysis, Medical Univ of Vienna, Vienna, Austria.*

Background: Catheter infections and dysfunctions cause morbidity and mortality in haemodialysis patients. There are data showing that taurolidine containing catheter lock solutions may reduce the risk of both of these complications. Yet, there are no consistent guidelines for the use of lock solutions in haemodialysis patients with tunneled central lines. We aimed to study whether a TauroLock™ based locking regimen reduced the incidence of catheter-related blood stream infections (CRBSI, at least one positive blood culture with no other source of infection) and catheter malfunction (inadequate blood flow during dialysis - defined as blood flow < 200ml/min or >30% less than the average of the previous 10 sessions or necessity of catheter rescue with alteplase).

Methods: In this randomized controlled trial with 106 haemodialysis patients with a newly inserted tunneled central line a taurolidine based locking regimen with TauroLock™-Hep500 2x/week after the first two dialysis sessions and TauroLock™-U25.000 1x/ week before the long interval was compared to 4% citrate (CitraFlow™) used after each dialysis 3x/week.

Results: 52 patients were assigned to TauroLock™ (8982 catheter days) and 54 patients to 4% citrate (6708 catheter days). Catheter-related blood stream infections occurred in 11.4 % of patients in TauroLock™- and in 33.3 % of patients in 4% citrate-group, corresponding to rates of 0.67 and 2.6 episodes of CRBSI per 1000 catheter days, respectively (p= 0.003). Similarly, the rates of catheter dysfunctions were significantly lower in the TauroLock™ regimen (18.7 /1000 catheter days) vs. 4% citrate (44.3/ 1000 catheter days; p= 0.001). As a consequence, patients in the citrate 4% group needed alteplase rescue intervention in a significantly higher rate (38 vs. 3.8/ 1000 catheter days Citrate 4% versus TauroLock™; p= 0.001).

Conclusions: The use of a taurolidine based locking regimen significantly reduced the incidence of catheter-related blood stream infections as well as catheter malfunction in tunneled central venous haemodialysis catheters when compared to 4% citrate.

TH-OR128

Renal Olfactory Receptor 1393 Contributes to Glucose Reabsorption Blythe D. Shepard,[1] Lydie Cheval,[3] Zita Peterlin,[4] Stuart Firestein,[4] Hermann Koepsell,[2] Alain Doucet,[3] Jennifer L. Pluznick.[1] *[1]Johns Hopkins Univ SOM, Baltimore, MD; [2]Univ Wurzburg, Julius-von Sachs-Inst, Wurzburg, Germany; [3]Centre de Recherche des Cordeliers UMRS 872, Paris, France; [4]Columbia Univ, New York, NY.*

Background: Olfactory receptors (ORs) are G protein-coupled receptors that detect odorants in the nose but also have functions beyond odorant detection; we previously determined that ORs (including Olfr1393) are expressed in the kidney.

Methods: Olfr1393 renal localization was determined by RT-PCR on RNA from microdissected renal segments and with overexpressed MDCK cells. We generated whole-animal knockout mice (KO) and measured plasma electrolytes by iStat, blood pressure by tail cuff, GFR by elimination of plasma sinistrin, blood glucose by glucometer and

urinary glucose and creatinine by VetACE Clinical Chemistry System. Sodium-glucose co-transporters (Sglt1 and Sglt2) were examined by western blotting and confocal microscopy of kidney cryosections.

Results: Olfr1393 is expressed in the renal proximal tubule (S1, S2, S3, n=3 mice), and is found on the apical plasma membrane, but not cilia, when expressed in polarized MDCK cells. Olfr1393 KOs are similar to wild-type (WT) with regards to plasma electrolytes, blood pressure and GFR. However, KOs exhibit urinary glucose wasting (1.4x increase in glucose/creatinine vs WT; P = 0.01) despite normal blood glucose (fed and fasted) and insulin levels. KOs also perform better in a glucose tolerance test (area under curve: WT 20.4±1.6 vs KO 16.3±1.1; P = 0.008) implicating a role in renal glucose handling. In support of this, KOs have a 22% decrease in luminal Sglt1, but not Sglt2, in the proximal tubule (confocal) despite similar total renal expression (western blot). Olfr1393 and Sglt1 co-immunoprecipitate when overexpressed. KO of the Sglts has been shown to attenuate diabetes-induced hyperfiltration due to increased distal Na^+ delivery. In preliminary data, the hyperfiltration induced after 16 weeks on high fat diet in WT mice appears to be attenuated in KO (GFR/BW: WT 576ml/min n=4; KO 435ml/min n=9; P=0.09).

Conclusions: These data suggest that Olfr1393 is a regulator of Sglt1 and presents a novel signaling pathway modulating renal glucose reabsorption.

Funding: NIDDK Support, Private Foundation Support

TH-OR129

Analysis of Vasopressin V1a Receptor Distribution and Function in the Mammalian Kidney Torsten Giesecke,[1] Taka-Aki Koshimizu,[2] Katsumasa Kawahara,[3] Sebastian Bachmann,[1] Kerim Mutig.[1] *[1]Charité Universitätsmedizin Berlin, Dept of Anatomy, Berlin, Germany; [2]Jichi Medical Univ, Dept of Molecular Pharmacology, Shimotsuke-shi, Tochigi-ken, Japan; [3]Kitasato Univ School of Medicine, Dept of Physiology, Kitasato, Sagamihara Kanagawa, Japan.*

Background: Apart from its effect on the renal concentrating mechanism, vasopressin (AVP) may affect acid-base regulation through its binding on the V1a receptor (V1aR). Activation of the V1aR appears to stimulate renal proton secretion, but information on this receptor is generally scarce. To extend available data we have analyzed segmental and cellular distribution of V1aR in mouse, rat, and human kidneys and performed functional studies using a V1aR agonist.

Methods: Antibody to V1aR was generated and controlled using V1aR knockout tissues. Its segmantal and cellular distribution along mouse, rat, and human renal tubule was characterized by immunofluorescence and high-resolution immunocytochemistry. Functional studies were performed in AVP-deficient Brattleboro rats using V1aR-specific agonist, AO-4-67.

Results: The V1aR antibody produced basolateral signal in α-type intercalated cells of connecting tubules and collecting ducts across the studied species. In contrast, beta-type intercalated cells showed punctate perinuclear and subapical V1aR signal which was partially colocalized with clathrin and the lysosomal marker, LAMP1. In the mouse kidney, macula densa cells were V1aR-positive as well. Administration of AO-4-67 to Brattleboro rats for 4h resulted in luminal trafficking of V-ATPase in alpha-type intercalated cells, whereas basolateral V-ATPase of luminal pendrin signals of beta-type intercalated cells were not affected by the stimulation.

Conclusions: In summary, the divergent cellular distribution patterns of V1aR in alpha- vs. beta intercalated cells provide morphological support for distinct responsiveness of these cells to the V1aR-agonist. These results corroborate and extend data on the role of AVP in the renal acid-based handling.

TH-OR130

Physiological Study of Urea Transporters Using Mice Lacking All Urea Transporters and Computational Model Baoxue Yang,[1] Tao Jiang,[1] Yingjie Li,[1] Anita T. Layton.[2] *[1]Dept of Pharmacology, Peking Univ, Beijing, China; [2]Dept of Mathematics, Duke Univ, Durham, NC.*

Background: Urea transporters (UT) are a family of transmembrane urea-selective channel proteins expressed in multiple tissues and play an important role in the urine concentrating mechanism of the mammalian kidney. UT inhibitors have been identified to have diuretic activity and may be developed as novel diuretics.

Methods: To determine if functional deficiency of all UTs in all tissues causes physiological abnormality, we established a novel mouse model in which all UTs were knocked out by deleting an 87 kb of DNA fragment containing most parts of *Slc14a1* and *Slc14a2* genes. A computational model was used to simulate the urine concentrating mechanism in wild-type and UT knockout rat.

Results: Western blot analysis and immunofluorescence confirmed the lack of expression of any urea transporter in all-UT-knockout mice. Their daily urine output was nearly 3.5-fold higher, with significantly lower urine osmolality than wild-type mice. All-UT-knockout mice were unable to substantially increase urinary urea concentration and osmolality after water deprivation, acute urea loading or high protein intake. Knocking out all UTs also decreased blood pressure and promoted the maturation of the male reproductive system. The computational model identified the contribution of each UT except for UT-A2, the knockout simulation of which yielded no significant impact on urine concentration and flow rate.

Conclusions: These results indicate that functional deficiency of all UTs may cause urea selective urine concentrating defect with little physiological abnormality in extrarenal organs.

TH-OR131

Src Kinase Inhibition by Dasatinib Induces Aquaporin-2 Membrane Accumulation in Kidney Principal Cells Richard Bouley, Pui Wen Cheung, Dennis Brown. *Medicine/Nephrology, Massachusetts General Hospital, Boston, MA.*

Background: Maintenance of water homeostasis is a vital function of the kidneys. In order to efficiently reabsorb water, the kidneys require a functional vasopressin (VP) signaling pathway to activate aquaporin-2 (AQP2). AQP2 trafficking is a balance between endocytosis and exocytosis, and src kinases are known to play important regulatory roles in membrane protein endocytosis; therefore, we explored the role of dasatinib, a src inhibitor, on AQP2 trafficking, and to investigate its potential role for treatments of water balance diseases.

Methods: We treated LLC-PK1 cells stably expressing AQP2 (LLC-AQP2) and mutant S256A cells with the src inhibitor dasatinib, and used immunocytochemistry to study AQP2 trafficking. We used western blot with specific phospho-antibodies against S256, S261 and S269 to measure phosphorylation. We treated rat kidney slices with dasatinib to follow AQP2 localization *in situ*. The effects of dasatinib treatment on AQP2 vesicle trafficking was also studied using exocytosis and endocytosis assays, actin depolymerization assay and clathrin-transferrin internalization assays to provide mechanistic information on its mode of action.

Results: Dasatinib increased apical membrane AQP2 accumulation in collecting duct principal cells in our *in situ* kidney slice model, and led to an increase in AQP2 membrane accumulation in the LLC-AQP2 cells. Western blots showed that dasatinib did not increase phosphorylation of S256, and this S256-independent effect was confirmed when dasatinib was able to induce AQP2 membrane accumulation in mutant S256A cells. Similar to VP, dasatinib increased exocytosis and decreased endocytosis, and these effects were specific to AQP2 containing cells. In contrast to VP, dasatinib did not activate PKA or MAP kinase, and did not de-phosphorylate S261. To our surprise, however, we observed a dose-dependent increase in S269 phosphorylation upon dasatinib treatment.

Conclusions: Src inhibition by dasatinib induced AQP2 membrane accumulation in a non-canonical fashion. The signaling pathway differs from that induced by VP, and represents a new approach to stimulating VP-independent AQP2 membrane accumulation.

Funding: NIDDK Support, Private Foundation Support

TH-OR132

CaSR and AQP2 Interplay in Pendrin/NCC dKO and the Impact on Water Excretion and Vascular Volume Depletion Marianna Ranieri,[1] Kamyar A. Zahedi,[2] Grazia Tamma,[1] Mariangela Centrone,[1] Manoocher Soleimani,[2] Giovanna Valenti.[1] *[1]Univ of Bari Aldo Moro; [2]Univ of Cincinnati.*

Background: Pendrin/NCC double KO (dKO) mice display significant calcium (and phosphate) wasting and develop severe volume depletion despite increased circulating vasopressin levels. It is known that high concentrations of urinary calcium in the renal collecting duct counteract vasopressin action, consequently impairing the trafficking of the vasopressin-sensitive water channel AQP2. This effect is mediated by the activation of the Calcium Sensing Receptor (CaSR) expressed in the luminal membrane of collecting duct cells. Here we tested the hypothesis that the vasopressin resistance in dKO mice is due to CaSR-mediated impairment of the AQP2 expression/trafficking.

Methods: Ex vivo experiments were performed in kidney slices from pendrin/NCC dKO mice. Modulation of AQP2 phosphorylation was tested using phosphospecific antibodies. The calcimimetic NPS-R568 and the calcilytic NPS2143 were used to activate or inhibit CaSR respectively.

Results: Pendrin/NCC dKO mice exhibit significantly reduced total AQP2 both at mRNA and protein levels. Interestingly, when normalized to total AQP2, dKO mice had significantly higher levels of AQP2-pS261 vis-à-vis WT mice, which paralleled higher levels of phosphorylated p38-MAPK, an enzyme activated by CaSR and known to phosphorylate AQP2 at ser261. Specific inhibition of p38-MAPK partially reversed the increase of AQP2-pS261 in double KO mice. Conversely, upstream inhibition of CaSR with the calcilytic NPS2143 in dKO mice resulted in 100% increase in basal levels of AQP2-pS256, suggesting that in addition to the up-regulation of AQP2-p261, CaSR mediates the downregulation of AQP2-pS256. Finally, preliminary data indicate that dKO mice have significantly higher AQP2-targeting miRNA-137, which is suggested to downregulate AQP2.

Conclusions: Together, these results point to a critical role of CaSR in impairing both AQP2 abundance, possibly through miRNA-137, and short-term vasopressin response by reducing AQP2 phosphorylation at S256 and increasing AQP2 phosphorylation at S261, contributing to water excretion and vascular volume depletion observed in Pendrin/NCC dKO mice.

Funding: Government Support - Non-U.S.

TH-OR133

Tamoxifen Restores Renal Fibrosis and Attenuates Reduced AQP2 and AQP3 Regulation in Response to Unilateral Ureteral Obstruction in Rats Stine Julie Tingskov Pedersen, Rikke Norregaard. *Dept of Clinical Medicine, Aarhus Univ, Aarhus N, Denmark.*

Background: Renal fibrosis is the final common pathway in chronic kidney diseases and is the most consistent predictor of irreversible loss of renal function. Previous studies have demonstrated that fibrosis reduces the amount of aquaporin (AQP)-2 and AQP3. Tamoxifen binds to estrogen receptor (ER) and has been used as an anti-estrogen for the prevention and treatment of breast cancer. In this study, we investigated the effect of tamoxifen on unilateral ureteral obstruction (UUO)-induced fibrosis and its regulation of AQPs.

Methods: Fibrosis was induced by 7 days UUO in rats. Tamoxifen (50 mg/kg) was given by oral gavage for 5 days before induction of renal fibrosis. Tamoxifen (TAM) treatment was continued for 7 days after UUO operation. Clearance experiments were performed and histologic changes were examined by HE stain and Masson's trichrome stain. Expression of α-smooth muscle actin, fibronectin, AQP2 and AQP3 were evaluated by immunohistochemistry and western blot analysis.

Results: Renal fibrosis was increased after UUO. TAM treatment significantly reduced fibrosis and fibroblast activation as well as increased the anti-fibrotic bone morphogenetic protein 7 (BMP7) in rats subjected to UUO. Furthermore, TAM decreased cross-sectional and gross-morphology changes in the obstructed kidney. In the UUO kidneys, AQP2, phosphorylated Ser256-AQP2 and AQP3 protein expression was reduced and TAM administration attenuated downregulation of the AQPs although no changed was observed in expression of the vasopressin V2 receptor. In addition, the expression of ERα, ERβ and GPER was not affected by TAM treatment in UUO rats. Urine samples collected from the pelvis of the obstructed kidney treated with TAM exhibited a higher urine osmolality compared to non-treated UUO kidneys. Plasma osmolality was not affected.

Conclusions: These findings indicate that TAM has beneficial effects on UUO-induced fibrosis and might have therapeutic potential in the management of obstruction-associated dysregulation of fluid metabolisms.

Funding: Private Foundation Support

TH-OR134

Metformin Improves Urine Concentration Ability in Rodent Models of Nephrogenic Diabetes Insipidus Orhan Efe,[1] Janet D. Klein,[1,2] Jeff M. Sands.[1,2] *[1]Dept of Medicine, Renal Div, Emory Univ; [2]Dept of Physiology, Emory Univ, Atlanta, GA.*

Background: Urine concentration is regulated by vasopressin. Congenital nephrogenic diabetes insipidus (NDI) is characterized by excessive polyuria and caused by vasopressin V2 receptor (V2R) mutations. Present treatment options are limited. We studied AMPK as an alternate pathway to stimulate transporters involved in urine concentration.

Methods: Tolvaptan (10 mg/kg/day) was given by oral gavage to rats for 4 or 10 days, +/- metformin (800 mg/kg/day). Tolvaptan (selective V2R antagonist) was used to produce a rat model of NDI. Metformin was used to stimulate AMPK. Urine volume and osmolality were measured daily. Kidneys were dissected into inner medullary (IM) tip, base, and outer medulla, and UT-A1, AQP2, pAQP2 and NKCC2 were analyzed by Western blot. Immunohistology was used to localize the same transporters. Tamoxifen-induced V2R knock-out mice (gift from Dr. Wess, NIH) were given metformin (600 mg/kg) or vehicle twice daily. Hourly and daily urine osmolalities were determined and transporter proteins analyzed.

Results: Metformin reduced urine volume in tolvaptan-treated rats by 110% in 3 days and the effect was stable for 10 days. Correspondingly, urine osmolality in tolvaptan-treated rats was restored to near control levels by metformin (mean: 1303±126 mOsM (-met) vs 2335±273 mOsM (+met), p<0.05). Metformin increased protein abundance of IM tip UT-A1 61% and AQP2 44% (p<0.05) in tolvaptan-treated rats but not in control rats. Outer medullary NKCC2 abundance was markedly increased (117%) with metformin in control rats (p=0.004) but not in V2R-blocked rats. Immunohistochemistry showed increased membrane accumulation of AQP2 and pSer256-AQP2 with acute (1 hr) and chronic (4 days) AMPK stimulation, both in control and V2R-blocked rats. Metformin treatment of V2R knock-out mice increased urine osmolality within 1 hr and was maintained for up to 10 hours. Repeated daily treatment maintained the higher 24-hr urine osmolality. Metformin increased AQP2 in the V2R knock-out mice similar to the tolvaptan-treated rats.

Conclusions: AMPK activators, such as metformin, might provide a promising treatment for congenital NDI due to V2R mutations.

Funding: NIDDK Support, Pharmaceutical Company Support - Otsuka Pharmaceuticals

TH-OR135

Genetic Deletion of ADP-Activated P2Y12 Receptor Ameliorates Lithium-Induced NDI in Mice Bellamkonda K. Kishore,[1] Noel G. Carlson,[1] Kenny M. Hansson,[2] Yue Zhang.[1] *[1]Univ of Utah & VA Medical Center, Salt Lake City, UT; [2]Cardiovascular and Metabolic Diseases, Innovative Medicines Biotech Unit, AstraZeneca AB, Mölndal, Sweden.*

Background: Previously we reported that pharmacological blockade of P2Y12 receptor (R) significantly ameliorates Li-induced nephrogenic diabetes insipidus (NDI) in rodent models. To establish that the observed protection is mediated through P2Y12-R, we evaluated the effect of genetic deletion of P2Y12-R on Li-induced NDI.

Methods: Groups (n = 5) of adult wild type (WT) C57/Bl6 and syngeneic P2Y12-R knockout (KO) mice were fed Li-added diet (40 mmol LiCl/kg food) for 12 days with free access to food and water. Cohorts of control mice (n = 4/genotype) were fed regular chow. Twenty-four hour urine samples were collected prior to and at the end of experimental period. Blood and kidney samples were collected at euthanasia.

Results: As expected, Li caused marked increases in water consumption and urine output, and decreases in urine osmolality and AQP2 protein in the kidney medulla of WT mice. These alterations were significantly ameliorated in KO mice (Table; mean ± se).

	Wild Type	P2Y12 KO	P Value
Water Intake*	366 ± 68	140 ± 63	< 0.05
Urine Output*	393 ± 50	182 ± 22	< 0.001
Urine Osmolality*	40 ± 3	60 ± 3	< 0.05
Urine Sodium**	240 ± 26	194 ± 6	< 0.05
Urine Potassium**	511 ± 63	454 ± 19	= 0.183
AQP2 Protein in Medulla†	26 ± 6	57 ± 14	< 0.05
Serum Li (mmol/l)	0.478 ± 0.031	0.462 ± 0.027	= 0.721

*terminal value as percentage of day 0 value in the same group
**terminal value (μmol/24 h/20 g body wt)
†terminal value as percent of values in WT control group

Serum osmolality and sodium levels were within the normal range in both genotypes after feeding Li. As expected, Li feeding resulted in significant increases in urinary AVP and PGE2 excretion, which were not affected by P2Y12-R deletion.

Conclusions: Thus, similar to pharmacological blockade, deletion of P2Y12-R significantly ameliorates Li-induced NDI, without reducing serum Li levels. Hence, targeting P2Y12-R offers a novel and safer method for treating NDI with fewer side effects.

Funding: VA Support

TH-OR136

Soluble (Pro)Renin Receptor Targets Renal V2 Vasopressin Receptor to Enhance Urine Concentrating Capability Fei Wang,[1,2] Nirupama Ramkumar,[2] Kexin Peng,[1,2] Xiaohan Lu,[1,2] Long Zhao,[2] Donald E. Kohan,[2] Tianxin Yang.[1,2] *[1]Inst of Hypertension, Zhongshan School of Medicine, Sun Yat-sen Univ, Guangzhou, Guangdong, China; [2]Dept of Internal Medicine, Univ of Utah and Veterans Affairs Medical Center, Salt Lake City, UT.*

Background: We recently discovered that soluble (pro)renin receptor (sPRR) derived from collecting duct intercalated cells acts in a paracrine fashion to regulate water transport in the principal cells. The present study attempted to define the role of sPRR in vasopressin (AVP) signaling with emphasis on V2R regulation.

Methods: Primary rat IMCD cells were used to assess the direct effect of a recombinant sPRR-His on V2R expression. The sPRR-His was infused to mice with CD-specific deletion (CD PRR KO) and nephron-specific deletion (Neph PRR KO) of PRR.

Results: In primary rat IMCD cells, sPRR-His at 10 nM induced a 2.8 –fold increase in V2R protein and a 2-fold increase in V2R mRNA. Following AVP treatment, V2R protein was increased by 3-fold, which was blunted by a PRR antagonist and a PRR neutralizing antibody. CD PRR KO mice developed a medium level of diabetes insipidus {urine volume (UV): KO: 2.2±0.4 versus Floxed: 1.2±0.3ml/d; $P<0.05$}, accompanied with a 60% reduction of renal V2R protein and a 25% reduction of urinary sPRR excretion. Administration of sPRR-His for 3 d almost completely rescued the polyuria phenotype (UV: KO+sPRR-His:1.6±0.3 vs. KO: 2.4±0.5 ml/d, $p<0.05$) associated with restoration of renal V2R and AQP2 expression. Interestingly, Neph PRR KO mice exhibited more robust polyuria (UV:KO:7.3±1.1 vs. Floxed: 1.2±0.5 ml/d, $p<0.01$) associated with suppressed renal expression of AQP2, NKCC2, and V2R. Administration of sPRR-His to Neph PRR KO mice partially attenuated polyuria (UV:KO+sPRR-His:4.1±1.2 vs. KO: 7.3±1.1 ml/d, $p<0.01$) accompanied by restored expression of V2R and AQP2. In contrast, the downregulation of NKCC2 expression in the null mice was unaffected by sPRR-His nor was the upregulation of autophagosome marker microtubule-associated protein 1A/1B-light chain 3 (LC3b).

Conclusions: The sPRR selectively targets the CD to determine V2R expression and hence AVP sensitivity and urine concentrating capability, independently of autophagosome accumulation.

Funding: NIDDK Support, VA Support

TH-OR137

Medullary Class I HDACs Are Critical for Fluid-Electrolyte Balance and Blood Pressure Control during High Salt Feeding Kelly A. Hyndman, Joshua S. Speed, Courtney M. Dugas, Andrew Abad, Chunhua Jin, David M. Pollock, Jennifer S. Pollock. *Medicine-Nephrology, Univ of Alabama at Birmingham, Birmingham, AL.*

Background: Histone deacetylase enzymes play a critical role in the regulation of transcription through epigenetic modification of chromatin structure. Consequently, deranged HDAC activity is causally linked to cancer, where three HDAC inhibitors (HDACi) are approved cancer treatments. Additional evidence suggests that HDACi may be beneficial in preventing inflammation in cardiovascular disease. However, the reported adverse events of HDACi use include hypertension, hyponatremia, and hypokalemia suggesting fluid-electrolyte disturbances. Thus we hypothesized that renal medullary class I HDACs are critical for homeostatic regulation of fluid-electrolyte balance and blood pressure control.

Methods: The class I HDACi, MS275, or vehicle was chronically infused into the medullary interstitium of the male rat kidney during high salt diet diet (HSD, 4% NaCl).

Results: Class I HDACs are expressed in the human and rat kidney, and inner medullary (IM) HDAC1 is significantly increased 4-fold with HSD in normotensive rats. During HSD, renal medullary HDACi resulted in a significant 15 ± 2.0 mmHg increase in mean arterial pressure. Furthermore, HDACi resulted in polydipsia, polyuria, a significant 50% reduction in IM aquaporin-2 expression and decreased plasma potassium (control = 4.4 ± 0.1 mM, MS275 treated = 3.5 ± 0.1 mM, $P < 0.05$). Furthermore, HDACi resulted in increased vasopressin and renal ET-1 production, and renal nitric oxide deficiency that are consistent with the fluid-electrolyte abnormalities observed in clinical studies with these

drugs. Our findings point to a mechanism whereby HDAC1 promotes nitric oxide synthase expression through regulation of chromatin structure at the *Nos1* and *Nos3* promoters. In agreement, increased HDAC1 expression resulted in a significant increase in IMCD *Nos1* mRNA expression (control = 1.0 ± 0.2 and HDAC1 = 2.5 ± 0.5 A.U) and a 30% increase in *Nos3* mRNA.

Conclusions: Given the promising research of HDACi to treat cardiovascular disease, this study provides insight on the mechanisms of the adverse events, which may be fatal to critically ill patients.

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FR-OR001

Randomized, Placebo Controlled Double Blind Clinical Trial of the Somatostatin Analog Pasireotide LAR for Patients with ADPKD or ADPLD with Severe Liver Involvement

Marie C. Hogan, Tetyana V. Masyuk, Troy G. Ofstie, Carly Banks, Marie E. Edwards, Maria V. Irazabal, Lisa E. Vaughan, Walter K. Kremers, Nicholas F. LaRusso, Vicente E. Torres. *Mayo Clinic, MN.*

Background: We previously reported the somatostatin (SST) receptor analog, octreotide LAR reduced liver volume (LV), improved quality of life in symptomatic polycystic liver disease (PLD) & retarded GFR decline in ADPKD. Here we assessed safety & efficacy of another SST analog, pasireotide (SOM230) in severe PLD & in ADPKD. SOM230 has a broader binding profile & higher affinity to SST receptors with potential for greater efficacy.

Methods: Eligible participants were assigned (2:1 ratio) in a 1 year double blind randomized trial (stratified ADPKD & ADPLD) to receive SOM230 / placebo every 28 days. Primary endpoint (EP) was change in LV; secondary EPs were change in kidney volume (KV) eGFR & QOL.

Results: Forty eight subjects were randomized (ADPKD n=40; ADPLD n=8); of these, 40 completed LV measurements at 12 mo. From baseline, there was a 3.3% decrease in annualized change in LV (4271±2373 to 4104±2265ml) in SOM230 group (n=28), compared with 6.3% increase (4047±1298 to 4294±1314ml) in placebo group (n=12; p=0.001) (fig 1†). KVs decreased -1.1% on SOM230 compared with a 3.9% increase on placebo (p=0.024). Changes in eGFR were not different between groups. Common adverse events (AEs) included hyperglycemia (24/33 (73%) SOM230 vs 3/15 (20%) placebo; p=0.003) & diabetes (10/33 (30%) vs 0/15 (0%); p=0.042). Most AEs were grade 1-2. † Results: mean±std dev. P-values: Wilcoxon.

	SOM230			Placebo			P for Delta %[a,b]
	Baseline	12 mo	Delta %[a,b]	Baseline	12 mo	Delta %[a,b]	
Blood glucose, (mg/dL)	92.3 ± 12.8	124.0 ± 28.0	36.1 ± 28.3	88.7 ± 12.6	89.8 ± 7.0	3.1 ± 16.3	<0.001
Hemoglobin A1C (%)	5.43 ± 0.48	6.31 ± 0.50	16.6 ± 10.1	5.20 ± 0.23	5.27 ± 0.26	1.3 ± 2.2	<0.001
Serum Creatinine (mg/dL)	1.00 ± 0.29	1.00 ± 0.32	4.3 ± 11.9	1.11 ± 0.36	1.10 ± 0.44	4.6 ± 11.5	0.87
eGFR (CKD-EPI)	75.2 ± 21.6	71.8 ± 20.0	-3.6 ± 13.3	72.0 ± 19.4	68.9 ± 19.8	-4.7 ± 11.4	0.69
Liver volume, (mL)	4271 ± 2373	4104 ± 2265	-3.3 ± 7.5	4047 ± 1298	4294 ± 1314	6.3 ± 7.0	0.001
Kidney volume, (mL)	927 ± 591	913 ± 572	-1.1 ± 3.6	671 ± 268	706 ± 299	3.9 ± 4.5	0.024

Conclusions: SOM230 versus placebo treatment significantly decreased the annualized liver & kidney volume & significantly increased the frequency of hyperglycemia & diabetes in patients with PLD and ADPKD. The eGFR declined in both arms, thus larger studies are needed to determine the impact of SSTs analogs on eGFR. **(NCT01670110)**

Funding: Pharmaceutical Company Support - Novartis

FR-OR002

Efficacy and Safety of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease Including Chroninc Kidney Disease G4

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Background: TEMPO3:4 trial showed the effect of tolvaptan (TLV) on total kidney volume (TKV) growth and decline of renal function among ADPKD with creatinine clearance (CCr) more than 30mL/min. However, effectiveness, safety, and optimal dose of TLV were uncertain in those with CCr less than 30mL/min. In addition, there is virtually no data of TLV influence to renal dysfunction on urine volume and osmolality.

Methods: Among ADPKD patients with TLV administration from 2014 to 2016, serum creatinine and estimated glomerular filtration ratio (eGFR) were measured at 1 week, 1, 3, 6 months, and TKV was calculated immediately before and 6 months after TLV treatment. TKV was estimated using ellipsoid approximation. Urine volume at 1 day, 1, 3, 6 months and urine osmolality at 0, 1 day, and each month until 8 months were evaluated.

Results: Chronic kidney disease (CKD) G2, G3 and G4 were 22%, 45% and 33%, respectively. ΔTKV was significantly decreased 6 months after TLV administration (24.8(7.7-56.5) vs -17.8(-37.9-1.9) %/year, P<0.05) while eGFR and serum creatinine was not changed during the same period. Urine volume variation especially observed immediately after TLV administration gradually disappeared. Water intake was significantly increased 6 months after TLV administration compared with the next day (3375(2723-3958) vs 3850(3468-4000) mL, P<0.05), whereas urine volume tended to increase between the same periods (3825(3210-5638) vs 3925(3588-4000) mL, P=0.07). The dose of TLV was larger in responders than non-responders when responders were defined as patients with improvement of TKV or eGFR after TLV administration. The dosage could not be increased because of hepatic dysfunction and polyuria in non-responders. TLV was discontinued in 2 cases with CKD G4, and both of them showed hepatic dysfunction 4-8 months after TLV initiation.

Conclusions: TLV was well tolerated in CKD G4. High dose TLV may mitigate TKV outgrowth.

FR-OR003

Toll-Like Receptors in the Progression of Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary cause of chronic kidney disease. The intriguing role of innate immune system and inflammation become a target for potential therapeutically approach to slow progression. Thus, we aim to investigate the association of Toll-like receptors(*TLRs*) between progression of ADPKD.

Methods: 90 ADPKD patients and ninety matched controls were enrolled this prospective study and were followed during three years. *TLR-2* and *TLR-4* gene polymorphisms and expressions were measured. Hypertension was diagnosed with ambulatory blood pressure monitoring. Rapid progression was defined as sustained decline in estimated glomerular filtration rate (eGFR) of more than 5 ml/min/1.73 m^2/year.

Results: *TLR-4Asp299Gly* polymorphisms were significantly different between patient and control group (p<0.05).Also,*TLR-2* and *TLR-4* geneexpressions were significantly different between the ADPKD patients and the control subjects (p<0.05). The expression levels of both *TLR-2* and *TLR-4* were found to be higher in the rapid progression groups comparing the slow progression group (p<0.05). *TLR-2* gene expression, hypertension and uric acid were found to be independent risk factors in identifying rapid progression in ADPKD patients.

Conclusions: *TLR-2* and *TLR-4* gene expressions are associated with rapid progression in ADPKD patients.*TLRs* may play a role in the progression of ADPKD.

FR-OR004

Copeptin, a Surrogate for Vasopressin, Predicts Disease Progression and Tolvaptan Treatment Efficacy in ADPKD. Results of the TEMPO 3:4 Trial

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Background: The TEMPO 3:4 Trial showed that 3 years treatment with tolvaptan, a vasopressin V2 receptor antagonist, slowed the increase in total kidney volume (TKV) and eGFR decline in ADPKD. We investigated determinants of baseline copeptin concentration, surrogate marker for vasopressin, to ascertain whether copeptin is associated with rate of ADPKD progression and whether treatment induced change in copeptin is associated with treatment efficacy.

Methods: Post-hoc analysis of prospective, blinded RCT including 1445 patients with ADPKD, aged 18-50, estimated creatinine clearance ≥60 ml/min and TKV ≥750 mL. Copeptin was measured by an automated immunofluorescence assay.

Results: Median baseline copeptin concentration was 6.4 (IQR 3.8-11.0) pmol/L. Baseline copeptin concentration was in a multivariate analysis associated with age, gender, BMI, plasma osmolality, eGFR and TKV (all p<0.001). In placebo treated patients baseline copeptin predicted TKV growth during 3 year of follow-up (p<0.0001). This remained significant after adjustment for sex, age and baseline eGFR. No significant association was found between baseline copeptin and eGFR change during follow-up. In subjects with higher baseline copeptin, a larger treatment effect of tolvaptan was noted with respect to TKV growth rate (p=0.008) and to some extent for eGFR decline (p=0.07). Tolvaptan induced an increase in copeptin (baseline 6.5 vs 19.6 pmol/L at yr 1,p<0.0001), whereas no change in copeptin was noted on placebo (baseline 6.5 vs 6.0 pmol/L at yr 1,p=0.15). The percent increase in copeptin from baseline to yr 1 was positively associated with tolvaptan treatment effect on TKV growth rate (p=0.02), but not on slope of eGFR decline (p=0.31).

Conclusions: In ADPKD patients higher baseline copeptin is associated with more rapid TKV growth, and with better tolvaptan treatment efficacy on TKV growth. In addition, tolvaptan induced change in copeptin predicted better treatment effect on TKV growth.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceuticals

FR-OR005

A New Clinical Entity: GANAB-Related Polycystic Kidney and Liver Disease Emilie Cornec-Le Gall,[1] Vladimir Gainullin,[1] Binu Porath,[1] Yannick Le Meur,[2] Marie-Pierre Audrezet,[2] Peter C. Harris,[1] Claude Ferec.[2] *[1]Mayo Clinic; [2]CHU Brest, France.*

Background: Genic variability in ADPKD/ADPLD has recently been refined with the description of a new gene, *GANAB*, encoding the α subunit of the glucosidase II; mutations impair polycystin trafficking (Porath et al, AJHG 2016). The aim of this study is to characterize the disease presentation in GANAB patients.

Methods: Molecular analysis of GANAB was conducted in 50 unresolved ADPKD/ADPLD unrelated patients. Clinical records and imaging data of recently reported and newly identified patients were reviewed.

Results: *GANAB* mutations were found in 2 new pedigrees.In the first (splice variant c.39-1G>C), a 75 y man was incidentally diagnosed with ADPKD at age 61 by a CT scan and had atrophic cystic kidneys (7.5 cm, ~20 cysts) and liver cysts. His two siblings had similar presentations at age 87 and 75 and did not require dialysis. In the second pedigree (frameshift variant c.2723del), a diagnosis of bilateral cystic kidneys was made in a 7 y.o boy following hematuria, and subsequently in his 9 y.o brother and 44 y.o father, who had normal kidney function and liver cysts. While all the 26 described GANAB patients (median age 50y (7-87), 14 males) had kidney cysts, kidney enlargement was only present in 18.5%, and was moderate, caused by a few large cysts. Kidney function was preserved, with 96% being CKD1-2 patients, and the only CKD3 patient (75y) had a partial nephrectomy at age 26. Hypertension was present in 39% of the adult patients. Liver cysts were reported in 81% of the adult patients and severe PLD was observed in 4 patients, clustered in 2 pedigrees, which suggests the existence of modifier genes modulating the severity of liver cystogenesis. Intracranial aneurysms were reported in 2 pedigrees.

Conclusions: In patients with normal-sized cystic kidneys and significant liver cysts, a GANAB diagnosis should be considered. GANAB patients typically present with milder kidney disease than PKD2 and do not seem at risk of CKD. As larger GANAB cohorts become available, better description of the disease penetrance and presentation will be possible. We are currently analyzing 200 other unresolved ADPKD/ADPLD cases.

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

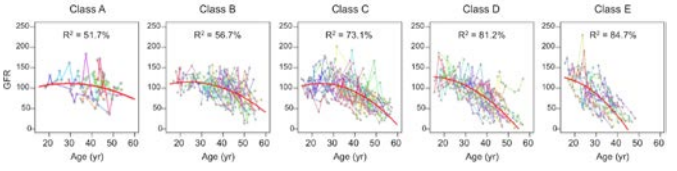
FR-OR006

Trajectory of the GFR in Autosomal Dominant Polycystic Kidney Disease Alan S.L. Yu,[1] Chengli Shen,[2] Doug Landsittel,[2] Jared J. Grantham,[1] Larry Cook,[1] Vicente E. Torres,[3] Arlene B. Chapman,[4] Kyongtae Ty Bae,[2] Michal Mrug,[6] Peter C. Harris,[3] Frederic F. Rahbari-Oskoui,[5] Michael F. Flessner,[7] William M. Bennett.[8] *[1]U Kansas; [2]U Pittsburgh; [3]Mayo Clinic; [4]U Chicago; [5]Emory Univ; [6]U Alabama; [7]NIH; [8]Legacy Good Samaritan Med Ctr.*

Background: In autosomal dominant polycystic kidney disease (ADPKD), cyst growth and kidney injury occur throughout life, leading to ESRD. The shape of the GFR trajectory over this period spanning several decades is not well defined, and the factors that influence this are unclear.

Methods: CRISP is a 13 yr observational study of 241 ADPKD pts. To predict trajectories of renal decline, a novel classification of kidney growth rates, based on age and height-adjusted total kidney volume (Irazabal, et al., 2014), was used to stratify participants into 5 classes. Within each group, a quadratic polynomial function was fit to the individual GFR trajectories using linear mixed models with a subject random effect and fixed effects for age and other covariates. Conditional R^2 is the variance explained by fixed and random factors.

Results: Irazabal classes effectively separated the cohort into individuals with similar trajectories. The overall curvilinear trend included a period of relatively stable GFR followed by accelerating decline. Increasing class (from A to E) was associated with earlier and steeper decline.



Increasing class was also associated with increased proportion of *PKD1* genotype and higher baseline urine sodium and osmolality. However, stratification effectively captured the related variability, as none of these covariates was independently associated with GFR.

Conclusions: Rate of kidney growth, as assessed by Irazabal class, is a powerful predictor of the shape and slope of the GFR trajectory. Results of the stratified polynomial linear mixed models have significant implications for predicting which individuals will more rapidly decline and where interventions should be focused.

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FR-OR007

Foam Sclerotherapy for Cystic Volume Reduction in Autosomal Dominant Polycystic Kidney Disease Ioan-Andrei Iliuta, Beili Shi, Silvio Giancarlo Bruni, John Conklin, Moumita Barua, Korosh Khalili, Eran Shlomovitz, York P. Pei. *Toronto General Hospital, Univ Health Network, Toronto, ON, Canada.*

Background: Kidney volume (KV) in autosomal dominant polycystic kidney disease (ADPKD) expands exponentially during adult life at ~5%/yr on average. Patients with total kidney volume >1,500 ml are at high risk of developing end-stage renal disease. Large cysts may be particularly detrimental by impeding regional kidney blood and urine flow. We examined the safety and effectiveness of foam sclerotherapy (FS) on KV reduction.

Methods: Thirty-one patients with typical or atypical ADPKD were treated with 3% sodium tetradecyl sulfate FS targeting 2 to 3 large (>5 cm) non-exophytic cysts in one or both kidneys between August 2014 and April 2016. Serum creatinine (sCr), measured 24 hour Cr clearance (Ccr), and KV were assessed before and after each intervention.

Results: The mean age and baseline sCr of our typical (n=27) and atypical (n=4) PKD patients were 51 vs. 63 years and 0.94 [95% CI:0.81-1.58] vs. 0.93 [0.75-1.43] mg/dL, respectively. Over a mean time of 12.5 months, the volume of kidneys targeted by FS decreased by 375 ml (-24%; p<0.0001) while the volume of non-targeted kidneys increased by 88 mL (15%; p=0.003).

	n	Pre	Post	Difference	Percentage change	p
Volume of targeted kidneys (mL)	31	1530	1155	-375	-24	<0.0001
Typical	26	1637	1293	-344	-19	0.0001
Atypical	5	973	437	-536	-48	
Volume of non-targeted kidneys (mL)	11	602	690	88	15	0.003
Typical	8	657	767	110	19	0.02
Atypical	3	457	484	27	6	
Measured CrCl (mL/min)	17	81.1 ±27.7	81.0 ±28.4	-0.1		0.96

Measured Ccr corrected for urinary Cr excretion rate was unchanged within 1 month after sclerotherapy. There were no significant complications (i.e. hypotension, bleeding, infection) other than self-limiting acute pain lasting for 2-5 days requiring analgesic treatment in ~10% of patients.

Conclusions: Foam sclerotherapy is well-tolerated in ADPKD and results in a significant kidney volume reduction. Further studies are required to examine whether this procedure can be used to improve kidney blood flow and delay kidney function decline.

Funding: Government Support - Non-U.S.

FR-OR008

Increased Risk of Kidney Cancer in Patients with Polycystic Kidney Disease: A Propensity Score Matching Analysis of a Nationwide, Population-Based Cohort Study Tung-Min Yu,[1] Kuo-Hsiung Shu,[1] Mei-Ching Yu,[2] Ya-Wen Chuang.[1] *[1]Div of Nephrology, Taichung Veterans General Hospital, Taichung, Taiwan; [2]Pediatric Nephrology, Chang-Gung Hospital, Taoyuan, Taiwan.*

Background: Data regarding the risk of kidney cancer and cancer at other sites in patients with polycystic kidney disease (PKD) are lacking. Therefore, we conducted a nationwide cohort study to determine the risk of cancer in patients with PKD.

Methods: From the National Health Insurance Research Database (NHIRD), we included 7080 patients aged >20 years and diagnosed with PKD between 1998 and 2010 in the PKD cohort. For each patient with PKD, one patient aged >20 years who was neither PKD nor cancer was randomly selected from the NHIRD, matched on the basis of the propensity score, and included as control group. The follow-up period was from the time of the initial PKD diagnosis until the date of the cancer diagnosis, censoring, or December 31, 2011. We used Cox proportional hazard regression models to analyze the risk of cancer.

Results: The overall incidence of cancer was significantly higher in the PKD cohort than in the non-PKD cohort [17.6 vs. 11.4 per 1000 person-years; crude hazard ratio (HR) = 1.82; 95% confidence interval (CI) = 1.61–2.06]. After adjustment for comorbidities including hypertension, chronic obstructive pulmonary disease, diabetes, alcoholism, alcoholic liver damage, and obesity, the patients with PKD had a higher overall risk of cancer [adjusted HR (aHR) = 1.74; 95% CI = 1.54–1.96]. The risk of kidney cancer was significantly higher in the PKD cohort than in the non-PKD cohort (aHR = 5.00; 95% CI = 2.86–8.75). After considering death as a competing risk factor, the risk of kidney cancer remained significantly higher in patients with PKD [adjustedsubhazard ratio (aSHR) = 3.69; 95% CI = 2.41–5.67]. Of note, a significantly higher risk of kidney cancer was observed in younger patients with PKD (<49 year old; aSHR = 4.70; 95% CI = 1.78–12.4).

Conclusions: This study is the first to report the association of PKD with a higher risk of cancer, particularly kidney cancer. When treating patients with PKD, a high index of suspicion for cancer should be maintained.

Funding: NIDDK Support

FR-OR009

Urinary Proteomic Analysis Revealed New Specific Medullary Sponge Kidney Disease (MSK)-Associated Proteins Gianluigi Zaza,[1] Antonia Fabris,[1] Maurizio Bruschi,[2] Giovanni Candiano,[2] Simona Granata,[1] Giovanni Gambaro,[3] Antonio Lupo.[1] *[1]Renal Unit, Univ of Verona, Verona, Italy; [2]Laboratory of Physiopathology of Uremia, Gaslini Inst, Genoa, Italy; [3]Renal Unit, Columbus-Gemelli Hospital/Univ, Verona, Italy.*

Background: MSK is a kidney malformation featuring nephrocalcinosis, recurrent renal stones, renal acidification and ectasias of pre-calyceal ducts. It generally occurs sporadically, but an autosomal dominant inheritance have been reported. Previous studies have suggested a putative point mutations of the *GDNF* gene as a cause of MSK but the precise molecular mechanisms leading to the disease remain poorly understood. Currently, MSK diagnosis is only radiographic and no molecular diagnostic biomarkers are available.

Methods: Therefore, we employed an innovative high-throughput methodology (proteomic analysis) to identify new specific urinary MSK diagnostic biomarkers. Briefly, urines from 21 MSK patients and 21 controls with idiopathic calcium nephrolithiasis (ICN) were collected and processed for proteomic analysis and ELISA. The urine of 11 MSK and 10 controls, randomly selected, were processed/analyzed by the mass spectrometer LTQ-Orbitrap Velos Pro. Subsequently, several statistical algorithms and bioinformatic analysis were undertaken to select most discriminative proteins between the 2 study groups. ELISA, performed on the entire patients' cohort, was used to validate proteomic results.

Results: After an initial statistical analysis, 249 (16%) and 396 proteins (26%) resulted exclusive for MSK and ICN (FC<2, p<0.001), respectively. Subsequently, several statistical algorithms and graphic representations (including Volcano Plot and ROC curve) restricted the number of proteins to 22 up- and 15 down-regulated in MSK compared to ICN. The use of a Support Vector Machine restricted the selection to 16 top ranked proteins (primarily involved in matrix remodeling and bone differentiation) hyper-expressed in urines of MSK (e.g., Glypican, Plexin). These biological elements were validated by ELISA.

Conclusions: Therefore, our study, for the first time, using a proteomic methodology was able to identify new diagnostic MSK urine biomarkers possibly employable in future in the "day by day" clinical practice.

FR-OR010

Recessive Mutations of TTC28 Cause a Ciliopathy Ankana Daga,[1] Joao Goncalves,[2] Kinga Maria Bujakowska,[3] Daniela A. Braun,[1] Jillian Kateri Warejko,[1] Laurence Pelletier,[2] Friedhelm Hildebrandt.[1] *[1]Div of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston, MA; [2]Lunenfeld-Tanenbaum Research Inst, Mount Sinai Hospital, Toronto, Canada; [3]Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA.*

Background: Retinal-renal ciliopathies are characterized by dysfunction of the primary cilium and centrosomes. More than 95 genes have been discovered in these single gene-disorders; however, about 30% of cases do not have a monogenic cause identified.

Methods: To identify novel ciliopathy genes, we analyzed whole exome sequencing (WES) data in individuals with ciliopathies who had no mutations in all known ciliopathy genes. We examined the cellular localization of *TTC28* using confocal immunofluorescence analysis in HEK293 and RPE-1 cells and performed co-immunoprecipitation to test the interactions with other known ciliopathy genes. We tested defects in ciliogenesis by using siRNA directed against *TTC28* in RPE-1 cells.

Results: By WES we identified 4 different mutations in exon 7 of the *TTC28* gene in 4 unrelated families with a brain-skeletal-retinal phenotype. The first patient presented with microcephaly and seizures. A homozygous missense mutation in an amino acid residue that is evolutionarily conserved to *Drosophila melanogaster* was discovered. The second patient with severe skeletal dysplasia and intellectual disability has a homozygous missense mutation in an amino acid residue that is evolutionarily conserved to *Caenorhabditis elegans*. The third and the fourth patients both with retinitis pigmentosa have two different, rare and well-conserved compound heterozygous mutations. We show that wild type GFP-*TTC28* localizes to the centrosome. By co-immunoprecipitation, we show that wild type *TTC28* interacts with *NIN*, mutated in Seckel syndrome and *CEP120*, mutated in Jeune asphyxiating thoracic dystrophy. SiRNAs directed against *TTC28* in RPE-1 cells show reduction in number of ciliated cells.

Conclusions: We identify mutations of *TTC28* as a novel monogenic cause of ciliopathy in humans. Further studies will elucidate allele specific expression and pathogenic pathways involved.

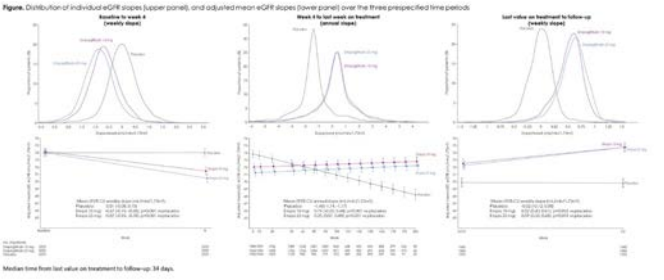
FR-OR011

Empagliflozin and Changes in Renal Function Decline in Type 2 Diabetes: Prespecified Slope Analyses from the EMPA-REG OUTCOME Trial Christoph Wanner,[1] Bernard Zinman,[2] Silvio E. Inzucchi,[3] John M. Lachin,[4] Maximilian von Eynatten,[5] Audrey Koitka-Weber,[5] Michaela Mattheus,[5] Erich Bluhmki,[5] Hans-Juergen Woerle,[5] Uli Christian Broedl,[5] Per-Henrik Groop,[6] Hiddo Jan Lambers Heerspink.[7] *[1]Dept of Medicine, Würzburg Univ Clinic, Würzburg, Germany; [2]Lunenfeld-Tanenbaum Research Inst, Mount Sinai Hospital, Toronto, Canada; [3]Section of Endocrinology, Yale Univ, New Haven, CT; [4]Biostatistics Center, George Washington Univ, Rockville, MD; [5]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; [6]Div of Nephrology, Helsinki Univ Central Hospital, Helsinki, Finland; [7]Dept of Clinical Pharmacy and Pharmacology, Univ of Groningen, Groningen, Netherlands.*

Background: CKD and progressive decline of renal function are common in patients with diabetes. In the EMPA-REG OUTCOME trial, empagliflozin (EMPA) slowed CKD progression in patients with type 2 diabetes and high cardiovascular risk. Here we report treatment differences in the rate of change in eGFR by utilizing linear regression models yielding mean and individual slopes.

Methods: 7020 patients were randomized (1:1:1) to EMPA 10 mg, 25 mg or placebo on top of standard of care. Treatment differences in the average rate of change in eGFR (MDRD) for pre-specified time periods were assessed using a random intercept and time coefficient model.

Results: Mean slopes with EMPA showed an acute fall in eGFR during the first 4 weeks, followed by stable eGFR during chronic treatment and a rapid return towards baseline after drug cessation (Figure [lower panel]). Individual slopes revealed a uniform shift with EMPA compared to placebo during all three periods (Figure [upper panel]).



Conclusions: EMPA exerted a uniform treatment effect on eGFR across the entire distribution of renal function. Therefore, our findings suggest that EMPA has the potential to slow rate of GFR decline independent of the individual renal function trajectory.

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

FR-OR012

Glycogen Synthase Kinase 3β Overexpression and Hyperactivity in Urinary Exfoliated Cells Predicts Progression of Diabetic Nephropathy Xianhui Liang,[1,2] Pei Wang,[1] Minglei Lu,[1] Yan Ge,[1] Zhangsuo Liu,[2] Rujun Gong.[1] *[1]Nephrology, Brown Univ; [2]The First Affiliated Hospital of Zhengzhou Univ, China.*

Background: Glycogen synthase kinase (GSK) 3β is a highly-conserved serine/threonine protein kinase that was originally identified as a key cellular signaling transducer involved in glycogenesis. Converging evidence recently points GSK3β as a key player in pathogenesis of diverse kidney diseases. However, its role in diabetic nephropathy (DN) remains unknown and was examined here.

Methods: The expression and activity of GSK3β were evaluated in kidney specimens from DN patients or db/db diabetic mouse models, and assessed in urinary exfoliated cells in patients with type 2 diabetes.

Results: In db/db mice, renal expression and activity of GSK3β were progressively elevated over time, in parallel with deterioration of signs of diabetic kidney injuries, characterized by albuminuria, extracellular matrix accumulation in glomerulus, podocytopathy and renal interstitial fibrosis. In consistency, in cultured kidney cells, including podocytes, mesangial cells and tubular epithelial cells, high glucose exposure markedly amplified GSK3β expression and activity, associated with cytopathic changes. In kidney biopsy specimens procured from patients with varying stages of DN, GSK3β expression and activity were progressively augmented in glomeruli and renal tubules, and correlated with the severity of DN, as assessed by albuminuria and glomerular pathology. In a cohort of patients with type 2 diabetes that were followed for 5 years, elevated expression of GSK3β in urinary exfoliated cells was found to precede the progression of proteinuria in patients diagnosed with diabetic nephropathy. In contrast, urinary GSK3β levels remained normal in diabetic patients with no normoalbuminuria or stable microalbuminuria. Moreover, receiver operating characteristic curve analysis revealed that urinary GSK3β was likely superior to microalbuminuria in predicting the progression of DN.

Conclusions: In aggregate, our studies demonstrated that renal expression and activity of GSK3β are amplified in animal and human diabetic nephropathy. GSK3β in urinary exfoliated cells may serve as a novel biomarker for predicting progression of DN.

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

FR-OR013

BP Levels Lower Than 120/70 mm Hg Associate with Lower Risk of Renal Events in Type I Diabetes Elaine Ku,[1] Charles E. McCulloch,[1] Michael Mauer,[2] Barbara A. Grimes,[1] Chi-Yuan Hsu.[1] *[1]UCSF; [2]Univ of Minnesota.*

Background: Optimal BP targets in diabetes continue to be debated. We compared different BP levels and their associations with adverse renal outcomes in type I diabetes (T1DM), and determined whether glycemic control modifies this association.

Methods: We included 1441 participants with T1DM ages 13-39 initially randomized to intensive vs. conventional glycemic control in the Diabetes Control and Complications Trial (DCCT) and subsequently followed in Epidemiology of Diabetes Interventions and Complications (EDIC) study. The predictors were time-updated systolic (SBP) and diastolic blood pressure (DBP) categories, ascertained one year before outcomes of interest, which included macroalbuminuria,CKD stage III,and ESRD.

Results: During median follow-up of 24 years, 84 cases of CKD stage III, 169 cases of macroalbuminuria, and 26 cases of ESRD occurred. In adjusted Cox models, there was a stepwise graded association between higher BP and risk of macroalbuminuria and CKD stage III.

	Risk of Macroalbuminuria Hazard ratio (95% CI)	**Risk of CKD** Hazard ratio (95% CI)
SBP category		
≥ 140 mm Hg	**2.64 (1.62-4.29)**	**2.61 (1.44-4.71)**
130-<140 mm Hg	Reference (Ref)	Ref
120-<130 mm Hg	0.65 (0.41-1.02)	0.91 (0.49-1.71)
< 120 mm Hg	**0.46 (0.29-0.73)**	**0.23 (0.10-0.53)**
DBP category		
≥ 90 mm Hg	**1.66 (1.00-2.73)**	**3.18 (1.72-5.87)**
80-<90 mm Hg	Ref	Ref
70-<80 mm Hg	**0.55 (0.38-0.79)**	0.84 (0.49-1.44)
< 70 mm Hg	**0.56 (0.35-0.90)**	**0.40 (0.19-0.85)**

Every 10 mm Hg increase in SBP and DBP also associated with 1.73 (95% CI 1.42-2.11) and 1.67 times (95% CI 1.14-2.45) higher risk of ESRD, respectively. No interaction was noted between BP and glycemic control strategy (HbA1C <6% vs. conventional therapy) during DCCT (p> 0.10). Similar results were observed when analysis was limited to participants receiving BP medications.

Conclusions: Lower BP (<120/70 mm Hg) was associated with a substantially lower risk of adverse renal outcomes, regardless of prior assigned glycemic control strategy. These findings suggest that current guideline-recommended target of 140/90 mm Hg for T1DM may be too high for optimal reno-protection.

FR-OR014

Intensified Multifactorial Intervention in Type 2 Diabetes and Microalbuminuria Reduces End Stage Renal Disease and Mortality: 21 Years Follow-Up of the Steno-2 Study Jens Christian Øllgaard,[1,2,3] Peter Gaede,[1,2] Peter Rossing,[3,4,5] Hans-Henrik Parving.[5,7] *[1]Slagelse Hospital, Slagelse, Denmark; [2]Univ of Southern Denmark, Odense, Denmark; [3]Steno Diabetes Center, Gentofte, Denmark; [4]Univ of Aarhus, Aarhus, Denmark; [5]Univ of Copenhagen, Copenhagen, Denmark; [6]Novo Nordisk Foundation Center for Basic Metabolic Research, Univ of Copenhagen, Copenhagen, Denmark; [7]Rigshospitalet, Copenhagen, Denmark.*

Background: Despite declining rates of late diabetic complications in other organ systems, renal complication rates do not decline to the same extent according to epidemiological studies. We report renal outcomes over 21 years in patients with type 2 diabetes and microalbuminuria and the influence of intensified, multifactorial treatment including strict control of blood glucose, lipids and blood pressure.

Methods: 160 patients with type 2 diabetes and microalbuminuria assigned to conventional or intensified multifactorial intervention targeting multiple risk factors in a prospective, open-label trial. The treatment regimen was target-driven and included behavioral and pharmacological modifications. Duration of the intervention was 8 years, where after all patients were recommended intensified treatment. Total follow-up of up to 21 years of albuminuria and GFR (^{51}Cr-EDTA-clearance) assessed at 6 study visits. Outcome measures were progression to macroalbuminuria (>300 mg/24h), decline-rate of GFR and progression to ESRD or death.

Results: Progression to macroalbuminuria was reduced in the original intensive-therapy group, HR 0.45 [95% CI 0.28–0.74; p=0.003]. The decline in GFR was 3.1 ml/min/year in the intensive group vs. 4.1 in the conventional group [difference 0.5 – 1.5 ml/min/year; p < 0.001]. Progression to ESRD trended towards a decreased HR with an adjusted (age and sex) HR of 0.36 [95% CI 0.12–1.05; p=0.061] (n 5 vs. 10) in the intensive group. ESRD combined with all-cause or cardiovascular mortality was reduced in the intensive group; adjusted HR 0.53 [95% CI 0.12–0.81; p = 0.003] and 0.35 [95% CI 0.19–0.65; p=0.001], respectively.

Conclusions: Intensified, multifactorial treatment for 8 years in type 2 diabetes patients with microalbuminuria slows long-term progression in nephropathy and reduces the risk of ESRD and mortality.

Funding: Pharmaceutical Company Support - Novo Nordisk A/S

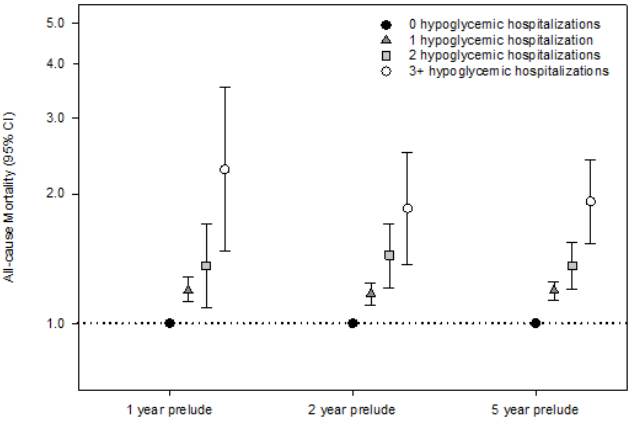
FR-OR015

Hypoglycemia-Related Hospitalizations and Mortality among Non-Dialysis Dependent CKD Patients Transitioning to Dialysis Connie Rhee,[1] Amy Seung You,[1] Melissa Soohoo,[1] Elani Streja,[1] John J. Sim,[2] Danh V. Nguyen,[1] Csaba P. Kovesdy,[3] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Kaiser Perm. Southern CA; [3]Univ of Tennessee Health Science Center.*

Background: Diabetic kidney disease patients with declining kidney function are at heightened risk for hypoglycemia due to impaired insulin degradation and clearance, as well as decreased renal gluconeogenesis. We sought to examine how hypoglycemia in the pre-dialysis (prelude) period impacts post-ESRD mortality in this population.

Methods: Among US veterans with diabetic kidney disease who transitioned to dialysis over 2007-11, we evaluated the occurrence and frequency of hypoglycemia-related hospitalizations during the 2-year pre-ESRD prelude interval. We then examined whether occurrence and frequency of pre-ESRD hypoglycemia-related hospitalizations are associated with post-ESRD all-cause mortality using unadjusted, minimally adjusted, and case-mix adjusted Cox models. We conducted sensitivity analyses examining 1-year and 5-year prelude intervals.

Results: Among 30,321 patients in the 2-year prelude period, occurrence of a hypoglycemia-related hospitalization was associated with higher mortality risk in case-mix analyses (ref: no hypoglycemia): HR (95%CI) 1.21 (1.14-1.28). Increasing frequency of hypoglycemia-related hospitalizations were associated with incrementally higher mortality risk in case-mix analyses (ref: no hypoglycemia): HRs (95%CI) 1.17 (1.10-1.24), 1.44 (1.21-1.70), and 1.85 (1.37-2.49) for 1, 2, and ≥3 hypoglycemia-related hospitalizations, respectively. Similar findings were observed for 1-year and 5-year prelude periods.



Conclusions: In diabetic kidney disease patients transitioning to dialysis, there is a dose-dependent relationship between frequency of pre-ESRD hypoglycemia and post-ESRD mortality. Further studies are needed to determine modifiable risk factors for hypoglycemia, and whether correction of these factors improves survival.

Funding: NIDDK Support

FR-OR016

Angiotensin Receptor Blockers Confer Cardioprotection in Males but Not in Females with Type 2 Diabetes Bauke Schievink, Dick de Zeeuw, Peter G.M. Mol, Michelle Pena, Petra Denig, Hiddo Jan Lambers Heerspink. *Univ Medical Center Groningen.*

Background: Previous studies showed that female patients with type 2 diabetes (T2D) have nearly 50% higher risk of cardiovascular (CV) complications compared to male patients. It is unclear if females also respond differently to therapy compared to males. We assessed gender differences in response to treatment with angiotensin receptor blockers (ARBs), a mainstay of cardiorenal protective therapy in T2D.

Methods: We used data from RENAAL and IDNT trials, which assessed the effect of losartan or irbesartan respectively on renal/CV outcomes in patients with T2D and nephropathy. The CV outcome in both trials was time to first event of a composite of stroke, myocardial infarction, CV death or hospitalization for heart failure. Gender differences in response to ARB treatment were assessed by a gender*treatment interaction term in a Cox model. Hazard ratios (HRs) were adjusted for baseline levels of systolic blood pressure, albuminuria, eGFR, HbA1c, total cholesterol and hemoglobin.

Results: 1737 males and 924 females were followed for a median 2.9 years. During follow-up 872 CV events were recorded. ARB treatment decreased CV risk in males (HR: 0.79, 95% CI: 0.67 - 0.94), but not in females (HR: 1.12, 95% CI: 0.88 - 1.43, p interaction=0.027). This interaction was driven by treatment differences in myocardial infarction (MI) and heart failure (Table 1). Males also had a larger, albeit non-significant, benefit for the renal endpoint of ESRD or doubling serum creatinine compared to females (Table 1).

Conclusions: ARB treatment confers cardioprotection in male but not female T2D patients. These results warrant more careful analysis of gender differences when determining treatment efficacy, as well as investigation of underlying mechanisms of drug response.

HR (95% CI) on ARB treatment			
Endpoint	Males	Females	P for gender interaction
CV composite	0.79 (0.67-0.94)	1.12 (0.88-1.43)	0.027
MI	0.60 (0.42-0.84)	1.42 (0.85-2.38)	0.007
Stroke	0.81 (0.54-1.24)	1.13 (0.64-2.01)	0.34
CV death	1.06 (0.78-1.44)	1.28 (0.83-1.98)	0.56
Heart failure	0.51 (0.38-0.70)	1.02 (0.72-1.44)	0.005
Renal composite	0.66 (0.54-0.81)	0.86 (0.69-1.09)	0.08

FR-OR017

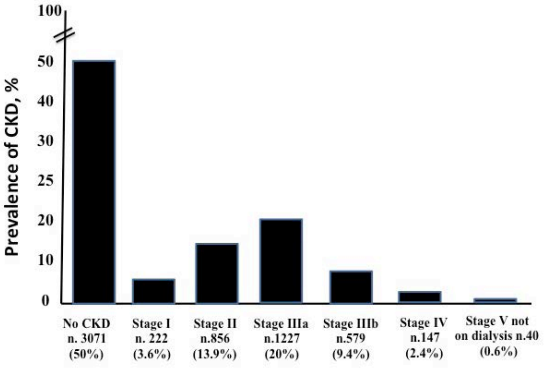
Development of a Service Interface Method (Webservice) between Family Care Physicians (FCPs) Operating in a Primary Care Setting and Nephrologists (NPs), for the Prevention, Diagnosis and Treatment of Kidney Damage in Patients with Type 2 Diabetes Mellitus (T2DM) Stefano Bianchi, Chiara Bilanceri, Elisa Poderelli, Silvia Campatelli, Francesca Nistri, Giada Santini, Roberto Bigazzi. *Nephrology and Dialysis, ASL Nordovest Toscana, Italy.*

Background: Chronic kidney disease (CKD) due to T2DM is a common and costly chronic disease and its complications are a major driver of health care (HC) costs worldlwide. Because of the large prevalence of such patients (pts), second care level of assistance (outpatient clinics and hospitals) is not able to screen and treat appropriately all of them. Information technology can be used effectively to track clinical and laboratory data and generate databases useful to follow these pts.

Methods: With this 3 years project (Italian HC system RF-2011-02346990) we realized a shared cumputerized (WEB connection) clinical chart (SCCC) allowing continuous updating of individual clinical data of pts with T2DM between NPs and FCPs. A SCCC allows an early diagnosis and would improve the treatment of DN and a reduction of cost of medications, diagnostic examinations and hospitalization rate.

Results: In the first year of the study, 106 FCPs have been enrolled, each of them caring for 1,000 pts. Therefore, the population of our study includes 106,000 subjects. We have screened 6,142 pts with T2DM, 2898 females and 3244 males, mean age 71,3±11.1 years. 3,071 out of 6,142 pts (50%) presented DN in different stage of CKD: 222 Stage I (3.6%), 856 Stage II (3.9%), 1227 Stage IIIa (20%), 579 Stage IIIb (9.4%), 147 Stage IV (2.4%) and 40 Stage V (0.6%).

Prevalence of renal damage (Stage of CKD) in 6,142 patients with type II Diabetes enrolled in the Study



Conclusions: A SCCC between NPs and FCPs is a feasible tool to early diagnose DN in pts with T2DM. DN has a high prevalence. 65% of pts with DN shows an advanced CKD stage. Screened T2DM pts with DN are now enrolled in a therapeutic protocol aimed to reduce the renal and cardiovascular complications of this high risk population.

Funding: Government Support - Non-U.S.

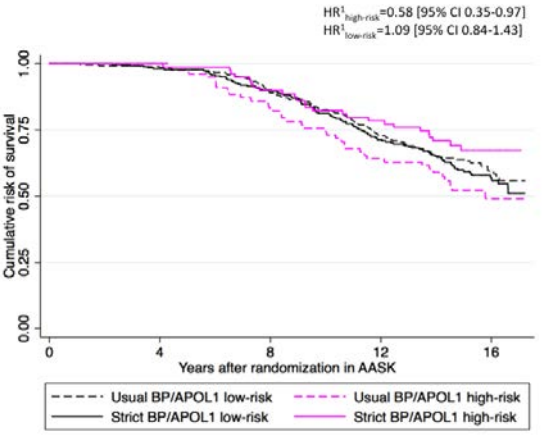
FR-OR018

Intensive Blood Pressure Control Associates with Lower Mortality Risk among Persons with High-Risk APOL1 Genotype Elaine Ku,[1] Michael S. Lipkowitz,[2] Lawrence J. Appel,[2] Afshin Parsa,[3] Jennifer J. Gassman,[2] David V. Glidden,[1] Miroslaw Smogorzewski,[2] Chi-Yuan Hsu.[1] *[1]UCSF; [2]AASK; [3]Univ of Maryland.*

Background: The association between *APOL1* and risk of death in black CKD patients is not well known. We determined whether *APOL1* status modifies the association between strict BP control and long-term mortality risk in former African American Study of Kidney Disease (AASK) trial participants.

Methods: We analyzed 682 AASK trial participants with CKD previously randomized to intensive (mean arterial pressure [MAP] ≤92 mm Hg) versus usual BP control (MAP 102-107 mm Hg) between 1995-2001. We determined risk of death by 1) *APOL1* genotype and 2) prior BP target assignment in analysis stratified by *APOL1* genotype. Deaths were ascertained through 2012 by linkage with the Social Security Death Index and US Renal Data System.

Results: During median follow-up of 14.5 years, risk of death did not differ between individuals with high- versus low-risk *APOL1* genotypes (unadjusted HR= 1.00 [95% CI 0.76-1.33]). However, an interaction was detected between *APOL1* risk group and BP control strategy during AASK trial (p=0.03). In the *APOL1* high-risk group (N=157), risk of death in long-term follow-up was 0.58 times lower comparing intensive versus usual BP control (unadjusted 95% CI 0.35-0.97), but in the *APOL1* low-risk group (N=525), risk of death was not different (unadjusted HR=1.09 [95% CI 0.84-1.43]).



In analysis adjusted for age, sex, baseline GFR, heart disease, smoking, and proteinuria, risk of death remained 0.48 times lower (95% CI 0.28-0.84) comparing intensive versus usual BP arms in the *APOL1* high-risk group, but was not different in the *APOL1* low-risk group (HR=0.98 [95% CI 0.74-1.28]).

Conclusions: Intensive BP control during CKD associates with lower risk of death in blacks with high-risk *APOL1* genotype. Knowledge of *APOL1* status may inform appropriate BP treatment targets in black CKD patients.

Funding: NIDDK Support, Other NIH Support - NHLBI

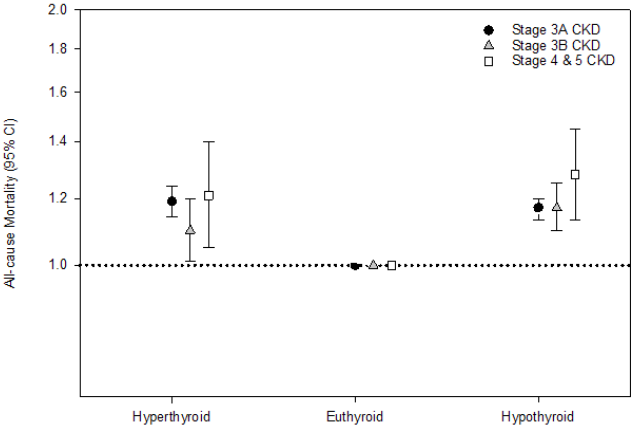
FR-OR019

Thyroid Functional Disease and Mortality in U.S. Veterans with Chronic Kidney Disease Connie Rhee,[1] Kamyar Kalantar-Zadeh,[1] Vanessa A. Ravel,[1] Elani Streja,[1] Steven M. Brunelli,[2] Danh V. Nguyen,[1] Gregory Brent,[3] Csaba P. Kovesdy.[4] *[1]UC Irvine; [2]DaVita Inc; [3]UCLA; [4]Univ of Tennessee Health Science Center.*

Background: Epidemiologic studies show that advanced chronic kidney disease (CKD) patients have a higher prevalence of thyroid dysfunction compared to their non-CKD counterparts. While hyper- and hypothyroidism have been associated with higher mortality in the dialysis population, no studies have examined the relationship between thyroid function defined by serum thyrotropin (TSH) and death risk in non-dialysis dependent chronic kidney disease (NDD-CKD) patients.

Methods: We examined the association of thyroid function with all-cause mortality among US veterans with Stage 3-5 NDD-CKD who underwent ≥1 TSH measure(s) over 2004-12. We examined the association between thyroid status, defined as hyper-, eu-, and hypothyroid (TSH levels <0.5, 0.5-5.0, and >5.0mIU/L, respectively), with all-cause mortality across CKD strata using case-mix adjusted Cox models.

Results: Among 232,524 patients with Stage 3-5 CKD, 4% (n=8154), 90% (n=209,438), and 6% (n=14,932) of patients had hyper-, eu-, and hypothyroidism, respectively. In the overall cohort, 98% (n=227,426), 2% (n=4248), and 0.4% (n=850) had Stage 3, 4, and 5 CKD, respectively. In adjusted analyses, hyperthyroidism was associated with higher mortality risk across all CKD strata: HRs (95% CI) 1.19 (1.14-1.24), 1.10 (1.01-1.20), and 1.21 (1.05-1.40) for Stage 3A, 3B, and 4+5, respectively. Similarly, hypothyroidism was associated with higher mortality risk across all stages of CKD: HRs (95% CI) 1.17 (1.13-1.20), 1.17 (1.10-1.25), and 1.28 (1.13-1.45) for Stage 3A, 3B, and 4+5, respectively.



Conclusions: Among US veterans with Stage 3-5 NDD-CKD, hyper- and hypothyroidism were associated with higher mortality. Further studies are needed to determine whether treatment that normalizes serum TSH ameliorates death risk in NDD-CKD patients with thyroid dysfunction.

Funding: NIDDK Support

FR-OR020

Equations Based on a Set of Novel Metabolites Markers Provide a More Precise Determination of the Glomerular Filtration Rate (GFR) Than the Standard Equations in a Swedish Population with Measured GFR

Regis Perichon,[1] Veronica Lindström,[2] Tiffany Freed,[1] Lisa Ford,[1] Ulf Nyman,[3] Jonas Björk,[2] Jacob Wulff,[1] Anders O. Grubb.[2] *[1]Metabolon, Durham, NC; [2]Univ Hospital Lund, Lund, Sweden; [3]Skane Univ Hospital, Lund, Sweden.*

Background: Creatinine and creatinine-based equations (eg, MDRD and CKD-EPI) are used in routine clinical practice to assess the kidney function. However, non-glomerular determinants affects the performance and clinical utility of creatinine-based equations. We previously identified new metabolites with high correlation with the measured (mGFR). Using quantitative assays for those new metabolites we developed equations that had better precision than the MDRD and CKD-EPI equations in a cohort of adult Swedish patients with mGFR (n=482). The aim of this study is to verify the performance of those new equations in an independent set of 803 patients with mGFR.

Methods: Plasma samples from 803 consecutive adult patients referred to the Lund Hospital (Lund, Sweden) for mGFR assessment by plasma clearance of iohexol were collected and the plasma levels of 5 metabolites were determined using quantitative mass spectrometry assays.The GFR was determined by using the new metabolite-based equations as well as with the MDRD and CKD-EPI equations. The performance of those 3 estimates of GFR was assessed against the mGFR.

Results: MDRD and CKD-EPI equations performed similarly in this patient cohort; about 78% and 64% of the GFR estimates were within 30% and 20% of the mGFR values, respectively. In contrast, with an equation based on acetyl-threonine, pseudouridine and age, 87% and 75% of the GFR estimates were within 30% and 20%, respectively. The rate of CKD Stage misclassification due to an error of more than 30% was 18% with MDRD and CKD-EPI equations. In contrast, this rate was only 8.3% (more than 50% reduction) with the equation based on the new metabolites.

Conclusions: The potential for new metabolites to provide significantly more precise and accurate estimates of GFR was verified in this large independent cohort. Full clinical validation of the new metabolite markers is underway in a larger and diverse cohort.

Funding: Pharmaceutical Company Support - Metabolon, Inc.

FR-OR021

Multiple Metabolites Correlate More Strongly with Measured Glomerular Filtration Rate Than Creatinine: A Verification Study

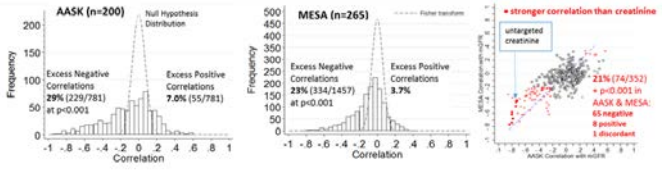
Josef Coresh,[1] Lesley Inker,[2] Yingying Sang,[1] Jingsha Chen,[1] Tariq Shafi,[1] Wendy S. Post,[1] Michael Shlipak,[3] Regis Perichon,[4] Tom Greene,[5] Andrew S. Levey.[2] *[1]JHMI; [2]Tufts MC; [3]UCSF; [4]Metabolon; [5]UU.*

Background: We previously showed that in 200 individuals from AASK measured glomerular filtration rate (mGFR) was highly correlated with many metabolites. We now test whether this is also true in a higher GFR range and evaluate which metabolites are strongly correlated with mGFR at both low and high mGFR providing a foundation for improved GFR estimation.

Methods: Study Population: 265 white or African-American participants at the JHU MESA site with mGFR by plasma clearance of iohexol. **Laboratory Methods:** Untargeted GC/MS^2 and LC/MS^2-based metabolomic quantification of serum (Metabolon) followed by development of targeted assays for 15 metabolites. **Data Analysis Methods:** Log metabolites were ranked by correlation with log mGFR and compared across AASK and MESA.

Results: In semi-quantitative untargeted metabolite assays more than a quarter of measured metabolites were significantly correlated ($p<0.001$) with mGFR in AASK and MESA, and 7 of 9 metabolites more negatively correlated than untargeted serum creatinine in AASK were also more negatively correlated in MESA (Figure). Targeted assays developed for promising metabolites showed higher correlations in the combined dataset with mGFR than creatinine (r=-0.82) for: acetyl-threonine (-0.90), pseudouridine (-0.89), acetyl-alanine (-0.84) and myo-inositol (-0.83).

Conclusions: We identified several metabolites which replicated as being more correlated with mGFR than serum creatinine across both a low and high GFR populations. Validation and testing of metabolite panels is underway with the goal of developing a more precise and robust GFR estimate. [Patents pending by Drs. Levey, Inker and Coresh and Metabolon].



Funding: NIDDK Support, Pharmaceutical Company Support - Metabolon

FR-OR022

Weak Performances of Glomerular Filtration Rate Equations in Stable Lung/Liver Transplant Recipients Compared to 51Cr-EDTA Clearance

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Background: Performance of the most common GFR equations (i.e. MDRD and CKD-EPI) is poorly described in transplant recipients. These populations exhibit frequent non-renal characteristics that influence serum creatinine. Exogenous marker, such as ^{51}Cr-EDTA, allows accurate GFR measurement but it remains cumbersome. Performance of MDRD-2006 and CKD-EPI-2009 equations was compared to the ^{51}Cr-EDTA clearance in lung or liver transplant recipients.

Methods: Retrospective monocentric study (Jan 2011-Sept 2015). GFR was measured by the intercept slope method (3 samples: 90,150 and 210 min). Bias, precision and accuracy defined the performance of GFR equations (IDMS traceable serum creatinine values). Bias was the difference between estimated and measured GFR. Precision was the standard deviation of this difference. Accuracy was rated by the percentage of estimations within 30% of the measured GFR. Risk of misclassification between chronic kidney disease categories (KDIGO 2012) was defined.

Results: 753 GFR measurements were performed for lung (n=152) and liver (n=124) transplant recipients. Mean GFR was 56±42 ml/min/1,73m², mean age was 56 years and 56% were male. Under 60 ml/min/1,73m² (n=444), bias was lower for MDRD (11±24 versus 14±25 ml/min/1,73m²; $p<0.001$). Between 60-90 ml/min/1,73m² (n=238), bias was lower for CKD-EPI (-13±25 versus -17±25 ml/min/1,73m²; $p<0.001$). Accuracy was similar but strikingly poor (43% MDRD and 41% CKD-EPI). The subsequent risk of misclassification was 75% with both equations. GFR overestimation was associated with an age <60 years, malnutrition and lung transplant. GFR underestimation was associated with an age >60 years, BMI >30 kg/m² and liver transplant.

Conclusions: Accuracy of MDRD and CKD-EPI equations was inadequate in this population precluding valid use in clinical routine. Clinicians should be aware of these limitations that may lead to a high risk of misclassification.

FR-OR023

Performance of the CKD-EPI BTP Equation in Kidney Transplant Recipients

Christine A. White,[1] Ayub Akbari,[2] Dean Fergusson,[3] Greg A. Knoll.[2] *[1]Dept of Medicine, Queen's Univ, Kingston, ON, Canada; [2]Dept of Medicine, Univ of Ottawa, Ottawa, ON, Canada; [3]Dept of Epidemeology and Community Medicine, Univ of Ottawa, Ottawa, ON, Canada.*

Background: Accurate estimation of GFR continues to be problematic in kidney transplantation. A new equation to estimate GFR based on serum concentrations of BTP has recently been proposed by the CKD-EPI consortium: BTP eGFR=55 * BTP $^{-0.695}$ * 0.998 ^{age} * 0.899 if female. The aim of this study was to examine the performance of this equation in a cohort of kidney transplant recipients and compare it to the CKD-EPI creatinine (Cr) eGFR and cystatin C (cysC) eGFR. Whether the average of the eGFRs of all three markers improves GFR estimation as compared to the average of Cr/cysC eGFR alone was also examined.

Methods: BTP, cysC, Cr and plasma clearance of ^{99m}Tc-DTPA were measured in 202 adult kidney transplant recipients. BTP and Cys C were measured using the Siemens' nephelometric assays. Equation performance was evaluated by equation bias (estimated – measured GFR), precision (standard deviation of the bias) and 10% and 30 % accuracy. Differences were assessed using paired test and McNemar's test as appropriate.

Results: Results are shown in table below.

CKD-EPI Equation	Bias (ml/min/1.73m²)	Precision (ml/min/1.73m²)	Accuracy % within	
			10%	30%
BTP eGFR	-11.9	17.4	25	65
Cr eGFR	-6.2*	14.8	29	79$^{\beta}$
CysC eGFR	1.6*	16.2	30	76$^{\alpha}$
Cr/CysC eGFR	-2.3**	12.9	37	87$^{\delta}$
Cr/CysC/BTP eGFR	-5.5	12.9	34	89

*P<0.0001 compared to CKD-EPI BTP; **P<0.0001 compared to CKD-EPI Cr/CysC/BTP; $^{\beta}$P=0.0009 compared to CKD-EPI BTP; $^{\alpha}$ P=0.02 compared to CKD-EPI BTP; $^{\Delta}$ P=0.55 compared to CKD-EPI Cr/CysC/BTP.

Conclusions: The CKD-EPI BTP equation is more biased, less precise and less accurate than either the CKD-EPI Cr or the CKD-EPI CysC equations. Incorporating the BTP equation to an average of the CysC and Cr equations does not provide any additional benefits.

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FR-OR024

Absence of Renal Hyperfiltration Imposes Adverse Pregnancy Outcome
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Background: Pre-gestational chronic kidney disease was related to worse pregnancy prognosis and failed hemodynamic adaptation was suspected to be the cause. However, the relationship between midterm renal hyperfiltration (RHF), a normal hemodynamic change during gestation, and adverse pregnancy outcome remains obscure.

Methods: This study included pregnancy cases from two tertiary hospitals in Korea from 2001 to 2015. We used CKD-EPI eGFR (estimated glomerular filtration rate, ml/min/1.73m^2) in the second trimester of each pregnancy to assess midterm RHF of mothers. Mothers were divided into four subgroups as follows: eGFR 60-90, 90-120, 120-150, and ≥150. Mothers with delivery done in the same trimester and eGFR<60 before or during pregnancy were excluded. Adverse pregnancy outcome was the composition of prematurity birth (gestational age<37 weeks), low birth weight (fetal birth weight<2.5 kilograms) and preeclampsia.

Results: A total of 1,936 deliveries were included in the study. Mothers with adverse pregnancy outcome had lower midterm eGFR than those without gestational complications, although their pre-gestational eGFR were not significantly different. When classified into subgroups, mothers with midterm eGFR 60-90 (adjusted OR 2.31, 1.41-3.79, *P*=0.001), eGFR 90-120 (adjusted OR 1.34, 1.004–1.80, *P*=0.047), and even mothers with eGFR≥150 (adjusted OR 2.31, 1.79–13.72, *P*=0.001) showed increased risk of adverse pregnancy outcome when compared to those with eGFR 120-150. Overall, midterm eGFR showed non-linear U-shape association with the risk of adverse pregnancy outcome. The results were similar with prematurity birth and low birth weight, respectively. In contrast, the risk of preeclampsia increased as midterm eGFR decreased, and was higher in the subgroup with midterm eGFR 60-90 (OR 8.27, 2.06-33.30, *P*=0.003).

Conclusions: We demonstrated a novel, non-linear, U-shaped relationship between midterm eGFR and the risk of adverse pregnancy outcome. The absence of adequate midterm RHF was a significant risk factor of worse pregnancy prognosis. Therefore, routine measurement of the midterm renal function should be considered.

FR-OR025

Chronic Kidney Disease (CKD) and Peripheral Nerve Function in the Health, Aging and Body Composition (HABC) Study
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Background: Peripheral neuropathy is prevalent in older adults and is associated with loss of mobility and balance. We hypothesize that CKD, akin to aging; will be associated with nerve function deficits.

Methods: We evaluated the cross-sectional relationship of CKD (defined by eGFR<60 ml/min/1.73 m2) with sensory, motor and autonomic function(Table) in 1483 participants of The HABC Study, a longitudinal cohort of community-dwelling white and black Medicare beneficiaries with 1997-98 baseline. Multivariable logistic regression (LR) model was used. Variables significant at p<0.1 in univariate analyses were adjusted.

Results: Mean(SD) age was 75(3) yrs, 46.1% were men, 35.7% were black and 18.5% had CKD. Participants with CKD had higher odds for having vibration detection deficit and abnormal autonomic function(Table).

Relationship of CKD (predictor) with nerve outcomes: LR				
NERVE FUNCTION	**Unadj model**		**Adj# model**	
	CKD (eGFR)			
	<60	**>60**	**<60**	**>60**
	ODDS RATIO (95% CI)			
SENSORY				
Monofilament insensitivity 1.4g 10g	 1.4(1.1-1.8)* 1.6(1.1-2.3)*	 - -	 1.4(0.8-2.3) 1.2(0.9 -1.7)	 - -
Vibration detection threshold, <130 Um	2.1(1.4-3.3)*	-	1.7(1.1-2.7)*	-
MOTOR				
Amplitude, CMAP<1 mV	1.4(1.0-2.0)	-	1.3(0.9-1.9)	-
Velocity, NCV <40 m/s	1.0(0.8-1.4)	-	1.0(0.7-1.3)	-
AUTONOMIC				
Heart rate range (HRR)$ Ref = >50 2nd tertile, 37-50 3rd tertile, <37	 1.6(1.2-2.3)* 1.6(1.2-2.3)*	 - -	 1.4(1.0-2.0) 1.6(1.1-2.2)*	 - -
Heart rate recovery (HRY)$ Ref = >21 2nd tertile, 14-21 3rd tertile, <13	 1.2(0.8-1.6) 1.5(1.1-2.0)*	 - -	 1.1(0.8-1.6) 1.5(1.1-2.0)*	 - -
# Adj for demographics, comorbidities (DM, HTN, CAD, PVD), lifestyle factors, pertinent labs (Vit B12, PTH) and meds (beta blockers) * Sig. at p < 0.05 $ HRR = HR at end of 400-m walk – HR at rest, HRY = HR at end of 400 m walk – HR after 2 min rest				

Conclusions: Early CKD is associated with sensory and autonomic nerve deficits.

FR-OR026

Association of Sleep Architecture and Stage of Chronic Kidney Disease in a Large Community Based Cohort Study
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Background: Individuals with progressive chronic kidney disease (CKD) frequently report increasing insomnia and poor sleep quality. There is also evidence that individuals with habitual sleep restriction have a more rapid decline in renal function. These finding indicate interplay between renal function and sleep which is not fully understood. To better understand the specific attributes of sleep disturbances that may associate with CKD, we performed a large cross-sectional analysis of polysomnography measures with stages of CKD.

Methods: In cross-sectional analyses of individuals from the Sleep Heart Health Study with sleep disturbances measured using polysomnography, we evaluated the association of baseline total sleep duration (primary exposure), arousal index, hypoxia index (% sleep time with oxygen saturation < 90%) , and respiratory disturbance index (secondary exposures) with baseline estimated glomerular filtration rate (eGFR,N=3597) and albuminuria-creatinine ratio (ACR, N=1567).

Results: Lower eGFR was associated with shorter total sleep duration, and higher indices of arousal, hypoxemia and respiratory disturbance, p-trend <0.005 for all. After adjustment for age, gender, race, smoking and diabetes only total sleep duration remained significantly associated with decreased eGFR, p-trend = 0.007. Higher indices for arousal, and hypoxia were associated with higher ACR, which remained significant after adjustment for age, gender, race, smoking and diabetes, p≤0.005. Neither total sleep duration nor respiratory disturbance index was associated with albuminuria.

Conclusions: Individuals with lower eGFR appear to have decreased sleep duration as measured by polysomnography, independent of age, gender or race, while individuals with more frequent arousals or hypoxemic episodes tend to have higher albuminuria. Prospective studies are required to more fully examine the direction of these associations and to better assess whether or not they may be causal.

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FR-OR027

Gait Speed Trajectory among Patients with CKD
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Background: Gait speed is an component of frailty and strongly associated with mobility disability and mortality across populations. Understanding the trajectory of gait speed decline and its determinants is critical to preventing functional impairment among CKD patients. For the first time we describe longitudinal change in gait speed in patients with CKD.

Methods: Longitudinal study of 213 participants with CKD I-V enrolled in the Seattle Kidney Study without ADL disability, lower extremity impairment, or dialysis treatment at baseline. Gait speed was measured yearly. Generalized estimating equations were used to estimate associations with annual change in gait speed. Kidney function was measured using eGFRcysc. Multiple imputation was performed for missing variables.

Results: Mean age of participants was 57±13 years with 81% male, and 22% black. Mean eGFRcysc was 48±18. Median follow-up was 3 years IQR[2, 4]. Mean annual change was -0.002m/s IQR[-0.05, 0.04]. Those with fastest tertile decline (17.5%/yr IQR[28.3, 12]) were more likely black, and had lower eGFRcysc at baseline. After adjustment, lower eGFRcysc was associated with more rapid decline in gait speed (-0.021 m/s/yr or -2.2%/yr per 1-SD (95% CI -0.03, -0.01; P<0.001). Diabetes was independently associated with -0.019m/s/yr decline. Further adjustment for hemoglobin attenuated the estimates for eGFRcysc and diabetes.

Conclusions: Among persons with CKD, lower eGFRcysc, diabetes, and low hemoglobin are associated with faster decline in gait speed, underscoring the importance of screening for mobility impairment in more severe kidney disease.

eGFRcysc	Baseline mean (SD) (m/s)	Model slope (m/s per yr) (95% CI)
≥60	1 (0.2)	Ref
40-59	0.96 (0.2)	-0.03 (-0.051, -0.009)
30-39	0.95 (0.2)	-0.046 (-0.076, -0.016)
<30	0.95 (0.2)	-0.067 (-0.095, -0.039)
per SD lower eGFRcysc		-0.021 (-0.03, -0.01)
DM		-0.019(-0.036, -0.002)
Model: Age, sex, black race, height, weight, education, smoking, DM, any CVD, CRP		

Funding: NIDDK Support, Private Foundation Support

FR-OR028

Cap Mesenchyme Cell Migration during Kidney Development Is Influenced by Attraction, Repulsion, and Adhesion to the Ureteric Tip
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Background: Morphogenesis of the mammalian kidney requires reciprocal interactions between two cellular domains at the periphery of the developing organ: the tips of the epithelial ureteric tree and adjacent regions of cap mesenchyme. While the presence of the cap mesenchyme is essential for ureteric branching, how the cap mesenchyme is specifically maintained at the tips is unclear.

Methods: Using *ex vivo* timelapse imaging we show that cells of the cap mesenchyme are highly motile.

Results: Individual cap mesenchyme cells move within and between cap domains. They also attach and detach from the ureteric tip across time. Timelapse tracks collected for >800 cells showed evidence that this movement was largely stochastic, with cell autonomous migration influenced by opposing attractive, repulsive and cell adhesion cues.

Conclusions: What was formerly considered a static cellular environment has proven to be dynamic. Continuous cell movement within the niche results in a constant change in the likely signalling environment of any given CM cell. As a result, the niche does not appear to be neatly segregated into spatial subdomains required for a linear differentiation of CM cells to an induced fate. Each CM cell is being simultaneously repelled from the tip, attached to the tip and attracted to tip. These competing forces facilitate the dynamic remodelling required to maintain a domain around the ureteric tips, which is vital for continued branching and nephron induction.

Funding: Government Support - Non-U.S.

FR-OR029

The Role of Megalin in Nephrogenesis and Its Expression in the Developing Human Kidney
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Background: Megalin is localized in the proximal tubule (PT) and rescues ligands like retinol-binding protein (RBP) and vitamin D-binding protein (VDBP) from urinary loss. RBP transports vitamin A, critical for kidney development. Premature neonates are at risk for CKD. Considering the role of megalin in vitamin conservation, we hypothesize that kidney formation in premature neonates is compromised by a relative megalin deficiency and ligand loss. Our aim is to determine if premature neonates excrete megalin ligands due to a developmental expression of megalin and if megalin deficiency during nephrogenesis interferes with kidney development, increasing CKD risk.

Methods: To study megalin expression during human renal development along with the uptake and urinary excretion of megalin ligands, two human cohorts were assessed (1) deceased cohort (20-40 wks gestation) to quantitate tissue megalin, RBP, VDBP and mature PT and (2) living cohort (28-40 wks gestation) to measure urinary RBP and VDBP. Imaging software calculated the area of protein expression. To assess the role of megalin during nephrogenesis, we used a kidney specific megalin deficient model to analyze GFR, nephron number, PT fraction and renal morphology.

Results: Human megalin expression in the PT increased over gestation from 20 to 33 wks as does the tissue level of RBP and VDBP from 20 to 29 weeks. There was a significant correlation between megalin expression and RBP and VDBP uptake. Urinary RBP and VDBP were found in higher concentrations in the 28-32 wk group as compared to the 38-40 week group at birth (RBP: $p<0.01$; VDBP: $p<0.05$) but by term corrected age they were no different compared to the term group at birth. Our analyses showed that 3 wk old megalin KO mice have fewer glomeruli with smaller kidneys and more atubular glomeruli. By the age of 60 days, these mice have a decreased GFR (WT: 401 µl/min; KO: 184 µl/min; $p=0.017$).

Conclusions: Premature infants represent a population with relative megalin deficiency with urinary wasting of megalin ligands. In mice, PT megalin deficiency results in interference of normal nephron formation and may play a role in the development of CKD.

FR-OR030

Nrp1 Is Essential for Glomerular Development and Chemoattraction of Mesangial Cells to PDGF
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Background: Nrp1 is a transmembrane co-receptor for SEMA3A, VEGF, HGF, FGF2, TGF-β, and PDGF. In the kidney Nrp1 is expressed in glomerular mesangial cells (GMCs) yet little is known about its physiological role in glomerular development and disease. An antibody against Nrp1, designed as anti-angiogenic therapy, inadvertently causes significant proteinuria indicating that Nrp1 function is vital in the glomerulus.

Methods: We created conditional knockout (cKO) mouse mutants specifically lacking Nrp1 expression in GMCs and vascular smooth muscle cells (vSMCs) and assessed glomerular development, structure, and function. Cellular behavior upon PDGFB stimulation were studied in human glomerular mesangial cells (hGMCs) following siRNA-mediated knockdown of Nrp1.

Results: PDGFRb-Cre-dependent deletion of *Nrp1* resulted in cKO mice with ~86% reduction in Nrp1 protein levels in the kidney, showing that renal Nrp1 expression is largely in PDGFRb+ GMCs and vSMCs. Nrp1 deficiency causes renal insufficiency, proteinuria and early lethality. Nrp1 cKOs have simplified glomeruli with poorly elaborated capillary tufts. By 2 weeks of age cKOs show glomerular abnormalities including endothelial detachment, podocyte effacement, glomerular basement membrane distortion, and mesangiolysis. Nrp1 is required for PDGFB-dependent migration of hGMCs but not proliferation or adhesion to collagen, laminin and fibronectin. Consistently, upon PDGFB stimulation, activation of p130Cas but not Erk or Akt is dependent on Nrp1.

Conclusions: Nrp1 is essential in GMCs and its loss results in glomerular maldevelopment and glomerulosclerosis. Nrp1 is needed for the structural support function of the mesangium as the glomerular capillary tufts are poorly branched and collapsed when Nrp1 is absent. Cell culture studies suggest that impaired chemotaxis of GMCs lacking Nrp1 to PDGFB, through loss of p130Cas activation, may contribute to aberrant glomerular development in Nrp1 cKO mutant mice.

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FR-OR031

A Novel Strategy to Identify the Role of Whole-Exome Sequencing Candidate Genes in Renal Hypo-Dysplasia
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Background: Next generation sequencing (NGS) has revolutionized genetic research, leading to fast and cost-efficient characterization of heritable pathologies. In particular, whole-exome sequencing (WES) has become the technology of choice to investigate monogenic diseases. However, WES leads to the identification of large numbers of candidate genes, which have to be individually validated. This part of the process is long and costly. Here we propose a novel approach to rapidly and inexpensively screen WES candidate genes in renal hypo-dysplasia.

Methods: Candidate genes obtained by WES were sorted in silico (functional and biological significance). The expression of each candidate gene was knocked down in murine kidney cultures, using a specific vivo-morpholino. Kidneys were analyzed after culture using a multiphoton fluorescent microscope. Candidate genes whose knockdown in culture recapitulated the phenotype observed in the families were defined as confirmed candidates.

Results: Six WES candidate genes were tested, accounting for renal hypodysplasia in 7 unrelated families. One candidate gene was identified by the presence of a heterozygous frameshift variant segregating with renal cystic dysplasia in one family. Its expression in culture was decreased by 65% ($p < 0.001$) using a specific vivo-morpholino. This finding was associated with cyst formation ($p < 0.001$). This phenotype recapitulated the patients' renal phenotype. Another gene was a candidate to account for multicystic hypodysplasia because of the identification of a homozygous, predicted as damaging missense variant in 3 fetuses from 1 family. Its expression in culture was decreased by 60%. This was associated with cyst formation. Ureteric bud branching was decreased by 45%. Tubular cell thickness was increased by 28%. The phenotype matched the patients' phenotype.

Conclusions: This novel approach is fast, inexpensive, and reliable, especially to characterize a frameshift or a loss-of-function missense mutation resulting in a decreased protein function in vivo. It is a strategy of choice to screen WES candidate genes potentially involved in renal diseases.

FR-OR032

Regulation of Kidney Field Size by Transcriptional Regulation of microRNAs
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Background: Renal progenitors arise from the intermediate mesoderm (IM), a germ layer that lies between the lateral & paraxial mesoderm. The transcription factor l*hx1* is expressed in the lateral & IM. Eventually *lhx1* becomes restricted to the IM becoming one of the earliest genes expressed in the kidney field. Lhx1 is essential to specify kidney; the molecular mechanism remains undefined and very few targets have been identified.

Methods: In *Xenopus* kidney cells, we identified proteins using tandem-affinity purified (TAP) proteins that could interact with constitutively active form of Lhx1 (TAP-LL-CA) & not a version lacking the C-terminal region (TAP-LL-delC). The C-terminal region of Lhx1 contains the functional domains necessary to confer transcriptional activity. Furry (Fry) was identified as a potential Lhx1 interacting protein that bound only to the TAP-LL-CA. In *Xenopus*, Fry acts as a transcriptional co-repressor of microRNA (miRNA) expression. We depleted Fry & Lhx1 utilizing antisense oligonucleotides & visualized their effects on the kidney by staining for pronephric kidney markers. We conducted miRNA deep sequencing on these embryos. miRNA mimics were injected into embryos and their effects on the kidney were analyzed as before.

Results: Here we show *fry* is expressed in the IM & pronephric anlagen. We determined that embryos depleted of *fry* show loss of the kidney field, phenocopying the *lhx1* depletion. We observed a synergistic requirement of these two proteins in the IM indicating the

potential interaction in the specification of the kidney field. To gain further insight of the mechanism for Fry & Lhx1 in the kidney field, we identified miRNAs regulated by the proteins using miRNA deep sequencing, & perturbed specification of the kidney field by expressing mimics for the identified miRNAs.

Conclusions: These results support a role of a Lhx1/Fry complex in specification of the kidney field by regulation of miRNAs expression.

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FR-OR033

Regulation and Function of Mural Cell-Derived p57Kip2 in Kidney Development

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Background: p57kip2 (Cdkn1c) is a cyclin-dependent kinase inhibitor that is implicated in Beckwith-Wiedemann Syndrome and IMAGe Syndrome. In the embryonic kidney, p57kip2 is expressed in podocytes and the medullary interstitium. Ablation of p57Kip2 in mice led to many defects resembling the Beckwith-Wiedemann Syndrome. The kidneys of p57Kip2 mutant mouse embryos exhibited a shorter renal medulla since the onset of renal medulla formation.

Methods: Immunohistochemistry, luciferase reporter analysis and Chromatin immunoprecipitation were performed on mice and cell culture.

Results: In Wnt7b mutant kidneys, where a renal medulla failed to form, p57Kip2 expression in the medullary interstitium was reduced to undetectable levels whereas its expression in the podocytes was unaltered. In the renal medulla, p57kip2 is expressed in the mural cells associated with peri-ureteric bud capillaries, the Wnt7b/canonical Wnt target cells. Luciferase reporter analysis in vitro and Chromatin Immunoprecipitation (ChIP) of the renal interstitium showed that p57Kip2 expressed in the mural cells is a direct transcriptional target of Wnt/β-catenin signaling. Further, tissue-specific manipulation of p57Kip2 expression in the embryonic kidney showed that mural cell-derived p57Kip2 is necessary and sufficient for renal medulla elongation, whereas podocyte-derived p57kip2 did not contribute to renal medulla elongation. In the renal medulla, p57Kip2 inhibits proliferation of mural cells and endothelial cells of peri-UB capillaries, and regulates oriented cell division of collecting duct cells and collecting duct elongation.

Conclusions: Our study of p57Kip2 reveals a cross-talk between the collecting duct and the vasculature during kidney formation where the collecting duct regulates gene expression in the vascular components and the vascular component regulates collecting duct and renal medulla elongation in return.

Funding: NIDDK Support

FR-OR034

Fibroproliferative Response to Urothelial Failure Obliterates the Ureter Lumen in a Mouse Model of Prenatal Congenital Obstructive Nephropathy

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Background: Congenital obstructive nephropathy (CON) is the most common cause of pediatric kidney disease and ESRD. Ureteropelvic junction (UPJ) obstructions are responsible for a large portion of CON cases. Based on histological observations the hypothesis arose that urothelial damage could be an underlying basis for some human UPJ obstructions, but this hypothesis has not been tested.

Methods: We have generated a novel genetic mouse model of prenatal UPJ obstructions by conditional deletion of Sec10, an exocyst trafficking complex subunit. We used Ksp-Cre mice to delete Sec10 in ureteric bud-derived epithelia, including the urothelial progenitor cells lining the ureters. Here, we use both *in vivo* and *ex vivo* approaches to investigate the failure of the Sec10-knockout urothelial layer to mature, the subsequent urothelial cell death, and the pathological obliteration of the ureter.

Results: $Sec10^{FL/FL}$;Ksp-Cre mice developed bilateral UPJ obstructions between E17.5 and E18.5, with severe hydronephrosis, anuria, and neonatal death. We found that without Sec10, the urothelial progenitor cells lining the ureter fail to differentiate into superficial cells, which are responsible for producing uroplakin plaques on the luminal surface. These Sec10-knockout urothelial cells undergo cell death by E17.5 and the urothelial barrier becomes leaky to urine. At E17.5, we measured an increased expression of TGFβ1 and genes associated with myofibroblast activation, increased mesenchymal cell proliferation, and found evidence of stromal remodeling. When ureters were removed at E15.5 and cultured for 72 hours, the urothelial defects persisted, but lumen obstructions did not occur in the absence of urine.

Conclusions: Our findings support the model that defective urothelial barrier allows urine to induce a fibroproliferative wound healing mechanism, which may contribute to UPJ obstructions in humans.

Funding: NIDDK Support, Other NIH Support - NIGMS, Private Foundation Support

FR-OR035

Epigenomic Profiles Identify Age Associated Chromatin State Transitions in Nephron Progenitors

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Background: $Cited1^{+}/Six2^{+}$ cells are lineage-restricted multipotent nephron progenitor cells (NPC). Unlike young NPC, which are actively engaged in self-renewal and are resistant to inductive signals, old NPC differentiate at a faster rate limiting their life span. We hypothesized that "aging" alters the epigenomic landscape of NPC, which favors differentiation over renewal.

Methods: NPC were isolated using a magnetic activated cell sorting protocol from E13 and E19 CD1 mouse kidneys and expanded in NPEM growth factor medium for 48 hrs to generate pure $Cited1^{+}/Six2^{high}$ NPC. To identify genome-wide open chromatin regions (OCR - nucleosome-free active promoters and enhancers), NPC were subjected in triplicates to ATAC-seq (Assay for Transposase-Accessible Chromatin with high throughput sequencing). Peak calling, annotation, transcription factor binding motifs and overlapping peaks between E13/E19 samples were performed using HOMER and iCis-Target. OCR were integrated with publicly available RNA-seq and ChIP-seq databases.

Results: We identified 956 and 1438 annotated genes carrying at least one OCR in E13 vs. E19 NPC, respectively, of which 5-7% are differentially expressed. OCR clustered around the transcription start site and at distant 5' or 3' or intragenic sites. Progenitor genes (e.g., c-Myc, Osr1, Six2, Meox1, Eya1, cell cycle and epigenetic regulators) featured age-related attenuation of OCR peak scores and density. Transcriptionally silent β-catenin target genes (e.g., Wnt4, Lef1, Axin2, Jag1, Pax8) consistently harbored OCR in curated enhancers as well as in novel candidate enhancers in old but not young NPC. AP-1, Six2, Sall1/2, WT1, Pax2, Smads, c-Myc, p53, and E2F were amongst the most commonly identified transcription factors in OCR footprints.

Conclusions: Young and old $Cited1^{+}$ NPC exhibit distinct epigenomic landscapes. OCR footprints identified candidate networks of transcriptional regulators in NPC. Chromatin of old NPC displays biochemical signs of epigenetic poising which may explain, at least partly, the enhanced propensity of old NPC to differentiation vs. self-renewal.

Funding: NIDDK Support

FR-OR036

RET Signaling Is Necessary for Survival of Progenitors in the Anterior Intermediate Mesoderm and Wolffian Duct - Cloaca Joining through a Novel Trans-Cloacal Cascade of Apoptosis before Ureteric Budding

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Background: The mammalian collecting system is derived from the ureteric bud (UB) at the caudal end of the Wolffian duct (WD). The UB progenitors originate in the anterior intermediate mesoderm (IM) at E8.5 in mouse. The specific mechanisms of how these IM progenitors generate WD and UB or join the cloaca before UB budding is not clear. These processes when disrupted are major causes of congenital anomalies of kidney and urinary tract (CAKUT). Global RET receptor tyrosine kinase signaling is required for UB induction and for WD to reach the cloaca. We recently showed that signaling through RET-Y1015 docking tyrosine inhibits ectopic UBs from WD and regulates CND apoptosis for ureter maturation after UB budding.

Methods: Here we used genetically encoded reporters, lineage tracing and mice deficient in RET-Y1062 or RET-Y1015 docking tyrosine activity to better understand the early events priming the formation of the metanephric kidney and its union with the cloaca beginning from the IM progenitors and through WD morphogenesis during the pronephros and the mesonephros stages in mice.

Results: We discovered that RET-Y1062 signaling controls IM cell number, the survival of WD leader cells and their migration to reach cloaca. We discovered a novel cascade of spatio-temporally controlled trans-cloacal apoptosis before ureteric budding and branching morphogenesis during normal development. The cloacal apoptosis at the site of putative WD insertion did not occur in WDs that do not reach the cloaca and it was dependent on RET-Y1015 signaling in WD tip cells.

Conclusions: These novel findings decipher how progenitors in IM lay this plumbing unique to amniotes and convey novel insights in the pathogenesis of CAKUT and rebuilding a kidney ex vivo.

Funding: NIDDK Support

FR-OR037

PI3K Pathway Potentiates Nephron Progenitor Cell (NPC) Renewal by Promoting Glycolysis

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Background: Energy metabolism pathways have emerged as critical regulators of stem/progenitor cell fate. We showed an age-dependent decrease in glycolysis in young (E13.5, predominantly self-renewing) vs old (P0, poised to differentiate) NPC. Glycolysis inhibition in organ culture promotes NPC differentiation. PI3K and Bmp/MAPK signaling pathways maintain NPC in a Cited1+/Six2+ self-renewing state. PI3K inhibition or Bmp/Smad activation promotes NPC differentiation. As the PI3K pathway is a positive regulator of glycolysis, we hypothesized that PI3K and Bmp/MAPK pathways converge on glycolysis to maintain NPC in a self-renewing state. To test our hypothesis we measured the glycolytic flux in isolated NPC after PI3K or Bmp/Smad pathway modulation.

Methods: E13.5 NPC were isolated by MACS, cultured in expansion (NPEM) or differentiation (DMEM) media ± treatments followed by glycolysis flux (extracellular acidification rate, ECAR) measurement at 18h or QPCR at 24h. Treatments: 10μM PI3K inhibitor LY294002, 100nM Akt inhibitor MK2206, Wnt activator CHIR 2μM or NPEM minus Smad inhibitor LDN to activate the Bmp/Smad pathway. Glycolysis enzyme PFKFB3 inhibitor YN1 20μM was used as a positive control.

Results: Compared to NPC/NPEM, NPC/DMEM showed 3-5 fold ECAR decrease, 10- and 12-fold decreased Cited1 and Six2 expression and 6-fold increased Wnt4 expression. In comparison, inhibition of PI3K or Akt, or Smad activation in NPC/NPEM was sufficient to cause a 2-4 fold ECAR decrease. Smad activation suppressed Cited1 and Six2 expression 8- and 1.8 fold, respectively, while Wnt4 expression increased 5.2 fold. YN1 reduced ECAR 2.4-fold without affecting Cited1, Six2 and Wnt4 expression. Inhibition of glycolysis in cultured E12.5 kidneys accelerated nephrogenesis. This effect was blocked by co-treatment with the canonical Wnt response inhibitor IWR1.

Conclusions: Glycolysis flux is a pivotal determinant of NPC fate. A high glycolysis flux is an essential intermediary of PI3K-mediated NPC self-renewal. Glycolysis inhibition promotes nephrogenesis via established β-catenin dependent pathways. Reduced glycolysis in itself is insufficient to activate NPC differentiation in the absence of β-catenin.

Funding: NIDDK Support

FR-OR038

Molecular Predictors of Proteinuria and Glomerular Filtration Rate in Patients with Focal Segmental Glomerulosclerosis Undergoing a Kidney Transplant Lilian A. Otalora,[1] Efren Alejandro Chavez,[1] Daniel J. Watford,[1] Viji Nair,[2] Dayami Hernandez,[1] Lissett Tueros,[1] Mayrin Correa,[1] Matthias Kretzler,[2] Phillip Ruiz,[1] George William Burke,[1] Sandra M. Merscher,[1] Alessia Fornoni.[1] *[1]Katz Family Drug Discovery Center and Div of Nephrology and Hypertension, Univ of Miami, Miami, FL; [2]Dept of Internal Medicine - Nephrology, Univ of Michigan, Ann Arbor, MI.*

Background: We recently demonstrated that sphingomyelinase phosphodiesterase acid like 3b (SMPDL3b) is a key modulator of podocyte architecture and function. Decreased SMPDL3b expression in post-reperfusion kidney biopsies predicted post-transplant proteinuria and occurred in association with foot process effacement in retrospective studies.

Methods: Thirty-nine patients with biopsy proven FSGS undergoing a kidney transplant were enrolled in a prospective clinical trial. Pre (PRE) and post-reperfusion (POST) kidney biopsies were collected. Histological analysis, immunohistochemistry (IHC) for SMPDL3b, microarray analyses of isolated glomeruli from PRE and POST biopsies, analysis by electron microscopy (EM) to assess foot process effacement (FPE) and correlation analyses with protein/creatinine ratios (PCR) and estimated Glomerular Filtration rate (eGFR) at 12 months (eGFR-12) after kidney transplantation were performed.

Results: We found a positive correlation between SMPDL3b positive glomerular cells and eGFR-12 ($p<0.05$) in POST biopsies. The degree of FPE positively correlated with PCR and with worsened eGFR-12 ($p<0.05$). Inflammation and lipid-related pathways were found to be significantly regulated in POST when compared to PRE biopsies. Transcript levels of several genes of these pathways significantly correlated with PCR or change in eGFR. In addition, the transcript levels of a subset of genes was found to correlate with the degree of FPE.

Conclusions: Decreases in SMPDL3B positive cells in POST biopsies is significantly associated with post-transplant loss of GFR in FSGS. FPE in POST biopsies is significantly associated with post transplant proteinuria and loss of renal function. Upregulation of certain genes associated with inflammation or lipid metabolism may predict the development of proteinuria or change in eGFR after transplantation.

FR-OR039

Molecular Significance of Peritubular Capillaritis in Early Transplant Kidney Biopsies of Donor-Specific Antibody Negative Patients Maria Ajaimy, Yi Bao, Enver Akalin. *Montefiore Transplant Center, Albert-Einstein College of Medicine.*

Background: Peritubular capillaritis (PTC) is a part of microvascular inflammation seen in antibody-mediated rejection (ABMR). However, it is observed in early transplant kidney biopsies with acute tubular necrosis (ATN) due to ischemia/reperfusion injury. We aimed to investigate intragraft gene expression of transplant kidney biopsies with PTC and ATN in kidney transplant recipients without donor-specific antibody (DSA).

Methods: We identified 19 early transplant kidney biopsies with ATN for gene expression profiling comparing to 12 normal transplant kidney biopsies (Group I). Biopsies with a diagnosis of acute or chronic rejection, recurrent or de novo glomerular disease, moderate to severe fibrosis or polyoma nephropathy were excluded. The gene expression profiles were studied by Affymetrix HuGene 1.0 ST expression arrays.

Results: Among the 19 biopsies with ATN, 7 patients (Group 2) had isolated PTC and 12 patients (Group 3) had no PTC. Both groups had similar demographics characteristics in terms of age, race, and sex, type of transplant, previous history of transplantation or acute rejection, donor characteristics, panel reactive antibody levels and immunosuppressive treatment. There was no statistically significant difference in gene expression profiles between the 3 groups including injury and response (IRIT), interferon-gamma and rejection associated transcripts (GRIT), cytotoxic T cell (CAT), regulatory T cell (TREG), B-cell (BAT) natural killer cell transcripts (NKAT) Constitutive Macrophage (CMAT), donor-specific antibody (DSAST) and endothelial cell associated transcripts.

Pathogenesis Based Transcripts	G2 vs G1	G3 vs G1	G3 vs G2
IRIT	0.57	0.58	0.18
GRIT	0.28	0.21	0.42
CAT	0.40	0.17	0.28
TREG	0.21	0.11	0.42
BAT	0.80	0.63	0.42
NKAT	0.73	0.71	0.50
CMAT	0.47	0.10	0.13
DSAST	0.48	0.88	0.93
ENDAT	0.86	0.68	0.28

Conclusions: Isolated peritubular capillaritis could be seen in early transplant kidney biopsies with ATN and intragraft gene expression profiles do not reflect immune activity.

FR-OR040

Molecular Evidence of Chronic Cellular Rejection in C4d and Microvascular Inflammation Negative Transplant Glomerulopathy Michelle Lubetzky, Yi Bao, Enver Akalin. *Montefiore Center for Transplantation, Albert Einstein College of Medicine, Bronx, NY.*

Background: Transplant glomerulopathy (TGP) is frequently found in the setting of chronic antibody mediated rejection along with microvascular inflammation (MVI) (peritubular capillaritis+glomerulitis score > 1) and/or positive c4d staining. We assessed the molecular profiles of TGP in the absence of microvascular inflammation and C4d staining as compared to TGP with positive MVI and/or C4d.

Methods: 42 for-cause renal allograft biopsies were studied using Affymetrix HuGene 1.0 ST expression arrays; 12 with normal biopsy findings (G1), 17 with a diagnosis of TGP, C4d positive and/or a MVI score >1 (G2), and 13 with a diagnosis of TGP and C4d negative and MVI score </=1 and (G3).

Results: There was no difference in sex, race, or type of transplant between the 3 groups. More patients had DSA in TGP with MVI or C4d (G2), 82.4%, as compared with normal (G1), 8.3% $p<0.001$ and TGP without MVI or C4d (G3), 38.4%, $p=0.02$. When comparing TGP with MVI and/or C4d (G2) to TGP without MVI or C4d (G3) and normal (G1), pathogenesis based transcripts revealed increased expression of gamma interferon and rejection (GRIT) and DSA associated transcripts (DSAST) consistent with the response seen in antibody-mediated rejection. However, when TGP without MVI or C4d (G3) compared to normal (G1), increased expression of Cytotoxic T cell (CAT), T-regulatory cell (TREG), and B cell associated transcripts (BAT) were observed but not GRIT or DSAST. There was no difference in expression of natural killer cell and endothelial cell associated transcripts between the 3 groups.

Conclusions: Gene expression profiles of TGP in the absence of microvascular inflammation and C4d lack molecular features of antibody-mediated rejection but suggest chronic cellular rejection.

Pathogenesis Based Transcripts	G2 VS G1	G2 VS G3	G3 VS G1
GRIT	0.02	0.04	0.15
CAT	0.002	0.12	0.007
TREG	0.008	0.07	0.034
BAT	0.11	0.60	0.04
NKAT	0.17	0.49	0.07
DSAST	0.012	0.017	0.19
ENDAT	0.30	0.29	0.46

FR-OR041

Angiotensin II Type 1 Receptor Antibodies Are Associated with Elevated TNF-α, IL-1β, IL-8, and Poor Allograft Outcomes in Pediatric Renal Transplantation Meghan Pearl,[1] Jonathan Grotts,[1] Maura Rossetti,[1] Qiuheng Jennifer Zhang,[1] Miguel Fernando Palma Diaz,[1] Patricia L. Weng,[1] Elaine F. Reed,[1] Eileen W. Tsai.[1,3] *[1]Univ of California Los Angeles, Los Angeles, CA; [2]Dept of Pediatrics, Duke Univ, Durhan, NC.*

Background: We recently found that angiotensin II type 1 receptor antibody (AT_1R-Ab) was associated with vascular injury and allograft failure in pediatric renal transplant recipients. TNF-α, IL-1β, IL-8, IFN-γ, IL-17, and IL-6 have been associated with vascular inflammation and AT_1R activity, but their role in renal transplant patients with AT_1R-Ab is unknown. We aimed to determine the relationship between cytokine profiles and AT_1R-Ab on renal function and allograft survival in pediatric kidney transplant recipients.

Methods: 65 pediatric kidney transplant recipients were monitored for 2 years post-transplant from August 2005 to November 2014. AT_1R-Ab (ELISA test, > 17 units/ml positive) and TNF-α, IL-1β, IL-8, IFN-γ, IL-17, IL-6 (Luminex assay) were measured pre-transplant and post-transplant at 6 months (m), 12m, 24m and during episodes of rejection. Renal function (Schwartz equation), rejection (2013 Banff criteria), and allograft loss were monitored.

Results: AT_1R-Ab positivity in the first 2 years post-transplant was associated with higher TNF-α (0.067), IL-1β ($p=0.055$), and IL-8 (0.006) levels (Figure 1a) but not IFN-γ, IL-17, or IL-6 (data not shown). Renal function at last follow up was worse in

patients positive for AT_1R-Ab, even in patients without rejection (p=0.049, Figure 1b). Furthermore, AT_1R-Ab positive patients with TNF-α were more prone to allograft loss (p=0.058, Figure 1c).

Conclusions: In pediatric renal transplant patients, AT_1R-Ab is associated with poor allograft function, survival and higher IL-8, IL-1β, and TNF-α levels. AT_1R-Ab monitoring used in conjunction with these cytokines may identify those at risk for poor allograft outcomes.

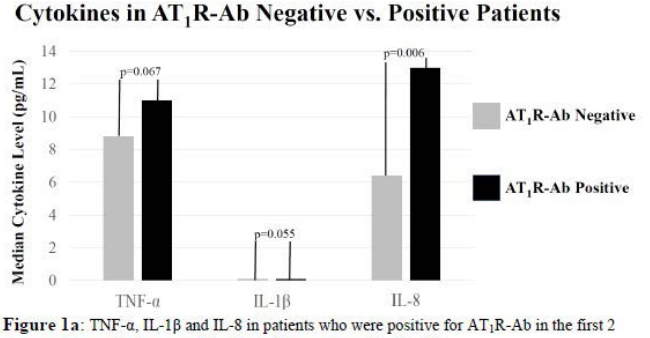

Figure 1a: TNF-α, IL-1β and IL-8 in patients who were positive for AT_1R-Ab in the first 2 years post-transplant compared to those who were negative (n=65).

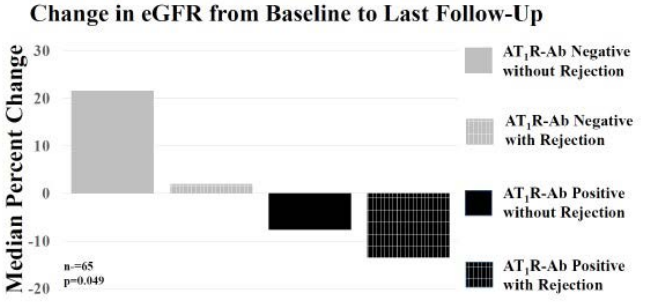

Figure 1b: Median percent change in estimated glomerular filtration rate (eGFR) between baseline and last follow up in patients with and without AT_1R-Ab with and without rejection.

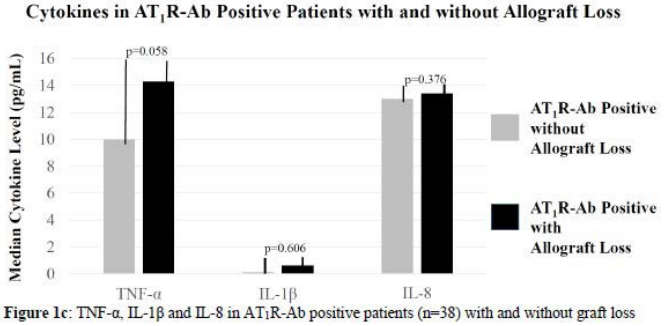

Figure 1c: TNF-α, IL-1β and IL-8 in AT_1R-Ab positive patients (n=38) with and without graft loss

Funding: NIDDK Support, Private Foundation Support

FR-OR042

Polyclonal Treg Adoptive Therapy for Control of Subclinical Kidney Transplant Inflammation: TASK Pilot Trial

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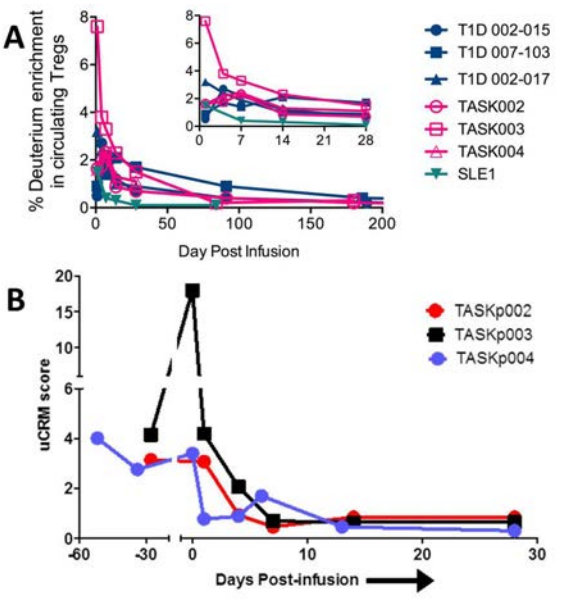
Background: Treg therapy can reverse established inflammation in animal models. We conducted a pilot safety & feasibility trial of Treg therapy for subclinical kidney transplant inflammation.

Methods: Peripheral blood $CD4^+CD25^+CD127^{lo/-}$ Tregs were isolated (FACS) & expanded *ex vivo* (anti-CD3/anti-CD28 stimulations/IL-2) in a deuterated glucose-containing medium. $320x10^6$ Tregs were infused into kidney transplant recipients with subclinical inflammation on 6-m protocol biopsy. %Deuterium enrichment by GC-MS allowed estimation of levels of infused (labeled) Tregs in circulation. Inflammation was assessed on follow-up biopsies using Banff scoring and leukocyte common antigen positive (LCA^+) cell density & in urine using common rejection module (uCRM), a biomarker of rejection.

Results: 3 patients on tac/MMF/prednisone received Treg infusions. Tregs expanded >100-fold (comparable to non-immunosuppressed patients) & met release criteria for infusion. One patient had transient lymphopenia (day 4-21) post-infusion. No infusion reactions or infections were seen & graft function remained stable. Infused Tregs peaked within week 1, up to 7.5% of all circulating Tregs. Decay of infused Tregs was similar to that seen in non-immunosuppressed patients (Fig 1A). Graft inflammation improved in two & uCRM scores improved in all cases (Table 1 & Fig 1B).



Subject	Kidney biopsy Banff score		LCA^+ cells/mm²	
	Baseline	2 weeks	Baseline	2 weeks
002	i1t1	i0t0	337	19
003	i0t1	i0t0	469	303
004	i1t1	i1t1	278	454

Conclusions: It is feasible to isolate & expand Tregs from transplanted patients. Infused Tregs were well tolerated & had pharmacokinetics similar to those in non-immunosuppressed patients. CTOT-21 will test the efficacy of Tregs for control of graft inflammation.

Funding: Private Foundation Support

FR-OR043

A Molecular Approach to Chronic Active T Cell Mediated Rejection

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Background: Banff classification only recognizes chronic allograft arteriopathy as chronic active T cell mediated rejection. We hypothesized that T cell-mediated immune injury plays role in two conditions; donor-specific antibody (DSA) negative transplant glomerulopathy (TGP) and interstitial fibrosis and tubular atrophy (IFTA) with inflammation (i> 0). We investigated gene expression profiles of those biopsies compared to biopsies with antibody-mediated rejection (ABMR) and to biopsies with non-specific IFTA and no inflammation (i=0).

Methods: A total of 62 for-cause renal allograft biopsies were studied using Affymetrix HuGene 1.0 ST expression arrays in the following groups; G1: normal transplant kidney biopsy, n=12, G2: ABMR (including TGP with DSA), n=24, G3: TGP without DSA or IFTA with i score > 0 and G4: IFTA without inflammation (i=0), n=10.

Results: There was no difference in sex, race, or type of transplant between the 4 groups. G2 biopsies showed significantly increased expression of gamma-interferon and rejection associated (GRIT), Cytotoxic T cell (CAT), regulatory T cell (TREG), constitutive macrophage (CMAT), and DSA associated gene transcripts (DSAST) when compared to G1 biopsies. While there were no statistically significant differences in expression of any pathogenesis based transcripts studied in G4 compared to G1 biopsies, G3 biopsies showed increased intragraft expression of CAT and TREG, suggesting T cell mediated immune mechanisms in its pathogenesis.

Pathogenesis Based Transcripts	G2 VS G1	G3 VS G1	G4 VS G1
GRIT	0.055	0.17	0.33
CAT	0.005	0.017	0.13
TREG	0.025	0.04	0.14
BAT	0.15	0.10	0.13
NKAT	0.19	0.24	0.34
CMAT	0.04	0.08	0.24
DSAST	0.005	0.35	0.39
ENDAT	0.35	0.57	0.63

Conclusions: DSA negative TGP and IFTA with inflammation biopsies have a unique molecular signature with significant expression of cytotoxic and regulatory T cells. This suggests that DSA negative TGP and IFTA with inflammation could be classified as chronic T cell mediated rejection.

FR-OR044

Identification of Urinary mRNA Expression for Diagnosing Acute Rejection by Meta-Analysis of Gene Expression in Kidney Transplantation

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Background: microarray data is a powerful source for identifying potential targets to diagnose acute rejection (AR) in kidney transplanted patients (KTPs). We performed a meta-analysis of gene expression profiles of stable graft function (STA) and AR from biopsy tissues in kidney transplantation and investigated expressions of candidate genes selected from meta-analysis in urine of KTPs.

Methods: The microarray data were obtained from the public repositories. Meta-analysis were conducted by 664 STA and 272 AR patients, with a total of 954 samples. 14 candidate genes selected after meta-analysis as biomarker of AR in urinary cells of KTPs. 120 urine samples (23 stable, 34 acute cellular rejection (ACR), and 17 acute antibody-mediated rejection (AMR), 23 long-term graft survival (LGS), 17 chronic antibody-mediated rejection (CAMR), and 6 tolerance (Tol)) were collected after kidney transplantation. The expression levels of transcripts were determined in urinary cells using real-time PCR.

Results: 14 candidate genes were selected by meta-analysis of gene expression for AR diagnosis, including CXCL9, PSMB9, INPP5D, LCK, ISG, RUNX3, CD3ε, IP-10, Tim-3, Foxp3, IDO1, PTPRC and C1QB. We determined expression levels of mRNA isolated from urinary cells with 14 candidates. 3 (Tim-3, CXCL9, and LCK mRNA) among them were significantly elevated in patients with acute cellular rejection, while Tim-3 was significantly higher expressed and ISG20 and OX40 were significantly decreased in patients with acute antibody-mediated rejection. In addition, the real change of CXCL9 mRNA level in biopsy tissue was confirmed by *in situ* hybridization. In ACR prediction model composed of 3 genes clearly discriminated the patients with acute cellular rejection from STA.

Conclusions: We developed ACR and AMR specific urine mRNA panel composed of 3 genes. We suggested that urinary mRNA is promising as a sensitive, non-invasive means to monitor kidney allografts.

Funding: Government Support - Non-U.S.

FR-OR045

The Association between Rapid BK Viremia Clearance and Graft Rejection in Kidney and Kidney/Pancreas Transplant Recipients

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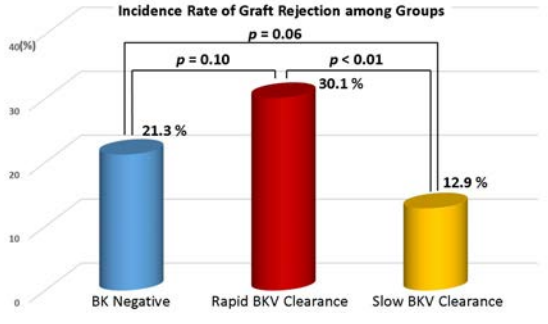
Background: BK polyoma virus reactivation is a serious complication after transplantation with no definitive treatment except reduction of immunosuppression. Patients are at risk of graft rejection after BK viremia (BKV) and reduction of immunosuppression. There is no published data on the association between BKV clearance rate and incidence of graft rejection. The objective of this study is to assess the relation between the rate of BKV clearance and graft rejection after kidney transplantation.

Methods: We screened 595 kidney transplants (2007-2011) for BKV by PCR in blood. One hundred and sixty two out of total 595 patients (27.2 %) developed BKV any time post-transplant. We classified BKV patients into 2 groups based on the duration from the time of peak to 50% reduction of BKV load as follows; A) rapid BKV clearance group (duration within 21 days) and B) slow clearance group (duration more than 21 days). The incidence of graft rejection after BKV was assessed among 2 BKV groups and BK virus negative group. Acute rejection was defined as Banff borderline or greater changes on either surveillance or for cause post-transplant biopsy.

Results: The rapid BKV clearance group was associated with higher incidence of allograft rejection after BKV (30.1 %) compared to the slow BKV clearance group (12.9 %), p <0.01 (Pearson's Chi-Square test). The rate of allograft rejection in BK virus negative group was 21.3 % and no statistical significance was observed in comparison to BKV groups.



Conclusions: Rapid BKV clearance is associated with higher rates of graft rejection after BKV, perhaps due to reconstitution of native immunity.

FR-OR046

20-Year Trends in Clinical Outcomes of Kidney Transplantation

William Irish,[1] Akinlolu O. Ojo,[2] Neetu Agashivala,[3] Larry M. Gache.[1] *[1]CTI Clinical Trial and Consulting Services, Inc.; [2]Univ of Arizona Health Sciences; [3]Novartis Pharmaceuticals Corporation.*

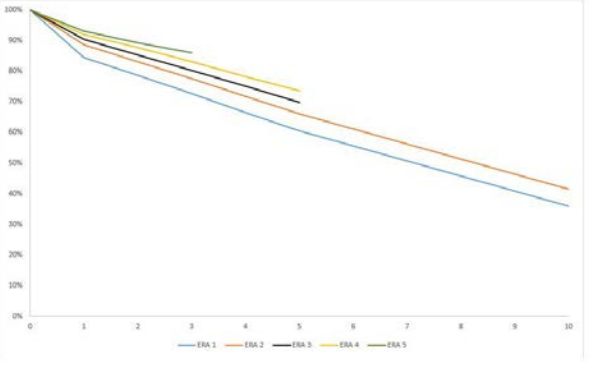
Background: The short term outcomes of KTx are excellent, but the long term outcomes have improved minimally despite advances in immunosuppression (IS). The purpose of this study was to examine historical trends using data from the United States Renal Data System (USRDS).

Methods: Adult primary Medicare beneficiaries in USRDS who received a kidney-only transplant from 1992-2012 and received pre-transplant dialysis were eligible for inclusion. Clinical outcomes included all-cause graft failure and death-censored graft loss. Trends were evaluated using transplant periods (eras 1-5): 1992-1996, 1997-2002, 2003-2006, 2007-2009, and 2010-2012. Eras were chosen to reflect major KTx milestones: tacrolimus approval (1997), organ allocation policy changes (2002), center-specific program evaluation initiative (2007), and the KDIGO guidelines (2009).

Results: 134,679 patients (77%/23% deceased [DD]/living donor [LD]) were eligible: 21%, 27%, 21%, 16% and 16% in ERAs 1, 2, 3, 4, and 5. Across ERAs**,** donors were older, prevalence of hypertension and terminal SCr>1.5 mg/dL increased, donation after cardiac death and extended criteria donor organs increased. Across ERAs, recipients were older, more often had diabetes, had higher pre-transplant Charlson Comorbidity Index scores, had more 6-antigen mismatches and were more often African American. Maintenance IS shifted from cyclosporine- to tacrolimus-based regimens with decreased use of corticosteroids. Graft survival trends are shown. Similar trends were observed for DD and LD. Death-censored graft loss at 3-years post-KTx was reduced by ~60% in ERA 5 compared to ERA 1 for DD and LD.

Conclusions: The net benefit of KTx has improved significantly across transplant eras despite worsening donor/recipient risk profiles.

Figure 1: Trends in Graft Survival by ERA Cohort



Funding: Pharmaceutical Company Support - Novartis Pharmaceuticals Corporation

FR-OR047

Does Cognitive Function Predict Waitlisting for Kidney Transplant?

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Background: Cognitive dysfunction is common in patients with advanced kidney disease. Being cognitively intact is vital for post-transplant care and medical compliance. Few studies have examined cognitive function in pre-kidney transplant patients. We hypothesized that lower scores on the Montreal Cognitive Assessment (MoCA) would be associated with a decreased rate of transplant (TXP) listing.

Methods: MoCA was performed as a part of routine pre-kidney transplant evaluation and at annual follow-up. Demographic, comorbidity, and clinical parameters were collected on all patients. Different MoCA versions were utilized as appropriate. Scoring of the MoCA was performed as recommended by the test developers. Cox proportional hazards models were used to assess associations between baseline MoCA and the subsequent occurrence of TXP listing. Linear mixed effects models were used to test for longitudinal changes in MoCA.

Results: 329 subjects had at least 1 MoCA and 183 had 2 during a 28 month period. The baseline mean composite MoCA score was 24.3±4.2. Hispanics, Native Americans, advanced age, and ESRD secondary to diabetes were associated with lower MoCA scores. Conversely, higher education level, peritoneal dialysis, and non-Hispanic White ethnicity were associated with higher MoCA scores. In patients who underwent 2 MoCA tests (n=183), the mean score increased by 1.2 from the first to the second test (95% CI: 0.8 – 1.7, p<0.001). Among patients not already waitlisted for TXP, those with baseline composite MoCA scores below 26 had a hazard ratio for subsequent listing of 0.44 (95% CI: 0.24-0.82, p=0.01), compared to those with higher scores.

Conclusions: This study demonstrates that patients evaluated for kidney transplant suffer from mild cognitive function impairment compared to the general population. Lower MoCA scores were associated with decreased waitlisting for renal transplant. MoCA scores were stable over time among patients evaluated for kidney transplant. Further studies are warranted to define cognitive changes in patients waiting for renal transplant.

FR-OR048

The lncRNA Tug1 Interacts Directly with PGC-1α to Regulate Mitochondrial Bioenergetics in Diabetic Nephropathy Jianyin Long,[1] Shawn S. Badal,[1] Zengchun Ye,[2] Yin Wang,[1] Farhad R. Danesh.[1] *[1]Section of Nephrology, The Univ of Texas, MD Anderson Cancer Center, Houston, TX; [2]Nephrology, 3rd Affiliated Hospital of Sun Yat-Sen Univ, Guangzhou, Guandong, China.*

Background: The regulatory roles of long noncoding RNAs (lncRNAs) on transcriptional coactivators are still largely unknown. Here we show that the peroxisome proliferator-activated receptor γ (PPARγ) coactivator α (PGC-1α) is functionally regulated by a lncRNA, and describe a previously unknown regulatory role for this lncRNA in the regulation of podocyte mitochondrial function.

Methods: Using experimental models of diabetic nephropathy (DN), we performed unbiased RNA-Seq profiling of kidney glomeruli, and identified lncRNA *Tug1* (Taurine upregulated gene 1) as a differentially expressed lncRNA in the diabetic milieu. To test the contribution of Tug1 to the progression of DN, we generated podocyte-specific transgenic mice to overexpress *Tug1* within the diabetic millieu of Type 2 diabetic (*db/db*) mice. Mechanistically, we performed genome wide transcriptome studies, lncRNA genome wide DNA binding profiling (ChiRP-Seq) and biochemical studies to investigate novel targets/pathways under the control of *Tug1* RNA.

Results: Podocyte-specificoverexpression of *Tug1* in diabetic (*db/db*) mice improved albuminuria levels, reduced mesangial matrix expansion, improved podocyte foot process effacement and prevented podocyte loss as quantified by WT1 positive podocytes. Unexpectedly, we found that podocyte-specific overexpression of *Tug1* in diabetic mice rescued expression of PGC-1α mRNA, improved mitochondrial copy number levels and mitochondrial bioenergetics. Mechanistically, we identified a *Tug1* Binding Element (TBE) upstream of the PGC-1α gene promoter. We demonstrate that the interaction of *Tug1* with TBE serves as a genomic tether, whereby *Tug1* acts as a scaffold to recruit PGC-1α protein to its own promoter, triggering its transcription.

Conclusions: We propose that a novel, physical interaction between PGC-1α protein and *Tug1* RNA contributes to modulating mitochondrial bioenergetics in podocytes via regulation of PGC-1α gene expression.

Funding: NIDDK Support

FR-OR049

FXR-TGR5 Agonists Prevent the Development of Diabetic Kidney Disease in Part by Increasing Mitochondrial Biogenesis and Function Xiaoxin Wang, Yuhuan Luo, Evgenia Dobrinskikh, Dong Wang, Moshe Levi. *Univ of Colorado Denver.*

Background: Diabetes mellitus continues to be the leading cause of kidney disease. Our purpose is to determine the role of the nuclear receptor farnesoid X receptor (FXR) and G protein coupled receptor TGR5 in prevention and treatment of diabetic kidney disease.

Methods: We have treated two distinct models of rodent diabetic nephropathy i) DBA/2J mice fed a western diet and made diabetic with streptozotocin and ii) db-db mice with a) FXR agonist INT-747 at 30 mg/kg/day, or b) TGR5 agonist INT-777 at 30 mg/kg/day, or c) FXR-TGR5 dual agonist INT-767 at 30 mg/kg/day, from 3 months of age until 6 months of age.

Results: All 3 agonists had no effects on the hyperglycemia but had very marked and significant effects to decrease urine albumin excretion, glomerular area and mesangial expansion, podocyte loss, inflammation, glomerulosclerosis and tubulointerstitial fibrosis (determined by Mason's trichrome and Picrosirius Red stains, immunostaining for extracellular matrix proteins, label free imaging with Two Photon Excitation and Second Harmonic Generation Microscopy, and expression of profibrotic growth factors). Further mechanistic studies indicated that these agonists also stimulate the mitochondrial transcription factors Nrf1 and Tfam, as well as AMPK, PGC-1α, Sirtuin 1, Sirtuin 3 and the nuclear receptor estrogen related receptor alpha (ERRα), major regulators of mitochondrial biogenesis and function. In fact there were increases in long-chain 3-hydroxy acyl-coenzyme A dehydrogenase (LCAD) and carnitine palmitoyltransferase IA (CPT1A) which are mediators of mitochondrial fatty acid β oxidation, resulting in decreased lipid accumulation in the kidney (as determined by lipid stains and lipid composition analysis), and mitochondrial superoxide dismutase 2 (SOD2) which is an antioxidant resulting in decreased oxidative stress in the kidney (as determined by decreases in oxidized proteins and lipids).

Conclusions: FXR and TGR5 agonists have renal protective effects independent of their effects on systemic glucose metabolism. They have a great potential for prevention and treatment of diabetic kidney disease by enhancing mitochondrial biogenesis and mitochondrial function.

Funding: NIDDK Support, VA Support, Pharmaceutical Company Support - Intercept Pharmaceuticals

FR-OR050

Enhanced Real-Time In Vivo Mitochondrial Redox in Diabetic Nephropathy Daniel L. Galvan,[1] Shawn S. Badal,[1] Paul T. Schumacker,[2] Farhad R. Danesh.[1] *[1]Section of Nephrology, The Univ of Texas MD Anderson Cancer Center, Houston, TX; [2]Dept of Pediatrics, Northwestern Univ, Chicago, IL.*

Background: The role of mitochondrial reactive oxygen species (mtROS) in the pathogenesis of diabetic nephropathy (DN) remains controversial. A major gap in further addressing the role of mtROS in DN is the real-time measurement of ROS inherent to the mitochondria *in vivo*.

Methods: To monitor mtROS *in vivo*, we utilized a recently described mouse model in which a CMV-driven roGFP redox sensor was specifically expressed in the mitochondrial matrix (mts). Transgenic CMV-mts-roGFP mice were intercrossed with mice harboring the *Lepr$^{db/+}$* mutation to generate a type 2 diabetic mouse model with a genetic redox biosensor(*db/db$^{TgCMV\text{-}mts\text{-}roGFP)}$*, hereafter referred to as *db/db^{roGFP}*). We employed excitation of the roGFP biosensor at the prescribed laser wavelengths for the oxidized (720nm) and reduced (860nm) forms. Emission spectra were collected and ratios of the oxidized to reduced signals determined.

Results: Using two-photon imaging, mitochondrial redox state was assessed in the kidneys of experimental models of diabetes of 16-weeks old diabetic (*db/db^{roGFP}*) and control (*db/m^{roGFP}*) mice *in vivo*. Live animal imaging of these mice revealed increased mtROS in kidneys of diabetic mice (~5-fold ratiometric increase). Pre-treatment with mitoTEMPO (10mg/kg for 3days) restored mtROS to normal levels in diabetic mice. Podocytes isolated from diabetic animals revealed reduced complex 1 activity relative to controls suggesting that mtROS might be generated by problems with electron transport at its entry point. Ectopic expression of yeast NADH-dehydrogenase (Ndi1), a mammalian complex 1 homolog, successfully prevented high-glucose induced increases in mtROS.

Conclusions: We provide evidence that diabetic animals have increased levels of ROS within the mitochondrial matrix of the kidney *in vivo*. These increases in mtROS could be ameliorated by quenching of the mtROS, as well as bypassing electron transport at complex 1.

Funding: NIDDK Support

FR-OR051

Pro-Oxidant Enzyme Nox5 Accelerates Renal Damage in Experimental Diabetes Jay Chandra Jha,[1] Claudine Banal,[1] Stephen P. Gray,[1] Harald H. Schmidt,[2] Mark E. Cooper,[1] Rhian Touyz,[3] Chris R. Kennedy,[4] Karin Jandeleit-Dahm.[1] *[1]Diabetes Complications, Baker IDI Heart and Diabetes Inst, Melbourne, Victoria, Australia; [2]Dept of Pharmacology, Maastricht Univ, Maastricht, Netherlands; [3]Inst of Cardiovascular and Medical Sciences, Univ of Glasgow, Glasgow, United Kingdom; [4]Dept of Medicine, Ottawa Hospital Research Inst, Ottawa, Canada.*

Background: Reactive oxygen species (ROS) play crucial role in diabetic nephropathy (DN).The more recently discovered pro-oxidant enzyme, Nox5 could play a role in DN. Nox5 is present in humans but not in rodents. Thus, there is a paucity of information about Nox5 in animal models of DN. We examined the role of Nox5 in a model of human inducible Nox5 transgenic mice expressing Nox5 selectively in vascular smooth muscle cells including the mesangial cells (SM22+Nox5+) in the setting of diabetes. In vitro, we examined the effect of Nox5 silencing in human renal cells.

Methods: SM22+Nox5- and SM22+Nox5+ transgenic mice were rendered diabetic via streptozotocin injections and followed for 10 and 15 weeks. Renal function including albuminuria and creatinine clearance, structural damage as well as gene and protein expression of markers of inflammation, fibrosis and oxidative stress were assessed. In vitro, Nox5 was silenced in human mesangial cells or in podocytes and exposed to high glucose and TGF-β for the measurement of ROS level and molecular analysis.

Results: Diabetes induced increase in albuminuria in Nox5 negative mice was further increased by 20% in Nox5 positive diabetic mice. In addition, a further increase in glomerulosclerosis and markers of fibrosis (fibronectin), inflammation (MCP-1 and F4/80) and oxidative stress (nitrotyrosine and DHE) were found in diabetic SM22+Nox5+ mice when compared to diabetic SM22+Nox5- mice. Creatinine clearance was unchanged in both group of diabetic mice. Moreover, silencing of Nox5 in human renal cells resulted in reduced ROS production and down-regulation of profibrotic and proinflammatory markers that are implicated in DN.

Conclusions: Collectively, these findings suggest that Nox5 derived ROS accelerates renal injury in diabetes and provide proof of principle for the innovation of a new renoprotective agent in diabetes.

FR-OR052

Myo-Inositol Oxygenase (MIOX) Accelerates Renal Tubular Injury via Oxidative Stress Utilizing Glucuronate-Xylulose (GX) Pathway in Experimental Diabetes Isha Sharma, Yashpal S. Kanwar. *Dept of Pathology, Northwestern Univ, Chicago, IL.*

Background: MIOX is exclusively expressed in renal proximal tubules. Subsequent to the distal events of glycolytic pathway it channels myo-inositol into glucuronic acid via G-X pathway. During the various steps of this pathway there are perturbations in the ratios of NADPH:NADP and NAD:NADP, as a result there is an excessive generation of reactive oxygen species (ROS) via G-X pathway.

Methods: A diabetic state was induced with the administration of streptozotocin in wild type (WT), MIOX transgenic (TG) and MIOX$^{-/-}$ (KO) mice to assess the degree of MIOX-induced oxidant stress that influences the outcome of tubular injury among these strains. The animals with blood glucose >250 mg/dl were evaluated and sacrificed 8 weeks after induction of diabetes.

Results: The MIOX expression was highly accentuated in diabetic MIOX TG mice compared to WT and normoglycemic untreated or KO mice. Serum creatinine and urea levels were found to be significantly elevated in MIOX TG mice. The proximal tubules had relatively more cytolysis and apoptosis with thickened basement membranes and increased interstitial fibronectin and collagen I staining in TG mice compared WT and KO mice. The cellular redox in the kidney tissues was relatively more adversely affected in TG mice compared to other strains of mice, as highlighted by increased DHE staining. Also, a markedly decreased in reduced glutathione (GSH) levels were noted TG mice. Analyses

of various signaling events revealed an increased activation of p-PDK1, p-PKC and p-Akt in kidneys of MIOX TG mice. Likewise expression of TGF-β and Smad4 along with HIF-1alpha was relatively high in TG mice. All these parameters were minimally affected in MIOX KO mice. In vitro, HK-2 cells treated with MIOX-siRNA reduced the expression of all the above indicated signaling molecules and the ROS generation, as assessed by FACS analysis and DHE staining.

Conclusions: These data indicate that MIOX is another one of the newly discovered mediator in STZ induced tubular injury via G-X with accentuated generation of ROS in diabetic tubulopathy.

Funding: NIDDK Support

FR-OR053

Stabilization of Endogenous Nrf2 by Minocycline Protects against Nlrp3-Inflammasome Induced Diabetic Nephropathy Fabian Bock,[1] Khurrum Shahzad,[1] Moh'd Mohanad Ahmad Al-Dabet,[1] Ihsan Khan Gadi,[1] Shrey Kohli,[1] Berend Heinrich Isermann.[1] *[1]Univ Klinikum Magdeburg, Inst of Clinical Chemistery und Pathobiochemistry, Magdeburg, Germany; [2]Univ of Heidelberg, Dept of Internal Medicine I and Clinical Chemistry, Heidelberg, Germany.*

Background: While a plethora of studies support a therapeutic benefit of Nrf2 activation and ROS inhibition in diabetic nephropathy, the Nrf2 activator bardoxolone failed in clinical studies in type 2 diabetic patients due to side effects. Intriguingly, the tetracycline antibiotic minocycline, which has been in clinical use for decades and limits mitochondrial dysfunction and apoptosis, has been shown to convey anti-inflammatory effects in diabetic patients. As the mechanism underlying minocycline's nephroprotection remains unknown we speculated that minocycline reduces renal ROS generation and inflammation, potentially through a Nrf2 dependent mechanism.

Methods: The effect of minocycline on inflammasome activation and oxidative stress was studied in murine models of diabetic nephropathy, db/db mice and the STZ diabetes model. We assessed albuminuria, glomerular extracellular matrix accumulation as well as expression of Nrf2 and inflammasome regulators. Nrf2-ubiquitination was analyzed by immunoprecipitation.

Results: Here we show that minocycline protects against dNP in mouse models of type 1 and type 2 diabetes, while caspase-3,-6,-7,-8 and -10 inhibition is insufficient, indicating a function of minocycline independent of apoptosis inhibition. Minocycline stabilizes endogenous Nrf2 in kidneys of db/db mice, thus dampening ROS-induced inflammasome activation in the kidney. Indeed, minocycline exerts antioxidant effects *in vitro* and *in vivo*, reducing glomerular markers of oxidative stress. Minocycline reduces ubiquitination of the redox-sensitive transcription factor Nrf2 and increases its protein levels. Accordingly, minocycline mediated Nlrp3 inflammasome inhibition and amelioration of dNP are abolished in diabetic $Nrf2^{-/-}$ mice.

Conclusions: Taken together, we uncover a new function of minocycline, which stabilizes the redox-sensitive transcription factor Nrf2, thus protecting from dNP.

Funding: Government Support - Non-U.S.

FR-OR054

Renal Tubular ACE Affects Microalbuminuria in Early Diabetic Nephropathy Masahiro Eriguchi,[1] Jorge F. Giani,[1] Mercury Y. Lin,[2] Tuantuan Zhao,[1] Zakir Khan,[1] Ellen A. Bernstein,[1] Xiao Shen,[1] Romer Andres Gonzalez-Villalobos,[3] Kenneth E. Bernstein.[1] *[1]Depts of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA; [2]Pathology & Lab Medicine, Cedars-Sinai Medical Center, Los Angeles, CA; [3]CVMET RU, Cedars-Sinai Medical Center, Groton/Cambridge, MA.*

Background: ACE inhibitors are mainstay treatment for diabetic nephropathy. Studies demonstrated that the intrarenal renin-angiotensin system plays a key role in the progression of diabetic nephropathy. However, the specific contribution of renal tubular epithelial ACE vs. other sources of ACE to diabetic nephropathy remains unknown.

Methods: To study this, we used two mouse models: it-ACE mice that specifically lack ACE in renal tubular epithelial cells and ACE 3/9 in which renal ACE is only expressed in renal tubular cells. Total renal ACE in it-ACE and ACE 3/9 mice is 48% and 83% of WT mice; GFR is equivalent to WT mice. Diabetic nephropathy was induced with streptozotocin. Glomerular filtration rate (GFR), albuminuria and urinary KIM-1, a specific marker for tubular injury, were monitored. All data are presented as % of untreated WT control mice.

Results: Total renal ACE activity was decreased in both diabetic WT and diabetic ACE 3/9 mice (54±15% and 56±7%, $p<0.001$, n=4 to 6). No changes in total renal ACE were observed between diabetic and non-diabetic it-ACE mice (46±7% and 48±6%, p=NS). After 3 months of diabetes, both WT and it-ACE mice have increased GFR (142±11% and 147±7%, $p<0.05$). In contrast, ACE 3/9 did not increase GFR (107±6%). After 4 months of diabetes, microalbuminuria and urinary KIM-1 levels were significantly higher in both diabetic WT mice (220±17% and 498±94%) and ACE 3/9 mice (292±29% and 534±147%) compared to untreated WT mice. In diabetic it-ACE mice, despite glomerular hyperfiltration, depletion of renal tubular ACE reduced both microalbuminuria and urinary KIM-1 levels (122±7% and 236±38%) compared to diabetic WT mice.

Conclusions: This study indicates that in early diabetic nephropathy, tubulointerstital injury is associated with renal tubular ACE while hyperfiltration is associated with endothelial ACE. Finally, renal tubular epithelial ACE, and not endothelial ACE, is associated with microalbumnuria.

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FR-OR055

A Potent Pan-AMPK Activator Improves Renal Structure and Function in the ZSF-1 Rat Model of Diabetic Nephropathy Maarten Hoek, Xiaoyan Zhou, Robin E. Haimbach, Eric Muise, Li-Jun Ma, Olga Price, Gail M. Forrest, Kithsiri Herath, Emanuel Zycband, Zadok Ruben, Yonghua Zhu, Shirly Pinto, David E. Kelley. *Merck Research Labs, Kenilworth, NJ.*

Background: Defects in mitochondrial function and renal metabolism have been hypothesized to play a causal role in the pathophysiology of diabetic nephropathy. Non-specific AMPK activators such as AICAR improve renal function in multiple animal models, which has been attributed to the ability of these agents to improve the metabolic state of the kidney. The goal of these studies was to determine whether a potent Merck pan-AMPK activator would be beneficial in animal models of diabetic nephropathy.

Methods: An intervention study was performed in the ZSF-1 rat in which the Merck AMPK activator (Cmpd A, potency 6-60 nM, dosed at 1 and 10 mpk in feed) was compared to enalapril (10 mpk in feed). Treatment was initiated at 20 weeks, a timepoint at which renal damage was evident, and continued for another 28 weeks. Cell based studies were performed in primary human renal proximal tubule cells to assess the direct protective effects of Cmpd A in the context of a lipotoxic challenge or a challenge with TGF-β.

Results: The 10 mpk dose of Cmpd A led to improvements in uPCR (48.6 vs 18.2 mg/mg), GFR (430 vs 779 ml/min/gm kid weight) and renal histology scores compared to vehicle. These effects were comparable to enalapril treatment. Treatment with Cmpd A was accompanied by decreases in plasma glucose, body weight, and plasma lipids. Distinct renal RNA expression profiles were noted between the enalapril and Cmpd A treatments, with the endothelin axis and oxidative phosphorylation more affected by Cmpd A, suggesting that pathways affected by these treatments were at least partially orthogonal. Cmpd A protected primary human proximal tubule cells from lipotoxic stress and attenuated collagen induction in response to TGF-β.

Conclusions: Treatment with a specific AMPK activator resulted in substantial improvements in renal function in the ZSF-1 model of diabetic nephropathy. Though the effects may be secondary to systemic metabolic improvement, cell based assays and RNAseq data suggest that some of the effects might be attributed to direct action on the kidney.

Funding: Pharmaceutical Company Support - Merck & Co.

FR-OR056

AdipoRon Prevents Diabetic Nephropathy through Improvement of Lipid Metabolism in db/db Mice Yaeni Kim, Sun Ryoung Choi, Ji Hee Lim, Min Young Kim, Seon Deok Hwang, Yu Ah Hong, Yong-Soo Kim, Cheol Whee Park. *Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.*

Background: Adiponectin, one of the numerous adipokines produced by adipose tissue, interplays with others to exert the milieu of metabolic syndrome. Orally active synthetic molecule AdipoR agonist, AdipoRon binds to both AdipoR1 and AdipoR2 and ameliorates diabetic nephropathy (DN) in type 2 diabetes. The connection between adiponectin and lipid metabolism is apparent and the ceramide subspecies of shingolipids have been related to inflammation, cell death, and insulin resistance, so called lipotoxicity. We investigated the possible role of AdipoRon in renal physiology in the view of prevention and development of DN in diabetic mice.

Methods: Male *db/db* and *db/m* mice were fed either a regular chow or a diet containing AdipoRon (30 mg/kg/day p.o. for 4 weeks from 17 to 20 weeks of age). Serum, urine and renal tissue were analyzed for changes in metabolic parameters, relevant molecular levels and their association with regard to renal structure.

Results: AdipoRon fed *db/db* mice showed decreased amount of albuminuria and lipid accumulation in the kidney with no significant changes in the levels of serum adiponectin, glucose, creatinine, and body weight. Increased expressions of AdipoR1 and AdipoR2 in the renal cortex were observed in *db/db* mice with AdipoRon administration. Consistent up-regulations of p-AMPK, PPAR-α, p-Akt, p-ACC and p-eNOS and down-regulations of protein phosphatase 2A, SREBP-1c and iNOS levels were shown, which were related to a decrease in ceramide to sphingosine-1 phosphate ratio. In glomerular endothelial cells (GECs), AdipoRon treatment reduced lipotoxicity via attenuating palmitate-induced oxidative stress and apoptosis.

Conclusions: AdipoRon prevents lipotoxicity in the kidney as represented by decreased ceramide versus sphingosines ratio. The protective role of AdipoRon against the development of DN seems to occur through a direct action on the kidney independently of systemic effects of adiponectin. Its reduction of oxidative stress and apoptosis provides protection against renal damage via ameliorating endothelial dysfunction in DN.

FR-OR057

Fatty Kidney by Clinical 1H-Magnetic Resonance Spectroscopy: A Dietary Intervention and Validation Study in Porcine Kidneys Jacqueline Jonker,[1] Paul de Heer,[2] Evelien van Rossenberg,[1] Celine Klessens,[3] Hans J. Baelde,[3] Sietse Jan Koopmans,[4] Paulo G. Coelho,[6] Ingeborg M. Bajema,[3] Trea C.M. Streefland,[5] Ilona Alexandra Dekkers,[2] Ton J. Rabelink,[1] Patrick Rensen,[5] Hildo Lamb,[2] Aiko P.J. De Vries.[1] *[1]Nephrology, Leiden Univ Medical Center, Leiden, Netherlands; [2]Radiology, Leiden Univ Medical Center, Leiden, Netherlands; [3]Pathology, Leiden Univ Medical Center, Leiden, Netherlands; [4]Veterinary Medicine, Wageningen Univ, Wageningen, Netherlands; [5]Endocrinology, Leiden Univ Medical Center, Leiden, Netherlands; [6]New York Univ.*

Background: Renal lipid accumulation has been experimentally linked to obesity and type-2 diabetic nephropathy. Human translation has been hampered by lack of noninvasive biomarkers. ^{1}H-MR spectroscopy is an established technique to study lipids in liver, muscle and heart and feasibility was shown for kidney, but few protocols underwent validation. We assessed agreement between our ^{1}H-MRS protocol and enzymatically determined lipids in porcine kidneys.

Methods: Renal lipid content was measured in 27 porcine kidneys by ^{1}H-MRS on a 7T scanner, of which 15 mini-pigs were randomized to either 9-months control diet, cafeteria diet (CAF), or CAF with low-dose streptozotocin (CAF-S) to induce obesity and insulin-independent diabetes, with the remainder being slaughter pigs. Renal biopsies were taken at the same location and lipids were measured enzymatically.

Results: Bland-Altman analysis of normalised data of all kidneys showed good agreement with bias of 0.0 (limits of agreement -0.8; 0.8) for ^{1}H-MRS and enzymatically assessed lipid. After 9-month diet, renal triglyceride (TG) content was higher in CAF-S group (134.0 (44.7-229.8) nmol/mg protein) compared to the control group (36.0 (30.6-52.3) nmol/mg protein, P=0.02). Renal TG content was not significantly different between the control and cafeteria diet group. Notably, renal and hepatic TG showed significant positive correlation (n=14, r=0.97, P<0.001).

Conclusions: Our clinical ^{1}H-MRS protocol agreed well with gold-standard assessment of lipids in porcine kidneys, which correlated closely with hepatic lipid. This offers unique opportunity to investigate the pathophysiology of fatty kidney clinically in obesity and diabetic nephropathy.

FR-OR058

Macrophage-Derived Wnts Contribute to Kidney Fibrosis after Injury Yuan Tian, Dong Zhou, Haiyan Fu, Youhua Liu. *Dept of Pathology, Univ of Pittsburgh School of Medicine, Pittsburgh, PA.*

Background: Activation of Wnt/*β*-catenin signaling plays a pivotal role in the pathogenesis of many forms of chronic kidney diseases (CKD). Wnt ligands are induced in a wide variety of kidney resident cells as well as infiltrated cells including macrophages. However, the relative contribution of Wnts from different sources in CKD progression is poorly understood. To address this issue, we utilized genetic approach by blocking Wnt secretion via conditionally knockout of Wntless (Wl), a cargo receptor that is obligatory for Wnt trafficking and secretion.

Methods: We generated Wl conditional knockout mice in macrophage by crossing Lyz-Cre mice and Wl-floxed mice. Control and macrophage-specific Wl knockout mice were then subject to renal unilateral ureteral obstruction (UUO), and kidney fibrotic lesions assessed at 7 days after UUO. Mice were also subjected to acute kidney injury (AKI) induced by ischemic/reperfusion injury (IRI). Bone marrow-derived macrophages were cultured and analyzed.

Results: Macrophage-specific ablation of Wl in mice were confirmed by Western blot analyses of bone marrow-derived macrophage. The Lyz-Wl-/- mice were phenotypically normal. We found that at 1 day after IRI, there was no difference in serum creatinine and kidney pathology betwenn control and Lyz-Wl-/- mice. In addition, the mRNA level of pro-inflammatory cytokines such as TNF-α, MCP1, RANTES in knockout mice was not significantly altered as well, compared to the controls. However, ablation of Wl in macrophage attenuated renal fibrotic lesion at 7 days after UUO, accompanied by reduction of fibronectin, plasminogen activator inhibitor-1 and Snail1. In vitro, conditioned medium derived from the bone marrow-derived macrophages of Lyz-Wl-/- mice reduced fibroblast activation and fibronectin expression, compared to the controls.

Conclusions: These results suggested that macrophage-derived Wnts does not affect the early kidney injury after ischemic AKI. However, it plays a critical role in promoting kidney fibrosis after UUO.

Funding: NIDDK Support

FR-OR059

A Critical Role for Rictor/mTORC2 in Promoting Macrophage Activation and Kidney Fibrosis Jiafa Ren, Chunsun Dai. *Center for Kidney Disease, Nanjing Medical Univ.*

Background: Our published study reported that Rictor/mTORC2 signaling mediates TGFβ1-induced fibroblast activation and kidney fibrosis. However, the role and mechanisms for Rictor/mTORC2 in macrophage activation and kidney fibrosis are not clear.

Methods: In this study, a mouse model with tamoxifen-induced macrophage-specific deletion of Rictor and primary cultural macrophages from bone marrow (BMMs) were generated.

Results: Rictor/mTORC2 signaling was activated in macrophages from mouse kidneys at 1, 2 and 4 weeks after ischemia/reperfusion (I/R). All mice were administrated with tamoxifen at 1 week and sacrificed at 4 weeks after kidney I/R. Compared with their control littermates, the knockout mice developed less kidney fibrosis and inflammatory cell accumulation in kidney tissue at 4 weeks after I/R. Rictor-/- macrophages expressed less CTGF, TGFβ1, TGFβ3, PDGFB, VEGFA and VEGFC than Rictor+/+ macrophages from kidneys at 4 weeks after I/R. Macrophage proliferation in the kidneys was enhanced after I/R, whereas it was much less in the knockouts. TGFβ1 could induce the mRNA expression of CTGF, PDGFA, PDGFB and VEGFC in primary cultured Rictor+/+ BMMs, which were much less in Rictor-/- BMMs. Conditioned cultural medium (CM) from Rictor+/+, but not Rictor-/- BMMs efficiently promoted fibroblasts to express Collagen I, FN and α-SMA. Furthermore, Rictor+/+ BMMs adoptive transfer could worsen UUO nephropathy in mice pretreated with clodronate to preclear macrophages, whereas mice with Rictor-/- BMMs adoptive transfer developed much less kidney fibrosis.

Conclusions: Together, these results suggest that Rictor/mTORC2 signaling plays an important role for promoting macrophage activation and kidney fibrosis.

Funding: Government Support - Non-U.S.

FR-OR060

HIPK2 in Renal Tubules Is a Key Regulator of Kidney Fibrosis Wenzhen Xiao,[1] Ying Fan,[2] Zhengzhe Li,[1] Kyung (Kim) Lee,[1] John C. He.[1] *[1]Medicine/Div of Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY; [2]Nephrology, Shanghai Jiao Tong Univ Affiliated Sixth People's Hospital, Shanghai, China.*

Background: Renal fibrosis is the common pathway for the progression of CKD to ESRD. However, no effective treatment exists against renal fibrosis. We have shown that HIPK2 is a key protein kinase that mediates both pro-fibrotic and pro-inflammatory pathways in kidney cells. We showed previously that global knockout of HIPK2 attenuates renal fibrosis in several animal models of renal fibrosis including models of unilateral ureteral obstruction (UUO), folic acid nephropathy, and HIV-associated nephropathy. Here, we sought to further determine the role of HIPK2 specifically in renal tubular epithelial cells in contributing to renal fibrosis by using tubule-specific HIPK2 knockout and overexpression mice.

Methods: We generated floxed HIPK2 mice, which were crossed with PEPCK-Cre mice to generate renal tubular cell specific HIPK2 knockout mice. We also generated Tet-On HIPK2 overexpression mice, which were crossed with Pax8-rtTA mice to generate renal tubular cell-specific HIPK2 overexpression mice. We induced UUO in these mice and renal fibrosis was assessed at day 10 post-UUO.

Results: We confirmed that HIPK2 expression was significantly reduced in renal cortices in tubule-specific knockout mice by both real-time PCR and western blot analysis. Immunostaining also confirmed a reduction of HIPK2 in renal tubules. Using the same approach, we also confirmed that HIPK2 expression was increased in renal tubules of HIPK2 overexpression mice. After UUO, we observed that HIPK2 knockout mice developed less renal fibrosis in comparison to wildtype (WT) controls, whereas HIPK2 overexpression mice had worsened progression of renal fibrosis than in WT mice. In addition, expression of fibrosis markers such as collagen I, α-SMA, fibronectin, and Snail1 was attenuated in the HIPK2 knockout UUO mice, while increased in the HIPK2 overexpression UUO mice.

Conclusions: We conclude that increased expression of HIPK2 in renal tubular cells contributes to the development of renal fibrosis. HIPK2 could be a potential target to treat patients with renal fibrosis.

Funding: NIDDK Support, VA Support

FR-OR061

Stromal Progenitor Cell Deletion of STAT3 Protects Mice from Folic Acid-Induced Kidney Fibrosis by Inhibiting Pericytes/Fibroblasts Migration, Differentiation and Proliferation Amrendra Kumar Ajay, Venkata Sabbisetti, Joseph V. Bonventre. *Renal Div, Brigham and Women's Hospital, Boston, MA.*

Background: STAT3 is a key transcription factor involved in inflammation, tissue regeneration, tumor growth, cell proliferation and migration. In the kidney the exact function of STAT3 remains unknown. We developed a stromal progenitor cells (pericytes/fibroblast) conditional knock out mouse to study the function of STAT3 in kidney fibrosis progression.

Methods: Breeding STAT3 floxed mice with FoxD1 Cre, we developed kidney pericyte/fibroblast knock out mice. Folic acid (250 mg/kg body weight) was injected and mice were sacrificed on day 7. Kidney fibrosis was evaluated by Masson's Trichrome and alpha-smooth muscle actin (α-SMA) staining. RT-PCR was performed to quantify fibrotic markers (fibronectin, alpha smooth muscle actin, collagen 1a1). STAT3 gain of function (constitutive active STAT3) and loss of function (siRNA mediated knock down as well as phosphorylation mutants) studies were performed in the pericyte (10T&1/2) and mouse fibroblast (NIH3T3) cell lines.

Results: Mice with STAT3 depletion in kidney pericytes were protected from folic acid-induced kidney fibrosis and had a decrease in the number of myofibroblasts as observed by Masson's Trichrome and a-SMA staining. RT-PCR analyses showed significant decreased expression of fibrotic markers in pericyte/fibroblast knock out mice as compared to the floxed littermates. Further, gain of function and loss of function studies of STAT3 in pericyte (10T&1/2) and fibroblast (NIH3T3) cell lines confirmed that STAT3 plays an important role in phosphorylation of SMAD2/3.

Conclusions: STAT3 signaling plays a crucial role in pericyte differentiation, proliferation and migration, which is one of the critical events for the progression of kidney fibrosis. Targeting STAT3 signaling in pericytes may help to slow or inhibit fibrosis progression.

Funding: NIDDK Support

FR-OR062

Fibroblast-Specific Loss of Krüppel-Like Factor 15 Exacerbates Kidney Fibrosis Xiangchen Gu,[1] Yiqing Guo,[3] Timothy W. Miller,[3] John C. He,[2] Sandeep K. Mallipattu.[3] *[1]Nephrology, Yueyang Hospital of Integrated TCM and Western Medicine, Shanghai, China; [2]MSSM, New York, NY; [3]Medicine/Nephrology, Stony Brook Univ, Stony Brook, NY.*

Background: Regulation of fibroblast to myofibroblast differentiation in kidney fibrosis remains poorly understood. Krüppel-Like Factor 15 (KLF15), a zinc-finger transcription factor, has been demonstrated to play a critical role in progression of cardiac and kidney fibrosis. We sought to determine the mechanism by which the loss of KLF15 increases fibroblast to myofibroblast differentiation in kidney fibrosis.

Methods: To assess the role of Klf15 specifically in fibroblasts, we generated pericyte and resident fibroblast specific *Klf15* knockout mice (*Klf15$^{\Delta FoxD1}$*) by crossing *Klf15$^{fl/fl}$*mice with *Foxd1-Cre mice.* We utilized unilateral uninephrectomy (UUO for 3 and 7 days) and Angiotensin II (Ang II infusion for 4 weeks) as murine models of fibrosis. Mouse embryonic fibroblasts (MEF) with stable knockdown of *Klf15* (*Klf15*-shRNA) and empty vector (*EV-shRNA*) were generated using lentiviral delivery.

Results: *Klf15$^{\Delta FoxD1}$* mice exhibited an increase in pro-fibrotic markers (αSMA, Col1α1, fibronectin, vimentin) and fibroblast proliferation (Ki67) as compared to wildtype mice at 3 and 7 days post UUO. Similarly, we observed an increase in pro-fibrotic markers and fibroblast proliferation in AngII-treated *Klf15$^{\Delta FoxD1}$* mice as compared to AngII-treated wildtype mice. Gene-set enrichment analysis of genes with KLF15 binding sites identified an increase in the pathways involved in suppression of Wnt/β-catenin pathway. We initially confirmed that *Klf15$^{\Delta FoxD1}$* mice exhibited an increase in Wnt/β-catenin signaling (activated-phospho β-catenin, c-Myc, Lef1) as compared to wildtype mice post UUO. We also observed that *Klf15-shRNA* MEFs exhibited a significant increase in Wnt/β-catenin signaling (activated-phospho β-catenin, c-Myc), pro-fibrotic markers (αSMA, Col1α1, fibronectin), and proliferation (Ki67 and MTT assay) as compared to *EV-shRNA* MEFs after Wnt1 ligand treatment for 72 hours.

Conclusions: These data suggest that the loss of *Klf15* in pericyte/resident fibroblast-specific accelerates fibroblast to myofibroblast differentiation in models of kidney fibrosis.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic Inc.

FR-OR063

Role of Lysophosphatidic Acid (LPA)/LPA Receptor in EGFR-Mediated Renal Fibrosis Jessica Marie Overstreet, Ming-Zhi Zhang, Raymond C. Harris. *Medicine, Vanderbilt Univ, Nashville, TN.*

Background: Excessive tissue scarring or fibrosis is a critical contributor to chronic kidney disease, which ultimately leads to organ failure. We have previously demonstrated that overactivation of EGFR in the proximal tubule epithelium of mice is sufficient to promote spontaneous, progressive renal fibrosis. The role of the lysophosphatidic acid (LPA)/LPA receptor axis in epithelial-fibroblast crosstalk and renal fibrosis is less understood.

Methods: For *in vivo* analysis, we generated male C57BL/6 mice with human HB-EGF selectively expressed in the renal proximal tubule epithelia (hHB-EGF$^{Tg/Tg}$) to overactivate EGFR. hHB-EGF$^{Tg/Tg}$ mice were crossed with *Waved2* mice (hHB-EGF$^{Tg/Tg}$;*Waved2*), which have a 90% reduction in EGFR kinase activity. Human proximal tubule epithelial cell line (hRPTEC) and mouse cortical fibroblasts were used for communication studies *in vitro*.

Results: Immunohistochemical analysis revealed an increase in LPA_1 and autotaxin, an enzyme that produces LPA, in the interstitium surrounding the tubule epithelium of hHB-EGF$^{Tg/Tg}$ mice compared to wildtype mice. The increased expression of LPA_1 and autotaxin observed in hHB-EGF$^{Tg/Tg}$ mice was attenuated in HB-EGF$^{Tg/Tg}$;*Waved2* mice. EGF-treatment induced LPA secretion from hRPTEC measured by high performance liquid chromatography. Conditioned media collected from EGF-treated hRPTECs increased fibroblast proliferation and activation as indicated by increased fibronectin, α-smooth muscle actin (α-SMA), and cyclin D protein expression in comparison to fibroblasts incubated in conditioned media from untreated hRPTECs. Further, conditioned media derived from hRPTECs exposed to EGF+ Erlotinib, an EGFR kinase inhibitor, induced less fibroblast proliferation. Fibroblasts treated with EGF-induced conditioned media + Ki16425, an LPA_1/LPA_3 inhibitor, prevented the increased proliferation seen with EGF-induced conditioned media from hRPTECs.

Conclusions: These results suggest that EGFR activation in the proximal tubule promotes the secretion of paracrine factors driving fibroblast activation and proliferation, likely through a LPA/LPAreceptor-dependent pathway.

Funding: NIDDK Support, VA Support

FR-OR064

Worn-out GBM Components, Particularly the Collagen IV-Alpha1 Chain, Account for Mesangial Matrix Expansion in Diabetic Nephropathy (DN) in Humans Wilhelm Kriz,[1] Jana Loewen,[1,2] Giuseppina Federico,[2] Elisabeth Groene,[2] Hermann-Josef Groene.[2] *[1]Dept of Neuroanatomy, Medical Faculty Mannheim, Univ of Heidelberg, Mannheim, Germany; [2]Dept of Molecular Pathology, German Cancer Research Center, Heidelberg, Germany.*

Background: Mesangial matrix expansion is a hallmark of DN and generally believed to emerge from the overproduction by mesangial cells; other sources have so far not been considered.

Methods: Re-evaluation of 918 biopsies of DN from the years 2007-2015 (types 1 and 2 were not separated) by light and electron microscopy (LM,TEM), immunofluorescence (IF) and in-situ hybridization (ISH).

Results: As seen by LM and TEM at least a major part of the accumulated matrix in the mesangium in DN is derived from the deposition of worn-out GBM-material. The process is as follows:

The DN specific thickening of the GBM causes a narrowing of the spaces within the GBM-infoldings compromising the situation of the podocytes therein. They retract out of them leaving back shedded cytoplasmic material that becomes included into the innermost portions of the GBM. These portions disconnect from the GBM and are dropped into the mesangium. The inclusions of podocyte cytoplasmic remnants provide a label proving that this material is derived from the GBM.

As seen by IF, the collagen IV-α1, α3 and α5 chains all contribute to mesangial matrix accumulation (other components so far not studied). Whereas the staining of the α3 and α5 chains fades out with time, the staining of the α1 chain is dominant and persists even in nodules.

As seen by ISH, the synthesis of the α3 and α5 chains by podocytes seems not to be changed in DN compared to controls. In contrast, the synthesis of the α1 chain by endothelial cells seems to be substantially increased (a contribution by mesangial cells cannot be excluded); however, the crucial derangement likely consists of its failed degradation.

Conclusions: These findings put the turnover of the GBM into centre stage of the pathogenesis of DN. They support the view (Walker F. 1973, J Pathol 110: 233) that components of the GBM are synthesized by podocytes and endothelial cells and degraded within the mesangium.

FR-OR065

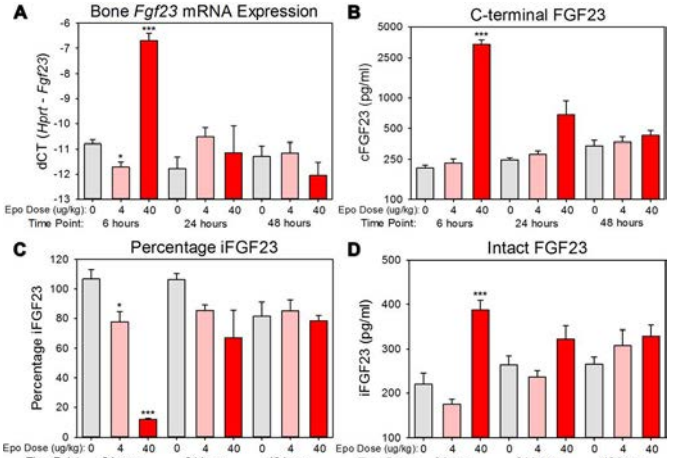
Erythropoietin Increases Bone FGF23 Expression and Circulating FGF23 Levels Mark R. Hanudel,[1] Maxime Rappaport,[1] Kristine Chua,[2] Erica Clinkenbeard,[3] Victoria Rivka Gabayan,[2] Tomas Ganz,[2] Kenneth E. White,[3] Isidro B. Salusky,[1] Elizabeta Nemeth.[2] *[1]Dept of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA; [2]Dept of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA; [3]Dept of Medical & Molecular Genetics, Indiana Univ School of Medicine, Indianapolis, IN.*

Background: Polycystic kidney disease is associated with higher levels of both erythropoietin (EPO) and FGF23. Iron deficiency anemia, which is also associated with higher EPO, increases bone *Fgf23* expression. These observations raise the possibility that EPO may affect FGF23 production and metabolism.

Methods: To assess the acute effects of EPO on FGF23 parameters, wild type (WT) C57BL/6 mice, and three anemic human subjects, were injected with a single dose of human recombinant EPO, and FGF23 parameters were measured at subsequent intervals. To assess whether the effects of EPO on FGF23 are mediated by erythroferrone, an EPO-responsive, marrow-produced, hepcidin suppressing hormone, WT and erythroferrone knockout mice were treated with 3 days of saline or EPO.

Results: At 6 hours after injection of 40 μg/kg EPO, the mice had significantly increased bone *Fgf23* mRNA expression, significantly increased circulating FGF23 levels, and significantly decreased percentage intact FGF23, suggesting concurrent effects on expression and post-translational cleavage. Similarly, in the three adults, C-terminal FGF23 levels increased 1.8-fold at 12 hours after injection of 20,000-40,000 units EPO, with less of an effect on intact FGF23. Erythroferrone knockout did not ameliorate EPO-induced increases in FGF23, suggesting an erythroferrone-independent effect.

Conclusions: Independent of erythroferrone, EPO increases bone *Fgf23* expression, coupled with increased FGF23 cleavage.



Funding: Other NIH Support - K12 Child Health Research Career Development Award (NIH 5K12HD034610-18)

FR-OR066

Cross-Talk of Anemia and Phosphate Metabolism via FGF23 in a Model of PKD Erica Clinkenbeard,[1] Hitesh Nidumanda,[1] Pu Ni,[1] Julia M. Hum,[1] Yves Sabbagh,[2] Kenneth E. White.[1] *[1]Dept Medical and Molecular Genetics, Indiana Univ, Indianapolis, IN; [2]Rare Diseases, Sanofi Genzyme, Framingham, MA.*

Background: Fibroblast growth factor 23 (FGF23) is a bone derived hormone responsible for maintaining phosphate homeostasis. We have found in addition to phosphate, FGF23 is also be significantly induced with iron-deficiency anemia. Interestingly, patients with polycystic kidney disease (PKD) maintain EPO production during anemia, whereas patients with CKD-MBD often demonstrate anemia with loss of EPO production in concert with phosphate homeostasis dysregulation. Therefore, the purpose of our study was to test the associations between FGF23 and anemia in a mouse model of PKD and to determine the molecular mechanism driving the cross-talk between iron and phosphate homeostasis.

Methods: Juvenile cystic kidney (Jck) mice harboring a *Nek8* mutation, were maintained on a normal chow and monitored from 4 to >20 weeks of age for complete blood counts, serum FGF23, erythropoietin (EPO) and total iron levels. Additionally, we tested factors important for iron handling on rat osteoblast cells (UMR-106) to determine EpoR and FGF23 mRNA levels.

Results: Serum intact FGF23 becomes significantly increased in Jck mice over normal controls during the course of disease (13-fold, $p<0.0005$). Jck mice also exhibited anemia with reductions in red blood cells, hematocrit and hemoglobin. We found a negative correlation between total iron and FGF23 ($p<0.005$), and the reciprocal strong positive correlation between serum EPO and FGF23 ($p=0.03$) in Jck mice across time. In UMR-106 cells, iron chelation stimulated EpoR mRNA expression. Human EPOR was transfected in the cells and upon EPO treatment initiated canonical JAK/STAT signaling which associated with induced FGF23 mRNA ($p<0.05$). Additionally, FGF23 promoter activity was stimulated by EPO administration.

Conclusions: During anemia, EPO is an independent regulatory factor for FGF23, and may be in part, responsible for elevated FGF23 in PKD, and EPO-treated CKD-MBD. This, in conjunction with iron deficiency may be modifiable risk factors in rare and common disorders of phosphate metabolism.

Funding: NIDDK Support, Other NIH Support - NIAMS F32; AHA fellowship

FR-OR067

The FGF Receptor Inhibitor Decreases FGF23 Levels in Uremic Rats Maria Lerche Mace,[1,2] Eva Gravesen,[2] Anders Nordholm,[1,2] Jacob Hofman-Bang,[2] Klaus Olgaard,[2] Ewa Lewin.[1,2] *[1]Dept of Nephrology, Herlev Hospital, Copenhagen, Denmark; [2]Dept of Nephrology, Rigshospitalet, Univ of Copenhagen, Denmark.*

Background: The phosphaturic hormone fibroblast growth factor 23 (FGF23) is severely increased in uremia, where it is associated with increased cardiovascular complications and mortality. Our aim was to study whether inhibition of the FGF receptor (FGFRi) had a regulatory impact on FGF23, Klotho and PTH.

Methods: Chronic kidney disease was induced in Wistar rats by 5/6 nephrectomy. After 8 weeks of uremia, uremic rats (U) and age-matched control rats (C) were randomized to FGFRi (20mg PD173074) or vehicle. Plasma FGF23 and PTH were measured along with gene expression of *FGF23* in bone and kidney expression of α*Klotho*, *NaPi2a, NaPi2c* and *FGFR1IIIc*.

Results: Uremic rats had increased p-creatinine (72±11 vs 32±1 μM), p-phosphate (2.57±0.18 vs 2.05±0.08 mM), p-PTH (932 (355-2929) vs 224 (169-290) pg/ml) and p-FGF23 (1925±554 vs 367±21 pg/ml) (all $p<0.05$). FGFRi resulted in a significant decrease in p-FGF23 to 154±18 pg/ml in C rats and 738±174 pg/ml in U rats, and in down-regulation of the *FGF23* mRNA in bone (C rats: 1.54±0.23 to 0.15±0.03. U rats: 2.79±0.61 to 0.14±0.03) (all $p<0.01$). Despite stable p-calcium^{2+} and p-phosphate, PTH rose significantly to 392 (281-2079) in C rats and to 2719 (1579-16912) in U rats after FGFRi ($p<0.05$). The present results didn't support the concept of parathyroid resistance to FGF23 in uremia, but demonstrated renal resistance to FGF23. In the kidney of C rats FGFRi resulted in a significant increase in the expression of *αklotho* (1.40±0.05 to 1.72±0.03), *NaPi2a* (1.48±0.05 to 1.72±0.05) and *NaPi2c* (1.44±0.03 to 1.73±0.11) (all $p<0.05$). In contrast, in the kidney rudiment of U rats FGFRi had no effect on the expression of *αklotho* (0.82±0.15 vs. 0.87±0.13), *NaPi2a* (0.83±0.18 vs. 0.83±0.14) and *NaPi2c* (0.80±0.16 vs. 0.90±0.15). FGFRi did not affect the expression of *FGFR1IIIc*.

Conclusions: Inhibition of the FGF receptor has a powerful down-regulatory impact on FGF23 levels in both normal and uremic rats. The expression of Klotho was up-regulated in the normal kidney, but unchanged in the injured kidney by PD173074. These results demonstrate renal, but not parathyroid resistance to FGF23 in chronic uremia.

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

FR-OR068

Acute Parathyroid Hormone (1-34) Challenge Increases C-Terminal Fibroblast Growth Factor 23 Levels but Not Intact Fibroblast Growth Factor 23 Levels Marta Christov,[1,2] Vanessa Maria Knab,[2] Braden A. Corbin,[2] Olena Andrukhova,[4] Julia M. Hum,[3] Pu Ni,[3] Seham M. Rabadi,[1] Akira Maeda,[2] Kenneth E. White,[3] Reinhold Erben,[4] Harald Jüppner.[2] *[1]Medicine, New York Medical College, Valhalla, NY; [2]Medicine, Massachusetts General Hospital, Boston, MA; [3]Medical and Molecular Genetics, Indiana Univ School of Medicine, Indiana, IN; [4]Univ of Veterinary Medicine of Vienna, Vienna, Austria.*

Background: The acute effects of parathyroid hormone (PTH) on fibroblast growth factor 23 (FGF23) *in vivo* are not well understood.

Methods: Injection of PTH into wild type and autosomal dominant hypophosphatemic rickets (ADHR) mice. Treatment of differentiated calvarial osteocytes with PTH.

Results: After a single s.c. PTH(1-34) injection (50nmol/kg) in mice, FGF23 levels were measured in plasma using assays that measure either intact alone (iFGF23) or intact/C-terminal FGF23 (cFGF23). Furthermore, FGF23 mRNA and protein levels were assessed in bone. In addition, we examined the effects of PTH treatment on FGF23 production *in vitro* using differentiated calvarial osteocytes. cFGF23 levels increased by 3- 5-fold within two hours following PTH injection, which returned to baseline by 4 hours. In contrast, iFGF23 levels remained unchanged for the first two hours, yet declined to approximately 60% by 6 hours and remained suppressed before returning to baseline after 24 hrs. Using mice that are homozygous for the ADHR-FGF23 mutation or animals treated with a furin inhibitor, we showed that cFGF23 and iFGF23 levels increased equivalently after PTH injection. These findings are consistent with increased FGF23 production in bone, yet rapid cleavage of the secreted intact protein. Using primary cultures of differentiated osteocytes, we showed that PTH increased FGF23 mRNA expression through cAMP/PKA, but not IP3/PKC signaling.

Conclusions: In conclusion, PTH injection rapidly increases FGF23 production in bone *in vivo* and *in vitro*. However, intact FGF23 is rapidly degraded. At later timepoints and through an as yet unidentified mechanism there is a sustained decrease in FGF23 production.

Funding: NIDDK Support, Private Foundation Support

FR-OR069

Paricalcitol and FGFR Blockade Synergistically Attenuate Uremic Cardiac Hypertrophy Michael Freundlich,[1] Christian Faul,[2] Saurav Singh,[2] Yasmir Quiroz,[3] Brian A. Czaya,[2] Keila Zulimi Yaguas,[3] Bernardo Rodriguez-Iturbe.[3] *[1]Pediatric Nephrology, Univ of Miami, Miami, FL; [2]Nephrology, Univ of Miami, Miami, FL; [3]Nephrology, Hospital Univ-IVIC, Maracaibo, Venezuela.*

Background: In uremic (U) rodents, FGF23 activates myocardial calcineurin/NFAT signaling causing cardiac hypertrophy (CH) that can be blocked by inhibiting FGF receptor (FGFR) 4, and paricalcitol (Pc) improves CH by suppressing the myocardial renin-angiotensin-system (RAS). Since Pc suppresses NFAT with CH attenuation in non-U animals, we studied whether Pc inhibits myocardial NFAT in U rats and if FGFR blockade amplifies the Pc effects.

Methods: 5/6 nephrectomized rats receiving Pc alone (0.3 mcg/kg x3/week) or Pc+pan-FGFR blocker PD173074 (PD; 1mg/kg), were compared to untreated (Nx) and sham (S). After 4 weeks, we analyzed heart /body weight (HW/BW) ratio, myocardial expression RT-PCR profiles, blood pressure (BP), and blood levels of creatinine and FGF23.

Results: Pc or Pc+PD versus Nx significantly attenuated renal dysfunction, hypertension and HW/BW with further elevation of FGF23. Pc+PD versus Pc significantly lowered HW/BW despite similarly elevated FGF23. Neither FGF23 nor BP correlated with HW/BW. Compared to S, myocardial expression markers for hypertrophy, fibrosis and inflammation, FGFR4, NFAT target genes (RCAN1, TRPC6), angiotensinogen and AT1R were significantly elevated in Nx and reduced by Pc and Pc+PD. Of note, some NFAT and hypertrophy markers were significantly lower in Pc+PD versus Pc, and associated with 80% higher cumulative Pc dose/prevailing log FGF23 ratio, a presumptive indicator of the anti-hypertrophic effect of Pc.

Conclusions: In addition to RAS suppression, and independently of FGF23/FGFR4 signaling, Pc suppresses cardiac NFAT in U animals. This VDR-mediated anti-hypertrophic effect is further magnified by PD co-administration, and may be dependent on the Pc dose relative to prevailing FGF23 levels. Based on the uncovered synergistic cardio-protective effects of Pc and FGFR blockade, future clinical studies should aim at targeting FGFR4 in addition to tailored Pc doses adjusted to the prevailing FGF23 levels, to effectively treat uremic CH.

Funding: Other NIH Support - NHLBI

FR-OR070

Endothelial Dysfunction in Experimental Chronic Kidney Disease Is Caused by FGF23 Melissa Verkaik,[1,2,3,4] Pieter M. Ter Wee,[1] Etto C. Eringa,[2] Marc G. Vervloet.[1] *[1]Dept of Nephrology, VU Univ Medical Center, Amsterdam, Netherlands; [2]Dept of Physiology, VU Univ Medical Center, Amsterdam, Netherlands; [3]Inst of Cardiovascular Research ICaR-VU; [4]On Behalf of the NIGRAM Consortium.*

Background: Cardiovascular causes account for approximately 50% of mortality in patients with chronic kidney disease (CKD). FGF23, a phosphate-lowering protein and elevated in CKD, is associated with endothelial dysfunction and cardiovascular mortality. We hypothesized that CKD impairs vascular function and that this can be attributed to FGF23.

Methods: Seven weeks old male wild type C57Bl/6J mice were subjected to partial nephrectomy (5/6Nx) or sham-surgery. After 6 weeks resistance arteries were isolated and subjected to a pressure myograph setup to test *ex vivo* vascular function. A second non-CKD group received either PBS or FGF23 i.p. injections for 7 consecutive days twice daily. To assess whether FGF23 mediates CKD-induced endothelial dysfunction, a third group received FGF23 antibodies by i.p. injections, in combination with a low phosphate diet, 6 weeks following 5/6Nx surgery. A control group received control antibodies and a normal diet. To assess eNOS uncoupling, femoral arteries were used to determine eNOS monomer and dimer protein expression by low-temperature SDS-PAGE.

Results: Plasma FGF23 significantly increased after 5/6Nx surgery (1.7-fold p=0.01), as well as fractional excretion of phosphate (FEP) (4-fold p=0.003). 5/6Nx blunted ex vivo vasodilator responses to acetylcholine (p=0.002), whereas responses to sodium nitroprusside (SNP) or endothelin were normal. Seven days *in vivo* FGF23 injections completely mimicked this vascular endothelial defect (p=0.021), and in accordance, responses to SNP and endothelin were not altered. Short-term *ex vivo* FGF23 administration to isolated vessels did not change vascular reactivity. FGF23 antibodies in CKD mice prevented development of endothelial dysfunction (p=0.048). eNOS uncoupling was not observed after either 5/6Nx or FGF23 injections.

Conclusions: Impaired endothelium-dependent vasodilatation in CKD mice is mediated by FGF23 and can be prevented by blocking FGF23. These data corroborate FGF23 as a main target to combat in cardiovascular disease in CKD.

FR-OR071

Regulation of Phosphate Homeostasis by the Central Nervous System Daniela Egli-Spichtig,[1] Martin Y.H. Zhang,[1] Komuraiah Myakala,[2] Evgenia Dobrinskikh,[2] Moshe Levi,[2] Farzana Perwad.[1] *[1]Pediatric Nephrology, Univ of California San Francisco, San Francisco, CA; [2]Dept of Medicine, Univ of Colorado, Aurora, CO.*

Background: Phosphate (Pi) homeostasis is determined by dietary intake, intestinal absorption, renal excretion and skeletal turnover and is tightly regulated by parathyroid hormone, fibroblast growth factor 23 (FGF23) and 1,25 dihydroxyvitamin D_3. Although several Pi cotransporters have been identified, Pi sensing mechanisms are still unknown. We hypothesize that Pi sensing in the central nervous system (CNS) plays a role in the regulation of systemic phosphate homeostasis in mice.

Methods: 12 weeks old C57/BL6 mice were fed a low Pi (0.02%) diet and received intracerebroventricular (ICV) injections of either vehicle (ICV-Veh) or 20 nmol potassium dibasic phosphate (ICV-Pi).

Results: Sodium-dependent Pi (NaPi) uptake and NaPi-IIc protein abundance in the kidney were reduced by 30% and urinary Pi excretion increased by 3-fold in ICV-Pi compared to ICV-Veh injected mice after one hour. Serum Pi and FGF23 levels were not significantly different in the two groups. We next determined whether increasing cerebrospinal fluid (CSF) Pi concentrations with ICV-Pi injections or by manipulating dietary Pi intake regulates CNS Klotho expression. We observed a 35% decrease in Klotho protein expression in the choroid plexus in ICV-Pi compared to ICV-Veh injected mice. In mice fed an acute high Pi (1.65%) diet which is known to increase CSF Pi, we observed a 56% decrease in Klotho protein abundance in the choroid plexus compared to mice fed a low Pi diet. As expected, serum Pi concentrations and urinary Pi excretion increased by 6- and 300-fold, respectively, in mice fed the high Pi diet compared to the low Pi diet group.

Conclusions: ICV Pi injections stimulate urinary Pi excretion independent of serum Pi and FGF23 levels providing evidence for a CNS-kidney signaling axis. Increased CSF Pi levels and high dietary Pi intake suppress Klotho expression in the choroid plexus. Our study provides evidence that Pi regulates CNS Klotho expression and suggests Pi sensing in the CNS plays a role in the regulation of systemic phosphate homeostasis in mice.

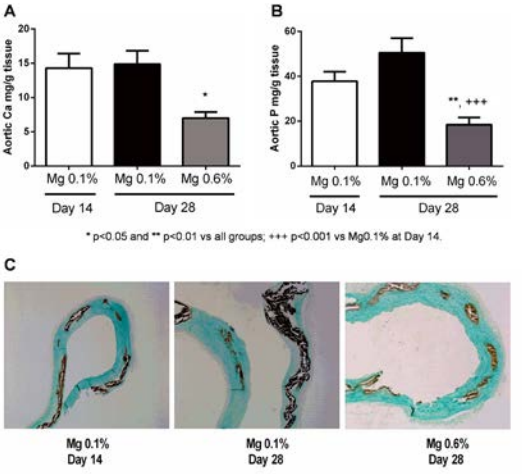
FR-OR072

Dietary Magnesium Supplementation Prevents and Reverses Vascular and Soft Tissue Calcifications in Uremic Rats Mariano Rodriguez,[3] Juan R. Munoz-Castaneda,[3] Alan Peralta-Ramirez,[2,3] Yolanda Almaden Peña,[4] Maria Encarnacion Rodriguez Ortiz,[7] Ignacio Lopez,[1] Carmen Maria Herencia,[3] Noemi Vergara Segura,[3] Sonja Steppan,[5] Julio Manuel Martínez Moreno,[3] Juan M. Diaz Tocados,[3] Antonio Canalejo,[6] Escolastico Aguilera-Tejero.[1] *[1]Medicina y Cirugía Animal, Univ Cordoba, Cordoba, Spain; [2]Univ Nac Autónoma de Nicaragua, Leon, Nicaragua; [3]Servicio de Nefrología (Red in Ren), IMIBIC/Hosp Univ Reina Sofia/Univ Cordoba, Cordoba, Spain; [4]Lipidos y Aterosclerosis, IMIBIC/ Hosp. Univ Reina Sofia/Univ Cordoba and CIBEROBN, ISCIII, Cordoba, Spain; [5]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [6]Biologia Ambiental y Salud Publica, Univ Huelva, Huelva, Spain; [7]Laboratorio de Nefrología, IIS Fundación Jiménez Díaz, Madrid, Spain.*

Background: There is an association between low serum Mg and mortality in CKD patients finding an inverse correlation with cardiovascular events. Although Mg has been shown to prevent vascular calcification (VC) *in vitro*, controlled *in vivo* studies in uremic models are limited.

Methods: To investigate the effect of different levels of dietary Mg intake (from 0.1 to 1.1%) on the prevention and treatment of VC in vivo studies through 5/6 Nx rats fed with a high P diet (1.2%).

Results: A moderate increase in dietary Mg (0.3%) was associated with a reduction in aortic Ca content together with an improvement in mineral metabolism parameters. In comparison with a restricted phosphate diet (P 0.7%), Mg supplementation (0.6%) reduced more efficiently aortic Ca and P content. The effects of Mg on VC were not only limited to phosphate binder action, finding a reduction of blood pressure and improving renal function. In a second study, uremic rats with established VC (Mg 0.1%, Day 14) were fed a diet with either normal (Mg 0.1%, Day 28) or moderately increased Mg (Mg 0.6%, Day 28).Dietary Mg supplementation reduced VC and mortality.



Conclusions: Dietary Mg prevented and reversed both VC and mortality in uremic rats.

Funding: Pharmaceutical Company Support - Fresenius Medical Care, Government Support - Non-U.S.

FR-OR073

The Kidney Is the Major Site for Fibroblast Growth Factor-23 Disposal in Humans Giacomo Garibotto, Daniela Verzola, Francesca Ansaldo, Samantha Milanesi, Francesca Viazzi. *Dept of Internal Medicine, Nephrology Div, Genoa Univ and IRCCS AOU San Martino-IST, Genoa, Italy.*

Background: Fibroblast Growth Factor 23 (FGF-23) accumulates in blood of patients with chronic kidney disease and is associated both with cardiovascular complications and disease progression. However, our knowledge of the sites and mechanisms which regulate plasma FGF-23 is still incomplete.

Methods: We measured plasma FGF-23 (ELISA assay Endo Millipore, Darmstadt, Germany) across the kidney, splanchnic organs and lung in nine patients (4 males, 5 females, median age 72 yrs, eGFR 65±6 ml/min) during elective diagnostic cardiac catheterizations.

Results: Arterial FGF-23 levels were in the normal range (median 14.3, range 10.5-32.7 pg/ml). Renal vein FGF-23 concentrations were remarkably lower (by ~21.6 %,$p < 0.01$) than the corresponding arterial values, indicating that plasma FGF-23 decreases substantially after a single pass across the kidney. Surprisingly, the fractional extraction (FE) of FGF-23 across the kidney was similar (p=NS) to that of creatinine (18.5%). FGF-23 level in the liver vein was quite similar (14.9±2 pg/ml) to that of arterial FGF-23. Arterial FGF 23 levels were almost identical to systemic venous (pulmonary artery) whole body levels (15.7±2 pg/ml), documenting zero balance of FGF 23 across these organs systems.

Conclusions: Our data show that the human kidney is the only site for FGF-23 removal from blood. Besides providing a better understanding of physiology of FGF-23 metabolism, the data reported in this study could be useful to understand the alterations in FGF-23 that are observed in CKD and many systemic and organ diseases.

Funding: Government Support - Non-U.S.

FR-OR074

Deletion of the Gene Encoding Transient Receptor Potential Canonical 1 (TRPC1) Channel in Mice Produces the Phenotypes of Familial Hypocalciuric Hypercalcemia (FHH) and Skeletal Parathyroid (PTH) Resistance Kai Lau,[1,2] Bonnie Eby,[1] Marybeth Humphrey,[1,2] Leonidas Tsiokas.[3] *[1]Medicine, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK; [2]Medical Service, VA Medical Center, Oklahoma City, OK; [3]Cell Biology, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK.*

Background: Previously we showed TRPC1 deficiency induces hypercalcemia, high PTH but increased bone mass, indicating TRPC1 controls Ca entry & cell [Ca] in concert with CaSR to regulate PTH secretion. Our 1st aim was to test the thesis that TRPC1 deficiency replicates FHH phenotypes. Our 2nd aim was to study skeletal resistance in null mice.

Methods: We studied wild-type & null mice by standard metabolic, clearance (Cl) & micro-CT techniques. Serum (S) PTH, 1,25 di(OH) vit D (1, 25 D), & calcitonin were analyzed by ELISA; alkaline (Alk) & acid phosphatases (Ptase), creatinine (creat), Ca, Mg, P & urine (U) hydroxproline (HP) by published method.

Results: We confirmed high SCa & high PTH in null males from 2nd to 12th m, without changes in S creat, 1,25 D, calcitonin, P or Mg. At 7 m, null males were normomagnesiuric but hypocalciuric [UCa (1 vs. 2 mg/d), UCa/creat (2 vs. 3), CaCl (14 vs. 26 ul/min)]. In null females, SCa (10 vs. 8.5 mg %) was up, PTH inversely related to SCa, & low urine Ca (1 vs. 1.6 mg/d), UCa/cre (2 vs. 3) & CaCl (13 vs. 22 ul/min). In null males & females, S AlkPtase was down by 20-40 % from 2nd-16th m. Osteoclastic activities were down (30% down in tartrate-resistant acid Ptase, 45% down in UHP, 3-fold up in trabecular

connectivity density, 37% more trabecular #, & 25% less trabecular spacing). At both 3 & 19 m, bone volume/tissue volume was higher in null mice. At 7th mon, their hind limbs were 25% heavier.

Conclusions: 1. TRPC1 deficiency impairs Ca entry, reduces cell [Ca] & stimulates PTH to cause hypercalcemia. 2. Similar to FHH, 1,25 D, P & Mg are normal, but hypocalciuria is prominent in both sexes like CaSR inactivation. 3. Despite chronic PTH excess, due to resistance, resorption is down & bone volume up in null mice. 4. These data support the key roles TRPC1 plays in PTH secretion, Ca absorption & bone biology.

Funding: NIDDK Support, Private Foundation Support

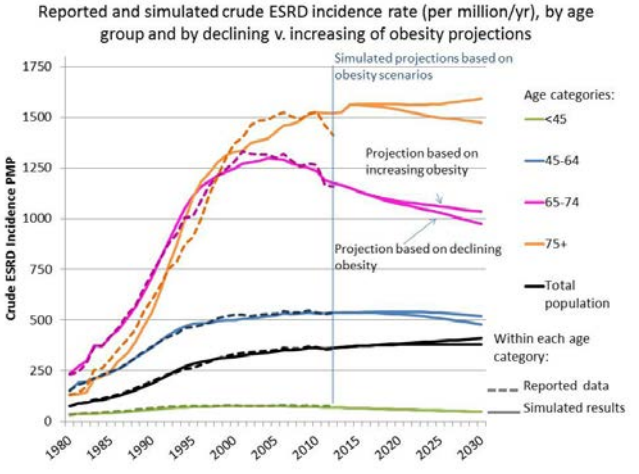
FR-OR075

Projecting End Stage Renal Disease (ESRD) Incidence and Prevalence in the United States through 2030 Keith McCullough,[1] Hal Morgenstern,[2] William H. Herman,[2] Rajiv Saran,[2] Bruce M. Robinson.[1,2] *[1]Arbor Research Collaborative for Health; [2]Univ of Michigan.*

Background: End-stage renal disease (ESRD) can be defined by receipt of chronic dialysis or transplantation. While the age-sex-race-adjusted incidence rate of ESRD has declined slightly since 2006, the crude incidence rate has risen. Future trends in the crude ESRD incidence are important because of the impact on healthcare utilization and cost. This analysis models incidence and prevalence of ESRD in the US through 2030.

Methods: We used an open compartmental simulation model to project diabetes, hypertension, and ESRD trends stratified by age and race categories using restricted cubic spline estimates of time-varying flow parameters optimized based on annual incidence. Future trends in population-level obesity were assumed to either plateau and start to decline or increase linearly; this range should cover every reasonable obesity prevalence scenario. We assumed ESRD mortality would either remain constant at 2013 levels or to continue to decline proportionately. We used data from the National Health and Nutrition Examination Survey, Centers for Disease Control and Prevention National Health Interview Survey, US Census, and United States Renal Data System, including population projections through 2030.

Results: While age-specific rates are projected to stay relatively constant or decline, the total crude annual ESRD incidence rate is projected to rise to 381-410 per million/year, a 5-13% increase, depending on obesity trends.



The prevalence is projected to rise to 2209-2757 per million, an increase of 9-36%, depending on trends in obesity and ESRD mortality.

Conclusions: Incidence within age groups have leveled off or tended to decline, suggesting better management, but crude incidence and prevalence will both rise through 2030, due to an aging population, the increasing prevalence of obesity and diabetes, and improved ESRD survival.

Funding: NIDDK Support, Other NIH Support - This project has been funded in whole or in part with Federal funds from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN276201400001C

FR-OR076

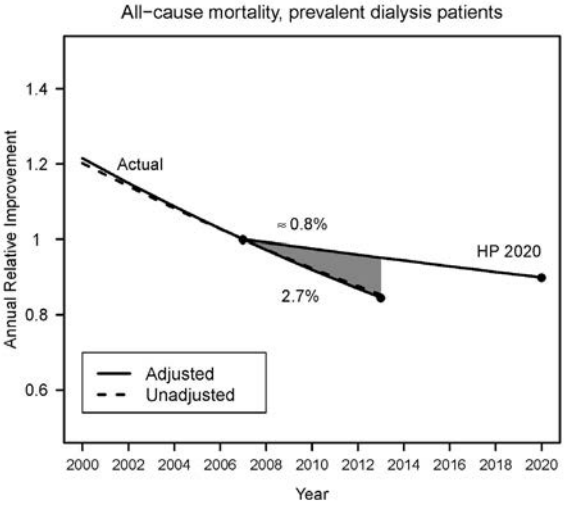
Healthy People 2020 Goals in CKD and ESRD: Measuring Progress to Date James B. Wetmore,[1] Peer Kidney Care Initiative Investigators.[2] *[1]Medicine, Div of Nephrology, Hennepin County Medical Center, Minneapolis, MN; [2]Peer Kidney Care Initiative.*

Background: We assessed progress towards key Healthy People (HP) 2020 goals CKD and ESRD. We hypothesized that these goals are in the process of being met.

Methods: Using the CMS ESRD database, we created yearly cohorts of incident and prevalent dialysis patients, 2000-2013. Change in event rate or proportion change over the study years was modeled using Poisson regression with adjustment for age, race, sex, and primary cause of ESRD.

Results: For all-cause mortality in prevalent patients, HP 2020 sought a <1% relative annual improvement; actual improvement was 2.7%. Improvement was greatest for patients aged 18-44 years (3.8%, P <0.01 versus 2.8% for ages 65-74 years), and was 2.3% even for patients aged ≥75 years. For mortality in incident patients, the relative annual decrease was 2.1% overall, a 2-fold improvement over the goal; mortality decreased nearly twice as much in black as in white patients (3.2% versus 1.8%, P <0.001). Geographic variation was substantial: the relative annual decrease was 0.6% in the Midwest and >4-fold greater (2.7%) in the South. Cardiovascular mortality in prevalent patients decreased dramatically at 5.0% per year, far exceeding the annual goal of <1%; the decrease was greatest in patients aged ≥75 years (5.5%, P <0.001 versus ages 65-74 years, 5.1%). The relative annual increase in percentages of patients with a fistula at dialysis initiation was 2.4%, roughly three times the goal; the increase was greater for black than for white patients (3.2% versus 2.3%, P <0.01).

Figure 1A.



Conclusions: While progress in meeting the HP 2020 CKD and ESRD goals has exceeded the targets, not all groups of patients have benefited equally. Goal development for HP 2030 should consider ever-more-aggressive targets as well as changes in goal paradigms, such as tailoring goals by geographic region.

Funding: Pharmaceutical Company Support - Financial support for the Peer Kidney Care Initiative is provided by the following participating provider organizations: American Renal Associates, Atlantic Dialysis Management Services, DaVita HealthCare Partners, Dialysis Clinic, Inc., Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Satellite Healthcare, The Rogosin Institute, U.S. Renal Care, and Wake Forest University

FR-OR077

Optimal Outcomes with Targeted Chronic Kidney Disease Management Meghan Martin Cockrell,[1] Todd Prewitt,[1] Yanting Dong,[1] Huyi Hines,[1] Gilbert Haugh,[1] Stephen D. McMurray,[2] Eric Franco.[2] *[1]Humana Inc., Louisville, KY; [2]Village Health.*

Background: Unprepared patient transitions from chronic kidney disease (CKD) to end stage renal disease (ESRD) can result in avoidable hospitalizations and initiation of dialysis with non-preferred central venous catheters (CVC). Our objective was to evaluate the impact of integrated care management (ICM) on dialysis transitions with preferred modality (peritoneal dialysis vs. hemodialysis) and vascular access (arteriovenous fistula or graft).

Methods: Between 2012 and 2015, Humana Medicare enrollees with CKD who were most likely to transition to ESRD within a year were identified and referred to ICM using clinical rules (e.g., glomerular filtration rate ≤20) and a predictive model. The program ensured nephrologist oversight and patient education on CKD, modality and vascular access through telephone and in-person contact. For patients who transitioned to dialysis in 2015, descriptive statistics were used to report the number of transitions with preferred modality and access.

Results: In 2015, an average of 3,552 patients per month with CKD participated in ICM, with a total of 690 transitioning to dialysis. Of those who transitioned, 338 (48.9%) started dialysis with preferred modality or access. Another 151 (21.7%) started dialysis with a maturing fistula or graft, for a total of 70.9% starting dialysis with preferred modality or access option in place or underway. Among all ICM patients who transitioned to dialysis and had at least 6 months of ICM enrollment, an additional 15% had nephrologist oversight, 44% had selected a modality, 47% had a vascular access plan, and 43% had permanent access in the month prior to starting dialysis, compared to their 1st month in ICM.

Conclusions: The observed outcomes of ICM were satisfactory for the health plan to continue the program. When these findings are viewed in context of national data from the 2015 Annual Data Report by the United States Renal Data System, patients in the ICM program had a 22.4% higher rate of transition to dialysis with preferred modality or access (48.9% vs. 26.5%), which can be extrapolated to 155 avoidable CVC placements with ICM. Focused, systematic care for patients with this high risk condition can have demonstrable clinical benefits.

Funding: Pharmaceutical Company Support - Humana Inc.

FR-OR078

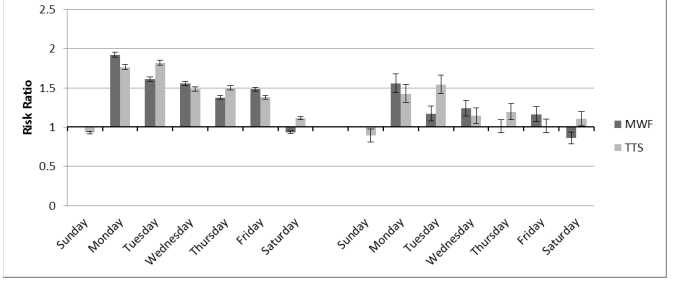
Hospitalization Rates among In-Center Hemodialysis (HD) Patients by Day of the Week Rajiv Saran,[1] Patrick J. Albertus,[1] Kevin He,[1] Francesca Tentori,[2] Brahmajee K. Nallamothu,[1] Yi Li.[1] *[1]KECC, Univ of Michigan; [2]Arbor Research Collaborative for Health.*

Background: Higher mortality on Monday/Tuesday has been reported in patients on thrice weekly hemodialysis, but the risk of other clinical outcomes remains uncertain. Therefore, we examined USRDS data to study the association of day-of-the-week with all-cause hospitalization and emergency department (ED) visits among Medicare-covered HD patients.

Methods: Prevalent in-center HD patients with Medicare as primary payer from 2013 with 3x/week dialysis sessions were identified in the USRDS database. Patients were followed through the end of 2013 for hospitalizations and ED visits, identified in Medicare claims. Poisson regression was used to calculate event rates and associated 95% confidence intervals (CI), characterized by the week day and stratified by dialysis schedule (Mon/Wed/Fri [MWF] or Tues/Thurs/Sat [TTS]), which was determined by the day of the week of a patient's first HD session. The model was adjusted for age, sex, race, ethnicity, and primary cause of ESRD.

Results: For 237,920 prevalent in-center 3x/week HD patients in 2013, 371,346 hospitalizations and 16,530 ED visits occurred. With adjustment, hospitalization rates were highest on Mondays for MWF patients (risk ratio: RR=1.92; 95% CI: [1.89, 1.96]) and on Tuesdays for TTS patients (RR=1.82 [1.79, 1.85]) (Fig. 1). Similarly, rates of emergency department visits after adjustment were highest on Mondays (RR= 1.55 [1.44, 1.68]) and on Tuesdays (RR=1.54 [1.42, 1.67]) for MWF and TTS patients, respectively.

Figure 1. Adjusted risk ratio (ref: Sunday, MWF) of (a) hospitalizations and (b) emergency department (ED) visits, by day of the week and dialysis schedule, among in-center hemodialysis patients, 2013



Conclusions: These findings, when combined with prior reports of higher mortality rates early in the week, call for a serious reconsideration of policy and practice with respect to the widely prevalent paradigm of the thrice weekly hemodialysis.

Funding: NIDDK Support

FR-OR079

Quantifying Risk of Increased All-Cause Hospitalization for Adult Hemodialysis Patients Who Skipped Seasonal Flu Vaccination Nien-Chen Li, Uddar Onta, Norma J. Ofsthun, Jeffrey L. Hymes, Franklin W. Maddux. *Fresenius Medical Care, Fresenius Kidney Care North America, Waltham, MA.*

Background: It is well known that skipping seasonal flu vaccination is at a risk of increased hospitalization. The study attempts to quantify such risk for adult hemodialysis (HD) patients (pts).

Methods: We selected active HD pts aged ≥ 18 years at Fresenius Medical Care North America for three flu seasons: 2013-14, 2014-15, and 2015-16. Each season covered August 1 to July 31 of the following year. Active pts were those who had records of treatments or laboratory work within 40 days prior to August 1. We calculated hospitalization rate per patient-year and rate ratio (RR). We also estimated RR using negative binomial regression model wherein hospitalization count was the dependent variable with logarithmic link function, offset with logarithmic transform of exposure time and adjusted for age, gender, race, DM, CAD, and CHF. The model yielded estimated RR and Chi-square test for testing whether RR = 1. For each of 3 cases the exposure time at risk was calculated as follows. First, for those pts who were active throughout the season but not vaccinated, the exposure time was 12 months. Secondly, for those pts who were vaccinated, the exposure time was the duration from the vaccination date to the end of the season. Thirdly, for pts vaccinated, the exposure time prior to vaccination was calculated from the start of the season until the vaccination date, and the pts were considered not vaccinated during this time period.

Results: The total active pts were 158326, 202793, and 220203, and % pts vaccinated were 60.1, 75.6, and 80.4 for seasons 2013-14, 2014-15, and 2015-16, respectively. The estimated RR of hospitalization for non-vaccinated vs. vaccinated were 1.53, 1.87, and 2.58 (all p<.0001) in three seasons, respectively.

Conclusions: Our study showed that the risk of increased all-cause hospitalization for adult hemodialysis patients who skipped seasonal flu vaccination were 53 to 158% higher in terms of average hospitalization rate. An aggressive program for promoting flu vaccination is well warranted.

FR-OR080

The Hemodialysis Schedule Affects Hospitalization by Day of the Week for Acute Cardiovascular Diseases: 20 Years' Experience Masataka Banshodani, Hideki Kawanishi, Misaki Moriishi, Sadanori Shintaku, Shinichiro Tsuchiya. *Artificial Organs, Tsuchiya General Hospital, Hiroshima, Japan.*

Background: An increase in deaths has been identified after a 2-day break (longest interdialytic gap) in hemodialysis (HD) in previous reports, and frequent HD has recently been recommended. However, no reports have evaluated how the dialysis schedule affects day-of-week hospitalization on a long-term basis.

Methods: We analyzed 11,111 hospitalizations of 1,955 HD patients and 1,969 hospitalizations of 497 peritoneal dialysis (PD) patients to clarify the association between the day-of-week hospitalizations for acute CVDs including pulmonary edema, cerebrovascular disease, heart failure, ischemic heart disease, cardiac arrhythmia, and aortic and peripheral vascular disease (HD: 1,705 times; PD: 261 times) and the dialysis schedule at our institution between January 1995 and December 2014.

Results: In HD patients, the rate of hospitalizations for acute CVDs on 1st-HD day (Monday or Tuesday, 42%) was significantly higher than that on 2rd- (Wednesday or Thursday, 24%) and 3rd- (Friday or Saturday, 22%) HD days (P<0.001), while there was no significant difference for PD patients. However, in the HD group, the hospitalization rate on the 1st-HD day has been decreasing in recent years (1st-5th yr, 48%; 2nd-5th yr, 41%; P=0.03; 3rd-5th yr, 40%; P=0.03; 4th-5th yr, 39%; P=0.009). Moreover, the rates of acute CVD contributing to overall hospitalizations have been decreasing in HD patients (1st-5th yr, 33%; 2nd-5th yr, 19%; P<0.001; 3rd-5th yr, 13%; P<0.001; 4th-5th yr, 9.6%, P<0.001). Frequent HD (≥4 times/week) at our institution increased from 1.0% (1st-5th yr) to 5.3% (4th-5th yr) (P<0.001), and the rate of hospitalizations for acute CVDs on 1st-HD day significantly decreased from 37% pre- to 24% post-initiative (P=0.04).

Conclusions: Day-of-week hospitalization was affected by the HD schedule, but the risk decreased over time. This result may be attributed to the advantages of frequent HD. Our findings can guide clinical management practices for CVDs in dialysis patients.

FR-OR081

Obstructive Sleep Apnea in Incident Hemodialysis Patients Significantly Increases Risk for Sudden Cardiac Death and Cardiovascular Mortality Eric S. Kerns,[1] Esther D. Kim,[2] Lucy A. Meoni,[3] Stephen M. Sozio,[3] Bernard G. Jaar,[3] Michelle M. Estrella,[3] Rulan S. Parekh,[2,3] Ghada Bourjeily.[1] *[1]Brown Univ, Providence, RI; [2]Univ of Toronto, Toronto, ON, Canada; [3]Johns Hopkins Univ, Baltimore, MD.*

Background: Mortality in ESRD approaches 20% per year predominantly from sudden cardiac death (SCD). Obstructive sleep apnea (OSA) is characterized by abnormal breathing during sleep and oxygen desaturations and is highly prevalent in patients with ESRD. Whether OSA increases the risk for SCD, cardiovascular (CV) and all-cause mortality in HD is unknown.

Methods: In a prospective cohort of 558 incident HD patients from the Predictors of Arrhythmic and Cardiovascular Risk in ESRD (PACE) study, we examined the association of OSA diagnosis ascertained by physician chart review with all-cause mortality, CV mortality, and SCD using Cox proportional hazards model. SCD was defined as out of hospital, non-ischemic coronary events adjudicated by the end point committee.

Results: Sixty-six incident HD patients (12%) were identified as having OSA. Median age and sex were similar in OSA and non-OSA groups. Those with OSA had fewer African Americans (53% vs 71%), and higher median BMI (37 [IQR 31, 42] vs 27 [IQR 24, 32]), median Charlson comorbidity index (6 [IQR 5, 7] vs 5 [IQR 4, 7]), prevalence of diabetes (76% vs 56%), coronary artery disease (47% vs 34%), and median left ventricular mass index (76 [IQR 59, 93] vs 61 [IQR 50, 79]) (all p <0.05). During 1080 person-years of follow-up, there were 104 deaths, including 30 CV and 16 SCD. OSA was associated with a higher risk of all-cause mortality, CV mortality, and SCD after adjustment.

Association of OSA compared to non-OSA with all-cause mortaltiy, cardiovascular mortality, and sudden cardiac death

Adjustment	All cause mortality	Cardiovascular mortality	Sudden cardiac death
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1: age, sex, ethnicity	1.27 (0.74, 2.18)	1.50 (0.66, 3.42)	3.28 (1.12, 9.57)
Model 2: model 1, Charlson comorbidity	1.10 (0.64, 1.89)	1.38 (0.60, 3.18)	3.00 (1.01, 8.86)
Model 3: model 1, BMI	1.90 (1.04, 3.46)	3.62 (1.36, 9.66)	12.12 (2.70, 54.40)

Conclusions: Incident HD patients with a known diagnosis of OSA are at significantly increased risk for all cause and CV mortality and SCD. Future studies should assess the impact of screening for OSA and OSA-targeted interventions on morbidity and mortality in ESRD.

Funding: NIDDK Support

FR-OR082

High Efficiency Hemodiafiltration (HDF) versus Hemodialysis (HD): A Comparison of Clinical Outcomes in EuroDOPPS Angelo Karaboyas,[1] Francesco Locatelli,[2] Ronald L. Pisoni,[1] Bruce M. Robinson,[1,3] Joan Fort,[4] Raymond C. Vanholder,[5] Hugh C. Rayner,[6] Werner Kleophas,[7,8] Stefan H. Jacobson,[9] Christian Combe,[10] Friedrich K. Port,[1] Francesca Tentori.[1,11] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]Alessandro Manzoni Hosp, Lecco, Italy; [3]U of Michigan, Ann Arbor, MI; [4]U Hosp Vall d'Hebron, Barcelona, Spain; [5]U Hosp, Gent, Belgium; [6]Heart of England NHS, Birmingham, United Kingdom; [7]MVZ DaVita, Dusseldorf, Germany; [8]Heinrich-Heine U, Dusseldorf, Germany; [9]Danderyd Hosp, Stockholm, Sweden; [10]Centre Hosp U de Bordeaux, France; [11]Vanderbilt U, Nashville, TN.*

Background: Online HDF is considered the most efficient dialysis technique, though only 1 of 3 recent randomized trials demonstrated a survival benefit vs. HD. Post-hoc analyses of all 3 studies showed patients who received the highest convection volumes had lower risk of adverse events. Use of high-volume HDF has consequently increased in many European countries, while online production of replacement fluid is not available in North America.

Methods: We analyzed n=8567 patients from 7 European countries in DOPPS phases 4-5 (2009-2015) with vintage >90 days. Among n=2012 (23%) HDF patients, about half had replacement fluid volume >20L. Adjusted Cox regression was used to estimate the association between mortality and HDF (vs. HD).

Results: Median follow-up was 1.6 years, and 2043 patients died. The adjusted HR (95% CI) of mortality was 1.13 (1.00-1.28) for any HDF vs. HD and 1.08 (0.92-1.28) for HDF > 20L vs. HD. Results were similar for CV and infection-related mortality. We did not observe lower mortality risk among facilities prescribing HDF to a greater % of patients.

Conclusions: Our results do not support the notion that online HDF achieves better patient survival vs. HD, even focusing on HDF with convection volumes >20L. Further trials specifically designed for testing the effect of increased convection of online HDF vs. HD on clinical outcomes are necessary before superiority of HDF can be accepted.

Adjusted HR (95% CI) of mortality: HDF vs. HD	
Overall, all-cause mortality	
Any HDF vs. HD	1.13 (1.00-1.28)
Cause of death	
CV mortality	1.20 (1.00-1.43)
Infection mortality	1.12 (0.82-1.54)
By volume replacement	
non-HDF (Ref.)	1 (Ref.)
HDF, 4-15L	1.25 (1.01-1.55)
HDF, 15-20L	1.14 (0.95-1.37)
HDF, >20 L	1.08 (0.92-1.28)
Facility % HDF use	
0%	1 (Ref.)
1-14%	1.17 (1.00-1.36)
15-49%	1.10 (0.93-1.30)
≥ 50%	1.28 (1.06-1.53)

Cox models stratified by phase*country, adjusted for age, sex, vintage, 13 comorbidities, vascular access, blood flow rate, BMI, albumin, Hgb, and accounted for facility clustering; Facility model additional adjusted for 5 fac-level confounders.

Funding: Pharmaceutical Company Support - AbbVie, Amgen, Baxter Healthcare, F. Hoffmann-LaRoche, Hexal, Keryx, Kyowa Hakko Kirin, Merck, Proteon, Relypsa, Sanofi, Shire, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, WiNe Institute, Societies for Nephrology in Germany, Italy, & Spain. All grants are made to Arbor Research Collaborative for Health and not to Mr. Karaboyas directly

FR-OR083

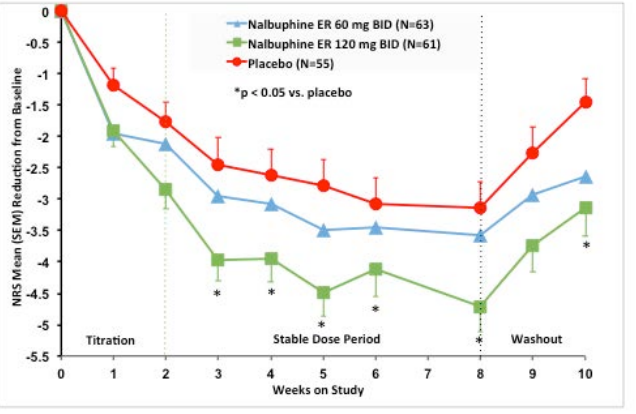
Time Course of Reduction in Itch Intensity during and following Treatment with Nalbuphine ER Tablets: A Randomized, Placebo-Controlled Trial in Patients with Uremic Pruritus Thomas Richard Sciascia,[1] Howard Hait,[1] Vandana S. Mathur.[2] *[1]Trevi Therapeutics, New Haven, CT; [2]MathurConsulting, Woodside, CA.*

Background: Clinical trials in uremic pruritus (UP) patients are typically powered to compare differences in itching intensity between the active treatment and placebo at the end of the treatment period. However, understanding the time course of loss of effect following treatment withdrawal is also important. Patients with severe baseline itching are of particular interest because they are the population with the greatest medical need.

Methods: This was a 3-arm randomized, double-blind, placebo-controlled trial comparing nalbuphine ER tablets 120 mg bid (NAL 120) and 60 mg BID (NAL 60) to placebo in 373 hemodialysis patients with UP. We measured change from baseline to the end of the treatment period (Week 8) in the worst itching intensity using an 11 point numerical rating scale (NRS) (0 = no itching; 10 = worst possible itching). The primary endpoint compared NAL 120 to placebo at the mean of Weeks 7 and 8. After completion of treatment, NRS data was additionally collected for 2 weeks.

Results: Among all patients and those with severe baseline itching (NRS >7, n = 179), NAL 120 consistently reduced itching from the end of the 2 week titration through the end of the treatment period. In the NAL 120 group, the mean (SEM) reduction in itching intensity at the end of treatment and end of washout was 3.8 (0.3) (p = 0.017 vs. placebo) and 2.2 (0.3) (p = NS vs. placebo) in the overall population and 4.7 (0.4) (p <0.01) and 3.1 (0.4) (p <0.05) in the severe pruritus population.

Reduction in Itching Intensity Among Patients with Severe Uremic Pruritus



Conclusions: In this randomized, controlled trial, NAL 120 significantly reduced itching in patients with moderate or severe pruritus. Among patients with severe pruritus, the anti-pruritic effects of NAL remained significantly better vs. placebo for at least 2 weeks after the last dose.

Funding: Pharmaceutical Company Support - Trevi Therapeutics

FR-OR084

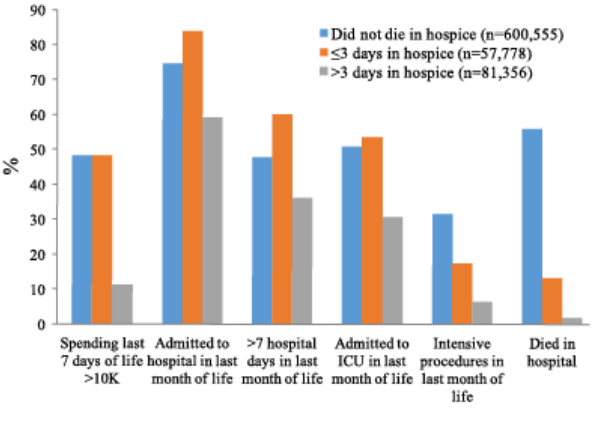
Timing of Hospice Enrollment and End-of-Life Utilization and Spending among Patients with ESRD Melissa Wachterman,[1] Susan M. Hailpern,[2] Nancy L. Keating,[1] Manjula Kurella Tamura,[3] Ann M. O'Hare.[2] *[1]Harvard Medical School; [2]Univ of Washington; [3]Stanford Univ.*

Background: Rates of hospice enrollment in patients with ESRD have increased over time, although remain low compared with the general population. Less is known about *timing* of hospice enrollment in ESRD patients. Because Medicare will not pay concurrently for dialysis and hospice for patients whose life-limiting illness is ESRD, these patients may be less often referred to hospice in a timely fashion. We examined the frequency and timing of hospice enrollment and patterns of end-of-life utilization and spending among ESRD patients.

Methods: Using USRDS data, we identified all ESRD patients who died between 2000 and 2012 who had Medicare Parts A & B. Patients were grouped according to whether and when they enrolled in hospice before death. We used a generalized linear model to examine the association of timing of hospice with healthcare utilization and spending at the end of life after adjustment for patient characteristics.

Results: Of the 739,689 ESRD patients who died, 19% were receiving hospice at the time of death, increasing from 10% in 2000 to 26% in 2012. Among hospice enrollees, 42% enrolled ≤3 days before death, decreasing slightly from 43% in 2000 to 40% in 2012. Adjusted measures of spending and utilization were significantly lower for those who received >3 days of hospice than for patients who did not use hospice (all p<.001). For patients who received ≤3 days of hospice, spending was not significantly different than for hospice non-users (p=.97), and hospital admission, length of stay, and ICU utilization were significantly higher (all p<.001).

End-of-life utilization and spending by length of time in hospice



Conclusions: While hospice use among ESRD patients has increased over time, almost half of patients enroll within 3 days before death. End-of-life spending and most measures of utilization for these patients are similar to or higher than for patients not enrolled in hospice.

Funding: Other NIH Support - K23AG049088 from National Institute on Aging, VA Support

FR-OR085

Efficacy of Endothelin Receptor A Blockade in Experimental Podocin Nephropathy Tanja Tamara Wlodkowski,[1] Mansoureh Tabatabaeifar,[1] Helga Denc,[1] Geraldine Mollet,[2] Corinne Antignac,[2] Franz S. Schaefer.[1] *[1]Pediatric Nephrology Div, Heidelberg Univ Hospital, Heidelberg, Germany; [2]Inserm U1163-Imagine Inst, Paris Descartes Univ, Paris, France.*

Background: Renal endothelin-1 expression is increased in various kidney diseases. Selective ET_A receptor blockade (ERA) improves renal function in various animal models of kidney disease. Here, we investigated antiproteinuric and nephroprotective effects of the ET_A receptor blocker Atrasentan in a mouse model of the most common human hereditary podocytopathy. Hemizygous R138Q-*NPHS2* knock-in mice develop heavy proteinuria, podocyte loss, focal segmental glomerulosclerosis (FSGS) and progressive renal failure.

Methods: In C57BL/6 mice with $Nphs2^{Flox/R140Q}$, Cre^{+} hemizygosity for mutant podocin was induced by tamoxifen injection. In a pilot study the animals were administered Atrasentan encompassing a sixfold dose range with food from time of induction or remained untreated (U). Furthermore, animals treated with a 4-wk delay ((D)elayed, n=14) were analyzed. Weight, blood pressure (MAP) and proteinuria were monitored weekly. Biochemical parameters and histopathological changes were examined after 4 wks treatment.

Results: Prophylactic ERA blockade demonstrated no attenuation in proteinuria and histological lesions at any dose level. Notably, intrarenal ET-1 expression increased only gradually as disease progressed, reaching significance by wk 5. When Atrasentan was administered at the time of maximal proteinuria and strong ET-1 expression, proteinuria decreased progressively and MAP was lowered significantly (wk7: 80.4 (D) v. 99.5 (U) mmHg, $p=0.001$) Preliminary histological evaluation (n=9) demonstrates attenuation in glomerulosclerosis (GSI: 1.69 (D) v. 2.27 (U wk 8), $p=0.0008$) and tubulointerstitial fibrosis (TIF % of total area: 4.18 (D) v. 7.56 (U wk 8), $p=0.008$; podocyte numbers tended to be better preserved (podocytes per glom: 54% (D) v. 32% (U wk 8) of healthy controls, n.s.). Furthermore, podocin protein abundance and mRNA expression was partly preserved in the treated animals.

Conclusions: In an *in vivo* model of hereditary podocin nephropathy, treatment with Atrasentan showed a beneficial effect on glomerulosclerosis and tubulointerstitial fibrosis.

Funding: Pharmaceutical Company Support - AbbVie

FR-OR086

DNA Copy Number Variations Associated with Vesicoureteral Reflux and Its Sequelae Dong Liang,[1] David S. Hains,[1] Andrew L. Schwaderer.[2] *[1]Innate Immunity Translational Research Center, Le Bonheur Children's Hospital, Memphis, TN; [2]CCTR, Nationwide Children's Hospital, Columbus, OH.*

Background: Copy number variations (CNV) represent a large class of structural genomic variations that have the ability modify susceptibility to a variety of human disorders such as cancer, obesity, schizophrenia, autism and infectious diseases. The RIVUR study followed 600 children with vesicoureteral reflux (VUR) and UTIs for two years, and DNA was collected on a subset of patients. We hypothesize that CNVs in pathways involving lower urinary tract development, innate immunity, or fibrosis will segregate to VUR patients that experience a complicated course.

Methods: Using high-resolution genome-wide, array comparative genomic hybridization (aCGH) experiment, using the genomic DNA from 298 RIVUR patients as well as 1440 matched healthy controls. The aCGH data was further processed and analyzed using Nexus 8 Copy Number software and DAVID bioinformatic resources. For each gene locus, a Fisher's Exact test was performed to access its association with disease susceptibility.

Results: Analysis identified a total of 612 common and 2659 rare CNVs differentially present in RIVUR compared to controls. 9 of the top 20 involved common pathways involved innate immunity/bacterial response. Furthermore, our analysis also revealed unique alterations (disease-specific CNVs) in genes related to renal development such as *PRKX* and *NOTCH1*, intercalated cell related genes such as *ATP6V1B1* and the bacterial defense such as *RNASE7* and *DEFA1A3* in RIVUR patients compared to controls.

Conclusions: Our study led to identification of over 3000 differentially presented rare and common CNVs in RIVUR patients compared to controls. These CNVs likely contribute to VUR sequelae and offer potential candidates for novel insights into disease pathogenesis as well as personalized medicine approaches to children with VUR.

Funding: NIDDK Support

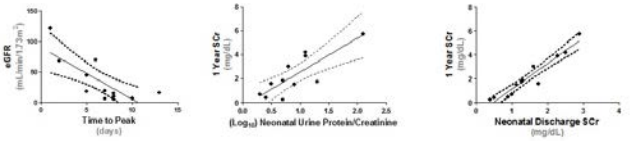
FR-OR087

Predictors of Progressive Kidney Disease after Definitive Vesicoamniotic Shunting for Lower Urinary Tract Obstruction Chryso P. Katsoufis, Marissa J. Defreitas, Wacharee Seeherunvong, Jayanthi Chandar, Michael Freundlich, Gaston E. Zilleruelo, Carolyn L. Abitbol. *Pediatrics/Pediatric Nephrology, Univ of Miami Miller School of Medicine/Holtz Children's Hospital, Miami, FL.*

Background: Lower urinary tract obstruction (LUTO) in the fetus is associated with poor postnatal outcomes, including chronic and end stage kidney disease, and high mortality. Studies of the effect of fetal intervention through vesicoamniotic shunting (VAS) are marred by a device malfunction rate of up to 60%. In this study, we delineate the postnatal course and infant renal function following definitive urinary diversion in utero.

Methods: This is a retrospective, cohort study of 17 male infants who survived the fetal intervention to birth. All had patent VAS in place at birth. Patients were followed for one year, or until demise, with serial measures of serum creatinine (SCr) and urine protein profile.

Results: Of the 17 males, 82% were non-white (35% black, 47% Hispanic). Shunts were placed at 21±3.5 weeks gestation. All neonates were born preterm (33.5±2.2 weeks) with low birth weight (2266±559 grams). 47% required respiratory support, for a duration of 2 days (IQR 0,9). Renal function at 1 year was predicted by neonatal discharge SCr [p<0.0001,r0.96] and time to peak SCr [p0.004,r-0.76]. It also correlated with neonatal random total proteinuria and albuminuria (p0.002,r0.67 and p0.02,r0.45, respectively). 3 patients died in the neonatal period, with 1 receiving renal replacement therapy (RRT). 3 additional patients required RRT at 8 months (IQR 5,28).



Conclusions: Even with definitive VAS for LUTO, postnatal morbidity and mortality remain high, emphasizing the role of renal dysplasia, in spite of urinary diversion, in postnatal kidney failure. Predictors of infant kidney function in the first year include neonatal SCr at discharge and time to peak SCr, along with neonatal proteinuria.

FR-OR088

Genomic Imbalances Associate with Cognitive Impairment and Anxiety/Depression in Children with Chronic Kidney Disease Amy Kogon,[1,3] Miguel Verbitsky,[2,3] Matthew Matheson,[3] Stephen R. Hooper,[3] Craig S. Wong,[3] Bradley Warady,[3] Susan L. Furth,[3] Ali G. Gharavi.[2,3] *[1]Nationwide Children's Hosp; [2]Columbia Univ; [3]Chronic Kidney Disease in Children Study Group.*

Background: Children with chronic kidney disease (CKD) are at an increased risk for neuropsychiatric (NP) complications. Our ability to identify those most at risk and provide early intervention is limited. Children with CKD harbor a 10.8-fold excess of large genomic imbalances (GI) that also confer risk of NP impairment. We hypothesized that GIs predispose to both CKD and NP dysfunction.

Methods: We examined the relationship of GIs to NP performance using data from the Chronic Kidney Disease in Children Study. NP outcomes included intelligence (IQ:Wechsler Abbreviated Scales of Intelligence or Preschool and Primary Scale of Intelligence-Revised), anxiety/depressive symptoms (internalizing problems(IP):Behavior Assessment System for Children-2) and executive function (global executive composite score(GEC):Behavior Rating Inventory of Executive Function). GIs were detected by chromosomal microarrays and defined as definitively pathogenic or likely pathogenic per American College of Medical Genetics recommendations for interpretation of microarray data(Verbitsky et al,JCI'15). Linear regression determined associations of GIs with NP scores after controlling for GFR, CKD duration, maternal education, low birth weight, seizures, and genetically defined ancestry using genomic SNP data. NP measure score ≥1 standard deviation worse than the standardized mean was considered at risk.

Results: Analysis included 31 children with and 388 children without GIs. There were no demographic or kidney disease parameter differences between the groups. By adjusted regression analyses, GIs associated with a 7.6 point lower IQ score (p=0.006), 6.6 point worse IP score (p=0.003) and 5.8 point worse GEC score (p=0.01). 40% of children with GIs were at risk for intellectual disability, 46% for anxiety/depression and 57% for executive function issues compared to 22%, 23% and 29% without GIs, respectively.

Conclusions: GIs may predict NP function in children with CKD. Identifying pathogenic CNVs may provide opportunity for early diagnosis and personalized intervention for this at-risk subgroup.

Funding: NIDDK Support

FR-OR089

Polymorphisms in Antimicrobial Peptide, Ribonuclease 7, Associate with Urinary Tract Infection Risk Keith Pierce,[1] David S. Hains,[1] Steven Creacy,[2] Andrew L. Schwaderer,[3] Brian Becknell,[3] John David Spencer.[3] *[1]Innate Immunity Translational Research Center, Children's Foundation Research Inst at Le Bonheur Children's Hospital, Memphis, TN; [2]YX Genomics, Cordova, TN; [3]CCTR, Research Inst at Nationwide Children's Hospital, Columbus, OH.*

Background: The mechanisms that maintain sterility in the urinary tract are not well understood. Recent studies emphasize the contribution of the innate immune system, which includes antimicrobial peptides (AMP), in protection from uropathogens. Previously, we have shown that the AMP, ribonuclease 7 (RNase 7), has broad-spectrum antimicrobial activity against uropathogenic bacteria and contributes to maintaining urinary tract sterility.

Methods: We used quantitative real–time PCR to investigate the prevalence of non-synonymous exonic single-nucleotide polymorphisms (SNPs) in *RNASE7* of 444 individuals with urinary tract infections (UTIs) and vesicoureteral reflux (VUR) from the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) Study, 160 individuals with non-VUR UTIs from the Careful UTI Evaluation (CUTIE) Study, and 482 matched controls. We also used a site-directed point mutagenesis strategy to create amino acid changes in the RNase 7 peptide corresponding to these SNPs. We evaluated the antimicrobial activity of the RNase 7 peptide variants against uropathogenic *E. coli* (UPEC) using minimum inhibitory concentration (MIC) kill assays.

Results: The allele frequencies of two *RNASE7* polymorphisms, rs1263872 and rs1243469, indicated a significant difference between the cohorts studied (P<0.001 and P<0.05, respectively). Additionally, haplotype analysis revealed these polymorphisms are linked (D'=0.946) and are associated with the risk of recurrent UTI of Caucasian female patients not receiving antibiotic prophylaxis in the RIVUR and CUTIE studies (P<0.05).

Recombinant RNase 7 UPEC kill assays demonstrate that wild-type RNase 7 had a MIC of 3-4 μM while the RNase 7 variant rs1263872, encoded by an alanine to proline mutation, had an MIC of 0.25-0.5μM.

Conclusions: Our research suggests these *RNASE7* polymorphisms confer a decreased antimicrobial activity and are associated with UTI risk in children.

Funding: NIDDK Support

FR-OR090

Prediction of Progression of Chronic Kidney Disease in Children by Various eGFR Markers in Comparison to Nuclear GFR

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Background: The accuracy of various eGFR formulas in comparison to nuclear GFR has been well documented. It is however unclear which eGFR is best suited for longitudinal follow-up and prediction of progression of chronic kidney disease (CKD). The aim of the study was to analyze the predictive power of various eGFRs obtained during follow-up for the prediction of measured GFR.

Methods: We performed a retrospective analysis of eGFR estimates in children with CKD followed in our institution over the last 8 years. All available results of urea, creatinine, cystatin C and height were used to calculate following eGFRs: Cystatin C eGFR (Pediatr Nephrol 2003;18:981), Schwartz eGFR(JASN 2009;20:629), CKiD eGFR (JASN 2009;20:629) and Lyon eGFR(NDT 2014;29:1082). Slopes of each eGFR were constructed by regression analysis in each patient; the intercepts of individual regression lines were then compared to nuclear GFR (nGFR) at the end of follow up. The ratios between predicted eGFR (PeGFR) and measured nGFR were analyzed by linear mixed effects models and intraclass correlation coefficient (ICC).

Results: A total of 366 eGFR values were collected in 23 patients (aged 11.8±5.0 years) with progressive CKD over a median of 400 follow-up days (range= 0 to 2821). There were significant differences among PeGFR/nGFR ratios (linear mixed effect model, $p<0.001$). In post-hoc Tukey tests, Cystatin C PeGFR was found to be significantly higher than Lyon PeGFR and Schwartz PeGFR (both $p<0.01$). The agreement between various PeGFR in the prediction of nGFR was modest (ICC=0.57, 95% CI=0.35 to 0.76). The most accurate prediction of the nuclear nGFR (PeGFR/nGFR ratio closest to 1) was obtained with CKiD PeGFR (mean ± SD ratio = 1.03 ± 0.20) followed by Schwartz PeGFR (0.97±0.23), Lyon PeGFR (0.95±0.23) and Cystatin C PeGFR (1.13±0.27; significantly different from 1.0, $p=0.02$).

Conclusions: There were significant differences among various eGFR formulas in the prediction of the measured nuclear GFR at the end of follow-up. The most accurate prediction of the nuclear GFR was obtained with the CKiD eGFR.

FR-OR091

Long-Term Clinical Outcomes and Risk Factors in Isolated Antenatal Hydronephrosis: A Prospective Cohort Study

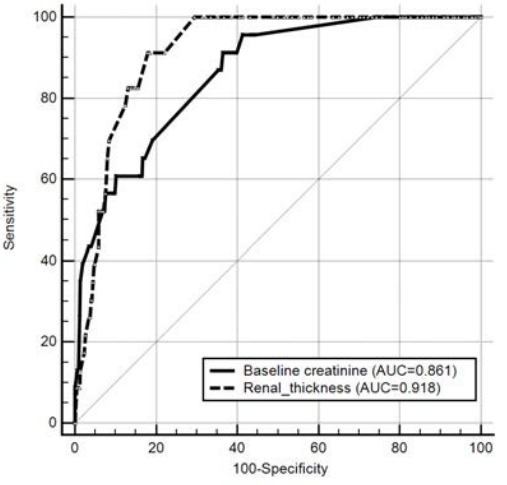
Eduardo A. Oliveira,[2] Robert H. Mak.[1] *[1]Pediatrics, UCSD, San Diego, CA; [2]Pediatrics, HC-UFMG, Belo Horizonte, MG, Brazil.*

Background: Antenatal hydronephrosis (ANH) affects approximately 1-5% of pregnancies. There are few studies on long-term clinical outcomes of infants with ANH. We evaluated the clinical outcomes of incident adverse health events (AHE) and the risk factors in a prospective cohort of 447 infants with isolated ANH in a single tertiary center.

Methods: ANH was classified according to the Society Fetal Urology (SFU) grading system into two groups (grades 0-2 vs. 3-4). The primary end-point was time until the occurrence of a composite of incident AHE, including proteinuria, hypertension and chronic kidney disease (CKD).

Results: Median follow-up time was 6.4 years (IQ range, 2.8 – 12.5). During follow-up, urinary tract infections (UTI) occurred in 89 (20%) children. Patients with SFU grades 3-4 had a greater risk of the occurrence of UTI ($P < 0.001$). Thirteen patients (3%) developed proteinuria, 6 (1.3%) hypertension, 14 (3.1%) CKD, and 23 (5%) the composite outcome. Estimated probability of occurrence of the composite outcome was 30% at 18 years. AHE occurred only in patients with SFU grades 3-4. After adjustment by Cox model, baseline creatinine, renal parenchyma thickness, and recurrent UTI were independent predictive factors of AHE. Renal parenchyma thickness at birth < 8.7 mm and a baseline creatinine > 0.37 mg/dl were strong predictors of AHE.

Risk factors	**Hazard Ratio (95% Confidence Interval)**	P-value
Baseline creatinine (mg/dl)	1.27 (1.05 - 1.56)	0.014
Renal parenchyma thickness at birth (mm)	0.78 (0.62 - 0.99)	0.042
Recurrent UTI	4.52 (1.49 - 13.6)	0.007



Conclusions: Our findings indicate a benign clinical course for ANH patients with SFU grades 0-2 without long-term AHE. Conversely, for patients with SFU grades 3-4 there is a clear increased risk of incident AHE, including proteinuria, hypertension and CKD.

Funding: Government Support - Non-U.S.

FR-OR092

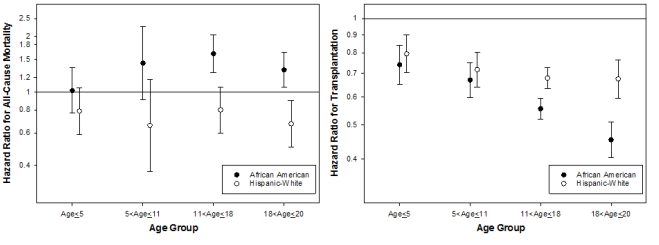
Association of Race with Risk of Mortality and Transplantation in Pediatric Dialysis Patients

Melissa Soohoo,[1] Elani Streja,[1] Marciana Laster,[2] Connie Rhee,[1] Keith C. Norris,[1] Rajnish Mehrotra,[3] Isidro B. Salusky,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]UCLA; [3]Univ of Wash.*

Background: Previous studies have shown that in adults, African-Americans and Hispanic treated with dialysis have a lower likelihood of renal transplantation compared to whites and African-Americans have a higher risk of death. However, racial-ethnic disparities outcomes in pediatric dialysis patients remains understudied and often have not examined Hispanic children.

Methods: We investigated a cohort of 18,108 pediatric (age<20 years) patients who initiated dialysis between 2000-2013, according to USRDS records. We used competing risk regression to examine the association of race/ethnicity with mortality and transplantation stratified by the age at initiation of renal replacement therapy. All models were adjusted for cause of end-stage renal disease (ESRD), demographic and socioeconomic factors.

Results: The pediatric cohort included 47% white, 27% African-American and 26% Hispanic White incident ESRD patients. Compared to whites , African-Americans had a higher risk of mortality (HR[95%CI]: 1.37[1.21,1.55]), whereas Hispanic patients experienced better survival (HR[95%CI]: 0.69[0.59,0.81]) (Ref: whites). These differences were modified by age, where African-American patients ≤5 years did not experience worse mortality compared to whites. Across all levels of adjustment and age strata, both minorities had a lower probability of undergoing transplantation compared to whites.



Conclusions: The lower risk of death for Hispanic White vs. white dialysis patients extends to the pediatric age range, but for African Americans there is a reversal with higher mortality rates than their White peers. Lower transplant rates for Hispanics and African Americans also extend across adult and pediatric populations. Future studies are needed to further understand the underlying causes of these contrasting findings in adult and pediatric ESRD patients.

Funding: NIDDK Support

FR-OR093

Antenatal Corticosteroids and the Renin-Angiotensin-Aldosterone System in Adolescents Born Preterm Andrew M. South,[1,2] Patricia A. Nixon,[1,3] Debra I. Diz,[2,4] Gregory B. Russell,[5] Beverly Snively,[5] Hossam A. Shaltout,[2,6] James C. Rose,[6] Michael H. O'Shea,[7] Lisa K. Washburn.[1,2] *[1]Pediatrics, Wake Forest School of Medicine, Winston Salem, NC; [2]Hypertension and Vascular Research Center, Wake Forest School of Medicine, Winston Salem, NC; [3]Health and Exercise Science, Wake Forest Univ, Winston Salem, NC; [4]Surgery, Wake Forest School of Medicine, Winston Salem, NC; [5]Biostatistical Sciences, Wake Forest School of Medicine, Winston Salem, NC; [6]Obstetrics and Gynecology, Wake Forest School of Medicine, Winston Salem, NC; [7]Pediatrics, Univ of North Carolina School of Medicine, Chapel Hill, NC.*

Background: Antenatal corticosteroid (ANCS) treatment hastens fetal lung maturity and improves survival of premature infants, but the long-term effects of ANCS are not well described. Animal models suggest ANCS increases the risk of cardiovascular disease through programmed changes in the renin-angiotensin (Ang)-aldosterone system (RAAS). We hypothesized that ANCS exposure alters the RAAS in adolescents born prematurely.

Methods: A cohort of 173 adolescents born prematurely was evaluated at age 14 years, of whom 92 were exposed to ANCS. We measured plasma and urine Ang II and Ang-(1-7) and calculated Ang II/Ang-(1-7) ratios. We used general linear regression models to estimate the difference in the RAAS between the ANCS-exposed and unexposed groups, adjusting for confounding variables.

Results: In unadjusted analyses, and after adjustment for sex, race, and maternal hypertension, ANCS exposure was associated with increased urinary Ang II/Ang-(1-7) [adjusted estimate 0.27 (95% CI 0.03, 0.5), $p = 0.03$], increased plasma Ang-(1-7) [0.66 (0.26, 1.07), $p = 0.002$], and decreased plasma Ang II/Ang-(1-7) [-0.48 (-0.91, -0.06), $p = 0.03$].

Conclusions: These alterations indicate an imbalance in the RAAS, promoting the actions of Ang II at the expense of Ang-(1-7), which over time may increase the risk of renal inflammation and fibrosis and ultimately hypertension and renal disease.

Funding: Other NIH Support - Program project grant P01 HD047584

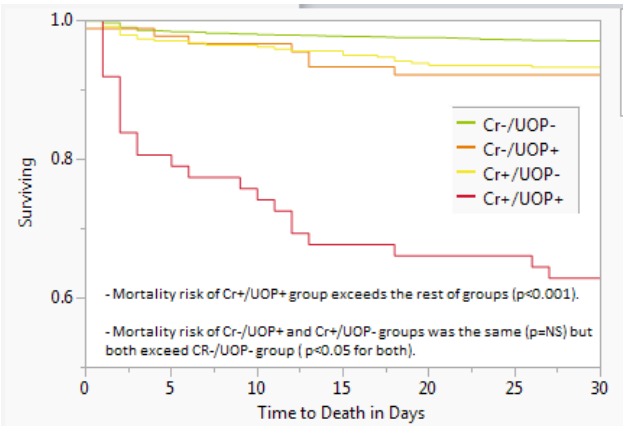
FR-OR094

Oliguria Is Independently Associated with Increased Mortality Risk amongst Critically Ill Children with Acute Kidney Injury Ahmad Kaddourah,[1,2] Rajit K. Basu,[2] Stuart Goldstein,[2] Scott M. Sutherland.[3] *[1]Sidra Medical and Research Center, Doha, Qatar; [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [3]Dept of Pediatrics at Stanford Univ, Stanford, CA.*

Background: Acute kidney injury (AKI) is associated with poor outcomes in critically ill children (CIC). While the KDIGO serum creatinine (SCr) AKI criteria have been widely applied, the urine output (UOP) criteria have not been studied. The impact of disregarding UOP criteria and effect of meeting both criteria remains unknown. We hypothesize the mortality risk associated with meeting both criteria exceeds that of meeting either alone.

Methods: We queried the database for AWARE, a prospective international multicenter study designed to assess AKI outcomes in CIC. We compared 28-mortality rates in CIC with Stage 2/3 AKI based upon whether they met both sets of criteria (SCr^+/UOP^+), SCr alone (SCr^+/UOP^-), or UOP alone (SCr/UOP^+).

Results: SCr and UOP data for 3318 CIC were available. 136(4.1%) deaths were reported. We observed poor agreement between SCr and UOP criteria to diagnose Stage 2/3 AKI (ƙ statistic 0.17, 95% CI:0.12-0.22). Kaplan-Meier survival analysis (figure 1) revealed that the mortality risk of the SCr^+/UOP^+ group exceeded all other groups (adjusted OR=20.9 [95% CI:11.7-35.6] p<0.001).



CIC meeting one but not both criteria (Cr^+/UOP^- and Cr/UOP^+) experienced similar mortality risk (p=0.21); this risk was greater than those without AKI (adjusted OR 2.4 [95% CI:1.5-3.8] and 2.8 [95%CI:1.2–5.9], respectively,p<0.05).

Conclusions: Application of the UOP criteria identified a cohort of CIC with AKI undiagnosed by SCr criteria. Notably, this cohort had similar mortality to those with SCr diagnosed AKI. Additionally, their use identified a subset of SCr diagnosed AKI with greater mortality risk. These findings underscore the importance of this definitional aspect and highlight the benefit of applying both KDIGO criteria in CIC.

FR-OR095

Loss of Serine Protease Hepsin Results in Defective Uromodulin Processing and Increased Activity of NKCC2 Eric Olinger,[1] Luca Rampoldi,[2] Ron Korstanje,[3] Olivier Devuyst.[1] *[1]Inst of Physiology, Univ of Zurich, Zurich, Switzerland; [2]San Raffaele Scientific Inst, Milan, Italy; [3]The Jackson Laboratory, Bar Harbor.*

Background: Uromodulin, the most abundant protein in healthy urine, is a zona pellucida (ZP)-type protein exclusively produced in the thick ascending limb (TAL), where it modulates NaCl handling by regulating the Na^+, K^+, $2Cl^-$ cotransporter NKCC2. The release and proper polymerization of uromodulin in urine was recently demonstrated to depend on a C-terminal proteolytic cleavage mediated by the serine protease hepsin (HPN). The functional consequences of defective HPN and uromodulin miscleavage are unknown.

Methods: We investigated an ENU mouse line harboring a splice site mutation in *Hpn,* which is predicted to reduce the transcription rate. Furthermore, we performed a knockdown of HPN using lentiviral shRNA in primary mouse TAL cells.

Results: We confirmed the predicted lack of HPN expression in the kidneys of HPN-ENU mice. In the urine of these mice, we detected a dramatic decrease of mature uromodulin excretion and evidence of miscleaved, polymerization-incompetent uromodulin isoforms. ShRNA-mediated knockdown of HPN in polarized primary mouse TAL cells led to a strong decrease in apical secretion of uromodulin as well as in the amount and size of uromodulin polymeric chains. In parallel with reduced urinary excretion, uromodulin massively accumulated both at the apical membrane and in the cytosol of TAL cells in HPN-ENU mice. These mice showed an exaggerated natriuretic response after furosemide and a better adaptation to 24h water deprivation, suggesting a hyperactivation of the TAL segment. This was supported by an increase in core and phosphorylated forms of NKCC2 in HPN-ENU kidneys, in absence of adaptations in the distal convoluted tubule.

Conclusions: These data expand the physiological role of HPN *in vivo* and in primary TAL cells, which endogenously express uromodulin and HPN. The loss of HPN results in intracellular and apical membrane accumulation of uromodulin and a specific activation of the TAL, suggesting that membrane-bound uromodulin activates NKCC2. They give new insights into the regulation of uromodulin processing and its role in the TAL.

Funding: Government Support - Non-U.S.

FR-OR096

Plasma K+ Dependent Regulation of NaCl Cotransporter in Native Distal Convoluted Tubules Involves SPAK/OSR1 and Calcineurin David Penton Ribas,[1] Jan Czogalla,[1] Agnieszka Wengi,[1] Nina Himmerkus,[2] Dominique Loffing-Cueni,[1] Olivier Staub,[3] Markus Bleich,[2] Frank Schweda,[4] Johannes Loffing.[1] *[1]Inst of Anatomy, Univ of Zurich, Zurich, Switzerland; [2]Inst of Physiology, Univ of Kiel, Kiel, Germany; [3]Dept of Pharmacology and Toxicology, Univ of Lausanne, Lausanne, Switzerland; [4]Inst of Physiology, Univ of Regensburg, Regensburg, Germany.*

Background: A high dietary potassium (K^+) intake causes a rapid dephosphorylation and hence inactivation of the thiazide-sensitive NaCl cotransporter (NCC) in the renal distal convoluted tubule (DCT). Based on experiments in heterologous expression systems and in mice, it has been proposed that changes in plasma K^+ concentrations ($[K^+]$) modulate NCC phosphorylation via changes in intracellular Cl^- concentrations that control the activity of the WNK/ SPAK kinase pathway.

Methods: We used isolated perfused mouse kidneys, isolated perfused DCTs, and mouse kidney slice preparations to test the physiological relevance of this model on native DCT cells *ex vivo*.

Results: We demonstrate that changes in extracellular $[K^+]$ ($[K^+]_{ex}$) rapidly (< 30 min) modulate NCC phosphorylation by direct effects on the DCT, with the most prominent changes occurring around physiological variations of plasma $[K^+]$. The inhibition of cellular Cl^- fluxes by removing extracellular Cl^- or by blocking Cl^- channels with DIDS abolished NCC phosphorylation in response to low $[K^+]_{ex}$, but did not blunt NCC dephosphorylation in response to high $[K^+]_{ex}$. Moreover, NCC dephosphorylation under low $[Cl^-]_{ex}$ and high $[K^+]_{ex}$ was independent from any significant changes in the phosphorylation status of SPAK. However, under these conditions, inhibition of protein phosphatase 3 (calcineurin) by tacrolimus diminished $[K^+]_{ex}$ induced dephosphorylation of NCC. Inhibition of protein phosphatases 1, 2A and 4 by calyculin A did not interfere with the response to $[K^+]_{ex}$, but increased NCC phosphorylation in general.

Conclusions: In the native DCT, changes in $[K^+]_{ex}$ directly and rapidly control NCC phosphorylation by Cl^- dependent and independent pathways that involve both SPAK and calcineurin.

Funding: Government Support - Non-U.S.

FR-OR097

Calcineurin Rapidly Dephosphorylates Sodium-Chloride Cotransporter in Response to High Potassium Intake Wakana Shoda, Naohiro Nomura, Fumiaki Ando, Yutaro Mori, Takayasu Mori, Eisei Sohara, Tatemitsu Rai, Shinichi Uchida. *Dept of Nephrology, Tokyo Medical and Dental Univ, Bunkyo, Tokyo, Japan.*

Background: Dietary potassium (K^+) intake is well known for reducing blood pressure and mortality. Moreover, the sodium-chloride cotransporter (NCC) plays an important role blood pressure regulation and urinary K^+ excretion in response to K^+ intake. In previous studies, it has been reported that NCC is activated by the With no lysine kinase (WNK) - Ste 20-related proline (SPAK) cascade in a low-K^+ diet. However, the mechanism

of NCC regulation with high K^+ intake is still unclear. A previous study showed rapid dephosphorylation of NCC after acute K^+ load, suggesting the involvement of phosphatases. Protein phosphatase (PP) 1 and PP2B (calcineurin) have been reported to dephosphorylate NCC. To identify the mechanism involved in the regulation of NCC with K^+ intake, we focused on rapid decrease of NCC phosphorylation during acute K^+ load.

Methods: We used adult C57BL/6 mice, which were fed with a 1.7% K^+ solution by oral gavage. Kidneys were collected 15 min after oral gavage. The effect of WNK4, SPAK, and PP1 on acute K^+ load was evaluated by Western blotting with specific antibodies. To investigate the involvement of calcineurin and calmodulin on NCC dephosphorylation, tacrolimus (5mg/kg) or W7 (20mg/kg) was injected in each mouse intraperitoneally 1 h before K^+ oral gavage. To evaluate the urine K^+ excretion, urine samples were collected every 30 minutes after K^+ oral administration.

Results: We confirmed that acute oral K^+ load rapidly dephosphorylated NCC. The dephosphorylation of NCC induced by acute K^+ load was clearly inhibited by tacrolimus and W7 treatment. We also found that hyperkaliuria induced by high K^+ intake was significantly suppressed by tacrolimus treatment. PP1 and its endogenous inhibitor, I-1, did not show significant change after K^+ intake. There was no significant difference in WNK4, total and phosphorylated SAPK expression after high K^+ intake.

Conclusions: This study showed that calcineurin is activated with acute K^+ load, which rapidly dephosphorylates NCC, leading to increase urinary K^+ excretion. The mechanism is independent of WNK4 and SPAK kinases.

Funding: Government Support - Non-U.S.

FR-OR098

The Kidney Specific WNK1 Isoform (KS-WNK1) Is a Potent Activator of WNK4 and NCC Eduardo R. Argaiz,[1] Maria Chavez-Canales,[2] Alejandro Rodriguez-Gama,[1] Norma Hilda Vázquez,[1] Juliette Hadchouel,[2] David H. Ellison,[3] Gerardo Gamba.[1] *[1]Molecular Physiolog Unit, INCMNSZ-IIB-UNAM, Mexico City, Mexico; [2]INSERM 970, París, France; [3]Oregon Health & Science Univ, Portland.*

Background: The observation that the kidney enriched WNK1 isoform lacking exon 11 (L-WNK1-Δ11) is an activator of NCC (Hypertension, 2014) and that WNK4 can have a dual effect on NCC, which depends on the intracellular Cl^- concentration (JASN, 2015) have changed our working model of NCC regulation by WNKs. We thus revisited the effect of the KS-WNK1-Δ11 isoform on NCC and WNK4 activity.

Methods: NCC activity was assessed in *Xenopus* oocytes by measuring the thiazide-sensitive $^{22}Na^+$ uptake and the N-terminal phosphorylation by Western blot, two days after microinjection with NCC cRNA alone or together human L-WNK1-Δ11, KS-WNK1-Δ11 and/or WNK4. WNK4-S335 phosphorylation was taken as a surrogate of activity. Antibodies used were against c-myc, flag, T60-NCC, S335-WNK4, SPAK or S373-SPAK.

Results: KS-WNK1-Δ11 induced a dramatic activation of NCC by 3 fold (N=30, $p<0.001$) that was accompanied by increased SPAK/OSR1 phosphorylation as well as NCC surface expression and phosphorylation. The effect of L-WNK1-Δ11 and KS-WNK1-Δ11 on NCC was additive. The effect of L-WNK1-Δ11, but not that of KS-WNK1-Δ11 on NCC was precluded by coinjection with WNK4. The presence of KS-WNK1-Δ11 increased WNK4 phosphorylation at S335 by 7.5 fold (N=6, $p<0.01$), despite no change in intracellular Cl^- concentration. KS-WNK1-Δ11 and WNK4 interaction was confirmed by immunoprecipitation. Increased WNK4-S335 phosphorylation in the presence of KS-WNK1-Δ11 was only seen in the immunoprecipitated fraction and was not observed with the KS-WNK1-Δ11 HQ mutant that lacks interaction with WNK4.

Conclusions: Our data show that KS-WNK1-Δ11 is a powerful activator of NCC. The mechanism appears to be due to KS-WNK1-Δ11-induced WNK4 autophosphorylation and activation that in turn promotes NCC N-Terminal phosphorylation by the WNK-SPAK/OSR1 pathway. Given the high expression of KS-WNK1-Δ11 in DCT, these observations may provide a mechanism to explain why the up-regulated WNK4 in PHAII remains active despite the salt sensitive, low renin hypertension and hyperkalemia, expected to inhibit the kinase.

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

FR-OR099

A Cysteine-Rich Motif Regulates KS-WNK1 Protein Localization and Abundance Cary R. Boyd-Shiwarski,[1] Kara L. McClain,[1] Daniel J. Shiwarski,[1] Lubika J. Nkashama,[1] Ankita Roy,[1] Olivier Staub,[2] Arohan R. Subramanya.[1] *[1]Univ of Pittsburgh; [2]Univ of Lausanne.*

Background: WNK1 coordinates tubular NaCl and K+ transport through the concerted action of two major gene products: a ubiquitously expressed full-length "Long" isoform with intact serine-threonine kinase activity (L-WNK1), and an N-terminally truncated kinase-defective "Kidney Specific" isoform (KS-WNK1) that is highly expressed in the DCT. KS-WNK1 is transcribed from an intronic promoter that replaces the first four exons of L-WNK1 with a short unique exon, termed exon 4a. In the DCT, WNK signaling complexes form discrete puncta of unknown function. The marked expression of KS-WNK1 in DCT suggests that it may play role in the formation of these structures.

Methods: WNK1 isoform localization in kidney was assessed by immunostaining and light microscopy. The role of specific residues in KS-WNK1 trafficking and stability was determined by gBlock mutagenesis, cDNA transfection into 293 and MDCK cells, confocal microscopy, cell fractionation, and CHX chase assays.

Results: In the human and rodent DCT, C-terminal pan-WNK1 antibodies recognized a punctate signal that differed strikingly from a diffuse localization pattern in other nephron segments where KS-WNK1 expression is low. In cultured kidney epithelia, KS-WNK1 collected in similar puncta, whereas L-WNK1 was distributed diffusely throughout the cytoplasm. Mutagenesis studies revealed that KS-WNK1 puncta formation was dependent on a cysteine-rich motif harbored in exon 4a. Mutation of this signature to serines shifted KS-WNK1 diffusely, rendering the protein unstable due to enhanced sensitivity to its cognate E3 ubiquitin ligase, the KLHL3/CUL3 complex. In coexpression studies, L-WNK1 redistributed into KS-WNK1 puncta, indicating that KS-WNK1 may act as a scaffold that sequesters WNK complexes in the DCT.

Conclusions: These results suggest that exon 4a acts as a cap to protect KS-WNK1 from disposal, and that the cysteines in exon 4a are necessary for its assembly into discrete structures that participate in DCT physiology. We propose that the punctate localization of WNK kinases in the DCT may reflect a KS-WNK1 dependent signaling response during oxidative or potassium stress.

Funding: NIDDK Support, VA Support

FR-OR100

Regulation of WNK4-SPAK-NCC Pathway by the Calcium Sensing Receptor Silvana Bazua-Valenti,[1] Lorena Leonor Rojas,[1] Maria Castañeda-Bueno,[1] Alejandro Rodriguez-Gama,[1] Norma Hilda Vázquez,[1] Luz Graciela Cervantes-Perez,[2] Jonatan Barrera-Chimal,[1] Paola De los Heros,[3] Gerardo Gamba.[1] *[1]Molecular Physiology Unit, INCMNSZ-IIB-UNAM; [2]Pharmacology, INCICH; [3]Faculty of Medicine, UNAM, Mexico City, Mexico.*

Background: Extracellular calcium inhibits salt reabsorption in the TAL through the basolateral Calcium Sensing Receptor (CaSR) inducing hypercalciuria. CaSR is also expressed in the apical membrane of the DCT, where we hypothesize plays a role in activating NCC via WNK4-SPAK pathway to prevent salt loss and further decrease the calcium reabsorption.

Methods: NCC activity (thiazide-sensitive $^{22}Na^+$ uptake) and the effect of the type I CaSR agonist gadolinium were analyzed in *X. leavis* oocytes in the absence or presence of mouse WNK4 and/or CaSR. Expression and phosphorylation of SPAK were assessed in HEK-293 cells co-transfected with WNK4 + wild type or mutant CaSR harboring the activating mutation E227K, in the presence or absence of the type 2 agonist R-568. Lastly, the WNK4-SPAK-NCC pathway was also studied by western blot analysis in kidneys of 12 mice administered with R-568 at 30 mg/kg or vehicle.

Results: In oocytes, gadolinium increased NCC activity by five-fold when co-expressed with WNK4 and CaSR ($p<0.001$). Absence of either WNK4 or CaSR precluded this effect. In R-568-stimulated HEK-293 cells, SPAK phosphorylation increased in a dose and time dependent manner only if both CaSR and WNK4 were present. Furthermore, co-transfection with the CaSR activating mutation, CaSR-E227K, phosphorylates SPAK in basal conditions ($p<0.05$). Interestingly, CaSR-E227K markedly increased WNK4 protein expression (almost two-fold, $p<0.0001$), a condition not observed with a WNK4 harboring PHAII mutation, suggesting a Kelch3-dependent mechanism. Finally, R-568 administration to wild-type mice showed increased NCC phosphorylation and increased WNK4 and SPAK protein expression (five-fold $p<0.05$).

Conclusions: Our results suggest that activation of CaSR can increase the activity of NCC via WNK4-SPAK pathway. It is possible that activation of CaSR by calcium in the apical membrane of DCT increases salt reabsorption via NCC to prevent salt loss and further decrease calcium reabsorption in this nephron segment.

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

FR-OR101

Collecting Duct Specific Deletion of the (Pro)renin Receptor Modulates ENaC Expression Nirupama Ramkumar, Deborah Stuart, Nikita Abraham, Kai Song, Shuping Wang, Donald E. Kohan. *Nephrology and Hypertension, Univ of Utah Health Sciences Center, Salt Lake City, UT.*

Background: The renal tubular (pro)renin receptor (PRR) has been shown to modulate water balance, blood pressure and Na^+ homeostasis. We recently reported that *inducible* nephron wide deletion of the PRR results in Na^+ wasting, reduced epithelial Na^+ channel (ENaC) expression in the kidney and attenuated hypertensive response to angiotensin-II (Ang-II) infusion.

Methods: In this study, we examined the effects of PRR deletion in collecting duct (CD) specific mouse models targeting either the principal cells (PC) or intercalated cells (IC).

Results: PC-specific PRR knockout (KO) mice were obtained by crossing floxed PRR mice with mice harboring AQP-2 Cre recombinase. Compared to floxed mice, PC specific KO PRR mice had no differences in PRR immunostaining but had 50% reduction in PRR mRNA in micro-dissected cortical CDs. No differences in blood pressure were observed between the two groups at baseline or following Ang-II infusion at 600 ng/kg/min. Similarly, plasma renin concentration and renal expression of ENaC protein isoforms were comparable between the two groups. To achieve IC-specific PRR deletion, floxed PRR mice were bred with mice expressing B-1 Cre recombinase. Compared to floxed controls, IC-specific PRR KO mice were smaller (KO body weight: 5.9 ± 1.3 g vs controls: 11.1± 1.2 g) and did not survive beyond 30 days after birth. IC-specific PRR KO mice also demonstrated marked reduction in renal medullary PRR immunostaining along with decreased renal expression of ENaC-α protein (50% reduction compared to controls), similar to the findings in nephron wide deletion of PRR.

Conclusions: Taken together, these findings suggest that IC specific deletion of PRR but not PC-specific deletion modulates renal ENaC expression. Further studies evaluating ENaC activity in isolated cortical CDs from PC and IC specific PRR KO mice will help delineate the functional role of CD PRR in Na^+ homeostasis.

Funding: Private Foundation Support

FR-OR102

(Pro)renin Receptor/ATP6AP2 Is Required for V-ATPase Assembly and Function but Not for the Renin-Angiotensin System Matias Simons,[1] Magda Cannata Serio,[1] Virginie Hauser,[1] Francesco Trepiccione,[2] Michael Schwake,[3] Dominique Eladari.[4] *[1]Inst Imagine, Paris, France; [2]Second Univ of Naples, Naples, Italy; [3]Northwestern Univ, Chicago, IL; [4]PARCC, INSERM 970, Paris, France.*

Background: The proton pump vacuolar (V)-ATPase acidifies intracellular organelles and is crucial for many cellular processes. The multisubunit complex is divided into the proton pore (V0 sector) and the ATP hydrolysis domain (V1 sector). Apart from the V1 and V0 subunits, there are two accessory subunits, ATP6AP1 and ATP6AP2. While ATP6AP1 seems to participate in V0 assembly in the endoplasmic reticulum (ER), ATP6AP2 has been proposed to function as a receptor for (pro)renin in the renin-angiotensin system (RAS).

Methods: This study aimed at characterizing ATP6AP2 functions in the kidney by combining phenotypic characterization in mouse and *Drosophila* models with interaction proteomics in cultured human cells.

Results: Using an inducible conditional deletion of ATP6AP2 in the tubular nephron of the mouse, we could recently show that acid-base regulation was decreased due to impaired V-ATPase expression and activity in the intercalated cells of the collecting duct. By contrast, RAS-dependent sodium and potassium handling as well as blood pressure control was unaffected. To identify novel binding partners of ATP6AP2, we performed a mass spectrometry-based proteomic approach. Among top-ranking interactors for ATP6AP2, we found both V0 subunits and ER-based V0 assembly factors, including ATP6AP1. We were able to demonstrate ER localization of ATP6AP2 using *Drosophila* wing epithelial cells. This localization depended on an ER retention motif in the extreme cytoplasmic tail of ATP6AP2. Overexpression and knockdown of ATP6AP2 led to Xbp1-dependent ER stress in wing epithelial cells. Moreover, fly wing phenotypes caused by ATP6AP2 overexpression were completely suppressed by co-expressing ATP6AP1.

Conclusions: Taken together, our results demonstrate that ATP6AP2 interacts with ATP6AP1 in the ER to control ER homeostasis. Together with the *in vivo*-analysis, our data argue for a main role of ATP6AP2 in V-ATPase assembly and function and against a role in the renin-angiotensin system.

Funding: Government Support - Non-U.S.

FR-OR103

Recombinant ApoL1 Confers pH-Dependent Anion Permeability to Phospholipid Vesicles John C. Edwards. *Internal Medicine, Saint Lousi Univ, Saint Louis, MO.*

Background: Variants in ApoL1 confer increased risk of certain types of chronic kidney disease in people of African ancestry. ApoL1 has been reported to function as an ion channel but reports vary on the nature of this activity. We sought to characterize ApoL1 channels with expectation that detailed properties of the channel activity of WT and variant ApoL1 may provide insight into the pathophysiology of ApoL1-associated kidney disease.

Methods: Recombinant N-terminal His-tagged ApoL1 was expressed in bacteria and purified by Ni-affinity and gel filtration using methods of Thompson and Finkelstein (PNAS 112: 2894 (2015)). Ion permeability was assessed using vesicle-based, voltage dependent Cl and K efflux assays employing ion selective electrodes. Single channel properties were investigated using the Tip-Dip lipid bilayer approach with ApoL1 added to the bath solution. Protein structure was probed using intrinsic tryptophan fluorescence.

Results: The purification method yields large amounts of very highly purified His-tagged ApoL1 which is active in a trypanosome killing assay. Direct addition of Apol1 to pre-formed phospholipid vesicles yields robust Cl selective permeability that supports voltage-driven chloride transport. The activity shows a strong dependence on pH at which protein and membranes interact, with a sharp drop in activity as pH is raised above 6.5. Activity is linearly dependent on mass of protein, and shows strong dependence on lipid composition of the vesicles, requiring the presence of negatively charged phospholipids. We do not find cation-selective permeability when assayed at either pH 5 or 7.5. Biophysical studies of ApoL1 in solution reveal a significant structural transition in the same range in which the channel is activated (pH 7 to 6.5). In tip-dip bilayer, ApoL1 spontaneously inserts at low pH, generating transitions with a range of single channel conductances between 2 and 10pS, and with a non-rectifying current-voltage relationship. We do not find enhanced channel activity if the bath solution is changed to pH 7.5.

Conclusions: Purified recombinant ApoL1 can insert directly into phospholipid membranes at low pH and function as an anion selective channel. Whether the disease associated variants show altered channel properties remains to be determined.

FR-OR104

Purinergic Modulation of V-ATPase-Dependent Proton Secretion in Type A Intercalated Cells Maria A. Battistone, Claire R. Barton, Rachel Nager Liberman, Anil V. Nair, Diane E. Capen, Dennis Brown, Sylvie Breton. *Prog. Membr. Biol./Nephrology Div, MGH/Harvard Med. Sch., Boston, MA.*

Background: Acid/base transport by renal intercalated cells (ICs) is central to the maintenance and regulation of blood pH. In particular, type A ICs (A-ICs) secrete protons (H^+) via the vacuolar H^+-ATPase (V-ATPase) located in their apical membrane. This process is regulated via recycling between sub-apical vesicles and the apical membrane, and activation of the cAMP/PKA pathway induces apical V-ATPase accumulation. The adenosine (Ade) P1 purinergic receptors A2A and A2B are linked to Gs and increase cAMP and we, therefore, investigated their role in the regulation of V-ATPase in A-ICs.

Methods: P1 receptor expression was evaluated by RT-PCR in $EGPF^+$ A-ICs isolated by FACS from B1-EGFP mice, and by immunofluorescence (IF) in mouse kidney. Mice were injected (i.v.) with Ade, agonists of A2A (PSB077) or A2B (BAY60-6583) (1.5 µmol/kg, 15 min) or saline. V-ATPase membrane accumulation was analyzed by IF, immunogold electron microscopy (EM), and Western blotting (WB) following cell fractionation. Moreover, isolated A-ICs were incubated for 15 min with PSB077 or BAY60-6583 (600 µM), or antagonists of A2A (ANR94) or A2B (PSB1115) (10 µM), and V-ATPase membrane accumulation and PKA substrate phosphorylation were evaluated by WB.

Results: RT-PCR revealed A2A and A2B expression in A-ICs, and IF showed their apical membrane expression in A-ICs. IF, EM, and WB following cell fractionation showed V-ATPase apical membrane accumulation (subunit A, a4) in mice treated with Ade, PSB077 or BAY60-6583, compared to control. A-ICs treated with the agonists showed an increase in PKA substrate phosphorylation, and V-ATPase redistribution from vesicles to plasma membrane. The A2A and A2B antagonists, added together with Ade, abolished these effects.

Conclusions: These results indicate the presence of an adenosine-dependent PKA activation pathway via A2A and A2B receptors, which leads to V-ATPase apical membrane accumulation in A-ICs. Our study reveals a novel mechanism by which A-ICs respond to luminal agonists via purinergic regulation, and provides new frameworks for the future development of treatments for acid/base balance disorders.

Funding: NIDDK Support

FR-OR105

Increased Concentration of the Vasoconstriction Inhibiting Factor (VIF), an Endogenous Cofactor of Angiotensin II Acting on the AT2 Receptor, in CKD Patients Joachim Jankowski,[1] Vera Jankowski.[1] *[1]Inst for Molecular Cardiovascular Research, Univ Hospital RWTH Aachen, Aachen, Germany; [2]Charite, Berlin, Germany.*

Background: The renin-angiotensin system (RAS) and especially the angiotensin peptides play a central role in blood pressure regulation. Here, we hypothesize that a yet unknown peptide is involved in the action of Ang 2 modulating the vasoregulatory Ang II effects as a cofactor.

Methods: The peptide was isolated from bovine adrenal glands chromatographically. Chromatographic fractions with vasodilatory properties were fractionated to homogeneity, and the underlying cofactor of Ang II was identified. The effects of this peptideon vasoconstriction were evaluated *in-vitro*, *in-vivo* in an animal model, and the affinity of the peptide to the receptor mediating these effects was identified. The plasma concentration in humans was quantified in CKD patients and controlls.

Results: The amino acid sequence of the endogenous cofactor of Ang II isolated from bovine adrenal glands was HSSYEDELSEVLEKPNDQAEPKEVTEEVSSKDAAE, which is a degradation product of chromogranin A. The amino acid sequence of the peptide isolated from human plasma was HSGFEDELSEVLENQSSQAELKEAVEEPSSKDVME. Both peptides diminished significantly the vasoconstrictive effect of Ang II *in-vitro*. Based on the vasoregulatory effects on the Ang II actions, we named the peptide "*vasoconstriction inhibiting factor*" (*VIF*). The vasoregulatory effects of *VIF* are mediated by the AT-2 receptor. VIF impairs Ang II-induced phosphorylation of the p38MAPK pathway but not of ERK1/2. The vasodilatory short-term and long-term effects were confirmed *in-vivo*. The plasma concentration of *VIF* was significantly increased in CKD patients compared to controls.

Conclusions: *VIF* is a novel vasoregulatory peptide which modulates the vasoconstrictive effects of Ang II by acting on the AT2 receptor. It is likely that this increase in *VIF* may serve as a counter-regulatory effect to defend against hypertension. The identification of this new target may help us to understand the pathophysiology of renal and heart failure and may form a basis for the development of new strategies for the prevention and treatment of cardiovascular disease in these patients.

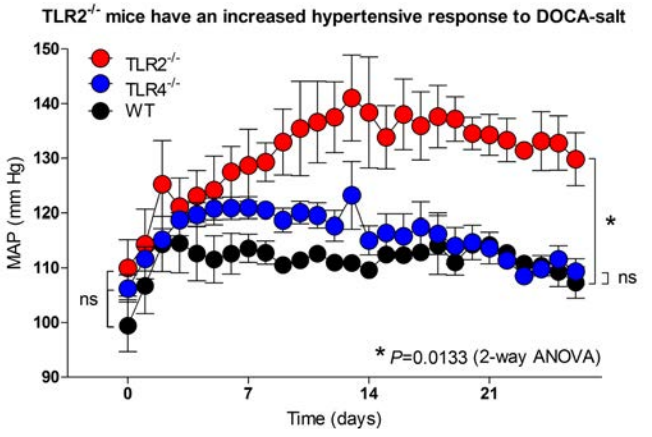
FR-OR106

Toll-Like-Receptor 2 Deficiency Exacerbates Deoxycorticosterone Acetate-Salt-Induced Hypertension David Severs, Estrellita Uijl, Alexander H. Danser, Robert Zietse, Ewout J. Hoorn. *Dept of Internal Medicine, Erasmus Medical Center, Rotterdam, Netherlands.*

Background: Emerging evidence suggests that inflammatory processes contribute to the development of hypertension. Specific damage-associated molecular patterns (DAMPs) may be increased in early stages of hypertension. Engagement of these DAMPs with Toll-like receptors (TLR) on innate immune and nonimmune cells initiates a cascade that could lead to worsening hypertension. Our aim was to assess the effect of deficiencies in TLR2 or TLR4 on the development of salt-sensitive hypertension.

Methods: We measured mean arterial pressure (MAP) in wild-type (WT, n=3), $TLR2^{-/-}$ (n=3) or $TLR4^{-/-}$ mice (n=6) by implanted radiotelemeters. We induced hypertension by deoxycorticosterone acetate and 0.9% NaCl as drinking water (DOCA-salt) during 4 weeks. We measured vascular reactivity in iliac arteries with wire myographs; these data are expressed as percentage of the maximum contractile response (E_{max}) to 100 mmol/L KCl.

Results: $TLR2^{-/-}$ mice had a much greater rise in MAP than did WT mice, while MAP in $TLR4^{-/-}$ was similar to that in WT (see figure). The angiotensin (Ang) II E_{max} did not differ between WT (60.3±6.9) and $TLR4^{-/-}$ mice (50±2.2%, P=0.41), but $TLR2^{-/-}$ mice had significantly greater contractility (93.2±5.9%, P=0.02). Irbesartan blocked Ang II-induced contractile responses in all mice, whereas the Ang II type 2 (AT2) receptor blocker PD123319 blunted the effects of Ang II only in $TLR2^{-/-}$ mice. Addition of the nitric oxide synthase blocker L-NAME did not significantly alter the contractile response to Ang II, and acetylcholine-induced vasorelaxation was similar in all mice.



Conclusions: Unexpectedly, TLR2 deficiency exacerbates experimental salt-sensitive hypertension. This effect may involve an increase in Ang II responsiveness, which may be partly explained by a constrictive rather than a vasodilatory response to AT2 receptor stimulation.

Funding: Government Support - Non-U.S.

FR-OR107

Renal-Specific Dendritic Cell Depletion Causes Hypotension via Reduced Sodium Chloride Cotransporter Expression Brandi M. Wynne,[1,2] Gillian Grace Hecht,[2] Trinity Kronk,[1] Henrieke Jacobien van Elst,[2] Robert S. Hoover.[1,2,4] *[1]Dept of Physiology, Emory Univ, Atlanta, GA; [2]Dept of Medicine, Renal Div, Emory Univ, Atlanta, GA; [3]Veteran's Administration Research Service, Atlanta, GA; [4]Atlanta VA Medical Center, Atlanta, GA.*

Background: During hypertension, dendritic cells (DCs) have been shown to activate immune cells and secrete cytokines, such as IL-6. Recently, DCs were found to form an intricate network within the renal cortex and especially along the distal nephron. Additionally, during AngII-mediated hypertension, a subset of DCs route to the kidney. Studies have shown that loss of renal-specific DCs (rDCs) reduce glomerulonephritis and play an important role in the progression of hypertension. We hypothesize that rDCs modulate blood pressure (BP) and sodium transporter expression.

Methods: Tail-cuff measurements were performed in rDC-depleted and Wt mice. rdas loss contributed to a decreased systolic blood pressure (94mmHg ± 17mmHg *vs.* 130mmHg ± 10mmHg *Wt*, n=5, $p<0.05$) at baseline. To determine a mechanism, protein expression of phospho-NCC (pNCC) and total NCC, along with IL-6 was determined. rDC-depleted mice had a lower expression of total NCC (48% decrease), with no changes in pNCC or IL-6. There were no differences in urinary sodium excretion at baseline.

Results: Tail-cuff measurements were performed in rDC-depleted mice and Wt (C57Bl6). Renal-specific loss of DCs contributed to a decreased systolic blood pressure (94mmHg ± 17mmHg *vs.* 130mmHg ± 10mmHg *Wt*, n=5, $p<0.05$). To determine a mechanism, protein expression of phospho-NCC (pNCC) and total NCC, along with IL-6 was determined. rDC-depleted mice had a lower expression of total NCC (48% decrease), with no changes in pNCC. In addition, no detectable changes in IL-6 were observed.

Conclusions: These data suggest that baseline BP is modulated by resident innate immune cells specific to the kidney. Our data also demonstrate that rDC-depleted mice have reduced levels of the distal nephron sodium transporter, NCC, which may be contributing to this phenotype. In addition, we observed no differences in IL-6, a predominate cytokine secreted by DCs. Together, our data demonstrate that rDCs contribute to reduced NCC expression and hypotension.

Funding: Other NIH Support - 2T32DK7656-21, VA Support

FR-OR108

Atrial Natriuretic Peptide Knockout Exacerbates Hypertension in Dahl Salt-Sensitive Rat Daria Ilatovskaya, Gregory Blass, Vladislav Levchenko, Alison J. Kriegel, Alexander Staruschenko. *Physiology, Medical College of Wisconsin, Milwaukee, WI.*

Background: Atrial Natriuretic Peptide (ANP) encoded by the *Nppa* gene is an osmoregulatory hormone known to promote salt excretion and therefore lower blood pressure. *Nppa* knockout mice were shown to exert a salt-sensitive (SS) phenotype; furthermore, *Nppa* was identified as one of causative genes at a GWAS locus relevant to blood pressure (BP) control. The current project was designed to study the effects of ANP deficiency under the condition of SS hypertension using the *Nppa* KO developed on the Dahl SS rat background.

Methods: A combination of *in vivo* (chronic BP monitoring and GFR measurement in conscious unrestrained animals), electrophysiological (single channel patch-clamp analysis of the freshly isolated split-open CCD), molecular and biochemical approaches and echocardiography were used here to characterize the role of ANP in the development of SS hypertension in Dahl SS rats.

Results: *Nppa* KO rat is viable; there was no difference observed in the body weight or kidney to body weight ratio of the 8 week old *Nppa* KO animals compared to wild type SS rat. However, heart weight is significantly higher in *Nppa* KO rat. Echocardiography revealed a striking hypertrophy of the right ventricle, and an increase in right ventricle wall thickness and chamber diameter. Furthermore, *Nppa* KO rats have lower 24 hr urine output compared to wild type SS rats, and show decreased GFR even when fed a normal salt diet. BP measurements indicate the *Nppa* KO rats exhibit exacerbated salt-sensitivity compared to wild type SS controls (mean arterial pressure after 21 days of a 4% NaCl diet was 183 ± 9 in *Nppa* KO and 144 ± 4 mmHg in SS control group). Additionally, electrophysiological analysis demonstrated that *Nppa* KO animals have higher Epithelial Sodium Channel (ENaC) activity in the distal nephron (CNT/CCD) compared to wild type rats.

Conclusions: ANP plays a critical role in the development of SS hypertension. Knock out of *Nppa* is SS rats results in significant abnormalities in heart and kidney function.

Funding: NIDDK Support, Other NIH Support - NHLBI, Private Foundation Support

FR-OR109

Slc26a11 Plays an Important Role in Salt Reabsorption in the Kidney Collecting Duct: Impact on Furosemide Diuresis and Salt/DOCA Hypertension Jie Xu,[1] Sharon L. Barone,[1,2] Marybeth Brooks,[1,2] Saeed Alshahrani,[1] Kamyar A. Zahedi,[1,2] Manoocher Soleimani.[1,2] *[1]Dept of Medicine, Univ of Cincinnati, Cincinnati, OH; [2]Research Services, Veterans Affairs Medical Center, Cincinnati, OH.*

Background: The identity and role of trans-cellular chloride reabsorbing pathways in medullary collecting ducts are poorly understood. We have localized Slc26a11 to the apical membrane of A-intercalated cells in the CCD, OMCD and iIMCD. Functional studies in cultured cells and oocytes indicate that Slc26a11 can function as a Cl^-/HCO_3^- exchanger, chloride conductive pathway and electrogenic Na-Cl co-transporter. Expression of kidney Slc26a11 increases in response to furosemide treatment or salt loading, raising the possibility that it is important in salt reabsorption in the setting of enhanced delivery of salt to the collecting duct.

Methods: To ascertain the role of Slc26a11 in the kidney, kidney specific Slc26a11-KO mice were generated by crossing floxed-Slc26a11 mice with Cadherin promoter-driven Cre-recombinase transgenic mice.

Results: Immunofluorescence microscopy, northern and western blot analyses showed more than 90% reduction in the expression of Slc26a11 in the kidneys of KO mice. These mice exhibited significant salt wasting in response to furosemide (sodium excretion of 0.44 in KO vs 0.32 mmole/day in WT mice, $p<0.03$, n=5). Baseline salt excretion was comparable in the two genotypes (0.18 vs 0.20 mmoles/day in WT and KO mice). Slc26a11 KO mice exhibited complete abrogation of high salt/DOCA-induced hypertension vs WT mice when animals were placed on a high salt diet for 10 days and injected with a DOCA (systolic blood pressure was 98 mm Hg in KBAT KO vs. 145 mm Hg in WT mice, as measured by computerized tail cuff method (n = 5, $p<0.01$). Pendrin KO mice were used for comparison and showed a significant protection against salt/DOCA-induced hypertension.

Conclusions: We conclude that Slc26a11 plays an important role in salt reabsorption along the length of the collecting duct following increased delivery of salt and is essential for the generation of salt/DOCA hypertension. Slc26a11 could be a novel target for diuretic therapy in fluid overloaded states and in aldosterone-induced hypertension.

Funding: VA Support

FR-OR110

MiR-204 Protects the Kidney against Hypertensive Injury Yuan Cheng,[1,2,4] Dandan Wang,[1,2,4] Baorui Huang,[3,4] Maria Angeles Baker,[4] Kristie Usa,[4] Yong Liu,[4] Congxiao Zhang,[5] Lijin Dong,[5] Aron M. Geurts,[4] Niansong Wang,[3,4] Sheldon S. Miller,[5] Yongcheng He,[1,2,4] Mingyu Liang.[4] *[1]Nephrology, The First Affiliated Hospital of Shenzhen Univ and Shenzhen Second People's Hospital, Shenzhen, Guangdong, China; [2]The Center for Nephrology and Urology at Shenzhen Univ,Shenzhen Univ Health Science Center, Shenzhen Univ, Shenzhen, Guangdong, China; [3]Nephrology and Rheumatology, Shanghai Jiaotong Univ Affiliated Sixth People's Hospital, Shanghai, China; [4]Center of Systems Molecular Medicine, Dept of Physiology, Medical College of Wisconsin, Milwaukee, WI; [5]Section of Epithelial and Retinal Physiology and Disease, National Eye Inst, National Insts of Health, Bethesda, MD.*

Background: Hypertension is the second leading cause of end-stage renal disease. The role of microRNA (miRNA) in hypertensive renal injury remains largely unknown.

Methods: Small RNA deep sequencing was performed to examine miRNA profiles in hypertensive nephrosclerosis patients. The functional role of a selected miRNA and the mechanisms involved were investigated in a rat model and a knockout mouse model.

Results: MiR-204-5p abundance was significantly lower in kidneys of hypertensive nephrosclerosis patients and Dahl salt-sensitive rats. Administration of anti-miR-204-5p in salt-insensitive $SS.13^{BN26}$ rats decreased detectable miR-204-5p in the kidneys and significantly exacerbated the thickening of interlobular artery and renal interstitial fibrosis without influencing salt-induced increases of blood pressure. Knockdown of miR-204-5p led to up-regulation of protein tyrosine phosphatase SHP2 and increased phosphorylation of signal transducer and activator of transcription 3 in the rat kidneys. The role of miR-204 was further examined in a mouse model of hypertensive renal injury induced by uninephrectomy, angiotensin II, and a high-salt diet. *Mir204* gene knockout significantly exacerbated albuminuria, renal interstitial fibrosis, and thickening of interlobular artery in this model despite an attenuation of hypertension.

Conclusions: These findings in patients, rat and mouse models indicate a new mechanism in hypertensive renal injury in which endogenous miR-204 protects the kidney against hypertensive injury.

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FR-OR111

MicroRNA-132 Regulates Renin Release via Targeting Cox-2 in the Macula Densa Roel Bijkerk,[1,2] Wendy Stam,[1,2] Sharon Van Gelderen,[1,2] Ton J. Rabelink,[1,2] Anton Jan Van Zonneveld.[1,2] *[1]Internal Medicine (Section Nephrology), Leiden Univ Medical Center, Leiden, Netherlands; [2]Einthoven Laboratory for Experimental Vascular Medicine, Leiden Univ Medical Center, Leiden, Netherlands.*

Background: Renin synthesis and release from the juxtaglomerular apparatus is the rate-limiting step in the activation of the renin– angiotensin system, which is central to the regulation of body fluid and electrolyte homeostasis and blood pressure. Generation of prostaglandin-E2 (PGE2) in a cyclo-oxygenase-2 (Cox-2)-dependent manner plays a dominant role in the stimulation of renin release.

Methods: We used miR-reporter constructs to validate Cox2 repression by microRNA-132 (miR-132) and generated antagomirs to silence miR-132 function. Mice were housed in metabolic cages and sacrificed 1 day after i.v. injection of the antagomirs or scrambled controls.

Results: We identified miR-132, using in situ hybridization, to be strongly expressed in the macula densa and found miR-132 to directly target Cox-2 *in vitro*. *In vivo* silencing of miR-132 resulted in increased PGE2 and subsequent renin production. Blocking PGE2 synthesis using the selective Cox-2 inhibitor Celecoxib abrogated the mir-132-antagonist induced increase in renin, further supporting a regulatory role for miR-132 in the Cox-2/PGE2 dependent release of renin. Previously, we found that silencing miR-132 resulted in acute diuresis by inhibiting hypothalamic AVP production, resulting in hypovolemia and increased plasma osmolality. To exclude secondary effects on PGE2 and renin production caused by this, we administered ddAVP which reversed these miR-132 mediated diuretic effects, and demonstrated that PGE2 and renin levels remained elevated independent of miR-132-antagonist induced diuresis.

Conclusions: Taken together, we demonstrated an essential posttranscriptional regulatory role for miR-132 in the synthesis and release of renin through Cox-2 mediated PGE2 synthesis in the macula densa.

FR-OR112

Detection of THSD7A Antibodies Is a Valuable Tool for the Differential Diagnosis of Membranous Nephropathy Elion Hoxha,[1] Laurence H. Beck,[2] Thorsten Wiech,[3] Nicola M. Tomas,[1] Christian Probst,[4] Catherine Meyer-Schwesinger,[1] Gunther Zahner,[1] Phillip Rolf Stahl,[3] Ulf Panzer,[1] Sigrid Harendza,[1] Udo Helmchen,[3] David J. Salant,[2] Rolf A. Stahl.[1] *[1]III. Medizinische Klinik, UKE-Hamburg, Hamburg, Germany; [2]Boston Univ School of Medicine, Boston, MA; [3]Inst für Pathologie, UKE-Hamburg, Hamburg, Germany; [4]EUROIMMUN AG, Lübeck, Germany.*

Background: Thrombospondin Type-1 Domain-Containing 7A (THSD7A) is a target antigen in membranous nephropathy (MN) in addition to the major antigen Phospholipase A_2 Receptor 1 (PLA_2R1). The prevalence of THSD7A antibody (THSD7A-Ab) positive patients is unknown and it is unclear whether differences occur in the clinical presentation between patients positive for PLA_2R1-Ab or THSD7A-Ab.

Methods: We screened sera of 1276 patients with MN from three cohorts by Western blot and an indirect immunofluorescence test (IFT) for THSD7A-Ab. Follow-up data over at least 12 months were available for 10 THSD7A-Ab positive patients.

Results: The IFT had a 92% sensitivity and 100% specificity compared to Western blot. The prevalence of THSD7A-associated MN in a prospective cohort of 345 consecutive patients with newly diagnosed MN was 2.6%; the majority of patients was female. 40 of 1276 patients were identified to have a THSD7A-associated MN, in eight of them a malignant tumor was diagnosed within a median time of 3 months from diagnosis of MN. In one patient with THSD7A-associated MN and metastases of an endometrial carcinoma, immunohistochemistry demonstrated THSD7A expression on the metastatic cells and within follicular dendritic cells of the metastasis-infiltrated lymph node. Complete remission of proteinuria was observed in only those 4 patients in whom THSD7A-Ab disappeared from the circulation. Five patients had a partial remission of proteinuria, THSD7A-Ab became negative in one and remained positive in four patients.One patient had no remission of proteinuria and THSD7A-Ab persisted.

Conclusions: The IFT allows a sensitive and specific measurement of THSD7A-Ab in patients with MN. Patients with THSD7A-associated MN differ in their clinical characteristics from patients with PLA_2R1-associated MN. Intensive screening for malignant tumors is warranted in patients with THSD7A-associated MN.

Funding: Government Support - Non-U.S.

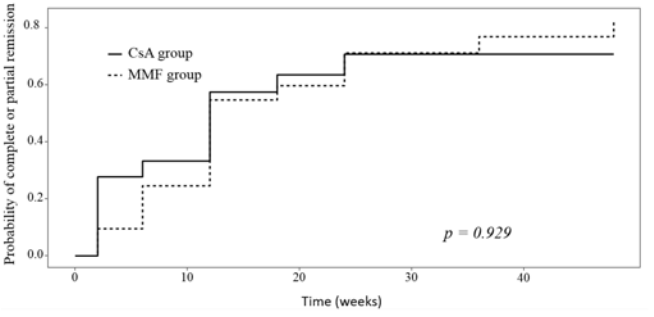
FR-OR113

The Effect of Mycophenolate Mofetil versus Cyclosporine as a Combination Therapy to Low Dose Corticosteroid in High Risk Patients with Idiopathic Membranous Nephropathy: A Multicenter Randomized Trial Ji-Young Choi,[1] Dong Ki Kim,[2] Yang Wook Kim,[3] Tae-Hyun Yoo,[4] Jung Pyo Lee,[2] Hyun Chul Chung,[5] Kyu-Hyang Cho,[6] Won Suk An,[7] Duk Hyun Lee,[8] Hee-Yeon Jung,[1] Jang-Hee Cho,[1] Chan-Duck Kim,[1] Yong-Lim Kim,[1] Sun-Hee Park.[1] *[1]Kyungpook National Univ; [2]Seoul National Univ; [3]Inje Univ; [4]Yonsei Univ; [5]Ulsan Univ; [6]Yeungnam Univ; [7]Dong-A Univ; [8]Fatima Hospital, Daegu.*

Background: The effect of mycophenolate mofetil (MMF) versus cyclosporin (CsA) combined with low-dose prednisolone was evaluated in patients with idiopathic membranous nephropathy (MGN) in a multicenter randomized trial (NCT01282073).

Methods: Biopsy-proven idiopathic MGN patients with severe proteinuria (> 8 g/day, n=39) were randomly assigned to MMF or CsA group combined with low dose prednisolone, respectively and followed up for 48 weeks. Complete or partial remission rate of proteinuria as well as eGFR at 48 weeks were compared between the two groups.

Results: Proteinuria at baseline and 48 weeks were 8.9 ± 5.9 and 2.1 ± 3.1 g/day in the MMF vs. 8.4 ± 3.5 and 3.2 ± 5.7 g/day in the CsA group. Cumulative incidences of complete or partial remission of proteinuria at 48 weeks were 76.1% in MMF and 66.7% in CsA group, a difference of 9.4% (95% CI -0.18 to 0.38) that did not exceed the predefined 20% margin.



eGFR at baseline and 48 weeks were 73.9 ± 31.0 and 70.1±19.2 ml/min/1.73m^2 in the MMF vs. 84.9 ± 25.2 and 84.0±32.6 ml/min/1.73m^2 in the CsA group. Adverse events occurred in 12 (57.1%) and 9 (50.0%) patients in MMF and CsA group (p=0.90). There were no significant differences in changes of gastrointestinal symptom rating scale and gastrointestinal quality of life index score from baseline to 48 weeks between the two groups.

Conclusions: Combined with low dose corticosteroid, the effect of MMF was comparable to CsA in patients with idiopathic MGN with similar adverse effects including gastrointestinal symptoms.

Funding: Pharmaceutical Company Support - Hanmi Pharmaceutical, Seoul, Korea

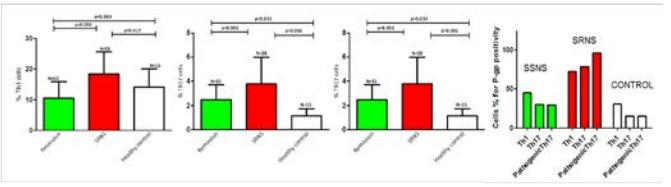
FR-OR114

Permeable Glycoprotein Expression on Pathogenic IL-17/IFN-γ Double-Positive Th17 Cells Is Responsible for Steroid Resistance in Minimal Change Disease Narayan Prasad,[1] Akhilesh Jaiswal,[1] Vikas Agarwal,[2] Raj K. Sharma.[1] *[1]Nephrology, SGPGIMS, Lucknow, UP, India; [2]Immunology, SGPGIMS, Lucknow, India.*

Background: Th17 cells and cytokine IL-17 are involved in many autoimmune diseases. Recently, IL-17/IFN-γ double-positive Th17 cell, called pathogenic Th17 cells were found to be associated with multiple autoimmune and inflammatory diseases. P-glycoprotein (P-gp, an efflux pump) positive Th17 cells are refractory to glucocorticoids. P-gp on lymphocytes efluxes out steroid and prevents its action. We conducted this study with hypothesis that P-gp expressing Th17 and IFN-γ are one of key pharmacokinetic and pharmacodynamic modulator responsible for steroid resistance in nephrotic Syndrome(NS), As it has not been studied in NS, we studied the frequency of P-gp expressing pathogenic Th17 cells in steroid sensitive (SSNS) and steroid resistant (SRNS) patients.

Methods: We analysed the frequency of pathogenic IL-17/IFN-γ double-positive Th17 lymphocytes and P-gp expression on their surface by flowcytometry in SSNS (n=32, mean age 9.06±5.84) and SRNS (n=28, mean age 11.29±3.73) patients. We also included 15 age and sex matched healthy controls. All patients were biopsy proven MCD and all patients were treated with steroid. All patients were recruited as per criteria of ISKDC.

Results: We found a significant increase in the frequency of Th1 (p=0.001), Th17 (p=0.006) and IL-17/IFN-γ double-positive Th17 (p<0.001) cells in SRNS as compared to SSNS patients and healthy controls (p<0.001). Of the total Th1, Th17 and pathogenic Th17; 78.45%, 72.37% and 95.8% cells expressed P-gp on their surface in SRNS;45.0%, 30.27% and 30.1% cells expressed P-gp in SSNS group; and 30.91%, 15.51% and 15.62% in healthy control respectively.



Conclusions: Higher frequency of IL-17/IFN-γ double-positive Th17 cell with P-gp expression may be associated immunological and pharmacological factor for steroid resistance in minimal change disease.

Funding: Government Support - Non-U.S.

FR-OR115

Angiopoietin-Like-4 and Minimal Change Disease Gabriel M. Cara-Fuentes,[1] Alfonso Segarra,[2] Cecilia Silva Sanchez,[1] Heiman Wang,[1] Miguel A. Lanaspa,[3] Richard J. Johnson,[3] Eduardo H. Garin.[1] *[1]Univ of Florida; [2]Hospital Vall D'Hebron; [3]Univ of Colorado.*

Background: Minimal change disease (MCD) is considered a podocytopathy. It has been hypothesized that in MCD podocyte Angiopoietin-like-4 (Angplt4) lacks sialic acid, and when bound to the glomerular basement membrane (GBM) proteoglycans, decreases GBM anionic charge allowing albumin to cross the capillary wall barrier into the urinary space. Objective: To evaluate the role of Angptl4 as a biomarker and/or mediator of proteinuria in MCD.

Methods: 60, 52 and 52 patients with MCD, FSGS and MN respectively and 18 control subjects were included. Urinary and serum Angptl4 were measured by Elisa. pI of Angptl4 in urine of MCD in relapse was determined by 2D electrophoresis. Frozen tissue sections were stained for Angptl4. Statistical analysis using Kruskal-Wallis, Mann-Whitney U test and Spearman correlation.

Results: Urinary Angptl4 was increased in patients with massive proteinuria regardless of the underlying glomerular disease compared to controls. No correlation was observed between proteinuria and urinary Angptl4 in MCD patients in relapse. Serum Angptl4 was higher in normal controls compared to MCD, FSGS and MN patients in relapse. Glomerular Angplt4 expression, by immunofluorescence (IF), was absent in MCD patients in relapse. Angptl4 detected in urine in MCD had a pI of 5.4.

Conclusions: 1) Serum and urinary excretion of Angptl4 were not specific for MCD patients, and there was no correlation of urinary Angptl4 with proteinuria in MCD patients. 2) Angptl4 detected in urine in MCD is likely freely filtered circulating Angptl4 given a) its MW, b) absent glomerular staining by IF in MCD patients in relapse. 3) Urinary Angptl4 in MCD in relapse is not cationic. In summary, our data do not support a role of Angplt4 as marker and/or mediator of proteinuria in MCD. Increased urinary Angplt4 is likely the result, rather than the cause, of a leaky glomerular filtration barrier.

Funding: Other NIH Support - NIHRO1DK080764

FR-OR116

Oxidized Low-Density Lipoprotein and Microparticle Tissue Factor Activity in the Nephrotic Syndrome Vimal K. Derebail,[1] Elizabeth J. Brant,[2] Carmen E. Mendoza,[1] Susan L. Hogan,[1] Nigel S. Key,[1] Nigel Mackman,[1] Heather N. Reich,[3] Patrick H. Nachman,[1] Donna O. Bunch.[1] *[1]Univ of North Carolina; [2]Dartmouth-Hitchcock Medical Center; [3]Univ of Toronto.*

Background: Venous thromboembolic (VTE) events are common in nephrotic syndrome (NS). Hypoalbuminemia is most consistently related to VTE risk. Profound hyperlipidemia, also characteristic of NS, leads to elevation of oxidized low-density lipoprotein (oxLDL). In turn, oxLDL stimulates monocytes to release microparticles bearing tissue factor that can initiate intravascular thrombosis. We examined the relationship between oxLDL and microparticle tissue factor activity (mpTFa) in individuals recruited to the Nephrotic Syndrome Study Network (NEPTUNE).

Methods: We included participants from NEPTUNE ages 13-80, with Membranous Nephropathy (MN), Focal Segmental Glomerulosclerosis (FSGS), or Minimal Change Disease (MCD). Inclusion required ***overt*** proteinuria ≥ 3.0 g/day by 24hr urine collection or urine protein/creatinine ratio (UPCR) ≥ 2 at screening. Baseline samples were used to measure oxLDL (by ELISA) and mpTFa (custom assay). Correlations of mpTFa, oxLDL and other clinical variables were assessed via Spearman's rank-order.

Results: 47 individuals (72.3% female, median age 47 [IQR 22, 62]) met inclusion criteria and had sample to measure mpTFa. 29.8% had FSGS, 53.2% had MN, 10.6% had MCD and 6.4% had other phenotype. Median albumin was 2.7 g/dl (IQR 2.0, 3.0), median UPCR was 4.2 (IQR 2.5, 7.1) and median mpTFa was 0.07 pg/mL (IQR 0, 0.21). oxLDL was measured in 34 individuals. Median oxLDL was 55.1 U/ml (IQR 40.5, 91.0). UPCR correlated with oxLDL (ρ=0.58, p=0.0003) and mpTFa (ρ=0.34, p=0.02). Albumin correlated negatively with oxLDL (ρ= - 0.63, p=0.0007). Only a weak correlation was noted between oxLDL and mpTFa (ρ=0.22, p=0.2) that was not statistically significant.

Conclusions: In a NEPTUNE participant sample with overt NS, serum albumin and UPCR strongly correlated with oxLDL suggesting severity of NS is pro-inflammatory; proteinuria correlated with mpTFa, indicating NS severity may also drive thrombotic risk. Future work will examine if oxLDL directly correlates with mpTFa and increased VTE risk in NS, an expected relationship limited by our sample size.

Funding: NIDDK Support, Private Foundation Support

FR-OR117

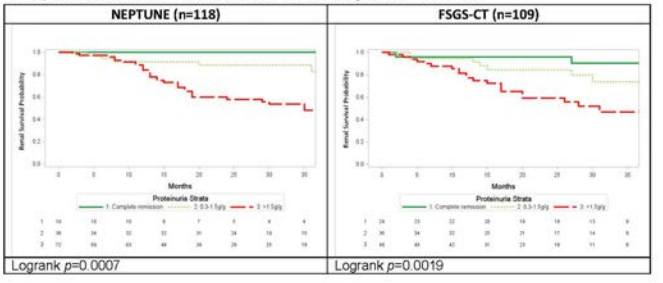
A Clinical Outcome Assessment of Proteinuria in Patients with Focal Segmental Glomerulosclerosis Jonathan P. Troost,[1] Howard Trachtman,[2] Cathie Spino,[1] Radko Komers,[3] Sarah E. Tuller,[3] Patrick H. Nachman,[4] Matthias Kretzler,[1] Debbie S. Gipson.[1] *[1]Univ of MI; [2]New York Univ; [3]Retrophin; [4]Univ of NC at Chapel Hill.*

Background: Proteinuria is used as an indicator of disease activity in FSGS, but its use as an end point for clinical trials is not universally accepted. The goal of this study is to examine the strength of the relationship between proteinuria and renal survival in patients with FSGS.

Methods: Data from 118 FSGS patients from the Nephrotic Syndrome Study Network (NEPTUNE) and 109 patients from the completed NIH sponsored FSGS Clinical Trial (FSGS-CT) were used for this discovery and replication analysis, respectively. Central measurements of urine protein: creatinine ratio (UP:C g/g) and serum creatinine were used and eGFR was calculated. Kaplan-Meier methods and log-rank tests were used to estimate the effect of proteinuria on subsequent ESRD or 40% reduction in eGFR. Proteinuria was categorized by conventional definitions of complete (UP:C<0.3, CR) and partial remission (50% reduction in UP:C and UP:C<3.5, PR). ROC analyses were performed to determine other important thresholds of proteinuria.

Results: In NEPTUNE and the CT, 40 and 47 patients progressed to ESRD or 40% reduction in eGFR, respectively. In NEPTUNE, reaching a CR, but not necessarily a PR, was associated with a decreased risk of disease progression (hazard ratio (HR) relative to no remission: CR=0.1, p<0.01; PR=1.0, p=0.90). ROC analyses identified a modified PR definition of UP:C 0.3-1.5 associated with a lower likelihood of progression to ESRD or 40% reduction in eGFR in NEPTUNE (HR=0.3 p<0.01), which was replicated in the FSGS-CT (HR=0.4, p=0.03).

FIGURE. Proteinuria Strata Using a Modified Definition of Partial Remission and Progression to ESRD/40% Reduction in eGFR. Results from NEPTUNE replicated in FSGS-CT.



Conclusions: Reaching either CR or a modified definition of PR, was associated with better long-term outcomes in patients with FSGS. From a regulatory perspective, this may help improve the feasibility of conducting clinical trials by using proteinuria as an endpoint.

Funding: NIDDK Support, Pharmaceutical Company Support - Retrophin (San Diego, CA, USA)

FR-OR118

Congophilic Fibrillary Glomerulonephritis: Clinicopathologic and Proteomic Characteristics Mariam P. Alexander,[1] Surendra Dasari,[1] Julie A. Vrana,[1] Glen S. Markowitz,[2] Vanesa Bijol,[3] Aviv Hever,[4] Navin Verma,[5] Julie Riopel,[6] Bhargavi Degapudi,[7] Lynn D. Cornell,[1] Mary E. Fidler,[1] Samar M. Said,[1] Sanjeev Sethi,[1] Loren Paola Herrera Hernandez,[1] Nelson Leung,[1] Paul J. Kurtin,[1] Samih H. Nasr.[1] *[1]Mayo Clinic, Rochester, MN; [2]Columbia Univ, New York, NY; [3]Brigham and Women's Hospital, Boston, MA; [4]Kaiser Permanente, Los Angeles, CA; [5]Hershey Medical center, PA; [6]L'Hotel-Dieu de Quebec, Quebec, Canada; [7]Atlantic Care, NJ.*

Background: Historically Congo red (CR) positivity has dichotomized organized glomerular deposits into amyloid and non-amyloid diseases. Fibrillary glomerulonephritis (FGN) is traditionally defined by CR negative randomly-oriented fibrils. We report the first series of Congophilic FGN (CFGN), defining its clinicopathologic and proteomic characteristics.

Methods: We identified 9 cases of CFGN from our archives from 2014-16. Histologic, clinical and outcome data were evaluated. Mass spectrometry (MS) was performed in all cases and on control cases (9 AL amyloidosis, 5 non-CFGN).

Results: Mean age was 59 yrs, 5 were female. Mean 24 h proteinuria and S. creatinine were 5.9 g and 1.5 mg/dl. 75% had hematuria. 7 of the cases were referred for amyloid typing by MS. 2 pts had hep C, 2 had carcinoma, and only 1 had monoclonal gammopathy. No pt had extrarenal amyloidosis. LM showed mesangial GN (N=6) or MPGN (N=3). All showed CR positivity with yellow (N=2) or apple green (N=7) birefringence. IF showed polyclonal staining for IgG, κ and λ. EM showed randomly-oriented fibrils (mean diameter 12-16 nm) in mesangium (N=9) and GBMs (N=7). By MS, the proteome of deposits in CFGN was identical to non-CFGN except for slightly higher spectra for ApoE in CFGN; CFGN and non-CFGN showed spectra for IgG, κ and λ, and small spectra for SAP with no/trivial spectra for ApoA4. The profile was different from AL which had abundant spectra for SAP, ApoE, ApoA4, and a single light chain. F/U was available in 8 pts (mean 13 mos, 2.5-20), including 4 treated with rituximab. 1 pt developed ESRD and none expired.

Conclusions: FGN can show CR positive deposits; therefore, Congophilia should not be the sole criterion used to distinguish FGN from amyloidosis; MS is useful in the distinction of these entities.

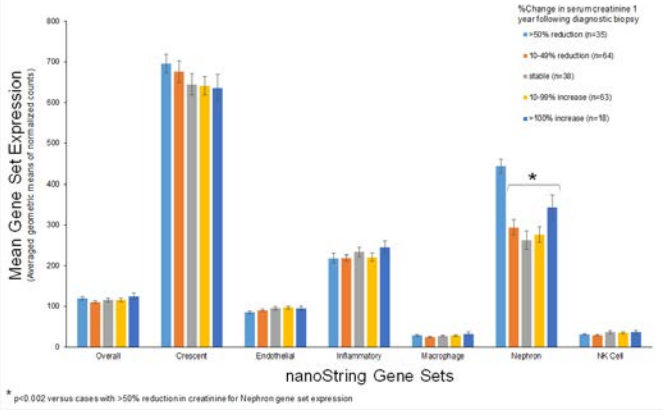
FR-OR119

Molecular Diagnostics for Glomerulonephritis in Routine Formalin-Fixed Paraffin-Embedded Native Kidney Biopsies Kristalee Watson,[1] Benjamin Alexander Adam,[1] Neesh I. Pannu,[2] Ainslie M. Hildebrand,[2] Michael Mengel.[1] *[1]Dept of Laboratory Medicine and Pathology, Univ of Alberta, Edmonton, AB, Canada; [2]Div of Nephrology, Univ of Alberta, Edmonton, AB, Canada.*

Background: Molecular diagnostics can potentially improve the classification and staging of native kidney diseases. The nanoString nCounter gene expression platform can use formalin-fixed paraffin-embedded (FFPE) tissue, representing a potential method for routine molecular diagnostics in renal pathology. We aimed to assess gene expression quantification in the diagnostics and staging in glomerulonephritis (GN) in FFPE native kidney biopsies.

Methods: A literature-derived gene set for renal injury was generated (54 genes related to nephrons, endothelium, and inflammation). RNA was isolated from 386 FFPE native kidney biopsies (275 crescentic GN, 82 non-crescentic immune complex GN, 29 non-crescentic non-proliferative disease). Gene expression was quantified with nanoString and correlated with histology, and clinical indices at biopsy and 1-year follow-up.

Results: Gene set expression was higher in cases with crescentic GN than non-crescentic GN ($p<0.001$). Gene set expression correlated with interstitial fibrosis and tubular atrophy ($r=0.34$, $p=0.001$). Expression of nephron transcripts correlated with the proportion of crescentic glomeruli ($r=0.39$, $p<0.001$). Expression of nephron transcripts was higher in patients with crescentic GN and recovery in renal function 1 year post biopsy versus those with stable or deteriorating serum creatinine ($p<0.002$).



Conclusions: The nanoString platform allows for robust gene expression quantification from FFPE native kidney biopsies. High expression of nephron genes is associated with functional recovery after crescentic GN. Molecular biopsy assessment has the potential to provide additional diagnostic and prognostic information in renal pathology.

Funding: Clinical Revenue Support

FR-OR120

Identification of Shared Molecular Targets across Glomerular Disease: Case Study in ANCA-Associated Vasculitis (AAV) and Nephrotic Syndrome (NS) Sean Eddy,[1,2] Viji Nair,[1,2] Hemang Parikh,[3,4] Laura H. Mariani,[1,2] Felix H. Eichinger,[1,2] Huateng Huang,[1,2] Wenjun Ju,[1,2] Casey S. Greene,[4,5] Peter C. Grayson,[4,6] Jeffrey P. Krischer,[3,4] Peter A. Merkel,[4,5] Matthias Kretzler.[1,2] *[1]Div of Nephrology, Univ of Michigan, Ann Arbor, MI; [2]NEPTUNE Consortium; [3]Univ of South Florida, Tampa, FL; [4]Vasculitis Clinical Research Consortium; [5]Univ of Pennsylvania, Philadelphia, PA; [6]Vasculitis Translational Research Program, NIAMS, NIH, Bethesda, MD.*

Background: Clinical trials in rare diseases typically test therapeutic efficacy in one disease defined by a particular clinical phenotype. An unbiased analysis of kidney diseases suggests many rare kidney diseases share common molecular profiles (Martini et al., 2014). To expand on these findings, we explored shared transcriptional responses in patients with AAV and NS to identify common targetable disease mechanisms.

Methods: Transcriptomic profiles were generated from renal biopsies from NS (MCD, FSGS and Membranous Nephropathy, n=126) from the NEPTUNE cohort and the European Renal cDNA Bank (ERCB, n=61), and from AAV (Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)) from the ERCB cohort (n=80) and living donors (n=37) on Affymetrix U133 and ST2.1 platforms. Functional networks were assessed for cross-cutting disease mechanisms, upstream regulators and potential therapeutic targets shared between both diseases.

Results: 5%-25% of expressed transcripts were differentially regulated compared to living donor (FDR<0.05, shared directionality of change) in both NS and AAV in glomerular and tubulointerstitial compartments and replicated across expression platforms. Functional analysis identified conserved, therapeutically targetable transcriptional networks in the glomeruli from NS and AAV patients including activation of Tec kinase, IL-8 signaling, TNF, IFNG, TGFB1, and NFkappaB, while alpha catenin and LXR/RXR signaling were suppressed. A causal analysis approach predicted increase TNF pathway activity across diseases.

Conclusions: AAV and NS, two rare kidney diseases, share common intra-renal transcriptional profiles that can be readily mined to identify shared molecular targets. Shared molecular targets can be leveraged for drug development and repurposing efforts.

Funding: Other NIH Support - NCATS

FR-OR121

ANCA Autoantigen Expression in Combination with ANCA Titer May Be More Useful to Assess Disease Activity Than Either Alone Jia Jin Yang,[1] Caroline J. Poulton,[1] Susan L. Hogan,[1] Yichun Hu,[1] Meghan A. Jobson,[1] Candace Henderson,[1] Britta E. Jones,[2] J. Charles Jennette,[2,1] Ronald J. Falk,[1,2] Dominic J. Ciavatta,[3] William Franklin Pendergraft.[1] *[1]Medicine, UNC-CH; [2]Pathology, UNC-CH; [3]Genectics, UNC-CH, Chapel Hill, NC.*

Background: We demonstrated aberrant up-regulation of autoantigen genes in mature neutrophils and monocytes from patients with ANCA disease (JASN 2004, 15:2103-14). Here, we compared the utility of *PRTN3* and *MPO* mRNA and ANCA titers to predict disease activity.

Methods: A total of 969 leukocyte RNA samples from 122 ANCA-patients were collected serially every 3 months over the past 6 years compared to 169 healthy controls. Levels of *PRTN3* and *MPO* gene transcripts were determined by Q-PCR and expressed as relative levels to standard curve. Active disease was defined as a Birmingham Vasculitis Activity Score (BVAS) ≥ 5 with clinical and /or laboratory evidence of disease active; remission as a BVAS=0 and no evidence of active disease. Fisher's exact test was used in this study.

Results: In samples with active disease (n=106), 60% and 67% of samples had significantly increased *PRTN3* (385±846, $p<0.0001$) and *MPO* (995±1900, $p<0.0001$) mRNA, respectively compared to healthy donors (*PRTN3*:16±33; *MPO*:57±57). Only 6% and 9% of remission samples (n=94) had increased *PRTN3* and *MPO, respectively*. In contrast, ANCA titer did not return to normal levels in 65% of PR3-ANCA (n=52) and 45% of MPO-ANCA (n=42) patients when remission was achieved. ANCA titers were increased in 92% of PR3-ANCA (n=59) and 81% of MPO-ANCA (n=47) samples with active disease. Specificity values for *PRTN3* (94%) and *MPO* (91%) mRNA were higher than PR3-ANCA (35%) and MPO-ANCA (55%) titers, while sensitivity values for *PRTN3* (60%) and *MPO* (67%) mRNA were lower than PR3-ANCA (92%) and MPO-ANCA (81%) titers. When both mRNA and ANCA titer tests were used to assess disease activity, specificity and sensitivity increased to 98% and 95% in PR3-ANCA and 98% and 89% in MPO-ANCA patients, respectively.

Conclusions: The combination of ANCA titer and ANCA autoantigen expression may be more useful to assess disease activity than either alone. Both expression of autoantigen genes and antibodies are involved in the pathogenesis of ANCA disease.

Funding: NIDDK Support

FR-OR122

Serum Klotho Levels Are Associated with Renal Function Recovery in Patients with Septic Acute Kidney Injury Undergoing Continuous Renal Replacement Therapy Ji Min Park,[1] Hyoungnae Kim,[1] Young Eun Kwon,[2] Min-Uk Cha,[1] Youn Kyung Kee,[1] Tae-Hyun Yoo.[1] *[1]Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea; [2]Div of Nephrology, Dept of Internal Medicine, Myongji Hospital, Seonam Univ College of Medicine, Goyang, Korea.*

Background: This study aimed to elucidate the role of klotho as a biomarker in septic acute kidney injury (AKI) patients requiring continuous renal replacement therapy (CRRT).

Methods: This is a post hoc analysis of HICORES study (HIgh-volume COntinuous REnal replacement therapy in patients with Septic AKI, NCT 01191905) conducted from January 2011 to August 2014 at two tertiary hospitals in Korea. A total of 165 septic AKI patients undergoing CRRT were eligible and serum klotho level at CRRT initiation was measured by ELISA. The patients were divided into high and low klotho groups based on the median value of klotho (244pg/ml). Primary outcome was CRRT weaning rate at 28 day and secondary outcomes were the proportion of intensive care unit (ICU) discharge at 28 day and all-cause mortality rate.

Results: Male was 110 (66.7%) and the mean age was 62.2 years. High klotho group was younger and showed significantly lower norepinephrine requirement, C-reactive protein, and log transformed interleukin (IL)-1β and IL-10 levels compared to low klotho group. Multiple Cox regression analysis revealed that the CRRT weaning rate at 28 day was significantly higher in high klotho group (hazard ratio [HR] 1.634; 95% confidence interval [CI] 1.004–2.659, P=0.048) compared to that in low klotho group. In addition, high klotho group showed more ICU discharges at 28 day (HR 2.959, 95% CI 1.493–5.864, P=0.002) than low klotho group after adjusting confounding factors. Meanwhile, the difference in all-cause mortality rate did not reach statistical significance between the two klotho groups (HR 0.709, 95% CI 0.480–1.049, P=0.085).

Conclusions: Present study suggests that baseline serum klotho might be a potential biomarker predicting renal function recovery in patient with septic AKI.

FR-OR123

Preoperative Plasma Monocyte Chemotactic Protein-1 Is Associated with Postoperative AKI and Long-Term Mortality after Cardiac Surgery: A Multicenter Prospective Cohort Study

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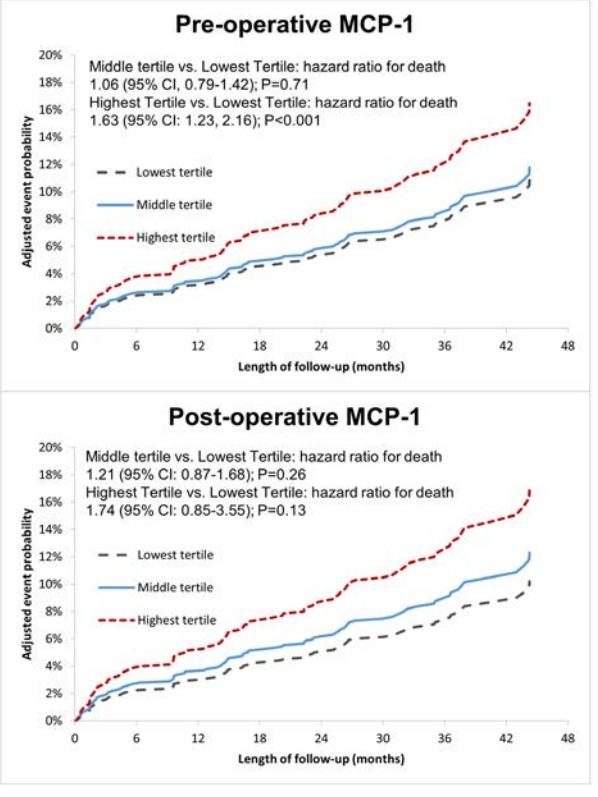
Background: Monocyte chemotactic protein-1 [MCP-1] is upregulated in ischemia-reperfusion injury and is a promising biomarker of inflammation in cardiac surgery. We evaluated the association of perioperative MCP-1 levels in patients undergoing cardiac surgery with AKI and mortality.

Methods: We measured pre- and postoperative plasma MCP-1 levels in TRIBE-AKI, a prospective, multicenter, observational cohort of patients undergoing cardiac surgery. Short-term outcomes were in-hospital AKI or severe AKI, and long-term outcome was all-cause mortality.

Results: Of the 972 participants in the study, 329 (34%) developed AKI and 45 (5%) developed severe AKI. Of the 957 patients alive at hospital discharge, 103 (11%) participants died during median follow-up of 2.9 (2.2-3.5) years. In fully adjusted analyses, patients with preoperative MCP-1 levels in the highest tertile (>196 pg/ml) had an increased risk of AKI as compared with the lowest tertile [<147 pg/ml; OR, 1.43(95% CI, 1.00-2.05)]; the association appeared similar but was not significant for the outcome of severe AKI [OR, 1.48 (0.62-3.54)]. As compared with patients with preoperative MCP-1 in the lowest tertile, those in the highest tertile had higher mortality risk [HR, 1.63 (1.23-2.16); P<0.001]. Postoperative MCP-1 concentrations were not associated with AKI or mortality.



Conclusions: Preoperative plasma MCP-1 level is associated with increased risk of AKI and long-term mortality after cardiac surgery. MCP-1 could be used as a biomarker to identify high-risk patients to enrich clinical trials for AKI prevention in the setting of cardiac surgery.

FR-OR124

Prediction of Acute Kidney Injury (AKI) and Clinical Outcomes Using a Combination of Routine Clinical Information and Novel Urinary Biomarkers: The Dublin Acute bioMArker Group Evaluation (DAMAGE) Study

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Background: Implementation of novel AKI biomarkers in practice has been hampered by a failure to integrate into routine clinical decision making, which involves standard clinical information, including demographics, acute and chronic illness information, and markers of kidney function (urine output, BUN, creatinine).

Methods: The DAMAGE Study is a prospective multicenter observational study investigating the utility of urinary biomarkers for diagnosis and prognosis of AKI in critically ill patients admitted to intensive care units in Dublin, Ireland. Clinical information and urine were collected on admission and daily for 7d. Urine biomarkers analysed were NGAL, α-GST, π-GST, KIM-1, L-FABP, Cystatin-C, creatinine, and albumin. ROC curves were constructed from logistic regression models that predicted AKI (by KDIGO) and adverse clinical outcomes (progression to death or RRT) in combination with APACHE II score, gender, admission serum creatinine, urea and urine output.

Results: The study enrolled 736 patients. 242 (37.4%) developed AKI within 7 days of ICU admission. 208 (31.6%) progressed to death or dialysis within 30d. A panel of admission biomarkers significantly improved prediction of AKI developing within 7d of admission (AUC; 95% CI: 0.77;0.72-0.82) over clinical covariates alone (0.73;0.68-0.79;p=0.029). Similarly, the admission values of Albumin and NGAL improved prediction of early AKI, developing within 48h (0.77;0.73-0.81), compared to clinical covariates alone (0.75;0.71-0.79;p=0.03). Finally, the addition of this biomarker pair improved prediction of 30d adverse clinical outcomes - RRT or death – (0.82; 0.78-0.86) when compared to clinical covariates alone (0.79; 0.75-0.83; p=0.0004).

Conclusions: Combined use of novel urinary AKI biomarkers with knowledge of patient clinical covariates on admission to the ICU significantly improved the prediction of AKI and 30d adverse clinical outcomes.

Funding: Pharmaceutical Company Support - Abbott Labs; Argutus/EKF Diagnostics, Government Support - Non-U.S.

FR-OR125

Saliva Urea Nitrogen Dipstick: A Simple Tool to Detect and Stratify Risk of Renal Disease in Low Resource Settings

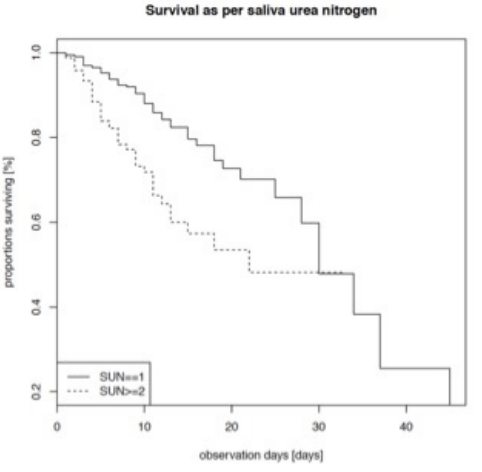
Viviane Calice-Silva,[1] Rhys David Russell Evans,[2,3,4] Jochen G. Raimann,[5] Ulla Hemmila,[2,3] Alison Craik,[3] Mwayiwathu Prince Mtekateka,[3] Fergus Hamilton,[3] Zuze Madalitso Kawale,[3] Gavin Dreyer,[6] Nathan W. Levin,[7] Peter Kotanko,[5] Roberto Pecoits-Filho.[1] *[1]Pontifícia Univ Católica do Paraná, Brazil; [2]College of Medicine, Malawi; [3]Queen Elizabeth Central Hospital, Malawi; [4]Bart's Health, United Kingdom; [5]Renal Research Inst; [6]Royal Free Hospital, United Kingdom; [7]Icahn School of Medicine at Mount Sinai.*

Background: Simple and non-expensive tools for the diagnosis of renal disease, in particular acute kidney injury (AKI), are lacking. We evaluated the diagnostic performance of a salivary urea nitrogen (SUN) dipstick and its ability to predict outcomes in a low-resource setting in Africa.

Methods: Adult patients presenting to general medicine at QECH, Blantyre, Malawi, were screened for kidney disease with serum creatinine (sCR) and SUN on admission. Patients with renal impairment were followed-up for up to 7 days. SUN level greater 14 mg/dL was the threshold to diagnose renal disease. Cox proportional hazard models were constructed to evaluate the predictors of death.

Results: 742 patients with SUN data were studied (40.9±17.3 years, 56.1% male). We diagnosed 146 patients with renal disease [114 AKI, 26 AK disease without AKI, 6 CKD] according to KDIGO sCr based criteria. The SUN performance to diagnose renal disease was good [AUC 0.83 (95% CI 0.79 to 0.87)]. SUN levels > 14 mg/dL was the optimal threshold (sensitivity 72%; specificity 87%). Out of 702 patients with complete outcome data, 104 died during hospitalization. Elevated SUN was an independent predictor of all cause mortality (**Figure 1**; HR=2.43 [95% CI 1.63 to 3.62]).

Figure 1: Kaplan-Meier curve survival analysis of all-cause mortality stratified by SUN results.



Conclusions: SUN showed good diagnostic performance to detect renal disease. SUN was an independent predictor of mortality in this population. Our data suggest that SUN may be used to diagnose kidney disease, particularly in limited health care settings.

Funding: Private Foundation Support

FR-OR126

Fluid Overload in Critically Ill Patients Is Predicted Using Single and Sequential Urinary Biomarker Measurements Erin K. Stenson,[1] Shina Menon,[2] Stuart Goldstein,[3] Rajit K. Basu.[3] *[1]Pediatric Critical Care, Cincinnati Children's Hospital; [2]Pediatric Nephrology, Seattle Children's Hospital; [3]Center for Acute Care Nephrology, Cincinnati Children's Hospital.*

Background: Fluid overload (FO) is independently associated with worsened outcomes in critically ill patients. Although urinary biomarkers have been studied in multiple populations for prediction of acute kidney injury (AKI), prediction of fluid overload has not been reported. Further, the predictive performance of biomarkers as they change over time has not been explored.

Methods: We leveraged data from a single-center, prospective study of children admitted to the intensive care unit (ICU). The primary outcome for this analysis was the development of >20% FO (derived by net fluid balance and weight) at any time from ICU admission to Day 7. Predictor variables were assessed at least 3 times during the first 36 hours of admission (urinary neutrophil gelatinase associated lipocalin (uNGAL), serum creatinine (sCr), and urine output (UOP)).

Results: 173 pts(51% male, median age 7.7 years) were included. Peak FO>20% occurred in 45 pts(26%) (Median 4 days). uNGAL was elevated over 200 in 52 pts (30%). uNGAL was persistently <200 in 115 pts (66%), intermittently elevated (spiked over 200, and then downtrended) in 29 (17%) and persistently>200 (at least 3 values over 200) in 29 (17%). Compared to UOP or sCr measurements, uNGAL levels demonstrated a significant association for prediction of FO > 20%. Persistently increased uNGAL strengthened this association (compared to persistently low uNGAL).

Variable	n	Odds for FO >20% (95% CI)	p Value
uNGAL persistently elevated	29	3.3 (1.4-7.7)	0.007
uNGAL spiked	29	1.8 (0.7-4.5)	0.205
uNGAL elevated day 1	52	2.4 (1.2-4.9)	0.016
Cr persistently elevated	12	2.7 (0.8-9.0)	0.100
Cr elevated day 1	31	1.0 (0.4-2.4)	0.977
UOP persistently decreased	21	1.1 (0.4- 3.1)	0.848
UOP decreased day 1	32	1.1 (0.5-2.7)	0.763

Conclusions: Our data suggest that >20% FO can be predicted. Single and sequential urinary biomarkers assessed early in ICU admission are predictive of FO while creatinine and urine output are not. These findings are clinically relevant as fluid accumulation is a modifiable outcome. Expanded analysis in larger populations is warranted to confirm these findings.

FR-OR127

Urinary Neutrophil Gelatinase-Associated Lipocalin Predicts Non Response to Therapy with Albumin and Terlipressin in Patients with Hepatorenal Syndrome Rafael Oliveira Ximenes,[1] Alberto Queiroz Farias,[1] Claudia Helou.[2,3] *[1]Gastroenterology, Univ of Sao Paulo School of Medicine, Sao Paulo, Brazil; [2]Nephrology, Univ of Sao Paulo School of Medicine, Sao Paulo, Brazil; [3]LIM 12, Univ of Sao Paulo School of Medicine, Sao Paulo, Brazil.*

Background: Current predictors of response to hepatorenal syndrome (HRS) treatment have limited accuracy, leading to administration of ineffective therapy. The aim of the study was to evaluate the utility of urinary *neutrophil gelatinase-associated lipocalin* (uNGAL) as a predictor of non response to albumin and terlipressin treatment in patients with HRS.

Methods: Prospective study conducted at a tertiary care unit between June 2013 and November 2015. Inclusion criteria: a) cirrhosis; b) age > 18 years; c) HRS diagnosis according to International Club of Ascites criteria; d) informed consent. Exclusion criteria: a) severe systemic comorbidities; b) shock; c) chronic kidney disease; d) intrinsic nephropathy; e) nephrotoxic drug use; f) previous dialysis; g) liver transplantation recipient. uNGAL was determined in the first day of treatment.

Results: Forty-nine patients (75% male, median age 59 years) were included. 24 (49%) did not respond to treatment. Median uNGAL levels were 728.8µg/L in non-responders, and 182.9 µg/L in responders (p=0.02).

	Responders, n=25	Non-responders, n=24	p
Albumin, g/dL	2.9 (2.6-3.8)	2.7 (2.4-3.0)	0.046
INR	1.9 (1.7-2.0)	2.2 (1.9-2.5)	0.015
Bilirrubins, mg/dL	3.0 (1.7-4.0)	5.2 (2.0-16.9)	0.101
Child (B/C)	10 (40%)/ 15 (60%)	3 (12.5%)/ 21 (87.5%)	0.050
MELD	25 (21-29)	30 (27-37)	0.009
Mean blood pressure, mmHg	78 (73-87)	81 (70-86)	0.294
Fractional excretion of urea, %	24 (16-32)	14 (8-23)	0.003
uNGAL	182.9 (104.8-378.6)	728.8 (235.3-1,050)	0.020

uNGAL had an AUC of 0.69 to predict non response to combined treatment, with the optimal cut-off value of 214.4µg/L (sensitivity 0.83, specificity 0.56, positive predictive value 0.65 and negative predictive value 0.78).

Conclusions: uNGAL is a useful predictor of unresponsiveness to treatment with albumin and terlipressin in patients who fulfill HRS diagnosis criteria.

Funding: Government Support - Non-U.S.

FR-OR128

Haemodialysis for Acute Kidney Injury Results in Myocardial Stunning Huda Mahmoud,[1,2] Christopher W. McIntyre,[3] Nicholas M. Selby.[1,2] *[1]Dept of Renal Medicine, Derby Royal Hospital, United Kingdom; [2]Centre for Kidney Research and Innovation, Univ of Nottingham, United Kingdom; [3]Schulich School of Medicine and Dentistry, Canada.*

Background: The circulatory stress of chronic haemodialysis (HD) results in repetitive subclinical myocardial ischaemia (myocardial stunning) contributing to adverse patient outcomes. Currently it is unknown if this process occurs during renal replacement therapy (RRT) for acute kidney injury (AKI). Acute RRT differs in both its delivery and because patients do not display the circulatory changes of chronic uraemia. We aimed to determine if acute RRT is capable of inducing myocardial stunning.

Methods: 12 patients requiring RRT for AKI participated. Serial echocardiography was performed before, during and after a single RRT session and images analysed off-line using speckle-tracking software. Myocardial stunning was defined as >2 new left ventricular (LV) regional wall motion abnormalities (RWMAs) during dialysis; global longitudinal strain (GLS) assessed LV contractility. Blood pressure (BP) and systemic haemodynamics were measured continuously.

Results: 10 patients were included in the analysis; 2 were excluded due to poor image quality. All 10 patients demonstrated dialysis-induced stunning (>2 new RWMAs), with partial recovery seen at 30min post dialysis. The median number of affected LV segments was 5 (IQR 4-6). GLS significantly declined from a pre-dialysis level of -17.8±3.7% (within normal range) to below the normal range during dialysis (-15.44±2.7%, p=0.05), remaining low at 30min post-dialysis to -14.77%±3, p=0.005. There were associations between number of stunned segments and dialysis ultrafiltrated volume (r=0.79, p=0.0061). 2 patients died at 150 and 153 days post discharge (both left HD dependant). One patient remains HD dependant.

Conclusions: HD induced myocardial stunning occurs during acute RRT in combination with reductions in LV contractility. This suggests that the process is driven by HD related factors (as opposed to patient phenotype) and opens up the possibility of therapeutic HD based interventions. Further study is required to determine whether dialysis induced stunning contributes to the very poor outcomes that are well recognised in this patient group.

FR-OR129

Effect of Acute Kidney Injury on Chronic Kidney Disease Progression and Proteinuria: Baseline Results from the ARID Study Nicholas M. Selby,[1,2] Kerry L. Horne,[1] Rebecca A. Packington,[1] Christopher Lee,[1] Timothy T. Reilly,[1] John Monaghan,[1] Nitin V. Kolhe,[1] Richard J. Fluck,[1] Maarten W. Taal.[1,2] *[1]Derby Teaching Hospitals NHS Foundation Trust; [2]Centre for Kidney Research and Innovation, Univ of Nottingham.*

Background: The long-term sequelae of acute kidney injury (AKI) on renal function and mortality are increasingly appreciated, but there remains the need for prospective studies in generalisable patient groups. We present baseline data from a large case-control study of AKI in an undifferentiated hospitalised population.

Methods: In a single UK centre, participants were identified with a hospital-wide electronic AKI detection system. Cases (hospitalised patients who sustained AKI) were matched 1:1 with controls (hospitalised patients without AKI) for age, baseline eGFR stage and diabetes. Biochemical parameters including renal function and proteinuria were measured 3 months post-AKI and will be measured at 1,3 and 5 years. Survival data will be tracked to 5 yrs. CKD progression is defined as ≥25% decline in eGFR with decline in eGFR stage.

Results: 1125 patients were recruited; 878 were successfully matched. There was no difference between cases and controls in age (70 yrs (IQR 14) vs 72 yrs (IQR 13), p=0.1) or baseline CKD-EPI eGFR (69.0±21.6 vs 69.0±21.2 ml/min/1.73m^2, p=1.0). AKI episodes were predominantly stage 1 with median duration 3 days (IQR 2.5). At 3 months, mean eGFR was lower in the AKI group than controls: 62.4±22.7 vs 72.0±20.9ml/min/1.73m^2, p<0.001. 84 cases (19%) demonstrated CKD development or progression compared with only 15 controls (3%), p<0.001. Albuminuria (ACR≥3mg/mmol) was more common in the AKI group; 184 (42%) cases had albuminuria compared with 109 (25%) controls, p<0.001. Median ACR in the AKI group was 1.9 (IQR 10.3)mg/mmol compared with 0.9 (IQR 3.0) mg/mmol in controls, p<0.001.

Conclusions: Non-recovery of renal function is common at 3 months following AKI, even in a general hospital population with predominantly AKI stage 1. Albuminuria is also common after AKI; it is currently unclear whether this reflects renal parenchymal injury at time of AKI or a pre-existing risk factor. Long-term follow-up is ongoing with the aim of developing strategies to better stratify individual risk.

Funding: Private Foundation Support

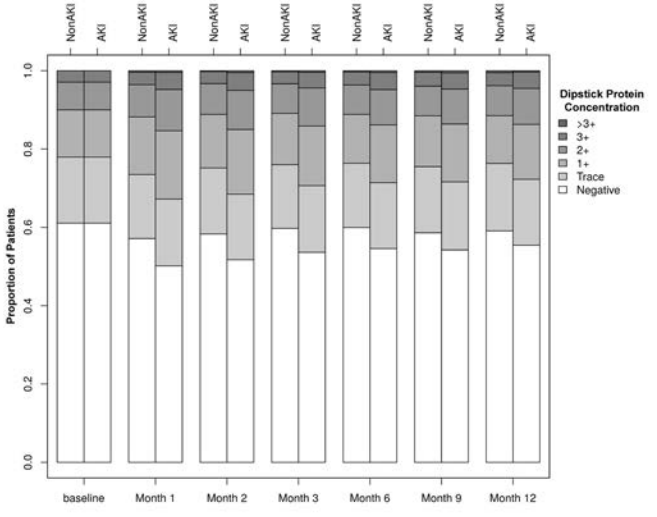
FR-OR130

Association between Acute Kidney Injury and Subsequent Proteinuria
Sharidan Parr,[1,2] Robert Greevy,[2] Aihua Bian,[2] James Fly,[1] Guanhua Chen,[2] Theodore Speroff,[1,2] Adriana Hung,[1,2] Khaled Abdel-Kader,[2] Michael Edwin Matheny,[1,2] Talat Alp Ikizler,[1,2] Edward D. Siew.[1,2] *[1]Tennessee Valley Healthcare System, Veterans Health Administration; [2]Vanderbilt Univ Medical Center.*

Background: Acute kidney injury (AKI) is associated with progressive chronic kidney disease (CKD), but this link is not well-understood. We evaluated the association between AKI and subsequent proteinuria, as a potentially modifiable risk factor in development or progression of CKD.

Methods: We identified 657,840 patients from a national retrospective cohort of US Veterans hospitalized between 2004-2012 with baseline creatinine and urine dipstick protein measurements in the year prior to admission. Patients with and without AKI were matched on Mahalanobis distances using demographics, comorbidities, baseline proteinuria, eGFR, blood pressure, RAAS use, and inpatient exposures. We performed inverse probability sampling weighted logistic regression to evaluate changes in proteinuria over 1 year post-discharge.

Results: Matching resulted in a cohort of 90,614 AKI and non-AKI pairs. Median patient age was 66 (IQR, 59-77) years, with baseline eGFR 62 (IQR, 47-77) mL/min/1.73m^2. At baseline, 49% of patients had diabetes, 78% had hypertension, and 61% had no proteinuria. Changes in proteinuria from baseline in AKI and non-AKI groups are shown in Figure 1. Among patients with AKI, the odds of having ≥1+ proteinuria was higher during each month of follow-up than in patients without AKI; OR's ranging 1.19-1.35 (P <0.001). This risk was highest at 2 months post-discharge, OR 1.35 (95% CI: 1.30-1.41).



Conclusions: We demonstrate that AKI is a risk factor for new-onset or worsening proteinuria, suggesting a potential mechanism linking AKI and future CKD. The type of proteinuria, its mechanisms, and clinical significance warrant further study, and represent a potentially modifiable risk factor in the pathway from AKI to CKD.

Funding: NIDDK Support, VA Support

FR-OR131

Use of Palliative Care Services for Patients with Acute Kidney Injury
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Background: Palliative care is underutilized in patients with chronic kidney disease, but its use in patients with acute kidney injury (AKI) is not well understood. We sought to determine the factors associated with palliative care use in hospitalized AKI patients.

Methods: Using data from the 2012 National Inpatient Sample, we identified patients with AKI and AKI-requiring dialysis (AKI-D) using validated ICD-9 codes. We compared demographics, hospital characteristics, comorbidities, and procedures between patients who did and did not receive palliative care (diagnosis code V66.7). We used logistic regression to assess associations with palliative care utilization. For the multivariable model, we used backwards selection to identify statistically significant associations.

Results: Palliative care was provided to 151,820 (5%) AKI patients and to 8370 (9%) AKI-D patients. On multivariable analysis, patients with AKI who received palliative were more likely to have cancer (OR 3.71, 95% CI 3.59-3.84), cardiogenic shock (2.39, 2.19-2.60), cirrhosis (3.50, 3.29-3.71), intracerebral hemorrhage (2.77, 2.50-3.06), or sepsis (2.00, 1.93-2.07). Several patient and hospital factors decreased the likelihood of palliative care involvement. Patient-level factors included black race (compared to white race, 0.77, 0.72-0.83), Hispanic race (compared to white race, 0.79, 0.72-0.87), chronic kidney disease (0.83, 0.81-0.86), and major surgery (0.53, 0.51-0.56); hospital-level factors included care at a rural hospital (compared to teaching hospital, 0.68, 0.59-0.78), care at a private (investor-owned) facility (compared to non-profit, 0.50, 0.44-0.57), and care at a hospital with a small number of beds (compared to large number, 0.73, 0.65-0.82).

Conclusions: Palliative care is not consistently utilized in patients with AKI, despite its many benefits in critically ill patients. More research is needed to determine reasons for patient and hospital differences in palliative care utilization, as well as to develop palliative care programs targeted at patients with AKI.

SA-OR001

The End-Stage Renal Disease Prospective Payment System Had Little Effect on Home Dialysis Usage in the United States
Eugene Lin,[1] Xingxing S. Cheng,[1] Kuo-Kai Chin,[3] Talhah Zubair,[3] Glenn Matthew Chertow,[1] Eran Bendavid,[2] Jay Bhattacharya.[2] *[1]Internal Medicine - Nephrology, Stanford Univ; [2]Centers for Health Policy and Primary Care and Outcomes Research, Stanford Univ; [3]Stanford Univ.*

Background: Home dialysis modalities (peritoneal dialysis and home hemodialysis) are touted as a way to help reduce the high cost of End-Stage Renal Disease (ESRD) in the United States. The Prospective Payment System (PPS) for ESRD, implemented by Centers for Medicare & Medicaid Services (CMS), in January, 2011, introduced financial incentives to increase home dialysis use.

Methods: In this study, we estimated the effect of the PPS on home dialysis use in adults who initiated dialysis between January 1, 2007 and August 31, 2012. We compared the estimated effect of the PPS in patients with a high incentive to use home dialysis (those with Medicare as primary insurer) with patients with a low incentive to use home dialysis (those with another primary insurer). Using a difference-in-differences method, we compared the estimated effect of the PPS in patients with Medicare as primary insurer versus those without.

Results: On average, home dialysis use increased over time in the pre-PPS era. Home dialysis use increased at a faster rate after the PPS, and by the end of the study period, the introduction of the PPS was associated with an increase in home modality use by 0.8% (CI: 0.3, 1.2%). An increase in home dialysis use was observed in both subgroups: 1.0% (CI: 0.5, 1.6%) in the Medicare as primary population and 0.4% (CI: -0.1, 1.6%) in the Medicare as secondary population. The estimated effect size was not statistically different between the two groups (p = 0.2).

Conclusions: Although the PPS was associated with an increase in home dialysis use in the United States, this increase was small relative to the baseline temporal trend, suggesting that the financial incentives for home dialysis instituted by CMS within the PPS were insufficient to yield major changes in practice.

Funding: NIDDK Support

SA-OR002

Early Technical Complications and Long Term Survival of Urgent Peritoneal Dialysis According to Break-In Period
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Background: Guidelines recommend a break-in period of at least 2 weeks before peritoneal dialysis(PD) start because of catheter-related technical complications. Recent study report that urgent-start PD within 14 days after PD catheter insertion is an acceptable and safe alternative to hemodialysis(HD) in patients who need to start dialysis urgently without established dialysis access. We investigated the effect of break-in periods for 48 hours less or more on early technical complications, long term PD maintenance and survival.

Methods: We included 360 patients percutaneously inserted PD catheter by surgical methods from a single center between 2007 and 2014. We excluded patients started HD before PD catheter insertion and retrospectively analyzed data of 293 PD patients. Finally we included 190 patients and grouped according to break-in period before PD solution dwell: 48 hours or less (<P2) and 2-13 days (P2-P13). We defined urgent PD patients had BUN > 100 mg/dL, creatinine >10 mg/dL, K > 6 mEq/L or pulmonary edema with a break-in period of less than 2 weeks. We defined early technical complications as malposition, leakage, obstruction, omental wrapping, change to HD within 6months after PD catheter insertion.

Results: Age of enrolled patients was 58.6, male was 62.6% and diabetes was 40.5%. 103 patients were started PD within 2 days and 87 patients within 2 to 13 days. Early technical complications was significantly higher in <P2 gorup(28.2%) than in P2-P13 group(10.3%). The incidence of re-positioning operation was higher in <P2 group(14.6%) than in P2-P13 group(3.4%). However, we observed no significant differences between the groups with respect to the prevalence of catheter dysfunction requiring change to HD within 6months or incidence of peritonitis or exit site infection. There was not significantly different in aspect of maintaining PD and survival according to break-in period.

Conclusions: Urgent PD may have few incidences of early technical complications if we avoid starting PD within 2 days after PD catheter insertion and it may warrant long term PD maintenance regardless of break-in period.

SA-OR003

Variability in Peritoneal Dialysis Patients' Training: The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) Ana Elizabeth Figueiredo,[1,4] Junhui Zhao,[2] Brian Bieber,[2] Helen Hurst,[3,4] Francesca Tentori.[2,4] *[1]Pontificia Univ Católica do Rio Grande do Sul, Porto Alegre, Brazil; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]Manchester Royal Infirmary, Manchester, United Kingdom; [4]On Behalf of the PDOPPS Patient Training and Education Workgroup, Ann Arbor, MI.*

Background: Controversy exists regarding optimal training practices for PD patients. This study provides important information on international variability in PD training practices across countries participating in PDOPPS.

Methods: Launched in 2013, the PDOPPS is a prospective cohort study of PD practices and outcomes ongoing in Australia, Canada, Japan, New Zealand, Thailand, the United Kingdom (UK) and the United States (US). Data on typical training practices were reported by nurse study coordinators at each facility.

Results: At the time of submission, data were availablefor138 facilities in Australia, Canada, Japan, UK, and the US. Training practices varied internationally and were dramatically different in Japan. Japan had the greatest proportion of facilities providing training greater than one week. Home only training was unique to the UK. Across all countries, the majority of facilities provided individualized training, by a specific nurse, two weeks after catheter implantation, for 16 to 30 hours, and an oral and practical demonstration of technical procedure as a final assessment of comprehension.

Table: PD training practices by PDOPPS country*

	Australia	Canada	Japan	UK	US
Number of facilities	13	20	25	19	61
When training occurs					
Prior to PD catheter insertion	8%	5%	62%	5%	2%
1 week after PD catheter insertion	0%	30%	27%	11%	16%
2-3 weeks after PD catheter insertion	61%	65%	0%	79%	66%
Other	31%	0%	11%	5%	16%
Training location					
Facility only	46%	84%	100%	26%	53%
Combination of home and facility	54%	16%		47%	48%
Home only				26%	
Duration of training, days					
2-3	17%	22%	39%	50%	14%
4-5	67%	56%	17%	44%	29%
6-7	8%	17%	13%	6%	34%
>7	8%	6%	30%		23%
Final training assessment					
Procedure demonstration	100%	100%	100%	100%	100%
Written test	23%	30%	8%	11%	89%
Oral test	54%	40%	24%	37%	67%
Other	8%	5%	0%	0%	10%
Number of nurses training one patient					
One nurse	67%	95%	28%	84%	97%
Several nurses	33%	5%	72%	16%	3%

* As reported by the nurse study coordinator at each facility

Conclusions: Large variation exists in PD training practices across PDOPPS countries. As the study proceeds, and accrues follow-up time, patient-level training practices, and patient reported perceptions of training quality, the PDOPPS will provide unique information regarding the association of specific training practices and outcomes, thus contributing to fill this knowledge gap.

SA-OR004

Complement Activation in PD Induced Arteriolopathy Maria Bartosova,[1] Betti Schaefer,[1] Justo Lorenzo Bermejo,[2] Felix Lasitschka,[3] Silvia Tarantino,[4] Christoph Aufricht,[4] Klaus Kratochwill,[4] Bradley Warady,[5] Karel Vondrak,[6] Claus P. Schmitt.[1] *[1]Center for Pediatric and Adolescent Medicine, Univ of Heidelberg, Germany; [2]Dept of Medical Biometry, Univ of Heidelberg, Germany; [3]Inst of Pathology, Univ of Heidelberg, Germany; [4]Zytoprotec GmbH, Austria; [5]The Children's Mercy Hospital; [6]Univ Hospital Motol, Czech Republic.*

Background: Exposure to high glucose concentrations and glucose degradation products (GDP) leads to angiogenesis and vasculopathy compromising ultrafiltration capacity of the peritoneum, ultimately resulting in PD failure. The underlying pathomechanisms are partly understood.

Methods: Omental arterioles were microdissected from non-uremic children, age and gender matched children at time of first PD catheter insertion and peritonitis free children on PD for 26 (2-72) months (n=6/group). Children with diseases potentially affecting vessel integrity were excluded. 4 arterioles / patient with similar morphology (EVG staining, Aperio® automated image analysis) were selected. Neighboured sections were used for transcriptome and proteome analysis.

Results: Uremia induced up-regulation of 173 and down-regulation of 117 arteriolar genes ($p<0.01$) compared to controls. In patients on low / high GDP PD, 88/139 genes were up- and 11/17 genes down regulated compared to uremic controls. Gene ontology analyses demonstrated activation of inflammatory, immunological and stress response cascades with uremia and even more with PD. In children on low GDP fluid the complement system and respective regulatory pathways were upregulated most significantly. Proteomics findings were concordant in 14 out of 15 complement factors. Findings were reconfirmed immunohistochemically in omental arterioles in independent cohorts of 15 children per group for C1q, C3c, C4d and TCC. In parietal peritoneum, we quantitated endothelial C1q, which inversely correlated with lumen/vessel ratio, i.e. vasculopathy ($r=-0.75$, $p=0.02$).

Conclusions: Omental arterioles are uniquely suited for global assessment of molecular mechanisms of uremia and PD induced arteriolopathy. Low GDP dialysis fluids predominantly activate arteriole and capillary complement cascades.

Funding: Government Support - Non-U.S.

SA-OR005

The Inhibition of CTGF Ameliorates Peritoneal Fibrosis through the Suppression of Fibroblast/Myofibroblast Accumulation Miki Nakamura,[1] Norihiko Sakai,[2] Kenneth E. Lipson,[3] Taito Miyake,[2] Yasutaka Kamikawa,[2] Akihiro Sagara,[2] Shinji Kitajima,[2] Tadashi Toyama,[2] Akinori Hara,[2] Yasunori Iwata,[2] Miho Shimizu,[2] Kengo Furuichi,[2] Takashi Wada.[1] *[1]Dept of Nephrology and Laboratory Medicine, Kanazawa Univ, Kanazawa, Japan; [2]Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Japan; [3]FibroGen, Inc., San Francisco, CA.*

Background: Peritoneal fibrosis is a severe complication of peritoneal dialysis, but the mechanisms driving it remain to be fully determined. Connective tissue growth factor (CTGF) has been known to regulate fibroblast activity such as proliferation and myofibroblast differentiation. We therefore examined if the inhibition of CTGF has anti-fibrotic effects on the peritoneal fibrosis.

Methods: Peritoneal fibrosis was induced by intraperitoneal injection of chlorhexidine gluconate (CG) in type I pro-collagen promoter-driven green fluorescent protein (GFP) mice to identify fibroblasts. The neutralizing anti-CTGF antibody (FG-3019) was used to inhibit CTGF functions.

Results: CG-induced increases in peritoneal thickness, type I pro-collagen mRNA expression and hydroxyproline content were significantly attenuated in FG-3019-treated mice (n=7). In addition, CG challenges induced a marked peritoneal accumulation of GFP^+ fibroblasts that was significantly reduced by FG-3019. To specifically identify proliferating fibroblasts, dual immunostainings of peritoneal sections were performed using anti-proliferating cell nuclear antigen (PCNA) antibody and anti-GFP antibody. The number of proliferating fibroblasts ($PCNA^+GFP^+$) in the peritoneum after CG challenges was significantly suppressed by FG-3019 (n=5). Peritoneal accumulation of a-smooth muscle $actin^+$ myofibroblasts was also reduced in FG-3019-treated mice. In addition, peritoneal CTGF expression was detected in peritoneal mesothelial cells and fibroblasts, and the levels of peritoneal CTGF expression were significantly suppressed in FG-3019-treated mice compared with those in control antibody-treated mice (n=6).

Conclusions: Our results suggest that the inhibition of CTGF by FG-3019 might be a novel treatment for peritoneal fibrosis through the regulation of fibroblast/myofibroblast accumulation.

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SA-OR006

Connective Tissue Growth Factor Is Correlated with Lymphangiogenesis in Peritoneal Fibrosis Hiroshi Kinashi,[1,2] Tri Q. Nguyen,[1] Roel Goldschmeding,[1] Yasuhiko Ito.[2] *[1]Pathology, Univ Medical Center Utrecht, Utrecht, Netherlands; [2]Nephrology and Renal Replacement Therapy, Nagoya Univ Graduate School of Medicine, Nagoya, Japan.*

Background: Lymphatic absorption in peritoneal cavity may contribute to ultrafiltration failure in peritoneal dialysis (PD). Lymphangiogenesis develops during PD-related peritoneal fibrosis (PF). Connective tissue growth factor (CTGF, aka CCN2) is an important determinant of fibrotic tissue remodeling, but its possible involvement in lymphangiogenesis has not been explored. We studied the relationship between CTGF and lymphangiogenesis in association with PD.

Methods: Messenger RNA (mRNA) for CTGF, lymphatic markers (lymphatic endothelial hyaluronan receptor-1 [LYVE-1] and podoplanin), and vascular endothelial growth factor-C (VEGF-C), a major lymphangiogenic factor, in human peritoneal biopsies (N=56) was analyzed by quantitative real-time polymerase chain reaction. CTGF and VEGF-C mRNA were assessed in human peritoneal mesothelial cells (HPMC) (N=21) treated with transforming growth factor-β1 (TGF-β1). Immunohistochemistry (IHC) for CTGF, LYVE-1, and VEGF-C in a rat chlorhexidine gluconate (CG) induced-PF model was performed.

Results: CTGF mRNA positively correlated with LYVE-1 ($R=0.638$, $P<0.001$), podoplanin ($R=0.592$, $P<0.001$), and VEGF-C ($R=0.670$, $P<0.001$) mRNA in human peritoneal biopsies. We cultured HPMC derived from 21 patients with variable peritoneal membrane transport. CTGF and VEGF-C mRNA expression were increased by TGF-β1 (5 ng/ml) treatment. There was a positive relationship between CTGF and VEGF-C mRNA increment at 12 ($R=0.722$, $P<0.001$) and 24 ($R=0.532$, $P<0.01$) hours after TGF-β1 treatment. IHC analysis indicated that the expression of CTGF ($P<0.01$), LYVE-1-positive lymphatic vessels ($P<0.001$), and VEGF-C ($P<0.01$) were increased in the rat diaphragm of CG models compared with controls. Moreover, CTGF expression positively correlated with expression of LYVE-1-positive lymphatic vessels ($R=0.775$, $P<0.05$) and VEGF-C ($R=0.952$, $P<0.001$) in the CG model. There was also a positive correlation between expression of VEGF-C and LYVE-1 in the CG model ($R=0.704$, $P<0.05$).

Conclusions: Our results suggest a close relationship between CTGF and PF-related lymphangiogenesis.

SA-OR007

The PD Membrane Microvasculature in Uremia and PD - Findings from the International Pediatric PD Biobank Maria Bartosova,[1] Betti Schaefer,[1] Stephan Macher-Goeppinger,[2] Peter Sinn,[2] Uwe Querfeld,[4] Ariane Zaloszyc,[5] Gema Ariceta,[6] Yok-Chin Yap,[7] Philipp Romero,[3] Franz S. Schaefer,[1] Bradley Warady,[8] Claus P. Schmitt.[1] *[1]Center for Pediatric and Adolescent Medicine, Univ of Heidelberg, Germany; [2]Dept of Pathology, Univ of Heidelberg, Germany; [3]Dept of Pediatric Surgery, Univ of Heidelberg, Germany; [4]Univ of Charité, Germany; [5]Univ Hospital Hautepierre, France; [6]Univ Hospital Vall d' Hebron, Spain; [7]Hospital Kuala Lumpur, Malaysia; [8]The Children's Mercy Hospital.*

Background: Based on modelling and experimental findings, peritoneal microvasculature primarily defines PD membrane transport function, respective human data is scant.

Methods: 30 centers collected 332 peritoneal and 256 omental specimens from 106 healthy individuals (0.1-60 yrs), 114 patients at time of PD catheter insertion and 112 on PD (0.1-20.1 yrs), 91 treated with low GDP fluid. Aperio® and Nanozoomer/NDP Systems® were used for automated analyses.

Results: Parietal peritoneal vessel density depends on age, with highest blood capillary density / endothelial exchange area in infancy and lowest values with 7-12 yrs. Lymphatic vessel density is low, but again highest in infants. Omental blood capillary density correlates with parietal capillary density, lymphatic vessels are few. Uremia reduces omental blood vessel density by 51%, Angp-2 protein by 78%, ACTG1 by 34%. The submesothelial three vessel layer structure dissipates with low GDP PD, blood vessel density increases 2-3 fold, as do TGF-ß/pSMAD, miR21, VEGF, ASMA pos. fibroblasts and CD45/CD68+ macrophages. Mild lumen narrowing develops in 31% of blood vessels, lymphatic vessel density remains low. Similar changes develop with high GDP PD, while EMT and profibrotic $CD90^{+}$ fibroblast subpopulations are more prominent. D/P creatinine ratios correlate with peritoneal vessel density ($r=0.33$, $p<0.05$), but not with lymphatic vessel density or submesothelial thickness; vessel density with PD duration and peritonitis number ($r=0.26/0.20$, $p<0.001/0.05$).

Conclusions: Peritoneal blood vessel density defines peritoneal solute transport. Despite low GDP fluid usage, progressive blood capillarisation develops with time on PD, while lymphatic vessel density and vasculopathy remain low.

Funding: Government Support - Non-U.S.

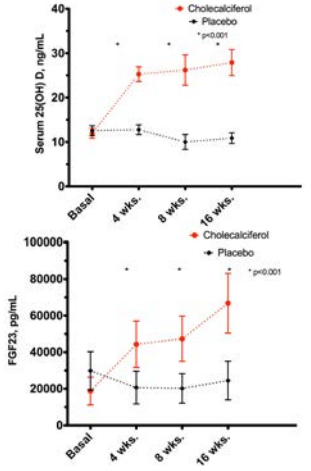
SA-OR008

Cholecalciferol Supplementation to Correct Hypovitaminosis D in Peritoneal Dialysis Patients Increases FGF23 but Not Other Osteogenic Proteins: A Randomized Clinical Trial Juan Carlos Ramirez-Sandoval, Mauricio Arvizu-Hernandez, Barbara Vazquez-Cantu, Cristinoc Cruz, Enrique Gómez, Ricardo Correa-Rotter. *Ins Nac de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.*

Background: Very low levels of 25-hydroxyvitamin D (25OHD) are common in peritoneal dialysis(PD) patients, and normalization has been advocated as potentially beneficial. The safety, eficacy, and effects of 25OHD correction on osteogenic biomarkers in this population remains uncertain.

Methods: We conducted a double-blind, placebo-controlled, randomized clinical trial to assess the effects of cholecalciferol supplementation on osteogenic biomarkers (osteoprotegerin, intact fibroblast growth factor-23[iFGF23], osteocalcin, osteopontin, iPTH) in PD patients with 25OHD<20 ng/mL;56 patients were randomized to 16 wks. of cholecalciferol (4,800 IU/daily,n=28) or placebo(n=28).

Results: Baseline characteristics were similar between groups. Mean±SD serum 25OHD increased from 10.5±3.6 ng/ml at baseline to 26.1±4.5 ng/ml in the cholecalciferol group and did not significantly change in the placebo group (11.9±4.1 ng/ml to 13.2±4.5 ng/ml). A larger proportion of the cholecalciferol supplemented subjects had an increase >30% in iFGF23 compared with placebo (95% vs 9%,p<0.0001). Extremely high iFGF23 levels (>30000 pg/ml) were observed in 74% of patients receiving cholecalciferol at 16 wks.



The observed changes in iFGF23 were not confounded by concurrent and sustained changes in urinary residual function, serum P, or iPTH levels. No difference was observed between arms in osteoprotegerin, osteocalcin, osteopontin, Ca, P, iPTH, IL-6, phosphate binder use or calcitriol dose.

Conclusions: Cholecalciferol supplementation increases serum 25OHD levels in patients on PD with levels<20 ng/mL, yet it induces an exponential increase of iFGF23 in most PD patients, which may be a major concern and contraindication for this manouever.

SA-OR009

Peritoneal Dialysis-Related Infection Rates and Outcomes: Early Results from the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) Jeffrey Perl,[1,6] Junhui Zhao,[2] Brian Bieber,[2] Ronald L. Pisoni,[2] Beth M. Piraino,[3,6] Yasuhiko Ito,[4,6] David W. Johnson.[5,6] *[1]Univ of Toronto, Toronto, ON, Canada; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]Univ of Pittsburgh, Pittsburgh, PA; [4]Nagoya Univ Graduate School of Medicine, Nagoya, Japan; [5]Univ of Queensland, Brisbane, Australia; [6]On Behalf of the PDOPPS Infection Prevention and Management Workgroup, Ann Arbor, MI.*

Background: Peritoneal dialysis (PD)-related infections are a major source of morbidity for PD patients. We describe preliminary peritonitis rates and outcomes among PDOPPS participants.

Methods: PDOPPS is an international prospective cohort study of PD treatment outcomes in Australia/New Zealand (ANZ), Canada, Japan, Thailand, the UK and the USA. Data was collected on peritonitis episodes, and outcomes from countries with ≥100 patient-years of follow-up.

Results: Peritonitis rates were comparable across countries with the exception of Japan which had a slightly higher peritonitis rate. Wide variation was seen in facility peritonitis rates in each country. Organism-specific information revealed: the proportion of fungal peritonitis was highest in ANZ (7%), lowest in Japan (0%), the proportion of peritonitis due to pseudomonas species was highest in Japan (7%) and ANZ (7%), and peritonitis due to CNST was lowest in Japan (13%), but culture-negative peritonitis was highest (34%). Peritonitis associated with a hospitalization was highest in Japan. The proportion of peritonitis episodes necessitating PD catheter removal was similar across countries.

	ANZ	Canada	Japan	US
Sample				
Facilities, N	15	20	28	27
Patients, N	237	716	609	782
Peritonitis rates				
Patient years, sum	100.9	645.8	285.6	632.6
Peritonitis episodes, N	30	203	128	228
Peritonitis rate, per patient year (95% CI)	0.30 (0.20,0.42)	0.31 (0.27,0.36)	0.45 (0.37,0.53)	0.36 (0.32,0.41)
Distribution of facility peritonitis rates, median (IQR)*		0.28 (0.23,0.43)	0.40 (0.37,0.48)	0.41 (0.29,0.44)
Organism category**				
Gram positive	38%	48%	40%	47%
Gram negative	10%	18%	15%	16%
Fungi	7%	2%	0%	3%
Polymicrobial	17%	13%	10%	12%
Unknown organism	7%	1%	1%	2%
Culture negative	21%	19%	34%	22%
Selected organisms**				
Coagulase negative staphylococcus (CNST)	24%	26%	13%	24%
Staphylococcus aureus	7%	12%	9%	10%
Streptococcus species	17%	14%	12%	9%
Pseudomonas species	7%	2%	7%	4%
Peritonitis episode details				
Concurrent exit site/tunnel infection	3%	7%	9%	2%
Hospitalized during peritonitis episode	50%	48%	86%	47%
PD catheter removed	17%	17%	18%	16%
Death within 90 days of diagnosis	3.3%	3.0%	5.5%	4.4%

*Restricted to facilities with at least 20 patient years (number of facilities: Canada 16, Japan 6, US 13).
**No Organism information available for 42 episodes (ANZ 1, Canada 11, Japan 10, and US 20).

Conclusions: Peritonitis rates vary widely across facilities. Country-specific differences need confirmation with extended follow-up. Variation in the characteristics and details regarding peritonitis episodes may guide the regional development of peritonitis prevention strategies.

SA-OR010

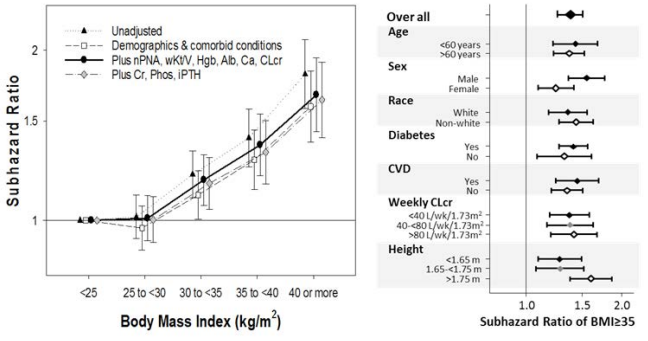
Morbid Obesity and Time to Transfer to Hemodialysis among Incident Peritoneal Dialysis Patients Yoshitsugu Obi,[1] Amanda R. Tortorici,[1] Connie Rhee,[1] Elani Streja,[1] Daniel L. Gillen,[1] Rajnish Mehrotra,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Univ of Wash.*

Background: The prevalence of obesity is increasing among dialysis patients in the USA and may be associated with higher risk of peritoneal dialysis (PD) modality interruption and transfer to hemodialysis (HD), notwithstanding the survival advantages of obesity in dialysis patients (obesity paradox).

Methods: In a national cohort of incident dialysis patients in the USA (2007–2011), we identified 15,112 patients who started PD as their 1st or 2nd dialysis modality and who had

data on body mass index (BMI) during the first 91 days. The association of BMI categories and the association of morbid obesity (BMI ≥35 kg/m^2) with transfer to hemodialysis (HD) were examined in competing risk regression models incorporating the competing risk for death and kidney transplantation. Hierarchical adjustments were employed using case-mix variables and clinically relevant laboratory variables.

Results: There was a higher likelihood of transfer to HD across higher BMI (*P*trend<0.001); BMI categories above 30 kg/m^2 were significantly associated with shorter time to transfer to HD. These associations were robust against any adjustment models (left panel). Overall the risk associated with morbid obesity (BMI ≥35 kg/m^2) was high (subhazard ratio 1.32 [95%CI, 1.21–1.45]) in the case-mix adjusted model. The risk of morbid obesity was pronounced among male or taller (height >1.75 m) patients (*P*interaction <0.05) but was consistently observed across all subgroups (right panel).



Conclusions: Obesity and morbid obesity are incrementally associated with a higher risk for PD patients to transfer to HD. This makes it imperative to identify interventions that would prolong patient time on PD in patients who are obese and morbidly obese.

Funding: NIDDK Support

SA-OR011

IL-33 Induces Innate Lymphoid Cells and Alternatively Activated Macrophages That Reduce Kidney Ischaemia-Reperfusion Injury

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Background: IL-33 is an important immune regulator which can promote Th2-dependent immunity, inflammation, and tissue repair in several important immune-mediated disorders. In the current study, we sought to determine whether IL-33 is an important regulator in renal ischaemia-reperfusion injury (IRI).

Methods: Renal IRI was induced in C57BL/6 mice by bilateral renal pedicle occlusion for 30 minutes. IL-33 was given by 5 consecutive daily injections starting at day 5 before IRI surgery. Separately, adoptive transfer of type 2 innate lymphoid cells into mice with IRI was used to assess their in vivo functions.

Results: IL-33 significantly improved kidney functional and structural injury in IRI mice, with lower serum creatinine and less tubular cell injury. The possible mechanisms underlying the protective effect of IL-33 were examined. IL-33 increased the levels of IL-4, IL-5 and IL-13 in serum and kidney and promoted induction of alternatively activated (M2) macrophages in kidney. Moreover, the number of NK cells and neutrophils was significantly reduced in IRI mice treated with IL-33. Of note, IL-33 increased the number of type 2 innate lymphoid cells (ILC2) and regulatory T cells (Tregs) in kidney. The depletion of ILC2 or Tregs by using CD90 or CD25 antibodies in vivo demonstrated that the protective effect of IL-33 in IRI is dependent on ILC2 cells, but not Tregs. Adoptive transfer of ILC2 not only reduced kidney injury of IRI mice but also induced M2 macrophages in kidney.

Conclusions: In conclusion, IL-33 elicits ILC2 and Tregs, regulates macrophage phenotype in kidney and prevents kidney IRI. ILC2 is primarily responsible for IL-33's protective effect in IRI.

Funding: Government Support - Non-U.S.

SA-OR012

Tubular Cell Endocycle-Related Hypertrophy and Renal Progenitor Mitosis Drive Kidney Function Recovery after AKI but Cannot Avoid Persistent Tubular Cell Loss

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Background: Acute kidney injury (AKI) is considered largely reversible based on an intrinsic regenerative capacity of tubules. As AKI can be followed by chronic kidney disease (CKD), we questioned this concept and hypothesized that tubular cell division is limited and other mechanisms account for kidney function recovery.

Methods: To this aim, we developed four conditional transgenic mouse models: 1. *Pax8.rtTA;TetO.Cre;R26.Confetti* (Pax8/Confetti) to track all tubular cells; 2. *Pax2.rtTA;TetO.Cre;R26.Confetti* (Pax2/Confetti) to track putative tubular progenitors; 3. *PAX8.rtTA;tetO.cre;R26.FUCCI2* (Pax8/FUCCI2) and 4. *PAX2.rtTA;tetO.cre;R26.FUCCI2* (Pax2/FUCCI2) to identify cell-cycle phase of Pax8+ and Pax2+ cells. Doxycycline administration followed by 1 week washout drove the reporters expression to track Pax2+ and Pax8+ progenies in healthy mice and after 30' of unilateral ischemia/reperfusion injury (IRI).

Results: To quantify irreversible cell loss we induced IRI in Pax8/Confetti mice where all tubular cells are tracked. Kidney function recovered, but 35% of total tubular cells were irreversibly lost. Clonal analysis disproved widespread tubular cell proliferation erroneously indicated by cell-cycle markers immunostaining. Simultaneous cell-cycle phase and DNA content assessment using Pax8/FUCCI2 mice and flow cytometry revealed endoreplication-related tubular cell hypertrophy as the predominant response and showed that cell-cycle markers indicated endoreplication but not true cell division. In contrast, Pax2/Confetti mice showed that Pax2+ tubular progenitors enriched by higher survival and clonogenic capacity after IRI. Consistently, Pax2/FUCCI2 mice demonstrated that Pax2+ tubular progenitors completed mitosis while Pax8+ cells endoreplicated.

Conclusions: These results 1. disprove common knowledge about the mechanisms of AKI recovery, 2. identify tubular cell hypertrophy related to endoreplication cycles as a critical response to AKI 3. explain the high incidence of CKD after an AKI episode.

SA-OR013

Genetic Lineage Analysis of Dedifferentiated Proximal Tubule Epithelia during Repair after AKI

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Background: Proximal tubule (PT) has a remarkable capacity for repair after acute injury. Whether dedifferentiation or a fixed progenitor population is responsible for this repair remains the subject of ongoing controversy. We have generated a novel genetic mouse model to address this question.

Methods: We generated a Kim1-GFPCreER^{t2} knockin mouse line (Kim1-GCE) by homologous recombination. Kim1 is expressed exclusively in dedifferentiated PT cells. After crossing to the R26-tdTom reporter line we performed lineage analysis to evaluate the fate and characteristics of these cells during repair.

Results: Heterozygote Kim1-GCE expressed half the level of Kim1 protein after IRI, and homozygote Kim1-GCE had undetectable endogenous Kim1 protein, as expected with our ATG replacement knock in strategy.In bigenic Kim1-GCE; R26tdTom mice, there was no labeling of any cells in healthy kidney, even after tamoxifen (TAM) administration. By contrast, bilateral IRI with TAM induced robust labeling of cells in the outer medulla. These cells co-expressed Kim1, Vimentin and Pax2, indicating a dedifferentiated state. These were Ki67+, indicating proliferative repair. We performed clonal analysis using low dose TAM. At day 2, 95% of clones were single cell but this decreased to 45% single cell clones by day 14, with mostly 2, 3 and 4 cell clones however a substantial number of 10+ cell clones was observed as well. The multicellular clones continued to express Pax2 by day 14, with a decrease in Vimentin expression. Importantly, TdTom+ cells cultured on day 2 after injury formed tubular structures in a tree-like pattern resembling branching morphogenesis, whereas cells cultured after redifferentiation at day 14 lacked this capacity.

Conclusions: The mechanism of repair after AKI is by dedifferentiation of bulk proximal tubule and not by a fixed progenitor population. Dedifferentiation confers unique properties that are lacking from differentiated proximal tubule.

Funding: NIDDK Support

SA-OR014

Fibroblast-Specific Integrin-Linked Kinase Signaling Is Required for Kidney Protection and Repair after AKI

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Background: Integrin-linked kinase (ILK) signaling plays a critical role in regulating cell proliferation, differentiation, matrix production and tissue hemostasis. Activation of ILK has been linked to the pathogenesis of tubular epithelial-mesenchymal transition (EMT) and kidney fibrosis. Whether ILK plays any role in the repair or progression after AKI is unknown.

Methods: To study this, we generated conditional knockout mice in which the ILK gene was specifically depleted in kidney fibroblasts (FC-ILK-/-) by mating ILK-floxed mice with Gli1-Cre transgenic mice. Sex- and age-matched control and FC-ILK-/- mice were subjected to ischemia/reperfusion injury (IRI).

Results: Mice with fibroblast-specific deletion of ILK (FC-ILK-/-) were phenotypically normal with no appreciable defects in kidney morphology and function. Following AKI induced by IRI, FC-ILK-/- mice developed more severe kidney injury, comparing to the controls. FC-ILK-/- mice had higher serum creatinine level and more severe morphologic injury. In addition, ablation of ILK in interstitial fibroblasts promoted chemokine expression and renal infiltration of inflammatory cells after IRI. Consistently, apoptosis was more prevalent in the kidneys of the FC-ILK-/- mice, which was accompanied by increased renal expression of soluble FasL and Fas-associated protein with death domain (FADD). Notably, the ability of fibroblasts activation and proliferation was largely abolished in the FC-ILK-/- mice, with downregulation of PDGFR-β, PCNA and increased P53 expression.

Conclusions: These results suggest that endogenous ILK in fibroblast is pivotal for proper fibroblast activation in response to acute injury. Such response from healthy fibroblasts is crucial for tubular cell survival, repair and regeneration after AKI.

Funding: NIDDK Support

SA-OR015

Renin Lineage Cells Do Not Participate in Endothelial but Mesangial Regeneration after Experimental Injury Leo Ruhnke, Jan Sradnick, Moath Al-Mekhlafi, Michael Gerlach, Florian Gembardt, Vladimir T. Todorov, Bernd Hohenstein, Christian Hugo. *Div of Nephrology, Dept of Internal Medicine III, Univ Hospital CGC, Dresden, Germany.*

Background: In response to kidney injury renin lineage cells (RLC) can give rise to different glomerular cell types such as mesangial cells (MC) or podocytes. Endothelial cells (EC) represent another major glomerular cell type frequently undergoing primary or secondary injury during kidney disease. Up to now it is unknown if RLC can also differentiate into EC. Thus, we investigated the role of RLC in endothelial regeneration.

Methods: We used a triple transgenic lacZ reporter mouse which allows specific detection and fate mapping of RLC via X-Gal staining. LacZ labeling of RLC in healthy adult mice was induced by doxycyclin/enalapril treatment. Left sided EC injury (ECI) was caused by renal-arterial administration of concanavalin A (conA)/anti-conA. Kidneys were harvested on day 0 (healthy control (HC)), 1, 7 and 28.

Results: ECI evaluation using CD31 densitometry showed significant decrease of positive staining area at day 1 and subsequent recovery to HC levels at day 7 (HC: 11.7 ± 1.7% d1: 6.7 ± 0.3% d7: 13.7 ± 1.5%). Accordingly AFOG staining revealed glomerular fibrin thrombi at d1. In conjunction with endothelial damage we detected pronounced MC injury by PAS staining, which could be verified by α8 integrin densitometry (HC: 16.5 ± 1.7% d1: 6.2 ± 1.5% d7: 13.9 ± 1.0%). Whereas X-Gal staining was restricted to the juxtaglomerulus apparatus (JGA) in healthy controls, 15.6 ± 0.8 % of glomeruli showed migration of RLC from the JGA into the glomerular tuft at d7. Immunohistological analysis revealed that these intraglomerular RLC show a transdifferentiation to mesangial phenotype expressing α8-integrin, NG2 and GATA3, but do not co-localize with EC (CD31, ERG) or podocytes (WT-1, synaptopodin). These findings could preliminarily be confirmed using fluorescent renin lineage mice.

Conclusions: In our model of renal ECI, RLC are recruited from the JGA to the glomerular tuft upon severe injury. These RLC do not show involvement in regeneration of damaged renal endothelium. Rather, recruitment of RLC seems to be specific for the repair of concomitantly injured mesangium.

SA-OR016

Exosomal Transfer of micro-RNA-486-5p Protects against Ischemia-Reperfusion Kidney Injury Kevin D. Burns, Joe A. Zimpelmann, Alex Gutsol, William A. Knoll, Dylan Burger, David Allan, Jose L. Vinas. *Medicine, KRC, OHRI, Univ of Ottawa, Ottawa, ON, Canada.*

Background: Exosomes derived from cord blood endothelial colony forming cells (ECFCs) reduce ischemia/reperfusion (IR) kidney injury in immuno-incompetent mice. ECFC exosomes are enriched in micro-RNA (miR)-486-5p, which we showed can transfer to cultured endothelial cells. We studied the role of miR-486-5p transfer in protection against IR kidney injury *in vivo*, and assessed phosphatase and tensin homolog (PTEN) as a potential target.

Methods: Immuno-competent mice with IR kidney injury were injected with ECFC exosomes (20 μg i.v.) at reperfusion. Some mice received exosomes derived from ECFCs that were transfected with antagomiR to miR-486-5p. After 24 h, mice were sacrificed, plasma was collected, and kidneys were analyzed by real-time PCR, immunoblots, histologic injury scores, and apoptosis assays. In cultured human umbilical vein endothelial cells (HUVECs), a luciferase reporter assay assessed targeting of PTEN by miR-486-5p, and silencing RNA determined the role of PTEN in apoptotic response to hypoxia.

Results: In mice with IR, exosomes increased kidney miR-486-5p levels, decreased PTEN, and increased phosphorylation of pro-survival Akt. These effects were blocked in mice receiving exosomes from antagomiR-transfected ECFCs. ECFC exosomes potently protected against IR kidney injury, determined by plasma creatinine and BUN, histologic injury, and apoptosis assays (plasma Cr: 117±26 μM (IR) vs 9±4 μM (IR + exosomes); P<0.01; n=5-7 mice). By contrast, the protective effects were not observed with exosomes derived from antagomiR-transfected ECFCs. In cultured HUVECs transfected with a luciferase reporter, miR-486-5p directly targeted the 3'-untranslated region of PTEN. Knockdown of PTEN in HUVECs inhibited hypoxia-induced apoptosis, to levels observed with exosome treatment (n=3).

Conclusions: In kidney IR injury, administration of ECFC exosomes causes transfer of miR-486-5p, which mediates protective effects on kidney function, histology and apoptosis. In endothelial cells, PTEN is directly targeted by miR-486-5p, which blocks apoptosis. Exosomes enriched in miR-486-5p could represent a viable strategy to protect against acute kidney injury.

Funding: Private Foundation Support, Clinical Revenue Support

SA-OR017

Proximal Tubule-Derived Amphiregulin and TNFα Crosstalk Promotes Progressive Fibrotic Kidney Disease Eirini Kefalogianni,[1] Vaishali Krishnadoss,[1] Muthu Lakshmi Muthu,[2] Helmut G. Rennke,[2] Benjamin D. Humphreys,[1] Joseph V. Bonventre,[2] Andreas Herrlich.[1] *[1]Nephrology, Washington Univ School of Medicine, St. Louis, MO; [2]Renal, Brigham and Women's Hospital, Boston, MA.*

Background: Using global and proximal tubule (PT)-specific knockout, we previously showed in ischemic and obstructive kidney injury mouse models that the metalloprotease ADAM17 is a key regulator of fibrosis via cleavage-activation of its substrates, epidermal growth factor receptor (EGFR) ligands and TNFα. However, apart from PT, injury also induced ADAM17 upregulation in the interstitial compartment. We thus now examined the effect of stromal- or myeloid linage-specific knockout of ADAM17 on injury-induced kidney fibrosis in vivo. Further, we studied pro-fibrotic and pro-inflammatory effects of specific PT-released ADAM17 substrates in vitro. Finally, we investigated activation of the EGFR and TNFα pathways in human AKI and fibrotic CKD kidney samples.

Methods: We used SLC34a1-Cre-ERt2/ADAM17fl/fl (PT-KO), FoxD1-Cre/ADAM17fl/fl (Stroma-KO) and LysM-Cre/ADAM17fl/fl (Myeloid-KO) and respective littermates and subjected them to UUO. ADAM17 and downstream pathways were studied in PT cells *in vitro* and in AKI and chronic kidney disease (CKD) patients.

Results: UUO-induced kidney fibrosis was significantly reduced in PT-KO but not in stroma-KO or myeloid-KO mice, suggesting that ADAM17 substrate release from PT is mainly responsible for its pro-fibrotic function. Among several EGFR ligand substrates released from injured PT, we identify AREG as inducing the strongest pro-inflammatory and pro-fibrotic cytokine expression in PT cells in vitro. This effect is strongly potentiated by TNFα. This newly identified EGFR-TNFα pathway cross-talk partially depends on TNFα-induced and ADAM17-dependent AREG cleavage. Finally, both EGFR and TNFα pathways are activated in human AKI and CKD samples, and ADAM17 and AREG protein expression are very strongly correlated with fibrosis markers in CKD biopsies.

Conclusions: ADAM17 substrates released from injured PT and their cross-talk, in particular of AREG and TNFα, exert ADAM17's pro-fibrotic role. Activation of ADAM17-pathways highly correlates with injury and fibrosis in human kidney samples.

Funding: NIDDK Support

SA-OR018

Elucidating the Cellular Mechanisms of a Pro-Regenerative Drug Therapy for Acute Kidney Injury Hwa In Han,[1] Lauren Brilli Skvarca,[1] Eugenel Bermudez Espiritu,[1] Maria Azzurra Missinato,[1] Michael Tsang,[1] Alan J. Davidson,[2] Neil A. Hukriede.[1] *[1]Dept of Developmental Biology, Univ of Pittsburgh, Pittsburgh, PA; [2]Molecular Medicine and Pathology, Univ of Auckland, Auckland, New Zealand.*

Background: Acute kidney injury (AKI) often progresses to chronic kidney disease and end stage renal disease due to inefficient renal tubular epithelial cell (RTEC) proliferation. Therefore, drugs that can enhance proliferation in post-AKI setting are urgently in need. We have identified a small molecule, methyl-4-phenylthiobutanoate (m4PTB), an HDAC inhibitor, which increases RTEC proliferation in zebrafish and rodent models of AKI. However, the mechanisms driving proliferation are not known. Here, we show that m4PTB enhances epithelial-to-mesenchymal transition, a hallmark of dedifferentiating cells. The dedifferentiating cells provide the source of RTEC proliferation, thereby enhancing post-AKI repair.

Methods: We injected gentamicin in larval zebrafish to induce a nephrotoxic model of AKI. We utilized immunohistochemistry to visualize expression of E-cadherin and Vimentin, markers of epithelial and mesenchymal cells, respectively. We stained tubules with Pax2, and PCNA, markers for renal progenitors and proliferation, respectively. Finally, we stained tubules with kidney injury molecule-1 (KIM-1) to quantify changes in injury level after m4PTB treatment.

Results: m4PTB treatment increased expression of mesenchymal marker and decreased epithelial marker in injured RTECs. Injury stimulated Pax2 reactivation in RTECs, further increasing with m4PTB. Pax2 expression colocalized with Vimentin, suggesting that RTECs expressing the embryonic gene simultaneously undergo dedifferentiation. To investigate whether the dedifferentiating cells provide the source of proliferation, we stained tubules with Pax2 and PCNA. m4PTB increased the number of Pax2 and PCNA positive cells, of which many colocalized. Finally, we show that m4PTB lowers KIM-1 expression, thereby reducing tubular injury.

Conclusions: Our work demonstrates that m4PTB promotes dedifferentiation of RTECs to increase proliferation and reduce injury level. This mechanism of dedifferentiation and proliferation enhances regenerative responses post-AKI.

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SA-OR019

Interaction of the EGF Receptor and the Hippo Pathway in Acute Kidney Injury Jianchun Chen, Raymond C. Harris. *Medicine, Vanderbilt Univ, Nashville, TN.*

Background: Activation of both EGFR and the Hippo signaling pathway can control cell proliferation, apoptosis and differentiation. Our previous studies have shown that activation of EGFR in renal proximal tubule epithelial cells plays a critical role in renal functional and structural recovery from Ischemia-reperfusion injury. YAP is a key transcriptional activator that associates with the highly conserved transcription factors, TEA domain (TEAD) proteins, to regulate transcription of multiple target genes.

Methods: Renal proximal tubule cell-specific EGF receptor knockout mice ($EGFR^{ptKO}$) or their wild type littermates (WT) were subjected to ischemia-reperfusion injury (IRI), and wildtype mice were subjected to IRI followed by administration with vehicle or verteporfin, an inhibitor of YAP-TEAD activation.

Results: In response to IRI, renal YAP expression and nuclear localization were markedly increased within 6 hours and persisted for at least 3 weeks after IRI. YAP activation was dramatically inhibited in $EGFR^{ptKO}$ mice. Administration of verteporfin significantly delayed renal functional and structural recovery from IRI. The BUN of vehicle-treated mice returned to basal levels (19.65 ± 1.44 mg/dl) at 7 days after IR, but remained elevated in verteporfin treated mice (43.33 ± 6.01 mg/dl, P<0.01, n=5). There was more severe proximal tubule dilation and epithelial simplification and cast formation

in verteporfin-treated mice. We also found that upregulation of cyclin D expression and phosphorylation of retinoblastoma protein (Rb) 24 h after IRI were dramatically blunted in EGFR^{ptKO} mice or in the mice given verteporfin.

Conclusions: This study demonstrates that EGFR-dependent YAP upregulation plays an important role in renal functional and structural recovery in response to acute kidney injury. The increases in cyclin D and Rb phosphorylation suggest that YAP activation is important for cell cycle activation and epithelial regeneration following AKI.

Funding: NIDDK Support, VA Support

SA-OR020

Kidney Injury Molecule-1 (KIM-1) Interacts with the Dynein Light Chain Tctex-1 to Mediate Efferocytosis Lakshman Gunaratnam,[1,2] Ola Ziyad Ismail,[1] Xizhong Zhang.[1] *[1]Matthew Mailing Centre for Translational Transplant Studies, Lawson Health Research Inst, London, ON, Canada; [2]Medicine, Western Univ, London, ON, Canada.*

Background: After tissue injury, the phagocytic clearance of apoptotic cells, or efferocytosis, attenuates inflammation and enables tissue repair. KIM-1 is an efferocytosis receptor specifically upregulated on proximal tubular epithelial cells during acute kidney injury (AKI). We previously showed that, after renal ischemia-reperfusion injury, mice deficient in KIM-1 have impaired efferocytosis, with greater tissue damage, renal dysfunction and death, compared to wild-type mice.

Methods: To uncover the phagocytic signalling pathway downstream of KIM-1, we utilized a yeast two-hybrid screening system and identified a potential KIM-1-interacting protein, the 14-kDa dynein light chain protein, Tctex-1. Tctex-1 is a component of the dynein microtubule motor complex involved in linking dynein to its cargo as an adaptor protein. It also plays dynein-independent roles in diverse cellular functions. Thus, we hypothesized that Tctex-1 is required for KIM-1-mediated engulfment of apoptotic cells.

Results: First, we confirmed the direct interaction between Tctex-1 and Kim-1 using co-immunoprecipitation, GST-Tctex-1 pull-down assay and immunofluorescence staining. When we stimulated KIM-1-expressing cells with apoptotic cells, the interaction between KIM-1 and Tctex-1 was sustained until the later stages of the efferocytosis. Knockdown of endogenous Tctex-1 expression with siRNA significantly inhibited efferocytosis by KIM-1-expresisng cells. To test if Tctext-1 the inhibitory effect caused by Tctex-1 knockdown was related to impaired cargo binding for dynein transport (i.e. dynein-dependent), we utilized a Tctex-1 mutant construct in which we replaced Threonine-94 with glutamic acid (T94E) to mimic the phosphorylated form that cannot bind dynein. Surprisingly, the phospho-mimic Tctex-1-T94E displayed decreased binding to Kim-1, but did not influence KIM-1-mediated uptake of apoptotic cells.

Conclusions: Our studies have uncovered a novel role for Tctext-1 in efferocytosis, which is crucial to tissue repair following AKI.

Funding: Government Support - Non-U.S.

SA-OR021

New Insights into the Function of Dendritic Cell Subsets in Glomerulonephritis Using Multi-Photon Imaging Sebastian Braehler,[1] Saravanan Raju,[1] Michael William Johnson,[1] Bernd H. Zinselmeyer,[1] Jeffrey H. Miner,[2] Kenneth M. Murphy,[1] Andrey S. Shaw.[3] *[1]Dept of Pathology and Immunology, Washington Univ School of Medicine, St. Louis, MO; [2]Div of Nephrology, Washington Univ School of Medicine, St. Louis, MO; [3]Genentech, South San Francisco, CA.*

Background: Glomerulonephritis (GN) is a major cause for end stage renal disease. The immunological mechanisms are not completely understood. Studies using CD11c as marker for dendritic cells (DC) have identified DCs as key players in a mouse model of GN (NTN). How to discriminate macrophages and dendritic cells in various tissues is a matter of ongoing debate. Recently, new markers allow the definition of subsets of macrophages and dendritic cells in the kidney.

Methods: Here we used multiphoton imaging of isolated kidney slices from three different fluorescent reporter mice (CD11c-YFP, ZBTB46-GFP for all classical DCs and SNX22-GFP for the CD103+ DC subpopulation) to analyze structure, migration and distribution of dendritic cells under healthy conditions and after NTN treatment. To determine the function of specialized DC subsets, we depleted the general classical DC lineage using zbtb46-DTR bone marrow chimeras and the CD103+ subset by using BATF3-knockout mice before inducing NTN.

Results: CD11c-YFP-positive cells form a continuous network with long cell processes, and with many cells in this population also expressing the macrophage markers F4/80 and CD64. In contrast, ZBTB46-GFP-positive and SNX22-GFP-positive DCs have a lower expression of these markers, exhibited shorter processes, higher motility and were found clustered around blood vessels. Depletion of ZBTB46+ DCs caused an attenuation of NTN, predominantly in the early stage, whereas depletion of only the CD103+ subset aggravated NTN with rapid crescent formation and excessive neutrophil invasion.

Conclusions: Here we provide evidence that CD11c-YFP identifies a mixed population of macrophages and dendritic cells. ZBTB46-depletion studies showed that the dendritic cells in toto have a proinflammatory effect, whereas the CD103+ subset represents an anti-inflammatory population, possibly balancing the immune response generated by their CD11b+ counterparts.

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SA-OR022

FcγRIV Is Important in the Pathogenesis of Anti-MPO Induced Crescentic Glomerulonephritis Hong Xiao, Peiqi Hu, Cheng Wan, Ronald J. Falk, J. Charles Jennette. *Pathology and Laboratory Medicaine, Univ of North Carolina, Chapel Hill, NC.*

Background: Anti-myeloperoxidase (anti-MPO) IgG causes crescentic glomerulonephritis (CGN) in mice that mimics human antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis in patients. Our prior studies have shown that knock out (KO) of all activating Fcγ receptors (FcγRs) prevents induction of anti-MPO CGN, but that KO of activating receptors FcγRI and FcγRIII does not prevent disease. In this study, we investigated the role of the activating receptor FcγRIV in anti-MPO induced CGN *in vivo*, as well as the effect of blocking anti-FcγRIV antibodies on neutrophil activation by anti-MPO IgG *in vitro*.

Methods: B6 mice with KO of FcγRIV (FcγRIV KO) and wild type (WT) B6 mice were injected i.v. with 50ug/g body weight anti-MPO IgG. Circulating anti-MPO IgG was determined by ELISA. Urine abnormalities were monitored, and mice were sacrificed at day 6 and kidney tissue obtained for pathologic examination. In vitro neutrophil activation by anti-MPO was measured by respiratory burst.

Results: At day 6, B6 WT and FcγRIV KO mice that received anti-MPO IgG showed similar levels of circulating anti-MPO. All WT B6 mice developed hematuria and CGN (mean 12% glomeruli with crescents). In contrast, FcγRIV KO mice had normal urine and less CGN with mean 2% crescents ($p<0.001$). Neutrophils deficient in FcγRIV-/- or treated with anti-FcγRIV blocking antibodies had less *in vitro* activation by anti-MPO than neutrophils from wild type mice as measured by respiratory burst.

Conclusions: 1) Absence of the FcγRIV greatly diminishes anti-MPO induced CGN *in vivo* and *in vitro* neutrophil activation, indicating the engagement of FcγRIV by anti-MPO IgG plays an important role in the pathogenesis of anti-MPO induced GCN. 2) Inhibitory effects of anti-FcγRIV antibody on anti-MPO induced activation of neutrophils suggests that blockade of FcγRIV engagement by ANCA may have a therapeutic role in ANCA disease.

Funding: NIDDK Support

SA-OR023

CD11b Activation Protects against Lupus Nephritis by Suppressing TLR-Dependent IFN Responses via AKT-FOXO3-IRF7 Samia Khan,[1] Mohd Hafeez Faridi,[1] Shehryar J. Khaliqdina,[1] David J. Cimbaluk,[1] Vineet Gupta.[1] *[1]Rush Univ Medical School; [2]NIAMS, NIH.*

Background: Genetic variations in the ITGAM gene (coding for CD11b) produce defective CD11b and associate with a risk for systemic lupus erythematosus (SLE, lupus) and lupus nephritis. Elevated level of IFN I in circulation is a heritable risk factor for SLE and promotes the immune dysregulation characteristic of this disease. Whether variations in ITGAM are linked to high IFN I and whether CD11b activation could be a therapeutic strategy is not known and is explored here.

Methods: We measured serum IFN I activity in 171 SLE patients and determined their *ITGAM* genotype to test for a direct link between *ITGAM* SNPs and the IFN I pathway. Given that ITGAM SNPs result in functionally deficient CD11b, we tested whether partial CD11b activation with small molecule agonist, leukadherin-1 (LA1), can reduce IFN I responses and determined the underlying mechanistic pathways. To test the efficacy of LA1 *in vivo*, we used the MRL/*lpr* mice that develop IFN I-dependent multi-organ lupus similar to human lupus with renal injury.

Results: We show that three *ITGAM* variants significantly associate with the elevated levels of IFN I in lupus, suggesting a direct link between reduced CD11b activity and elevated inflammation in patients. Partial CD11b activation with LA1 reduced IFN I responses and protected lupus-prone MRL/*lpr* mice from kidney injury. LA1-treated mice had reduced proteinuria, IgG renal immune complex deposition, and glomerular damage as compared to controls. CD11b activation reduced TLR-dependent pro-inflammatory signaling in leukocytes and suppressed IFN I signaling, via an AKT-FOXO3-IRF7 pathway. TLR-stimulated macrophages from CD11b SNP carriers showed increased basal expression of IRF7 and IFNB, as well as increased nuclear exclusion of FOXO3, which was suppressed by LA1.

Conclusions: LA1 suppresses TLR-stimulated overproduction of cytokines *in vivo*, which have been directly linked to exacerbation of lupus nephritis. These findings suggest that pharmacological CD11b activation should be explored as a potential novel therapeutic target in SLE, particularly in patients identified as carriers of specific genetic polymorphisms.

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SA-OR024

Endothelial NF-κB Blockade Abrogates Anti-MPO Antibody-Induced Glomerulonephritis Mira Choi,[1] Adrian Schreiber,[1] Claudia Eulenberg-Gustavus,[2] Claus Scheidereit,[3] Jan A.A.M. Kamps,[4] Ralph Kettritz.[1] *[1]Nephrology, Experimental and Clinical Research Center, Berlin, Germany; [2]Experimental and Clinical Research Center, Berlin, Germany; [3]Max-Delbrueck-Center for Molecular Medicine, Berlin, Germany; [4]Dept of Pathology and Medical Biology, Univ Medical Center Groningen, Groningen, Netherlands.*

Background: ANCA vasculitis is a highly inflammatory condition where ANCA-activated neutrophils interact with endothelium resulting in necrotizing vasculitis. We tested the hypothesis that endothelial NF-κB mediates necrotizing crescentic glomerulonephritis (NCGN) and can be therapeutically targeted.

Methods: P65 siRNA was formulated in liposomes conjugated with anti-E-selectin antibodies to target activated endothelial cells (EC). Mice were injected with low dose TNFa to upregulate E-selectin on EC, followed by SOS siRNA or control compound. Anti-MPO antibodies and LPS were injected 48h later for disease induction. After 7 days urine analysis was done by dipsticks, albuminuria. Glomerular crescents and necrosis were assessed by histology. Neutrophil and monocyte influx into the kidney were measured by flow cytometry. NF-κB activity was quantified in nuclear extracts using electrophoretic mobility shift assays using EMSA and by RT-PCR for TNFa mRNA.

Results: Retrospective analysis of kidneys from murine NCGN revealed that p50/p65 NF-κB is activated in affected kidneys, resulted in increased NF-κB gene transcription, correlated with crescent formation, and possibly involved the endothelial compartment. ANCA-stimulated primed neutrophils activated endothelial NF-κB in neutrophil:endothelial cell co-cultures. This resulted in increased transcription and protein production of NF-κB dependent genes, and promoted neutrophil adhesion to an endothelial monolayer. We used a passive anti-MPO antibody transfer model for NCGN and treated mice with p65 siRNA. Active treatment significantly reduced urine abnormalities, myeloid cell influx into the kidneys, and glomerular necrosis and crescent formation. Finally, increased phospho-p65 staining in glomeruli with active lesions indicates that NF-κB is also activated in patients with ANCA-associated NCGN.

Conclusions: We suggest that endothelial NF-κB contributes to NCGN and provides a therapeutic target.

SA-OR025

Transcriptome Analysis of CD4-Lymphocytes Specifically Deleted of NEMO or IKKβ in an Experimental Model of Rapid Progressive Glomerulonephritis

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Background: Experimental nephrotoxic nephritis (NTN) is a model for T-cell mediated human rapid progressive glomerulonephritis. T-cell stimulation leads to activation of transcription factors, such as NF-kappa B. Recently we published the role of a specific IKK2 (β)-inhibitor in this model. We therefore now examined T-cell specific ablation of IKK2 or NEMO.

Methods: T-cell specific ablation of IKK2 or NEMO was achieved through deletion of IKK2 or NEMO by Cre-recombinase under control of the CD4*cre* transgene. NTN-antiserum was injected and function, histology and kidney chemokines determined during a 10-days period. T cells, Th1, Th17 and Treg infiltration into the kidney were analysed by FACS. Nephritic CD4*cre* animals were used as controls. Transcriptome analysis was performed of CD4+ T-cells isolated from spleens before and after NTN induction.

Results: Nephritic CD4*cre*IKK2*fl/fl* and CD4*cre*NEMO*fl/fl* mice had an increase in albumin/creatinine-ratio at day 3 and increased glomerular crescents at day 10. Although the percentage of CD4+ T cells infiltrating kidneys was not different between the groups examined further analysis showed significantly reduced Tregs but a significant increase in Th1- and Th17-cells in CD4*cre*IKK2*fl/fl* and CD4*cre*NEMO*fl/fl* animals. As a spleen–kidney axis has been described recently next transcriptome analysis of CD4+ splenocytes was performed. Volcano plot revealed 97 genes differentially down- and 120 genes up-regulated in CD4+ splenocytes of nephritic mice. The results of DiRE analysis showed IKK2 and NEMO dependent differential transcription factors activation.

Conclusions: Our data demonstrate that ablation of IKK2 or NEMO specifically in CD4+ T-cells significantly increased Th1 and Th17 cells infiltrating kidneys after NTN. We have identified genes involved in T cell differentiation that were differentially expressed between IKK2 and NEMO deficient CD4+ T-cells. Better understanding the role of IKK2 and NEMO in T-cell regulation will help to recognize the role of IKK2- and NEMO- kinase inhibitors in patients with glomerulonephritis.

Funding: Government Support - Non-U.S.

SA-OR026

Therapeutic Induction of Antigen Specific Tolerance in MPO-ANCA GN Using MPO-Conjugated Apoptotic Splenocytes

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Background: Loss of tolerance to myeloperoxidase (MPO) results in MPO-ANCA associated glomerulonephritis (MPO-ANCA GN). Splenic clearance of senescent leukocytes by apoptosis induction is a homeostatic pathway and maintains self-tolerance. We sought to co-opt this pathway by injecting apoptotic MPO peptide conjugated splenocytes (MPO-Ap-Sp) to induce MPO tolerance in MPO-ANCA GN.

Methods: Murine Sp underwent simultaneous $MPO_{409-428}$ (the nephrogenic MPO peptide) or control, $OVA_{323-339}$ conjugation and apoptosis induction *ex vivo* using ethylenecarbodiimide; MPO-Ap-Sp and OVA-Ap-Sp respectively. MPO autoimmunity was induced by $MPO_{409-428}$ immunization and GN triggered by a subnephritogenic dose of anti-GBM Ig.

Results: Treatment of mice with MPO-Ap-Sp prior to MPO-ANCA GN attenuated MPO autoimmunity compared with control OVA-Ap-Sp mice (MPO induced DTH swelling; 0.11±0.02 vs 0.02±0.01Δmm P<0.05) and GN (43±5% of glomeruli with segmental necrosis [gsn] vs 19±1% P<0.05). Treatment of mice with established MPO autoimmunity immediately prior to inducing GN also afforded significant protection (gsn; 31±4 vs 44±4% P<0.05). Adoptive transfer of CD4+ cells from mice receiving MPO-Ap-Sp to mice with established MPO autoimmunity significantly decreased induced GN compared to mice receiving CD4+ cells from OVA-Sp treated mice (gsn; 45±4% vs 23±3% P<0.05). Confirming that MPO-Ap-Sp induces antigen specific suppressive CD4+ cells. The requirement for Tregs in mediating MPO-Ap-Sp protection against GN was confirmed by comparing GN in 1) Treg depleted mice (anti-CD25 mAb) receiving MPO-Ap-Sp, 2) Control Treg intact (irrelevant mAb) receiving MPO-Ap-Sp and 3) Untreated mice developing MPO-ANCA GN. Untreated mice developed GN with 46% gsn, not significantly different from mice given MPO-Ap-Sp but depleted of Tregs (46% gsn) whereas Treg intact mice given MPO-Ap-Sp were significantly protected (24% gsn, P<0.05).

Conclusions: MPO-Ap-Sp is a preventative and therapeutic in experimental MO-ANCA GN by enhancing antigen specific tolerance mediated by Tregs.

Funding: Government Support - Non-U.S.

SA-OR027

The Role of Th1 and Th17 CD4 T Cells in Experimental Autoimmune Myeloperoxidase ANCA Associated GN

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Background: Current evidence suggests that CD4 T helper (Th) subsets, Th1 and/or Th17 direct MPO-ANCA GN. Defining the dominant cytokines directing this disease allows for therapeutic targeting using emerging biologicals.

Methods: Mice deficient in Th1 (IL-12p35; $p35^{-/-}$) and Th17 capacity (IL-23p19; $p19^{-/-}$) were immunized with MPO and GN triggered early (day 16) and late (day 28) with a low dose of anti-GBM Ig and culled 4 days later. Biologicals targeting the dominant cytokines (α-p35 and α-p19 monoclonal antibodies [mAb]) directing each phase were then assessed as therapeutics immediately prior to triggering GN.

Results: Early in the development of MPO autoimmunity (day 20), $p19^{-/-}$ mice were protected from the development of GN (albuminuria; 297.0±33.9vs421.1±44.5 μg/24hr and glomerular segmental necrosis; 11±2 vs 34±7%, all $P<0.05$) compared to WT mice, wherease $p35^{-/-}$ mice were not protected from MPO-ANCA GN (albuminuria; 282.9±20.6 vs WT mice 304.3±21.2 μg/24hr, $P=0.5$). Administration of α-p19 mAb starting day 16 attenuated induced GN (albuminuria; 105.3±28.2 vs IgG2a treated controls 325.4±60.5 μg/24hr, $P<0.01$). When MPO autoimmunity was established (day 32), Th1 was dominant as $p35^{-/-}$ mice had reduced MPO autoimmunity (MPO DTH swelling and *ex vivo* MPO stimulated draining lymph node cell proliferation) and attenuated GN (significantly reduced glomerular leukocytes, segmental necrosis and albuminuria). Therapeutic administration of α-p35 mAb at day 28 also attenuated GN. In $p19^{-/-}$ mice, MPO autoimmunity was not reduced (similar to WT mice), however glomerular leukocytes and albuminuria were reduced. Subsequent experiments show that IL-23 and the Th17 axis play a critical innate immune role in recruiting glomerular neutrophils and depositing MPO initiating GN, accounting for the protection from GN observed in $p19^{-/-}$ mice.

Conclusions: Established MPO autoimmunity is Th1 dominant while Th17 is important early in establishing adaptive MPO autoimmunity and playing an innate immune role in facilitating glomerular neutrophil infiltration and deposition of MPO required to induce MPO-ANCA GN.

Funding: Government Support - Non-U.S.

SA-OR028

Interferon Regulatory Factor 5 Promotes Disease in the FcgRIIB-/- Mouse Model of Lupus through TLR7-Dependent and -Independent Pathways

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Background: Polymorphisms in interferon regulatory factor 5 (IRF5) are strongly associated with an increased risk of developing systemic lupus erythematosus. We previously demonstrated that IRF5 is required for disease development in the $FcgRIIB^{-/-}$ lupus mouse model. The exact pathways through which IRF5 acts to promote disease in this model are not known. As IRF5 plays a central role in signaling through TLR7, a TLR involved in pathogenesis in other lupus models, we investigated the relative effects of TLR7 deficiency, and combined TLR7 and IRF5 deficiency in the $FcgRIIB^{-/-}$ mouse model, on disease manifestations as well as on the severity of lupus nephritis.

Methods: We generated the following experimental groups of $FcgRIIB^{-/-}$ female mice: $TLR7^{+/+}IRF5^{+/+}$ mice, $TLR7^{+/+}IRF5^{-/-}$ mice, $TLR7^{-/-}IRF5^{+/+}$ mice and $TLR7^{-/-}IRF5^{-/-}$ mice. Mice were analyzed at the age of 8 months. Experimental groups were compared for disease manifestations including autoantibody production, serum IgG levels, and kidney disease severity.

Results: We found that TLR7 deficiency reduces disease severity and that TLR7 is required not only for the production of autoantibodies against RNA-containing autoantigens but also for autoantibodies against double-stranded DNA. $FcgRIIB^{-/-}$ mice deficient in both TLR7 and IRF5 developed less disease than mice deficient in TLR7 alone, with lower titers of anti-RNA autoantibodies, lower levels of the pathogenic IgG isotypes, and less severe renal disease.

Conclusions: We have identified TLR7-dependent and TLR7-independent roles for IRF5 in the development of lupus autoimmunity and lupus nephritis. $FcgRIIB^{-/-}$ mice deficient in both TLR7 and IRF5 developed less disease than mice deficient in TLR7 alone, with lower titers of anti-nuclear autoantibodies, lower levels of the pathogenic IgG isotypes, and less severe renal disease. This suggests that therapies targeting IRF5 may offer some additional benefit compared to therapies targeting only TLR7 for the treatment of lupus and lupus nephritis.

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SA-OR029

Treatment with the Natural VEGF Inhibitor Soluble Flt-1 Reduces Renal Complications, Endothelial Activation and Inflammation in Long-Term Type 1 Diabetic Mice Pascal Bus, Marion Scharpfenecker, Jan A. Bruijn, Hans J. Baelde. *Pathology, LUMC, Leiden, Zuid-Holland, Netherlands.*

Background: It has been shown that VEGF-A is involved in diabetic nephropathy (DN). Animal models for diabetic nephropathy have shown that glomerular VEGF-A levels are increased, and that reducing VEGF-A is beneficial in preventing renal complications. Besides its role in angiogenesis, VEGF-A is also involved in endothelial activation and macrophage migration. The aim of the current study was therefore to investigate if treatment with the natural VEGF-A inhibitor sFlt-1 reduces inflammation and endothelial activation.

Methods: Diabetes was induced in C57BL/6 mice with injection of streptozotocin. After five weeks of diabetes mice were transfected with a sFlt-1 construct via electroporation. 15 weeks after the induction of diabetes mice were sacrificed. Collection of urine and blood was performed at baseline, and subsequently every other week. Albuminuria was measured using Rocket Electrophoresis. Kidneys were sectioned and stained for PAS, collagen IV, fibronectin, wt1, fa-11, tnf-a, pecam-1, vcam-1 and icam-1, and quantified using ImageJ. One-way ANOVA was performed to measure differences between groups. Differences with a probability level ($p < 0.05$ were considered statistically significant.

Results: Diabetic mice transfected with sFlt-1 had lower urine albumin/creatinine ratios compared to mice with diabetes alone and reduced glomerular damage ($p<0.001$). In addition, vcam-1 and icam-1 ($p<0.001$), the number of glomerular macrophages ($p<0.01$) and glomerular tnf-alpha expression ($p<0.001$), were reduced to basal levels in sFlt-1 treated diabetic mice compared to control diabetic mice.

Conclusions: Our results show that inhibiting VEGF-A levels by sFlt-1 has beneficial effects on inflammation, besides the effect on renal function and morphology. These effects could be attributed to a decreased number of glomerular macrophages, potentially due to the inhibitory effect of sFlt-1 on macrophage migration and by reducing endothelial activation.

SA-OR030

Absence of the Endogenous A2B Adenosine Receptor Increases Severity of Immune-Associated Inflammation Gabriela E. Garcia,[1] Luan D. Truong,[2] Kelley S. Brodsky,[3] Holger Eltzschig,[3] Richard J. Johnson.[1] *[1]Medicine, Univ of Colorado Denver, Aurora, CO; [2]Pathology, The Methodist Hospital, Houston, TX; [3]Anesthesiology, Univ of Colorado Denver, Aurora, CO.*

Background: Adenosine functions as a signaling molecule through the activation of four adenosine receptors. During conditions in which adenosine levels are elevated such as hypoxia, ischemia or inflammation A_{2B} adenosine receptor (A_{2B}AR) increases ischemia tolerance and attenuates acute inflammation.

Methods: Using an A_{2B}AR knockout/reporter gene-knock-in, we investigated the role of A_{2B}AR in kidney injury in the cytokine-dependent anti-glomerular basement membrane glomerulonephritis (anti-GBM GN).

Results: We found that A_{2B}AR is slightly expressed in the vascular pole and that in nephritic kidneys A_{2B}AR expression is highly induced in the vascular pole and also in glomeruli and arteries. Mice with less kidney injury expressed less A_{2B}AR. In contrast, higher expression of A_{2B}AR expression was observed with more kidney injury, suggesting that increased A_{2B}AR is a counter-regulatory response to inflammation. Importantly, nephritic kidneys from A_{2B}AR -/- mice showed more severe kidney injury compared with those in WT control mice. Glomerular proliferation, crescent formation, tubulointerstitial injury and inflammatory cell infiltration were significantly higher in A_{2B}AR -/- mice. A_{2B}AR promoter contains a binding site for the transcription factor hypoxia-inducible factor (HIF)-1 that increases A_{2B}AR expression. To investigate if HIF-1 is induced in GN and could be responsible for A_{2B}AR upregulation, we used a HIF-1α reporter mouse (ODD-Luc) and found that HIF-1 is induced in nephritic kidneys as early as day 3 after induction of the disease. Next, to determine if endothelial A_{2B}AR mediates kidney protection in GN, we compared mice with deletion of A_{2B}AR in endothelial cells with controls. Mice with endothelial-specific A_{2B}AR-/- showed increased in disease susceptibility. Moreover, use of an A_{2B}AR agonist significantly attenuated GN.

Conclusions: These findings suggest that A_{2B}AR is a natural mechanism of inhibition of inflammation and protection from tissue damage.

Funding: NIDDK Support

SA-OR031

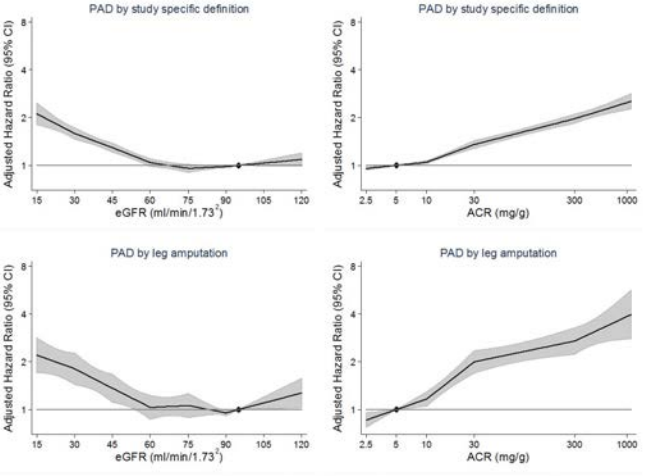
eGFR, Albuminuria, and Future Risk of Peripheral Artery Disease: The Chronic Kidney Disease Prognosis Consortium Kunihiro Matsushita, Shoshana Ballew, Josef Coresh, Hisatomi Arima, Johan Arnlov, Massimo Cirillo, Natalie Ebert, Jade S. Hiramoto, Michael Shlipak, Frank L.J. Visseren, Ron T. Gansevoort, Csaba P. Kovesdy, Varda Shalev, Mark Woodward, Florian Kronenberg. *Chronic Kidney Disease Prognosis Consortium.*

Background: Peripheral artery disease (PAD) is one of the most common cardiovascular outcomes in patients on dialysis. However, the full spectrum associations of eGFR and albuminuria with future PAD risk are yet to be investigated.

Methods: We studied 784,342 participants without a history of PAD from 13 cohorts. Cox models were used to quantify the associations of creatinine-based eGFR and urine albumin-to-creatinine ratio (ACR) with incident PAD (composite of hospitalizations with PAD diagnosis, intermittent claudication, leg revascularization, and leg amputation) beyond potential confounders such as diabetes. We also evaluated whether eGFR and ACR improve PAD risk prediction.

Results: There were 19,574 PAD cases over a median follow-up of 3.4-14.9 years across cohorts. Both low eGFR and high ACR were associated with PAD risk independently of each other and known PAD risk factors (Figure). Of note, the association of ACR appeared to be more evident with leg amputation than overall PAD. Both eGFR and ACR improved PAD risk discrimination beyond known risk factors (Δc-statistic: 0.013 [95% CI: 0.011-0.015] and 0.008 [0.006-0.010], respectively). Risk discrimination for leg amputation was improved with ACR (Δc-statistic: 0.037 [0.024-0.050]) but not necessarily with eGFR (0.012 [-0.001-0.025]).

Conclusions: Both low eGFR and high ACR were independently associated with future PAD risk and significantly improved its prediction. ACR was particularly relevant to leg amputation, even independently of diabetes. These results suggest the usefulness of CKD measures to identify patients who are at high risk of PAD and may benefit from PAD examination, monitoring, and prevention.



Adjusted for age, sex, race, smoking, diabetes, systolic blood pressure, antihypertensive drugs, total and high-density lipoprotein cholesterols, history of coronary disease, stroke, and heart failure, and each CKD measure.

Funding: NIDDK Support

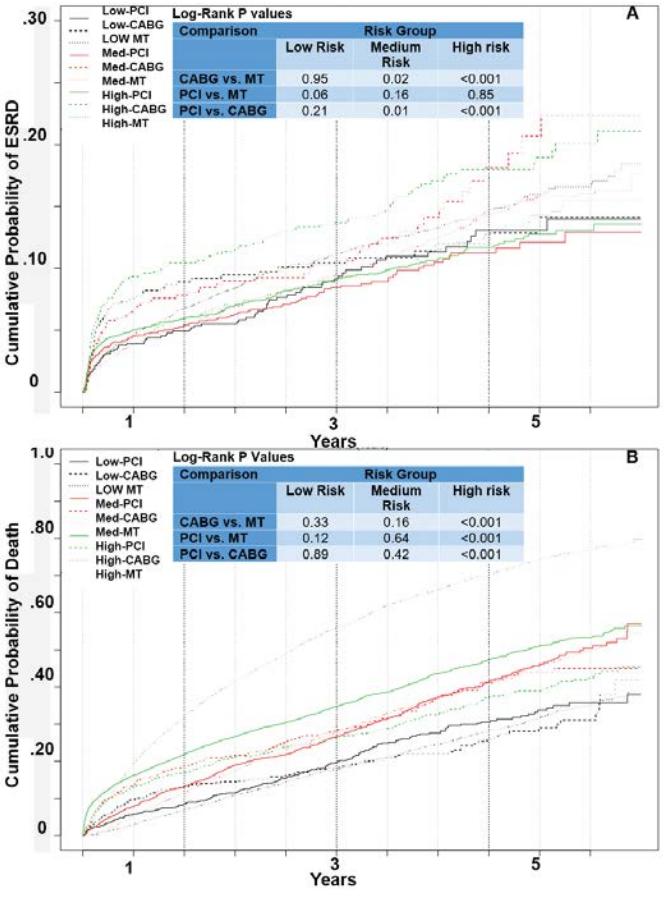
SA-OR032

ESRD and Mortality after Medical Therapy Compared with Percutaneous and Surgical Coronary Revascularization in Individuals with CKD at Low, Medium, or High Cardiovascular Risk David M. Charytan,[1] Tanya Natwick,[2] Craig Solid,[2] Shuling Li,[2] Charles A. Herzog.[2] *[1]Brigham & Women's Hospital, Boston; [2]Chronic Disease Research Group, MMRF, Minneapolis.*

Background: Prior analyses suggest that medical therapy (MT) is inferior to percutaneous (PCI) or surgical coronary revascularization (CABG) for the treatment of coronary disease in individuals with CKD, but did not assess ESRD risks and may be confounded by definition of MT as the absence of revascularization as well as failure to stratify by baseline cardiovascular (CV) risk.

Methods: CV risk groups were defined in the 2007-2012 Medicare 20% sample. Low risk: angiography or stress testing without prior CV disease (CVD); Medium risk: stress test or angiography with prior CVD; High risk: admission for acute coronary syndrome (ACS); CKD and ESRD were defined by diagnostic codes, and PCI and CABG as procedures within 60 days of risk group entry. MT was defined as use of new CV medications.

Results: For low risk pts 1000 had PCI, 571 CABG, and 6848 MT. For medium risk 1751 PCI, 718 CABG and 9670 MT. For high risk 4542 PCI, 1481 CABG and 8287 MT. Mortality and CV outcomes increased across risk groups, consistent with excellent discrimination of our metric. Cumulative probability of ESRD was similar with CABG and MT in the low risk group, but was worse with CABG in medium and high risk groups. Notably, ESRD probability was similar with PCI and MT in all groups (figure 1) . Mortality rates per hundred patient years were lowest with MT in the low risk group—PCI 9.1, CABG 8.9, MT 8.1--and medium risk groups—PCI 13.5, CABG 14.6, MT 13.2, but was markedly better with CABG or PCI in high risk patients—PCI 18.4, CABG 13.1, MT 33.5.



Conclusions: MT, PCI and CABG benefits in CKD vary by baseline CV risk and may be equivalent in low or moderate risk. CABG is associated with improved survival but also increased ESRD risk compared to MT after ACS.

Funding: Other NIH Support - NHLBI

SA-OR033

Renal Impairment and Stroke: The INTERSTROKE Study Andrew Smyth,[1,2] Martin O'Donnell,[1,2] Michelle Canavan,[1] Sumathy Rangarajan,[2] Salim Yusuf.[2] *[1]HRB Clinical Research Facility Galway, National Univ of Ireland, Galway, Ireland; [2]Population Health Research Inst, McMaster Univ, Hamilton, ON, Canada.*

Background: Renal impairment and stroke share pathogenic mechanisms and risk factors, particularly hypertension. Previous studies report conflicting associations between renal impairment and stroke. In these analyses, we explore if renal impairment is an independent risk factor for stroke.

Methods: INTERSTROKE is a large, case-control study in 32 countries in Asia, America, Europe and Africa. Cases were defined as acute first stroke and were age and sex matched to controls without a history of stroke (hospital or community based). We include participants with available serum creatinine measurement, the CKD-EPI formula was used to estimate GFR and renal impairment defined as eGFR<60ml/min/1.73m^2. Multivariable-adjusted conditional logistic regression was used to explore the association between renal impairment and stroke.

Results: Of 21,127 participants, 10,610 were cases and 10,517 were controls. Mean age was 62.3 (13.4) years and 59.6% (n=16,039) were male. Mean eGFR was 79.9 (23.5) ml/min/1.73m^2 and 20.3% (n=4,296) had renal impairment, with higher prevalence in cases (23.4%, n=2,477) than controls (17.3%, n=1,819) (p<0.01). After adjustment for age, sex, ethnicity, hypertension, diabetes, cardiovascular disease, physical activity, waist hip ratio, diet, antihypertensives, analgesics and anti-inflammatories, renal impairment was associated with increased odds of all stroke (OR 1.25 [1.15-1.36]), ischemic stroke (OR 1.17 [1.06-1.29]) and intracerebral hemorrhage (OR 1.50 [1.25-1.79]). The association was similar between men (OR 1.28 [1.14-1.44]) and women (OR 1.22 [1.07-1.38]), but significant only in those <65 years of age (OR 1.73 [1.50-2.00]). Overall, there was evidence of a dose response for all stroke: eGFR>90 (Reference), eGFR 60-90 (OR 0.94 [0.87-1.03]), eGFR 30-60 (OR 1.13 [1.01-1.25]) and eGFR<30 (OR 2.01 [1.59-2.55]).

Conclusions: We report that renal impairment is associated with an increased risk of in the largest case-control study of stroke with evidence of a dose response. Importantly, there was no effect modification by gender, but those <65years of age were most vulnerable.

SA-OR034

The Incidence of Atrial Fibrillation by Chronic Kidney Disease Stage and Proteinuria Amber O. Molnar,[1] Anan Bader Eddeen,[5] Robin Ducharme,[5] Amit X. Garg,[5,6] Ziv Harel,[4] Megan K. Mccallum,[5] Jeffrey Perl,[4] Ron Wald,[4] Manish M. Sood.[2,3] *[1]Nephrology, McMaster Univ, Hamilton, ON, Canada; [2]Nephrology, Univ of Ottawa, Ottawa, ON, Canada; [3]Epidemiology, Ottawa Hospital Research Inst, Ottawa, ON, Canada; [4]Nephrology, St. Michael's Hospital, Univ of Toronto, Toronto, ON, Canada; [5]Inst for Clinical Evaluative Sciences, Ottawa, ON, Canada; [6]Medicine and Epidemiology, Western Univ, London, ON, Canada.*

Background: Prior studies examining the association of CKD with incident atrial fibrillation (AF) are limited by heterogeneous definitions of CKD. Many studies define CKD as a dichotomous outcome and most fail to include albuminuria, which is an important component of new staging systems for CKD.

Methods: In this retrospective cohort study (2002-2015), we grouped 736,666 adults ≥40 years of age with no prior history of AF by eGFR (≥90, 60 to <90, 45 to <60, 30 to <45, 15 to <30, or <15 mL/min per 1.73 m^2) and urine albumin-to-creatinine ratio (ACR >300, 30-300 or <30 mg/g) to examine the incidence of new onset AF. Cox models were used to estimate the hazard ratios (HR) for AF. Patients were censored upon death, dialysis or end of follow up.

Results: Median follow up 6 years. 45,499 (6.2%) patients developed AF, 62,243 (8.4%) died and 6,667 (0.9%) patients required dialysis. The incidence rate of AF increased more than 40 fold across declining eGFR and increasing ACR groupings (eGFR >90/ACR <30: 3.29 per 1000 person-years; eGFR <15/ACR >300: 137.3 per 1000 person-years). In adjusted models using the eGFR >90 and ACR <30 grouping as the referent, patients with an eGFR=15-<30 mL/min per 1.73 m^2 had adjusted HR's for AF of 2.4 (95% CI, 2.2-2.6) for the lowest ACR group and 5.5 (95% CI, 4.5-6.7) for the highest ACR group. Patients with an eGFR >90/ACR >300 had an adjusted HR of incident AF of 3.9 (95% CI, 2.9-5.4), higher than the adjusted HR of 2.6 (95% CI, 1.7-3.9) for patients with an eGFR <15/ACR <30. Urine ACR altered the association of eGFR with incident AF (p<0.001).

Conclusions: This study shows that declining eGFR and increasing albuminuria each independently increase the risk of AF. Strategies for the prevention of AF should consider CKD, defined by both eGFR and urine ACR, as a risk factor for AF.

Funding: Government Support - Non-U.S.

SA-OR035

CKD Modifies the Association of Brain Natriuretic Peptide (BNP) and High Sensitivity-Troponin T (TnT) with CV Events and Death L. Parker Gregg,[1,2] Xilong Li,[1] Beverley Adams-Huet,[1] James Delemos,[1] Susan Hedayati.[1,2] *[1]UT Southwestern; [2]Dallas VA, TX.*

Background: Few data exist assessing associations of traditional cardiac biomarkers and outcomes in non-dialysis CKD patients. We evaluated whether associations between BNP and N-Terminal-pro-BNP (NT-BNP) ≥75th percentile for sex and TnT ≥3 ng/L with death and CV events were modified by CKD in 3,303 asymptomatic Dallas Heart Study participants followed for 10 years.

Methods: Cox proportion hazards assessed associations between biomarkers and all cause death or CV death/event, adjusted for age, sex, race, diabetes, hypertension, smoking, total and HDL cholesterol. Effect modification of CKD (eGFR<60 mL/min/1.73m^2 or ACR≥17 mg/g in men or ≥25 mg/g in women) was significant if interaction p<.1.

Results: The cohort was 50% Blacks, 31% Caucasians, 17% Hispanics, and 2% other races. Compared to 3,014 non-CKD, 289 CKD patients were older with a higher percentage of Blacks and diabetics. Proportions with stages 1, 2, 3, and 4-5 CKD were 50, 26, 20, and 3%. There were 302 deaths and 224 CV deaths/events. Of non-CKD patients 11% died and 6% had CV death/event vs. 42% and 29% of CKD patients, p<.0001 for both. The interaction between BNP and CKD on death was significant so that the aHR was intensified and significant in CKD but not significant in the non-CKD group. CKD also modified associations of BNP and TnT with CV death/event, with stronger associations in CKD (**Table**).

Conclusions: BNP, NT-BNP, and TnT provide independent prognostic information in early stage CKD, with stronger associations for BNP and TnT in CKD than non-CKD. Future studies should investigate whether these biomarkers differentially add to the prognostic ability of traditional CV risk factors in asymptomatic CKD patients.

Outcome	Main Effects aHR (95% CI)	No CKD	CKD
All-Cause Death			
BNP	1.32 (1.03, 1.68)	1.04 (0.77, 1.41)	2.11 (1.39, 3.21)*
NT-BNP	2.14 (1.67, 2.72)	1.90 (1.43, 2.53)	2.93 (1.82, 4.72)
TnT	1.67 (1.27, 2.21)	1.74 (1.29, 2.36)	1.45 (0.87, 2.44)
CV Death/Event			
BNP	1.92 (1.46, 2.52)	1.61 (1.17, 2.23)	3.02 (1.82, 5.01)*
NT-BNP	2.64 (2.01, 3.48)	2.54 (1.84, 3.50)	2.96 (1.73, 5.05)
TnT	1.83 (1.34, 2.52)	1.62 (1.15, 2.30)	3.17 (1.53, 6.56)*

*Interaction p<.1.

Funding: Other NIH Support - The Dallas Heart Study was supported by a grant from the Donald W. Reynolds Foundation and by USPHS GCRC grant #M01-RR00633 from NIH/NCRR-CR. Supported in part by grant UL1TR001105 from the National Center for Advancing Translational Sciences, National Institutes of Health

SA-OR036

The Association between Rate of Change in Albuminuria and Clinical Outcomes Min Jun,[1,2] Matthew T. James,[1] Braden J. Manns,[1] Marcello Tonelli,[1] Jianguo Zhang,[1] Vlado Perkovic,[2] Brenda Hemmelgarn.[1] *[1]Univ of Calgary, Canada; [2]George Inst for Global Health, Australia.*

Background: Change in albuminuria may have important prognostic utility in determining the future risk of outcomes. We sought to assess the association between change in urine albumin-creatinine ratio (UACR) and the risk of acute myocardial infarction (AMI), end-stage renal disease (ESRD), and all-cause death.

Methods: We identified 170,515 adults (age ≥18 years) in Alberta, Canada, who had ≥2 outpatient UACR measurements (1-2 years apart) within a 2-year period between May 1, 2003 and March 31, 2012. Rate of change in UACR (during a 2-year period; mg/mmol/year) was defined based on 3 groups: 1) decrease (≥-4.6 decrease; 5th percentile of change), 2) stable (-4.6 to 6.1), 3) increase (≥6.1 increase; 95th percentile of change). Follow-up for outcome (AMI, ESRD, and all-cause death) ascertainment commenced at the last UACR measurement during the 2-year period (defined as baseline). We used adjusted Cox regression models to estimate the hazard ratio for each outcome, adjusting for sociodemographic information, baseline eGFR and UACR, and comorbidities at baseline.

Results: Over the outcome ascertainment period, 4100 (2.4%) AMI events, 849 (0.5%) ESRD events, and 14450 (8.5%) deaths occurred. Compared with stable UACR, increase in UACR was associated with 56%, 721%, and 50% higher risk of AMI, ESRD, and death, respectively.

Outcome	UACR change	Adjusted HRs	
		HR	95% CI
AMI	Decrease	1.08	0.95 – 1.22
	Stable (Reference)	**1.00**	-
	Increase	1.56	1.41 – 1.74
ESRD	Decrease	3.26	2.61 – 4.08
	Stable (Reference)	**1.00**	-
	Increase	7.21	5.90 – 8.81
All-cause death	Decrease	1.33	1.25 – 1.41
	Stable (Reference)	**1.00**	-
	Increase	1.50	1.42 – 1.58

However, decrease in UACR was also associated with greater risk for ESRD and all-cause death, resulting in a U-shaped relationship between UACR change and these outcomes.

Conclusions: Change in UACR over time is associated with future risk of clinically important outcomes. However, given the observed U-shaped relationship between albuminuria change and outcomes, its utility as a prognostic tool among high-risk patient groups requires further assessment.

SA-OR037

Adverse Events in Advanced Chronic Kidney Disease: The Chronic Renal Insufficiency Cohort Study Morgan Grams,[1] Wei Yang,[2] Casey Rebholz,[1] Xue Wang,[2] Anna C. Porter,[2] Lesley Inker,[2] Edward J. Horwitz,[2] James H. Sondheimer,[2] L. Lee Hamm,[2] Jiang He,[2] Matthew R. Weir,[2] Bernard G. Jaar,[1] Tariq Shafi,[1] Lawrence J. Appel,[1] Chi-Yuan Hsu.[2] *[1]Johns Hopkins Univ; [2]CRIC Study, Univ of Pennsylvania.*

Background: People with advanced chronic kidney disease (CKD) are at risk for the development of end-stage renal disease (ESRD), but also many other adverse outcomes, including cardiovascular disease (CVD) events and death. Determination of risk factors that explain the variability in prognosis and timing of these adverse outcomes can aid patient counseling and medical decision-making.

Methods: We followed 1,798 participants with eGFR <30 ml/min/1.73 m² in the Chronic Renal Insufficiency Cohort (CRIC) study for a median of 5.5 years, evaluating risks of ESRD, CVD (congestive heart failure, stroke, myocardial infarction, peripheral artery disease), and death.

Results: Baseline age of the cohort was 60 years; 46% were women, and 46% were African American. While 52.3% of participants progressed to ESRD during follow-up, the path by which this occurred varied by baseline patient characteristics. For example, the predicted 1-year probabilities for a 60-year old white woman with eGFR 30 ml/min/1.73 m², 1.8 grams/day of proteinuria, and no diabetes or CVD (risk characteristics similar to the average participant), were 3.3%, 4.1%, and 0.3%, for first developing CVD, ESRD, and death, respectively. For a 40-year-old African-American man with similar characteristics but higher systolic blood pressure, the corresponding 1-year probabilities were 2.4%, 13.2%, and 0.1%. For all participants, the development of ESRD or CVD increased the risk of subsequent mortality, with no differences by patient race or body-mass index.

Table. 1-year probability of remaining event-free, or first developing CVD event, ESRD, or death for various hypothetical patient scenarios

Scenario	Event-Free	CVD Event	ESRD Event	Death
40-year-old white man with diabetes*	85.3%	5.4%	9.2%	0.2%
40-year-old black man with high blood pressure (systolic 150 mmHg)	84.3%	2.4%	13.2%	0.1%
60-year-old white man with EF 35% and CVD	84.2%	12.3%	3.1%	0.4%
60-year-old black man with diabetes and 5 g/day proteinuria	78.1%	8.5%	12.4%	0.9%
60-year-old white woman	92.3%	3.3%	4.1%	0.3%
60-year-old black woman with diabetes and cardiovascular disease	86.9%	7.0%	5.3%	0.8%
70-year-old white woman with 0.1 g/day proteinuria	97.2%	2.0%	0.4%	0.4%

*Unless otherwise specified, other covariates include non-Hispanic ethnicity, eGFR 30 ml/min/1.73 m², systolic blood pressure of 130 mmHg, proteinuria of 1.8 g/day, EF of 50%, BMI of 30 kg/m², no cardiovascular disease, no diabetes mellitus, and a non-smoker.

Conclusions: With replication in additional cohorts, these results can help guide personalized approaches for managing patients with advanced CKD.

Funding: NIDDK Support

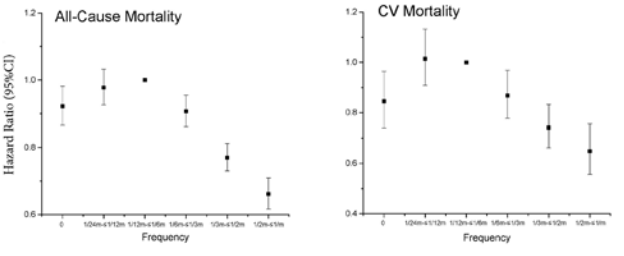
SA-OR038

Association of the Frequency of Pre-ESRD Medical Care with Post-ESRD All-Cause and CV Mortality Csaba P. Kovesdy,[1,3] Jun Ling Lu,[1] Miklos Zsolt Molnar,[1] Keiichi Sumida,[1] Praveen Kumar Potukuchi,[1] Elani Streja,[2] Kamyar Kalantar-Zadeh.[2] *[1]Univ of Tennessee Health Science Center, Memphis, TN; [2]Univ of California, Irvine, CA; [3]VA Medical Center, Memphis, TN.*

Background: Some studies found that receiving Nephrology care in the pre-ESRD period is associated with improved outcomes in dialysis patients. Less is known about the association between the frequency of pre-ESRD laboratory testing and post-ESRD mortality in incident ESRD patients.

Methods: We examined 23,089 US veterans who initiated RRT between 10/2007-09/2011, and had outpatient laboratory tests performed during the last two years prior to RRT (prelude). The association of the frequency of the combined measurement of serum creatinine, potassium and hemoglobin with post-ESRD all-cause mortality and cardiovascular (CV) mortality was examined in Cox proportional hazard regression models adjusted for socio-demographics, comorbidities, BP variability, and CV medication adherence.

Results: The mean age (SD) was 66.2 (11.3) years, and the mean estimated GFR (SD) was 46.8 (23.9) ml/min/1.73m² entering the 2-year prelude period. 32.3% of the cohort had the lab test trio performed between once-a-year to once every two years; 9.3% had no lab test trio measured during prelude, and 8.9% had the trio measured more often than every other month. Over a 2.5-year median follow-up period, 15,303 (66.3%) patients died (mortality rate: 260/1000 patient years, 95% CI: 256-264). More frequent lab testing was associated with lower post-ESRD mortality (Figure). The adjusted hazard ratio (95%CI) associated with lab testing done more than once every other month compared to once every 6-12 month was 0.66 (0.62-0.71). Associations were similar for CV mortality (Figure).



Conclusions: More frequent laboratory testing during the 2 years prior to RRT initiation is associated with lower post-ESRD all-cause and CV mortality.

Funding: NIDDK Support, VA Support

SA-OR039

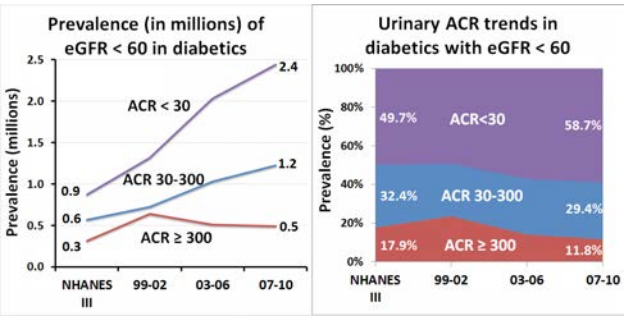
Changing Phenotype of CKD in Diabetes Mellitus (DM) and Its Implications Srini Beddhu,[1] Alfred K. Cheung,[1] Linda F. Fried,[2] Guo Wei,[1] R. E. Boucher,[1] Rabia Nadeem Kiani,[1] Julia Lewis,[3] Tom Greene.[1] *[1]Univ of Utah; [2]VA Pittsburgh; [3]Vanderbilt Univ.*

Background: Classic phenotype descriptions of CKD in DM are based upon studies conducted in the 80's and 90's. However, therapies for CKD in DM have evolved. We hypothesized that the phenotype and hence, implications of CKD in DM has changed in the US.

Methods: We examined the prevalence of CKD (eGFR < 60 ml/min/1.73 m²) and the distribution of urinary albumin-creatinine ratio (ACR) (mg/g) in DM in the US using National Health And Nutrition Examination Survey (NHANES) III (1988-1994) and recent

surveys (1999-2010). We also examined whether diabetics with eGFR< 60 and ACR < 30 compared to diabetics with eGFR ≥ 90 and ACR < 30 have ↑ risk of cardiovascular (CV) or renal events using data from NHLBI funded ACCORD Study. CV outcome was a composite of CV death, MI, CHF or stroke. Kidney outcome was a composite of 50% drop in eGFR, dialysis or serum creat >3.3 mg/dl.

Results: Prevalence of eGFR < 60 in DM has dramatically increased; in this population, nearly 60% have urinary ACR < 30 (fig).



This segment of the DM population is at ↑ risk of CV events but not CKD progression (table).

	CV composite		Kidney composite	
ACR and eGFR groups	Events /100 person-yrs	HR(95% CI)*	Events /100 person-yrs	HR(95% CI)*
ACR<30				
eGFR≥ 90	1.45	Ref	0.53	Ref
60-90	2.42	1.32(1.10, 1.59)	0.46	0.91(0.65, 1.29)
< 60	3.58	1.44(1.10, 1.89)	0.31	0.61(0.29, 1.29)
ACR ≥30				
eGFR≥ 90	3.62	2.12(1.74, 2.58)	0.63	1.08(0.72, 1.62)
60-90	4.85	2.12(1.75, 2.58)	0.85	1.49(1.02, 2.18)
< 60	6.27	2.34(1.82, 3.00)	1.79	3.17(2.02, 4.96)
*adjusted for age, gender, race, Rx arm, study network, CVD, CHF, retinopathy, HbA1C, DM duration, SBP, DBP, ACE/ ARB and statin use				

Conclusions: The phenotype of CKD in DM is changing. The most common phenotype (eGFR < 60 and ACR < 30) confers ↑ CV risk but not CKD progression risk.

Funding: NIDDK Support

SA-OR040

Glucose Targets for Renal, Mortality, and Cardiovascular Outcomes: A Meta-Analysis of Randomized Trials Marinella Ruospo,[1,2] Valeria M. Saglimbene,[1] Suetonia Palmer,[3] Salvatore De Cosmo,[4] Antonio Pacilli,[4] Jonathan C. Craig,[5] Giovanni F.M. Strippoli.[1,5,6] *[1]Diaverum Medical Scientific Office; [2]Amedeo Avogadro Univ of Eastern Piedmont; [3]Univ of Otago Christchurch; [4]Scientific Inst CSS; [5]Univ of Sydney; [6]Univ of Bari.*

Background: Blood pressure lowering and glucose control are used to reduce diabetes-associated disability including end-stage kidney disease. However, the benefits and harms of tight glycemic control on renal outcomes among patients with kidney disease are uncertain. We summarized the evidence in randomized clinical trials (RCTs) of intensive versus standard glycemic control for preventing the onset and progression of kidney disease among adults with diabetes.

Methods: A Cochrane systematic review with meta-analysis was conducted including trials in which adults with type 1 or 2 diabetes with and without kidney disease were randomly allocated to tight or less stringent blood glucose targets. Treatment effects were estimated using random-effects meta-analysis. Risks of bias were adjudicated using Cochrane methods.

Results: Eleven studies involving 29,140 patients were eligible. Trial follow up was 56.7 months on average. In moderate to high quality evidence, a tight glucose target conferred uncertain risks of serum creatinine doubling (relative risk (RR) 0.84, CI 0.59-1.18), ESKD (RR 0.88, CI 0.70-1.11); all-cause mortality (RR 0.99, CI 0.86 to 1.13), cardiovascular mortality (RR 1.19, CI 0.73-1.92), and sudden death (RR 0.82, CI 0.26-2.57). Tighter glycemic control reduced risks of nonfatal myocardial infarction (RR 0.82, CI 0.69-0.99), and onset (RR 0.85, CI 0.77-0.94) and progression of microalbuminuria (RR 0.50, CI 0.36-0.69).

Conclusions: Tight glycemic control for treatment of diabetes provided uncertain risks of ESKD, death and major cardiovascular events compared with less stringent glycemic control, while lowering risks of myocardial infarction and onset and progression of microalbuminuria. The long-term clinical benefit of glycemic management on microalbuminuria is uncertain until sufficiently powered RCTs evaluate hard renal outcomes.

SA-OR041

Generation and Analysis of KLHL3 Knockout Mice Emi Sasaki, Koichiro Susa, Takayasu Mori, Kiyoshi Isobe, Yuya Araki, Yuichi Inoue, Tatemitsu Rai, Shinichi Uchida, Eisei Sohara. *Nephrology, Tokyo Medical and Dental Univ, Bunkyo, Tokyo, Japan.*

Background: Mutations in with-no-lysine kinase 1 (WNK1), WNK4, Kelch-like 3 (KLHL3) and Cullin 3 (CUL3) genes are reported to cause PHAII. Recently, we generated KLHL3 $^{R528H/+}$ mice and demonstrated that mutant KLHL3 resulted in defective degradations of WNK1 and WNK4, leading to PHAII, indicating that KLHL3/CUL3 ubiquitin ligase complex interacts and degradates WNK kinases. However, pathophysiological roles of KLHL3 other than PHAII are still unclear.

Methods: To answer these questions, we generated two KLHL3-/- mice lines; conventional KLHL3-/- mice and KLHL3-/- mice that express β-gal under endogenous KLHL3 promoter in this study. Using these mice, we sought to determine the tissue distribution of KLHL3 and its role in regulating WNK protein level in each tissue.

Results: At first, we investigated the tissue distribution of KLHL3 using β-gal expression. Immunoblots of β-gal showed the strong expression in brain and kidney, and the lower expressions in eye, testis, heart, lung and pancreas. Strong LacZ staining was observed in hypocampus and distal tubules in brain and kidney, respectively. Next, we investigated the protein levels of WNK1, WNK3 and WNK4 in the whole tissues of KLHL3+/- and KLHL3-/- mice where KLHL3 expression was detected. In the brain and other tissues showing the lower expression levels of KLHL3, expression levels of WNK1, WNK3 and WNK4 were not increased in KLHL3+/- and KLHL3-/- mice. However, only in kidney, WNK1 and WNK4 were significantly increased in KLHL3-/- mice, but not in KLHL3 +/- mice. KLHL3-/- mice also showed PHAII-like phenotypes, but KLHL3+/- mice did not.

Conclusions: Our data clearly showed that the WNK protein levels in KLHL3-expressing tissues might not be governed only by KLHL3. Lack of PHAII phenotypes in KLHL3+/- mice clearly showed the heterozygous deletion of KLHL3 was not enough to cause PHAII in the kidney, indicating that PHAII phenotypes in KLHL3$^{R528H/+}$ heterozygous mice we previously observed are caused by the dominant-negative effect of R528H KLHL3 mutant. Dimer formation of wild-type and R528H KLHL3, which we could demonstrate, would explain the dominant-negative effect of this mutant.

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SA-OR042

KLHL3-Knockin Mice Featuring Pseudohypoaldosteronism Type II Do Not Correct the Phenotype of WNK4-Null Mice Chien-Ming Lin,[1,2] Chih-Jen Cheng,[3] Sung-Sen Yang,[2,3] Shih-Hua P. Lin.[2,3] *[1]Dept of Pediatrics, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; [2]Graduate Inst of Medical Sciences, National Defense Medical Center, Taipei, Taiwan; [3]Div of Nephrology, Dept of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan.*

Background: Enhanced SPAK/OSR1-NCC signal cascade caused by mutations in Kelch-like 3 (KLHL3) or Cullin3 (Cul3) involved in WNK1/4 ubiquitination is known to cause pseudohypoaldosteronism type II (PHAII). It remains unclear that which WNK kinases is the major regulator in the pathogenesis of KLHL3 mutation-causing PHAII.

Methods: We generated mutant KLHL3 ^{M131V} knockin mice (corresponding to human M78V)in BTB domain and WNK4 null mice. KLHL3^{M131V} mutant mice were crossed with WNK4 null mice. The genotype, phenotype, and the relevant protein expression in the kidneys were examined in these transgenic mice.

Results: Both heterozygous and homozygous KLHL3^{M131V} knockin mice exhibited typical feature of PHAII with hypertension (SBP: KLHL3$^{M131V/-}$ 118.3± 13.5 mmHg, KLHL3$^{M131V/ M131V}$119.4± 11.5 mmHg, WT 107.0± 11.3mmHg) with suppressed PRA (KLHL3$^{M131V/-}$ 4.5 ± 1.9 ng/mL/hr, KLHL3$^{M131V/ M131V}$3.8± 1.1 ng/mL/hr, WT 6.5 ± 1.4 ng/mL/hr), hyperkalemia (KLHL3$^{M131V/-}$ 5.5 ± 0.3 mmol/l, KLHL3$^{M131V/ M131V}$6.0 ± 0.6 mmol/l, WT 4.5 ± 0.3 mmol/l) with decreased FE_K, and mild metabolic acidosis. Although KLHL3 M131V protein expression was unchanged as wild type, marked increase in WNK1 and WNK4 expression and the phosphorylation of SPAK, ORS1 and NCC were observed in heterozygous and homozygous KLHL3 knockin mice. WNK4knockout mice exhibited all phenotypic features of Gitelman syndrome (GS) with an increased WNK1 expression but remarkably reduced SPAK, ORS1 and NCC phosphorylation. Of note, KLHL3$^{M131V/M131V}$, WNK4 $^{-/-}$double transgenic mice still showed the overwhelming phenotype of GS with an increased expression of WNK1 but a decreased phosphorylation of SPAK, ORS1 and NCC.

Conclusions: KLHL3 knockin mice featuring PHAII with increased expression of WNK1 and WNK4 fail to correct the GS phenotype of WNK4 null mice, indicating that WNK4 is the most paramount kinase in SPAK/OSR1-NCC cascade in the PHAII caused by KLHL3 mutation.

SA-OR043

Identification of the Cullin 3 Domain Responsible for Defective COP9 Signalosome Binding in Familial Hyperkalemic Hypertension Ryan J. Cornelius,[1] Chong Zhang,[2] Kayla J. Erspamer,[1] Jeffrey Singer,[3] Chao-Ling Yang,[1] David H. Ellison.[1] *[1]Oregon Health and Science Univ, Portland, OR; [2]Shanghai Jiao Tong Univ, Shanghai, China; [3]Portland State Univ, Portland, OR.*

Background: Familial hyperkalemic hypertension (FHHt) can result from mutations in cullin 3 (CUL3), which increase abundance of WNK kinases and activate the thiazide-sensitive NaCl cotransporter. CUL3 is a member of the cullin-RING ligase (CRL) family

that ubiquitinates proteins, targeting them for degradation. The mechanism by which deletion of exon 9 (CUL3 Δ403-459) leads to the disease is unknown, but an important feature in CRL activity is cycling between neddylated (active) and unneddylated (inactive) states. The COP9 signalosome (CSN) deneddylates CRLs utilizing the catalytically active subunit JAB1. It has been reported that the cullin 1 CSN-binding region contains the 4HB and α/β domains. Since exon 9 in CUL3 encodes the 4HB domain, we determined whether this region binds to the CSN and if the altered function of CUL3 Δ403-459 results from enhanced neddylation, caused by decreased CSN binding.

Results: Co-immunoprecipitation from HEK 293 cells of JAB1 with CUL3 or CUL3 Δ403-459 indicated that the mutant had lower binding affinity. Further, JAB1 and CUL3 constructs containing deletions in certain domains showed that removal of the α/β domain, adjacent to the 4HB domain, abrogated binding to JAB1; in contrast deletion of the 4HB domain itself did not. Suppression of JAB1 using siRNA resulted in enhanced neddylation of CUL3 and a lower abundance of KLHL3 protein. To determine whether neddylation has functional consequences, we used a neddylation-deficient CUL3 construct (CUL3 Δ403-459 K712R). The abundance of KLHL3 and WNK4 protein was higher and lower, respectively, with CUL3 Δ403-459 K712R compared to CUL3 Δ403-459.

Conclusions: The results demonstrate that (1) the CUL3 binding site for the CSN is located in the α/β domain; deletion of the 4HB domain must lead to less CSN binding by altering protein structure; and (2) the enhanced neddylation of CUL3 Δ403-459, caused by the lower affinity for the CSN, results in over activation of CUL3 leading to degradation of KLHL3 and a greater WNK abundance.

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SA-OR044

Roles of Cytoplasmic Hsp40 and Hsp70 Molecular Chaperones in NKCC2 Stability and Maturation

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Background: We recently showed that MAGE-D2 mutations causes polyhydramnios with prematurity and a severe but transient form of antenatal Bartter's syndrome associated with inappropriate expression of the sodium–chloride transporters NKCC2 and NCC (Laghmani et al, N Engl J Med. 2016 May 12;374(19):1853-63). Moreover, MAGE-D2 interacts specifically with heat shock protein Hsp40/DnaJB1, raising the possibility that MAGE-D2 promotes expression of the co-transporters through this cytoplasmic Hsp40. In support of this notion, using the yeast two-hybrid system, we identified Hsp40/DnaJB1 as a specific binding partner of NKCC2. Consequently, the aim of the present study was to investigate the role of Hsp40 in NKCC2 biogenesis.

Methods: Protein-protein interaction was assessed by co-immunopreciptation (CO-IP) assay. NKCC2 protein expression was monitored in transiently transfected OKP and HEK cells, using immunoblot and confocal imaging. NKCC2 stability was assessed by cycloheximide chase assay.

Results: CO-IP assay in renal cells showed that Hsp40 association involves only the immature form of NKCC2. Accordingly, immunocytochemistry analysis revealed that NKCC2 and Hsp40 co-localize at the ER. Hsp40 co-expression strikingly increased total cellular NKCC2 protein in a dose dependent manner. Cycloheximide chase assay showed that in cells over expressing Hsp40, NKCC2 stability and maturation are improved. Mutation of the conserved HPD motif of Hsp40 J-domain, that is essential for Hsp70 activation, abolished Hsp40 effect indicating that Hsp40-induced increase in NKCC2 maturation is Hsp70 dependent. Accordingly, similar to Hsp40, Hsp70 co-expression increased also strikingly NKCC2 expression and maturation.

Conclusions: Our data strongly suggest that Hsp40 and Hsp70 are crucial for the stability and maturation of NKCC2 . They suggest a model whereby, MAGE-D2 cooperates with Hsp40 and Hsp70 co-chaperones to protect NKCC2 from ER associated degradation and promote proper folding and maturation of the co-transporter.

Funding: Government Support - Non-U.S.

SA-OR045

The Basolateral Kidney Anion Exchanger 1 Regulates Tight Junction Integrity by Interacting with Claudin-4

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Background: Patients with distal renal tubular acidosis (dRTA) have impaired renal acid secretion and, as a consequence, abnormal bicarbonate reabsorption from their distal nephron. dRTA patients develop kidney stones, hypokalemia, hyperchloremia, nephrocalcinosis, metabolic acidosis and difficulties to thrive. Mutations in the SLC4A1 gene encoding the anion exchanger 1 can cause dRTA. Kidney anion exchanger 1 (kAE1) is a transmembrane Cl^-/HCO_3^- exchanger that is expressed in a-intercalated cells in the collecting duct. Using a membrane yeast two-hybrid assay, we found that kAE1 interacts with Claudin-4 (Cldn-4). Cldn-4 is a tight junction protein, which is expressed in many tissues including intercalated cells. Cldn-4 forms a paracellular Cl^- selective pore and has been implicated in Cl^- reabsorption from the collecting duct. We therefore hypothesized that a kAE1/Cldn-4 interaction regulates pH and electrolyte homeostasis in the distal nephron.

Methods: To confirm a close proximity between the two proteins, we performed immunofluorescence and proximity ligation assays. Immunoprecipitations were used to confirm the physical interaction. kAE1 function was assessed with BCECF-based assays. Finally, the integrity of tight junctions was examined using Ussing chambers.

Results: We observed co-localization between kAE1 and Cldn-4 in polarized murine inner medullary collecting duct cells. Immunoprecipitations confirmed the physical interaction. Cldn-4 over-expression did not affect kAE1 function. Upon kAE1 expression, there was a decrease in transepithelial electrical resistance and an increase in paracellular Cl^- & Na^+ permeability, indicating that expression of the basolateral anion exchanger altered the tight junction integrity. Finally, kAE1 effect on tight junction properties was independent of changes in intracellular pH.

Conclusions: Our results demonstrate a physical interaction between kAE1 and Cldn-4 and have uncovered an un-expected role of a basolateral anion exchanger on tight junction integrity, and possibly further on electrolyte homeostasis and blood pressure regulation.

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SA-OR046

High Na Diet Causes Increased Na Retention and Impaired Dipsogenic Response in HKα1 H,K-ATPase Knockout Mice

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Background: Purinergic regulation of the epithelial Na channel (ENaC) is an important mechanism that regulates external Na balance. Loss of this regulation contributes to salt-sensitivity and has been implicated in mineralocorticoid escape. ENaC activity is inversely related to dietary Na intake, in part, due to inhibitory purinergic signaling in the collecting duct (CD), with increasing Na intake stimulating luminal ATP secretion. We previously showed that Na reabsorption in CD of $HK\alpha_1$ H,K-ATPase null ($HK\alpha_1^{-/-}$) mice was benzamil-insensitive, and ENaC activity in $HK\alpha_1^{-/-}$ mice was uncoupled from Na intake. ENaC activity on a 2.0% Na (HS) diet was greater in the $HK\alpha_1^{-/-}$ versus wild-type (WT), and dietary Na did not normally modulate ENaC activity in the $HK\alpha_1^{-/-}$. Purinergic signaling of ENaC was abnormal in $HK\alpha_1^{-/-}$ mice, with markedly reduced urinary ATP that did not increase in response to the HS diet. ENaC activity in the $HK\alpha_1^{-/-}$responded normally to exogenous ATP, suggesting a pre-receptor defect. The present studies tested the contribution of this uncoupling at the whole animal level.

Methods: Total Na balance was measured in $HK\alpha_1^{-/-}$ and WT mice placed in metabolic cages and fed a normal Na diet for 7 days followed by HS for 7 days. Blood hematocrit and plasma Na and vasopressin (AVP) were measured in mice on Day 1 of the HS diet.

Results: On day 1 of the HS diet, $HK\alpha_1^{-/-}$ mice had three times greater Na retention ($p<0.01$) compared to WT and markedly impaired dipsogenic response (50% lower fluid intake vs. WT, $p<0.001$) with higher urine osmolality. Hematocrit and plasma Na and AVP were significantly greater in $HK\alpha_1^{-/-}$ than WT on the HS diet. During the entire period of HS feeding, Na retention in $HK\alpha_1^{-/-}$ was greater than WT (days 1, 2&4, $p<0.05$).

Conclusions: These results suggest an important role for the $HK\alpha_1$ subunit in the regulation of purinergic signaling in the CD. $HK\alpha_1$ is physiologically important in the acute regulation of Na balance, affects the dipsogenic response to a high NaCl diet, and is part of a previously undiscovered element in Na regulation in the CD.

Funding: VA Support

SA-OR047

A Missense Mutation in the Extracellular Domain of α-ENaC Causes Liddle Syndrome

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Background: Liddle syndrome or pseudoaldosteronism is an autosomal dominant form of hypokalemic hypertension that has been linked to mutations in the *SCNN1B* or *SCNN1G* gene, encoding the β- or γ-subunit of the epithelial sodium channel (ENaC). Here, we describe one generation of a family with Liddle syndrome due to a novel mutation in *SCNN1A* and functionally characterize the α-ENaC mutation.

Results: The proband (63-y.o. man) was referred because of unexplained hypertension (since age 26), hypokalemia, metabolic alkalosis, and suppressed plasma renin and aldosterone. Previous genetic testing had not identified mutations in *SCNN1B* or *SCNN1G*. Because of a positive family history for hypertension, whole-exome sequencing was performed and revealed a novel mutation in the amiloride-sensitive domain of α-ENaC. This missense mutation was identified in a highly conserved region of the extracellular domain of α-ENaC. Family analysis (5 siblings) identified one affected sister (hypertension, no hypokalemia) and showed that suppressed plasma renin and aldosterone completely segregated siblings with or without the mutation. Hypertension did not segregate because three other siblings also had (primary) hypertension. Open exome analysis did not identify additional causes of genetic hypertension in the family. A "triamterene test" was performed (adapted from the thiazide test) showing a 2-fold greater natriuresis to 100 mg triamterene (an ENaC blocker) in the two affected siblings than in healthy volunteers. Daily treatment with triamterene quickly normalized blood pressure and serum potassium in the affected siblings. Functional analysis of ENaC carrying the missense mutation in oocytes confirmed a channel gain-of-function (2-3-fold increase in Na^+ current), predominantly due to an increase in intrinsic activity of the channel.

Conclusions: We report the first mutation in the extracellular domain of α-ENaC causing Liddle syndrome. The mild phenotype correlates with the function studies. This mutation may be present in other unrecognized cases of hypertension with suppressed renin and aldosterone, and also provides novel insight in regulation of ENaC activity.

SA-OR048

Principal Cell Aerobic Glycolysis, Induced by ENaC-Mediated Lithium Entry, Likely Underlies Collecting Duct Remodeling Mohammad Alsady, Peter M.T. Deen, Theun de Groot. *Physiology, Radboud Univ Medical Center, Nijmegen, Netherlands.*

Background: Lithium, given to bipolar disorder patients, causes Nephrogenic Diabetes Insipidus (Li-NDI) and an increased intercalated/principal cell ratio of the collecting duct (CD remodeling). Whereas Li-NDI is due to downregulation of principal cell (PC) AQP2, The cause of CD remodeling is unknown, but has been ascribed to metabolic acidosis due to H-ATPase/H-K-exchanger inhibition in α-intercalated cells. However, as we showed that lithium induces PC proliferation, which might coincide with aerobic glycolysis-induced lactic acid formation, we investigated whether the latter process may underlie lithium-induced CD remodeling.

Methods: In Transwell grown polarized mouse collecting duct (mpkCCD) cells were exposed to LiCl on the apical (10 mM) and basolateral side (1 mM) for 1-2 days. C57BL6/J mice and rats were fed a normal diet with/without 40 mmol LiCl/kg for 10 and 28 days, respectively. 24-hrs water intake and urine output/osmolality was obtained. Kidneys were analyzed for remodeling.

Results: In mpkCCD cells and mice, lithium induced cell proliferation (increased PCNA levels) coincided with aerobic glycolysis (increased se/excretion of lactate elevated abundance of lactate dehydrogenase, and hexokinase-2, decreased ratio of phospho-pyruvate dehydrogenase (pPDH)/PDH). Lithium-increased urinary lactatewas absent in mice lacking the epithelial sodium channel ENaC, the PC entry site for lithium. Moreover, ENaC inhibition via amiloride in rats attenuated lithium-induced CD remodeling.

Conclusions: We show that ENaC-mediated lithium influx in principal cells induces aerobic glycolysis and that inhibition of principal cell lithium entry attenuates the extent of aerobic glycolysis and CD remodeling. Our data indicate that the lithium-induced aerobic glycolysis of principal cells and the consequent acidification of the micro-environment underlies CD remodeling.

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

SA-OR049

Dysregulation of Acid Base (H+/HCO3-) Transport Machinery in the Kidney Collecting Duct in Cystic Fibrosis: Role in the Pathogenesis of Metabolic Alkalosis Mujan Varasteh Kia,[1] Sharon L. Barone,[1,2] Alicia A. McDonough,[3] Jie Xu,[1] Kamyar A. Zahedi,[1,2] Manoocher Soleimani.[1,2] *[1]Dept of Medicine, Univ of Cincinnati, Cincinnati, OH; [2]Research Services, Veterans Affairs Medical Center, Cincinnati, OH; [3]Dept of Cell and Neurobiology, Univ of Southern California, Los Angeles, CA.*

Background: Patients with cystic fibrosis (CF) are prone to the development of metabolic alkalosis; however, the pathogenesis of this life threatening derangement remains unknown. We hypothesized that altered acid base transport machinery in the kidney collecting duct underlies the mechanism of impaired bicarbonate elimination in CF kidney.

Methods: CFTR knockout (CF) mice with the intestinal rescue were examined for acid base homeostasis in response to bicarbonate loading or salt restriction, as well as for the expression of bicarbonate transporters in the collecting duct.

Results: Baseline parameters, including acid-base status were comparable in CF and WT mice. Compared to WT animals, CF mice demonstrated a significant increase in their blood HCO_3^- concentration (21.87 in WT vs. 26.83 mEq/l in CF mice, $p<0.004$) and pH (7.33 in WT vs. 7.42 in CF mice, $p<0.003$) and exhibited impaired kidney HCO_3^- excretion (urine pH 8.10 in WT vs. 7.35 in CF mice, $p<0.002$) following a 3-day oral bicarbonate load. When subjected to salt restriction, CF mice developed a more noticeable increase in their blood HCO_3^- concentration (29.26 +/- 0.53 in CF mice vs. 26.72 +/- 0.80 mEq/l in WT; $p<0.05$). Immunofluorescence labeling demonstrated a profound reduction in the apical expression of the Cl^-/HCO_3^- pendrin in intercalated cells and the unexpected induction of the apical Na^+/H^+ exchanger, NHE3, and the basolateral $Na^+:HCO_3^-$ co-transporter, NBC-e1, in the principal cells of cortical collecting duct in CF mice.

Conclusions: We propose that patients with cystic fibrosis are prone to the development of metabolic alkalosis secondary to the inactivation of the bicarbonate secreting transporter, pendrin, and the transformation of principal cells into a bicarbonate absorbing system in the cortical collecting duct, specifically during volume depletion, which is a common occurrence in CF patients.

Funding: NIDDK Support, VA Support

SA-OR050

Metabolic Acidosis Enhances Innate Immune Defense against Urinary Pathogenic *E. coli* Hu Peng, Jeffrey M. Purkerson, George J. Schwartz. *Pediatrics, Univ of Rochester Medical Center, Rochester, NY.*

Background: Intercalated cells (ICs) of the kidney mediate H^+ and HCO_3 secretion, and anion exchange. Our laboratory recently reported in collecting ducts (CDs) of kidney that adaptation to metabolic acidosis is mediated at least in part by SDF-1 signaling via CXCR12 (JCI 125:4365, 2015). SDF-1 is a target gene of hypoxia-inducible transcription factor (HIF-1α), both of which are stimulated by acidosis.

Methods: To test the effect of acidosis on pH-independent antimicrobial activity in urine, we developed an assay for activity of antimicrobial peptide (AMPs) in rabbit urine utilizing a functional model of *ex vivo* Uropathogenic *Escherichia coli* (UPEC) infection. Overnight cultured UPECs were added to diluted normal and acidotic urines (pH adjusted to 7.0), incubated at 37°C for 10 h, and bacteria growth was monitored by measuring turbidity (OD) at 600nm.

Results: Acidosis induced expression of cathelicidin (2.8 fold ±0.48, n=4), neutrophil gelatinase-associated lipocalin (NGAL) (6 fold ±2.1 n=4), and rabbit defensin neutrophil peptide 5 (NP-5) mRNA (1.76 fold ±0.42, n=6) in the CCDs micro-dissected from rabbit kidney; there was also a large increase in NP-5 mRNA (5.8 fold ±1.1, n=6) in proximal tubule (PST). Growth was attenuated in acidotic urine compared to normal. Antibody mediated blockade of cathelicidin activity promoted UPEC growth in pH neutralized acidotic urine. Conventional qRT-PCR from 4 pairs of Dolichos biflorus agglutinin (DBA)-selected kidney CDs showed that metabolic acidosis induced cytokine mRNA expression for IL-1β, TNFα, and IL-6, 2-4 fold. A rabbit cytokine/chemokine/receptor PCR array from one pair of DBA-selected kidney CDs showed induction of chemokines CXCL8 (IL-18), CXC3L, tumor necrosis factor receptor superfamily member 11b (TNFRSF-11b), and LOC100354804, a permeability factor 2-like gene, 3-7 fold by acidosis.

Conclusions: Metabolic acidosis, possibly via activation of HIF-1α, induces expression and function of innate immune defense peptides as well as pro-inflammatory cytokine/chemokine expression in renal tubules.

Funding: NIDDK Support

SA-OR051

Kruppel-Like Factor 4 Is a Key Mediator of Renal Endothelial Injury in Antibody Mediated Rejection Chelsea C. Estrada, Edward P. Nord, Sandeep K. Mallipattu. *Medicine/Nephrology, Stony Brook Medicine, Stony Brook, NY.*

Background: Yearly mortality for patients with end-stage renal disease on dialysis is 5-times higher than their counterparts who are transplanted, however sustained graft survival is impeded by antibody-mediated rejection (ABMR) with the renal endothelium as the primary target. Mechanism(s) mediating endothelial injury in ABMR are unclear. Endothelial-associated transcripts (ENDATs), reflecting activation and injury were recently incorporated into diagnostic criteria for ABMR, and Krüppel-Like Factor(KLF4), a zinc-finger transcription factor, exhibited the highest expression by microarray in biopsies from ABMR compared to T-cell rejection (TCR). KLF4 is known to have anti-inflammatory and anti-thrombotic effects on endothelial cells in the cardiovascular system but its actions in the renal endothelium have not been delineated.

Methods: Immunofluorescence (IF) for KLF4 and isolectin B4 (endothelial marker) was performed in human and mouse control kidneys. Wild-type mice were injected with lipopolysaccharide (LPS) 10 ug/g IP or buffer and sacrificed at 48 hours. Human umbilical vein cells (HUVECs) were incubated with LPS or the endothelial specific lectin, concanavalin A (20 ug/ml, 30 minutes) followed by anti-concanavalin A, (200 ug, 6 hours).

Results: We demonstrated KLF4 has high baseline expression in all renal endothelial cells by IF. We observed a 4-fold increase in *KLF4* by rt-PCR in HUVECs treated with LPS, 1 and 10 ug/ml for 8 hours. Similarly, wild-type mice treated with LPS had a 3-fold increase in endothelial-specific expression of Klf4 as compared to controls by IF and rt-PCR. Both LPS groups exhibited an increase in the adhesion molecules *VCAM-1* and *ICAM-1*, confirming endothelial injury. Subsequently, in a model of antibody mediated endothelial injury, HUVECs incubated with concanavalin A followed by anti-concanavalin A, also demonstrated significant induction of *KLF4*. Finally, kidney biopsies from patients with ABMR demonstrated a significant increase in endothelial-specific expression of KLF4 compared to healthy donors, TCR, and non-rejecting acute kidney injury by IF.

Conclusions: Our data suggests that KLF4 is a key mediator of endothelial injury in ABMR.

Funding: Private Foundation Support

SA-OR052

Differences in Inflammation and Fibrosis in Deceased and Living Renal Donors Determine Long-Term Renal Function Montserrat M. Diaz Encarnacion, Elena Guillen-Gomez, Irene Silva, Iara Karlla Dasilva, Yolanda Arce, Jose Ballarin. *Fundacio Puigvert.*

Background: It is known that living donor (LD) transplants present better outcome than deceased ones (DD). Renal fibrosis and tubular atrophy (IF/TA) is the best predictor of renal function and it could be induce by chronic inflammation. The aim of this study is to analyze the influence of donors in renal outcome.

Methods: Pre-implantational (basal) and 4 month biopsies were analyzed by Remuzzi and Banff scores, respectively. Inflammation and fibrosis markers were quantified by qPCR and IHQ ammation. The aim of this study is to analyze the influence of donors in renal outcome.

Results: Our results show that basal inflammation measured by CD68 positive cells (24 mo, p=0.006 and 5 yr, p=0.005) and Remuzzi score (24 mo, p=0.0003; 5 yr, p=0.0468) correlate with medium- and long-term renal function in DD, whereas we did not found it in LD. At 4 months, Banff'05 inflammation (24 mo, p=0.010 and 5 yr, p=0.0233) and inflammatory and fibrosis markers in DD correlated with medium- and long-term renal function (IL-1β, 24 mo, p=0.0187 and 5 yr, p=0.0003; ICAM-1, 24 mo, p=0.0473 and 5 yr, p=0.0007; MCP-1, 24 mo, p=0.0212 and 5 yr, p=0.0011 and TNF-α, 24 mo, p=0.0209 and 5 yr, p=0.0202; TGF-β1, 24 mo, p=0.0026 and 5 yr, p<0.0001; fibronectin, 5 yr, p=0.0007). On the other hand, in LD, 4 months fibrosis but not inflammation, correlated with renal function only at 24 months, but none of the markers studied by qPCR did it. Moreover, sustained inflammation and fibrosis (Δ 4M-basal) correlated with medium- and long-term renal function (MCP1, p=0.0003; TNF-α, p=0.0241; IL-1β, p=0.0102 and ICAM-1, p=0.0026; TGF-β1, p= 0.0210; fibronectin, p=0.0258).

Conclusions: In conclusion, early and sustained inflammation in DD are predictors of long-term graft outcome and could be essential in dissimilarities between DD and LD renal outcome.

Funding: Government Support - Non-U.S.

SA-OR053

Loss of Regulatory Anti-Angiogenic Protease Activated Receptor-1 (PAR-1) Antibodies Associate with the Development of Metastatic Cancer Post Renal Transplantation and Patient Death

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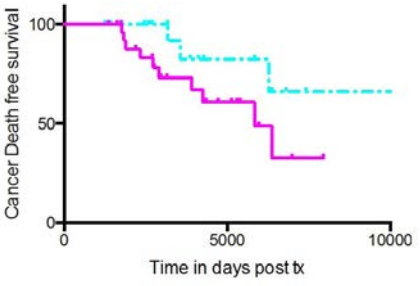
Background: VEGF is crucial for neoangiogenesis in tumors. The GPCR Protease-activated receptor 1 (PAR-1) is closely involved in VEGF regulation. We hypothesized that autoimmune GPCR targeting process may disturb VEGF induced angiogenesis.*in vitro* we found that PAR-1 is a novel activating autoantibody target. We then assessed the presence of PAR-1 autoantibodies in 20 Kidney Transplant Recipients (KTR) with and 29 KTR without metastatic cancer.

Methods: Human microvascular endothelial cells (HMEC-1) were stimulated with IgG isolated from sera of kidney transplant recipients (KTx-IgG). regulation of VEGF was studied by promoter deletion assay. qRT-PCR, western blot, EMSA and cFOS knockdown. VEGF secretion was determined by ELISA. Tube formation on matrigel served to study endothelial neoangiogenic response. All 49 patients had sera for assessment of PARab and at the time of transplantation and 2014.

Results: PARab levels were lower at the time of transplant in KTR who developed metastatic cancer after transplant compared to those who did not. Levels were also different at the time of cancer diagnosis compared to those who had not developed cancer when assessed in 2014.



Time to cancer death in 49 KTR where pre transplant PARab were assessed. Upper line (dotted cyan) represents KTR (n=27) who had PARab >2.85 u/ml at the time of transplant. Lower line (pink full line) represents KTR (n=22) who had PArab <2.85 U/ml at the time of transplant. KTR with low PARab were more likely to die a cancer death (Log Rank Chi Square 3.19 p=0.074).

Conclusions: The PAR-1 receptor is a new target for functional antibodies in the context of kidney transplantation and tumor angiogenesis. KTx-IgG disturb VEGF transcriptional regulation resulting in reduced VEGF secretion and inability of endothelial cells to form tubes. KTR with low PARab <2.85 U/ml were more likely to die a cancer death, larger cohort studies are on going.

Funding: Government Support - Non-U.S.

SA-OR054

Molecular Markers Predicting Delayed Graft Function in Renal Transplantation

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Background: Ischemia reperfusion injury (IRI) occuring during peri-transplantation can lead to acute injury (AKI) and in 25-50% of cases to delayed graft function (DGF). Drug candidates identified and clinically tested to date, have not led to appreciable improvements in DGF outcome.

Methods: Cortex biopsies were taken immediately before transplant (pre-perfused) and following anastomosis after 45 minutes reperfusion (post-perfused). 22 biopsy pairs representing extreme phenotypes of immediate and delayed graft function underwent RNAseq. DESeq2 was used to identify differentially expressed transcripts while qPCR was used for target validation. Methylation status was determined in 10 paired biopsies using WGBS.

Results: 55 transcripts indicative of DGF, independent of IRI were identified, amongst them 20 were validated as related to DGF e.g. FCGR1C was upregulated (p=0.0006 and p=0.016 for pre and post-perfusion, respectively), pre-perfusion HSPB7 (p=0.007) and LPGAT1 (p=0.006) were downregulated. These represent immune, chaperone, and lipid metabolic functions, respectively. Further analyses in relation to CIT, WIT, DBD/DCD, SCD/ECD, MDRD4 at 3, 6 and 12 months post-transplant were also performed. DGF was associated with decreased methylation in promoter and intragenic regions in pretransplant biopsies.

Conclusions: Specific transcriptional and epigenome signatures provide evidence for molecular changes detectable in donor kidneys prior to transplantation and immediately following kidney transplantation independently of IRI and predict post-transplant outcomes. These signatures and pathways drive molecular events leading to impaired graft function and represent potential nodes for therapeutic intervention.

Funding: Pharmaceutical Company Support - GlaxoSmithKline

SA-OR055

Complement Modulation Abrogated Ischemia/Reperfusion (I/R) Induced Inflammaging by Inhibiting Senescence-Associated Secretory Phenotype (SASP) in Tubular Epithelial Cells (TEC)

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Background: Renal senescence is associated to the development of a subclinical, low-grade inflammatory state called inflammaging, as first described in diabetic nephropathy. This process is associated with the diminished regenerative potential of TEC. However, the role of cellular senescence and its modulation in I/R injury is not known.

Methods: Ten pigs underwent to 30min of renal warm I, followed by 24h of R (T24 CTRL). Five pigs were treated with C1-Inhibitor (C1-Inh, 500U/Kg, 5 min before reperfusion) (T24 C1-INH). Biopsies were analyzed for markers of SASP (SA-βGal, $p16^{INK4a}$, $p21^{WAF1}$ and IL-6) by IHC. In addition, TEC were exposed to C5a and then analyzed after culture in normal medium (24h, 48h) for SA-βGal, p53,NOX-4,IL-6,MCP-1 and CTGF by WB and qPCR.

Results: I/R injury induced tubular senescence by increasing SA-βGal, p21 and nuclear p16 expression (IHC T24CTRL:12.74±1.2 vs T0:3.75 ±0.84,$p<0.05$) typical of SASP accompanied by IL-6 production ($p<0.05$). Pigs treated by C1-INH efficiently antagonized SASP by restoring p16 (T24 C1-INH 4.93±0.92 vs T24 CTRL), p21, IL-6 expression and SA-βGal at basal level ($p<0.05$). In accordance, short stimulation of TEC with C5a (3h) induced senescence in vitro by up-regulating SA-β Gal (%SA-βGal+cells C5a 3h:13,5%±0.58 vs Basal 3.6%±0.8) IL-6, MCP-1 and CTGF gene expression ($p<0.05$). SASP were characterized by increase in p53 protein (WB/p53: C5a 24h: 1.45±0.84 vs basal 0.76±0.24, $p<0.05$) as sign of stable cell cycle arrest and up-regulation of p65 NF-κB subunit ($p<0.05$). Finally, NOX-4 protein levels significantly increased after C5a stimulation indicating the activation of oxidative stress pathway.

Conclusions: Renal I/R can induce TEC senescence by promoting the development of SASP. C1-INH might be a therapeutic approach to prevent graft senescence in renal transplantation.

SA-OR056

Natural Killer Cells in Renal Transplant Rejection and Ischemia

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Background: The role of natural killer (NK) cells in induction and prevention of cellular damage relies on the balance of activating and inhibitory receptor signaling. NKp46 is a natural cytotoxicity receptor; its activation in NK cells disrupts this balance, leading to a cytotoxic phenotype. To date, the mechanism by which innate immunity contributes to kidney damage in solid organ transplant rejection remains elusive. Herein, we investigate the role of NKp46-positive NK cells in organ dysfunction using porcine models of renal ischemia and transplantation.

Methods: We performed allogeneic kidney transplantation (n=10) or auto-transplantation (n=4). Pairs of pigs were operated on simultaneously with left kidneys exchanged or reimplanted for allotransplantation and autotransplantation, respectively. All pigs underwent right nephrectomy prior to closure and transplant nephrectomy upon sacrifice at 72 hours. No immunosuppression was used. Renal function was determined by serum creatinine. Pathology was assessed with H&E. NK cells were identified with immunohistochemical staining using NKp46 receptor antibody.

Results: Creatinine was significantly elevated in the allotransplant group as compared to the autotransplants (8.18±1.80 vs 2.83±0.60 mg/dL, p=0.009). All of the allotransplanted kidneys demonstrated SLA mismatches and some degree of acute cellular rejection. Autotransplants exhibited intact renal architecture with only mild tubular necrosis. When compared to right kidney controls, autotransplants showed no significant change in baseline NK cell population. Allotransplantation with rejection but preserved renal architecture demonstrated a 2.2 fold increase in renal NK cell population. Allotransplants with severe rejection associated with tubular damage demonstrated a 6.5 fold increase in NKp46-positive NK cell population.

Conclusions: The dramatic increase in NKp46-positive cells observed in damaged renal allografts suggests that NK cells play a role in renal allograft injury and subsequent dysfunction. Thus, inhibition of NK cell infiltration of the allograft may improve transplant outcomes.

Funding: Pharmaceutical Company Support - Mallinckrodt Pharmaceuticals

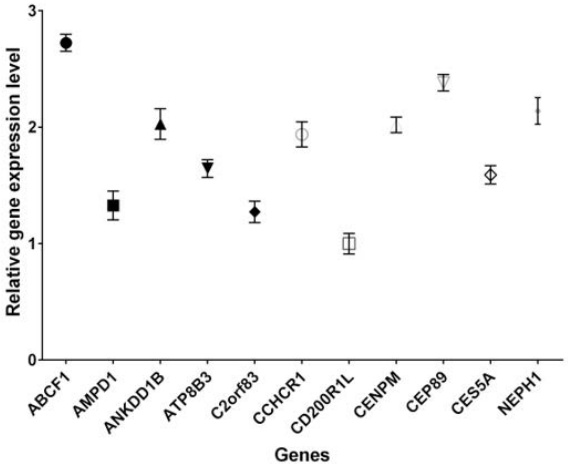
SA-OR057

Prediction of Genome-Wide Donor-Specific Minor Histocompatibility Antigens (mHA) Based on Genotyping of Donor and Recipient Pairs Roman Reindl-Schwaighofer, Alexander Kainz, Rainer Oberbauer. *Nephrology and Dialysis, Medical Univ of Vienna, Vienna, Austria.*

Background: Two random individuals differ by millions of genetic variants that include several thousands of protein polymorphisms based on sinlge nucleotide polymorphisms (SNP) as well as complete gene losses caused by "loss of function" (LoF) variants. We have established a workflow to identify genome wide genetic incompatibility based on genotyping data from donor and recipient pairs. A complete gene loss in the recipient (compound LoF variant affecting both alleles) with at least one functioning copy in the donor represents a plausible target for an alloimmune response.

Methods: We have genotyped 400 donor / recipient pairs using the iGeneTRAiN transplant array V1.0 based on Affymetrix Axiom technology that contains 750k genomic markers, including 10k specific markers for LoF variants. Following imputation we are able to cover almost 80 million different genetic markers for each individual. We then used gene expression data from kidney biopsy samples to verify if the identified proteins are expressed in transplanted kidneys.

Results: We created a candidate gene set containing more than 100 proteins with predicted homozygous gene loss. Based on the gene expression data from transplant kidney biopsies we verified that almost 70% of these proteins are transcribed in transplanted kidneys.



Conclusions: Using genomic tools new and donor-specific mHAs can be predicted on a genome-wide level.

SA-OR058

Angiotensin Receptor Antibodies Are Associated with Hypertension and Proteinuria in the Setting of Ischemia-Reperfusion Injury Gaurav Gupta, Siddhartha S. Ghosh, Todd W. Gehr, Irfan Ahmed Moinuddin, Dhiren Kumar, Anne L. King, Pam Kimball. *Nephrology, Virginia Commonwealth Univ, Richmond, VA.*

Background: Agonistic antibodies against the angiotensin II type 1 receptor (AT1R-Ab) have been linked with acute and chronic vascular kidney transplant rejection. Preliminary data has also linked AT1R-Ab with proteinuric conditions including focal segmental glomerulosclerosis and transplant glomerulopathy. In this study we investigated the effects of AT1R-Ab in an ischemia-reperfusion injury (IRI) model.

Methods: AT1R-Ab obtained from transplant patient serum was semipurified. IRI was induced in Sprague dawley rats by clamping the left renal pedicle for 45 minutes followed by reperfusion. Control animals underwent sham surgery. Alzet pumps containing AT1R-Ab (AT1R group) or human IgG (IgG group) were placed in 5 animals each with IRI. The pump was programmed to deliver 1µg/g antibody per day for 7 days. We also investigated the effect of AT1R-Ab on TGF-β secretion in a human proximal tubular (PT) cell line.

Results: Six hours after surgery, serum creatinine (SCr) in AT1R group (1.34±0.09 mg/dl) was higher than IgG group (0.78± 0.1 mg/dl) and they were both higher than in controls (0.4±0.1 mg/dl; $p<0.01$). By 7 days the SCr in IgG group dropped to normal (0.38±0.08mg/dL) but SCr in AT1R (0.8+0.1mg/dL) remained higher than in controls (0.32±0.09 mg/dl; $p<0.01$). Mean arterial pressure (MAP) of IgG group after 4 and 7 days was similar to controls at 73±12 and 71±14 mm Hg, respectively. The MAP in AT1R group after 4 and 7 days were 122+7 and 125±12 mm Hg, respectively. These were significantly higher ($p<0.01$) than the IgG group. Similarly, proteinuria in AT1R group at 7 days (227±36 mg) was also significantly higher than in IgG (44±22; $p<0.01$) and controls (24±11 mg; $p<0.01$). Finally, PT cells treated with either 75 ng of AT1R-Ab, or Angiotensin II (10^{-7}M) significantly increased production of TGF-β. This effect was abated by losartan (10^{-6}M).

Conclusions: These preliminary data suggest that AT1R-Ab is associated with worsened kidney function, hypertension and proteinuria in rats subjected to ischemia-reperfusion injury. In addition, AT1R-Ab seems to be associated with formation of pro-fibrotic TGF-β.

SA-OR059

Therapeutic Modulation of the Tie2 Receptor in Experimental Kidney Transplantation Kristina Thamm,[1] Paul Van Slyke,[2] Joon-Keun Park,[1] Hermann G. Haller,[1] Sascha David.[1] *[1]Dept of Nephrology and Hypertension, Medical School Hannover, Hannover; [2]Biological Sciences, Sunnybrook Research Inst, Toronto.*

Background: Early graft dysfunction as well as acute rejection after solid organ transplantation are characterized by a proinflammatory endothelium. The Angiopoietin/Tie2 system plays an important role in endothelial barrier function and its response to injury. Activation of the Tie2 receptor promotes endothelial homeostasis as well as anti-inflammatory properties. We therefore analyzed the potential of the Tie2 activating PEGylated 7-mer HHHRHSF, termed vasculotide (VT), as a therapeutic strategy in an MHC-mismatched renal transplant model.

Methods: We performed a murine MHC-mismatched renal transplant model (C57Bl/6 male into Balb/c female). 500ng VT was administered i.p. to C57Bl/6 1h before transplantation. Balb/c received 500ng VT i.p. directly and 3 days after surgery. Survival was monitored and remaining animals were sacrificed after 28 days. We analyzed 1) organ function, 2) Kaplan-Meier survival, 3) organ damage (PAS staining) 4) expression of endothelial adhesion molecules via immunofluorescence staining (IF), immunoblotting and qPCR, 5) infiltration of inflammatory cells (IF Gr-1, F4/80) and 6) fibrosis(IF αSMA, Sirius red staining and immunoblotting of SMAD3 activation).

Results: VT treatment resulted in diminished expression of peritubular and glomerular endothelial adhesion molecules. Consequently, infiltration of inflammatory cells (ICAM-1, Gr-1 and F4/80) was reduced in VT-treated mice compared to controls. Additionally, VT was protective against fibrogenesis. Trends towards lower serum creatinine (vehicle: 142±17 µmol/l vs. VT: 94±23 µmol/l), urea (vehicle: 76±5 mmol/l vs. VT: 60±8 mmol/l) and lactate dehydrogenase (vehicle: 1288±383 iU vs. VT: 870±275 iU) were observed. Kaplan-Meier survival analysis showed improved survival rates in the VT-treated mice (27% vs. 54%, p=0.24).

Conclusions: Exogenous activation of Tie2 via VT might reduce infiltration of inflammatory cells into renal tissue thereby protecting the renal transplant from early graft dysfunction. Thus, protection of the endothelial microvasculature via the Tie2 axis might hold promise as a therapeutic target.

Funding: Government Support - Non-U.S.

SA-OR060

Effects of Anti-Human-Leucocyte-Antigen Antibodies on Endothelial Expression and Serum Levels of Thrombomodulin in Transplant Recipients Stephanie Beland, Olivier Desy, Patrice Vallin, Sacha A. De Serres. *Renal Div, Univ Health Center of Quebec, Laval Univ, Quebec, QC, Canada.*

Background: Thrombomodulin (TBM) is an anticoagulant and anti-inflammatory transmembrane protein expressed on endothelial cells. Mutations of TBM are seen in thrombotic microangiopathies due to atypical hemolytic-uremic syndrome. DSA, particularly those against HLA class II (anti-HLA-II), are involved in endothelial allograft damage during ABMR, but mechanistic knowledge is still lacking. Thus far, the effects of anti-HLA antibodies on thrombomodulin, and the differential effects of anti-HLA class I (anti-HLA-I) compared with anti-HLA-II have not been characterized.

Methods: We used human glomerular microvascular endothelial cells to examine TBM expression by fluorescence microscopy and western blot on anti-HLA-treated cells. We then tested sera from 55 kidney recipients for soluble TBM by ELISA.

Results: Treatment of endothelial cells with anti-HLA-I led to a dose-dependent increase in membrane TBM expression, whereas treatment with anti-HLA-II and TNF-α led to minimal levels of the protein. Western Blot on extracted membrane proteins confirmed these results and showed a different molecular weight for TBM in the anti-HLA-II well. Neither stimulation with anti-HLA-I nor II increased TBM levels in cell culture supernatants, but TNF-α stimulation induced high levels, suggesting different pathways between TNF-α and anti-HLA-II. We next measured cytosolic TBM and observed an accumulation upon stimulation with anti-HLA-II, but not with stimulation with TNF-α. In patients, we found a significant association between the presence of circulating anti-HLA-II DSA and low serum levels of TBM.

Conclusions: Ligation of anti-HLA-I and II produces different effects on the endothelial surface expression of TBM and on serum levels in kidney recipients. Anti-HLA-II stimulation leads to a cytosolic accumulation of TBM with little membrane expression, suggesting a modification of the protein. This phenotype may be associated with a prothrombotic state, which could explain the higher occurrence of transplant glomerulopathy and the poor outcomes observed in patients with these antibodies.

SA-OR061

Humanized Readout of Diabetic Nephropathy in Mice Using Urinary Peptidomics Joost Schanstra,[1] Julie Klein,[1] Adela Ramirez-Torres,[2] Anette E. Ericsson,[3] Yufeng Huang,[4] Benjamin Breuil,[1] Justyna Siwy,[2] Harald Mischak,[2] Xiao-Rong Peng,[4] Jean-Loup Bascands.[1] *[1]U1048, INSERM, Toulouse, France; [2]Mosaiques Diagnostics GmBH, Hannover, Germany; [3]AstraZeneca R&D, Mölndal, Sweden; [4]Univ of Utah School of Medicine, Salt Lake City.*

Background: Diabetic nephropathy (DN) is among the most frequent complications of diabetes and the first cause of end-stage renal disease. Despite being successful in animal models, the majority of clinical trials for novel drugs targeting DN failed.This lack of translational value may in part be due to an inadequate comparability of human disease

and animal models that often capture only a few aspects of disease. Here we overcome this limitation by developing a multi-molecular non-invasive humanized readout of DN based on urinary peptidomics.

Methods: The urinary peptidome of the two most frequently used models of type 2 diabetic (T2D) DN, the BTBRob/ob mice and the uninephrectomized db/db mice on a C57BLKS background (UNxdb/db), treated or not with enalapril, was analyzed using capillary electrophoresis coupled to mass spectrometry.

Results: The disease-modified urinary peptides of the two T2D DN mouse models were identified and compared with previously validated urinary peptide markers of DN in humans to generate a classifier composed of 21 ortholog peptides. This classifier predicted the response to disease and treatment with inhibitors of the renin-angiotensin system (RASi) in mice. The humanized classifier was significantly correlated with glomerular lesions. Using a human T2D validation cohort consisting of 207 patients, the classifier also distinguished between patients with and without DN, and response to RASi.

Conclusions: Our approach demonstrates that a combination of multiple molecular features similar in both human and animal disease could provide a step change in translational drug discovery research in T2D-DN nephropathy.

SA-OR062

Linking Renal Structure to Molecular Function for Outcome Prediction in Diabetic Kidney Disease Viji Nair,[1] Jennifer L. Harder,[1] Wenjun Ju,[1] Carine Boustany,[5] Kevin V. Lemley,[3] Robert G. Nelson,[2] Matthias Kretzler.[1] *[1]UM; [2]NIH; [3]Children's Hospital Los Angeles; [4]Univ of Erlangen; [5]Boehringer Ingelheim.*

Background: Genome wide transcriptional profiling identifies active regulatory and transcriptional networks in kidney disease. Integrating structural changes with molecular profiles may identify functional correlates of early structural damage that predict subsequent disease progression.

Methods: Gene expression profiling and quantitative morphometric analysis was performed on protocol kidney biopsies from 49 type 2 diabetic Pima Indians with pre-symptomatic Diabetic Kidney Disease(DKD). Transcriptional co-expression modules were generated and associated with morphometric and long term clinical traits using Weighted Gene Coexpression Network Analysis. Urinary protein Epidermal Growth Factor (uEGF) levels were assessed for their correlation with the cortical interstitial fractional volume (VvInt) and GFR.

Results: Several structural parameters were associated with molecular profiles. The degree of tubulointerstitial damage, assessed by measurement of VvInt, showed a strong association with molecular signatures and was linked to long term clinical outcomes. Enrichment for migratory, inflammatory and cell-cell/cell-matrix interaction pathways was found in the transcripts that correlated positively with VvInt and enrichment for metabolic pathways, turnover of amino acids, sugars and lipids in those that correlated negatively. A subset of VvInt associated transcripts correlated with GFR and ACR measured ~10 years after biopsy, including EGF. uEGF showed strong positive correlation with intrarenal EGF transcript and negative correlation with VvInt. uEGF was strongly associated with GFR measured at baseline and 10 years after biopsy.

Conclusions: Cortical interstitial fractional volume-associated gene expression in pre-symptomatic to early DN was associated with ACR/GFR progression. 81% of these transcripts were also regulated in a diabetic European cohort with more advanced DKD. Molecular-morphometric approaches may allow a better understanding of the molecular events activated at a early DKD stage and provide starting points for therapeutic patient stratification.

Funding: NIDDK Support, Pharmaceutical Company Support - Boehringer Ingelheim

SA-OR063

Inactivation of Placental Growth Factor Is Associated with Perirenal Inflammation and Renal Impairment Yaeni Kim, Ji Hee Lim, Min Young Kim, Eun Nim Kim, Yu Ah Hong, Sun Ryoung Choi, Hoon Suk Park, Seon Deok Hwang, Yong-Soo Kim, Cheol Whee Park. *Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.*

Background: An excess of adipose tissue displays impaired angiogenesis that can lead to local hypoxia and apoptosis, resulting in chronic inflammation. Placental growth factor (PlGF) has favorable angiogenetic activity through its interaction with VEGFR1. We investigated the role of PlGF in adipose tissue–related angiogenesis in perinephric fat and whether the inactivation of PlGF would promote renal phenotypical and functional deterioration.

Methods: Male wild-type, PlGF-deficient (PlGF KO), and PlGF transgenic mice (PlGF TG) were fed regular chow. Mice were sacrificed at 13th and 32nd weeks to compare biochemical parameters, relevant molecular expressions and phenotypes of perinephric fat and the kidney at each distinct time point.

Results: PlGF KO mice developed features of metabolic syndrome at week 32; body weight and systolic blood pressure significantly increased with concurrent increases in serum insulin level and AUC of IGTT. While perinephric fat of 13 week old PlGF KO mice showed decreased number and increased size of adipocytes with no significant difference in F4/80 positive cells as compared to the others, 32 week old PlGF KO mice revealed increased number of F4/80 positive cells. Vessel density of perinephric fat was decreased with corresponding increase in HIF-1α expression in PlGF KO mice. 32 week old PlGF KO mice showed unfavorable renal phenotypical changes as compared to PlGF TG and controls while these changes were insignificant in those at week 13. Consistent down regulations in the renal expressions of p-AMPK, LKB1, PPARα, PGC1α, ERRα, eNOS, SOD, Bcl2/Bax ratio were shown in 32 week old PlGF KO mice with increased albuminuria. Intrarenal p-AMPK-PGC1α axis was accentuated in PlGF TG mice and this was associated with attenuated albuminuria.

Conclusions: Our study suggests that PlGF-deficiency represents impaired vasculature and adipogenesis. This derangement promotes hypoxia, inflammation, and oxidative stress in the perirenal adipose tissue which deteriorates renal functional and phenotypic parameters.

SA-OR064

miR-221-Containing Exosomes from Vascular Endothelial Cells Promote Mesangial Hypertrophy in Diabetic Nephropathy Qi Sun, Junwei Yang. *Center for Kidney Disease, Second Affiliatted Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Diabetic nephropathy (DN) is a major microvascular complications of diabetes that is structurally characterized by extracellular matrix (ECM) accumulation in glomeruli. Hyperglycemia-induced mesangial cell injury has been proved to play a key role in ECM expansion, but the mechanism under this progression has not been fully elucidated. Recently, exosome-associated microRNA transferring represent a newly identified mechanism of intercellular communication. Therefore, we hypothesize that miRNA expression in endothelium-derived exosomes may be critical in the crosstalk between mesangial cell injury and surrounding endothelium under DN condition.

Methods: Exosomes were isolated from endothelial cell cultures using exosome isolation reagent and characterized by electron microscopy. The uptake of exosomes by the mesangial cells was assessed by flow cytometry and flourescent microscopy. The abundance of miR-221 was measured by real-time quantitative PCR in serum, urine and kidney tissues of diabetic mice. Adeno-associated virus (AAV)-mediated miRNA inhibitor was used to explore the role of miR-221 in vivo by tail vein injection.

Results: Hyperglycemia upregulates miR-221 expression in cultured HMECs and in glomeruli from db/db type 2 diabetic mice. Incubation cultured mesangial cells with miR-221-containing exosomes can significantly downregulate matrix metallopeptidase 9 (MMP-9) expression by targeting transcription factor Ets-1. Then, we evaluated the efficacy of AAV-mediated inhibitor of miR-221 in db/db mice. AAV-anti-miR-221 reduced levels of miR-221 in kidneys of both normal and db/db mice. Inhibition of miR-221 in diabetic mice significantly increased Ets-1/MMP9 expression and promoted ECM degration.

Conclusions: In summary, our study provides the first evidence that endothelial cells can promote mesangial hypertrophy by releasing miR-221-containing exosomes, which may create a "pro-hypertrophic" microenvironment and further be delivered to mesangial cells to inhibit ECM degration by targeting Ets-1/MMP9 pathway. More importantly, we found that inhibition of miR-221 might be an effective therapy for diabetic nephropathy.

Funding: Government Support - Non-U.S.

SA-OR065

Follistatin Is a Novel Protective Agent for Diabetic Nephropathy Dan Zhang, Agata Gava, Bo Gao, Tony Nuo Wang, Richard Van Krieken, Neel Mehta, Renzhong Li, Liliana K. Wolak, Joan C. Krepinsky. *Nephrology, McMaster Univ, Hamilton, ON, Canada.*

Background: The kidney is a major site of diabetic microvascular complications. We previously showed that caveolin-1 knockout (KO) mice are protected from diabetic glomerular sclerosis, and KO mesangial cells (MC) are deficient in matrix protein synthesis in response to high glucose (HG) and the profibrotic cytokine TGFβ. A screen identified significant upregulation of the secreted antifibrotic protein follistatin (FST) in KO MC. Here we evaluated the *in vitro* and *in vivo* role of FST in DN.

Methods: *In vitro* studies used primary mouse MC and standard molecular biology techniques. For *in vivo* studies, type 1 diabetic Ins2^{Akita} or control mice were given vehicle or 3μg recombinant FST (Paranta Biosciences) IP every other day for 12 weeks and assessed for renal function, proteinuria and pathology.

Results: FST inhibited HG-induced matrix upregulation in wild-type MC, and its downregulation with siRNA enabled matrix synthesis by HG in KO MC. TGFβ is a well-recognized mediator of HG-induced matrix production. FST, however, does not inhibit its actions, but primarily neutralizes TGFβ family members called activins. HG and TGFβ increased MC production of Activin A (ActA) as assessed by ELISA. ActA was also increased in serum and kidneys of diabetic mice. Inhibition of ActA signaling by siRNA downregulation of its type I receptor ALK4 prevented HG-induced matrix upregulation. Interestingly, HG-induced TGFβ upregulation was also prevented by ALK4 siRNA and FST. Treatment of MC with recombinant ActA confirmed that it can induce the production of TGFβ. These data suggest that ActA is a key mediator of HG- and TGFβ-mediated matrix accumulation in MC. We thus tested the efficacy of FST administration in type 1 diabetic Akita mice which developed early signs of DN by 18 weeks of age. FST protected against the development of albuminuria, basement membrane thickening and collagen upregulation.

Conclusions: ActA is a major mediator of MC matrix production in response to HG. Its antagonist FST prevents matrix upregulation *in vitro* and protects against the development of DN *in vivo*. FST thus represents a novel and promising therapeutic approach to DN.

SA-OR066

CCR2 Expression in Podocytes Mediates Diabetic Renal Injury Hanning You,[1] Ting Gao,[1] Timothy K. Cooper,[2] Sarah K. Bronson,[3] William Brian Reeves,[1] Alaa S. Awad.[1] *[1]Medicine, Pennsylvania State Univ College of Medicine, Hershey, PA; [2]Comparative Medicine, Pennsylvania State Univ College of Medicine, Hershey, PA; [3]Cellular and Molecular Physiology, Pennsylvania State Univ College of Medicine, Hershey, PA.*

Background: Inflammation is a central pathophysiologic mechanism that contributes to diabetes mellitus and diabetic nephropathy (DN). Recently, we showed that macrophages directly contribute to diabetic renal injury, and that pharmacological blockade or genetic deficiency of CCR2 confers kidney protection in DN. However, the direct role of CCR2 in kidney-derived cells such as podocytes in DN remains unclear. Here, we report that CCR2 in podocytes mediates diabetic renal injury *in vivo*.

Methods: We developed a transgenic mouse expressing CCR2 specifically in podocytes (Tg(*NPHS2-Ccr2*)) in a nephropathy prone CCR2 deficient ($Ccr2^{-/-}$) background, with heterozygous $Ccr2^{+/-}$ littermate controls. Type 1 diabetes was induced by multiple low doses of intraperitoneal streptozotocin (STZ) injection.

Results: As expected, absence of CCR2 conferred kidney protection after 9 weeks of diabetes as evidenced by significantly reduced albuminuria ($p<0.05$), blood urea nitrogen (BUN) ($p<0.05$), histopathologic changes, and kidney fibronectin ($p<0.01$) and type-1 collagen expression ($p<0.05$) compared to diabetic $Ccr2^{+/-}$ littermate controls. In contrast, diabetic $Ccr2^{-/-}$ mice with podocyte-specific CCR2 expression displayed significantly increased albuminuria ($p<0.05$), BUN ($p<0.05$), histopathologic changes, and kidney fibronectin ($p<0.05$) and type-1 collagen ($p<0.05$) expression compared to diabetic $Ccr2^{-/-}$ after 9 weeks of diabetes. Of interest, there was no increase in kidney macrophage recruitment or inflammatory cytokine levels in diabetic $Ccr2^{-/-}$ mice with podocyte-specific CCR2 expression.

Conclusions: These findings support a direct role for CCR2 expression in podocytes to mediate diabetic renal injury independent of monocyte/macrophage recruitment. Targeting the CCR2 signaling cascade in podocytes could be a novel therapeutic approach for treatment of DN.

Funding: NIDDK Support

SA-OR067

Effect of Janus Kinase 2 on Kidney Serum Amyloid A in a Mouse Model of Diabetic Kidney Disease Rick L. Meek,[1] Brad Dieter,[1] Robert J. Anderberg,[1] Sheryl K. Cooney,[1] Hongyu Zhang,[2] Viji Nair,[2] Frank C. Brosius,[2] Matthias Kretzler,[2] Katherine R. Tuttle.[1,3] *[1]Providence Sacred Heart Medical Center, Providence Health Care, Spokane, WA; [2]Internal Medicine, Univ of Michigan, Ann Arbor, MI; [3]Inst of Translational Health Sciences, Univ of Washington, Seattle, WA.*

Background: Janus kinase 2 (JAK2) signaling and expression of the pro-inflammatory mediator serum amyloid A (SAA) are increased in the kidneys of humans with diabetic kidney disease (DKD) and in diabetic mouse models. We hypothesize that JAK2 induces a mouse-kidney-isoform of SAA, SAA3, which is associated with injury in mouse DKD models.

Methods: Podocyte specific JAK2 overexpressing type 1 diabetic Akita mice were infused with angiotensin II to enhance kidney disease. A JAK2 inhibitor (LY03103801, 3 mg/kg/day) was administered for the last 2 weeks of the study. Kidney sections were immunostained for SAA3 and assessed by standard histopathology. Glomerular SAA3 mRNA (RNAseq) and urine albumin-to-creatinine ratio were measured. Cultured mouse podocytes were exposed to recombinant SAA or advanced glycation end products (AGE) with and without the JAK2 inhibitor (Tyrphostin AG 490, 50μM). JAK2 activity (Western blot) and SAA3 mRNA (qRT-PCR) were measured.

Results: Diabetes increased kidney SAA3 protein and overexpression of podocyte JAK2 augmented SAA3 protein in both the tubulointerstitium and glomeruli (19.3 fold vs control, p=0.005; 3.1 fold vs diabetic mice, p=0.003). JAK2 inhibition attenuated the increases of SAA3 protein immunostaining and reduced glomerular SAA3 mRNA. SAA3 protein correlated with increased Periodic Acid Schiff staining (r=0.51, p=0.02), mesangial index (r=0.64, p=0.001), and urine-albumin-to-creatinine ratio (r=0.49, p=0.03). Exposing podocytes to exogenous SAA or AGE increased JAK2 activity (6.2 fold, p=0.03; 3.2 fold, p=0.03, respectively) and SAA3 mRNA expression (9.0 fold, p=0.01; 8.2 fold, p=0.02, respectively), whereas inhibiting JAK2 activity attenuated the increases in SAA3 mRNA.

Conclusions: Kidney SAA3 is up-regulated downstream of JAK2 and acts locally in the kidney of diabetic mice, indicating that SAA may mediate inflammatory mechanisms in DKD.

SA-OR068

Telomerase Deficiency Increases Glomerular Endothelial Cell Senescence in Diabetic Nephropathy Huifang Cheng,[1] Xiaofeng Fan,[1] William E. Lawson,[1] Paisit Paueksakon,[2] Raymond C. Harris.[1] *[1]Medicine, Vanderbilt Univ School of Medicine, Nashville, TN; [2]Pathology, Microbiology and Immunology, Vanderbilt Univ School of Medicine, Nashville, TN.*

Background: Aging is a risk factor for Diabetic Nephropathy (DN), and shorter telomere length (TL) has been observed in patients with diabetes mellitus. Both telomerase reverse transcriptase (TerT) and telomerase RNA (TerC) are essential to maintain telomere length.

Methods: To investigate the mechanism of telomerase dependent vulnerability to DN, we used streptozotocin to induce diabetes in fourth generation TerC and TerT KO mice and measured their TL and senescence in kidneys, compared with wild type (Wt) and used primary cultured glomerular endothelial cells (GEnCs) for *in vitro* studies.

Results: TL was significantly shorter in kidneys from TerC and TerT KO mice compared with Wt. STZ injection reduced TL in Wt, and further decreased it in TerC and TerT KO mice. After 26 weeks of diabetes, TerC and TerT KO mice had greater decrease in expression of renal SIRT1 and increased P53 and P16. Similarly SIRT activity was profoundly diminished in TerC /T KO mice compared to Wt. TerC /T KO mice had increased renal injury (assessed by albuminuria and GBM thickness) and glomerular senescence. Senescence was predominately detected in endothelial cells. Primary GEnCs from TerC KO mice proliferated slower. After incubation for 96 hours in high glucose (HG, 30 mM), GEnCs exhibited cellular senescence, with a marked increase in cells with TerC deletion. There was only minimal senescence with incubation in normal glucose medium or with a mannitol osmolality control. HG decreased SIRT 1 expression and activity, especially in GEnCs from TerC KO mice, with up-regulation of P16 and P53, especially acetylated P53. The SIRT1 activator, SRT1720, partially counteracted these alterations.

Conclusions: Inhibition of SIRT1 pathway contributes to telomerase deficiency-dependent susceptibility to DN progression and GEnCs senescence. Telomere shortening of aging may be a predisposing factor for development of diabetic nephropathy.

Funding: NIDDK Support, VA Support

SA-OR069

Roles of Hedgehog Interacting Protein in Diabetic Nephropathy Xin-Ping Zhao,[1] Shiao-Ying Chang,[1] Min-Chun Liao,[1] Chao-Sheng Lo,[1] Isabelle Chenier,[1] Stephan Troyanov,[2] Julie R. Ingelfinger,[3] John S.D. Chan,[1] Shao-Ling Zhang.[1] *[1]CRCHUM, Univ of Montreal, Montreal, QC, Canada; [2]Res. Ctr., l'Hôpital du Sacré-Cœur de Montréal, Univ of Montreal, Montreal, QC, Canada; [3]Pediatr Nephrol Unit, Mass. Gen. Hosp., Boston, MA.*

Background: We previously reported thathigh glucose (HG) stimulates Hedgehog Interacting Protein (*Hhip*)gene expression, impairing nephrogenesis; whether Hhip contributes to the *pathophysiology* of diabetic nephrology (DN) is unknown. Here we examined potential mechanisms of hyperglycemia induced renal Hhip gene expression, leading to endothelial to mesenchymal transition (EndoMT) related renal fibrosis. We asked if urinary soluble Hhip (sHhip) might be a marker of DN onset and/or progression.

Methods: We examined the role of renal Hhip expression in diabetic murine models—T1DM (*Akita* mice) and T2DM (*db/db* mice), as well as in kidney biopsies from T1DM and T2DM patients cf. to non-diabetic patients. We determined HG-mediated renal Hhip cleavage/shedding and HG-regulated renal Hhip expression at both transcriptional and translational levels *in vivo* and *in vitro*.

Results: Hhip expression in renal cells (glomerular endothelial cells, podocytes and glomerular and tubular epithelial cells) was significantly elevated in both murine diabetes models and diabetic patients. Urinary sHhip/Creatinine (Cre) ratio positively correlated with the time-course of diabetes in our murine models. Hyperglycemia activated ADAM 17, which subsequently cleaved/shed Hhip, contributing to urinary sHhip formation. In mouse endothelial cells (mECs) *in vitro*, H_2O_2 and angiotensin II (Ang II) directly up-regulated Hhip gene expression. HG and recombinant Hhip (rHhip) stimulated mouse Hhip and TGFβ1 promoter activity dose-dependently; recombinant TGFβ1 (rTGFβ1) had no impact on *Hhip* promoter activity, suggesting that Hhip acts upstream of TGFβ1 signaling. In sum, enhanced Hhip, via TGFβ1 receptors targets TGFβ1-Smad2/3 cascades, promoting endothelial to mesenchymal transition (EndoMT), associated with renal fibrosis.

Conclusions: Hyperglycemia induced Hhip expression is important in the pathogenesis of DN, promoting EndoMT via the TGFβ1-Smad2/3 pathway. Urinary sHhip/Cre ratio may indicate onset and/or progression.

Funding: Government Support - Non-U.S.

SA-OR070

PACSIN2 Is Increased in Podocytes in Diabetic Kidney Disease and Regulates Nephrin Turnover at the Plasma Membrane Sanna H. Lehtonen, Tuomas Aleksi Tolvanen, Sara Kuusela, Hong Wang, Sonja Lindfors, Vincent Dumont. *Univ of Helsinki, Finland.*

Background: Reduced expression or abnormal localization of nephrin has been observed in experimental models of diabetes and human diabetic nephropathy. Here we aim to define whether PACSIN2, known to participate in vesicle trafficking in various cell types, regulates localization of nephrin at the plasma membrane.

Methods: Immunohistochemistry and Western blotting were used to quantify the expression of PACSIN2 in the glomeruli of Zucker Diabetic Fat (ZDF) rats. Immunofluorescence and confocal microscopy were used to study the localization of nephrin in ZDF rat glomeruli. Complex formation between PACSIN2 and nephrin in glomeruli and podocytes overexpressing nephrin was studied by co-immunoprecipitation and *in situ* proximity ligation assay (PLA). PACSIN2 was overexpressed in nephrin-expressing podocytes followed by On-cell/In-cell Western to quantify the effect on nephrin insertion and turnover at the plasma membrane.

Results: PACSIN2 was found to be expressed in podocytes *in vitro* and *in vivo*. It colocalized with nephrin, and was found to be expressed at higher level in the glomeruli of obese, highly albuminuric ZDF rats compared to lean controls. The distribution of nephrin changed from linear to granular pattern in the glomeruli of obese ZDF rats. Co-immunoprecipitation and *in situ* PLA indicated that PACSIN2 and nephrin form a complex in cultured podocytes and in isolated human and rat glomeruli. On-Cell Western revealed that PACSIN2 overexpression reduces the amount of nephrin inserted in the plasma

membrane compared to empty vector-transduced podocytes. Furthermore, time series In-Cell Western experiments revealed quicker turnover of nephrin at the plasma membrane in PASCIN2 overexpressing cells.

Conclusions: PACSIN2 is upregulated in glomeruli in diabetes, and *in vitro* experiments revealed that PACSIN2 enhances nephrin trafficking. This suggests that increased PACSIN2 expression associates with loss of glomerular permselectivity and proteinuria. Further studies are needed to define the molecular mechanisms by which PACSIN2 regulates nephrin trafficking and whether increased expression of PACSIN2 helps in preventing or accelerates loss of renal function.

Funding: Private Foundation Support

SA-OR071

Polycystin 1 Regulates WWTR1/TAZ, a Non-Canonical WNT and Hippo Signaling Target Nikolay P. Gresko,[1] David Merrick,[2] Kavita Mistry,[1] Michael J. Caplan.[1] *[1]Cellular and Molecular Physiology, Yale Univ, New Haven, CT; [2]Univ of Pennsylvania.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations in the *PKD1* and *PKD2* genes, which encode PC1 and PC2, respectively. PC1 is a 460kD multi-spanning membrane protein that undergoes multiple proteolytic cleavages, at least two of which release C-terminal fragments. One of these fragments includes the last 200 amino acids of PC1 (PC1-CTTp200) and possesses a functional nuclear localization sequence (NLS) that drives its nuclear accumulation. Nuclear PC1-CTTp200 regulates several transcription pathways.

Methods: One of the top hits in a screen for transcription factors and co-regulators whose activities are modulated by PC1-CTTp200 was TAZ (also known as WWTR1), which is an important component of several signalling cascades, including the Hippo pathway.

Results: We found that TAZ protein expression in the nephron is localized to the basolateral compartment of S3 segment epithelial cells and to the principal cells of the collecting duct. Interestingly, it has previously been shown that TAZ deficient mice develop severe renal cysts. Moreover, we find that exogenous expression of an active form of TAZ in PC1 null cells prevents them from forming cyst-like structures in the 3D Matrigel culture. Expression of the active form of TAZ also corrects the curly tail phenotype that is seen in PKD1a/b morphant zebra fish. We find that PC1 interacts with TAZ, and furthermore that PC1 expression upregulates TAZ abundance at the mRNA and protein levels. TAZ abundance and activity have been shown to be upregulated through the non-canonical Wnt signalling. A recent study demonstrates that PC1 can serve as a receptor for Wnt ligands. We find that HEK293 cells that express PC1 and PC2 respond to treatment with recombinant Wnt5a protein by increasing the abundance of TAZ mRNA as compared to wild type HEK293 cells.

Conclusions: Taken together, our data suggest that PC1 may participate in a novel signalling pathway that links detection of non-canonical Wnt ligands to the positive regulation of TAZ, a multifaceted signalling molecule whose absence is sufficient to induce renal cystic disease.

Funding: NIDDK Support

SA-OR072

Polycystin-1 Regulates EZH2 Expression through the cAMP/PKA/CREB Pathway and EZH2 Inhibition Delays ADPKD Progression Na Qi, Ming Wu, Changlin Mei. *Dept of Nephrology, Shanghai Changzheng Hospital, Second Military Medical Univ, Kidney Inst, Shanghai, China.*

Background: Enhancer of zeste homolog 2 (EZH2) plays important roles in tumor formation and growth, however it is not known whether EZH2 promotes cyst expansion in autosomal dominant polycystic kidney diseases (ADPKD). The aim of this study is to determine the effect and mechanism of EZH2 inhibition in ADPKD.

Methods: $Pkd1^{+/-}$ and $Pkd1^{-/-}$ mice were treated with 30 mg/kg/day EZH2 specific inhibitor GSK126 or vehicle from day15 to day 35 by IP injection. ADPKD cells were treated with various concentration of GSK126. The upstream signaling pathway of EZH2 was analyzed by using PKD1 siRNA, cAMP agonists or antagonists, PKA inhibitor, CREB siRNA or plasmids in control or ADPKD cells.

Results: EZH2 expression and the methylation of histone and STAT3 are increased in ADPKD kidney tissues. Four weeks of treatment by EZH2 specific inhibitor GSK126 reduced BUN and creatinine levels by 26.9% and 29.5%, respectively, in Pkd1-/- mice. Administration of GSK126 decreased two-kidney/total body weight ratio by 30.5% and cyst volume density by 36% in $Pkd1^{-/-}$ mice. Moreover, exogenous expression of human EZH2 induced pronephic cysts in zebrafishes. The effect of EZH2 inhibition *in vivo* was evaluated, GSK126 treatment reduced cell proliferation in cystic kidneys as shown by Ki-67 staining. *In vitro* study further confirmed that EZH2 ablation inhibited cell proliferation and cell cycle of ADPKD cells. Western blot analysis showed that EZH2 inhibition reduced phosphorylation of STAT3 *in vivo* and *in vitro*, which were correlated with decreased methylation of STAT3. Further *in vitro* studies showed that EZH2 is up-regulated by PKD-1 siRNA, cAMP agonists (forskolin or 8-Br-cAMP) and CREB over-expression. Moreover, the cAMP antagonist Rp-camp, the PKA inhibitor H89 and CREB siRNA down-regulated EZH2 expression in ADPKD cells.

Conclusions: Polycystin-1 regulates EZH2 expression through the cAMP/PKA/CREB pathway. Inhibition of EZH2 mediated protein methylation could be a new strategy for ADPKD therapy.

Funding: Government Support - Non-U.S.

SA-OR073

Global Profiling in Polycystic Kidney Disease Reveals a Metabolic Rewiring Reminiscent of Cancer Christine Podrini,[1,2] Isaline Rowe,[1] Roberto Pagliarini,[3] Silvia Raineri,[1] Ivano Di Meo,[4] Marco Chiaravalli,[1] Valeria Tiranti,[4] Diego Di Bernardo,[3] Alessandra Boletta.[1] *[1]DGCB, San Raffaele Scientific Inst, Milan; [2]Univ Vita-Salute San Raffaele, Italy; [3]TIGEM, Pozzuoli, Italy; [4]IRCCS Foundation Neurological Inst, Italy.*

Background: We and others have previously uncovered metabolic alterations in ADPKD including defective glycolysis. Global metabolic profiling was performed in a murine model of PKD carrying kidney-specific inactivation of *Pkd1* as to avoid confounding effects caused by inactivation in other organs.

Methods: We collected 16 newborn (P4) kidneys of *Ksp*-Cre;$Pkd1^{flox/-}$ mice and littermate controls from a total of 4 litters containing each 2 cystic and 2 control (half male, half female) kidneys. Ultrahigh performance liquid and gas chromatography followed by mass spectrometry was used.

Results: 550 metabolites were named. An unsupervised statistical analysis (PCA) revealed a clear separation between mutant and control kidneys with a significant upregulation of 196 and downregulation of 292 metabolites (total 488). Alterations include defective glycolysis, fatty acids biosynthesis, β-oxidation and TCA cycle. The last suggested a mitochondrial defect. To test this, oxygen consumption rates were measured in a 96 wells SeaHorse. $Pkd1^{-/-}$ MEFs (immortalized and primary) presented decreased maximum respiration and increased extracellular acidification rates as compared to controls, suggesting a switch from mitochondrial oxidation to glycolysis. Analysis suggested that $Pkd1^{-/-}$ cells have glutamine anaplerosis. We applied metabolic deprivation to $Pkd1^{+/+}$ and $Pkd1^{-/-}$ MEFs. $Pkd1^{-/-}$ cells were more sensitive to glucose deprivation. Deprivation of both glutamine and glucose resulted in a more detrimental effect on $Pkd1^{-/-}$ cells than $Pkd1^{+/+}$ suggesting that mutant cells are addicted to glucose and glutamine.

Conclusions: A major metabolic rewiring is identified in PKD unexpectedly similar to cancer. Defective TCA cycle and mitochondrial activity likely drive "Warburg effect" in *Pkd1* mutants which is accompanied by glutamine anaplerosis, again showing similarities with cancerous cells. Thus metabolic alterations are a hallmark of PKD. Further analysis is required to understand why transformation is not a feature of this disease.

SA-OR074

Inhibition of CamKII Reduces ER Stress, Oxidative Damage, Improves Mitochondrial Integrity, and Attenuates Polycystic Kidney Disease Nikolay Bukanov,[1] Christina M. Bracken,[3] Philippe Beauverger,[2] Olivier Duclos,[2] Ryan J. Russo,[1] Kelly A. Rogers,[1] Herve Husson,[1] Thomas A. Natoli,[1] Steven R. Ledbetter,[1] Philip Janiak,[2] Oxana Beskrovnaya.[1] *[1]Rare Diseases, Sanofi-Genzyme R&D Center, Framingham, MA; [2]Cardiovascular Research, Sanofi, Chilly-Mazarin, France; [3]Mitobridge Inc., Cambridge, MA.*

Background: Polycystic kidney diseases (PKD)s comprise a large family of cilia-associated genetic diseases characterized by formation and progressive growth of renal cysts, eventually leading to end-stage renal disease. Despite recent advances in understanding of PKD pathogenesis, the exact mechanisms of cystogenesis are not completely understood. We show a new role for calcium/calmodulin-dependent protein kinase II (CaMKII) as a pathological mediator of oxidative damage, maladaptive ER stress response and mitochondrial dysfunction in progression of cystic kidney disease.

Methods: Western blot analysis of kidney tissue was used for assessment of integral mitochondrial membrane proteins and proteins responsible for oxidative damage, mitochondria-related apoptotic pathway, and ER stress response. Mitochondrial membrane potential was assessed by MitoTracker and flow cytometry analysis of JC-1 dye uptake; mitochondrial antioxidant gene expression was evaluated with PCR. Efficacy of CaMKII small molecule inhibitor in jck mice was measured by kidney to body weight ratio, blood urea nitrogen, and cystic volume.

Results: Here we show that that CaMKII is activated in renal cystic epithelia in human ADPKD and in the jck mouse model of PKD. These data is also confirmed by western blot analysis of normal and human ADPKD and jck kidney lysates. Pharmacological blockade of pCaMKII by a novel and selective small-molecule inhibitor significantly attenuates PKD in jck mice, reducing cystic disease endpoints, namely K/BW ratio, cystic volume and BUN levels. Mechanistic analyses show that treated kidneys are characterized by decreased unfolded-protein response, oxidative stress and restoration of mitochondrial membrane potential and integrity.

Conclusions: Taken together, our data show that inhibition of CaMKII may be a viable therapeutic approach for the treatment of PKD.

Funding: Pharmaceutical Company Support - Sanofi-Genzyme

SA-OR075

Re-Expression of Polycystin-1 in Polycystic Kidneys Antagonizes Cyst Progression and Prolongs Survival Stephen C. Parnell, Archana Raman, Timothy A. Fields. *Kidney Inst, Univ of KS Medical Center.*

Background: Mutations in the *PKD1* gene disrupt the function or cause decreased amounts of its protein product, polycystin-1 (PC1), and are responsible for most cases of autosomal dominant polycystic kidney disease (PKD). However, after cysts have initiated it is not known whether ongoing PC1 deficiency is necessary for cyst progression, or whether re-expression of PC1 in cystic kidneys will halt or reverse cyst growth.

Methods: To determine the effects of PC1 re-expression in cystic kidneys, we engineered an inducible functional allele of mouse *Pkd1*, $Pkd1^{NEO\ WT}$. In the absence of

Cre, *Pkd1*$^{NEO\ WT}$ is a non-functional allele. However, Cre-mediated recombination produces a re-arranged allele, *Pkd1*^{WT*}, that expresses functional PC1. *Pkd1*$^{NEO\ WT}$ mice were mated to mice with hypomorphic *Pkd1* alleles (*Pkd1*^{V} or *Pkd1*^{RC}) and ubiquitously expressed *ROSA26-Cre*^{ERT2}. PC1 re-expression was induced in 1 week-old cystic mice by tamoxifen injection, thereby converting the non-functional *Pkd1*$^{NEO\ WT}$ allele to the functional *Pkd1*^{WT*} allele, and the effects on cystic kidney disease were determined.

Results: *Pkd1*$^{NEO\ WT/V}$ and *Pkd1*$^{NEO\ WT/RC}$ pups survived embryogenesis but displayed early cystic kidney disease, with death of *Pkd1*$^{NEO\ WT/V}$ pups occurring at 3-4 weeks. Control *Pkd1*$^{WT*/WT*}$ mice were normal. Two weeks of PC1 re-expression improved cystic kidney disease in 3 week-old pups, with a decrease in kidney weight to body weight (KW/BW) and an improved cystic index compared to pups that did not re-express PC1. A single cystic mouse was sacrificed at 11 weeks following re-expression of PC1. While this mouse exhibited prominent cystic kidney disease, its KW/BW was less than that of 1 week-old *Pkd1*$^{NEO\ WT/V}$ pups. Moreover, there was significant preservation of normal parenchyma, and evidence of cystic epithelial cell apoptosis.

Conclusions: These results suggest that re-expression of PC1 provides a significant benefit to cystic mice, and further suggests that rescue of PC1 function (*e.g.*, chaperone-mediated therapy for *PKD1* mutations that result in misfolded and/or mis-localized PC1, or small molecules that stimulate polycystin-2 channel activity for *PKD1* loss-of-function mutations) may be an ideal therapeutic approach for PKD.

Funding: Other U.S. Government Support, Private Foundation Support

SA-OR076

Loss of Cilia Does Not Inhibit Pkhd1 Dependent Cyst Growth in the Liver

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Background: Loss of polycystin in ADPKD and complete removal of cilia by inactivation of intraflagellar transport-related proteins both give rise to cysts in the kidney and liver. Recently it has been shown that inactivation of both polycystin and cilia concurrently results in a protective effect on ADPKD dependent cystogenesis, revealing the existence of a novel signaling pathway of polycystin-dependent inhibition and cilia-dependent cyst activation (CDCA). We and others have previously shown that there is a genetic interaction between *Pkhd1* and *Pkd1* dosage, we proposed to inactivate cilia in the livers of the ARPKD mouse model *Pkhd1*$^{del4/del4}$ to determine if the CDCA pathway plays a role in cyst progression in ARPKD.

Methods: The animals models used in this study are *Pkhd1*^{del4}, *Kif3a* floxed allele and ERT2;UBCCre. All animals used in this study were induced with Tamoxifen at postnatal day 28 for 5 days and then aged to 17 weeks. The livers and kidneys were examined for disease progression.

Results: At the start of cilia inactivation, the *Pkhd1*$^{del4/del4}$ livers show mild bile duct proliferation. At 17 weeks, the body weights of the *Kif3a*$^{fl/fl}$*:UbcCRE* were higher than the *Pkhd1*$^{del4/del4}$ animals [33.39 ± 5.592 g compared to 25.98 ± 2.584 g]. It has been well described that loss of cilia results in increased body weight.The body weight of the double knockout were similar to the *Kif3a* single knockouts at 30.44 ± 1.304 g. No significant difference was detected in kidney weights across all genotypes. The liver cystic disease progression which is evident in the *Pkhd1*$^{del4/del4}$ animals at 17 weeks, remained unchanged in the absence of cilia: *Pkhd1*$^{del4/del4}$(1.63 ± 0.28), *Kif3a*$^{fl/fl}$*:UbcCRE* (1.69 ± 0.50), *Pkhd1*$^{del4/del4}$*;Kif3a*$^{fl/fl}$*;UbcCRE* (1.71 ± 0.43). The slight increase in liver weights in the cilia mutant animals was due to fat deposits and not increased cyst formation.

Conclusions: Taken together our data demonstrate that loss of cilia in an ARPKD mouse model is not sufficient to slow disease progression. These data suggest that the cyst formation in the liver due to loss of *Pkhd1* is not dependent on the presence of intact cilia.

Funding: NIDDK Support

SA-OR077

Primary Cilia Regulate Interstitial Macrophage Proliferation and Polarization in an Acute Kidney Injury Model of Polycystic Kidney Disease

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Background: The mechanism responsible for renal cyst formation often involves defects in primary cilia related proteins including intraflagellar transport proteins (e.g., IFT88) or polycystins. Induction of cilia loss in adult mice leads to slow and focal cyst formation; however, rapid cyst formation can be initiated in these mice by ischemic reperfusion (IR) injury. Over the last two decades, studies have demonstrated that inflammatory cells, including macrophages, are involved in the pathogenesis of IR injury suggesting a role for inflammation in IR induced cyst formation.

Methods: To better define the role of macrophage populations prior to and during cyst formation, we studied effects of IR injury in adult induced Ift88^{tm1Bky} (Ift88$^{fl/fl}$), CAGG-Cre/Esr1/5Amc/J (CAGG-CreER) cilia mutant mice.

Results: Following the primary cilia loss, cyst formation began ~14 days following IR and gradually progressed to post-injury day 28. Throughout the time course, there is a persistent increase in the level of pro-inflammatory and pro-fibrotic cytokines including MCP-1, TNF-α, activin A, IL-1β, and TGF-β in the injured cilia mutant mice. We also observed significantly higher number of interstitial resident macrophages at post-injury day 7 (prior to cyst initiation). Compared to controls, resident macrophage subtypes (F4/80^{hi}, CD11b^{lo}, CD11c^{-}) and their proliferation was increased in the cilia mutant mice. Interestingly, membrane bound CSF-1, which is a cytokine responsible for resident macrophage proliferation, was overexpressed in proximal tubule epithelial cells isolated from cilia mutant mice suggesting that cilia on epithelial cells may regulate resident macrophage proliferation and kidney repair after injury.

Conclusions: In conclusion, defects in communication between cilia containing epithelial cells and resident macrophages through upregulated CSF-1 results in persistent resident macrophage proliferation that contributes to initiation and progression of polycystic kidney diseases.

Funding: NIDDK Support

SA-OR078

Tubule-Expressed Mcp-1 Promotes Macrophage Homing and Cyst Growth in Polycystic Kidney Disease (PKD)

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Background: Macrophages accumulate around cysts in models of polycystic kidney disease (PKD), and macrophage depletion with clodronate has been shown to slow cyst growth. Macrophage chemoattractant protein-1 (MCP1) is highly expressed in orthologous mouse models of ADPKD and by polycystin-1 null renal tubular cells in culture, leading us to hypothesize that loss of tubular cell PC1 leads to over-expression of MCP1 and promotes MCP1 receptor (CCR2) dependent macrophage homing and cyst growth.

Methods: *Mcp1*$^{(fl/fl)}$*;Pkd1*$^{(fl/fl)}$*;Pax8TetOn-Cre* mice (termed DKO) were generated and induced from 4-6 weeks of age with doxycycline to simultaneously knock-out tubular cell MCP-1 and PC1 expression and compared to *Pkd1*$^{(fl/fl)}$*;Pax8TetOn-Cre* mice (SKO) induced at the same age. Some SKO mice were given daily IP injections of the CCR2-antagonist INCB3344 for 6 weeks beginning at the completion of doxycycline induction. Kidneys were analyzed at 12 weeks of age.

Results: DKO mice demonstrated significantly reduced Mcp1 expression, macrophage numbers, kidney weight/body weight, cystic index, and BUN at 12 weeks of age (table 1) with improved survival at 18 weeks (94% vs. 50%).

*p<0.05 **p<0.01 ***p<0.001

12 weeks of age	n	*Mcp-1* expression (dCt)	Macrophage number (%)	Kidney/ Body ratio	Cystic Index (%)	BUN (mg/ dL)
SKO	5	0.1705 (+/- 0.013)	22.47 (+/-2.11)	0.0592 (+/- 0.013)	38.88 (+/- 2.23)	53.6 (+/- 3.7)
DKO	8	0.0207 (+/- 0.013)***	2.97 (+/- 0.75)***	0.0127 (+/-0.003)**	22.32 (+/-2.25)*	35.1 (+/- 3.0)*
SKO (Vehicle)	5	NA	NA	0.0571 (+/- 0.009)	38.04 (+/- 2.13)	44.7 (+/- 3.8)
SKO (INCB3344)	6	NA	NA	0.0191 (+/-0.007)**	25.65 (+/-2.37)*	26.9 (+/- 1.3)*

Similarly, daily injection of INCB3344 resulted in a significant decrease in cyst growth and BUN at 12 weeks of age as compared to vehicle controls.

Conclusions: The Mcp1-CCR2 pathway appears to be critical for macrophage homing to murine polycystic kidneys and interruption of this pathway slows cyst growth and loss of renal function.

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

SA-OR079

Investigating the Role of T Cells in Autosomal Dominant Polycystic Kidney Disease Progression

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Background: While ADPKD is the most common monogenic renal disease, no treatment exists to slow its progression. Much research has focused on aberrations in epithelial cell signaling, but little is known about the role of the microenvironment in disease progression. Specifically, the role of T lymphocytes in ADPKD is unknown.

Methods: We used flow cytometry and immunofluorescence to identify distinct immune cell populations in mouse models of ADPKD. We used the slower progressing *Pkd1* p.R3277C (RC) model in the C57Bl/6,129S6, and Balb/c strain, which show increasing disease severity, respectively, and the rapidly progressive *Pkd1*$^{RC/-}$ model in the C57Bl/6 strain.

Results: We observed a significant increase in immune cells in all ADPKD mice compared to their respective wildtype mice. In the *Pkd1*$^{RC/-}$ model at P20, this increase was primarily mediated by macrophages, while in 9-month-old *Pkd1*$^{RC/RC}$ mice, the increase was driven by T lymphocytes (CD4 and CD8 T cells), which accumulated around cystic lesions. Importantly, the increase in T cell populations correlated with severity of disease. We also observed higher numbers of T regulatory cells (T_{Regs}) in the *Pkd1*$^{RC/RC}$ model, which generally are immunosuppressive. In a preliminary experiment, antibody depletion of CD8+ cells from 1-3 months in C57Bl/6 *Pkd1*$^{RC/RC}$ mice, resulted in a significant increase in %kidney weight/body weight compared to IgG-control, suggesting a protective role for CD8 cells in ADPKD progression. Furthermore, *Pkd1*$^{RC/RC}$ CD8 and epithelial cells expressed more PD1 and PD-L1 respectively, indicating activation of an immune checkpoint, leading to inhibition of CD8 function. Targeting this pathway has shown great promise as a cancer therapeutic, and antibodies against PD1 and PD-L1 have been approved by the FDA for multiple cancers.

Conclusions: Together, these data indicate that T cells are upregulated in ADPKD and likely play an important role in slowly progressive cystogenesis. Here, CD8 cells may play an important protective role, which could be disrupted by checkpoint activation, hence leading to more rapidly progressive disease. Targeting T cells may represent a novel therapeutic approach to inhibit ADPKD progression.

Funding: Other NIH Support - T32

SA-OR080

New In Vitro Model for the Study of Phenotypes Associated with Polycystic Kidney Disease: "Pseudonephrons" and "Pseudovessels" Generation

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Background: Polycystic kidney disease (PKD) is a group of genetic disorders that cause renal failure and are originated by abnormal tubular morphology by the presence of multiple cysts along the nephron. PKD is associated with other extrarenal manifestations (hepatic and pancreatic cysts, aneurysms…). Up to the moment, *in vitro* studies of PKD are based on 2 dimensional (2D) culture or 3 dimensional (3D) collagen culture. An *in vitro* culture model that mimic the shape or the arrangement of cells, cell-to-cell junctions or extracellular matrix environment (ECM) applying a fluid shear stress (FSS) is essential to replicate more accurately the *in vivo* conditions.

Results: We have developed a 4 dimensional (4D) culture where flow is the fourth dimension. This model is based on creation of channels embedded in collagen by 3D bioprinting of filaments of gelatin (within or without cells). This gelatin is a temporary material that leaves a hollow channel inside collagen where cells can grow. This technic allow us replicated pseudonephrons and pseudo-blood vessels to monitor different mechanisms related to cell flow sensing and orientation/organization. We have designed a device where can to apply a flow through these channels. We were able to print in a tube different serial nephron segment cell types, identifying phenotypical specific characteristics like ciliated cells. Same strategy was applied for endothelial and epithelial cells, and extended to immortal conditional primary cells derived from Pkd mouse models, allowing us to induce the inactivation of pkd genes.

Conclusions: This new 4D model of collagen channels will allows to study molecular mechanisms underlying cystogenesis and aneurysms, in a context where flow can be apply and mutations can be induce under controlled mimicking in vivo conditions.

Funding: Government Support - Non-U.S.

SA-OR081

Cross Talk between Myostatin and BMP Signaling Regulates Muscle and Bone Mass in CKD

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Background: metabolic defects in CKD include losses of muscle and bone but if and how these defects are linked. We have found that muscle of CKD mice expresses myostatin to cause muscle wasting and now we examine if myostatin-induced intracellular signaling interacts with bone morphogenetic protein (BMP) signaling, regulates muscle and bone mass.

Methods: CKD mice with BUN >80 mg/dL were treated with an antimyostatin peptibody. We monitoring body weight, bone mass, mineral density and muscle strength. Cell signaling pathways were assessed in C2C12 myoblasts and MC3T3 osteoblast cells.

Results: mice with CKD had increased myostatin expression but decreased muscle mass and reduced bone mineral density. When the peptibody blocked myostatin in mice with CKD, both body weight and bone mineral density (g/cm^2) were 18% higher vs. CKD mice treated with PBS. Skeletal muscle mass was increased 15-32% and blood glucose was decreased as was glucose tolerance. There were no changes in fat mass vs. control, CKD mice. Muscle grip strength of myostatin-blocked, CKD mice were 21% higher vs CKD mice treated with PBS. The changes were independent of serum PTH levels. To explain how myostatin changes both muscle and bone, we examined tissue lysates and found that the peptibody decreased p-Smad2/Smad3 and increased p-Smad1/5, p-S6, p-mTOR, and p-Akt in both tissues of mice with CKD. We hypothesized that myostatin could influence bone responses by changing BMP signaling. It was tested in both C2C12 myoblasts or MC3T3 osteoblastswhen myostatin production was blocked using a SiRNA to myostatin. In the absence of myostatin, both osteoblasts and myotubes exhibited increased p-Smad1/5, p-mTOR, p-Akt plus the differentiation of both osteoblasts and myotubes. Likewise, treatment of myotubes with recombinant BMP7 produced increases in p-Smad1/5, mTOR and p-Akt.

Conclusions: our results indicate that in CKD mice, myostatin exhibits cross talk with BMP to regulate intracellular signaling, inhibiting differentiation of myoblasts and osteoblasts. The result is reduced muscle and bone mass. Anti-myostatin peptibody may be a potent therapeutic strategy for improving muscle and bone growth in CKD.

Funding: NIDDK Support

SA-OR082

A Ligand of the Activin Receptor Type IIA Mediates Osteoclast Stimulation of Bone Remodeling in Diabetic Mice with CKD

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Background: Dysregulation of skeletal remodeling is a component of renal osteodystrophy. We have reported that activin receptor signaling is differentially affected in various tissues in CKD, and here, using a ligand trap for the activin receptor type 2A (RAP-011), we demonstrate that inhibition of skeletal activin receptor signaling has efficacy in the CKD-MBD osteodystrophy.

Methods: CKD, with 70% reduction in GFR, was induced at 14 weeks of age in the *ldlr-/-* high fat fed model of atherosclerotic vascular calcification and diabetes. CKD mice, with hyperphosphatemia, hyperparathyroidism, and elevated activin A, were treated with RAP-011 10mg/kg (n=20) or vehicle (Veh, n=19), injected SC twice weekly beginning at 22 weeks of age until euthanasia at 28 weeks and study by skeletal histomorphometry, micro CT, mechanical testing and *ex vivo* bone cell cultures.

Results: Results were compared to sham operated *ldlr-/-* high fat fed mice (Sham, n=16). Sham mice had a low-turnover osteodystrophy and skeletal frailty that was converted by CKD to a higher turnover bone remodeling state with increases in osteoclast and osteoblast numbers and bone resorption, p<0.01. RAP-011 treatment eliminated the CKD induced increase in these histomorphometric parameters and increased trabecular bone fraction compared to CKD and sham mice. RAP-011 increased cortical bone area and thickness, p<0.05. Activin A enhanced osteoclastogenesis was mediated through p-smad2 association with c-fos and activation of NFATc1.

Conclusions: In conclusion, an ActRIIA ligand trap reversed CKD stimulated bone remodeling, likely through inhibition of activin A induced osteoclastogenesis.

Funding: NIDDK Support, Pharmaceutical Company Support - Celgene

SA-OR083

In Uremic Rats, the Calcimimetic Maintains Bone Turnover in a Parathyroid Hormone-Independent Manner

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Background: Calcimimetics decrease PTH secretion resulting in reduction of bone turnover. Here we evaluated the effects of CaSR activation by calcimimetic (AMG641) on bone in uremic rats with clamped high PTH levels.

Methods: Rats on a 0.9%P, 0.6 %Ca diet were divided in four groups: **Sham**; **5/6Nx**; **5/6Nx+PTx+PTH** (5/6Nx rats underwent parathyroidectomy and received constant infusion of PTH and vehicle) and **5/6Nx+PTx+PTH+AMG641**. After 28d, animals were euthanized and blood and bone were collected. Mineralization was assessed by double-calcein labeling.

Results: In 5/6Nx, PTH increased, bone volume decreased and bone turnover was augmented as compared with sham. In 5/6Nx+PTx+PTH rats, AMG641 increased bone cells activity , while bone volume was similar vs vehicle. Moreover, bone formation rate was slight but not significantly higher in rats on AMG641 than vehicle.

	Sham	5/6Nx	5/6Nx+PTx+PTH	5/6Nx+PTx+PTH+AMG641
	n=5	n=7	n=8	n=5
BV/TV (%)	30.9±1.75	21.3±1.28[a]	20.6±2.29[a]	20.1±1.21[a]
OS/BS (%)	2.89±1.01	20.7±2.06[a]	13.9±2.39[a]	23.3±1.27[ac]
Ob.S/BS (%)	0.27±0.11	13.0±0.99[a]	4.36±0.46[b]	11.7±1.44[ac]
Oc.S/BS (%)	1.02±0.20	6.42±1.22[a]	2.25±0.42[b]	5.23±1.38
BFR/BS (%/year)	192±5.80	463±46.4[a]	253±28.6[b]	379±24.6[a]

Bone Histomorphometry. Values are mean±SEM. [a]p<0.05 vs Sham; [b]p<0.05 vs 5/6Nx; [c]p<0.05 vs 5/6Nx+PTx+PTH. **BV**: Bone Volume. **TV**: Tissue Volume. **OS** Osteoid Surface. **BS**: Bone Surface **Ob.S**: Osteoblast Surface **Oc.S**: Osteoclast Surface. **BFR**: Bone Formation Rate.

Conclusions: In conclusion, the calcimimetic AMG641 increases bone turnover in uremic rats with clamped PTH. These results are in agreement with in vitro studies that demonstrate a bone anabolic effect of CaSR activation.

SA-OR084

Metabolic Acidosis Increases IFRD1 Expression in Primary Mouse Osteoblasts

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Background: Chronic metabolic acidosis (MET), a systemic increase in proton concentration [H^+], stimulates cell-mediated net calcium (Ca) efflux from bone. This Ca efflux is mediated primarily through increased osteoblastic cyclooxygenase 2, leading to prostaglandin E_2-induced stimulation of RANKL and increased osteoclastic bone resorption.

The response to MET is initiated through OGR1, a specific osteoblastic proton receptor, which results in increased intracellular Ca. To further understand the intracellular signaling events involved in the osteoblastic response to MET, we utilized primary osteoblasts to study potentially important gene expression pathways, including IFRD1, interferon-related developmental regulator 1. IFRD1 modulates the wnt/β-catenin signaling pathway and has recently been shown to play a pivotal role in activating osteoclastic bone resorption.

Methods: Confluent osteoblastic cells isolated from neonatal mouse calvariae were incubated in neutral (NTL, pH=7.50, Pco_2=39 mmHg, [HCO_3^-]=30 mM) or acid (MET, pH=7.20, Pco_2=39 mmHg, [HCO_3^-]=14 mM) medium up to 24h. Specific RNA gene expression was analyzed by real time PCR with expression normalized to RPL13A and calculated relative to non-incubated cells.

Results: MET-induced significant stimulation of IFRD1 mRNA expression in osteoblasts after 6h in culture (NTL=1.60±0.08 vs MET=1.95±0.11, p<0.05). We have previously shown that MET-induced bone resorption, as well as MET induced stimulation of FGF23 is inhibited by treatment with 50 μM 2-APB, which blocks intracellular Ca signaling or by treatment with 1 μM NS398, which blocks cyclooxygenase 2, both integral steps in MET stimulation of bone resorption. Comparable inhibition of MET-induced IFRD1 was also observed after incubation of osteoblasts with 2-APB or NS398.

Conclusions: Thus, IFRD1, a transcription factor which modulates the wnt/β-catenin pathway, was stimulated by MET and may be important in the mechanism of MET-induced bone resorption as well as MET-induced stimulation of FGF23 production. These results suggest that the wnt/β-catenin pathway could be a therapeutic target to decrease MET-induced bone loss.

Funding: Private Foundation Support

SA-OR085

The Association between Skeletal Muscle Mass Surrogates and the Risk of Bone Fracture in Patients Undergoing Hemodialysis: The Q-Cohort Study Shunsuke Yamada,[1] Masatomo Taniguchi,[3] Masanori Tokumoto,[2] Narihito Tatsumoto,[1] Hideki N. Hirakata,[3] Takanari Kitazono,[1] Kazuhiko Tsuruya.[1] *[1]Dept of Medicine and Clinical Science, Kyushu Univ, Fukuoka, Japan; [2]Dept of Internal Medicine, Fukuoka Dental College, Fukuoka, Japan; [3]Fukuoka Renal Clinic, Fukuoka, Japan.*

Background: CKD is an independent risk factor for bone fracture. There is a close interplay between bone and skeletal muscle. It still remains unknown whether lower skeletal muscle mass increases the risk of bone fracture in hemodialysis (HD) patients.

Methods: The present study was an prospective, observational study consisting of 3030 outpatients undergoing HD. As surrogates of skeletal muscle mass, we used both serum creatinine (Cr) and Cr index. Cr index was calculated using age, sex, serum Cr level, and Kt/V for urea. The association between the incidence of bone fracture and the baseline creatinine (Cr) index or serum Cr level was examined. Patients were stratified by sex-specific quartiles based on serum Cr or Cr index. Cox proportional hazard model was used for analyses.

Results: During the median observational period of 3.9 years, 140 patients developed bone fracture. In the multivariable analysis, the risk of bone fracture was significantly higher in the lowest Cr index quartile (Q1) compared to the highest Cr index quartile (Q4) as the reference value in both male and female (multivariable-adjusted hazard ratio [95% confidence intervals]: men; Q1, 6.26 [1.87-23.66]; Q2, 4.33 [1.49-14.62]; Q3, 1.68 [0.55-5.75]; Q4, 1.00; *P*=0.008 for trend, women; Q1, 4.25 [1.45-13.77]; Q2, 3.00 [1.19-8.23]; Q3, 1.92 [0.81–4.93]; Q4, 1.00; *P*=0.007 for trend). Similarly, lower serum Cr level was associated with the increased risk of bone fracture in both men and women. Effects modification regarding the association between bone fracture and Cr index or serum Cr level was not observed across baseline characteristics.

Conclusions: Lower skeletal muscle mass surrogates were associated with the increased risk of bone fracture in HD patients. Further studies are required to know whether maintaining skeletal muscle mass prevents bone fracture in HD population.

SA-OR086

Progression of Medial Arterial Calcification in End-Stage Renal Diseaase W. Charles O'Neill, Shumila Manzoor, Syed Mustafa Ahmed. *Renal Div, Emory Univ, Atlanta, GA.*

Background: Medial arterial calcification is an important lesion in end-stage renal disease (ESRD) but little is known about its progression and the effect of different treatments because of the inability of previous studies to quantify it and distinguish it from atherosclerotic calcification. Breast arterial calcification, which is readily apparent on mammograms (MGs), exclusively medial, and correlates with peripheral arterial calcification and clinical outcomes, provides a unique opportunity to follow the progression of medial calcification.

Methods: Women with at least 2 MGs performed while receiving hemodialysis (HD) or peritoneal dialysis (PD), or after renal transplantation were identified from a computerized search of medical records. Warfarin use was an exclusion. Lengths of calcified arteries were summed and expressed as mms per breast (+/- SE). Intraobserver and interobserver correlations were 0.99 and 0.98, and interstudy variability was 9.8%. Significance was by nonparametric testing.

Results: Progression of breast arterial calcification (BAC) was 8.7 +/- 4.4 mm/y pre-ESRD (mean: 0.36 yrs; n=30) and 30.4 +/- 7.1 mm/y during HD (n=42; p<0.01). The rate during PD was 4.7 +/- 2.5 mm/y (n=24) and did not differ from the pre-ESRD rate. To exclude other patient effects, rates were compared in the same patients before and after initiation of HD and increased from 3.6 +/- 1.8 to 18.9 +/- 8.8 mm/y (n=17; p<0.05). Progression was less frequent (25% vs. 95%) and slower (3.5 +/- 1.5 vs. 44.9 +/- 11.4 mm/y) in patients with no baseline BAC, but was still greater during HD (4.5 +/- 2.2 mm/y) than PD (1.3 +/- 0.8 mm/y; p=0.01). After renal transplantation, BAC rate was 3.8 +/- 1.8 mm/y (n=27; mean serum creatinine 1.17 +/- 1.2 mg/dl), less than the pre-ESRD rate (p<0.01). There was no significant reversal of BAC in any patient.

Conclusions: Medial arterial calcification accelerates in patients on hemodialysis but not peritoneal dialysis. Renal transplantation slows progression to below pre-ESRD rates but does not reverse calcification. These results indicate that hemodialysis or related factors promote medial arterial calcification and that calcification persists when normal renal function is restored.

Funding: Clinical Revenue Support

SA-OR087

Small Vessel and Soft Tissue Histology in End-Stage Renal Disease: Specificity of Diagnostic Criteria for Calciphylaxis Carla L. Ellis,[1] W. Charles O'Neill.[2] *[1]Pathology and Laboratory Medicine, Emory Univ, Atlanta, GA; [2]Renal Div, Dept of Medicine, Emory Univ, Atlanta, GA.*

Background: Calciphylaxis (calcific uremic arteriolopathy) is a rare disease characterized by skin ulceration and tissue necrosis presumably resulting from vascular calcification that typically occurs in end-stage renal disease (ESRD). Histologic criteria include intimal hypertrophy, medial calcification, and/or thrombosis of small arteries, and extravascular (soft tissue) calcification, but their specificity is unknown. These features were examined in tissue from the margins of amputations performed in ESRD patients.

Methods: 26 amputations above (11) and below (15) the knee in 21 ESRD patients were identified from pathology records for 2014-2015. Sections from the margins were retrieved and both H & E and von Kossa stains were prepared and reviewed by a single pathologist. Chart review was performed by a single nephrologist.

Results: None of the patients had a clinical presentation suggestive of calciphylaxis. Average age was 63.7 years (range 43-83), 16 (76%) were male, 14 (67%) had diabetes, and 5 (24%) were treated with warfarin. Bulky, large vessel calcifications were identified in 24/26 (92%) of specimens, consistent with peripheral arterial disease (PAD). However, 8/26 (31%) also showed dermal/epidermal arteriolar calcification, and 11/26 (42%) showed extravascular soft tissue calcification. Intimal hyperplasia and small vessel thrombosis were observed in 3 and 4 cases respectively (12 and 15%). Arteriolar calcification and thrombosis were observed in 5 and 3 of the 13 patients with diabetes mellitus but only 1 and none of the 8 patients without diabetes. There was no association with warfarin use.

Conclusions: Histopathologic findings historically associated with calciphylaxis on skin biopsies can also be seen in viable tissue from unaffected ESRD patients. While the results are not necessarily applicable to patients without PAD, they do indicate that histologic findings ascribed to calciphylaxis can be seen in the absence of clinical manifestations, particularly in diabetics. This calls into question the specificity of the histologic diagnosis of calciphylaxis.

SA-OR088

Gli1+ Adventitial MSC Are Vascular Smooth Muscle Cell Progenitors and Key Drivers of Vascular Calcification in CKD Rafael Kramann,[1] Janewit Wongboonsin,[2] Nadine Kaesler,[1] Christoph Kuppe,[1] Benjamin D. Humphreys.[2] *[1]Div of Nephrology, RWTH, Aachen, Germany; [2]Div of Nephrology, Washington Univ, St. Louis.*

Background: We recently demonstrated that Gli1 expression defines perivascular mesenchymal stem cells (MSCs). A role for adventitial MSCs in vascular injury, repair and calcification has been hypothesized but the absence of a specific *in vivo* marker for MSCs has prevented progress.

Methods: We used genetic lineage analysis to trace the fate of $Gli1^+$ cells in Gli1CreER;tdTomato mice subjected to femoral artery wire injury. Triple transgenic Gli1CreER;tdTomato;ApoEKO and Gli1CreER;iDTR,ApoEKO mice subjected to subtotal nephrectomy or sham surgery followed by western diet versus standard chow were used for fate tracing and ablation experiments during vascular calcification.

Results: We demonstrate that FACS isolated adventitial $Gli1^+$ cells are MSC that can differentiate into mature VSMCs *in vitro*. Single cell qPCR of adventitial $Gli1^+$ cells indicates a heterogeneous population that gradually loses expression of progenitor markers and acquires expression of VSMC markers. *In vivo* genetic fate tracing experiments demonstrate that adventitial $Gli1^+$ MSC migrate into the vascular media to become mature VSMCs during aging. Following acute injury to the femoral artery >50% of newly formed VSMCs in media and neointima are derived from adventitial $Gli1^+$ MSC. During chronic arterial injury with vascular calcification $Gli1^+$ cells robustly migrate into media and neointima where they differente into $Runx2^+$ calcifying vascular cells (CVCs). Costaining experiments with markers of secretory and contractile VSMCs suggest that $Gli1^+$ cells first acquire a VSMC phenotype but subsequently maldifferentiate to CVCs during vascular calcification. Genetic ablation of $Gli1^+$ cells by diphtheriatoxin before onset of CKD in Gli1CreER;tdTomato;ApoEKO mice completely abolished calcification of both media and intima.

Conclusions: Adventitial $Gli1^+$ MSC are progenitors of VSMCs during aging and acute arterial injury repair. However, in CKD with vascular calcification $Gli1^+$ cells are the key progenitors of CVCs in media and intima. They represent an important and novel therapeutic target.

Funding: NIDDK Support

SA-OR089

Coronary Calcification and Mortality in Patients with Advanced Chronic Kidney Disease: A 10-Year Follow-Up Marta Cano Megías,[1] María Perez Fernandez,[1] Gabriel De Arriba,[2] Diego Rodriguez Puyol,[1] Concepcion Alvarez Sanz,[4] Patricia De Sequera,[3] Hanane Bouarich.[1] *[1]Nephrology, Hospital Univ Principe de Asturias, Alcalá de Henares, Madrid, Spain; [2]Nephrology, Hospital Univ de Guadalajara, Guadalajara, Spain; [3]Nephrology, Hospital Univ Infanta Leonor, Madrid, Spain; [4]Radiology, Hospital Univ Principe de Asturias, Alcalá de Henares, Madrid, Spain.*

Background: Haemodialysis and advanced CKD patients have a higher prevalence of coronary calcification (CC) than general population. Previous studies have suggested a potential predictive value of CC on mortality, regardless of traditional cardiovascular (CV) risk factors. However, this mortality predictive ability is not well defined in long-term follow-up in CKD population.

Methods: A 10-year prospective longitudinal study was conducted in 137 CKD patients (stage IV-V and dialysis). A non-enhanced multi-slice coronary computed tomography was performed at baseline. CC was assessed with the Agatston method. Patients were stratified according to its coronary calcium score (CCS): CCS<400, n=53;and CCS≥400,n=84. Patients were followed for median 88 months (30-111), all-cause and CV mortality were recorded.

Results: The median age was 66 years. The median CCS was 600 (70-1794). The overall mortality rate was 58% (40% to CV events). Patients with severe calcification (CCS≥400) showed higher total and CV mortality than those with lower calcification (CCS<400); 75% vs. 30% and 34,5% vs. 5,6% respectively (p<0.001). Patients with CCS≥400, were older, have a previous history of type 2 DM and cardiac events, and lower serum albumin levels. In a multivariate Cox model, severe CCS (≥400) was a significant predictor of total mortality in haemodialysis patients (HR 4.12; 95%CI 1.83 to 9.3,p=0.001), whereas it reached significance in the CV mortality in the whole serie (HR 5.01; 95%CI 1.28 to 19.59,p=0.02). The Kaplan-Meier curves of total and CV mortalities were statistical different according to CCS (p<0,001).

Conclusions: During 10-years follow-up period mortality rate was higher among patients with severe coronary calcifications, especially CV mortality. Coronary calcifications might be a proper marker to estimate cardiovascular risk in CKD patients.

SA-OR090

Assessment of Arterial Calcification, Vascular Inflammation, Bone Mineral Density and Metabolism Using Fluorodeoxyglucose-PET/CT in Patients on Maintenance Dialysis: Focused on Relationship with PTH Level Young-Joo Kwon, Jieun Kim, Gang Jee Ko, Yoonkyung Song. *Div of Nephrology, Korea Univ, Seoul, Republic of Korea.*

Background: Aims of our study are to find factors associated with, and relationships between, aortic and coronary vascular calcification, vascular inflammation, vertebral bone mineral density(VBMD) and bone metabolism in patients on maintenance dialysis with FDG PET-CT, focused on the relationships with PTH level. Furthurmore, we tried to assess simple X-ray methods in predicting vascular calcification scores.

Methods: Thirty patients on hemodialysis (HD, n=15) or peritoneal dialysis (PD, n=15) were enrolled (both >6month). Calcification scores of thoracic (TCS), abdominal (ACS), total aorta (TACS), coronary arteries (CCS) were assessed by Agatston method. Right carotid SUV and target-to-background-ratio(CSUV/CTBR) was used for vascular inflammation measurement and L-spine maximal SUV(MSUV) for bone metabolism. VBMD was measured as 'trabecular' and 'total' by single slice QCT method. Patients were classified into 3 groups based on K/DOQI and KDIGO PTH target level. In addition, L-spine lateral and chest PA/Lateral films were used to assess various scoring methods in predicting CT-based scores.

Results: Significant calcification was found in 93%(aorta) and 62%(coronary) of the patients. The calcification scores were significantly related to one another. CCS correlated with HbA1c, and was higher in HD patients. Aortic calcification score(AC) was associated with age and serum calcium level. 'Optimal' PTH group by KDOQI tended to have lower CCS and AC. VBMD was only related to duration of dialysis. MSUV was not related to other variables. CSUV/CTBR correlated with LDL level. Simple X-ray scores well correlated with AC.

Conclusions: It seems reasonable to maintain optimal PTH levels according to KDOQI, not KDIGO guideline, in terms of vascular calcification. Our patients on maintenance dialysis had no significant vascular inflammation but showed highly prevalent vascular calcifications. The relationship between bone mineral density/bone metabolism and vascular calcification is unclear by FDG-PET/CT. Simple X-ray methods can predict CT-based aortic calcification scores.

Funding: Private Foundation Support

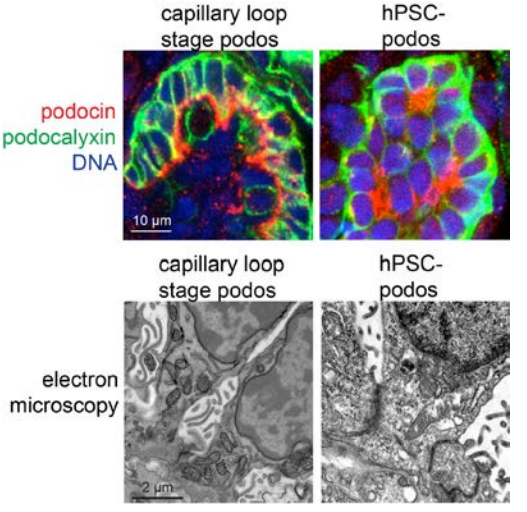
SA-OR091

Modeling Podocyte Development with Human Kidney Organoids Derived from Pluripotent Stem Cells Yong Kyun Kim,[1] Ramila E. Gulieva,[1] Stefan Czerniecki,[1] Nelly M. Cruz,[1] Laura V. Islas,[1] Craig R. Brooks,[2] Benjamin S. Freedman.[1] *[1]Div of Nephrology, Kidney Research Inst, and Inst for Stem Cell and Regenerative Medicine, Dept of Medicine, Univ of Washington, Seattle, WA; [2]Renal Div, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.*

Background: Podocytes derived from human pluripotent stem cells (hPSC-podos) have recently been generated in kidney organoids, with great potential for modeling complex development and regeneration. We investigated the structure and function of hPSC-podos, compared to developing mammalian podocytes.

Methods: hPSC-podos in kidney organoids were analyzed by confocal immunofluorescence and transmission electron microscopy. CRISPR/Cas9 was applied to hPSCs to knock out podocalyxin, a heavily sialylated podocyte glycoprotein. Kidney sections from wild-type or *Podxl*$^{-/-}$ mice were also examined.

Results:



Localization of nephrin, podocin, synaptopodin, podocalyxin, and WT1 in kidney organoids closely resembled developing capillary loop stage podocytes *in vivo*. Ultrastructurally, hPSC-podos formed basement membrane junctional domains containing slit diaphragm components. The apicolateral membranes of hPSC-podos were covered with microvilli and podocalyxin, and did not form junctions. Genetic knockout of podocalyxin resulted in ablation of apicolateral microvilli and failure of junctional components to migrate basally. These features precisely phenocopied developing mammalian podocytes in wild-type and *Podxl*$^{-/-}$ mice.

Conclusions: hPSC-podos *in vitro* correspond to capillary loop stage podocytes *in vivo*. Podocalyxin-mediated microvillus formation regulates podocyte cell spacing and junctional migration in mouse and man. The capacity of hPSC-podos to reveal and recapitulate developmental mechanisms makes them a powerful new tool for kidney disease modeling and regeneration. (Supported by Northwest Kidney Centers).

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SA-OR092

Localized mRNA Translation Mediated by Staufen Is a Novel Mechanism Regulating Cytoskeletal Reorganization in Response to Podocyte Injury Valerie A. Schumacher,[1] Jessica J. Harris,[1] Astrid Weins,[2] Britta George,[3,4] Benjamin D. Humphreys,[5] Shuang Yang.[1,6] *[1]Urology, Boston Children's Hospital, Boston, MA; [2]Pathology, Brigham and Women's Hospital, Boston, MA; [3]Renal-Electrolyte and Hypertension Div, Univ of Pennsylvania, Philadelphia, PA; [4]Medizinische Klinik und Poliklinik D, Universitätsklinikum Münster, Muenster, Germany; [5]Renal Div, Washington Univ School of Medicine, St. Louis, MO; [6]Medical College of Nankai Univ, Tianjin, China.*

Background: Podocytes sometimes recover from foot process effacement indicating that there is an intrinsic plasticity inherent in foot process architecture. Our study focuses on the role of localized mRNA translation as a mechanism to dynamically regulate reorganization of the actin cytoskeleton in foot processes and modulate podocyte cell-matrix adhesion, thereby maintaining the glomerular filtration barrier during injury.

Methods: A cell biological and gene targeting approach was used to study the role of local mRNA translation in podocytes.

Results: We show that the RNA-binding protein Staufen2, previously demonstrated to mediate RNA transport and localized translation in neurons, is expressed in podocytes and localizes to focal adhesions *in vitro* and foot processes *in vivo*. Moreover, Staufen2 and translating ribosomes are increased in areas of foot process effacement. Next, we show that Staufen2-bound RNAs in podocytes are enriched for cytoskeletal assembly and cell-matrix adhesion regulators, one example being the GEF *Dock5*. *Stau2* knockdown in immortalized

podocytes affects *Actb* mRNA localization and *Dock5* mRNA stability and results in cell detachment as well as impaired re-establishment of actin stress fibers upon recovery from injury. Lastly, we generated *Stau2* single and *Stau1/2* double knockout (DKO) mice; these mice had normal baseline kidney function but DKO mice developed massive proteinuria and foot process effacement in response to Adriamycin, far greater than observed in control, or *Stau1* and *Stau2* single knockouts.

Conclusions: Localized mRNA translation mediated by Staufen represents a novel mechanism to regulate cytoskeletal reorganization and cell-matrix adhesion in response to podocyte injury.

Funding: NIDDK Support, Private Foundation Support

SA-OR093

Novel Mat of Contractile Actin Filaments Formed at the Base of Podocytes during the Process of Foot Process Effacement

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Background: Because the diffraction limit of light microscopy restricts the resolution of structures smaller than 200 nm such as podocyte foot processes and slit diaphragms, imaging the podocyte cytoskeleton is challenging. Traditional tissue preparation methods don't preserve the actin cytoskeleton enough, further restricting our ability to view changes after podocyte injury. We developed a new method of cytoskeletal preservation that allowed us to image actin and actin-associated molecules in kidney glomeruli. 2D and 3D superresolution imaging enabled us to study the architecture of the podocyte in normal and diseased states.

Methods: Two superresolution methods, STORM and Airyscan, were used to study the changes of the podocyte foot process in healthy and injured mouse glomeruli. Antibodies used are: synaptopodin (synpo), α-actinin-4 (Actn4), myosin IIa (myh9), nephrin, podocin.

Results: Synpo and Actn4 stained the center of healthy podocytes foot processes, while nephrin and podocin labeled between the foot processes. In injured podocytes, slit diaphragm proteins moved apically inside the effaced foot processes. While synpo and Actn4 clusters did not change upon injury, there was robust recruitment of myh9 to the base of the podocytes. Myh9 stained in alternating stripes with synpo and Actn4, suggesting the formation of contractile actin fibers during podocyte foot process effacement. 3D superresolution imaging confirmed that myh9 is part of sarcomere-like structures near the GBM in different injury models. In contrast, normal podocytes show myh9 staining only in primary podocyte processes. En face views of effaced foot processes showed that myh9, intertwined with synpo, covered the entire effaced area.

Conclusions: Using a new way of imaging the actin cytoskeleton, we visualized podocyte foot processes in healthy and diseased conditions. In the normal podocyte, contractile actin cables are present in primary processes, while the actin filaments in the foot processes are non-contractile. After foot process effacement, a mat of actin filaments form at the base of effaced podocytes and arrange in a sarcomere-like contractile network near the GBM.

Funding: NIDDK Support, Private Foundation Support

SA-OR094

Dynamics and Importance of Slit Diaphragm Molecules in Adulthood

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Background: Little is known on the inherent dynamics of the slit diaphragm proteins NEPHRIN, PODOCIN and NEPH1. While constitutive deletion of any of these genes leads to early perinatal lethality adult knock-out has so far only been described for *Nphs2*. We therefore generated inducible, podocyte-specific *Nphs1, Nphs2* and *Neph1* knock-out mice to assess whether adult deletion leads to divergent phenotypes.

Methods: 5 week old, inducible *Nphs1*NEFTA8rtTA*TeTOCre* (*Nphs1$^{\Delta pod}$*), *Nphs2*NEFTA8rtTA*TeTOCre* (*Nphs2$^{\Delta pod}$*) and *Neph1*NEFTA8rtTA*TeTOCre* (*Neph1$^{\Delta pod}$*) mice were treated with oral doxycycline for 7d and were analyzed functionally, biochemically and histologically.

Results: Kinetics of proteinuria considerably differed between the 3 genes. While *Neph1$^{\Delta pod}$* mice were the first to show proteinuria after 7d of treatment, *Nphs2$^{\Delta pod}$* mice followed at 11d. In both lines proteinuria rose quickly. Although proteinuria had reached an ACR of ~70 after 4w in *Neph1$^{\Delta pod}$* no histological changes were detectable, while *Nphs2$^{\Delta pod}$* showed severe glomerulosclerosis. Most interestingly *Nphs1$^{\Delta pod}$* mice despite a knock-out efficacy of 95% on mRNA and protein level at 1w did not show any proteinuria until 5w post induction, after which proteinuria only rose very slightly till 12w where a considerable acceleration could be noted. IF indicated that the remaining NEPHRIN resided within the plasma membrane pointing to potentially different pools of NEPHRIN within podocytes.

Conclusions: Adult inducible knock-out of *Nphs1, Nphs2* and *Neph1* revealed that especially NEPHRIN has a different dynamic and turnover than PODOCIN and NEPH1. While *Nphs2$^{\Delta pod}$* and *Neph1$^{\Delta pod}$* mice developed proteinuria after 50% of their protein content had vanished, *Nphs1$^{\Delta pod}$* mice could maintain a tight barrier with as little as 5% of protein.

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SA-OR095

Mechanical Overload May Lead to Podocyte Damage by Increasing Podocyte [Ca2+] through TRPC6 Channels and P2Y2 Receptors

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Background: TRPC6 channels are known to be one of the important Ca^{2+} influx pathways. The effect of extracellular nucleotides by the activation of TRPC6 through P2Y receptors on podocyte [Ca^{2+}] has also been reported. However, the molecular mechanism how mechanical overload leads to podocyte injury is still elusive. We aimed to study and quantitatively visualize the dynamic effects of high intra-glomerular capillary pressure, a solely mechanical stimulation on podocyte [Ca^{2+}] and the role of TRPC6 and P2Y2 receptors in mechanosensation.

Methods: Time-lapse high resolution multiphoton microscopy imaging on intact living kidneys and freshly dissected in vitro microperfused glomerulus of wild type (WT), TRPC6 transgenic (TG), TRPC6 knockout (KO), and P2Y2 KO mice was used to directly visualize the changes in podocyte [Ca^{2+}] after acute isolated intra-glomerular capillary pressure elevation. All mice expressed the intensely green calcium indicator, GCaMP3, only in podocytes. Changes in single cell GCaMP3 fluorescence intensity were used as an indicator for podocyte [Ca^{2+}] changes.

Results: Acute intra-glomerular capillary pressure elevation was induced by obstructing the efferent arteriole with laser induced microthrombus in vivo and by a micropipette in vitro. In WT mice GCaMP3 fluorescence intensity in podocytes increased 2.9-fold in vitro and more than 2-fold in vivo as compared to baseline. Podocyte GCaMP3 fluorescence intensity in TRPC6 TG mice increased more than 5-fold. In TRPC6 KO and P2Y2 KO mice the effect of acute mechanical overload on podocyte [Ca^{2+}] was significantly reduced, the increase in GCaMP3 fluorescence intensity was 1.3-fold and 1.41-fold, respectively.

Conclusions: This study demonstrated direct visual evidence of the effect of high intra-glomerular capillary pressure on podocyte [Ca^{2+}] and the important pathological role of TRPC6 channels and P2Y2 receptors in the related podocyte injury. Podocyte TRPC6 and P2Y2 are promising therapeutic targets in conditions with high intra-glomerular capillary pressure, such as diabetic and hypertensive nephropathy for the prevention of CKD.

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SA-OR096

Dynamic Control of Focal Adhesions in Podocyte Health and Disease

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Background: Pericyte-like podocytes form the outer part of the glomerular filter where they have to withstand the enormous transcapillary filtration forces driving glomerular filtration. Detachment of podocytes from the glomerular basement membrane is a common hallmark and final pathway in various glomerular diseases. However, little is known about the regulation of podocyte adhesion in response to continous physical filtration and under disease conditions *in vivo*.

Methods: We screened for podocyte specific focal adhesome (FA) components employing genetic reporter models in combination with iTRAQ-based quantitative mass spectrometry. Applying bioinformatic filtering algorithms allowed for the idenfitication of podocyte specific FA components. Super resolution microscopy (STORM) was employed to validate candidates. In vivo characterization was performed using newly generated mouse models for EPB41L5 and CORO2B. CRISPR/CAS9 genome edited immortalized podocyte cell lines as well as primary podocytes were analyzed *in vitro* using life imaging.

Results: The MS-based FA mapping approach led to the identification of two novel podocyte specific FA components, the FERMT protein EPB41L5 and the WD40 protein CORO2B. Genetic deletion of *EPB41L5 in vivo* resulted in severe proteinuria, detachment of podocytes and development of FSGS. By binding and recruiting the RhoGEF ARGHEF18 to the leading edge EPB41L5 directly controls actomyosin contractility and subsequent maturation of focal adhesions. Furthermore, these effects were mediated in an ECM-dependent manner. Surprisingly, deletion of CORO2B *in vivo* prevented podocyte damage in two different stress models, via modulating focal adhesion disassembly.

Conclusions: Collectively, these observations support a novel concept of podocyte intrinsic balancing of FA turnover to maintain the integrity of the kidney filtration barrier.

SA-OR097

The Podocyte-Specific Induction of Krüppel-Like Factor 15 Attenuates Glomerulosclerosis in FSGS

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Background: Krüppel-Like Factor 15 (KLF15) is a critical regulator of podocyte differentiation. Klf15 is also required for steroid-induced restoration of podocyte differentiation markers. Podocyte-specific loss of *Klf15* exacerbates podocyte injury in proteinuric murine models. Furthermore, the level of KLF15 expression in podocytes correlates with steroid-responsiveness MCD and primary FSGS. We now hypothesize whether the podocyte-specific induction of *hKLF15* in mice attenuates FSGS.

Methods: Full-length ORF cDNA of *KLF15* was cloned into a TRE plasmid. Mice with *TRE-hKLF15* and *Nphs2-rtTA* transgenes (*ΔhKLF15*) exhibited doxycycline (DOX) inducible podocyte-specific KLF15mRNA and protein expression. HIV-1 transgenic (Tg26) mice were crossed with *ΔhKLF15* mice to assess the role of KLF15 in FSGS murine model.

Results: DOX-treated Tg26;*ΔhKLF15* exhibited a significant reduction in albuminuria (40-fold), foot process effacement, glomerulosclerosis, serum BUN and creatinine, interstitial inflammation, glomerular epithelial cell proliferation (Claudin1, Ki67), podocyte differentiation markers (Nephrin, Synaptopodin, Podocin, WT1), kidney fibrosis (αSMA, Col1α1, Fibronectin, Vimentin) as compared to DOX-treated *Tg26* mice. In addition, DOX-treated Tg26;*ΔhKLF15* exhibited a 50% increase in survival as compared to DOX-treated *Tg26* mice at 10 weeks of age. TRANSFAC promoter analysis was performed to identify genes with binding sites for KLF15. Gene-set enrichment analysis of these genes identified a significant increase in the pathways involved in suppression of Wnt/β-catenin pathway. Finally, we validated that DOX-treated *Tg26;ΔhKLF15* exhibited a reduction in Wnt/β-catenin pathway (*C-myc, Lef1*) compared to DOX-treated *Tg26* mice in isolated glomeruli.

Conclusions: Taken together, these data suggest that upregulation of *KLF15* in the podocyte abrogates FSGS, kidney fibrosis, and overall mortality by inhibiting Wnt/β-catenin signaling in HIV-1 transgenic mice.

Funding: NIDDK Support

SA-OR098

Excessive Proliferator-Activated Receptor Gamma Coactivator 1a (PGC1a) Expression and Mitochondrial Biogenesis in Podocytes Results in Cell Cycle Entry and Collapsing Glomerulosclerosis Szu-Yuan Li,[1,2] Jihwan Park,[1] Chengxiang Qiu,[1] Matthew Palmer,[3] Katalin Susztak.[1] *[1]Medicine, Univ of Pennsylvania, Philadelphia, PA; [2]Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [3]Pathology and Laboratory Medicine, Univ of Pennsylvania, Philadelphia, PA.*

Background: Mutations in mitochondrial genes can result in FSGS. Acquired mitochondrial defects in podocytes have been described in other forms of glomerular disorders. We hypothesized that increasing mitochondrial biogenesis in podocytes would be beneficial for glomerular disease. Pgc1a is the main transcriptional regulator of mitochondria biogenesis and tubule specific expression of PGC1a has been beneficial in acute and chronic kidney injury.

Methods: Gene expression were analyzed in microdissected human glomeruli using Affymetrix gene expression arrays. Podocyte specific inducible PGC1a transgenic mice were created by breeding Nephrin rtTA with tetO-PGC1α mice. We have studied PGC1α function in cultured murine podocytes using an adenoviral expression system.

Results: Glomerular expression of mitochondrial specific genes and PGC1a showed significant positive correlation with kidney function, indicating that mitochondrial content likely decreased with GFR. PGC1a expression was also decreased in diabetic mouse models. Cell type specific inducible expression of PGC1a in podocytes increased mitochondrial number and size, however, animals developed albuminuria. Histologically examination showed glomerular hypercellulcarity, cellular crescent formation and glomerular sclerosis and podocytes were positive for proliferation marker PCNA, resembling collapsing FSGS. Overexpression of PGC1a in cultured podocytes resulted in an increase in metabolism related gene expression and oxygen consumption rate. Excess PGC1a also caused uncontrolled mitochondria biogenesis and fusion, accompany with cell cycle reentry.

Conclusions: Decreased podocyte PGC1a expression and mitochondrial content is a consistent feature of chronic glomerular disease. While PGC1a improves podocyte energy metabolism, excessive activation promotes podocyte proliferation and result in glomerulosclerosis, indicating that there is a narrow therapeutic window for PGC1a.

Funding: NIDDK Support

SA-OR099

SGPL1 Mutations Lead to Sphingosine-1-Phosphate Lyase 1 Deficiency with Nephrotic Syndrome, Deficiency of Cellular Immunity, Adrenal Insufficiency, and Ichthyosis in Humans Svjetlana Lovric,[1] Sara Gonçalves,[2,5] Heon Yung Gee,[1] Babak Oskouian,[3] Shazia Ashraf,[1] Won-Il Choi,[1] David Schapiro,[1] Martin Zenker,[4] Corinne Antignac,[5] Julie D. Saba,[3] Friedhelm Hildebrandt.[1] *[1]Div of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston, MA; [2]Imagine Inst, Paris, France; [3]Children's Hospital, Oakland Research Inst, Oakland, CA; [4]Inst of Human Genetics, Univ Hospital Magdeburg, Magdeburg, Germany; [5]Dept of Genetics, Necker Hospital, Paris, France.*

Background: SGPL1 *(*sphingosine-1-phosphate lyase) is an intracellular enzyme responsible for the final step in sphingolipid breakdown, converting S1P into ethanolamine phosphate and hexadecenal. S1P functions as a ligand for G protein coupled receptors that mediate autocrine and paracrine signals controlling cell migration and proliferation. Mouse models of *Sgpl1* exhibit proteinuria and mild acanthosis with orthokeratotic hyperkeratosis.

Methods: We performed homozygosity mapping (HM) and WES to identify loss of function mutation in >200 individuals with steroid resistant nephrotic syndrome (SRNS). The function and localization of SGPL1 protein were examined in podocytes and mesangials cells.

Results: We identified 6 different recessive mutations in *SGPL1* (p.S3Kfs*11, p.R222Q, p.S346I, p.Y416C, p.E132G and p.R278Gfs*17) in 5 families. Affected individuals exhibited SRNS, acanthosis and orthokeratosis, deficiency of cellular immunity and facultative adrenal insufficiency. All identified mutations resulted in reduced or absent SGPL1 protein and/or enzyme activity. Overexpression of cDNA representing mutations of SRNS patients resulted in subcellular mislocalization of SGPL1. Immunofluorescence revealed SGPL1 expression in mouse podocytes and mesangial cells. Knockdown of Sgpl1 in rat mesangial cells (RMC) reduced cell migration rate, which was partially rescued by VPC23109, an S1P receptor antagonist. Knockdown of SGPL1 in RMC resulted in a decrease of active RAC1.

Conclusions: We have identified *SGPL1* mutations as a novel cause of human SRNS, acanthosis and adrenal insufficiency. Our findings delineate a new RAC1-mediated molecular pathogenesis of syndromic SRNS that may be amenable to treatment.

Funding: Other NIH Support - R01

SA-OR100

APOL1 Risk Alleles (G1, G2) Induced Kidney Disease Development Is Dose Dependent and Reversible Jing Bi Karchin,[1] Pazit Beckerman,[1] Ae Seo Deok Park,[1] Matthew Palmer,[2] Jeffrey H. Miner,[3] Katalin Susztak.[1] *[1]Div of Renal-Electrolyte and Hypertension, Univ of Pennsylvania, Philadelphia, PA; [2]Dept of Pathology and Laboratory Medicine, Univ of Pennsylvania, Philadelphia, PA; [3]Div of Nephrology, School of Medicine, Washington Univ, St. Louis, MO.*

Background: Two coding variants (G1 and G2) in the Apolipoprotein L1 (APOL1) gene increase the risk of developing chronic kidney disease (CKD) by 2-80 fold in African Americans. However, it remains unclear what triggers disease development in 2 risk allele carriers. Endogenous APOL1 expression can be stimulated by inflammatory cytokine interferon γ (IFNγ), which also triggers albuminuria in 2 risk allele subjects. Therefore, we hypothesized that the APOL1-associated kidney disease development depends on risk allele APOL1 expression levels.

Methods: We generated conditional inducible G0, G1 and G2 APOL1 transgenic animals and crossed them with the nephrin rtTA to induce podocyte specific expression. In these animals transgene expression can be controlled by doxycycline. Renal function was evaluated by albumin ELISA and structural changes by light and electron microscopy. *In vitro* cytotoxicity was analyzed by propidium iodide and intracellular ATP content.

Results: APOL1 expression levels showed significant variations between the different founder lines. Risk allele APOL1 levels (G1 and G2) strongly correlate with the severity of albuminuria, which was 20 fold higher than in mice expressing reference allele (G0). Similarly, glomerulosclerosis was more severe in mice with higher expression of risk allele APOL1. *In vitro* experiments supported the *in vivo* results and indicated that risk allele APOL1 causes an increased inflammatory type cell death (pyroptosis) in a doxycycline-dose dependent manner. Furthermore, initial studies indicated that albuminuria development was reversible; upon discontinuation of doxycycline diet, APOL1 expression and albuminuria returned to baseline.

Conclusions: APOL1 risk (G1 or G2) variant levels likely play an important role in disease development. Our results suggest that reducing risk allele APOL1 expression could be a realistic targeting strategy in patients with high-risk genotype.

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SA-OR101

Does Acute Declines in Renal Function during Intensive BP Lowering Associate with Higher Risk of ESRD during Long-Term Follow-Up? Elaine Ku,[1] Kirsten L. Johansen,[1] Vito M. Campese,[2] Jennifer J. Gassman,[3] Miroslaw Smogorzewski,[2] Chi-Yuan Hsu.[1] *[1]UCSF; [2]USC; [3]AASK.*

Background: Intensive blood pressure (BP) lowering frequently leads to acute declines in renal function, which was demonstrated in the recent Systolic Blood Pressure Intervention Trial (SPRINT).The long-term implications of such declines–which have been thought to be "hemodynamic"/functional in nature -are unclear. We determined whether acute declines in renal function during the first three months of intensive BP lowering in the African American Study of Kidney Disease (AASK) trial (1995-2001) were associated with a higher long-term risk of ESRD.

Methods: The percent decline in renal function (by CKD-EPI equation) in AASK CKD trial participants (N=899) randomized to mean arterial pressure (MAP) target of <92 mm Hg (Strict BP arm) versus 102-107 mm Hg (Usual BP arm) was determined between time of randomization and month 3 of the trial (period of intensive BP lowering to achieve MAP goals). Risk of ESRD (ascertained through 2012) was compared among those with a <5%, 5-<20%, versus ≥20% decline in eGFR in adjusted Cox models.

Results: Up to a 20% decline in eGFR during anti-hypertensive therapy intensification in the Strict BP arm was not associated with a statistically significantly higher risk of ESRD during mean follow-up of 14.4 yrs, compared to the reference group of <5% decline in the Usual BP arm (HR 1.16; 95% CI 0.79-1.69). In contrast, a ≥5% decline in the Usual BP arm and ≥ 20% decline in Strict BP arm was associated with a higher risk of ESRD.

% decline in renal function	N	ESRD incidence (per 100 person years)	Hazard ratio (95%CI)	N	ESRD incidence (per 100 person-years)	Hazard ratio (95%CI)
	Usual BP Arm			Strict BP Arm		
<5%	307	2.8	1.0 (Reference)	265	2.9	1.05 (0.78-1.40)
5-<20%	76	5.8	2.14 (1.48-3.09)	107	3.2	1.16 (0.79-1.69)
≥ 20%	68	7.5	2.77 (1.92-4.00)	76	6.0	2.23 (1.53-3.24)

Conclusions: Acute declines in eGFR up to 20% during intensive BP lowering appears to be safe and is not associated with a higher long-term risk of ESRD.Further studies are needed to confirm the long-term safety of a <20% decline in eGFR during intensive BP lowering.

SA-OR102

Blood Pressure Parameters and Their Associations with Various Causes of Death in Chronic Kidney Disease Sankar D. Navaneethan,[1] Jesse D. Schold,[2] Susana Arrigain,[2] Stacey Jolly,[2] Matthew F. Blum,[2] Wolfgang C. Winkelmayer,[1] Joseph V. Nally.[2] *[1]Baylor College of Medicine, Houston, TX; [2]Cleveland Clinic, Cleveland, OH.*

Background: Previous observational studies reported higher risk for death with lower blood pressure levels in CKD. However, recent clinical trial evidence suggest targeting BP <120/80 mm Hg results in better cardiovascular outcomes even among those with CKD. We examined the associations of different BP levels with various causes of deaths in a CKD population.

Methods: We included 45,433 patients with eGFR 15-59 ml/min/1.73 m^2 (twice 90 days apart) with underlying hypertension and taking at least one antihypertensive agent. We ascertained overall and cause-specific deaths from State department of health mortality data and classified deaths into three major categories: a) cardiovascular b) malignancy and c) non-cardiovascular/non-malignancy conditions. We fitted Cox models for overall mortality and separate competing risk regression models for each major cause of death categories to evaluate their associations with various SBP (<110, 110-119, 120-129, 130-139, 140-149 and >150 mm Hg) and DBP levels (<50, 50-59, 60-69, 70-79, 80-89, >90 mm Hg) adjusting for relevant covariates.

Results: During a median follow-up of 3.9 years, 13,343 patients died. SBP <110,110-119 and >150 mm Hg (vs. 130-139) were associated with all-cause mortality and cardiovascular mortality (Table). DBP <50, 50-59 mm Hg (vs. 70-79 mm Hg) were associated with all-cause and non-cardiovascular/non-malignancy related deaths. DBP >90 mm Hg was associated with higher cardiovascular mortality.

Table. Associations of systolic blood pressure with all-cause and cause-specific mortality

SBP levels (mm Hg)	Overall* HR (95%CI)	Cardiovascular deaths SHR (95% CI)	Malignancy related deaths SHR (95% CI)	Non-cardiovascular/Non-malignancy deaths SHR (95% CI)
<110 mm Hg	**1.32 (1.24, 1.41)**	**1.42 (1.28, 1.58)**	1.07 (0.94, 1.21)	1.16 (1.04, 1.29)
110-119	**1.14 (1.07, 1.21)**	**1.19 (1.07, 1.31)**	0.92 (0.81, 1.04)	1.09 (0.98, 1.20)
120-129	0.99 (0.94, 1.05)	1.00 (0.91, 1.10)	0.95 (0.86, 1.06)	0.97 (0.89, 1.07)
130-139	Ref	Ref	Ref	Ref
140-149	1.01 (0.95, 1.07)	1.07 (0.97, 1.19)	0.98 (0.87, 1.10)	1.01 (0.92, 1.12)
> 150	**1.09 (1.03, 1.15)**	**1.24 (1.13, 1.36)**	1.01 (0.90, 1.13)	1.00 (0.91, 1.11)

Conclusions: Among non-dialysis dependent CKD population, SBP <120 and >150 mm Hg were associated with all-cause cardiovascular deaths, and DBP <60 mm Hg was associated with all-cause and non-cardiovascular/non-malignancy related deaths. Additional studies examining the differential associations with cause-specific death are needed.

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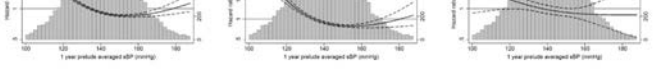
SA-OR103

Pre-ESRD Systolic Blood Pressure and Post-ESRD Mortality in Advanced CKD Patients Transitioning to Dialysis Keiichi Sumida,[1,2] Miklos Zsolt Molnar,[1] Praveen Kumar Potukuchi,[1] Fridtjof Thomas,[1] Jun Ling Lu,[1] Connie Rhee,[3] Elani Streja,[3] Kunihiro Yamagata,[2] Kamyar Kalantar-Zadeh,[3] Csaba P. Kovesdy.[1,4] *[1]Univ of Tennessee Health Science Center, Memphis, TN; [2]Univ of Tsukuba, Ibaraki, Japan; [3]Univ of California, Irvine, CA; [4]VA Medical Center, Memphis, TN.*

Background: Previous studies of non-dialysis dependent (NDD)-CKD patients have shown a J-shaped association of systolic blood pressure (SBP) with mortality. However, the association of SBP in late-stage NDD-CKD with post ESRD mortality remains unknown.

Methods: We identified 17,994 US veterans with advanced CKD transitioning to dialysis between 10/2007-9/2011 who had at least 3 outpatient BP measurements within 1 year prior to dialysis initiation. Associations of 1-year averaged pre-ESRD SBP categories (<120, ≥160 mmHg; and increments of 10 mmHg in between) with all-cause and cause-specific mortality during the 2-year period following dialysis initiation were examined using Cox (for all-cause) and competing risk (for cause-specific mortality) regressions and cubic splines adjusted for demographics, comorbidities, medications, CV medication adherence, and BMI, eGFR, and access type at dialysis initiation.

Results: The mean±SD of SBP was 141±16 mmHg. There was a reverse J-shaped association of SBP with all-cause and CV mortality (Figure). The lowest mortality was associated with SBP of 140-149 mmHg (multivariable adjusted hazard/subhazard ratios [95% CI] for SBP <120 [vs. 140-149] mmHg: 1.64 [1.51-1.79] and 2.01 [1.72-2.35] for all-cause and CV mortality, respectively). There was an inverse linear trend of association between SBP and infectious mortality, none of which were statistically significant.



Conclusions: Low SBP in late-stage NDD-CKD are associated with higher post-ESRD all-cause and CV mortality, but not infectious mortality. Further studies are needed to clarify ideal SBP levels among these patients.

Funding: NIDDK Support, VA Support

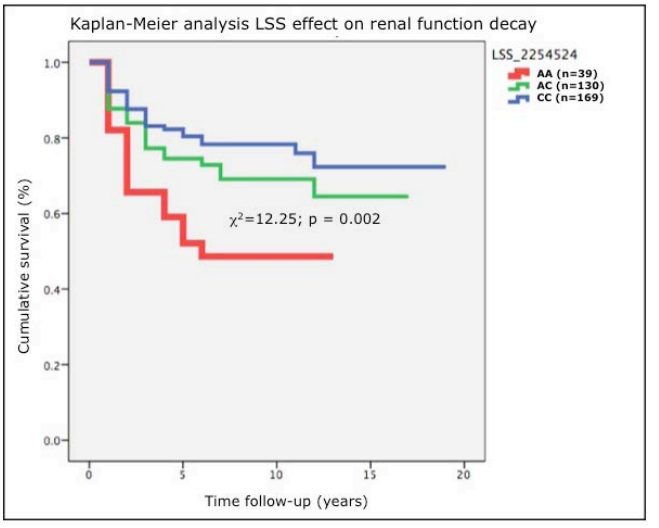
SA-OR104

Lanosterol Gene Polymorphisms Impact the Decline in Renal Function among Hypertensive Patients: A Follow-Up Study Simone Fontana,[1] Chiara Lanzani,[1] Rossella Iatrino,[1] Lorena Citterio,[1] Marco Simonini,[1] Simona Delli Carpini,[1] John Hamlyn,[2] Elena Brioni,[1] Stefano Tentori,[1] Paolo Manunta.[1] *[1]H San Raffaele, Italy; [2]Univ Maryland.*

Background: Cholesterol is an essential component of mammalian cell membranes and serves as a precursor for bile acids and various steroid hormones. The gene for Lanosterol (LSS), the first committed intermediate in cholesterol biosynthesis, has a missense polymorphism that affects EO biosynthesis in adrenocortical cells. Recently, we reported *(Hypertension 2016)* that the LSS AA genotype is associated with salt-sensitive hypertension. Exposure to increased circulating EO causes glomerular damage, and is a risk factor for acute kidney injury (*Cri Care Med 2015*). Furthermore, LSS gene is transcribed in discrete nephron sites (*JASN 2015*). In this report, we explore the importance of LSS in the progression of chronic kidney disease (CKD).

Methods: A cohort of 421 naïve hypertensive patients (female 188, male 233, age 42.7 ± 8.41 years), were enrolled in a follow-up study (5.32 ± 4.37 years) in which BP values were kept at goal with ACEi plus diuretic and, when needed, a Ca^{2+} channel antagonist. Renal function and other kidney parameters were evaluated every six months.

Results: BP values (SBP/DBP) after 4.6 years of follow-up were at target (LSS AA 138/85 AC 140/86 CC 141/85, respectively). The slope in eGFR (CKD-EPI) was 1.43±0.47 ml/1.73m^2/yr in the whole study population. When analysed according to the LSS genotype, the decline in renal function was double in the AA homozygotes (LSS AA -2.01±2.4 vs CC 2.23 ± 1.20 ml/1.73m^2/yr;p= 0.024). The impact of LSS polymorphisms was also reflected in patient renal survival (see Fig. 1).



Conclusions: Our findings further support the role of LSS polymorphisms and circulating EO in the progression of CKD. This metabolic pathway may accelerate the decline in renal function via its effects on glomerular podocyte and tubular components.

SA-OR105

Prevalence of White-Coat (WCH), Masked (MH), and Sustained Hypertension (SH) Using Uniform Definitions across Multiple Cohorts - The International Database of Ambulatory Blood Pressure in Renal Patients (I-DARE) Collaborative Group Paul E. Drawz,[1] Luca De Nicola,[2] Naohiko Fujii,[3] Francis B. Gabbai,[4] Jennifer J. Gassman,[4] Jiang He,[5] Satoshi Iimuro,[3] James P. Lash,[5] Roberto Minutolo,[2] Robert A. Phillips,[4] Luis M. Ruilope,[5] Susan P. Steigerwalt,[5] Raymond R. Townsend,[5] Dawei Xie,[5] Mahboob Rahman.[4,5] *[1]Univ of Minnesota; [2]Italian Cohort; [3]CKD-JAC; [4]AASK Cohort; [5]CRIC Cohort.*

Background: Differences in ABPM profiles based on ethnicity and geography have not been well studied. In addition, differences in definitions have made it hard to compare the prevalence of WCH, MH, and SH across cohorts.

Methods: A database of demographic, clinical, and ambulatory BP (ABP) data from renal patients from AASK, CRIC, Italy, CKD-JAC, and Spain was established. Participants with CKD, either eGFR <60ml/min/1.73m^2 or proteinuria, were included in this cross-sectional analysis. Cutoffs for controlled clinic and 24h ABP were 140/90 and 130/80mmHg, respectively.

Results: Characteristics of the 9,293 participants are shown in the table. The prevalence of MH was higher in AASK, CRIC, and CKD-JAC (30-38%) compared to the Italian and Spanish cohorts (7-10%) in which WCH was higher.

Covariate	Overall	AASK	CRIC	Italy	CKD-JAC	Spain
N	9293	581	1306	444	1017	5945
Age	64.5 (12.3)	62.1 (10.4)	63.8 (10.1)	65.3 (13.9)	61.2 (11.3)	65.5 (12.9)
Male (%)	51.8	62.5	56.6	59.0	63.3	47.2
eGFR (CKD-Epi)	46.7 (22.6)	34.4 (14.8)	38.3 (15.0)	38.5 (18.1)	34.2 (15.9)	52.5 (23.8)
Proteinuria (% pts)	35.1	48.0	49.7	71.4	40.7	26.9
BP category (%)						
- Controlled BP	23.7	30.8	46.6	21.2	37.3	15.8
- WCH	22.0	2.2	4.4	28.6	5.3	30.1
- MH	15.1	38.2	30.5	10.1	32.8	6.7
- SH	39.2	28.7	18.3	40.1	24.4	47.3

Conclusions: This international database of ABP in renal patients reveals a large heterogeneity of BP profiles across countries. This project represents an important advance in our ability to study racial/ethnic/geographic variations in ABP profiles. Future analyses will evaluate factors that contribute to elevated ABP, the effect of elevated ABP on adverse cardio-renal outcomes, and whether there are any ethnic or geographic differences in these associations.

Funding: NIDDK Support

SA-OR106

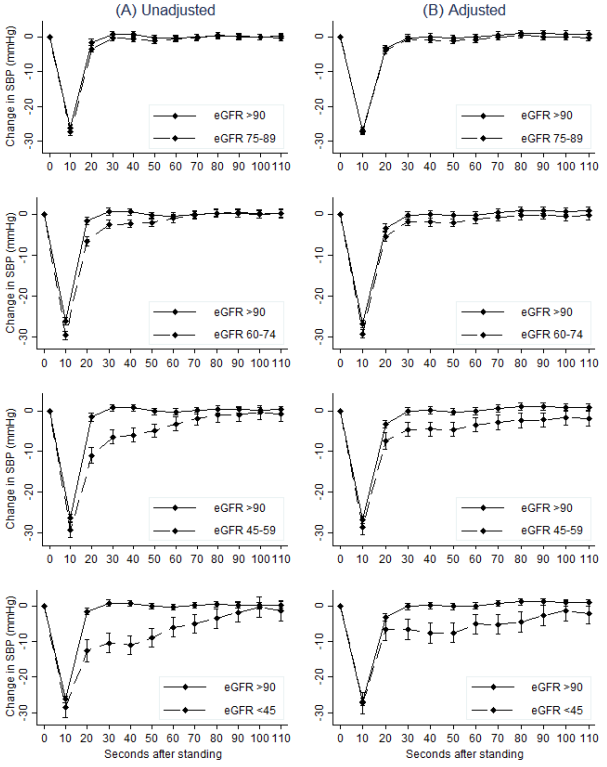
Graded Association between Kidney Function and Postural Blood Pressure Instability

Mark Canney,[1,2] Matthew D.l. O'Connell,[1] Donal J. Sexton,[1,2] Neil O'Leary,[1] Rose Anne M. Kenny,[1] Mark Alan Little,[2] Conall M. O'Seaghdha.[3] *[1]The Irish Longitudinal Study on Ageing, Trinity College Dublin; [2]Trinity Health Kidney Centre, Trinity College Dublin; [3]Nephrology Dept, Beaumont Hospital, Dublin.*

Background: Postural blood pressure (BP) instability is a predictor of cognitive dysfunction, falls and mortality. We sought to characterize postural BP behavior across the spectrum of estimated glomerular filtration rate (eGFR) in older adults.

Methods: Cross-sectional analysis of 4204 participants from The Irish Longitudinal Study on Ageing, a representative national cohort of community-dwelling adults aged ≥50yrs. Beat-to-beat BP was measured by finometry during a 2 minute active stand test. The primary predictor was cystatin C eGFR categorized as follows (mL/min/1.73m^2): ≥90(ref);75-89;60-74;45-59;<45. We used multivariable linear regression to model the association between eGFR groups and postural BP behavior, defined as the change from baseline in mean systolic BP (SBP) at 10 second(s) intervals. In a secondary analysis we modeled the association between creatinine eGFR and postural BP behavior.

Results: Mean(sd) age was 61.6(8.2)yrs, 53% were female and mean(sd) eGFR was 81(17.6)mL/min/1.73m^2. We observed a graded association between postural BP instability and cystatin C eGFR. This was evident within 20s of standing and was robust to multivariable adjustment.



At 40s participants with eGFR<45 had a mean SBP deficit of 8(95%CI, 5 to 11)mmHg vs the reference group. There was no evidence of effect modification by antihypertensive therapy. The association between creatinine eGFR and postural BP behavior was comparatively modest.

Conclusions: We report a novel relationship between postural BP instability and eGFR in a large representative sample of older adults using beat-to-beat data. This graded association was marked within the first minute of standing, a time window not captured by conventional BP measurements.

SA-OR107

Intensive Blood Pressure Lowering Will Prevent over 100,000 Deaths Annually

Tisha Joerla M. Tan,[1] Adam Bress,[3] Richard Cooper,[1] Paul Muntner,[2] Srini Beddhu,[3] Holly J. Kramer.[1] *[1]Loyola Univ; [2]Univ of Alabama; [3]Univ of Utah.*

Background: The Systolic Blood Pressure Intervention Trial (SPRINT) trial randomized 9,361 adults aged ≥50 years at high cardiovascular disease (CVD) risk without diabetes or stroke to intensive systolic blood pressure (SBP) lowering (≤120 mmHg) or standard SBP lowering (≤140 mmHg). After a median follow up of 3.26 years, all-cause mortality was 27% (95% CI 40%, 10%) lower with intensive SBP lowering. We estimated the potential number of prevented deaths with intensive SBP lowering in the U.S. population meeting SPRINT criteria.

Methods: SPRINT eligibility criteria were applied to the National Health and Nutrition Examination Survey 1999-2006, a representative survey of the U.S. population, linked with the mortality data through December 2011. Eligibility included (1) age ≥50 years with (2) SBP 130-180 mmHg depending on number of antihypertensive classes being taken, and (3) presence of ≥1 CVD risk conditions (history of coronary heart disease, estimated glomerular filtration rate (eGFR) 20 to 59 ml/min/1.73 m^2, 10-year Framingham risk score ≥15%, or age ≥75 years). Adults with diabetes, stroke history, >1 g/day proteinuria, heart failure, or eGFR<20 ml/min/1.73m^2 were excluded. Annual mortality rates for adults meeting SPRINT criteria were calculated using Kaplan-Meier methods and the expected reduction in mortality rates with intensive SBP lowering in SPRINT was used to determine the number of potential deaths prevented. Analyses accounted for the complex survey design.

Results: An estimated 18.1 million U.S. adults met SPRINT criteria with 7.4 million taking blood pressure lowering medication. The mean age was 68.6 years and 83.2% and 7.4% were non-Hispanic white and non-Hispanic black, respectively. The annual mortality rate was 2.2% (95% CI 1.9%, 2.5%) and intensive SBP lowering was projected to prevent 107,453 deaths per year (95% CI 45,374, 139,490). Among the estimated 4.1 million adults with eGFR 20-59 ml/min/1.73 m2 meeting SPRINT criteria, the annual mortality rate was 2.9% (95% CI 2.3%, 3.6%) and intensive SBP lowering was projected to prevent 32,145 deaths per year (95% CI 25,493 - 39,903) in this group.

Conclusions: We project intensive SBP lowering could prevent over 100,000 deaths per year of intensive treatment.

SA-OR108

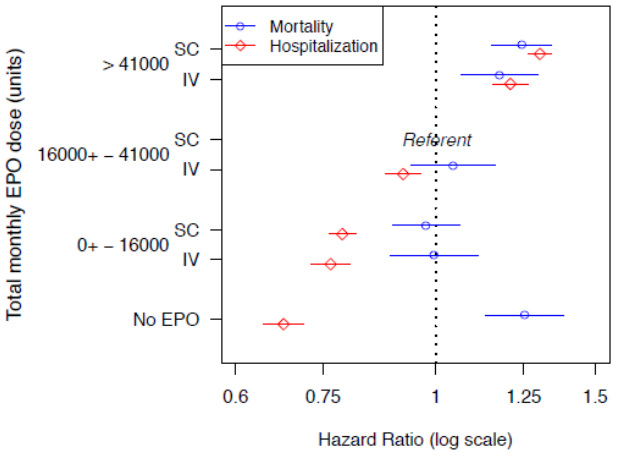
Dose Requirements, Hospitalization, and Mortality Are Similar with Subcutaneous versus Intravenous Erythropoietin Administration

Ambreen Gul,[1] R. Schrader,[1] D. Miskulin,[1,2] S. Paine,[1] Antonia Harford,[3] Philip Zager.[1,3] *[1]DCI; [2]Tufts; [3]UNM.*

Background: Erythropoietin (EPO) is indicated for the treatment of the anemia of ESRD. Results of the CREATE and CHOIR trials as well as implementation of the bundle payment system led many providers to switch from intravenous (IV) to subcutaneous (SC) EPO administration. A retrospective analysis of hemodialysis (HD) patients enrolled in the CMS Clinical Performance Measures Project from 1997 to 2005 found that IV vs. SC EPO administration was associated with 25% higher doses and an increased risk for the composite outcome of death or cardiovascular hospitalization. However, only 8% of patients received SC EPO. Since then, target hemoglobin (Hgb) values, EPO doses and the percent of patients treated with IV EPO have decreased significantly. Therefore, it is unknown if the alleged advantages of SC over IV are still operative.

Methods: We conducted a retrospective study of 24,957 HD patients treated between 2011 and 2014 at DCI facilities. The majority of SC and IV doses were administered once and thrice weekly, respectively. We used linear mixed models to compute mean weekly EPO doses and associated Hgb levels. To assess the relationships of IV and SC EPO to hospitalization and mortality, we constructed Cox models with time varying covariates to adjust for age, vintage, race, sex, BMI, albumin and Hgb.

Results: From 2011 to 2014, the proportion of patients treated with SC EPO increased from 41% to 69%. For a given achieved Hgb there were no significant differences between SC and IV mean weekly EPO doses. High doses, whether IV or SC, were associated with increased risks of hospitalization and mortality. However, there were no differences in hospitalization or mortality risk by route of administration.



Conclusions: Mean weekly doses of EPO and the risks for hospitalization and mortality were similar for IV and SC EPO administration.

SA-OR109

Mortality among Undocumented Hispanic ESRD Patients with Different Availability to and Access for Dialysis Lilia Cervantes,[1] Delphine S. Tuot,[2] Rajeev Raghavan,[3] Jeff Zoucha,[1] Lena C. Sweeney,[2] Chandan Vangala,[3] Madelyne L. Hull,[1] Mario Andres Camacho,[1] Jessica B. Kendrick,[1] Neil R. Powe,[2] Stuart L. Linas.[1] *[1]Univ of Colorado; [2]Univ of California, San Francisco; [3]Baylor College of Medicine.*

Background: Treatment strategies for undocumented end-stage renal disease (ESRD) patients in the U.S. varies between and within states. Most states provide dialysis to undocumented patients only when they present to an emergency department with life-threatening complications. We sought to determine whether the frequency of available treatment and access to AVF/AVG placement yielded mortality differences in three cities.

Methods: We conducted a retrospective cohort study of undocumented Hispanics who initiated hemodialysis January 2007 through July 2014 at three sites with different approaches: Denver Health (DH) (n = 45) in Colorado, Harris Health (HH) (n = 47) in Texas, and Zuckerberg San Francisco General (ZSFG) (n = 119) in California. Standardized mortality ratios (SMR) were calculated using participant gender and age at initiation. Sites were individually and collectively compared to the documented Hispanic population in the U.S. Renal Data System (USRDS). A Kaplan-Meier curve described one, three, and five year survival across sites.

Results: Compared to the USRDS Hispanic population, undocumented Hispanics had greater risk of mortality at three and five years following dialysis initiation (Table). SMRs show patients who received emergent dialysis with either a catheter or AVF/AVG experienced higher rates of mortality compared to counterparts who received routine dialysis with access to AVF/AVG placement. Kaplan-Meier curves were consistent.

	1-year		3-year		5-year	
Treatment group	Gender	Age	Gender	Age	Gender	Age
HH: Emergent care with non-permanent access	0.62	0.95	1.55	2.35	1.80	2.77
DH: Emergent care with access to AVF/AVG placement	1.04	1.31	1.77	2.23	2.36	3.00
ZSFG: Routine care with access to AVF/AVG placement	0.53	0.63	0.90	1.08	0.93	1.12
All undocumented Hispanics	0.69	0.96	1.46	1.99	1.74	2.40

Conclusions: Availability of routine dialysis and permanent vascular access for undocumented Hispanics is strongly associated with improved mortality.

Funding: Private Foundation Support

SA-OR110

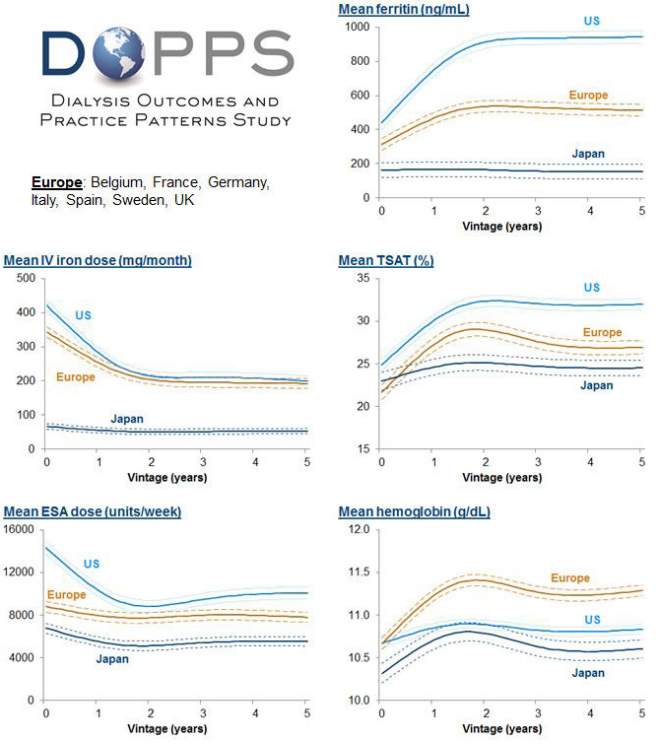
Anemia and Iron Management over the First 5 Years after Dialysis Start: Results from the DOPPS Angelo Karaboyas,[1] Bruce M. Robinson,[1,2] Yvonne Meier,[3] Lisa Loram,[4] Masaaki Inaba,[5] Stefan H. Jacobson,[6] Raymond C. Vanholder,[7] Ronald L. Pisoni.[1] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]U of Michigan, Ann Arbor; [3]Vifor Pharma Ltd, Glattbrugg, Switzerland; [4]Keryx Biopharmaceuticals, Boston, MA; [5]Osaka City U, Japan; [6]Danderyd Hosp, Stockholm, Sweden; [7]Univ Hosp, Gent, Belgium.*

Background: Hemodialysis (HD) patients are at an especially high risk of adverse events in the period following HD initiation. Optimizing treatment practices before, during, and after this transition is paramount, particularly for anemia management. Hemoglobin (Hgb) levels typically rebound on HD due to substantial ESA and IV iron dosing, but the trajectory of ferritin and TSAT levels after the transition to dialysis has not been well-studied.

Methods: Restricted cubic splines were used to model the mean (SE) of ferritin, TSAT, Hgb, IV iron and ESA dose over the first 5 years of HD using longitudinal data from 6612 patients in phase 5 (2012-2015) of the Dialysis Outcomes and Practice Patterns Study (DOPPS) in Europe (EUR), Japan, and the US.

Results: In the first year after HD initiation, IV iron and ESA doses were higher in the US vs. EUR, but achieved mean Hgb levels were lower in the US. In contrast, iron parameters increased more quickly in the US and remained high, reaching a mean plateau of 900 ng/mL (ferritin) and 32% (TSAT) after 2 years, despite IV iron doses declining to EUR levels. Anemia treatments and measures were generally more stable across HD vintage in Japan.

Conclusions: Regional differences in anemia management are accentuated during the early HD period, when US patients receive the highest IV iron and ESA doses and have larger, sustained increases in ferritin and TSAT levels. Because early HD mortality is high, future investigation is needed including identifying pre-HD practices that can support the use of lower IV iron and ESA doses soon after HD start, and what effect if any this might have on clinical outcomes.



Funding: Pharmaceutical Company Support - AbbVie, Amgen, Baxter Healthcare, F. Hoffmann-LaRoche, Hexal, Keryx, Kyowa Hakko Kirin, Merck, Proteon, Relypsa, Sanofi, Shire, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, WiNe Institute, Societies for Nephrology in Germany, Italy, & Spain. All grants are made to Arbor Research Collaborative for Health and not to Mr. Karaboyas directly

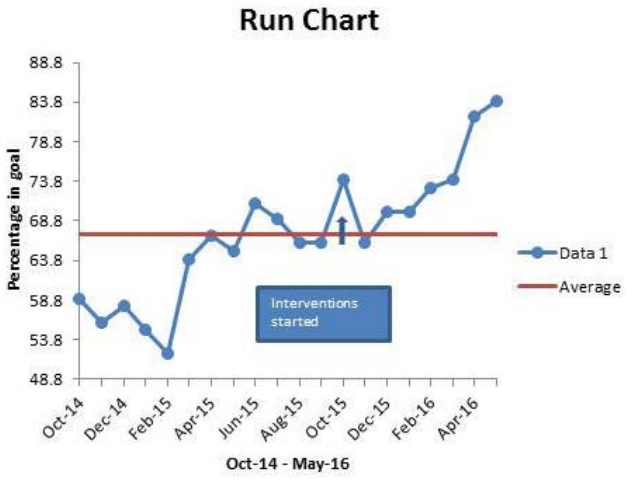
SA-OR111

Improving Interdialytic Weight Gain in Dialysis Patients Chandandeep Takkar,[1] Karen D. Burchell,[1] Laura Montes,[2] Wajeh Y. Qunibi.[1] *[1]Nephrology, UTHSCSA, San Antonio, TX; [2]UHS, San Antonio, TX.*

Background: UF Rate (UFR) above 13 ml/Kg/ hour (vs 10-13 ml/kg/hour) in hemodialysis (HD)patients is associated with increase in mortality. Moreover, UFR is being considered as a reportable quality measure for HD by the CMS. Aim of our project is to improve interdialytic weight gain (IDWG) to keep UFR <12ml/Kg/hour in at least 65% of HD patients.

Methods: A multidisciplinary team was convened in Sept 2015. Baseline IDWG (average of 13 /month/ patient) was recorded from 10/2014-9/2015. Goal IDWG was calculated for each patient to keep maximum UFR<12ml/Kg/hour as follows: 12 X Estimated Dry Weight X treatment duration (in hr)-Rinse back. Patients met goal the preceding month if their average IDWG was at/below maximum goal. Volume overload-related admissions, pre-and post-dialysis BP and hypotensive episodes during dialysis were recorded. A fishbone diagram was used to identify barriers to goal IDWG and a driver diagram to identify key actionable items. We counseled patients extensively regarding sodium and fluid restriction, adjusted their dialysate sodium (DNa) prescription according to the 3-month pre dialysis average serum sodium concentration (SNa), in order to reduce the DNa to SNa gradient. Standardized educational process and material for counseling was also developed. For sustainability, IDWG calculation, maximum goal and monthly average IDWG report was incorporated in EMR.

Results:



Compared to baseline, average percentage of patients at goal increased from 62% pre intervention to 74% by May 2016. Average UFR improved from 11.4 ml/kg/hour pre intervention to 9.7 ml/kg/hour. We noticed fewer hypotensive episodes, decreased use of antihypertensive agents, and improved staff and patient engagement.

Conclusions: A team based approach involving intensive patient counseling and attention to dialysis prescription are effective means to reduce IDWG in dialysis patients.

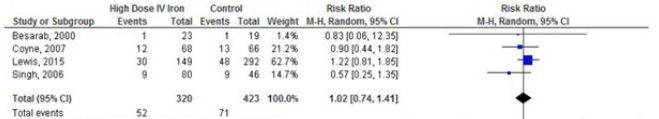
SA-OR112

Intravenous Iron Dosing and the Risk of Adverse Events in End Stage Renal Disease: A Systematic Review and Meta-Analysis Ingrid Hougen, Mathieu Bourrier, David Thomas Collister, Thomas W. Ferguson, Paul Komenda, Claudio Rigatto, Navdeep Tangri. *Max Rady College of Medicine, Univ of Manitoba, Winnipeg, MB, Canada.*

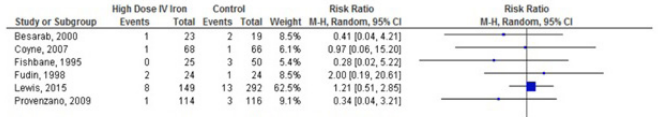
Background: Anemia and relative iron deficiency are common in patients with end stage renal disease (ESRD) and contribute to morbidity and mortality. The optimal intravenous (IV) iron dosing strategy in dialysis patients is unclear with controversy regarding the safety of high versus low dosing. We performed a systematic review and meta-analysis in order to assess the safety of IV iron dosing in adults with ESRD on dialysis.

Methods: A search strategy was developed for searching Medline, PubMed, EMBASE, Cochrane Central and CINAHL databases from inception until July 15, 2015. We included randomized controlled trials that compared high dose IV iron to low dose IV iron in the adult ESRD population on hemodialysis (HD) or peritoneal dialysis (PD) with follow-up of at least 30 days. Outcomes included infections, hospitalizations, cardiovascular events, and mortality.

Results: Seven studies met the criteria for inclusion with five in HD, one in PD, and one in both HD and PD. Four studies reported infections (n=743) and six reported mortality (n=970). Only two studies reported hospitalizations and none reported cardiovascular events. Meta-analysis with a random effects model showed that higher doses of IV iron were not associated with an increased risk of infection (HR 1.02 [95% C.I. 0.74, 1.41]) or mortality (HR 0.93 [95% C.I. 0.47, 1.84]). No significant statistical heterogeneity was detected.



Meta-Analysis Comparing the Safety of High Dose IV Iron versus Control for Relative Risk of Infection Events.



Meta-Analysis Comparing the Safety of High Dose IV Iron versus Control for Relative Risk of Mortality Events.

Conclusions: High dose IV iron does not appear to increase the risk of infection or mortality in adult ESRD patients on dialysis. However, our results are limited by the generally low quality of included studies and clinical heterogeneity among anemia management, as well as possible publication bias. Additional studies are needed to elaborate on these findings.

SA-OR113

Continuous ECG Recording of Cardiac Rhythm Shows That Pre-Hemodialysis (HD) Potassium (K+) Levels Need To Be Tightly Controlled between 4 to 5.5 mM Christian Combe,[1,2,6] Antoine Benard,[3,6] Hélène Savel,[3,6] Virginie Rondeau,[4,6] F. Sacher.[5,6] *[1]Nephrologie, CHU Bordeaux, Bordeaux, France; [2]INSERM 1026, Univ Bordeaux, Bordeaux, France; [3]Sante Publique, CHU Bordeaux, Bordeaux, France; [4]INSERM 1219, Univ Bordeaux, Bordeaux, France; [5]LYRIC Inst, CHU Bordeaux, Bordeaux, France; [6]Rythmodial, Study Group, France.*

Background: Sudden cardiac death is the commonest mode of death in HD patients (pts). Our objective was to identify mechanisms which may lead to SCD using an implantable loop recorder (ILR).

Methods: Pts from 9 HD centers were included. Cardiac rhythm was monitored with the ILR. Clinical, biological, & HD parameters & medications were recorded for ≥1 year. General joint frailty model for recurrent event data were used to analyze associations between these parameters & the occurrence of cardiac rhythm events (RE).

Results: 71 pts (65.1±8.6 y, 52M) have been included, with diabetes (n=32) & hypertension (n=19) as ESRD causes. 22 pts had ischemic cardiomyopathy. 66.2% pts had at least one RE, with a 198.8 patients-years (py) incidence (95%CI 196.3-201.4). Incidence was 55.6 py (54.2-56.9) for conduction abnormalities (CA); 9.6 py (9.0-10.1) for ventricular arrhythmias (VA); 100.7 py (98.9-102.6) for atrial fibrillation >2min (AF); 33.0 py (31.9-34.0) for bradycardia. In multivariate analyses, CA was linked to high K+ (K+>5mM, RR=4.0, p<0.0002), to high hemoglobin (Hb>11.5, RR=3.3, p<0.005), & to ischemic cardiopathy (RR=18.3, p<0.01), to a high-risk day for HD (RR=6.4, p<10-9), to a history of any RE (RR=9.3, p<10-7). VA incidence was higher with low K+ (<4mM, RR=12.8, p<0.005), & lower with anti-arrhythmic drugs (RR=0.1, p<0.005). AF was more frequent in males (RR=73.0, p<0.002), with low K+ (<4mM, RR=2.5, p<0.02), & high phosphorus (>45mg/L, RR=1.9, p<0.01). Bradycardia was linked to high K+ (>5mM, RR=13.7, p<0.002), to low K+ (<4mM, RR=9.2, p<0.05), & to shortened HD sessions (RR=7.6, p<0.02. In 6 SCD pts, ILR showed bradycardia followed by asystole.

Conclusions: Serum K+ levels need to be tightly controlled, since levels>5mM are associated to CA and bradycardia, while levels <4mM are associated to VA, AF, and bradycardia. Pts treated with anti-arrhythmic drugs had a much lower rate of VA.

Funding: Pharmaceutical Company Support - Medtronic, Government Support - Non-U.S.

SA-OR114

Daprodustat, a HIF-Prolyl-Hydroxylase Inhibitor, Maintains Hemoglobin Levels over 24 Weeks in Anemic Hemodialysis Subjects Switching from Recombinant Human Erythropoietin Alexander Ralph Cobitz,[1] Amy M. Meadowcroft,[1] Borut Cizman,[1] Louis Holdstock,[1] Nandita Biswas,[1] Delyth Jones,[1] Brendan M. Johnson,[2] John J. Lepore,[1] A. Kaldun Kaldun Nossuli.[3] *[1]GlaxoSmithKline; [2]Roivant Sciences; [3]Nossuli Research.*

Background: This study examined the relationship between daprodustat (GSK1278863) dose and hemoglobin (Hgb) level at 4 weeks (4w), and the efficacy and safety of daprodustat over 24 weeks (24w), in 216 subjects on hemodialysis (HD) previously receiving a stable dose of recombinant human erythropoietin (rhEPO).

Methods: Subjects with a baseline Hgb of 9-11.5 g/dL discontinued rhEPO and were randomized to receive daily oral daprodustat 4, 6, 8, 10, 12 mg or control (placebo for 4w; then open-label rhEPO as required). After 4w, doses were titrated to a Hgb target of 10-11.5 g/dL.

Results: Mean baseline Hgb was 10.4 g/dL. Switching from rhEPO to daprodustat produced dose-dependent mean changes in Hgb (g/dL) from baseline after 4w (placebo: -0.72; 4mg: -0.29; 6mg: 0.18; 8mg: 0.40; 10mg: 0.69; 12mg: 0.69). The mean change from baseline in Hgb at 24w for the combined daprodustat group was 0.03 g/dL (control: -0.11 g/dL). Mean hepcidin levels were reduced from baseline at 24w by 20.6% in subjects in the combined daprodustat group (control: 3.6%). The median maximum observed plasma EPO levels in the control group during rhEPO therapy were ~14-fold higher than the combined daprodustat group (control: 522.9 IU/L; daprodustat: 36.5 IU/L). There was no effect on plasma VEGF for either group. Daprodustat demonstrated an adverse event profile consistent with the HD population; however, the incidence of overall mortality and major cardiovascular events were lower than expected across all treatment arms.

Conclusions: These data inform the Hgb dose-response relationship of daprodustat in anemic HD subjects who were switched from a stable dose of rhEPO and demonstrate daprodustat can maintain Hgb at target levels for 24w. In the same time frame, daprodustat reduced hepcidin levels, maintained physiologic levels of plasma EPO, and there was no effect on plasma VEGF. These data support future long-term clinical studies in the dialysis population using daprodustat to treat anemia of CKD.

Funding: Pharmaceutical Company Support - This study was funded by GlaxoSmithKline

SA-OR115

Effects of Hemodialysis and Dialysate Potassium on Maximum P Wave Duration and P Wave Dispersion Yi-Lun Zhou. *Dept of Nephrology, Tian-Tan Hospital, Capital Medical Univ.*

Background: Atrial fibrillation (AF) is a frequent arrhythma in hemodialysis (HD) patients and is associated with increased morbidity and mortality. Maximum P wave duration (Pmax) and P wave dispersion (Pd) are effective electrocardiographic predictors of AF. This study was designed to evaluate the influence of HD session and dialysate potassium concentration (K_d) on Pmax and Pd.

Methods: 117 chronic HD patients with sinus rhythm and 50 healthy controls were included. K_d 2.5mmol/L (K_d 2.5) was normally used and then once raised to 3.0mmol/L (K_d3.0). Blood samples were drawn and twelve-lead electrocardiograms (ECG) were recorded immediately before and after HD session. Pd was defined as the difference between the maximum and minimum P-wave duration on ECG. Home blood pressure monitoring was performed and home systolic blood pressure (home-SBP)≥150mmHg was defined as uncontrolled hypertension. Left atrial diameter was measured by ultrasound.

Results: Pmax and Pd were significantly increased in HD patients than healthy controls. Multiple stepwise regression analysis relveald that left atrial enlargement ($p< 0.001$) and uncontrolled home blood pressure ($p=0.030$) were indiependent predictors of prediaysis Pmax and Pd among HD patients. Pmax significantly increased during both HD sessions compared with prediaylsis values (121.1±11.6 vs. 105.4±11.6ms, 115.8±10.7 vs. 106.1±11.3ms, respectively, $p<0.001$), either did Pd (46.2±10.3 vs. 32.8±8.8ms, 40.4±9.7vs. 33.2±8.4ms, respectively, $p<0.001$) after HD sessions. Furthermore, postdiaysis Pmax and Pd were decreased in K_d3.0 group than K_d2.5 (115.8±10.7 vs. 121.1±11.6ms, 40.4±9.7ms vs. 46.2±10.3ms, respectively).

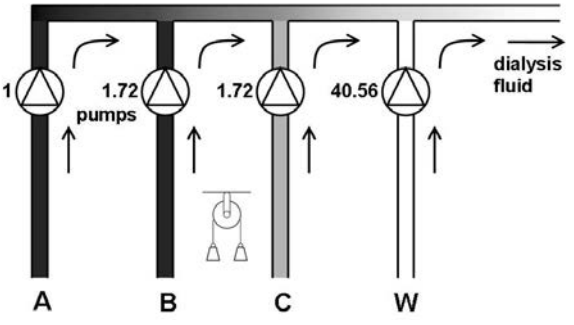
Conclusions: Pmax and Pd increase significantly after HD sessions. Raising dialysate potassium concentration can shorten postdialysis Pmax and Pd, and this may help to decrease the incidence of AF among HD patients.

SA-OR116

A Novel Method of Delivering Bicarbonate-Based Dialysis Fluid: A 4-Stream Approach Susie Q. Lew,[1] Yuk Lun Cheng,[2] Todd S. Ing.[3] *[1]Medicine, George Washington Univ, Washington, DC; [2]Medicine and ICU, Alice Ho Miu Ling Nethersole Hospital, Hong Kong, China; [3]Medicine, Stritch School of Medicine, Loyola Univ Chicago, Maywood, IL.*

Background: A conventional 45X, 3-stream method of delivering a bicarbonate-based dialysis fluid (DF) uses an acid concentrate stream (CS), **A**; a bicarbonate (BIC) CS, **B**; & H_2O stream, **W**. The flow rate ratios (FRR) for **A**:**B**:**W** are: 1:1.72:42.28, respectively (totaling 45 or 45X). By altering the **B** flow rate, BIC level in the final DF ranges from 20 to 40 mM. Variations beyond these limits leads to excessive reciprocal changes in the DF levels of **A** ingredients.

Methods: We have devised a 4-stream method to overcome the above range limitation by adding a NaCl CS, **C**. **B** & **C**'s FRR are controlled by an electronic pulley-like mechanism.



Results: The FRR for the 4-streams **A**:**B**:**C**:**W** are: 1:1.72:1.72:40.56 (45X). Contributions to the final DF are: **A:** Chlorides of Na (63 mM), K, Ca, & Mg, & glucose; **B:** 37 mM $NaHCO_3$; **C:** 37 mM NaCl, and **W**: H_2O. With **B** & **C**, when the FRR changes in 1 stream, the other changes by the same magnitude but in the opposite direction. For example, **B**'s FRR decreases by 0.2 to 1.52 in order to lower the DF $NaHCO_3$ level to 32.7 mM to treat metabolic alkalosis, then **C**'s FRR will reciprocally increase by 0.2 to 1.92 to raise the DF NaCl level to 41.3 mM. The opposite sequence of events occur if FRR of **B** increases to treat metabolic acidosis. The 2 fluid volumes responsible for diluting the ingredients derived from **A**, namely, the sum of the FRR for **B** & **C** (3.44) and the FRR for **W** (40.56) remain unchanged. Hence, the levels of **A** ingredients in the final DF will remain untouched. Since **B** & **C** are isonatric, their reciprocal changes described will not affect the final DF Na level either.

Conclusions: This 4-stream approach allows a wider [BIC] range in the final DF without changing the levels of Na or **A** ingredients.

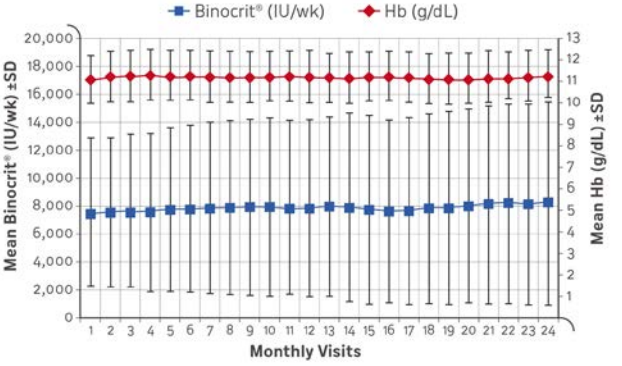
SA-OR117

Real-World Effectiveness of Biosimilar Epoetin α: 2-Year Outcomes in the Monitor-CKD5 Study Johannes F. Mann,[1] Gerard M. London,[2] Christian Combe,[3] David Goldsmith,[4] Philippe Zaoui,[5] Frank Dellanna,[6] Michael Gorray,[7] Nadja Hoebel,[7] Karen Macdonald,[8] Ivo Abraham.[9] *[1]Friedrich Alexander Univ Erlangen-Nürnberg, Erlangen, Germany; [2]Centre Hospitalier F.H. Manhés, Fleury-Mérogis, France; [3]Centre Hospitalier de Bordeaux, Bordeaux, France; [4]Guy's and St. Thomas' NHS Foundation Hospital, London, United Kingdom; [5]Univ de Grenoble-Alpes, Grenoble, France; [6]Dialysezentrum, Düsseldorf, Germany; [7]Sandoz/Hexal AG, Holzkirchen, Germany; [8]Matrix45, Tuscon, AZ; [9]Univ of Arizona, Tuscon, AZ.*

Background: Biosimilar erythropoiesis-stimulating agents (ESAs) are not yet available in the US, but longitudinal evidence on real-world use abroad is growing. MONITOR-CKD5 is a European study examining long-term safety and effectiveness of biosimilar epoetin α (Binocrit®) in hemodialysis (HD) patients (pts).

Methods: Prospective 24-month (24m) pharmacoepidemiological study of 2023 HD pts with renal anemia treated with Binocrit® in 10 European countries. Binocrit® dosing and hemoglobin (Hb) outcomes over 24m are presented.

Results: Mean±SD age was 64.8±14.95y; 59.3% were male. Mean time on HD was 3.8±4.6y. Most had received an ESA previously (82.5%). Primary CKD etiology: diabetic nephropathy (25.4%), chronic glomerulonephritis (20.4%), renal vascular disease (16.4%). At enrollment 73.0% had adequate iron stores, 22.2% had functional and 4.8% absolute deficiency. Over 24m, mean serum ferritin ranged from 466±320 to 581±434ng/mL; supplemental iron was given to 59.7-67.5% and transfusion to 0.3-1.2% of pts. Baseline Hb was 11.1±1.1g/dL, with 68% between 10-12g/dL; mean weekly Binocrit® dose at baseline was 106.5±78.7 IU/kg. Mean Hb and Binocrit® dose remained stable over 24m (both *p*=ns)



Conclusions: In this real-world study Binocrit® maintains stable Hb over 24m, consistent with originator. This is the first 2-year evidence of the effectiveness of Binocrit® in HD.

Funding: Pharmaceutical Company Support - SANDOZ

TH-PO001

Discontinuation of Eculizumab in a Patient with Atypical HUS Mamta Shah, Juan Calderon, Anushree C. Shirali. *Dept of Nephrology, Yale School of Medicine, New Haven, CT.*

Introduction: Since atypical HUS (aHUS) is a disease of disordered serum complement activation, eculizumab has been used successfully in its treatment. While this approach has been beneficial in the acute treatment of aHUS, the optimal duration of therapy remains unknown, particularly in patients with mutations of complement regulatory proteins. We report a case of aHUS in a patient with a membrane cofactor protein (MCP) mutation who was successfully treated with eculizumab and remains without disease recurrence after its discontinuation.

Case Description: A 26 year-old man was diagnosed with aHUS after presenting with influenza, non-bloody diarrhea, hematuria and a serum creatinine (Cr) of 5.1mg/dL. He had 4gms of proteinuria, hemolytic anemia and thrombocytopenia. He showed improvement in hematologic parameters with steroids and plasmapheresis but had persistently elevated Cr prompting initiation of eculizumab. Within 6 months his Cr was 1.1mg/dL with minimal proteinuria. Direct sequencing analysis revealed that he had a heterozygous MCP missense mutation c.586G>A (G196R). Two years later, in consultation with hematology, eculizumab was stopped. He is being followed with monthly labs. Over the past year, he has shown no evidence of disease recurrence, with stable Cr at 1.1mg/dL and no significant proteinuria, hematuria or hemolysis.

Discussion: Approximately 60%-70% of aHUS patients have mutations in the genes encoding complement factor H (CFH), factor I, MCP, factor B, thrombomodulin or C3. In a study of 10 aHUS patients with different mutations who were taken off eculizumab maintenance, 3 patients had recurrent disease, all of whom had CFH mutations. Immediate improvement was seen with reinstitution of eculizumab. Our patient with a MCP mutation has been recurrence free for a year following discontinuation of eculizumab. The rationale for this approach includes avoiding high drug cost,and minimizing risk of meningococcal infection and immune-mediated drug reactions. Frequent laboratory testing is necessary for early detection of recurrence. Improved understanding of specific genotypes and aHUS recurrence will help tailor therapy individually and maximize benefit while minimizing risk.

TH-PO002

Two Cases of Adult Onset Henoch-Schönlein Purpura with Acute Kidney Injury and Severe Gastrointestinal Manifestations: Successful Treatment with Factor XIII Replacement Therapy Takeyuki Takamura, Fumihiko Furuya, Kenichiro Kitamura. *Third Dept of Internal Medicine, Univ of Yamanashi, Chuo, Yamanashi, Japan.*

Introduction: Gastrointestinal involvement occurs in 50-75% of Henoch-Schönlein Purpura (HSP) patients. Several prior studies have identified a correlation between the decreased FXIII activity and the severity of gastrointestinal manifestations or kidney injury in HSP patients.

Case Description: [Case 1] A 48-year-old-woman was hospitalized with purpura, gastrointestinal hemorrhage, proteinuria, and macroscopic hematuria. Kidney biopsy revealed granular deposition of IgA and C3 in the mesangial region with crescent formation. She was initially treated with intravenous methylprednisolone pulse therapy followed by oral prednisolone 40mg daily, but her symptoms were not improved. Since her plasma level of FXIII was substantially decreased, we added FXIII replacement therapy and intravenous cyclophosphamide (IVCY) on oral prednisolone therapy. Her gastrointestinal manifestations and renal function were significantly ameliorated. [Case 2] A-78-year-old-man was admitted complaining of purpura, melena, proteinuria, and macroscopic hematuria. His pathological findings indicated leukocytoclastic vasculitis and IgA deposition of vessel walls. Nine severe gastrointestinal hemorrhages occurred and he received red blood cell transfusion and endoscopic clipping therapy. He was also treated with intravenous methyl prednisolone pulse therapy, IVCY, intravenous immunoglobulin, and plasma exchange. His plasma level of FXIII was significantly reduced and FXIII replacement therapy was performed. His kidney function and gastrointestinal bleeding were improved.

Discussion: We report 2 cases of HSP with acute kidney injury and severe gastrointestinal manifestations and successfully treated with FXIII replacement. In both cases, immunosuppressive therapy did not improve the kidney or gastrointestinal injury, but FXIII replacement therapy or combination of plasmapheresis and FXIII replacement substantially ameliorated the both injury. These findings strongly suggest the possibility that FXIII plays critical roles in the pathogenesis and the progression of kidney and gastrointestinal injury that are associated with HSP.

TH-PO003

A Case of Nephrotic Syndrome Secondary to Kimura Disease Divya Raghavan,[1] Mazdak A. Khalighi,[2] Laith Al-Rabadi,[1] Josephine Abraham.[1] *[1]Dept of Nephrology, Univ of Utah, Salt Lake City, UT; [2]Dept of Pathology, Univ of Utah, Salt Lake City, UT.*

Introduction: Kimura disease (KD) is a rare chronic inflammatory disorder typically presenting with head and neck masses, peripheral eosinophilia and elevated serum IgE levels. Etiology is unclear and it is usually seen in East Asians. A multitude of renal lesions have been described with KD, including membranous glomerulonephritis (GN), mesangioproliferative GN, minimal change disease (MCD) and IgA nephropathy. We report a case of KD in a Caucasian male patient who initially presented with MCD.

Case Description: A 70 year old Caucasian man with a history of diabetes mellitus and recurrent skin lesions (lymphocytoma cutis on biopsy) was admitted to the hospital with complaints of leg swelling and dyspnea on exertion. Physical exam revealed pitting pedal edema and enlarged right post-auricular and right cervical lymph nodes. Labs showed a serum creatinine (SCr) of 2.44 mg/dl (baseline 1.1mg/dl), eosinophilia (14%), and urine total protein-to-creatinine ratio of 8.8 g/g. Kidney biopsy showed MCD. Prednisone 1mg/kg PO QD was started soon after he underwent a CT scan of head, neck, chest, abdomen and pelvis to evaluate for lymphoma as the etiology of MCD. A large infiltrative soft tissue mass involving the right parotid gland was identified. Patient underwent an ultrasound-guided fine needle aspiration of the post-auricular lymph node which showed atypical lymphoid cells but no monoclonality. Patient declined biopsy of the parotid mass after discussing potential surgical complications. Dermatopathology obtained slides of previous skin lesions (''lymphocytoma cutis'') which showed numerous eosinophils with dilated vascular spaces, a finding consistent with KD. IgE level was elevated at 1084 kU/L (<214). Patient was discharged on oral prednisone. SCr improved to 1.1 mg/dl three months later (peak value 4.9 mg/dl) with resolution of proteinuria.

This is a unique case of KD causing nephrotic syndrome in a 70 year old Caucasian man. A multidisciplinary approach was important in identifying the etiology of the patient's nephrotic syndrome. This unifying diagnosis obviated the need for further invasive procedures.

TH-PO004

Effect of Single-Dose Rituximab in IgA Nephropathy Presenting as Nephrotic Syndrome: A Report of Two Cases Roxana Adriana Jurubita, Bogdan Obrisca, Florentina Wagner, Andreea Andronesi, Bogdan Marian Sorohan, Nicu Caceaune, Gener Ismail. *Nephrology and Internal Medicine, "Carol Davila" Univ, Bucharest, Romania.*

Introduction: Nephrotic syndrome (NS) is a rare manifestation of IgA nephropathy (IgAN) usually associated with widespread proliferative lesions or coexistent minimal-change disease. Rituximab has shown efficacy in the treatment of membranous nephropathy and ANCA-associated vasculitis, but wasn't evaluated as a therapeutic option for IgA nephropathy.

Case Description: Case 1: A 27 year-old male presented with edemas, NS (proteinuria of 8 g/day), altered renal function with estimated glomerular filtration rate (eGFR-CKD-EPI) of 63 ml/min and microscopic hematuria. Kidney biopsy revealed IgAN with fibrocellular crescents involving more than 50% of the examined glomeruli, with no endocapillary hypercellularity. The serologic studies (ANA, pANCA, cANCA, anti-GBM antibodies) were negative. After an initial 6-month course of corticosteroid therapy, the NS persisted. In this setting, 500 mg of Rituximab was administered. Subsequent check-ups are shown in table. Case 2: A 21 year-old male is admitted for edemas and hypertension. Initial testing revealed NS with proteinuria of 8,74 g/day, serum albumin 2,8 g/dl, eGFR 58 ml/min and microscopic hematuria. Kidney biopsy showed intense mesangial IgA staining on immunofluorescence and fibrocellular crescents in less than 50% of the examined glomeruli. The patient received a 6-month course of corticosteroid therapy and mycophenolate mofetil 2g/d, with partial remission of the NS. However, after completing the immunosuppressive regimen, the NS relapsed and eGFR decreased to 41 ml/min, so it was decided upon administration of 500 mg of Rituximab. Subsequent check-ups are shown in table.

Variables	Case 1				Case 2		
	Baseline	3 months	6 months	9 months	Baseline	3 months	6 months
eGFR (ml/min)	75	58	50	56	41	34	39
Serum Albumin (g/dl)	3.3	3.6	4	4.2	2.9	3.5	3.7
Proteinuria (g/day)	5.53	2.5	1	0.7	10	7	4

Discussion: In the cases described, Rituximab treatment was associated with a clear improvement of NS and stabilization of renal function. Still, randomized clinical trials to assess the efficacy of rituximab in IgAN treatment are needed.

TH-PO005

Acute Kidney Injury and Possible Thrombotic Microangiopathy Associated with EGFR Inhibitor Osimertinib Nuha Ibrahim, Antoney Joseph Ferrey, Yongen Chang. *Nephrology, UC Irvine, Orange, CA.*

Introduction: Osimertinib is a small molecule inhibitor of epithelial growth factor receptor (EGFR) tyrosine kinase approved to treat non-small cell lung cancer (NSCLC). Here, we report a case of acute kidney injury (AKI) associated with the use of osimertinib.

Case Description: A 68 year old female with metastatic NSCLC presented with dyspnea, hypertension and swelling after taking osimertinib for one month. Exam was remarkable for +JVD and peripheral edema. Serum creatinine (SCr) was 4.4mg/dL from baseline 0.89mg/dL. Urine protein creatinine ratio was 3.9 g/g and albumin creatinine ratio was 1905mg/g. Urine sediment revealed many nondysmorphic RBCs but no casts. Echocardiogram showed ejection fraction of 33%. Patient was oliguric and hemodialysis was initiated. Renal biopsy was performed. Light microscopy showed severe acute tubular epithelial cell injury with tubular basement membrane rupture and secondary interstitial inflammation. Both LM and electron microscopy showed extensive glomerular and arteriolar endotheliosis and glomerular basement membrane (GBM) wrinkling. No endocapillary fibrin thrombi were observed. There was also mild effacement of podocyte foot processes. Given the severity of endotheliosis, the possibility of early TMA was considered. Further laboratory studies showed no thrombocytopenia or evidence of hemolysis. On hospital day 7, her urine output improved and dialysis was held. Her SCr was 2.8mg/dL upon discharge and 1.3 mg/dL two months later. Repeat urine PCR was 0.57g/g and ACR 208mg/g. Osimertinib was held indefinitely.

Discussion: In summary, we presented a case of new onset heart failure (HF), AKI and proteinuria in association with osimertinib use. HF is a known adverse effect of osimertinib. Unlike vascular endothelial growth factor (VEGF) receptor inhibitors, EGFR inhibitors were not known to be nephrotoxic. To our knowledge, this is the first report of EGFR inhibitor associated AKI. Interestingly, renal biopsy not only demonstrated ATN but also features of TMA and podocyte injury. This case expands the current knowledge of the renal effects of tyrosine kinase inhibitors in the era of biologics.

TH-PO006

A Report of 3 Cases of MPGN Type III, Strife and Anders Type: A Definitive Diagnosis by EM-PAM Proposes a Negative Application to C3 Glomerulonephritis Naomi Sato,[1] Yasuhiro Nakamura,[2] Takashi Takaki,[1] Kensuke Joh.[1] *[1]Pathology, Tohoku Univ Graduate School of Medicine, Sendai, Miyagi, Japan; [2]Pathology, Tohoku Medical and Pharmaceutical Univ, Sendai, Miyagi, Japan.*

Introduction: C3 glomerulopathy is an umbrella term comprising of dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). C3GN is composed of primary membranoproliferative GN (MPGN) type I and type III after differentiation of DDD. Since primary MPGN type III, second form, "Strife and Anders" type (MPGN III S&A) can be a candidate of C3GN. We experienced 3 cases of MPGN III S&A, which were definitely diagnosed by electron microscope with Periodic Acid-Methenamine-Silver stain (EM-PAM) according to the original articles of Strife and Anders. The purpose was to analyze these rare cases and to estimate whether MPGN III S&A can be categorized into C3GN.

Case Description: Patients (pts) were 57 yrs male, 23 yrs male and 20 yrs female, respectively. All pts showed no clinical symptoms of secondary GN. Only one presented C3 hypocomplementemia. Renal biopsy revealed MPGN-like lesion with double contour. Immunoglobulins (heavy and light chains) besides C3 deposition were demonstrated as glomerular peripheral pattern. In EM, all cases showed a large amount of lumpy intramembranous continuous dense deposits in the glomerular basement membrane (GBM) with mesangial interposition, whereby a continuity of lamina rara externa was well preserved. EM-PAM demonstrated a disruption of lamina densa of the GBM, which may relate to immunoglobulins deposition.

Discussion: EM-PAM proposed substantial reasons to diagnose these all cases as MPGN III S&A, which consists of first, a disruption of lamina densa, which can differentiate a diagnosis of DDD without GBM disruption and second, intact lamina rara externa, which can differentiate MPGN type III Burkholder with epimembranous deposits showing destruction of lamina rara externa. The term C3 GN is coined to describe glomerular lesions in which there is glomerular accumulation of C3 with little or no immunoglobulin. Since our all 3 cases showed immunoglobulins deposition, which may relate to a disruption of lamina densa as a definition of MPGN III S&A, C3 GN may not be applied to MPGN III S&A.

TH-PO007

A Complex Case - Solitary Kidney with Crescentic IgA Nephropathy during Pregnancy Rekha Kambhampati, Daphne Harrington Knicely. *Nephrology, Johns Hopkins Univ School of Medicine, Baltimore, MD.*

Introduction: IgA nephropathy is the most common glomerular disorder. We present a complex case of successfully treated crescentic IgA nephropathy in a solitary kidney diagnosed in early pregnancy.

Case Description: A 28 year old Caucasian G1P0101 at 14 weeks and 5 days gestation with a past medical history of left donor nephrectomy and gestational hypertension presented with acute kidney injury. Fifteen days prior to admission, her creatinine was 0.95 and 24-hour urine protein was 4448 mg. Five days prior to admission, she developed group A streptococcal infection. One day prior to admission, her creatinine rose to 2.4 with gross hematuria. On admission, she was found to be hypertensive with a creatinine of 3.2 and 36 red blood cells per high power field on urinalysis. A renal biopsy revealed 70% crescentic and necrotizing proliferative glomerulonephritis with IgA dominant deposits.

She was treated with methylprednisolone 1 gram daily for three days and then transitioned to prednisone 60 mg daily. Her creatinine improved to 1.0-1.1. Her pregnancy was complicated by variable fetal heart decelerations requiring delivery of a live infant at 28 weeks gestation. Post-partum, her prednisone was tapered at monthly intervals. Her creatinine remained stable at 1.5-1.7. Maximum 24-hour urine protein was 14.6 gm and improved to 1 gram. Post-partum, she was started on an ACE inhibitor.

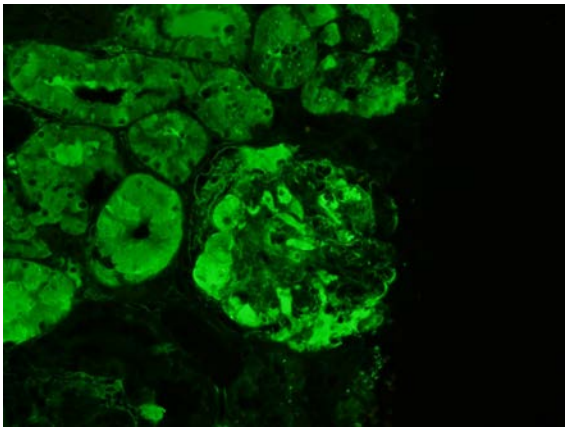
Discussion: There is very little literature on treatment of crescentic necrotizing glomerulonephritis in pregnancy. Current recommendations advise for corticosteroids and cyclophosphamide as initial therapy in non-pregnant individuals. However, given its teratogenic side effects, cyclophosphamide was not a feasible option for our patient. A case report by Komatsuda, et al (1994) revealed successful treatment of a patient with crescentic IgA nephropathy diagnosed at 21 weeks gestation with corticosteroids. No literature currently exists regarding treatment of crescentic IgA nephropathy in a solitary kidney during pregnancy. We were able to successfully treat our patient with pulse dose steroids followed by high dose oral steroid therapy for the duration of her pregnancy with favorable post-partum outcomes.

TH-PO008

Proliferative Glomerulonephritis with Masked Monoclonal Deposits Responsive to Myeloma Chemotherapy Anjuman A. Howlader,[1] Amy Nicole Sussman,[1] Erika R. Bracamonte,[2] Samih H. Nasr,[3] Bijin Thajudeen.[1] *[1]Nephrology, Banner Univ of Arizona, Tucson, AZ; [2]Pathology, Banner Univ of Arizona Medical Center, Tucson, AZ; [3]Pathology, Mayo Clinic, Rochester, MN.*

Introduction: MPGN with masked monotypic immunoglobulin(IG) deposits is a recently described entity. In the absence of an electron microscopy(EM), some of these patients can be misdiagnosed as having post-infectious glomerulonephritis(PIGN).

Case Description: A 48-year-old Hispanic male transferred to our institution with a diagnosis of biopsy-proven PIGN. His lab evaluation: urine 82 RBC/HPF, urine pro/cr 6100 mg/gm, alb/cr 5403 mg/gm, BUN 208 mg/dl, serum: Cr 4.6 mg/dl. Serum electrophoresis: monoclonal gammopathy(MG) with predominant IgG kappa on immunofixation. Serum free kappa elevated(1246 mg/l) and lambda fraction normal. A repeat kidney biopsy was performed. LM demonstrated diffuse endocapillary proliferative GN. IF was negative except for trace granular staining for C3. EM showed large non-organized intraluminal electron dense deposits. In view of histopathology and MG, IF study on pronase-digested, paraffin embedded tissue was performed which showed bright (2-3+) staining for IgG kappa.



The findings were consistent with diffuse endocapillary proliferative GN with masked monoclonal IgG kappa deposits. Bone marrow aspiration showed myeloma, treated with revlimid-velcade-dexamethasone. He also received HD support for 3 weeks with subsequent improvement in renal function. The most recent serum Cr and urine pro/cr ratio were 0.8 mg/dl and 300 mg/gm respectively.

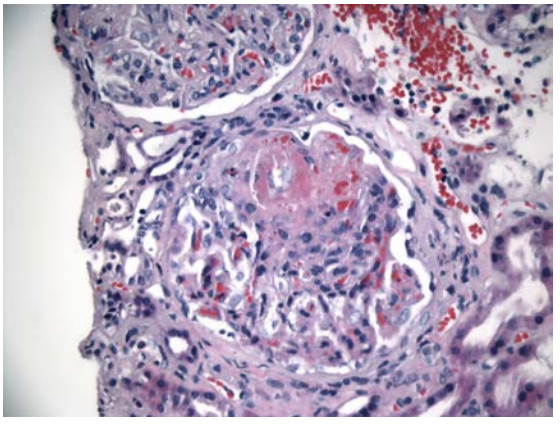
Discussion: This case highlights the importance of performing paraffin IF for GN associated with C3 deposits in adults, especially in the presence of MG regardless of the ultrastructural appearance and location of deposits. It is also recommended when the findings by routine IF do not match either the clinical scenario or EM findings.

TH-PO009

Concomitant Heparin Induced Thrombocytopenia and Hemolytic Uremic Syndrome Sarthak Virmani,[1] Ari B. Geller.[2] *[1]Internal Medicine, Univ of Connecticut School of Medicine, Farmington, CT; [2]Div of Nephrology, St. Francis Hospital, Hartford, CT.*

Introduction: Thrombotic microangiopathy (TMA) with renal failure has a broad differential including TTP, HUS, DIC, APLS and renal scleroderma crisis.

Case Description: A 54 year old female presented with with blurry vision, unilateral leg weakness and altered mental status 11 days after a bio-prosthetic valve repair for critical aortic stenosis. Initial blood work showed hemolytic anemia (Hb 10.7 g/dl, haptoglobin < 6 mg/dl), AKI (Cr 2.4 mg/dl, baseline 0.9 mg/dl) and thrombocytopenia (60,000/mm^3). MRI of the brain showed multifocal acute infarcts of the anterior and posterior circulation. ANA titers were found to be 1:160. Plasma exchange (PLEX) therapy was initiated for a clinical diagnosis of TTP while awaiting ADAMTS13 levels. After 5 days of therapy, her initial ADAMTS13 measured 50% activity and her heparin PF4 antibody screen was positive. This effectively ruling out TTP and established a diagnosis of Heparin Induced Thrombocytopenia (HIT).PLEX therapy was then stopped and Argatroban was initiated. Soon after this intervention, her platelet counts, LDH and other hemolysis markers improved. However, progressive renal failure (Cr 5.0 mg/dl) prompted a biopsy which demonstrated thrombotic microangiopathy. This raised a concern for concomitant atypical HUS.



She received a total of 4 weekly doses of Eculizumab for presumptive diagnosis of atypical HUS. She had significant improvement of her renal function (Cr 1.9 mg/dl). She was continued on anticoagulation. On follow up, she reports improvement in all her symptoms, with improving hemolysis parameters. She will be continued on Eculizumab for 6 months.

Discussion: This case not only highlights the need to have a broad differential diagnosis for TMAs and renal failure, but also the complex management of a patient with overlapping syndromes of HIT and HUS.

TH-PO010

Association of Atypical ANCA with Glomerular Disease Ali I. Gardezi, Tripti Singh, Sana Waheed. *Div of Nephrology, Univ of Wisconsin SMPH, Madison, WI.*

Introduction: Anti neutrophilic cytoplasmic antibodies (ANCA) include a wide range of antibodies directed against cytoplasmic antigens of neutrophils. Indirect Immunofluorescence (IIF) is commonly used to identify ANCA with different patterns. Cytoplasmic pattern (cANCA) is mostly caused by proteinase-3 (PR3) whereas perinuclear pattern (pANCA) is mostly caused by Myeloperoxidase (MPO) antibodies. Any pattern other than these two is labeled atypical ANCA (aANCA). Whereas cANCA & pANCA have been associated with small vessel vasculitis in the kidneys, aANCA has never been associated with any glomerular pathology.

Case Description: We reviewed cases of 7 patients who had aANCA positive on serological testing with negative MPO and PR3 antibodies on ELISA. The details of clinical course and biopsy findings are mentioned in the table included.

Sr. No	Clinical presentation	Initial Creatinine mg/dl	Urine Protein g/g	Hematuria	ANA	Biopsy findings	Treatment and outcome
1	29 y/o male, SLE with flare, mucositis, leukopenia	0.5	0.5	Present	1:640	Class IV Lupus Nephritis	Steroids and IV Cyclophosphamide. Stable creatinine and proteinuria
2	65 y/o male, Hypertension, CKD, Proteinuria & family h/o autoimmune disease	1.26	0.5	Absent	1:320	Secondary membranous nephropathy due to mixed connective tissue disorder	Creatinine and Proteinuria has remained stable without any immunosuppressive treatment
3	44 y/o female, h/o Lung transplant, CKD 4, New onset nephrotic range proteinuria	2.26	4.1	Absent	Negative	Mesengial Proliferative Glomerulonephritis with IgM deposits	Already on immunosuppression for lung transplant. Progression to End stage renal disease within four months of diagnosis.
4	64 y/o male, AKI on CKD 3, Hypertension, NSAIDs	1.56	14	Present	Negative	Membranoproliferative Glomerulonephritis with Cryoglobulins	Rituximab. Significant improvement in serum creatinine and proteinuria
5	76 y/o male, AKI	2.79	2.21	Present	Negative	Pauci Immune Glomerulonephritis	Cytoxan initially, then switched to Rituximab. Significant improvement in creatinine and proteinuria
6	57 y/o male, Nephrotic range proteinuria, Sarcoidosis	0.8	4.36	Present	1:640	Pauci Immune Glomerulonephritis	Oral Cytoxan. Creatinine has been stable, Proteinuria is improving
7	40 y/o male, AKI on CKD 3, DM, Nephrotic range proteinuria	4.58	14.7	Present	Not checked	Pauci Immune Glomerulonephritis	IV Cytoxan, Steroids & Plasma Exchange. Required dialysis on presentation and never came off.

Discussion: As opposed to cANCA and pANCA, target antigens for aANCA have not been identified but have been associated with inflammatory bowel disease, autoimmune hepatitis, primary sclerosing cholangitis, rheumatoid arthritis and certain chronic infections. All seven patients with aANCA showed glomerular damage but no common pattern was identified. A strongly positive antinuclear antibody (ANA) can lead to cross reactivity with ANCA and three of our patients had concurrent ANA positivity. Interestingly, three patients were diagnosed with pauci-immune glomerulonephritis despite having a negative MPO and PR3 antibodies. The presence of aANCA in our patients could be due other antibodies implicated in ANCA negative vasculitis like leukocyte associated membrane protein 2 (LAMP-2) or anti-pantrexin 3 antibodies and might have been the direct pathogenic cause of the disease process. Even though, historically, a positive aANCA test with negative PR3 and MPO antibodies is ignored; findings of glomerular damage with positive aANCA warrants further studies to explore this association.

TH-PO011

Catastrophic Hemodialysis Failure Secondary to Hydroxocoblamin Exposure Kenneth Lim,[1] Eliot C. Heher,[1] David J.R. Steele,[1] Andrew Z. Fenves,[1] Ravi I. Thadhani,[1] Kenneth Christopher,[2] Nina E. Tolkoff-Rubin.[1] *[1]Div of Nephrology, Massachusetts General Hospital, Boston, MA; [2]Renal Div, Brigham and Women's Hospital, Boston, MA.*

Introduction: Hydroxocobalamin is an antidote for the treatment of cyanide poisoning. We describe a case of a young patient administered empiric hydroxocobalamin due to suspected cyanide overdose with failure of emergent hemodialysis secondary to interference from hydroxocobalamin.

Case Description: A 24 year old man was found unresponsive and profoundly hypotensive. On arrival to the emergency room, he was in extremis with significant agonal breathing. Following emergent intubation and despite IV fluid resuscitation, he required rapid escalation to multiple vasopressor requirements. Due to profound acid-base disturbance and concern for intentional overdose, emergent dialysis was considered. Physical examination was notable for a glasgow coma scale of 3, temp 35.3°C, BP 60/46 mm Hg, HR 74 beats/min, RR 24 breaths/min, and cool extremities. Laboratory investigations revealed a Cr of 1.3mg/dL, Na 145mmol/L, K+ 4.6mmol/L, HCO3 10mmol/L, AG 39, phos 4.9, lactate 21.3mmol/L, WBC 27.3K/uL. A rapid bedside echocardiogram showed severely diminished cardiac function. Blood and urine toxicology screen were negative. Hemodialysis was initiated emergently using a Fresenius 2008K machine, however this was confounded by a recurrent "blood leak alarm" that repeatedly shut down the machine. Following multiple trials to initiate hemodialysis, this was aborted with plans to initiate CVVH. Emergent salvage extracorporeal membrane oxygenation (ECMO) was commenced, however the patient expired prior to CVVH initiation. Collateral history later revealed likely sodium azide intoxication.

Discussion: Hydroxoobalamin causes orange/red discoloration of bodily fluids and can permeate dialysate. This can lead to catastrophic dialysis failure due to defraction of light from discolored dialysate, resulting in triggering of the blood leak sensor in certain hemodialysis machines. The case highlights the need for increased awareness of hydroxocobalamin effects in hemodialysis and its potential to delay initiation of emergent dialysis in critically-ill patients.

TH-PO012

Focal Segmental Glomerulosclerosis Associated with Mitochondrial Disease Kenneth Lim,[1] David J.R. Steele,[1] Ravi I. Thadhani,[1] Eliot C. Heher,[1] Amel Karaa.[2] *[1]Div of Nephrology, Massachusetts General Hospital, Boston, MA; [2]Pediatrics, Massachusetts General Hospital, Boston, MA.*

Introduction: Primary mitochondrial diseases (MD) are complex, heterogeneous inherited diseases caused by mutations in either the mitochondrial or nuclear DNA. Glomerular diseases in MD have been reported with tRNA mutation m.3243A>G causing a syndrome of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS). We present a case of focal segmental glomeruloscerosis (FSGS) associated with a new tRNA mutation site.

Case Description: A 34 year old man with a history of ESRD s/p living related kidney transplantation, diabetes, hearing loss and developmental delay presented to outpatient clinic with complaints of new behavioral changes. At age 12 he developed hearing loss and at age 14 non-nephrotic range proteinuria secondary to FSGS. He now presents with new behavioral difficulties and disorganized thought processes. Based on this set of clinical circumstances, concern for an underlying genetic abnormality was raised. Physical examination was remarkable for difficulty hearing, a pattern of dysarthric speech and cerebellar gait. Laboratory investigations including lactate levels were unremarkable. Serial brain MRIs revealed multiple areas of abnormal signal intensity in the basal ganglia and deep white matter, prominent 4th ventricle and cerebellar atrophy. Multiple metabolic testings were unremarkable and whole exome sequencing revealed a mitochondrial MT-TW tRNA change at position m.5538G>A as well as a PDGFRB p.R695C variant. This gene is associated with primary familial brain calcification. Genotype-phenotype correlations in this case are more consistent with a tRNA mutation as a cause of his symptoms. Biochemical investigations are currently in process to further evaluate the pathogenicity of the mutation found.

Discussion: Patients presenting with deafness and proteinuria can be misleadingly diagnosed with Alport's syndrome. Consideration of an underlying MD should be made in patients presenting with deafness, neurologic changes, diabetes and renal failure. To the best of our knowledge, this is the first case describing FSGS-associated MD caused by a m.5538 G>A mutation.

TH-PO013

A Confounding Case of Type 1 Cryoglobulinemic Vasculitis Nishkarsh Saxena, Tripti Singh, Sana Waheed. *Nephrology, Univ of Wisconsin School of Medicine and Public Health, Madison, WI.*

Introduction: Membranoproliferative glomerulonephritis (MPGN) associated with cryoglobulins (CG) is often seen in the setting of hepatitis C (HCV) infection, hematologic malignancies or autoimmune conditions. Rarely, no etiology is found, limiting therapeutic options in these patients. We present a case of type 1 CG associated GN caused by monoclonal IgM heavy chain (HC) successfully treated with rituximab.

Case Description: A 64-year-old white male with history of hypertension and sporadic NSAID use presented to the kidney clinic with a creatinine (Cr) of 4.2mg/dL and a spot urine protein to Cr ratio (UPCR) of 9g/g with dysmorphic RBCs. Serologic work up was significant for normal complements, negative ANA and negative HCV antibody and PCR.

His CG test was positive for type 1 CG (monoclonal IgM HC). His serum immunofixation (IF) showed three distinct monoclonal bands – two IgG kappa and one IgG lambda. Bone marrow biopsy and CT scan of the chest, abdomen and pelvis were negative for malignancy. Renal biopsy showed MPGN pattern of glomerular injury with a full-house immunofluoresence pattern and subendothelial deposits with electro-lucent areas inside and severe podocyte foot process effacement. He was treated with pulse dose steroid followed by 4 weekly doses of rituximab 375 mg/m^2. His renal function improved to a Cr of 1.97mg/dL and UPCR 0.43g/g.

Most cases of CG associated GN are seen in the setting of mixed CG. Type 1 CG associated GN without an underlying hematologic malignancy is rare. Interestingly our patient had multiple oligoclonal bands of IgG on regular IF but his renal disease was likely caused by IgM HC. This monoclonal IgM HC was detectable only on IF done on serum for testing of CG due to its precipitation at a lower temperature. Data regarding optimal therapy for such patients is scarce. A study of 23 patients with type 1 CG treated with rituximab had shown a response rate of 80%, however, one-third had relapse by 12 months. Another case series of 2 patients with type 1 CG, rituximab therapy was associated with treatment failure.

Discussion: Further data is needed to evaluate the efficacy of rituximab monotherapy for type 1 CG associated GN, which was successful in our patient.

TH-PO014

The Importance of Renal Biopsy in the Diagnosis of Fabry Nephropathy

Eduarda Tenorio Leite,[1] Luiz Antonio Magnata Da Fonte Filho,[1] Jose Edevanilson Gueiros,[1] Ana Paula Gueiros,[1] Luiz A. Moura.[2] *[1]Nephrology, IMIP, Recife, Brazil; [2]Pathology, UNIFESP, Sao Paulo, Brazil.*

Introduction: Fabry disease (FD) is caused by mutations in the α-galactosidase A gene resulting in progressive accumulation of globotriaosylceramide (GL-3) in various tissues including the kidney, brain and heart. The current challenge is the search for biomarkers that allow early identification of patients with progressive disease, mainly in asymptomatic young people. In this context, the renal biopsy (RB) is gaining importance in the diagnosis of Fabry nephropathy, in the indication and evaluation of the response of enzyme replacement therapy (ERT).

Case Description: A female patient was diagnosed as a carrier of the p.R356W mutation at 14 years old through family screening after her father, (already on hemodialysis) had been diagnosed with FD. At first, the asymptomatic patient rejected the diagnosis and only later at 17 years old, sought medical help. She remained asymptomatic, denied having neuropathic pain, hypohidrosis or anhidrosis or gastrointestinal symptoms. She not had angiokeratoma. Laboratory tests showed serum creatinine 0.64mg/mL, urinary albumin-creatinine ratio 29 mg/g and normal urinalysis. Normal echocardiography. With the medical history of the father, coupled with the fact that a cousin had a kidney transplant at age 32 (daughter of a deceased uncle), we opted to do a RB. Light microscopy revealed vacuolization of podocytes, tubules with small and sparse atrophy foci and discreet interstitial fibrosis. Small-size arteries showed discrete fibrous intimal hyperplasia. In electron microscopy, podocytes were observed with large cytoplasm containing inclusions in concentric lamellar (myelin figures) and periodic band (zebra bodies) configuration. In these, there is effacement of foot processes. When evaluated by the renal scoring system for FD Proposed by Fogo, the podocytes received a GL-3 score 2 and 3.2 in PAS and semi thin sections, respectively. The percentage of interstitial fibrosis was 5%. On the findings of RB the patient was advised to start ERT.

Discussion: RB is of fundamental importance for early therapeutic intervention in FD in order to mitigate or prevent progressive nephropathy and other life threatening complications.

TH-PO015

Novel Treatment of HCV Induced Cryoglobulinemia Glomerulonephritis

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Introduction: Current standard treatment of HCV-induced cryoglobulinemia GN (Cryo GN) in severe cases include plasmapheresis plus steroids with induction immunosuppressive (IS) (i.e. cytoxan), but in era of the antiviral therapy with 96-100% Sustained virologic response, it is unclear if standard therapy remains the best option.

Case Description: 66 year old white man with history of HTN, HLD, history of bladder cancer s/p resection, presented to renal clinic for evaluation of elevated creatinine (Cr) [6.3 mg/dl] from his baseline 1mg/dl [4month ago], he was complaining from generalized fatigue, joint pain, no joint swelling, redness, mouth ulceration, skin rash, no fever, no history of NSAID or herbal medication. His physical examination was unremarkable. His labs revealed elevated serum Cr, pyuria, hematuria, proteinuria (1.3 g/g), small monoclonal spike 0.57, free light chain normal 1.9, rheumatoid factor 85, HCV viral load 170K , kidney biopsy revealed a diagnosis of Cryo GN. The patient was treated with plasmapheresis, pulse steroids and initiated on the newer antiviral therapy [Elbasvir,grazoprevier], without induction IS. Patient's serum Cr decreased from 6.3 to 3.4 in less than 1month preventing him from being dialysis dependent.

Discussion: The treatment of cryoglobulinemia depends upon the underlying disorder and upon the severity and nature of the renal involvement. In this patient he responded well to plasmapheresis, steroids, and newer antiviral therapy alone. Raising the question in Cryo Gn secondary to HCV, the treatment may include standard therapies plus the new antiviral treatment with or without the need for induction immunosuppressive medication. To our knowledge this is the first case using newer antiviral treatment strategies and plasmaphereses without immunosuppressive medication in Cryo GN with a good response.

TH-PO016

Do Genetic Defects in Complement Regulation Underlie Invasive *S. pneumoniae* - Associated HUS?

Selasie Goka, Joshua Zaritsky. *Pediatrics, Nemours, Wilmigton, DE.*

Introduction: *Streptococcus pneumoniae*- associated HUS (Strep-HUS) has been thought to be a result of neuraminidase activity of pneumococci leading to endothelial damage and thrombotic microangiopathic anemia (TMA). However recent data suggests that mutations in the genes encoding complement proteins may potentiate complement dysregulation leading to the full clinical manifestation of HUS. We present a case of Strep-HUS associated with a known gene mutation of complement factor I (CFI).

Case Description: An otherwise healthy 10 month old male presented with 5 days of fever, and 2 days of vomiting and diarrhea. Initial and subsequent lab findings were significant for a TMA (Table) with a peripheral smear significant for helmet cells and RBC schistocytes and severe AKI with anuria.

	Presentation	6h later	40h later
Hemoglobin (g/dL)	11.4	9.5	6.7
Platelets (k/uL)	18	12	57 (post transfusion)
Sodium (mm/L)	136	146	144
Potassium (mm/L)	5.1	5.4	5.7
Chloride (mm/L)	102	114	114
TCO2 (mm/L)	24	22	19
BUN (mg/dL)	16	23	55
Creatinine (mg/dL)	0.5	0.6	1.6

Blood culture was positive for *S. pneumoniae.* Given an ADAMTS13 activity of 41%, a haptoglobin of 109 mg/dl and a LDH of 14, 645 U/L the patient was diagnosed with Strep-HUS. The patient was admitted to the PICU due to altered mental status with bradycardia and hypertension necessitating intubation. MRI brain demonstrated restricted diffusion, multiple hemorrhagic foci and elevated lactate on spectroscopy concerning for HUS. Unfortunately despite rapid treatment with eculizumab the patient developed brainstem herniation within 18 hours of presentation and was pronounced dead 4 days after admission. Genetic testing showed patient to be positive for a heterozygous missense mutation (c. 355G>A, p. Gly119Arg) in exon 3 of CFI, which has been previously shown to be associated with aHUS.

Discussion: This case suggests that underlying congenital abnormalities of complement regulation may play a significant pathogenic role in the development of Strep-HUS. Future studies are needed to clarify this association as rapid identification of these genetic abnormalities may allow for targeted therapy and improved patient outcomes.

TH-PO017

Renal Medullary Angiitis: Another Manifestation of ANCA - Associated Vasculitis

Swetha Rani Kanduri, Jorge Luis Castaneda. *Div of Nephrology, Univ of Mississippi, Jackson, MS.*

Introduction: Renal Medullary Angiitis is a lesion involving the vasa recta of the medulla. It has been reported previously in association with and without Anti-Cytoplasmic Neutrophil antibodies (ANCA). This lesion can be easily mistaken for acute interstitial nephritis owing to the acute inflammatory infiltrate. We report a case of Pulmonary-Renal Syndrome associated with ANCA and Myeloperoxidase antigens (MPO) with medullary involvement and no significant glomerular involvement.

Case Description: Our patient was a 74 years old AAF with previous history of Diabetes and HTN and no renal disease, who presented with 2-week history of shortness of breath, hemoptysis and AKI with a Serum Creatinine of 2.5mg/dl. The Urine analysis was positive for hematuria and minimal proteinuria. The bronchoscopy revealed a diffuse alveolar hemorrhage. She was immediately started on pulse dose steroids while the renal biopsy was prepared. Serology was positive for ANA, MPO-ANCA and negative for Anti-dsDNA, anti-GBM and normal Complement levels. Renal Biopsy showed mostly unremarkable glomeruli with only one cellular crescent formation, several areas of interstitial inflammatory infiltrates and one area of medullary angiitis, IF was negative. Renal function recover even before the institution of Rituximab as induction of remission regimen.

Discussion: Medullary angiitis is a lesion seen on kidney biopsy characterized by the combined morphologic findings of interstitial hemorrhage in the medulla with associated polymorphonuclear leukocyte infiltrate. The presence of karyorrhectic debris surrounding peritubular capillaries and interstitial hemorrhage may be the clue to distinguish from interstitial nephritis. The exact pathogenesis of medullary angiitis is unknown however we want to stress the importance of recognition of this presentation since it may be the only clue suggesting the presence of systemic vasculitis.

TH-PO018

Treatment of Fibrillary Glomerulonephritis with Use of Repository Corticotropin Injections (Acthar®) Sharon Reuben,[1] Natallia Maroz.[1,2] *[1]Dept of Medical Education, Kettering Medical Center, Kettering, OH; [2]Wright State Univ, Dayton, OH.*

Introduction: Fibrillary glomerulonephritis (FG) is a rare idiopathic condition, which is linked to malignancy, autoimmune disorders, or monoclonal gammopathies in a third of the cases. It carries a poor prognosis resulting in progression to end stage renal disease (ESRD) within 2-6 years depending on severity of disease and histological findings. Immunosuppressive agents (IA) have been used in uncontrolled studies with inconsistent results.

Case Description: A 66 year old African American male with a history of hypothyroidism and hypertension was referred to outpatient nephrology consultation in 10/2013 for worsening renal insufficiency over the prior of 2 years. Physical exam was notable for uncontrolled HTN, obesity, and 2+ pitting edema of lower extremities. Elevated creatinine of 2.7mg/dl and nephrotic range proteinuria 5.9gm/day prompted renal biopsy in 12/2013, which showed advanced fibrillary glomerulonephritis with proliferative features, extensive interstitial scarring, and tubular atrophy. Serological work up was negative for autoimmune disorders, hepatitis C or monoclonal gammopathy. No malignancy was identified. Initially, treatment was deferred due to patient preference, advanced disease, and consideration of adverse effects of IA. Four months later, he was started on *Acthar*®80 units three times weekly in hopes to slow progression to ESRD while avoiding the potentially more severe systemic immunosuppressive effects of alternative cytotoxic agents. Within 8 months he had resolution of nephrotic range proteinuria (from a peak of 8.1gm/day to 600mg/day). *Acthar*® was further tapered to 40 units twice weekly and eventually 20 units twice weekly. Creatinine peaked at 3.8mg/dl in 09/2015 but improved to 2.8mg/dl within 8 months and remained stable over subsequent 18 months.

Discussion: FG has no standardized treatment regimen owing to the lack of clinical trials. The use of corticotrophin injections have been seen to mitigate nephrotic proteinuria in variety of glomerular diseases. We report a case of partial remission in FG with complete resolution of nephrotic syndrome and stabilization of renal function over 26 months of therapy.

TH-PO019

Nephrotic Syndrome in a Patient with Mitochondrial Trifunctional Protein Deficiency Bakri Alzarka, Avi Rosenberg, Larry T. Patterson. *Nephrology, Children's National Medical Center, Washington, DC.*

Introduction: Mitochondrial trifunctional protein (MTP) deficiency is a rare autosomal recessive disorder of mitochondrial fatty acid β-oxidation caused by mutations in HADHA or HADHB. Nephrotic syndrome is not a reported feature of MTP deficiency.

Case Description: An 18 month old female had developed severe hypoglycemia and acidosis after birth. Her acylcarnitine profile was consistent with long-chain-3-hydroxyacyl-CoA dehydrogenase deficiency or MTP deficiency. She was found to have a heterozygous deletion, c.1059delP, in HADHB that is predicted to cause truncation and loss of MTP function. Her father had the same mutation, but is asymptomatic. At 18 months of age, she developed nephrotic syndrome. Her renal biopsy contained segmental and global sclerosing glomerular lesions. Her renal function rapidly declined leading to dialysis and nephrectomies. Collapsing glomerulopathy (CG) was seen on microscopy. Gene analysis showed a heterozygote variant in COQ6, which is predicted to have abnormal function.

Discussion: Our patient had a heterozygous mutation in COQ6, an enzyme needed for production of an integral member of the mitochondrial electron transport chain. Homozygous and compound heterozygote mutations in COQ6 cause coenzyme Q10 deficiency and nephrotic syndrome. Susceptibility genes for CG in mouse encode proteins directly involved in mitochondrial function suggesting that the glomerulopathy can be induced by mitochondrial dysfunction. A mutation in COQ2, which encodes an enzyme in CoQ10 pathway, leads to collapsing lesions resembling those in a murine model having a mutation in a gene with homology to the human PDSS2, another member of the CoQ10 synthesis pathway. We speculate that heterozygosity for both HADHB and COQ6 in our patient led to the metabolic disease as well as the nephrotic syndrome. Neither mutation alone would be expected to cause disease, but together could alter mitochondrial function. Collapsing glomerulopathy, which is found in other conditions with mitochondrial dysfunction, supports this idea. Further study will be needed to evaluate the effect of a combined HADHB and COQ6 heterozygosity and to determine whether supplementation might effectively treat disease.

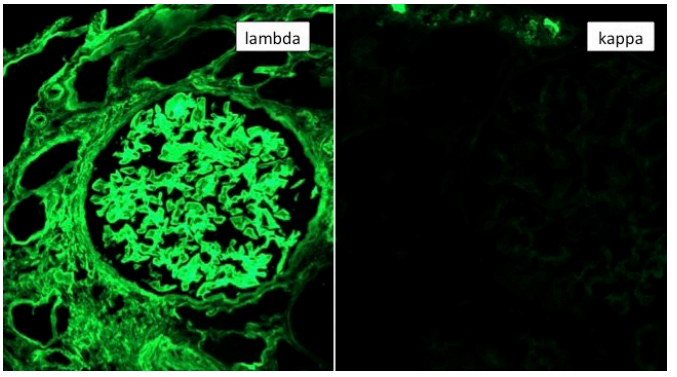
TH-PO020

De Novo Multiple Myeloma in a Kidney Transplant Recipient Presenting with Asymptomatic Proteinuria Anne D. Sebastian,[1] William Luke Whittier,[2] David J. Cimbaluk.[3] *[1]Internal Medicine, Rush Univ Medical Center, Chicago, IL; [2]Nephrology, Rush Univ Medical Center, Chicago, IL; [3]Pathology, Rush Univ Medical Center, Chicago, IL.*

Introduction: Multiple myeloma (MM) is a plasma cell malignancy that can cause renal failure in native kidneys and recur in kidney transplants (RT) but is rarely reported *de novo*. We present a case of an asymptomatic RT recipient with proteinuria whose biopsy revealed *de novo* light chain deposition disease.

Case Description: A 65 y.o. black man with a PMH of HTN, DM2, and ESRD due to FSGS s/p RT in 1982 presented for routine follow up in 2015. His baseline SCr was 2.0 mg/dL from chronic allograft nephropathy (CAN) on biopsy in 1990. Microalbumin/Cr and p/c ratio in 2014 were 53 mcg/mg and 170 g/g respectively. Physical exam was normal. SCr: 2.1 mg/dL, Calcium: 10.4 mg/dL, total protein: 7.0 g/dL, albumin 4.4 g/dL. UA: 2+protein, 1+blood. Urine p/c 2.1 g/g.

Renal biopsy in 2015 redemonstrated CAN without nodularity or acute rejection. Congo red was (-). IF revealed strong, linear staining of glomerular and tubular basement membranes for lambda (λ) light chain and no staining for kappa (κ) (see Figure). EM contained no deposits or granules in the GBM.



SPEP showed κ 1.96 mg/dL, λ 93.0 mg/dL, and κ/λ 0.021. UIEP had monoclonal free lambda light chains. Marrow bx confirmed lambda light chain MM with 25% plasma cells. After starting bortezemib and dexamethasone, SCr and lambda light chains improved to 1.8 mg/dL and 34 mg/dL respectively. Treatment was held after a cavitary lung lesion was found. He eventually expired due to infectious complications.

Discussion: We present a patient found to have *de novo* lambda light chain nephropathy from MM 33 years after his renal transplant. This case highlights the importance of considering *de novo* pathology in transplant patients presenting with proteinuria.

TH-PO021

Successful Treatment of Resistant Mixed Class IV/V SLE with Adrenocorticotropic Hormone (ACTH) Amtul Aala,[1] Ali Yalcindag,[2] M. Khurram Faizan.[2] *[1]Dept of Medicine, Rhode Islad Hospital, Providence, RI; [2]Dept of Pediatrics, Hasbro Children's Hospital, Providence, RI.*

Introduction: Numerous immunosuppressive medications have been used in the treatment of resistant mixed class IV/V lupus nephritis (LN) such as mycophenolate mofetil (MMF), cyclophosphamide, cyclosporine, rituximab and tacrolimus. We present a 13 y.o. girl with resistant mixed class IV/V lupus nephritis treated successfully with ACTH.

Case Description: 13 y.o. African American girl presented with new onset proteinuria with urine protein to creatinine ratio (UPCR) of 2.7, creatinine 0.5 mg/dL, ANA 1:10240, C3 52.0 (low), C4 10.9 (low) and serum albumin (Alb) 2.7 g/dL. Renal biopsy revealed diffuse proliferative and membranous glomerulonephritis consistent with Mixed Class IV/V LN. She was started on oral prednisone and MMF 1000 mgs bid. Due to persistent proteinuria, MMF was increased to 1500 mg bid, prednisone was increased to 20 mg bid and Lisinopril to 20 mg daily with minimal improvement. Repeat renal biopsy 3 yrs later showed focally proliferative and predominantly membranous glomerulonephritis, consistent with LN classes III (A/C) and V, with <10% interstitial fibrosis. This time Rituximab was given (2 doses) with no change in serologies and worsening UPCR to 4. Tacrolimus was added, but UPCR increased to 6 with Alb 1.9 gms/dL and patient remained persistently nephrotic. ACTH (Acthar Gel) 80 units IM twice a week was added to her previous immunosuppressive regimen. Her UPCR improved remarkably to 4.1 in 6 months, and to 2.06 in 10 months on ACTH. She reports marked improvement in fatigue, swelling and joint stiffness with improved but low complements (C3 66, C4 18), ANA titer 1:2560, and creatinine 0.79 mg/dL.

Discussion: Patients with concurrent membranous LN and proliferative or diffuse LN are treated according to the proliferative lesion. Such patients have a worse prognosis. Numerous immuno-suppresive drugs have been used but none of these treatments produce a satisfactory response on class IV/V LN. So far, there is no known data on the use of ACTH in such patients. We hypothesize that for select patients with resistant mixed LN with proteinuria, adding ACTH to their immunosuppressive regimen may be beneficial with improvement in lupus symptoms.

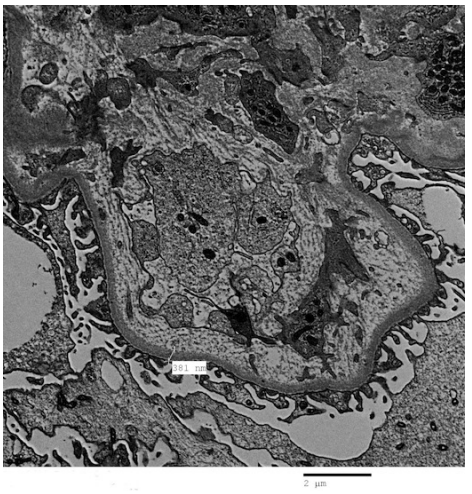
TH-PO022

Preeclampsia in a Man? Idiopathic Endotheliosis Successfully Treated with Plasmapheresis Jennifer A. Lazor, William Luke Whittier, David J. Cimbaluk. *Nephrology, Rush Univ Medical Center, Chicago, IL.*

Introduction: Glomerular endotheliosis is a distinct lesion characterized by endothelial swelling. The glomeruli are "bloodless" due to endothelial swelling causing occluded capillary lumens. We report a case of anasarca, hematuria and AKI with biopsy findings characteristic of endotheliosis. Our patient failed Rituxan therapy but responded rapidly to plasmapheresis.

Case Description: A 50 yo male presented with anasarca. Past medical history was significant for colon CA treated by surgical resection alone (no chemotherapy). On physical exam, BP 112/70 mmHg. He had rales, ascites, and 3+ leg edema. SCr 1.9 mg/dl, UA 3+ prot, 1+ bld, P/C ratio of 0.5 g/g. Secondary serological workup was negative. Biopsy revealed

glomerular capillaries occluded by swollen endothelium without thrombi. IF was negative. On EM, the capillary lumen was occluded by endothelial swelling, electron-lucent widening and subendothelial flocculent material. Podocyte foot processes were preserved (Figure 1).



Therapy with Rituxan was unsuccessful. His SCr rose to 2.9 mg/dl and plasmapheresis was initiated. With 8 treatments over 10 days, his SCr was 1.3 mg/dl and his anasarca resolved. After 6 months, he remains in remission.

Discussion: Circulating endogenous anti-angiogenic substances such as sFLt-1 and KDR antagonize VEGF when over-expressed. This dysregulated signaling deprives the glomerular endothelium of growth factors needed for maintenance. The patient had an excellent sustained response with resolution of AKI and edema following plasmapheresis. We theorize there is an auto-antibody against the VEGF receptor, excess levels of sFLt-1 or KDR, or another anti-endothelial vascular protein that is removed with plasmapheresis allowing restoration of glomerular maintenance.

TH-PO023

Antineutrophil Cytoplasmic Antibodies-Positive Pauci-Immune Crescentic Glomerulonephritis Associated with Acquired Angioedema Siwadon Pitukweerakul, Sai Prasad Gadapa, Sree V. Pilla, Pye Phyo Aung. *Medicine, Presence Saint Francis Hospital, Evanston, IL.*

Introduction: The association of hereditary angioedema with different types of glomerulonephritides has been previously reported. To our knowledge, there has been no reports of acquired or hereditary angioedema associated with pauci-immune vasculitis or glomerulonephritis.

Case Description: A 76 years old African American man with past medical history significant for hypertension and diabetes presented with 2 years of recurrent lip and tongue swelling. He had similar symptoms in the past over past 2 years which required multiple hospitalizations. Physical examination revealed upper lip swelling tongue swelling. Comprehensive metabolic panel revealed Blood urea nitrogen of 49 mg/dL, creatinine of 3.8 mg/dL. Urine analysis was significant for hematuria and proteinuria without casts or abnormal cells. His last known historic creatinine was 1.5 mg/dL 6 months prior to admission. Vasculitis workup was positive for Myeloperoxidase(MPO) ANCA, negative for anti-Glomerular basement membrane(GBM)and proteinase 3(PR3) ANCA. Serum C3 was normal. Serum C4, Serum C1 and C1q were decreased. These complement profiles were compatible with diagnosis of acquired angioedema(AA). According to rapid decline in kidney function he underwent left core needle kidney biopsy which showed focal necrotizing and crescentic glomerulonephritis, pauci-immune type. Patient was started on methylprednisolone and cyclophosphamide. At 1-month follow up and 6-month follow up, creatinine decreased to 2.7 and 1.7 mg/dL,respectively. He also denied episodes of lip and tongue swelling.

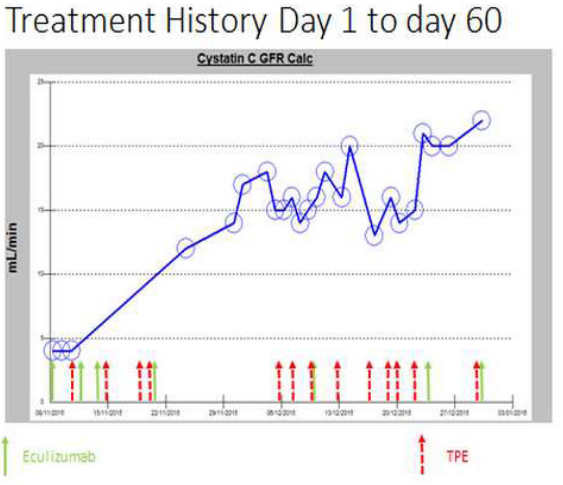
Discussion: Common causes of acquired angioedema(AA) includes non-Hodgkin's lymphoma, monoclonal gammopathy. Other nonhematologic malignancy, infections, and a variety of autoimmune diseases have also been reported as causes of AA. In our case, compatible chronology, complement level and lack of other possible causes of angioedema made pauci-Immune crescentic glomerulonephritis likely the cause of AA. The exact mechanism of recurrent angioedema in this case remains unclear. We would like to add this pauci-immune vasuculitis as a rare cause of AA.

TH-PO024

Atypical Histopathological Findings in a Child with Atypical Hemolytic Uremic Syndrome Treated Successfully with Eculizumab Gurinder Kumar,[1] Bassem Soliman Mohamed Hendawy,[2] Zubaida Al-Ismaili,[1] Omar Nihad Al Masri,[1] Eslam Mohamed Saleh Tawfik,[1] Eihab Al Khasawneh.[1] *[1]Dept of Pediatric Nephrology, Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates; [2]Dept of Pathology, Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates.*

Introduction: Atypical hemolytic uremic syndrome (aHUS) is a rare disease due to dysregulated alternate complement pathway. Histologically it is rare to have crescents on renal biopsy in aHUS. We report a case of 9 year old male presenting with renal failure and renal biopsy showed diffuse crescentic glomerulonephritis(GN) with only few glomeruli showing rare tiny intracapillary fibrin thrombi. Child subsequently developed features of thrombotic microangiopathy(TMA) and successfully treated with eculizumab(Ecu).

Case Description: We report a case of a 9-year-old male presenting with oligoanuric renal failure. Initial labs did not suggest TMA. He required hemodialysis for 2 weeks. Renal biopsy on day 2 showed more than 75% of glomeruli with cellular crescents and negative immunofluorescence. However subsequent labs showed TMA. ANA,ANCA, antiDsDNA were negative and C3 was low. Course in hospital was complicated with seizures and severe hypertension. Repeat renal biopsy after 10 days showed clearing of crescents(60%). He was started on Ecu and plasmapheresis with good response. Genetic testing for aHUS showed hetereozygous variance in genes coding for CFH, CFB,CFI,CFHR5. Currently child improved with gfr of 75 ml/min/1.73m2 and on regular follow up with Ecu q2weeks.



Discussion: Though unusual, aHUS may rarely present histologically with crescentic morphology rather than the expected TMA like picture. aHUS may be considered as a cause of diffuse crescentic GN, especially if ANCA serology is negative and with the presence of other supportive histologic, serologic and clinical signs of TMA. Testing for gene mutations may be helpful for confirmation.

TH-PO025

A Case of Hereditary Fibrinogen A-α-Chain Amyloidosis: Clinical and Counseling Challenges Alison F. Fitzgerald, Alan Segal. *Nephrology, Univ of Vermont Medical Center, Burlington, VT.*

Introduction: Hereditary fibrinogen Aα-chain renal amyloidosis—characterized in 1993—is a form of autosomal dominant renal amyloidosis. Patients invariably present with proteinuria and usually progress to ESRD in their 50s. Our asymptomatic patient first developed isolated proteinuria at age 52. A few months later, her fraternal twin brother developed proteinuria. Four other members of their family (father, older brother, uncle, and uncle's son) had previously developed ESRD and are deceased. Her father had a kidney biopsy in 1971 (age 51) that showed "amyloidosis," which recurred in 2 kidney transplants over the next 6 years.

Case Description: In light of her family history, our patient was convinced that she would "develop ESRD and die of amyloidosis" and was terrified that one or both of her children would meet the same fate. As she feared and predicted, her kidney biopsy showed enlarged glomeruli stuffed with amyloid. No extraglomerular amyloid was apparent. Analysis of the tissue at Mayo Clinic revealed a mutation (E545V) in the fibrinogen Aα-chain made by the liver. Learning this and realizing the significance, this sophisticated patient immediately rejected the idea of "waiting for kidney failure just to have a kidney transplant fail within a few years" and instead advocated that she should pursue a curative liver transplant now, before she gets sick. Yet, a liver transplant is based on a MELD score, which she does not have.

Discussion: It is unclear why this genetic disease does not become clinically evident for 45-55 years, but then recurs within 5 years in a transplant kidney. Should we advocate for pre-emptive liver transplantation for our patient and her children (while their livers can be used for domino transplants), or have them wait for a liver-kidney transplant when they have advanced kidney disease? Finally, when would be the ideal time to transplant her children if they do in fact have the mutation?

TH-PO026

IgA-Dominant Acute Post-Infectious Glomerulonephritis in a Kidney Transplant Recipient Hassan Alhalabi, Manish Anand, Juan Pablo Arroyo, Timothy E. Thayer, Mark Lusco, Anthony J. Langone, Beatrice P. Concepcion. *Vanderbilt Univ Medical Center.*

Introduction: IgA-dominant acute post-infectious glomerulonephritis (IgA-APIGN), a morphologic variant of APIGN, is a rare disease in which IgA is the dominant immunoglobulin found in glomerular immune deposits. All prior reported cases have been in native kidneys. Here we present the first reported case of IgA-APIGN in a kidney transplant recipient, successfully treated with steroids.

Case Description: A 62/M with ESRD secondary to DM underwent kidney transplantation in 2012 and was maintained on tacrolimus and MMF. He was admitted in 2015 with right foot osteomyelitis and MSSA bacteremia and was treated with antibiotics and BKA. Twelve days after initial presentation, he was readmitted with oligoanuric AKI with a Cr of 8.2 mg/dL (baseline 1.4 mg/dL), low C3 and normal C4, UA 2+ protein, 122 WBC's, 133 RBC's, and urine PCR of 1. Biopsy was performed and LM revealed diffuse global endocapillary hypercellularity with frequent neutrophils and 2/10 glomeruli with fibrinoid necrosis. By IF, IgA was the dominant Ig with stronger C3 staining in a diffuse global granular mesangial and irregular chunky capillary loop pattern. By EM, there were frequent mesangial, scattered subendothelial and rare subepithelial deposits. He was given pulses of methylprednisolone (1.5 g) then prednisone 40 mg daily. Renal function improved rapidly with a discharge Cr of 2.1 mg/dL. Steroids were tapered over 3 months and on last follow-up 5 months after presentation Cr was 1.7 mg/dL, UA 1+ protein, 1 RBC, 18 WBC's, urine PCR 0.3.

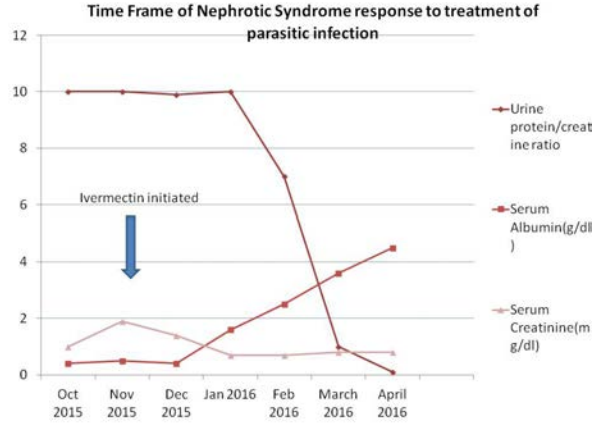
Discussion: IgA-APIGN is often associated with a staphylococcal infection and usually presents with AKI, hematuria and proteinuria. Antibiotics are the mainstay of treatment and prognosis is generally poor. All prior 85 reported cases of IgA-APIGN have been in native kidneys. This is the first reported case of IgA-APIGN in a kidney transplant recipient, illustrating that this disease can occur despite ongoing immunosuppression. Early recognition of IgA-APIGN is an important first step in determining appropriate management. Steroids may have a therapeutic role in cases where renal function continues to deteriorate despite appropriate management of infection.

TH-PO027

Tip Variant Focal Segmental Glomerulosclerosis Associated with Strongyloides Stercolaris Massini Merzkani,[1] Vivette D. D'Agati,[2] Pranisha Gautam-Goyal,[3] Kenar D. Jhaveri.[1] *[1]Nephrology, Hofstra Medical School; [2]Pathology, Columbia Univ Medical Center; [3]ID, Hofstra Medical School.*

Introduction: Although parasitic infections are known to be associated with glomerular lesions, strongyloidiasis-associated glomerulopathy has not been well documented. We report a case of tip variant focal segmental glomerulosclerosis(FSGS) associated with strongyloides stercorali (SS).

Case Description: A 36 year old male from Guatemala presented with sudden onset of lower extremity and facial edema. Lab data revealed urinary protein/creatinine ratio of 10.6 g with serum albumin(Alb) 0.4 g/dl and serum creatinine 0.5mg/dl. Past medical history included tip variant FSGS in childhood that had responded to steroids. A repeat kidney biopsy showed tip variant FSGS with marked podocyte effacement. A detailed history revealed that the patient had recently traveled and had suffered episodic abdominal pain and diarrhea with peripheral eosinophilia of 41 % (2.7 k/ul). His stool studies confirmed SS. Conservative management with lisinopril, atorvastatin and diuretics was initiated with no improvement in edema. He was not given steroids. Ivermectin was initiated to treat the parasitic infection. His edema improved one month after ivermectin treatment, and his nephrotic syndrome resolved in 2 months. Changes in proteinuria, Alb and creatinine over time are graphed below.



Discussion: This is the first case report of tip variant FSGS secondary to SS. Given his predilection for podocytopathy, the parasitic infection was likely the precipitating immune stimulus as "second hit". Surprisingly, the nephrotic syndrome resolved with antihelminthic therapy alone. This case suggests a possible causal relationship between SS infection and FSGS. Even in primary podocytopathies, it is important to consider precipitating infectious triggers that can be specifically treated without resorting to steroid therapy.

TH-PO028

IgM Nephropathy: Achievement of Steroid Free Remission with Rituximab Fatima Khalid,[1] Catherine A. Moore.[1] *[1]Nephrology, Univ of Rochester; [2]Nephrology, Univ of Rochester.*

Introduction: Immunoglobulin M (IgM) nephropathy often presents as nephrotic syndrome in childhood which is poorly responsive to steroids. Likelihood of steroid free remission is very low in the long term, and this exposes individuals to long term complications of steroid therapy. Rituximab has been successfully used in cases of steroid resistant/refractory nephrotic syndrome. However, there are only a few case reports of use in IgM nephropathy, all early in the course of disease.

Case Description: We present a case of a 22 year old female with history of nephrotic syndrome, initially diagnosed at age 20 months. Her first biopsy was at age 6 year old, revealed minimal change disease and possible early cyclosporine nephrotoxicity. Immunofluorescence was not performed on this specimen. Subsequent biopsies have revealed mesangial hyper-cellularity with mesangial IgM consistent with IgM nephropathy. Her most recent biopsy, performed at age 17, revealed 40% global glomerulosclerosis and mild interstitial fibrosis with tubular atrophy. She was steroid-resistant until age 8, and subsequently was steroid dependent. Cyclophosphamide and cyclosporine therapy were used without clear response. This was followed by a trial of tacrolimus and mycophenolate mofetil. She was in complete remission with the above regimen and steroid free for two years. She then relapsed and was steroid dependent again. Infections, particularly upper respiratory infections, tend to trigger relapses. She has experienced significant toxicity from her chronic immunosuppression. Considering steroid dependence with chronic glucocorticoid toxicity, and lack of remission with tacrolimus and mycophenolate mofetil, we decided to initiate rituximab treatment. The patient underwent induction with 2 doses of rituximab 375 mg/m^2, with mycophenolate mofetil as maintenance. The patient has been in remission on less than 20 mg of steroids in the last 6 months and completely off of steroids in the last 6 weeks with no evidence of relapse.

Discussion: We describe a case demonstrating achievement of steroid-free remission using rituximab in a patient with longstanding IgM Nephropathy.

TH-PO029

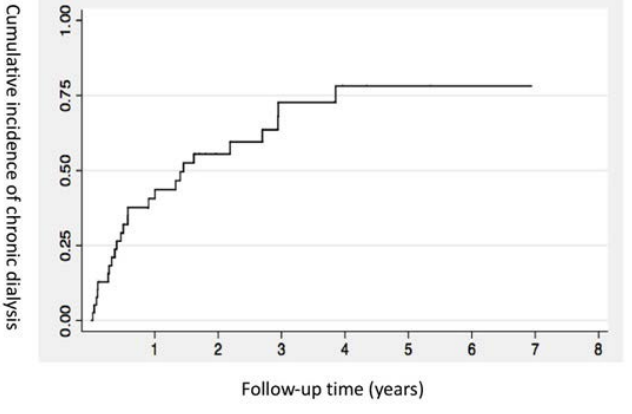
Intravenous Heroin Use Associated with AA Amyloidosis Arjun V. Sharma, Priyanka Govindan, Bryan R. Kestenbaum. *Dept of Nephrology, Univ of Washington, Seattle, WA.*

Introduction: Secondary (AA) renal amyloidosis is characterized by the deposition of serum amyloid A within the glomerular basement membrane, mesangium, tubules, and blood vessels. Affected patients typically present with nephrotic range proteinuria and rapid loss of kidney function. We and others have observed renal AA amyloidosis among patients who use intravenous (IV) heroin; however, the association of IV drug use and renal AA amyloidosis is incompletely described.

Case Description: We evaluated all biopsy proven cases of renal AA amyloidosis within native kidneys at the University of Washington Medical Center and Harborview Medical Center, in Seattle Washington, from 2005-2015. We extracted medical data via chart review. We used Kaplan-Meier estimation to describe renal and overall survival of affected patients.

We identified 43 patients who had biopsy proven renal AA amyloidosis from 2005-2015. Among this group, 42 patients (97%) had chart documentation of IV heroin use with 29 (67%) with use within 6 months prior to biopsy. In addition to IV heroin use, "muscling" and "skin-popping" were also common (83% and 70%, respectfully). Cocaine (72%) use was frequent. Renal co-morbidities included hepatitis C (81%), HIV (9%), and rheumatic disease (5%). At time of biopsy, the mean protein to creatinine ratio was 13.3 ±8.1 g/g and the mean serum creatinine concentration was 4.0 ±2.6 mg/dL. Among 39 of the 43 patients who were not receiving dialysis at the time of biopsy, 25 initiated dialysis over a maximum of 6.9 years of follow-up. Overall patient survival at 5 years was 47%.

Figure. Time to dialysis initiation among 39 patients with AA amyloidosis.



Discussion: Nearly all patients who have renal AA amyloidosis in Seattle, WA use IV heroin. The marked geographical variation in the association of IV heroin use with AA amyloidosis strongly suggests that specific components of street heroin and/or local patterns of use are a cause of this disease.

TH-PO030

Membranous Nephropathy Related to the Checkpoint Inhibitor Nivolumab Jonathan T. Lin,[1] Morgan A. Schiff,[2] Steven Salvatore,[3] Alexander N. Shoushtari,[4] Ilya Glezerman.[5] *[1]Div of Nephrology, New York Presbyterian / Weill Cornell, New York, NY; [2]Critical Care Service, Memorial Sloan Kettering, New York, NY; [3]Pathology and Laboratory Medicine, New York Presbyterian / Weill Cornell, New York, NY; [4]Melanoma and Immunotherapeutics, Memorial Sloan Kettering, New York, NY; [5]Renal Service, Memorial Sloan Kettering, New York, NY.*

Introduction: Programmed cell death (PD) inhibitors are novel anti-cancer immunotherapy, and cases of autoimmune nephritis have been described. We report the first case of nephrotic syndrome with membranous nephropathy associated with the IgG4 PD-1 inhibitor nivolumab.

Case Description: A 75 year-old male presented with metastatic melanoma of unknown primary. He was treated with nivolumab and tolerated bi-weekly infusions with few adverse effects, including mild pruritus and mild colitis. After his fifth treatment, he noted scrotal and lower extremity edema. Subsequent labs revealed hypoalbuminemia to 1.4 (4-5.2) mg/dL with stable creatinine at 1.2 (0.6-1.3) mg/dL. Urine studies were notable for 12 g proteinuria/24 hours, without RBCs, WBCs, or casts on urine microscopy. Serological workup including Anti-Phospholipase-A2-Receptor (PLA_2R) antibody testing was negative. Nivolumab infusions were held, and the patient was started empirically on steroids with prednisone 0.5 mg/kg for presumed autoimmune nephritis. A renal biopsy was performed, with electron microscopy revealing scattered subepithelial electron dense deposits with nearly complete podocyte effacement and immunofluorescence revealing predominantly granular IgG capillary wall staining, consistent with membranous nephropathy. PLA_2R staining was negative. Imaging one month later showed interval decrease in size of both masses. Repeat spot urine protein-to-creatinine was 4.0, plasma albumin was 3.2 g/dL, and his edema resolved.

Discussion: Membranous nephropathy has been linked to solid malignancies including melanoma, but the timing of nephrotic syndrome in this patient coincided with treatment with nivolumab. Clinicians should be aware of this risk, and additional cases may help elucidate alterations in the immune response and mechanisms of renal injury by therapy with PD-1 inhibitors.

TH-PO031

Spontaneous Clinical Resolution in Dense Deposit Disease Anna Lane Baldwin, Katherine D. Westreich, Akhil Hegde, Volker Nickeleit, Harsharan Kaur Singh, Gerald A. Hladik. *UNC Kidney Center, UNC Hospitals, Chapel Hill, NC.*

Introduction: Dense deposit disease (DDD) is often progressive and incurs high morbidity. We present two atypical cases of DDD that are somewhat atypical with spontaneous remission of proteinuria and renal dysfunction.

Case Description: Case 1: 24-year-old white woman with acute kidney injury (AKI) and nephritis. She had a recent minor skin infection of the hand that resolved. C3 was <40 mg/dl and anti-DNAse B titer was elevated at 862 U/ml. Biopsy: DDD, with proliferative GN, C3 deposits, and electron dense deposits (EDD) within the glomerular basement membrane (GBM). C3 nephritic factor (C3NeF) was detected; extensive testing of the complement system, including sequencing of 6 genes with known mutations causing C3GN/DDD, was normal. Serum creatinine (Scr), C3, and urine protein normalized in 1 month without treatment; microscopic hematuria persists. **Case 2:** 8-year-old white girl with AKI and nephritis during an upper respiratory infection; anti-streptococcal antibodies were[-]. 1st Biopsy: proliferative GN, C3 deposits, scattered EDD. Scr, C3, and urine protein normalized in 3 months after a short course of steroids. 7 months later developed recurrent nephritis during confirmed strep pharyngitis. 2nd biopsy: DDD with no significant chronic tissue injury. Complement analysis as described in case 1 showed elevated C3NeF and no other abnormality. Creatinine, cystatin C, C3, and urine protein all normalized within 6 weeks.

Discussion: The two patients under discussion had DDD with self –limited clinical findings. Both had increased C3NeF with relatively limited intramembranous deposits . In Case 2, a second biopsy showed no evidence of chronic kidney injury. The underlying etiology remains undetermined. We speculate that infection, autoimmune, or inflammation-related complement activation may cause transient and rudimentary forms of DDD in patients with elevated C3NeF. Alternatively, these might reflect early clinical expression of DDD. Overall, these cases illustrate that the clinical manifestations may largely resolve without treatment Similar cases require further study to identify distinguishing features in order to avoid immunosuppression (IS) in cases that improve, at least in the short term, without IS.

TH-PO032

Membranous Nephropathy in a Patient with Common Variable Immune Deficiency Teena Zachariah, Syed Ali Husain, Jordan Gabriela Nestor, Renu Regunathan-Shenk, Glen S. Markowitz, Andrew S. Bomback. *Nephrology, Columbia Univ Medical Center, New York, NY.*

Introduction: Secondary membranous glomerulonephritis occurs in patients with systemic lupus erythematosus, infections such as hepatitis B and C, and solid tumors. There have been no prior case reports of membranous nephropathy in adult patients with common variable immune deficiency (CVID).

Case Description: A 36 year old Caucasian woman with CVID on weekly subcutaneous immunoglobulin G (IgG) therapy presented with fluid overload. Labs were notable for 8 g/day proteinuria, albumin 2.0 g/dL, and creatinine of 0.6 mg/dL. She underwent renal biopsy revealing membranous nephropathy (MN) with negative staining for anti-PLA2R on immunofluorescence. She was initially treated conservatively; within two weeks, she was admitted for worsening lower extremity edema, abdominal pain, and nausea. Her creatinine had risen to 2.0 mg/dL on admission, and she subsequently developed oliguric renal failure with a peak creatinine of 5.8 mg/dL. Serologic test for PLA2R antibody was negative. A repeat renal biopsy revealed acute tubular injury in addition to prior findings of PLA2R negative membranous nephropathy. She was treated with 6 sessions of hemodialysis, two doses of intravenous rituximab (1 g), and a prednisone taper. At 2 months after starting treatment, her creatinine had returned to 0.6 mg/dL, urine microalbumin:creatinine ratio was 345 mcg/mg, and serum albumin was 3.4 g/dL.

Discussion: The treatment of membranous glomerulonephritis in an immunocompromised patient poses a challenge. A previous case report of MN in a child with CVID reported remission of proteinuria with cyclosporine, and here we report successful response to rituximab-based therapy. CVID, a rare disease, may be an even rarer etiology of secondary membranous nephropathy that, nonetheless, appears to respond to immunosuppressive therapy.

TH-PO033

Kidney Disease and Neurologic Deficits from a Rare Collagen Type 4 Mutation Dominique Dorsainvil, Jeffrey M. Turner. *Nephrology, Yale School of Medicine, New Haven, CT.*

Introduction: Type 4 collagen is the main component of the basement membrane in the filtration barrier of the glomerulus. Mutations in the genes coding for the six alpha chains lead to various disorders with renal and non-renal manifestations. Mutations in COL4A5 cause Alport syndrome, the most common inherited type 4 collagen disorder. Recently an autosomal dominant disorder termed hereditary angiopathy with nephropathy, aneurysms and muscle cramps (HANAC) has been described due to mutations in the COL4A1 gene.

Case Description: 24 year old female with isolated persistent microscopic hematuria in the setting of recurring acute intermittent headaches with transient neurologic deficits. Her neurologic symptoms began as migraine episodes as a teenager. They severely worsened at the age of 22 during the postpartum period of her second pregnancy. MRI was notable for periventricular and deep subcortical white matter changes. Her family history is notable for several family members with neurologic deficits ranging from migraines to strokes at a young age. Two maternal aunts had end stage renal disease of unknown etiology. Kidney biopsy in this patient showed thin basement membrane with an average thickness of 139nm and diffuse foot process effacement on electron microscopy. Whole exome sequencing showed a heterozygous mutation of the COL4A1 gene leading to amino acid changes G->E at codon 805.

Discussion: Case series have reported a wide spectrum of renal manifestations from COL4A1 mutations, ranging from no proteinuria, persistent hematuria, cystic disease to end stage kidney disease with diffuse fibrosis. Our patient had persistent hematuria with a preserved glomerular filtration rate, consistent with the previous descriptions. Electron microscopy findings in published case series have shown irregularities in the basement membrane structure, also present in our case. Unique to our case, as it has not yet been described in the literature, is the finding of diffuse podocyte foot process effacement. For that reason, this case expands our understanding of the different renal patterns of injury associated with COL4A1 mutations.

TH-PO034

Patient with Thrombotic Microangiopathy: Thrombotic Thrombocytopenic Purpura and Atypical Hemolytic Uremic Syndrome at the Same Time Ahmed Daoud, Lauren L. Pacheco, Umbar Ghaffar. *Nephrology, UAMS, Little Rock, AR.*

Introduction: Thrombotic microangiopathy (TMA) is a pathological process characterized by microangiopathic hemolytic anemia, thrombocytopenia and microvascular occlusion. TMAs are classified into 4 major syndromes: Hemolytic uremic syndrome (HUS), Atypical HUS (aHUS), Thrombotic thrombocytopenic purpura (TTP) and other disorders including malignant hypertension. We are reporting a case of a patient presenting with clinical features of a TMA who was diagnosed with both aHUS & TTP at the same time.

Case Description: A 24-year-old African American man with a past medical history of Klinefelter Syndrome and hypertension was transferred from an outside facility with the chief complaint of generalized fatigue. Labs showed renal failure, thrombocytopenia, and hemolytic anemia. He underwent workup for TMA which revealed low ADAMTS13 level of 15% with a positive ADAMTS13 inhibitor screen. The ADAMTS13 inhibitor Bethesda titer was elevated at 5.2. His genetic testing revealed CFHR1/CFH3 homozygous deletion, which is strongly associated with the presence of Factor H auto-antibodies and a heterozygous, missense variant in exon 20 of CFH which was recently cited as a mutation associated with aHUS. Patient was treated with plasmapharesis, eculizumab, rituximab, vincristine, cyclophosphamide, and prednisone with resolution of thrombocytopenia and anemia. However, he remained dialysis dependent for his renal faliure. Near discharge, his ADAMTS13 level was 31% with a negative inhibitor. He was discharged home on infusions of cyclophosphamide and prednisone and with follow-up appointments for labs and on weekly eculizumab.

Discussion: TTP is an uncommon TMA-related disorder that occurs mainly in adults, and is associated with acquired (or rarely genetic) severe deficiency of the cleaving protease for Von Willebrand Factor (vWF), ADAMTS13. aHUS is a rare disease associated with genetic or acquired factors that cause defective regulation of the alternative complement pathway. This patient had low ADAMTS 13 levels indicating TTP & complement gene mutations indicating aHUS. The occurrence of both these conditions together is extremely rare,and has not been reported before.

TH-PO035

A Case of Glomerular Capillary Endotheliosis due to Multicentric Castleman's Disease Vahagn A. Zakaryan, Anjali A. Satoskar, Tibor Nadasdy, Brad H. Rovin, Samir Parikh. *The Ohio State Univ Medical Center.*

Introduction: Glomerular capillary endotheliosis (GE) is the result of severe endothelial cell injury and manifests histologically with endothelial swelling, glomerular hypertrophy, and capillary lumen narrowing. GE has been previously associated with thrombotic microangiopathy and pre-eclampsia. Here, we report a case of severe GE causing acute renal failure in a patient with Multicentric Castleman's Disease (MCCD).

Case Description: A 59-year-old male presented with anasarca, hypoalbuminemia, and orthostatic hypotension consistent with systemic capillary leak syndrome (SCLS). He developed acute renal failure requiring hemodialysis. Workup was negative for autoimmune disease, infection, or malignancy. A kidney biopsy showed severe glomerular capillary endothelial swelling with acellular closure of capillary loops consistent with GE. Empiric treatment with high dose prednisone led to remission but disease relapsed after steroids were stopped. He had nephritic urine sediment and 750mg/d proteinuria. A second renal biopsy showed severe GE. Remission was again achieved after 6 months of oral cyclophosphamide and prednisone taper. Maintenance mycophenolate mofetil was given for 3 years without relapse. Therapy was stopped and disease relapsed but this time with diffuse lymphadenopathy and a circulating monoclonal IgG-kappa light chain in addition to SCLS and nephritis. A lymph node biopsy was consistent with MCCD. IL-6, CRP, and VEGF levels were markedly elevated. Anti-IL-6 antibody therapy was started and a complete remission was achieved after 2 months of treatment.

Discussion: This is the first report of GE as a manifestation of MCCD. MCCD is a rare, life threatening lymphoprolfierative disease associated with hyperactivation of the immune system causing excessive release of IL-6 and similar cytokines. The hypercytokinemia seen in MCCD is likely responsible for the increased vascular permeability and GE seen in this case. In summary, MCCD should be considered in patients found to have acute glomerulonephritis due to capillary endotheliosis. If recognized, therapy with immunosuppression is effective and may prevent life-threatening complications.

TH-PO036

Using Steroids for Nephrotic Syndrome in Proliferative Glomerulonephritis with Monoclonal IgG Deposits Sean Verma,[1] Emmanuel Bassily,[1] Claude Bassil.[3] *[1]Internal Medicine, Univ of South Florida; [2]Nephrology, Univ of South Florida.*

Introduction: Proliferative Glomerulonephritis with Monoclonal IgG Deposits (PGNMID) is a rare disorder associated with monoclonal gammopathy of renal significance (MGRS) that has unique pathological and glomerular histological features from other MGRS disorders. The pathogenesis and best treatment options remain unknown.

Case Description: A 57-year-old man was found to have nephrotic range proteinuria of 8 grams/24 hours. On exam he had 2+ pitting edema to the knees. Labs showed hemoglobin 12.2 mg/dL, creatinine 1.3 mg/dL, calcium 8.6 mg/dL, and albumin 2.7 mg/dL. Renal biopsy revealed glomerular basement membranes (GBM) with irregular thickening with "tram tracking" and diffuse moderate mesangial expansion. Immunofluorescence showed 3+ granular staining for IgG3, 3+ kappa light chains, 2-3+ C3, and 2-3+ C1q. Electron microscopy showed irregular thickness of the GBM with subendothelial electron dense granular deposits and podocyte foot process effacement. Serum and urine protein were negative for monoclonal proteins. Skeletal survey had no lytic lesions and bone marrow biopsy showed plasma cells less than 5% of total cellularity. He was started on lisinopril and prednisone taper. His 24-hour urine protein was 800 mg at 6 month follow up.

Discussion: We report an uncommon case of PGNMID responding to steroid therapy and renin angiotensin-system (RAS) blockade. PGNMID has been associated with myeloma, chronic lymphocytic leukemia, parvovirus and hepatitis C infection. In a study of 37 PGNMID patients, Nasr et al. suggest PGNMID is not a precursor to hematological malignancies in most patients. However, the best treatment option remains elusive and prognosis typically is poor. Biopsy may show endocapillary proliferation, membranoproliferative features, membranous features, or mesangial proliferation. Possible treatments include, RAS blockade alone, cyclophosphamide, rituximab, and bortezomib. Komatsudu et al. described the first case of steroid responsive nephrotic syndrome in PGNMID with pure mesangial features, and it is unclear whether this unusual form has a better response to steroids.

TH-PO037

Characteristics of Genetic and Biomolecular Backgrounds in Patients with LAMB2 Related Nephropathy Shogo Minamikawa,[1] Kandai Nozu,[1] Tomohiko Yamamura,[1] Takeshi Ninchoji,[1] Yuko Shima,[2] Koichi Nakanishi,[2] Kazumoto Iijima.[1] *[1]Dept of Pediatrics, Kobe Univ Graduate School of Medicine, Hyogo, Japan; [2]Dept of Pediatrics, Wakayama Medical Univ, Wakayama, Japan.*

Introduction: Null mutations in *LAMB2* cause Pierson syndrome (PS), a severe congenital nephrotic syndrome with ocular and neurologic defects, and show completely negative expression of laminin β2 on glomerular basement membrane (GBM). However, recently some cases with milder phenotypes in *LAMB2* mutations have been reported. Here we report 3 cases with milder phenotypes who were diagnosed as PS by next generation sequencing (NGS). We also identified characteristics of genetic and biomolecular backgrounds in these patients.

Case Description: Case 1 is a 3 yo boy; developed nephrotic syndrome at 6 mo. Case 2 is a 1yo girl, younger sister of the case 1. She presented nephrotic syndrome at 1 mo. Case 3 is 2 yo boy, exhibited hematuria and non-nephrotic range proteinuria at 1 mo. None of these three patients showed kidney dysfunction, ocular or neurological defects until now. Renal biopsy showed mesangial proliferation, and electron microscopy findings showed thinning and Basket-weave change of the GBM in all cases. As a result of genetic analysis by NGS, novel frameshift mutation: c.225delC and known pathogenic missense mutation: p.Gly699Arg in *LAMB2* were detected in case 1 and case 2. In case 3, novel frameshift mutation: c.5073-5076dupCCAG and novel splicing-site mutation: c.3797+5G>A in *LAMB2* were detected whichresulted in whole intron 24 (96bp) insertion between exon 24 and exon 25 at the transcript level. Laminin β2 positive expression on GBM was evaluated by immunohistochemistry in all cases.

Discussion: We detected compound heterozygous mutations in *LAMB2* gene in all patients. One family showed missense mutation and another showed in-frame mutation. We proved laminin β2 positive expression in all cases. These results might reflect milder phenotypes for PS in our cases. In conclusion, we clarified the genetic and biomolecular backgrounds for milder phenotypes in our cases with *LAMB2* mutations. NGS is a powerful tool to make genetic diagnosis of inherited kidney diseases showing atypical phenotypes.

TH-PO038

ANCA Vasculitis Induced Aortitis Rawan T. Al-Odat, Faisal Anwar, Hafiz Ali Sroya, Saeed Kamran Shaffi. *Nephrology, UNM, Albuqerque, NM.*

Introduction: ANCA vasculitis primarily affects small vessels; however, large vessel involvement has been reported in literature. We present a case of aortitis caused by ANCA vasculitis.

Case Description: We evaluated a 49 years old male with history of granulomatosis with polyangitis (GPA), that was diagnosed 15 years ago and was treated with induction therapy (steroids, cyclophosphamide and plasmapheresis) followed by maintenance therapy (azathioprine) for 5 years, in the nephrology clinic. He was recently admitted to the hospital for chest pain that had been worsening over the last few days with a chest CT showing an ascending aortic aneurysm that mandated urgent repair. Physical examination during the clinic visit was unremarkable. Pertinent diagnostic data is shown in Figure 1. The patient is currently receiving induction therapy for anti-proteinase 3 (PR3) positive ANCA vasculitis with monthly intravenous cyclophosphamide doses and oral steroids.

Figure 1

Lab data	Result
BUN (mg/dL)	40
Cr (mg/dL)	2.16
ANCA	Positive for PR3*
PR3*	4.4 (normal 0.0-0.9)
Urine analysis	Protein 2+, Blood 3+
Urine microscopy	> 5 dysmorphic RBCs per high power field
Spot urine protein to creatinine ratio (g/g)	1.3
Kidney ultrasound	Normal sized kidneys with preserved cortices.
Kidney biopsy	Few crescents with focal necrosis, and scarring; Pauci-immune
* PR3; Anti proteinase 3 antibody	

Discussion: The pathogenesis of large vessel involvement by ANCA vasculitis is not entirely clear. Intimal injury may be the initial insult followed by the inflammation of the media and adventitia resulting in trans-mural aortitis. It occurs in both myeloperoxidase (MPO) and PR3 ANCA vasculitis. The presentation is varied with instances of stenosing large vessel arteritis, aneurysmal disease, aortic dissection, and aortic rupture reported in literature. Most of the reported cases were managed with an extended period of immunosuppression using corticosteroids and cyclophosphamide with good outcomes.

TH-PO039

Mixed Cryoglobulinemic Glomerulonephritis Associated with Ulcerative Colitis in a Liver Transplant Patient Rungwasee Rattanavich, Ali I. Gardezi, Dr Salahuddin, Arjang Djamali, Didier A. Mandelbrot. *Div of Nephrology, Dept of Medicine, Univ of Wisconsin School of Medicine and Public Health, Madison, WI.*

Introduction: Mixed Cryoglobulinemic vasculitis is most commonly associated with Hepatitis C infection but rarely reported in chronic autoimmune disorders. We present a patient who developed cryoglobulinemic vasculitis with membranoproliferative glomerulonephritis after ulcerative colitis (UC) flare.

Case Description: 47 y/o male with ulcerative colitis, primary sclerosing cholangitis s/p post liver transplant, CKD III presented with an ulcerative colitis flare which was treated with adalimumab and prednisone with improvement in symptoms. He was also found to have AKI on CKD with new onset nephrotic range proteinuria, hematuria. He also developed violaceous discoloration of his toes. Hepatitis B & C panel, HIV, CMV, EBV, ANA and ANCA were negative. LFTs and serum free light chain ratio were normal. C3 was low but C4 was normal. Serum cryoglobulins were negative. Kidney biopsy showed Membranoproliferative glomerulonephritis. Electron microscopy showed electron dense deposits with ultrastructural features of cryoglobulinemic glomerulonephritis. Skin biopsy of the rash was consistent with cryoglobulinemic vasculitis. He developed anuric AKI requiring temporary hemodialysis. He was given rituximab due to severity of his AKI and no improvement with treatment of ulcerative colitis. He subsequently came off dialysis and his GFR improved back to baseline. His urine protein to creatinine ratio improved from 4.81 to 0.73.

Discussion: This case highlights the rare association between ulcerative colitis(UC) and cryoglobulinemia. Studies have shown the presence of autoantibodies to Saccharomyces cerevisiae (ASCA) in patients with UC as well as in those with cryoglobulinemia which could explain the association. Although this is rare, but clinicians treating IBD should have a high suspicious for cryoglobulinemic vasculitis especially in patients with vasculitic rash or AKI. Rituximab has been shown to be effective in treating both Hepatitis C and Non HCV related cryoglobulinemic vasculitis and should be considered in severe glomerulonephritis with nephrotic range proteinuria.

TH-PO040

Rituximab Therapy Worsens Hepatitis C Associated Cryoglobulinemic MPGN Post Kidney Transplant Despite HCV Eradication Samuel Chakola,[1] Nomsa Musemwa,[1] Swati Rao,[1] Mythili Ghanta,[1] Duncan B. Johnstone,[1] Xu Zeng,[2] Serban Constantinescu,[1] Avrum Gillespie,[1] Crystal A. Gadegbeku,[1] Iris J. Lee.[1] *[1]Section of Nephrology and Transplantation, Temple Univ, Philadelphia, PA; [2]Section of Pathology, Temple Univ, Philadelphia, PA.*

Introduction: Chronic Hepatitis C virus infection (HCV) is prevalent in end stage renal disease and kidney transplant recipients (KTR). Polyclonal B-cells stimulation by HCV leads to cryoglobulin and rheumatoid factor (RF) production, manifesting as systemic vasculitis and/or MPGN in KTR. Standard of care is therapy with steroids, Rituximab (RTX), plasmapheresis (PP) and eradication of HCV with anti-viral regimens. We report a case of persistent cryoglobulinemia with vasculitis and MPGN, despite eradication of HCV in a KTR.

Case Description: A 63 year old AA male with HCV on hemodialysis received a cadaveric KT from a HCV positive donor. Proteinuria, HCV, high RF and low complement levels prompted an allograft biopsy which showed cryoglobulinemic MPGN. Therapy was initiated with steroids, PP, and RTX (375mg/m2) for 2 doses, with remaining doses of RTX held due to sepsis. Despite rapid resolution of HCV with an IFN-free regimen cryoglobulinemia persisted. Work up for a monoclonal lymphoproliferative disorder was negative. A third dose of RTX was given but the patient subsequently developed gross hematuria, proteinuria, acute kidney injury and a purpuric rash. Allograft biopsy showed progressive MPGN with crescents improved by aggressive PP and steroids. We reasoned that RTX triggered an acute vasculitis and MPGN, and therefore opted to give 2 cycles of Bortezomib along with PP and achieved complete clinical remission.

Discussion: RTX is a chimeric molecule possessing a humanized IgG tail, a potential target for IgM with RF activity. The resulting increase in IgG-IgM complex could have precipitated acute vasculitis and organ damage in our patient. In addition, RTX alters B-cell populations by upregulating BAFF receptor on B-cells favoring mature B-cell development, counter-productive to treatment goals. Our case highlights the complications of RTX in HCV cryoglobulinemia and suggests studying the role of bortezomib in resistant cases likely driven by plasma cell dyscrasia.

TH-PO041

Hydralazine-Induced ANCA Vasculitis with Glomerulonephritis and Diffuse Alveolar Hemorrhage Josef Bautista, Katherine Mikovna Scovner. *Section of Kidney Diseases and Hypertension, Brown Univ - Rhode Island Hospital, Providence, RI.*

Introduction: Hydralazine is known to cause drug-induced lupus. However, this entity has very limited renal involvement. In contrast, hydralazine-induced ANCA vasculitis, a rarer pathology, may result in catastrophic renal and pulmonary disease.

Case Description: This is a 71-year-old woman with hypertension who had been on hydralazine 50 mg twice daily for 2.5 years. She presented with hematuria, acute renal failure, hemoptysis and hypoxic respiratory failure. Physical exam was notable for hypertension, coarse lung sounds and bilateral pitting edema. Serum creatinine was 5.4 mg/dL. Her UA showed 3+ blood and 100mg/dL protein. ANA was 1:1,280, p-ANCA was 1:80, anti-histone antibody was elevated to 2.8, anti-double-stranded (ds) DNA antibody was elevated at 155, and C3/C4 were low. Renal ultrasound showed increased echogenicity concerning for medication-induced renal disease. Renal biopsy showed diffuse acute tubular necrosis with RBC casts and active vasculitis in 5 of 23 glomeruli. 10 of 18 glomeruli had fibrocellular crescents. Immunofluorescence was negative for immune complex deposition while electron micrograph showed no deposits in the glomerular basement membrane or mesangium. Hydralazine was discontinued. The patient received stress dose steroids and was started on plasmapheresis. She was also started on rituximab 375 mg/m2 weekly for 4 weeks for induction immunosuppression. 1 week after the diagnosis, labs showed improvement in her ANA, anti-histone and myeloperoxidase titers. Her complement levels remained low. After 2 months, she remained dialysis-dependent.

Discussion: This case illustrates an exceedingly rare complication of hydralazine. Hydralazine may alter the expression of MPO and other neutrophilic antigens (e.g. histone, ANA, anti ds DNA) by inhibiting DNA methyltransferases in the neutrophils. The presence of P-ANCA, positive anti-histone antibodies, and pauci-immunity are consistent with drug-induced ANCA vasculitis rather than with drug-induced lupus or primary vasculitis. Treatment of this condition is similar to that of idiopathic ANCA vasculitis but, in addition, the offending agent must never be reintroduced to the patient.

TH-PO042

Rituximab for Proliferative Glomerulonephritis with Monoclonal IgG Deposits in Two Kidney Allografts Josef Bautista, Basma Omar Merhi. *Section of Kidney Diseases and Hypertension, Brown Univ - Rhode Island Hospital, Providence, RI.*

Introduction: Proliferative glomerulonephritis with monoclonal IgG deposit (PGNMID) in the allograft is a rare condition with IgG3 Kappa being the most common subtype. It could be de novo or recurrent disease. There is no standardized treatment protocol yet due to the limited case reports published. Here, we present 2 cases of PGNMID in the allograft and their response to Rituximab.

Case Description: We present two kidney transplant cases of nephritic syndromes with sub- and nephrotic-range proteinuria and allograft dysfunction. Serologies for hepatitis B & C, anti-nuclear antibodies, cryoglobulins, SPEP/UPEP were negative in both patients. Allograft biopsy of the two patients met the pathologic criteria for PGNMID with IgG1 kappa subtype in one case and IgG3 kappa subtype in the second case. Both cases were treated with two doses of 375mg/m2 of Rituximab given two weeks apart. Both had improvement in their hematuria, proteinuria and allograft function after 2 years of follow-up with improving pathologic biopsy one year after Rituximab in one patient.

Discussion: PGNMID in the allograft creates a diagnostic and therapeutic dilemma to the clinician. The pathophysiology appears to be persistence of monoclonal IgG molecule that is readily fixed by the complement system and subsequent glomerular deposition and activation of downstream inflammatory reaction. B cell apoptosis by rituximab, a chimeric anti-CD20 monoclonal antibody, decreases immunoglobulin production and this is the rationale behind its use in the transplant population especially in the treatment of steroid-resistant antibody mediated rejection, post-transplant lymphoproliferative disorder, recurrent glomerular disease after transplant. Its use in our 2 cases seems promising as a potential treatment of PGNMID after transplantation.

TH-PO043

Acquired Gitelman Syndrome from Bendamustine Josef Bautista, Jie Tang, Andrew Rogers. *Section of Hypertension and Nephrology, Dept of Medicine, Rhode Island Hospital - Brown Univ, Providene, RI.*

Introduction: Gitelman's syndrome, caused by loss-of-function mutations in the thiazide-sensitive Na-Cl cotransporter (NCC), is characterized by hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria. Acquired Gitelman-like syndromes have also been described, commonly with cisplatin use. Bendamustine is a nitrogen mustard routinely used in the treatment of chronic lymphocytic leukemia (CLL) and indolent B-cell non-hodgkin lymphoma (NHL). Although hypokalemia has been observed in about 5% of patients taking it, the underlying causes have never been established, the mechanism is unknown.

Case Description: Herein, we report a case of bendamustine-induced hypokalemia that satisfied the diagnostic criteria for Gitelman's syndrome. The patient is a 51-year-old male who had recently completed bendamustine and rituximab therapy for follicular lymphoma who presented to the hospital with leg cramps and with serum potassium 1.6 mEq/L, magnesium 1.6 mEq/L and bicarbonate 36 mEq/L. Physical exam showed hypotension, dry mucosa, and poor skin turgor. Laboratory test prior to his chemotherapy showed serum creatinine of 0.9 mg/dl, potassium of 3.7 meq/L and bicarbonate of 27 meq/L. Subsequent work-up revealed 24-hour urine potassium 88 meq, sodium 206 meq and calcium 8 mg. Serum aldosterone was undetectable while the renin activity was elevated at 6.82 ng/mL/hr. Diuretic screen was negative. The patient was treated with oral and intravenous potassium, which normalized his serum potassium and improved his symptoms. Follow-up laboratory test after one month showed a potassium of 5.4 meq/L and a bicarbonate of 22 meq/L while still on 80 meq/day of oral potassium.

Discussion: To our knowledge, this is the first documented case of acquired Gitelman's syndrome from bendamustine. Now that bendamustine is more commonly used, this rare but serious complication with hypokalemia should be recognized. Future studies are needed to elucidate mechanisms of the pathophysiological effects of bendamustine on the distal tubule.

TH-PO044

Successful Treatment with Spironolactone and Acetazolamide for Severe Metabolic Alkalosis and Hypokalemia Secondary to Ectopic Adrenocorticotropic Hormone-Secreting Extrapulmonary Small Cell Neuroendocrine Carcinoma of the Rectum Luis A. Vazquez, William Chastant, Jonathan G. Owen. *Nephrology and Hypertension, Louisiana State Univ Health Sciences Center, New Orleans, LA.*

Introduction: Metabolic alkalosis is life threatening with reported mortality of 45% with arterial blood pH of 7.55. We present a case of severe metabolic alkalosis and hypokalemia secondary to an ACTH-secreting neuroendocrine tumor.

Case Description: 58 year old man with hypertension and HIV on HAART therapy, presented to his PCP with edema, hypertension and fatigue after no improvement from doubling his valsartan-HCTZ. Labs showed creatinine 5.6 mg/dL, hypokalemia (2.3 mmol/L) and serum CO2 level of 42mmol/L, prompting admission. Arterial blood gas showed pH 7.57, HCO3 42.8 mmol/L, pCO2 45.8 mmHg. Nephrology consulted after no improvement with a liter of normal saline and 80 meq potassium chloride (KCl). Exam was notable for buffalo hump and striae and mineralocorticoid excess was suspected; patient started on spironolactone 25mg daily, and hydration and KCl replacement continued. After 24 hours, despite improving creatinine, the pH peaked at 7.596. Spironolactone increased to 50mg daily, oral KCl 40meq started thrice daily, and acetazolamide 500mg IV started q12 hours for two doses, followed by acetazolamide 500 mg orally q12 hours for 4 doses.

His pH improved to 7.577 at 24 hours, 7.505 at 48 hours, and to 7.442 at 72 hours upon completion of acetazolamide. He was maintained on spironolactone 50mg daily and KCl 40meq orally thrice daily with no return of severe alkalosis or hypokalemia. Creatinine improved to 1.2 mg/dL. Cortisol level resulted greater than 110 µg/dL, and ACTH level of 1585 pg/mL. Work-up suggested non-pituitary source, and CT-imaging revealed concern for metastatic involvement of rectum and liver. Biopsy of the rectal mass confirmed extrapulmonary small cell ACTH-secreting neuroendocrine carcinoma.

Discussion: Severe metabolic alkalosis and hypokalemia secondary to mineralocorticoid effects of cortisol in ACTH-secreting neuroendocrine tumors has been rarely reported. Our case demonstrates the potential severity and a treatment regimen that has not previously been reported in this rare condition.

TH-PO045

Novel Treatment: Nephrogenic DI Swapna P. Vantzelfde, Jean M. Francis, Craig E. Gordon. *Boston Medical Center, Boston, MA.*

Introduction: A patient with lithium-induced nephrogenic diabetes insipidus (NDI) was treated with acetazolamide. This was modeled after a trial in mice.

Case Description: 49 year old male with bipolar disorder on chronic lithium therapy, admitted for resection of acoustic schwannoma due to ipsilateral hearing loss. Post-operatively, he was delirious with limited water intake. Lithium was discontinued on day 3 for worsening mental status. Serum sodium ranged from 153mmol/L to 164mmol/L and urine output ranged from 8 to 12L per day. Urine osmolality was 150mosm/kg H20. The free water deficit was initially treated with D5W IV without improvement. His mental status continued to deteriorate and his serum sodium remained elevated. DDAVP was administered with no change in the urine osmolality or serum sodium, conferring the diagnosis of complete NDI. Hydrochlorothiazide was started, and 4 days into treatment his urine output had increased to 14L per day. On day 18, acetazolamide started and hydrochlorothiazide stopped. By day 20 of admission there were dramatic improvements; urine output dropped to 3 to 5L per day, urine osmolality increased to 330mosm/kg H20 and serum sodium normalized. The beneficial effects of acetazolamide persisted, but were confounded by recent cessation of lithium and thus the acetazolamide was stopped which led to rise in urine output, to 7L per day. The acetazolamide was resumed on day 34, with marked reduction in polyuria to 1.5-3.5L per day for the duration of admission.

Discussion: The most common cause of NDI is chronic lithium use. Traditionally, the therapeutic approach emphasizes reduced sodium intake and thiazide diuretics with or without amiloride. Recent data from animal models of lithium-induced NDI delineate that hydrochlorothiazide reduces polyuria in mice lacking the thiazide-sensitive sodium-chloride co-transporter. This suggests an alternative mechanism of action than previously accepted. Carbonic anhydrase inhibition was proposed and a trial utilizing mice and collecting duct cells showed that acetazolamide was at least as effective for treatment of NDI. We utilized acetazolamide monotherapy in a patient with severe lithium-induced NDI and to our knowledge this is the first case with successful use of acetazolamide in humans with NDI.

TH-PO046

Attempt to Treat Anti-Brush Border Antibody-Mediated Tubulointerstitial Nephritis with Rituximab Emily Dryer,[1] Robert B. Colvin,[2] Ivy A. Rosales,[2] A. Bernard Collins,[2] Katherine Westin Kwon.[1] *[1]Lakeland Health, Saint Joseph, MI; [2]MGH Pathology, Boston, MA.*

Introduction: A case of immune complex tubulointerstitial nephritis due to autoantibodies to the proximal tubule brush border was recently described. We describe a second case, identified prior to the onset of end stage renal disease, and the lack of response to therapy with rituximab.

Case Description: A 76 year old man was referred to nephrology for evaluation after routine labs revealed his serum creatinine had risen from 1.1 to 1.5 over a year's time. He had 510 mg of proteinuria and transient microhematuria. He had no history of diabetes or hypertension. His blood pressure was 118/56, and physical exam revealed no edema. Kidney biopsy showed segmental membranous glomerulopathy. Immunofluorescence identified immune complex deposits along tubular basement membranes (TBM). This was consistent with a primary immune complex tubulointerstitial nephritis associated with anti-brush border antibodies (ABBAs). To confirm, the patient's serum was incubated with normal renal tissue and similar immune complexes developed. The patient was treated with prednisone 40 mg daily and rituximab 375 mg/m2 weekly for four weeks. Over the next five months, his serum creatinine rose further, reaching 3.5 mg/dL. He had profound functional decline, and his BMI fell from 18.8 to 15.9, ultimately requiring inpatient evaluation for failure to thrive. Admission was complicated by respiratory failure due to pneumonia in the setting of advanced chronic obstructive lung disease, and he expired in the hospital. Postmortem evaluation revealed no occult malignancy or extrarenal autoimmune disease. The kidneys had widespread tubular injury and atrophy with extensive diffuse fibrosis, progressive from prior biopsy. Interstitial inflammation was mild, but immune complex deposits were present in the TBM and Bowman's capsule. Serum was positive for ABBAs.

Discussion: In this case of anti-brush border antibody-mediated tubulointerstitial nephritis, administration of rituximab and prednisone early in the course of the disease did not halt the progression of renal decline. In the future, alternative therapy options should be considered for this disease process.

TH-PO047

Inherited Salt-Losing Tubulopathy: A Case Series Zhen Cheng,[1,3] Jing Lin,[2,3] Qi Qian.[3] *[1]Nephrology, Jinling Hospital Nanjing Univ, Rochester, MN; [2]Nephrology, Zhongshan Hospital Fudan Univ, Rochester, MN; [3]Nephrology and Hypertension, Mayo Clinic College of Medicine, Rochester, MN.*

Introduction: Two major syndromes of salt-losing nephropathy are Bartter syndrome (BS) and Gitelman syndrome (GS). We presented a series of GS and BS with unique mutations and some atypical presentations.

Case Description: Clinical data were collected through Mayo Clinic Electronic Medical Records with the IRB approval.

Five cases were identified (2010-2015). Average age was 37.2 yr (range: 20-50), BP 113.2/65.2 mmHg (96-140/48-88), common presentations were fatigue/muscle cramps and hypokalemia 2.82 mmol/L (2.0-3.3) while on K supplementation. Mutation analysis showed SLC12A3 gene mutations in 4 patients, consistent with GS, and CLCNKB mutation in 1, consistent with classic BS (cBS). The SLC12A3 mutations were (1) novel combination of double heterozygous c.184G>C and c.1964G>A; (2) novel combination of double heterozygous c.533C>T and c.815T>C; (3) homozygous mutations in two positions c.2221G>A and c.791C>G; and, (4) novel combination of heterozygous c.1315G>A and c.1964G>A. The remaining patient had CLCNKB mutation c.508G>A combined with an allelic deletion. Atypical presentations included (1) normotensive and hypertensive in 4 cases, 2 were on treatment; (2) erythrocytosis requiring phlebotomy in 1; (3) reversible hypercalcemia (11.5 mg/dL) associated with Ca supplement (1250 mg 2xdaily) and with fixed low urine Ca excretion (65 and 67 mg/24 hr urine before and after serum Ca correction [9.6 mg/dL]) by discontinuation of Ca intake; and, (4) the most severe hypokalemia (1.8-2.0 mmol/L on 160 mmol KCl/day) in a GS patient and the mildest hypokalemia (3.5-4.0 mmol/L on 20 mmol KCl/day) in the cBS patient. Combination treatments of oral KCl (20-160 mEq daily), amiloride (5-10 mg daily), and MgOx (400 -1800 mg daily) improved symptoms and serum K rose to 3.27 mmol/L (2.1-4.1).

Discussion: We describe unique mutant alleles in five unrelated adults. 8 mutations were predicted to be pathogenic, of which 7 missense mutations and 1 deletion. Differentiation of BS and GS based on clinical presentations is difficult. Normotension and hypertension are common. Genetic testing is informative.

TH-PO048

Pseudonormalization of the Serum Anion Gap in a Patient with Ketoacidosis Caused by Bromvalerylurea Intoxication Yatsumu Saito, Akiko Soda, Shuichiro Yamanaka, Kyoko Kishida, Yasuyuki Nakada, Taketo Uchiyama, Izumi Yamamoto, Ichiro Ohkido, Takashi Yokoo. *Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Minato-ku, Tokyo, Japan.*

Introduction: Although nonsteroidal anti-inflammatory drugs (NSAIDs) containing bromvalerylurea are prohibited in the United States, such drugs are commonly available over-the-counter in Asian countries. The clinical features of acute intoxication include nausea, vomiting, and disturbed consciousness. Chronic intoxication induces irreversible neurological deficits and cerebellar atrophy. Importantly, the commonly used assays cannot distinguish bromides from chlorides, with the result that serum hyperchloremia may be a key feature of bromvalerylurea intoxication.

Case Description: A 50-year-old woman had a history of Neuro-Behçet's disease from the age of 48 years. She felt nauseous, and vomited repeatedly for 3 weeks prior to admission. These symptoms and her disturbance of consciousness became gradually worse to the point where she could not eat. On admission, ketone body levels in urine and blood were markedly elevated and her serum levels of bicarbonate were extremely low at 8.8 mmol/L. However, blood gas analysis revealed a paradoxical normal anion gap of 7.7 with hyperchloremia (127 mmol chloride/L). Furthermore, a magnetic resonance imaging brain scan revealed severe cerebellar vermis atrophy compatible with chronic bromvalerylurea intoxication. A medical interview revealed a history of common use of NSAIDs containing bromvalerylurea. Ultimately, we diagnosed her with acute to chronic bromvalerylurea intoxication. Prohibition of drug use resolved the digestive symptoms quickly, resulting in normalization of chloride levels and the metabolic acidosis. She was discharged, ambulating, 21 days after admission.

Discussion: Bromvalerylurea intoxication is uncommonly encountered in modern practice but has not disappeared; cases are still reported in Asian countries. Our case suggests that pseudohyperchloremia and pseudonormalization of the anion gap in patients with severe acidosis could be key features in the diagnosis of bromvalerylurea intoxication.

TH-PO049

Succinylcholine Induced Hyperkalemia in Pregnancy: A Unique Clinical Presentation Maria Theodorou, Jennifer K. Bond, Kavitha Vellanki. *Loyola Univ Medical Center, Maywood, IL.*

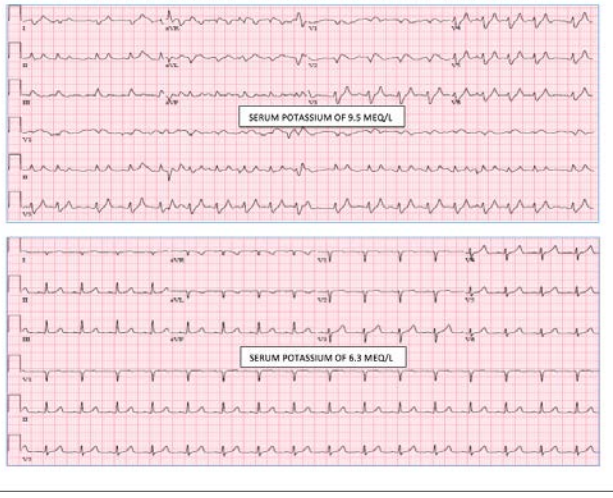
Introduction: Succinylcholine is used as a paralytic for endotracheal intubation, especially when rapid onset and offset of effect is needed. One adverse effect in certain patients is acute onset hyperkalemia and associated cardiovascular instability. Little is known about such effects in pregnancy. Here we report one such rare case.

Case Description: A 38 year old primigravida at 16 weeks with poorly controlled asthma presented with severe acute asthma exacerbation. Over 36 hours, she deteriorated despite maximal medical support, requiring emergent intubation for severe hypercapnic respiratory failure with succinylcholine and propofol induction. 7 hours post-intubation, wide QRS complexes were noted on cardiac monitor. STAT workup revealed a serum potassium of 9.5 MM/L (Table 1).

Table 1: Laboratory Data Pre & Post Succinylcholine Induction		
	Pre-Induction	7 Hours Post
Na (136-144 MM/L)	138	133
K (3.3-5.1 MM/L)	3.6	9.5
HCO3 (20-32 MM/L)	24	30
Cl (98-108 MM/L)	107	103
Glucose (70-100 MG/DL)	96	226
BUN (7-22 MG/DL)	6	11
Cr (0.6-1.4 MG/DL)	0.49	0.79

EKG showed wide QRS complexes. She was treated with calcium gluconate, sodium bicarbonate, insulin drip, sodium polystyrene sulfonate, and inhaled isoflurane. Hyperkalemia and EKG abnormalities improved in 4 hours (Figure 1).

FIGURE I : EKG CHANGES WITH SEVERE HYPERKALEMIA AND POST TREATMENT



Her hospital course was complicated by severe hypercapnia requiring extracorporeal membrane oxygenation, however she was eventually extubated and delivered a healthy child.

Discussion: Succinylcholine induced hyperkalemia in pregnancy has rarely been described. Cardiac arrest was reported in a pregnant female who had recovered from Guillain-Barre syndrome and developed hyperkalemia and cardiac arrhythmia within 1 minute of receiving succinylcholine. The 7 hour time delay to hyperkalemia and absence of neuromuscular disorder make our patient's clinical presentation unique.

TH-PO050

Persistent Hyperkalemia Post-Adrenalectomy Rami Mouayad Azem,[1,2] George Thomas.[1] *[1]Nephrology, Cleveland Clinic Foundation, Cleveland, OH; [2]Internal Medicine, Summa Health System, Akron, OH.*

Introduction: Primary aldosteronism should be suspected in resistant hypertension with hypokalemia. Adrenal vein sampling (AVS) can differentiate unilateral from bilateral secreting lesions. Adrenalectomy should result in normalization of potassium (K) levels. We describe a patient with adrenal adenoma who underwent unilateral adrenalectomy, with subsequent persistent hyperkalemia.

Case Description: A 62 year old male with resistant hypertension and hypokalemia presents with a plasma aldosterone (PA) level of 203 ng/dl and plasma renin activity (PRA) of 0.4 ug/dl/hr. CT showed a 1.5 cm right adrenal adenoma with left adrenal hyperplasia. AVS showed lateralization to the right, and the patient underwent right adrenalectomy. ACTH stimulation test showed appropriate cortisol response. He was discharged 2 days post-operatively on nifedipine XL, lisinopril, and K supplementation because of a persistently low K of 3.0 mmol/l and hypertension. On follow-up after 3 days, his K was 5.4 mmol/l and creatinine was 1.5 mg/dl from pre-operative level of 1.1 mg/dl. His lisinopril and K supplementation were discontinued. His post-operative PA and PRA levels were 3 ng/dl and 3.5 ug/l/hr respectively. Because of persistent hyperkalemia with K up to 5.8 mmol/l and creatinine up to 2.6 mg/dl 2 weeks post-operatively, he was hydrated with IV normal saline. His renal function and K improved, but on follow-up one month post-operatively, he was persistently hyperkalemic with K of 5.3 mmol/l. Fludrocortisone 0.1 mg daily was started.

Discussion: Unilateral adrenalectomy should correct hypokalemia in primary aldosteronism. Case series have described hyperkalemia post-adrenalectomy. Incidence is 16-29 percent and hyperkalemia can persist from 1 week to 46 months. Fludrocortisone is needed in rare cases. The etiology is likely selective hypo-aldosteronism due to suppressed contralateral adrenal gland, along with volume depletion. Factors that increase risk include long duration of hypertension and decreased eGFR. Patients who undergo unilateral adrenalectomy for primary aldosteronism should increase fluid intake, liberalize dietary sodium, and have close follow-up of renal function and electrolytes.

TH-PO051

Hyperphosphatemia, Normal eGFR, and Complete Tubular Phosphate Reabsorption Leading to a Pituitary Tumor Diagnosis Jwalant R. Modi, Ghurulakshmi Moorthy, Michael T. Eadon. *Medicine, Indiana Univ, Indianapolis, IN.*

Introduction: The classic presentation of a pituitary tumor is comprised of hormonal symptoms related to gonadal hormone deficiency or neurological symptoms including diplopia, headache, or visual field defects. However, these tumors may be dormant clinically, be found incidentally on brain imaging, or provide subtle clues which can be easily overlooked.

Case Description: A 49 year old African American woman was seen following hospitalization for sudden-onset hand cramping and facial contracture due to hypokalemia for evaluation of hypokalemia induced nephrogenic diabetes insipidus. History was notable for hypertension, normal eGFR, fibroids, colonic polyps, wrist fracture and a 15 lb weight loss in 1 year. She complained of diffuse body aches, fatigue, and poor appetite, but denied any nipple discharge, major headaches, or visual symptoms. She no longer menstruated as she had undergone hysterectomy. On lab studies, she had hypokalemia, recurrent hyperphosphatemia, hypomagnesemia, TTKG 6.5, urine K+/Creatinine ratio 20 meq/g; Fractional excretion (FE) of Mg 1.3% and FE-phos 0%. Her aldosterone level was low with a normal renin level. The most differential-focusing aspect was the complete tubular reabsorption of phosphate in the setting of hyperphosphatemia and normal eGFR. Her 25-OH and 1,25-OH vitamin D were suppressed. It is known that acromegaly with IGF-1 secretion may lead to phosphorus reabsorption. Even though she had no phenotypic features of acromegaly, we checked growth hormone, IGF-1, and IGF-BP3, as well as an MRI brain. Her growth hormone axis was suppressed, but the MRI revealed a heterogeneous sellar mass, suspicious for a pituitary macro adenoma. Her endocrine work-up revealed pan-hypopituitarism, except for a prolactin level of 72.4 - elevated, but atypical for a prolactinoma. She was started on hydrocortisone and levothyroxine and will undergo transsphenoidal tumor removal.

Discussion: Since this patient had hyperphosphatemia with normal eGFR and complete tubular reabsorption of phosphate, this case raises the question of whether pituitary hormones (other than IGF-1) contribute to the regulation of FGF-23 and the sodium phosphate co-transporter.

TH-PO052

TB or Not TB.. That Is the Question Miraie Wardi,[1] Angelica Aurora Nunez,[2] Dubier Matos,[2] Hasan Joseph Salameh.[1] *[1]Internal Medicine - Div of General Internal Medicine, TTUHSC Paul L. Foster School of Medicine, El Paso, TX; [2]Internal Medicine - Div of Nephrology, TTUHSC Paul L. Foster School of Medicine, El Paso, TX.*

Introduction: *Mycobacterium wolinskyi* , a member of the *Mycobacterium smegmatis* group of rapidly growing mycobacteria (RGM), is a rare cause of infection in humans. To date, less than 20 cases have been reported, most of which are associated with post-traumatic and post-surgical wound infections. We report a case of *M.wolinskyi*-induced peritoneal dialysis (PD) catheter exit-site infection, an entity never before reported in the literature.

Case Description: A 46 year old female with a past medical history of end-stage renal disease secondary to lupus nephritis on chronic PD presented for constant abdominal pain of 3 days duration after manual exchanges. Pain was localized in the epigastrum and lower abdomen with no radiation with associated nausea and vomiting. Upon initial evaluation, she was found to be afebrile and normotensive. Abdominal examination was significant for a tender abdomen in the lower and epigastric regions with thick purulent discharge easily expressed from the exit site. A CT of the abdomen failed to show infectious changes tracking along the catheter tunnel. Peritoneal fluid analysis was unremarkable. Bacterial and AFB cultures of the purulent discharge were taken and the patient was initiated on empiric levofloxacin. Initial cultures were negative. The patient with discharged home on topical gentamicin. Upon follow up, the purulent discharge remained. Analysis of exit-site cultures at 168 hours revealed growth of *M. wolinksyi*. Long-term dual antibiotic therapy was initiated and currently pending follow up.

Discussion: M. wolinskyi was discovered in 1999 using 16sRNA sequencing. Only 19 cases of *M.wolinskyi* infections in humans have been described, the majority of which are associated with post-orthopedic surgical site infections, although a few cases of post-operative *M. wolinskyi* bacteremia have been described. It has also been described in one case of PD catheter-related acute peritonitis within 6 months of surgical placement of PD catheter. To our knowledge, this is the first case of M. wolinskyi-induced PD catheter exit-site infection.

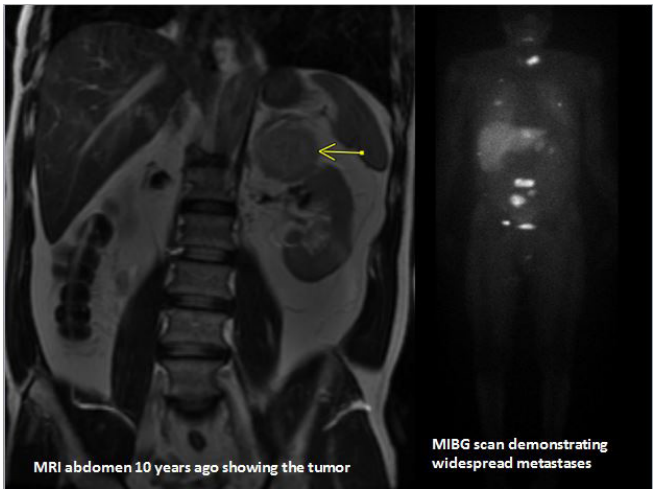
TH-PO053

The Tale of a Forgotten Tumor Abhilash Koratala, S. Irfan Qadri, Vikrampal Bhatti, Volodymyr Chornyy. *Nephrology, Univ of Florida.*

Introduction: Pheochromocytoma (PCC) is a rare catecholamine-secreting neuroendocrine tumor that arises from chromaffin cells of the adrenal medulla. Approximately 10% are malignant, often diagnosed as a result of local invasion into surrounding organs or distant metastases. We present a case of an apparently benign PCC that presented 10 years after diagnosis as metastatic disease.

Case Description: A 64 year old Caucasian man was seen by us for hypertension (HTN) and an adrenal mass. 10 years prior to presentation, he was diagnosed with a left adrenal mass while undergoing work up for uncontrolled HTN. He underwent laparoscopic left adrenalectomy and pathology confirmed PCC. The tumor was 8.3 cm in size with focal areas of hemorrhage and necrosis, but confined to the adrenal gland. His BP normalized

and he was tapered off of anti-hypertensives a few weeks later. He was then lost to follow up. 3 months ago, he saw his primary care physician for a 40 lbs unintentional weight loss. He was found to be hypertensive & hyperglycemic. He denied headache, palpitations or sweating. 24 hour urine studies confirmed elevated (~1,000x normal) metanephrines & normetanephrines. CT revealed a 3.8cm left adrenal mass with focal calcification. PET CT identified multiple areas of bony involvement suggestive of metastatic disease. Biopsy of the sacral mass was attempted, but the blood pressures rose to 240/124. He was started on phenoxybenzamine & labetalol with good response. He is currently being treated with I-131 metaiodobenzylguanidine. Prior MRI and current MIBG are shown.



Discussion: Malignant PCCs are histologically and biochemically similar to benign ones with the only reliable clue to malignancy being local invasion or distant metastases, which may be missed during initial diagnosis. Although benign appearing PCCs are completely excised, we recommend continued follow up of these patients until reliable predictors of malignancy are defined.

TH-PO054

Severe Hypertriglyceridemia and Fasting Ketoacidosis Associated with Clevidipine

Daniel Dudenkov,[1] Insara Jaffer Sathick,[1] Robert C. Albright.[1] *[1]Internal Medicine, Mayo Clinic, Rochester, MN; [2]Nephrology, Mayo Clinic, Rochester, MN; [3]Nephrology, Mayo Clinic, Rochester, MN.*

Introduction: Clevidipine (CLV) is a newer intravenous calcium channel blocker used to treat high blood pressure in acute settings. Although CLV is generally considered safe, clinical experience is limited, especially pertaining to rare adverse effects.

Case Description: Patient is a 60 year-old male with a history of allogenic cardiac transplantation for ischemic cardiomyopathy, immunosuppressed with mycophenolate mofetil and cyclosporine. He gradually developed cardiac allograft vasculopathy and cyclosporin-related nephrotoxicity. On hospital day (HD) 1, he underwent kidney allotransplantation and second cardiac allotransplantation. On HD3, he was initiated on CLV drip for hypertension. Over the next two days he developed progressive metabolic acidosis with bicarbonate 13 mmol/L and anion gap 23 (Figure 1). Due to increased work of breathing, he was placed on BiPAP support, with arterial blood gas showing pH 7.37, pCO2 27, and pO2 81. Other labs revealed a lactate 1.0 mmol/L, creatinine 1.0 mg/dL, glucose 121 mg/dL, beta-hydroxybutyrate (BHB) 5.9 mmol/L, and triglycerides (TG) 2000 mg/dL. Due to concern for CLV toxicity, he was transitioned to a nicardipine drip. He was also given IV dextrose with insulin. Within 24 hours, the patient's acidosis resolved with a repeat BHB 0.2 mmol/L and TG 280 mg/dL.

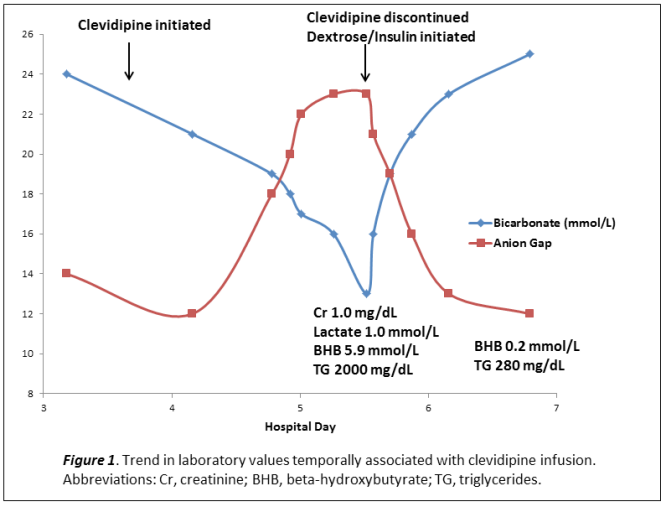


Figure 1. Trend in laboratory values temporally associated with clevidipine infusion. Abbreviations: Cr, creatinine; BHB, beta-hydroxybutyrate; TG, triglycerides.

Discussion: To our knowledge this is the first reported case of severe hypertriglyceridemia and fasting ketoacidosis associated with intravenous CLV. CLV is formulated within a 20% fat emulsion. For patients with low insulin states from fasting, the production of ketoacids is potentiated by a high lipid load. For fasting patients receiving CLV, close monitoring of triglycerides and administration of glucose with insulin should be considered.

TH-PO055

Coexistence of Proximal and Distal Renal Tubular Acidosis

Soham Gohil, Hemant J. Mehta, Jhoomar R. Makhija, Wasi Shaikh. *Nephrology, Lilavati Hospital & Research Center, Mumbai, India.*

Introduction: Renal tubular acidosis (RTA) is a group of transport defects in the reabsorption of bicarbonate, the excretion of hydrogen ion (H+), or both, resulting in systemic acidosis and hypokalemia with a normal glomerular filtration rate. Isolated proximal (type 2) or distal (type 1) tubular pathologies are well characterized, a combined pathology leading to type 3 RTA is very rare. We report a case with features of type 1 and type 2 RTA. We wonder if this is a case of type 3 RTA, a term, which is not in use.

Case Description: 20 years old female presented with diarrhea and weakness of all 4 limbs. She had 5 episodes of weakness over past 10 years, and fracture of left shaft of femur. She had growth retardation, left genu valgum, power was 4 in all 4 limbs. She was 1st of 4 siblings of parents, and no family history of similar disease. Clinical diagnosis: renal tubular acidosis with rickets. Investigations: isosthenuria, urine pH 9.0; urine protein creatinine ratio 0.47 mg/mg, normal renal function, hypokalemia, hypocalcemia, hypophosphatemia, normal blood sugars, glycosuria, phosphaturia, bicarbonaturia, with venous bicarbonate of 18 mEq/L. Specific aminoaciduria could not be demonstrated. Urinary calcium excretion, serum Vit D and PTH levels were normal. X-rays showed fractures and looser's zone in many bones. CT KUB showed non obstructing renal calculi and amorphous chunky calcification in renal medulla suggestive of medullary nephrocalcinosis. Patient was treated with potassium, calcium, phosphorus and alkali supplements. Her power returned to normal and she could walk with support.

Discussion: Our patient has features of proximal (p) and distal (d) RTA. The term Type 3 RTA is not in use, but it is an extremely rare autosomal recessive syndrome. Combined dRTA and pRTA is also observed in inherited carbonic anhydrase II deficiency. Patients with pRTA may have high urinary calcium excretion; however, nephrocalcinosis and renal calculi are rare in type 2 but common in type 1 RTA. Stunted growth is a prominent clinical feature in children. Rickets and osteomalacia are never observed unless hypophosphatemia is present as occurs in the Fanconi syndrome. We feel this patient has Type 3 RTA.

TH-PO056

Acute on Chronic Osmotic Demyelination in Binge Alcoholism

Mark A. Kleman, Ion D. Bucaloiu. *Nephrology, Geisinger Health System, Danville, PA.*

Introduction: Osmotic Demyelination is a devastating neurological complication of hyponatremia and a consequence of rapid increase in serum tonicity in patients with chronic hyponatremia. We present a rare case of acute on chronic pontine and extra pontine demyelination in the setting of binge alcoholism.

Case Description: A 24-year-old male admitted with ataxic gait, slurred speech, nausea, and vomiting of five days duration. He also had blurred vision and fell several times but denied significant head injury or loss of consciousness. He was habitually drinking 24 bottles of beer per weekend over the last year. He also reported craving and licking salt upon regaining sobriety. His medical history was significant only for depression. On physical examination he was hypotensive and appeared hypovolemic. Neurological examination revealed significant dysmetria, ataxic gait, and intentional tremor. Initial laboratory data showed serum sodium level of 118, serum osmolality 263, urine osmolality 565, and urine sodium <10. Computed Tomography of the head showed a lucent area in the central pons concerning for myelinolysis. The patient was treated with normal saline infusion, followed by 5% dextrose in normal saline infusion containing thiamine and folic acid. Serum sodium level corrected to 123 mEq/dL (5 mEq/dL) over the next 6 hours. Desmopressin was administered and the rate of correction of serum sodium stabilized to an average rate of 7 mEq per 24 hours over the next three days. Neurologic symptoms resolved during the first 48 hours of admission. Magnetic resonance imaging scan of the brain showed T2 hyperintensity and restricted diffusion in the middle cerebellar peduncles suggestive of acute osmotic demyelination and myelomalacia in the central pons likely secondary to remote episodes of osmotic demyelination.

Discussion: It is unlikely that the radiological findings were caused by the presenting hyponatremic event, rather prior episodes of alcohol binges may have caused rapidly correcting hypotonic states, resulting in the chronic demyelinating lesions. This case underscores the the spectrum of demyelination that can be present in the setting of repeated osmotic injury associated with the pattern of binge alcoholism.

TH-PO057

Tubulointerstitial Nephritis and Renal Tubular Acidosis Are Important Complications of Primary Biliary Cirrhosis - A Case Report

Anjushree Kumar, Pooja Budhiraja, Amna Ilahe. *Nephrology, Kansas Univ Medical Center, Kansas City, KS.*

Introduction: Primary biliary Cirrhosis (PBC)is a liver disease that is characterized by the progressive destruction of the bile ducts.T cell dependent immune reaction has been thought as the major mechanism of bile duct destruction.This mechanism may play role in renal dysfunction in these patients.We describe a case of Renal Tubular acidosis (RTA) and tubulointerstitial nephritis (TIN) associated with PBC.

Case Description: A 53 years old female was diagnosed with PBC with elevated antimitochondrial antibodies(AMA)of 1:320 and high IgM levels(500 mg/dl).Laboratory results at the time of diagnosis-

Serum Creatinine-3.1 mg/dl	Serum Potassium -3.4 mEq/L	Serum Phosphate -2.6 mg/dl	Serum bicarbonate -15 mEq/L	Serum uric acid -2.0 mg/dl
Serum alkaline phosphatase-134 U/L	Urine PH -5.5	Glycosuria ++	Proteinuria ++	Aminoaciduria +
RBC in urine -0-2 cells/hpf	WBC in urine -0-2 cells/hpf	Protein /cr -2.9 g/g	SPEP-absent	UPEP-absent

She underwent kidney biopsy which showed normal Glomeruli.Interstitial edema,marked tubulo-interstitial inflammatory infiltrates and significant fibrosis were present.Significant deposits of calcium phosphate were also noted in the tubules. Immunofluorescence showed C3 activity in arterioles.EM showed extensive mononuclear infiltrate.Proximal and distal RTA and TIN was likely related to PBC in this patient. Patient was started on potassium citrate.Due to significant fibrosis steroids were not given.Later her renal function worsened and she needed dialysis.

Discussion: PBC can be associated with TIN and RTA which can be easily missed. Possible mechanisms include autoreactive T lymphocytes driven by abnormal antigen expression in both hepatocytes and similar antigen expression in renal tubules might be involved leading to T lymphocyte infiltration into the interstitium.Also,AMA by reducing activity of mitochondrial enzymes in renal tubular cells may also play a role in genesis of TIN and RTA.Physician acquaintance regarding these mechanisms is needed as these processes can cause renal dysfunction in subjects with PBC and early treatment with steroids may prevent further renal damage.

TH-PO058

A Heterozygous Mutation in NPT2c (SLC34A3) Is Associated with Marked Hypercalciuria and Kidney Stones during Infancy Maryam Gondal, Olivera Marsenic Couloures, Neera K. Dahl, Clemens Bergwitz. *Yale Univ School of Medicine, New Haven, CT.*

Introduction: The SLC34A3 gene encodes for the renal sodium-phosphate co-transporter NPT2c. A homozygous or compound heterozygous inactivation results in Hereditary hypophosphatemic rickets with hypercalciuria (HHRH, OMIM#241530). Affected individuals present with hypophosphatemia and hypercalciuria . Heterozygous carriers of SLC34A3 mutations often present with idiopathic hypercalciuria (IH). Here we present the case of a child with multiple kidney stones and hypercalciuria since birth. His father was also found to have marked hypercalciuria.

Case Description: The child was born prematurely (29GW), and presented as a new born with hypertension.Renal imaging revealed bilateral kidney stones and nephrocalcinosis. Urine analysis showed calcium oxalate crystals with calcium excretion of 4.9mg/kg/day.His most recent laboratory studies at age 10 yrs show serum calcium of 9.8mg/dl , phosphorous 4.9 mg/dL, PTH 12 pg/ml, 1,25-OH vitamin D 78 pg/ml and 25-OH vitamin D 27 pg/ml. His 24-hr urine calcium is 8.6 mg/kg/day. Prompted by his son's findings, the father's evaluation at age 43 was significant for urine calcium 609 mg/day and urine oxalate 40mg/day. Serum Parathyroid hormone (PTH) was 13pg/ml, 1-25 OH vitamin D was 105pg/ml, 25 OH vitamin D 53 pg/ml, phosphate 3.7mg/dL and calcium was 10mg/dL. An ultrasound of his kidneys revealed a left calcified renal cyst and left sided renal mass, found to be renal cell cancer and he underwent partial nephrectomy. Whole exome sequencing (WES) of the child revealed a heterozygous mutation SLC34A3: c.575C>T (p.S192L).

Discussion: SLC34A3: c.575C>T (p.S192L) was previously reported in compound heterozygous individuals affected by HHRH and has a minor allele frequency in the general population of 0.03%. This mutation likely contributes to the idiopathic hypercalciuria in the current kindred. Interestingly, penetrance appears variable, causing early onset nephrocalcinosis and symptomatic stone disease in the son, while only a calcified cyst was found upon ultrasound in the father. Based on genetic diagnosis, son is managed on high phosphorous diet with resolution of hypercalciuria. The father is monitored off therapy.

TH-PO059

Nephrolithiasis and Nephrocalcinosis Associated with 1,25(OH)2D-24 Hydroxylase Deficiency M. Lourdes Gonzalez Suarez,[1] Robert A. Wermers,[2] Ravinder Singh,[3] Stephen B. Erickson.[1] *[1]Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [2]Endocrinology, Mayo Clinic; [3]Lab. Medicine and Pathology, Mayo Clinic College of Medicine.*

Introduction: Vitamin D plays a major role in calcium (Ca) homeostasis. $1,25(OH)_2D$-24 Hydroxylase is the enzyme that converts active vitamin D to its inactive metabolites. It is codified by the gene CYP24A1. If deficient, it may cause hypercalcemia, nephrolithiasis, nephrocalcinosis and renal failure. We describe two cases of $1,25(OH)_2D$ mediated hypercalcemia associated with nephrolithiasis and nephrocalcinosis with biochemical evidence of possible biallelic CYP24A1 mutation.

Case Description: Case 1: 50 year old man with kidney stones (Ca phosphate) since age 14 with a strong family history of kidney stones. He had persistent hypercalcemia (13 mg/dL), PTH 22 pg/mL, serum creatinine (sCr) 1 mg/dl, and hypercalciuria (349 mg/24h). $1,25(OH)_2D$ 77 ng/ml, 25(OH)D 32 ng/ml, $24,25(OH)_2D$ 0.3 ng/ml; 25(OH) $D/24,25(OH)_2D$=107(ratio >80 consistent with biallelic CYP24A1mutation). Patient was treated with fluconazole attempting to downregulate conversion of 25(OH)D to $1,25(OH)_2D$, prednisone and potassium citrate. **Case 2:** 33 year old man with failure to thrive as a child. He had chronic hypercalcemia (13-14 mg/dL), sCr 2.6 mg/dl, PTH 62 pg/ml, $1,25(OH)_2D$ 38 ng/ml, 24h urinary Ca 152 mg/dl. Kidney biopsy showed nephrocalcinosis. Parathyroid scan showed left lower adenoma -removed without improvement. Repeat scan showed right lower adenoma, he underwent a second partial parathyroidectomy. 25(OH)D 35 ng/ml; $24,25(OH)_2D$ 0.1 ng/ml; $25(OH)D/24,25(OH)_2D$=350. Drug therapy included furosemide, prednisone and cinacalcet. He was approved for kidney transplant. Genetic testing is pending.

Discussion: This study highlights the importance of recognizing clinical presentation of patients who may have CYP24A1mutations. This may have a varied presentation including longstanding $1,25(OH)_2D$mediated hypercalcemia, nephrocalcinosis and nephrolithiasis, progressive chronic kidney disease (CKD). Case 2 presented signs of CKD –lower $1,25D_2$ level and lower 24h urine calcium–as CYP24A1 gene is expressed in the kidney, kidney transplant should be curative.

TH-PO060

Glucocorticoid Therapy for the Treatment of Oxalate Nephropathy Dominique Dorsainvil, Bryan Tucker, Randy L. Luciano. *Nephrology, Yale School of Medicine, New Haven, CT.*

Introduction: Oxalate nephropathy is an uncommon form of kidney injury marked by calcium oxalate crystals in kidney tubules leading to acute tubular injury and interstitial inflammation. Supportive treatment includes intravenous fluids to flush crystals out of the tubules. However in severe injury, renal replacement therapy may be required. No studies report the use of anti-inflammatory medications to treat oxalate induced kidney injury. Here we present two patients who presented with acute kidney injury (AKI) attributed to oxalate nephropathy. Both patients had significant acute interstitial inflammation resulting in prolonged AKI that improved with glucocorticoids.

Case Description: The first patient was a 54 year old man with bipolar disorder who presented obtunded after ethylene glycol ingestion. He had AKI, a high anion gap metabolic acidosis and an osmolar gap in the setting of high serum ethylene glycol. The patient was treated with intravenous fluids but kidney injury was so severe that he required hemodialysis. Six weeks into hemodialysis recovery was not apparent. At that time a biopsy revealed persistent calcium oxalate crystals and interstitial inflammation. The patient was pulsed with intravenous solumedrol and transitioned to prednisone 60 mg with a gradual taper over 4 weeks. Two weeks after starting glucocorticoids the patient was able to stop hemodialysis. The second patient was a 71 year old gentleman with hypertension, non insulin dependent diabetes mellitus, mild dementia, prior stroke, and CKD stage III presenting with AKI of unclear origin. Creatinine increased from 1.5 mg/dL to 8.4 mg/dL, all the while receiving intravenous isotonic fluid and antibiotics for a pneumonia. Due to the continued rising creatinine a biopsy was performed and unexpectedly revealed diffuse oxalate crystals with a reactive peri-tubular interstitial infiltrate. The patient was started on prednisone 60 mg daily. His renal function subsequently improved. In retrospect, it was noted that he ate copious amount of chocolate and peanut butter.

Discussion: Both cases demonstrate the importance of identifying oxalate nephropathy early and treating inflammation with glucocorticoids if there are no underlying contraindications.

TH-PO061

Xanthine Oxidase Deficiency: A Very Rare Cause of Recurrent Nephrolithiasis Madhura S. Borikar, Kevin Fleming. *Internal Medicine, Mercy Catholic Medical Center, Darby, PA.*

Introduction: Xanthine Oxidase deficiency with resulting xanthinuria causing nephrolithiasis is a very rare disorder. We present a rare such case which exemplifies importance of understanding pathophysiology of purine metabolism and clinical correlation to pathophysiology.

Case Description: A 32 year old African-American female with PMHx of recurrent renal stones, presented with 2 day history of right flank pain radiating to RUQ, fevers and nausea. She was previously diagnosed with nephrolithiasis with hydronephrosis requiring ureteral stent. Her physical examination was notable for an elevated temperature, tachycardia, RLQ and CVA tenderness. A CT scan of the abdomen and pelvis showed a staghorn calculi in the right pelvicalyceal system, along with the previously placed stent and perinephric stranding. She underwent lithotripsy and stone extraction. The chemical analysis revealed that the stone was composed of 100% Xanthine. Serum uric acid level was less than 0.2 mg/dl, which was consistent with Xanthine Oxidase deficiency. Her treatment involved aggressive intravenous hydration and alkalization of the urine, recurrent lithotripsy and stone extraction procedures.

Discussion: Xanthine oxidase deficiency is extremely rare autosomal recessive disease resulting in hereditary xanthiuria. The enzyme is a catalyst of the final two steps in the metabolism of Purine leading to the formation of Xanthine and Uric Acid. Its deficiency causes increased urinary excretion of relatively insoluble xanthine which leads to development of xanthine stones in approximately one-third of patients. Diagnosis is suspected by hypouricemia (uric acid level less than 1.0 mg/dl), reduced urinary uric acid levels and increased xanthine excretion and is confirmed by liver or intestinal biopsy with measurement of enzyme activity. Management of xanthine stones involves intravenous isotonic saline administration to increase urine output. Although alkanization of the urine with sodium bicarbonate anecdotally successful, xanthine is poorly soluble in both acidic and alkalized urine. Anecdotally, aggressive fluid intake and low purine diet helps prevent such stones.

TH-PO062

Combined Liver/Kidney Transplantation in a Patient with Primary Hyperoxaluria Type 2 Tsering Dhondup, Elizabeth C. Lorenz, Dawn S. Milliner, John C. Lieske. *Dept of Nephrology and HTN, Mayo Clinic, Rochester.*

Introduction: Liver transplantation is an accepted therapy for primary hyperoxaluria type 1 (PH1), but has not been shown to correct the enzyme defect causing PH2. Unlike PH1, the enzyme deficiency in PH2 is found not only in the liver, but also in cells in multiple body organs. To date, the question of whether liver transplantation can provide sufficient correction of the metabolic deficiency in PH2 has remained unanswered. We report a case of a 44-year-old man with PH2 who had successful reduction in plasma oxalate (POx) and urine oxalate (UOx) after combined liver/kidney transplantation.

Case Description: Born with a solitary kidney, the patient's first symptomatic stone event occurred at the age 6. The next symptomatic nephrolithiasis was at age 37 when he presented with an elevated creatinine and a large obstructing renal stone requiring endoscopic removal. Progressive chronic kidney disease ensued and he underwent a preemptive living donor kidney transplant elsewhere. Allograft dysfunction occurred 6 months post-transplant and a biopsy revealed oxalate nephropathy. Urine studies showing elevated urine glycerate and normal glycolate suggested PH2. Multiple stone events and progressive allograft dysfunction followed. Genetic testing confirmed PH2 with a nonsense mutation in *GRHPR (*c.139C>T; p.R47X). Creatinine was 4.1 and both UOx (1.51 mmol/24hr) and POx (22.1 umol/L) were markedly elevated. Because of the marked hyperoxaluria, frequency of stone events, and loss of the first renal allograft to oxalate nephropathy, he was listed for combined liver/kidney transplant at our center. The combined transplant occurred 1 year later at age 44 before dialysis was required. He developed delayed renal allograft function and received hemodialysis daily for the 1st 9 days post-transplant. By postoperative day 26, creatinine had improved to 1.4 and both POx and UOx had normalized [1.2 umol/L (reference < 1.8 umol/L) and 0.23 mmol/ 24 hr (reference 0.11-0.46 mmol/ 24hr)] respectively.

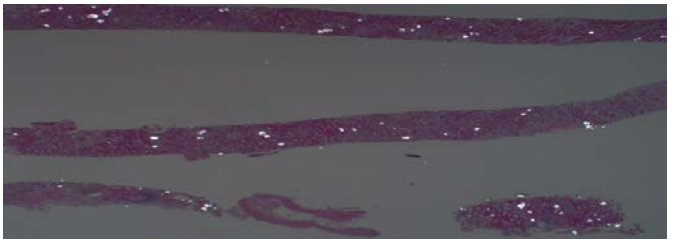
Discussion: Although GR/HPR is expressed throughout the body, this case suggests that a liver transplantation may normalize oxalate generation in PH2. Thus the role of liver transplantation in PH2 merits further study.

TH-PO063

Alternative Chemotherapy Resulting in Pancreatitis, Ketoacidosis and Oxalate Nephropathy Caroline Johnson, Lindsay Sanders, Ayan Sen, Mira T. Keddis, Leslie F. Thomas. *Nephrology, Mayo Clinic Hospital, Phoenix, AZ.*

Introduction: Alternative treatments for cancer are used increasingly in the United States. Unintended harms of these novel regimens may be profound but underreported. Here,we describe a non-diabetic patient with solitary kidney who developed pancreatitis, ketoacidosis and oxalate nephropathy quickly following the use of high dose vitamin C and 3-bromopyuruvate.

Case Description: A 72 year old man presented with progressive fatigue,nausea,and mid-epigastric pain.Two weeks prior to admission,he initiated an 8-day course of an alternative chemotherapeutic regimen for metastatic bladder cancer consisting of oral vitamin C 2g daily,IV vitamin C 50g daily, and IV 3-bromopyruvate 90mg daily. CT and laboratory studies confirmed pancreatitis(lipase >3,000 U/L).A high anion gap metabolic acidosis(pH 7.14, AG 36),elevated beta-hydroxybutyrate(15.6mmol/L (<0.4))and elevated oxalate (23.4mmol/L (<1.8)) were noted. Acute kidney injury was revealed by the serum creatinine (3.8mg/dL (patient's baseline 1.7)).Kidney biopsy revealed acute tubular necrosis and diffuse oxalate crystal deposition.



Lack of meaningful renal recovery led to initiation of hemodialysis.

Discussion: We posit the infusion of cellular stressors vitamin C and 3-bromopyuruvate induced his pancreatitis.Severe ketoacidosis in this non-diabetic patient may be explained by the acute pancreatitis and exacerbated by the direct effect of 3-bromopyuruvate on inhibition of glycolysis and diverting ATP production to fatty acid utilization.This is the first reported case of the triad of pancreatitis,oxalate nephropathy, and non-diabetic ketoacidosis secondary to alternative therapy.Complications associated with alternative therapies needs further reporting in literature.This would enable active evidence-based discussion and improved risk counseling to patients regarding harm associated with unproven alternative therapies.

TH-PO064

Hypervitaminosis A: A Rare Case of Hypercalcemia Divya Sharma, Ramapriya Sinnakirouchenan. *Nephrology, Medical College of Wisconsin, Milwaukee, WI.*

Introduction: Serum Vitamin (Vit) A levels are raised in chronic kidney disease (CKD). Chronic Vit A toxicity occurs with ingestion of 10 times the recommended daily allowance. It occurs at lower doses in patients with CKD. We present a case of hypercalcemia in a CKD patient taking toxic levels of beta-carotene.

Case Description: A 59 year old male presented for routine nephrology follow up. His past medical history was significant for CKD stage 3 and liver transplant 10 years prior for alcoholic cirrhosis. He had no complaints and felt well overall. Routine labs revealed an elevated serum calcium level of 12.4 mg/dL. Subsequent workup for hypercalcemia showed 25 hydroxy Vit D of 50.7 ng/mL (normal 32-100), 1,25 hydroxy Vit D of 92.1 pg/mL (normal 10-75), intact parathyroid hormone (PTH) of 11.0 pg/mL (normal 15-72), and an undetectable PTH related peptide level. Hypercalcemia persisted despite discontinuing calcium and Vit D supplements. On further review, the patient reported he started taking 50,000 units of beta-carotene daily 3 months prior. Hypercalcemia resolved after cessation of the Vit A supplement.

Discussion: While hypervitaminosis A is a well-documented cause of hypercalcemia, the association is rarely seen in clinical practice. Vit A stimulates osteoclastic resorption and inhibits osteoblastic formation. Patients with underlying CKD are more sensitive to its effects and have higher Vit A concentrations even if ingested below toxic doses. Possible explanations include decreased retinol and retinol binding protein excretion by the kidneys. This case illustrates the importance of obtaining a complete history, including all nonprescription medications. Additionally, as illustrated by our patient taking 50,000 units of beta-carotene daily instead of the recommended 3,000 units daily, the clinician must be mindful of recommended doses as patients may unknowingly be taking toxic doses of seemingly benign substances. Nephrologists should be especially vigilant of this phenomenon, as risk for toxicity remains higher in our patients with underlying CKD. Care should be taken in prescribing multivitamins with Vit A to CKD patients.

TH-PO065

Stone or Pseudo-Stone? S. Irfan Qadri,[1] Abhilash Koratala,[1] Vincent G. Bird,[2] Rupam Ruchi.[1] *[1]Nephrology, Univ of Florida; [2]Urology, Univ of Florida.*

Introduction: We report a case of Keratinizing Desquamative Squamous Metaplasia (KDSM) of the upper urinary tract, which is an uncommon and under-recognized condition that mimics Nephrolithiasis in symptomatology.

Case Description: 66 year old Caucasian male with history of hypertension, hyperlipidemia, osteoarthritis and 16 pack-year smoking was referred to us for evaluation of recurrent right sided flank pain and suspected Nephrolithiasis. He had the first episode of pain about 2 years prior to presentation that was recurrent. There was no associated hematuria, dysuria, fever, chills, urinary hesitancy or incontinence. No family history of stones or other kidney disease. He saw multiple urologists and underwent multiple ureteroscopies some of which showed glistening, soft, acellular debris in the upper ureter. Last available pathology showed minute fragments of acellular keratin debris. Interestingly, he never had imaging evidence of renal stone, though had mild hydronephrosis one time. During the episodes of flank pain, he can feel 'something' sloughing off and traversing through the ureter. Excreted material is shown.

We diagnosed KDSM and managed conservatively with adequate hydration and supportive measures.

Discussion: KDSM is a condition in which the urothelium of the urinary tract is replaced with keratinized squamous epithelial cells. It can be confused with nephrolithiasis and/or neoplasia based on symptoms and appearance on imaging. It has been associated with chronic infection or irritant exposure including smoking. Management is largely conservative with invasive treatment reserved for those with ureteral obstruction by desquamated keratinous material. Renal parenchymal involvement is rare. KDSM has been associated with squamous cell carcinoma without any proven causative relationship. Given the unlikely, but possible transition to SCC, it is prudent to monitor these patients with annual imaging.

TH-PO066

Refractory Hungry Bone Syndrome in a Patient with Prior Roux-en-Y Gastric Bypass Surgery Jared Crisafi,[1] Natallia Maroz.[2,3] *[1]Kettering Medical Center; [2]Boonshoft School of Medicine, Wright State Univ; [3]Univ of Florida.*

Introduction: Hungry bone syndrome (HBS) with hypocalcemia is a known complication following parathyroidectomy (PTX) for hyperparathyroidism with incidence reported up to 20%. Risk factors include volume of resected adenoma, age, azotemia, and elevated alkaline phosphatase. Few cases have attributed prolonged hypocalcemia to prior gastric bypass surgery.

Case Description: A 64 year-old-female with past medical history of chronic kidney disease stage IV (CKD) and Roux-en-Y gastric bypass (RYGB) underwent subtotal PTX for primary hyperparathyroidism. Pathology revealed three hyperplastic glands and an adenoma. PTH was reduced from 1,452.9 pg/ml to 187 pg/mL. She subsequently developed symptomatic hypocalcemia with facial and acral paresthesias secondary to HBS with calcium <5 mg/dl and urine calcium <5mg/dl. During this time she became dialysis dependent. Patient's symptomatic hypocalcemia was unresponsive to oral therapy necessitating intravenous calcium replacement for 253 days to date.

Days from PTX	Calcium mg/dl	Ionized Calcium mmol/L	PTH pg/ml	Therapy (dose/day)
Reference	8.5-10.5	1.09-1.3	15-65	
Preoperative	7.7		788	Calcitriol 0.5 µg
Day 1	5.7	0.90	187	Calcitriol 0.5 µg
Day 30	5.3	0.88	49.4	Calcitriol 0.5 µg Calcium carbonate 15 g
Day 253	6.7	0.96		Calcitriol 2 µg Calcium carbonate 5 g Calcium acetate 6003 mg Calcium gluconate IV 3-8g three times per week High-calcium dialysate bath

Discussion: This case demonstrates HBS in a patient with prior RYGB lasting 253. The duration of hypocalcemia is unlikely due to CKD given an undetectable urine calcium suggesting minimal renal calcium loss. Additionally, Mittendorf demonstrated HBS in patients with CKD had a mean duration of only 4.7 days. We propose that prior surgical diversion of the duodenum where intestinal calcium is preferentially absorbed resulted in calcium malabsorption which impaired bone mineralization and lead to hypocalcemia refractory to oral calcium. Prior case reports by Petras and by Panazolla have also attributed prolonged HBS to prior gastric bypass. History of bariatric surgery should be considered a risk factor for development of HBS.

TH-PO067

Pancreaticobiliary Adenocarcinoma Secreting Fibroblast Growth Factor 23 Valerie Suzanne Barta, Mala Sachdeva. *Hypertension, Northwell Hofstra School of Medicine, Great Neck, NY.*

Introduction: Oncogenic renal phosphate wasting secondary to fibroblast growth factor 23 (FGF23) secretion is a rare paraneoplastic syndrome, causing tumor induced osteomalacia (TIO). The majority of cases reported are benign mesenchymal tumors. Malignant FGF23 secreting tumors have been reported in lung, colon, prostate, ovarian cancer, osteosarcoma, multiple myeloma and lymphoma. We report the first case of a malignant pancreaticobiliary tumor secreting FGF23.

Case Description: We present a 71yr old female with no past medical history who was admitted for progressively worsening abdominal pain and weight loss over 6 weeks. Labs were pertinent for calcium 11.6 mg/dL, albumin 2.8 g/dL, magnesium 2.0 mg/dL, and phosphorus ranging from 1.4 to 2.4 mg/dL with supplementation. Further workup revealed intact PTH 6 pg/mL, 25-hydroxyvitamin D 18.9 ng/mL, 1-25-hydroxyvitamin D level 28.6 pg/mL, and normal PTHrP, Kappa/Lambda ratio and SPEP. Fractional excretion of phosphorous was 48%. Abdominal CT showed cirrhosis with multiple hepatic masses. Biopsy of the liver mass revealed pancreaticobiliary adenocarcinoma. Due to hypophosphatemia being persistent and refractory, an FGF23 level was checked and returned as 1310 RU/mL (normal <= 180). A diagnosis of oncogenic renal phosphate wasting was made.

Discussion: TIO is characterized by oversecretion of FGF23 by tumor cells causing marked hypophosphatemia. We report the first case of malignant pancreaticobiliary related oncogenic renal phosphate wasting. In our patient, the hypophosphatemia and the pancreatobiliary malignancy were diagnosed simultaneously. There was no evidence of osteomalacia, likely because the short duration of hypophosphatemia had not yet impaired bone mineralization. She had typical biochemical features of TIO however atypical was her slight Vitamin D insufficiency, which was unlikely the sole cause of her hypophosphatemia. Hypercalcemia was thought to be malignancy related.

TH-PO068

B-Type Natriuretic Peptide and Renal Physiology Taranpreet Kaur,[1] Joseph V. Nally,[1] Hernan Rincon-Choles.[1] *[1]Nephrology and Hypetension, Cleveland Clinic, Cleveland, OH; [2]1; [3]1.*

Introduction: B- Type natriuretic peptide (BNP) related peptides are mainly produced by ventricular myocytes in response to stretch. Its production is upregulated in cardiac failure. However its exact effect on renal function is poorly understood. Total artificial heart (TAH) implantation provides a unique scenario where the role of BNP in renal physiology is highlighted.

Case Description: A 60 year old Amish male with end stage heart disease from familial hypertrophic cardiomyopathy and cardio renal syndrome underwent total ventriculectomy and TAH implantation as a bridge to heart transplantation. Two weeks prior to surgery, amino-terminal pro-BNP (NT-proBNP) level was 1318 pg/ml and serum creatinine (SCr) was 1.8 mg/dl. Nesiritide infusion was started on post- operative Day 2 (POD) after surgery when he failed to respond to intravenous high dose diuretics. Immediately the urine output improved and over the next few days SCr improved to a nadir of 1.2 mg/dl. Blood NT-proBNP level was 349 pg/ml on POD 4. On POD 6 Nesiritide was stopped and again he did not respond to high dose diuretics. Nesiritide was resumed after 24 hours with marked improvement in urine output. Further attempts of weaning off Nesiritide drip were futile and led to worsening of renal function. Unfortunately, he developed acute tubular necrosis (ATN) and had to be started on dialysis. He ultimately succumbed to sepsis before heart transplant could take place.

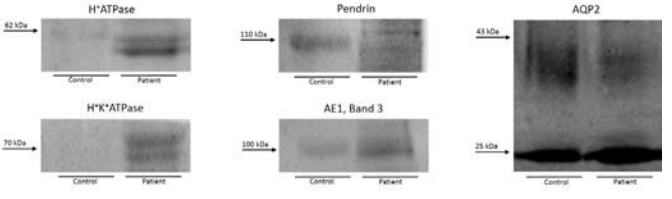
Discussion: In heart failure, BNP and intracellular cyclic GMP synthesis is upregulated, causing vasodilation, diuresis and inhibition of the renin–aldosterone system. With total ventriculectomy as part of TAH implantation, there is a sudden marked decline in endogenous BNP production. Thereupon, renal function declines and diuretic resistance develops. Low-dose BNP infusions post operatively restores the urine output. This finding suggests that BNP has direct renal effects in patients with congestive heart failure. Literature review showed that Nesiritide can be weaned off once endogenous production of BNP from extra cardiac tissue (e.g., brain) is restored usually between POD 7 to 30. In our case, it could not be stopped even 8 weeks after surgery until patient develop ATN and needed dialysis.

TH-PO069

An Atypical Case of Renal Tubular Acidosis Type I Laura Onuchic, Talita R. Sanches, Camila Eleuterio Rodrigues, Antonio C. Seguro, Lucia Andrade. *Nephrology, Univ of São Paulo, Brazil.*

Introduction: Distal renal tubular acidosis (RTA type I) is characterized by impaired urine distal acidification and can be associated with multiple etiologies, including autoimmune diseases, hereditary disorders and drugs.

Case Description: A 34 y/o male presented with a year history of diffuse weakness, vomiting and a 20-kg weight loss. He denied relevant medical history other than alcohol abuse. Laboratory data at admission revealed: serum creatinine 3.9 mg/dL, BUN 47.2 mg/dL, Na 114 mEq/L, K 1.2 mEq/L, Mg 1.8 mg/dL, iCa 3.9 mg/dL, pH 7.22, bicarbonate 9 mEq/L, CPK 1039 IU/L and urinary pH 7.0. TTKG was 10 and the FEK was 25%, extremely high considering low serum K. CT scan revealed a slightly enlarged pancreas and no renal abnormalities. He was started on intravenous saline 0.9% and electrolyte reposition, presenting no recovery of laboratory abnormalities within the following 5 days. Further on he was started on metimazol based on a TSH of 0.02 mU/L and free T4 of 2.2 mg/dL.Due to uremic symptoms he was submitted to a dialysis session, followed by electrolyte normalization and renal function improvement. Urine analysis revealing K loss and RTA type I excluded the hypothesis of pancreatitis associated with hypokalemia, leading to protein expression evaluation of the main H+ transporters located in the final distal tubule and collecting duct cells through urinary exosome western-blot analysis.



Discussion: This case is consistent with RTA type I, possibly associated with a systemic disease such as Sjogren's or IgG4, considering hypothyroidism as a manifestation of his underlying disease. Exosome analyses, in turn, revealed an appropriate physiological response to a severe metabolic acidosis: H+ATPase, H+K+ATPase and AE1 overexpression and pendrin underexpression. We hypothesize that defects in other distal nephron transporters may have significantly impaired urinary acidification.

Funding: Government Support - Non-U.S.

TH-PO070

Effect of Lowering Hemoglobin S Level to Less Than 30 Percent on Renal Physiology and Pathology in Sickle Cell Disease Olorunkemi O. Oluwole,[1] Julie Kanter Washko,[2] Milos N. Budisavljevic,[1] Ndidiamaka O. Obadan.[1] *[1]Nephrology, Medical Univ of South Carolina, Charleston, SC; [2]Pediatric Hematology & Oncology, Medical Univ of South Carolina, Charleston, SC.*

Introduction: Sickled red blood cells in sickle cell disease (SCD) cause repeated episodes of ischemia and reperfusion in all organs, including the kidney.The most common marker of nephropathy from SCD is albuminuria, occurring in 19% of children age 10 and older and 68% of adults. Red blood cell exchange (RBCE) has been documented to prevent stroke, acute chest syndrome, and recurrent pain crises. Thus we investigated the role of RBCE on renal function in SCD patients.

Case Description: Charts of 61 patients with SCD undergoing monthly prophylactic RBCE were reviewed. Excluded were patients with diabetes (1), advanced chronic kidney disease (1), missing data (12), the deceased (2) and those less than 15 years old (7). Variables collected on the remaining 42 patients included age, sex, number of RBCEs, albuminuria, urine specific gravity, blood pressure, and serum chloride and bicarbonate concentrations.

Parameters of the 20 males and 22 females were: mean age 21 ± 5 years, time on therapy (median 8 years, range 2 - 10), and median RBCEs 100, microalbuminuria (median 34 mg/g creatinine, range 4 – 1772) present (ie > 30) in 19%, mean systolic and diastolic blood pressure 120 ± 16 and 75± 8 mmHg respectively, mean urine specific gravity of 1.013 ± 0.003, and mean serum chloride and bicarbonate concentrations 107 ± 3 and 23 ± 2 respectively. Albuminuria was not different between patients receiving RBCE for less than 6 years (N = 9) of therapy compared to those receiving RBCE for more than 6 years (N = 33). Diastolic blood pressure and serum bicarbonate concentrations dropped with duration of RBCEs ($p < 0.04$, $p < 0.001$, respectively).

Discussion: This study establishes relevant renal clinical and laboratory data in a cohort of SCD patients who received RBCEs over an extended period of time. We did not find that RBCE reduced albuminuria over time. Currently we are matching our patients with SCD patients not undergoing prophylactic RBCE, to determine if RBCE protects the kidney against SCD nephropathy.

TH-PO071

A Rare Case of End Stage Renal Disease Chidinma N. Enyinna, Amir Abdi Pour. *Medicine, Loma Linda Univseristy Medical Center, Loma Linda, CA.*

Introduction: Chronic tubulointerstitial nephritis (CTIN) is a type of renal injury associated with progressive decline in renal function characterized histopathologically by epithelial tubular cell atrophy, tubular dilation, interstitial fibrosis, and lymphocyte-and macrophage-predominant cell infiltration. Multiple conditions including medications, metabolic disorders, immune-mediated disease, infection, and hematologic disease can result in CTIN.

Case Description: A 69 year old male with history of hypertension, basal cell skin cancer, prostate cancer, and recently diagnosed small cell lymphocytic leukemia was seen for elevated creatinine. He exhibited features of Fanconi syndrome with mild proteinuria. Except for mildly decreased C4, all serologic tests including anti-GBM were negative. Abdominal CT showed a retroperitoneal mass encasing multiple vessels including bilateral renal arteries. Kidney ultrasound was unremarkable. Kidney biopsy showed advanced interstitial fibrosis and tubular atrophy without significant glomerular abnormalities. Immunofluorescence demonstrated diffuse linear IgG staining of tubular basement membranes, but no staining of glomeruli (Figure 1). Electron microscopy showed proximal tubular basement membrane thickening without significant glomerular disease. A diagnosis of anti-tubular basement membrane (anti-TBM) nephritis was made based on these collective biopsy findings.

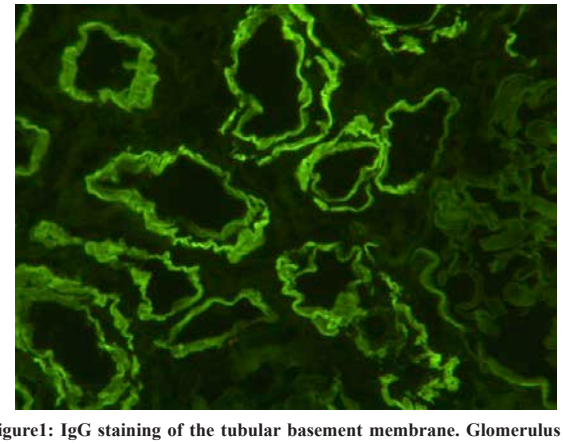


Figure1: IgG staining of the tubular basement membrane. Glomerulus on the right shows no staining of the basement membranes.

Discussion: Primary anti-TBM nephritis is a rare disease and has been associated with membranous nephropathy in children. Circulatory anti-TBM antibody has been seen in many renal diseases including post-infectious,lupus and drug-induced nephritis, and also post-kidney transplant. We report a case of advanced renal failure due to anti-TBM nephritis. It is not clear if his underlying leukemia may have played a role.

TH-PO072

A Rare Case of Calciphylaxis in a Renal Transplant Patient with a Glomerular Filtration Rate of More Than 60ml/min/1.73m2 Jean Luc Franck, Abduljalil Elfasi, Jason Cobb. *Nephrology, Emory Univ Hospital, Atlanta, GA.*

Introduction: Calcific Uremic Arteriolopathy (CUA) or calciphylaxis is a life-threatening ischemic vasculopathy confined primarily to patients with ESRD. We report a case of calciphylaxis in a renal allograft recipient with a GFR of more than 60ml/min/1.73m2.

Case Description: A 55 year old female patient with a transplanted kidney was referred to our institution for evaluation of multiple necrotic skin lesions in her legs. Her past medical history beside hypertension, diabetes mellitus type 2, coronary artery disease was significant for being on hemodialysis for five years before receiving a cadaveric renal transplantation two years prior to presentation. Her post surgical course was uneventful and her current immunosuppressant regimen consisting of tacrolimus, mycophenolate mofetil, and prednisone. Her physical exam was remarkable for a functioning left brachio-cephalic arteriovenous fistula and the presence of multiple necrotic ulcerations with eschar formation in her lower extremities, the largest measuring 13cmx8cm in her left crural region. Admission labs notable for a BUN/Cr (mg/dl)18/0.8, calcium 8.9mg/dl, phosphorus 3.6mg/dl, PTH 128pg/ml and albumin 2.4g/dl. An incisional skin biopsy was performed and the histopathological findings were consistent with CUA by the presence of dermal fibrosis with prominent calcium deposition within the vessel walls and lumina of small to medium sized blood vessels. Despite intensive combined management with wound care and hyperbaric oxygen therapy, the patient expired within a year from sepsis.

Discussion: Risks factors implicated in the development of calciphylaxis include perturbation of the calcium and phosphate homeostasis, type 2 diabetes mellitus, Vitamin K antagonists, hypoalbuminemia and more recent evidence also suggests the use of prednisone. The disease is almost always described in ESRD patients and despite intensive combined treatments, the prognosis of CUA remains poor. This case of calciphylaxis in a renal transplant patient was reported to emphasize the need to maintain a high degree of suspicion in the renal transplant population even more when other risk factors are present.

TH-PO073

Hypokalemic Flaccid Paralysis Induced by Distal RTA Associated with Primary Hyperparathyroidism: Case Report Adriana Belo Lopes Prazeres, Marclebio M.C. Dourado, Ana Paula Gueiros, Jose Edevanilson Gueiros. *Nephrology, UFPE, Recife, Pernambuco, Brazil.*

Introduction: Primary hyperparathyroidism (PHP) is a condition in which one or more of the parathyroid glands becames overactive due to an abnormal regulation by calcium and produce parathyroid hormone (PTH) in excess. The prevalence of PHP is 21 cases per 100.000 person-year, with hyperfunctioning single adenoma of the parathyroid accounting for approximately 85% of cases of PHP. The major renal clinical presentation includes polyuria, nephrolithiasis, hypercalciuria and rarely nephrocalcinosis and renal tubular acidosis (RTA).

Case Description: A 30 year-old man was admitted in the emergency department with subtle weakness in lower limbs. Laboratory studies revealed normal renal function, serum sodium 142 mEq/L, serum potassium 2mEq/L, serum chloride 116 mEq/L and CPK 116 U/L. Venous blood gas analysis showed hyperchloraemic metabolic acidosis. Urinalysis with density 1010, pH 6,5 and negative proteinuria and hematuria. He had no known diseases and was not taking any medication. He had a family history of nephrolithiasis. The weakness improved with venous potassium replacement. Subsequent laboratory studies revealed PTH 601 pg/ml, phosphate 1,9 mEq/L, calcium 11,7 mEq/L, albumin 4,5 mg/dL, 25-hydroxyvitamin D 19,9 ng/mL, thyroid stimulating hormone 2,2 nUI/mL and a 24 hour urine calcium of 449mg. The sestamibi parathyroid scintigraphy showed hyperfunction of the lower left gland. After partial parathyroidectomy (PTX) the patient had resolution of the distal RTA.

Discussion: The type 1 RTA represents the inability of the distal tubule to acidify the urine. The major acquired causes of distal RTA includes Sjögren syndrome, HIV, hyperthyroidism, use of amphotericin or lithium and vitamin D intoxication. PHP is a rare cause of distal RTA with 5 previous reports (4 indian and 1 philippine) and in 4 of these, PTX solved the RTA. In our case, PTX also treated the patient.

Funding: Government Support - Non-U.S.

TH-PO074

IgG4-Related Kidney Disease in HIV Infection: Coincidence or Something More? Christina L. Bradshaw,[1] Brian Y. Young.[1,2] *[1]Nephrology, Stanford Univ, Palo Alto, CA; [2]Nephrology, Santa Clara Valley Medical Center, San Jose, CA.*

Introduction: IgG4-related disease (IgG4-RD) is characterized by tissue lymphoplasmacytic infiltration with IgG4-positive plasma cells and CD4+ T lymphocytes. The role of IgG4 in the pathogenesis of the disease is poorly understood and association with autoimmune or infectious triggers is unclear. We describe here an unusual presentation of IgG4-RD in an HIV-positive patient.

Case Description: A 68-year-old male patient with history of HIV infection (CD4 count >600, viral load undetectable) presented with elevated creatinine (Cr) to 1.8 mg/dL from a baseline of 0.8 mg/dL. No inciting event was evident from review of medical history and HAART regimen did not include a tenofovir-based agent. Urinalysis was bland with urine protein/Cr ratio of 0.44 mg/mg and no microalbuminuria. UPEP showed a monoclonal IgA kappa band and serum free light chain ratio was abnormal. Other serologic markers included a positive ANA, reduced C3 and C4 levels, and negative HBsAg and anti-HCV Ab. An increase in Cr to 3.3 mg/dL prompted a kidney biopsy, which showed an interstitial

lymphoplasmacytic infiltrate and no significant glomerular abnormalities. Immunostaining showed >100 IgG4-positive cells per HPF and serum IgG4 level was >300 mg/dL. Bone marrow biopsy performed to rule out lymphoma was unremarkable and lymph node biopsy showed an average of 130 IgG4 cells per HPF. Once malignancy was excluded and undetectable HIV viral load confirmed, patient was started on prednisone 0.6 mg/kg/day for IgG4-related tubulointerstitial nephritis. Cr level thereafter improved from 3.1 mg/dL to 2.6 mg/dL over the first 10 days of therapy.

Discussion: IgG4-RD is a rare multi-systemic disorder, initially described as a cause of autoimmune pancreatitis. To our knowledge, this is the first report of IgG4-RD in an HIV-positive patient, with its only manifestation being renal dysfunction. HIV is known to target CD4+ T cells and some reports have suggested abnormal IgG4 regulation. Given that many patients are now surviving with a long-term diagnosis of HIV, further investigation may be warranted to determine if IgG4-RD is a more frequent, yet less considered, cause of renal dysfunction in HIV.

TH-PO075

Apolipoprotein L1 and Soluble Urokinase Receptor in the Activation of Integrin Avb3 and Incident Kidney Disease Salim Hayek,[1] Kwi Hye Koh,[2] David Changli Wei,[2] Cheryl Ann Winkler,[3] Jeffrey B. Kopp,[4] Jochen Reiser.[2] *[1]Emory Univ; [2]Rush Univ Medical Center; [3]NCI, NIH; [4]NIDDK, NIH.*

Introduction: Apolipoprotein L1 (APOL1) genetic variants are strongly associated with but only partially explain the increased risk of chronic kidney disease (CKD) in African Americans (AA). Immunologic factors such as HIV may synergistically increase the risk of CKD associated with APOL1. Soluble urokinase receptor (suPAR) is a marker of immune activation and a predictor of CKD. Mechanistically, suPAR activates podocyte αvβ3 integrin. An interaction between suPAR and APOL1 with regards to kidney disease is however unknown.

Case Description: We measured plasma suPAR and characterized APOL1 genotype in 825 AA patients (mean age 58±12, male 52%, eGFR<60 in 27%) enrolled in the Emory Cardiovascular Biobank. Follow-up serum creatinine was collected (median measures =7, median follow-up =10 years). We characterized the cross-sectional association between suPAR and APOL1 genotype and determined the interaction between future eGFR decline, suPAR and APOL1 risk alleles. We studied the biochemical interaction between APOL1, suPAR, and integrin β3 by co-immunoprecipitation (Co-IP) and surface plasmon resonance (SPR).

Patients with 2 APOL1 risk alleles (14%, median suPAR 3300 pg/mL) had significantly higher levels of suPAR compared to those with 1 (44%, median suPAR 2770 pg/mL) or 0 (42%, median suPAR 2827 pg/mL), after adjusting for baseline eGFR, age, gender and BMI. In longitudinal analyses, patients with 2 APOL1 risk alleles and high suPAR levels had a steeper decline in eGFR compared to those with 1 or no alleles (β-2.96, P=0.04 for three-way interaction). Co-IP data show that APOL1 wild type protein binds both suPAR and integrin β3. In SPR analysis, APOL1 directly binds suPAR (K_D ~11.71 nM). APOL1 binds strongly to integrin αvβ3 (K_D ~6.27 nM) but not α3β1. Interestingly, the binding affinity of APOL1 to integrin αvb3 increased 100-fold upon activation of the integrin.

Discussion: A synergistic, eGFR independent relationship between suPAR and APOL1 explains the heightened risk for kidney disease in patients with 2 APOL1 risk alleles. suPAR mediated integrin αvb3 activation facilitates a high affinity binding of APOL1.

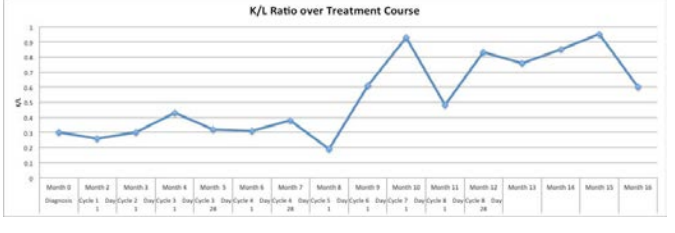
Funding: NIDDK Support

TH-PO076

Serum Free Kappa/Lambda Ratio in Primary Amyloidosis: Can It Be Abnormally Normal? Arouna Senthilkumar, Saud Rana, Kavitha Vellanki. *Loyola Univ, Maywood, IL.*

Introduction: Free light chain quantification is considered to be highly sensitive for diagnosis of primary renal amyloidosis, reported sensitivity as high as 95 to 100%. Here we report a rare case of Primary renal amyloidosis with normal serum and urine free light chain ratio.

Case Description: A 67 year old male with no past medical history was referred for evaluation of worsening lower extremity swelling after negative cardiac work up. He reported generalized fatigue and exam revealed diffuse anasarca with dark macular lesions on bilateral shins. Initial work up revealed nephrotic range proteinuria (25grams) with serum albumin of 1.1. Further serological work up is shown in Table 1. Serum free K/L ratio was within normal range for few months as shown in figure 1.



Kidney biopsy revealed lambda light chain amyloidosis and subsequent bone marrow biopsy revealed lymphoplasmacytic lymphoma.

Lab (reference range)	Result
Sodium (136-144mmol/L)	140
Potassium (3.3-5.1mmol/L)	3.7
Bicarbonate (20-32 mmol/L)	27
Chloride (98-108 mmol/L)	107
Glucose (70-100 mg/dL)	109
Blood Urea Nitrogen (7-22mg/dL)	16
Creatinine (0.6-1.4mg/dL)	1.07
Albumin (3-5 gm/dL)	1.1
24 hr urine Protein	25.3 grams
Serum free light chain K/L ratio (0.26-1.65)	0.3
Urine free light chain K/L ratio (0.46-4.00)	3.23

Discussion: Free light chain quantification may abnormally be normal in lambda light chain amyloidosis and hence, should not be used as a sole criteria to rule out paraproteinemias.

TH-PO077

A Case of IgG4-Related Kidney Disease with Predominantly Unilateral Renal Atrophy Akari Wada,[1] Kazunori Yamada,[1] Ichiro Mizushima,[1] Satoshi Hara,[1] Kiyoaki Ito,[1] Hiroshi Fujii,[1] Kazuaki Mizutomi,[2] Mitsuhiro Kawano.[1] *[1]Div of Rheumatology, Kanazawa Univ Graduate School of Medicine, Kanazawa, Ishikawa, Japan; [2]Internal Medicine, Kaga Medical Center, Kaga, Ishikawa, Japan.*

Introduction: Patients with IgG4-related kidney disease (IgG4-RKD) may reveal various renal abnormalities on imaging tests, such as multiple low-density lesions on contrast-enhanced computed tomography (CE-CT), diffuse bilateral renal swelling, and hypovascular solitary nodules, as well as renal atrophy. Here, we describe a patient with IgG4-RKD manifesting as predominantly unilateral renal atrophy.

Case Description: A 73-year-old woman with obstructive jaundice was first referred to our hospital 6 years prior. At that time, an elevated serum IgG4 level (378 mg/dL) was found and CE-CT revealed a mass in the pancreatic head. Renal lesions were absent. The patient was diagnosed with autoimmune pancreatitis (AIP) and treated with prednisolone (PSL) 30 mg/day. As her AIP symptoms improved and serum IgG4 level decreased, the PSL dose was gradually tapered to 5 mg/day. Her renal function had been normal (Cr 0.7 mg/dL) until 1 year before the current admission, and CT showed no renal atrophy. During the intervening 12 months her renal function declined (Cr 1.1 mg/dL), and she was admitted to our hospital. A urinalysis showed no abnormality. CE-CT revealed marked right renal atrophy and multiple low-density lesions on both kidneys. Serum IgG4 level was elevated (204 mg/dL). A renal biopsy was not performed because of the right renal atrophy and malformation of the left renal vein. Through careful examination, we ruled out vascular diseases and clinically diagnosed IgG4-RKD. PSL dose was increased to 30 mg/day. One month later, her renal function improved, with no obvious change in CE-CT findings. Six months later, PSL dose was tapered to 10 mg/day. Her renal function was stable, and no worsening of renal atrophy was seen.

Discussion: Bilateral renal atrophy sometimes occurs in patients with IgG4-RKD. However, this patient presented with predominantly unilateral renal atrophy. Renal lesions are sometimes asymptomatic in patients with IgG4-RKD; therefore, when caring for such patients, careful examination is required if the patients' renal function declines.

TH-PO078

Adenovirus Related Granulomatous Interstitial Nephritis Masquerading as Sarcoidosis in Renal Transplant Recipient Dilek Yarar,[1] Pradeep Vaitla,[2] Stephen O. Pastan,[2] Carla L. Ellis.[3] *[1]Nephrology Dept, Emory Univ, Atlanta, GA; [2]Transplant Nephrology Dept, Emory Univ, Atlanta, GA; [3]Renal Pathology Dept, Emory Univ, Atlanta, GA.*

Introduction: Granulomatous interstitial nephritis is an uncommon entity in kidney transplant recipients.

Case Description: A 42 year-old African-American female with a history of sarcoidosis, and end stage renal disease presumed secondary to hypertensive nephrosclerosis, received a deceased donor renal transplant in 2012. The immunosuppresssive regimen was prednisone, mycophenolate mofetil and belatacept. She was admitted in 2016 with fever, chills, myalgia, gross hematuria and acute kidney injury. The patient's creatinine was 2.6 on admission with baseline creatinine of 1.2-1.5. Workup showed no growth on urine and blood cultures, serum PCR was negative for BK and CMV viruses. Renal ultrasound showed hydronephrosis, but renal function did not improve with percutaneous nephrostomy. She continued to experience fever spikes and intermittent gross hematuria despite broad spectrum antibiotics. Renal biopsy showed severe granulomatous interstitial nephritis with focal areas of necrosis. Given the history of sarcoidosis, she was started on high dose Prednisone. Serum angiotensin converting enzyme level, vitamin D and calcium were normal. Kidney tissue stained positive for adenovirus in the areas of the granulomas; serum PCR was strongly positive for adenovirus. The patient's symptoms significantly improved with steroids and supportive care. The infectious disease specialist recommended brincidofovir, which the patient refused due to her clinical improvement. She was discharged home on steroid taper. The hematuria resolved and the creatinine decreased down to baseline.

Discussion: We report a case of granulomatous interstitial nephritis affecting a renal transplant secondary to adenovirus infection, a known but uncommon entity

that can be confused with sarcoidosis. Adenovirus infection should be considered in immunocompromised patients with acute kidney injury, hematuria and granulomatous inflammation on renal biopsy.

TH-PO079

Reno-Cerebral Reflex Activates Renin-Angiotensin System and Promotes Renal Damage after Ischemia-Reperfusion Injury Wei Cao, Fan Fan Hou. *Div of Nephrology, Nanfang Hospital, Southern Medical Univ, Guangzhou, Guangdong, China.*

Background: A kidney-brain interaction has been described in AKI but the mechanisms are uncertain. Since we recently described a reno-cerebral reflex, we tested the hypothesis that renal ischemia-reperfusion injury activates a sympathetic reflex that interlinks the renal and cerebral renin-angiotensin axis to promote oxidative stress and progression of the injury.

Methods: Ischemic AKI in C57BL/6J mice was induced by bilateral clamping of the renal pedicles for 45 minutes. The status of renin-angiotensin system, oxidative stress, and activity of sympathetic nervous were studied in AKI mice with or without various inhibitors.

Results: Bilateral ischemia-reperfusion activated the intrarenal and cerebral, but not the circulating, renin-angiotensin system, increased sympathetic activity in the kidney and the cerebral sympathetic regulatory regions, and induced brain inflammation and oxidative stress, and kidney injury. Central blockade of central renin-angiotensin system or oxidative stress by intracerebroventricular losartan or tempol reduced the renal ischemic injury score by 65% or 58%, respectively, and reduction of renal efferent sympathetic signal by intracerebroventricular clonidine decreased the score by 52% (all $P<0.05$). Remarkably, selective blockade of renal afferent sympathetic signal by capsaicin inhibited the upregulation of the brain renin-angiotensin system, and decreased brain oxidative stress, sympathetic activity and inflammation after ischemia-reperfusion injury. Ischemia-reperfusion-induced renal damage and dysfunction persisted after controlling blood pressure with hydralazine.

Conclusions: In conclusion, this study demonstrates that ischemia-reperfusion induces AKI in a mouse model, at least in part, by activation of a reno-cerebral RAS axis interlinked by renal afferent and efferent sympathetic nerves. This identifies a novel mechanism underlying reno-cerebral interaction in response to renal ischemia-reperfusion, and thereby could lead to new interventional approaches, such as the use of RAS inhibitors, sympatholytic agents or even renal nerve ablation.

TH-PO080

The Effect of Circulating Extracellular Vesicles on the Response of the Kidney Proximal Tubule to Injury Emma E. Morrison, Marion Rook, Iqbal Singh Toor, Alexandra Inés Thompson, Neil Henderson, Gillian A. Gray, Matthew A. Bailey, James W. Dear. *Univ of Edinburgh, Edinburgh, United Kingdom.*

Background: Acute kidney injury can complicate liver or heart failure and increase mortality. Acute liver injury (ALI) causes a characteristic microRNA (miRNA) signature in blood.[1] Circulating miRNAs are encapsulated in extracellular vesicles (EVs) that can be taken up by kidney tubules with subsequent delivery of functional miRNA into the cell.[2] We hypothesized that circulating miRNA changes that accompany liver and/or cardiac cell death could affect the response of the kidney proximal tubule (PT) to injury.

Methods: To complement our ALI profiling data [1], the circulating miRNA response to cardiac injury was determined by small RNAseq. Samples were collected from patients undergoing cardiac bypass surgery (CABG n=23) and orthopedic surgery (control n=23). MiRNAs of interest were quantified in additional human samples and in mice. In mouse models, miRNA containing circulating EVs were isolated after myocardial infarction (MI) or paracetamol-induced acute liver injury (ALI). Murine kidney primary PT cells were co-cultured with fluorescently-labeled EVs and their uptake was quantified by flow cytometry. PT cells exposed to EVs were injured and their viability was determined.

Results: 333 miRNAs increased or decreased more the 1.5 fold after CABG compared with control. miR-22, -30a, -30d, -145, -140, -99b, -499, -1, -133a, -23 were successfully back-translated into mice. EVs from MI and ALI models entered PT cells (control EVs: mean fluorescence intensity±SD 12,989±8282a.u.; ALI: 17,689±10782a.u.; MI: 23,541±26915a.u.). ALI EVs reduced PT cell injury induced by cisplatin (10μM) (ATP luminescent assay ALI:142,300±17307u; control: 84,373±13861u; n=6; P=0.03). MI EVs had no effect.

Conclusions: Liver and cardiac injury induced significant but distinct changes in circulating miRNA. Only EVs from mice with ALI protected PT cells. EVs represent a potential mechanism of liver to kidney signaling that is amenable to therapeutic modulation. 1. Vliegenthart, A.D., et al. Sci Rep, 2015. 5: p. 15501. 2. Oosthuyzen, W., et al. J Am Soc Nephrol, 2016.

Funding: Government Support - Non-U.S.

TH-PO081

Long-Acting Albumin-Thioredoxin Fusion Protein Prevents AKI-Associated Acute Lung Injury Kento Nishida,[1] Hiroshi Watanabe,[1] Masafumi Fukagawa,[2] Toru Maruyama.[1] *[1]Dept of Biopharmaceutics, Graduate School of Pharmaceutical Sciences, Kumamoto Univ, Kumamoto, Japan; [2]Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Japan.*

Background: Respiratory complications are frequently occur after acute kidney injury (AKI), and are associated with increased mortality. Therefore, an effective strategy for preventing AKI-induced acute lung injury (ALI) due to increasing oxidative stress and inflammatory response is highly desirable. Thioredoxin-1 (Trx) is a redox-active protein that has anti-oxidative and anti-inflammatory properties. Although, Trx has great potential for use as a therapeutic agent against several types of oxidative stress-related diseases, its short half-life limits its clinical application. To overcome this problem, we produced a recombinant fusion protein that is comprised of human serum albumin and Trx (HSA-Trx), and examined its preventive effect against AKI-induced ALI.

Methods: Recombinant HSA-Trx was expressed using *Pichia* expression system. AKI-induced ALI mice were produced by renal ischemia/reperfusion (I/R).

Results: A pharmacokinetic study of HSA-Trx or Trx in mice showed that the plasma retention and lung distribution of Trx were markedly increased by fusion with HSA. Renal I/R mice showed not only an increase in BUN and serum creatinine levels, but also an increase in neutrophil infiltration in lung and protein concentration in bronchoalveolar lavage fluid (BALF)compared to sham mice. In contrast, systemic administration of HSA-Trx significantly decreased the number of neutrophils in lung and BALF protein compared with PBS administration. HSA-Trx also suppressed the elevation of plasma IL-6 level, CXCL1/CXCL2 chemokine and oxidative stress in lung.

Conclusions: HSA-Trx has potential for use in the treatment of AKI-induced ALI via its extended effects of modulating oxidative stress and inflammation.

TH-PO082

Prevention of Liver Inflammation in a Rodent Model of Acute Kidney Injury following Selective Gut Decontamination Chen Yu, Jiangtao Li. *Dept of Nephrology, Tongji Hospital, Tongji Univ School of Medicine, Shanghai, China.*

Background: Recent studies have indicated that the intestinal integrity and barrier function is disrupted during acute kidney injury(AKI)and blood from the intestines containing endotoxin and inflammatory mediators are presumed to activate Kupffer cell and further augment the systemic consequences of AKI . We investigated the effects and underlying mechanisms of oral norfloxacin on liver inflammation in renal ischemia reperfusion (RIR) model of AKI.

Methods: Sprague–Dawley rats were divided into 3 groups: Sham, RIR+saline and RIR + norfloxacin. The RIR animals were treated with oral norfloxacin 20 mg/kg/day or saline for 2 weeks before operation. For RIR induction, the bilateral kidneys were subjected to 60 min of ischemia and followed by 24h reperfusion. Plasma biochemistry and cytokines were measured. Endotoxemia was measured using Limulus amoebocyte lysate (LAL) assays. Protein expression of CD68, NFκB and cytokines were measured in the liver homogenate.

Results: Severity of endotoxemia was reduced in norfloxacin treated animals($p<0.05$). The RIR group treated with norfloxacin showed significant attenuation of the increasing liver TNF-a and IL-6($p<0.05$). The increased expression of CD68 and NFκB of liver tissues in the untreated animals was significantly attenuated in the norfloxacin treated animals.

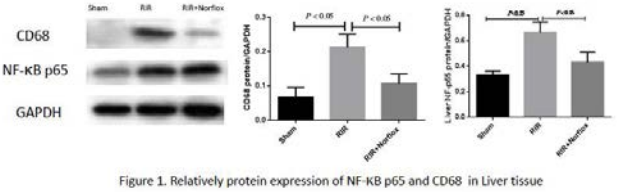


Figure 1. Relatively protein expression of NF-KB p65 and CD68 in Liver tissue

However, norfloxacin administration failed to improve the liver and renal function and down-regulate the circulation level of cytokines ($p<0.05$).

Conclusions: The results showed for the first time that translocation of endotoxin from the gut can contribute to endotoxinemia in AKI. As a result, the liver becomes an important affected organ system in the context of remote organ injury. Liver inflammatory insult due to AKI can be prevented with selective decontamination, providing novel insights into the cross-talking between gut and liver in AKI.

Funding: Government Support - Non-U.S.

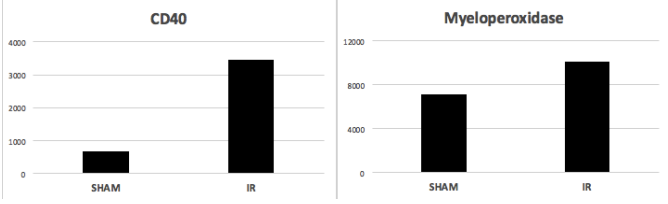
TH-PO083

Pulmonary CD40 Levels Are Increased 24 Hours after Ischemia-Reperfusion Kidney Injury Mark Hepokoski,[1] Laura E. Crotty Alexander,[1] Prabhleen Singh.[2] *[1]Div of Pulmonary and Critical Care Medicine, Univ of California San Diego, La Jolla, CA; [2]Div of Nephrology and Hypertension, Univ of California San Diego, La Jolla, CA.*

Background: Pulmonary complications are known to significantly increase the mortality of acute kidney injury (AKI) up to 80%. Multiple mediators of lung injury after AKI have been identified, the majority of which induce damage within 24 hours. The purpose of this study was to identify mediators of lung injury that are present 24 hours after AKI, as this is potentially a more useful time point for interventions.

Methods: Mice were randomized to ischemia-reperfusion (IR) kidney injury via 15 minutes of bilateral renal arterial clamping or sham operation (n=4 for each group). Pulse oximetry measurements were obtained prior to surgery and at harvest. At 24 hours, the pulmonary arteries were perfused with PBS to wash out blood and lung parenchyma was harvested, lysates prepared, and levels of 111 common inflammatory mediators were analyzed (Proteome Profile Mouse XL Cytokine Array, R&D Systems).

Results: Only 10 inflammatory mediators showed increased levels at 24 hours in IR mice compared to sham controls. Of these, CD40 had the most robust change with a 5-fold increase. There was no difference in mean pulse oximetry measurements between groups, 96.2% in sham compared to 95.8% in IR. However, lung myeloperoxidase, an indicator of neutrophil influx and thus a marker of lung injury, was elevated 30% compared to sham.



Conclusions: CD40 is a costimulatory protein known to amplify inflammatory cascades, such as NF-κB, a previously described mediator of lung injury after AKI. We show that IR kidney injury leads to a remarkable increase in pulmonary CD40 expression at 24 hours. CD40 may be a mediator of lung injury in the later phases of AKI, and further research into the role of CD40 in lung injury after AKI is warranted.

Funding: NIDDK Support, VA Support

TH-PO084

Antithrombin III Protects against AKI following Acute Severe Pancreatitis and Contrast Medium Administration Feng Wang,[1] Zeyuan Lu,[1,2] Jianyong Yin,[1] Nian-Song Wang.[1] *[1]Nephrology, Shanghai Jiao Tong Univ Affiliated Sixth People's Hospital, Shanghai, China; [2]Physiology, Medical College of Wisconsin, Milwaukee, WI.*

Background: We previously reported that insufficiencies of antithrombin III (ATIII), the major anti-coagulation molecule in vivo, exacerbated renal ischemia-reperfusion injury in animal models and possibly humans.

Methods: In the present study, we investigated the relationship between ATIII levels and two additional types of acute kidney injury in patients and examined therapeutic effects of ATIII in animal models.

Results: Patients with low ATIII activity presented a higher incidence of acute kidney injury (AKI) following severe acute pancreatitis (SAP). Intravenous injection of ATIII (500μg/kg) before or after the induction of SAP in Sprague-Dawley rats did not attenuate pancreatic injury, but significantly attenuated the elevation of serum creatinine, blood urea nitrogen, and renal histological injury. The beneficial effects of ATIII were accompanied with diminished renal inflammatory response, oxidative stress, and tubular cell apoptosis. Similarly, patients with low ATIII activity showed a higher incidence of contrast induced nephropathy (CIN), and the ATIII treatment significantly attenuated contrast induced AKI and improved renal blood flow in rats. In cultured renal tubular epithelial cells, ATIII attenuated tumor necrosis factor α (TNFα) -stimulated intercellular cell adhesion molecule 1(ICAM)-1 and monocyte chemotactic protein 1 (MCP-1) upregulation.

Conclusions: In conclusion, ATIII administration may represent a promising strategy for the prevention and treatment of SAP or contrast-induced AKI.

TH-PO085

Transcutaneous Measurement of Glomerular Filtration Rate to Assess the Progression from Acute to Chronic Kidney Disease following Bilateral Ischemic Injury in Mice Danielle Soranno, Chris Altmann, Sarah Faubel. *Univ of Colorado, Aurora, CO.*

Background: AKI is common and predisposes patients to developing CKD. Biomarkers used to estimate kidney function (BUN and Cr) are less accurate than measurement of GFR.

Methods: 8-10 week WT C57BL/6 mice underwent bilateral ischemia-reperfusion with clamp-time of 22 minutes. Mice received 0.5 mL saline resuscitation subcutaneously daily for 5 days. tGFR measurement: Mice were put under anesthesia via 2% inhaled isoflurane and the hair was removed from the dorsum. The NIC-Kidney device was attached to the dorsum of the mouse. After 1-5 minutes, FITC-sinistrin (15 mg/100 g body weight) was injected via tail vein injection. The mouse was monitored for 1 hour; the device was removed. The half-life of the FITC-sinistrin was calculated using MPD Lab Version 1.0a software, and the tGFR was calculated: tGFR [μL· min ·100 g body weight] = 14616.8 [μL/100g body weight]/$t_{1/2}$ FITC-sinistrin[min]. tGFR was measured pre-AKI, 1 day after and then weekly until 28 days. BUN (BioAssay Systems) and serum Cr (Point Scientific) were analyzed per manufacturer instructions. Picrosirius Red staining was performed tissue using standard histological staining procedures and imaging software was used to calculate the percent area of fibrosis.

Results:

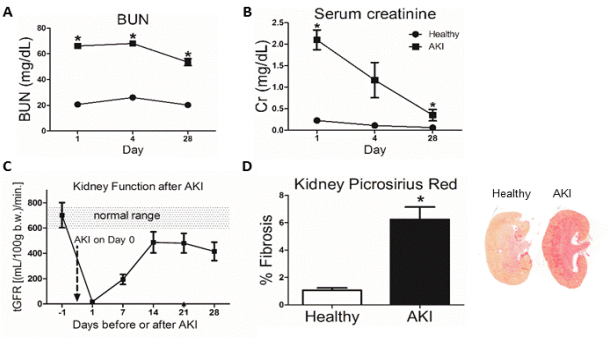


Figure 1: Assessment of kidney function 28 days following acute kidney injury (AKI). Serial (**A**) blood urea nitrogen (BUN) and (**B**) serum creatinine (Cr) to *estimate* kidney function over time. (**C**) Serial tGFR to *measure* function over time. (**D**) Quantification and representative images of Picrosirius Red stain 28 days following AKI. n = 5, p < 0.01.

Serial BUN and Cr used to estimate kidney function, demonstrates a persistent elevation in BUN and a mild increase in Cr 28 days after AKI. Serial tGFR used to measure kidney function demonstrates a persistent decrease in GFR 28 days following AKI. Picrosirius Red staining demonstrates the presence of cortical fibrosis 28 days following AKI.

Conclusions: We have demonstrated both histological and functional evidence of CKD in a murine model of bilateral ischemia-reperfusion AKI. The utilization of non-invasive tGFR monitoring allows for accurate, serial measurements of kidney function following injury.

Funding: Private Foundation Support

TH-PO086

Mir-219 Is a Pro-Fibrotic MicroRNA That Is Hyper-Methylated and Suppressed in Kidney Injury Associated Fibrosis Qingqing Wei,[1] Chunyuan Guo,[1] Xiao Xiao,[1] Huidong Shi,[3] Zheng Dong.[1,2] *[1]Cellular Biology & Anatomy, Medical College of Georgia, Augusta Univ, Augusta, GA; [2]Charlie Norwood VA Hospital, Augusta, GA; [3]Georgia Cancer Center, Medical College of Georgia, Augusta Univ, Augusta, GA.*

Background: Epigenetic regulation, including DNA methylation, plays important roles in gene expression under various patho-physiological conditions.

Methods: To understand DNA methylation after kidney injury, we analyzed the global DNA methylation change in different mouse kidney injury models.

Results: Interestingly, in addition to protein coding genes, the global analysis revealed the hyper-methylation of mir-219-2 in kidney tissues of 3 days of cisplatin nephrotoxicity, 25 minutes of ischemia with 1 week or 1 month reperfusion, and 1 week of unilateral urinary obstruction (UUO). The hyper-methylation was associated by a significant decrease in mir-219 expression in the injured kidneys. In vitro, 48 - 72 hours of hypoxia also led to a decrease in mir-219 in BUMPT proximal tubular cells. Overexpression of mir-219 in BUMPT cells enhanced the pro-fibrotic reaction during hypoxia or TGF-β treatment, as shown by significantly higher induction of fibronectin. Though immunoblotting did not show obvious difference of TGF-β signaling pathway activation, GSK-3beta phosphorylation was significantly increased by mmu-mir-219 overexpression. The KEGG pathway analysis of the predicted mmu-mir-219 targets from TargetScan indicated that mmu-mir-219 may regulate several important pathways related to renal fibrosis regulation, which include insulin signaling pathway, phosphatidylinositol signaling system, MAPK signaling pathway, and WNT signaling pathway.

Conclusions: These results suggest that intrinsic anti-fibrotic mechanisms are activated in response to kidney injury and fibrosis. DNA hyper-methylation of mir-219 may be one of these anti-fibrotic mechanisms, which is activated to repress mir-219, a pro-fibrotic microRNA.

Funding: NIDDK Support, Private Foundation Support

TH-PO087

Expression of Endomucin, an Endothelial-Specific Sialomucin in Normal and Injured Kidneys Li Li, Xiaoyan Xiao, Takaharu Ichimura, Hong Liu, Seiji Kishi, Joseph V. Bonventre. *Brigham and Women's Hospital, Boston, MA.*

Background: Endomucin (EMCN) is a membrane bound O-sialoglycoprotein expressed on the surface of endothelial cells. Its role in inflammation has been controversial. Early studies reported that EMCN bears a peripheral node addressin (PNAd) epitope and binds to L-selectin on high endothelial venules (HEVs) in lymph nodes. Recent studies suggest that EMCN is part of endothelial glycocalyx and maintains the anti-adhesive property of normal endothelium. The role of EMCN in kidney injury is unknown.

Methods: We investigated the expression of EMCN and PNAd using immunofluorescence in both normal and injured kidneys. In male BALB/c mice, ischemia-reperfusion injury (IRI) was induced by clamping the renal pedicle of both kidneys for 27 min at 37.0 °C. Aristolochic acid nephropathy (AAN) was induced by a one-time intraperitoneal injection AA (5 mg/kg BW).

Results: EMCN stained glomerular and peritubular capillaries in normal kidney, co-localizing with CD 31. In post-ischemic mouse kidneys, EMCN staining became significantly thicker and more intense at 1 day. EMCN continued to co-localize with CD31, but did not overlap with F4/80 (macrophages), Ly6G (neutrophils), KIM-1 (injured tubules) and PDGFRβ (pericytes and fibroblasts) staining. A similar pattern of EMCN staining was observed at day 2, 4, 7 and 9 post-ischemia. At day 28 post-ischemia, EMCN staining returned to baseline thin capillary morphology as observed in normal kidney. In contrast,there was significant loss of the EMCN staining in the AAN model associated with much more fibrosis at day 21 and 42. EMCN co-localized with CD 31 in AAN model. On the other hand, PNAd was not expressed in the day 2 post-ischemic kidneys.

Conclusions: These data suggest that EMCN is expressed in normal and injury kidney. Up-regulation of EMCN expression after ischemic injury suggests that EMCN might serve as a specific marker for activated remodeling endothelium. Loss of EMCN in AAN may facilitate endothelial rarefaction. No PNAd expression in ischemic kidney suggests EMCN bears a different glycosylation epitope and may serve different function in kidney compared to EMCN in HEVs in lymph node.

Funding: Other NIH Support - T32

TH-PO088

Stromally Derived Endothelial Progenitors Mediate Injury after Acute Kidney Injury Katherine V. Maringer,[1] Jeffrey S. Isenberg,[2] Sunder Sims-Lucas.[1,2] *[1]Pediatric Nephrology, Rangos Research Center Childrens Hospital of Pittsburgh of UPMC, Pittsburgh, PA; [2]Vascular Medicine Inst, Univ of Pittsburgh, Pittsburgh, PA.*

Background: Acute Kidney Injury (AKI) is characterized by an abrupt decrease in renal function leading to renal failure, and contributing to high percentages of morbidity and mortality. The kidney contains a complex and high degree of vascularization making it susceptible to ischemic injury. We have identified a subset of stromally derived endothelium (SDE) that is important for kidney vascular development. We hypothesize that SDE are critical to the kidneys ability to recover from AKI.

Methods: To confirm the importance of SDE following ischemia reperfusion injury (IRI) we performed lineage tracing, using a TdTomato reporter (permanently labeling all SDE cells) and interrogated the percentage of SDE cells that were present in the IRI and contralateral control kidneys. Furthermore, we generated mice with a conditional deletion of Flk1 (floxed) in the Foxd1cre positive renal stroma ($Flk1^{SY-/-}$), and evaluated the tissue after IRI, focusing on the recovery phase (7 days) post injury.

Results: We determined in control mice following IRI that stromal genes were re-expressed suggesting that the stroma may be undergoing de-differentiation and subsequently driving SDE proliferation. Furthermore, using lineage tracing we found that SDE preferentially increase during the repair phase (7 days) of IRI. To evaluate the role of SDE during IRI we used $Flk1^{SY-/-}$animals subjected to IRI and found that mutants had less perfusion and an increase in hypoxia at 7 days. This was coupled with inappropriate continued expression of de-differentiation markers in the proximal tubules, which failed to re-differentiate in the hypoxic environment causing exasperated kidney damage in the mutant animals.

Conclusions: Taken together we determined that SDE are important mediators of vascular perfusion after kidney injury. Furthermore, SDE play a vital role in reestablishing normal oxygen concentrations after AKI to regulate the repair of the de-differentiated proximal tubules.

Funding: NIDDK Support

TH-PO089

Genetic Deletion of Endogenous Proangiogenic Factor Vasohibin-2 Exacerbates Renal Ischemic Reperfusion Injury Katsuyuki Tanabe, Kana Masuda, Yuka Arata, Hitoshi Sugiyama, Jun Wada. *Dept of Nephrology, Rheumatolgy, Endocrinology and Metabolism, Okayama Univ Graduate School of Medicine, Okayama, Japan.*

Background: During the progression of acute kidney injury (AKI), dramatic alteration in the expression of various mediators including angiogenesis-related factors has been reported. Understanding the role of such mediators in AKI may lead to development of novel therapeutic strategies. Vasohibin-2 (VASH2) was originally identified as a proangiogenic factor secreted by bone marrow-derived mononuclear cells and it has been shown to be upregulated in various malignant tumor tissues. However, its pathogenic role in kidney diseases has not been elucidated yet. In the present study, we examined the effects of lacking endogenous VASH2 deficiency on renal function and histology in murine AKI model.

Methods: Ischemic-reperfusion (I/R) injury was induced by clumping bilateral renal pedicles for 25 min in eight to nine week-old C57BL6/J wild type (WT) and VASH2 knockout ($VASH2^{-/-}$) mice (n=6 in each group). Blood samples were collected and kidneys were harvested 24 hours after the reperfusion.

Results: I/R injury caused marked increase in serum creatinine and blood urea nitrogen in WT mice, and such increase was significantly accelerated in $VASH2^{-/-}$ mice (1.05±0.51 vs 2.20±0.41mg/dl and 143±26 vs 203±25mg/dl, respectively). Histologically, renal tubular injury (ATN score) following I/R in $VASH2^{-/-}$ mice was significantly exuberated compared with WT mice. Likewise, increased oxidative stress associated with the accumulation of malondialdehyde and 4-hidroxynonenal was more prominent in $VASH2^{-/-}$ I/R mice. VEGF mRNA level was significantly reduced after I/R in both WT and $VASH2^{-/-}$ mice. By immunostaining, VASH2 expression was observed in fibroblast-like cells in normal kidney interstitium. In the course of I/R, renal VASH2 mRNA markedly elevated on 24 hours but not six hours. Increased immunoreactivity of VASH2 on injured tubules 24 hours after I/R was observed.

Conclusions: These results suggested that endogenous VASH2 was upregulated in late phase of I/R injury, and thus may exert certain beneficial effects on the tubular repair process.

Funding: Government Support - Non-U.S.

TH-PO090

Activated CD47 Dysregulates Metabolic Pathways and Cellular Reprogramming in Acute Kidney Injury Natasha M. Rogers,[1,4] Takuto Chiba,[1,2] Elina Mukherjee,[2] Zheng Jenny Zhang,[3] Jiao-Jing Wang,[3] Angus W. Thomson,[4,5] Dennis Kostka,[3,6] Sunder Sims-Lucas,[1,2] Jeffrey S. Isenberg.[1] *[1]Medicine, Univ of Pittsburgh, PA; [2]Children's Hospital, Univ of Pittsburgh, PA; [3]Comprehensive Transplant Center, Northwestern Univ, Chicago, IL; [4]Starzl Transplantation Inst, Univ of Pittsburgh, PA; [5]Immunology, Univ of Pittsburgh, PA; [6]Developmental Biology, Univ of Pittsburgh, PA.*

Background: Acute kidney injury (AKI) is a serious disorder that is identified in 50% of ICU patients. We have previously shown that 1) TSP1-CD47 signaling exacerbates ischemia reperfusion (IR)-mediated AKI in mice, 2) in some non-renal tissue beds, absence of CD47 was associated with improved mitochondrial function, and that 3) multiple self-renewal factors including Oct4, Sox2, Klf4 and c-Myc (OSKM) are increased in murine $CD47^{-/-}$ primary renal tubules. We hypothesize that AKI-induced TSP1-CD47 signaling dysregulates PTEC metabolic pathways and cellular reprogramming to limit kidney healing.

Methods: To localize TSP1-CD47 signaling, we utilized antibodies bound to magnetic beads to selectively enrich for PTEC and renal arterial endothelial cells as compared to whole kidneys from age/ gender matched $CD47^{-/-}$ and wild type (WT) mice. RNA sequencing (RNA-seq) was performed with whole kidneys of age/ gender-matched WT and $CD47^{-/-}$ mice 24 hours after IR.

Results: TSP1 and CD47, mRNA levels were increased in WT PTEC and endothelial cells compared to whole kidneys. Conversely, cMyc and Klf4 mRNA expression was elevated in $CD47^{-/-}$ PTEC as was VEGF mRNA in $CD47^{-/-}$ renal arterial endothelial cells compared to WT cells. *In vitro*, hypoxic $CD47^{-/-}$ PTEC maintained enhanced OSKM levels in the face of TSP1 induction and showed increased proliferation under normoxia. OSKM protein and mRNA levels were increased in whole kidneys from $CD47^{-/-}$ mice at day1, 3 and 7 post-IR. RNA-seq followed by a pathway analysis revealed that genes of oxidative phosphorylation pathway as well as of mitochondrial and glycolysis were upregulated in $CD47^{-/-}$ kidneys.

Conclusions: TSP1-CD47 signaling is maladaptively upregulated in IR-mediated AKI in a cell type specific fashion, suppresses expression of self-renewal factors OSKM, dysregulates oxidative phosphorylation, and suppresses proliferation of PTEC to limit tubule repair.

Funding: Other NIH Support - P01 HL103455, R01 HL-108954, 1R01HL112914-01A1, P30-DK079307

TH-PO091

Role of IL-17 in the Induction of Fibrosis and Neutrophil Recruitment in Post AKI Rats Fed on High Salt Diet Purvi Mehrotra, Jason Andrieu Collett, Seth D. Mckinney, Jackson Stevens, David P. Basile. *Cellular and Integrative Physiology, Indiana School of Medicine, Indianapolis, IN.*

Background: T cells have been implicated in the pathogenesis of acute kidney injury (AKI) as well as its progression to chronic kidney disease (CKD). Previous studies from our laboratory suggest that a specific subset of T helper cells, Th17, characterized by IL-17 secretion, is the predominant subtype activated during AKI to CKD transition. Further, inhibition of T cell activity by mycophenolate mofetil (MMF) or losartan, protected from fibrosis in post AKI rats fed on high salt diet, but the role of Th17 cells in AKI-CKD transition is not clear. We hypothesized that T cell deficient rats, may have reduced cytokine levels leading to decrease fibrosis.

Methods: Ischemia and reperfusion was performed on T cell deficient athymic rats ($Foxn1^{rnu-/rnu-}$) and control heterozygote control euthymic rats ($Foxn1^{rnu-/+}$) and allowed to recover for 35 days. CKD progression was hastened by unilateral nephrectomy and high salt diet for an additional 4 weeks. These rats were also treated with MMF or vehicle along with high salt diet.

Results: As expected, I/R and high salt diet increased fibrosis in euthymic rats (206%;p³0.05) as indicated by an increase in picosirus red staining, which was reduced by MMF treatment (66%; p³0.05). However, the degree of fibrosis was similar in the athymic rat (266%) as compared to euthymic controls (206%). Surprisingly, MMF treated had no effect on AKI induced fibrosis in athymic rats. This may be due to the compensatory role, MMF-insensitive natural killer (NK) T-cells in IL-17 production in athymic rats. Blockade of IL-17 activity using IL-17RC soluble receptor (150ng/day), significantly decreased fibrosis in both euthymic (66%) and athymic (71%) rats as compared to vehicle treated controls. Further, we also observed a significant decrease in neutrophil recruitment in IL-17RC-treated rats as compared to vehicle-treated rats.

Conclusions: Taken together, we conclude that IL-17 cytokine secretion from any source plays a central role in the pathogenesis of fibrosis during AKI to CKD transition.

Funding: NIDDK Support

TH-PO092

Adenine Overload Causes Severe AKI Progressing to CKD by Activation of Innate Immunity in Rats and Mice Gizely C.S. Moreira,[1,2] Flavia G. Machado,[2] Clarice K. Fujihara,[1] Benjamin D. Humphreys,[2] Roberto Zatz.[1] *[1]Renal Div, Univ of Sao Paulo, Sao Paulo, SP, Brazil; [2]Div of Nephrology, Washington Univ in St. Louis, St. Louis, MO.*

Background: Adenine (ADE) overload is a known model of kidney injury due to precipitation of crystals in the tubular lumen leading to epithelial damage and interstitial expansion. Here we investigated glomerular filtration rate (GFR), the role of innate immunity and tubular damage in both rat and mouse models of tubulointerstitial nephritis.

Methods: Adult male Munich-Wistar rats were fed with chow containing 0.5% of ADE for 1 week and analyzed 4 and 24 weeks after cessation of ADE. A separate group of mice were fed with 0.25% ADE chow for 10 days and evaluated 4 weeks after ADE cessation. GFR was measured through transcutaneous elimination kinects of FITC-Sinistrin.

Results: At the end of 1 week under ADE overload in rats, innate immunity components such as IL1β, IL6, NLRP3 and TLR4 were upregulated. After 4 and 24 weeks of ADE cessation intratubular rare crystals could be observed and innate immunity protein expression had fallen back to normal levels, translating a foreign body reaction against ADE crystals in tubulointerstitial compartment. At 24 weeks, glomerulosclerosis and collagen interstitial deposition indicating irreversible tubulointersititial fibrosis. A similar overall pattern was observed in mice, where ADE induced KIM-1 and NGAL mRNA expression to 620-fold and 3810-fold over control. Four weeks after ADE, their expression fell but remained elevated at 20-fold and 555-fold over control. Fibronectin, collagen 1α1, αSMA and F4/80 mRNA were also induced over the 4 weeks time course. Importantly, acute ADE overload in mice caused a 64% reduction in GFR (1049±96 µl/min/100*g* bw at baseline vs. 380±60 µl/min/100*g* bw ADE 10d, $p<0.05$) that made an incomplete recovery 4 weeks after discontinuation of ADE (792±18 µl/min/100*g* bw, $p>0.05$ *vs.* baseline).

Conclusions: ADE overload causes severe AKI that progresses to CKD in both rats and mice. This is mediated by activation of innate immunity. The ADE model is an attractive one to study AKI to CKD transition because it is associated with GFR reduction.

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

TH-PO093

Effects of Acute Coxsackievirus Infection on the Kidneys of Non-Obese Diabetic Mice Debra L. Walter,[1,4] Kelly D. Mccall,[2,4] Karen T. Coschigano.[3,4] *[1]Biological Sciences, College of Arts and Sciences, Athens, OH; [2]Specialty Medicine, Heritage College of Osteopathic Medicine, Athens, OH; [3]Biomedical Sciences, Heritage College of Osteopathic Medicine, Athens, OH; [4]The Diabetes Inst at Ohio Univ, Athens, OH.*

Background: Enteroviruses, like coxsackievirus, are one of the most common virus genera infecting humans worldwide. Enterovirus infections have been documented to mediate a wide range of insults including direct injury as well as indirect injury through mechanisms such as autoimmune disease. Chronic kidney disease (CKD) can result from each type of damage (direct or indirect), however, little work has been done to differentiate the effects of each type of damage as a cause of CKD. This study, therefore, evaluates acute coxsackievirus infection in the kidneys of non-obese diabetic (NOD) mice that are genetically susceptible to develop autoimmune diseases that can ultimately result in CKD. Characterizing the effects of an acute viral infection in the kidneys of these mice will strengthen our understanding of direct virus-induced injury which can then be used to understand chronic kidney disease with respect to virus infection and autoimmune disease both alone and together.

Methods: In the current study, NOD mice were infected with coxsackievirus at 8 weeks of age and euthanized 3, 7, 10 and 14 days post infection.

Results: Coxsackievirus infection within the kidneys of NOD mice peaked at 3 days and disappeared by 14 days post infection. While morphological evaluation has not yet revealed any significant changes, genes involved in kidney damage and the inflammatory response (e.g. IL-6, TLR3, TNFα, CCL2, and others) were found to be significantly upregulated 3 days post infection.

Conclusions: Characterizing the direct effects of an acute virus infection within the kidneys of these mice will strengthen our understanding of the nature of virus-induced acute kidney injury that may trigger CKD resulting from either virus infection (direct), autoimmunity (indirect) or both together. Together, these data will help identify how CKD develops in different situations and reveal potential treatment strategies for each causative agent.

TH-PO094

Macrophage Promoted Kidney Repair in the Ischemia-Reperfusion Injury via the Activation of IKKα Xin Wan, Changchun Cao. *Dept of Nephrology, Nanjing First Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Macrophage played a notable role in the renal ischemia-reperfusion injury(IRI). IKKa, a key mediator of NF-κB nonclassical pathway was considered could inhibit the progression of imflammation. The roles and underlying mechanisms of IKKa in macrophage was not clear in kidney IRI.

Methods: To investigate the performance of IKKa in macrophages, we generated a *chuk* knock mouse ($IKK\alpha^{F/F}$:MlysCre, $IKK\alpha^{MKO}$) and they were submitted to unilateral renal IR or sham operation. Histomorphological, immunohistochemical methods were performed to judge the kidney samples.

Results: Compared to WT, KO mouse was smaller ($P<0.05$). After IRI, the ratio of left kidney and whole weight was higher in KO mouse then they survived more than WT (Figure 1, 2). KO group showed less SDF-1, IL-10 expression in renal epithelial cells than another group, accompanied with a higher injury score (Figure 3, 4).

Conclusions: The IKKα in macrophage was essential for the restoration of kidney injury.

Funding: Government Support - Non-U.S.

TH-PO095

Splenic Marginal Zone Macrophages Regulate NKT Cell Activation in Acute Kidney Injury Elvira Kurmaeva, Liping Huang, Amandeep Bajwa. *Medicine, Univ of VA, Charlottesville, VA.*

Background: Marginal zone macrophages (MZM) are present in lymphoid and non-lymphoid organs and regulate innate immune responses. In spleen MZM are arranged around the marginal sinus lining and consist of several subsets: $CD169^+$, $CD209^+$ or $MARCO^+$. $CD169^+$ MZM are involved in erythropoiesis, capture blood born particles and target endogenous glycolipids to activate splenic NKT cells. In kidney ischemic reperfusion injury (IRI), NKT cell activation through production of IFN-γ is crucial in initialing innate injury. Depletion of NKT cells or use of NKT KO mice protects kidneys from injury. We functionally evaluated the role of splenic $CD169^+$ MZM to present endogenous glycolipid to activate NKT cells to initiate injury in kidney IRI.

Methods: Renal injury was assessed by plasma creatinine (PCr; mg/dl). 8-wk old $CD169^{WT/WT}$ and $CD169^{DTR/WT}$ male mice were used for all IRI studies. Mice were injected with 10ng/g of diphtheria toxin (DT) one day prior to 24 mins or 26 mins of IRI. For NKT functional studies, α-galactosylceramide (α-GalCer, 10µg/mouse, i.p.) was administered 2 days after CD169-depletion and all samples were collected after 2 hrs.

Results: CD169-depleted mice are partially protected compared to WT mice (PCr; 0.8±0.2 vs 0.6±0.01; 26-mins). However, with sub-threshold clamp time of 24 mins, CD169-depleted mice have significantly lower PCr compared to littermates (2.14±0.15, $p<0.001$). Sham and CD169-depleted IRI mice had comparable injury (PCr; 0.23±0.05 vs 0.27±0.01). Additionally, CD169-depleted mice have less infiltration of $CD11b^+Gr1^{high}Ly6C^{int}$ (neutrophils) and $CD11b^+Gr1^{neg}Ly6C^{high}$ (monocyte) in IRI kidneys compared to controls. Additionally, administration of α-GalCer to CD169-depleted mice results in two times less IFN-γ production by splenic NKT cells (%NKT^+, 38.28 ± 2.831vs 14.74 ± 4.103, $p=0.0003$).

Conclusions: Depletion of $CD169^+$ MZM in CD169-DTR mice reduced IFN-γ production by NKT cells, neutrophil and monocyte infiltration into IRI kidneys. Due to prime location of $CD169^+$ macrophages at the MZ of the spleen, our data further demonstrates that endogenous glycolipid presentation takes place in the spleen to regulate ischemic injury and depletion of $CD169^+$ MZM protests kidneys from IRI.

Funding: NIDDK Support

TH-PO096

Acute Splenic Iron Loading Protects against Ischemic AKI Yogesh M. Scindia, Ewa U. Mandziak, Liping Huang, Saleh Mohammad, Sundararaman Swaminathan. *Medicine, Univ of Virginia, Charlottesville, VA.*

Background: We have previously demonstrated that hepcidin (*Hamp*) mitigates renal ischemia reperfusion injury (IRI) by inducing splenic iron retention. In these studies, we observed that renal protection was associated with splenic iron accumulation that far out weighed that in the liver and kidney. We therefore hypothesized that strategically iron overloading the spleen with iron preparations known to be targeted to splenic macrophages may be beneficial in renal IRI.

Methods: Mice, C57Bl/6 (WT), and $Hamp^{-/-}$ (on B6 background) were injected with saline or 14 mg/kg Ferumoxytol (Feraheme™) (i.v.), a FDA approved iron nanoparticle preparation in current use for treating anemia of chronic kidney disease. Twenty-four hours later, mice were subjected to renal IRI (24-26 min). In some experiments, WT mice were injected with Ferumoxytol, 2 h post reperfusion. Outcomes (renal function, injury markers, histopathology and inflammation) were examined after 24-72 h of reperfusion.

Results: Ferumoxytol significantly reduced IRI-induced kidney injury in WT mice as measured by plasma creatinine (WT P_{Cr}: IRI; 2.5±0.32 vs Ferumoxytol+IRI; 0.38±0.01 mg/dl, $p < 0.005$), NGAL, acute tubular necrosis score and immune cell infiltration. Ferumoxytol protected hepcidin-deficient ($Hamp^{-/-}$) mice against renal IRI despite the presence of kidney iron overload. Splenic iron accumulation was a common feature in the protected WT and $Hamp^{-/-}$ mice. In contrast, the spleens of injured mice were iron depleted. Mice injected with Ferumoxytol after the onset of AKI had significantly lower plasma creatinine, after 72 h of reperfusion (WT P_{Cr}: IRI; 1.2 vs Feraheme+IRI; 0.50 mg/dl, $p < 0.05$). The kidneys of the protected mice had more M2 macrophages and less neutrophils.

Conclusions: Our results reveal a novel protective effect of Ferumoxytol in renal IRI. Moreover, its actions are independent of hepcidin or kidney iron content. The ability of Ferumoxytol to protect against IRI even when administered after the onset of injury highlights its therapeutic potential. These observations validate our previous studies suggesting the critical importance of splenic iron content for inducing protection in ischemic AKI.

Funding: NIDDK Support

TH-PO097

A Novel Mice Model of Acute Kidney Injury Induced by Hemorrhagic Shock Lei Wang, Jin Wei, Shaohui Wang, Jie Zhang, Ruisheng Liu. *Molecular Pharmacology and Physiology, Univ of South Florida, Tampa, FL.*

Background: Current animal models for hemorrhagic shock-induced acute kidney injury (HS-AKI) need extensive surgery and monitoring which are very time consuming. The goal of the present study is to develop an easy and reliable mouse model of HS-AKI.

Methods: C57BL/6J mice were implanted with radio-transmitters for mean arterial pressure (MAP) measurement. Hemorrhagic shock was induced by left retro-orbital bleeding of 0.4 ml blood. After 30 min, bilateral pedicels were clamped for 18 min at 36.8-37.0^{0}C. One group of mice were then resuscitated with 0.2 ml of collected blood 2-fold diluted with Lactate Ringer's solution. Another group was not given resuscitation. The clamps were then released to start the reperfusion. Renal blood flow (RBF) was measured in separate non-survival experiments.

Results: Hemorrhagic shock reduced MAP from 77 ± 4 to 35 ± 3 mmHg, which returned to 90% of baseline in 3 hours in the resuscitation group and in 8 hours in the non-resuscitation group. Plasma creatinine levels increased from 0.09 ± 0.01 mg/dl to 1.71 ± 0.08 mg/dl in the resuscitation group and from 0.08 ± 0.01 mg/dl to 2.03 ± 0.12 mg/dl in the non-resuscitation group 24 h after HS-AKI. GFR was decreased by 69% in the resuscitation group and by 78% in the non-resuscitation group. ($p<0.05$, resuscitation group vs non-resuscitation group, n=6/group) All of the above parameters returned to near baseline at 4 weeks after HS-AKI. Hemorrhagic shock reduced RBF from 0.68 ± 0.13 to 0.24 ± 0.09 ml/min. RBF was returned about 92% of baseline with resuscitation, but remained low in the non-resuscitation group. ($p<0.01$ resuscitation group vs non-resuscitation group, n=5/group).

Conclusions: We propose to generate this HS-AKI mouse model without MAP and RBF monitoring by: 1) retro-orbital bleeding 0.4 ml blood; 2) bilateral pedicles clamping for 18 min at 36.8-37 °C; 3) with or without resuscitation of 0.2 ml LR + blood via retro-orbital sinus. This new HS-AKI model is a well-controlled, easy and reliable mouse model, which may facilitate investigators to further investigate and understand the mechanisms of HS-AKI.

Funding: NIDDK Support

TH-PO098

Development of a Cellular Assay for Ischemic Acute Kidney Injury David J. Rickard,[1] Robert S. Geske,[1] Cathy Simmons,[1] Jean-Louis D. Klein,[1] Robert Kirkpatrick,[2] Craig Leach,[3] Luke Devey.[4] *[1]Target Sciences, GlaxoSmithKline R&D, Collegeville, PA; [2]Pipeline Futures Group, GlaxoSmithKline R&D, Collegeville, PA; [3]Platform Technology and Science, GlaxoSmithKline R&D, King of Prussia, PA; [4]Heart Failure DPU, GlaxoSmithKline R&D, King of Prussia, PA.*

Background: In AKI, tubular epithelia respond to ischemia-induced hypoxia and nutrient deprivation with oxidative and metabolic stress, leading to cell death, inflammation and impaired kidney function in severe cases. A possible reason for the failure of several promising therapeutic approaches is poor predictability of preclinical models of renal ischemia. We sought to develop a cellular model of renal tubular ischemia amenable to the identification of potential therapeutic targets and agents. Precision-cut kidney slice cultures were used for comparison with the cell model.

Methods: HK-2 proximal tubule and primary human renal epithelial cells subjected to chemically-induced redox, hypoxic, metabolic and fibrotic stresses were analyzed for changes in mitochondrial activity, cell death, as well as expression of genes associated with hypoxia, nephrotoxicity and genes identified from patient samples exhibiting delayed graft function (DGF) after renal transplant (see abstract by Kirkpatrick R, et al).

Results: HIF hydroylase inhibitors (hypoxia mimic) and TGFβ1 (fibrosis) both had little effect on cell death, while ATP and glucose deprivation (metabolic stress) induced apoptosis and hydrogen peroxide (oxidative stress) increased necrosis. Despite differing effects on cell death, metabolic and hypoxic stressors caused time-dependent mitochondrial damage. Consistent with their divergent effects on cell health, each stress treatment produced distinct changes in gene expression. Importantly however, the effect of each stressor in epithelial cell culture correlated poorly with the DGF-induced change for a subset of differentially expressed genes. Moreover, gene expression analysis in cultured cortical slices demonstrated a greater number of hypoxia rather than DGF-mediated changes.

Conclusions: The DGF tissue dataset indicates that our in vitro models may require an immune component to better recapitulate the complex pathology of AKI.

Funding: Pharmaceutical Company Support - GlaxoSmithKline

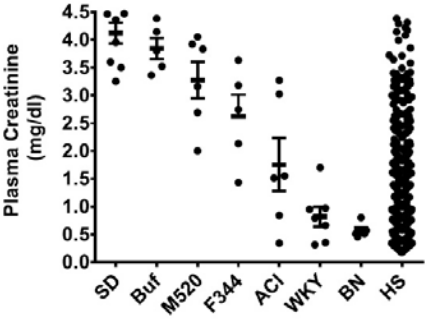
TH-PO099

Differential Susceptibility to Renal Ischemia-Reperfusion Injury in Heterogeneous Stock Rats David Charles,[1] David Houser,[1] Bohan Xing,[1] Leah C. Solberg Woods,[2] Kevin R. Regner.[1] *[1]Nephrology; [2]Pediatrics, Medical College of Wisconsin.*

Background: Renal ischemia-reperfusion injury (IRI) is a common cause of acute kidney injury (AKI). In animal models of AKI, we and others have demonstrated that genetic factors may play a role in modulating the severity of AKI. Heterogeneous stock (HS) rats are outbred from eight inbred founder strains and can be used to fine map genes involved in complex traits. The aim of the present study was to evaluate the range of phenotypes in HS rats and HS founder strains following renal IRI.

Methods: Groups of eight week old male outbred Sprague-Dawley (SD), inbred HS founder (ACI, BN, BUF, F344, M520, WKY), and outbred HS rats underwent 30 min bilateral renal ischemia and 24 hrs reperfusion or sham surgery. Renal function was assessed by measurement of serum creatinine (sCr) by LC-MS/MS. Tubular injury (TI) was assessed by histologic analysis in kidney sections and immunblot analysis of neutrophil gelatinase-associated lipocalin (NGAL) expression.

Results: TI scores and sCr did not significantly differ between groups 24 hrs after sham surgery. Following IRI, sCr was 4.1 ± 0.22 mg/dl in SD rats. In comparison to SD rats, sCr was significantly lower in the BN and WKY founder strains (see Figure). As expected, sCr in HS rats varied across the range found in the inbred HS founder strains (see Figure). Similar trends in TI scores were found in HS founder strains and HS rats. NGAL expression correlated with sCr ($r = 0.7$, $P < 0.01$) and with renal cortex TI scores ($r = 0.5$, $P<0.01$) in HS rats.



Conclusions: In conclusion, we found that susceptibility to renal IRI varied between HS founders and that HS rats exhibited a high degree of variability in response to renal IRI, with some rats completely protected from AKI. This variability indicates that HS rats can be used to fine-map genetic loci and to uncover the causal genes that alter susceptibility to AKI in HS founder strains.

Funding: NIDDK Support

TH-PO100

Estrogen Receptor Alpha Mediates Female Protection from Renal Ischemia-Reperfusion Injury David Dean Aufhauser,[1] Douglas R. Murken,[1] Zhonglin Wang,[1] Guanghui Ge,[1] Tricia Bhatti,[2] Matthew H. Levine.[1] *[1]General Surgery, Hospital of the Univ of Pennsyvania and the Childrens's Hospital of Philadelphia, Philadelphia, PA; [2]Pathology and Laboratory Medicine, Hospital of the Univ of Pennsyvania and the Childrens's Hospital of Philadelphia, Philadelphia, PA.*

Background: Female protection from renal ischemia-reperfusion injury (IRI) is observed in both mouse and human renal transplantation. We have previously shown that both estrogen and androgens contribute to the gender dichotomy following this injury pattern. We wished to assess the role of estrogen receptor alpha (ERα) in mediating this process.

Methods: Wild type (WT) and ERα knockout (ERαKO) C57BL/6 mice underwent standardized 28-min (female) or 15-min (male) warm IRI with clamping of the left renal pedicle and contralateral nephrectomy. BUN was measured daily for 4 days following injury and kidneys were collected for histology after 28 days.

Results: Female ERαKO mice demonstrated significantly diminished survival after renal IRI compared to WT controls with universal lethality from renal failure within 96 hours of the ischemic injury (n=5 per group, $p<0.01$, Fig 1). Male ERαKO mice demonstrated equivalent biochemical renal injury (n=5 per group, $p=0.81$, Fig 2) and fibrosis compared to WT controls.

Figure 1. Survival After 28-min IRI

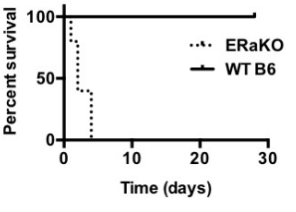
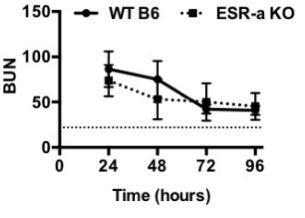


Figure 2. Renal Function after 15 min IRI



Conclusions: Genetic deletion of ERα leads to profound reduction in renal IRI tolerance in female but not male mice. This finding confirms that gender-specific phenotypes in renal IRI arise from both protective actions of estrogens and detrimental effects of androgens and suggests that ERα plays a mechanistic role in female protection. Further investigations are necessary to identify specific actions of ERα responsible for protection and possible avenues to translate the protective action of ERα after renal transplantation and in other clinical scenarios of AKI.

Funding: NIDDK Support

TH-PO101

Influence of Gender and Regulatory T Cells on Acute Aristolochic Acid Nephropathy in Mice Gilbert R. Kinsey, Brian K. Stevens, Mana Yang. *Div of Nephrology and Center for Immunity, Inflammation and Regenerative Medicine, Univ of Virginia.*

Background: Aristolochic acid has been identified as the cause of several outbreaks of ESRD around the world. Clinical studies revealed extensive inflammation in kidneys of patients with aristolochic acid nephropathy (AAN). AAN involves acute toxic injury to tubular epithelial cells that leads to immune cell infiltration and progressive fibrosis over time. Regulatory T cells (Tregs) protect the kidney from acute and chronic disease in other models and we sought to test the role of Tregs in AAN.

Methods: Male and female C57Bl/6 mice were treated with AA 5 – 10 mg/kg/day for 1 to 3 days by i.p. injection. Tregs were partially (~50%) depleted using the anti-IL-2 receptor antibody PC61. Five to 14 days after initiating AA treatment renal function, injury and inflammation were assessed.

Results: Male mice developed dose-dependent renal dysfunction, inflammation and tubular necrosis by day 5, whereas female mice were markedly resistant to renal injury. For example, one dose of 5 mg/kg in males induced consistent kidney injury and dysfunction in males at day 5, whereas 2 doses of 10 mg/kg caused no significant renal injury in females. Renal inflammation at day 5 in males consisted mainly of monocyte/macrophages ($CD11b^{+}F4/80^{int}$) and to a lesser extent neutrophils ($CD11b^{+}SSC^{high}Ly6G^{high}$), with few T or B cells observed. At day 14, a significant increase in the abundance of renal $CD4^{+}$ and $CD8^{+}$ T cells was noted in males ($CD3^{+}CD4^{+}$ T cells per gram: Veh 49,000 ± 22,000; AA 440,000 ± 123,000) . In contrast, AA treatment in female mice did not increase renal immune cells above control levels at 5 or 14 days after AA treatment. Treg depletion in males had no effect on plasma creatinine or BUN levels, but led to elevated tubular necrosis, KIM-1, NGAL, CXCL1 and MCP-1 expression in the kidney compared to non-Treg-depleted mice treated with AA at day 5.

Conclusions: These results demonstrate a significant difference in the acute response to AA between male and female mice. In males, Tregs appear to act as a barrier to kidney damage in the acute phase of this nephrotoxic injury model.

Funding: NIDDK Support

TH-PO102

Gender Differences in Response to Ischemia-Reperfusion as Determined by RNA Sequencing of Pre- and Post-Ischemic Human Kidney Biopsies Hannes Olauson,[1] Johan E. Nordström,[2] Julia Wilflingseder,[1] M. Todd Valerius,[1] Lars Wennberg,[2] Annika Wernerson,[2] Joseph V. Bonventre.[1] *[1]Div of Renal Medicine, Brigham and Women's Hospital, Boston, MA; [2]CLINTEC, Karolinska Inst, Stockholm, Sweden.*

Background: Ischemia-reperfusion injury (IRI) is implicated in many common diseases, including acute kidney injury (AKI). Patients with AKI are seldom biopsied, and most of our knowledge about the kidney's response to ischemia-reperfusion is derived from animal studies.

Methods: Twenty paired kidney biopsies were obtained before and after 3-15 min warm ischemia, 60-120 min cold ischemia and ca 60 min reperfusion during living donor transplantation. Glomeruli were removed and mRNA was extracted from the tubulointerstitial fraction and subjected to RNA Sequencing. Genes with a 2-fold up- or downregulation and a FDR < 0.05 were considered to be differentially expressed.

Results: Histological analysis showed no major differences between pre- and post-ischemic samples. RNA Sequencing, however, revealed a robust tissue response to ischemia-reperfusion, with upregulation of 259 genes, and downregulation of 72 genes. When compared to published datasets, there was a significant overlap with the transcriptional profile in rodents subjected to IRI. Shared pathways included the MAPK pathway and the transcription factors KLF4 and KLF6. Furthermore, we systematically analyzed gender differences between samples. Genes located on the male-specific region of the Y chromosome and their X-linked homologues were differentially expressed and accounted for a large portion of the variability between samples. When these genes were removed from the analysis the gender differences disappeared.

Conclusions: This study demonstrates that RNA Sequencing is a feasible and sensitive method to study genome-wide gene expression changes in kidney biopsies, and establishes living donor transplantation as a suitable human model to study the immediate response to ischemia-reperfusion. Additionally, we demonstrate that differences between genders were largely driven by sex-specific genes, and that the response to ischemia-reperfusion appears similar in men and women when these sex-specific gene expression differences are removed.

Funding: Private Foundation Support

TH-PO103

Age and Sex Dependent HO-1 Expression Regulates Autophagy in Cisplatin Induced AKI Ravindra Boddu,[1] Sunil Rangarajan,[1] Bhuvana Sunil,[1] Lisa M. Curtis.[1,2] *[1]Medicine, Univ of Alabama at Birmingham; [2]Birmingham VA Medical Center, Birmingham, AL.*

Background: Cisplatin (Cp)-induced AKI is a major complication of chemotherapy in patients with solid organ cancers. Previous studies using pharmacological and genetic manipulations in animal models have demonstrated a protective role for heme oxygenase-1 (HO-1), an inducible heme catabolizing enzyme, in Cp-induced AKI, effects that are mediated via anti-oxidant, anti-apoptotic, and anti-inflammatory properties.

Methods: To study the influence of age and sex on HO-1 expression in response to AKI, 4 month (young) and 16-17 month (aging) old male and female C57BL/6 mice were injected with a single intra-peritoneal injection of Cp (20 mg/kg body weight) or saline as control. 1 and 3 days post injections, the kidneys were processed for western blot analyses. Serum creatinine (SCr) was measured by LC-MS/MS. Data and statistical values indicate mean±SEM using one way ANOVA with Tukey's post-test.

Results: SCr values in aging males (3.64±0.40 mg/dL) and females (3.40±0.44 mg/dL) showed worsening of kidney function as compared to the young males (1.69±0.66 mg/dL) and females (0.61±0.12 mg/dL)($p<0.01$ and $p<0.0001$, respectively), after 3 days post Cp injection. Western blot data from kidney lysates indicate that young males had significantly higher HO-1 induction as compared to young females 1 day post Cp injection. Young females and males had significantly higher HO-1 induction as compared to aged females and males, respectively, at 1 day after Cp. 3 days post Cp, in contrast to aging females, HO-1 expression in young females returned to values comparable to baseline saline control treated levels. The increased HO-1 protein levels persisted in young and aging males 3 days after Cp as compared to saline treated control mice. ATG5, a marker of autophagy, was significantly decreased in aging females compared to young females at 3 days post Cp. Levels of p62 were significantly higher in all the aging mice as compared to their younger counterparts after 1 and 3 days of Cp injection.

Conclusions: These results indicate that age and sex influence renal HO-1 expression and alter the autophagy pathway after Cp-induced AKI and may contribute to worse outcomes in this setting.

Funding: VA Support

TH-PO104

Protective Effects of Heme Oxygenase-2 in Ischemic Acute Kidney Injury Karl A. Nath,[1] Joseph P. Grande,[2] John D. Belcher,[5] Anthony J. Croatt,[1] Gianrico Farrugia,[3] Zvonimir S. Katusic,[4] Gregory M. Vercellotti.[5] *[1]Div of Nephrology and Hypertension, Mayo Clinic; [2]Dept of Pathology, Mayo Clinic; [3]Div of Gastroenterology and Hepatology, Mayo Clinic; [4]Dept of Anesthesiology, Mayo Clinic, Rochester, MN; [5]Div of Hematology, Oncology and Transplantation, Univ of MN, Mpls., MN.*

Background: Heme oxygenase (HO) exists as an inducible (HO-1) and a constitutive (HO-2) isoform. HO-1 is widely recognized as a protectant against ischemic and nephrotoxic AKI. Our prior studies demonstrate that HO-2 protects against heme protein-induced AKI. The present study examined whether HO-2 is protective in ischemic AKI.

Methods: Bilateral renal ischemia (15 minutes) was imposed on young (18-19 wk) and old (80-85 wk) $HO\text{-}2^{+/+}$ and $HO\text{-}2^{-/-}$ mice of either gender. Renal function (BUN and serum creatinine) and relevant gene expression were then assessed.

Results: We observed no significant differences in BUN or serum creatinine in young $HO\text{-}2^{+/+}$ and $HO\text{-}2^{-/-}$ mice (either male or female) on days 1 and 2 following ischemic AKI. However, for aged male mice, HO-2 deficiency significantly worsened renal function: BUN on day 1 (73 ± 10 vs 113 ± 6 mg/dl) and day 2 (94 ± 15 vs 156 ± 17 mg/dl); serum creatinine on day 1 (0.9 ± 0.1 vs 1.5 ± 0.2 mg/dl) and day 2 (0.9 ± 0.2 vs 1.9 ± 0.3 mg/dl). No significant differences in function were observed in similarly aged female $HO\text{-}2^{+/+}$ and $HO\text{-}2^{-/-}$ mice. In aged male mice, HO-2 deficiency also significantly increased the upregulation of a number of genes at day 2 after ischemia, including proinflammatory genes which contribute to ischemic AKI, such as CCL2 (9.8 ± 1 vs 18.3 ± 1.8 AU) and IL-6 (18.9 ± 1.6 vs 36.8 ± 8.3 AU).

Conclusions: We conclude that the protective effects of HO-2 in ischemic AKI are evinced in aged male mice and involve, at least in part, suppression of proinflammatory pathways. These effects of HO-2 are not observed in aged female mice, or in young mice of either gender. These studies underscore the exacerbatory effects of age and male gender as determinants of the severity of AKI, and support the recent emphasis that analyses of putative protective and exacerbatory pathways in AKI should accommodate studies of age and gender.

Funding: NIDDK Support

TH-PO105

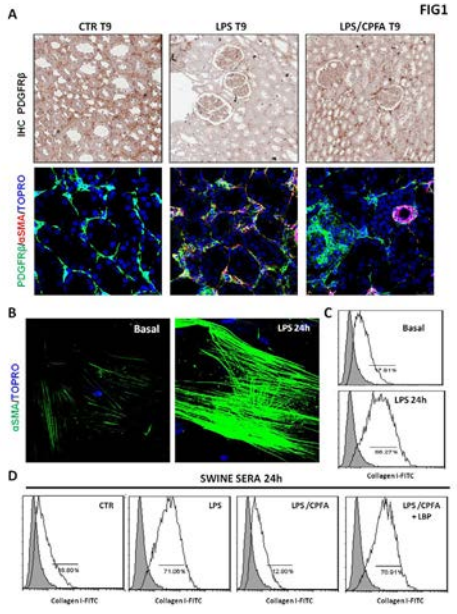
LPS Binding Protein (LBP) Amplifies TLR-4 Signaling and Pericyte (PC) to Myofibroblast Trans-Differentiation (PMT) in LPS-Induced Acute Kidney Injury (AKI) Giuseppe Castellano,[1] Alessandra Stasi,[1] Rossana Franzin,[1] Chiara Divella,[1] Alessandra Spinelli,[1] Margherita Gigante,[1] Paola Pontrelli,[1] Giuseppe Grandaliano,[2] Giovanni B. Pertosa,[1] Loreto Gesualdo.[1] *[1]Univ of Bari; [2]Univ of Foggia.*

Background: During sepsis, serum LBP levels increase and maximize the activation of TLR4-signaling leading to AKI. PC are pivotal in myofibroblasts generation during chronic kidney disease but little is known in AKI.

Methods: AKI was induced by i.v. LPS infusion in 8 pigs (LPS group). After 3h from LPS infusion, 8 pigs were treated with coupled plasma filtration adsorption (CPFA) to remove LBP. Renal biopsies, performed at 9h from LPS infusion (T9), were analyzed by IHC and IF. PC (PDGFRβ+) were stimulated in vitro and analyzed by FACS, IF and WB. Serum LBP and TGFβ were quantified by ELISA.

Results: In endotoxemic pigs, we found the occurrence of acute PMT by reduction of PDGFRβ expression and αSMA increase in peritubular PC (**Fig.1A**, T9LPS vs CTR). CPFA treatment restored PDGFRβ expression and significantly decreased $\alpha SMA^{+}PC$ (**Fig.1A**, T9LPS/CPFA vs T9LPS) in accordance with reduced serum levels of LBP and TGF-β ($p<0.05$). LPS and endotoxemic sera led to PMT in vitro with Collagen I synthesis and αSMA ($p<0.05$) reorganization in contractile fibers (**Fig.1B-C**). The removal of LBP from septic plasma ($p<0.05$) maintained Collagen I and αSMA expression ($p<0.05$) at basal

level. On the contrary, LBP supplementation completely reversed CPFA effects (**Fig.1D**). Finally, LPS induced acute PMT by both canonical TGFβ-Smad2/3 dependent and non-canonical TGF-β-Smad independent signaling (MAPK), by increased phosphorylation of Smad2/3 and ERK1, respectively ($p<0.05$).



Conclusions: PC might be pivotal in the generation of renal myofibroblasts by PMT during AKI upon LPS/TLR4 signaling pathways. Removal of LBP might represent a potential novel strategy to hamper the acute development of renal fibrosis.

TH-PO106

Role of Adenosine 1a Receptor Signaling on GFR Early after the Induction of Sepsis Jonathan Street, Erik H. Koritzinsky, Peter S.T. Yuen, Robert A. Star. *NIDDK, Bethesda, MD.*

Background: Sepsis is a common condition with a high mortality and morbidity. Organ dysfunction, including acute kidney injury (AKI), strongly predicts adverse outcomes. Kidney injury is diagnosed by a reduced glomerular filtration rate (GFR). The mechanisms underlying a reduced GFR are poorly characterized and have been proposed, in part, to be an adaptive, protective response limiting the metabolic demand on the kidney tubules. The extent of reabsorption by the tubules can be sensed at the macula densa, and adenosine 1a receptor (A1aR) signaling reduces GFR via tubuloglomerular feedback (TgF). We tested whether TgF contributes to sepsis-AKI using A1aR knockout mice.

Methods: Cecal ligation and puncture (CLP) was used as a model of sepsis in A1aR knockout (KO) and wild type (WT) littermate control mice. GFR was monitored using a miniaturized fluorimeter on the back of a mouse measuring the plasma disappearance of FITC-Sinistrin. Hemodynamics were monitored in conscious mice using implantable pressure transducer telemetry devices.

Results: In WT, GFR was stable for the first hour following CLP surgery to induce sepsis and then declined rapidly over the next 4 hours. In the KO, GFR was lower immediately following CLP surgery ($p=0.0226$) and declined gradually over the next 4 hours. Mean arterial pressure and heart rate declined during the third and fourth hours, respectively, and were not significantly different between WT and KO. Systemic hemodynamics cannot account for the difference in GFR at 1 hour.

Conclusions: In the absence of A1aR, unexpectedly, GFR began to decrease immediately after CLP surgery. The sudden decrease in GFR in the WT mice 2 hours after surgery occurs before clinical symptoms or hemodynamic changes and does not occur in the A1aR KO mice. GFR may initially be supported by A1aR signaling (GFR is initially higher in WT) and is only later suppressed.

Funding: NIDDK Support

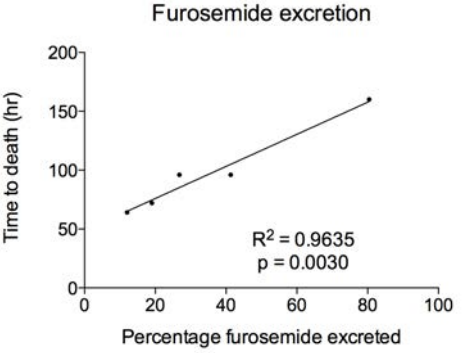
TH-PO107

A Furosemide Excretion Stress Test (FEST) Predicts Mouse Mortality after Sepsis Jonathan Street,[1] Erik H. Koritzinsky,[1] Tiffany R. Bellomo,[1] Hiroshi Kojima,[1] Lakhmir S. Chawla,[2] Peter S.T. Yuen,[1] Robert A. Star.[1] *[1]NIDDK, Bethesda, MD; [2]VA, Washington, DC.*

Background: The furosemide stress test (FST) measures urine production after a furosemide bolus. FST is a sensitive and specific predictor of mortality and a need for renal replacement therapy in the ICU. Furosemide must be actively secreted into the proximal tubule lumen to then inhibit NKCC2 in the thick ascending limb, causing a diuresis. Tubule damage should thus reduce furosemide excretion (FEST) and prevent a subsequent increase in urine volume (FST). As filtration markers have limited predictive value of sepsis mortality in mice, we tested FST and FEST in a murine model of sepsis.

Methods: We developed a sensitive reverse phase HPLC assay for urine furosemide. Male CD-1 mice underwent cecal ligation and puncture (CLP) to induce sepsis. 48 hrs post-CLP 1 mg/kg furosemide was given s.c. and urine was collected for the next 12 hrs to allow for intermittent urination. The mice were monitored every 8 hrs and euthanized if their clinical score exceeded the protocol threshold.

Results: A moderate severity of CLP injury was used; 20 of 32 mice survived to 48 hr and underwent FST/FEST, and 15 mice survived 7 d. Urine production during 12 hr varied from 0.08 to 2.62 ml. Both urine production and the fraction of furosemide recovered in the urine predicted mortality [AUC ROC values of 0.92 ($p<0.01$) and 0.87 ($p<0.05$), respectively]. There was a strong correlation between time to event and fraction of furosemide recovered in the urine among mice that died, $R^2=0.96$ ($p<0.01$).



Conclusions: The furosemide excretion stress test and furosemide stress test strongly predict post-sepsis mortality in mice, allowing for early stratification by severity in future drug studies.

Funding: NIDDK Support

TH-PO108

RIPK3 Is a Mediator of Oxidative Stress, Mitochondrial Dysfunction and Necroptosis in Sepsis-Induced Kidney Injury in Mice Sureshbabu Angara, Oleh M. Akchurin, Sung Il Kim, Augustine M.K. Choi, Mary E. Choi. *Weill Cornell Medicine, New York City, NY.*

Background: Sepsis causes multi organ dysfunction including acute kidney injury (AKI). Recent studies have identified Receptor Interacting Protein Kinase-3 (RIPK3) and Mixed Lineage Kinase domain-Like protein (MLKL) as key mediators of necroptosis.

Methods: We sought to investigate the role of RIPK3 in sepsis-induced AKI using cecal ligation and puncture (CLP) sepsis model in mice.

Results: We showed that RIPK3 deficiency (*Ripk3*$^{-/-}$ mice) significantly decreased intracellular vacuolization and improved brush border in proximal tubular epithelial cells compared to *Ripk3*$^{+/+}$ mice at 24 h CLP. Furthermore, proteinuria and lipocalin-2 (both in urine and serum) induced in *Ripk3*$^{+/+}$ mice at 6 h CLP were significantly reduced in *Ripk3*$^{-/-}$ mice. We showed increased expression of p-RIPK3, RIPK3, p-MLKL and NOX4 upon 6h LPS treatment in human proximal tubular epithelial (HK-2) cells. Pharmacological inhibition of RIPK3 and NOX4 significantly reduced lactate dehydrogenase levels as compared to LPS treatment alone in HK-2 cells. Knock down of RIPK3 by specific siRNA in HK-2 cells decreased expression of NOX4/1 but not NOX2 as compared to scrambled siRNA-treated cells after LPS treatment. Similarly, kidney tissue lysates of *Ripk3*$^{-/-}$ mice showed decreased expression of NOX4 and MLKL as compared to *Ripk3*$^{+/+}$ mice at 6h CLP. Also, elevated mitochondrial DNA levels in the plasma of *Ripk3*$^{+/+}$ mice at 6h CLP were reduced in *Ripk3*$^{-/-}$ mice. Using transmission electron microscopy, we noted increased swelling of intracellular organelles, rupture of outer mitochondrial membrane and poorly defined mitochondrial cristae in proximal tubular epithelial cells of *Ripk3*$^{+/+}$ mice compared to *Ripk3*$^{-/-}$ mice at 24 h CLP. Using immunohistochemistry, we noted decreased nitrotyrosine staining in tubular epithelial cells in *Ripk3*$^{-/-}$ mice compared to *Ripk3*$^{+/+}$ mice at 6h CLP. Furthermore, kidney tissue lysates of *Ripk3*$^{-/-}$ mice showed significantly reduced ROS and MDA levels as compared to *Ripk3*$^{+/+}$ mice at 6h CLP.

Conclusions: Together, our data suggest that RIPK3 acts as mediator of oxidative stress and mitochondrial dysfunction and resultant necroptosis in CLP-induced kidney injury in mice.

TH-PO109

Sphingosine Kinase-2 Inhibitor ABC294640 Attenuates Endotoxin-Induced Acute Kidney Injury Zhi Zhong,[1] Yasodha Krishnasamy,[1] John J. Lemasters,[1] Rick G. Schnellmann.[1,2] *[1]Medical Univ of South Carolina; [2]Ralph H. Johnson VA Medical Center.*

Background: Sepsis is the most common cause of acute kidney injury (AKI), and mortality of septic AKI is up to 70%. Inflammatory responses and mitochondrial dysfunction contribute to septic AKI. ABC294640, a specific sphingosine kinase-2 (SK2) inhibitor, suppresses inflammatory responses in many diseases and prevents mitochondrial dysfunction after hepatic ischemia/reperfusion. The purpose of this study was to examine if ABC294640 decreases endotoxin-induced AKI.

Methods: Mice were treated with lipopolysaccharide (LPS, 10 mg/kg, ip), and ABC294640 (50 mg/kg) was gavaged 2 h later.

Results: At 24 h after LPS treatment, renal pathological changes were mild. Tubular necrosis was absent, but cast formation and inflammatory cell infiltration occurred. TUNEL-positive cells, cleaved caspase-3, and NGAL expression increased, and serum creatinine increased 2.6 folds, indicating LPS-induced AKI. ABC294640 decreased kidney injury and

serum creatinine after LPS treatment. LPS increased NFκB p65 phosphorylation and TLR4 and ICAM-1 expression, indicating increased inflammatory signaling. Myeloperoxidase, F4/80, and CD4, markers of neutrophils, monocyte/macrophages, and T lymphocytes, respectively, also increased, confirming leukocyte infiltration. ABC294640 decreased these inflammatory responses and inflammatory cell infiltration. In control mice by intravital imaging, TMRM fluorescence, a marker of mitochondrial membrane potential, was bright and punctate in tubular cells, indicating mitochondrial polarization. Depolarization occurred in >60% tubular cells after LPS, indicating mitochondrial dysfunction. Reactive nitrogen species are known to cause mitochondrial dysfunction. iNOS expression increased in the kidney after LPS treatment. ABC294640 blunted iNOS expression and mitochondrial depolarization.

Conclusions: SK2 inhibition by ABC294640 attenuates endotoxin-induced AKI, most likely by inhibition of inflammatory responses and prevention of mitochondrial dysfunction.

Funding: NIDDK Support

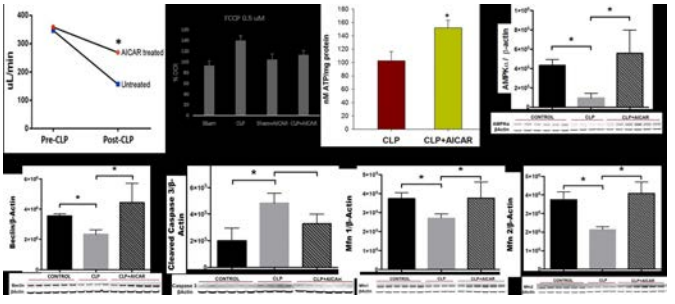
TH-PO110

Protective Role of AMPK in Sepsis-Associated AKI Ying Li, Elanore Hall, Hai Pham, Prabhleen Singh. *Medicine, UC San Diego & VASDHS, San Diego, CA.*

Background: Sepsis-associated acute kidney injury (s-AKI) significantly contributes to morbidity and mortality in critically ill patients. Effective therapeutic strategies for s-AKI are limited due to incomplete understanding its pathogenesis.

Methods: We performed FITC inulin clearance to examine renal function and other functional and molecular analyses to examine mitochondrial dysfunction in the pathogenesis of sepsis using a model of cecal ligation and puncture (CLP) 24 hours post-injury. Mitochondrial function was evaluated in fresh isolated proximal tubules by assessing oxygen consumption rates (OCR) during oxidative phosphorylation with a high-throughput XF96 Seahorse® analyzer.We also evaluated the role of AMPK in mitochondrial function in sAKI.

Results:



At 24 hours post-CLP, GFR was significantly reduced in CLP mice (345±19 vs. 155±35 uL/min; p=0.004). AICAR (AMPK activator) treatment 24 hours prior to CLP significantly improved GFR. CLP mice displayed elevated basal OCR rates, and significantly increased maximal respiratory OCR in the presence of uncoupler, FCCP. This was eliminated by pre-treatment with AICAR. AMPK was decreased in CLP kidney, along with decreased fusion proteins (Mfn1 and Mfn2). Expression of an autophagy protein Beclin was decreased while apoptosis protein cleaved caspase 3 was increased. Pre-treatment with AICAR increased AMPK and ATP levels in CLP kidney and increased fusion and autophagy proteins in the CLP kidney.

Conclusions: Our findings indicate cellular stress with decreased AMPK is associated with abnormal regulation of signaling pathways involving autophagy, apoptosis, mitochondrial function and mitochondrial biogenesis, which may play an important role in the pathogenesis of sepsis associated AKI. AMPK and its signaling pathway may serve as novel therapeutic targets in s-AKI.

Funding: NIDDK Support, VA Support

TH-PO111

Oxidative Stress and HMGB1 Redox during Acute Kidney Injury Wasan Abdulmahdi, Devika Patel, Rahul N. Pawar, Tala F. Azar, Anitsire Collado-Polanco, May M. Rabadi, Brian B. Ratliff. *New York Medical College.*

Background: A common factor in many forms of kidney disease is increase of reactive species of oxygen (ROS) and nitrogen (RNS). Enhanced production of ROS/RNS affects the redox state of molecules such as the alarmin high mobility group box 1 (HMGB1). HMGB1 is released from the kidney following sepsis-induced acute kidney injury (AKI), and can promote repair or damage depending on its redox state. We hypothesize that during sepsis-induced AKI, elevated ROS/RNS cause an imbalance of antioxidants and promote HMGB1 oxidation and its pro-damage effects.

Methods: After injection of either a low or high dose of lipopolysaccharide (LPS) to induce sepsis in mice, kidney samples were fractionated, and the redox of HMGB1 and antioxidant activity measured. Experiments also measured cytokine release in mice plasma after injection of reduced or oxidized HMGB1. In cell culture experiments, endothelial and proximal tubule cells were treated with LPS and glutathione/thioredoxin inhibitors, with subsequent analysis of HMGB1 redox.

Results: High dose LPS enhanced ROS/RNS and blunted thioredoxin activity in the kidney, while lower dose caused less pronounced ROS/RNS increase and enhanced thioredoxin activity. Glutathione activity paralleled thioredoxin, except demonstrated less nuclear activity. High LPS dose enhanced HMGB1 oxidation in the cytoplasm, plasma and especially in the nucleus. Administration of oxidized HMGB1 to healthy mice triggered release of anti-inflammatory cytokines, while reduced HMGB1 stimulated release of reparative anti-inflammatory cyto-/chemokines. In cell culture experiments, glutathione and thioredoxin activity inhibitors augmented HMGB1 oxidation. However, glutathione inhibition was more effective in endothelial cells, while thioredoxin inhibition was more effective in proximal tubular cells.

Conclusions: Low dose LPS upregulated antioxidants, while higher dose enhanced ROS/RNS, increased oxidation of HMGB1, and altered levels of antioxidants which maintain HMGB1 in a reduced state. Release of pro-inflammatory cytokines after injection of oxidized HMGB1 is indicative of the alarmin's role in inflammation, while reduced HMGB1 promotes reparative processes.

TH-PO112

Real-Time Quantification of Temporal and Cell Specific Oxidative Stress in the Ischemic Kidney Tomoaki Miyazaki, Yun-Wei A. Hsu, Neal A. Paragas. *Medicine, Univ of Washington, Seattle, WA.*

Background: A key factor in acute kidney injury (AKI) has been oxidative stress (OS) after the ischemic event. A classic model of AKI is renal ischemia and reperfusion (I/R) which leads to OS due to hypoxia during ischemia and subsequent generation of reactive oxygen species (ROS) during reperfusion. A major ROS is hydrogen peroxide (H202) and excess H202 can be injurious, however to date, there has never been a cell-specific, non-invasive, real-time, and longitudinal method to quantitate this H202 after an acute kidney injury.

Methods: We created the following mice expressing the luciferase (luc) gene in a cell specific manner: Aquaporin2, HoxB7, Podocin, and E2a. Luc cell-specific reporter mice were injured by 30 min bilateral I/R and H202 activity imaged at 3, 6, 12 and 24 hrs after perfusion using an optical imaging system. Using a novel H202 sensitive caged-luciferin substrate, that only releases luciferin to react with luciferase in the presence of H202, we quantified cell specific changes of H202 after I/R.

Results: Aqp2-Luc, HoxB7-Luc, and E2a-Luc H202 activity peaked 6 hours after surgery while Podocin-Luc2 showed increasing H202 activity after 24 hrs. At the peak, E2a-Luc2 mice, the global luciferase expressers, had 10^8 increase in H202-luminescent flux while both Aqp2-Luc2- and HoxB7-Luc2 both had 10^6 increase in H202-luminescent flux. Podocin-Luc2 mice had log orders less increase in H202-luminescent flux within the 24 hr reperfusion period.

Conclusions: For the first time, we demonstrate the feasibility of quantifying kidney ROS non-invasively and longitudinally in the living animal in a cell-type specific manner. These early data reveal that the cells of the nephron and the collecting duct have logarithmic order differences in ROS generation after AKI. Here we prove that the ability to monitor H202 generation non-invasively in a cell-specific manner will permit the identification of cell-types susceptible to OS during an AKI and ultimately lead to mapping the time-course of kidney OS. This is a powerful new system to better understand the pathophysiology of renal disease progression and to test the specificity and efficacy of novel therapeutics.

Funding: NIDDK Support

TH-PO113

Interleukin(IL)-36 Axis Is Modulated in Mice Acute Kidney Injury Model and Human Urine Hirofumi Nishikawa, Naoki Arima, Tatsuki Matsumoto, Yoshiko Shimamura, Kosuke Inoue, Yoshinori Taniguchi, Taro Horino, Shimpei Fujimoto, Yoshio Terada. *Dept of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi Univ, Nankoku, Kochi, Japan.*

Background: IL-36 is a newly named cytokine of the IL-1 cytokine family comprising three members, IL-36α, IL-36β and IL-36γ. All three IL-36 isoforms bind to a heterodimer consisting of IL-36 receptor (IL-36R). IL-36 axis plays roles in inflammation in psoriasis. However, little is known about the role of IL-36 axis in acute kidney injury (AKI) pathogenesis.

Methods: We evaluated the role of IL-36 in renal function in bilateral renal ischemia (28 min)/reperfusion injury (IRI) model using IL-36R knock-out (KO) and wild type (WT) mice. We evaluate the localization of IL-36R in WT mice kidney by confocal microscopy. Plasma was evaluated creatinine (PCr), BUN, IL-6 and kidneys were prepared for histology. Total kidney tissue mRNA was measured by RT-qPCR. The effects of IL-36α on NF-κB and Erk activities were examined in cultured renal tubular cells. In clinical study, we measured urine IL-36α in AKI patients, and immunohistological examination of IL-36α in AKI and minimal change renal biopsy sample.

Results: IL-36R was expressed in mainly proximal tubules in WT mice. IL-36R KO mice had significantly lower PCr (0.41+0.12 versus 1.08 + 0.21 mg/dl), BUN (65.3+14.8 versus 158+31.5 mg/dl) and IL-6 (24.3 + 5.7 versus 39.6+7.9 pg/ml) at 24h after IRI compared to WT. Immunohistological examination showed mild tubular injury in IL36R KO mice compared to WT mice. IL-36α, IL-36β, and IL-36γ expression were up-regulated at 24h post IRI. IL-36α expressions were observed at neutrophil (7/4+) and proximal tubules. IL-6 and TNF-α expressions after AKI were lower in IL36R KO mice compared to WT. In vitro experiments, up-regulation of NF-κB and Erk activity was observed by IL-36α in NRK-52E cells. Urinary IL-36α levels and renal staining of IL-36α were increased in AKI patients (n=7).

Conclusions: These data demonstrate that IL-36 axis plays pathological roles IRI induced mice AKI. IL-36α is up-regulated in renal tissue not only mice AKI but also human AKI. These results indicate that IL-36 blockage could be a potential therapeutic target of AKI.

TH-PO114

Dysregulated Chromogranin A Expression in Acute Kidney Injury
Saiful A. Mir, Jacob Story, Anneke Arlene Stenger, Linda Awdishu, Prabhleen Singh, Ravindra L. Mehta, Sucheta M. Vaingankar. *Medicine, Univ of California at San Diego, La Jolla, CA.*

Background: Chromogranin A (CHGA) is a component of the adrenergic pathway and the index granin protein in dense core vesicles of the adrenal medulla and sympathetic axons. It is co-stored and co-released with catecholamine and is elevated in human hypertension and renal failure. Hypertension is a complication associated with AKI, therefore CHGA expression was investigated in AKI patients. Mouse model over-expressing CHGA was employed to understand the consequence of dysregulated CHGA expression.

Methods: Serum samples from AKI patients and healthy controls were tested for CHGA expression and kidney injury biomarkers by multi-plex and elisa assays. Mouse models 'humanized' for the *CHGA* loci expressing *CHGA* at normal and excess levels were phenotyped for BP and HR by telemetry; eGFR; adrenal ultrastructure and *in vivo* and *in vitro* analysis of dense core vesicles.

Results: Sympathetic over-activity established by higher BP, HR and circulating CHGA accompanied elevated creatinine, albumin, b-2 microglobulin, cystatin C, NGAL, NAG, KIM-1 in AKI patients. Mice mimicking this human phenotype of elevated CHGA, also displayed higher BP and HR contrasting with mice expressing normal levels of CHGA. The adrenal medullary cells of mice expressing excess CHGA showed an increase in total number and size of vesicles and mitochondrial abundance. This resulted in elevated expression of electron transport chain enzymes but surprisingly 2-fold decrease in ATP. This was delineated to be due to higher expression of mitochondrial uncoupling protein 2 (UCP2). This was recapitulated *in vitro* in which, CHGA overexpression in the PC12 cell line, caused upregulation of UCP2.

Conclusions: CHGA the catecholamine storage protein is elevated in the circulation of AKI patients and has predictive potential for consideration as a biomarker for the disease. The physiological consequences of elevated CHGA is increased adrenergic tone in humans and mice. We hypothesize that elevated CHGA disrupts mitochondrial electron transport chain causing ATP decline through the upregulation of UCP2 protein.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-PO115

JNK Signaling in the Proximal Tubule Is Critical for Renal Ischaemia Reperfusion Injury
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Background: Activation of the JNK signalling pathway in tubular epithelial cells is evident in most forms of acute and progressive renal injury, including renal I/R injury. However, the specific contribution of tubular JNK signalling in kidney disease remains to be established. Kidney cells express the two main JNK isoforms (Jnk1 and Jnk2), with considerable redundancy. We created mice lacking the *Jnk1* gene in proximal tubules (via gamma-glutamyl transpeptidase Cre) with global *Jnk2* gene deletion (termed Jnk^{PT}). These mice are viable with normal kidney structure and function but lack JNK expression in the S3 segment of the proximal tubule.

Methods: Bilateral warm I/R injury was induced in groups (n=8) of; Jnk^{PT}, $Jnk2^{-/-}$, and wild type (WT) mice. Mice were killed 24hr after I/R surgery. Controls underwent sham surgery.

Results: Renal I/R injury caused acute renal failure in both WT and $Jnk2^{-/-}$ mice (178±6 and 170±23 umol/L serum creatinine, respectively; both $P<0.001$ vs 12±4 umol/L in sham operated). In contrast, Jnk^{PT} mice undergoing I/R showed marked protection from renal failure (61±21 umol/L; $P<0.01$ vs other I/R groups). This protection was associated with reduced tubular damage [79±3% WT, 75±4% $Jnk2^{-/-}$, 61±8% Jnk^{PT}; $P<0.01$ vs other I/R groups and a 35% reduction in KIM-1 mRNA levels in JNK^{PT} vs other I/R groups; $p<0.05$]. A 60% reduction in infiltrating neutrophils and a 40% reduction in macrophages was evident in JNK^{PT} vs other I/R groups ($p<0.01$). Up-regulation of mRNA levels for pro-inflammatory molecules (CCL2, NOS2, IL-6) was substantially reduced in JNK^{PT} vs other I/R groups ($p<0.05$).

Conclusions: This study establishes that JNK signalling in proximal tubular epithelial cells plays a critical role in cell damage and renal dysfunction in acute I/R injury.

Funding: Government Support - Non-U.S.

TH-PO116

P2X7 Receptor Activation Induces Renal Tubular PAD4 to Exacerbate Ischemic AKI
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Background: Acute kidney injury (AKI) due to ischemia and reperfusion (IR) is a major clinical problem without effective therapy. We recently demonstrated that peptidylarginine deiminase-4 (PAD4) is induced after renal IR to exacerbate ischemic AKI. Moreover, ATP is a recently recognized DAMP molecule and exacerbates ischemic AKI via P2X7 purinergic receptor (P2X7R) activation. Here, we tested the hypothesis that ATP released from necrotic kidney cells activates P2X7R to induce renal tubular PAD4.

Methods: To test whether ATP induces renal tubular PAD4, cultured mouse or human proximal tubule cells were treated with vehicle, with 0.5-1mM ATP or with 100-500μM ATPγS for 1-24hr. To determine whether P2X7R is involved in ATP-mediated PAD4 induction, some proximal tubule cells were pretreated with 20μM A804598 (a selective P2X7R antagonist) before ATP treatment or treated with 50μM BzATP (a selective P2X7R agonist) in lieu of ATP. To determine whether P2X7R activation directly exacerbates ischemic AKI by inducing PAD4, PAD4 WT or PAD4 KO mice were pretreated with 5mg/kg BzATP or with vehicle 24 hr prior to 20 min renal IR injury.

Results: ATP and ATPγS induced PAD4 expression and activity in mouse and human renal proximal tubule cells. Implicating a critical role for P2X7R activation, A804598 blocked and BzATP mimicked the ATP-mediated induction of renal tubular PAD4, respectively. Consistent our *in vitro* findings, BzATP significantly increased mouse kidney PAD4 expression and activity *in vivo*. Supporting a critical role for PAD4 in ischemic AKI, PAD4 KO mice were protected against ischemic AKI (Cr(mg/dL)=0.6±0.1, N=5) when compared to PAD4 WT mice (Cr=1.4±0.2, N=5). Finally, supporting a critical role for P2X7R-mediated induction of PAD4 in the pathogenesis of ischemic AKI, pretreatment with a selective P2X7R agonist BzATP exacerbated ischemic AKI in PAD4 WT mice (Cr=2.4±0.3, N=5) but not in PAD4 KO mice (Cr=0.7±0.2, N=5).

Conclusions: Taken together, our studies show that ATP via P2X7R activation induces renal tubular PAD4 *in vitro* and *in vivo*. We also show here a critical role for P2X7R-mediated exacerbation of ischemic AKI via induction of PAD4.

Funding: NIDDK Support, Other NIH Support - NIGMS

TH-PO117

Benefit of Mineralocorticoid Receptor Antagonism in Acute Kidney Injury (AKI): Role of Smooth Muscle Rac1
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Background: Renal ischemia/reperfusion (IR) is a major cause of AKI. The benefit of novel non-steroidal MR antagonists such as finerenone in the IR context has not been evaluated and the mechanisms underlying the benefit of MR antagonism remain unclear. Here we tested the efficacy of finerenone in ischemic AKI and to evaluate the specific contribution of the MR expressed in endothelial or smooth muscle cell (SMC) in renal IR injury.

Methods: We included 18 male C57/B6 mice that were divided in: sham, renal ischemia for 20 min and IR plus treatment with finerenone (10 mg/kg) by gavage once a day at -48, -24 and -1 h before IR. Alternatively, MR inactivation in endothelial cells (MR^{endoKO} mice / Vecadh-cre) or in smooth muscle cells (MR^{SMCKO} mice/SMA-cre) was induced in 3-month-old mice. Sham surgery or bilateral renal IR for 20 min was performed and mice were studied 24 h after reperfusion. Primary rat SMC cultures were used to assess the signaling pathways modulated by MR.

Results: In C57/B6 WT, $MR^{fl/fl}$ and MR^{endoKO} mice, IR induced kidney dysfunction and tubular injury. After IR, Finerenone-treated mice and the MR^{SMCKO} mice presented normal renal function and a significant reduction of histological alterations, while MR^{endoKO} mice were not protected. The benefit of finerenone and MR KO in SMC was associated with reduced oxidative stress-mediated lipid peroxidation as compared to $MR^{fl/fl}$ or WT mice. In aldosterone-stimulated rat SMC, we observed a 100% increase in hydrogen peroxide production and a 2-fold increase in Rac1 activity; MR and Rac1 antagonism blunted these effects. Moreover, mice deficient of Rac1 in SMC were also protected against ischemic AKI.

Conclusions: Finerenone limits renal injury induced by IR. Moreover, genetic deletion of MR in SMC only has similar effects. This benefit was associated with reduced oxidative stress, by affecting oxidative stress production via SMC Rac1.

Funding: Pharmaceutical Company Support - BAYER Pharma AG, Government Support - Non-U.S.

TH-PO118

Renal Afferent Neurons Are Altered by Lipopolysaccharides
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Background: Sympathetic renal nerve activity (RSNA) is increased in lipopolysaccharide (LPS)-induced SIRS probably due to altered properties of renal afferent nerves (RANs), which exert complex sympatho-modulatory and paracrine effects. We tested the hypotheses that LPS alters the firing patterns and acid dependant inward currents in cultured renal neurons as well as CGRP release from afferent renal nerves.

Methods: In rats treated with LPS (E.coli O127/B8,20mg/kg iv) blood pressure (BP), heart rate (HR)and RSNA were measured. Dorsal root ganglion neurons (Th11-L2) of rats with renal afferents were cultivated and incubated with LPS 12h before patch clamp recordings. Inward currents were assessed during neuronal stimulation with protons (pH 6,9 and 5,0). Current clamp recordings were also done after 12h LPS-incubation and in controls. Neurons were characterized as tonic, i.e. sustained AP firing or phasic, i.e.<5 APs in response to current injections. In an organ bath of kidney slices (with/without LPS) Capsaicin, a TRPV1 receptor agonist, was used to induce CGRP release.

Results: LPS induced high increases of RSNA (+250%, $p<0.05$) and HR (+25%, $p<0.05$), BP remained unchanged. Under control conditions, acidic superfusion of 246 renal neurons was followed in 59% by tonic firing patterns, a portion that were significantly reduced to 49 % after LPS exposure ($p<0,05$) suggesting altered sympathetic control by renal afferents in vivo. LPS exposure significantly increased acid dependant inward currents in renal neurons (-793,18+/-66pA vs.-1224+/-200pA,$p<0,05$) putatively involved in paracrine functions of neurons. Neurogenic CGRP release from kidney slices due to capsaicin was significantly increased after LPS incubation (LPS: 58+20 pg/ml, control: 14+2, $*p<0.05$).

Conclusions: LPS significantly decreased the ease of AP production of renal neurons while the responsiveness to acidic milieu was increased. Neurogenic renal CGRP release was also increased by LPS. These finding may contribute to the complex sympatho-paracrine alterations seen in SIRS affecting kidney and the cardiovascular system.

Funding: Other NIH Support - Deutsche Forschungsgemeinschaft

TH-PO119

Resolvin D1 Modulates Renal Cell Apoptosis in Lipopolysaccharide-Related Acute Kidney Injury Yuliang Zhao, Ping Fu. *Nephrology, West China Hospital, Chengdu, Sichuan, China.*

Background: Resolvin D1 (RvD1) is a newly found anti-inflammatory bioactive compound derived from polyunsaturated fatty acids. Our previous research revealed a renal protective effect on Lipopolysaccharide (LPS) -related AKI of RvD1 by down-regulating NF-κB signaling pathway. The current study aims to observe the influence of RvD1 on renal cell apoptosis during LPS-related AKI *in vivo* and *in vitro*.

Methods: Male BALB/c mice and human proximal tubule epithelial cells (HK-2) were randomly divided into control group (saline), LPS group (LPS) and RvD1 group (LPS+ RvD1) and blockage group (LPS+ RvD1+Boc-MLP). Boc-MLP is a RvD1 receptor blocker. The drugs were intraperitoneally injected or added into culture medium at targeted concentrations. The mice kidneys and HK-2 cells were harvested at different time points respectively.

Results: In *in vivo* experiment, RvD1 inhibited the up-regulation of Bax/Bcl-2 mRNA ratio by LPS, which was mitigated in blockage group. LPS activated the expression of Caspase-3 mRNA in mice kidney, but RvD1 inhibited its activation. TUNEL staining indicated RvD1 suppressed cell apoptosis in mice kidney. In *in vitro* study, RvD1 was effective in down-regulating Caspase-3 mRNA expression in renal tubular epithelial cells. Interestingly, RvD1 also increased Bax/Bcl-2 mRNA ratio. Flow cytometry recorded a higher proportion of apoptosis in RvD1 group than in LPS group (P=0.002) and control group (P<0.001)(figure 1).

Conclusions: In LPS-related AKI, the effect of RvD1 on renal cell apoptosis is complex. RvD1 imposed a pro-apoptotic influence directly on tubular epithelial *in vitro*, while showing a general anti-apoptotic effect *in vivo. T*he underlying mechanism needs further research.

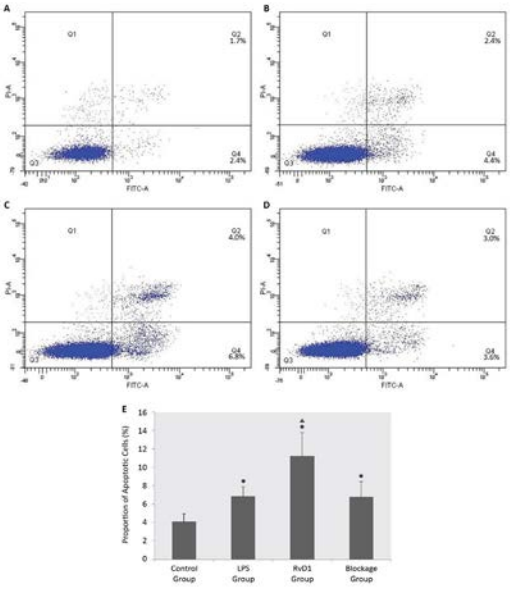


Figure 1. flow cytometry of HK-2 cell apoptosis (A: control group; B: LPS group; C: RvD1 group; D: blockage group; *indicates P<0.05 compared with control group; Δindicates P<0.05 compared with LPS group; time point: 24h).

TH-PO120

Shikonin Elicits a Nephropreventive Effect in a Murine Model of LPS-Induced Septic AKI by Triggering Nrf2 Activation with Anti-Oxidative Responses Go Yoneda,[1] Madoka Kawara,[1] Yuko Yamamoto,[1] Rika Matsunaga,[1] Hirofumi Jono,[1,2] Hideyuki Saito.[1,2] *[1]Dept of Clinical Pharmaceutical Sciences, Kumamoto Univ Graduate School of Pharmaceutical Sciences, Kumamoto, Japan; [2]Dept of Pharmacy, Kumamoto Univ Hospital, Kumamoto, Japan.*

Background: Sepsis-induced AKI is developed frequently in the patients with decreased immunocompetence, resulting in severe renal failure. For the effective treatment of septic AKI, infusion therapy and/or anti-inflammatory treatments are provided, however, the efficacy is insufficient to reach recovery of survival rates, requiring development of therapeutics. Shikonin is a naturally occurring herbal medicine extracted from the red-root gromwell, possessing proteasome inhibition and antioxidant effects. The present study explored a preventive effect of shikonin against LPS-induced septic AKI and its molecular events.

Methods: Septic AKI was induced in C57BL mice with intraperitoneally administration of LPS (20 mg/kg). Shikonin (5 mg/kg) was administered intraperitoneally to mice 1 h before the LPS treatment. Development of AKI, Nrf2 expression and anti-oxidant responses (HO-1 and NQO1) in LPS-treated mice with or without shikonin were compared 48 hr after the treatment.

Results: Survival rates of LPS-treated mice and LPS & shikonin-treated mice were 36 and 82%, respectively. Histochemical examination revealed that glomerular and tubular injuries in LPS-mice was partially restored by shikonin treatment. Serum levels of creatinine (SCr), BUN, IL-6 and TNF-α were markedly elevated in LPS-mice. Shikonin treatment resulted in significant decreases in the elevated SCr (P<0.05), BUN (P<0.05), and serum levels of IL-6 (P<0.01) and TNF-α (P<0.01). Shikonin significantly suppressed serum hydroperoxide and malondialdehyde levels evoked by LPS treatment. Shikonin treatment induced a marked expression of Nrf2 protein in the nuclear fraction of kidney, which was associated with a significant induction of mRNA expressions of HO-1 (P<0.01) and NQO1 (P<0.01) in LPS-mice kidney.

Conclusions: These results suggested that shikonin could have a renopreventive potency against septic AKI, at least in part, through the transient activation of renal Nrf2 followed by the downstream antioxidant responses.

Funding: Government Support - Non-U.S.

TH-PO121

Paricalcitol Pretreatment Attenuates Lipopolysaccharide-Induced Inflammation in Human Renal Proximal Tubule Cells through the EP4 Receptor Yu Ah Hong, Yoon-Kyung Chang, Cheol Whee Park, Chul Woo Yang, Suk Young Kim, Hyeon Seok Hwang. *Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Republic of Korea.*

Background: Paricalcitol is thought to exert protective effects on various renal diseases, but the underlying molecular mechanism remains unclear. We investigated whether paricalcitol attenuates renal proximal tubule cell injury after lipopolysaccharide (LPS)-exposure, and evaluate the prostaglandin E_2 receptor (PGE_2) EP4 pathway as an anti-inflammatory mechanism of paricalcitol.

Methods: Human renal tubular epithelial cells (HK-2 cells) were exposed to LPS with or without paricalcitol pretreatment. The effects of paricalcitol and its protective mechanisms were investigated using EP4 antagonist or small interfering RNA EP4.

Results: Paricalcitol pretreatment significantly increased the expression of vitamin D receptor and cyclooxygenase-2 in LPS-exposed HK-2 cells. The PGE2 and cellular membrane expression of EP4 was increased in paricaliol-treated cells. Paricalcitol prevented cell death induced by LPS exposure, and the co-treatment of EP4 antagonist offset these cell-protective effects. The phosphorylation and nuclear translocation of p65 nuclear factor-κB (NF-κB) were decreased in LPS-exposed cells with paricalcitol pretreatment. EP4 antagonist and EP4 siRNA reversed the inhibitory effects of paricalcitol on p65 NF-κB nuclear translocation.The production of regulated upon activation normal T cell expressed and secreted (RANTES), tumor necrosis factor-a (TNF-a), interleukin-1b (IL-1b), interferon-g (IFN-γ), and macrophage inflammatory protein-1a (MIP-1a) were attenuated by paricalcitol pretreatment in LPS-exposed HK-2 cells. The co-treatment with EP4 antagonist abolished all of these suppressive effects on inflammatory cytokine productions.

Conclusions: Paricalcitol prevents LPS-induced renal proximal tubule cell injury, and EP4-dependent pathway isone of the anti-inflammatory mechanisms of paricalcitol.

TH-PO122

Curcumin Therapy Attenuates the Severity of Acute Kidney Injury in a Mouse Model of Hepatorenal Syndrome Type 1 Sindhura Bobba, Manoj Das, Siddhartha S. Ghosh, Todd W. Gehr, Daniel E. Carl. *Div of Nephrology, Virginia Commonwealth Univ Health System, Richmond, VA.*

Background: Hepatorenal syndrome (HRS) type 1 is a life threatening complication of cirrhosis with limited therapeutic options. We hypothesized that Curcumin will attenuate severity of HRS by improving intestinal barrier function, via tight junctions (TJ). We tested this hypothesis in a mouse model of HRS. TJ proteins, such as Zonula occludens protein-1 (ZO-1), are responsible for restricting the paracellular movement of compounds across the intestinal mucosa. Therefore, impaired intestinal barrier function can result from decreased TJ protein expression.

Methods: C57BL/6 mice received 1ml/kg of carbon tetrachloride (CCl4) biweekly for 12 weeks to induce cirrhosis. A 6 mg/Kg of Lipopolysaccharide (LPS) was given intraperitoneally to induce acute kidney injury by simulating the inflammatory stressor caused by acute infection. Curcumin 100mg/ kg body weight was co-administered with CCL4 for 4 weeks. Four mouse populations were studied: (1) control mice (2) CCl4 treated mice (3) CCl4 + LPS mice (4) CCl4+LPS+curcumin mice (N=4 per group). Urine output, urinary sodium, and serum creatinine (SCr) were measured 10 hrs after LPS. Mice intestines were homogenized, and ZO-1 expression determined by western blot.

Results: Control and CCl4 treated mice showed no change in renal function. CCL4+LPS treated mice had renal phenotype suggestive of HRS, including a higher SCr, lower UNa and UOP compared to CCL4 mice (p<0.05). Moreover, CCl4+LPS+curcumin treated mice had a significant improvement in renal function (p<0.05) compared with CCl4+LPS mice. ZO-1 protein expression was significantly low (p<0.05) in both CCL4 and CCL4+ LPS groups compared with control. ZO-1 expression was significantly increased (p<0.05) in CC4+LPS+ curcumin mice compared to CCL4+LPS.

Conclusions: CCL4 induced cirrhotic and in CCL4+LPS (HRS) mice have decreased ZO-1 protein expression compared to controls. Curcumin administration attenuates the severity of AKI in this mouse model of HRS. Moreover, the expression of ZO-1 protein was increased in this cohort of mice, suggesting improved intestinal barrier function compared to cirrhotic and HRS mice.

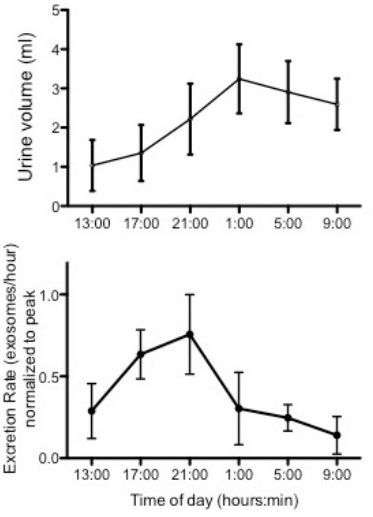
TH-PO123

Urine Exosome Excretion Varies Diurnally in Rats Erik H. Koritzinsky, Jonathan Street, Robert A. Star, Peter S.T. Yuen. *NIDDK, Bethesda, MD.*

Background: Urine exosomes are a promising source of non-invasive biomarkers for kidney health. Kidney transport and function have circadian patterns. Normalization by urine creatinine is thought to account for most physiologic diurnal variation in kidney function, allowing for diagnosis using a spot urine collection rather than a timed 24 hr collection. It is unknown if urine exosome excretion similarly varies throughout the day in normal animals.

Methods: Timed 4-hour urine collections were obtained from healthy, untreated male SD rats over a 24 hour period with free access to food and water and housed in a facility with a 24 hr light/dark cycle [Light: 6AM – 6PM; Dark: 6PM – 6AM]. Exosomes were isolated from 4 hr urine fractions by ultracentrifugation. Quantification of exosome concentration (number/mL) was assessed by Nanosight analysis. Because of variability in total 24 hr urine exosome excretion rate between animals, hourly exosome excretion rates for each 4-hour fraction were normalized to peak exosome excretion in each animal.

Results: The normalized urine exosome excretion rate increased during the light period, peaking at the start of the dark period, then subsequently fell during the dark period. The observed circadian pattern of exosome excretion did not temporally correspond to that of urine flow rate. The relative amplitude of the variation (peak to trough ratio) was 5.4-fold for exosome excretion and 3.85-fold for urine flow.



Conclusions: Urine exosome excretion in rats displayed a circadian pattern that was not directly linked to that of urine flow. Because of a large daily variation in normal urine exosome excretion rates, the time urine of collection must be considered. Prospective urine exosomal biomarkers should be evaluated for circadian rhythms. As exosomes serve as a form of cell-cell communication in other contexts, the functional significance of this circadian pattern in urine exosome excretion is unknown.

Funding: NIDDK Support

TH-PO124

Enrichment of miR192 in Urinary Exosomes following Ischemia-Reperfusion Injury in Rats Erik H. Koritzinsky, Jonathan Street, Tiffany R. Bellomo, Hua Zhou, Robert A. Star, Peter S.T. Yuen. *NIDDK, Bethesda, MD.*

Background: We previously identified urine exosomal miR192 as a candidate biomarker for renal ischemia-reperfusion injury in rats (Zhou et al, ASN 2008). Two hypotheses arose from these observations: a) the number of exosomes were increasing with a constant abundance of miR192 or b) the number of exosomes was relatively unchanged with an increased abundance of miR192 per exosome. We used Nanosight analysis to determine exosome number, and then measured the temporal excretion of exosomes by collecting timed urine fractions.

Methods: Male Sprague-Dawley rats (250-290 g) underwent bilateral ischemia-reperfusion injury (IRI) with a 40 minute clamp. Acute kidney injury was confirmed by a rise in BUN 24 hours after surgery. Urine was collected in metabolic cages for 24 hours before (baseline) and immediately following IRI surgery. Six 4-hour urine samples were collected by an automated fraction collector. Urinary exosomes were isolated by ultracentrifugation. After isolation of miRNA by miRNeasy, the absolute concentration of miR192 was determined by RT-qPCR using purified, synthetic miR192. The concentration of exosomes was determined by Nanosight analysis.

Results: Exosomal excretion rate varied from 6.89 x 10^9 to 1.04 x 10^{11} exosomes per hour and was not significantly different between baseline and post-AKI, nor across the 24 hour period. Similarly, miR192 excretion rate was not significantly different between baseline and AKI, nor across the 24 hour period. However, the number of miR192 molecules per exosome increased at the earliest time point, and persisted throughout the 24 hr period ($p<0.05$). The average number of miR192 molecules/exosome over the 24 hour collection after ischemia-reperfusion was 62-fold higher than baseline ($p<0.05$).

Conclusions: Ischemia-reperfusion injury does not significantly change exosome excretion rates, nor does it significantly change the excretion of miR192; however, the abundance of miR192 per exosome increases 62-fold, consistent with an enrichment of miR192 within urinary exosomes.

Funding: NIDDK Support

TH-PO125

Stoichiometry of the Protein TSG101 in Urine Exosomes Erik H. Koritzinsky,[1] Jonathan Street,[1] Tiffany R. Bellomo,[1] Angel M. Aponte,[2] Robert A. Star,[1] Peter S.T. Yuen.[1] *[1]NIDDK, Bethesda, MD; [2]NHLBI, Bethesda, MD.*

Background: Novel biomarkers for kidney health, including miRNAs, have been identified in urine exosomes. Surprisingly, miRNAs are stoichastically present in a small fraction of biofluid-derived exosomes (≤1%), making miRNA unsuitable to normalize exosomal biomarkers. As TSG101 is a protein in the ESCRT complex involved in exosome biogenesis, it is assumed to be present in exosomes in high copy number, and thus is commonly used as a surrogate marker for exosome number. However, the number of molecules of TSG101 per exosome is not known, nor is it known to be constant.

Methods: Spot urine samples were obtained from 7 healthy volunteers (3 M, 4 F; Age 21-55) then treated with protease inhibitors. Urine exosomes were isolated by ultracentrifugation. Absolute quantification of molecules of exosomal TSG101/mL was assessed by Western blot using a 4 point dilution series (standard and samples) with a TSG101 standard of known concentration. Quantification of exosome concentration (number/mL) was assessed by Nanosight Nanoparticle Tracking Analysis.

Results: In 7 healthy adults, values ranged from 4.39x10^9 to 7.87x10^{10} exosomes/mL urine and 3.37x10^{10} to 1.08x10^{12} exosomal TSG101 molecules/mL urine. The stoichiometry of molecules of TSG101 per exosome in urine averaged 10.2 ± 4.0 (SD) copies per urine exosome (range of 5.2 to 15.8).

[Exosome] (number/mL urine)	[Exosomal TSG101] (molecules/mL urine)	TSG101 Molecules/Exosome
7.67 x 10^{10}	1.08 x 10^{12}	13.4
7.87 x 10^{10}	4.34 x 10^{11}	5.2
4.06 x 10^{10}	4.72 x 10^{11}	11.8
2.40 x 10^{10}	1.93 x 10^{11}	6.9
4.39 x 10^{9}	3.37 x 10^{10}	6.6
1.07 x 10^{10}	1.45 x 10^{11}	15.8
1.94 x 10^{10}	2.02 x 10^{11}	11.3

Conclusions: Exosome concentration and TSG101 concentration varied 18-fold and 32-fold from person to person, but the stoichiometry of TSG101 per urine exosome was relatively stable across healthy human subjects. There were ~10 TSG101 molecules/urine exosome. TSG101 may be a valid surrogate for exosome number to normalize urine exosomal biomarkers. Normalization using TSG101 is easier and less costly than Nanosight analysis, and easier to interpret than normalization using miRNA.

Funding: NIDDK Support

TH-PO126

Urinary Activin A: A Novel Urinary Biomarker for Acute Kidney Injury Shunsuke Takahashi, Akito Maeshima, Yoshinori Takei, Masao Nakasatomi, Hidekazu Ikeuchi, Toru Sakairi, Yoriaki Kaneko, Keiju Hiromura, Yoshihisa Nojima. *Dept of Medicine and Clinical Science, Gunma Univ Graduate School of Medicine, Maebashi, Gunma, Japan.*

Background: Activin A, a member of TGF-β superfamily, is known to regulate cell growth and differentiation in various tissues. We previously reported that activin A, which was absent in normal kidney, was increased in the post-ischemic rat kidney and negatively regulates the repair process of renal tubules after injury (Maeshima et al. JASN 2001). This study was conducted to examine whether activin A can be detected in the urine from mice with renal ischemia-reperfusion injury and patients with acute kidney injury (AKI).

Methods: Ischemia-reperfusion injury was induced in C57BL/6 mice. Mice were sacrificed at 6, 24, 48, 72, 120 hours after operation, and the kidneys and urine were collected for analysis. Urine samples were collected from ten patients with AKI as well as from eight healthy volunteers. Urinary activin A was measured by ELISA. Correlation of urinary activin A with urinary N-gal, urinary KIM-1, and clinical parameters were analyzed.

Results: The expression of activin A was markedly up-regulated in the post-ischemic mouse kidney. Immunoreactive activin A was detected in KIM-1-positive proximal tubular cells of the outer medulla in ischemic kidneys, but not in normal kidneys. Activin A was absent in the urine of normal mice. In contrast, activin A was detectable in the urine of ischemic mice. Urinary activin A was almost undetectable in healthy volunteers, but was significantly increased in patients with AKI (9.6 ± 2.3 vs. 257.9 ± 174.6 ng/gCr, $p<0.001$). There was a significant correlation of urinary activin A level with urinary N-gal and follistatin (activin antagonist), but not with urinary KIM-1 or eGFR.

Conclusions: Activin A can be detected in the urine of patients with ATN and may serve as a useful biomarker for renal proximal tubule injury.

Funding: Pharmaceutical Company Support - Astellas Pharma Inc.

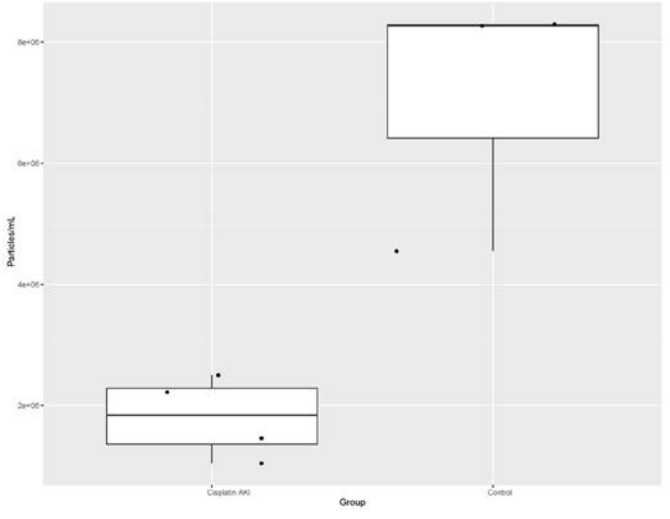
TH-PO127

Profile of Urinary Microparticles in Cisplatin Nephrotoxicity in Mice Gabor Bodonyi-Kovacs, Christine Rudy, Thu H. Le, Uta Erdbruegger. *Renal Div, Univ of Virginia, Charlottesville, VA.*

Background: Acute kidney injury (AKI) is associated with increased mortality and risk of progression to chronic kidney disease. Its diagnosis is based on rising levels of serum creatinine - a late and nonspecific marker of reduced kidney function. Urinary microparticles (uMP) are candidate biomarkers for earlier and non-invasive diagnosis and prognosis of AKI. We hypothesized that a distinct uMP profile characterizes cisplatin-induced AKI.

Methods: 11-19 week old 129S6 male mice received either ip. injection of 25 mg/kg cisplatin or equal volume of saline. Serum and urine were collected 72 hours later. Serum creatinine was measured using an enzymatic, colorimetric kit (Crystal Chem). Urine was frozen and stored in -80 C. A uMP pellet was generated from thawed urine with differential centrifugation. Enumeration and phenotyping of uMPs was performed with imaging flowcytometry using the following markers: podocalyxin (podocyte derived), Insulin-like growth factor-binding protein 7 (IGFBP7, inducer of G1 cell cycle arrest, implicated in AKI), collectrin (tubular cell marker) and Annexin V. Results were analyzed by a two sided t-test.

Results: The cisplatin treated mice had significantly elevated serum creatinine (n=4, 2.35 ± 0.54 mg/dl) compared to saline treated controls (n=4, 0.1 ± 0.07 mg/dl), p=0.003. Animals with AKI had lower level of IGFBP7 positive microparticles compared to controls, 1.8 x 10^6 and 7 x 10^6 particles per ml respectively, (p=0.044), Figure 1.



Urinary concentrations of MPs stained with other markers were not statistically different between AKI and control groups.

Conclusions: Severe cisplatin induced AKI is associated with significantly lower IGFBP7 positive uMP levels. Future studies are needed to examine the diagnostic role of these vesicles in earlier stages of AKI and assess their potential mechanistic and prognostic roles.

Funding: NIDDK Support

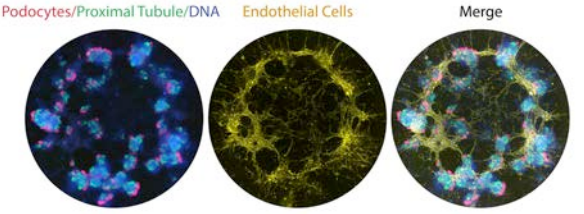
TH-PO128

Differentiation of Human Kidney Organoids in High Throughput-Compatible Formats Modeling Nephrotoxic Injury Stefan Czerniecki, Ramila E. Gulieva, Laura V. Islas, Yong Kyun Kim, Neal A. Paragas, Benjamin S. Freedman. *Div of Nephrology, Kidney Research Inst, and Inst for Stem Cell and Regenerative Medicine, Dept of Medicine, Univ of Washington, Seattle, WA.*

Background: Kidney organoids derived from human pluripotent stem cells (hPSCs) are a potentially powerful tool for high throughput discovery, but their complexity poses a challenge for miniaturization and automation. We tested whether kidney organoids could be generated in high throughput formats for modeling nephrotoxicity.

Methods: hPSCs were seeded and differentiated in 96-well and 384-well plates both 1) manually, using multi-channel pipettors, and 2) automatically, using liquid handling robots to perform all steps. Kidney markers were characterized by high content imaging analysis, compared to kidney tissue sections. Injury biomarker induction was monitored in cisplatin-treated organoids by ELISA and immunofluorescence.

Results: Differentiation was robustly achieved in 96-well and 384-well formats with several hPSC lines using both manual and fully-automated protocols. Each 384-well contained ~ 30 miniature kidney organoids (~ 300 organoids/cm^2). Analysis of > 20 tubular and podocyte markers revealed transporters and nephron sublineages similar to developing kidneys. Cisplatin treatment induced 4-fold upregulation of kidney injury molecule 1 (KIM-1) in proximal tubules, using a high throughput-compatible assay.



Conclusions: hPSC-derived kidney organoids can be generated and analyzed in fully-automated, high throughput-compatible formats. Miniaturized cultures retain sufficient complexity to model nephrotoxicity in proximal tubules. High throughput compatibility, coupled with human specificity, makes this platform an attractive starting point for screening approaches focusing on therapeutic discovery, toxicology, and regenerative medicine. (Supported by Northwest Kidney Centers)

Funding: NIDDK Support, Pharmaceutical Company Support - Northwest Kidney Centers (Unrestricted Gift), Private Foundation Support

TH-PO129

Probiotics Attenuate Progression of CKD via Expanding Tregs in Mesenteric Lymph Node Sang-Kyung Jo, Jihyun Yang, Sung Yoon Lim, Young Ju Na, Myung-Gyu Kim, Won-Yong Cho. *Dept of Internal Medicine, Div of Nephrology, Korea Univ Medical College, Seoul, Republic of Korea.*

Background: Emerging evidence showed the presence of kidney-gut crosstalk and alterations in intestinal barrier or dysbiotic gut microbiota have been demonstrated in diverse pathological processes including chronic kidney disease (CKD). Regulatory T cells (Tregs) exert anti-inflammatory effect and the decrease of Tregs has been shown to be associated with inflammatory phenotype and disease severity. The purpose of this study was to investigate the effect of probiotics on the progressive CKD and also the mechanisms.

Methods: CKD was induced in 6 week old C56BL/6 mouse by 5/6 nephrectomy. *Lactobacillus Rhamnosus* R0011 and *Lactobacillus Acidophilus* R0052 and proton pump inhibitor mixture were administered via oral gavage starting 1 day after the operation and continued for 8 weeks following intestinal decontamination. Biochemical, histological as well as flow cytometric analyses were performed at 4 weeks after 5/6 nephrectomy.

Results: Increased serum creatinine and substantial fibrosis in CKD mice were associated with increased plasma and kidney TNF-a, IL-6 level. In addition, significantly decreased percentage of mesenteric LN Tregs, colonic Foxp3 mRNA expression as well as increased colon epithelial cell apoptosis were observed in CKD mice. Treatment with probiotics resulted in significantly decreased serum creatinine level as well as kidney fibrosis. The beneficial effect on progressive CKD was also associated not only with reduction of systemic and kidney iniflammation, but also with partial expansion of mesenteric lymph node Tregs, increase of colonic Foxp3 expression and also decreased colon epithelial cell apoptosis.

Conclusions: This study first demonstrated that alteration of normal intestinal immune homeostasis (decreased Tregs in colon, mesenteric LN) and barrier disruption (colon epithelial cell apoptosis) was associated with inflammation, progression of CKD. Probiotics seem to be promising as one therapeutic strategy in progressive CKD via their immune modulatory mechanisms.

Funding: Private Foundation Support

TH-PO130

Toll-Like Receptor 4 Is Dominantly Expressed Compared to Toll-Like Receptor 2 and 9 in Kidneys of Patients with Anti-Neutrophil Cytoplasmic Antibody Associated Vasculitis Kim M. O'Sullivan,[1] Sharon Lee Ford,[1] A. Richard Kitching,[1,2] Stephen R. Holdsworth.[1,2] *[1]Centre for Inflammatory Diseases, Dept of Medicine, Monash Univ, Clayton, Australia; [2]Dept of Nephrology, Monash Health, Clayton, Australia.*

Background: Infections can initiate and exacerbate disease in patients with anti-neutrophil cytoplasmic antibody associated vasculitis (AAV). Toll-like Receptors (TLRs) may be the link between infection and autoimmunity. This study investigates the distribution of kidney TLR2, 4 and 9 and evaluates altered TLR expression in relation to the severity of renal injury.

Methods: Kidney biopsies from patients with a first presentation of AAV (38), Lupus (8), and controls (minimal change and thin membrane disease, 10) were examined by confocal microscopy for the distribution of TLR2, 4 and 9 and co-localized with CD34, CD68, CD15, nephrin, and TLR ligands fibrinogen and high mobility group box 1(HMGB1).

Results: AAV+ renal biopsies had significant glomerular and tubular expression of TLR2, 4 and 9 compared to controls (all, P<0.05). TLR2 and 4 co-localized with endothelial cells, podocytes and leukocytes, whereas TLR9 was predominantly expressed by podocytes. The functional relevance of TLR2, 4 and 9 expression was supported by the observation that TLR expression was co-localised with known endogenous TLR ligands HMGB1 and fibrinogen. Infiltrating neutrophils were highly positive for TLR4, however the largest degree of TLR staining was observed within intrinsic renal cells. The predominant glomerular TLR assessed by percentage area was TLR4 (31.2±3.8%), compared to TLR2 expression (5.2±1.9%) and TLR9 expression (13.5±2.1% P<0.0001). Tubulointerstitial TLR4 was significantly more expressed (29.3 ±3.3%) than TLR2 (9.1±1.8%) and TLR9 (17±2.5%, P<0.05). Glomerular TLR2 correlated with glomerular segmental necrosis (SN) (r=.44,

P<0.05) and TLR4 correlated with SN and cellular crescents (r= .57, P<0.01). Increased glomerular TLR 2 and 4 inversely correlated with presenting eGFR (r=-.39, P=0.02 and r=-3.9, P=0.01, respectively).

Conclusions: The extent of TLR4 expression correlates with renal injury and is the predominant TLR expressed within intrinsic renal cells, and may be a potential target for therapeutics.

TH-PO131

Elevated Microparticle Tissue Factor Activity Predicts Venous Thromboembolism in ANCA Vasculitis Elizabeth J. Brant,[1,2] Carmen E. Mendoza,[1] Matthew L. Mcdermott,[1] Yichun Hu,[1] Susan L. Hogan,[1] J. Charles Jennette,[1] Ronald J. Falk,[1] Patrick H. Nachman,[1] Vimal K. Derebail,[1] Donna O. Bunch.[1] *[1]UNC Kidney Center; [2]Dartmouth-Hitchcock Medical Center.*

Background: Venous thromboembolism (VTE) is a complication of ANCA vasculitis (AAV). Mechanisms of VTE and the cells involved have not been elucidated, but tissue factor (TF)-bearing microparticles (MP) may play a role. We hypothesized that elevated microparticle tissue factor activity (MPTFa) is associated with VTE in AAV and explored the cellular source.

Methods: Patients without VTE (VTE^{neg}, n=21) were enrolled during active disease. Patients with VTE (VTE^{pos}, n=11) were included whether active or in remission at the time of VTE. Longitudinal platelet-free plasma samples were assayed for MPTFa and compared to 15 healthy controls (HC). Isolated MP were incubated with Factor VIIa and Factor X. Absorbance was measured after adding Factor Xa chromogenic substrate. Recombinant, relipidated human TF was the standard used to determine TF concentration. Values were expressed as percent relative to positive controls. Surface expression of TF was measured by flow cytometry. A Mann-Whitney test was used to compare continuous variables.

Results: Demographics were similar among patients and HC. VTE^{pos} and VTE^{neg} patients did not differ in ANCA serotype or titer, BVAS, D-dimer or other laboratory data, or organ involvement. VTE^{pos} patients had significantly higher peak MPTFa than VTE^{neg} patients (median 16.1 vs 3.4; p<0.0001). MPTFa of VTE^{neg} patients was similar to HC (2.4, p=0.3). Four of 6 VTE^{+} patients with available stored samples had elevated MPTFa within 6 months prior to VTE. VTE^{pos} patients had higher $\%TF^{+}$ $CD14^{+}$ monocytes than HC (median 19.9 vs 1.8; p=0.009), and $CD14^{+}CD16^{+}$ inflammatory monocytes than HC (23.8 vs 9.5; p=0.03) and VTE^{neg} patients (4.1, p=0.04). Our other preliminary in vitro data show that ANCA IgG triggers release of MP with TFa in HC blood.

Conclusions: Patients with AAV who develop VTE have increased MPTFa, whereas those without VTE rarely exhibit MPTFa higher than HC. Our data suggest that elevated MPTFa identifies AAV patients at high risk for VTE and that effects of ANCA IgG on monocytes may contribute to thrombogenesis.

Funding: NIDDK Support

TH-PO132

Quantification of the Average Creatinine-Clearance and Proteinuria per Nephron in Murine Nephritic Kidneys by Tissue Clearing and Light Sheet Microscopy Christian Kurts.[1] *[1]Inst for Experimental Immunology, Rheinische Friedrich-Wilhelms-Univ, Bonn, Germany; [2]Inst for Experimental Immunology and Imaging, Univ Duisburg-Essen, Essen, Germany.*

Background: The number of nephrons is a fundamental parameter of kidney function, but very difficult to determine using standard methodology. This precludes analysis of kidney function per nephron.

Methods: Here we enumerated nephrons by a combination of in vivo fluorescence labeling of endothelial cells, a novel tissue clearing technique, light sheet microscopy and automated enumeration of glomeruli by a computer algorithm. Our clearing technique is superior to other reagents because of its non-toxicity and because its maintenance of fluorescence over weeks.

Results: The average creatinine-clearance per nephron declined already in the first week of murine nephrotoxic nephritis, whereas nephron numbers started doing so after day 7. Focal glomerular inflammation was accompanied by periglomerular accumulation of dendritic cells. Only inflamed glomeruli showed protein leakage, indicating that large proteinuria may result from damage to a few glomerular filters only. Finally, using a model of crystal proteinuria by alimentary adenine overload, we quantified the number of intrarenal microstones.

Conclusions: Our novel technique delivers fundamental parameters of renal function and should facilitate the analysis of various models of experimental kidney disease.

Funding: Government Support - Non-U.S.

TH-PO133

Myeloid-Specific Deletion of MRP8 Ameliorates Glomerulonephritis through Affecting Macrophage Characterization Takashige Kuwabara,[1,3] Kiyoshi Mori,[2] Manabu Hayata,[1] Shuro Umemoto,[1] Hideki Yokoi,[3] Masashi Mukoyama.[1,3] *[1]Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan; [2]Medical Innovation Center, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; [3]Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan.*

Background: Our previous report indicated that myeloid-related protein 8 (MRP8) and toll-like receptor 4 (TLR4) play an important role in diabetic nephropathy in mice. We observed that glomerular-infiltrated macrophages (Mφ) expressed MRP8 much more robustly than tubulointerstitial Mφ in diabetic mice, which has also been observed in human diabetic kidney and glomerulonephritis. However, these mechanisms and roles are still unknown.

Methods: We generated myeloid-lineage cell-specific conditional knockout mice (MRP8cKO), and induced experimental nephrotoxic glomerulonephritis (NTN). Co-culture of Mφ with mesangial cells (Mes) or proximal tubular cells (PT) was performed to investigate potential mechanisms of intraglomerular crosstalk. The effects of MRP8 on Mφ were evaluated with phalloidin staining in bone marrow-derived Mφ (BMDM) generated from MRP8cKO. Mφ were characterized as M1/M2 ratio determined by real-time PCR.

Results: Effective 60-80% reduction of MRP8 was achieved in target organs of MRP8cKO. Ablation of MRP8 in myeloid-lineage cells significantly ameliorated glomerulonephritis as indicated by proteinuria, glomerular exudative lesions and pro-inflammatory gene expressions in isolated glomeruli. In vitro study revealed that MRP8 expression in Mφ was dramatically induced by co-culture with Mes but not with PT. Such results were recapitulated by stimulation with Mes-cultured supernatant (Mes-sup). Mes-sup stimulation tended to increase M1/M2 less in BMDM generated from MRP8cKO than that from wild-type. M1/M2 was also significantly suppressed in isolated glomeruli of MRP8cKO NTN mice in vivo. Phalloidin staining of Mφ revealed that deletion of MRP8 resulted in less stress fiber formation.

Conclusions: Myeloid-lineage cell-derived MRP8 potentially contributes to glomerular injury through intraglomerular cell-cell crosstalk affecting Mφ characterization.

TH-PO134

NLRP3 Inflammasome Activation Contributes to Aldosterone-Induced Podocyte Injury Aihua Zhang,[1] Mi Bai,[1] Yue Zhang,[1] Zhanjun Jia,[2] Songming Huang.[1] *[1]Dept of Nephrology, Nanjing Children's Hospital affiliated to Nanjing Medical Univ, Nanjing, China; [2]Nanjing Key Lab of Pediatrics, Nanjing, China.*

Background: Recently, the pathogenic role of NLRP3 inflammasome in mediating renal tubular damage was identified, while its role in podocyte injury still needs evidence. Thus the aim of the present study was to investigate the role of NLRP3 inflammasome in aldosterone (Aldo)-induced podocyte damage.

Methods: Aldo was administered to the cultured podocytes and NLRP3 WT and KO mice. Renal biopsy specimens and urine samples from nephrotic syndrome patients were used to test the activation of NLRP3 inflammasome.

Results: In vitro, exposure of podocytes to Aldo enhanced NLRP3, caspase-1 and IL-18 expressions in dose and time-dependent manners by around 2 to 4 folds, respectively, indicating an activation of NLRP3 inflammasome. Silencing NLRP3 by a siRNA approach strikingly attenuated Aldo-induced podocyte apoptosis and nephrin protein downregulation in line with the blockade of caspase-1 activation and IL-18 production. In NLRP3 WT mice, since day 5 of Aldo-infusion, NLRP3 inflammasome activation and podocyte injury evidenced by nephrin reduction occurred concurrently. More importantly, immunofluorescence analysis showed a significant induction of NLRP3 in podocytes of glomeruli following Aldo infusion. In the mice with NLRP3 gene deletion, Aldo-induced downregulation of nephrin(-53%) and podocin (-50) and podocyte foot processes (electron microscopy) were largely diminished. Consistently, a 5-fold increase of urinary albumin output was blocked by 55% in the KO mice, indicating a protective role of NLRP3 deletion in Aldo-induced podocyte injury. Finally, we observed a striking induction of NLRP3 in both glomeruli and renal tubules in line with an enhanced urinary IL-18 output (around 5.5 folds) in nephrotic syndrome patients with pathological feature of MCD or FSGS.

Conclusions: These results demonstrated an important role of NLRP3 inflammasome in mediating the podocyte injury induced by Aldo.

TH-PO135

ABIN1 Contributes to the Severity of Antibody-Mediated Glomerulonephritis via an Intrinsic Podocyte-Neutrophil Axis David W. Powell,[1] Erik Korte,[1] Dawn J. Caster,[1,2] David J. Salant,[3] Kenneth R. McLeish.[1,2] *[1]Nephrology, Univ of Louisville; [2]Dept of Veterans Affairs; [3]Boston Univ Medical Center.*

Background: Transcription factor (NF)-κB regulates expression of hundreds of genes that control inflammation and NF-κB is activated in glomerular cells in glomerulonephritis (GN). We previously identified genetic variants for a NF-κB regulatory, ubiquitin binding protein ABIN1 as risk factors for GN in autoimmune diseases. The goal of the current study was to determine if disruption of glomerular ABIN1 function contributes the development of GN.

Methods: Nephrotoxic serum nephritis (NTN) was induced in wild-type (WT) and ubiquitin binding null ABIN1[D485N] mice; and proteinuria, kidney pathology, glomerular leukocyte accumulation, and glomerular inflammatory mediator expression were assessed 24 hours post nephrotoxic serum injection. Proteinuria was also measured in ABIN1[D485N] mice transplanted with wild-type mouse bone marrow and following administration of recombinant TAT-SNAP-23 protein, an inhibitor of neutrophil degranulation. The interaction of neutrophils with WT and homologous ABIN1 mutant cultured podocytes was assessed by functional assays.

Results: Disruption of ABIN1 function exacerbated proteinuria, podocyte injury, glomerular expression of inflammatory mediators, and glomerular recruitment and retention of neutrophils, but not mesangial cell proliferation, in NTN. Bone marrow transplantation of WT bone marrow did not prevent increased proteinuria. TAT-SNAP-23 attenuated proteinuria and foot process effacement in WT and ABIN1 mice. TNF-stimulated supernatant from homologous ABIN1 mutant podocytes stimulated neutrophil chemotaxis and degranulation. Incubation with neutrophil granule contents disrupted cytoskeletal organization and morphology of ABIN1 mutant podocytes.

Conclusions: We conclude that ABIN1 dysfunction mediates a novel intrinsic podocyte-neutrophil inflammatory axis that determines the severity of podocyte injury in GN. Our data suggest that genetic regulation of podocyte NF-κB activity controls injury through release of cytokines that recruit neutrophils. Inhibition of neutrophil granule release is a novel therapeutic intervention for preventing podocyte injury in GN.

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TH-PO136

Function of the Atypical Chemokine Receptor 2 in Murine Immune Complex Glomerulonephritis Andrei Bideak, Volker Vielhauer. *Nephrologisches Zentrum, Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians-Univ, Munich, Germany.*

Background: The atypical chemokine receptor 2 (ACKR2), also named D6, is unable to induce cell signaling but can regulate local chemokine levels by internalization and degradation. Here we characterize the role of ACKR2 in murine autologous nephrotoxic nephritis (NTN).

Methods: NTN was induced in C57/BL6 wild-type and Ackr2-deficient mice by injection of sheep antibodies against mouse glomerular basement membrane.

Results: At 2 weeks Ackr2-/- mice showed increased albuminuria, serum creatinine and urea levels than wild-type controls. Histological analysis revealed increased structural damage in the glomerular and tubulointerstitial compartment of Ackr2-/- kidneys. By flow cytometry these findings correlated with a higher renal leukocyte infiltration of CD4+ T cells and mononuclear phagocytes in Ackr2-/- mice. As a possible cause, Ackr2-/- mice demonstrated higher levels of inflammatory chemokines CCL2 and CCL5 in nephritic kidneys. Further histological analysis revealed that increased leukocyte infiltration resulted from higher numbers of T cells and macrophages in the tubulointerstitial compartment of Akcr2-/- mice, whereas leukocyte numbers in glomeruli were comparable. Accordingly, in-vitro experiments with TNF-stimulated renal cells showed that increased chemokine levels in Ackr2-/- mice resulted from a reduced ACKR2-mediated chemokine degradation in the tubulointerstitial compartment. Furthermore, Ackr2-/- mice showed decreased T-cell activation resulting in a reduced adaptive cellular immune response.

Conclusions: These results are consistent with the known expression of Ackr2 in interstitial lymphatic endothelial cells, assuring efflux of activated leukocytes into locoregional lymph nodes. However, the decreased adaptive immune response did not result in decreased renal inflammation during NTN because of simultaneously increased tubulointerstitial chemokine levels and a higher renal leukocyte infiltration in Ackr2-deficient mice. Our data indicate that ACKR2 plays an important role in limiting renal inflammation in NTN and therefore identifies ACKR2 as a potential target molecule for therapeutic approaches in immune complex-mediated glomerulonephritis.

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TH-PO137

A Novel Targeting Strategy to Inhibit Deleterious TNF Signaling in Nephrotoxic Nephritis Rudolf Lucas, Maggie McMenamin, Nino Kvirkvelia, Supriya Sridhar, Maritza J. Romero, Istvan Czikora, Michael P. Madaio. *Vascular Biology Center and Dept of Medicine, Medical College of Georgia, Augusta Univ, Augusta, GA.*

Background: Activation of the p38 MAPK pathway by TNF in glomerular endothelial cells (GEC) represents a central mechanism of renal inflammation in nephrotoxic serum (NTS)-induced nephritis (NTN). Strategies to inhibit TNF receptor signaling, using neutralizing antibodies or soluble TNF receptors, can impair host defense to infection. In this study, we evaluated the therapeutic potential of the TNF-derived TIP peptide in NTN. This peptide mimics the lectin-like domain of TNF, blunts acute lung injury in several species and does not affect TNF receptor-mediated anti-bacterial activities.

Methods: TIP peptide or inactive mutant peptide were evaluated when applied systemically in murine NTN (13.5 µl/g NTS). To determine whether the effects were local or systemic, glomerular targeting was evaluated after linking the peptide to the human F1.1 mAb directed against α3(IV) collagen, in more severe NTN (14.5 µl/g NTS). All agents were given i.p. after induction of nephritis every second day from day 2 on (n=10 per group). To further evaluate the glomerular specific effects of TIP peptide its actions on TNF-induced p38 MAPK activation in GEC were assessed using Western blotting analysis of the phospho-p38/total p38 ratio.

Results: Systemic delivery of active, but not mutant TIP peptide significantly reversed nephritis (histology, proteinuria, BUN, macrophage infiltration) on day 7, and this was associated with reduced plasma levels of TNF, IL-6, IL-1β and MCP-1. Renal delivery of TIP peptide-F1.1 complex reduced mortality from 100% to 20% on day 6 and improved pathology in more severe NTN. In culture, TIP peptide abrogated hTNF-induced activation of p38 MAP kinase in GEC.

Conclusions: Local actions of TNF-derived TIP peptide ameliorate ongoing nephritis, at least in part due to direct effects on glomerular cells. Therefore, application of strategies that specifically target deleterious effects of TNF in acute glomerulonephritis (GN) locally, without either interfering with beneficial anti-bacterial activities of the cytokine or inciting inflammation, has therapeutic potential.

Funding: NIDDK Support

TH-PO138

APOL1 mRNA Is Partially Retained in the Nucleus and Is Associated with Increased Levels of Phosphorylated Protein Kinase R Koji Okamoto,[1] Maarten Hoek,[2] Myung Shin,[2] Jeffrey B. Kopp.[1] *[1]NIDDK, NIH, Bethesda, MD; [2]Merck Research Laboratories, Kenilworth, NJ.*

Background: APOL1 coding variants G1 and G2, compared to ancestral G0, are strongly associated with glomerular diseases. We have previously found that APOL1 renal risk variants contribute to podocyte injury by activating interferon-inducible, double-stranded RNA-activated protein kinase (PKR). Cytoplasmic PKR is central to the cell stress pathway, activating the metabolic inflammasome and suppressing protein synthesis. PKR also resides in the nucleus where its function is unclear, although nuclear PKR levels are increased in leukemia and neurogenerative disease (e.g. Huntington disease, in which PKR preferentially binds mutant *huntingtin* transcripts).

Methods: BAC/APOL1 transgenic mice bear the APOL1 gene locus. We conducted knock-down experiments using conditionally immortalized human podocyte cell lines established from human urine and we generated stable HEK293 cell lines over-expressing *APOL1* variants.

Results: In BAC/APOL1 transgenic mice, the amount of nuclear phosphorylated PKR was increased, G1=G2>G0. By confocal microscopy, phosphorylated PKR formed nuclear speckles. APOL1 G1/G2 heterozygous podocytes manifested strong signals for nuclear phosphorylated PKR (intensity: 759±169), which was lacking in G0/G0 podocytes (intensity: 328±119). In APOL1 G1/G2 dual heterozygous podocytes but not in G0/G0 podocytes, knock down of APOL1 RNA reduced nuclear phosphorylated PKR by 28.7%. In APOL1 over-expressing HEK293 cells, APOL1 nuclear mRNA was increased with the G1 (152±9%)and G2 variants (176±8%) compared to cells that were transfected with the G0 variant (106±13%) (100% set as nuclear ratio in housekeeping genes). Nuclear mRNA retention was 70-fold higher than housekeeping genes (β-actin, GAPDH), and APOL1 nuclear RNA levels were 12-fold higher following transfection of the coding sequence and 3' UTR, compared with transfection of coding sequence alone.

Conclusions: APOL1 mRNA and phosphorylated PKR were present in the nucleus, at higher levels with the risk variants. The APOL1 3' UTR contributes to nuclear localization of mRNA. Nuclear PKR may serve as a reservoir for delivery to the cytoplasm, contributing to the stress response.

Funding: NIDDK Support

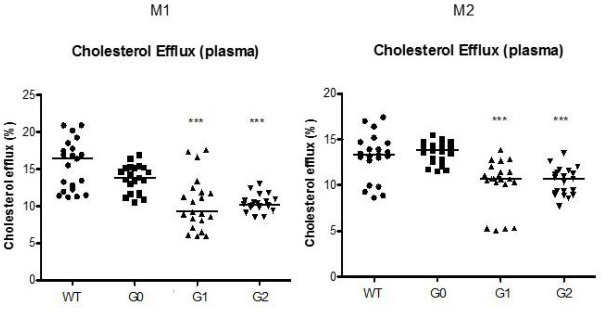
TH-PO139

APOL1 Renal Risk Variant Alleles Reduce Cholesterol Efflux in Murine Bone Marrow-Derived Macrophages Jung-Hwa Ryu,[1] Hidefumi Wakashiu,[1] Alex Dinh,[1] Alan Remaley,[1] Maarten Hoek,[2] Myung Shin,[2] Alessia Fornoni,[3] Jeffrey B. Kopp.[1] *[1]NIDDK, National Insts of Health, Bethesda, MD; [2]Merck, Kenilworth, NJ; [3]Univ of Miami School of Medicine, Miami, FL.*

Background: Apolipoprotein L1(APOL1) genetic variants G1 and G2, compared to the common allele G0, are major risk factors for non-diabetic kidney disease in African descent populations. APOL1 is a protein component of HDL. Reverse cholesterol transport(RCT) involves the transport of cholesterol to HDL by cellular ABCA1, with subsequent delivery from peripheral tissues to the liver. With impaired RCT, macrophages become foam cells, releasing inflammatory factors. We asked whether the APOL1 risk variants alter macrophage cholesterol efflux.

Methods: Bone marrow monocytes were isolated from wild-type mice(WT) and from BAC-APOL1 transgenic(G0, G1, and G2) mice, which carry a bacterial artificial chromosome with the human *APOL1* genomic region. Monocytes were differentiated into macrophages using M-CSF(50 ng/mL) for 7d. Macrophages were stimulated for 24h with IFN-γ(20 ng/mL) to induce the M1 phenotype or with IL-4(20 ng/mL) to induce the M2 phenotype. For cholesterol efflux assays, cells were incubated with [^{3}H]-cholesterol for 24h. After incubation with efflux ligands for 4h, [^{3}H]-cholesterol in the supernatant and cell lysates were quantified.

Results: M1 and M2 macrophages showed the expected polarization according to cytokine stimulation. M1 and M2 macrophages derived from APOL1 G1 and G2 mice showed significantly decreased cholesterol efflux compared to WT or G0 macrophages.



N=6 mice per group, 3-5 samples per mouse. ***$P < 0.001$ vs. WT and vs. G0.

Conclusions: M1 and M2 macrophages from APOL1 G1 and G2 mice showed decreased cholesterol efflux compared to cells from WT or G0 mice. This process would tend to promote macrophage foam cell formation, driving inflammation in the glomerulus and interstitium.

Funding: NIDDK Support

TH-PO140

Spleen Tyrosine Kinase Inhibitor Ameliorates Tubular Inflammation in IgA Nephropathy Wai Han Yiu, Dickson W.L. Wong, Haojia Wu, Kam Wa Chan, Yang Liu, Loretta Y.Y. Chan, Joseph C.K. Leung, Kar Neng Lai, Sydney C.W. Tang. *Dept of Medicine, The Univ of Hong Kong, Queen Mary Hospital, Hong Kong.*

Background: Spleen tyrosine kinase (Syk) is a non-receptor tyrosine kinase involved in signal transduction in a variety of immune responses. It has been demonstrated that inhibition of Syk has renoprotective effects in antibody mediated glomerulonephritis and this protein tyrosine kinase plays a pathogenic role in orchestrating inflammatory responses and cell proliferation in human mesangial cells in IgA nephropathy (IgAN). However, the therapeutic potential of Syk inhibition in tubulointerstitial damage in IgAN remains unknown.

Methods: Cultured human proximal tubular epithelial cells (PTECs) were stimulated with conditioned medium prepared from human mesangial cells incubated with polymeric IgA (IgA-HMC) from patients with IgAN or healthy control subjects. The effect of Syk inhibitor R406 on the expression of inflammatory cytokines was detected by real-time qPCR and ELISA, and NFκB signal transduction in activated PTECs was determined by Western blotting. Furthermore, expression of phosphorylated Syk protein was examined on renal biopsies from patients with IgAN and normal control by immunohistochemistry.

Results: The synthesis of IL-6, IL-8 and ICAM-1 in PTECs were upregulated at both mRNA and protein levels after incubating with IgA-HMC conditioned medium from IgAN patients when compared to that from healthy control subjects. Pretreatment with R406 significantly suppressed IgA-HMC conditioned medium-induced pro-inflammatory cytokine production and also attenuated the phosphorylation of NFκB p65 subunit in the activated PTECs. Finally, the phosphorylated level of Syk was increased in renal tubules of patients with IgAN compared to that of the healthy controls.

Conclusions: Syk mediates inflammatory responses in tubular cells, suggesting a role for this kinase in tubulointersitial damage of IgAN. These data also supported a therapeutic potential of Syk inhibitor in treating IgAN. Fund support: Hong Kong Society of Nephrology and Hong Kong Kidney Foundation Research Grant (2015).

TH-PO141

TLR9 Activation Induced Overproduction of Aberrantly Glycosylated IgA via Activation of BAFF in Patients with IgA Nephropathy Yuko Makita,[1] Hitoshi Suzuki,[1] Toshiki Kano,[1] Akiko Takahata,[1] Bruce A. Julian,[2] Jan Novak,[2] Yusuke Suzuki.[1] *[1]Nephrology, Juntendo Univ Faculty of Medicine; [2]Univ of Alabama at Birmingham.*

Background: Involvement of Toll-like receptor9 (TLR9) has been discussed in the pathogenesis of IgA nephropathy (IgAN). There is increasing evidences that galactose-deficient IgA1 (Gd-IgA1) and immune complexes (ICs) consisting of Gd-IgA1 are important players in the pathogenesis of IgAN. We recently demonstrated that IL-6 can enhance the production of Gd-IgA1 by IgA1-producing cells. Moreover, B-cell activating factor (BAFF) and A proliferation-inducing ligand (APRIL) may be involved in the overproduction of nephritogenic IgA1. However, the mechanisms leading to overproduction of nephritogenic IgA and progression of IgAN are still unclear. In present study, we studies the mechanisms of TLR9-mediated activation of IgA-producing cells.

Methods: Commercially available quiescent ddY mice were divided into two groups with (n=18) or without (n=18) stimulation by TLR9 agonist (CpG-ODN) for 12 weeks. Renal histological lesions and serum levels of IgA, IgG, IgA-IgG ICs and aberrantly glycosylated IgA were evaluated. The expression of TLR9, MyD88, BAFF, APRIL, and BCMA were quantitatively evaluated. We also examined the mechanisms of production of Gd-IgA1 in human IgA1-secreting cell lines with or without stimulation of TLR9.

Results: Mice treated with CpG-ODN showed overexpression of TLR9, MyD88, BAFF, APRIL and BCMA. These mice had elevated serum levels of aberrantly glycosylated IgA and IgA-IgG ICs. Serum levels of aberrantly glycosylated IgA and IgA-IgG IC correlated with BAFF expression. *In vitro*, CpG-ODN stimulation induced secretion of soluble BAFF *via* elevation of IL-6, resulted in production of aberrantly glycosylated IgA. The production of aberrantly glycosylated IgA correlated with increase of soluble BAFF. In human IgA1-secreting cell lines, TLR9 activation enhanced production of Gd-IgA1 through the same pathways, *i.e.,* IL-6-mediated BAFF production.

Conclusions: TLR9 activation exacerbated murine IgAN by enhancing production of aberrantly glycosylated IgA and nephritogenic ICs. This TLR9-mediated activation involved IL-6 and BAFF overproduction in murine as well as human IgA-secreting cells.

TH-PO142

(Pro)renin Receptor-Mediated ERK1/2 and Wnt Signaling Pathway in Crescent Glomerulonephritis Maki Urushihara,[1] Takashi Nagai,[1] Shuji Kondo,[1] Yasumasa Ikeda,[2] Toshiaki Tamaki,[2] Shoji Kagami.[1] *[1]Dept of Pediatrics, Inst of Biomedical Sciences, Tokushima Univ Graduate School, Tokushima, Japan; [2]Dept of Pharmacology, Inst of Biomedical Sciences, Tokushima Univ Graduate School, Tokushima, Japan.*

Background: (Pro)renin receptor ((P)RR)-bound renin and (pro)renin not only become enzymatically active but also cause intracellular signaling pathway activation. We recently showed that direct renin inhibition ameliorated the magnitude of crescent glomerulonephritis (GN) using rat experimental model and suggested that inflammation and cell proliferation via (P)RR involved in the pathophysiology of glomerular crescent formation.

Methods: To clarify the mechanism of (P)RR-mediated intracellular signaling in glomerular crescent formation, we induced crescentic GN model by anti-glomerular basement membrane antibodies in WKY rats and treated with direct rein inhibitor (DRI). Furthermore, we examined the signal transduction in cultured mesangial cell (MCs) and parietal epithelial cell (PECs) transfected with (P)RR specific small interference RNA (siRNA).

Results: Anti-GBM nephritis model developed severe glomerular crescent, accompanied by increased CD68 positive macrophage infiltration and glomerular expression of (P)RR and phospho-ERK1/2 by immunohistochemistry, and mRNA levels of MCP-1 and Wnt4 in isolated glomerulus. Treatment with DRI markedly suppressed those augmentations. Recombinant renin (rRenin) stimulation induced cell proliferation in cultured PECs and increase of monocyte chemoattractant protein-1 (MCP-1) mRNA in cultured MCs, but not in (P)RR siRNA transfected PECs or MCs. PECs stimulated with rRenin showed ERK1/2 phosphorylation and MEK1/2 inhibitor PD98059 abolished cell proliferation, suggesting that (P)RR-mediated ERK1/2 regulated cell proliferation of glomerular crescent. Wnt4 siRNA transfected MCs suppressed the elevation of MCP-1 mRNA by stimulation with rRenin, indicating that (P)RR-mediated Wnt4 signal regulated MCP-1 expression leading to macrophage infiltration into glomerular crescent.

Conclusions: These data suggest that ERK1/2 and Wnt4 signaling pathways via (P)RR are involved in cell proliferation and macrophage infiltration in crescentic GN.

TH-PO143

Autotaxin Inhibition Decreases Inflammation and Fibrosis in Experimental Model of Crescentic Glomerulonephritis Marco Prunotto,[1] Solange Moll,[2] Christos Chatziantoniou,[3] Susanne Raab,[1] Laura Badi,[1] Christoph Ullmer.[1] *[1]Roche Basel Innovation Center, Hoffmann- La Roche, Basel, Bs, Switzerland; [2]Clinical Pathology Dept, Univ of Hospital of Geneva, Geneva, Ge, Switzerland; [3]INSERM UMR S 1155, Hôpital Tenon, Paris, France.*

Background: Autotaxin (ATX) is a secreted enzyme catalyzing the conversion of lysophosphatidyl choline to produce the majority of extracellular lysophosphatidic acid (LPA), a bioactive phospholipid that exerts its action through binding to specific LPA activated G-protein coupled receptors (LPARs). In a number of organs, elevated plasma levels of LPA have been associated to fibrosis. Specifically in kidney, preclinical evidence in the UUO model showed LPA levels to be associated to fibrosis and causal role has been demonstrated in the same model where fibrosis was significantly attenuated in LPA1R-KO mice compared with wild type mice. In addition to that specific role in fibrosis, LPA has been associated by a vast number of papers to inflammation. All findings let us investigate the role of autotaxin inhibition in preserving renal function and its specific mode of action (MoA) in that model.

Methods: Sv129 mice were injected with nephrotoxic serum (NTS) and a selective ATX inhibitor was administered 1 day prior lesion induction. Functional assessment was carried out at 4, 7 and 14 days post NTS injection with evaluation of blood urea nitrogen, proteinuria or urine cystatin C. Mice were euthanized 14 days post NTS injection and kidney collected for histology, immunohistochemical and morphometric analysis. Gene expression profile was performed for all mice.

Results: ATX inhibition significantly improved renal function measured by proteinuria or urine cystatin C. These functional results were paralleled by a correspondent effect on tubule-interstitial fibrosis, tubular injury or total number of infiltrating inflammatory cells. Gene expression profile of all treated animals pointed out to a key role of ATX inhibition on T-cell recruitment.

Conclusions: Our findings support a key role of LPA axis in renal function preservation in NTS model of crescentic glomerulonephritis and possibly in other renal diseases.

TH-PO144

DDR1 Inhibition Decreases Experimental Induced Glomerulosclerosis Marco Prunotto,[5] Takeshi Murata,[1] Hideaki Shimada,[1] Akira Maeda,[1] Naoshi Fukushima,[1] Christos Chatziantoniou,[2] Marcus J. Moeller,[4] Diana Rubel,[3] Oliver Gross,[3] Yukari Yasui.[1] *[1]Fuji-Gotemba Research Labs, Chugai Pharmaceutical Co., Ltd., Gotemba, Japan; [2]INSERM UMR S 1155, Hôpital Tenon, Paris, France; [3]Clinic of Nephrology and Rheumatology, Univ Medicine Goettingen, Goettingen, Germany; [4]Dept of Nephrology and Clinical Immunology, RWTH Univ, Aachen, Germany; [5]I2O, Clinical Development, Roche Product Ltd., Basel, Switzerland.*

Background: Discoidin Domain receptor 1 (DDR1) is tyrosine kinase collagen receptor that has been shown to be involved in progression of cancer and fibrosis. Specifically in kidney, an impressive series of papers highlighthed a major role for this receptor in the pathogenesis of renal fibrosis, crescentic glomerulonephritis and in Alport syndrome. The present abstract describes the effects of selective DDR1 pharmacological inhibition in experimental-induced glomerulosclerosis models.

Methods: Selective DDR1 pharmacological inhibition on progression of experimental-induced glomerulosclerosis by injection of alloimmune sheep nephrotoxic serum (NTS) in Sv129 mice and in a model of acquired progressive glomerular sclerosis (NEP25) was tested. Functional parameters were collected during the study and tissues submitted to histology, immunohistochemistry and gene expression profile.

Results: DDR1 selective inhibition, assessed by reduction of DDR1 phosphorylation in renal parenchyma, showed a dose-dependent decrease in disease severity assessed by blood urea nitrogen and albuminuria in both models. This functional improvement was paralleled by a marked reduction of expression levels of the principal fibrotic markers. Network analysis on gene expression profile from all treated mice showed a preserved renal tissue gene signature and a decreased signature of inflammation & fibrosis in both anti-GBM and NEP25 model with a marked effect on podocin/nephrin network preservation.

Conclusions: Our preclinical data suggest DDR1 inhibition as a possible therapeutic intervention strategy in treating glomerulosclerosis and in advanced stages of chronic kidney disease.

TH-PO145

Intraglomerular Crosstalk between Mesangial Cells and Macrophages in Glomerular Injury Shuro Umemoto, Takashige Kuwabara, Manabu Hayata, Daisuke Fujimoto, Tomoko Kanki, Yuichiro Izumi, Yutaka Kakizoe, Masashi Mukoyama. *Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto City, Kumamoto, Japan.*

Background: We previously reported that myeloid-related protein 8 (MRP8: S100A8)–toll-like receptor 4 (TLR4) signaling activated by ER-stressed macrophages (Mφ) could be involved in the progression of diabetic nephropathy. Besides, ER stress associated with glucolipotoxicity might contribute to diabetic complications along with the MRP8/TLR4 upregulation in the kidney. Since glomerular infiltrated Mφ showed obviously high MRP8 positivity compared to tubulointerstitial Mφ, we speculated the intraglomerular crosstalk between infiltrated Mφ and resident cells in glomeruli. However, detailed mechanisms remain to be elucidated.

Methods: Macrophages (mouse RAW264.7 cells) were co-cultured or stimulated with rat mesangial cells (Mes) or Mes-conditioned media (Mes-sup), respectively. Expressions of mRNA of MRP8, pro-inflammatory genes and ER stress-associated genes were determined with TaqMan real-time PCR. Inflammation and ER stress were evaluated using THP1-dual reporter cell line enabling to monitor activation of both NFκB and interferon regulatory factor (IRF) pathways. Furthermore, the effects of a TLR4 antagonist on this crosstalk were also examined.

Results: MRP8 and pro-inflammatory genes in Mφ were dramatically induced by co-culture with Mes (by 25-fold and 12-fold, respectively). These results were mostly reproduced by stimulation with Mes-sup, rather than that with proximal tubular cell-conditioned media. Furthermore, experiments using the dual reporter assay revealed that Mes-sup stimulation induced IRF signaling, which could cause ER stress, as well as NFκB pathway in a concentration-dependent manner. Such induction was partially (by ~50%) abrogated by the TLR4 antagonist.

Conclusions: These results indicate that humoral factors secreted from Mes would contribute to the intraglomerular crosstalk between Mes and Mφ during the course of MRP8 activation, which might play an important role in the inflammation and ER stress partly through TLR4 signaling.

TH-PO146

CXCL10-Deficient Mice Reveal a Pro-Proliferative Role for IP-10 in Mesangial Proliferative Glomerulonephritis Xiang-Mei Chen, Lingling Wu. *Dept of Nephrology, Chinese PLA General Hospital, Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing.*

Background: IFN-γ-inducible protein 10 (IP-10, CXCL10), a small chemokine belonging to the CXC chemokine family, has been widely documented to be involved in chemokine activity, cell proliferation and angiogenesis inhibition. It has also been pointed out that the CXCL10 expression increased significantly in patients with mesangial proliferative glomerulonephritis (MesPGN). However, the role and the underlying mechanism of CXCL10 in MesPGN reminds unclear.

Methods: MesPGN was induced in both CXCL10-/- and CXCL10+/+ mice. The glomerular lesions were examined by PAS staining. Immunohistochemistry staining of PCNA was performed to detect the cell proliferation in glomerulus. The expression levels of cell cycle-related proteins were determined by western blotting.

Results: Typical pathological phenotypes were observed in both CXCL10-/- and CXCL10+/+ mice, but the CXCL10-/- mice showed more severe accumulation of extracellular matrix and proliferation of mesangial cells. The PCNA-positive cells in the CXCL10+/+ mice were much more than that in CXCL10-/- mice at day 7. In addition, the results of western blotting showed that the expression levels of cell cycle-related proteins, including Cyclin D3, Cdk2 and Cdk4, were all higher in CXCL10+/+ mice compared with those in CXCL10-/- mice. Furthermore, we observed that CXCL10-/- mice showed less activation of PI3K-AKT signaling pathway than that in CXCL10+/+ mice at day 7.

Conclusions: CXCL10 may aggravate the mesangial proliferation in MesPGN through activating the PI3K-AKT signaling pathway. These results provide a novel insight into the mechanism and a potential therapy target of MesPGN.

TH-PO147

Transcriptome Analysis Suggests That Vorinostat Is Antiapoptotic and Anti-Inflammatory in Experimental Alport Syndrome Vanessa R. Williams,[1] Eun Hui Bae,[2] Ana Konvalinka,[3] York P. Pei,[3,4] James W. Scholey.[1,3] *[1]Medical Science, Univ of Toronto, Canada; [2]Internal Medicine, Chonnam National Univ, Korea; [3]Nephrology, Univ Health Network, Canada; [4]Genomic Medicine, Univ Health Network, Canada.*

Background: Alport syndrome (AS) is a hereditary disorder characterized by early proteinuria and progressive chronic kidney disease (CKD). Currently few effective treatments are available. We previously identified vorinostat, a lysine deacetylase (KDAC) inhibitor, as a novel therapeutic approach to AS. Here, we used systems biology to examine effects of vorinostat treatment on molecular mechanisms affecting progression of AS.

Methods: *Col4a3*$^{-/-}$ (KO) and wild-type (WT) mice on a congenic 129 background were treated with vorinostat (50 mg/kg/day) or vehicle from 4 to 7 weeks of age ($n = 8$ per group). Plasma and urine samples were collected, and kidney histological analyses were performed. Global RNA expression profiling of renal cortical samples was performed with Affymetrix Mouse Gene 2.0 ST arrays at 7 weeks, followed by differential expression, gene ontology (GO), and pathway analyses.

Results: KO mice developed proteinuria, elevated plasma creatinine and blood urea nitrogen, glomerulosclerosis, and tubulointerstitial fibrosis, however vorinostat treatment tended to attenuate these changes. Transcriptional profiles of untreated KO mice compared to WT mice showed enrichment of genes involved in activation of NF-κB, toll-like receptor, and TNF inflammatory signaling pathways. Genes involved in apoptosis, and lipid and carbohydrate metabolism were also enriched. Interestingly, vorinostat-treated KO mice showed downregulation of pathways involved in apoptosis, particularly p53 signaling, compared to untreated KO mice. GO analysis of vorinostat-treated KO mice revealed enrichment of biological processes involved in negative regulation of inflammation and metabolism.

Conclusions: Unbiased transcriptome analysis suggested that vorinostat exerts therapeutic effects by reversing changes in gene expression and biological processes contributing to progression of CKD in AS, particularly apoptosis, inflammation, and metabolism. Future studies will thoroughly investigate specific mechanisms of KDAC inhibition in AS.

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

TH-PO148

Capillary Mechanical Tension Cause Glomerular Injury through Activation of Innate Immunity in the Remnant Kidney Simone C.A. Arias, Victor F. Avila, Camilla Fanelli, Denise M. Malheiros, Niels O.S. Camara, Roberto Zatz, Clarice K. Fujihara. *Univ of Sao Paulo.*

Background: Mechanical tension (MT) is thought to initiate and perpetuate glomerular injury, a notion supported by in vitro studies. The mechanisms of the deleterious action of MT remain unclear. We hypothesized that at least part of these effects may be mediated by innate immunity (InIm), activated as part of a nonspecific cell response to aggression.

Methods: We analyzed retrospectively, by IHC, renal tissue from 15 sham-operated (S) and 30 adult male Munich-Wistar rats subjected to 5/6 renal ablation (Nx). For each experiment, glomerular transcapillary hydraulic pressure difference (ΔP), glomerular volume (V_G) and glomerulosclerosis index (GSI) had been obtained 30 (Nx30) or 60 (Nx60) days after Nx. The ($\Delta P \times V_G^{1/2}$) product was used as a simple estimate of mean glomerular wall MT (GWMT), according to Laplace's law. We assessed the glomerular infiltration (cells/mm^2) by PCNA+ cells and macrophages (MΦ), and the glomerular content (% area) of zonula occludens-1 (ZO-1), α-actin and TGF-β. Glomerular InIm activation was evaluated by the % area of Caspase-1, TLR4, IL-1β and NLRP3.

Results:

	S	Nx30	Nx60
GWMT	40±1	63±2[a]	91±3[ab]
GSI	0±0	10±4[a]	30±11[ab]
TGF-β	3±2	22±6[a]	31±9[a]
α-actin	2.1±0.3	3.8±0.9[a]	11.3±2.5[ab]
MΦ	1.4±0.3	3.0±0.4[a]	4.3±0.7[a]
PCNA	0.7±0.2	2.4±0.3[a]	3.4±0.8[a]
ZO-1	59±2	50±5	42±4[a]
Caspase-1	0.4±0.1	1.8±0.4[a]	4.1±0.1[ab]
TLR4	0.3±0.1	2.0±0.3[a]	2.3±0.3[a]
IL-1β	5±2	11±1[a]	24±3[ab]
NLRP3	0.9±0.6	3.9±0.7[a]	7.1±0.7[ab]
Mean±SE, [a]p<0.05 vs. S; [b]p<0.05 vs. Nx30			

Among Nx rats, GWMT correlated positively with GSI ($p<0.02$) and α-actin ($p<0.005$), and negatively with ZO-1 ($p<0.03$), indicating that it may participate in glomerular inflammation and podocyte injury. In addition, GWMT correlated with % area for Caspase-1 ($p<0.05$), NLRP3 ($p<0.05$), IL1β ($p<0.001$) and TLR4 ($p<0.05$), suggesting that glomerular MT activated InIm.

Conclusions: InIm activation may mediate the adverse effects of GWMT and participate in the initiation and perpetuation of progressive glomerular injury in the Nx model. FAPESP/CNPq.

TH-PO149

Suppression of Inflammation by Leukadherins Ameliorates Diabetic Kidney Disease Mohd Hafeez Faridi,[1] Samia Khan,[1] Shehryar J. Khaliqdina,[1] Alessia Fornoni,[2] Vineet Gupta.[1] *[1]Internal Medicine, Rush Univ Medical Center, Chicago, IL; [2]Div of Nephrology and Hypertension, Miller School of Medicine, Univ of Miami, Miami, FL.*

Background: Systemic Inflammation governs the pathology of several diabetic complications including diabetic nephropathy (DN). Increased infiltration of inflammatory leukocytes in the glomerular milieu has been reported in DN in recent studies. We recently described that CD11b activation using a novel compound, Leukadherin-1 (LA1), suppresses tissue infiltration of leukocytes by reducing transmigration. Here, we tested our hypothesis that CD11b-activation mediated suppression of leukocyte kidney infiltration reduces diabetic kidney injury.

Methods: BTBR ob-/ob- mice were treated with LA1 at 2mg/kg/day for 8 weeks. Blood glucose level, body weight, and urine albumin-creatinine ratio were measured weekly. Histochemical and immunofluorescence analyses were used to quantify LA1 treatment mediated tissue protection.

Results: Diabetic BTBR ob-/ob- mice showed increased albuminuria with age that correlated with leukocyte infiltration into the kidney. LA1 treatment of diabetic mice

significantly reduced albuminuria and improved renal function. Histochemical analyses showed that LA1 significantly reduced leukocyte infiltration and glomerular injury, including mesangial sclerosis, as compared to the untreated animals.

Conclusions: Pharmacologic activation of CD11b with allosteric agonists can be a therapeutically relevant strategy to reduce leukocyte kidney infiltration and inflammatory injury in the setting of diabetes.

Funding: NIDDK Support

TH-PO150

Integrative Analysis of Transcriptome Alterations in Kidney Tissues of Diabetes Nephropathy Revealed Significant Enrichment of M1 Macrophages, Mature Dendritic Cells and Activated Helper T Cells Tao Wei, John N. Calley, Philip Ebert, Suntara Cahya, Zhonghua Qi, Bhaskarjyoti Sarmah, Matthew D. Breyer, Kevin L. Duffin. *Eli Lilly and Company, Indianapolis, IN.*

Background: Recent studies suggested tissue inflammation may play a significant pathogenic role in diabetes kidney disease (DKD). We carried out an integrative analysis with objectives to identify major cellular players associated with diseased kidney tissues.

Methods: Multiple independently generated DKD transcriptome datasets involving different cohorts of human subjects were analyzed to identify a consensus set of differentially expressed genes (DEGs) in kidney tissues (glomeruli and tubuli) associated with DKD. Pathway analysis and leukocytes specific gene signatures were employed to identify major pro-inflammatory leukocytes.

Results: ~2000 genes were identified as DEGs by at least two different studies. Pathway enrichment and coherence analysis revealed significant up-regulation of inflammatory pathways and down-regulation of metabolism and mitochondrial activities. Leukocyte specific gene signatures for macrophages, dendritic cells (DCs), neutrophils, natural killer cells (NKs), T cells and B cells were developed from a published human immune cell transcriptome profile. Enrichment analysis, together with pathway analysis, revealed significant enrichment of macrophages, DCs and helper T cells in diseased kidney tissues. Further analysis revealed significant enrichment of pro-inflammatory M1 macrophages when compared to M2 macrophages, and mature or activated DCs when compared to immature or tolerogenic DCs. Metabolic and mitochondrial activity profiles of M1 and mature dendritic cells are similar to what was observed in DKD kidney tissue, further confirming the involvement of M1 macrophages and mature dendritic cells in DKD development.

Conclusions: Integrated analysis confirmed the significant association of chronic tissue inflammation with DKD. We discovered the dis-regulated enrichment in kidney tissues of M1 macrophages, mature DCs and activated helper T cells is the main cellular basis that underlies the chronic tissue inflammation observed in DKD kidney.

Funding: Pharmaceutical Company Support - Eli Lilly and Company

TH-PO151

A Macrophage COX-2/PGE2/EP4 Axis Protects against Development of Diabetic Nephropathy Xin Wang,[1] Yinqiu Wang,[1] Suwan Wang,[1] Xiaofeng Fan,[1] Haichun Yang,[2] Agnes B. Fogo,[2] Ming-Zhi Zhang,[1] Raymond C. Harris.[1] *[1]Medicine, Vanderbilt Univ School of Medicine, Nashville, TN; [2]Pathology and Microbiology and Immunology, Vanderbilt Univ School of Medicine, Nashville, TN.*

Background: Alterations of intrinsic kidney cyclooxygenase-2 (COX-2) expression are observed in development of diabetic nephropathy (DN), and increased COX-2 expression in macula densa contributes to hyperfiltration in the early stage of diabetes. More advanced DN is characterized by increased infiltration of macrophages. COX-2-derived PGE2 plays an important role in macrophage polarization. In the present studies, we investigated the potential roles of macrophage COX-2 in development of DN.

Methods: Mice with hematopoietic cell COX-2 knockout (129J/sv) and mice with deletion of macrophage COX-2 (CD11b-Cre; COX-$2^{flox/flox}$) or EP4 receptors (CD11b-Cre; $EP4^{flox/flox}$) on an FVB background were used. Type I diabetes was induced by streptozotocin.

Results: At 20 weeks of diabetes, hematopoietic cell COX-2 deletion increased albuminuria, in association with increased renal profibrotic and fibrotic markers (CTGF, fibronectin) and macrophage infiltration. Similarly, macrophage COX-2 deletion also significantly increased albuminuria (ACR: 314 ± 43 vs. 137 ± 32 μg/mg of WT, $P < 0.01$, $n = 5$-9) with increased renal fibrotic markers (α-SMA, collagen I) and macrophage infiltration. Macrophage COX-2 deletion also led to greater glomerulosclerosis index (0.48 ± 0.09 vs. 0.24 ± 0.04 $P < 0.05$, $n = 5$) and podocyte loss (podocytes/glomerulus: 13.65 ± 0.54 vs. 21.34 ± 0.95, $P < 0.001$, $n = 4$). Macrophage COX-2 deletion resulted in decreases in mRNA levels of M2 markers (mannose receptor and YM-1) as well as the number of M2 macrophages (mannose receptor positive macrophages). Finally, macrophage COX-2 deletion caused reduction in autophagy (lower LC3A expression) and increases in endoplasmic reticulum (ER) stress (higher CHOP expression). Similar results were also observed in mice with macrophage EP4 deletion.

Conclusions: Our studies indicate that macrophage COX-2 protects against development of DN through multiple mechanisms, including modulation of macrophage polarization and infiltration, decreases in autophagy and increases in ER stress.

Funding: NIDDK Support, VA Support

TH-PO152

High Glucose Induces Dedifferentiation in Podocytes but Prevents Parietal Epithelial Cells Transition through Up Regulation of Micro-RNA193a Manoj K. Tembhre,[1] Waqaar Khawar,[1] Seyedeh Shadafarin Marashi Shoshtari,[1] Judith Eng,[1] Catherine Meyer-Schwesinger,[2] Ashwani Malhotra.[1] *[1]Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY; [2]Medicine, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany.*

Background: In recent studies, MicroRNA (miR) 193a has been implicated for the development of glomerulosclerosis in several models of chronic kidney diseases. miR193a is a regulator of Wilms tumor (WT1) suppressor gene. Enhanced expression of WT1 in glomerular epithelial cells is associated with the expression of podocalyxin and nephrin, markers of podocytes. On the other hand, down regulation of WT1 enhances the expression of PAX2, a marker of parietal epithelia cell (PEC). A subset of PECs acts as progenitor cells to replenish injured podocytes. We hypothesize that high glucose milieu up regulates miR193a contributing to dedifferentiation of podocytes and preventing the transition of PECs to podocytes.

Methods: Renal tissues of 8 week wild type and $BTBR^{ob/ob}$ mice were evaluated for the expression of WT1, nephrin, and PAX2. In *in situ* hybridization studies, renal cortical sections of control and diabetic mice were labeled for miR193a. In *in vitro* studies, human podocytes and human parietal epithelial cells were incubated in media containing either normal glucose (5mM) or high glucose (30 mM) for 48 hours and probed for miR193a. In other sets of experiments, control and high glucose treated (48 hours) podocytes were evaluated for the expression of podocalxin, PAX2, and nephrin.

Results: *In situ* hybridization studies revealed podocyte expression of miR193 in diabetic mice. In *in vitro* studies showed enhanced miR193a expression in high glucose treated podocytes and PECs. Renal tissues of diabetic mice displayed attenuated expression of WT1 and nephrin. High glucose treated podocytes also displayed attenuated expression of podocalyxin and nephrin. High glucose did not alter PAX2 expression in PECs.

Conclusions: High glucose down regulates podocytes's but preserves PECs's molecular phenotype through modulation of miR193a. The present study provides mechanistical insight into the development of glomerulopathy in majority of diabetic patients.

Funding: NIDDK Support

TH-PO153

IL17A Blockade Improves Renal Damage en BTBR ob/ob Animal Model Carolina Lavoz,[1] Yenniffer Sanchez,[1] Maria Alejandra Droguett,[1] Paola Krall,[1] Daniel Carpio,[1] Marta Ruiz-Ortega,[2] Sergio A. Mezzano.[1] *[1]Div of Nephrology, School of Medicine, Univ Austral, Valdivia, Chile; [2]Renal Diseases Laboratory, Univ Autónoma Madrid, Madrid, Spain.*

Background: Chronic inflammation is a main feature of the progressive renal diseases, including diabetic nephropathy (DN), the most prevalent chronic kidney disease. Among potential therapeutic targets of diabetic renal damage the Interleukin 17A might be a promising one. IL17A is the hallmark cytokine of the T helper 17 cell. The mouse model strain BTBR obob (leptin deficiency mutation) has been widely used for the study of DN, develops histological features that resembles human DN, and offer an opportunity to study the mechanisms that may lead to more specific therapies aimed at regression of DN. Our aim was to investigate the involvement of the Th17 effector cytokine IL17A in the pathogenesis of DN.

Methods: To evaluate the direct effects of IL17A on DN progression, a neutralizing antibody against IL17A (osmotic mimipumps, 5 ng/gr of b.w) was administered to mice between 15 and 20 weeks (sacrifice) . The results were analyzed by Western blot, ELISA, and RTPCR.

Results: In the obob animal model, IL17A renal production was observed at 16 weeks, sustained up to 20 weeks as well as activated RORγT. Moreover, positive IL17A expressing CD4 lymphocytes, mastocytes and tubular epithelial cells were found. IL17A neutralization diminished blood glucose and body weight compared to IgG control-treated mice, whereas renal weight and serum creatinine levels were not affected. Importantly, IL17A blockade improved Albumin/Creatinine Ratio during all period of study. Moreover, downregulation of the kidney damage markers (KIM1 and Ngal) and the proinflammatory factors (MCP1 and Rantes) were found in response to IL17A neutralization. Podocytes markers like WT1 and Pdcn tend to recover after treatment. Histologically was observed a decreased inflammatory infiltrating cells in anti-IL17A-treated mice. In biopsies of DN patients we have detected IL17A expression in tubular epithelial cells.

Conclusions: These data demonstrate that IL17A participates in diabetic-mediated renal damage and could be a novel therapeutic target for ND. PAI 82140017.

Funding: Government Support - Non-U.S.

TH-PO154

Tissue Plasminogen Activator Modulates Macrophage Polarity Shift Ling Lin, Kebin Hu. *Medicine, Penn State Univ College of Medicine, Hershey, PA.*

Background: Macrophage polarization plays an important role in tissue inflammation and fibrogenesis. Generally, M1 macrophages promote inflammation, whereas, M2 macrophages are anti-inflammatory and promote tissue remodeling. Recent work indicates that macrophages, in response to kidney injury, can shift their polarity. However, the underlying mechanisms remain largely unknown.

Methods: We investigated the role of tissue plasminogen activator (tPA) in macrophage polarity shift using integral in vivo and in vitro approaches.

Results: We found that there were more $CD11b^+TNF\alpha^+$ or $CD11b^+F4/80^{lo}$ M1 macrophages in the obstruction-induced fibrotic kidneys from wildtype mice than that from tPA knockout mice. tPA also induced M1 chemokines expression, including IFN-γ, IL-1β, and TNF-α, both in vivo and in vitro, suggesting that tPA may be an endogenous factor that modulates M2 macrophages shift towards M1 phenotype. J774 macrophages were treated with IL-4 to induce M2 phenotype as indicated by de novo expression of arginase 1, SOCS3, and Ym1. Intriguingly, it's found that IL-4-induced M2 macrophages, after tPA treatment, lost their M2 markers such as arginase 1 and SOCS3, indicating that tPA promotes a polarity shift of macrophages from M2 skewed towards M1. Possible contamination of endotoxin was also excluded as heat-inactivated tPA lost its effect. Additionally, knockdown of LRP-1 by siRNA, one of the known tPA receptor, had little effect on tPA-induced macrophage polarity shift. Instead, it's found that annexin A2 mediated tPA-induced macrophage polarity shift, because annexin A2 siRNA abolished tPA effects.

Conclusions: Thus, it's clear that tPA promoted macrophage polarity shift from M2 to M1 through annexin A2-mediated pathway.

Funding: NIDDK Support, Private Foundation Support

TH-PO155

Cell Specific Targeted PCR and RNA Sequencing of Renal Collecting Duct Epithelial Cells Reveals Novel Innate Immune Signature in Murine Intercalated Cells Andrew L. Schwaderer,[1] Vijay Saxena,[1] Raoul D. Nelson,[3] George J. Schwartz,[4] David S. Hains.[2] *[1]CCTR, Nationwide Children's Hospital, Columbus, OH; [2]Pediatrics, Le Bonheur Children's Hospital, Memphis, TN; [3]Pediatrics, Univ of Utah, Salt Lake City, UT; [4]Pediatrics, Univ of Rochester Medical Center, Rochester, NY.*

Background: The urinary tract is usually culture negative despite its close proximity to microbial flora. The precise mechanisms by which the kidneys and urinary tract defends against infection is not well understood. The initial kidney cells to encounter ascending pathogens are the collecting tubule cells which consist of principal cells (PC) that express the aquaporin 2 (AQP2) and intercalated cells (IC) which express vacuolar H^+-ATPase (V-ATPase). We have previously shown that intercalated cells are involved in the innate immune defense of the kidney in humans.

Methods: In this study we generated two reporter mice, V-ATPase-cre^+Tdt^+ mice to fluorescently tag IC and AQP2-cre^+Tdt^+ mice to fluorescently tag PC and enriched them by flow sorting to ≥90% purity. Isolated IC and PC cells were studied for targeted anti-microbial peptide mRNA expression. Unbiased RNA sequencing (RNA-Seq) was performed on IC and non-IC cell fractions.

Results: ICs were significantly enriched for anti-microbial peptides (AMPs), *Defb1*, *Defb26* and *RNase4*. ICs responded rapidly to uropathogenic *E. coli* challenge *in vitro* by rapidly up-regulating *RNase4* gene expression. Pathway analysis of RNA-Seq data identified, LPS/IL1 mediated inhibition of retinoic acid receptor function as the primary pathway involved in the collecting tubule compared to the remainder of kidney cells. Additionally AMP and/or innate immune gene expression including *Defb11*, *Scg5*, *Cav1*, *Cav2*, *IL-17RE*, *IL-23R* and *CXCR4* was increased in ICs.

Conclusions: Key collecting tubule innate immune genes include *Defb1*, *Defb11*, *SCG5*, *Cav1*, *Cav2* and *RNase4*. To our knowledge, this is the first report of isolating murine collecting tubule cells and identifying their innate immune gene profile.

Funding: NIDDK Support

TH-PO156

BET Bromodomain Inhibition Ameliorates Experimental Renal Damage Jose Morgado-Pascual,[1] Beatriz Suarez-Alvarez,[4] Sandra Rayego-Mateos,[1] Raúl R. Rodrigues Díez,[1] Pierre-Louis Tharaux,[2] Jesus Egido,[3] Alberto Ortiz,[3] Carlos Lopez-Larrea,[4] Marta Ruiz-Ortega.[1] *[1]Univ Autónoma Madrid, Spain; [2]Paris Cardiovascular Centre, France; [3]ISS Fundacion Jimenez; [4]Hospital Univ Central de Asturias, Spain.*

Background: Renal inflammation plays a key role in the onset and progression of immune and non-immune renal diseases. Here, we evaluated whether the epigenetic inhibitor of bromodomain and extraterminal (BET) proteins JQ1 could modulate renal inflammation.

Methods: In vitro studies were done in TNF-α treated tubuloepithelial cells. Experimental models of unilateral ureteral obstruction (UUO), infusion of Angiotensin II and anti-glomerular basement membrane nephritis induced by nephrotoxic serum (NTS) administration were used. Mice were treated with JQ1 (100 mg/ mouse/day).

Results: The *in vitro* evaluation of JQ1 on cytokine-inducible genes in renal cells showed that BET inhibition modulates several biological processes, including inflammation and immune response. Gene silencing of BDR4, one of the most important BET proteins, and chromatin immunoprecipitation assays demonstrated that JQ1 alters the direct association of BRD4 with acetylated histone-packaged promoters and reduces the transcription of proinflammatory genes (IL-6, CCL-2 and CCL-5). These data suggest that JQ1 by chromatin remodelling might regulate renal inflammation. Interestingly, several JQ1-downregulated genes were under nuclear factor-kB (NF-κB) control, a key inflammatory signaling pathway. The RelA NF-κB subunit is activated by acetylation of lysine 310. In damaged kidneys and in cytokine-stimulated renal cells, JQ1 inhibited RelA/NF-κB nuclear levels and down-regulated NF-κB-mediated gene expression. Additionally, JQ1 dampens the activation of the Th17 immune response in experimental renal damage.

Conclusions: Our results demonstrate that BET inhibition reduces renal inflammation by several mechanisms: chromatin remodeling in promoter regions of specific genes, blockade of NF-κB pathway activation and modulation of the Th17 immune response. These results suggest that BET inhibitors could have important therapeutic applications in inflammatory renal diseases.

Funding: Government Support - Non-U.S.

TH-PO157

Cisplatin(CP)-Induced Chronic Kidney Disease (CKD): Failed Healing and the Conversion of AKI to CKD Robert L. Safirstein,[1,2] Heino Velazquez,[1,2] Richard Torres,[2] Gilbert W. Moeckel,[2] Gary V. Desir.[1,2] *[1]Medicine/Nephrology, CVAHS, West Haven, CT; [2]Medicine/Nephrology, Yale Univ, New Haven, CT.*

Background: CP causes AKI and CKD but the mechanism of this conversion is unknown. We have shown that the induction of CKD after 2 doses of CP is characterized by changes in physiologic, molecular, and three dimensional histologic parameters. We report now the molecular and morphologic events that mark this interface.

Methods: We compared changes evident 1,3,5 days and 2 and 4 week after a single dose to those noted after two CP doses given 2 weeks apart. Function by inulin clearance and morphology by light and electron microscopy (EM), and multiphoton microscopy was evaluated. Molecular changes were assessed by cDNA microarrays, PCR, western blotting, and immunohistochemistry (IHC).

Results: Mice given 1 dose of CP recover nearly completely. By contrast, CKD develops fully 2 weeks after the 2nd dose of CP. 3-D morphology shows the same degree of capsular cuboidal cell loss and atubular glomeruli at 2 weeks as that seen after 9 weeks following the second CP dose. The renal transcriptome was similar between acutely and chronically injured kidneys and include activation of stress response, inflammatory, cell cycle, and cell death genes. Expression of the damage markers NGAL and KIM-1, which had returned to normal after 1 dose, was re-activated in a sustained manner after the second dose. Proximal tubule Ki67 staining was reduced compared to single dose exposure and the cell cycle inhibitor p21 gene was activated as well. IHC showed widespread molecular responses in the PT, distal tubule and collecting duct. EM of PT cells revealed severe injury and autophagy and pericytes in the outer medulla showed evidence of transdifferentiation.

Conclusions: These studies show that persistent injury and inflammatory responses characterize the transition from AKI to CKD. The failure to replace damaged and dying tubule cells suggests a causal relationship between failed repair of this segment and the conversion of AKI to CKD. We propose that the source of the continued injury response and the check on cell cycle activity are linked and is central to the development of CKD.

Funding: NIDDK Support, VA Support

TH-PO158

Role of Claudins in Tumor Necrosis Factor-Induced Permeability and Migration Changes in Tubular Cells Katalin Szaszi,[1,2] Shaista Anwer,[1] Yasaman Amoozadeh,[1] Emily Branchard,[1] Qinghong Dan.[1] *[1]Keenan Research Center St. Michael's Hospital, Toronto, ON, Canada; [2]Surgery, Univ of Toronto, Toronto, ON, Canada.*

Background: Tumor Necrosis Factor-α (TNF) is a key pathogenic cytokine in kidney disease. We showed that TNF causes a biphasic transepithelial resistance (TER) change in tubular cells that consists of an early drop followed by recovery (1-3h), and a late increase (>8h). TNF also enhances tubular cell migration. However, the underlying mechanisms are not fully known. TER is determined by the claudin (Cldn) family of tight junction proteins. The combination of claudin isoforms expressed determines paracellular permeability of a cell. Claudins were also shown to affect migration. The aim of this work was to assess how claudins contribute to TNF-induced changes in permeability and motility of tubular cells.

Methods: We used LLC-PK1 tubular cells. TER and cell migration was quantified by Electric Cell-substrate Impedance Sensing (ECIS). Claudin expression was followed using western blotting. Specific claudins were silenced using siRNA.

Results: TNF alters expression of several claudins. It causes a biphasic change in Cldn-2 and 3 expression. Specifically, an initial transient increase due to reduced degradation (1-3h) is followed by a drop in mRNA and protein levels (>8h). Prolonged TNF treatment also increases claudin-1, 4 and 7 protein and mRNA . The ERK and JNK pathways are required for the expression changes of Cldn-1, 4 and 7, and have a key role in the late TER increase. To correlate TNFα-induced claudin expression and TER changes, we silenced each claudin and monitored TER using ECIS. Cldn-1 is necessary for the early TNFα-induced TER change. In contrast, Cldn-2 decrease is the main contributor to the late TER increase, with only minor roles for Cldn-1, 4 and 7. Finally, we assessed the role of the various claudins in migration. Silencing Cldn-1, 2 or 3 significantly slowed wound healing in LLC-PK1 cells. Our ongoing studies explore the role of these claudins in migration-associated cytoskeleton remodeling.

Conclusions: Altered claudin expression may have consequences beyond permeability changes. By affecting epithelial regeneration following injury claudins may contribute to the pathogenesis of kidney disease.

Funding: Government Support - Non-U.S.

TH-PO159

Fibroblast CD73 Controls the Interstitial Adenosine Microenvironment, Inflammation and Fibrosis after Kidney Ischemia-Reperfusion Injury (IRI) Nicole Görldt,[1] Sun-Sang J. Sung,[1] Liping Huang,[1] Jessica R. Lawler,[1] Hong Ye,[1] Jurgen Schrader,[3] Diane L. Rosin,[2] Mark D. Okusa.[1] *[1]Div of Nephrology and Center for Immunity, Inflammation and Regenerative Medicine, Univ of VA; [2]Dept of Pharmacology, Univ of Virginia, Charlottesville, VA; [3]Inst of Molecular Cardiology, Heinrich-Heine-Univ, Duesseldorf, Germany.*

Background: Molecular mechanisms after IRI are poorly understood. ATP, released by apoptotic/necrotic cells, promotes pro-inflammatory responses but is rapidly metabolized by CD39 to AMP and then by CD73 to adenosine, which activates its specific receptors to regulate immune response and healing processes. Loss of CD73 increases inflammation

after IRI, but its contribution to late kidney fibrosis has not been examined. We hypothesize that CD73 mediates fibrosis after AKI by blocking inflammation-induced fibroblast-myofibroblast transformation.

Methods: *Foxd1^{Cre}CD73$^{fl/fl}$* (fibroblast CD73KO) and *Foxd1^{Cre}* (control; C) mice were subjected to 20' unilateral IRI, and kidney function, immune cell infiltration and histology were assessed at 14d. In a subset of mice simultaneous unilateral IRI and contralateral nephrectomy were performed to compare initial effects of IRI after 24h.

Results: 24h after IRI, fibroblast CD73KO and C mice had similar initial injury as assessed by plasma creatinine (PCr), KIM-1 and NGAL mRNA, but 14 d after IRI, PCr was higher in fibroblast CD73KO. Collagen formation, myofibroblast marker expression and the area occupied by PDGFR-β^{+} cells were higher in fibroblast CD73KO 14d after IRI, suggesting a role of CD73 in regulating fibroblast-myofibroblast transformation. Furthermore inflammation was higher in fibroblast CD73KO 14d after IRI resulting in impaired resolution of immune cell infiltration. Fibroblasts from *CD73$^{-/-}$* mice cultured *in vitro* showed a hyperproliferative phenotype.

Conclusions: These results demonstrate that mice with fibroblasts deficient in CD73 have increased fibrosis after injury and enhanced fibroblast-myofibroblast transformation, and their fibroblasts have a hyperproliferative phenotype. Understanding the molecular mechanism of regulation by fibroblast CD73 on phenotype transformation could provide an important therapeutic approach to blocking progressive kidney fibrosis.

Funding: NIDDK Support

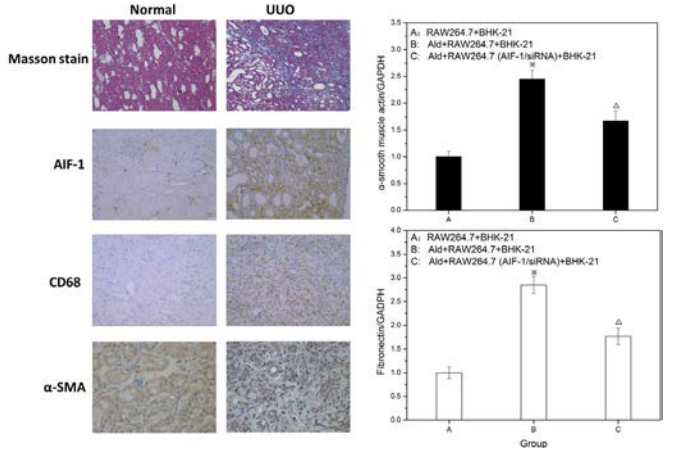
TH-PO160

AIF-1 Expression in Macrophages Promotes Fibroblasts to a Pro-Fibrotic Phenotype and Renal Interstitial Fibrosis Yushu Li, Lirong Hao, Xingzhi Wang. *Nephrology, The 1st Hospital Affiliated of Harbin Medical Univ, Harbin, Heilongjiang, China.*

Background: Macrophages have been identified as key cells in the pathogenesis of renal interstitial fibrosis, but the mechanism is still unclear.This research focus on effects and possible mechanism of Allograft Inflammatory Factor-1 (AIF-1) in promoting of renal interstitial fibrosis.

Methods: Mice were subjected to Unilateral Ureteric Obstruction (UUO), and sacrificed after 14 days. Kidney sections were analyzed by Masson stain. Presence of AIF-1, CD68 and α-smooth muscle actin (α-SMA) were analyzed by immunohistochemistry. Double immunofluorescence stain of AIF-1 and CD68 was also used. AIF-1 expression in RAW264.7 stimulated by aldosterone was detected in vitro. To identify the role of AIF-1 in promoting fibrosis, AIF-1 expression was reduced by transfection of AIF-1 small interfering RNA (siRNA) in RAW264.7. Expressions of α-SMA, Phosphorylation P38 kinase (P-P38) and fibronectin (FN) in BHK-21 (fibroblasts cell line) were examined after co-culture with normal or AIF-1/siRNA RAW264.7.

Results:



Expressions of AIF-1, CD68 and α-SMA were up-regulated in UUO model. AIF-1 expression colocalized with CD68-positive macrophages in kidneys. The increase of AIF-1 expression (above basal levels) was confirmed in RAW264.7 responsed to aldosterone. After 24 hours of co-culture between fibroblasts and macrophages, the α-SMA expression was induced in BHK-21 with increasing expressions of FN and P-P38.Expressions of α-SMA,P-P38 and FN were reduced in BHK-21 co-cultured with RAW264.7 with AIF-1/siRNA.

Conclusions: The expression of AIF-1 in macrophages is critical for the activation of renal fibroblasts to a pro-fibrotic phenotype. AIF-1 expression could be up-regulated in macrophages, and it is a novel mechanism linking macrophages to the promotion of renal interstitial fibrosis, which should be via P38 pathway.

Funding: Government Support - Non-U.S.

TH-PO161

Nrf2 Dependent Inflmmasome Activation Contributes to Maintain M1 Macrophage but Not M2 Infiltration in Kidney Disease Model Yuji Sogawa, Hajime Nagasu, Atsushi Uchida, Seiji Itano, Minoru Satoh, Tamaki Sasaki, Naoki Kashihara. *Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Okayama, Japan.*

Background: Inflammasome activation contributes progression of chronic kidney diseases (CKD) in animal disease model but the molecular mechanism was unknown. We focused on the transcription factor Nrf2 to reveal the mechanism of inflammasome activation in kidney injury. Nrf2 is a master transcription factor for cellular defense against oxidative stress, on the other side, Nrf2 play an important role in inflammasome activation. We investigated the contribution of Nrf2 dependent inflammasome activation for the progression of CKD.

Methods: (1) Male Nrf2 knockout mice (Nrf2$^{-/-}$) and Wild-type mice (WT) underwent UUO (unilateral ureteral obstruction). Histological change, inflammasome activity and fibrotic changes in kidney were examined. The polarity of the macrophages were assessed using FACS. (2) Bone marrow cells were harvest from WT or Nrf2$^{-/-}$ as a donor, then injected to tail vein of WT which were irradiated lethal dosage (Nrf2$^{-/-}$-BMT and WT-BMT). Two weeks after BMT, UUO were performed. Kidney were harvested to examine kidney damage at 14 days. (3) WT were also treated with AtRA (all trans retinoic acid) which is known as Nrf2 inhibitor, for daily 2 weeks after UUO.

Results: (1) Expression of inflammasome related genes is increased in 7 days, and fibrosis-related gene was increased to one-way from 3 days to 14 days in WT. These was reduced in Nrf2$^{-/-}$. Although inflammatory macrophage (M1; CD11b^{+}F4/80^{low}) was increased to one-way in both group until 7 days,it was significantly reduced in Nrf2$^{-/-}$ to 14 days. Anti-inflammatory macrophage (M2; CD11b^{+}F4/80^{high}) was similar in both group. (2) Fibrosis was histologically remarkably suppressed in Nrf2$^{-/-}$-BMT group compared with WT-BMT group.Furthermore expression of fibrosis-related gene and inflammasome-related gene has been suppressed in Nrf2$^{-/-}$-BMT group. (3) Compared to Control, fibrosis is suppressed histologically in AtRA group. Inflammasome activation and fibrosis-related genes was also suppressed.

Conclusions: Inflammatory macrophages sustain infiltrating by Nrf2-dependent inflammasome activation and contribute to kidney disease progress.

TH-PO162

eNOS-NO Pathway Attenuates Chronic Inflammation via Nitric Oxide in Hypertensive Kidney Disease Yuji Sogawa, Hajime Nagasu, Atsushi Uchida, Seiji Itano, Minoru Satoh, Tamaki Sasaki, Naoki Kashihara. *Kawasaki Medical School, Nephrology and Hypertension, Kurashiki, Okayama, Japan.*

Background: It is widely known that chronic inflammation is a common pathway of various progressive kidney diseases (CKD). We previously reported that NLRP3 inflammasome activation plays an important role in the progression of CKD. However, it is unclear how NLRP3 inflammasome is regulated in the kidney. We investigated whether or not NO suppresses inflammasome activation in hypertensive kidney disease because it is well known that endothelial dysfunction promotes progressive kidney disease. We used wild-type (WT) and enos knockout (eNOS$^{-/-}$) mice to determine the role of endothelial function, especially with nitric oxide, for inflammasome dependent chronic inflammation of the kidney.

Methods: [1] WT and enos$^{-/-}$ underwent unilateral nephrectomy (Nx). After NX, these mice were divided into four groups (WT-Nx, WT-Nx-Ald, eNOS-Nx, and eNOS-Nx-Ald). Aldosterone (Ald) was continuously administered with 1% NaCl drinking water. The mice were sacrificed after four weeks of Ald administration, and the kidney tissue was examined. [2] We used bone marrow-derived macrophages (BMDMs) to examine the molecular mechanism. After LPS priming, the BMDM were stimulated with ATP to activate NLRP3 inflammasome. We simultaneously primed with S-nitrosoglutathione (GSNO) as an NO donor or Bay41-2272 as a sGC stimulator.

Results: [1] In the WT-Nx-Ald, blood pressure increases were seen after administration of Ald. Fibroses were observed in the kidneys of the WT-Nx-Ald but not the WT-Nx. These changes were much more exacerbated in the eNOS-Nx-Ald compared with the WT-Nx-Ald. Expression of inflammatory genes was also much higher in the eNOS-Nx-Ald than in the WT-Nx-Ald. [2] ATP stimulation with LPS priming caused NLRP3 inflammasome-dependent cell death and IL1beta secretion. While GSNO inhibited this activation, it did not affect the sGC stimulator. This data suggests that NO can suppress NLRP3 inflammasome activation directly in macrophages.

Conclusions: Endothelial cell-induced NO inhibits inflammasome activation, which regulates chronic intra-renal inflammation. Additionally, endothelial dysfunction might promote chronic inflammation in CKD.

TH-PO163

Role of TLR4-MyD88 Regulation in the Renal Inflammation and Fibrosis Induced by C-Reactive Protein Jiao Hai Bao, Zi Li. *Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan, China.*

Background: Our previous study indicated CRP was not only a biomarker, but also a mediator of the pathogenesis of early renal fibrosis and inflammation. TGF-β/Smad and NF-κB signaling pathways activation but the underlying mechanism remains unclear. In present study, we hypothesis inflammation triggered by the NF-κB signaling pathway would subsequently activate Toll-like receptor 4, and then activates TGF-β/Smad and to mediates the acfute renal fibrosis and inflammation induced by CRP.

Methods: The expression of TLR4, MyD88 , NF-κB signaling pathway and TGF-β/Smad pathway, renal inflammation and fibrosis factors in both human renal proximal tubular epithelial cells(HK2) and human CRP-transgenic mice were detected. HK2 were cultured and stimulated with CRP, TLR4 siRNA, pyrrolidine dithiocarbamate (PDTC) (inhibitor for NF-kapa B). TLR4, MyD88 and other cytokines were assessed by real-time PCR and westernblot analysis . In vivo, unilateral ureteral obstruction model was mad in human CRP-transgenic and wild-type mice. Assessment of renal inflammation, fibrosis,NF-κB signaling pathway and TGF-β/Smad pathway, expression of TLR4 were evaluated by realtime PCR and immunohistochemistry staining.

Results: We found that HK2 incubation with CRP induced an significantly increase in expression of TLR4, MyD88, pro-inflammatory cytokines (IL-1β, TNF-α), chemokines (MCP-1) and pro-fibrotic growth factors (TGF-β, collegen-1,α-SMA) . Silencing of TLR4 with siRNA attenuated CRP-induced TGF-β/Smad signaling pathways activation, inhibited the downstream synthesis of MyD88, TGF-β, collegen-1 and α-SMA. Block NF-κB signal pathway inhibited expression of TLR4, MyD88, and all the inflammation and fibrosis cytokines. Compared with wild-type (Wt) mice at 3 days after UUO, CRPtg mice expressed more TLR4, MyD88 and developed more severe renal inflammation and fibrosis with a significant upregulation of proinflammatory cytokines , chemokines and pro-fibrotic growth factors.

Conclusions: CRP induced early renal inflammation by activating NF-κB signaling pathway, then lead to renal fibrosis through TLR4-MyD88-TGF-β/Smad dependent pathway.

Funding: Government Support - Non-U.S.

TH-PO164

Activation of Angiotensin II Receptors on T Cells Attenuates Renal Fibrosis

Nathan Rudemiller, Jiandong Zhang, Alexander David Jeffs, Steven D. Crowley. *Medicine/Div Nephrology, Duke Univ and Durham VA Medical Centers, Durham, NC.*

Background: Most forms of chronic kidney disease (CKD) culminate with renal fibrosis that heralds organ failure. Although global blockade of type 1 angiotensin (AT_1) receptors attenuates hypertension and kidney fibrosis, we have recently discovered that activating AT_1 receptors directly on T lymphocytes limits their differentiation toward a pro-inflammatory Th1 phenotype by blunting expression of the Th1 transcription factor TBET. As activated T cells have recently been implicated in the pathogenesis of kidney fibrosis, we hypothesized that AT_1 receptor activation on T cells may ameliorate kidney fibrosis.

Methods: We subjected mice with GFP^+ T cells (Lck Cre mT/mG) or T cell-specific deletion of the dominant murine AT_1 receptor isoform, AT_{1A}, (Lck Cre $Agtra^{flox/flox}$; "TKO"; 90% deletion) and wild-type (WT) controls to the unilateral ureteral obstruction (UUO) model of kidney fibrosis.

Results: In Lck Cre mT/mG reporter mice, renal infiltration of GFP^+ T cells peaked at day 14 UUO. Compared to WTs, obstructed TKO kidneys at day 14 had increased expression of mRNA for TGF-B (1.0 ± 0.1 vs 1.6 ± 0.4 au; P = 0.04) and more collagen 1 protein deposition (1.8 ± 0.4% vs 3.7 ± 0.9% of section; P = 0.05). Obstructed TKO kidneys also had elevated mRNA levels for TNF-α (1.0 ± 0.1 vs 1.6 ± 0.3 au; P = 0.03) and interleukin-1B (IL1B) (1.0 ± 0.1 vs 2.2 ± 0.6 au; P = 0.02), suggesting that activation of the AT1 receptor on infiltrating T cells mitigates renal fibrosis by suppressing their generation of profibrotic Th1 cytokines. To test the contribution of the Th1 response to kidney fibrosis, we examined kidney scar formation in TBET deficient (KO) mice and controls. At day 14 after UUO, TBET KO kidneys contained less collagen 1 mRNA (1.3 ± 0.1 vs 1.0 ± 0.1 au; P = 0.01) and protein (P<0.006) and expressed lower levels of IL1B (1.5 ± 0.2 vs 1.0 ± 0.1 au; P = 0.02).

Conclusions: We conclude that activating the T cell AT_1 receptor mitigates renal fibrogenesis by inhibiting their elaboration of pro-inflammatory and pro-fibrotic cytokines. These studies illustrate important tissue-specific actions of the renin angiotensin system in modulating the progression of CKD.

Funding: NIDDK Support, VA Support

TH-PO165

Factor XII Deficiency Confers a Modest Renal Beneficial Effect in 5/6 Nephrectomy-Induced Chronic Kidney Disease in Rats

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Background: Coagulation Factor XII (FXII) was previously reported as one of the candidate genes in proximity of the single-nucleotide polymorphisms (SNPs) significantly correlated with GFR. FXII mRNA levels in the kidney are negatively correlated with eGFR in chronic kidney disease (CKD) patients. We therefore were interested in evaluating whether FXII plays a causal role in CKD development and progression by studying the FXII knockout (KO) rat in a CKD model. The present study was designed to assess blood pressure, renal function and histology in wild type (WT) and FXII KO rats with surgically induced CKD via 5/6 nephrectomy (NX).

Methods: Four experimental groups were included: WT sham surgery; WT with 5/6 NX; FXII KO sham surgery; FXII KO with 5/6 NX. Blood pressure was measured by radiotelemetry. Renal function was assessed in metabolic cage studies. Kidney fibrosis was assessed by collagen synthesis rate and collagen trichrome staining. Kidney gene profiling was determined by RT-PCR. Plasma bradykinin was measured by ELISA and LC/MS.

Results: FXII KO animals exhibited markedly prolonged activated partial thromboplastin time (aPTT) and lower basal and stimulated bradykinin levels than WT animals, as expected. WT 5/6 NX animals developed hypertension, kidney hypertrophy, proteinuria, GFR reduction, kidney fibrosis and tubular injury, consistent with our understanding on the model. FXII KO 5/6NX group displayed significantly lower blood pressure and proteinuria, and a trend toward less GFR declining and less severe kidney fibrosis than the WT 5/6NX group.

Conclusions: Our data suggest that FXII deficiency confers a modest renal beneficial effect in 5/6 NX rat model. Future studies will be necessary in further determining the role of FXII-mediated activation of Plasma Kallikrein-kinin system (PKKS) in CKD development in the 5/6 NX rat model.

Funding: Pharmaceutical Company Support - Merck & Co.

TH-PO166

Renal Pharmacology and Preclinical Attributes of Sparsentan, a Dually Active Endothelin A and Angiotensin 1 Receptor Antagonist

Kevin Leach, Xin-Ru Pan-Zhou, Wayne Deats, Maria Beconi. *Retrophin, Inc., Cambridge, MA.*

Background: Sparsentan (RE-021) is a first-in-class, potent, dual endothelin A (ET_A) and angiotensin 1 (AT1) receptor antagonist currently in clinical development to treat focal segmental glomerular sclerosis (FSGS). Here we report the results of in vitro potency studies and in vivo toxicology studies and the effects of sparsentan in 2 different renal pharmacological models.

Methods: In vitro potency was assessed by competition with the appropriate ligand. Pharmacological activity was measured in either the 5/6 nephrectomy or Passive Heymann Nephritis models in rats. Long-term toxicology studies were performed in the Sprague Dawley rat and the Cynomolgus monkey.

Results: In vitro, sparsentan is a potent antagonist of the AT1 receptor (Ki=0.9 nM) and the ET_A receptor subtype (Ki=13 nM), with selectivity over the endothelin B subtype (Ki=6582 nM). In the 5/6 nephrectomy rat model of glomerular sclerosis, where animals received a single daily oral dose of sparsentan at 6, 18, or 60 mg/kg/day for 8 weeks, sparsentan reduced systolic blood pressure compared with the 5/6 nephrectomized control rats at the 18- and 60-mg/kg/day doses. At 60 mg/kg/day, sparsentan significantly reduced proteinuria compared with the control group after 4 (-65%, $P<.05$) and 8 weeks (-84%, $P<.05$) of treatment. The 18-mg/kg/day dose showed a positive trend toward reduction in proteinuria at 8 weeks. In the anti-FX1A-induced passive Heymann Nephritis model, 60 mg/kg/day oral sparsentan led to a 59% ($P=.009$) decrease in proteinuria, significant preservation of podocytes in the glomeruli ($P=.02$) and significant reduction in fibrosis in the kidney ($P=.03$) as measured by alpha smooth muscle actin staining. In long-term toxicology studies the no observed adverse effect level for sparsentan was 50 mg/kg/day in Cynomolgus monkeys and 80 mg/kg/day in Sprague-Dawley rats; the corresponding $AUC_{0\text{-last}}$ were 14 and 209 μg×hr/mL, respectively.

Conclusions: The combined preclinical characteristics of sparsentan—potency, selectivity, pharmacology, and toxicology—are consistent with a molecule that may be safe and effective to treat FSGS.

Funding: Pharmaceutical Company Support - Pharmacopeia, Inc. funded the long-term toxicity studies. Retrophin, Inc. acquired sparsentan from Ligand Pharmaceuticals (formerly Pharmacopeia) and funded the other preclinical studies. Retrophin, Inc., participated in the writing, reviewing, and approving this abstract for presentation

TH-PO167

T-Type Calcium Channel Blocker Attenuates Renal Interstitial Fibrosis Induced by Unilateral Ureteral Obstruction via Activating the Nrf2 Antioxidant Pathway

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Background: T-type calcium channel blocker has been reported to have a renoprotective effect in experimental models of renal fibrosis. We investigated whether the renoprotective effect of T-type calcium channel blocker is associated with modulation of the signaling of oxidative stress-induced renal fibrosis.

Methods: Treatment with a non-hypotensive dose of efonidipine, a T-type calcium channel blocker, or nifedipine, an L-type channel blocker, was initiated one day before unilateral ureteral obstruction (UUO) in C57BL6/J mice, and was continued until 3 and 7 days after UUO. Oxidative stress, inflammation and fibrosis in renal tissues were evaluated.

Results: In the obstructed kidneys, treatment with efonidipine significantly attenuated interstitial fibrosis, collagen deposition and inflammatory cell infiltration compared with those of treatment with nifedipine on day 7 after UUO. Additionally, efonidipine significantly increased the expression of the antioxidant enzymes heme oxygenase-1, NAD(P)H:quinone oxidoreductase 1 and superoxide dismutase 1 on day 3 and 7 after UUO, and Nox4 and catalase on day 3 after UUO. Increased apoptotic cell death and decreased Bcl-2 were also significantly ameliorated by efonidipine. Furthermore, the expression of the histone acetyltransferase p300/CBP-associated factor (PCAF), a regulator of inflammatory molecules, was significantly inhibited by efonidipine, on the contrary, nifedipine decreased the expression of PCAF. These beneficial effects of efonipidine were attributed to the increased nuclear expression of nuclear factor-erythroid-2-related factor 2 (Nrf2) on UUO day 3 and the increased expressions of both total and nuclear Nrf2 with elevated Kelch-like ECH-associated protein 1 on UUO day 7.

Conclusions: T-type calcium channel blocker could attenuate UUO-induced renal tubulointerstitial inflammation and fibrosis, via increased expression of PCAF and activation of the Nrf2 followed by upregulation of its subsequent antioxidants.

Funding: Private Foundation Support

TH-PO168

HDAC1 Inhibition Ameliorates Renal Inflammation in Unilateral Ureteral Obstruction Induced Renal Fibrosis Jin Han Lim,[1,2] Kyung Pyo Kang,[1] Tung Nguyen-Thanh,[1] Won Kim,[1] Sik Lee,[1] Sung Kwang Park.[1] *[1]Dept of Internal Medicine, Chonbuk National Univ Medical School, Jeonju, Korea; [2]Dept of Internal Medicine, Research Inst of Clinical Medicine, Chonbuk National Univ Hospital.*

Background: Renal fibrosis begins from localized activation of inflammatory processes, which include infiltration of inflammatory cells and production of proinflammatory cytokines and chemokines. Histone deacetylases can remove acetyl-residue from histones and result transcriptional regulation of DNA. Inhibition of these histone deacetylase (HDAC) might have potential protective effect against fibrosis of the liver, heart and kidney. However, modulation of renal inflammation by HDAC inhibition was still elusive in renal fibrosis process. Therefore, we evaluate whether class I HDAC inhibitor have anti-inflammatory effect on unilateral ureteral obstruction (UUO)-induced renal fibrosis.

Methods: Renal fibrosis was induced by UUO in the six-week-old C57BL/6 mice for 14 days. Class I HDAC inhibitor, vaproic acid (VPA, 300 mg/kg), was treated by intraperitoneal injection for 5 days before induction of renal fibrosis and continued for 14 days. Tubular injury, fibrosis and macrophage infiltration were evaluated by histologic examination. Expression of inflammatory cytokines and chemokines were evaluated by Western blot analysis and ELISA.

Results: After 14 days of ureteral obstruction, renal tubular injury and fibrosis were significantly increased compared to sham operation group. VPA treatment group has significantly attenuated the UUO-induced renal tubular injury and fibrosis. The number of F4/80 (+) macrophage infiltration after UUO surgery was significantly decreased after VPA treatment. In immunohistochemistry study, VPA treatment significantly decreased UUO-induced increase of ICAM-1 and MCP-1 expression in the tubule-interstitial area. We also found that total kidney ICAM-1 and MCP-1 expression were decreased after VPA treatment in UUO model by Western blot analysis and ELISA.

Conclusions: In conclusion, VPA have anti-inflammatory effect on UUO-induced renal inflammation through regulation of ICAM-1 and MCP-1 expression and decreases renal fibrosis.

Funding: Government Support - Non-U.S.

TH-PO169

D-Pinitol Alleviates Cyclosporine-Induced Renal Fibrosis via the Activation of Sirt1 and Nrf2 Antioxidant Pathways Minyoung Kim,[1] Soojeong Kim,[2] Eun Sil Koh,[1] Hyung Wook Kim,[1] Sungjin Chung,[1] Seok Joon Shin.[1] *[1]Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Korea; [2]Dept of Biochemistry, College of Medicine, The Catholic Univ of Korea, Seoul, Korea.*

Background: D-Pinitol, 3-methoxy analogue of D-chiroinositol, is one of the most abundant cyclitol present in soybean seeds, legumes and soy food. According to previous studies, D-pinitol has been suggested to possess multifunctional properties including anti-inflammatory, anti-lipidemic and anti-diabetic effects. The aim of this study was to evaluate of the effect of D-pinitol on renal fibrosis through the antioxidant signaling pathway in an experimental model of cyclosporine A (CsA)-induced nephropathy.

Methods: Renal effect of oral treatment of D-pinitol at 50 mg/kg body weight for 28 days was evaluated against CsA-induced renal injury in male ICR mice.

Results: Treatment with D-pinitol significantly prevented the rise in albuminuria, urine volume and urine osmolality and the decrease in renal function as compared to CsA control group. Additionally, D-pinitol attenuated CsA-induced tubulointerstitial fibrosis and inflammation as assessed by Masson's trichrome and α-SMA staining. Administration of D-pinitol increased the expression of heme oxygenase-1, NAD(P)H:quinone oxidoreductase 1 and catalase in CsA-treated kidneys. These renoprotective effects of D-pinitol were attributed to the increase in level of sirtuin 1 (Sirt1) and total and nuclear expressions of nuclear erythroid factor 2-related factor 2 (Nrf2), as well as an elevated level of Kelch-like ECHassociated protein 1, indicating that Sirt1 increased by D-pinitol regulates Nrf2 and in turn the activated Nrf2 affects the cellular antioxidant system.

Conclusions: These findings show that the renoprotective effect of D-pinitol against renal fibrosis in CsA-induced nephrotoxicity may result from the inhibition of oxidative stress through Sirt1 and Nrf2 activation and subsequent enhancement of antioxidant enzymes.

TH-PO170

Ligand-Bound Thyroid Hormone Receptor on Macrophages Ameliorate Kidney Injury via Inhibition of Nuclear Factor-κB Activities Toshihisa Ishii, Fumihiko Furuya, Kenichiro Kitamura. *Third Dept of Internal Medicine, Univ of Yamanashi, Chuo, Yamanashi, Japan.*

Background: In chronic kidney disease (CKD) patients, inflammation plays a pivotal role in the tubulointestitial injury and the progression of renal fibrosis, however it remains unclear how its processes are initiated and regulated. Hypothyroidism is associated with an increased occurrence of atherosclerosis and inflammation, suggesting the protective roles of thyroid hormones and its receptors against inflammatory processes. However, the contribution of thyroid hormone receptors to the macrophage differentiation has not been well documented.

Methods: We focused on the endogenous thyroid hormone receptor α (TRα) in macrophages and examined the role of ligand-bound TRα in the macrophage polarization-mediated anti-inflammatory effects.

Results: TRα-deficient irradiated chimeric mice exacerbated tubulointerstitial injury in the UUO model when compared with wild type mice. Macrophages isolated from obstructed kidneys of mice lacking TRα were mainly derived from bone marrow and displayed increased expression of proinflammatory cytokines such as IL-1β. In bone marrow-derived macrophages from wild type mice, T3-depleted culture medium augmented the phosphorylation of IκBα and enhanced the translocation of p65 to the nucleus via MAPK/MAPK phosphatase pathway. TRα-deficient macrophages also increased the release of proinflammatory cytokines accompanied with the increased nuclear translocation of p65. Evaluation of TRα-deficient bone marrow-derived macrophages confirmed the propensity of these cells to produce exaggerated levels of IL-1β, and co-culture of TRα-deficient bone marrow-derived macrophages with renal epithelial cells induced more severe damages to the epithelial cells via IL-1 receptor (IL1R) activation compared with wild type bone marrow-derived macrophages.

Conclusions: Our study indicates that ligand-bound TRα on macrophages plays protective roles in the kidney inflammation through the inhibition of NF-κB pathway, possibly by affecting the pro- and anti-inflammatory balance that controls the development of CKD.

TH-PO171

Canonical Wnt Signaling Promotes Macrophage Proliferation and Migration and Potentiates Kidney Fibrosis in Mice with Obstructive Nephropathy Ye Feng, Jiafa Ren, Chunsun Dai. *Nanjing Medical Univ.*

Background: Macrophage accumulation plays a critical role for kidney fibrosis in chronic kidney diseases. However, the underlying mechanisms regulating macrophage accumulation during kidney fibrosis remain to be investigated.

Results: In this study, we found that canonicalWnt/β-catenin signaling was robustly activated in macrophages from the fibrotic kidneys after UUO or IRI. A mouse model with specific deletion of β-catenin in macrophages was generated by using the Cre-LoxP system. Compared to control littermates, the knockouts developed less kidney injury, interstitial extracelluar matrix deposition, macrophage accumulation or macrophage proliferation in kidney tissue at 2 weeks after UUO. In the primary cultured bone marrow–derived macrophages (BMMs), compared with wild type macrophages, cell proliferation and cyclin D1 expression stimulated by M-CSF were markedly decreased in β-catenin–deficient macrophages. Additionally, cell motility for β-catenin–deficient macrophages was also largely inhibited compared to the wild type macrophages.

Conclusions: Taken together, this study suggests that Wnt/β-catenin signaling may regulate macrophage proliferation and migration, which may potentiate kidney fibrosis in mice with UUO nephropathy.

Funding: Government Support - Non-U.S.

TH-PO172

Inhibition of Inflammasomes Activation Attenuates Hypertensive Renal Injury Satoru Oka,[1] Yoko Obata,[1] Kenta Torigoe,[1] Miki Sawa,[1] Takehiko Koji,[2] Tomoya Nishino.[1] *[1]Dept of Nephrology, Nagasaki Univ Hospital, Nagasaki, Japan; [2]Dept of Histology and Cell Biology, Nagasaki Univ Graduate School of Biomedical Sciences, Nagasaki, Japan.*

Background: Chronic inflammation is closely linked to the development of organ damage by hypertension. Inflammasomes are involved in the production of IL-1b and play an important role in the progression of inflammation. Thus, inflammasomes may be involved in the development of hypertensive renal injury.

Methods: Using the Dahl salt-sensitive (DS) rats as a model of hypertensive renal injury, we examined the involvement of inflammasomes in the development of hypertensive renal injury and investigated whether colchicine (Col), an inhibitor of tubulin polymerization which is essential for activation of inflammasomes, attenuated hypertensive renal injury. We divided three groups: (1) DS rats fed a normal-salt diet, defined as DS + NS group, (2) DS rats fed a high-salt diet, defined as DS + HS group, (3) DS rats fed a high-salt diet with oral Col administration, defined as DS + HS + Col group. After 6 weeks salt loading, we collected renal tissue, blood and urine sample. We examined the morphological changes, the expression of inflammasomes associated protein (NLRP3 and caspase-1) by immunohistochemistry, and measured the urinary IL-1b by ELISA.

Results: Systolic blood pressure significantly elevated from 2 weeks after salt loading, but Col administration did not affect blood pressure. Serum creatinine, interstitial fibrosis and glomerulosclerosis significantly increased in the DS + HS group than those in the DS + NS group. These changes were significantly suppressed by Col administration. NLRP3 and caspase-1 expressions were limited to renal tubules and these expressions in the DS + HS group were significantly enhanced than those in the DS + NS group. Col administration significantly suppressed these expression. Moreover, urinary IL-1b was significantly increased in the DS + HS group than that in the DS + NS group, but Col tend to decrease urinary IL-1b levels.

Conclusions: Our results suggest that the inhibition of inflammasomes activation may be a therapeutic target in the hypertensive renal injury.

TH-PO173

shRNA Mediated Knockdown of DPP4 in the Kidney Ameliorates Kidney Inflammation and Proteinuria Ravi Nistala, Jianzhong An. *Medicine, Univ of Missouri-Columbia, Columbia, MO.*

Background: Dipeptidyl peptidase 4 (DPP4) inhibition is widely used for type 2 diabetes mellitus (T2DM) management. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus - Thrombolysis in Myocardial Infarction 53

(SAVOR-TIMI 53) trial showed that DPP4 inhibition improves proteinuria in T2DM subjects with chronic kidney disease (CKD). Our lab and others have observed that kidney DPP4 activation in rodents is associated with proteinuria in conditions of RAAS activation including diabetes and obesity. However, the role of kidney DPP4 is not clear.

Methods: To test our hypothesis, we uninephrectomized mice, knocked down DPP4 via lentiviral based shRNA injections into the contralateral kidney through the renal veins. After a recovery period of 2-3 wks, we implanted Ang II osmotic pumps (1000ng/kg/min), DOCA pellet (50mg) and provided 0.9% NaCl in drinking water for an additional 2 wks.

Results: Ang II-DOCA salt caused heart hypertrophy (Ang II/DOCA salt, 174±16mg vs. Saline, 140mg±8.2mg) as expected accompanied by left kidney hypertrophy. DPP4 knockdown was not protective of this hypertrophy. However, DPP4 knockdown prevented kidney injury as assessed by reduction in albuminuria (Sham controls+Ang II/DOCA 80.18 ug/mg crt vs. DPP4shRNA+Ang II/DOCA 25.76 ug/mg crt). Flow cytometry assessment showed that DPP4 knockdown prevented activation of CD4+ T-cells by Ang II/DOCA salt as indicated by reduced expression of DPP4 on CD4+, CD44+CD127+ central memory and CD44+CD127- effector cells. In addition, DPP4 knockdown prevented the Ang II/DOCA salt mediated infiltration of Ly6ChiCD11bhiF4/80lo macrophages and decreased CD11bloF4/80hi resident dendritic cells. DPP4 knockdown decreased pro-fibrotic markers such as Col1A and CTGF. Lastly, DPP4 knockdown decreased glomerulomegaly, mesangial expansion and interstitial inflammation as assessed by trichrome stain.

Conclusions: In summary, RAAS activation is a prominent mechanism for kidney injury in diabetes and obesity and kidney DPP4 is an important effector of RAAS mediated effects. Kidney specific DPP4 inhibition may ameliorate kidney injury and proteinuria through reduction in activation of the immune system and pro-fibrotic markers.

Funding: Pharmaceutical Company Support - Dialysis Clinics Inc.

TH-PO174

Allopurinol Diminished NLRP3 and Attenuated Hypertension and Renal Inflammation in the Chronic NO Inhibition and Salt Overload Model

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Background: Chronic NO synthase (NOS) inhibition with Nω-nitroarginine methylester (NAME) is a model of renal inflammation leading to hypertension (HT). Concomitant salt overload (HS) aggravates renal injury/inflammation and exacerbates HT. The pathogenesis of these processes remains unclear. Here, we investigated whether in this model: 1) Innate immunity (InIm) is activated; 2) Allopurinol (Allo), which has been reported to inhibit the NLRP3 inflammasome, attenuates renal damage.

Methods: Male Munich-Wistar rats received oral NAME (32 mg/Kg/d) and HS (HS+NAME, N=10). Other rats received HS+NAME and Allo, 36 mg/kg/d, (HS+NAME+Allo, N=10). Control rats received HS only (N=9). Tail-cuff pressure (TCP, mmHg), albuminuria (ALB, mg/d) and glomerulosclerosis (GS, %) were assessed after 4 weeks. In addition, we evaluated % interstitial collagen 1 (COLL1) and α-actin, and macrophages (MΦ, cells/mm^2). Glomerular (%area) and interstitial (cells/mm^2) NLRP3 was estimated by IHC. Renal content of IL1β (pg/mg), Caspase1, TLR4 and nuclear p65 (NFκB) were also measured (x HS).

Results:

	HS	HS+NAME	HS+NAME+Allo
TCP	148±2	211±4[a]	192±4[ab]
ALB	11±3	144±13[a]	79±18[ab]
GS%	0.3±0.2	4.5±1.2[a]	3.8±1[a]
COLL1%	1±1	3±1[a]	2±1[ab]
MΦint	23±2	133±7[a]	88±10[ab]
α-actin	0.7±0.1	10±1[a]	5±1[ab]
NLRP3int	0.8±0.1	2.4±0.3[a]	1.1±0.2[b]
NLRP3glom	1.4±0.2	4.5±0.8[a]	2.1±0.4[b]
IL1β	1.6±0.3	4.5±0.8[a]	2.0±0.3[b]
Caspase1	1.0±0.2	1.6±0.3	1.8±0.3
TLR4	1.0±0.1	2.6±0.4[a]	1.7±0.4
p65	1.0±0.1	2.9±0.3[a]	2.7±0.3[a]
Mean±SE;[a]p<0.05 vs HS,[b]p<0.05 vs HS+NAME			

These results suggest that severe HTN and renal inflammation/injury were associated with activation of both NLRP3/IL1β and TLR4/NFkB pathways. Allo normalized renal NLRP3/IL1β, attenuating HTN, ALB, renal inflammation and fibrosis, although NFkB remained activated.

Conclusions: Allo prevented NLRP3 activation and attenuated HT and renal injury in the HS+NAME model. Allo may exert renoprotection by mechanisms additional to, or independent of, its effect on uric acid. FAPESP/CNPq.

TH-PO175

Role of Innate Immunity in the Progressive Nephropathy That Ensues after Brief NO Inhibition and Salt Overload

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Background: NO inhibition by L-NAME plus salt overload (HS) leads to marked hypertension (HT) and renal injury. With cessation of treatment, most of these changes subside, but progressive renal injury/inflammation develops. Here we investigated whether activation of innate immunity (InIm) is involved in this process.

Methods: Male Munich-Wistar rats received HS and L-NAME, 32 mg/Kg/d. Control rats received HS only. Treatments ceased at 4 wk (18 rats studied). Additional rats (N=36) were studied at 8 and 28 wk. Assessed at each time point: tail-cuff pressure (TCP, mmHg), albuminuria (ALB, mg/d), glomerulosclerosis (GS, %), ischemic glomeruli (IG, %), interstitial collagen 1 (COLL, %), AngII+ and macrophages (Mø), cells/mm^2, and the renal protein content of IL1β (pg/mg), Casp1, TLR4, and NFkB (x HS).

Results:

	4wks		8wks		28wks	
	HS	HS+N	HS	HS+N	HS	HS+N
TCP	146±3	213±3*	146±3	164±4*[#]	131±2	162±8*
ALB	9±2	160±27*	5±1	25±6[#]	18±4	68±13*[&]
GS%	0±0	2±1*	0±0	1±0*	1±1	7±2*[&]
GI%	0±0	17±2*	0±0	7±1*[#]	0±0	4±0*[&]
COLL	1±0	4±1*	2±0	4±0*	1±1	4±0*
MΦ	26±4	225±19*	34±5	85±15*[#]	34±4	104±17*
AngII	2±0	10±1*	3±0	14±3*	3±1	10±2*
Casp1	1±0	4±1*	1±1	2±1	1±1	2±1
IL1β	2±0	4±1*	2±1	2±1	1±1	2±0.1
NFκB	1±1	2±1	1±1	2±1	1±1	1±1
TLR4	1±1	2±1*	1±1	2±1*	1±1	2±1*
*p<0.05 vs HS [#]p<0.05 vs 4 wk [&]p<0.05 vs 8 wk						

Expectedly, 4 wk HS+N caused severe HT, ALB and renal injury and increased Casp1, IL1β and TLR4. At 8 wk, renal injury/inflammation regressed partially, but InIm remained activated. At 28 wk, GS worsened, while inflammation and InIm activation persisted.

Conclusions: InIm activation may contribute to the initiation of renal injury in the HS+L-NAME model, and for autonomous progression of the nephrophaty even after cessation of the original insult. FAPESP/CNpq.

Funding: Government Support - Non-U.S.

TH-PO176

Useful of Presepsin and Procalcitonin in Cardiorenal Syndrome Type 5 Diagnosis

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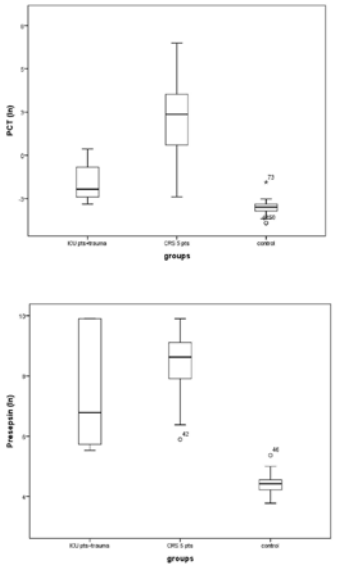
Background: Procalcitonin (PCT) has been shown to predict bacteremia and bacterial DNAemia. Presepsin is the soluble N-terminal fragment of CD14, which is the receptor for LPS and LPS-binding protein complexes; its level increases in response to bacterial infections, and it is considered a new, emerging, early marker for sepsis. The aim of this study was to investigate the role of Presepsin and PCT in the diagnosis of patients with Cardiorenal Syndrome Type 5 (CRS5).

Methods: we enrolled 8 ICU patients with trauma (4 male; age 61.6±22.9), 36 CRS5 patients (30 male; age 64.8±15.7) and 19 healthy controls (CTR) (10 male; age 42.3.±11.4). Plasma levels of Presepsin and PCT, IL6; IL18, TNFα, NGAL and endotoxin level were detected at diagnosis. Serum endotoxin activity was measured by the EAA^{tm}.

Results: Accordingly to EAA levels, patients were divided into two groups: 25% of patients had low endotoxin activity level (negative EAA), while 75% of patients showed high endotoxin activity level (positive EAA). Plasma PCT in CRS5 patients were significantly higher than those in ICU patients with trauma and CTR (both p=0.000). PCT levels was higher in pts with positive EAA results compared to negative EAA pts (p=0.000). Presepsin was significantly higher in trauma and in CRS5 patients than in CTR (both p=0.000). There were a positive correlations between Presepsin and IL6 (rho=0.583), TNFα (rho=0.411), IL18 (rho=0.636) and NGAL (rho=0.646)(all p<0.001).



Conclusions: Our results suggest that the levels of PCT are increased in CRS5 patients compared to trauma patients and CTR and PCT discriminate patients with positive EAA from the others. Presepsin correlates with pro-inflammatory cytokines and NGAL level, but it cannot discriminate between CRS5 and trauma pts in our ICU population. In conclusion, presepsin may underline an inflammatory process and PCT may be useful as a biomarker of systemic process and in particular of septic condition.

TH-PO177

Identification of Myeloid-Derived Fibrosis-Inducing Cells Presumably Accounting for Cardiorenal Connection in Chronic Kidney Disease Akihiro Sagara,[1] Norihiko Sakai,[1] Yasunori Iwata,[1] Kengo Furuichi,[1] Yasuhiko Yamamoto,[2] Takashi Wada.[1] *[1]Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Japan; [2]Dept of Biochemistry and Molecular Vascular Biology, Kanazawa Univ Graduate School of Medical Sciences, Kanazawa, Japan.*

Background: Chronic kidney disease (CKD) is a serious risk factor for cardiovascular diseases, which is known as cardio-renal syndrome (CRS). Dysregulation of tissue repair such as fibrosis is a pathological process leading to the end stage of organ failure. However, fibrosis mediators in CRS under CKD are not fully defined.

Methods: To seek the functional cell mediator, unilateral ureteral obstruction (UUO) plus angiotensin II (AII) infusion (AII+UUO) CRS model was established and used with employing CAG-GFP mice and Col1a2 (Col)-GFP mice along with procedures of parabiosis and bone-marrow transplantation (BMT). We performed flow cytometry to identify newly recruited cells into hearts or kidneys and gene expression analyses followed by cell sorting. We also used immunohistochemistry and co-culture system of sorted cells with mouse embryonic fibroblasts (MEFs) from Col-Luciferase mice.

Results: We newly identified a cluster of myeloid cells, which was tracked by GFP using mouse parabiosis or BMT and thereby found to be double-positive for CD45 and Sca1 in hearts as well as kidneys of the CRS model. The cells of the cluster were oval-shaped and mononuclear and significantly increased in number in proportion to heart fibrosis. Gene chip analyses further led to subdividing the population and then identifying fibrosis-triggering cells using Col-reporter MEF co-culture system. The number of the fibrosis-inducing cells in peripheral blood was also significantly increased in the CRS model.

Conclusions: We identified a new population of myeloid-derived fibrosis-inducing cells which were associated with cardiac and kidney fibrosis using our CRS mouse model. Novel strategies targeting the cell population would be therapeutic means against CRS in CKD.

Funding: Government Support - Non-U.S.

TH-PO178

Lineage Tracing Analysis Elucidating the Behaviors of Erythropoietin Producing Cells Keiichi Kaneko, Misako Asada, Motoko Yanagita. *Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto-shi, Kyoto-hu, Japan.*

Background: We previously reported that resident fibroblasts in the kidney including erythropoietin (Epo)-producing cells transdifferentiate into myofibroblasts with concomitant loss of Epo production during renal fibrosis. However, previous reports including ours cannot distinguish current Epo-producing cells from resident fibroblasts, and the behavior of Epo-producing remains unclear.

Recently Epo-Cre mice were generated which enabled the lineage tracing of the cells with the history of Epo production. With Epo-Cre mice, the transdifferentiation of Epo-Cre labeled cells into myofibroblasts during fibrosis has been demonstrated. As Epo-Cre mice labeled Epo-producing cells from fetal period to adult life, we tried to narrow down the period of labeling and trace current Epo-producing cells at desired time points.

Methods: We generated a novel mouse strain in which inducible form of Cre, Cre^{ERT2} is knocked-in at the locus of Epo gene (Epo-Cre^{ERT2} mice). Epo-Cre^{ERT2} mice were crossed with R26TdTomato mice, and tamoxifen was administered to activate Cre^{ERT2}.

Results: Epo-Cre^{ERT2} labeled cells were located in the interstitium of the cortex and corticomedullary region of the kidney, and expressed PDGFRb and CD73, indicating that these cells are resident fibroblasts. Double in situ hybridization confirmed that Epo-Cre^{ERT2} labeled cells expressed Epo mRNA, indicating that Epo-Cre^{ERT2} mice labeled Epo-producing cells faithfully. The numbers of Epo-Cre^{ERT2} labeled cells were increased with the induction of anemia. After unilateral ureteral obstruction, Epo-Cre^{ERT2} labeled cells expressed aSMA and increased in parallel with the progression of fibrosis, indicating the transdifferentiation to myofibroblasts.

Conclusions: We generated a novel mouse strain, Epo-Cre^{ERT2} mice, which faithfully label current Epo-producing cells at desired time points. Epo-Cre^{ERT2} labeled cells transdifferentiated into myofibroblasts and increased during renal fibrosis. Further analysis of Epo-producing cells with this strain will provide clues to the unsolved questions whether Epo-producing cells are distinct population in resident fibroblasts.

TH-PO179

Abstract Withdrawn

TH-PO180

microRNAs Are Essential for Maintenance of Postnatal Collecting Duct Homeostasis Sachin S. Hajarnis,[1] Matanel Yheskel,[1] Darren Williams,[1] Michel G. Baum,[1] Olivier Devuyst,[2] Vishal Patel.[1] *[1]UT Southwestern Medical Center, Dallas, TX; [2]Univ of Zurich, Zurich, Switzerland.*

Background: miRNA biogenesis involves the sequential processing of primary miRNA transcripts by two enzymes Dgcr8 and *Dicer*,while miRNA-induced gene silencing is aided by Argonautes1,2,3 and 4.In embryonic kidney,*Dicer* knockdown produces tubular cysts. In contrast,*Dicer* ablation from postnatal proximal tubules (PT) has no effect on kidney histology.However, whether miRNAs are required for maintenance of other segments of postnatal renal tubule is not known.

Methods: To study the role of miRNAs in renal tubule homeostasis,we ablated *Dicer* specifically from postnatal collecting ducts (CD) using the Pkhd1/Cre driver.Dicer is also involved in repair of damaged DNA and generation of small non-coding RNAs.To exclude miRNA-independent effects of *Dicer* deletion,we generated and analyzed CD-specific *Dgcr8*-KO,CD-specific *Ago*2-KO,Ago1,3,4-null,and combined Ago1-4-KO mice.

Results: *Dicer*-KO mice were born with histologically normal kidneys.By postnatal day(P)21,*Dicer* deletion evoked an increase in kidney injury markers *Ngal* and *Kim1*,which led to progressive interstitial fibrosis,tubular atrophy and inflammatory infiltration.*Dicer*-KO mice exhibited gradual increase in serum creatinine levels and shortened life-span (median survival of ~6 months).*Dgcr8*-KO mice were born with histologically normal kidneys but eventually developed progressive chronic kidney disease (CKD).While adult CD-*Ago2*-KO and global *Ago*1,3,4-KO mice had histologically normal kidneys,CD *Ago*1-4-KO recapitulated the *Dicer* and *Dgcr8*-KO phenotype.Microarrays on microdissected (MD) postnatal renal tubules revealed that CD have a unique miRNA expression pattern compared to PT.miR-200c was ~80-fold more enriched in CDs compared to PTs.miR-200c levels were reduced in MD *Dicer*-KO CDs compared to ctrl CDs.Levels of miR-200c targets *Zeb1 and Zeb2*,two regulators of epithelial-to-mesenchymal transition (EMT),were increased in CDs of *Dicer*-KO compared to ctrl kidneys but levels of epithelial markers Hnf-1β and E-cadherin were unchanged.

Conclusions: Inhibition of miRNAs in CD produces progressive CKD.Loss of CD-enriched miRNAs is associated with partial EMT,inflammatory and pro-fibrotic response.

Funding: NIDDK Support, Private Foundation Support

TH-PO181

Serum Levels of a Type VI Collagen Fragment Predict Mortality in Chronic Kidney Disease Daniel Guldager Kring Rasmussen,[1] Anthony Fenton,[2] Mark David Jesky,[2] Charles Ferro,[2] Morten Asser Karsdal,[1] Paul Cockwell,[2] Federica Genovese.[1] *[1]Fibrosis Biology and Biomarkers, Nordic Bioscience, Herlev, Denmark; [2]Dept of Nephrology, Univ Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom.*

Background: Chronic kidney disease (CKD) is associated with increased mortality. Systemic fibrosis may be a central component of this increased risk. Collagen type VI (COL6) is a major extracellular matrix protein that is over-expressed in fibrosis and mechanistically associated with vascular and myocardial injury. We hypothesized that increased COL6 expression represents a novel pathway for early mortality.

Methods: We used an immunoassay that binds a specific fragment of COL6, which is cleaved off after secretion from the cell (Pro-C6) and reflects COL6 formation. Serum Pro-C6 levels were measured in 500 patients from the Renal Impairment In Secondary Care (RIISC) study, which is a prospective cohort of patients with high risk of CKD progression as defined by the UK NICE criteria (2008). Patients were followed up for mortality; Cox regression analysis was used to assess risk of death.

Results: The cohort was 61.6% male, with a median age of 64 years (IQR 50-76), and 72.2% Caucasian. Median eGFR was 26.5 mL/min/1.73m^2 (19.5-34.6), and median ACR was 32.4 mg/mmol (6.2-128.0). Median follow-up time was 37 months. 66 (13.2%) patients had died at time of analysis. Median Pro-C6 level was 23.1 ng/mL (IQR 16.8-30.0) and on log transformation had a linear association with CKD-EPI eGFR ($r=-0.74$, $p<0.0001$). An increase in Pro-C6 of 10 ng/mL was associated with a mortality hazard ratio of 1.60

(95% CI 1.35-1.89, p<0.0001), and patients in the highest quartile had a 12-fold increase in hazard relative to the lowest quartile. After adjusting for confounding variables (age, eGFR, ACR, blood pressure, co-morbidities), Pro-C6 was independently associated with mortality (HR 1.51 [1.07-2.12], p=0.019).

Conclusions: Serum Pro-C6 is an independent marker for mortality in CKD after adjustment for confounders, and may reflect a pathological role for COL6 in the increased mortality associated with CKD.

TH-PO182

Selective Tubular Activation of Hypoxia-Inducible Factor-2α Has Dual Effects on Renal Fibrosis Kyoung Hye Kong,[1] Seung-Jung Kim,[2] Duk-Hee Kang,[2] Kyu Bok Choi,[2] Dong-Ryeol Ryu.[2] *[1]Graduate School, Ewha Womans Univ, Seoul, Korea; [2]Dept of Internal Medicine, Ewha Womans Univ, Seoul, Korea.*

Background: Hypoxia-inducible factor (HIF) is a key transcriptional factor in the response to hypoxia. This study aimed to investigate the effects of HIF-1α or HIF-2α activation on renal fibrosis according to activation timing in inducible tubule-specific transgenic mice with non-diabetic chronic kidney disease (CKD).

Methods: Mice with tubular selective HIF activation were generated by multiple breeding strategies. For the induction of renal fibrosis and CKD, the mice were fed a custom-made diet containing 0.2% adenine for 4 weeks, and HIF activation was done at day 0 or day 14. Mice were sacrificed at 4 weeks, and the kidneys were removed for histological evaluation and molecular analysis. We also performed in vitro experiments with cultured renal tubular epithelial cells.

Results: In transgenic mice with CKD, activation of HIF-2α at the beginning of CKD significantly aggravated renal fibrosis, whereas activation at a late-stage of CKD abrogated renal fibrosis, which was associated with restoration of renal vasculature and amelioration of hypoxia. Similarly, renal function assessed by serum creatinine in mice with HIF-2α activation at the beginning of CKD was comparable to that of wild-type CKD mice, but serum creatinine in CKD mice with activation at a late-stage was significantly lower than in wild-type CKD mice. HIF-2α activation in renal tubular cells upregulated mRNA expression of VEGF, PAI-1, lysyl oxidase, Bnip3, type I collagen, fibronectin, and PGK1, suggesting that it induced both profibrotic and antihypoxic pathways. However, tubule-specific HIF-1α activation had no significant effect on increased serum creatinine level or on histologic change in CKD mice, though its late activation decreased fibronectin expression.

Conclusions: Renal tubular HIF-2α activation has dual effects on renal fibrosis, and it could represent a therapeutic target in late-stage CKD when HIF-2α expression is not sufficient to maintain renal vascular integrity.

TH-PO183

Instructive Role of the Microenvironment in Preventing Renal Fibrosis (RF) Kei Matsumoto,[1] Sandhya Xavier,[2] Jun Chen,[2] Yujiro Kida,[2] Mark Lipphardt,[2] James R. Dutton,[3] Brian B. Ratliff,[2] Stefan Rose-John,[4] Michael S. Goligorsky.[2] *[1]Showa Univ, Tokyo, Japan; [2]New York Medical College, Valhalla, NY; [3]Univ of Minnesota, MN; [4]Christian-Albrechts Univ, Kiel, Germany.*

Background: Accumulation of myofibroblasts is a hallmark of renal fibrosis (RF). A significant proportion of myofibroblasts has been reported to originate via endothelial-mesenchymal transition. We initially hypothesized that exposing myofibroblasts to the extract of endothelial progenitor cells (EPC extract) could reverse this transition.

Methods: Studies were performed in cultured renal fibroblasts and in α-SMA mice subjected to UUO or folic acid-induced nephropathy (FAN).

Results: In vitro EPC extract prevented expression of α-SMA in TGF-β1-activated fibroblasts, however, it did not enhance expression of endothelial markers. In two models of RF, (UUO) and chronic phase of FAN, subcapsular injection of EPC extract to the kidney prevented and reversed accumulation of α-SMA-positive myofibroblasts and reduced fibrosis. Screening the composition of EPC extract for cytokines revealed that it is enriched in LIF and VEGF, but only LIF reduced fibroblast-to-myofibroblast transition of TGF-β1-activated fibroblasts. In vivo subcapsular administration of LIF reduced the number of myofibroblsts, improved the density of peritubular capillaries, however, it did not reduce the degree of RF. A receptor-independent ligand for gp130/STAT3 pathway, Hyper-IL-6, not only induced a robust downstream increase in pluripotency factors Nanog and c-Myc, but also exhibited a powerful anti-fibrotic effect.

Conclusions: 1) EPC extract prevents and reverses fibroblast-to-myofibroblast transition and RF. 2) The component of EPC extract, LIF, was capable of preventing development of the contractile phenotype of activated fibroblasts, but did not eliminate TGF-β1-induced collagen synthesis in cultured fibroblasts and models of RF. 3) In contrast, a receptor-independent gp130/STAT3 agonist, Hyper-IL-6, prevented fibrosis. 4) These studies through the evolution from EPC extract to LIF and then to Hyper-IL-6 demonstrate the instructive role of microenvironmental cues and may offer a strategy to prevent and reverse RF.

Funding: NIDDK Support

TH-PO184

TGF-β1 Represses Expression of the Antifibrotic Protein Follistatin in Mesangial Cells Neel Mehta, Tony Nuo Wang, Dan Zhang, Renzhong Li, Bo Gao, Joan C. Krepinsky. *Nephrology, McMaster Univ, Hamilton, ON, Canada.*

Background: The TGF-β superfamily member Activin A is emerging as an important mediator of the development and progression of renal fibrosis in chronic kidney disease (CKD). Follistatin (FST) is a secreted glycoprotein inhibitor of activin A. The balance between FST and activin A is an important determinant of fibrosis. Here we determined whether TGF-β1, a known key mediator of fibrosis in CKD, influenced the expression of FST.

Methods: Studies used primary mouse mesangial cells (MC) and standard molecular biology techniques including immunoblotting, qRT-PCR and luciferase reporter assays. Immunohistochemistry was used to assess FST in CKD mouse kidneys.

Results: Renal FST expression was decreased in the 5/6 nephrectomy mouse model of CKD. In MC, TGF-β1 potently suppressed FST transcript as early as 2 hours, associated with decreased FST protein expression. Inhibition of methyltransferase activity using 5-azacytidine reversed the repression of FST transcript by TGF-β1. Histone deacetylase inhibition with TSA and sodium butyrate also reversed this repression, suggesting that epigenetic mechanisms are involved in TGF-β1 regulation of FST. Interestingly, TGF-β1 did not affect activity of a FST mouse promoter (-2.9kb) reporter. However, TGF-β1 destabilized the FST 3'UTR as assessed by activity of a reporter construct. This was found to be dependent on Smad3 in studies using the Smad3 inhibitor SIS3 and MC from Smad3 knockout mice.

Conclusions: We show for the first time that TGF-β1 is a potent repressor of FST expression in MC through epigenetic regulation of its 3'UTR. Importantly, FST is decreased in CKD. This reduction of a major antifibrotic protein likely contributes significantly to the development of renal fibrosis. Future studies will delineate the molecular mechanism by which this occurs, and test the use of FST as a novel antifibrotic agent in CKD.

Funding: Government Support - Non-U.S.

TH-PO185

Hippo-YAP Signaling in the Regulation of Fibroblast Activation and Renal Fibrosis Zhengmao Zhang,[1] Yanlin Wang.[1,2] *[1]Medicine, Baylor College of Medicine, Houston, TX; [2]Center for Translational Research on Inflammation Diseases, Michael E. DeBakey VA Medical Center, Houston, TX.*

Background: Renal fibrosis is characterized by fibroblast activation and excessive accumulation of extracellular matrix proteins. However, the molecular mechanisms underlying fibroblast activation are incompletely understood. In this study, we investigated the role of Hippo-YAP signaling in fibroblast activation and fibrogenesis.

Methods: Fibroblasts were used to examine the role of Hippo-YAP signaling in fibroblast activation. To examine the functional role of YAP in vivo, we generated mice with fibroblast-specific deletion of YAP by crossing $YAP^{flox/flox}$ mice with tamoxifen-inducible collagen type I promoter/enhancer-driven Cre recombinase transgenic mice. Unilateral ureteral obstruction (UUO) and ischemia-reperfusion injury (IRI) models were used to induce renal fibrosis.

Results: In cultured fibroblasts, TGF-β1 led to phosphorylation of YAP at serine 127 and cytoplasmic translocation of YAP. Knockdown of YAP with shRNA enhanced α-smooth muscle actin (α-SMA) protein expression and promoter activity and ECM protein expression. Conversely, expression of constitutively active YAP (YAP-5SA) suppressed α-SMA protein expression and promoter activity and ECM protein expression. Mechanically, YAP interacted with Smad3 and inhabited its transcriptional activity. Mice with fibroblast-specific deletion of YAP were born normal and had no obvious morphological abnormality in the kidney. Compared with Cre negative, floxed YAP control mice, mice with fibroblast-specific deletion of YAP exhibited larger number of α-SMA-positive myofibroblasts and expressed higher levels of α-SMA protein in the kidneys following UUO or IRI. Furthermore, fibroblast-specific deletion of YAP significantly enhanced total collagen deposition and increased expression of extracellular matrix proteins in the kidneys in response to UUO or IRI.

Conclusions: Our results have shown that YAP functions as a corepressor in fibroblast activation through inhibition of Smad transcriptional activity. Therefore, activation of YAP signaling may represent a novel therapeutic strategy for fibrotic kidney disease.

Funding: NIDDK Support, VA Support

TH-PO186

The Ins and Outs of Nuclear TAZ Transport: More Than Retention Andras Kapus,[1,2] Pamela Speight,[1] Katalin Szaszi,[1,2] Michael M. Kofler.[1] *[1]Keenan Research Centre, St. Michael's Hospital, Toronto, ON, Canada; [2]Surgery & Biochemistry, Univ of Toronto, Toronto, ON, Canada.*

Background: Yap and TAZ are cell fate-determining transcriptional coactivarors, with key roles in the pathogenesis of organ (kidney) fibrosis. Their main regulators include the Hippo pathway and mechanical factors (via cytoskeleton remodeling), which impact their nucleocytoplasmic shuttling. According to the current view, Yap/TAZ traffic is controlled by stimulus-regulated binding to cytosolic or nuclear "retention factors" (e.g. 14-3-3 in the cytosol or TEAD transcription factors in the nucleus). However, several major aspects of Yap/TAZ shuttling remain unknown. It is unclear if nuclear entry occurs via an active process or passive diffusion, and neither the potential nuclear localization and efflux signals (NLS, NES) nor their putative regulation have been identified. Further, a simple retention model seems inadequate since the sequestering partners also shuttle.

Methods: To address these questions and identify key regions responsible for nucleocytoplasmic TAZ traffic, we generated a "molecular-mass ruler" toolkit fusing wild type or mutant TAZ or its fragments to a large tag (5mCitrine) that cannot passively diffuse through the nuclear pore. We expressed these in LLC-PK1 proximal tubular cells and tested their distribution under various conditions.

Results: We show that TAZ transport is active. We identify a conserved and unique (non-canonical), *negatively* charged NLS in the C-terminal half. The NLS is both necessary and sufficient for nuclear TAZ entry; its uptake is mediated in an unusual, Ran-GTPase activity-independent manner; and is mitigated by charge neutralization. Importantly cyclic stretch or the expression of active Rho promote the nuclear entry of the 5mCitrine-NLS, which binds neither 14-3-3 nor TEAD. Using mutagenesis and rapamycin-sensitive TAZ constructs, we also identify an N-terminal NES, which is masked by TEAD binding, but exposed through 14-3-3 mediated displacement of TEAD.

Conclusions: Thus, we have found a unique NLS in TAZ that is mechanosenstive and an NES which is controlled by a masking mechanism. Our findings shed light on fundamental aspects of TAZ regulation and offer new ways for pharmacological interventions.

Funding: Government Support - Non-U.S.

TH-PO187

Gremlin1 Signaling in Kidney Development and Disease Derek P. Brazil,[1] Rachel H. Church,[1] Imran H.A. Ali,[1] Mitchel Tate,[1] Deborah P. Lavin,[1] Ellen Kok,[2] Roel Goldschmeding.[2] *[1]Centre for Experimental Medicine, Queen's Univ, Belfast, Northern Ireland, United Kingdom; [2]Dept of Pathology, Univ Medical Centre Utrecht, Utrecht, Netherlands; [3]UCD Conway Inst, Univ College Dublin, Dublin, Ireland.*

Background: Grem1 is a secreted glycoprotein antagonist of bone morphogenetic proteins (BMPs) that is found in the extracellular matrix. Grem1 homodimers bind to and antagonise BMP homodimers, regulating normal limb, kidney and lung formation. *Grem1*-/- mice on a C57Bl/6 background die at birth due to renal agenesis, and display lower limb abnormalities. Grem1 is implicated in fibrotic diseases of kidney, lung and other tissues. Recent data has demonstrated increased levels of Grem1 in a range of cancers of the colon, brain and pancreas. Levels of Grem1 are elevated in rheumatoid arthritis in both synovial fluid and chondrocytes. Grem1 has also been suggested to drive angiogenesis via activation of VEGFR2 signalling.

Results: We generated *grem1*-/- mice on a mixed C57Bl6J/FVB background, and showed that levels of Grem1 were highest in colon, brain and spleen. In contrast, levels of Grem2 were highest in kidney, followed by colon, brain and liver. Only 8 % of *grem1*-/- offspring were viable, and these surviving *grem1*-/- mice were, on an average, 33 % smaller in size and weight compared to wild-type. Grem1 staining was evident in the muscularis layer of the colon, and elevated pSmad1/5/9 levels were detected in *grem1*-/- colon. The right kidney was absent in the majority of *grem1*-/- mice of both genders, with an enlarged left kidney evident, likely explaining the survival of these animals. Mice lacking Grem1 specifically in the kidney tubule epithelial cells (Grem1-TEC-/-) developed normal kidneys and were partially protected from acute kidney injury induced by folic acid. Compensatory increases in Grem2 expression were seen in Grem1-TEC-/- kidneys. Grem1 and Grem2 displayed differing affinities for BMP-2, 4 and 7 using C2C12 BRE-luciferase readouts, with Grem2, but not Grem1 inhibiting BMP-7.

Conclusions: We also show that Grem1 but not Grem2 are weak activators of VEGFR2 activation, suggesting that the current model of Grem1-mediated angiogenesis needs to be reconsidered.

TH-PO188

Extracellular Matrix Alterations Induced by Renal Fibrosis Perturb Epithelial Tubulogenesis in a Decellularized Whole-Kidney Model Joseph S. Uzarski,[1] Ryan C. Hill,[2] Kirk Hansen,[2] William M. Miller,[3] Jason Wertheim.[1,4] *[1]Comprehensive Transplant Center, Northwestern Univ Feinberg School of Medicine, Chicago, IL; [2]Dept of Biochemistry and Molecular Genetics, Univ of Colorado Denver, Denver, CO; [3]Dept of Chemical and Biological Engineering, Northwestern Univ, Evanston, IL; [4]Dept of Surgery, Jesse Brown VA Medical Center, Chicago, IL.*

Background: The growing number of patients suffering from renal failure has led to a severe shortage of donor kidneys for transplantation. Development of functional renal tissue by combining recipient cells with a scaffold derived from an unsuitable kidney would alleviate this shortage and create new platforms for modeling diseases or drug-induced nephrotoxicity.

Methods: Rat kidneys with or without 7 days of ureteral obstruction to induce extracellular matrix (ECM) accumulation were decellularized to produce normal or fibrotic ECM scaffolds. Proteomic analysis was performed for quantitative comparison of various protein fractions comprising normal, fibrotic, and decellularized kidney matrices. Scaffolds were repopulated with human distal tubule-derived renal cortical tubular epithelial cells (RCTECs) and cultured in a perfusion bioreactor for 7 days.

Results: Decellularization reduced the cellular fraction of kidneys by >97%, yet scaffolds retained fibrillar collagens (types I, III) basement membrane proteins (collagen IV, laminin), and proteoglycans (perlecan) organized in a 3D framework. Fibrotic ECM scaffolds were characterized by excessive interstitial collagen deposition. RCTECs cultured within normal ECM scaffolds formed tubules displaying proper basolateral (Na^+/K^+-ATPase, E-cadherin) and apical (a-tubulin+ cilia) protein expression. In contrast, RCTECs injected into fibrotic ECM scaffolds formed non-polarized, multi-layered interstitial aggregates.

Conclusions: ECM scaffolds derived from healthy or diseased kidneys are useful to investigate cell-matrix interactions that mediate renal tubule development or degeneration. These studies will also inform on the use of healthy or abnormal kidney scaffolds as 3D biological templates for generating patient-customized renal tissue for transplantation.

Funding: NIDDK Support, VA Support, Private Foundation Support

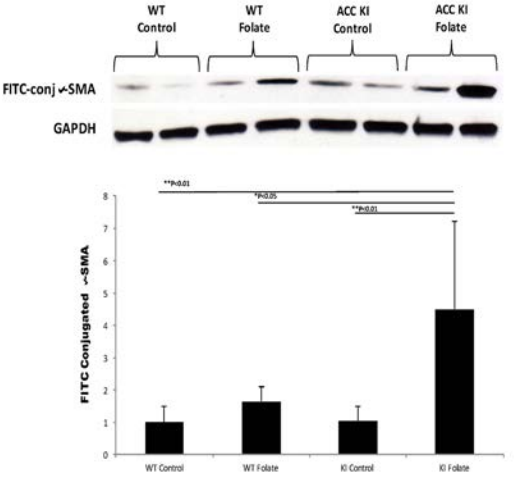
TH-PO189

Deletion of AMPK Regulatory Sites in ACC 1 and 2 Increases Epithelial Mesenchymal Transformation following Renal Injury Mardiana Lee,[1,2] Peter F. Mount,[1,2] Marina Katerelos,[1] Kurt Gleich,[1] David A. Power.[1,2] *[1]Nephrology, Austin Health, Melbourne, Victoria, Australia; [2]Medicine, The Univ of Melbourne, Heidelberg, Victoria, Australia.*

Background: AMP-activated protein kinase (AMPK) is a major regulator of fatty acid oxidation in tissues, mainly through phosphorylation of acetyl CoA carboxylase 1 and 2 (ACC1 and 2), which increase fatty acid (FA) oxidation and reduce FA synthesis. Previous studies have shown that activation of AMPK reduces renal fibrosis following injury, and also has an effect on epithelial-mesenchymal transformation (EMT). It is not known, however, whether these effects are mediated through regulation of fatty acid metabolism by AMPK. The aim of this study is to determine the effect of phosphorylation of ACC by AMPK on renal interstitial fibrosis and EMT in a model of renal tubular injury.

Methods: Male C57/BL6 mice with a combined knock-in mutation of the regulatory S79 and S212 phosphorylation sites in ACC1 and 2, respectively (ACC1/2 KI mice), were given an intraperitoneal injection of folic acid to induce renal injury. Kidneys were removed for analysis after 2 weeks.

Results: There was increased expression of α-smooth muscle actin (α-SMA) by Western blot analysis in the ACC1/2 KI mice when compared to the WT folate group (P<0.01).



There was no difference in expression of E-cadherin by Western blot. Interstitial fibrosis was not increased in the ACC1/2 KI mice, as determined by Sirius Red staining measured by image analysis. Measurement of the expression of key regulatory enzymes by PCR suggested that FA oxidation (ACox1, CPT1) and glycolysis (PK) were reduced in the mice receiving folate compared to untreated controls, but there was no difference between WT and ACC1/2 KI mice.

Conclusions: The data suggests that control of energy metabolism by AMPK following tubular injury is of particular importance in preventing EMT, and that EMT and fibrosis are controlled separately in these mice.

TH-PO190

Loss of β-1 Integrin in Collecting Duct Principal Cells Downregulates AQP2 Expression and Induces Severe Renal Fibrosis and Kidney Failure Fahmy Mamuya,[1,2] Lei Lei,[1] Dongping Xie,[1] Kenji Tsuji,[1,2] Diane E. Capen,[1] Teodor G. Paunescu,[1,2] Hua Ann Jenny Lu.[1,2] *[1]Program in Membrane Biology and Div of Nephrology, Massachusetts General Hospital; [2]Harvard Medical School, Boston, MA.*

Background: Renal collecting duct principal cells are highly regulated epithelial cells and play a major role in salt and water transport via ENaC sodium channels and aquaporin-2 (AQP2) water channels, respectively. Understanding their signaling mechanisms is crucial for developing therapeutic approaches to enhance and support the role of the kidney in homeostasis. A major cause of kidney failure is renal fibrosis, and β-1 integrin has been shown to play a role in fibrosis in the kidney and other organs. Recent studies are now showing interaction between AQP2 and β-1 integrin in principal cells, suggesting that β-1 integrin is involved in AQP2 trafficking.

Methods: To investigate the role of β-1 integrin in principal cells we conditionally deleted β-1 integrin in mouse medullary principal cells under a specific AQP2 Cre promoter. We investigated water homeostasis in these mutant mice by urine osmolarity measurements, and occurrence of fibrosis through histopathological analyses and transmission electron microscopy. We also characterized AQP2 expression by immunohistochemistry, immunoblotting, and RT-PCR.

Results: Although the mutant mice appeared normal at birth and successfully grew into adulthood, they died around 10 to 12 weeks, weighing about half of their wild type littermates' weight. Remarkably, the mutant mice exhibited very low urine osmolarity (404 ± 52 mOsm/kg, compared to 2403 ± 203 mOsm/kg in wild types). Starting around 5 weeks of age, we observed a steep time-dependent decrease in AQP2 protein levels in the mutant mouse collecting ducts along with increased evidence of fibrosis and cell death. Towards the end of their lives, AQP2 expression was barely detectable in mutant mice. This phenotype progressed to renal medullary fibrosis, which ultimately caused kidney failure and premature death.

Conclusions: Our data strongly suggest that β-1 integrin is required for maintaining AQP2 expression in medullary collecting duct principal cells, and that its loss induces renal medullary fibrosis and kidney failure.

Funding: NIDDK Support

TH-PO191

Muscle-Kidney Crosstalk via A Myokine, Irisin, Suppresses Renal Metabolic Reprogramming and Fibrosis in Mice Hui Peng,[1,2] Qianqian Wang,[1,2] Yanlin Wang,[2] William E. Mitch,[2] Zhaoyong Hu.[2] *[1]Div of Nephrology, Dept of Medicine, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China; [2]Div of Nephrology, Dept of Medicine, Baylor College of Medicine, Houston, TX.*

Background: Beneficial effects of exercise on muscle metabolism are associated with improved survival of patients with ESRD but the mechanisms underlying this observation are unknown. Potential mediators are myokines which are released from muscle by exercise. We hypothesized that myokines could mediate muscle-kidney crosstalk to limit the development of renal fibrosis and chronic kidney disease (CKD).

Methods: Since skeletal muscle-specific PGC-1a overexpression (mPGC-1a) stimulates myokines expression, we created several CKD models in the transgenic mice and evaluated the kidney function and the degree of fibrosis. Using a metabolomics approach, we accessed energy metabolic reprogramming in kidneys of wild-type and mPGC-1a with or without CKD. We also performed a PCR-based myokines array in muscle of PGC-1a mice and serum fraction assay to identify renal protective myokines.

Results: In mPGC-1α mice with CKD, we found that serum creatinine was lower than it in wild-type mice with CKD, this response was associated with less degree of interstitial fibrosis and glomerulosclerosis. Using a metabolomics approach, we found that CKD-induced energy metabolic reprogramming in kidney cells was blocked in kidney of mPGC-1a mice. To identify renal protectivemyokines present in serum of mPGC-1a mice, we divided serum from mPGC-1a mice into 4 fractions and found that only the fraction3 (10kD~30kD) significantly increased mitochondrial respiration capacity in kidney cells. We then analyzed the myokines array in muscle of PGC-1a mice and identified that irisin was the most likely candidate to protect kidney. The underneath mechanism is that irisin counteracts TGF-β1 signaling by competitive inhibiting TGF-β1 type 1 receptor.

Conclusions: Based on previous identification that metabolic reprogramming in kidney cells contribute to the development of fibrosis and CKD, we conclude that myokine irisin can block metabolic reprogramming in kidney cells and limit the development of renal fibrosis and CKD.

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TH-PO192

Oral Treatment with PBI-4050 Reduces Kidney Fibrosis Lyne Gagnon,[1] Brigitte Grouix,[1] Ming-Zhi Zhang,[2] Martin Leduc,[1] Mikaël Tremblay,[1] François Sarra-Bournet,[1] Lilianne Geerts,[1] Kathy Hince,[1] Liette Gervais,[1] Marie-Pier Cloutier,[1] Shaun Abbott,[1] Jean-Simon Duceppe,[1] Boulos Zacharie,[1] Raymond C. Harris,[2] Pierre Laurin.[1] *[1]ProMetic BioSciences Inc., Laval, QC, Canada; [2]Vanderbilt Univ School of Medicine, Nashville, TN.*

Background: PBI-4050 is a first-in-class novel orally active compound which displays anti-inflammatory/antifibrotic activities via a novel mechanism of action. PBI-4050 also displays metabolic properties by reducing blood glucose levels. In a double-blind single ascending dose (400 to 2400 mg) in healthy volunteers, PBI-4050 was found to be safe and well tolerated up to 2400 mg without any significant adverse effects (SAEs). Similarly, PBI-4050 was well tolerated in chronic kidney disease (CKD) patients with no SAEs observed at 800 mg. PBI-4050 is presently in Clinical Phase II in diabetes (T2D) associated with metabolic syndrome and in idiopathic pulmonary fibrosis (IPF). Preliminary data from the open-labeled T2D associated with metabolic syndrome clinical phase shows that PBI-4050 significantly reduced glycated hemoglobin (HbA1c, -0.77%, $p<0.001$), and biomarkers (IL-18, resistin, and pentraxin-3) from the first 12 enrolled patients.

Results: PBI-4050 has demonstrated strong anti-fibrotic activities in different kidney models: 5/6-nephrectomized rats (end-stage renal failure, early and late treatment), doxorubicin-induced nephrotoxicity (acute kidney injury), renal ischemia, db/db and db/db eNOS-/- mice (diabetic kidney disease), DTR (a spontaneous tubulointerstitial fibrosis in homozygous HB-EGF mice), and unilateral ureteral obstruction (UUO). PBI-4050 plays a key role in inflammation/fibrosis regulation by reducing pro-fibrotic cytokines and growth factors (MCP-1, CTGF, CCL11, IL-5, endothelin 1 (EDN1), EGF, PDGFα, VEGFα, Inhibin βE, TGF-β2), myofibroblast activation and epithelial-to-mesenchymal transition markers (α-SMA, collagen III, ILK, MMP2, MMP9, and TGF-β1, 2 and 3), remodeling enzymes (LOX, MMP1, MMP2, MMP9, MMP13, uPA, PAI-1, TIMP3 and ILK) and fibrotic markers, resulting in improvement of organ function.

Conclusions: Taken together, these pre-clinical results suggest that PBI-4050 offers the potential as a novel therapy for the treatment of kidney fibrosis.

TH-PO193

Imaging Renal Fibrosis with Two Photon Excitation (TPE), Second Harmonic Generation (SHG), and Fluorescence Lifetime Imaging Microscopy (FLIM) Evgenia Dobrinskikh,[1] Xiaoxin Wang,[1] Yuhuan Luo,[1] Suman Ranjit,[4] Avi Rosenberg,[3] M. Scott Lucia,[1] Vivette D. D'Agati,[2] Moshe Levi.[1] *[1]Univ of Colorado; [2]Columbia Univ; [3]NIH; [4]UC Irvine.*

Background: Glomerulosclerosis and tubulointerstitial fibrosis occurs in many diseases and signals poor renal functional outcomes. In view of recent therapies aimed at the pathogenesis of fibrosis, sensitive and quantitative techniques for documenting fibrosis have become highly desirable. Current stains have limited use for 3D imaging and they do not allow for determination of the metabolic state of the kidney.

Methods: We have applied TPE, SHG, and FLIM for label-free imaging of kidney sections. We have then applied the phasor approach for FLIM analysis, which allows for the determination of collagens and other extracellular matrix components, and metabolic state of the kidney (free to bound NADH ratio) taking advantage of the specific autofluorescence characteristics of these molecules. These techniques can be used in fresh or frozen or FFPE tissues. We have furthermore applied the novel multiphoton imaging microscope known as the DIVER which enables for imaging of thick tissues.

Results: In kidney biopsies obtained from diabetic humans, compared to biopsies obtained from nondiabetic subjects, we have determined that there is a strong SHG signal around the glomerulus and tubulointerstitial areas, which indicates presence of fibrosis. FLIM shows shift to the shorter lifetime in diabetic kidneys that corresponds to different metabolic state of the tissue and different matrix composition. FLIM also may determine relative degree of the disease progression based on differential lifetimes in diabetic compared to nondiabetic control kidneys. Application of the DIVER allows for 3D imaging of thick sections made from biopsies, which should give a better vision of the kidney ultrastructure and disease progression.

Conclusions: TPE, SHG and FLIM imaging allows for label-free and 3D imaging of the extracellular matrix and metabolic state of the kidney based on the autofluorescence of the corresponding molecules. In addition to the quantitative advantage it also allows for further processing of the same kidney biopsy slides for additional histochemical stains or biochemical studies.

Funding: NIDDK Support

TH-PO194

PHF14 as an Innate Brake to the Progression of Renal Fibrosis following Acute Kidney Injury Bo Yang, Zhiguo Mao. *Div of Nephrology, Changzheng Hospital, Shanghai, China.*

Background: PHF14 is a newly identified regulator of mesenchyme growth in embryonic tissues. Studies showed that PHF14-null mutants were neonatally lethal due to interstitial tissue hyperplasia in major organs including kidney. We hypothesize that PHF14 may plays a protective role in renal fibrosis progression after the pro-fibrotic insults. It will help to elucidate the interactions of mediators in the process of renal fibrogenesis by illuminating the function of PHF14.

Methods: We determined the expression profile of PHF14 in fibrotic kidneys after folic acid (FA) injection in mice. Then, we generated PHF14 inducible knockout mice to explore the biological role of PHF14 in the progression of renal fibrosis following FA administration. Relationship of PHF14 expression with TGF-β signaling pathway was also examined in rat renal fibroblast cells. We also validated whether PHF14 performed as negative regulator of platelet-derived growth factor receptor-α (PDGFR-α) and eventually suppressed the expression of fibrosis related biomarkers.

Results: PHF14 was upregulated in fibrotic kidneys after FA insults in mice. Compared with sham control, induced PHF14 deletion in adult mice exacerbated renal fibrosis following FA associated renal injury. TGF-β stimulation induced the upregulation of PHF14 *in Vitro*, and p-smad3 acts as transcription factor to enhance the PHF14 expression, which was proved by immunoprecipitaion assay. Lack of PHF14 expression enhances collagen I and α-SMA synthesis induced by TGF-β *in Vitro.*

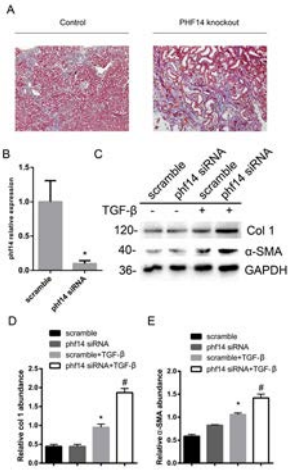

Figure 1: (A) Representative Masson (200x) images demonstrating the severity of renal fibrosis in the PHF14 knockout mice at day 28 after FA administration compared with sham control. (B) Q-PCR demonstrating the transcriptional activity of PHF14 mRNA. (C-E) Lack of PHF14 expression enhances collagen I and α-SMA synthesis induced by TGF-β. * P < 0.05 compared with NRK-49F cells untreated with TGF-β; # P < 0.05 compared with NRK-49F cells pretreated with scramble control siRNA and cultured in the media with TGF-β.

PHF14 was involved in the inhibition of the PDGF signaling overactivation by selectively repressing PDGFR-α transcription.

Conclusions: PHF14 expression was upregulated in fibrotic models *in vivo* and *in vitro* with anti-fibrotic functions. The TGF-β /smad3/PHF14 pathway acted as a self-limiting mechanism in TGF-β dominated renal pro-fibrotic signaling by suppressing PDGFR-α expression.

Funding: Government Support - Non-U.S.

TH-PO195

A Step Towards Clinical Application of Acellular Matrix: A Clue from Macrophage Polarization

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Background: The outcome of tissue engineered organ transplants depends on the capacity of the biomaterial to promote a pro-healing response once implanted in vivo. Multiple studies, including ours, have demonstrated the possibility of using the extracellular matrix (ECM) of animal organs as a platform for tissue engineering and more recently, discarded human organs have also been proposed as a scaffold source. It is known that natural matrices present diverse immune properties when compared to artificial biomaterials. However, how these properties compare between diseased and healthy ECM and artificial scaffolds has not yet been defined.

Methods: We used decellularized renal ECM derived from WT mice and from mice affected by Alport Syndrome as a model of renal failure with extensive fibrosis, at different time-points of disease progression. We characterized the morphology and composition of these ECMs and compared their in vitro effects on macrophage activation with that of synthetic scaffolds commonly used in the clinic (collagen type I and poly-L-(lactic) acid, PLLA).

Results: We showed that ECM derived from Alport kidneys differed in fibrous protein deposition (col I, col IVα1,2 and fibronectin) and cytokine content (Resistin, TIM-1/KIM-1, DPPIV/CD26 and Reg3G) when compared to ECM derived from WT kidneys. Yet, both WT and Alport renal ECM induced macrophage differentiation mainly towards a reparative (M2) phenotype (reduced CD80), while artificial biomaterials towards an inflammatory (M1) phenotype. Anti-inflammatory properties of natural ECMs were lost when homogenized, hence three-dimensional structure of ECM seems crucial for generating an anti-inflammatory response.

Conclusions: Together, these data support the notion that natural ECM, even if derived from diseased kidneys promote a M2 protolerogenic macrophage polarization, thus providing novel insights on the applicability of ECM obtained from discarded organs as ideal scaffold for tissue engineering.

TH-PO196

Human Discarded Kidneys as a Source of Protolerogenic Extracellular Matrix Scaffolds for Bioengineering

Astgik Petrosyan,[1] Stefano Da Sacco,[1] Chiara Donadei,[2] Giuseppe Orlando,[3] Laura Perin,[1] Paolo Cravedi.[2] *[1]Children's Hospital Los Angeles; [2]Icahn School of Medicine at Mount Sinai; [3]Wake Forest School of Medicine.*

Background: Human extracellular matrix (ECM) scaffolds produced through the decellularization of discarded kidneys represents a potential platform for kidney bioengineering. Studying their immune properties is crucial for their future implementation in the clinic.

Methods: We decellularized adult human kidneys not suitable for transplantation, dissected medulla from cortex and evaluated their relative immune effects on human naïve T cell proliferation (CFSE dilution in response to aCD3/aCD28 mAb) and conversion into functional regulatory T cells (cells were cultured with aCD3/aCD28 mAb, IL2 and no TGF-β, since we previously showed the TGF-β is present in ECM). We also seeded human macrophages on ECM and evaluated their cytokine expression.

Results: ECMs obtained from the cortex of discarded human kidneys inhibited expansion of activated human naïve CD4+ T cells and promoted their conversion into FoxP3+ regulatory T cells (Treg) (Figure) . Macrophages adhered onto human ECM and showed cellular activity including survival and proliferation. In addition after 5 days they secreted significant amounts of anti-inflammatory cytokine such as IL10, but no pro-inflammatory cytokines like INFγ and TNFα.

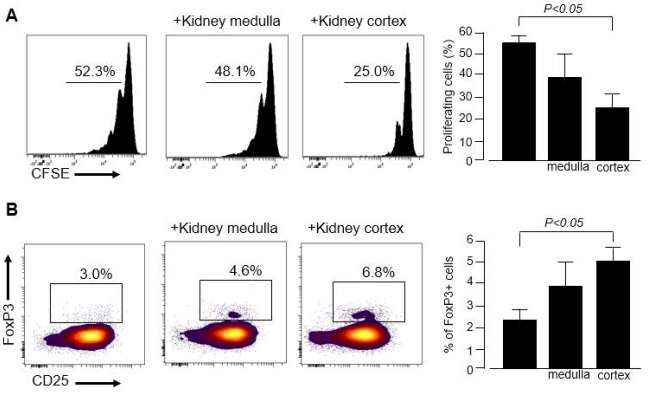

Figure. Human renal ECM inhibits naïve CD4+ T cell expansion and promotes their conversion into regulatory T cells. (A) CFSE-labeled naïve CD4+ T cells were activated with anti-CD3/anti-CD28 mAb with or without ECM from kidney medulla of cortex. Cell division was quantified on day 5 with CFSE dilution by flow cytometry. Representative histograms (left) and data quantification (right) of 6 independent experiments from 6 different donors. (B) Naïve CD4+ T cells were activated with anti-CD3/anti-CD28 mAb and IL-2 with or without ECM from kidney medulla of cortex. On day 5, the percentage of CD4+CD25+FoxP3+ regulatory T cells was quantified by flow cytometry. Representative histograms (left) and data quantification (right) of 4 independent experiments from 4 different donors.

Conclusions: Our data demonstrate that hrECMs inhibit effector T cell expansion and promote naïve CD4 T cell conversion into FoxP3+ Treg, possibly through a TGF-β mechanism. They stimulate macrophages to secrete anti-inflammatory cytokines, supporting further studies for their clinical use.

Funding: Private Foundation Support

TH-PO197

Podocyte-Derived Microparticles Induce Pro-Fibrotic Responses in Human Promote Proximal Epithelial Cells: Role of Scavenger Receptors

Dylan Burger, Mercedes N. Munkonda, Shareef Akbari, Maddison Turner. *Kidney Research Centre, Ottawa Hospital Research Inst, Ottawa, ON, Canada.*

Background: Tubulo-interstitial fibrosis (TF) is a hallmark of advanced diabetic kidney disease that is linked to renal decline. Cross-talk between podocytes and the tubular epithelium has been implicated in TF however the pathogenic mechanisms are poorly understood. Microparticles (MPs) are 100-1000 nm membrane vesicles shed from stressed/injured cells that have been implicated in cell-cell communication. Our lab recently showed that podocytes release MPs following stress/injury and that urinary podocyte MPs are increased in animal models of diabetes. The purpose of the present study was to assess whether podocyte MPs play a role in podocyte-epithelial cell cross-talk.

Methods: MPs were isolated from the media of cultured human podocytes (hPODs) and administered to cultured human proximal tubule epithelial cells (PTECs). PTEC/MP interaction was assessed by fluorescence microscopy and intracellular signaling responses were assessed by Western blot analysis.

Results: Podocyte MPs physically interacted with PTECs immediately after administration and continuing over 24 hours. Podocyte MP treatment increased phosphorylation of protein kinases p38 and Smad3 and increased expression of the extracellular matrix (ECM) proteins fibronectin and collagen type IV. All MP-induced responses were attenuated by co-treatment with the p38 inhibitor SB202190 (10 uM). The transforming growth factor beta (TGF-β) receptor inhibitor (SB431542, 10 uM) blocked MP-induced Smad3 phosphorylation and ECM protein expression but not p38 phosphorylation suggesting that these responses occurred downstream of p38. Finally, inhibition of the class B scavenger receptor CD36 with Sulfo-N-succinimidyl oleate (10 uM) completely blocked

MP-mediated effects on PTECs. Similarly, MP-induced activation of p38 and Smad3 was attenuated by a neutralizing antibody to kidney injury molecule-1, a putative scavenger receptor linked to tubular injury.

Conclusions: Taken together, our results suggest that podocyte MPs induce pro-fibrotic responses in PTECs. Such effects may involve activation of scavenger receptors and contribute to fibrosis and renal decline in diabetes.

TH-PO198

Core Fucosylation Regulates the Transition of Pericytes to Myofibroblasts in Renal Interstitial Fibrosis

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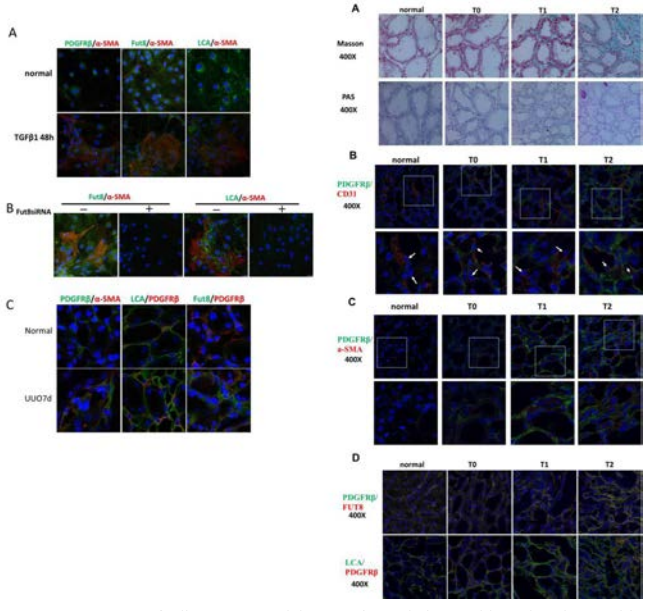
Background: Chronic kidney diseases are irreversible diseases with high mortality. Renal interstitial fibrosis is the final common outcome of CKD. While myofibroblasts are the main contributors to the progress of RIF. Recently pericytes have been confirmed as the main source of myofibroblasts in RIF. Cross-talks of multiple signaling pathways, such as TGF-β, PDGF pathways, are known to activate pericytes in the process of RIF. Researches have found that single receptor blockage of these pathways can alleviate RIF. Our previous researches have found that some key receptors of these pathways are modified by fucosyltransferase 8-regulated core fucosylation.

Methods: Pericyte-myofibroblast transition and the expressions of core fucosylation were observed in renal biopsies of IgAN patients, UUO mice model and primary pericytes cultivation *in vitro*. *FUT8*shRNA-Adenovirus and *FUT8*siRNA were used for the knockdown of FUT8 *in vivo* and *in vitro*, Pericyte-myofibroblast transition and the expressions of core fucosylation were then observed.

Results: We found that core fucosylation of pericytes was increased with the severities of renal interstitial injuries in IgAN patients. Similar elevations of core fucosylation were found in UUO mice model and pericytes-myofibroblasts transition model *in vitro*. Adenoviral-mediated *FUT8*shRNA *in vivo* and *FUT8*siRNA *in vitro* were then used to inhibit the expressions of FUT8. Interestingly, we found that the inhibitions of core fucosylation could alleviate RIF dramatically and prevent pericytes transition both *in vivo* and *in vitro*.



Conclusions: Our findings suggested that core fucosylation could regulate the transition of pericytes to myofibroblasts in the progress of RIF. We believed that glycosylation may provide a novel hub target to prevent RIF and CKD.

Funding: Government Support - Non-U.S.

TH-PO199

The BET Bromodomain Inhibitor JQ1 Diminished Renal Fibrosis

Sandra Rayego-Mateos,[1] Jose Morgado-Pascual,[1] Beatriz Suarez-Alvarez,[4] Pierre-Louis Tharaux,[2] Alberto Ortiz,[3] Carlos Lopez-Larrea,[4] Marta Ruiz-Ortega.[1] *[1]Univ Autónoma Madrid; [2]Paris Cardiovascular Centre, France; [3]ISS-Fundación Jimenez Diaz; [4]Hospital Univ Central de Asturias, Spain.*

Background: Bromodomain and extraterminal domain (BET) proteins participates in tumor development, autoimmunity, inflammation, and fibrosis. BET proteins bind to acetylated lysine residues on proteins to regulate the transcriptional program. Sex determining region Y-box 9 (SOX9) is a transcription factor involved in kidney regeneration, proliferation and migration. JQ1, a selective BET inhibitor, have demonstrated beneficial effects on murine pulmonary and liver fibrosis, but there is no data in renal fibrosis.

Methods: Experimental models of anti-glomerular basement membrane nephritis, induced by nephrotoxic serum (NTS) administration and unilateral ureteral obstruction (UUO) were used. Mice were treated with JQ1 (100 mg/mouse/day). In vitro studies were done in TGF-β-treated mesangial cells and renal fibroblasts.

Results: NTS-injected mice presented extracapillary proliferation and increased of podocyte damaged (evaluated by WT-1 levels) and gene upregulation of biomarkers of renal injury (*Ngal* and *Kim-1*) after 10 days. JQ1 restored changes in renal function (as serum creatinine and urinary albumin), downregulated renal injury biomarkers and fibronectin expression, and ameliorated glomerular lesions. Obstructed kidneys presented tubulo-interstitial fibrosis after 5 days. JQ1 markedly diminished gene overexpression of profibrotic factors (TGF-β and PAI-1) and renal overproduction of matrix components (Fibronectin and type I collagen). In vitro, JQ1 dose-dependently inhibited TGF-β-mediated Fibronectin and type I collagen gene expression and protein production. In injured kidneys of both models, Sox9 activation was found. In obstructed kidneys nuclear Sox9 was colocalized with SMA-positive cells, mainly in areas of matrix accumulation. JQ1 blocked Sox9 nuclear localization in injured kidneys and in TGF-β-treated cells.

Conclusions: Our results demonstrate that JQ1 regulates profibrotic and matrix-related components and reduces experimental renal fibrosis. These results suggest that BET inhibitors could have important therapeutic applications in chronic kidney diseases.

Funding: Government Support - Non-U.S.

TH-PO200

Niclosamide Ameliorates Fatty Acid Metabolism Disturbance of Tubular Epithelial Cells in Renal Fibrosis

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Background: Renal fibrosis is the common pathological and histological pathway of chronic kidney disease.Mitochondrial dysfunction promotes tubular epithelial cells injury, playing a vital role in the progress of renal fibrosis. As the mitochondria rich cells, tubular epithelial cells are mainly using fatty acid oxidation (FAO) as the energy fuel. Uncoupling proteins function as mitochondrial fatty acid anion exporters, modulating cellular fatty acid homeostasis. Niclosamide is a teniacide mediating the uncoupling of mitochondria. In this study, we investigate the role of niclosamide in the fatty acid metabolism of tubular epithelial cells in renal fibrosis.

Methods: C57BL/6J mice were randomly assigned into control group and three folic acid groups, mice in the folic acid groups sacrificed in the day 1,day 7 and day 30. The bilateral kidneys were used for morphology, western blot and RT-PCR analysis. C57BL/6J mice after injecting folic acid were treated with niclosamide, while the morphology of renal sections and the function of fatty acid oxidation were observed.

Results: 1.Folic acid induced the mitochondrial injury and fatty acid oxidation defect of the tubular epithelial cells. 2. The fibrotic matrix was expanded and the markers of collagen fibrils such as α-SMA, fibronectin (FN), Collagen I were increased in the kidneys after folic acid injecting in a time depended manner. 3.Niclosamide restored the structure and function of the tubular epithelial cells' mitochondria after folic acid injecting. The fatty acid oxidation of the tubular epithelial cells was resumed by niclosamide treatment. 4.Niclosamide could alleviate the progress of renal fibrosis induced by folic acid.

Conclusions: These results demonstrate that mitochondrial dysfunction leading to fatty acid metabolism disturbance in the tubular epithelial cells contribute to renal fibrosis. Niclosamide-induced mitochondrial uncoupling improves the mitochondrial structure and the fatty acid oxidation in the progress of renal fibrosis, and finally resisting the lesion of renal fibrosis. Targeting mitochondrial uncoupling may be a potential treatment for renal fibrosis.

Funding: Government Support - Non-U.S.

TH-PO201

Proteomic Analysis of Glomerular Extracellular Matrix Demonstrates Differences between FSGS Variants

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Background: Histologic evidence for abnormal remodeling of the glomerular extracellular matrix (ECM) is a prominent feature of FSGS, however, the differences in glomerular ECM composition are unknown. The current study used laser capture microdissection (LCMD) of glomeruli from human biopsy specimens and mass spectrometry (MS) to compare glomerular ECM composition among patients with FSGS NOS, collapsing FSGS (CFSGS), and normal subjects.

Methods: Glomerular sections were obtained by LCMD from de-identified formalin-fixed paraffin embedded renal biopsy tissue from 6 patients with FSGS NOS, 7 patients with CFSGS, and from 2 kidneys retrieved, but not used, for transplantation. Proteins were extracted by sequential decellularization with NH4OH/triton X-100 and extraction of the remaining matrix with protease MAX surfactant. Peptides obtained by proteolysis with trypsin were identified by MS. Peptide data was analyzed by Mascot/Sequest, and label-free quantification compared among groups.

Results: Of the 1271 unique proteins identified, 161 were determined to be ECM proteins by comparison to the matrisome database and previously published glomerular ECM identification. 110 ECM proteins were identified from normal glomeruli, 136 from FSGS NOS, and 155 from CFSGS. 106 ECM proteins were common between normal and FSGS NOS, while 30 proteins were unique to FSGS NOS. 109 ECM proteins were common between normal and CFSGS, while 46 were unique to CFSGS. 130 ECM proteins were common between FSGS NOS and CFSGS, 6 unique to FSGS NOS, and 25 unique to CFSGS. Protein quantification identified 8 proteins differentially expressed in CFSGS and 10 proteins differentially expressed in FSGS NOS, compared to the other two groups.

Conclusions: Proteomic analysis of glomeruli isolated by LCMD from renal biopsy tissue successfully identified differences in ECM protein expression in FSGS NOS and CFSGS. Differential ECM protein expression provides targets for biomarker identification for specific FSGS variants and suggests unique differences in ECM remodeling between FSGS NOS and CFSGS.

TH-PO202

Fibroblast Growth Factor 23 Exacerbates Kidney Fibrosis Involving β-Catenin Signaling Activation and Extracellular Matrix Production in Tubular Cells Xin Liu, Chunsun Dai. *Nanjing Medical Univ.*

Background: The concentration of fibroblast growth factor 23 (FGF23) in the circulation is closely correlated with the decline of renal function in patients with chronic kidney diseases. However, whether FGF23 can directly promote kidney fibrosis and its underlying mechanisms are not clear.

Methods: In this study, we generated a mouse model with ectopic expression of exogenous FGF23 in CD-1 mice through tail vein hydrodynamic injection of FGF23 expression plasmid once a week.

Results: FGF23 was largely increased at as early as one day and maintained at high level in the circulation during the observation period. The mice developed hypertension, anemia and hypokalemia but little kidney morphological damage after four times of pFGF23 injection. We then generated mouse models with kidney fibrosis including UUO nephropathy, adriamycin nephropathy and ischemia/reperfusion injury. The mice with ectopic FGF23 expression developed more severe kidney fibrosis and inflammatory cell accumulation in kidney tissue after UUO, adriamycin injection or ischemia/reperfusion compared to those injected with control plasmid. In cultured NRK-52E cells, FGF23 treatment could exacerbate TGFβ1-induced extracellular matrix production with a time and dose dependent manner. Additionally, in both FGF23 treated NRK-52E cells and UUO kidneys from mice with ectopic FGF23 expression, p-β-catenin (Ser675), an active form of b-catenin, was robustly elevated.

Conclusions: Thus, these results suggest that FGF23 exacerbates UUO nephropathy in mice, which may be associated with b-catenin signaling activation and extracellular matrix production in tubular cells.

Funding: Government Support - Non-U.S.

TH-PO203

Proximal Tubule Specific COMP-Angiopoetin-1 Overexpression Decreases Renal Injury in a Mouse Unilateral Ureteral Obstruction Model Woong Park, Yujin Jung, Tung Nguyen-Thanh, Kyung Pyo Kang, Won Kim. *Dept of Internal Medicine, Chonbuk National Univ Medical School, Jeonju, Korea.*

Background: Preservation of renal endothelial cells is one of promising strategies for renal fibrotic process. Angiopoietin-1 (Ang1) is an angiogenic factor through its endothelial receptor tyrosine kinase, Tie2. We have reported that adenoviral transfer of cartilage oligomeric matrix protein(COMP)-Ang1 decreases the progression of renal fibrosis by regulation of Tie2 and Akt phosphorylation in mouse unilateral ureteral obstruction (UUO) model. It also has been demonstrated that Ang1 is expressed on renal tubular epithelial cells of normal mice. In this study, we investigated whether the COMP-Ang1 in the mouse proximal tubules has protective effect on UUO-induced renal inflammation and fibrosis.

Methods: We generated proximal tubule specific COMP-Ang1 overexpression mice, constitutively expressing COMP-Ang1 under the control of a gamma-glutamyltransferase 1 (gGT1, a proximal tubular cell marker) promotor (COMP-Ang1 TG mice). Renal fibrosis was induced by UUO in the six-week-old COMP-Ang1 TG and WT mice for 7 days. Histologic examination and Western blot analyses for alpha-smooth muscle actin (α-SMA), intercellular adhesion molecule 1 (ICAM-1), F4/80 and *granulocyte* receptor-1 (Gr-1) were performed.

Results: COMP-Ang1 overexpression from renal proximal tubular epithelial cell ameliorated the UUO-induced decrease of PECAM-1-positive endothelial cells. After ureteral obstruction, tubular dilatation, desquamation and mononuclear cell infiltrations were increased in WT mice. However, UUO-induced tubular injury and fibrosis were significantly decreased in proximal tubular COMP-Ang1 overexpression mice. Immunofluorescence data for neutrophils (Gr-1-positive cells) and macrophages (F4/80 positive cells) showed that proximal tubular COMP-Ang1 overexpression mice suppressed UUO-induced increase of Gr-1 and F4/80 positive cells infiltration. In Western blot analyses, α-SMA and ICAM-1 expression were significantly decreased in proximal tubular COMP-Ang1 overexpression mice compared to WT mice.

Conclusions: Proximal tubular COMP-Ang1 overexpression might have a protective role in UUO-induced renal fibrosis and inflammation.

Funding: Government Support - Non-U.S.

TH-PO204

ErbB4 Deletion Accelerates Renal Fibrosis and Inflammation after Unilateral Ureteral Obstruction Fenghua Zeng,[1] Lance A. Kloepfer,[1] Tomoki Miyazawa,[2] Raymond C. Harris.[1] *[1]Medicine, Vanderbilt Univ Medical Center, Nashville, TN; [2]Pediatrics, Kindai Univ School of Medicine, Sakai, Osaka, Japan.*

Background: Tubulointerstitial injury/fibrosis is a histological feature involved in the progression of chronic kidney disease (CKD) regardless of etiology. Our preliminary results showed increased ErbB4 expression in the glomeruli and tubular epithelium of CKD kidneys. However, its role in the tubulointerstitial injuries remains to be determined.

Methods: Heart rescued ErbB4 deletion (ErbB4^{del}ht^{+}) and wild-type (WT) mice were subjected to unilateral ureteral obstruction (UUO) or sham operation. Renal function and pathological changes were examined.

Results: ErbB4^{del}ht^{+} mice tended to have higher BUN levels compared to WT mice after UUO, but the levels were not significantly different. However, in UUO kidneys, ErbB4^{del}ht^{+} mice displayed accelerated interstitial fibrosis as early as 3 days after UUO, whereas similar levels of fibrosis shown by trichrome staining were only evident after 6 days of UUO in WT mice. ErbB4^{del}ht^{+} kidneys had increased collagen I, SMA, and FSP-1 immunoreactivity. Macrophage infiltration as shown by F4/80 immunostaining and renal cell apoptosis by cleaved caspase 3 levels were also increased in ErbB4^{del}ht^{+} kidneys.

Conclusions: ErbB4 deletion accelerates the development and progression of renal fibrosis in obstructive nephropathy. Increased expression of ErbB4 seen in the kidneys of CKD may reflect a compensatory effect to overcome the tubulointerstitial injury.

Funding: NIDDK Support, VA Support

TH-PO205

Serum Levels of a Type VI Collagen Fragment Predict Progression of Chronic Kidney Disease Signe Holm Nielsen,[1] Anthony Fenton,[2] Mark David Jesky,[2] Charles Ferro,[2] Morten Asser Karsdal,[1] Paul Cockwell,[2] Federica Genovese.[1] *[1]Fibrosis Biology and Biomarkers, Nordic Bioscience, Herlev, Denmark; [2]Dept of Nephrology, Univ Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom.*

Background: Progressive renal fibrosis is the dominant process that leads to end stage renal disease (ESRD) in patients with chronic kidney disease (CKD). Collagen type VI (COL6) is over-expressed in progressive fibrosis, with prominent expression in renal disease. Pro-C6 is a COL6 fragment which reflects COL6 expression. We hypothesized that Pro-C6 levels were associated with CKD progression.

Methods: We measured Pro-C6 levels in the serum of 500 patients from the Renal Impairment in Secondary Care (RIISC) study. This is a prospective cohort study of patients with high risk CKD, as defined by the UK NICE criteria (2008). Participants were followed up and data collected at 12 months for progression of CKD, defined as either commencement of RRT or decline in eGFR of >30%. Logistic regression was performed to assess Pro-C6 as a marker of progression of CKD at 12 months.

Results: The cohort was 61.6% male, with a median age of 64 years (IQR 50-76), and 72.2% caucasian. Median eGFR was 26.5 mL/min/1.73m^2 (19.5-34.6), and median ACR was 32.4 mg/mmol (6.2-128.0).

417 patients had 12-month follow-up, and of these 46 (11.0%) had experienced progression of CKD at 12 months. Median Pro-C6 level was 23.1 ng/mL (IQR 16.8-30.0), and on log transformation had a linear association with CKD-EPI eGFR ($r=-0.74$, $p<0.0001$). An increase in Pro-C6 of 10 ng/mL was associated with a hazard ratio of 1.96 (95% CI 1.50-2.55, $p<0.0001$) for CKD progression, and participants in the highest quartile had a 9-fold higher risk than those in the lowest quartile. After adjusting for eGFR and ACR, a significant association between Pro-C6 and CKD progression at 12 months remains (HR 1.44 [01.02-2.04], $p=0.039$).

Conclusions: Serum Pro-C6 is an independent marker for CKD progression at 12 months. This indicates a potential pathological role for collagen type VI in progressive CKD.

TH-PO206

Inhibition of K-Ras in the Peri-AKI Period in a Murine Model of Aristolochic Acid Nephropathy Reduces Long-Term Progression to CKD in a Murine Model of Aristolochic Acid Nephropathy Sujit Kumar Saha, Bruce M. Hendry, Claire C. Sharpe. *Dept of Renal Sciences, King's College London, London, United Kingdom.*

Background: Acute Kidney Injury (AKI) is a recognised early forerunner of Chronic Kidney Disease (CKD). K-Ras expression is up-regulated in renal fibrosis and chronic K-Ras inhibition post-injury prevents scarring. Our aim was to investigate whether transiently reducing K-Ras expression prior to an AKI reduces progression to CKD.

Methods: CD1 mice received intra-peritoneal injections of 3.5mg/kg Aristolochic Acid (AA) or saline (NS) on Day 1 & on Day 5. A treatment group also received a single subcutaneous dose of 100mg/kg K-Ras murine Antisense Oligonucleotide (ASO) 2 days prior to the 1st AA dose. A vehicle group received NS 2 days prior instead. Blood urea nitrogen (BUN), Creatinine (Cr), Haemoxygenase 1 (HO-1) and urinary NGAL were measured at multiple time points. The degree of fibrosis was ascertained through a Hydroxyproline assay, Western blot (WB) for alpha SMA and Picrosirius Red (PSR) & Masson Trichrome (MT) staining. The effect on K-Ras was determined by QPCR and WB.

Results: Mice given AA transiently developed an AKI at day 5-20 before then recovering. There was a further rise in both BUN & Cr at day 80 indicating CKD. Administration of Murine K-Ras ASO reduced both the BUN & Cr at day 80 compared to vehicle by 37%. Fibrosis quantification through PSR & MT staining showed AA caused a 5 fold increase in collagen deposition by day 80. ASO treatment halved this amount of fibrosis at day 80 and reduced both hydroxyproline & αSMA. AA resulted in raised K-Ras expression throughout the model. ASO only transiently reduced K-Ras at day 0 as it was raised again by day 12 and remained elevated throughout the model before falling again at day 80. It is this initial fall in K-Ras with ASO that has resulted in the reduction in the CKD demonstrated at day 80.

Conclusions: Transiently reducing K-Ras expression in the peri-AKI period in a murine model of AA nephropathy reduces downstream fibrosis and prevents the decline in renal function. Targeting K-Ras may provide a future therapeutic option for preventing renal fibrosis and CKD following AKI.

TH-PO207

Lipoxins Attenuate Kidney Disease Progression in Diabetic ApoE-/- Mice Phillip Kantharidis,[1] Mark E. Cooper,[1] Muthukumar Mohan,[1] Aaron D. McClelland,[1] Karin Jandeleit-Dahm,[1] Catherine Godson,[2] Eoin P. Brennan,[1,2] Stephen P. Gray,[1] Raelene J. Pickering,[1] Chris Tikellis.[1] *[1]JDRF Danielle Alberti Memorial Centre for Diabetes Complications, Baker IDI Heart and Diabetes Insitute, Melbourne, Victoria, Australia; [2]UCD School of Medicine and Medical Sciences, UCD Conway Inst of Biomolecular & Biomedical Research, Dublin, Ireland.*

Background: Strategies based on the resolution of inflammation are an attractive approach for the treatment of diabetic kidney disease (DKD). Endogenous lipid mediators including Lipoxins (LXs) actively promote the resolution of inflammatory responses. Here we investigated the potency of endogenous (LXA_4) and stable LX analogues (Benzo-LX) in attenuating kidney disease in diabetic $ApoE^{-/-}$ mice.

Methods: 6-week-old apolipoprotein E ($ApoE^{-/-}$) mice were randomly divided into control and diabetes groups. Diabetes was induced with low-dose streptozotocin. Mice in both groups were randomly divided into vehicle, LXA_4, and Benzo-LX analogue groups, and followed for 10 or 20 weeks.

Results: Diabetic $ApoE^{-/-}$ mice presented with DKD, as evidenced by albuminuria and renal injury. Diabetes-induced glomerular expansion and mesangial matrix expansion were significantly attenuated by LXA_4 and Benzo-LX (Glomerulosclerotic index: control 1±0.1, diabetic+vehicle 2.3±0.2, diabetic+LXA4 1.8±0.01, diabetic+Benzo-LX 1.5±1 arbitrary units, $p<0.01$ Benzo-LX vs vehicle; n=9). The increase in renal cortical collagen (COL1, COL3, COL4), alpha-smooth muscle actin (α-SMA), transforming growth factor beta 1 (TGF-β1), ICAM-1, VCAM-1, MCP1, IL-6 and TNFA seen in diabetic $apoE^{-/-}$ mice was attenuated by both LXA4 and Benzo-LX. The Lipoxins had no significant effect on albuminuria.

Conclusions: Taken together, our data demonstrate that LXs may be used as novel anti-fibrotic and anti-inflammatory therapeutics in DKD.

Funding: Government Support - Non-U.S.

TH-PO208

Smad Anchor for Receptor Activation, which Regulates Wnt/β-Catenin Signaling, Is Transcriptionally Suppressed by Dec1 Constance Runyan, Tomoko Hayashida, H. William Schnaper. *Pediatrics, Northwestern Univ, Chicago, IL.*

Background: We previously reported that cultured renal epithelial cells (HKC) lacking Smad Anchor for Receptor Activation (SARA) spontaneously undergo mesenchymal transition and become more fibrogenic, expressing higher TGF-β-stimulated COL1A2 mRNA content . In unilateral ureteral obstruction-mediated renal fibrosis, SARA is significantly downregulated, suggesting that SARA loss is a key event for progression. At least four mRNA species for human SARA exist and one major form, Z2.1 lacks the FYVE domain, thought to be required for SARA membrane localization. The Smad-binding domain and following C-terminal portion remain intact. Functions of the Z2.1 isoform are not well characterized. Here we evaluate transcriptional regulation of SARA, and compared effects of Z2.1 and full-length SARA on Wnt/β-catenin signaling.

Methods: The SARA promoter region from -1036 to TSS or its truncation mutants were cloned into pGL2-basic vector. Expression vectors carrying the full-length or Z2.1 form of human SARA cDNA were transfected in HKC. β-catenin or Smad2/3 dependent transcriptional activity was evaluated using TOPflash/FOPflash or ARE/SBE-luciferase reporter systems.

Results: Consistent with our previous finding that TGF-β decreases SARA mRNA expression, SARA -1036 promoter activity was reduced by TGF-β by 50%. A -814 promoter construct demonstrated 3-fold higher basal transcriptional activity compared to the -1036 promoter. Analysis identified a binding site between -814 and -1036 for Dec1, and Dec1 knockdown yielded higher levels of SARA protein and resistance to TGF-β-mediated SARA downregulation. Cells expressing either Z2.1 or full-length SARA suppressed Wnt3a-induced β-catenin activity to a similar degree, while neither Smad2-dependent ARE nor Smad3-dependent SBE reporter was affected by Z2.1 or full-length SARA overexpression. Both SARA isoforms interacted with β-catenin and rendered β-catenin for degradation.

Conclusions: Dec1 ablation inhibits TGF-β-stimulated SARA downregulation. Despite lacking the membrane localization sequence, Z2.1 suppresses Wnt/β-catenin signaling. These findings suggest possible novel approaches to suppressing progression of renal fibrosis.

Funding: NIDDK Support

TH-PO209

Renoprotective Effects of Angiotensin III: Role of Oxidative Stress and Extracellular Matrix Expansion Rita de Cassia Cavaglieri, Doug Yoon Lee, Robert T. Day, Yves C. Gorin, Denis Feliers. *Dept of Medicine/Nephrology, Univ of Texas Health Science Center at San Antonio, San Antonio, TX.*

Background: Glomerular injury is a prominent pathological feature of diabetic nephropathy (DN). Hyperglycemia promotes extracellular matrix protein accumulation by glomerular mesangial cells (MCs) and oxidative stress plays an important role in the pathogenesis of glomerular fibrotic lesions in DN.

Results: Type 1 diabetic mice displayed higher renal angiotensin (Ang) II and lower renal levels of Ang III, which correlated with a downregulation of aminopeptidase-A, which generates Ang III from Ang II. Mice lacking Ang II type 2 receptor (AT2R) lower renal Ang III even in the absence of diabetes. Reduced Ang III was associated with enhanced oxidative stress and glomerular fibrotic injury in these mouse models, suggesting that Ang III may be protective in DN. We studied the effect of Ang III on high glucose (HG)-induced oxidative stress and fibrotic injury in cultured MCs. Ang III blocked rapid upregulation of Nox4 NADPH oxidase expression and reactive oxygen species (ROS) generation induced by HG in the cells and the mitochondrial fraction. Ang III negatively regulated HG-mediated Nox4 expression via inhibition of Nox4 mRNA translation, and significantly attenuated upregulation of fibronectin induced by HG at 24 h. All these effects of Ang III were reversed by pharmacologic or genetic inhibition of the AT2R. The relevance of this pathway was confirmed by the finding that Nox4 expression, ROS production and fibrotic injury are exacerbated in both control and type 1 diabetic mice lacking AT2R. The signs of renal disease in these mice are linked to a reduction in Ang III generation in the kidney.

Conclusions: We provide the first evidence that Ang III, acting through the AT2R, protects MC from HG-induced oxidative stress and fibrotic injury via inhibition of Nox4 expression. Our data unveil the anti-oxidant and anti-fibrotic effects of Ang III and demonstrate that a functional interplay between AT2R and Ang III accounts for these renoprotective action in the diabetic environment. Targeting of Ang III/AT2R axis may represent a promising therapeutic approach for the treatment of DN.

Funding: NIDDK Support, Private Foundation Support

TH-PO210

The Cys-Knot C Terminal Motif of CTGF Modulates Fibrotic Effects in Proximal Tubule Cells Alone and in Concert with TGFβ1 Matthew Pottle, Mysore Keshavmurthy Phanish, Mark E. Dockrell. *Renal, SW Thames Inst for Renal Research, Carshalton, Surrey, United Kingdom.*

Background: Connective tissue growth factor (CTGF, CCN2) and Nov(CCN3) are both members of the CCN family of matricellular proteins; they are structurally similar, both consist of an IGFBP motif and a von Willebrand factor type C motif linked by a hinge region to the thrombospondin and CYS knot motifs. CTGF in particular has been shown to play an important role in cell proliferation and extracellular matrix remodelling regulated by different motifs and is widely recognised as a key mediator of glomerular and tubulointerstitial fibrosis in the context of renal disease. Work by ourselves and others supports the hypothesis that CCN3 acts in opposition to CTGF with regard to the regulation of fibrosis.

Methods: Primary human PTEC were cultured on collagen IV in supplemented medium. At 75-80% confluence cells were treated with: the 11 kDa C-terminus form of CTGF (Peprotech, 0.5-50 nMol) for 24hr and 48 hr; or both TGFβ1 (30 pMol) and C-terminus CTGF (0.5-50 nMol) for 60min and 24hr. The medium was collected and cells lysed. Western Blotting was used to detect protein expression and qPCR for mRNA expression. Antibodies (Ab) to the hinge regions of CCN3 and CTGF were used for protein detection.

Results: Exogenous Cys Knot C-terminus CTGF treatment at 24hr resulted in a dose dependent increase in CCN3 expression ($p<0.05$) in contrast to U – shaped response by CTGF with a trough at 5nMol. Cys Knot CTGF also caused a dose dependent inhibition of cell proliferation as determined by by expression of proliferating cell nuclear antigen (PCNA) No intracellular signalling by Cys Knot CTGF was detected but a selective increase in phosphor-Smad3 induction by threshold concentrations of TGFβ1was observed.

Conclusions: Primary human PTEC in culture are sensitive to the effect Cys Knot CTGF protein. The effects observed were distinctively different from those reported for the c-terminus CTGF including the hrombospondin but possibly consistent with the binding of the 11 KDa Cys Knot protein.

TH-PO211

Mechano Growth Factor Stimulated Collagen IV Expression Is Dependent on Connective Tissue Growth Factor Yongxin Gao,[1] Raafat Farag Makary,[2] Leighton R. James,[1] Charles W. Heilig.[1] *[1]Dept of Medicine, Div of Nephrology and Hypertension, Univ of Florida, Jacksonville, FL; [2]Dept of Pathology and Laboratory Medicine, Univ of Florida - Jacksonville, Jacksonville, FL.*

Background: Increased extracellular matrix production is a hallmark of diabetic and hypertensive nephrosclerosis, yet the pathogenesis of nephrosclerosis is incompletely understood. Amongst various signaling pathways associated with sclerosis, connective tissue growth factor (CTGF) has been implicated in mediating extracellular matrix production in diabetic and hypertensive kidney disease. Mechano growth factor (MGF) is implicated in skeletal and cardiac muscle growth and survival; MGF has proliferative and anti-apoptotic properties. We have shown that MGF is glucose-response in that its expression is increased by high glucose in culture and in kidney of diabetic mice models.

Methods: To ascertain the interaction between CTGF and MGF in expression of matrix protein, we examined collagen IV and fibronectin levels in mesangial cells expressing MGF sense (MGF-S) and anti-sense (MGF-AS) transcripts. Immunohistochemistry (IHC) was performed for MGF, GLUT1, Type IV Collagen (Col-IV), Fibronectin, CTGF, NFkB p50 and NFkB p65 in cultured mouse MC's, +/- MGF-overexpression or MGF-suppression.

Results: Both CTGF and collagen IV protein levels were increased in MGF-S cells (1.5 and 2-fold respectively, $P<0.001$) and significantly reduced in MGF-AS cells. NF-κB (p50 and p65) was translocated to the nuclei (activated) in MGF-S MC's. Activated NFkB p50 was increased 2.4-fold in MGF-S MC's, while activated NFkB p65 was increased 2.1-fold in MGF-S vs MGFEV control MC's. In human kidneys from patients with interstitial fibrosis and tubular atrophy, CTGF and MGF were increased. Treatment of MGF-S cells with anti-CTGF antibody attenuated expression of collagen and fibronectin in MGF-S cells.

Conclusions: Thus, both CTGF and MGF expression associate with increased matrix protein levels and NF-KB nuclear translocation. Attenuation of ECM protein by CTGF antibody, suggest that CTGF may mediate part of the increased collagen production seen in MGFS cells.

Funding: Private Foundation Support

TH-PO212

Rac1 Is a Novel Fibrotic Transducer of TGF-β Pathway in Chronic Kidney Disease Rohan Samarakoon,[1] Samik H. Patel,[1] Lucas Falke,[2] Jessica Marie Overstreet,[3] Jiaqi Tang,[1] Roel Goldschmeding,[2] Paul J. Higgins.[1] *[1]Dept of Regenerative and Cancer Biolgy, Albany Medical Center, Albany, NY; [2]Dept of Pathology, Univ Medical Center Utrecht, Uttecht, Netherlands; [3]Div of Nephrology and Hypertension, Vanderbilt Medical School, Nashville, TN.*

Background: Rac-GTPase, a major regulator of cytoskeletal remodeling, is a subunit of NADP(H) oxidases which generate reactive oxygen species. While the causative role of Rac in cancer progression and skin fibrosis is documented, whether Rac relays profibotic TGF-β1 signals and contributes to CKD progression is not known.

Methods: We used both genetic and pharmacological approaches in vitro and in vivo to definitively implicate Rac1 in renal maladaptive repair responses associated with fibrosis.

Results: TGF-β1 promotes rapid Rac-GTP loading in HK-2 human renal epithelial cells. Pharmacological blockade of Rac activation with a specific inhibitor, EHT1684 abrogated the expression of a battery of TGF-β1 induced genes, including fibronectin, PAI-1, CTGF, p21 and vimentin in renal epithelial cells and fibroblasts. Stable Rac1 silencing in HK-2 cells eliminated not only fibrotic gene expression but bypassed growth arrest induction by TGF-β1 evident in control transductants. ROS generation by TGF-β1 is also substantially retarded in epithelial cells with Rac1 depletion, consistent with the role of Rac1 in the assembly of free radical generating NOX1/2 complexes. Expression of Rac1b isoform is significantly elevated in mouse models of UUO compared to contralateral controls, correlating with fibrosis gene expression. Intraperitoneal administration of EHT-1684 significantly attenuated UUO-induced fibrosis compared to vehicle treated control mice with ureteral ligation.

Conclusions: Rac1 is novel non-SMAD control element of the TGF-β1 pathway necessary for ROS generation and subsequent induction of epithelial fibrogenesis and growth arrest. Pharmacological targeting of Rac pathway suppressed obstructive nephropathy, strongly implicating Rac as a novel therapeutic target against CKD.

Funding: Other NIH Support - GM057242

TH-PO213

Autotaxin Promotes Renal Interstitial Fibrosis by Inducing Vascular Leak and Fibroblast Accumulation Norihiko Sakai,[1] Gretchen Bain,[3] Miki Nakamura,[2] Taito Miyake,[1] Yasutaka Kamikawa,[1] Akihiro Sagara,[1] Shinji Kitajima,[1] Tadashi Toyama,[1] Akinori Hara,[1] Yasunori Iwata,[1] Miho Shimizu,[1] Kengo Furuichi,[1] Andrew M. Tager,[4] Takashi Wada.[2] *[1]Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Japan; [2]Dept of Nephrology and Laboratory Medicine, Kanazawa Univ, Kanazawa, Japan; [3]PharmAkea, Inc., San Diego, CA; [4]Pulmonary and Critical Care Unit, Massachusetts General Hospital, Boston, MA.*

Background: The expansion of fibroblasts is an important step in the development of organ fibrosis, but the mechanisms driving this in renal fibrosis remain to be fully clarified. Lysophosphatidic acid (LPA), a bioactive lipid, has been reported to promote organ fibrosis by regulating multiple fibroblast functions. Autotaxin (ATX) is a major LPA-producing enzyme, and we hypothesized that ATX contributes to the development of renal fibrosis through LPA-mediated fibroblast accumulation.

Methods: Renal fibrosis was induced by unilateral ureteral obstruction (UUO) in type I pro-collagen promoter-driven green fluorescent protein (GFP) mice to identify fibroblasts. The selective ATX inhibitor was used to inhibit ATX activity.

Results: Renal activity and protein levels of ATX increased with the progression of fibrosis, despite concurrent reductions in renal ATX mRNA levels. UUO enhanced vascular permeability in the renal interstitium, and ATX protein localized to areas of vascular leak, suggesting that ATX enters the renal interstitium from the circulation in this model. Pharmacological inhibition of ATX activity protected mice from UUO-induced fibrosis, reducing the accumulation of fibroblasts. Renal vascular leak was also suppressed by ATX inhibition. *In vitro* studies showed that ATX induced the migration and proliferation of renal fibroblasts and enhanced the vascular permeability of endothelial monolayers.

Conclusions: These results suggest that during the development of renal fibrosis, ATX accumulates in the renal interstitium, and ATX produces LPA that drives fibroblast accumulation and further exacerbates renal interstitial vascular leak, thereby creating a vicious circle that amplifies fibrosis. Taken together, ATX inhibition may be a novel therapeutic strategy to combat renal fibrosis.

Funding: Government Support - Non-U.S.

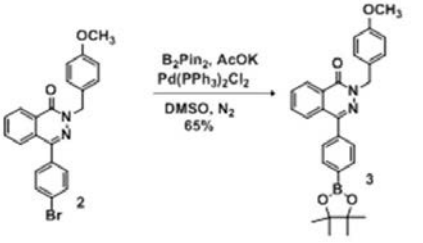
TH-PO214

Development and Synthesis of Boron Containing Low Molecular Weight Candidate Mimetics of Hepatocyte Growth Factor (HGF) for Treating Renal Fibrosis Sasmita Das,[1] Anna Fantinati,[2] Ram Sharma,[3] Bhaskar Chandra Das,[1] Mukut Sharma.[1,3,4] *[1]KU Medical Center, Kansas City, KS; [2]Univ of Ferrara, Ferrara, Italy; [3]KCVA Medical Center, Kansas City, MO; [4]MBRF, KCVA Medical Center, Kansas City, MO.*

Background: Renal fibrosis is associated with chronic kidney disease progression. HGF activates c-Met to initiate anti-fibrotic effects through opposing TGFβ1-Smad signaling. HGF mimetics are promising therapeutic agents for treating renal fibrosis. However, available HGF-derived peptide and c-Met activating protein mimetics are unstable and expensive. Introduction of boron in suitable scaffolds provides stable and versatile compounds for receptor-activation by hydrogen and covalent binding.

Methods: Computational Limited Rational Design Approach (LRD) was used. Protein crystal structures and their predicted ligands from protein-ligand data banks (PBB and EBI) were used to identify compatible small molecules with drug properties based on similarity search methods and Tanimoto similarity scores. Initial search identified phthalazin-1(2H)-one based heterocyclic compounds containing pharmacophore groups that complex with HGF and also bind c-Met. We synthesized compound based on phthalazinone scaffold and the product was used for borylation (3).

Results: Phthalazinone scaffold (Compound 2, Figure) developed by us was used for Miyaura borylation reaction. Bis (pincoloto) diboron (B_2pin_2)was used with potassium acetate as the base and $Pd(PPh_3)_2Cl_2$ as the catalyst to obtain the boron-containing derivatives (Compound 3) as a white solid in 65% yield at 99.9% purity. Structure was confirmed by Proton NMR, Carbon NMR and High Resolution mass spectrometry.



Conclusions: This novel approach for the first time provides boron-containing phthalazinone derivatives as potential HGF mimetics.

Funding: Other NIH Support - NIAAA/NIH R21 AA020630, Private Foundation Support

TH-PO215

Pro-Inflammatory Mediator Exocytosis from Murine Primary Macrophages Is Dependent on Protein Kinase C-θ Anna Bertram,[1] Natalia Ronkina,[2] Yulia Kiyan,[1] Hermann G. Haller,[1] Nelli Shushakova.[1] *[1]Nephrology and Hypertension, Hannover Medical School, Hannover, Germany; [2]Physiological Chemnistry, Hannover Medical School, Hannover, Germany.*

Background: The cooperation of several cell types is critical for a functioning inflammatory response to different kinds of injury. Protein kinase C-theta (PKC-θ) is well-known for its role in T-cells. Recently we could demonstrate a function for PKC-θ in neutrophil adhesion and recruitment, as well as cytokine release in chemical peritonitis in mice. Since the release of pro-inflammatory mediators from resident macrophages is a critical initial step in inflammation, we investigated the role of PKC-θ in this process.

Methods: Resident peritoneal macrophages isolated from healthy wild type (WT) or PKC-θ knockout (KO) mice were stimulated with LPS or vehicle with or without brefeldin A. Levels of the pro-inflammatory mediators TNF-α, CXCL1 and CXCL2 were measured by ELISA in conditioned cell culture medium and by Western Blots in cell lysates. Immunofluorescence microscopy in adherent stimulated macrophages and Western Blots were performed for evaluation of p38 MAPK activation and NFkB nuclear translocation. mRNA analysis was performed by RT-PCR.

Results: The release of pro-inflammatory mediators from LPS-stimulated KO macrophages was strongly impaired compared to WT, but no clear difference could be detected in mRNA levels. In line with the latter finding, neither activation of p38 MAPK nor nuclear translocation of NFkB was impaired in KO macrophages, suggesting a downstream target of PKC-θ. The analysis of exocytosis of WT and KO macrophages was further performed for TNF-α. LPS stimulation of WT macrophages resulted in transient intracellular accumulation of TNF-α with a maximum at 1h and declining within 2-4h. In line with the reduced TNF-α levels in conditioned medium from stimulated KO macrophages, intracellular TNF-α accumulation was significantly increased compared to WT starting 1h after stimulation. This difference was abrogated by co-incubation with brefeldin A, suggesting a defect in cytokine transport and exocytosis.

Conclusions: Our data demonstrates a role for PKC-θ in exocytosis of pro-inflammatory mediators from LPS-stimulated resident peritoneal macrophages.

TH-PO216

Suppressed microRNA-214 (miR-214) Dictates IGF-1 Receptor (IGF-1R) Expression to Stimulate mTORC1 Signaling for Proliferation of Renal Cancer Cells Falguni Das,[1] Nandini Ghosh-Choudhury,[2] Balakuntalam S. Kasinath,[1] Goutam Ghosh-Choudhury.[1] *[1]Medicine, UTHSCSA, San Antonio, TX; [2]Pathology, UTHSCSA, San Antonio, TX.*

Background: Elevated expression of IGF-1R in renal cell carcinoma correlates with tumor development and progression. The mechanism of hyper-expression of IGF-1R is not known.

Methods: VHL positive and negative renal cancer cells, immunoblotting, real-time qRT-PCR, site-directed mutagenesis, reporter transfection assays, DNA synthesis and proliferation assays were used.

Results: VHL positive and deficient renal cancer cells (ACHN, 786-O, RCC4 and A498) showed significantly reduced expression of mature, pre- and pri-miR-214 as compared to normal proximal tubular epithelial cells (HK2 and HRPTEC). Interestingly, in the 3'UTR of IGF-1R we identified a miR-214 recognition element (MRE) that responded to miR-214. When the MRE was mutated, the miR-214 responsiveness was abolished confirming its specificity. Overexpression of miR-214 inhibited IGF-1R mRNA and protein expression. IGF-1 increased phosphorylation of PRAS40 by Akt, leading to the activation of mTORC1

and phosphorylation of S6 kinase and 4EBP-1. miR-214 blocked the phosphorylation of PRAS40, S6 kinase and 4EBP-1. Phospho-deficient mutants of PRAS40 and 4EBP-1 and overexpression of miR-214 significantly inhibited IGF-1R-induced proliferation of renal cancer cells. Finally, expression of a 3'UTR-less IGF-1R or constitutively active mTORC1 reversed the miR-214-mediated inhibition of IGF-1-induced renal cancer cell proliferation.

Conclusions: These results provide the first novel evidence that reduced expression of miR-214 causes IGF-1-induced renal cancer cell proliferation via mTORC1 activation. Furthermore, we uncover the requirement of phosphorylation of PRAS40 and 4EBP-1 for IGF-1-stimulated proliferation of renal carcinoma cells. Thus we propose that use of miR-214 may represent an attractive therapy to test in preclinical models of renal carcinoma.

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TH-PO217

The Contribution of Transient Receptor Potential Channel 6 to Motility and Adhesion in the Podocyte and Identification of Novel Binding Partners

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Background: Several genetic mutations in TRPC6 have been linked to familial forms of FSGS, identifying it as a treatment target for nephrotic syndrome. TRPC6 is a membrane expressed calcium channel and it has previously been suggested that several of these mutations cause a gain of function and subsequent increase in calcium influx. However the role of TRPC6 in disease progression is still unclear.

Methods: Conditionally immortalised podocyte cell lines have been generated from TRPC3 KO, TRPC6 KO and TRPC3/TRPC6 double KO C57Bl/6 mice. GFP tagged TRPC6 was stably reintroduced into the KO cell line through generation of a lentiviral construct. These cell lines were then characterised to determine cell motility and adhesion using scratch and adhesion assays. GFP TRAP beads were used to pull down TRPC6 and proteomics was performed to identify novel binding partners. These interactions were confirmed through immunoprecipitation.

Results: Glomeruli from TRPC6, TRPC3 and TRPC3/6 KO mice were isolated and used to generate conditionally immortalised podocyte cell lines. All three cell lines appeared morphologically normal and expressed podocyte markers. Adhesion assays showed a significant increase in the adhesiveness of TRPC6 KO cells, whilst the TRPC3 KO and double KO cells were unaltered. The TRPC6 KO cells were also significantly less motile in a scratch assay. Reintroduction of GFP-TRPC6 to the TRPC6 KO cells returned the adhesive and motility phenotype towards that of the WT cell line. Immunoprecipitation with GFP TRAP beads identified interactions between TRPC6 and a number of calcium regulated proteins and proteins involved in regulating actin dynamics.

Conclusions: These results suggest that TRPC6 plays a considerable role in the adhesion and motility of the podocyte. This contribution could be occurring through the novel protein interactions that have been identified in this study, giving new insight into the role of TRPC6 in glomerular injury.

TH-PO218

The N-Recognin Ubr4 Controls Posttranslational Stability of Podocin/MEC-2 Supercomplexes

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Background: The PHB-domain protein podocin maintains the renal filtration barrier. Podocin mutation causes hereditary nephrotic syndrome. Podocin and its Caenorhabditis elegans orthologue MEC-2 are components of mechanosensitive membrane protein signalling complexes. Whereas podocin resides at a specialized cell junction at the podocyte slit diaphragm, MEC-2 is found in neurons required for touch sensitivity.

Methods: We performed mass-spectrometry based interactome analysis of podocin in vivo and in vitro to determine its interaction partners. We performed knockdown and knockout studies of Ubr4 in cell culture and C. elegans to determine its effect on podocin/MEC-2. We performed mass-spectrometry based ubiquitylomic analysis (using a Di-gly-gly antibody) to determine native podocin ubiquitylation sites in vivo. We modeled the biophysical effect of podocin ubiquitylation on the podocin structure using molecular dynamics simulations.

Results: Ubr4 was a key component of the podocin interactome purified both from cultured podocytes and native glomeruli. It localizes at the slit diaphragm and to the leading edge of podocytes in cell culture. Ubr4 regulates podocin stability in cell culture. In C. elegans, this process is conserved. Ubr4 knockdown or knockout increased the expression of Mec-2, the podocin orthologue. Ubr4 is also responsible for the degradation of mislocalized MEC-2 multimers. Ubiquitylomic analysis of mouse glomeruli revealed that podocin is ubiquitylated at two lysine residues. These sites were increasingly ubiquitylated in the presence of Ubr4 and were conserved across species, also based on mass-spectrometry dependent evidence. Molecular dynamics simulations revealed that ubiquitylation of one site, K301, does not only target podocin/MEC-2 for proteasomal degradation, but may also affect stability and disassembly of the multimeric complex. Mutation of K301 and K370 shifted podocin to the lysosomal compartment, indicating that K301 and K370 are essential for degrading podocin.

Conclusions: We suggest that podocin degradation is tightly controlled and that Ubr4 is a key regulator of podocyte foot process proteostasis.

Funding: Government Support - Non-U.S.

TH-PO219

HGF, a Novel Activator for Neph1 Signaling

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Background: Podocytes are the critical components of the glomerular filtration system and signaling from podocyte proteins Nephrin and Neph1 contributes towards their function. Despite numerous advancements, an extracellular ligand/s involved in their activation remains unknown. This is the first report demonstrating that the Hepatocyte Growth Factor (HGF) may induce Neph1 and Nephrin signaling in podocytes.

Methods: Proteomics, substrate trapping and mRNA profiling approaches were used to identify and investigate the role of HGF ligand in Neph1 signaling.

Results: HGF is known to signal through the phosphatase SHP2 and our preliminary results demonstrate that SHP2 may directly regulate Nephrin and Neph1 activation. Using a large scale mass spectrometric-based screen, we found that SHP2 interacts with Nephrin and Neph1 in a phosphorylation dependent manner. Using a substrate trapping mutant we demonstrate that SHP2 binds Neph1 in a substrate-specific manner, providing direct evidence that Neph1 is a substrate for SHP2. Additionally, HGF that stimulates SHP2 pathway was found to increase Neph1 phosphorylation only in SHP2 knock down cultured podocytes, suggesting that Neph1 participates in HGF induced signaling in podocytes. Since injury to podocytes has been shown to induce Neph1 phosphorylation we hypothesized that such induction may affect SHP2 expression. Indeed, mRNA profiling of cultured podocytes treated with puromycin aminonucleoside showed fivefold reduction in SHP2 expression. These results are consistent with a role for SHP2 in regulating Neph1 phosphorylation and activation. We further hypothesized that HGF induced Neph1 phosphorylation may initiate Neph1 endocytosis and to test this we created a chimeric Neph1 where Flag tag was introduced in the N-terminus of Neph1 that allows Neph1 to be extracellularly labeled with Flag antibody. Indeed, treatment of podocytes with HGF but not with other growth factors induced Neph1 endocytosis.

Conclusions: Collectively, these results provide compelling evidence that HGF can stimulate the signaling of slit diaphragm protein Neph1 in podocytes.

Funding: NIDDK Support

TH-PO220

Nephrin Tyrosine Phosphorylation Regulates Its Endocytosis through the Nck Adaptor Proteins

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Background: Nephrin is a key structural component of the podocyte slit diaphragm, and proper expression of nephrin on the cell surface is critical to ensure integrity of the blood filtration barrier. Maintenance of nephrin within the slit diaphragm is proposed to require endocytic recycling, although the molecular mechanisms that regulate such trafficking are poorly understood. We have recently demonstrated that tyrosine phosphorylation of nephrin is central to its function, via recruitment of intracellular signaling proteins including the Nck family of SH2/SH3 domain-containing cytoskeletal adaptors. We now reveal that Nck provides a connection between phosphorylated nephrin and the endocytic machinery, and that changes in nephrin tyrosine phosphorylation dynamically alter its expression on the cell surface.

Methods: Mice expressing a nephrin variant that cannot undergo tyrosine phosphorylation (nephrin-Y3F) were used to characterize trafficking dynamics in healthy and injured podocytes. Complementary cell-based approaches were employed to assess molecular interactions that regulate nephrin endocytosis.

Results: We demonstrate that the nephrin-Y3F protein is overexpressed on the cell surface, and localized within tubulated pits both *in vitro* and *in vivo*. Remarkably, mutations in the SH3 domain of Nck2 induce a similar pattern of nephrin localization, and fusion of the intact Nck2 SH3 domains to the nephrin-Y3F protein can rescue this phenotype. We confirm that Nck2 preferentially associates with the endocytic regulator dynamin, and that disruption of dynamin GTPase activity promotes accumulation of nephrin on the cell surface. Lastly, we show that nephrin is transiently hyperphosphorylated and removed from the cell surface in a reversible model of proteinuric kidney injury, and that nephrin-Y3F mice are protected from this injury.

Conclusions: Together these findings underscore the link between actin signaling and endocytosis in podocytes, and they suggest that precise regulation of nephrin tyrosine phosphorylation is required to maintain barrier homeostasis.

Funding: Government Support - Non-U.S.

TH-PO221

Ephrin-B1 Interacts with the Basal Site of the Extracellular Domain of Nephrin in Cis and Regulates the Barrier Function and the Signal Transduction Pathway of the Slit Diaphragm

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Background: We have previously reported that Ephrin-B1 is the component of the slit diaphragm (SD) (KI, 2008) and plays a role in the arrangement of the SD molecules (ASN, 2015). However, the role of Ephrin-B1 in regulating the SD function is not well understood.

Methods: (i)The molecular association between Ephrin-B1 and nephrin was analyzed with HEK cells. (ii) The phenotype of the podocyte-specific Ephrin-B1 knockout (KO) mice induced by tamoxifen administration was precisely analyzed. (iii)To explore novel molecules associated with Ephrin-B1, gene expression profile of glomeruli of the KO mice was analyzed by the RNA-seq with next-generation sequencer.

Results: (i)Ephrin-B1 interacted with the basal site of the extracellular domain (7th immunoglobulin (Ig) domain-fibronectin domain) of nephrin and did not interact with the tip (N-end-1st Ig domain) of the extracellular domain or cytoplasmic domain of nephrin. Tyrosine residue (324/329) at the most C-terminal region of Ephrin-B1 was phosphorylated by the stimulation to nephrin by an anti-nephrin antibody in the HEK cells co-transfected with Ephrin-B1 and nephrin. (ii)The mice of which Ephrin-B1 gene was knocked out after birth showed disarrangement of the SD molecules and proteinuria (KO 5.33 mg/24 h vs. control 1.55, p<0.0001). Although the expression of Ephrin-B2 was not increased in the mice knocked out after birth, Ephrin-B2 expression was increased (to compensate the lack of the Ephrin-B1) in the mice knocked out at E18.5. The mice knocked out at E18.5 showed disarrangement of the SD molecules, but proteinuria was not observed in these mice. (iii) Five transmembrane proteins, of which expressions in glomeruli were evidently downregulated (< 30%) in the KO mice, were identified by the RNA-seq analysis.

Conclusions: Ephrin-B1 interacts with the basal site of the extracellular domain of nephrin in cis and plays a crucial role in the accumulation of the SD molecules and in the maintenance of the barrier function and the signal transduction system of nephrin.

Funding: Government Support - Non-U.S.

TH-PO222

KIBRA Promotes Podocyte Injury by Inhibiting YAP Pro-Survival Signaling Kristin Meliambro, Jenny Wong, Justina Ray, John C. He, Evren U. Azeloglu, Kirk N. Campbell. *Nephrology/Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: KIBRA, an upstream regulator of the Hippo signaling pathway encoded by the *Wwc1* gene, shares the pro-injury properties of its putative binding partner dendrin and antagonizes the pro-survival signaling of downstream Hippo pathway effector YAP (Yes-associated protein) in *Drosophila* and MCF10A cells. Our group recently identified YAP as an essential component of the glomerular filtration barrier that promotes podocyte survival by inhibiting dendrin pro-apoptotic function. Despite recent advances, the signaling pathways that mediate podocyte survival and injury remain poorly understood. Here we test the hypothesis that similar to its role in other model systems, KIBRA promotes podocyte injury and death.

Methods: KIBRA/*Wwc1* was overexpressed in murine podocytes using retrovirus and high content image analysis characterized YAP localization, focal adhesion metrics, and actin cytoskeleton. KIBRA/*Wwc1* was silenced in human podocytes using lentivirus. Apoptosis was assessed via caspase 3/7 activity assay. Quantitative PCR determined expression levels of YAP-associated genes. Albuminuria was qualitatively assessed via Coomassie staining. Mouse kidneys were harvested following pericardial perfusion with HBSS or protamine sulfate and/or 4% PFA. Foot processes were quantified using transmission EM images.

Results: We found increased KIBRA/*Wwc1* gene expression in patient cohorts with biopsy-proven FSGS and CKD. Constitutive KIBRA/*Wwc1* knockout mice were protected from protamine-sulfate induced foot process effacement and KIBRA/*Wwc1* silencing in podocytes protected against adriamycin-induced apoptosis. Conversely, KIBRA/*Wwc1* overexpression enhanced podocyte susceptibility to staurosporine-induced apoptosis, disrupted actin cytoskeletal architecture, and reduced focal adhesion size and number. KIBRA promoted LATS phosphorylation leading to subsequent YAP S127 phosphorylation, YAP cytoplasmic sequestration, and reduction in target gene expression.

Conclusions: These findings suggest an important role for KIBRA in the pathogenesis of podocyte injury and the progression of proteinuric kidney disease.

Funding: NIDDK Support, Private Foundation Support

TH-PO223

SLIT2-ROBO2 Signaling Pathway Inhibits Non-Muscle Myosin IIA Activity and Destabilizes Kidney Podocyte Adhesion Xueping Fan,[1] Hongying Yang,[2] Sudhir Kumar,[1] Kathleen Tumelty,[2] Anna Pisarek-Horowitz,[1] Hila Milo Rasouly,[1] Richa Sharma,[1] Stefanie Chan,[1] Edyta Tyminski,[2] Michael Shamashkin,[2] Mostafa Belghasem,[1] Joel M. Henderson,[1] Anthony J. Coyle,[2] David J. Salant,[1] Stephen Berasi,[2] Weining Lu.[1] *[1]Nephrology and Pathology, Boston Univ Medical Center, Boston, MA; [2]Pfizer Centers for Therapeutic Innovation, Pfizer Inc, Boston, MA.*

Background: The repulsive guidance cue SLIT2 and its receptor ROBO2 are required for kidney development and podocyte foot process structure, but the SLIT2-ROBO2 signaling mechanism regulating podocyte cellular function is not known. Here we report that a novel signaling pathway of SLIT-ROBO Rho GTPase activating protein 1 (SRGAP1) and non-muscle myosin IIA (NM-IIA) regulates podocyte adhesion downstream of ROBO2.

Methods: We performed yeast two-hybrid assay, co-precipitation and western blot analyses, immunofluorescent staining, podocyte cell culture and adhesion assays, MRLC phosphorylation assay, in vivo mouse genetic interaction studies, and deoxycorticosterone (DOCA)-salt-uninephrectomy injury model study.

Results: We found that the myosin II regulatory light chain (MRLC), a subunit of NM-IIA, interacts directly with SRGAP1 and forms a complex with ROBO2-SRGAP1-NM-IIA in the presence of SLIT2. Immunostaining demonstrated that SRGAP1 is a podocyte protein and is co-localized with ROBO2 on the basal surface of podocytes. In addition, SLIT2 stimulation inhibits NM-IIA activity, decreases focal adhesion formation, and reduces podocyte cell attachment to collagen. In vivo studies further showed that podocyte-specific knockout of *Robo2* protects mice from hypertension-induced podocyte detachment and albuminuria and also partially rescues the podocyte loss phenotype in *Myh9* knockout mice.

Conclusions: We have identified SLIT2-ROBO2-SRGAP1-NM IIA as a novel signaling pathway in kidney podocytes, which may play a role in regulating podocyte adhesion and attachment. Our findings also suggest that inhibition of SLIT2-ROBO2 signaling could be beneficial for kidney diseases associated with podocyte detachment and loss.

Funding: NIDDK Support, Private Foundation Support

TH-PO224

Novel Mouse Models Overexpressing TRPC5 Xuexiang Wang, Hao Yu, Ranadheer Dande, Beata Tryniszewska, Mehmet M. Altintas, Jochen Reiser. *Dept of Medicine, Rush Univ Medical Center, Chicago, IL.*

Background: Transient receptor potential channel (TRPC) family is a nonselective calcium–permeable cation channels that is widely expressed in cells and critical to cell behavior, physiology and pathology. The subfamily 5 of TRPC (TRPC5) is highly expressed in brain and kidney, and it mediates Ca2+ influx induced promoted cell migration. In the kidney, TRPC5 is related to podocyte cytoskeletal remodeling and filtration barrier modulating. One study suggested that knockout of TRPC5 in mice protects podocytes and the kidney filter. However, the effect of TRPC5 overexpression in mice has never been shown and the pathogenic role of TRPC5 in causing proteinuria is not clear.

Methods: Two novel transgenic mouse models (C57BL/6 background) were developed by overexpressing either wild-type TRPC5 (TG) or the dominant negative TRPC5 (DN, pore mutant) respectively. Overexpressed animals were validated by genotyping. TRPC5 level in the animal tissue was measured through mRNA expression, western blot and glomerular immunofluorescence (IF). Urinary albumin levels were measured and histology analysis was performed up to 6 month. LPS-induced albuminuria was quantified and compared among TG, DN and Bl/6 at baseline (0 hour), and at 24 hours and 48 hours after injection.

Results: In our transgenic mice, TRPC5 mRNA was significantly higher than control. Western blot exhibited abundant TRPC5 protein throughout various tissues. IF demonstrated stronger staining of TRPC5 in glomeruli of TG and DN compared with Bl/6. Histology analysis of TG and DN appeared to have no abnormalities at birth and after month 6. Neither TRPC5 mouse line did develop proteinuria. Kidney injury after LPS injection was similar among TG, DN and Bl/6 at 0, 24 and 48 hour with no significant differences in albumin/creatinine ratio (ACR).

Conclusions: TRPC5 was overexpressed in our novel transgenic mice. However, overexpression of TRPC5 does not cause kidney damage per se. LPS treatment resulted in similar levels of glomerular injury among TG, DN and Bl/6.

Funding: NIDDK Support

TH-PO225

The Mechanisms of Dendrin Nuclear Translocation in Kidney Podocytes Naritoshi Shirata,[1,2] Kan-Ichiro Ihara,[3,4] Motoko Yanagita,[1,5] Katsuhiko Nishimori,[4] Katsuhiko Asanuma.[1,5] *[1]Medical Innovation Center, TMK Project, Graduate School of Medicine, Kyoto Univ, Kyoto, Japan; [2]Research Unit/Nephrological & Endocrinological Science, Sohyaku, Innovative Research Div, Mitsubishi Tanabe Pharmaceutical Corporation, Toda, Saitama, Japan; [3]Dept of Molecular Genetics, Inst of Biomedical Sciences, Fukushima Medical Univ, Fukushima, Japan; [4]Dept of Molecular and Cell Biology, The Laboratory of Animal Breeding and Genetics, Graduate School of Agricultural Science, Tohoku Univ, Sendai, Miyagi, Japan; [5]Dept of Nephrology, Graduate School of Medicine, Kyoto Univ, Kyoto, Japan.*

Background: Previously we reported that dendrin, which is a component of the slit diaphragm, translocates to the injured podocyte and that nuclear translocated dendrin promotes podocyte apoptosis. We also demonstrated that dendrin nuclear translocation was detected in human renal diseases with glomerulosclerosis. However, the regulatory mechanisms of dendrin localization have been still unknown.

Methods: In this study, we investigated the regulatory mechanisms of dendrin nuclear translocation using yeast two hybrid screening, Co-IP and newly generated the podocyte specific MAGI-2 KO mice.

Results: We identified Fyn (tyrosine kinase) and Nedd4-2 (ubiquitin ligase) as putative interacting proteins with dendrin. Proteolysis of dendrin was regulated by Fyn-mediated phosphorylation and Nedd4-2-mediated ubiquitination. Dendrin was downregulated and accumulated in the nuclei in podocyte of MAGI-2 KO mice. These KO mice exhibited podocyte apoptosis leading to glomerulosclerosis. Dendrin at the slit diaphragm was phosphorylated and that in the nuclei was dephosphorylated.

Conclusions: Localization and expression of dendrin is controlled by Fyn, Nedd4-2 and MAGI-2.

Funding: Pharmaceutical Company Support - Mitsubishi Tanabe Pharma

TH-PO226

New Structural and Biomechanical Insights Reveal the Importance of α-Actinin-4 Phosphorylation in Mediating Cytoskeletal Network and Glomerular Podocyte Function Di Feng,[1] Ramaswamy Krishnan,[2] Gabriel Birrane,[3] Johannes S. Schlondorff,[1] Martin R. Pollak.[1] *[1]Nephrology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA; [2]Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA; [3]Experimental Medicine, Beth Israel Deaconess Medical Center, Boston, MA.*

Background: Mutations in the alpha-actinin-4 gene (ACTN4) cause podocyte injury and familial focal segmental glomerulosclerosis (FSGS) in humans. We recently found that in cultured human podocytes, ACTN4 can be phosphorylated at the serine 159 site (S159), which is within the same actin-binding domain (ABD) as all of the known disease-causing ACTN4 mutations. Phosphomimetic S159D ACTN4 protein (which mimics the effect of phosphorylation at S159), recapitulates the altered actin bundling activity of FSGS-associated mutant ACTN4. This study seeks to further investigate the mechanism by which phosphorylation of ACTN4 affects podocyte function.

Methods: We used x-ray crystallography to solve the structure of the ACTN4 ABD protein, and traction force microscopy to quantify contractile forces exerted by human podocytes transfected with different ACTN4 constructs.

Results: We crystalized the ABD of phosphomimetic S159D ACTN4 protein. Similar to the previously solved crystal structures for the disease-causing K255E ACTN4, S159D ACTN4 showed a compact conformation with altered charge distribution compared to WT ACTN4. Across time, contractile force was consistently higher in S159D ACTN4 podocytes (commensurate with K255E podocytes) than in non-phosphorylatable S159A ACTN4 podocytes. However, WT ACTN4 podocytes initially exerted similar contractile force as S159D and K255E podocytes, but later decreased to lower levels comparable with S159A podocytes. This decrease in force could be in part due to decreased phosphorylation of WT ACTN4.

Conclusions: Our results suggest that phosphorylation of ACTN4 at S159 alters ACTN4 protein characteristics and podocyte biomechanical force. These observations support our hypothesis that an intracellular signal "switch" can convert normal ACTN4 to a form similar to the human mutation associated forms, therefore mediating podocyte injury in non-genetic forms of FSGS.

Funding: NIDDK Support

TH-PO227

Physiological Roles of Ezrin in the Regulation of Podocyte Foot Process Formation Ryo Hatano, Kotoku Kawaguchi, Shinji Asano. *Dept of Molecular Physiology, Ritsumeikan Univ, Kusatsu, Shiga, Japan.*

Background: Ezrin is highly expressed in the glomerular podocytes, and is reported to form multi-protein complex with a scaffold protein Na^+/H^+ exchanger regulatory factor 2 (NHERF2), and podocalyxin, a major sialoprotein. Podocalyxin deficient mice died within 24 hrs after birth with anuric renal failure, whereas NHERF2 knockout mice did not show apparent renal phenotype. On the other hand, physiological roles of ezrin in glomerular podocytes still remain unclear.

Methods: To investigate the physiological roles of ezrin in the regulation of glomerular podocyte function, ezrin knockdown mice ($Vil2^{kd/kd}$) were used in this study. Histological analysis of glomerulus was performed by H&E staining and electron microscopy. Western blotting and immunofluorescent analysis were performed to investigate the expression and localization of related proteins in the podocytes. Rho activities were investigated by ELISA-based pull down assay using isolated mouse glomeruli from WT and $Vil2^{kd/kd}$ mice before and 7 days after adriamycin treatment.

Results: $Vil2^{kd/kd}$ mice did not exhibit apparent glomerular dysfunction, morphological defects, and disturbance in the localizations of podocalyxin and NHERF2 in podocytes. In $Vil2^{kd/kd}$ glomeruli, RhoA activity was increased 1.3-fold compared to WT glomeruli, while Rac1 and Cdc42 activities in $Vil2^{kd/kd}$ glomeruli were comparable with those in WT glomeruli at baseline. Interestingly, in adriamycin-induced nephrotic condition, $Vil2^{kd/kd}$ mice showed reduced susceptibility to the drug-induced glomerular injury. In $Vil2^{kd/kd}$ glomeruli after adriamycin treatment, RhoA activity was increased 1.5-fold, but Rac1 activity showed 2-fold decrease compared to adriamycin-treated WT mice. Furthermore, interaction of ezrin with Rho GDP dissociation inhibitor (RhoGDI), a key regulator of Rho activities, was confirmed by coimmunoprecipitation in WT glomeruli.

Conclusions: Our results suggest that loss of ezrin protect the podocytes from injury-induced dynamic morphological change, and ezrin plays important roles in the regulation of podocyte motility by regulating Rho activities via the interaction with RhoGDI in glomerular podocytes.

TH-PO228

ARF6 Activation Is Necessary for Nephrin-Dependent Changes in Podocyte Cytoskeletal Dynamics Jamie Lin,[1] Qingfeng Fan,[1] Hetty N. Wong,[1] Jin Seok Jeon,[2] Lawrence B. Holzman.[1] *[1]Renal-Electrolyte and Hypertension Div, Univ of Pennsylvania, Philadelphia, PA; [2]Dept of Nephrology, Soon Chun Hyang Univ Hospital, Seoul, Korea.*

Background: Nephrin is a slit diaphragm protein that regulates podocyte actin dynamics and cell signaling. Nephrin is tyrosine-phosphorylated and undergoes endocytosis subsequent to podocyte injury. This triggers cellular remodeling necessary for podocyte effacement. The functional significance of nephrin endocytosis remains uncertain. We hypothesized that ARF6, a small GTPase necessary for endocytic trafficking and cell motility, is necessary for nephrin activation-induced podocyte cytoskeletal dynamics that results in injury-induced effacement.

Methods: These experiments were performed in an inducible nephrin-expressing podocyte cell culture model or in a newly engineered podocyte-specific ARF6 null mouse model.

Results: ARF6 is enriched in human podocytes *in vitro* and *in vivo*. In culture, nephrin activation resulted in increased ARF6 activity. Following nephrin activation, ARF6 was necessary for nephrin endocytic recycling, but not early nephrin trafficking, and was necessary for focal adhesion turnover and cellular ruffling. Mice deleted of ARF6 in podocytes had normal glomerular development and developed no evidence of proteinuria even when aged to eight months. When challenged with protamine sulfate, podocyte-specific ARF6 null mice exhibited protection from injury.

Conclusions: Our data show that nephrin tyrosine phosphorylation dependent focal adhesion turnover and cellular ruffling in cell culture are ARF6 dependent. *In vivo*, ARF6 appears to be dispensable for normal podocyte development and maintenance, yet is necessary for changes in podocyte morphology following injury with protamine sulfate. More studies are necessary to clarify the specific role and mechanism of ARF6 involvement in podocyte pathophysiology.

Funding: NIDDK Support

TH-PO229

Von Willebrand Factor Release and Weibel-Palade Body Fusion Maintain Endothelial Cell Homoeostasis after Complement Activation Magdalena Riedl,[1] Daniel Schlam,[1] Damien Gerard Noone,[2] Christoph Licht.[1,2] *[1]Cell Biology, The Hospital for Sick Children, Toronto, Canada; [2]Nephrology, The Hospital for Sick Children, Toronto, Canada.*

Background: Complement dysregulation on endothelial cells causes EC activation and injury and leads to thrombotic microangiopathy. Different from previous concepts, our data demonstrate that complement dysregulation does not result in EC death. The current study focuses on EC complement evasion strategies, especially plasma membrane (PM) repair. We particularly focused on von Willebrand Factor (VWF), which we recently identified as new complement regulator on ECs. VWF is stored in EC Weibel-Palade bodies(WPB) and known to be released by ECs due to activation.

Methods: Complement was activated via a previously established protocol on blood outgrowth endothelial cells (BOECs) from healthy controls and patients with two types of von Willebrand disease (VWD): VWD type 2a with dysfunctional VWF, and VWD type 3 lacking both VWF and their storage organelle WPBs. Calcein release was used to determine plasma membrane (PM) integrity.

Results: Complement activation resulted in PM insertion of C5b-9 pores in control followed by rapid intracellular Ca^{2+} elevation. In response, VWF was recruited to the EC surface via WPBs merging with the PM and releasing VWF multimers. Importantly, only BOECs with WPBs (control and VWD type 2a BOECs) were able to reseal the PM within 30 min. VWD type 3 BOECs - lacking WPBs - were not able to reseal. In control BOECs known cellular mechanisms for PM repair (endocytosis of C5b-9, lysosomal recruitment) were not critically involved in PM repair. Defective or missing VWF also resulted in increased C3b deposition on the EC surface.

Conclusions: ECs have evasion strategies allowing for survival of complement attack. We have identified a new mechanism of complement evasion via VWF: release of VWF reduces complement activation on ECs, and PM fusion of WPBs repairs complement induced PM injury. This repair mechanism may contribute to EC homoeostasis beyond complement-mediated injury.

TH-PO230

Activated Neurotrophin-3 Receptor TrkC Transmits Signals to the Podocyte Actin Cytoskeleton Sascha Gromnitza, Hermann Pavenstaedt, Britta George. *Molecular Nephrology, Inst of Internal Medicine D, Univ Hospital Münster, Münster, Germany.*

Background: Podocyte malfunction is central to glomerular disease and is characterized by defective podocyte intercellular junctions and actin cytoskeletal dynamics. Recently, TrkC was shown to be located at the podocyte slit diaphragm. TrkC knockout mice developed proteinuria shortly after birth (Lefevre et al., PLoS Genet., 2010). The aim of this study is to further investigate the role of TrkC in podocytes and its relevance in glomerular disease.

Methods: Mouse podocyte lines were generated that inducably express wild-type TrkC or TrkC with mutations of specific tyrosine-residues known to mediate TrkC signaling. Wound healing assays following live cell imaging were performed. Glomeruli were isolated from murine kidneys and treated with Lipopolysaccharide (LPS) or Adriamycin (ADR) to induce podocyte injury.

Results: We confirmed that TrkC was expressed in mouse glomerular podocytes and co-localized with the slit diaphragm marker Nephrin. Activation of endogenous TrkC by adding the ligand Neurotrophin-3 (NT-3) to cultured mouse podocytes resulted in tyrosine-phosphorylation of TrkC as well as activation of the downstream target proteins Erk and Akt. Activation of overexpressed or endogenous TrkC by NT-3 lead to increased formation of filopodia in cultured mouse podocytes. Increased filopodia formation could not be observed in podocytes expressing kinase dead TrkC. Consistently an increased migration of podocytes *in vitro* was observed upon TrkC activation. Injury induced by treating isolated murine glomeruli with ADR or LPS resulted in a significant increase in tyrosine-phosphorylation of endogenous TrkC.

Conclusions: Currently, genetic mouse models with the potential to conditionally express or knockout TrkC in podocytes or nephrons are generated to test whether TrkC is essential for the podocyte and to dissect TrkC signaling in vivo. These mouse models will be employed to test whether TrkC can be therapeutically-targeted to treat glomerular disease. Our results imply that TrkC is activated during glomerular injury, signals to the podocyte actin cytoskeleton and regulates cell migration.

Funding: Government Support - Non-U.S.

TH-PO231

Dasatinib Induces Nephrotoxicity through Selective Disruption of Podocyte Biomechanics Rhodora C. Calizo,[1] Johan G.C. Van Hasselt,[1] Gomathi Jayaraman,[1] Jenny Wong,[2] Kirk N. Campbell,[2] Evren U. Azeloglu.[1] *[1]Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY; [2]Nephrology (Medicine), Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: The toxicity induced by kinase inhibitors (KIs) is a bottleneck in targeted oncological therapies, where it may limit the efficacy of treatment or lead to the failure of a trial. It is thought that KIs lead to nephrotoxicity through nonspecific inhibition of VEGF; however the exact mechanisms are poorly understood.

Methods: We used retrospective data mining of FDA Adverse Event Reporting System (FAERS) to rank clinical nephrotoxicity of all FDA-approved KIs. We then used atomic

force microscopy (AFM), high-content imaging, and differential phospho-proteomics to assess the cytoskeletal biomechanics of cultured podocytes under different KI treatments and to identify the mechanisms through which dasatinib induced podocyte cytoskeletal remodeling.

Results: Dasatinib had the highest odds ratio for glomerulonephritis within FAERS compared to other KIs. Interestingly, VEGF inhibitor vandetanib was ranked very low as well as other Bcr-Abl inhibitors such as imatinib. High-content imaging of cultured podocytes showed significant and specific alterations to the actin cytoskeleton, number and size of focal adhesions, and cell morphology under dasatinib but not with other VEGF or BCR-Abl inhibitors. AFM elastography also revealed that elastic modulus of podocytes was significantly reduced under dasatinib treatment alone. Network analysis of differential phospho-proteomics of dasatinib treated podocytes showed "protein-protein interaction in the podocyte" and "regulation of actin cytoskeleton" as the highest enriched terms, and highlighted a number of upstream kinases that may be responsible for dasatinib's effects.

Conclusions: We conclude that dasatinib induces nephrotoxicity independent of VEGF inhibition. Its unique mechanism of action is specific to podocytes, and it acts through altered cellular cytoskeleton and biomechanics. Our results suggest that leukemia patients that are receiving targeted therapy with dasatinib should be monitored closely for nephrotoxicity.

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TH-PO232

Mediation Complex Protein 22 Is Essential for the Maintenance of the Glomerular Filtration Barrier Patricia Rodriguez,[1,2,3] Jing Guo,[1,3] Lwaki Ebarasi,[1] Jaakko Patrakka.[1,2] *[1]KI/AZ Integrated CardioMetabolic Center, Dept of Medicine, Karolinska Inst, Huddinge, Stockholm, Sweden; [2]Clinical Research Center, Dept of Laboratory Medicine, Karolinska Inst, Huddinge, Stockholm, Sweden; [3]Div of Matrix Biology, Dept of Medical Biochemistry and Biophysics, Karolinska Inst, Stockholm, Sweden.*

Background: Mediator complex protein 22 (Med22) is a component of the mediator complex, a multisubunit assembly that mediates signals from DNA bound transcription factors to RNA polymerase II. The role of Med22 in the biology of cells and organisms is not known. In this study, we identified Med22 as a highly podocyte-enriched transcript.

Methods: To establish its biological role in podocytes, we inactivated Med22 in zebrafish and mouse.

Results: In zebrafish larvae, Med22 knockdown prevents the formation of pronephros capillary loops and proper kidney filtration at 4dpf. Dye filtration assay shows that Med22 knockdown results in proteinuria in zebrafish larvae. Mice lacking Med22 specifically in podocytes develop normal kidneys and appear healthy until 8 weeks of age. After this the mice develop progressive albuminuria and renal insuffiency resulting in death by 16 weeks of age. Histologically, Med22-deficient mice exhibit large cytoplasmic vacuoles in podocytes that are positive for endosomal marker caveolin and lysosomal marker LAMP2.

Conclusions: Thus, Med22 is critical for the maintenance of podocyte homeostasis probably by regulating endosomal trafficking. This is the first time that a component of the mediator complex is shown to have a critical role in the kidney.

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TH-PO233

Nanoscopy of Slit Diaphragm Proteins in Optically Cleared Kidney Tissue David Unnersjö-Jess,[1] Lena Scott,[2] Hans Blom,[1] Hjalmar Brismar.[1,2] *[1]Applied Physics, Royal Inst of Technology, Solna, Sweden; [2]Women's and Children's Health, Karolinska Inst, Solna, Sweden.*

Background: Previously, the finest elements of the filtration barrier have only been possible to visualize using electron microscopy. However, electron microscopy is mostly restricted to ultrathin two-dimensional samples, and the possibility to simultaneously visualize different proteins is limited. With the advent of super-resolution light microscopy new possibilities are available. We have developed a fluorescence-based protocol for studying the filtration barrier in human and rat kidneys. The strict requirements of staining quality needed for super-resolution imaging are normally hard to meet when working with tissue samples due to high background. We overcome this by applying an optical clearing protocol, drastically increasing the signal-to-noise ratio as well as the staining homogeneity.

Methods: Our hydrogel-based optical clearing protocol can be applied to both human and rat kidney samples to remove lipids without interfering with tissue integrity. Samples are stained by immunohistochemistry, mounted in a saturated fructose solution and imaged using a Leica SP8 3X STED system.

Results: We show that an optical clearing protocol in combination with super-resolution microscopy allows us to resolve the slit diaphragm and the localization of proteins in this region. In non-cleared samples the slit diaphragm could not be resolved, showing that optical clearing is a necessary part of the protocol. We compared the localization of proteins in control samples to samples from rats with induced nephropathy, and observed alterations of the nanoscale distributions.

Conclusions: We show that optical clearing in combination with super-resolution microscopy can be used as a tool to study the finest parts of the slit diaphragm in kidney tissue. We also show alterations of slit diaphragm protein localizations under pathological conditions, making our protocol a possible tool for diagnosis.

Funding: Government Support - Non-U.S.

TH-PO234

Angiomotin Mutation in Rats Causes Proteinuria and Podocyte Foot Process Effacement Yaochun Zhang, Isaac Liu, Chang-Yien Chan, Hui Kim Yap, Kar Hui Ng. *Paediatrics, National Univ of Singapore, Singapore.*

Background: Using next generation sequencing, we identified in a Singapore Chinese family with X-linked recessive nephropathy a putative missense mutation in the *AMOT* gene which codes for angiomotin. The mutation segregates with renal disease, is not present in the exomes of healthy population and public databases. It changes a hydrophilic to hydrophobic amino acid. Although the amino acid is not conserved across different species, all species carry hydrophilic amino acids. *AMOT* occurs in the X chromosome in humans and rats and is known to affect tight junctions and actin cytoskeleton in epithelial cells. This study aimed to elucidate the function of *AMOT* in rat kidneys.

Methods: Using CRISPR/Cas9 system, we created a founder rat with a missense mutation corresponding to the human mutation. The phenotypes of the mutant F2 generation rats were compared with control rats. Total RNA were extracted from peripheral blood mononuclear cells and sent for RNA-Seq.

Results: All male mutant rats developed significant proteinuria by 6 months old and had significantly higher body weight than controls at 10 months old. Light microscopy showed minor glomerular changes but electron microscopy confirmed podocyte foot process effacement at 8 months old. There appeared to be no involvement in other organ systems. The renal tubular function was normal in mutant rats as shown by similar serum electrolytes and acid-base compared to controls. In contrast, both heterozygous and homozygous mutant females had no or very mild proteinuria, affirming the X-linked recessive inheritance. RNA-Seq results showed more than 300 differentially expressed genes including Smad7, Rac1 and pdlim1. Analysis using IPA revealed altered effector pathways in glomerular injury, renal necrosis, and nephritis.

Conclusions: To our knowledge, this is the first study that suggests that *AMOT* play important roles in podocytes. AMOT may exert its function in podocytes through Rich1/Gap complex affecting activation status of Rho GTPases or via interactions with slit diaphragm and actin cytoskeleton proteins. More studies are needed to further elucidate the mechanism.

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TH-PO235

Podocyte-Based HCS Assays Identify Paullone Derivatives as Novel Reno-Protective Agents Ha Won Lee,[1] Ehtesham Arif,[2] Deepak Nihalani,[2] Vineet Gupta.[1] *[1]Dept of Internal Medicine, Rush Univ Medical Center, Chicago, IL; [2]Dept of Medicine, Nephrology Div, Medical Univ of South Carolina, Charleston, SC.*

Background: Injury and loss of podocytes are early hallmarks of a variety of glomerular diseases. Targeting podocytes is an approach for the kidney-directed therapeutics. Damaged podocytes change their morphology and skeleton structure. To identify small molecules that protect podocytes from injury, we performed cell-based high content screening (HCS) using a phenotypic assay. The HCS assay revealed a family of small molecules, paullones, which are GSK3β inhibitors as potent podocyte-protective agents.

Methods: Phenotypic changes of podocytes were analyzed using automated methods. For in vitro podocyte damage, murine podocytes were treated with puromycin aminoglycoside (PAN). qPCR was used for the quantification of mRNA expression. Caspase 3/7 activities were measured using luciferase substrate-based system. Annexin V-positive cell population was quantified using flow cytometry. For glomerular injury in zebrafish, Adriamycin was added in growth medium. Pericardial edema was calculated by dividing cardiac area by whole body area.

Results: 3 paullone derivatives showed dose-dependent protection of podocytes from PAN-induced injury. Alsterpaullone, which showed most protective effects reduced the expression of a podocyte damage marker, *Desmin*, and inhibited PAN-induced increase in podocyte migration. Furthermore, alsterpaullone reduced PAN-induced apoptosis of podocytes. As a control, GSK3β inhibitor, SB216763, also protected podocytes from PAN-mediated injury apoptosis. Both alsterpaullone and SB216763 protected zebrafish from Adriamycin-induced glomerular damage.

Conclusions: Screening of a chemical library using our newly developed podocyte-based HCS assay resulted in identification of paullone family of compounds as novel podocyte-protective compounds. Paullones mediate their protective effects by targeting GSK3β, a well-known protein target in podocytes and showed protection of podocytes from injury in both in vitro and in vivo assays.

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TH-PO236

A T2A-Peptide Based Knock-In Mouse Model for Enhanced Cre Recombinase Activity and Fluorescent Labeling of Podocytes
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Background: Podocyte injury is a key event in glomerular disease leading to proteinuria and opening the path towards glomerular scaring. As a consequence glomerular research strives to discover molecular mechanisms and signaling pathways affecting podocyte health.

Results: Here, we generated a novel podocyte-specific Cre mouse model combining enhanced Cre efficiency and fluorescent cell labelling. To this end, we targeted the *Nphs2* locus to generate a tricistronic mRNA linking *Nphs2* to a codon improved Cre recombinase (iCre) via a viral 2A sequence followed by a second 2A sequence and mTomato allowing direct podocyte labelling. Podocin.T2A, iCre.T2A and mTomato are expressed in equimolar amounts under the control of the endogenous *Nphs2* promoter. Immunofluorescence and FACS-analysis revealed exclusive mTomato expression in podocytes. Nphs2.T2A.iCre.T2A.mtTomato mice did not develop glomerular disease confirming that the knock-in *per se* was not harmful. We assessed Cre recombinase efficiency by mating the mice to $Phb2^{fl/fl}$ mice. $Phb2^{fl/fl}$;$Pod2ACre^{tg/wt}$ mice presented with aggravated glomerular injury already evident after 2-3 weeks of age and premature lethality after 4 weeks while the onset of disease in conventional $Phb2^{fl/fl}$;$Pod.cre^{tg/wt}$ mice was delayed by approximately 7 days.

Conclusions: Taken together, we generated a tricistronic podocyte reporter mouse that combines improved Cre recombinase activity and expression of a membrane-tagged tomato for easy visualisation and identification of podocytes.

TH-PO237

VEGFA Expression by the Stromal Lineage Is Critical for Glomerular and Peritubular Capillaries in Kidney
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Background: VEGFA produced by podocytes and renal tubular epithelial cells is essential for the glomerular endothelium and peritubular capillaries, respectively. Given the important role of VEGFA in maintaining select microvascular beds, we aimed to determine whether the stromal compartment in kidney could be important for renal microvasculature by modulating the VEGFA system.

Methods: Expression of *Vegfa* in kidney was visualized using reporter mice with a *LacZ* gene inserted downstream of the *Vegfa* locus. Stromal-specific *Vegfa* deficient mice ($Vegfa^{Foxd1}$) were generated through crosses between Foxd1-Cre transgenic mice and floxed *Vegfa* animals, resulting in deletion of the *Vegfa* gene in interstitial pericytes and mesangial cells.

Results: During renal embryogenesis *Vegfa* was highly expressed in stromal cells. Elimination of *Vegfa* from the $Foxd1^{+}$ stroma resulted in proteinuria by postnatal day 14 (P14). Kidneys from $Vegfa^{Foxd1}$ showed abnormal mesangial expansion and thickening of the glomerular basement membrane at P7. Progressive worsening of the phenotype followed in $Vegfa^{Foxd1}$ with loss of glomerular endothelial cells, obliteration of the capillary lumen, and severe expansion of the mesangium. By P21, glomeruli appeared hypocellular with collapse of capillary tufts. Additionally, reduced peritubular capillary density was observed in $Vegfa^{Foxd1}$ kidneys.

Conclusions: VEGFA produced by renal $Foxd1^{+}$ stromal derivatives appear critical for proper maintenance of glomerular and peritubular microvasculature. The present data suggest that VEGFA may act as a paracrine factor mediating cellular communication towards renal endothelial cells by adjacent pericytes and mesangial cells.

TH-PO238

Unbiased Phosphoproteomic Approach Identifies Podocyte Protective Pathways Downstream the Melanocortin-1 Receptor
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Background: Adrenocorticotropic hormone (ACTH) has shown to be efficient in treatment of patients with nephrotic syndrome. Activation and upregulation of the ACTH receptor in podocytes, the melanocortin-1 receptor (MC1R), following renal damage has been proposed to be the protective mechanism of action.

Methods: To further understand the effector pathways downstream of the MC1R in podocytes, phosphoproteomic mass spectrometry was used on podocytes overexpressing wt-MC1R treated with the MC1R agonist, BMS. Stress fiber rearrangement was studied in real-time using LifeAct on podocytes treated with protamine sulfate, either overexpressing a constitutively active MC1R or a wt-MC1R treated with BMS.

Results: 299 significant MC1R regulated phosphoproteins were identified, with the top ranked regulated pathways at the early timepoint (15 min of BMS exposure) being actin cytoskeleton signaling followed by integrin, paxillin, FAK and RhoGTPase signaling. At a later stage (60 min of BMS) the activated pathways were shifted to tight junction followed by integrin, actin cytoskeleton and adherent junction signaling. The regulation of the actin cytoskeleton signaling by MC1R was further supported by LifeAct experiments where both BMS activation of wt-MC1R overexpressing cells and overexpression of the constitutively active MC1R showed a protective effect against PS induced stress fiber rearrangement.

Conclusions: This study presents the mechanisms behind the beneficial effects of MC1R-activation, with the top ranked function being actin cytoskeleton stabilization in podocytes, which is known to be crucial for the maintenance of kidney filtration barrier function. It also demonstrates how an unbiased phosphoproteomic approach can be used to identify regulated signaling pathways important in podocyte function.

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TH-PO239

Epidermal Growth Factor Receptor Augments Nephrin Tyrosine Phosphorylation
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Background: Phosphorylation of nephrin cytoplasmic tyrosines is thought to regulate podocyte morphology and actin cytoskeletal dynamics by inducing downstream signaling events. Here, we studied the ability of epidermal growth factor (EGF) receptor (EGFR) to participate in nephrin signaling.

Methods: Human podocytes were engineered with stable expression of chimeric nephrin (CD16 extracellular domain, CD7 transmembrane domain, and nephrin cytoplasmic domain). Nephrin phosphorylation was induced through antibody-mediated clustering (AMC) of nephrin and EGFR was activated with recombinant human EGF. Protein phosphorylation and protein complex formation were measured by immunoblotting and immunoprecipitation. Formation of endocytic structures and protein colocalization were quantified through analysis of fluorescence microscopy images.

Results: We found that the tyrosine phosphorylation that occurs normally in response to AMC was significantly augmented by concurrent EGFR activation. This effect was most apparent when EGFR and nephrin colocalization had increased substantially above baseline levels (≥10 min of AMC+EGF). The augmentation was abrogated through inhibition of Src family kinases (SFK), which were activated by EGFR and trafficked with EGFR-containing endosomal vesicles. Across all signals, phospho-nephrin signal correlated linearly with colocalization of nephrin and phospho-SFK ($R^2 = 0.87$). Interestingly, at early time points (≤2 min), concurrent EGFR activation suppressed nephrin tyrosine phosphorylation. This effect appeared to result from EGFR, which internalizes faster than nephrin, sweeping active SFK away from nephrin.

Conclusions: EGFR augments nephrin phosphorylation in a SFK-dependent manner by bringing active SFK into physical proximity of nephrin through EGFR–nephrin colocalization in endosomal compartments. EGFR's ability to influence nephrin signaling could play a role in slit diaphragm integrity.

TH-PO240

Role of the Rac1 Guanine Nucleotide Exchange Factor, Trio, in the Regulation of Rac1 Activity in Podocytes
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Background: Hyperactivation of the small GTPase, Rac1, has been shown to contribute to podocyte injury and development of focal segmental glomerulosclerosis (FSGS). We hypothesize that Rac1 is activated by one or more guanine nucleotide exchange factors (GEFs).

Methods: Nephromine was used to identify genes that are differentially expressed in FSGS and minimal change disease (MCD). Immuoblotting (IB) and immunofluorescence (IF) staining were used to detect proteins. Focal adhesion complex (FAC) was detected by vinculin IF. Trio knockout human podocyte (HP) lines (Trio KOs) were generated by the Cas9/CRISPR system. HP expressing Cas9 alone was used as control. Cell proliferation was studied by MTT assay. Motility was studied by wound healing. GST-bound Cdc42-Rac1 Interactive Binding domain (GST-CRIB) was used to pull-down (PD) active Rac1, followed by IB. GST-Rac1G15A was used to PD active Trio, followed by IB.

Results: RNA-seq showed high mRNA expression of the Rac1-GEF, Trio in two lines of HP. Glomerular mRNA of Trio was significantly upregulated in FSGS (1.24 fold) and MCD (1.18 fold) in the Ju podocyte dataset. Trio protein expression was detected by IB in HP and mouse glomerular lysates, and by IF staining in the mouse kidney, most notably in podocytes colocalizing with WT1. In HP, TGFβ1 activated Trio and Rac1 by 60 min and induced FAC relocalization toward the cell periphery. Compared to control, Trio KOs showed lower basal (24 ± 5% of control, n=3, $p<0.001$), as well as TGFβ1-induced (control: 1.72 ± 0.21 fold increase from basal, Trio KOs: 0.59 ± 0.13 fold from basal, n=4, $p<0.01$)

Rac1 activity. Trio KOs showed decreased motility (control: 21.4 ± 0.6 %, Trio KOs: 17.3 ± 1.0 %, wound closure at 5 h, n=4, p<0.05), while cell size, proliferation rate, and F-actin pattern were comparable to control HP. When the active form of Trio (GEF-D1 domain) was expressed in HP, it increased cell size and relocalized FAC to the cell periphery.

Conclusions: Trio contributes to basal and TGFβ1-induced Rac1 activity and regulates motility and FAC localization in podocytes. Trio may be one of the GEFs that contribute to the pathogenesis of FSGS and MCD via Rac1 activation.

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

TH-PO241

TGF-β1-Induced Changes of DNA Methylation Levels in Promoter and Enhancer Regions of WT1 Gene in Human Podocytes Hiroko Hamatani, Toru Sakairi, Hidekazu Ikeuchi, Yoriaki Kaneko, Akito Maeshima, Yoshihisa Nojima, Keiju Hiromura. *Dept of Medicine and Clinical Science, Gunma Univ Graduate School of Medicine, Maebashi, Japan.*

Background: Wilms' Tumor Suppressor (WT1) is essential for normal podocyte function. Previous reports have shown that WT1 promoter is often methylated in cancers, leading to transcriptional silencing. We have reported that TGF-β1 downregulates WT1 expression in podocytes. Based on the hypothesis that epigenetic modification plays a role in this process, we examined if TGF-β1 changes WT1 methylation levels in its promoter and three enhancer regions.

Methods: Conditional immortalized human podocytes were treated with 3 ng/ml of TGF-β1 for 10 days. A human renal tubular epithelial cell line (HK-2) was used as the control cells, which do not express WT1. The degree of DNA methylation was determined by quantitative methylation-specific PCR (Q-MSP), bisulfate sequencing, and pyrosequencing.

Results: Both WT1 mRNA and protein expression were reduced by the treatment of TGF-β1, as previously reported. Interestingly, TGF-β1 reduced mRNA expression of WT1 +KTS isoform, but not of -KTS isoform. The examination of methylation status of WT1 promoter by Q-MSP revealed that higher levels of methylation in HK2 (99.1±1.0% P<0.01) compared to untreated podocytes (2.9±4.5%), and that TGF-β1-treated podocytes tended to increase DNA methylation (14.3±10.5%, P=0.16, vs untreated podocytes). In contrast, examination of WT1 5' enhancer and intron 3 enhancer showed lower levels of methylation in HK2 (10.7±2.8% and 47.3±13.1%, P<0.01 and P<0.05) compared to untreated podocytes (53.7±10.3% and 74.5±8.9%), and that TGF-β1 tended to reduce or significantly reduced methylation at 5' enhancer and intron 3 enhancer (40.7±6.0% and 43.1±16.0%, P=0.13 and P<0.05, vs untreated podocytes). Bisulfite sequencing and pyrosequencing showed similar results. Finally, methylation levels at 3' enhancer did not differ among HK2, untreated podocytes and TGF-β1-treated podocytes.

Conclusions: Our data suggest that TGF-β1 changes the methylation levels of WT1 promoter and enhancers of podocytes. The reduction of WT1 expression by TGF-β1 may be partly due to the DNA methylation changes.

Funding: Government Support - Non-U.S.

TH-PO242

FRMD3/Protein 4.1O Is a Novel Linker of Nephrin to the Actin Cytoskeleton Eva Koenigshausen,[1] Aida Bajraktarevic,[1] Sinja Ohlsson,[1] Klaus Stahl,[2] Marie Schönberger,[1] Magdalena Woznowski,[1] Ivo Quack,[1] Mario Schiffer,[2] Lars C. Rump,[1] Lorenz Sellin.[1] *[1]Univ Hospital Duesseldorf, Germany; [2]Hannover Medical School, Germany.*

Background: FRMD3 has been proposed as a candidate gene for susceptibility of diabetic nephropathy (DN). FRMD3 encodes for protein 4.1O, which is a member of the 4.1 protein family. Members of the protein 4.1 family link membrane proteins to the actin cytoskeleton. The molecular function of protein 4.1O is unknown so far. Linkage of the slit diaphragm protein nephrin to the actin cytoskeleton via adapter proteins like nck are essential for the integrity of the slit diaphragm.

Methods: FRMD3 expression was analyzed in human podocytes. The interaction of nephrin with protein 4.1O and its truncations was examined by co-immunoprecipitation. Phospho-specific antibodies to nephrin and PP2 were used to investigate the role of nephrin Y-phosphorylation. Zebrafish larvae were treated with morpholinos against the orthologue of FRMD3 in zebrafish. Injection of fluorescently labeled FITC-dextran was monitored via eye fluoescence. A reduction of fluorescence was an indirect sign of glomerular tracer loss. For rescue experiments, morpholino treated larvae were injected with protein 4.1O truncations.

Results: Protein 4.1O is expressed in human podocytes and interacts with nephrin. Truncation mapping reveals the interaction domain of nephrin to protein 4.1O AA 506-554. Nephrin-protein 4.1O interaction is dependent on Src-family kinases. Interestingly, protein 4.1O reduces nephrin Y-phosphorylation at nephrin-nck binding sites and reduces nck binding to nephrin. Protein 4.1O directly interacts with actin. Injection of FRMD3 orthologue morpholinos in zebrafish larvae leads to yolk sac edema, slit diaphragm disruption and increase in glomerular permeability. This increase can be rescued by reconstitution of protein 4.1O AA 506-554, the nephrin binding domain.

Conclusions: Protein 4.1O is a novel linker of nephrin to the actin cytoskeleton and essential for the integrity of the glomerular filtration barrier. Our data point to a protective role of protein 4.1O in podocytes. Understanding of the physiological role of protein 4.1O will help to understand its role in diabetic nephropathy that has been implicated by GWAS.

TH-PO243

c-Abl Is Involved in the Cytoskeleton Remodeling of Podocytes via Interaction with Nephrin Yiqiong Ma, Qian Yang, Dingping Yang, Guohua Ding. *Div of Nephrology, Renmin Hospital of Wuhan Univ, Wuhan, Hubei, China.*

Background: Previous studies have showed that nephrin is required for cytoskeleton remodeling in podocytes. However, the molecular mechanism remains incompletely understood. c-Abl is a non-receptor tyrosine kinase involved in cytoskeleton regulation, which may be a candidate of signaling proteins interacting with SH2/SH3 domains of nephrin. The present study has explained whether c-Abl contributes to nephrin-dependent cytoskeleton remodeling of podocytes.

Methods: Colocalized expression of nephrin and c-Abl was evaluated in glomeruli of patients with nephrotic syndrome (NS) by double immunolabeling analysis. In *vitro*, Angiotensin II (Ang II) was used to promote cytoskeleton remodeling of podocytes. Differentiated murine podocytes were exposed to Ang II for 24 h. Cytoskeleton configuration was evaluated by FITC-phalloidin staining. Western blotting was performed to evaluate the expression of nephrin and c-Abl. Colocalization of nephrin and c-Abl was determined by confocal microscopy and co-immunoprecipitation analysis. Cell migration assays were used to evaluate the function of cytoskeleton remodeling. Co-immunoprecipitation was conducted in COS7 cells co-transfected with CD16-CD7-nephrin and SH2/SH3-defective c-Abl vectors to identify the domain of c-Abl binding with nephrin.

Results: The glomerular staining of nephrin and c-Abl indicated that the colocalization in patients with NS was decreased compared with that in control patients. In cultured podocytes, Ang II exposure induced dephosphorylation of nephrin and diminished the interaction between nephrin and c-Abl. In addition, F-actin disruption was aggravated by exposure of both Ang II and overexpression of c-Abl. Furthermore, the disorganized cytoskeleton stimulated by cytochalasin D in COS7 cells was restored by cotransfection with phosphorylated CD16-CD7-nephrin and c-Abl full-length constructs. Co-immunoprecipitation showed that phosphorylated CD16-CD7-nephrin interacted with wild type c-Abl, not with SH2/SH3-defective c-Abl.

Conclusions: This study suggests that phosphorylated nephrin is able to recruit c-Abl in a SH2/SH3-dependent manner, which modulates cytoskeleton remodeling in podocytes.

Funding: Government Support - Non-U.S.

TH-PO244

Novel Role of Proteasomes in Glomerular Disease Radhakrishna Baliga,[1] Allyson E. Bradley,[1] Himanshu Vashistha,[1] Sudhir V. Shah.[2] *[1]Inst of Translational Research, Ochsner Clinic Foundation, New Orleans, LA; [2]Nephrology, Univ of Arkansas for Medical Sciences, Little Rock, AR.*

Background: Proteasomes have been implicated in the pathophysiology of several disease processes in part through its action on a crucial transcription factor, nuclear factor-kappa B (NF-KB). NF-KB is a transcription factor that regulates the expression of a wide variety of inflammatory genes including cytochrome P450 (CYP). We have shown that CYP plays a major role in glomerular injury in a model of Minimal Change Disease (MCD). The role of proteasomes in MCD has not been explored. The current study examined the role of proteasomes in vitro utilizing cultured human podocytes (HP) and in vivo in a model of MCD.

Methods: MCD was induced in rats by injecting puromycin aminonucleoside (PAN) and the effect of proteasome inhibitors (PI) on proteinuria was measured as urinary albumin to creatinine ratio (ACR)(μg/mg) until day 10. Protein from PAN treated HP were analyzed by Western Blot. CYP2B6 was identified to the human kidney by immunohistochemistry and in cultured HP by W-B and RT-PCR.

Results: Exposure of HP to PAN resulted in nuclear translocation of NF-KB, activation of IL-6 and upregulation of CYP2B6. There was marked generation of H_2O_2 associated with significant increase in 8-oxo-2-deoxyguanosine (8-oxo-dG) accompanied by disorganization of actin cytoskeleton. PI, MG-132, significantly increased the expression of Nrf2 and its downstream antioxidant enzyme heme oxygenase-1 (HO-1), blunted the nuclear translocation of NF-KB and activation of IL-6 with no further upregulation of CYP2B6. There was marked reduction in H_2O_2 release and 8-oxo-dG expression with preservation of actin cytoskeleton. Administration of two PI, Carfilzomib(CAR) and MG-132, to rats resulted in marked and significant protection against PAN-induced ACR (Day 4:PAN 75 ±14, MG + PAN 31 ±1, CAR + PAN 36 ±6 ;Day 10:PAN 147 ±13, MG + PAN 97 ±16, CAR + PAN 75 ±9).

Conclusions: These studies indicate a pivotal role of proteasomes in the pathophysiology of MCD most likely through its effects on NF-KB and CYP2B6. Carfilzomib, a novel irreversible PI, is currently used in humans and may be potentially useful for the treatment of glomerular disease.

TH-PO245

Targeting mTOR Signaling Can Prevent the Progression of Focal Segmental Glomerulosclerosis Tillmann Bork, Stefan Zschiedrich, Wei Liang, Nicola Wanner, Markus Gödel, Tobias B. Huber. *Dept of Nephrology, Univ Hospital Freiburg, Freiburg, Germany.*

Background: Mammalian Target of Rapamycin (mTOR) signaling is involved in a variety of kidney diseases. Clinical trials administering mTOR inhibitors to patients with focal segmental glomerulosclerosis (FSGS), a prototypic podocyte disease, led to conflicting results ranging from remission to deterioration of kidney function.

Methods: Here we combined complex genetic titration of mTORC1 levels in murine glomerular disease models, pharmacologic studies and human studies to precisely delineate the role of mTOR in FSGS.

Results: mTORC1 target genes were significantly induced in both human FSGS cohorts and murine FSGS models. Mouse models with constitutive mTORC1 activation closely recapitulated human FSGS. Unexpectedly, the complete knockout of mTORC1 by induced deletion of both *Raptor* alleles accelerated the progression of murine FSGS models. However, curtailing mTORC1 signaling by genetically deleting just one *Raptor* allele ameliorated progression of glomerulosclerosis in murine FSGS model. This non-linear mTORC1 gene dosage effect was further substantiated by low dose Rapamycin treatment of murine FSGS models ameliorating disease progression. Mechanistically, complete mTOR inhibition shifted the cellular energy metabolism towards reduced rates of oxidative phosphorylation and anaerobic glycolysis, which was linked to an increased reactive oxygen species production. Moderate mTOR inhibition however preserved mitochondrial function in the presence of FSGS.

Conclusions: Together these data suggest that podocyte injury and loss is initially followed by an adaptive mTOR activation precluding the use of long-term and high dose mTOR inhibition. However as prolonged mTOR activation results in podocyte dedifferentiation and cellular stress with our models we propose incomplete mTOR inhibition as a novel and individualized treatment rationale.

Funding: Government Support - Non-U.S.

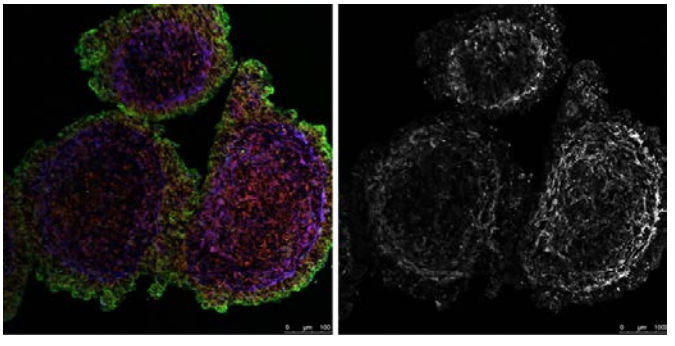
TH-PO246

An In Vitro Model of the Glomerulus Jack P. Tuffin,[1] Gavin Iain Welsh,[1] Moin Saleem,[1] Simon C. Satchell.[1] *[1]Bristol Renal, Univ of Bristol, Bristol, United Kingdom; [2]UCB Pharma Ltd, Slough, United Kingdom.*

Background: Our lab has previously developed conditionally immortalised human podocytes and glomerular endothelial cell (GEnC) lines. The purpose of this project has been to develop a 3D in-vitro model of the glomerulus for the purpose of developmental research as well as pharmaceutical-compound screening.

Methods: Cells were cultured using a variety of scaffold culture techniques including a novel gel/scaffold hybrid platform utilizing cocultured, growth factor-treated cells. Magnetic levitation as well as magnetic bioprinting techniques were also used. Cell types were identified using stable GFP/RFP labelling. Cultured tissues were paraffin embedded, sectioned and stained for confocal immunofluorescence microscopy.

Results: Experiments show that 3D cocultured podocytes and GEnCs reorganise in a similar, glomerular-like manner regardless of the culture platform used. Podocytes were seen to wrap around GEnCs, with tube formation identified. Magnetic spheroids were used to manually and rapidly organise cells in this way to form glomerulus sized tissues that express the glomerular basement membrane protein collagen IV in a location concurrent with its in-vitro deposition.



Conclusions: We have developed an in-vitro 3D coculture model of human podocyte and GEnC glomerular cell lines, with self organizing properties, that show early hallmarks of GBM formation.

Funding: Pharmaceutical Company Support - UCB pharma, Government Support - Non-U.S.

TH-PO247

Akt Pathway Plays a Critical Role in Podocyte Injury and Recovery in Glomerular Disease Tetsuya Kitao,[1,2] Melinda A. Chanley,[1] Kazunari Kaneko,[2] William E. Smoyer,[1,3] Shipra Agrawal.[1] *[1]CCTR, The Research Inst at Nationwide Children's Hospital, Columbus, OH; [2]Pediatrics, Kansai Medical Univ, Osaka, Japan; [3]Pediatrics, The Ohio State Univ, Columbus, OH.*

Background: Tight regulation of mTOR and Akt pathways has recently been reported in the context of chronic kidney disease and in apoptosis control of podocytes. Furthermore, we have previously reported the beneficial roles of glucocorticoids (GCs) and pioglitazone (Pio) in nephrotic syndrome (NS). We hypothesized that Akt pathway downstream of PI3K and/or mTOR plays a critical role in podocyte injury and recovery in NS.

Methods: Phosphorylated and total forms of Akt and Mdm2 were analyzed in the glomeruli or kidney sections of rats and mice injured with single puromycin aminonucleoside (PAN) and Adriamycin (Adr) injections, respectively. In vitro, differentiated immortalized human podocytes were injured with PAN and Adr at various time points and treated with GCs and Pio. Apoptosis was analyzed by TUNEL assay in the presence or absence of Akt activator (SC79) and inhibitor (MK2206).

Results: Akt phosphorylation was inhibited under the mTORC2 (site Ser473) pathway in PAN-treated rat glomeruli which correlated with proteinuria and inhibited under both mTORC2 and the PI3K (site Thr308) pathways in differentiated human podocytes which was restored by GC and Pio treatment. Adr-treated human podocytes also showed decreased Akt phosphorylation at earlier time point while it was activated in the Adr- treated mice cortices at 7 and 21 days. This activation was however attributed to proximal tubule cells and not podocytes as assayed by immuno-fluorescence microscopy. Moreover, while PAN induced apoptosis in cultured differentiated human podocytes and treatment with GCs inhibited apoptosis, activator of Akt at Ser473/Thr408 enhanced the anti-apoptotic effects while the inhibitor at Ser473/Thr408 enhanced apoptosis and reduced the anti-apoptotic effects of GCs.

Conclusions: Akt regulation by both mTORC2 and PI3K pathways is associated with podocyte injury and recovery in glomerular disease and its activation provides beneficial protective effects.

Funding: NIDDK Support

TH-PO248

Glomerular Podocyte to Endothelial Cell Cross-Talk in Kidney Disease Jia Fu,[1] Kyung (Kim) Lee,[1] Stuart J. Shankland,[2] John C. He.[1] *[1]Icahn School of Medicine at Mount Sinai, New York; [2]Univ of Washington School of Medicine, Seattle.*

Background: Podocytes and glomerular endothelial cells (GECs) are major components of the glomerular filtration barrier, and cross-talk between these two cell types is critical for maintaining this barrier. Recent studies suggest that podocyte injury leads to the progression of glomerular disease. It is hypothesized that podocyte injury could cause GEC injury through a cross-talk mechanism. Here, we sought to test this hypothesis in vivo using RNA sequencing of GECs in an animal model of podocyte injury.

Methods: We used a transgenic mouse model in which GECs are labeled with yellow-fluorescent protein (YFP) in the nuclei which allowed us to effectively sort GECs by flow cytometry. Podocyte injury was induced by injection of mice with a specific anti-podocyte antibody generated in Dr. Stuart Shankland's laboratory. Mice were sacrificed at day 14 after antibody injection, glomeruli were isolated and YFP-positive GECs were sorted for RNA sequencing. The key pathways were validated by real-time PCR, western blot analysis, and functional assays for apoptosis and ROS production.

Results: Antibody-injected mice developed significant proteinuria, focal glomerulosclerosis, and podocyte depletion. Interestingly, number of GECs was also reduced and appeared detached from glomerular basement membrane. GECs were sorted from these mice and expression of endothelial cell-specific markers was confirmed in the sorted cells. Analysis of the differentially expressed genes (DEGs) in GECs between the diseased and control mice revealed significant alteration of the pathways related to apoptosis, tight-junction, and oxidative stress. Expression of key DEGs was confirmed by real-time PCR and western blot analysis. We validated that apoptosis and production of ROS increased in the GECs of the diseased mice.

Conclusions: Podocyte injury can propagate to GEC injury through a crosstalk mechanism that mediates the progression of glomerular disease.

Funding: Other NIH Support - NIH 1R01DK078897; NIH 1R01DK088541; NIH P01-DK-56492, VA Support

TH-PO249

Mutant Actinin-4 in the Pathogenesis of Focal Segmental Glomerulosclerosis Albert Yee, Joan Papillon, Julie Guillemette, Daniel Robert Kaufman, Andrey V. Cybulsky. *Medicine, McGill Univ, Montreal, Canada.*

Background: Mutations in actinin-4 are associated with heritable focal segmental sclerosis (FSGS) in humans. Previously, we showed that actinin-4 K256E is a misfolded protein that undergoes aggregation and degradation in cultured glomerular epithelial cells (GECs). There is associated proteotoxicity, i.e. induction of endoplasmic reticulum (ER) stress and "choking" of the proteasome. The present study examined whether small molecules could improve the folding and function of mutant actinin-4, and if autophagy is upregulated by actinin-4 K256E and is responsible for its degradation.

Methods: GFP-tagged actinin-4 wild type (WT) or K256E were expressed in GECs or COS-1 cells by transfection. Interaction of actinin-4 with the cytoskeleton was assessed by detergent-extraction of cells and monitoring actinin-4 by immunoblotting. Autophagy was monitored by immunoblotting of endogenous LC3II or by expression of RFP-LC3 and quantifying formation of LC3II puncta.

Results: After extraction of cells with Triton X-100, actinin-4 WT was found mainly in the Triton-soluble fraction (69.8%); however, K256E was predominantly Triton-insoluble (81.6%), reflecting abnormally tight binding to F-actin. Incubation of cells with the chemical chaperone, 4-phenylbutyrate, decreased the proportion of Triton-insoluble actinin-4 K256E (from 81.6% to 68.6%), but celastrol, a drug that enhances expression of cytosolic and ER chaperones, had no effect. After treatment of cells with chloroquine (to block fusion of autophagosomes with lysosomes), actinin-4 K256E stimulated autophagy, as reflected by a 1.5-fold greater accumulation of endogenous LC3II, compared to WT. Moreover, RFP-LC3II puncta occupied a 45% greater area in cells expressing actinin-4 K256E, compared to WT. Surprisingly, actinin-4 K256E did not colocalize with RFP-LC3II, and was not degraded by autophagy, but rather by the proteasome.

Conclusions: A small molecule chemical chaperone improved the function of actinin-4 K256E. Mutant actinin-4 stimulated autophagy, but this process was not responsible for its degradation. The combination of a chemical chaperone and proteasome inhibitor may become a novel therapeutic approach to actinin-4-mutant associated FSGS.

Funding: Government Support - Non-U.S.

TH-PO250

CD147/Basigin Deficiency Prevents the Development of Podocyte Injury through the Integrin/FAK Signaling Pathway Tomoki Yoshioka, Tomoki Kosugi, Kayaho Maeda, Tomohiro Masuda, Yuka Sato, Hiroshi Kojima, Noritoshi Kato, Takuji Ishimoto, Shoichi Maruyama. *Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya-shi, Aichi-ken, Japan.*

Background: CD147/Basigin (Bsg) is a glycosylated transmembrane protein belonging to the immunoglobulin superfamily. Bsg contributes to cell survival, migration, cancer invasion and inflammation. We have so far demonstratedits pathophysiological roles in the kidney diseases, ranging from the occurrence of acute kidney injury accompanied by ischemia and inflammation to progression of renal fibrosis and lupus nephritis. However, little is known in the development of proteinuria. We therefore investigated the role of Bsg in the development of podocyte injury leading to the augmentation of proteinuria, using adriamycin nephropathy mice model.

Methods: Wild-type ($Bsg^{+/+}$)or Bsg-deficient ($Bsg^{-/-}$)mice were injected with adriamycin (16mg/kg BW), and were then sacrificed at 2 weeks later for histological and biochemical analyses. Blood, urine samples and kidney tissues were analyzed. In *in vitro* study, conditionally immortalized human podocyte cell lines were used.

Results: $Bsg^{-/-}$ mice ameliorate the development of proteinuria compared to $Bsg^{+/+}$ mice in adriamycin nephropathy.Marked podocyte injuries and the progression of foot process effacement were observed in $Bsg^{+/+}$ mice. Podocyte rarely expressed Bsg, but began to exhibit Bsg induction upon adriamycin exposure, using in situ hybridization and immnohistochemistry. Furthermore, Bsg expression was observed in immortalized human podocyte cells, and Bsg silencing with siRNA in podocyte cells suppressed the phosphorylation of focal adhesion kinase (FAK) under TGF-β stimulation. Interestingly, Bsg expression in podocyte has the association of integrin. Additionally, Bsg silencing on podocytes after TGF-β stimulation caused the decreases of endothelin-1 and MMP expressions, which are regarded as key molecules in the development of podocyte and glomerular injuries.

Conclusions: Bsg plays an indispensable role in the development of podocyte injury leading to the augmentation of proteinuria through the activation of FAK signaling pathway.

TH-PO251

Podocyte Effacement Precedes Albuminuria and Glomerular Hypertrophy in CD2 Assosicated Protein Deficient Mice John M. Basgen,[1] Susanne B. Nicholas,[2] Jenny Wong,[3] Kirk N. Campbell.[3] *[1]Charles Drew Univ, LA, CA; [2]Univ of California, Los Angeles, Los Angeles, CA; [3]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: CD2AP-deficient mice show podocyte foot process effacement, mesangial expansion, massive proteinuria and decreased kidney function by 4 weeks of age eventually resulting in glomerulosclerosis and death. We previously demonstrated crosstalk between podocytes and mesangial cells in this model but it is unclear which cell type was affected first. Here we sought to determine the sequence of early structural podocyte and mesangial changes in $Cd2ap^{-/-}$ mice at 2 weeks of age.

Methods: At age 14 days urine was collected and the mice perfused with fixative. After genotyping five $Cd2ap^{+/+}$ and four $Cd2ap^{-/-}$ mice were available for analysis. Urine albumin and creatinine were measured using appropriate ELISA kits. The albumin/creatinine ratio (ACR) was calculated for each animal and log-transformed for statistical analysis. Glomerular volume was measured by light microscopy using the Cavalieri principle. The volume densities of glomerular components (mesangium, podocyte and capillary) were measured on low magnification electron microscopy images using the Delesse principle. The volume of a component was then calculated by multiplying the volume density of the component by the glomerular volume. Foot process width was measured on high magnification EM images. Five glomeruli were measured per kidney.

Results: There was no difference in ACR between the $Cd2ap^{+/+}$ group (median [range] mg/g): 183 [160-1138] and the $Cd2ap^{-/-}$ group: 242 [176-388]. Foot process width was increased (p-value = .008) in the $Cd2ap^{-/-}$ group (mean [SD] nm): 1128 [286] vs. $Cd2ap^{+/+}$ group: 374 [42]. There was no difference in glomerular volume between $Cd2ap^{+/+}$ (mean [SD] μm^3): 68,307 [10,931] and $Cd2ap^{-/-}$: 66,844 [13,022] or the volumes of the glomerular components.

Conclusions: Podocyte effacement precedes albuminuria and changes in glomerular volume and the volumes of glomerular components in the CD2AP-deficient mouse. These findings suggest that podocyte injury is the initiating event in CD2AP-deficient mice leading to subsequent mesangial volume expansion and disease progression.

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TH-PO252

Podocyte Vitamin D Receptor Deficit Induces Activation of Renin Angiotensin System via SIRT1 Modulation Nirupama Chandel, Vinod Sharma, Waqaar Khawar, Nairuti H. Shah, Vinita Vishnoi, Ashwani Malhotra, Pravin C. Singhal. *Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY.*

Background: Vitamin D receptor (VDR) deficient status has been shown to be associated with the activation of renin angiotensin system (RAS). However, the involved mechanism is not clear. We hypothesized that lack of VDR would enhance p53 expression in podocytes through down regulation of SIRT1; the former would enhance the transcription of angiotensinogen (Agt) and angiotensinogen type 1 receptor (AT1R) leading to the activation of RAS.

Methods: Renal tissues of 4 week old control and VDR mutant (M, n=4) were analyzed for expression of p53, angiotensinogen (Agt), renin, SIRT1, PPAR--y and AT1R (mRNA and proteins). Human podocytes (HPs) were transfected with either scrambled or VDR siRNAs and evaluated for expression of above mentioned molecules. Renal tissues from VDR(M) and HPs lacking SIRT1 were evaluated for acetylation of p53 and lysine (K) 382 residues.

Results: Renal tissues of VDR mutant (M) mice displayed increased expression of p53, Agt, renin, PPAR-y, and AT1R. *In vitro* studies, VDR knockout podocytes not only displayed up regulation p53 but also displayed enhanced expression of Agt, renin and AT1R. VDR deficient podocytes also displayed an increase in mRNA expression for p53, Agt, renin, and AT1R. Interestingly, renal tissues of VDR-M as well as VDR heterozygous (h) mice displayed attenuated expression of deacetylase SIRT1. Renal tissues of VDR-M mice showed acetylation of p53 at lysine (K) 382 residues inferring that enhanced p53 expression in renal tissues could be the result of ongoing acetylation, a consequence of SIRT1 deficient state. Notably, podocytes lacking SIRT1 not only showed acetylation of p53 at lysine (K) 382 residues but also displayed enhanced p53 expression. Since renal tissues of VDR-M mice also showed enhanced expression of PPAR-y, it is plausible that either the deficit of SIRT1 has de-repressed expression of PPAR-y or enhanced podocyte expression of PPAR-y (in the absence of VDR) has contributed to the down regulation of SIRT1.

Conclusions: VDR deficit activates the RAS via SIRT1 modulation.

Funding: NIDDK Support

TH-PO253

Mapping Podocyte Mechanical Force In Vitro Kathryn E. Haley,[1] Nils Michael Kronenberg,[2] David James Harrison,[1] Malte C. Gather,[2] Paul Reynolds.[1] *[1]School of Medicine, Univ of St. Andrews, United Kingdom; [2]SUPA, School of Physics and Astronomy, Univ of St. Andrews, United Kingdom.*

Background: Podocyte damage is a pivotal event underlying the pathogenesis of multiple glomerular diseases. When damaged podocytes lose the ability to adhere to the glomerular basement membrane, they detach, resulting in impaired glomerular filtration. However, the mechanism underlying podocyte detachment remains poorly understood. In this study we sought to characterize the mechanical forces exerted by differentiated podocytes by using a novel force detection assay.

Methods: A human podocyte cell line containing a SV40/hTERT temperature-sensitive transgene was differentiated over the course of 12 days at the non-permissive temperature of 37°C. Differentiated podocytes were treated with 25μg/mL Puromycin Aminonucleoside (PAN) for 24 hours, followed by washout with fresh RPMI for 5 days. Podocyte mechanical forces were assessed with a novel continuous force detection assay, Elastic Resonator Interference Stress Microscopy (ERISM).

Results: Podocytes demonstrated a pulling force at focal points around the cell periphery that co-localized with foot processes. A pushing force was observed under the cell body that was 3 times greater than the force exerted by 3T3 fibroblasts (n=18). PAN treatment resulted in foot process effacement and membrane blebbing as evidenced by scanning electron microscopy, F-actin rearrangement, and a reduction in expression of NPHS1, NPHS2, CD2AP, and SYNPO. PAN treatment resulted in an initial increase in podocyte force transmission by a factor of 1.4, followed by a complete loss of either pushing or pulling force (n=4), despite continued cell attachment. Following PAN washout, partial recovery of force transmission of up to 60% of the initial value was observed.

Conclusions: Herein we present a novel biological application of the ERISM force detection assay. Our results indicate that, in a PAN model of glomerular injury, loss of podocyte mechanical force transmission is partially reversible. These results highlight podocyte mechanical force transmission as an integral feature of healthy podocytes, and suggest that changes in mechanical force play a pivotal role in the development of podocytopenia.

TH-PO254

Functional Interaction of USP40 with Nestin in Podocyte Shohei Takahashi, Yukino Nishibori, Kunimasa Yan. *Pediatrics, Kyorin Univ School of Medicine, MKtaka, Tokyo, Japan.*

Background: We previously showed that gene knockdown of ubiquitin specific protease-40 (USP40) leads to disorganized glomerulus in zebrafish morphants. Nestin is currently speculated to be a protective molecule against podocyte injury. The aim of the present study was to explore a functional role of USP40 in the acquired podocyte disease.

Methods: USP40 KO mice were generated and assessed for the kidney morphology and urinary abnormality. The isolated glomeruli from 3 KO mice and 3 wild type mice were analyzed to integrate the data of proteomic analysis. Cultured mouse podocytes were subjected to dual-labeling immunofluorescence, immunoprecipitaion and gene knockdown experiments to determine a functional relationship between USP40 and nestin. Glomeruli and kidney sections from adriamycin nephropathy and control mice were analyzed to compare protein expression of USP40 and nestin in podocytes.

Results: KO mice did not reveal pathological proteinuria and apparent alterations in kidney morphology. However, proteomic analysis revealed a predominant increase of nestin in KO mice compared to wild type. In the cultured podocytes, apparent protein binding and colocalization between USP40 and nestin were determined. Gene knockdown of USP40 revealed significant decrease of nestin in cultured podocytes. Finally, colocalization between USP40 and nestin was also apparent in the glomerular podocytes in the control mice. In the podocytes of adriamycin nephrosis, the expression of both USP40 and nestin were reduced in the sclerotic region whereas those were predominantly increased in the hypertrophic region.

Conclusions: Our findings collectively show that USP40 is a novel ligand protein for nestin and suggest that their interaction may be involved in the pathophysiology of the acquired podocyte disease. Absence of phenotypic change of USP40 KO mice suggests the possible presence of the compensatory mechanism for nestin protein turnover in podocytes.

TH-PO255

Mechanism of TIMAP Action: Competition with MYPT1 for the PP1c Catalytic Subunit Xin Wang,[2] Laiji Li,[1] Barbara J. Ballermann.[1] *[1]Medicine, Univ of Alberta, Edmonton, AB, Canada; [2]Nephrology, The First Affiliated Hospital of Sun Yat-Sen Univ, Guangzhou, China.*

Background: Actomyosin activation by phosphorylated myosin-light chain 2 (MLC2) increases endothelial permeability in glomeruli and other capillaries, and myosin phosphatase inhibition maintains MLC2 phosphorylation (pMLC2). Myosin phosphatase consists of regulatory (MYPT1) and catalytic protein phosphatase I (PP1c) subunits, and is inhibited by Rho-kinase-dependent phosphorylation of MYPT1. TIMAP is an endothelial cell (EC)-predominant member of the MYPT family. Surprisingly, overexpression of TIMAP increases pMLC2 in glomerular EC by inhibiting myosin phosphatase activity without activating Rho or MYPT1 phosphorylation. We investigated how TIMAP inhibits MYPT1/PP1c action in EC.

Methods: Western blots (WB) with densitometric quantification were performed on lung (rich in EC) lysates from wild-type and TIMAP deficient mice, and cultured human glomerular EC lysates. Glomerular EC were transduced with Adenoviruses (Ad) expressing GFP (Ad-GFP), GFP-TIMAP (Ad-GFP-TIMAP^{WT}) or the PP1c binding mutant Ad-GFP-TIMAP^{PP1-}. PP1c was specifically precipitated with microcystin sepharose.

Results: Similar to our findings of increased pMLC2 in glomerular EC overexpressing TIMAP^{WT}, the pMLC2:Actin ratio was higher in lung lysates of WT than TIMAP deficient mice (0.56 ± 0.19 *vs.* 0.32 ± 0.07, mean ± SD, n=4, *P*=0.019). The MYPT1:Actin ratio was 57 ± 23% (mean ± SD, n=3, *P*=0.026) lower in glomerular EC expressing GFP-TIMAP^{WT} vs. GFP. GFP-TIMAP^{PP1-}, which cannot bind PP1c, had no discernable effect on pMLC2 or MYPT1 abundance. Microcystin co-precipitated PP1c and MYPT1, but not TIMAP, from EC expressing GFP or GFP-TIMAP^{PP1-}, but co-precipitated only PP1c and TIMAP, and not MYPT1 from EC expressing GFP-TIMAP^{WT}, even when equivalent MYPT1 was loaded.

Conclusions: The data indicate that TIMAP competes for PP1c with MYPT1, implying that PP1c regulatory subunits like MYPT1 and TIMAP exist in excess over their catalytic subunits in EC, and that TIMAP inhibits, while MYPT1 potentiates PP1c activity towards pMLC2. Also, expression of TIMAP^{WT}reduces the MYPT1 abundance in EC. Hence, pMLC2-dependent EC permeability may be controlled in a Ying-Yang fashion by TIMAP and MYPT1.

Funding: Clinical Revenue Support

TH-PO256

Loss of Nonmuscle Myosin II in Postnatal Mouse Renal Tubules Results in Chronic Kidney Disease Indra Chandrasekar,[1] Karla L. Otterpohl,[1] Ryan G. Hart,[1] Kameswaran Surendran,[1] Bruce A. Molitoris.[2] *[1]Sanford Children's Health Research Center, Sanford Research, Sioux Falls, SD; [2]Dept of Medicine, Indiana Univ, Indianapolis, IN.*

Background: Nonmuscle myosin II (M2) is an actin associated motor protein that contributes to the cellular processes of migration, adhesion, and division and is essential for brain and heart development. Our recent work demonstrated that MII function (isoforms M2A and M2B) is critical for both compensatory and constitutive receptor mediated endocytosis. Previous studies have shown that point mutations in the M2A gene, *MYH9*, are associated with human diseases involving blood, eye, ear and kidney disorders. Additionally, two genome wide association studies have identified *MYH9* as a major locus for susceptibility to end-stage renal disease.

Methods: We hypothesized that the underlying mechanism in M2 related kidney disorders is compromised renal tubular endocytosis resulting in decreased protein reabsorption. We inactivated one or both M2 genes, *Myh9* and *Myh10*, within the postnatal renal tubules using the doxycycline inducible Pax8->rtTA; Tet-O-Cre system. Doxycycline was administered in the drinking water to mice at 1 month of age to inactivate the Myh9 and Myh10 genes.

Results: Urine analysis revealed proteinuria as early as two months after starting doxycycline. Histological evaluation of kidney from single MII gene knock-out revealed mild tubular dilation and inflammation younger mice, that progressed to glomerular sclerosis, loss of cytosolic staining in the proximal tubules and the presence of polymorphonuclear leukocytes and macrophages. Interestingly, knockout of both *Myh9* and Myh10 in the postnatal tubules results in dysplastic kidney disease within two months of starting doxycycline treatment.

Conclusions: Our data support the hypothesis that postnatal loss of M2 in renal tubules results in tubular dysfunction and progresses to chronic kidney disease.

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TH-PO257

mPGES-1-Derived PGE2 Stimulates Stat3 to Promote Podocyte Injury Jing Yu,[2] Zhanjun Jia,[2] Wei Gong,[2] Shuzhen Li,[2] Yue Zhang,[1] Guixia Ding,[1] Aihua Zhang,[1] Songming Huang.[1] *[1]Dept of Nephrology, Nanjing Children's Hospital affiliated to Nanjing Medical Univ, Nanjing, China; [2]Nanjing Key Lab of Pediatrics, Nanjing, China.*

Background: We previously reported that microsomal prostaglandin E synthase-1 (mPGES-1) contributed to Adriamycin (Adr)-induced podocyte injury (Yu et al. AJP-renal, 2015). However, the molecular mechanisms mediating mPGES-1 effect on inducing podocyte damage is still unknown. Here to performed experiments to test the role of mPGES-1/PGE2 cascade in activating Stat3 and its contribution in PGE2- and Adr-induced podocyte injury.

Methods: PGE2 and Adr were administered to the podocytes to induce podocyte injury. Specific Stat3 inhibitor and mPGES-1 siRNA were used to determine the roles of Stat3 and mPGES-1-derived PGE2 in this pathological process.

Results: By administration of PGE2 to podocytes, we observed a dose- and time-dependent upregulation of p-Stat3 (>3folds), indicating an activation of Stat3, in line with the significant podocyte injury as evidenced by the remarkable cell apoptosis and the reduction of nephrin expression. Consistently, Stat3-drived cytokines like IL-6, IL-17, and MCP-1 were enhanced by 2-4 folds ($p<0.05$) by PGE2 treatment. By inhibiting Stat3 with a specific Stat3 inhibitor S3I-201, PGE2-induced podocyte apoptosis was blocked by 51% ($p<0.05$) in parallel with attenuated nephrin downregulation by 55% ($p<0.05$). Then the podocytes were further subjected to the Adr treatment. As expected, Adr remarkably elevated p-Stat3 levels by more than 3-folds after 6 h treatment in line with the stimulation of mPGES-1/PGE2 cascade. Blockade of Stat3 by S3I-201 significantly ameliorated Adr-induced cell apoptosis by 60% and nephrin reduction by 45%. More interestingly, silencing mPGES-1 in podocytes by mPGES-1 siRNA almost abolished Adr-induced increments of Stat-3 phosphorylation, PGE2 production, and Sta3-drived inflammatory cytokines.

Conclusions: The current study highly suggested that mPGES-1-derived PGE2 could activate Stat3 signaling to promote podocyte injury. Targeting mPGES-1/PGE2/Stat3 signaling might be a potential strategy for the treatment and prevention of podocytopathy.

TH-PO258

Tracking the Fate of Single Glomerular Endothelial Cells with Serial Multiphoton Imaging in a New Cdh5-Confetti Mouse In Vivo Dorinne Desposito, Anne Riquier-Brison, Janos Peti-Peterdi. *Physiology and Biophysics, Univ of Southern California, Los Angeles, CA.*

Background: Endothelial cells are critical in the maintenance of a healthy glomerular filter and in the development of glomerular disease. However, the origin, proliferation, migration and regeneration of glomerular endothelial cells have been difficult to study in vivo. We aimed to develop a direct visual approach to track the fate of single endothelial cells over several days-weeks in the same glomerulus in vivo.

Methods: Endothelial cell-specific confetti mice featuring tamoxifen-inducible expression of 4 different fluorescent proteins (CFP/GFP/YFP/RFP) were developed by crossing Cdh5 (VE-cadherin) CreERT2 and floxed confetti reporter mice. Cdh5-Confetti mice (3 to 5 weeks of age) were subjected to implantation of a dorsal abdominal imaging window, which allowed non-invasive multiphoton microscopy (MPM) of the same kidney volume in vivo on a daily basis. To induce kidney injury, the streptozotocin (STZ) model of diabetes and L-NAME treatment, or unilateral ureteral ligation (UUO) were applied.

Results: MPM imaging of Cdh5-Confetti mice revealed strong expression of all confetti FPs (colors) at baseline. Individual glomerular endothelial cells were clearly identifiable based on their unique color, with random distribution of all four colors. High resolution MPM imaging observed thickened cytoplasmic ridges of endothelial cells that appeared as primary and secondary cell processes. Endothelial injury by STZ+L-NAME triggered rapid cellular remodeling of the glomerular endothelium judged by the changing confetti colors. Within four days of injury, multi-cellular endothelial cell tracing units developed in the same color suggesting that the newly formed cells were daughter cells of the same parent endothelial cell. Entirely monochromatic glomeruli developed. In UUO mice, multi-color afferent arterioles were seen transitioning into monochromatic glomeruli, suggesting rapid proliferation of single endothelial precursor cells within glomeruli.

Conclusions: In summary, glomerular endothelial cells show highly dynamic and robust proliferation/migration after injury, which may be consistent with glomerular and vascular regeneration.

Funding: NIDDK Support

TH-PO259

The Role of FcRn in the Expression of MHC II and Trafficking of Antibody-Antigen Complexes to Lysosomes in Glomerular Endothelial Cells James Francis Dylewski, Evgenia Dobrinskikh, Linda Lewis, Judith Blaine. *Dept of Medicine, Div of Renal Disease and Hypertension, Univ of Colorado, Aurora, CO.*

Background: Glomerulonephritis (GN) has been shown to occur via activation of CD4+ T cells by intrinsic renal cells expressing MHC II. Glomerular endothelial cells can express MHC II but it is unclear if they are able to process antigen for presentation. Neonatal Fc receptor (FcRn) is a trafficking protein that is required for antigen processing & presentation in dendritic cells. Renal endothelial cells are known to express FcRn and it has been demonstrated that when FcRn is knocked out of the kidneys, GN is prevented. We believe that glomerular endothelial cells can traffic antibody-antigen complexes utilizing FcRn for presentation on MHC II. Furthermore, we hypothesize that if FcRn is absent, antibody-antigen complex trafficking & antigen presentation via MHC II is altered.

Methods: We first isolated & purified glomerular endothelial cells (GECs) from wild type (WT) & FcRn knockout (KO) mice by isolating glomeruli. We then grew the cells and used von Willebrand factor coated dynabeads to isolate endothelial cells. The cells were then characterized using IF for vWF & a podocyte specific marker (WT1) to check for podocyte contamination. After characterization, WT and KO GECs were treated with INFγ. Flow cytometry was used to evaluate the expression of MHC II. To study antigen-antibody trafficking, we treated both WT & KO cells with antigen-antibody complexes, then used IF to identify co-localization of lysosomes with antibodies.

Results: We demonstrated that endothelial cells isolated from both WT & KO mice can express MHC II when treated with INFγ but the percentage of cells that express MHC II in the KO cells was significantly less than that in WT cells. We also discovered that WT cells had a higher rate of co-localization of antibody-antigen complexes with lysosomes than in the KO cells suggesting that FcRn directs lysosomal trafficking of immune complexes in glomerular endothelial cells.

Conclusions: These findings suggest that FcRn is needed to optimize the expression of MHC II as well as facilitate trafficking of antigen-antibodies to lysosomes.

Funding: NIDDK Support, Private Foundation Support

TH-PO260

C14orf142 Is the 5th Member of the Highly Conserved KEOPS Complex and Is Mutated in Galloway-Mowat Syndrome (GMS)

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Background: The evolutionarily conserved KEOPS complex is composed of at least 4 subunits (LAGE3, OSGEP, TP53RK and TPRKB), Gon7 being the 5th subunit in yeast. In model organisms, KEOPS was shown to catalyze an essential tRNA modification, and in yeast it plays a role in transcription and telomere maintenance. However, KEOPS function in humans is unknown. We have recently identified mutations in all four members of KEOPS in patients with GMS associating nephrotic syndrome with microcephaly and neurological impairment.

Methods: To identify new genes involved in GSM and characterize new potential partners of the KEOPS complex, we performed exome sequencing, proteomic and coIP/co-purification experiments. To assess one of the known functions of KEOPS, we performed Telomere Restriction Fragment analysis and Telomere dysfunction-Induced Foci.

Results: We identified 2 homozygous truncating mutations in the *C14orf142* (C14) gene in 5 families with GMS and showed that the C14 protein, which is predicted to be largely unstructured and of similar size as Gon7, strongly interacts with LAGE3. We further demonstrated that his-tagged C14 co-purified with all KEOPS members when over-expressed in bacteria and that this complex is stable during gel filtration purification. We did not find any telomere length modifications or telomere dysfunction suggesting that telomere maintenance is not the primary function of KEOPS in humans.

Conclusions: Here, we identified C14 as being the 5th element of the human KEOPS complex binding to the LAGE3 subunit, in a similar way as does Gon7 in yeast. The role of C14 within the KEOPS complex and the role of this complex in the pathogenesis of GMS remain unclear.

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

TH-PO261

Induction of Interdigitating Cell Processes in Cultured Podocytes

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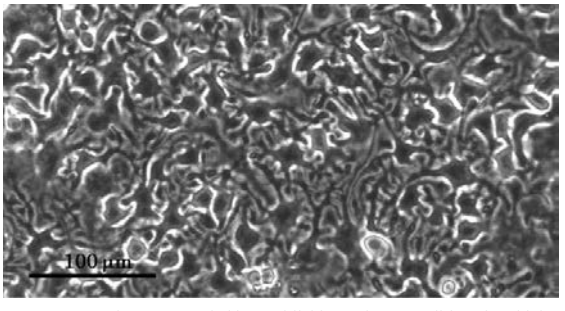
Background: Interdigitating cell processes characterize glomerular podocytes in vivo. However, podocytes in primary culture and in cell lines have a simple morphology lacking cell processes, especially upon reaching confluence. Some culture conditions have been reported to upregulate podocyte-specific gene expressions, but no reports have succeeded in inducing morphology close to that of in vivo conditions. In this study, we tried to establish culture conditions under which cultured cells spread cell processes at confluence.

Methods: Rat primary cultured podocytes were used to investigate the effects of cell density, low concentrations of fetal bovine serum (FBS), heparin, retinoic acid (RA), and extracellular matrices (collagen type I, fibronectin and laminin) on their morphology.

Results: Cell processes were extensively induced when cells were seeded at a cell density equivalent to in vivo and cultured in the presence of heparin and RA on laminin-coated dishes, and in decreasing concentration of FBS as shown in the phase-contrast micrograph figure. Cell seeding density and decreasing FBS concentrations were critical to interdigitating cell process formation. Without laminin coating, heparin or RA, cell processes were formed, although limited to a small area. Like primary processes in vivo, the processes contained vimentin filaments, occasionally overlapping each other, and stretched under adjacent cell bodies. Intercellular junctions as shown by staining for podocin, nephrin or ZO-1 were located between the cell processes and under cell bodies as elaborate squiggles, where actin filaments accumulated, suggesting primitive foot processes. Local formation of slit diaphragms was demonstrated by electron microscopy.



Conclusions: We have succeeded in establishing culture conditions in which cultured cell phenotypes are closer to those in vivo.

TH-PO262

A Small Molecule Screening to Detect Potential Therapeutic Targets in Human Podocytes

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Background: Steroid resistant nephrotic syndrome (SRNS) inevitably progresses to end-stage kidney disease, requiring dialysis or transplantation for survival. However, treatment modalities and drug discovery remain limited. Mutations in over 30 genes have been discovered as monogenic causes of SRNS. Most of these genes are predominantly expressed in the podocyte, placing it at the center of the pathogenesis of SRNS. Podocyte migration rate (PMR) represents a relevant intermediate phenotype of disease in monogenic causes of SRNS (Gee 2013; Ashraf 2013; and Gee 2014). We therefore adapted PMR in a high-throughput manner to screen small molecules as potential therapeutic targets for SRNS.

Methods: We performed a high-throughput drug screening of an NIH Clinical Collection (NCC) library (n=725 compounds) measuring PMR by video-microscopy. We used the Woundmaker™ to perform individual 96-well scratch wounds and screened compounds using a quantitative kinetic live cell imaging migration assay using IncuCyte ZOOM® technology.

Results: Using a normal distribution for the average PMR in wild type podocytes with a vehicle control (DMSO), we applied a 90% confidence interval to define "outliers" (5% faster/slower PMR) and found that 12 of 725 compounds (at 10 μM) reduced PMR. Clusters of drugs that alter PMR included actin/tubulin modulators such as the azole class of antifungals and anti-neoplastic vinca-alkaloids.

Conclusions: We hereby identify compounds that alter PMR. The PMR assay provides a new avenue to test therapeutics for nephrotic syndrome. Positive results may reveal novel pathways in the study of glomerular diseases such as SRNS.

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TH-PO263

The Donnai-Barrow Syndrome, Megalin Deficiency: A New Context

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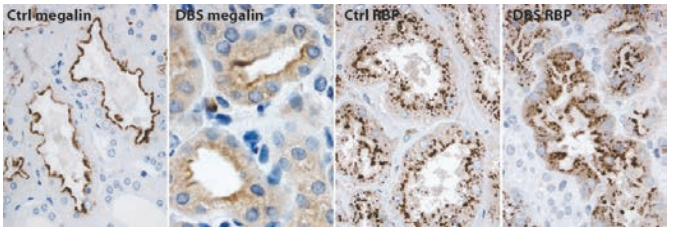
Background: Donnai-Barrow syndrome (DBS) is caused by deficiency of the endocytic receptor megalin and is characterized by low-molecular weight proteinuria, craniofacial, CNS, and ocular abnormalities. Herein we present a family with DBS who harbor a missense mutation in the megalin encoding gene, *LRP2*, and whose protein reabsorptive capacity has largely continued.

Methods: In a consanguineous Arabic family, a homozygous mutation (p.Y2522H) in exon 41 of *LRP2* was detected in two sisters who have the phenotype of the DBS: hypertelorism, broadened forehead, enlarged globes, high degree of myopia, bilateral sensorineural hearing loss and developmental delay. Both demonstrate proteinuria with urine protein to creatinine ratios from 1.8-3 mg/mg and high levels of β2-microglobulin. The mutation segregates completely with affected status.

Results: The immunohistochemical findings in both sisters were similar. The brush border megalin staining was largely reduced, while its functional conjoiner cubilin was maintained. The "normal" tubular content of albumin, α-1 microglobulin (megalin/cubilin ligands) and retinol binding protein (megalin ligand) was present in the proximal tubule, implying appropriate binding with endocytotic receptors (Fig. 1).

Conclusions: The missense mutation may allow for continued endocytic function of the largely intact protein; but to some extent has lost its immunohistochemically recognized epitope(s). The case is complicated by the fact that both sisters have an immune complex glomerulonephritis, which in one could be categorized as IgA nephropathy, a finding which may have broader implications (Kiryluk JASN epub, May 17, 2016).



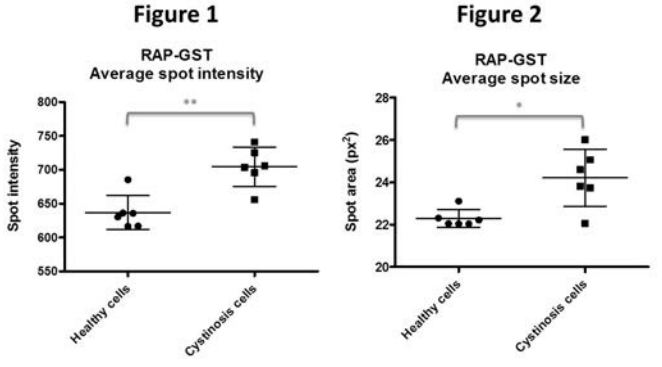
TH-PO264

High Throughput In Vitro Drug Screening Assay for Proximal Tubule Cell Function in Cystinosis Manoe J. Janssen,[1] Nienke Van Andel,[1] Martijn J. Wilmer,[2] Elena N. Levtchenko,[3] Rosalinde Masereeuw.[1] *[1]Pharmacology, UIPS, Netherlands; [2]Pharmacology-Toxicology, Radboudumc, Netherlands; [3]Pediatric Nephrology & Growth and Regeneration, KU Leuven, Belgium.*

Background: Cystinosis is a lysosomal storage disorder caused by mutations in cystinosin (*CTNS*). Patients develop renal Fanconi syndrome at 6 months and kidney failure before the age of ten. Here we developed a high-throughput *in vitro* assay to evaluate proximal tubular cell function for identification of potential drugs.

Methods: Receptor-mediated endocytosis was determined in conditionally immortalised proximal tubular cells (ciPTEC) from cystinotic patients and healthy controls by uptake of receptor associated protein (RAP-GST). RAP-GST uptake and transport to early endosomes (EEA1 staining) and late endosomes/lysosomes (LAMP1 staining) was quantified using a CV7000 high-content confocal imager. Cell viability was determined by PrestoBlue conversion.

Results: RAP-GST was efficiently taken up by ciPTEC in a vesicular pattern co-localizing with endosomes and lysosomes. After 1 hr incubation RAP-GST staining was significantly increased in cystinotic cells (28% ±10, $p<0.03$) and vesicles were prone to forming larger clusters (Figure 1, $p<0.02$) with higher intensity (Figure 2, $p<0.003$). This suggest a delay in protein degradation rather than protein uptake in cystinotic cells. Next, we determined the toxicity of two potential drug candidates selected after Prestwick library screening and found that the TC50 values after 7 days exposure were 49±2 and 54±3 µM ($R^2>0.99$). Pathological cystine accumulation is reduced at 10 µM, suggesting that the compounds will be non-toxic in the pharmacological range in cystinotic patients.



Conclusions: Our assay provides insight into lysosomal patterning and protein degradation in proximal tubule cells and can be used as a functional readout to identify drug compounds that may improve kidney function in cystinosis.

Funding: Government Support - Non-U.S.

TH-PO265

Determination of Plasma 2,8-Dihydroxyadenine with Ultra-Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS/MS) Vidar O. Edvardsson,[1,2] Unnur A. Thorsteinsdottir,[2,3] Hrafnhildur L. Runolfsdottir,[1,2] Inger M. Agustsdottir,[1] Finnur Freyr Eiriksson,[3] Margret Thorsteinsdottir,[2,3] Runolfur Palsson.[1,2] *[1]Landspitali - The National Univ Hospital of Iceland, Reykjavik, Iceland; [2]Univ of Iceland, Reykjavik, Iceland; [3]ArcticMass, Reykjavik, Iceland.*

Background: Adenine phosphoribosyltransferase deficiency (APRTd) is a hereditary disorder of purine metabolism characterized by excessive urinary 2,8-dihydroxyadenine (DHA) excretion, causing nephrolithiasis and crystal nephropathy. Allopurinol treatment reduces DHA production and ameliorates renal manifestations in affected individuals. We have recently developed a UPLC- MS/MS method for quantification of urinary DHA for diagnosis of the disorder and therapeutic monitoring. The objective was to modify this method for determination of DHA in plasma.

Methods: A UPLC- MS/MS plasma DHA assay was optimized utilizing chemometric approach. Experimental screening was conducted using D-optimal design in both negative and positive ionization mode. Optimization of the DHA response was performed by applying central composite face design, including 3 quantitative variables, and related to peak area of DHA utilizing partial least square regression. Protein precipitation (PPT) plate was used for clean-up of plasma samples from 2 patients with APRTd and one healthy subject. Following PPT, the plasma samples were evaporated and redissolved in 10 mM NH_4OH prior to analysis. Plasma specimen from a healthy control spiked with 1000 ng/mL of the DHA standard was included in the measurements for relative quantification.

Results: DHA was detected in plasma samples from the 2 APRTd patients and in the spiked control sample, but not in a plasma sample from the healthy control. The DHA signal intensity observed in the 2 patient samples indicated a concentration of 786 and 371 ng/mL, respectively.

Conclusions: For the first time, DHA was detected in plasma samples from patients with APRTd. This new assay may enhance the diagnosis and monitoring of pharmacotherapy in APRTd, particularly in patients with kidney failure.

Funding: NIDDK Support, Other NIH Support - Rare Kidney Stone Consortium (U54KD083908), Rare Diseases Clinical Research Network, Government Support - Non-U.S.

TH-PO266

2,4-Dihydroxybenzoic Acid Improves Survival and Demonstrates Reno-Protective Effect in a Podocyte-Specific Coq6-Knockout Mouse Model of Nephrotic Syndrome Eugen Widmeier,[1,2] Merlin Airik,[1] David Schapiro,[1] Hadas Ityel,[1] Rannar Airik,[3] Friedhelm Hildebrandt.[1] *[1]Div of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston, MA; [2]Dept of Medicine, Univ of Freiburg Medical Center, Freiburg, Germany; [3]Div of Nephrology, Children's Hospital of Pittsburgh, Pittsburgh, PA.*

Background: Steroid resistant nephrotic syndrome (SRNS) inevitably progresses to end-stage renal disease. Human mutations in the *COQ6* gene cause SRNS (Heeringa *JCI* 121:2013, 2011). To study the function of *COQ6* in podocytes we generated a podocyte-specific *Coq6*-knockout mouse model.

Methods: *Nphs2.Cre* mice were crossed with $Coq6^{lox/lox}$ mice, to generate podocyte specific *Coq6*-knockout mice ($Coq6^{\Delta Podocyte}$) on a C57BL/6 background. Treatment with 2,4-dihydroxybenzoic acid (2,4-diHB) at a 25 mM concentration in the drinking water was started at 5 months. Kidneys were harvested for histological and ultrastructural analysis at 10 months, and urine was collected monthly for metabolic studies.

Results: $Coq6^{\Delta Podocyte}$ mice displayed an onset of proteinuria at 4 months. Non-treated $Coq6^{\Delta Podocyte}$ mice displayed a significant reduction in survival, with all mice being moribund at 10 months of age (n=5). In contrast, $Coq6^{\Delta Podocyte}$ mice treated with 2,4-diHB (n=5) showed significantly improved survival, comparable to their untreated $Coq6^{\Delta Podocyte}$ and wild type littermates. Histological analysis of $Coq6^{\Delta Podocyte}$ kidneys at 10 months demonstrated severe global and focal segmental glomerular sclerosis (FSGS) with extensive interstitial fibrosis and tubular atrophy. Electron microscopy studies revealed severe foot process effacement and disturbed podocyte cell morphology. In contrast, treatment of $Coq6^{\Delta Podocyte}$ mice with 2,4-diHB significantly reduced the levels of urinary protein and prevented the development of FSGS as well as foot process effacement in all treated mice (n=5).

Conclusions: Our data demonstrate that 2,4-diHB, an intermediary metabolite of the CoQ10 biosynthesis pathway efficiently ameliorates proteinuria and prevents FSGS in $Coq6^{\Delta Podocyte}$ mice. Further, our study reveals a potential novel treatment strategy for human SRNS caused by dysfunction in the CoQ10 biosynthesis pathway.

Funding: Other NIH Support - DK076683, Government Support - Non-U.S.

TH-PO267

A Genetically Defined RhoA-Regulating Protein Module Elucidates Effects of Steroid Treatment in Steroid-Dependent Nephrotic Syndrome Friedhelm Hildebrandt, Jia Rao, Jennifer A. Lawson, Weizhen Tan, Eugen Widmeier, Svjetlana Lovric, Jillian Kateri Warejko, Daniela A. Braun, Shazia Ashraf. *Div of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston, MA.*

Background: Nephrotic syndrome (NS) is categorized into steroid sensitive (SSNS) and steroid resistant forms (SRNS). For SRNS no efficient treatment exists. And mechanisms of steroid action in SSNS are still unknown. We recently identified multiple novel recessive genes as causing NS if mutated: *MAGI2, TENC1, DLC1, CDK20,* and *ITSN1*. We showed that DLC1 molecularly interacts with TENC1 and CDK20. Interestingly, the affected individuals had steroid-dependent nephrotic syndrome (SDNS).

Methods: Because the individuals with mutations in these genes shared the clinical phenotype of SDNS, and because DLC1 is a known GTPase activating protein of RhoA/Rac1/Cdc42, and ITSN1 is a known GTPase exchange factor of the same, we hypothesized that the pathogenesis of mutations in these genes involves steroid-dependent dysregulation of RhoA/Rac1/Cdc42 activation. We performed a G-LISA assay to quantitate the active components of RhoA/Rac1/Cdc42 in a HEK293Ts, following knockdown (kd) *versus* overexpression (oe) of *MAGI2, TENC1, DLC1,* or *CDK20.*

Results: No effects were observed for the active Rac1 and Cdc42. However, we found that kd of *DLC1* increased active RhoA, while oe of *DLC1* decreased active RhoA. Kd and oe of the *DLC1* interaction partners *MAGI2*, *TENC1* and *CDK20* behaved opposite to the effects of *DLC1*, revealing a RhoA regulatory cluster of interacting proteins in HEK293Ts. We then demonstrated that steroid treatment with dexamethasone at >50 uM abolished the effects on RhoA activation by kd or oe of *TENC1, DLC1,* or *CDK20.* This indicates that the beneficial effect of steroids in patients with SDNS and mutations in these genes is likely mediated by the RhoA-regulating module *MAGI2, TENC1, DLC1,* and *CDK20.* We are seeking the direct target of steroid action, which is likely part of this genetically defined RhoA regulating module.

Conclusions: Our findings for the first time may elucidate cell autonomous podocytic mechanisms of treatment response in SDNS, and may make specific genetic variants of NS amenable to treatment.

Funding: Other NIH Support - DK076683

TH-PO268

Mutation in Human Class II α-Isoform of Phosphatidylinositol 3-Kinase Cause a Syndrome with Kidney, Bone and Retinal Involvement

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Background: Phosphatidylinositol 3-kinases (PI3Ks) are lipid kinases involved in a large set of biological processes, including membrane receptor signaling, cytoskeletal organization, and endocytic trafficking. PI3KC2A has been proposed to play an important role in endothelial cells, where it promotes endosomal trafficking and regulation of PtdIns3P levels. Whole exome sequencing (WES) provides a novel means of establishing an etiologic diagnosis. By revealing the causative monogenic mutation, it thereby contributes to our knowledge of the gene function, biological mechanisms and pathways, and will provide important knowledge about disease mechanisms the underlying pathophysiology.

Methods: In one affected child of consanguineous parents we performed WES to identify the underlying single-gene disease-causing mutation. We then harvested fibroblasts from skin biopsies of the affected individual and healthy control for performing immunofluorescence and immunoblotting studies.

Results: Through WES we detected a homozygous obligatory splice site mutation (c.1640+1 G>T) in the gene *PIK3C2A* (phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 alpha) in the affected individual. The mutation segregated with the affected status in this family and was absent from healthy controls. The affected individual showed right kidney agenesis and a complex tubulopathy, retinal degeneration with severe and progressive visual impairment,skeletal dysplasia, dental anomalies, brachydactyly and disproportionate short stature. By immunofluorescence studies we demonstrate that *PIK3C2A* localizes in endosomes, the trans-Golgi network and clathrin-coated vesicles, whereas the mutation of PIK2C2A lacks this. By immunoblotting we show that the mutation alters the phosphorylation status of GSK3beta, a major player of Wnt signaling.

Conclusions: We show that in humans *PIK3C2A* is critically involved in development and function of the kidney, bone and retina.

TH-PO269

Variant-Prioritization Coupled with Ontology-Based Algorithm Identified Disease-Causing Mutation in a Family with Atypical Hemolytic Uremic Syndrome

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Background: Atypical hemolytic uremic syndrome (aHUS) is a rare form of thrombotic microangiopathy. Recently, personal genome sequence analysis identified numerous disease-causing variants in aHUS, mainly in complement-related genes. However, variant-prioritization tools are needed to effectively discriminate true causative variants from a number of non-related variants, especially in a small family. To dissect causative genes in a family with aHUS, we applied prioritization strategies (pedigree VAAST) coupled with an ontology-based algorithm (Phevor) to whole exome sequence analysis.

Methods: We carried out an exome sequence analysis of a Japanese multiplex family composed of three patients diagnosed with aHUS in infancy, clustered in a dominant transmission mode. Variants identified by exome sequencing were prioritized by pVAAST, which combines variant frequency data, mutation severity, and conservation into a single score with linkage analysis, that is compared genome wide. Then, the prioritized gene ranking were re-ranked by Phevor, based on the phenotype information in the biomedical ontologies.

Results: Exome sequencing in this family detected a total of 83 heterozygous and non-synonymous variants shared only by the affected individuals. Filtering against several variant databases, we identified 20 variants, which have been reported in allele frequencies of less than 1%. To determeine which of the shared variants were most likely causative, pVAAST was carried out and 18662 genes were ranked according to the scores. Then, Phevor re-ranked the genes, and *C3* (p.W1034R) was selected as a top candidate gene with Phevor score of 7.4. p.W1034R in *C3* have been reported in aHUS patients (Blood 2015;125:2359), and predicted to have substantial effect on the protein C3d structure or function.

Conclusions: We identified *C3* mutation in a family with aHUS using prioritization and ontology-based algorithm. Functional analyses of the mutation in C3d domain are in progress to uncover the role in the pathogenesis of aHUS.

TH-PO270

A Recessive ETV4 Mutation Causes Urinary Tract Malformation via Abrogation of its DNA Binding Affinity

Amelie van der Ven,[1] Jing Chen,[1,2] Asaf Vivante,[1,3] Nina Mann,[1] Shirlee Shril,[1] Hadas Ityel,[1] Johanna Magdalena M. Schmidt,[1] Elijah O. Kehinde,[4] Friedhelm Hildebrandt.[1] *[1]Dept of Medicine, Boston Children's Hospital/Harvard Medical School, Boston, MA; [2]Dept of Nephrology, Children's Hospital of Fudan Univ, Shanghai, China; [3]Talpiot Medical Leadership Program, Sheba Medical Center, Tel-Hashomer, Israel; [4]Div of Urology, Dept of Surgery, Kuwait Univ, Safat, Kuwait.*

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common reason for chronic kidney disease in children. Although over 30 monogenic causes have been implicated in isolated forms of human CAKUT so far, the vast majority of causes for the development of CAKUT remain elusive.

Methods: To identify novel monogenic causes of CAKUT we applied homozygosity mapping, together with whole exome sequencing (WES) to a patient of consanguineous descent with isolated CAKUT. We performed electrophoretic mobility shift assay (EMSA) to analyze the DNA binding affinity of the mutated protein, and dual-luciferase reporter assay to test its transcriptional activity. Furthermore, we investigated a potential impact of the mutant protein onto cell migration by using scratch wound migration assays in two different stable knock-down cell-lines.

Results: We identified a highly conserved homozygous missense mutation (p.R415H) of the *Ets Variant Gene 4* (*ETV4*) in a CAKUT patient from consanguineous descent. The transcription factor ETV4 is a downstream target of the GDNF/RET signaling pathway and plays a crucial role in kidney development. By means of EMSA we show that the R415H ETV4 mutant causes loss of the DNA binding affinity of ETV4, and fails to activate transcription in a cell-based luciferase reporter assay. Unlike wildtype *ETV4*, the *ETV4* R415H mutant fails to rescue migration defects observed in stable ETV4 knock-down PC3 and U-2OS cells.

Conclusions: We identified and functionally characterized a recessive mutation in *ETV4* as a novel monogenic cause of isolated CAKUT. Possible pathomechanisms include impairment of proper GDNF/RET/ETV4 signaling. A.vdV. and J.C. are co-first authors.

Funding: Other NIH Support - R01

TH-PO271

A Dominant Mutation in NRIP1 Causes Urinary Tract Malformations via Dysregulation of Retinoic Acid Signaling

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Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) are the most common cause of chronic kidney disease in the first three decades of life. Identification of monogenic mutations that cause CAKUT permits insights into related disease mechanisms.

Methods: We performed whole exome sequencing, transcriptional reporter assay, protein-protein interaction studies, as well as in vivo studies in *Xenopus laevis*.

Results: We investigated a three-generation Yemenite Jewish family with an autosomal dominant form of CAKUT. By whole exome sequencing, we identified a heterozygous truncating mutation (c.279delG, p.Trp93fs*) of the *NRIP1* gene in all seven affected members. *NRIP1* encodes a nuclear receptor transcriptional co-factor, which directly interacts with the retinoic acid receptors to modulate retinoic acid transcriptional activity. By functional studies we reveal that the NRIP1 altered protein does not translocate to the nucleus, does not interact with retinoic acid receptor alpha (RARα) and fails to inhibit retinoic acid dependent transcriptional activity. In addition, we show that both *NRIP1* expression and its binding to RARα, are enhanced in the presence of retinoic acid. By expression and knockdown experiments in *Xenopus laevis* we confirm an evolutionary conserved role for *NRIP1* in renal development.

Conclusions: These data indicate that dominant *NRIP1* mutations cause CAKUT by interference with retinoic acid transcriptional signaling, thus shedding light on the well documented association between abnormal vitamin A levels and renal malformations in humans, and suggest a possible gene environment pathomechanism.

TH-PO272

Misidentification of Dihydroxyadenine Kidney Stones by Conventional Stone Analysis Techniques

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Background: Adenine phosphoribosyltransferase deficiency (APRTd) is an inherited disorder of purine metabolism that leads to excessive renal excretion of 2,8-dihydroxyadenine (DHA), resulting in kidney stones and crystal nephropathy. Analysis of crystal or kidney stone material using infrared (IR) spectroscopy has been considered diagnostic of APRTd. Recently, we have encountered cases misidentified as DHA stone formers by IR spectroscopy. The objective of this study was to examine the accuracy of stone analysis for identification of DHA kidney stones.

Methods: Records of all 40 patients referred to the APRTd Research Group of the Rare Kidney Stone Consortium from 2010 to 2016 were reviewed.

Results: Fifteen patients were referred to our program with the presumptive diagnosis of APRTd based on stone analysis. Seven of these 15 patients did not have APRTd as DHA had been misidentified as a stone component in 2 cases from the US, 2 from the UK, 2 from South Africa and 1 from Australia. The median age at referral was 26.6 (6-45) years. IR spectroscopy was the stone analysis technique used in 6 cases, yielding 12-100% (median of 60%) DHA in stone samples from 5 patients, while only trace amounts were found in a stone from 1 individual. X-ray diffraction was applied in one case suggesting 90% DHA.

None of the 7 patients had APRTd, demonstrated by undetectable DHA in spot urine samples using a novel mass spectrometry assay. The absence of APRTd was further confirmed by APRT enzyme activity measurements in 4 cases and genetic testing in 1 case.

Conclusions: Misidentification of kidney stones as DHA stones using gold standard stone analysis techniques appears to be more common than previously thought. The results of kidney stone analysis are based on human interpretation of different spectra and thus subject to error. The diagnosis of the APRTd should be confirmed by more reliable diagnostic methods, such as enzyme activity measurements or genetic testing.

Funding: NIDDK Support

TH-PO273

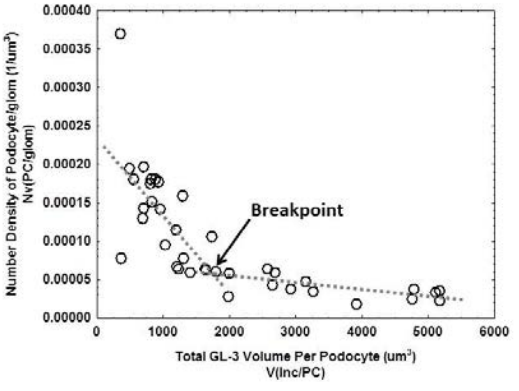
Podocyte Hypertrophy and Globotriaosylceramide (GL-3) Accumulation Are Strong Predictors of Podocyte Loss in Enzyme Replacement Therapy Naïve Male Patients with Fabry Disease

Behzad Najafian,[1] Camilla Tøndel,[2] Einar Svarstad,[2] Michael Mauer.[3] *[1]Univ of Washington; [2]Haukland Univ; [3]Univ of Minnesota.*

Background: Podocyte (PC) injury and loss play crucial roles in progressive chronic kidney disease (CKD) in Fabry disease. While PCs accumulate more GL-3 than other renal cells, they are far more resistant to GL-3 clearance following enzyme replacement therapy (ERT). Identifying parameters associated with PC loss may be crucial to halt CKD in Fabry disease. We assessed the relationship between PC GL-3 accumulation and PC number density per glomerulus [Nv(PC/glom)].

Methods: Biopsies from 38 male ERT-naïve Fabry patients aged 33[13-60], median [range], years with GFR 114±45 ml/min/1.73 m^2 were studied using electron microscopy unbiased stereology, including modified point-sampled intercept method.

Results: By linear regression, age correlated directly with protein creatinine ratio (PCR) (r=0.55, p=0.001) and inversely with GFR (r=-0.47, p=0.006). Nv(PC/glom) correlated inversely with mean PC volume (VPC) (r=-0.77, p=0.0001) and total GL-3 inclusion volume/PC [V(Inc/PC)] (r=-0.69, p=0.0001), but not with GL-3 volume fraction [Vv(Inc/PC)] or foot process width (FPW). Using piecewise linear regression analysis, 88% of Nv(PC/glom) variability was explained by VPC and V(Inc/PC), p=0.000001, with the V(Inc/PC) breakpoint at 1965 um^3 and the VPC breakpoint at 5201 um^3, beyond which the slope of decline in Nv(PC/glom) was markedly increased.



PCR correlated with VPC (r=0.44, p=0.01) and V(Inc/PC) (r=0.40, p=0.02), but not with Vv(Inc/PC) or FPW.

Conclusions: PC enlargement and total GL-3 accumulation are important determinants of PC loss in Fabry disease. The observed V(Inc/PC) and VPC breakpoints suggest thresholds beyond which PC hypertrophy and GL-3 content are associated with marked acceleration of PC loss. Such thresholds may suggest new treatment targets for Fabry nephropathy.

Funding: Other NIH Support - NCATS

TH-PO274

Aging Is Associated with Reduced %Podocytes (Podo), but Not %Parietal Epithelial Cells (PECs) with Fabry Phenotype in Females with Fabry Disease

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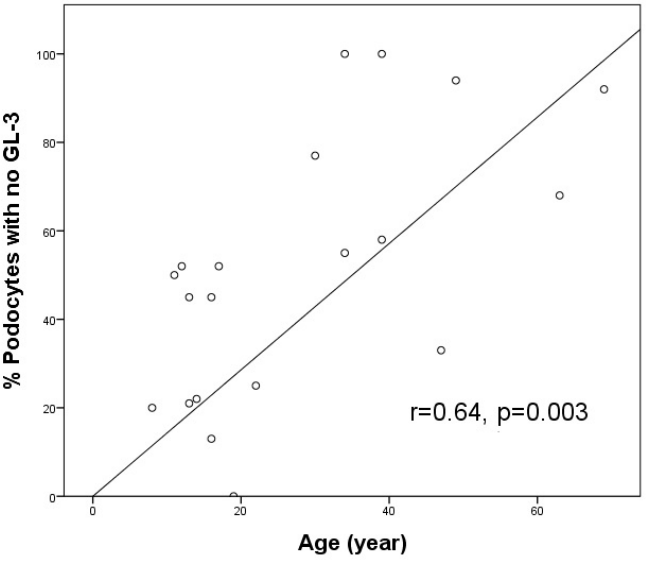
Background: In Fabry nephropathy (FN), globotriaosylceramide (GL-3) accumulation in Podo leads to disease progression. In females with FN, due to X-inactivation, the distribution of GL-3 inclusions in Podo is heterogeneous, and related to Podo injury. Recent studies suggest PECs may replace lost Podo. Thus, PECs may be important in pathophysiology of FN. We studied the distribution of Podo and PEC involvement in female Fabry patients, and their relationships to clinical parameters.

Methods: Kidney biopsies from 20 treatment-naïve female Fabry patients (age 20.5 [8–69], median [range]) were studied by electron microscopy. Urine protein excretion (UPE) was estimated by urine protein creatinine ratio (UPCR) (n=12) or total urine protein/day (n=8).

Results: GFR was 96.64±21.01 ml/min/1.73 m^2. UPE was 61 (0-1150) mg/day. In all 20 biopsies, 51±30% (mean ± SD) of Podo per glomerulus contained no GL-3 inclusions, classified as non-Fabry Podo (NFPodo). In 14 biopsies which allowed reliable evaluation of PECs, 47±31% of PECs per glomerulus had no GL-3 inclusions, classified as non-Fabry PECs (NFPEC). %NFPodo per glomerulus (%NFPodo/glom) was directly correlated with age (r=0.64, p=0.003), but %NFPEC per glomerulus (%NFPEC/glom) was not. %NFPodo/glom and %NFPEC/glom were not correlated. Neither %NFPodo/glom nor %NFPEC/glom showed relationships with GFR or UPE. The inter-glomerular variation in %NFPodo/glom in a given patient's biopsy was smaller than %NFPEC/glom.

Conclusions: Direct relationship between age and %NFPodo/glom is suggestive of a survival disadvantage for Podo with Fabry phenotype. The differential relationships of %NFPodo/glom and %NFPEC/glom to patients' age may reflect different regeneration capacity or injury response to GL-3 inclusions in Podo and PECs.



TH-PO275

High Prevalence of Proteinuria and Reduced Renal Function in 14 Adolescents and Young Adults with Antenatal and Classic Bartter Syndrome

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Background: Antenatal Bartter syndrome (aBS) and classic BS (cBS) are characterized by renal salt wasting resulting in hypokalemia, enhanced production of prostaglandin E_2, renin and aldosterone as well as hypercalciuria in aBS. The long-term outcome of glomerular and tubular function in adolescents and young adults is largely unknown. We here describe extensive follow-up data based on our single center experience with aBS and cBS.

Methods: 14 adolescents and young adults (seven females and males; aBS type I: n=7; aBS type II: n=3; and cBS: n=4), with a mean age of 21.2 years. All subjects were continously treated with prostaglandin synthesis inhibitors and supplemental electrolytes. We analyzed retrospectively endogenous creatinine clearance (CCR), the urinary excretion of electrolytes and protein and 24 h-ABDM.

Results: The average renal excretion of sodium and chloride were 153±75.1 and 185.5 ± 90.6 mmol/d, respectively. FE_{Na} correlated with systolic day blood pressure SDS (r=0,46, p=0.015). CCR was 81.5 ± 29.9 ml/min/1,73m², ten patients had a CCR<90, three patients < 50ml/min/1.73m². Proteinuria was detected in 11/14 patients (Alb/Crea 189 ± 288,6 mg/g), of these, five patients had tubular proteinuria. CCR correlated negatively with proteinuria (r=-0.4, p<0.01). Patients with aBS type I showed the most pronounced renal impairment (CCR: 68.5 ± 15.6, Alb/Crea 290 ± 379 mg/g), followed by patients with aBS type II (CCR: 77.6 ± 15.1, Alb/Crea 171 ± 261 mg/g) and patients with cBS (CCR: 107 ± 44, Alb/Crea 50 ± 40 mg/g). Two patients had increased blood pressure on 24 h-ABDM.

Conclusions: Reduced CCR and proteinuria were present in the majority of patients and clearly exceeded values from two previously published case series describing younger patients (Reinalter et al., 2001; Puricelli et al, 2010). Genotype, chronic renal salt wasting with continuous activation of renin and aldosterone synthesis and the cumulative exposure to prostaglandin synthesis inhibitors may all contribute to this so far unanticipated impairment in renal function.

TH-PO276

Defects in N-Glycosylation of Cubilin Result in Tubular Proteinuria

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Background: Mutations of either cubilin (*CUB*) or amnionless (*AMN*) cause low-molecular weight proteinuria and megaloblastic anemia, due to defects in endocytosis through cubilin-amnionless receptor complex (IGS: Imerslund-Gräsbeck Syndrome). The pathogenic mechanism of IGS is largely unknown. We found a novel missense G653R mutation of *CUBN* in a boy with IGS. Renal histology demonstrated that cubilin and amnionless were not targeted to brush border of proximal tubular cells in the patient.

Methods: To analyze the pathogenic mechanism of the mutations found in IGS, we quantitatively determined the membrane targeting of cubilin and amnionless in cultured cell by flow cytometry. We analyzed the effect of mutations causing IGS on glycosylation and membrane targeting of cubilin and amnionless.

Results: While wild-type cubilin and amnionless were interdependently targeted to the cell membrane, G653R and previously reported missense mutations of *CUBN* inhibited amnionless-dependent glycosylation, membrane expression of cubilin and amnionless, and endocytosis. Notably, all the previously reported missense mutations of *AMN* also inhibited cubilin glycosylation, and causes ER retention of amnionless and cubilin. N-linked glycosylation of cubilin did not affect cubilin-amnionless interaction, but was required for transport from ER to Golgi. Mass spectrometric and mutagenesis analysis identified the combination of glycosylations in CUB domain of cubilin which are crucial for surface expression of cubilin and amnionless.

Conclusions: N-glycosylation of cubilin is essential for endocytosis in renal and intestinal epithelial cells, and its defects result in tubular proteinuria.

TH-PO277

Morphological and Immunohistochemical Presentation of Complement Disorders in Native and Transplant Renal Biopsies Christof Aigner,[1] Martina M. Gaggl,[1] Zoltan Prohaszka,[2] Ahmad Altaleb,[3] Gere Sunder-Plassmann,[1] Alice Schmidt,[1] Renate Kain.[3] *[1]Dept of Medicine III, Div of Nephrology and Dialysis, Medical Univ of Vienna, Vienna, Austria; [2]IIIrd Dept of Internal Medicine, Research Laboratory, Semmelweis Univ, Budapest, Hungary; [3]Clinical Dept of Pathology, Medical Univ of Vienna, Vienna, Austria.*

Background: Complement-mediated Thrombotic Microangiopathy (TMA), C3-glomerulonephritis (C3GN) and Dense Deposit Disease (DDD) are diseases of the alternative complement pathway and associated with the same genotypic background. However, the reasons for the different phenotypes remain unexplained.

Methods: We analysed 35 biopsies of 5 patients followed for an average of 14 years. All underwent renal transplantation (KTX) and analysis of morphologic and immunohistochemical parameters included light-, electron-microscopy, and detection of immunoglobulins and proteins of the complement pathway (C1q,C3c,C3d,C4d,C5b-9).

Results: We identified 5 patients with complement associated disorders, all of which developed C3GN in the transplants**.** Treatment followed standard regimens in patients with biopsy proven rejection and 3 patients with persistent TMA received Eculizumab. All patients developed GN with a range of morphological presentation and variable C3d,C4d, no C5b-9, but prominent C3c deposits.

Pat	Muta-tion	Presen-tation	KTX1	Rejection (BANFF)	KTX2	Rejection	KTX3	Rejec-tion
1	THBD	TMA	TMA+C3GN	vascular(II)				
2	C3	TMA	TMA+C3GN					
3	-	TMA	C3GN					
4	CFH	TMA	TMA+C3GN					
5	CFH	DDD	TMA	vascular	TMA	ABMR, vas-cular (IIb), interstitial	C3GN	vascular (IIa), ABMR (II)

Conclusions: We present 5 patients, all of which developed C3GN after KTX, which indicates a phenotype-switch between complement associated disorders. Neither mutations nor deposition of complement products in renal biopsies allowed to predict presentation or outcome of disease. Our data indicate that a phenotype-switch may not be as rare as reported however morphological presentation may be influenced by therapies or immunological events in graft rejection.

TH-PO278

Focal Global Glomerulosclerosis Is Common in Dent Disease and Associates with Kidney Function Xiangling Wang,[1] Franca Anglani,[2] Lada Beara Lasic,[3] Anila Mehta,[1] Lisa E. Vaughan,[1] Loren Paola Herrera Hernandez,[1] Andrea G. Cogal,[1] Steven J. Scheinman,[4] Gema Ariceta,[5] Lawrence A. Copelovitch,[6] Felicity T. Enders,[1] Peter C. Harris,[1] John C. Lieske.[1] *[1]Mayo Clinic; [2]Uof Padua; [3]NYU; [4]TCMC; [5]U Hospital Vall d'Hebron; [6]U Penn.*

Background: Dent disease (DD) is a rare X-linked disorder characterized by low molecular weight proteinuria and considered a tubular disorder. However, focal global glomerulosclerosis (FGGS) was recently reported in several patients.

Methods: To characterize pathological findings in a cross section of DD patients, renal pathology reports and slides (where available) were obtained from 30 male patients in eight countries who had undergone clinically indicated renal biopsy.

Results: Median (25th, 75th) age at biopsy was 7.5 (5, 19) years with an estimated glomerular filtration rate (eGFR) of 69 (44, 94) ml/min/1.73m^2 and a 24hr protein excretion of 2000 (1325, 2936) mg. A repeat biopsy for steroid-resistant proteinuria was performed in 13% (4/30) of the patients. Prominent histological findings included FGGS in 83% of patients (25/30) affecting 16% ± 19% glomeruli, mild segmental foot process effacement in 57% (13/23), focal interstitial fibrosis in 60% (18/30), interstitial lymphocytic infiltration in 53% (16/30) and tubular damage in 70% (21/30).

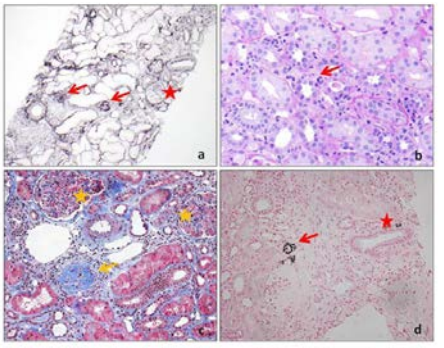


Figure 1. Renal histopathological features in Dent Disease 1. (a) Glomeruli with global sclerosis (arrows) and intact glomerulus (star). **(b)** Tubulitis (arrow). **(c)** Globally sclerotic glomerulus adjacent to the interstitium with lymphocytes infiltration (arrow) and intact glomeruli (stars). **(d)** Calcium phosphate crystals in the tubule (arrow) and interstitium (star).

Lower eGFR at biopsy associated with a higher percentage of globally sclerotic glomeruli, foot process effacement, and interstitial inflammation, while steeper annual eGFR decline during follow-up was associated with foot process effacement.

Conclusions: Glomerulosclerosis is common in DD. Glomerular pathology, specifically involving the podocyte,may play a role in disease progression in DD, which deserves further studies to understand the underlying mechanism(s). Furthermore, Dent disease should be suspected in unexplained proteinuric male patients with focal global glomerulosclerosis and segmental foot process effacement on renal biopsy.

Funding: Other NIH Support - Rare Kidney Stone Consortium (U54KD083908)

TH-PO279

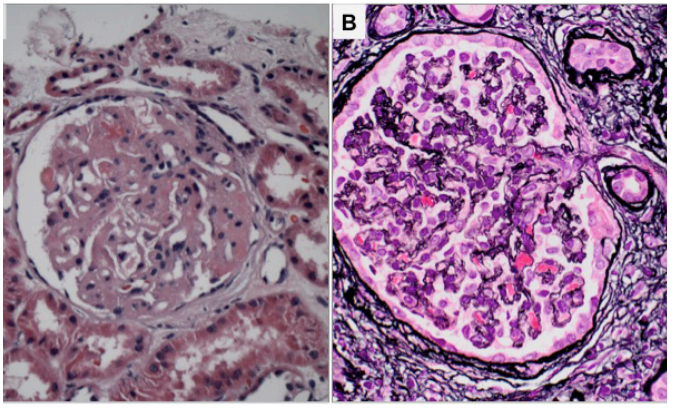
Thrombotic Microangiopathy: A Novel Presentation for TREX1 Mutation Ashima Gulati,[1] Gabriel M. Danovitch,[2] Margaret J. Bia,[1] Allen E. Bale,[1] Gilbert W. Moeckel,[1] Stefan Somlo,[1] Neera K. Dahl.[1] *[1]Yale Univ School of Medicine, CT; [2]David Geffen School of Medicine at UCLA, CA.*

Background: Thrombotic microangiopathy (TMA) is a systemic condition with predilection for the kidney. Genetic determinants have been identified mainly related to complement dysregulation. Since a significant proportion of TMA remains etiologically undefined, exome sequencing may uncover novel genotype correlations.

Methods: Genomic DNA from proband with familial TMA was subjected to exome sequencing and variant filtering using bioinformatics pipeline and data analyzed on *a priori* suggestion for autosomal dominant TMA.

Results: Proband is a Caucasian male (5th decade) with persistent proteinuria (1g/d) and gradual serum creatinine elevation during 3-yr follow up (eGFR 48 ml/min/1.73m^2) with controlled hypertension. He had no neurologic or visual symptoms and unremarkable physical examination. Kidney biopsy (fig.A) showed TMA with duplication of glomerular basement membrane. Family history is significant for kidney transplant in deceased father; retinal hemorrhage and chronic kidney disease with TMA in his brother (fig.B). CBC, CFH, CFI, C3, antiphospholipid panel were unremarkable. Proband exome sequencing revealed a heterozygous 4 bp duplication in carboxyl terminus of *TREX1* (Three Prime Repair Exonuclease) resulting in a non-truncating frame shift (NM_033629:exon1: c.828_831dupGAAG:p.D278Efs*48).

Conclusions: C-terminal mutations in *TREX1* known to alter its subcellular localization while preserving exonuclease activity cause microangiopathy predominantly of retina and brain. We report an exclusive renal phenotype of TMA and chronic kidney disease with mutation in *TREX1* in absence of symptomatic multisystem microangiopathy. While awaiting familial genetic testing, we emphasize the clinical importance of recognizing *TREX1* mutation as a cause of non complement mediated TMA and an opportunity for delineating novel TMA pathophysiology.



TH-PO280

Clinical Follow-Up of Female Fabry Disease Patients Receiving Enzyme Replacement Therapy for up to 2 Years Fellype C. Barreto,[1,2] Tammy Vernalha Rocha Almeida,[1] Bruna Fernanda de Castro,[1] Felipe T.M. Novak,[2] Lidio Derossi,[3] Caroline de Paula Cassanego,[1] Mariza G. Rosa,[3] Gilson Biagini.[1] *[1]Pontificia Univ Católica do Paraná; [2]Univ Federal do Paraná; [3]Health Center Clinic - Tapejara.*

Background: Fabry disease (FD) is an X-linked lysosomal storage disorder resulting from a deficiency of the hydrolytic enzyme α-galactosidase A (α-Gal-A). Heterozigous female patients may develop clinical manifestations and require enzyme replacement therapy (ERT) as homozygous males.

Methods: A review of clinical and laboratorial data of females FD patients followed up in Tapejara - Brazil, with serum creatinine and albuminuria measured before ERT (agalsidase-beta; 1 mg/kg; eow) Cardiac and cerebral involvements were evaluated by echocardiography and/or magnetic resonance imaging. The follow up period was divided in two time points. T1: up to 12 months (6.1±2.8 months, n=17); T2: up to 24 months (22.1±3.3 months, n=7) of ERT.

Results: Seventeen female patients (age: 29.1 ± 16.2 years) were included. The median age at diagnosis was 21 (13-65) years. The most frequent clinical manifestations were as follows: left ventricular hypertrophy (59%), septal hypertrophy (29%), cardiac fibrosis (35%), white matter lesion (43%), acroparesthesia (59%) and nephropathy (59%). 6/17 and 2/17 patients were at CKD stage 2 and 3a at baseline, respectively. ERT was initiated after 5 yrs (median) of the diagnosis. All patients received antiproteinuric medication. Renal function remained stable for most patients at the two different time points of follow up, including the patient with the lowest eGFR (49.5 ml/min) and the highest proteinuria (2500mg/24h) at baseline. Kidney biopsy performed before ERT in a patient without overt proteinuria and normal eGFR unveiled effacement of foot processes of the podocytes. No cardiac or cerebrovascular event was observed during the follow up.

Conclusions: Heterozygous female FD patients may present a broad spectrum of clinical manifestations of FD and should not be neglected. ERT, combined with renin-angiotensin system blockade, seems to be a safe and effective strategy to prevent progression of Fabry nephropathy in females.

TH-PO281

Proteogenomic Analysis of a Disease-Causing Actinin-4 Mutation Markus M. Rinschen,[1] Malte P. Bartram,[1] Caroline Pahmeyer,[1] Thomas Benzing,[1] Bodo B. Beck.[2] *[1]Internal Medicine, Univ Hospital Cologne, Cologne, Germany; [2]Human Genetics, Univ Hospital Cologne, Cologne, Germany.*

Background: In children, genetic diseases are the most important cause for end-stage renal disease. Mutations in the ACTN4 gene are a rare cause of autosomal dominant familial focal segmental glomerulosclerosis (FSGS). We here identified a novel, disease-causing ACTN4 mutation (p.G195D, de novo) in a sporadic case of childhood FSGS.

Methods: We utilized next generation sequencing to identify a novel ACTN4 mutation in a sporadic case of childhood FSGS. In vitro studies (actin sedimentation assay, immunofluorescence analyses and migration assays) were used to judge actin cytoskeleton function. Primary urinary epithelial cells of the patient were subjected to proteomic analysis. Results were complemented with interactomic and ubiquitylomic analyses of ACTN4 G195D in vitro.

Results: In vitro studies demonstrated that ACTN4 G195D had a detrimental effect on actin cytoskeletal function. Proteome analysis by quantitative mass spectrometry of patient-derived urinary epithelial cells indicated that ACTN4 levels were significantly decreased when compared with healthy controls. By resolving the allele bearing the mutated residue on a protein level, we demonstrated that the mutant protein is less abundant when compared with the wild-type protein. Molecular dynamics simulations revealed a decrease in ACTN4 CH-domain stability upon mutation. Further analyses revealed that the decreased stability of p.G195D is associated with increased ubiquitylation in the vicinity of the mutation site. We next defined the ACTN4 interactome, which was predominantly composed of LIM domain proteins. Interestingly, this entire group of proteins, including several ACTN4 interactors, was globally decreased in the patient-derived cells. Further ACTN4 mutations may demonstrate a similiar phenotype.

Conclusions: Our findings advance the understanding of dominant effects exerted by ACTN4 mutations in FSGS. This study illustrates the potential of genomics and complementary, high-resolution proteomics analyses to study the pathogenicity of rare gene variants (“proteomendeliomics”).

Funding: Government Support - Non-U.S.

TH-PO282

Recessive Mutations in 5 Novel Genes of Interaction Partners Elucidate Steroid Sensitivity in Nephrotic Syndrome Shazia Ashraf,[1,2] Jia Rao,[1] Jennifer A. Lawson,[1] Weizhen Tan,[1] Eugen Widmeier,[1] Svjetlana Lovric,[1] Jillian Kateri Warejko,[1] Daniela A. Braun,[1] Heon Yung Gee,[1] Mohamad Aman Jairajpuri,[2] Martin Zenker,[3] Friedhelm Hildebrandt.[1] *[1]Div of Nephrology, Boston Childrens’ Hospital, Harvard Medical School, Boston, MA; [2]Dept of Biosciences, Jamia Millia Islamia, New Delhi, India; [3]Inst of Human Genetics, Univ Hospital Magdeburg, Magdeburg, Germany.*

Background: Idiopathic nephrotic syndrome is a common pediatric kidney disease. 80% of all cases are steroid sensitive (SSNS). First insights into the pathogenesis of steroid-resistant nephrotic syndrome (SRNS) came from identification of ~30 single-gene causes. However, mechanisms of treatment sensitivity *vs.* resistance remain unknown.

Methods: We performed homozygosity mapping (HM) and whole exome sequencing (WES) to identify novel disease-causing genes in a worldwide cohort of ~2,000 individuals with severe NS.

Results: By WES and high-throughput sequence analysis, in families who mostly had steroid-dependent NS (SDNS), we identified multiple recessive mutations in the following genes: *MAGI2, TENC1, DLC1, CDK20,* and *ITSN1* in 2, 5, 4, 1, and 3 unrelated families, respectively. Knockout mice of *Magi2* or *Tenc1* have been previously shown to develop NS. By Co-IP, we now show that MAGI2 interacts with TENC1 and DLC1 and these interactions are abrogated by the two MAGI2 mutants. Knockdown of *MAGI2*, *DLC1* or *ITSN1* in cultured podocytes exhibited a decreased podocyte migration rate. Immunofluorescence studies showed that TENC1 and DLC1 colocalize with phosphotyrosine at focal adhesions in human podocytes. We discover CDK20 as a novel renal regulator of DLC1. In addition, we discover ITSN as a novel GEF for Cdc42, relevant for podocyte function.

Conclusions: Thus, by identification of 5 novel monogenic causes of NS we define a functional network of proteins at the intersection between steroid sensitivity *vs.* steroid resistance of NS. These findings for the first time may elucidate cell autonomous podocytic mechanisms of treatment response in NS and will make specific genetic variants of NS amenable to treatment.

Funding: Other NIH Support - DK076683

TH-PO283

IgA Glomerulonephritis Caused by ENTPD3 Mutations; and with Drusen Suggesting Low Grade Complement Activation Judith A. Savige,[1] Terence L. Kirley,[2] Deb J. Colville.[1] *[1]Medicine and Nephrology, The Univ Dept of Medicine, Melbourne, VIC, Australia; [2]Dept of Pharmacology and Cell Biophysics, Univ of Cincinnati College of Medicine, Cincinnati, OH; [3]The Univ of Queensland, QLD, Australia.*

Background: IgA disease is the commonest glomerulonephritis worldwide affecting 1% of the population, one third of whom go on to develop end-stage renal failure. The aim of this study was to use whole exome sequencing and bioinformatics analysis in a family with biopsy-proven IgA glomerulonephritis to identify the mutant gene.

Methods: Nine members of the family provided DNA that underwent whole exome sequencing (Otogenetics, Atlanta). The results were analysed for variants that segregated with affected status in an in-house bioinformatics pipeline. Pathogenicity was then confirmed with protein modelling experiments and functional assays using cells from family members.

Results: The whole exome sequencing demonstrated a missense mutation (R143C, rs 369719510) in the ectonucleoside triphosphate diphosphohydrolase 3 (*ENTPD3*) gene that segregated with disease in this family. ENTP3 is important in purinergic signalling, with roles in phagocytosis, inflammation and apoptosis. The R143C variant is very rare (0.0001%, www.exac.broadinstitute.org/). It affected enzyme function in modelling experiments, and in an in vitro transfection system. Affected peripheral blood monocytes from family members with the R143C mutation also demonstrated reduced enzyme activity and abnormal phagocytosis. We identified a further pathogenic variant (rs34266806, R264Q) that resulted in the same phagocytic defects in an unrelated individual with apparently sporadic IgA disease.

Conclusions: These results indicate a novel gene locus for IgA glomerulonephritis, and that some apparently sporadic cases also have a genetic basis. *ENTPD3* mutations impair phagocytosis which potentially contributes to the development of mesangial deposits. This represents the second gene identified in IgA glomerulonephritis, and the corresponding proteins belong to interacting pathways.

TH-PO284

Retinal Temporal Thinning Is More Pronounced in Males with X-linked Alport Syndrome and Early Onset Renal Failure Judith A. Savige, Yan Hong Chen, Andrew S. Talbot, Deb J. Colville. *Medicine and Nephrology, The Univ of Melbourne (MH and NH), Melbourne, VIC, Australia.*

Background: Alport syndrome is an inherited disease characterised by renal failure, hearing loss, and ocular abnormalities including retinal temporal thinning. This study examined retinal thinning in Alport syndrome.

Methods: Alport syndrome was diagnosed on renal biopsy or genetic testing, and the mode of inheritance was determined by genetic testing. Age at end-stage renal failure and current eGFR were recorded. Retinal thinning was determined from optical coherence tomography (OCT), using the formula of temporal thickness index (TTI) = (nasal – temporal thickness) ÷ nasal thickness x 100% compared with the normal range for age group (Ahmed, 2013). Statistical analysis was performed using Stata (StataCorp).

Results: Temporal thickness index was 11.47 + 5.3% in males (n=20) and 7.51 + 1.79% in females (n=28) with X-linked disease; 14.5 + 1.36% (n=5) in recessive disease; 7.03 + 2.12% (n=12) in Thin membrane nephropathy ; and 6.34 + 2.53% (n=12) in other causes of renal failure. In X-linked disease, 15 males (75%) and 19 females (68%) had retinal thinning, and thinning was more pronounced in males ($p< 0.01$), and, in males, correlated with early onset renal failure ($p<0.01$). Thinning did not correlate with eGFR in females ($R2 = 0.016$). The degree of thinning did not distinguish X-linked disease in women from Thin basement membrane nephropathy. Overall the sensitivity of retinal thinning for Alport syndrome was 72% and specificity was 58%.

Conclusions: The difference in retinal thinning in males and females with X-linked Alport syndrome and renal failure suggests that the loss of the collagen IV a5 chain from affected membranes contributes to renal failure in men, but that there is a further non-genetic contribution to renal deterioration in women such as hypertension.

Funding: Clinical Revenue Support

TH-PO285

Function of Focal Segmental Glomerulosclerosis Disease Protein Inverted Formin 2 (INF2) in Podocytes

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Background: Mutations in Inverted formin 2 (INF2) gene cause an autosomal dominant human kidney disease characterized by focal segmental glomerulosclerosis (FSGS) with or without Charcot-Marie-Tooth disease. Aberration in actin dynamics are manifested due to pathogenic mutations *in vitro* and have been hypothesized to play a major role in INF2 mediated FSGS. In addition, recent studies with a human pathogenic R218Q knockin mutant mouse model showed impaired podocyte recovery with protamine sulfate followed by heparin sulfate treatments, which associates with defective cell protrusions and actin structures in mutant podocytes. While these studies highlight the importance of INF2 in actin dynamics, its correlation with podocyte structure and function remains largely unknown. The purpose of this study was to understand the INF2 function in podocytes, and advance our knowledge in INF2 associated FSGS.

Methods: Human podocyte specific INF2 splice variant expressions were analyzed both by RT-PCR and Immunoblotting. CRISPRed INF2 knockout cells were generated and evaluated for changes in cytoskeleton and lipid raft trafficking using migration assays.

Results: Splice variant analysis of INF2 in human podocytes showed the expression of INF2-CAAX isoform (NCBI ID: NM_022489.3) and a short splice-isoform corresponding to a region from N-terminus exon 1 start to exon 5 end (NCBI ID: NM_032714.2). Unlike in normal cells, CRISPRed INF2 knockout podocytes lacking these isoforms exhibited polyglutamylated tubulin and cortactin structure defects in the lamellipodium region during migration. In addition, lipid raft trafficking, an actin and polyglutamylated tubulin structure dependent process, as measured through GM1 marker also exhibited defects in INF2 knockout podocytes.

Conclusions: INF2 functions in podocytes are associated with the regulation of podocyte cytoskeleton and lipid raft trafficking. Further understanding of INF2 function in these processes and their relation to slit diaphragm proteins would provide the critical mechanistic insights into INF2 associated FSGS.

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TH-PO286

The Acadian Variant of Fanconi Syndrome Is Caused by Mitochondrial Respiratory Chain Complex 1 Deficiency due to a Non-Coding Mutation in NADH Dehydrogenase Complex 1 Assembly Factor 6 (NDUFAF6)

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Background: The Acadian Variant of Fanconi Syndrome (AVFS) occurs in the Acadian population of Canada and is characterized by autosomal recessive inheritance of Fanconi syndrome and progressive CKD with ESRD between age 21 and 40.

Methods: 12 individuals with AVFS were identified and phenotyped. Fibroblasts were obtained from a skin biopsy of an affected patient. Whole exome sequencing, homozygosity mapping, whole genome sequencing (WGS), and Sanger sequencing were performed.

Results: Whole exome sequencing identified a region on chromosome 8(chr8:90958422-95690579) that was homozygous in 3 affected but not present in one unaffected family member. Using WGS, we identified one ultra-rare noncoding variant, chr8:96046914T>C in the gene *NDUFAF6* that was homozygous in the 9 affected individuals, whereas 13 healthy siblings were either heterozygotes or lacked the mutant allele. *NDUFAF6* encodes assembly factor 6 of the NADH dehydrogenase (ubiquinone) complex1 (NDUFAF6). This variant is located in intron 2. Mutation interpretation software predicted that the c.298-768 T>C nucleotide change would create a novel splice acceptor site. Western blot analysis of affected and control skin fibroblasts revealed loss of the mitochondrial NDUFAF6 isoform V-1 in affected fibroblasts, while the NDUFAF6 isoform V_2 was reduced but present in the cytoplasmic fraction. Affected fibroblasts had defects in mitochondrial respiration and complex 1 biogenesis that corrected with *NDUFAF6* cDNA transfection. All affected individuals had progressive pulmonary fibrosis leading to death.

Conclusions: AVFS is caused by a mutation in *NDUFAF6* that results in mitochondrial respiratory chain complex 1 deficiency. Progressive pulmonary fibrosis occurs in all affected individuals.

Funding: Clinical Revenue Support

TH-PO287

Prevalence of UMOD and MUC1 Mutations in Families with Autosomal Dominant Tubulo-Interstitial Kidney Disease

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Background: Mutations in *UMOD*, *MUC1*, *REN*, and *HNF1beta* genes are known causes of autosomal dominant tubulo-interstitial kidney disease (ADTKD). We analyzed the relative prevalence of these conditions in ADTKD.

Methods: Since 1996 we have been referred 698 families. We suspected ADTKD in 446 of these families and were able to obtain 2076 DNA samples on 1702 individuals from 308 families. These families underwent analysis for *UMOD*, *MUC1*, *REN*, and *HNF1beta* mutations. We also obtained information regarding a family history of gout. *UMOD* mutational analysis was performed at Athena Diagnostics, Worcester, MA, or the First Faculty of Medicine, Charles University, Prague, Czech Republic. Genetic analysis for a cytosine duplication in the variable number of tandem repeat region of the *MUC1* gene was performed at the Broad Institute, Cambridge, MA. Other mutational analyses were performed at Charles University.

Results: Of the 308 families, 140 (45.5%) had *UMOD* mutations, 59 (19.2%) *MUC1* mutations, 11(3.7%) *REN* mutations, one family (0.3) had an *SEC61A1* mutation and 1 (0.3%) a *hepatocyte nuclear factor one beta* mutation. 86 of 140 families with *UMOD* mutations (62%) had a strong family history of gout, and 21 of 59 (36%) families with *MUC1* mutations had a strong history of gout. All 11 *REN* families had a history of gout. We also performed mutational analysis in 23 individuals with tubulo-interstitial kidney disease of unknown cause and no family history of kidney disease; one individual(4.3%) was found to have a *MUC1* mutation, while no mutations were found in the other individuals.

Conclusions: *UMOD* and *MUC1* mutations make up the majority of mutations causing autosomal dominant tubulo-interstitial kidney disease, though the cause of inherited kidney disease remains unclear in a number of families. Gout is more prevalent in *UMOD* families, but can be seen in both disorders. Patients with tubulo-interstitial kidney disease and no family history of ADTKD rarely are found to have a *UMOD* or *MUC1* mutation.

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TH-PO288

The Genetic and Phenotypic Spectrum of DGKE Nephropathy

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Background: Diacylglycerol kinase ε (DGKE) is a recently discovered gene that causes a novel form of glomerulopathy. Our objective is to combine data from 9 new cases with previously published reports to gain insights into the phenotype and natural history of DGKE nephropathy.

Methods: Genetic testing was done in certified laboratories. Previously reported cases were identified with PubMed search. Time to ESRD was assessed by Kaplan-Meier analysis.

Results: We present the clinical characteristics for 9 patients from 8 unrelated kindreds. Novel disease-causing genotypes were found in Polish, Emirati, Korean and Indian kindreds. Published reports contained data on 34 children. Renal biopsies were consistent with thrombotic microangiopathy (TMA) in 15 patients, MPGN-like features in 9, and mixed TMA/MPGN in 1. While 30/33 of patient with aHUS were diagnosed in the first year of life, patients with MPGN were diagnosed later (range 2-17 years). Thus far, 11 children have progressed beyond CKD stage 3. Of these, 5 were transplanted with excellent outcomes. The phenotype of patients harboring the same pathogenic genotypes - in particular, mutation-concordant siblings - was more heterogenous than expected. Mild hypocomplementemia was observed in 8/43.

Conclusions: DGKE nephropathy presents either as infantile aHUS or pediatric MPGN, usually without hypocomplementemia. Substantial phenotypic disconcordance between affected siblings was observed. The risks of CKD/ESRD are high but kidney transplantation is a safe option.

TH-PO289

Abstract Withdrawn

TH-PO290

Acute and Stable CRISPR/Cas9 Zebrafish Models of KEOPS Protein Defects Recapitulate Microcephaly of Galloway-Mowat Syndrome Tilman Jobst-Schwan,[1] Johanna Magdalena M. Schmidt,[1] David Schapiro,[1] Daniela A. Braun,[1] Corinne Antignac,[2] Friedhelm Hildebrandt.[1] *[1]Div of Nephrology, Boston Children's Hospital, Boston, MA; [2]Imagine Inst, Univ Paris Descartes, Sorbonne Paris Cité, Paris, France.*

Background: Galloway-Mowat syndrome (GMS) is a severe neurorenal disorder that combines nephrotic syndrome with microcephaly. We performed whole exome sequencing and homozygosity mapping on a cohort of GMS patients and identified in a total of 31 families recessive missense mutations in the 4 genes *LAGE3*, *OSGEP, TP53RK* and *TPRKB* which constitute the evolutionary conserved KEOPS complex. To study the pathogenesis of this newly defined disease entity, we generated zebrafish animal models.

Methods: We used CRISPR/Cas9 to develop an acute knockdown (KD) approach based on injections of multiple guide RNAs to study larval-onset developmental phenotypes for the zebrafish orthologues *osgep, tp53rk* and *tprkb*. Also by CRISPR/Cas9, we generated stable knockout (KO) zebrafish lines for *osgep* and *tprkb*. Survival curves were generated by monitoring larvae twice a day until reaching a steady state. The microcephaly phenotype was determined by measuring the head diameter to body length ratio (HD/BL-R).

Results: All gene specific groups in the acute KD show a significant reduction of HD/BL-R and long term survival compared to scrambled and uninjected controls for *osgep, tp53rk* and *tprkb*. Immunoblotting shows efficient KD of all 3 proteins in protein extracts from pooled zebrafish larvae. DNA damage response (DDR) is induced in the *osgep* group compared to controls. Stable zebrafish KO lines reproduce the microcephaly phenotype for *osgep* and *tprkb*. No larvae homozygous for truncating mutations survived for more than 15 days.

Conclusions: CRISPR/Cas9 zebrafish models of KEOPS protein defects partially reflect the human disease phenotype in GMS patients, including microcephaly and early mortality. Early death in zebrafish may mask a nephrotic phenotype. Acute CRISPR/Cas9 KD reproduces the early phenotype in stable KO lines and provides a viable alternative to morpholino KD. Our zebrafish models implicate DDR in the pathogenesis of KEOPS related GMS.

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TH-PO291

"Humanize" Zebrafish to Model Nephrotic Syndrome Weibin Zhou, Mi-Sun Lee, Sulochana Devi. *Pediatrics and Communicable Diseases, Univ of Michigan, Ann Arbor, MI.*

Background: Nephrotic syndrome (NS) is a disease characterized by proteinuria caused by disruption of the glomerular filtration barrier (GFB). The *NPHS1* gene encodes NEPHRIN, a protein component of the interpodocyte-spanning slit diaphragm essential for the normal GFB. Our objective is to study the function of *nephrin* mutations *in vivo* and model NS in zebrafish.

Methods: Zebrafish *nphs1* mutants were made using CRISPR targeted to exon 2 of *nphs1*. *nphs1* heterozygotes were crossed to obtain *nephrin* homozygotes for morphological and histological analyses. The pathogenic human NPHS1 mutations were introduced into zebrafish *nphs1* and specifically expressed in the podocytes of zebrafish.

Results: We have established two zebrafish *nphs1* mutant lines carrying 5 bp or 28 bp deletion that leads to ORF shifts and hence a premature stop-codon. Different from a previous report that morpholino-mediated knockdown of *nphs1* in zebrafish resulted in pericardial edema at 4 days post fertilization (dpf), these mutants did not show any morphological abnormality until after 5 dpf, when periorbital edema (POE) (similar to the phenotype seen in children with NS) was observed. The edematous phenotype become progressively severe and led to whole-body edema and lethality within two weeks of age. We generated transgenic fish expressing wild-type zebrafish *nphs1* in podocytes to rescue the edematous phenotype. We also generated transgenic fish to model two new NPHS1 mutations discovered in NS patients (p.Asp105Asn and (p.Tyr638Cys) to demonstrate their functional consequences *in vivo*.

Conclusions: The zebrafish *nphs1* mutants generated by CRISPR genome editing avoid the possible off-target effect by morpholino-mediated knockdown and thus demosntrate a more reliable and convicing nephrotic phenotype for zebrafish, which is consistent with that of the zebrafish model of inducible podocyte injury previously published by us. Given the efficiency of generating transgenic zebrafish, our new zebrafish model is potentially a useful platform to perform functional studies of pathogenic alleles for *nphs1* and other genes related to podocyte diseases. The "humanized" zebrafish model of NS will be used to screen for therapeutical compounds for this disease.

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TH-PO292

OSGEP and TP53RK, Two Novel Monogenic Causes of Steroid Resistant Nephrotic Syndrome, Interact with Components of the ARP2/3 Complex and Regulate Cell Migration David Schapiro,[1] Daniela A. Braun,[1] Jennifer A. Lawson,[1] Jia Rao,[1] Geraldine Mollet,[2,3] Olivier Gribouval,[2,3] Christelle Arrondel,[2,3] Weizhen Tan,[1] Tilman Jobst-Schwan,[1] Olivia Boyer,[2,3] Johanna Magdalena M. Schmidt,[1] Svjetlana Lovric,[1] Shazia Ashraf,[1] Shirlee Shril,[1] Martin Zenker,[4] Corinne Antignac,[2,3] Friedhelm Hildebrandt.[1] *[1]Div of Nephrology, Boston Children's Hospital, Boston, MA; [2]INSERM, Laboratory of Hereditary Kidney Diseases, Paris, France; [3]Univ Paris Descartes, Sorbonne Paris Cite, Imagine Inst, Paris, France; [4]Inst of Human Genetics, Univ Hospital of Magdeburg, Magdeburg, Germany.*

Background: Steroid resistant nephrotic syndrome (SRNS), an inherited disease of the renal glomerular filter, is one of the most frequent causes of end-stage renal disease in childhood. We have recently identified mutations of *OSGEP* and *TP53RK*, two components of the highly conserved KEOPS complex, as novel monogenic causes of SRNS and microcephaly in humans. The role of the KEOPS complex in higher organisms is not well understood.

Methods: We generated human podocyte cell lines with stable knockdown of *OSGEP* and *TP53RK,* and examined the effect of loss-of-function of these genes on cytoskeletal architecture and cell migration using videomicroscopy.

Results: We show that knockdown of *OSGEP* and *TP53RK* impairs cell migration as well as lammelipodia formation in immortalized human podocytes. Both proteins show distinct localization to lammelipodia and co-localize with components of ARP2/3 complex in this compartment. Upon overexpression, OSGEP and TP53RK interact with four proteins of the ARP2/3 complex, which was confirmed with half-endogenous CoIP.

Conclusions: We have recently identified mutations of *OSGEP* and *TP53RK* as novel monogenic causes of SRNS. Here, we show that OSGEP and TP53RK interact with components of the ARP2/3 complex and that knockdown of these genes impairs cell migration, a well-established surrogate phenotype of SRNS. We thus show for the first time that the KEOPS complex may regulate cytoskeletal architecture and cell migration *via* ARP2/3 in human podocytes and that this might represent the pathogenic link between *OSGEP* and *TP53RK* mutations and SRNS in humans.

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TH-PO293

AVIL Mutations Are a Novel Cause of Steroid-Resistant Nephrotic Syndrome Jia Rao,[1] Shazia Ashraf,[1] Weizhen Tan,[1] Amelie van der Ven,[1] Svjetlana Lovric,[1] Eugen Widmeier,[1] Tobias F. Hermle,[1] Daniela A. Braun,[1] Heon Yung Gee,[1] Krisztina Feher,[2] Mohan Shenoy,[3] Yincent Tse,[4] Martin Bald,[5] Jose C. Martins,[2] Friedhelm Hildebrandt.[1] *[1]Div of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston, MA; [2]Dept of Pediatric Nephrology, NMR and Structural Analysis Group, Univ of Gent, Krijgslaan, Belgium; [3]Royal Manchester Children's Hospital, Manchester, United Kingdom; [4]Great North Children's Hospital, Newcastle, United Kingdom; [5]Inst of Pathology, Univ Hospital Hamburg-Eppendorf, Stuttgart, Germany.*

Background: Steroid resistant nephrotic syndrome (SRNS) is the second most frequent cause of end-stage renal disease in the first 3 decades of life. Identification of single-gene causes of SRNS has furthered the understanding of its pathogenesis.

Methods: We combined homozygosity mapping with whole exome sequencing (WES) in 100 families with SRNS. To identify additional mutations, we screened a cohort of ~800 individuals with SRNS by microfluidic multiplex PCR and next generation sequencing.

Results: By WES and next generation sequencing, we identified 4 recessive mutations of the *advillin* (*AVIL*) gene in three unrelated families with SRNS.A homozygous missense mutation in *AVIL* was found in an individual of consanguineous parents with SRNS, deafness, cataracts, microcephaly, mental retardation. The other two individuals had compound heterozygous mutations in *AVIL*. AVIL is a member of the gelsolin superfamily of actin binding proteins with 6 gelsolin domains. We show that AVIL localizes to WT1 positive podocytes in rat kidney. Molecular dynamics stimulations with enhanced sampling for changes of AVIL indicate that the two missense mutant alleles potentially influence the structure and therefore the function of AVIL. In human podocytes the truncating mutant allele of *AVIL* caused miscolocalization of F-actin. We identified PLCε1 and ARP2/3 as new interaction partners of advillin which regulate podocyte migration through the EGF-induced DAG signal pathway.

Conclusions: We identified recessive mutations of *AVIL* as a novel monogenetic cause of SRNS. Further genetic and functional studies will shed light on the pathogenic pathway involved.

TH-PO294

Mutations in Genes Encoding Members of the KEOPS Complex Are a Novel Cause of Nephrotic Syndrome with Microcephaly Daniela A. Braun,[1] Jia Rao,[1] Geraldine Mollet,[2,3] Olivier Gribouval,[2,3] David Schapiro,[1] Christelle Arrondel,[2,3] Weizhen Tan,[1] Tilman Jobst-Schwan,[1] Olivia Boyer,[2,3] Johanna Magdalena M. Schmidt,[1] Jennifer A. Lawson,[1] Svjetlana Lovric,[1] Shazia Ashraf,[1] Shirlee Shril,[1] Martin Zenker,[4] Corinne Antignac,[2,3] Friedhelm Hildebrandt.[1] *[1]Nephrology, Boston Children's Hospital, Boston, MA; [2]Laboratory of Hereditary Kidney Diseases, INSERM, Paris, France; [3]Imagine Inst, Univ Paris Descartes, Paris, France; [4]Inst of Human Genetics, Univ Hospital of Magdeburg, Magdeburg, Germany.*

Background: Galloway-Mowat syndrome (GMS) is an autosomal-recessive disorder that manifests with steroid-resistant nephrotic syndrome (SRNS) and severe developmental anomalies of the central nervous system. So far, mutations in the gene *WDR73* are the only identified monogenic disease cause.

Methods: To identify novel mongenic causes of GMS, we performed whole exome sequencing, homozygosity mapping, and targeted exon sequencing. To investigate molecular mechanisms of 4 newly identified GMS genes *in vitro*, we generated immortalized human podocyte cell lines with stable knockdown of the genes of interest.

Results: By next-generation sequencing, we identified mutations of the genes *LAGE3, OSGEP, TP53RK,* and *TPRKB* that encode proteins of the evolutionary highly conserved KEOPS complex (Kinase, Endopeptidase and Other Proteins of Small size) in 31 families with microcephaly and childhood-onset nephrotic syndrome. We show that knockdown of *OSGEP, TP53RK,* and *TPRKB* results in severe proliferation defects, and upregulation of the CDK inhibitor p21 in human podocytes. To confirm pathogenicty of the idenitified alleles, we show that wildtype but not mutant constructs rescue the proliferation deficiency. Furthermore, knockdown of *OSGEP, TP53RK,* and *TPRKB* increased phosphorylation of γH2AX as an indicator of activated DNA damage response signaling, and ultimately resulted in apoptotic cell death.

Conclusions: We here identified recessive mutations of all four members of the KEOPS complex, i.e. *LAGE3, OSGEP, TP53RK,* and *TPRKB* as novel monogenic causes of GMS. We generate evidence that the disease phenotype is caused by defects in cell proliferation, accumulation of DNA damage, and induction of apoptosisupon loss-of-function of *OSGEP*, *TP53RK*, and *TPRKB*.

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TH-PO295

Applying the Drosophila Garland Cell Nephrocyte to Model Mechanisms of Monogenic Forms of Human Nephrotic Syndrome Tobias F. Hermle, Daniela A. Braun, Friedhelm Hildebrandt. *Nephrology, Boston Children's Hospital/Harvard Medical School, Boston, MA.*

Background: Steroid-resistant nephrotic syndrome (SRNS) is characterized by podocyte dysfunction. The Drosophila garland cell nephrocyte (GCN) is a podocyte-like cell that forms membrane invaginations bridged by autocellular slit diaphragms (SD). GCN represent a potential *in vivo* model to study the pathogenesis of SRNS. However, relevant pathomechanisms of SRNS such as interaction with the extracellular matrix (ECM) or CoQ_{10}-deficiency have not been studied in GCN.

Methods: RNAi and CRISPR/Cas9 in larval GCN, transmission electron microscopy, confocal imaging of immunostainings of SD-proteins and uptake of fluorescent tracers.

Results: Drosophila SD-proteins colocalize within a fingerprint-like staining pattern that correlates with ultrastructural morphology of SD. Using RNAi and conditional CRISPR/Cas9 in GCN we found this pattern to be mutually dependent on the orthologues of *NPHS1* and *KIRREL*. We show that tracer endocytosis occurs through Cubilin and also reflects size selectivity analogous to mammalian glomerular function. Thus we establish significant tools to study GCN. Using RNAi for gene silencing and tracer endocytosis as a read-out of GCN-function we screened 29 Drosophila orthologues of human monogenic causes of SRNS. Silencing of 15 genes mainly involved in the SD-complex, ECM-interaction, and CoQ_{10}-synthesis impaired GCN-function. This supports the usefulness of GCN to study SRNS pathogenesis. We focused on the CoQ_{10}-biosynthesis gene *Coq2,* whose silencing by RNAi we found to disrupt SD morphology and function. Restoration of CoQ_{10}-synthesis by vanillic acid resulted in partial rescue of the phenotype of *Coq2*-RNAi. We show that *Coq2* resides in mitochondria and *Coq2*-silencing increased formation of reactive oxygen species (ROS). We observed phenocopy of *Coq2*-RNAi by knockdown of *ND75,* a subunit of the mitochondrial respiratory chain complex that controls ROS formation CoQ_{10}-independently. Moreover, ROS scavenger glutathione partially rescued *Coq2*-RNAi.

Conclusions: Drosophila GCN represent a useful model to study the pathogenesis of SRNS, and our findings implicate ROS formation as a potential pathomechanism of *COQ2*-nephropathy.

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TH-PO296

Ctns Loss-of-Function Zebrafish Mutant Shows Early Larval Glomerular and Tubular Dysfunction: A New Animal Model for Nephropathic Cystinosis Mohamed A. Elmonem,[1,2] Ramzi Khalil,[3] Ladan Khodaparast,[4] Laleh Khodaparast,[4] Hans J. Baelde,[3] Lambertus P.W.J. Van den Heuvel,[1,5] Elena N. Levtchenko.[1] *[1]Pediatric Nephrology & Growth and Regeneration, Univ Hospitals Leuven, KU Leuven, Leuven, Belgium; [2]Clinical and Chemical Pathology, Faculty of Medicine, Cairo Univ, Cairo, Egypt; [3]Pathology, Leiden Univ Medical Center, Leiden, Netherlands; [4]Cellular and Molecular Medicine, Univ Hospitals Leuven, KU Leuven, Leuven, Belgium; [5]Pediatric Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands.*

Background: The human ubiquitous protein cystinosin is essential for transporting the amino acid cystine out of the lysosomal compartment into the cytosol. Pathogenic mutations of the coding gene *CTNS* lead to defective cystinosin function and the intralysosomal accumulation of cystine. kidneys are first affected with renal Fanconi syndrome; however, unless properly treated the diseases progresses rapidly towards end stage renal disease and multiple organ dysfunction. Animal models to study nephropathic cystinosis are limited, with only a *Ctns*-knockout mouse reported, showing cystine accumulation and signs of tubular dysfunction but lacking the early glomerular phenotype.

Methods: In our study we used a morpholino injected knock-out model (MO) and established a stable model ($ctns^{-/-}$) with a homozygous nonsense mutation in exon 8 of the zebrafish *ctns* gene. We evaluated early development, morphology, motor activity and cystine levels in mutant larvae. We further investigated the glomerular and tubular renal functional involvement.

Results: $ctns^{-/-}$ mutant larvae showed cystine accumulation, delayed development, signs of glomerular and tubular proteinuria and significantly reduced glomerular filtration rate, which closely resemble the early phenotype observed in cystinotic patients. Furthermore, $ctns^{-/-}$ larvae showed a gradual and significant decrease in cystine levels when treated with increasing concentrations of cysteamine, the only available cystine depleting therapy for human patients.

Conclusions: Taken together, Our Ctns loss-of-function zebrafish mutant seems like a suitable animal model for studying the mechanisms involved in the pathogenesis of the disease and for the experimentation of potential new therapeutic agents.

Funding: Private Foundation Support

TH-PO297

Early Induction of MMCP-4 in Podocytes May Underlie Endothelin-1 Activation in Alport Glomeruli Dominic E. Cosgrove, Daniel T. Meehan, Brianna M. Dufek, Duane C. Delimont. *Genetics, Boys Town National Research Hospital, Omaha, NE.*

Background: We recently showed that active endothelin-1 protein, but not mRNA, is elevated in glomeruli and urine of pre-proteinuric Alport mice. In this same study we showed that endothelin-1 activation of endothelin A receptors plays a key role in the initiation of glomerular pathogenesis in this same model. The mechanism underlying elevated active endothelin-1 peptide was unclear. Here we show induction of the murine homologue of human chymase, mast cell protease-4 (mMCP-4) in podocytes of pre-proteinuric Alport mice. mMCP-4 processes big endothelin to the active peptide, and is thus as a likely candidate for elevated endothelin-1 in Alport glomeruli.

Methods: Isolated glomeruli from (pre-proteinuric) 2 week-old 129 Sv autosomal Alport mice and 7 week old C57Bl/6 X-linked Alport mice and wild type littermates were analyzed by real time RT-PCR and by western blot for mMCP-4 mRNA and protein. Cryosections from these same mice were analyzed by immunofluorescence for mMCP-4 expression. Glomerular podocyte, endothelial, and mesangial cell lines were analyzed for mMCP-4 mRNA expression.

Results: mMCP-4 mRNA and protein were significantly elevated in glomeruli from both the autosomal and X-linked Alport mouse models before the onset of proteinuria. The mMCP-4 protein localized to the podocyte foot processes and the GBM. Cultured podocytes and glomerular endothelial cells express mMCP-4 mRNA. Expression was not detected in cultured mesangial cells.

Conclusions: Elevated expression of mMCP-4 in pre-proteinuric Alport glomeruli may account for elevated active endothelin-1 at this same time-point. Drugs that block endothelin receptors are toxic. Targeting the protease that processes big endothelin-1 to active endothelin-1 might provide a less toxic alternative.

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TH-PO298

COL4A3/4/5-Sequencing by NGS in Chilean Alport Patients: Significant Applications in Diagnosis and Renal Transplant Paola Krall,[1] Daniela Paz Nualart,[1] Daniel Carpio,[2] Carolina Lavoz,[1] Sergio A. Mezzano.[1] *[1]Unidad de Nefrologia, Univ Austral de Chile, Valdivia, Region de los Rios, Chile; [2]Inst de Anatomia Patológica, Univ Austral de Chile, Valdivia, Region de los Rios, Chile.*

Background: Alport syndrome (AS) is an inherited kidney disease associated with mutations in COL4A3/4/5 genes. Altogether the three genes contain 151 exons turning genetic analysis by Sanger sequencing (SS) a challenge. NGS emerges as a cost-time-labor effective tool to identify mutations in benefit of AS patients and their families.

Methods: 7 Chilean males with AS clinical diagnosis were recruited; 6 of them were in dialysis and/or waiting for cadaveric donor transplantation. Genomic DNA was extracted

from blood samples and analyzed with the ALPORT MASTR kit covering COL4A3/4/5 in 149 amplicons, combined with Illumina MID barcodes and sequenced with MiSeq Reagent Kit (600c).

Results: 100% of exonic and exon-intron regions in COL4A3/4/5 were covered with more than 100x. Data analysis resulted in the identification of 345 SNV, which represent 86 different SNV. After filtering procedures, 6 different SNV were identified as "disease causing" (table 1) and confirmed by SS.

Case	Mutation	Protein prediction effect
#1	*COL4A5* (IVS36) c.3246 +1G>A	p.Pro1037TyrfsX560
#2	COL4A5 (IVS48) c.4688 +5G>A	p.Gly1504AspfsX11
#3	COL4A5 (EX9) c.525 T>A	p.Tyr175*
#4	COL4A3 (EX38) c.3270 A>C	p.Pro1090Pro
#5	COL4A3 (IVS15) c.888 +2T>C	p.aaΔ297-316
#6	COL4A3 (IVS15) c.888 +2T>C COL4A3 (EX3) c.172 G>A	p.aaΔ297-316 p.Gly58Ser
#7	-	-

In silico tools predicted truncating, missense, in-frame deletion and synonymous mutations. In case #1, skipping of exon 36 was observed by cDNA(RNA) sequencing in blood and hair root. Genetic analysis by SS of the mutated exon was offered to families.

Conclusions: NGS is being implemented worldwide as a very useful tool to identify mutations. To our knowledge, NGS has never been offered to AS patients in Chile. Our results allowed as to confirm diagnosis in 6 AS patients carrying different mutations. Additionally, we were able to identify three first-degree relatives as safe kidney donors, discard AS in one patient´s sister and provide early diagnosis in one patient´s son. FONDECYT #11140242.

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TH-PO299

Pathogenicity of the Human LamininB2 S80R Mutation Revealed by Its Impact on Alport Syndrome

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Background: Mutations that affect the GBM component laminin β2 (LAMB2) cause either Pierson syndrome or isolated congenital nephrotic syndrome, depending on the severity of the mutation. We investigated the pathogenicity of LAMB2-S80R, a mutation reported as homozygous in a child with nephrotic range proteinuria, ocular abnormalities, and mild diffuse mesangial sclerosis, which are all features consistent with Pierson syndrome. LAMB2-S80R resides in the laminin polymerization domain and is predicted to affect GBM integrity.

Methods: *Lamb2*-/- mice were engineered to express a rat Lamb2-S80R transgene driven by the nephrin promoter (Neph-Lamb2-S80R) or mated to mice carrying the S80R point mutation that was knocked into *Lamb2* with CRISPR technology (*Lamb2*-S80RCr). To determine if the LAMB2-S80R mutation could exacerbate kidney disease in another GBM disease model, *Lamb2*-S80RCr mice were mated to *Col4a3*-/- Alport mice and analyzed for proteinuria and GBM defects.

Results: *Lamb2*-/- mice with uniform Neph-Lamb2-S80R expression or exclusively *Lamb2* S80RCr expression never showed signs of proteinuria up to ~1 year of age. Interestingly, the *Lamb2*-S80RCr allele exacerbated proteinuria in *Lamb2* S80RCr/+; *Col4a3*-/- mice, and all *Lamb2* S80RCr/+; *Col4a3*-/- mice reached ESRD at 36-63 days, earlier than *Lamb2*+/+; *Col4a3*-/- littermates and pure 129 *Col4a3*-/- mice (typically 75 to 90 days).

Conclusions: A lack of significant proteinuria in mice expressing only the LAMB2-S80R mutant protein was unexpected. This result could stem from an inherent difference between human and mouse laminin or GBM biology, a resistance to proteinuria in the mixed C57BL/6 x CBA strain background being used, or a lack of pathogenicity of the homozygous LAMB2-S80R point mutation despite the Pierson-like features of the patient. However, the enhanced proteinuria and reduced survival of Alport mice harboring just one Lamb2-S80RCr allele indicates that the LAMB2-S80R variant is pathogenic in the context of glomerular stress. Our results demonstrate the power of modelling specific human variants in mice and using genetic interactions to identify pathogenicity that would otherwise be missed.

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TH-PO300

Functional Assessment of a Novel COL4A5 Splice Region Mutation in an Alport Family

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Background: Alport syndrome is a hereditary disease caused by mutations in *COL4A5* in 85% of cases. Approximately 13% of variants described in Alport Syndrome patients are splice site or splice region variants. Many of these have not been validated as pathogenic by functional studies.

Methods: Targeted-exome sequencing was performed on the proband of a family with biopsy-confirmed Alport syndrome. Sanger sequencing was performed on all affected family members and married-in individuals. In silico splicing analyses and an in vitro splicing reporter minigene assay were used to assess the functional consequences of the *COL4A5* variant discovered in this family.

Results: Our family is a 3 generational family with X-linked Alport Syndrome. There are no extra-renal manifestations of disease in this family. Targeted-exome sequencing revealed a novel splice region variant, c.1780-6T>G, in *COL4A5*. There were no other pathogenic variants found in *COL4 genes*. This variant was confirmed by Sanger sequencing and segregated with disease. Different in silico models were inconsistent with respect to the likely impact of the variant on splicing. However, the splicing reporter minigene assay clearly showed that c.1780-6T>G causes frequent skipping of exon 25. Skipping of exon 25 appeared incomplete, as the variant minigene assay showed some properly spliced transcript (exon 25 retained).

Conclusions: We identified a novel splice region variant in *COL4A5* in a family with X-linked Alport Syndrome. We confirmed that this variant causes frequent but incomplete skipping of the downstream exon 25. We hypothesize that the variable expression of normal and abnormal transcripts may explain phenotypic variation within this family.

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TH-PO301

Appropriate Use of a Rapid Genetic Assay to Confirm the Diagnosis of Complement-Mediated Thrombotic Microangiopathy

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Background: Improved diagnostic tests and greater understanding of thrombotic microangiopathy (TMA) have led to rapid differentiation of various types of TMAs. Availability of "Next-Gen" aHUS genetic testing (GT) allowing rapid detection (2-5 days) of >230 known or suspected polymorphisms possibly associated with aHUS, including 12 common mutations, (sensitivity ~70%) has enabled faster assessment of TMA cases.

Methods: From 4/14-4/16, we evaluated 124 patients (pts) with TMA. 86/124 (69%) pts had TTP (ADAMTS13 activity <5%), 9/124 (7%) pts had shiga-toxin ecoli (STEC) HUS, and 29/124 (24%) pts had neither. TTP pts presented with (p/w) mean platelet count (plt ct) 14 x 10^9/L (5-27 x 10^9/L), LDH 2816 U/L (844-5213), creatinine (Cr) 0.9 mg/dl (0.5-2.2); 32/86 (37%) had CNS abnormalities (abn), 9/86 (10%) had renal insufficiency (RI) (Cr>1.5). STEC HUS pts p/w mean plt ct 44 x 10^9/L (33-57 x 10^9/L), LDH 567 (390-694), Cr 3.1 (2.6-4.1); 2/9 (22%) had CNS abn, 9/9 (100%) had RI. Non-TTP/non-STEC TMA (TMA) pts p/w mean plt ct 59 x 10^9/L (18-153 x 10^9/L), LDH 827 (457-1336), Cr 4.3 (2.0-17.7), and ADAMTS13 of 78% (15-130%); 9/29 (31%) had CNS abn, 27/29 (93%) had RI.

Results: TTP pts received mean 14.8 plasma exchange (PE) treatments (txs) (5-43 txs); 63/86 (73%) received rituximab. STEC HUS pts received supportive care, including mean 5.3 PE txs (4-7). TMA pts received mean 6.1 PE txs (0-13); 17/29 (59%) required hemodialysis, 6/29 (21%) had RI which resolved. 14/29 (48%) TMA pts with unexplained, persistent RI received aHUS GT; 15/29 (52%) pts did not get aHUS GT and were treated for assoc. conditions: sepsis/DIC (3 pts), SLE flare (3 pts), malignant HTN (3 pts), pre-eclampsia (2 pts); HIV TMA, gemcitabine-assoc. TMA, CAPS, and scleroderma renal crisis (1 pt each). 10/14 (71%) of aHUS GT were positive (CFH, CFI, C3, MCP, DGKE, thrombomodulin, or plasminogen genetic abn) or equivocal; 29% were negative. 11/14 (79%) pts received eculizumab.

Conclusions: With development of improved genetic testing (ie, increased speed and sensitivity), aHUS genetic assays may represent a "real-time" diagnostic tool enabling more rapid assessment of complex TMA cases.

TH-PO302

A Monogenic Cause in Half Cases of Autosomal Dominant FSGS

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Background: The advent of next generation sequencing (NGS) has tremendously facilitated the genetic diagnosis in hereditary FSGS, and podocyte gene panels are increasingly used as the first step of genetic analyzes in familial cases.

Methods: We aimed to determine the causative gene mutations through Sanger sequencing and NGS in a large worldwide cohort of 140 families (253 patients) with FSGS starting during childhood or adulthood and an apparent autosomal dominant (AD) inheritance.

Results: Monogenic cause was identified in 67 families (48%). The mutation rate did not differ according to the size of pedigrees or the number of affected generations. The most prevalent gene mutations were the following: INF2 (20/67 families, 30%), COL4A3-5 (17/67, 25%), and WT1 (10/67, 15%). ACTN4 and TRPC6 mutations were detected in only 1 and 5 families (1.5% and 7.5%) respectively. An X-linked transmission was also possible in the 8 families with COL4A5 mutations and at least one affected relative had microscopic hematuria in 5/8, but no deafness was reported. Interestingly, we identified WT1 mutations in families with late-onset FSGS diagnosed at a median age of 19 years and no Wilm's tumor, including 3 pedigrees with fertile males who transmitted the mutation. Among the 60 different mutations identified, 30 were published pathogenic mutations (50%), 6 were novel truncating mutations (10%), 12 were novel missense variants in functional domains of the protein (20%) and 12 were predicted damaging missense variants (20%).

Conclusions: We conclude that 1) a high mutation rate is observed in families with AD-FSGS 2) isolated FSGS could result from mutations in collagen and developmental podocyte genes that should be included in all NGS diagnosis approaches to FSGS 3) a third of mutations are only probably pathogenic requiring further segregation/functional studies. This highlights the complexity of mutational analysis in identifying the true and nothing but the true pathogenic mutations in hereditary FSGS.

Funding: Government Support - Non-U.S.

TH-PO303

Novel TRPC6 Loss-of-Function Mutations Associated with FSGS Mario Kassmann,[1] Marc Riehle,[2] Anja K. Büscher,[3] Björn-Oliver Gohlke,[1] Jan H. Braesen,[4] Mato P. Nagel,[5] Jan U. Becker,[6] Peter F. Hoyer,[3] Robert Preissner,[1] Dietmar Krautwurst,[7] Maik Gollasch,[1] Christian Harteneck,[2] Stefanie Weber.[8] *[1]Experimental and Clinical Research Center (ECRC), Charité Univ Medicine Berlin, Berlin, Germany; [2]Eberhard Karls Univ Tubingen, Tubingen, Germany; [3]Univ of Duisburg-Essen, Essen, Germany; [4]Univ Hospital of Hannover, Hannover, Germany; [5]Center of Nephrology and Metabolism, Weisswasser, Germany; [6]Univ Hospital of Cologne, Cologne, Germany; [7]Deutsche Forschungsanstalt für Lebensmittelchemie, Molekulare Zellphysiologie und Chemorezeption, Freising, Germany; [8]Philipps-Univ Marburg, Marburg, Germany.*

Background: FSGS is a CKD with heavy proteinuria that eventually progresses to ESRD. Hereditary forms of FSGS have been linked to mutations in the transient receptor potential cation channel, subfamily C, member 6 (TRPC6) gene encoding a nonselective cation channel. Most of these TRPC6 mutations cause a gain-of-function phenotype, leading to calcium–triggered podocyte cell death, but the underlying molecular mechanisms are unclear.

Methods: We studied the molecular effect of disease-related mutations using tridimensional in silico modeling of tetrameric TRPC6. Our results indicated that G757 is localized in a domain forming a TRPC6-TRPC6 interface and predicted that the amino acid exchange G757D, a mutation which was found in FSGS-affected patients earlier, causes local steric hindrance and disruption of the channel complex. Notably, functional characterization of model interface domain mutants suggested a loss-of-function phenotype.

Results: Characterizing 19 human FSGS–related TRPC6 mutations by Ca2+-fluorescence measurements, we found that the majority caused gain-of-function mutations. However, five mutations (N125S, L395A, G757D, L780P, and R895L) caused a loss-of-function phenotype. For G757D and L780P these findings were confirmed by electrophysiology.

Conclusions: Our comprehensive analysis of human disease–causing TRPC6 mutations reveals loss of TRPC6 function as an additional concept of hereditary FSGS and provides molecular insights into the mechanism responsible for the loss-of-function phenotypes of TRPC6 G757D and L780P in humans.

Funding: Government Support - Non-U.S.

TH-PO304

The Prevalance of Fabry Disease in Patients with Chronic Kidney Disease in Turkey: The Results of Multicentric TURKFAB Study Kultigin Turkmen,[7] Aydin Guclu,[1] Garip Sahin,[2] Ismail Kocyigit,[3] Faruk Turgut,[4] Hilmi Umut Unal,[5] Cengizhan Açikel,[6] Mahmut Ilker Yilmaz,[5] Alberto Ortiz.[8] *[1]Nephrology, Kirsehir Ahi Evran Univ, Kirsehir, Turkey; [2]Nephrology, Eskisehir Univ, Eskisehir, Turkey; [3]Nephrology, Erciyes Univ, Kayseri, Turkey; [4]Nephrology, Mustafa Kemal Univ, Hatay, Turkey; [5]Nephrology, GATA Univ, Ankara, Turkey; [6]Epidemiology and Biostatistics, GATA Univ, Ankara, Turkey; [7]Nephrology, Necmettin Erbakan Univ, Konya, Turkey; [8]Nephrology, Unidad de Dialisis, HS-Fundaction Jimenez Diaz, U Automatica de Madrid, IRSIN, Madrid, Spain.*

Background: Fabry disease (FD) is a multisystemic X-linked disorder characterized by the accumulation of lysosomal globotriaosylceramide. In the literature, there has been no data regarding the prevalance of FD in Turkish CKD patients. We aimed to investigate the prevalance of FD in CKD population in Turkey.

Methods: This was a prospective study involving 313 stage 1-5 CKD patients not receiving hemodialysis or peritoneal dialysis. Patients with FD were confirmed by α-Gal A activity via DBS test and α-Gal A gene mutation analysis.

Results: Three patients among 313 CKD patients (0.95%) were identified as CKD patients with FD. After family screening of the 3 index patients, 11 patients (7male,4female) with CKD were diagnosed FD. Median age at onset of first symptoms of FD was lower in males compared to females (26years vs 38 years, respectively). The most frequent presenting symptoms in male patients were fatigue (100%), tinnitus (85%), acroparestesia (85%), vertigo (85%), hot intolerance (71%), abdominal pain (57%), cold intolarance (57%) The most frequent presenting symptoms in female FD patients were fatigue (50%), tinnitus (25%) and vertigo (25%). Male patients with FD had cornea verticillata (50%), cataract (25%), and angiokeratoma (25%). EM revealed Zebra bodies and miyeline figures. 6 male patients had started agalsidase-α, 1 male had started agalsidase-β along with previously prescribed RAS blockers. None of the female patients did not receive ERT. After six months of ERT, proteinuria significantly decreased in male patients.

Conclusions: FD was not uncommon among CKD patients in Turkey.

Funding: Pharmaceutical Company Support - Sanofi-Genzyme Company

TH-PO305

Multigene Panels Resolve Clinical Diagnosis for Multiple Inherited Kidney Disease Phenotypes in a Multidisciplinary Laboratory Service Andrew John Mallett,[1] Hugh J. Mccarthy,[2] Gladys Ho,[2] Amali Mallawaarachchi,[3] Chirag Patel,[1] Elizabeth Ann Farnsworth,[2] Cathy Quinlan,[4] Bruce Bennetts,[2] Stephen I. Alexander,[2] Katherine Jane Holman.[2] *[1]Royal Brisbane and Women's Hospital, Australia; [2]Children's Hospital Westmead, Australia; [3]Nepean Hospital, Australia; [4]Royal Children's Hospital, Australia.*

Background: Inherited kidney disease (IKD) spans a wide variety of phenotypes. Achieving genetic diagnosis is hypothetically feasible for many patients. The Australian Renal Gene Panels (ARGP) was established to realise this. Here we aim to describe its process and results (approval LNR/15/SCHN/505).

Methods: Consecutive patients (12/2013-03/2016) were referred for diagnostic genetic sequencing (10 multilane panels; 137 genes). DNA was sequenced (Illumina TruSightOne, HiSeq2500) and variants assessed with bioinformatic filters and a multidisciplinary team (MDT). Pathogenic variants were confirmed (Sanger). MLPA/microarray were utilized to identify copy number variants.

Results: 135 families (140 patients) were referred from all Australian states/territories. Probands were paediatric in 68/135 families (50%). Median/mean ages were 18/24yrs (IQR 33yrs, range 0-71yrs). 53% were female. Panels most requested were atypical haemolytic uraemia syndrome/C3 glomerulopathy (aHUS/C3GN, n=33), Alport Syndrome/thin basement membrane nephropathy (AS/TBMN n=27), nephrotic syndrome (NS, n=28), and nephronophthisis/related disorders (NPHP-RD, n=17). Pathogenic variants were confirmed in 58/135 families (43%). There was not a significant difference between paediatric and adult cohorts (31/68 vs 27/67, p0.53). The subcohorts with the greatest diagnostic rate were paediatric AS/TBMN (7/8, 88%), tubular (5/6, 83%) and adult AS/TBMN (15/19, 79%). Variants of uncertain significance (VOUS) were identified in an additional 22/135 (16%) families. Median age and gender proportion were similar between adults and children respectively with pathogenic, VOUS or negative results.

Conclusions: The diagnostic rate of this nephrogenetic service is 43% demonstrating the utility and cost-effectiveness of a MDT variant assessment approach. The absence of diagnostic rate difference between adults and children challenges dogma that such testing is less successful amongst adults.

TH-PO306

Whole Exome Sequencing in a Large International Cohort of 430 Pediatric Patients with Nephrotic Syndrome Jillian Kateri Warejko, Weizhen Tan, Svjetlana Lovric, Ankana Daga, Jia Rao, Shazia Ashraf, David Schapiro, Jennifer A. Lawson, Daniela A. Braun, Tobias F. Hermle, Tilman Jobst-Schwan, Eugen Widmeier, Shirlee Shril, Friedhelm Hildebrandt. *Div of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston, MA.*

Background: Steroid resistant nephrotic syndrome (SRNS) inevitably progresses to end-stage renal disease, requiring dialysis or transplantation for survival. To date, more than 40 monogenic causes of SRNS have been identified. Prior work (Sadowski et al, *JASN*, 26, 2015, pp 1279-89.) with targeted panel sequencing has shown that approximately 30% of cases of SRNS can be explained by a monogenic cause. However, panel sequencing can be limited by a high false positive rate and large numbers of Sanger sequencing required to confirm variants.

Methods: We therefore studied the underlying genetic cause of 382 patients from 295 families with nephrotic syndrome (NS) by employing whole exome sequencing (WES).

Results: Samples were recruited from April, 1998 to July, 2015 (17 years). WES was performed at the Yale Center of Mendelian Genomics. By using a candidate gene approach, we examined the sequenced exome data for mutations in 40 genes known to cause proteinuria and SRNS. During the time frame of the study, 10 of these genes were identified, characterized, and published by our laboratory. In 99/382 individuals (26.1%), we identified mutations in 27 of the known genes with this approach. There were also 8 genes that were identified as phenocopies of SRNS. In addition to an overall molecular solving rate of 26.1% of cases, we recapitulated what has been previously published with a 39% solve rate in consanguineous individuals and 15.5% solve rate in non-consanguineous individuals (Sadowski 2015).

Conclusions: This study confirms that ~26% of families with NS in our cohort are due to monogenic causes. WES is a viable and now cost-effective way to diagnose the underlying cause of NS in children. With our candidate gene approach, our report is the largest and most in-depth study of monogenic causes of NS in children using WES to date.

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TH-PO307

Whole Exome Sequencing of 121 Unrelated CAKUT Patients Identifies Novel Pathogenic Variants in Kidney Development Genes and in Genes Previously Not Associated with CAKUT Madhurima Kaushal, Amy B. Wilfert, Donald Conrad, Sanjay Jain. *Washington Univ in Saint Louis.*

Background: Congenital anomalies of the kidneys or lower urinary tract (CAKUT) encompass a spectrum of more than 10 different kidney malformations and are collectively the biggest cause of renal failure in children. These are genetically heterogeneous disorders with high heritability. The prevailing view is that these are monogenic or single pathway disorders. While a number of CAKUT genes have been implicated from discoveries in animal models or large pedigrees (mainly outside the US) the pathogenic variations in these genes or novel causes are largely undefined in US cohorts. By drawing on concepts

and discoveries in mechanisms of early kidney development and resulting defects , we focused on CAKUT phenotypes that are more likely due to defects in UB induction, ureter maturation and branching morphogenesis.

Methods: We performed Whole Exome Sequencing using Illumina platform and 50Mb Agilent clinical exome kit on 121 unrelated CAKUT cases with renal agenesis, hypoplasia, dysplasia and ureter defects to identify pathogenic rare or novel variants.

Results: By first interrogating 81 genes implicated in kidney development or CAKUT we found pathogenic variants identified by at least 3 different tools in 28 of these 81 genes in 48 cases. Many of these variations occurred in key functional domains that explain the likely mechanisms of these defects. While the common polymorphism frequencies in CAKUT cases and public datasets were similar, there was significant difference in rare variants in our cases compared to controls. We then used an unbiased approach that combined the prediction tools above, survey of large public datasets including 1000 genome, ESP6500, and Population Sampling Probabilities or PSAP tool that ranks pathogenicity from variant data of > 60000 exomes in ExAC and found pathogenic variants in 24 novel genes in additional 22 cases with a PSAP probability <1E-05. The novel ones includes genes important in histone and tRNA modification and apoptotic signalling.

Conclusions: Our work provides one of the first reports of the exomic landscape of CAKUT cohort that informs on pathogenetic mechanisms and diagnosis of these disorders.

Funding: NIDDK Support, Private Foundation Support

TH-PO308

Exome Sequencing in Patients with Rhabdomyolysis Reveals Heterogeneous Single-Gene Etiology in 47% of Cases

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Background: Rhabdomyolysis is a clinical emergency accounting for around 10% of all cases of acute kidney injury (AKI) in the US. Rhabdomyolysis can be acquired or due to single-gene causes. In the clinical setting, identifying the underlying molecular diagnosis is challenging, due to nonspecific presentation, high number of causative genes and lack of data regarding the prevalence of monogenic forms.

Methods: We employed whole exome sequencing (WES) to reveal the percentage of rhabdomyolysis cases that can be explained by single-gene mutations. We investigated a cohort of 19 unrelated families, in whom no underlying etiology was previously established.

Results: Using WES, we identified the causative mutation in nine of the 19 families (47%). We detected disease causing mutations in eight different known genes which can be grouped into the following categories: 1) disorders of glycogen metabolism (*PFKM* and *PGAM2*), 2) disorders of fatty acid metabolism (*CPT2*), 3) disorders of abnormal skeletal muscle relaxation and contraction (*RYR1*, *SCN4A*, *CACNA1S* and *MYH3*), and 4) disorders of purine metabolism (*AHCY*).

Conclusions: Our findings suggest a high prevalence for monogenic etiologies as well as broad genetic heterogeneity for rhabdomyolysis. This highlights the importance of molecular genetic diagnostics by WES of rhabdomyolysis to allow for personalized therapy. In addition, it helps establishing an etiologic diagnosis for an important subgroup of recurrent acute kidney injury.

TH-PO309

Exome Sequencing Discerns Syndromes in Patients from Consanguineous Families with Congenital Anomalies of the Kidneys and Urinary Tract

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Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) are the leading cause of CKD in children, featuring a broad variety of malformations. A monogenic cause can be detected in around 12% of patients. Nevertheless, in clinical practice, the genetic basis of most patients with CAKUT is elusive because of a very weak genotype-phenotype correlation.

Methods: To determine the likelihood of detecting causative recessive mutations, we performed whole exome sequencing (WES) and homozygosity mapping to identify such mutations that might also cause CAKUT. We screened and analyzed individuals with CAKUT from 33 different consanguineous families.

Results: Using homozygosity mapping and WES, we identified the causative mutations in nine of the 33 families studied (27%). We detected recessive mutations in nine known disease–causing genes: *ZBTB24*, *WFS1*, *HPSE2*, *ATRX*, *ASPH*, *AGXT*, *AQP2*, *CTNS*, and *PKHD1*. Notably, when mutated, these genes cause multiorgan syndromes that may include CAKUT as a feature (syndromic CAKUT) or cause renal diseases that may manifest as phenocopies of CAKUT. None of the above monogenic disease–causing genes were suspected on clinical grounds before this study. Follow-up clinical characterization of those patients allowed us to revise and detect relevant new clinical features in a more appropriate pathogenetic context.

Conclusions: Applying WES to the diagnostic approach in consanguineous families with CAKUT provides opportunities for an accurate and early etiology–based diagnosis and improved clinical management.

Funding: Other NIH Support - R01

TH-PO310

The Circadian Clock Provides Beneficial Effects against the Endothelial Dysfunction to Promote Atherogenesis by Regulating PDGF and TGF Generation

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Background: The circadian clock is a molecular mechanism that confers 24 hour variations in gene expression and function to regulate number of physiological functions in humans. Disruption of the clock is associated with pathological remodeling in the arterial structure and vascular stiffness. Chronic circadian clock disruption is also associated with dysfunction in endothelial signaling and responses. In this study, we observed if the deletion of Bmal1, a critical component of the circadian clock, can influencegrowth factors, such as platelet-derived growth factor (PDGF) and transforming growth factor (TGF)-β which play an important part in the progression of vascular diseases.

Methods: Congenic 12- to 16-week-old male, wild-type and Bmal1-KO littermate mice were generated from heterozygote breedings to be used for these studies. We also knocked down Bmal1 to evaluate the protein levels of PDGF and TGF-β in the knocked down cells.

Results: Endothelial function was reduced in aorta from Bmal1-KO mice. In aorta from Bmal1 KO mice, there was an increase in PDGF and TGF-β expression in mice with a dysfunctional circadian rhythm. Moreover, Bmal1 KO mice display pre-mature aging to have a dramatic prothrombotic phenotype. This phenotype is linked to changes in the regulation of key risk factors for cardiovascular disease. These include PDGF and TGF-β, which are significantly elevated in Bmal1 KO mice. We also confirmed that plasminogen activator inhibitor-1 and PDGF levels follow a circadian pattern and this pattern was absent in Bmal1 KO mice.

Conclusions: These findings indicate that circadian clock provides beneficial effects against the endothelial dysfunction to promote atherogenesis by regulating PDGF and TGF-β generation. This study establishes a mechanistic connection between Bmal1 and cardiovascular phenotype.

Funding: Other U.S. Government Support

TH-PO311

Therapeutic Restoration of Endothelial Glycocalyx in Sepsis

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Background: Endothelial glycocalyx (EG) is disintegrated during sepsis. We (Zullo et al. Am J Pathol, 2016) showed that this occurs very early in the course of sepsis and its prevention improves survival of mice with sepsis. The goal of the present study was to investigate pharmacologic tools capable of accelerating the restoration of disintegrated EG in sepsis.

Methods: We used a soilage injection model to induce sepsis in C57/Bl6 mice. We measured total body EG by comparing the dilution curves of dextran-40 and dextran-500 and their subtraction approximated the volume of EG. *En face* aortic preparations were used for staining with antibodies against heparan sulfate (HS) and atomic force microscopy (AFM) was used in vitro to measure EG.

Results: In vitro studies conducted in cultured endothelial cells exposed to LPS showed a robust ability of HS, sulodexide [Alfa Wassermann S.p.A., Alanno (PE), Italy], or high-molecular weight hyaluronic acid (HA) to accelerate EG regeneration (immunofluorescence and AFM). In vitro studies revealed the potential for inhibitors of hyaluronidase (Hase) and heparanase (HEPase) to accelerate EG regeneration. We demonstrated through In vivo studies showed that total volume of EG in control mice averaged 57±24 um^3, whereas in septic mice it was reduced to 1±30 um^3 within 24 hours of sepsis. Administration of components of the EG such as HA or HS did not produce dramatic acceleration of EG restoration. When HA or HS were administered in combination with inhibitors of Hase and HERase, the restoration of EG was remarkably accelerated. Notably, a heparan-sulfate like compound resistant to HEPase degradation, sulodexide, demonstrated a remarkable capacity for regeneration in vitro and in vivo. This combined treatment instituted 24 hr after induction of severe sepsis was also associated with the improved animal survival.

Conclusions: 1) EG is disintegrated in sepsis, the event which contributes to animal survival; 2) the process of endogenous restoration of EG is protracted; 3) pharmacologic acceleration of EG restoration can be achieved using the combination of hyaluronan and sulodexide with inhibitors of hyaluronidase and heparanase.

Funding: NIDDK Support

TH-PO312

Thrombospondin-1 and Its Glycocalyx Binding Partners Are Enriched in Endothelial Microparticles Formed under High Glucose Conditions

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Background: Diabetes is typified by the development of endothelial dysfunction; an independent predictor of poor prognosis linked to renal and cardiovascular disease. Microparticles are small (0.1-1.0 μm) membrane vesicles secreted following cell stress/

injury. Our previous work has shown that endothelial microparticles (eMPs) are sensitive markers of vascular injury and shown that eMPs themselves promote endothelial injury. However the effect of high glucose and diabetes on eMPs is unclear.

Methods: eMPs were isolated by centrifugation from the media of cultured human umbilical vein endothelial cells treated with normal D-glucose (5.6 mM), 25 mM D-glucose, or L-glucose (osmotic control, 5.6 mM D-Glucose + 19.44 mM L-Glucose). eMP levels were then assessed by nanoparticle tracking analysis. To assess the protein composition of eMPs formed under each condition, eMP protein lysates were separated by SDS-Page and the tryptic digests were analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Relative differences in protein levels between the conditions were assessed by label-free spectral counting and candidate proteins were verified by Western blot analysis.

Results: MP formation increased following 24 hour treatment with D-glucose (25mM) compared to the normal D-glucose or osmotic controls (~3-fold, $P<0.05$). LC-MS/MS analysis identified 14,631 unique peptides and 220 independent proteins with at least 2 peptides per protein and an average sequence coverage of ~16%. Amongst the 10 proteins most highly enriched in high glucose eMPs were the pro-coagulant protein thrombospondin-1 (~4-fold increase vs normal glucose eMPs) and its glycocalyx binding partners Versican (~8-fold enrichment), Agrin (~5-fold), and Perlecan (~11-fold). These observations were confirmed via Western blot analysis.

Conclusions: In summary we show that high glucose increases the formation of eMPs and leads to alterations in their molecular composition including the enrichment in thrombospondin-1. Such alterations may contribute to the development of vascular and renal injury in diabetes.

TH-PO313

CD4+CD28- T-Cells Are Cytomegalovirus Specific Cytotoxic Endothelial Targeting Cells and Are Independently Associated with Increased Arterial Stiffness in Renal Disease Dimitrios Chanouzas, Lovesh Dyall, Michael Sagmeister, Charles Ferro, Paul Moss, Matthew David Morgan, Lorraine Harper. *Univ of Birmingham, UK.*

Background: CD4+CD28- T-cells have been linked to cardiovascular disease (CVD) in inflammatory conditions. We previously showed that in ANCA associated vasculitis (AAV) they are associated with mortality and are specific to Cytomegalovirus (CMV) seropositivity. Using AAV as a model, we sought to characterize these cells further and determine their contribution to arterial stiffness, an independent predictor of CVD.

Methods: Peripheral blood mononuclear cells from 53 CMV seropositive AAV patients with renal involvement in remission and 30 age-matched healthy volunteers (HV) were cultured overnight with CMV lysate and stained for surface and intracellular markers by flow cytometry. Pulse wave velocity (PWV) was measured using the Vicorder device.

Results: AAV patients had higher % of CD4+CD28- cells compared to HV (median 11.3%[IQR 3.4-19.8] vs 6.7%[2.3-8.9],p=0.02). In comparison to CD4+CD28+ cells, CD4+CD28- cells displayed a CXCR3+CCR6- Th1 phenotype (80.5%[65.0-89.8] vs 31.0%[25.0-35.4],p<0.01) and expressed the Th1 transcription factor T-bet (83.5%[47.5-89.9] vs 12.9%[4.7-22.2],p<0.01). They expressed endothelial receptors (CX3CR1+CD49d+CD11b+ 51.6%[42.7-64.4] vs 4.9%[1.7-6.3],p<0.01) and cytotoxic molecules (perforin+granzymeB+ 74.5%[63.5-92.7] vs 2.9%[1.8-5.4],p<0.01) at high levels and produced IFN-γ (21.2%[8.2-37.0] vs 0.7%[0.3-1.4],p<0.01) following CMV lysate stimulation compared to CD4+CD28+ cells. The CD4+CD28- % was independently linked to increased PWV in AAV after controlling for age, mean arterial pressure, proteinuria, CD4 count and CD8+CD28-% ($R^2$0.482, B=0.075[0.018-0.132],p=0.01).

Conclusions: CD4+CD28- cells are a CMV specific, cytotoxic, proinflammatory Th1 subset that possess endothelial targeting receptors and are independently associated with increased arterial stiffness in renal disease. In a linked clinical trial submitted for ASN 2016, we also show that blocking subclinical CMV reactivation in AAV led to a reduction in CD4+CD28- cells, implicating CMV as the driving force behind their expansion and offering novel therapeutic opportunities in inflammatory renal disease.

TH-PO314

Creation of the CD148-Specific TSP1 Fragment and Its Effects in Glomerular Endothelial Cells Keiko Takahashi, Rachel H. Kim, Katherine Sumarriva, Ray Mernaugh, Takamune Takahashi. *Medicine, Vanderbilt Univ, Nashville, TN.*

Background: CD148 is a transmembrane tyrosine phosphatase expressed in renal endothelium including glomerulus. Previous studies showed its role in negatively regulating cell growth and growth factor signaling. Furthermore, we recently found that thrombospondin-1 (TSP1) serves as a ligand for CD148 (PNAS 109:1985), then characterized its interaction and created the CD148-specific TSP1 fragment (148-TSP1) (PLoS One 11:e0154916). This study aimed to define its effects in glomerular endothelial cells (GECs).

Methods: Human GECs were treated with monomeric or trimeric 148-TSP1 fragments and its effects on GECs proliferation and tube formation were assessed. CD148 catalytic activity was measured by IP/PTP assay and oligomerization status was assessed by immunostaining. GEC growth factor signaling was assessed by Western or IP/Western using phospho-specific antibodies. The effect on angiogenesis was assessed by mouse sponge assay using VEGF as an inducer. Specificity of the effects was evaluated by CD148 knockdown or knockout (mice).

Results: Trimeric, but not monomeric, 148-TSP1 fragment; 1) increased CD148 catalytic activity with its accumulation on cell surface in GECs, although both forms bound to CD148 effectively, indicating CD148 oligomerization is required for this effect.; 2) dose-dependently inhibited GEC proliferation (~80%) and tube formation (~50%) in culture; 3) remarkably (~80%) suppressed VEGF angiogenesis *in vivo*. These effects were largely attenuated or abolished by CD148 knockdown or knockout (mice). Furthermore, the 148-TSP1 fragment reduced tyrosine phosphorylation of VEGFR2, HGFR, Tie2, ERK1/2, and Src pY529 in GECs, while it showed no effects for EphA2, FGFR, Akt, and Src pY416.

Conclusions: The trimeric 148-TSP1 fragment increases CD148 activity and inhibits GEC proliferation and tube formation in culture and angiogenesis *in vivo*. This fragment suppresses multiple growth factor signaling (VEGFR, HGFR, Tie2, ERK1/2) in GECs without altering Akt or Src activity. Given the fact that Akt cell survival signal is preserved, this agent and pathway may provide a new and safer strategy for inhibiting glomerular angiogenesis.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-PO315

Vascular Endothelial Growth Factor Augments Arginine Transport and Nitric Oxide Generation via a KDR Receptor Signaling Pathway Idit F. Schwartz, Moshe Shashar, Doron Schwartz. *Nephrology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.*

Background: Vascular endothelial growth factor (VEGF) is an endothelium-specific peptide that stimulates angiogenesis via two receptor tyrosine kinases, Flt-1 and KDR. Endothelial nitric oxide synthase (eNOS) plays a major role in VEGF signaling. Delivery of arginine to membrane bound eNOS by the cationic amino acid transporter-1 (CAT-1) has been shown to modulate eNOS activity. The current studies were designed to test the hypothesis that VEGF enhances eNOS activity via modulation of arginine transport by CAT-1.

Methods: Using radio-labeled arginine {[^{3}H] L-arginine} uptake was determined in HUVEC following incubation with VEGF with and without silencing the VEGF receptors Flt-1 or KDR. Subsequently, western blotting for CAT-1, PKCα, ERK 1/2, JNK, and their phosphorylated forms were performed. NO generation was measured by the Griess reaction.

Results: VEGF (50 and 100 ng/ml) significantly augmented endothelial arginine transport in a time dependent manner, an effect which was prevented by Sunitinib (2 μM), a multi targeted receptor tyrosine kinase inhibitor.

The increase in arginine transport velocities by VEGF was not affected by silencing Flt-1 while silencing KDR abrogated VEGF effect. Furthermore, incubating cells with 50 and 100 ng of VEGF for 30 minutes significantly augmented CAT-1 abundance. The expression of PKC-α, JNK, and ERK1/2 and their phosphorylated forms were unchanged following incubation of HUVEC with VEGF. The concentration of NO2/NO3 following incubation with VEGF was significantly higher than from untreated cells.

Conclusions: VEGF increases arginine transport via modulation of CAT-1 in endothelial cells. This effect is exclusively dependent on KDR rather than Flt-1.

TH-PO316

Akt Signaling Modulates a Novel Transcription Factor to Promote the Re-Vascularization of Kidney Microvascular Endothelial Cells following Injury Lan Dang, Bryce Gordon Johnson, Graham Marsh, Ivan G. Gomez, Jeremy Stuart Duffield. *Cell Stress and Innate Immunity, Biogen, Cambridge, MA.*

Background: Acute kidney injury and chronic kidney disease are characterized by the progressive loss of kidney peritubular capillaries, which leads to local areas of hypoxia, induction of profibrotic responses, and ultimately the deterioration of renal functions. While many vascular beds have significant regenerative potential following tissue injury, the renal microvasculature fails to adequately regenerate. The unique property of the kidney microvasculature has prompted the investigation of new tissue-specific regulatory mechanisms that can provide new therapies for promoting re-vascularization following injury and thereby minimize the progression to chronic kidney disease.

Methods: We have developed new methods to isolate and study mouse and human Kidney Microvascular Endothelial Cells (KMVECs) *ex vivo*. Using *in vitro* and *ex vivo* assays that recapitulate features of angiogenesis, we demonstrated that both mouse and human derived KMVECs fail to generate new vascular sprouts in response to VEGF stimulation, compared to endothelial cells isolated from large vessel beds, such as Human Umbilical Vascular Endothelial Cells.

Results: Western blotting analysis showed that the PI3K/Akt pathway in KMVECs was severely attenuated in response to VEGF. PI3K/Akt signaling plays a critical role during endothelial invasion and sprouting and its activation is inhibited by the phosphatase PTEN. We observed that KMVECs treated with the PTEN inhibitor showed an increased capacity to invade and form new sprouts compared to the untreated control. Furthermore, we evaluated whether the inhibition of PTEN can ameliorate the re-vascularization capacity of KMVECs following ischemia re-perfusion injury in adult mice. Interestingly, PTEN inhibition greatly enhanced the capacity of KMVECs to form new blood vessels *in vivo,* as shown by the increase in vessel density.

Conclusions: These results provide critical insight into the role of the PI3K/Akt signaling pathway in regulating functional re-vascularization of injured kidneys to prevent progressive capillary regression and chronic kidney disease.

Funding: Pharmaceutical Company Support - Biogen

TH-PO317

Increased Angiogenic Potential of Endothelial Cells Isolated from Patients with End-Stage Kidney Disease Using Combined Cell Therapy
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Background: We have recently shown that the administration of the anti-fibrotic hormone, relaxin (Rln) in combination with mesenchymal stem cells (MSCs) abrogates fibrosis in a model of obstructive nephropathy, yet their effect on revascularization is still to be elucidated. Endothelial progenitor cells (ECPs) play a key role in this process and it is known that patients on dialysis have reduced circulating EPCs. Therefore, enhancing angiogenic potential of end-stage kidney disease (ESKD) patients warrants investigation.

Methods: Mononuclear cells were isolated from patients with ESKD and control subjects. Colony forming units (CFU) were quantified and Dil-AC-LDL/lectin binding confirmed endothelial cell function. Endothelial lineage was determined using immunocytochemistry and confirmed with flow cytometry. Tube formation in matrigel was assessed over 6hours using live cell time-lapse microscopy in the presence of MSCs/Rln. Wound healing over 24hours and proliferative capacity with/without MSC or Rln further quantifed angiogenic potential. All assays were replicated and compared with primary human endothelial cells (HECs).

Results: Patient EPCs were positive for Dil-AC-LDL/lectin and had impaired CFU compared to controls. EPCs transitioned into mature endothelial cells as confirmed by morphology and positive immunolabelling for vWF, CD31 and VEGFR2. Flow cytometry identified CD34+CD31+KDR+CD45- cells confirming endothelial lineage. HECs cultured directly with MSCs and Rln had a significant increase in branch points and length in tube forming assays ($p<0.05$). Additionally, wound closure was accelerated ($p<0.01$) and proliferation capacity was increased ($p<0.05$) when combination therapy was used.

Conclusions: EPCs can be successfully isolated from patients with ESKD and matured into endothelial cells. Their angiogenic potential can be modulated and enhanced with MSCs and Rln, which may have implications in kidney revascularization after injury.

Funding: Government Support - Non-U.S.

TH-PO318

Direct Evidence of Vascular Oxidative Stress and Inflammation in Chronic Kidney Disease
Kristen L. Nowak,[1] Wei Wang,[1] Laurel Thur,[1] Heather Farmer-Bailey,[1] Anna Jeanette Jovanovich,[1,2] Michel Chonchol.[1] *[1]Univ of Colorado Anschutz Medical Campus; [2]Denver VA Medical Center.*

Background: Chronic kidney disease (CKD) is associated with vascular dysfunction, as indicated by impaired vascular endothelial function and increased large-elastic artery stiffness. Vascular dysfunction in CKD is thought to be related to vascular oxidative stress and inflammation, but direct evidence is lacking.

Methods: We studied 21 patients (60±12 years) with stage 3-4 chronic kidney disease (CKD; mean estimate glomerular filtration rate (eGFR) 34±11 ml/min/1.73 m^2) and 15 healthy controls (42±4 years; eGFR 102±12 ml/min/1.73 m^2) and assessed brachial artery flow-mediated dilation (FMD_{BA}), aortic pulse-wave velocity (aPWV), and the carotid artery β-stiffness index. Vascular endothelial cells were collected from a peripheral vein and were available for analysis in 18 CKD patients and 11 controls. Vascular endothelial cell protein expression of the oxidant enzyme NADPH oxidase and pro-inflammatory cytokine interleukin-6 (IL-6) were measured using quantitative immunofluorescence.

Results: Consistent with previous evidence, FMD_{BA} was lower and aPWV and the β-stiffness index were higher in CKD patients ($p<0.01$) compared to healthy controls. Vascular oxidative stress was also higher in CKD patients, as indicated by greater endothelial cell protein expression of NADPH oxidase (0.94±0.06 vs. 0.80±0.08 [intensity relative to human umbilical vein endothelial cell (HUVEC) control; $p<0.001$). Vascular inflammation was also higher, as indicated by greater endothelial cell protein expression of IL-6 (0.87±0.06 vs. 0.66±0.05 [intensity vs. HUVEC control; $p<0.001$). These differences persisted after statistical correction for age ($p<0.001$). Participants with NADPH oxidase above the median had lower FMD_{BA} and higher aPWV and β-stiffness index compared to those below the median.

Conclusions: These results provide direct support for the hypothesis that endothelial oxidative stress and inflammation develop with CKD and are related to vascular dysfunction. Therapies targeting a reduction in oxidative stress and/or inflammation may improve vascular dysfunction in CKD.

Funding: Private Foundation Support

TH-PO319

Elevated Serum Platelet Microparticles Contribute to Aorta Endothelial Injury: A Potential New Mechanism for Atherosclerosis in Diabetes
Gui Hua Wang, Kun Ling Ma, Yang Zhang, Zebo Hu, Liang Liu. *Inst of Nephrology, Southeast Univ, Nan Jing City, JIang Su Province, China.*

Background: An early complication in diabetes is the development of endothelial dysfunction, characterized by altered endothelial cell function, impaired nitric oxide (NO) bioavailability and accelerated thrombosis. Platelet microparticles (PMPs) are arousing interest due to their pro-inflammatory effects. This study aimed to investigate the role of PMPs in aortic endothelial injury in diabetes.

Methods: Eight-week old male *Sprague-Dawley* rats were divided into three groups: nondiabetic rats (control), streptozotocin-induced diabetic rats (DM), and diabetic rats treated with Aspirin (DM+ Aspirin). The determination of PMPs was used by flow cytometry and confocal microscopy. The inflammatory cytokines released from PMPs was checked by protein microarray, immunohistochemical staining, or Western blot. The aortic endothelial injury was evaluated through determination of NO concentration, measuring the expression of endothelial nitric oxide synthase (eNOS), the change of glycocalyx and aortic endothelial permeabilityby electron microscopy, immunofluorescent staining and Western blot.

Results: Compared to the control, the serum level of PMPs increased significantly in DM rats, which was inhibited by Aspirin. Aspirin treatment decreased the production of inflammatory cytokines from serum PMPs and aorta. Using confocal microscopy, the enhanced interaction between PMPs and aortic endothelium was observed in DM rats, which was inhibited by Aspirin. Interestingly, the elevated PMPs and production of inflammatory cytokines from PMPs were correlated with the aortic endothelial injury by decreasing the NO excretion, the expression of eNOS, glycocalyx thickness and increasing endothelial permeability in DM rats. Decreased serum PMPs and production of inflammatory cytokines by Aspirin ameliorated the aortic endothelial injury compared to the DM group.

Conclusions: Elevated serum PMPs contribute to aorta endothelial injury through the release of inflammatory cytokines from PMPs, which accelerate the progression of atherosclerosis in diabetes.

TH-PO320

Myeloperoxidase and Altered Arginine Methylation Drive Chronic Kidney Disease Accelerated Atherosclerosis
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Background: Atherosclerosis is the leading cause of morbidity and mortality in chronic kidney disease (CKD) patients, but the underlying factors are not fully understood. In this study, we sought to determine the specific role of myeloperoxidase (MPO) mediated oxidative stress and the arginine -nitric oxide pathway in CKD accelerated atherosclerosis in a pathophysiologically relevant mouse model.

Methods: Male LDL receptor deficient mice were subjected to sham (CTL) or 5/6 nephrectomy (CKD) surgery and maintained on either low fat diet (LFD) or high fat diet (HFD) for up to 24 weeks. In addition to biological parameters, the extent of atherosclerosis was assessed at 24 weeks. Expression of MPO and its oxidation products 3-chlorotyrosine, 3-nitrotyrosine and *o,o'*-dityrosine were demonstrated using both immunohistochemistry and immunofluorescence and quantified using liquid chromatography / mass spectrometry (LC/MS). Targeted LC/MS was also utilized to profile the arginine metabolome.

Results: As anticipated, the CKD mice had significantly higher plasma creatinine, urea nitrogen, and intact parathyroid hormone while having lower hematocrit and body weight when compared to CTL mice. The CKD mice had similar blood pressure as CTL mice but had decreased cholesterol and triglycerides in the VLDL and LDL fractions. CKD mice on HFD had significantly increased aortic plaque area fraction compared to the CTL mice on similar diet. Additionally, CKD animals on HFD demonstrated increased MPO expression, and co-localization of macrophages, MPO and its specific oxidation products in the atherosclerotic lesions when compared to the CTL mice. Importantly, these modified aortic proteins were markedly elevated in the CKD HFD mice ($p<0.05$) when quantified by MS and consistent with increased MPO-mediated oxidation. Also, higher asymmetric dimethyl arginine (ADMA) levels in CKD mice correlated with atherosclerotic lesion area implicating altered arginine methylation and ADMA accumulation in these mice.

Conclusions: Together, these findings demonstrate the important role of macrophage derived MPO and its oxidants and altered arginine methylation in CKD accelerated atherosclerosis.

Funding: NIDDK Support, Pharmaceutical Company Support - Boehringer-Ingelheim

TH-PO321

Scavenging of Lipid Aldehydes Lessens Kidney Injury-Driven Atherosclerosis
Yan Shen,[1] Sean Stephen Davies,[2] Macrae F. Linton,[2] Valentina Kon.[1] *[1]Pediatrics, Vanderbilt Univ Medical Center, Nashville, TN; [2]Medicine, Vanderbilt Univ Medical Center, Nashville, TN.*

Background: Chronic kidney disease (CKD) accelerates atherogenesis. Reactive aldehydes, including isoprostanes and isolevuglandins (IsoLG) are lipoxidation products carried by high density lipoprotein (HDL). These aldehydes promote cellular dysfunction underlying atherosclerosis and their levels are increased in CKD. We previously used aldehyde scavenger, eg., IsoLG scavenger - salicylamine (SAM)) to lessen lipoxidation-induced cytotoxicity and now investigate the impact of this treatment on kidney-injury driven acceleration of atherosclerosis.

Methods: 11 week old female apolipoprotein E-/- mice underwent 5/6 nephrectomy (sNx) or sham-operation (sham), then treatment with SAM (1g/L) or vehicle for 6 weeks. Extent and characteristics of atherosclerotic lesions were assessed; cultured THP-1 macrophages were used to examine effects of IsoLG modified HDL on macrophage inflammatory response.

Results: Compared to sham, sNx increased atherosclerosis. SAM reduced the atherosclerotic lesion area in sNx ($121100 \pm 18760 \mu m^2$ *vs* 217600 ± 19890 in sNx+vehicle, $P<0.01$), but had little effect in sham. Assessment of plaques revealed greater necrotic area in sNx than sham ($9.4 \pm 0.8\%$ *vs* 3.7 ± 1.2, $P<0.01$). SAM significantly lessened necrotic areas in sNx+SAM ($6.2 \pm 0.5\%$, $P<0.01$), and did not affect the macrophage area or collagen content of plaques. Amelioration in atherosclerosis in sNx was not accompanied by changes in body weight, blood pressure, serum cholesterol, triglycerides, or BUN. In vitro, compared

to significant dampening of LPS-induced macrophage cytokine (IL-6) response to normal HDL, oxidative modification of HDL with IsoLG caused significant amplification in the inflammatory response (2.22 ± 0.16*vs* 0.78 ± 0.27in normal HDL, P<0.05).

Conclusions: Aldehyde scavengers ameliorate renal injury-induced acceleration in atherosclerosis and reduce necrotic area in plaques.These benefits are independent of effects on blood pressure or renal function but are linked to HDL aldehyde modification of macrophage inflammatory cytokine response.

Funding: Other NIH Support - NHLBI

TH-PO322

Extracellular Nucleosomes, Markers of Cell Death, Are Elevated in End-Stage Renal Disease Independent of Circulating Microparticle-Associated Tissue Factor Trung Phan,[1] Ryan Mcmillan,[1] Amanda Walborn,[1] Debra Hoppensteadt,[1] Jawed Fareed,[1] Vinod K. Bansal.[2] *[1]Pathology, Loyola Univ Medical Center, Maywood, IL; [2]Nephrology, Loyola Univ Medical Center, Maywood, IL.*

Background: Extracellular nucleosomes in plasma (PNs) are complexes of DNA and histones that are released during cell death. In acute kidney injury, there is an increased release of nucleosomes with decreased nucleosome clearance. Nucleosomes mediate inflammatory and thrombotic responses and could serve as biomarkers in chronic kidney diseases. Microparticle-associated tissue factor (MP-TF) are released during cell death and mediate thrombosis.

Methods: The concentrations of PNs in ESRD patients (n = 90) and healthy volunteers (n = 50) were measured using the Cell Death Detection ELISA PLUS assay (Roche Diagnostics, Mannheim, Germany). MP-TF levels were measured using the ZYMUPHEN MP-TF kit (Hyphen BioMed, Neuville-sur-Oise, France). The levels of both PNs and MP-TF were also correlated with WBCs, RBCs and platelets to determine their origin.

Results: In comparison to the plasma from healthy volunteers (6.74 ± 13.7 Arbitrary Units (AU)), the levels of PNs in ESRD patients were higher (15.5 ± 14.1 AU; $p < 0.0001$). Similarly, MP-TF levels were elevated in ESRD patients (3.00 ± 1.42 pg/mL; $p < 0.0001$) compared to normal (0.363 ± 0.263 pg/mL). There was no correlation between PNs and MP-TF in ESRD patients ($r = 0.077$; $p = 0.501$). Moreover, there was no correlation between PNs and platelets ($r = 0.067$; $p = 0.543$) and RBCs ($r = 0.083$; $p = 0.447$). However, the PNs showed a positive correlation with WBCs ($r = 0.223$; $p = 0.042$). There was no correlation between MP-TF and WBCs ($r = -0.057$; $p = 0.632$) and RBCs ($r = -0.042$; $p = 0.722$), but a positive correlation was observed between MP-TF and platelets ($r = 0.237$; $p = 0.042$).

Conclusions: PNs were elevated in ESRD patients, indicating an increased release of nucleosomes, suggesting increased cell death. The observed correlation between PNs and WBCs suggests that the detected PNs are derived from WBCs. A lack of correlation between PNs and MP-TF suggests that the MP-TF increase is independent of the pathogenesis responsible for abnormal PN generation in ESRD patients.

TH-PO323

FGF-23/Klotho System and Inflammation in Atherosclerotic Disease Ernesto Martín, Javier Donate, José Cruz, Angel López-Castillo, Sergio Rodríguez, Purificación Cerro, Nayra Pérez-Delgado, Anabel Rodriguez, Virginia Dominguez, Carmen Mora, Juan F. Navarro-Gonzalez. *Univ Hospital Nuestra Señora de Candelaria (Santa Cruz de Tenerife).*

Background: Several studies have shown the cardiovascular implications of the FGF-23/Klotho system. The aim of this work was to characterize the relationship between FGF-23/Klotho system, atherosclerotic disease and the underlying inflammatory process.

Methods: Forty-five patients with atherosclerotic vascular disease and 17 healthy organ donors (control group) were included in this work. The mRNA expression levels of *KLOTHO*, *FGF-23*, *TNF-α*, *IL-6* and *IL-10* were measured in vascular tissue samples and peripheral blood mononuclear cells (PBMC). Serum levels of KLOTHO, FGF-23 and IL-6 were also determined.

Results: Regarding vascular expression, *FGF-23* transcript was not detected in any individual in the control group, whereas it was present in 29 subjects (64.4%) with atherosclerosic vascular disease. *KLOTHO mRNA* levels were significantly lower in atherosclerotic patients ($P<0.05$). Regarding inflammatory cytokines, atherosclerotic patients had a lower expression of *IL-10* ($P<0.05$), with no differences in *IL-6* and *TNF-α*. Concerning gene expression in PBMC, atherosclerotic subjects had significantly lower mRNA levels of *KLOTHO* ($P<0.0001$) and *IL-10* ($P<0.001$), with higher expression of *TNF-α* ($P<0.001$). There were no differences for *IL-6* or *ADAM-17*. Finally, serum concentrations of KLOTHO and IL-6 were significantly lower in the atherosclerotic group ($P <0.0001$ and $P <0.05$, respectively).

Conclusions: These results indicate a relationship between vascular atherosclerotic disease and the regulation of FGF-23/KLOTHO system. The lower expression levles of *KLOTHO* in vessels and PBMCs, as well as the reduced serum concentrations of this protein, point to the atherosclerotic disease as a state of KLOTHO deficiency. In addition, *FGF-23* expression in vessels from atherosclerotic patients as compared with the lack of FGF-23 expression in control subjects might suggest that vascular tissue affected by the atherogenic process is a potential extra-bone source of this factor.

Funding: Government Support - Non-U.S.

TH-PO324

KLOTHO Expression in Different Vascular Territories and Its Relationship with Atherosclerosis Ernesto Martín, Javier Donate, Angel López-Castillo, Raúl Portas, Anabel Rodriguez, Sergio Rodríguez, Purificación Cerro, Nayra Pérez-Delgado, Carmen Mora, Juan F. Navarro-Gonzalez. *Univ Hospital Nuestra Señora de Candelaria (Santa Cruz de Tenerife).*

Background: The anti-aging factor Klotho has been related to protective effects on the vascular wall, while a decrease on its serum levels has been related with the presence and severity of coronary artery disease and an increased mortality in hemodialysis patients. The objectives of this study are (i) to determine the relationship between vascular expression of *KLOTHO* and the presence of atherosclerotic disease, and (ii) to assess potential differences in *KLOTHO* gene expression among different vascular territories.

Methods: Vascular tissue samples were collected from 44 patients with atherosclerotic disease under elective vascular surgery, and from 10 healthy organ donors (control group). Samples were obtained from different vascular territories: aorta (n=13), carotid (n=15) and femoral (n=16). *KLOTHO* gene expression levels were assessed by qPCR with TaqMan probes.

Results: In the overall group of patients with atherosclerotic disease, *KLOTHO* gene expression levels were significantly lower compared to healthy individuals [0.276 (-0,193 - 0.642) vs. 2.239 (0.017-2.756); $p<0.0001$]. Likewise, *KLOTHO* expression in every vascular territory was lower respect to controls (femoral, $p<0.05$; aorta and carotid, $p<0.01$). Within the group of patients affected of atherosclerosis, *KLOTHO* expression levels were significantly higher in the femoral territory respect to aorta [0,577 (0,29-0,93) vs. -0,053 (-0,17- 0,52); $p<0,01$] and to carotid [-0,234 (-0,46- 0,66); $p<0,01$], whereas there was no difference between the latter two regions.

Conclusions: The lower *KLOTHO* expression in patients with established vascular disease suggests a relationship between this factor and the pathophysiology of the atherosclerotic process. In addition, the differences observed in the expression of the *KLOTHO* gene among different vascular territories might suggest the existence of mechanisms of regulation dependent on the specific vascular territory.

Funding: Government Support - Non-U.S.

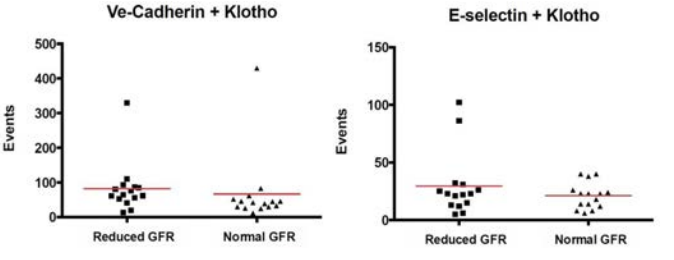
TH-PO325

Expression of Klotho on Endothelial Derived Microparticles Josefin L.G. Mörtberg, Fariborz Mobarrez, Kristina Lundwall, Hakan Wallen, Stefan H. Jacobson, Jonas Spaak. *Dept of Clinical Sciences, Danderyd Hospital, Karolinska Inst, Stockholm, Sweden.*

Background: Klotho is mainly expressed in the renal tubules, but also exists in a soluble form, where reduction is associated with renal disease, increased oxidative stress, endothelial dysfunction, and diffuse vascular calcification. Overexpression of Klotho promotes cardiovascular and renal protection. Endothelial derived microparticles (EMP) is considered a micro-biopsy of the endothelium. We investigated wheter Klotho is found on endothelial cells in patients with myocardial infarction and renal failure, by measuring Endothelial derived microparticles.

Methods: Blood samples were collected from 30 patients (21 men, 9 women), after acute myocardial infarction. Patients were stratified according to renal function, above or below eGFR 60 ml. Cystatin C eGFR was 81±7 ml/min/m^2, and 34±14 respectively in the groups. EMP:s were detected with antibodies towards CD144 (VE-cadherin), and also towards CD62E (E-selectin), a cell adhesion molecule expressed on cytokine activated endothelium. Klotho was identified on endothelial cells using a KLH conjugated polyclonal IgG antibody against human Klotho. All samples were analyzed using a Beckman Coulter Gallios flow cytometer and microparticles were defined as particles less than 1.0 µm in size.

Results: Our result indicate that Klotho is exposed on endothelial cells and on cytokine-activated vascular endothelium, (figure 1) without significant correlation with kidney function. There was no significant correlations between Klotho EMP levels and CRP, phospate, urea, urate, calcium, or urinary albumine excretion levels.



Conclusions: Klotho is found on endothelial cells and on cytokine-activated vascular endothelium, but levels do not correlate with kidney function. Further studies are warranted to investigate whether endothelial cells express trans-membrane Klotho, or Klotho receptors for soluble klotho.

Funding: Government Support - Non-U.S.

TH-PO326

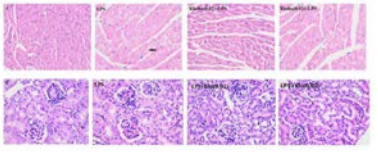
α-Klotho Alleviates LPS Induced Cardiorenal Syndrome Type 5 Chen Yu, Xi Liu. *Dept of Nephrology, Tongji Hospital, Tongji Univ School of Medicine, Shanghai, China.*

Background: Cardio-renal syndrome type 5occurs when an overwhelming insult leads to the simultaneous development of acute kidney injury and acute cardiac dysfunction. The α-klotho protein is a pleiotropic protein with a multitude of renal and extrarenal effects. Whether α-klotho can alleviate cardiorenal syndrome type 5is lack of research. We designed this study to study the effect and mechanism of α-klotho on cardiorenal syndrome type 5.

Methods: C57BL/6 micewere randomly assigned to following four groups: The CON group; the LPS group; the LPS+α-klotho (0.01mg/kg) group; and the LPS+α-klotho (0.02mg/kg) group. The dose of LPS is 10mg/Kg. Plasma creatinine, NGAL, BNP and troponin was measured at 24hours after LPS treatment, as same as myocardial apoptosis, inflammation, oxidation stress and endoplasmic reticulum stress levels.

Results: The result showed that Klotho gene was highly expressed in kidney but undetectable heart tissue. LPS induced the reduction of the klotho expression in kidney as early as 6 hours after LPS injection. The α-klotho protein (0.01~0.02mg/kg) reduced the levels of plasma creatinine, NGAL, BNP and troponin, and the protective effects were dose-dependent.

The α-klotho protein alleviates LPS induced cardiorenal syndrome type 5



α-klotho also reduced myocardial apoptosis and regulated the balance of proinflammation/anti-inflammation in both plasma and heart tissue. α-klotho reduced oxidative stress and increased endoplasmic reticulum stress level in myocardial tissue.

Conclusions: The α-klotho protein ameliorated the cardiac injury and renal injury in cardiorenal syndrome type 5 induced by LPS. The mechanism included reducing myocardial apoptosis and oxidative stress, regulating inflammatory cytokine and improving endoplasmic reticulum stress levels.

Funding: Government Support - Non-U.S.

TH-PO327

p66Shc Mediates ET-1 Induced Intracellular Calcium Mobilization in Renal Resistance Arteries Bradley S. Miller,[1] Oleg Palygin,[2] Alexander Staruschenko,[2] Andrey Sorokin.[1] *[1]Medicine Div of Nephrology, Cardiovascular Center, Medical College of Wisconsin, Milwaukee, WI; [2]Physiology, Medical College of Wisconsin, Milwaukee, WI.*

Background: Increased renal perfusion pressure activates renal autoregulation mediated in part by vasoconstriction of smooth muscle cells of preglomerular vessels, leading to reduction of blood flow to normal levels. The Dahl salt-sensitive (SS) rat model of hypertension is characterized by loss of renal vascular responsiveness upon increased dietary salt intake despite elevated levels of circulating Endothelin-1 (ET-1), a potent vasoconstrictor peptide. ET-1 mediates smooth muscle cell (SMC) contraction via elevated intracellular calcium signaling. In addition, ET-1 induction of p66Shc phosphorylation on serine 36 is essential for the promotion of mitochondrial oxidative stress, a potential factor in vascular dysfunction. The purpose of this study was to determine the role of p66Shc in ET-1 induced intracellular calcium mobilization in intact smooth muscle cells in isolated renal microvessels.

Methods: p66Shc knockout and p66Shc Ser36Ala substitution knock-in rats were generated on the SS genetic background using engineered Zinc Finger nucleases. Renal microvessels dissected from hypertensive WT SS rats and p66Shc mutant rat strains were loaded with calcium-sensitive fluorescent dye Fluo4-AM. Localization and quantification of calcium signaling was evaluated using two-photon excitation microscopy.

Results: We report that SMC, embedded in vascular wall of renal resistance arteries from p66Shc knockout rats, demonstrate an elevated level of intracellular calcium concentration in response to ET-1, when compared to SMC of renal resistance arteries isolated from wild type SS rats.

Conclusions: Our data suggest that the increased expression of p66Shc contributes to reduced vascular responsiveness which accompany the progression of salt-sensitive hypertension in SS rats through p66Shc-dependent modulation of intracellular calcium levels. It appears that p66Shc inhibitory effect occurs independently of its mitochondrial action. The p66Shc deficiency restores or enhances intracellular calcium levels, resulting in increased vascular response to ET-1.

Funding: NIDDK Support

TH-PO328

Cholecalciferol Supplementation Improves Vascular Function in Non-Diabetic Chronic Kidney Disease Patients with Vitamin D Deficiency: A Self-Controlled Study Ashok Kumar Yadav,[1] Vivek Kumar,[1] Manphool Singhal,[2] Vivekanand Jha.[1,3] *[1]Nephrology, PGIMER, Chandigarh, India; [2]Radiodiagnosis, PGIMER, Chandigarh, India; [3]George Inst for Global Health, New Delhi, India.*

Background: Vitamin D deficiency is common and associated with mortality in chronic kidney disease (CKD) patients. Its supplementation might improve endothelial and vascular function in patients with CKD. We studied the influence of vitamin D supplementation on vascular function and inflammatory biomarkers in patients with non-diabetic CKD stage 3-4 and vitamin D deficiency.

Methods: In this self-controlled study, 31 patients with non-diabetic stage 3-4 CKD and vitamin D deficiency [serum 25(OH)D levels <20 ng/ml] were assessed at 0, 16, and 32 weeks. All patients received directly observed cholecalciferol supplementation (300,000 I.U.) at 16 and 24 weeks. Endothelium dependent brachial artery flow mediated dilatation (FMD), pulse wave velocity (PWV) and circulating biomarkers were analyzed at 0, 16 and 32 weeks. The primary outcome was change in FMD at 16 and 32 weeks.

Results: 25(OH)D levels remained similar to baseline at 16 weeks but significantly increased at 32 weeks (13.0±5.4, 15.7±9.8 and 34.7±15.2 ng/ml at 0, 16 and 32 weeks, respectively, p<0.0001). FMD, PWV and biomarkers were similar at 0 and 16 weeks (table 1). However, after cholecalciferol supplementation at 16 and 24 weeks, FMD increased significantly at 32 weeks (p<0.0001). Similarly, significant changes in $1,25(OH)_2D$, IL-6, FGF-23 and PWV were seen at 32 weeks.

	Baseline	16 weeks	P value	32 weeks	P value
$1,25(OH)_2D$ (pg/ml)	22.3±13.9	21.4±20.2	0.974	40.1±18.9	**0.001**
iFGF-23 (pg/ml)	82.7±58.1	70.3±50.5	0.151	48.9±45.6	**0.005**
IL-6 (pg/ml)	5.5±5.8	5.0±4.0	0.653	3.3±2.5	**0.002**
E-selectin (ng/ml)	57.9±25.2	54.2±22.0	0.281	51.6±18.0	0.581
vWF (mU/ml)	1128±656	1076±379	0.689	1225±253	0.103
FMD (%)	7.6±2.3	8.0±2.7	0.231	13.8±4.3	**<0.0001**
PVW (ng/ml)	7.9±1.4	8.0±1.3	0.092	7.3±1.3	**0.005**

Conclusions: Cholecalciferol supplementation corrected vitamin D deficiency, improved FMD and PVW, and decreased serum levels of FGF-23 and IL-6 in subjects with non-diabetic CKD.

Funding: Government Support - Non-U.S.

TH-PO329

The Impact of Dietary Phosphate on Erectile Function in an Experimental Model of CKD Mandy E. Turner, Melanie Wilson, Cynthia M. Pruss, Emilie C. Ward, Paul S. Jeronimo, Bruno Svajger, Rachel M. Holden, Martin P. Petkovich, Michael A. Adams. *Biomedical and Molecular Sciences and Medicine, Queen's Univ, Kingston, ON, Canada.*

Background: CKD patients are at a markedly increased risk of CVD and CVD-related mortality. Phosphate dysregulation and pathological consequences, such as vascular calcification(VC), are key to this increased CVD risk. Erectile dysfunction(ED) is one of the earliest predictors CVD and ~80% of CKD patients self-report ED. Erectile function is a complex process dependent endothelial and vascular health, both of which are negatively impacted by phosphate. In a model of CKD, we sought to determine the impact of increased dietary phosphate on the development of ED and VC.

Methods: CKD was induced in male Sprague-Dawley rats(N=51, 15 wks) for 5 weeks using a 0.5% PO_4 0.25% adenine diet. They were then stratified by serum creatinine and phosphate in to either low(0.5%,N=14), medium(1%,N=13) or high (1.5%,N=15) phosphate diets for 3 weeks. ED was characterized using a pharmacological erectile bioassay (apomorphine 80ug/kg; no. of erectile responses(ER) per 30 min). Serum PTH, FGF23, creatinine, and phosphate were measured weekly. At sacrifice, vessels were harvested and calcium was measured. Urinary NO metabolites were measured in 10 animals.

Results: During the induction of CKD(0-5 wks), animals incurred a severe decline in erectile function (3.0±1.5 to 1.2±1.2 ER, p<0.001), while controls were constant. Serum phosphate was significantly elevated at week 3 despite low dietary phosphate. At week 5, the severity of ED was associated with higher serum phosphate but not with increased FGF23 or PTH. Increasing dietary phosphate (1.0, 1.5%) elevated serum phosphate, aortic and pudendal VC and decreased NO metabolites(p<0.05), however, there was no difference in ER between phosphate groups.

Conclusions: Increased serum phosphate was linked to early ED, however, increasing dietary phosphate at late stages of CKD did not have an impact on already declined erectile function. This occurred despite the higher phosphate diets worsening VC and markers of endothelial dysfunction. These results suggest that early interventions in CKD, possibly in phosphate, are more likely to impact ED.

Funding: Pharmaceutical Company Support - OPKO Health Renal, Government Support - Non-U.S.

TH-PO330

Transcriptomic Analysis Reveals Molecular Mechanisms Underlying the Beneficial Effect of Lipoprotein-Apheresis (LA) in Blunting Atherosclerosis Progression in Familiar Hypercholesterolemia

Simona Simone,[1] Annarita Chieti,[1] Maria Grazia Zenti,[3] Matteo Accetturo,[1] Paola Pontrelli,[1] F. Rascio,[2] Gianluigi Zaza,[3] Antonio Lupo,[3] Loreto Gesualdo,[1] Giuseppe Grandaliano,[2] Giovanni B. Pertosa.[1] *[1]Univ of Bari; [2]Univ of Foggia; [3]Univ of Verona.*

Background: LA is a potentially valuable treatment applied to conventional therapy-resistant hypercholesterolemic patients. Several clinical studies suggest that LA may reduce the recurrence of cardiovascular events, but the molecular mechanisms underlying this effect are still unknown. The aim of the study was to identify the modulation of peripheral blood mononuclear cell (PBMC) transcriptomic profile induced by LA.

Methods: The transcriptomic profile was evaluated in PBMCs isolated from 6 FH patients before and after LA by Microarray (Agilent Technologies). The results were evaluated by statistical (Genespring software) and functional pathway analysis (Ingenuity Pathway Analysis, IPA). The transcriptomic data were validated by real-time PCR in an independent testing-group (n=10).

Results: Using a fold-change (FC)≥2, we demonstrated that LA modulates the expression of 240 genes. The top canonical pathways were: communication between innate and adaptive immune cells (p=.00004), natural killer cell signaling (p=.00004) and atherosclerosis signaling (p=.0003). Many pro-inflammatory cytokines involved inthe development and progression of the atherosclerotic process were significantly down-regulated: Interleukin 1 (IL-1 FC=-2.97), IL-6 (FC=-2.07), IL-8 (FC=-3.56) ed Amphiregulin (AREG FC=-3.5). Quantitative real-time PCR confirmed that IL-1 (-84%; p=0.0004) IL-6(-69%; p=0.01) IL-8 (-75%; 0.005) ed AREG (-96% p=0.0002) were down-regulated after LA.

Conclusions: Our data suggest that LA may contribute to cardiovascular risk reduction through the modulation of different pathways involved in the progression of atherosclerotic disease and improvement of microcirculation. This observation might open new perspectives in the prevention of cardiovascular risk in patients with FH.

Funding: Government Support - Non-U.S.

TH-PO331

Adipose-Derived Mesenchymal Stem Cells (MSCs) from Human Atherosclerotic Renovascular Disease (RVD) Have Increased DNA Damage and Lower Angiogenesis as Compared with Normal Kidney Donors That Can Be Modified by Hypoxia

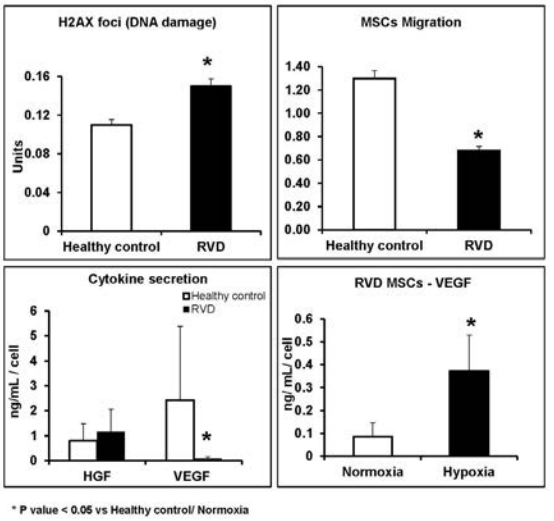
Ahmed Saad, Allan B. Dietz, Sandra Herrmann, LaTonya J. Hickson, Andre J. Van Wijnen, Lilach O. Lerman, Stephen C. Textor. *Mayo Clinic.*

Background: MSCs support angiogenic and immuno-modulatory processes. Whether these properties are modified in older patients with RVD is not known. Hypoxic conditions modify functional and growth characteristics of MSCs and may affect their role in ischemic kidney tissue. We tested the hypothesis that MSCs from RVD patients differ from MSCs from healthy kidney donors, and that hypoxia changes their functional and molecular properties to promote angiogenesis.

Methods: MSCs obtained from adipose tissue of 11 patients with RVD (age =74.5 ±3.9) and 10 healthy subjects (age= 51.2±16.7) cultured under normoxia (20% O_2) or hypoxia (1% O_2) for 3-4 days. Expression of genes and microRNAs analyzed using RNA-sequencing and rt-Quantitative PCR, H2AX and MSC migration using western blot. Secretion of VEGF and HGF was quantified in supernatant using ELISA, and apoptosis using Annexin-V flow cytometry.

Results: MSCs from RVD patients proliferated normally, but exhibited increased DNA damage and reduced migration. VEGF protein secretion was lower in RVD MSCs ($p< 0.05$) while HGF was slightly higher. Both patterns were reversed during growth under hypoxic conditions.

Figure



* P value < 0.05 vs Healthy control/ Normoxia

Hypoxia upregulated expression of pro-angiogenic mRNAs in MSCs (VEGF, FGF, STC and ANGPTL4) and downregulated expression of related miRNAs (e.g., miR-15a, miR-16, miR-93 and miR-424) whereas miR-210 was upregulated.

Conclusions: Adipose derived MSCs from older patients with RVD had more DNA damage and reduced migration and angiogenic properties, yet hypoxia stimulated pro-angiogenic responses by increasing expression of angiogenic genes and VEGF secretion. These data support a potential role for hypoxic preconditioning as a maneuver to enhance the angiogenic potency of MSCs in patients with RVD.

Funding: NIDDK Support

TH-PO332

Intraarterial Autologous Mesenchymal Stem Cells (MSC) Increase Renal Blood Flow and Preserve Kidney Function in Patients with Atherosclerotic Renovascular Disease (RVD)

Ahmed Saad, Sandra Herrmann, Alfonso Eirin, LaTonya J. Hickson, Michael A. Mckusick, Allan B. Dietz, Lilach O. Lerman, Stephen C. Textor, James Glockner, Andre J. Van Wijnen. *Mayo Clinic.*

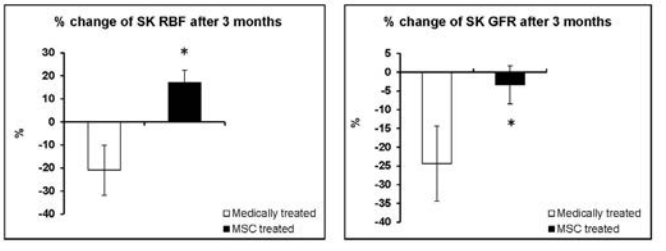
Background: Atherosclerotic RVD reduces renal blood flow (RBF), GFR and accelerates both hypertension and post-stenotic kidney (SK) tissue injury. Preclinical studies indicate that MSCs stimulate angiogenesis and modify immune function in experimental RVD. We tested the hypothesis that autologous MSCs would be safe and improve SK perfusion and function in a phase-I study of patients with RVD.

Methods: Adipose derived MSCs were collected from 14 RVD patients and expanded in platelet lysate media. Inpatient studies performed during fixed Na+ intake and ACE/ARB Rx before and 3 months after unilateral intra-arterial injection of 1.0-2.5 x 10^5/kg MSCs into the SK. Patients with RVD treated with standardized medical therapy alone (n=14), matched for age, severity of stenosis, and GFR, served as a control group. SK cortical perfusion and RBF were measured using multidetector CT, GFR by iothalamate clearance, and renal tissue oxygenation by BOLD-MRI at 3T.

Results: Age, GFR, and degree of stenosis did not differ between groups. MSC infusions were well-tolerated with no adverse effects. SK-RBF and cortical perfusion increased after 3 months ($p<0.05$). Fractional hypoxia (%R2*>30 sec-1) decreased in MSCs group. Iothalamate SK-GFR remained stable during 3 months after MSC, but fell in the control group.

	MSCs + Medical Rx (N=14)		*Medically Rx alone (N=14)*	
Age (years)	74.4 ± 3.4		71.1 ± 6.9	
Baseline iothalamate clearance GFR (mL/min)	51.2 ± 18.6		54.9 ± 20.4	
SK artery U/S Doppler velocity (cm/sec)	303.7 ± 64.5		331 ± 119.4	
Stenotic kidney	***Baseline***	***3 months***	***Baseline***	***3 months***
Cortical perfusion, mL/min/mL tissue	2.02 ± 0.69	2.4 ± 1*	2.1 ± 0.76	2.0 ± 0.53
RBF, mL/min	151.8 (63.7, 222)	185.5 (72.3, 259)*	132.5 (96, 255)	128.1 (77.2, 233)
Cortical flow, mL/min	125.6 (54.7, 192)	138.3 (60.3, 226)*	114 (75.7, 221)	106 (54, 186.3)
Medullary flow, mL/min	31(14.8, 38.9)	29.4(14.5, 36.9)	26.3(11.5, 42.3)	20.3(17.8, 36.4)
Renal hypoxia (% R2* > 30 sec^{-1})	12.1 (3.3, 17.8)	6.8 (1.8, 12.9)*	10 (6.3, 25.1)	9.6 (2.4, 37.7)

*P< 0.05 vs baseline (Wilcoxon signed-rank test). Values are presented as mean ± SD or median (IQR)



* P<0.05 vs Medically treated kidneys (Wilcoxon signed-rank test)

Conclusions: In this "first-in-man" study in 14 patients with atherosclerotic RVD, a single infusion of MSCs into the SK increased cortical perfusion and RBF after three months. Increased perfusion was associated with reduction in tissue hypoxia and preserved GFR. Our results demonstrate the capability of MSCs to improve oxygenation and RBF in the human kidney in-vivo and support a potential role for MSCs in the management of ischemic renal disease.

Funding: NIDDK Support

TH-PO333

Notch Signaling Mediates Indoxyl Sulfate-Induced Atherogenesis in Chronic Kidney Disease

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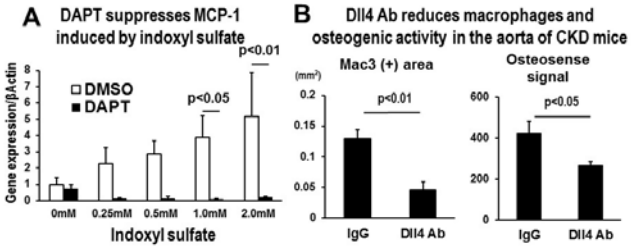
Background: Chronic kidney disease (CKD) increases cardiovascular risk, however, the mechanisms of atherogenesis in CKD remain obscure. We previously demonstrated that the Notch signaling ligand Delta-like 4 (Dll4) promotes macrophage activation. We investigated the causal role of the Dll4-Notch pathway in vascular inflammation in CKD.

Methods: We examined pro-inflammatory effects of indoxyl sulfate in human primary macrophages and C57BL/6 mice. To evaluate the role of Notch signaling in atherogenesis in CKD, we performed 5/6 nephrectomy in high fat-fed LDL receptor-deficient (Ldlr-/-) mice and administered Dll4 neutralizing antibody (Ab) or control IgG for 19 weeks (n=13-14/group).

Results: [In vitro] In human macrophages, clinically relevant concentrations of indoxyl sulfate (0.5-1.0 mM) induced the expression of pro-inflammatory molecules IL-1β, TNFα, and MCP-1 and Notch-related genes (e.g., Dll4, Notch1, Hey2), which was suppressed by Notch inhibition with the γ-Secretase inhibitor DAPT (fig.A). [In vivo] Indoxyl sulfate administration in C57BL/6 mice (100mg/kg/day, 7 days) induced activation of peritoneal macrophages, which Dll4 Ab treatment suppressed. In Ldlr-/- mice, 5/6 nephrectomy induced IL-1β, IL-6, TNFα, and MCP-1 in splenic macrophages, and accelerated aortic atherosclerosis and calcification. Dll4 blockade reduced the size of atherosclerotic lesions and macrophage accumulation as compared to IgG treatment (fig.B). Dll4 Ab also suppressed aortic calcification as gauged by alkaline phosphatase activity and molecular imaging of osteogenic activity (OsteoSense, fig.B).



Conclusions: Dll4-Notch signaling mediates indoxyl sulfate-induced macrophage activation and promotes atherosclerotic plaque inflammation and calcification in CKD.

TH-PO334

Atherosclerosis a Circulatory Disease: The Pivotal Role of Primed Neutrophils Eynav Kliger,[1,3] Shifra Sela,[1,3] Ronit Geron,[2,3] Galina Shapiro,[1] Batya Kristal.[2,3] *[1]Eliachar Research Laboratory, Galilee Medical Center, Nahariya, Israel; [2]Nephrology Dept, Galilee Medical Center, Nahariya, Israel; [3]Bar-Ilan Univ Faculty of Medicine in the Galilee, Safed, Israel.*

Background: Endothelial dysfunction and monocytes transmigration and differentiation underlie the development of atherosclerosis. Increased counts and priming of circulating neutrophils are associated with atherosclerosis however, the role of neutrophils in the accelerated atherosclerotic process of hemodialysis (HD) patients is still unclear. We hypothesize that atherosclerosis is a circulatory disease, where peripheral primed neutrophils activate monocytes and endothelium concomitantly, at the blood-tissue interface. Our aims were to examine monocytes transmigration through endothelial layer and their post-transmigration activation, induced ex-vivo by primed neutrophils, separated from HD patients.

Methods: A unique ex-vivo co-culture system of 3 cell types was developed in this study, enabling interactions among: primary endothelial cells (HUVEC), monocytes (THP-1, cell line) and in-vivo primed neutrophils from HD and Healthy Controls (HC), in order to mimic the initiation of the atherosclerotic process. The interactions among these cells were examined at the cellular, protein and gene expression levels.

Results: Pre-exposed HUVEC to HD/HC neutrophils showed a significant monocytes transmigration yield, 120-170% above HC. Monocyte exposure to HD neutrophils induced pre- and post-transmigration activation compared to HC. When the 3 cell types were co-cultivated at the same time, MCP-1 protein levels released from HUVEC, activation markers on HUVEC (CD54, CX3CL1) and monocytes (CX3CR1, CCR2) were increased. We have found that when the 3 cell types were co-cultivated with HD neutrophils at the same time, monocytes transmigration yield decreased to 70% (compared to HC) due to adherence and aggregation of monocytes to HUVEC.

Conclusions: We conclude that peripheral primed neutrophils play a pivotal role in the initiation of the atherosclerotic process suggesting atherosclerosis as a circulatory disease. Primed neutrophils can be used as a mediator and a biomarker of atherosclerosis even before plaque formation.

TH-PO335

Cardiac and Inflammatory Biomarkers and Their Role in the Pathogenesis of Heart Failure in ESRD Ryan Mcmillan,[1] Vinod K. Bansal,[2] Debra Hoppensteadt,[1] Jawed Fareed.[1] *[1]Pathology, Loyola Univ Medical Center, Maywood, IL; [2]Nephrology, Loyola Univ Medical Center, Maywood, IL.*

Background: Heart failure (HF) is highly prevalent in patients with End-Stage Renal Disease with a presence of approximately 40 %. HF is characterized by left ventricular hypertrophy, diastolic and systolic left ventricular dysfunction and cardiomyopathy. The purpose of this study was to determine the role of cardiac and inflammatory biomarkers in the pathogenesis of HF in ESRD patients.

Methods: Blood samples from maintenance hemodialysis patients were collected and stored at -70° C. Fifty plasma samples from healthy individuals were used as control. These samples were used to profile KIM-1, NT-pro BNP, NGAL, IL-18, PDGF, Vitamin D, PTH, Endothelin, Endocan, MPTF, Heparin anti Xa, Lp(a) using commercial sandwich and competitive ELISA kits and assays (R&D Systems, Minneapolis, MN | RayBiotech, Norcross, GA | Hyphen Biomed, Neuville-sur-oise, France).

Results: All biomarkers, except PDGF, Endothelin and Vitamin D, were increased in ESRD compared to normal ($P < 0.05$). Vitamin D was decreased in patients with ESRD compared to normal ($P < 0.05$). HF patients with ESRD, as compared to non-HF patients with ESRD, had significantly elevated NT-pro-BNP ($P = 0.0194$ | % change = 52.9) and KIM-1 ($P = 0.0485$ | % change = 58.5%). There were no differences found between age groupings, except <60 y.o KIM-1 vs 60-69 y.o KIM-1. NT-pro-BNP in ESRD patients with HF was found to correlate with K+ ($P = 0.023$ | $R = -0.39$), Ca+ ($P = 0.029$| $R = -0.38$), and Heparin anti Xa ($P = 0.045$ | $R = 0.35$). KIM-1 in ESRD patients with HF was found to correlate with Creatinine ($P = 0.0175$ | $R = -.41$), EGFR ($P = 0.008$ | $R = 0.45$), Phosphate ($P = 0.002$ | $R = -0.51$), Intact PTH ($P = 0.043$ | $R = -0.36$), Calcium Phosphate Product ($P = 0.002$ | $R = -0.52$), and Vitamin D ($P = 0.037$ | $R = 0.36$).

Conclusions: Elevated plasma NT-pro-BNP and KIM-1 in all of the ESRD patients and ESRD patients with HF suggest that natriuretic peptides and KIM-1 may contribute to the pathogenesis of HF in ESRD patients. Elevated NT-pro-BNP further supports previous studies demonstrating NT-pro-BNP's potential diagnostic and prognostic utility.

TH-PO336

Glomerular Hyperfiltration Is Associated with Elevated Urinary Mitochondrial-DNA Copy Number in African American Hypertensive Patients Alfonso Eirin,[1] Ahmed Saad,[1] John R. Woollard,[1] Luis A. Juncos,[2] Hui Tang,[1] Amir Lerman,[1] Lilach O. Lerman.[1] *[1]Mayo Clinic; [2]Univ of Mississippi.*

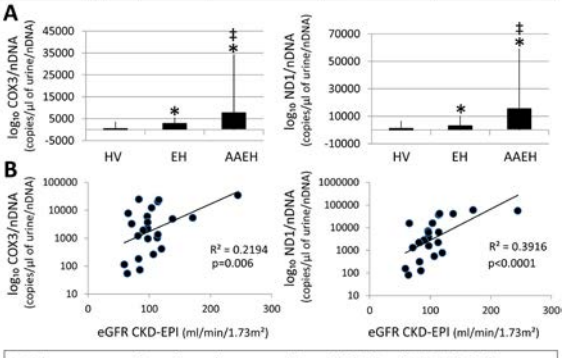
Background: Glomerular hyperfiltration may contribute to the high incidence of renal disease in African Americans essential hypertensive (AAEH) patients, but the precise mechanisms responsible for renal injury have not been elucidated. Mitochondria are important determinants of renal injury in hypertension, and increased levels of mitochondrial DNA (mtDNA) in the urine may indicate renal mitochondrial injury. We hypothesized that urine mtDNA copy numbers would be higher in AAEH compared to Caucasian essential hypertensive (EH) patients.

Methods: We prospectively measured systemic and urinary copy number of the mtDNA genes COX3 and ND1 by quantitative-PCR in Caucasian EH and AAEH patients during constant sodium intake and anti-hypertensive regimens, and compared them with healthy volunteers (HV) (n=23 each). Urinary mtDNA levels were corrected to the nuclear control gene RNAse-P and expressed as mtDNA/nDNA to identify mitochondrial-specific cellular damage.

Results: Blood pressure was similarly elevated in EH and AAEH, yet body mass index (BMI) and estimated glomerular filtration rate (eGFR) were higher and age lower in AAEH versus HV and EH (Table). Urinary (but not plasma) COX3 and ND1 were higher in EH compared to HV, and further elevated in AAEH patients (Figure). In AAEH patients, urinary COX3 and ND1 directly correlated with eGFR. In multivariate analysis, eGFR remained the only predictor of elevated urinary COX3 and ND1 levels.

Conclusions: Urinary fragments of the mitochondrial genome are elevated in AAEH patients and correlate with glomerular hyperfiltration. These results are consistent with mitochondrial injury that may aggravate renal damage and accelerate hypertension-related morbidity/mortality rates in AAEH.

	HV	EH	AAEH
Age (years)	67 (55-76)	67 (54-72)	50 (47-53)*‡
Gender (F/M)	12/11	13/10	5/18*‡
BMI (kg/m²)	26.4 (23.4-29.6)	26.4 (23.9-30.6)	31.6 (25.9-37.1)*‡
Mean arterial pressure (mmHg)	83.9±9.1	93.3±10.7*	98.4±13.7*
eGFR CKD-EPI (ml/min/1.73m²)	76.5 (66.4-85.0)	85.6 (64.0-94.5)	97.4 (82.6-114.1)*‡
Proteinuria (mg/24h)	63.0 (26.0-112.0)	55.0 (37.8-111.3)	48.0 (30.0-69.1)



A: Urinary copy number of cytochrome-c oxidase-3 (COX3) and NADH dehydrogenase subunit-1 (ND1) in HV, EH, and AAEH patients. B: Urinary COX3 and ND1 copy number directly correlated with eGFR. *p≤0.05 vs. HV.*p<0.05 vs. HV; ‡p<0.05 vs. EH

Funding: NIDDK Support

TH-PO337

VE-PTP Inactivation Enhances TIE2-AKT-ENOS Signaling Lowering Blood Pressure and Elevating GFR Isabel Anna Carota,[1,2] Christina S. Bartlett,[1] Rizaldy P. Scott,[1] Sunday S. Oladipupo,[2] Yazan M. Alia,[1] Matthew D. Breyer,[2] Susan E. Quaggin.[1] *[1]Div of Nephrology,Feinberg Cardiovascular Research Inst, Northwestern Univ, Chicago, IL; [2]Bio TDR, Eli Lilly & Co, Indianapolis, IN.*

Background: Chronic kidney disease affects 26 million Americans. Hence, discovery of novel therapeutic targets to slow its progression is urgently needed. Disruption of the angiopoietin-TIE2 signaling pathway occurs in CKD and is often associated with worsened outcomes in inflammatory diseases such as diabetic nephropathy and macular edema,

and sepsis. An imbalance between TIE2 ligands, specifically an increase in antagonistic ANGPT2 at the expense of agonistic ANGPT1 levels, is linked to vascular destabilization, leakage, and inflammation. We evaluated how augmentation of TIE2 activation, through genetic deletion of its inactivating phosphatase VE-PTP (PTPRB), affects renal function and blood pressure.

Methods: Using an inducible knockout mouse model, we induced deletion of VE-PTP in neonates and assessed potentiation of TIE2 autophosphorylation. Glomerular filtration rates (GFR) were determined by FITC-sinistrin clearance while blood pressure (BP) values were measured by tail cuff plethysmography. Nitric oxide production was reduced in mice by blocking the enzyme ENOS through a week-long administration on the drug L-NAME in drinking water.

Results: TIE2 phosphorylation is elevated in VE-PTP iKO mice versus control littermates. GFR increased 53.1±9% while systolic BP dropped 25±8% in VE-PTP iKO mutants relative to control cohorts. AKT and ENOS phosphorylation were also higher in VE-PTP iKO mutant kidneys suggesting that increased NO production might underlie altered GFR and BP. Consistently, L-NAME treatment normalized GFR and BP values in VE-PTP iKO mutants to wild-type control levels.

Conclusions: Genetic loss of VE-PTP causes increased TIE2 activity leading to sustained AKT-dependent ENOS signaling and eventual rise in circulating levels of NO. Loss of VE-PTP thus promotes vasodilation and vascular compliance resulting in lower BP and enhanced renal blood flow and glomerular filtration. Targeted inhibition of VE-PTP therefore holds promise in maintaining renal function in conditions such as CKD.

Funding: Other NIH Support - RC1HL124120, Pharmaceutical Company Support - Eli Lilly & Company

TH-PO338

Novel Mechanism for Cardiovascular Protective Effect of Vitamin D and ACE-Inhibitors in Chronic Kidney Disease: Correction of Impaired Cholesterol Efflux Induced by Plasma from Patients with Chronic Kidney Disease Nobuyuki (Bill) Miyawaki, Nicolle Marie Siegart, Heather Anne Renna, Hirra A. Arain, Farah Daccueil, Joseph Mattana, Joshua De Leon, Allison B. Reiss. *Medicine, Winthrop Univ Hospital, Mineola, NY.*

Background: In chronic kidney disease (CKD) and dialysis, ACE-inhibitors (ACEi) and Vitamin D (Vit D) reduce mortality/cardiovascular disease (CVD) risk while statins lose efficacy. Hence the atherosclerotic mechanism with advancing CKD likely differs from the general population. Macrophage lipid handling defect may be a pivotal proatherogenic factor in CKD. This study aims to detect changes in reverse cholesterol transport gene expression and foam cell accumulation in the setting of CKD in the presence and absence of Vit D or ACEi.

Methods: Following THP-1 human macrophage (10^6/ml) incubation for 24h with pooled plasma from 5 CKD Stage 4+5 patients or with control media ± Vit D (calcitriol, 10^{-8} M), or ACEi (enalapril, 50 μM), mRNA was isolated and reverse transcribed. The resulting cDNA was subjected to quantitative real-time PCR using specific primers for ATP binding cassette transporter (ABC)A1 and G1 (cholesterol efflux proteins). Foam cell quantification using Dil-acetylated-LDL with VectaShield mounting medium was used.

Results: CKD plasma suppressed ABCA1 in macrophages while concurrent Vit D restored ABCA1 mRNA, increasing it by 44±2.8% ($p<0.0001$). Concurrent exposure to CKD plasma + ACEi increased ABCA1 dramatically by 148±4.9% ($p<0.001$). ABCG1 expression did not increase (8±5.8%, nonsig) with Vit D, but increased 52±15% ($p<0.0001$) with ACEi. In control media, neither Vit D nor ACEi elicited significant response. In macrophages exposed to CKD plasma, foam cell accumulation decreased with addition of Vit D by 54±22% ($p<0.01$).

Conclusions: This is the first direct demonstration of an atheroprotective mechanism from Vit D and ACEi in the CKD milieu. ACEi and Vit D each promote cholesterol efflux with ACEi affecting ABCA1 and G1, while Vit D restored ABCA1 alone. Vit D reduced foam cell accumulation; ACEi study is planned. Further studies of mechanism, synergy of Vit D + ACEi and cholesterol handling in CKD are planned. This novel insight may define viable therapeutic targets.

Funding: Private Foundation Support

TH-PO339

Differential Role of Vascular Contractile Reactivity in Salt Wasting- and Salt Restriction-Induced Hypotension Saeed Alshahrani,[1,2] Robert Rapoport,[1] Manoocher Soleimani.[1,2] *[1]Pharmacology and Cell Biophysics, Univ of Cincinnati, Cincinnati, OH; [2]Nephrology and Hypertension, Univ of Cincinnati, Cincinnati, OH.*

Background: Although both salt wasting and salt restriction associated with Na-Cl-Co-transporter (NCC) dysfunction result in hypotension, whether decreased vascular contractility *per se* contributes to the hypotension in these models of volume depletion has not been entertained. This study investigated vascular contractility in mouse aorta in models of 1) sodium wasting due to double knockout (KO) of NCC and pendrin (the apical chloride/bicarbonate exchanger in B-intercalated cells) and 2) NCC KO with salt restricted diet, both of which are associated with hypotension.

Methods: To determine vascular contractility, aorta was removed from 8-12 months male and female mice, and 4-5 mm ring segments placed in an isometric contractile apparatus under optimal resting tension of 3 g-force. Vessels were then challenged with maximal or near maximal agonist concentrations.

Results: Maximal contraction of aorta segments to KCl and phenylephrine in the NCC/pendrin double KO compared to wild type were decreased by 30% and 55%, respectively. Sensitivity to these agents remained unaltered. In contrast, maximal contractions to KCl, and to phenylephrine, were similar in NCC KO with and without salt restricted diet and sensitivity also remained unchanged.

Conclusions: These findings suggest that decreased vasoreactivity associated with severe salt wasting contributes to the hypotension. The decreased reactivity occurs post receptor and does not involve membrane hyperpolarization.We suggest that compensatory vasoconstriction due to elevated circulating constrictors (angiotensin II) in response to hypovolemia may result in lowered amounts of contractile proteins while constrictor mechanisms remain intact. Lack of decreased vasoreactivity under conditions of NCC dysfunction and salt restriction reflect lower levels of circulating constrictor factors due to less severe hypotension and volume depletion.

Funding: VA Support

TH-PO340

Role of AT1a Receptor in 2K1C Model of Renovascular Hypertension and Its Impact on Renal ACE2 and NEP Protein Expressions Nadja Grobe, Laale F. Alawi, Rucha Fadnavis, Khalid M. Elased. *Pharmacology & Toxicology, Wright State Univ, Dayton, OH.*

Background: Angiotensin (Ang) II is the major biologically active peptide of the renin angiotensin system (RAS). Elevated formation of Ang II contributes to initiation and progression of chronic kidney disease via its action as a vasoconstrictor through binding to the Ang II type 1 receptor (AT1R). Ang II is antagonized by the vasodilator Ang (1-7), partly generated by angiotensin converting enzyme 2 (ACE2) and neprilysin (NEP). The two-kidney, one clip (2K1C) Goldblatt model is an experimental approach designed to mimic renovascular hypertension. We tested the hypothesis that renovascular hypertension in the 2K1C model is mediated by AT1AR and investigated its role on renal ACE2 and NEP.

Methods: For blood pressure (BP) measurements, a radiotelemetric probe was inserted into the left carotid artery of $AT1_AR$ knockout (KO) and wild type (WT) mice. 2K1C was induced by constricting the left renal artery using a u-shaped silver clip leaving a 0.12 mm gap for ischemic blood flow. Histochemistry, Immunofluorescence, Western blot, and RAS enzyme assays were used to study renal histology, protein expression and activity.

Results: At baseline, BP was significantly lower in KO compared to WT (90.4± 8.4 mm Hg vs. 152.1± 5.9 mm Hg, $p<0.05$). BP measurements revealed a significant increase of 46.1±3.6 mm Hg in 2K1C WT compared to 2K1C KO (145.3 ± 12.9 mm Hg vs 92.3 ± 6.4 mmHg, $p<0.05$). Renal pathologies were exacerbated in the 2K1C model as revealed by a significant increase in mesangial expansion and renal fibrosis. Immunofluorescence demonstrated that ACE2 and NEP were mainly co-localized in the proximal and distal renal tubules. Western blot analysis showed renal ACE2 and NEP were significantly reduced in clipped 2K1C kidneys in both WT and KO compared to the unclipped kidneys or to sham controls. However, renal and urinary ACE2 activity was not altered by 2K1C.

Conclusions: Taken together, these results suggest that renovascular hypertension are mediated via $AT1_AR$, and that the receptor has no impact on the decreased expression of renal ACE2 and NEP in renovascular hypertension.

TH-PO341

Impact of Soluble Epoxide Hydrolase Inhibition on the Cardiovascular Consequences of Chronic Kidney Disease Dominique Guerrot,[1,2] Clothilde Roche,[2] Mouad Hamzaoui,[1,2] Valéry Brunel,[3] Vincent Richard,[2] Jeremy Bellien.[2] *[1]Nephrology, Rouen Univ Hospital, Rouen, France; [2]U1096, INSERM, Rouen, France; [3]Biochemistry, Rouen Univ Hospital, Rouen, France.*

Background: Cardiovascular (CV) events are the leading cause of morbi-mortality in chronic kidney disease (CKD). Epoxyeicosatrienoic acids (EETs) are endothelium-derived metabolites of arachidonic acid, with vasodilatory, anti-inflammatory, natriuretic and antiproliferative properties. The aim of this project is to study, in experimental CKD, the cardiac impact of the pharmacological inhibition of soluble epoxide hydrolase (sEH), which degrades EETs.

Methods: 129/Sv mice were subjected to 5/6 nephrectomy, and were assigned to t-AUCB, amiloride or placebo for 10 weeks. Echocardiography was performed before sacrifice. Hearts were weighed and histological analyses were performed to evaluate fibrosis. Vascular function was studied ex vivo on the mesenteric artery. Sequential blood and urine tests were performed to assess kidney function.

Results: Following 5/6 Nx, mice developed CKD. The CV consequences were heart hypertrophy (heart weight/tibia length Nx vs Sham 7.9±0.3 vs 6.5±0.5 mg/mm, $p<0.05$), diastolic dysfunction (E/A ratio Nx vs Sham 1.29±0.05 vs 0.97±0.04, $p<0.001$) and diffuse fibrosis (Nx vs Sham 57.8±8.8 vs 1.8±1.8 %, $p<0.001$). t-AUCB significantly prevented left ventricular hypertrophy (Nx t-AUCB 6.7±0.2 mg/mm, $p<0.05$ vs Nx), diastolic dysfunction (Nx t-AUCB 1.12±0.04 $p<0.05$ vs Nx), while effects on fibrosis were not significant. These effects were independent of plasma FGF-23 concentrations. No beneficial effects were present with amiloride. No vascular dysfunction was observed in our study.

Conclusions: Inhibition of sEH reduces the cardiac hypertrophy and diastolic dysfunction associated with CKD. These beneficial effects of inhibiting sEH hold a therapeutic potential in CKD patients to treat type 4 cardiorenal syndrome.

TH-PO342

Rats with Adenine-Induced Chronic Renal Failure Develop Left Ventricular Hypertrophy with Selective Diastolic Dysfunction Pavlos Kashioulis,[1] Emman Shubbar,[1] Lisa Nguy,[1,2] Cecilia W. Guron,[1] Gregor S. Guron.[1] *[1]Dept of Molecular and Clinical Medicine, Inst of Medicine; [2]Dept of Physiology, Inst of Neuroscience and Physiology, the Sahlgrenska Academy at the Univ of Gothenburg, Sweden.*

Background: Rats with adenine-induced chronic renal failure (ACRF) develop severe renal insufficiency and metabolic abnormalities characteristic of uremia. The aim of the present study was to analyze left ventricular (LV) morphology and function in rats with ACRF.

Methods: Male Sprague-Dawley rats received either chow containing adenine or were pair-fed an identical diet without adenine (controls, C). After 9 weeks rats were anesthetized with isoflurane and cardiac function was assessed by echocardiography. At 12-13 weeks isoflurane-anesthetized rats were instrumented for measurements of aortic and LV pressures.

Results: Rats with ACRF showed an increase in mean arterial pressure (115±6 vs. 106±7 mmHg, P<0.05) and LV weight (3.4±0.3 vs. 2.5±0.2 mg/kg, P<0.05) vs. controls. Rats with ACRF had reduced early diastolic tissue Doppler velocities, enlarged left atrial diameter (4.8 ±0.8 vs. 3.5±0.4 mm, P<0.05) but increased cardiac output (211±66 vs. 149±24 ml/min, P<0.05). LV end-diastolic pressure was elevated in ACRF rats (15±5 vs. 8±1 mmHg, P<0.01). In the LV of ACRF animals there were statistically significant (P<0.05) increases in cardiomyocyte diameter, proliferation and apoptosis vs. controls.

Conclusions: Rats with ACRF develop LV hypertrophy, increased cardiomyocyte apoptosis, and diastolic dysfunction with preserved systolic function. These cardiac abnormalities resemble those in uremic patients making this a promising animal model for future studies of uremic cardiomyopathy.

TH-PO343

Disruption of Angiopoietin-TIE2 Signaling Causes Cystic Kidney Disease Yael Kenig-Kozlovsky, Rizaldy P. Scott, Benjamin R. Thomson, Shinji Yamaguchi, Hyea Jin Gil, Christine Jiang Wu, Susan E. Quaggin. *Feinberg Cardiovascular Research Inst, Chicago, IL.*

Background: The angiopoietin ligands ANGPT1 and ANGPT2, and their cognate receptor TIE2 are well recognized for their important roles in the development and remodelling of blood and lymphatic vessels. In this study, we sought to determine how angiopoietin-TIE2 signaling regulates the development and organization of the complex renal vasculature. Surprisingly, we found that loss of ANGPT1 and ANGPT2, or TIE2 causes a rapid onset of cystic kidney disease.

Methods: Using a Cre-based inducible gene targeting strategy we deleted *Angpt1*, *Angpt2,* and *Tie2* at mid-gestation or postnatally in the mouse in order to overcome null mutant embryonic lethality.

Results: Compound ablation of *Angpt1* and *Angpt2*, or *Tie2* leads to a reduction of renal blood vascular density. Unexpectedly, mice lacking *Angpt1* and *Angpt2*, or *Tie2* develop renal cysts evident early as P10. These cysts are lined by myofibroblast-like cells. Cysts do not express epithelial, endothelial, or lymphatic markers. Vascular-specific deletion of these genes postnatally (P1-P3) does not lead to cysts suggesting that TIE2 signaling within late gestation is likely mitigating abnormal vascular development and cysts if perturbed. While investigating the lymphatic vasculature in the kidney using Prox1 reporter mice we discovered novel "hybrid" vessels that co-express lymphatic (Prox1) and blood vessel (CD31, CD34) markers, but not other classic lymphatic markers like Lyve1 and podoplanin.

Conclusions: Inactivation of ANGPT-TIE2 signaling affects the gross architecture and density of the renal vasculature, and a subsequent emergence of renal cysts. Newly identified novel hybrid vascular bundles in the kidney raises the question of whether such vessels are deficient, in a manner reminiscent of Schlemm's canal defects in the eye, when ANGPT-TIE2 signaling is absent. These findings highlight a hitherto unidentified link between attenuated angiopoietin-TIE2 signaling and the pathogenesis of renal cysts suggesting a potential therapeutic target that can be used to treat cystic kidney disease.

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TH-PO344

CPAP Treatment for Obstructive Sleep Apnea Improves the Heart Rate Variability Response to Angiotensin II David Donald McTavish Nicholl,[1] Patrick Hanly,[1] Michelle C. Mann,[1] George Handley,[2] Darlene Y. Sola,[1] Sofia B. Ahmed.[1] *[1]Univ of Calgary, Calgary, AB, Canada; [2]Healthy Heart Sleep Company, Calgary, AB, Canada.*

Background: Obstructive sleep apnea (OSA) is common in chronic kidney disease (CKD). Both conditions are associated with decreased heart rate variability (HRV) and increased renin-angiotensin system activity, each a risk factor for progression of kidney and cardiovascular disease.

Methods: We aimed to determine the effect of continuous positive airway pressure (CPAP) treatment on HRV at baseline and in response to a physiological stress. Twenty normotensive, non-diabetic, newly diagnosed OSA subjects with normal kidney function (75% male; 50±2y; respiratory disturbance index [RDI] >15hr^{-1}) and hypoxia (oxyhemoglobin saturation [SaO_2] <90% for >12% of night) were studied in high-salt balance pre- and post-CPAP (≥4h/night x 1 month). Utilizing a 3-lead Holter monitor with a sampling frequency of 125Hz, HRV was calculated by spectral power analysis (low-frequency [LF], high-frequency [HF], standard deviation of the normal R-R wave [SDNN]) at baseline and in response to graded Angiotensin II (AngII) infusion (3ng/kg/min•30min, 6ng/kg/min•30min).

Results: CPAP corrected OSA and hypoxia (RDI, 43.1±4.1 vs 3.8±0.6hr^{-1}, p<0.001; SaO_2<90%, 36.3±5.0 vs 5.6±2.0%, p<0.001). There was no change in baseline LF (45±2 vs 46±3nu [normalized units], p=0.4) or HF (81±4 vs 83±10nu, p=0.8), but there was trend to improved SDNN (63±6 vs 75±9ms, p=0.087) post-CPAP. There was a greater reduction in LF (Δ30min, -1±2 vs -6±2nu, p=0.047; Δ60min, -2±3 vs -6±2nu, p=0.2), no change in HF (Δ30min, -7±5 vs -16±7nu, p=0.3; Δ60min, -9±5 vs -16±10nu, p=0.5), and SDNN was decreased (Δ30min, 14.1±6.8 vs 8.2±8.2ms, p=0.022; Δ60min, 14.9±6.1 vs 5.5±7.7ms, p=0.082) in response to AngII post-CPAP therapy. Norepinephrine decreased post-CPAP (2.6±0.3 vs 1.9±0.2nmol/L, p=0.001).

Conclusions: Treatment of OSA, a common condition in CKD, with short-term CPAP improved HRV and may have important implications in mitigating cardiovascular risk in CKD patients.

Funding: Government Support - Non-U.S.

TH-PO345

Normalization of Arterial Pressure in Rats with Adenine-Induced Chronic Renal Failure Does Not Attenuate the Defect in Aortic Relaxation Gregor S. Guron, Olof Arvidsson, Emman Shubbar, Lisa Nguy. *Molecular and Clinical Medicine, Medicine, Sahlgrenska Academy at Gothenburg Univ, Gothenburg, Sweden.*

Background: Cardiovascular disease is the major cause of death in chronic kidney disease. We have previously shown that rats with adenine-induced chronic renal failure (CRF) develop a markedly reduced rate of aortic relaxation. The aim was to examine whether reduced aortic relaxation rate in rats with adenine-induced CRF was caused by hypertension.

Methods: Experiments were carried out on male Sprague Dawley rats and CRF was induced by feeding rats an adenine-containing diet. Rats were randomized into 4 Groups (n=10 per group); adenine diet (adenine-induced CRF, A); adenine diet plus antihypertensive therapy (A-AHT); control diet (Controls, C); control diet plus antihypertensive therapy (C-AHT). Antihypertensive drugs (hydrochlorothiazide, metoprolol, and reserpine) were provided in the drinking water. Systolic arterial pressure (SAP) was measured weekly by tail-cuff plethysmography. Ex-vivo analyses of thoracic aortic function was assessed after 7 weeks using myography. Aortic relaxation rate was determined in vessels precontracted by KCl by calculating the area under the curve (AUC) for the initial 50% reduction in force following washout of KCl. Values are means±SEM.

Results: Antihypertensive triple therapy normalized SAP in rats with adenine-induced CRF. Average SAP during the treatment period was 126±4, 141±4 and 121±3 mmHg in groups C, A, and A-AHT, respectively. Groups A and A-AHT developed severe renal failure and showed similar plasma concentrations of creatinine, phosphorous and calcium. Aortic relaxation rates were significantly reduced (corresponding to increased AUCs for force) in groups A and A-AHT vs. controls (AUCs: 1980±292, 2440±929, and 960±105 s%, in groups A, A-AHT and C, respectively, P<0.01 ANOVA for adenine effect). Antihypertensive therapy had no statistically significant effect on aortic relaxation rate.

Conclusions: Normalization of SAP in rats with adenine-induced CRF did not attenuate the reduction in aortic relaxation rate. Hypertension does not seem to be the primary cause of reduced aortic relaxation rate in rats with adenine-induced CRF.

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

TH-PO346

Epigenetic Control Mechanisms Explain the Two Distinct CD177/mPR3 Subsets of Human Neutrophils with Relevance to ANCA Vasculitis Claudia Eulenberg-Gustavus,[1] Sylvia Bähring,[1] Friedrich C. Luft,[1] Ralph Kettritz.[1,2] *[1]Experimental and Clinical Research Center, a Joint Cooperation between the Charité Medical Faculty and the Max-Delbrück Center for Molecular Medicine at the Charité, Berlin, Germany; [2]Nephrology and Intensive Care Medicine, Campus Virchow, Medical Faculty of the Charité, Berlin, Germany.*

Background: The CD177 receptor presents the ANCA autoantigen PR3 on the neutrophil surface. Individuals can be either CD177-deficient, or harbor two distinct $CD177^{neg}/mPR3^{low}$ and $CD177^{pos}/mPR3^{high}$ neutrophil subsets. A larger percentage of the latter is clinically important in ANCA vasculitis. The molecular genetic mechanisms that control subset-restricted CD177, and therefore bimodal mPR3 expression, are not known.

Methods: We performed haplotype analyses, methylation studies,chromatin immunoprecipitation (ChIP) analyses, immunoblotting, and CD177 expression studies (TaqMan), reporter assays, as well as transcription factor transfection studies in hematopoietic stem cells, neutrophils, and HeLa cells.

Results: In our healthy cohort, 94 % of 165 individuals showed a $CD177^{pos}$ neutrophil subset with a median size of 60 %. $CD177^{pos}$, but not $-^{neg}$ neutrophils, produced CD177 protein and mRNA. Haplotype analysis indicated parental-inherited monoallelic CD177 gene expression. Hematopoietic stem cells silenced one CD177 allele during neutrophil differentiation. A HeLa cell model recapitulated key neutrophil findings of CD177 transcription and allowed reporter assays that characterized the CD177 promoter in euchromatin configuration containing a TATA box, 16 CpGs, CG-rich regions, and several binding sites for the AP-1 transcription factors (TFs) c-Jun and c-Fos. Reporter activity declined with vector methylation *in vitro* and CD177 monoallelic expression became biallelic with HeLa cell demethylation. c-Jun and c-Fos bound to the CD177 promoter and transfection with both TFs upregulated CD177 mRNA. Most importantly, $CD177^{pos}$, but not$-^{neg}$ neutrophils, exhibited euchromatin configuration, demethylated CpGs, c-Jun, and c-Fos binding in the CD177 promoter.

Conclusions: We propose that epigenetic mechanisms are responsible for the two distinct CD177 neutrophil subsets.

TH-PO347

The Effect of Resveratrol on the Vascular Renin-Angiotensin-System in Aging Mice Hye Eun Yoon, Eun Nim Kim, Min Young Kim, Ji Hee Lim, Seok Joon Shin, Cheol Whee Park, Bumsoon Choi. *Internal Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.*

Background: Aging is a major risk factor of cardiovascular disease and the renin-angiotensin system (RAS) is the key player in cardiovascular diseases. Resveratrol is known to have protective effects on inflammation and oxidative stress. This study evaluated the effect of resveratrol on arterial aging and the vascular RAS in mice.

Methods: Histologic changes and expressions of collagen IV, fibronectin, angiotensin II (Ang II), Ang II type 1 receptor (AT1R), Ang II type 2 receptor (AT2R), prorenin receptor (PRR), Mas receptor (MasR), angiotensin converting enzyme (ACE), ACE2, endothelial nitric oxide synthase (eNOS), NADPH oxidase 2 and 4 (NOX2 and NOX4), superoxide dismutase 1 and 2 (SOD1 and SOD2), silent information regulator T1 (SIRT1), peroxisome proliferator-activated receptor (PPAR)ɣ co-activator 1α (PGC-1α), and PPARα were measured in the thoracic aortas from 24-month-old C57/BL6 mice with or without resveratrol treatment.

Results: The aorta media thickness significantly decreased in the resveratrol-treated mice compared to the control mice (77.07±15.90 μm vs. 95.20±18.55 μm, $P < 0.001$). The aortic expressions of collagen IV and fibronectin decreased in the resveratrol-treated mice compared with the control mice. Resveratrol treatment decreased the aortic expressions of Ang II, ACE, AT1R and PRR, and increased those of AT2R and MasR. The expressions of eNOS, SOD1, SOD2, PPARα, SIRT1, PGC-1α increased with resveratrol treatment, while the expression of NOX4 decreased.

Conclusions: The results suggest that resveratrol has protective effects on arterial aging by amelioration of oxidative stress and inflammation, which was associated with the reduction in the PRR-ACE-Ang II-AT1R axis and enhancement of the ATR2-MasR axis.

Funding: Government Support - Non-U.S.

TH-PO348

Erythropoiesis-Stimulating Agent for Treatment of Anemia Ameliorates Deterioration of Erythrocyte Deformability Associated with Chronic Kidney Disease Ken Aizawa, Ryohei Kawasaki, Yoshihito Tashiro, Kumiko Kondoh, Yasushi Shimonaka, Michinori Hirata, Hideyuki Yasuno. *Product Research Dept, Chugai Pharmaceutical Co., Ltd., Kamakura, Japan.*

Background: Erythropoiesis-stimulating agents (ESAs) are commonly used to treat anemia associated with chronic kidney disease (CKD). Although ESAs contribute to increasing erythrocytes, erythrocyte lifespans in CKD patients are thought to be shortened by qualitative changes such as deterioration of deformability and stability, and shortened erythrocyte lifespans in CKD patients may result in poor prognosis. Therefore, ensuring appropriate hemoglobin (Hb) levels may not be sufficient to provide an effective treatment for CKD-associated anemia. However, it is not yet clear whether therapeutic treatment of anemia with ESAs affects erythrocyte quality in CKD.

Methods: CKD model rats were produced by anti-Thy1.1 antibody injection plus uninephrectomy (Week 0). After the surgery, vehicle or epoetin beta pegol (C.E.R.A., 0.6 μg/kg) was intravenously injected every 2 weeks from Week 4 to 16. Blood and urine was collected until Week 18. Therapeutic control of anemia was assessed by Hb level, and deformability and stability of erythrocytes was quantified by laser diffraction ektacytometry and hemolysis test, respectively. To explore the effect on kidney and cardiovascular status, total urinary protein (uTP) and heart weight/body weight (HW/BW) were assessed, respectively.

Results: CKD model rats showed anemia and impaired erythrocyte deformability and stability. Deformability significantly improved and stability tended to recover by C.E.R.A. treatment. In the sham-operated group, C.E.R.A. treatment did not change erythrocyte deformability or stability. In this experimental procedure, C.E.R.A. treatment did not change the significant increase in uTP and HW/BW in the CKD model rats.

Conclusions: In CKD rats, not only did Hb decrease but qualitative deterioration of deformability and stability in erythrocytes was also observed. These aspects were improved by therapeutic administration of C.E.R.A. The appropriate ESA therapy for anemia may contribute to a better understanding of the therapeutic benefits of ESA treatment in CKD-associated anemia.

TH-PO349

Far Infrared Irradiation Inhibits Platelet Adhesion through the Induction of ADAMTS-13 Wen-Yi Chen,[1] Daw-Yang Hwang,[1,3] Shang-Jyh Hwang.[1,2,3] *[1]Divsion of Nephrology, Dept of Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung, Taiwan; [2]Faculty of Renal Care, Kaohsiung Medical Univ, Kaohsiung, Taiwan; [3]Faculty of Medicine, Kaohsiung Medical Univ, Kaohsiung, Taiwan.*

Background: Far-infrared Ray (FIR) is an invisible electromagnetic waves with wavelength between 3-1000μm, which has multiple effects on the cardiovascular system. FIR irradiation improved dialysis fistula function through diverse mechanisms. We ever reported FIR irradiation reduced Thromboxan A2 recetor (TBXA2R)and von Willebrand factor (vWF) protein expression of on the surface of endothelial cells, which decreased platelet adhesion to HUVECs. VWF can be cleaved by the metalloprotease ADAMTS13, and the cleavage site in the VWF A2 domains is also cryptic in normal circulating plasma VWF. We hypothesize that FIR may induce ADAMTS-13 release and decrease platelet adhesion to endothelial cells.

Methods: Cultured HUVECs were treated with or without FIR irradiation for 30 minutes. In culture media, the levels of VWF and ADAMTS-13 were measured by immunoassay. The VWF on the surface of endothelial cells was detected by immunofluorescence staining. To examine platelet-HUVEC interactions, we co-cultured calcein AM-labeled platelet with FIR-treated or controlled HUVECs, followed by fluorescence microscopy analysis. Peripheral blood samples were obtained from healthy adult volunteers before and after FIR irradiation for 40 minutes, which were analyzed for the concentrations of ADAMTS-13 by immunoassay.

Results: The immunoassay results showed increased level of ADAMTS13 and VWF D4-CK domain in culture media after FIR irradiation. Significant reduced VWF D4-CK terminal expressions of on the surface of endothelial cells were observed after FIR irradiation. The platelet binding to HUVEC cells was significantly less in FIR-treated versus control. The ADAMTS-13 levels in healthy adult were significantly higher after FIR-treated.

Conclusions: These data suggest that far infrared Irradiation inhibits platelet adhesion to endothelial cell through the induction of ADAMTS-13. Our results may provide information for further exploring the mechanisms of FIR in the prevention of thrombus formation.

Funding: Government Support - Non-U.S.

TH-PO350

Not All Elastic Fibers Are Created Equally: Differential Role of Fibulin-4 in Large versus Small Arteries Carmen M. Halabi,[1] Robert P. Mecham.[2] *[1]Pediatrics, Washington Univ School of Medicine, Saint Louis, MO; [2]Cell Biology and Physiology, Washington Univ School of Medicine, Saint Louis, MO.*

Background: Homozygous or compound heterozygous mutations in Fibulin-4 (*FBLN4*) lead to autosomal recessive cutis laxa type 1B (ARCL 1B), a multisystem disorder characterized by inelastic skin, arterial tortuosity, aortic aneurysms, and pulmonary emphysema and thought to be the result of aberrant elastic fiber formation. We sought to determine the consequences of a disease-causing mutation in *FBLN4* (E57K) on the cardiovascular system and vascular elastic fibers in a mouse model of ARCL 1B.

Methods: The vasculature of mice homozygous for E57K *Fbln4* (*Fbln4*$^{E57K/E57K}$) were examined by visual inspection, histology and electron microscopy. Blood pressure and large artery compliance were assessed, as were vascular elastin and collagen levels and smooth muscle cell (SMC) organization.

Results: *Fbln4*$^{E57K/E57K}$ mice were hypertensive and developed arterial elongation, tortuosity and ascending aortic aneurysms. SMC organization within the wall of conduit arteries was abnormal and elastic fibers were fragmented and had a moth-eaten appearance. *Fbln4* E57K homozygosity led to a modest increase in elastin content in large arteries without a change in extracellular matrix gene expression. Surprisingly, elastin and smooth muscle cells in the mesenteric, saphenous, and renal arteries of homozygous mutant mice were normal and seemingly unaffected by the E57K mutation. In addition, elastin content of *Fbln4*$^{E57K/E57K}$ mesenteric arteries was unchanged.

Conclusions: These results suggest a differential role of FBLN4 in elastic fiber assembly, not only between different tissues, but also between conduit and resistance arteries. Future studies investigating tissue-specific elastic fiber assembly may lead to novel therapeutic interventions for ARCL 1B and other disorders of elastic fiber assembly.

Funding: Other NIH Support - NHLBI and K12 (Child Health Research Center Training Grant)

TH-PO351

Single Cell Gene Expression of Adventitial Gli1+ MSC Indicates a Heterogeneous Pool of Myofibroblast and VSMC Progenitors Janewit Wongboonsin,[12] Rafael Kramann,[3] Harald Grove,[2] Prapat Suriyaphol,[2] Benjamin D. Humphreys.[1] *[1]Div of Nephrology, Washington Univ in St. Louis; [2]Siriraj Hospital, Mahidol Univ, Bangkok, Thailand; [3]Div of Nephrology and Clinical Immunology, RWTH Aachen Univ, Aachen, Germany.*

Background: Progenitor cells are known to reside in the vascular adventitia but their precise cellular potential and gene expression profile remains unknown. We identified Gli1 as a marker of perivascular MSC that are important progenitors both of myofibroblasts in fibrosis but also vascular smooth muscle cells (VSMC). Whether Gli1^{+} stem cells are homogeneous, or alternatively represent a heterogenous population of myogenic and myofibroblast progenitors remains unknown. To address this question, we performed single cell gene expression analysis and looked for cell subpopulations expressing perivascular or smooth muscle gene markers.

Methods: 10 days after tamoxifen was given to bigenic Gli1CreER;tdTomato mice, the aorta was harvested and dissociated. Single Gli1+ progenitor cells were sorted and single cell qPCR was performed using TaqMan expression probes on a 96.96 Fludigm array for 32 genes of interest. Data was analyzed using the R package SINGuLAR Analysis Toolset.

Results: Three distinct cell clusters were identified from this gene panel. Seventeen genes were differentially expressed between the clusters (ANOVA, $p<0.0016$): Ly6a,Endoglin,Tek, IGF2,Kdr,Tagln,CD34,Ccnd2,TSC22d3,Nestin,Smtn,Ptch1,CD140a, CD140b,Sox10,Msx1 and CNN1. Principal component analysis showed the top four most influential genes were CNN1(calponin),Tagln(SM22),CD140a and CD34. Tagln, a VSMC gene, was negatively correlated with MSC markers such as CD140a ($R2 = -0.32$) and CD34 ($R2 = -0.13$). Cross validation confirmed a subpopulation of cells that always clustered together providing strong evidence that Gli1+ cells are heterogeneous. This subpopulation had low expression of CD140a and Thy1, and high expression of Kdr,Tek,IGF2 and Tagln.

Conclusions: Single cell qPCR strongly suggests the presence of distinct subpopulations among adventitial Gli1^{+} MSC. As VSMC marker expression increases, MSC marker expression decreases reflecting differentiation and commitment to the VSMC lineage of Gli1+ progenitors.

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TH-PO352

Association of Vascular Injury Markers with Rate of GFR Decline in Type 2 Diabetes Alexander Mohtadi, Olufemi B. Aina, Ameet Kumar, Candace D. Grant, Joseph Mattana, Shayan Shirazian. *Winthrop-Univ Hospital.*

Background: Urine microalbumin levels are the most commonly used biomarker for vascular injury and progression of chronic kidney disease (CKD) in patients with type 2 diabetes (T2DM). However, nonalbuminuric patients with T2DM and CKD are also prone to vascular injury and CKD progression, warranting study of additional biomarkers. This study examines the association between vascular injury markers and CKD progression in patients with T2DM and CKD.

Methods: This is a retrospective study of 40 subjects with T2DM and stage 3 CKD with prior vascular injury marker testing including urine microalbumin to creatinine ratio (UACR), von-Willebrand factor antigen, high sensitivity C-reactive protein, uric acid and circulating endothelial cell (CEC) levels. CEC levels were tested by Veridex® using an immune-magnetic bead based assay. The primary outcome, slope of estimated glomerular filtration rate (GFR) decline, was calculated in subjects with over 16 months of follow-up from vascular injury marker testing, and at least 3 measured creatinines separated by 3 months using a line of best fit. Pearson correlations were performed between slope of eGFR decline and other demographic and clinical predictors including vascular injury markers.

Results: Of the original 40 subjects, 30 had sufficient follow-up data for slope of eGFR decline calculation. This group was 53.3% male, 70% Caucasian, 23.3% African American, 6.7% Asian, and had a mean age of 69.8±8.1 years, diabetes duration of 16.5±5.9 years, UACR of 393.5±896.1 mcg/mg, slope of eGFR decline of -1.5±4.25 mL/min/1.73m^2/year, and median follow-up time of 23 months. UACR levels (r=-0.37, p=0.042) and hemoglobin $A1_c$ (r=-0.3198, p=0.08) were negatively correlated with slope of eGFR decline. There were no significant correlations between slope of eGFR decline and other vascular injury markers.

Conclusions: In this pilot study, only urine microalbumin levels showed a significant negative correlation with slope of eGFR decline in patients with T2DM and stage 3 CKD over a median of 23 months of follow-up. Longer term follow-up is needed to determine whether other vascular injury markers associate with eGFR decline in this population.

TH-PO353

IRE1 Activation Is Required for Collagen Secretion by Vascular Smooth Muscle Cells Victor Tat, Jeffrey G. Dickhout. *Dept of Medicine, Div of Nephrology, McMaster Univ and St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada.*

Background: Vascular stiffening is positively associated with both hypertension and aging and is a strong predictor of end-organ damage. Fibrotic remodeling of the extracellular matrix by vascular smooth muscle cells (VSMCs) contributes to the stiffening of conduit arteries such as the aorta. Activation of the IRE1 pathway within the unfolded protein response (UPR) results in adaptive programs that increase protein folding capacity. We hypothesize VSMCs transitioning to a collagen-secreting phenotype in response to TGF-β1 require the activation of IRE1. Inhibition of this pathway is hypothesized to reduce collagen secretion and hence prevent the development of fibrosis in the aorta.

Methods: Aortic smooth muscle cells were isolated from Wistar-Kyoto rats. Small molecule inhibitors of the IRE1α endonuclease domain, 4μ8c and STF-083010, were used to block IRE1 activity. Collagen production was measured using a dot blot for Type I collagen and a Picrosirius red-based microplate assay. Markers of UPR activation and ER stress were assessed with Western blot. Aortic rings were harvested from 5-7 week old WKY rats and cultured for 5 days in the presence of TGF-β1 (5 ng/ml) and 4μ8c (30 μM). Arterial compliance was measured using a wire myograph.

Results: Inhibition of IRE1 endonuclease activity dose-dependently reduced the production of collagen by VSMCs in response to either L-ascorbic acid or TGF-β1. 4μ8c blocked the splicing of the transcription factor XBP1 and prevented the induction of the collagen-folding chaperones GRP78, GRP94 and PDI by tunicamycin. Aortic rings incubated with TGF-β1 had reduced compliance, which was improved by co-treatment with 4μ8c.

Conclusions: These results suggest that activation of the IRE1 pathway is required for the secretion of collagen by VSMCs, leading to vascular fibrosis and stiffening. It is hypothesized that IRE1 blockade will have similar antifibrotic effects in other tissues such as the kidney by limiting the secretory capacity of collagen-producing cells. This presents a novel target for the treatment of fibroproliferative diseases. Funding:CIHR MOP-133484, Kidney Foundation of Canada Krescent New Investigator (Dr. Dickhout).

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TH-PO354

Role of Interleukin 17 Receptor A in Enhanced Atherosclerotic Inflammation in Renal Impairment Johannes Nordlohne,[1] Shuwang Ge,[1] Ari Waisman,[2] Hermann G. Haller,[1] Sibylle Von Vietinghoff.[1] *[1]Nephrology and Hypertension, Hannover Medical School, Hannover, Germany; [2]Inst of Molecular Medicine, Inst of Molecular Medicine, Mainz, Germany.*

Background: Patients with chronic kidney disease (CKD) suffer from increased atherosclerosis and its complications. This is only partly amenable to control of traditional risk factors. The T cell cytokine Interleukin (IL)-17A enhances myeloid inflammation via IL-17 receptor A. This project investigated the role of IL-17 receptor A in enhanced atherosclerotic inflammation in renal impairment.

Methods: LDL receptor (LDLr-/-) deficient mice with and without IL-17 receptor A (Il17ra-/-) underwent unilateral nephrectomy or sham surgery and were maintained on a high-fat diet. Bone marrow transplantation was conducted after lethal irradiation. Aortic leukocyte infiltration was determined by flow cytometry. Interaction of myeloid cells with aortic explants in response IL-17A was studied in vitro.

Results: Unilateral nephrectomy significantly decreased GFR in LDLr-/- mice. The number of aortic total leukocytes, CD11b+ myeloid cells and among them, both neutrophils and CD11c+ and MHCII high-expressing cells, both indicators of antigen presenting function, increased significantly in renal impairment after 10 weeks of high fat diet. This was completely abolished in the absence of IL-17 receptor A. In vitro, IL-17A enhanced adhesion of myeloid cells to aortic explants. Aortic myeloid cell homing in atherosclerosis was investigated in mixed bone marrow chimeric mice (50% wt/50% *Il17ra*$^{-/-}$ bone marrow). In the identical environment of mixed bone marrow chimeric mice, *Il17ra*$^{-/-}$ cells had a significant aortic homing defect in renal impairment.

Conclusions: IL-17 receptor A is instrumental in prevention of enhanced atherosclerotic inflammation in renal impairment. IL-17 inhibition should be further tested as an anti-inflammatory target in atherosclerosis and CKD.

Funding: Government Support - Non-U.S.

TH-PO355

Myostatin: A New Player in Uremic Vascular Remodelling and Fibrosis in Uremia Pasquale Esposito,[1] Daniela Verzola,[2] Edoardo La Porta,[1] Samantha Milanesi,[2] Maria Antonietta Grignano,[1] Antonio Dal Canton,[1] Giacomo Garibotto.[2] *[1]Nephrology, Dialysis and Transplantation, Fondazione IRCCS Policlinico San Matteo, and Univ of Pavia, Pavia, Italy; [2]Nephrology, Dialysis and Transplantation, Genoa Univ IRCCS AOU San Martino-IST, Genoa, Italy.*

Background: Myostatin (MSTN), a member of the TGFβ superfamily that exerts pleiotropic effects on skeletal muscle and bone, has been recently recognized as a mediator of cardiovascular cachexia, heart dysfunction and fibrosis. Accordingly, in this study we assessed the role of MSTN in arterial vascular remodelling and fibrosis in patients with end-stage renal disease (ESRD).

Methods: We studied gene expression (RT-PCR) and protein (immunohistochemistry) of myostatin, smoothelin-A (a marker of the smooth muscle cell contractile phenotype), klotho and periostin (an early marker of vascular calcification) in aortic patches from ESRD patients (n=16, 9M, 56.4±7.9 years) at the time of renal transplantation, and from paired deceased kidney donors–(Controls) (n=15, 8M, 55.4±12.1 years) at the time of organ removal. Von Kossa stain was used to quantify vascular calcium deposition. In addition we tested, *in vitro,* the effect of uremic serum on the expression of MSTN, klotho and smoothelin in primary human Vascular Smooth Muscle Cell line (VSMC), obtained from a kidney donor.

Results: There was a 15-fold increase in myostatin-mRNA levels in ESRD patients compared with age-matched control subjects ($P < 0.05$), while klotho was markedly downregulated ($p<0.001$). In addition, smoothelin-A and klotho immunohistochemical signals were lower in ESRD than in controls ($P<0.001$-$P<0.01$). Moreover, MSTN m-RNA was inversely correlated with klotho and smoothelin-A m-RNA (r=-0.5, p=0.05; r=0.6, p=0.01, respectively). In vitro studies on VSMC showed that uremic serum increased MSTN-mRNA (+ 70% respect to normal serum), and downregulated smoothelin and klotho (both - 40%), suggesting that the uremic milieu is responsible for inducing the observed changes.

Conclusions: Uremia increases MSTN gene expression in vascular tissues and blunts Klotho and smoothelin, suggesting that MSTN has a role in uremic-related vascular remodelling and fibrosis.

TH-PO356

Aryl Hydrocarbon Receptor Signaling Is an In Vivo Targetable Antithrombotic Pathway Mostafa Belghasem,[1] Moshe Shashar,[2] Jamaica Siwak,[2] Faisal F. Alousi,[2] Anqi Zhang,[3] Jean M. Francis,[2] Joel M. Henderson,[1] Vipul C. Chitalia.[2] *[1]Dept of Pathology, Boston Univ Medical Center, Boston, MA; [2]Nephrology, Boston Univ Medical Center, Boston, MA; [3]Metabolomics Core, Boston Univ Medical Center, Boston, MA.*

Background: CKD is characterized by the retention of several solutes of which indoxyl sulfate (IS) is highly thrombogenic. It enhance thrombosis by activating AHR to increase tissue factor levels, a key procoagulant. Though AHR inhibitors (AHRi) significantly suppressed thrombosis in an *ex vivo* model, there is a dearth of *in vivo* proof of AHRi as antithrombotics. There are limitations to current CKD animal models in that they retain numerous solutes precluding specific examination of IS and also fail to recapitulate the prothrombotic phenotype of human CKD.

Methods: We generated a uremic thrombosis model by combining IS administration along with the inhibition of its urinary excretion using Probenacid (Prob) in C57BL/6 mice. The protocol with high IS levels similar to stage 5 CKD was used. The effect of AHRi was examined in three groups **I**: Prob (CTL), **II**: IS + Prob, and **III**: IS + Prob+ AHRi (CH223191 10 mg/kg IP). Plasma IS levels were measured on day 0, 2, and 5 using LC/MS, and the animals were subjected to ferric chloride-mediated carotid injury. The onset of thrombosis was defined as the reduction of blood flow to the background and time to thrombosis served as a primary end point.

Results: IS in water (4mg/ml) along with Prob IP (150mg/kg) twice daily for 5 days resulted in a significant increase in IS levels greater than stage 5 CKD patients. The IS levels remained significantly higher from day 2 onwards. The time to thrombosis was significantly lower in IS + Prob (315.9±163.3 sec) compared to Prob (673.7±395.6 sec), and was significantly prolonged with AHRi (655.7±342.8 sec), despite similar IS levels in group II and III (p=0.49).

Conclusions: With the IS levels similar to stage 5 CKD patients, this first uremic thrombosis model faithfully recapitulates enhanced thrombotic phenotype in humans CKD. Validating IS as a thrombogenic uremic solute *in vivo*, the above observations confirm the *in vivo* druggability of AHRi as a novel class of antithrombotic.

TH-PO357

Disruption of Glomerular Permeability Barrier Increases Apolipoprotein AI (ApoAI) Ultrafiltration which Regulates Interstitial Lymphangiogenesis
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Background: Lymphatics not only return fluids/lipoproteins from the periphery to the circulation but have critical pathophysiologic/therapeutic roles in disease e.g., atherosclerosis, cancer, hypertension. Lipoproteins themselves appear to regulate lymphangiogenesis, however, little is known about lipoprotein modulation of the intrarenal lymphatic network. We examined ApoAI modulation of lymphangiogenesis in proteinuric kidney injury.

Methods: We studied Nphs1-hCD25 mice (NEP25) expressing human CD25 in podocytes which can be injured by immunotoxin, LMB2. Six weeks after LMB2, we assessed glomerular filtration, excretion of albumin and ApoAI, examined the intrarenal lymphatic network with podoplanin, localized endogenous ApoAI, and stained for lipoprotein transporters (scavenger receptor class B member 1, SRB1). In vitro, we examined lymphatic endothelial cells exposed to ApoAI with/without transporter blocker.

Results: Lymphatic endothelial cells exposed to ApoAI showed increased cell viability, lower migration, and reduced lymphangiogenesis compared to vehicle-exposed cells. Blocking SRB1 with BLT1 reduced cell viability and promoted more migration than ApoAI alone. In vivo, NEP25 mice had glomerulosclerosis, albuminuria and increased ApoAI excretion. Podocyte injury also caused more tubulointerstitial injury and more ApoAI localized to tubular epithelial cells and interstitium. After injury, tubular cells showed more SRB1 and VEGF-C, a powerful lymphaniogenic stimulus, compared to nonproteinuric mice. NEP25 mice had a dramatically more dense and complex lymphatic network than wild type mice. Lymphatic vessels expressed SRB1 that co-localized with reabsorbed ApoAI.

Conclusions: Proteinuric glomerular injury leads to more ApoAI in the ultrafiltrate, greater reabsorption by the proximal tubules into the interstitium and more ApoAI uptake by lymphatic endothelial cells via SRB1. We conclude that tubular VEGF-C secretion and lymphatic ApoAI absorption promote renal lymphangiogenesis.

TH-PO358

Abnormalities in Cholesterol Flux Pathway Induced by Plasma from Patients with Chronic Kidney Disease
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Background: The mechanism underlying chronic kidney disease (CKD) as a major risk factor for atherosclerosis and cardiovascular disease (CVD) has not been elucidated. Lipid profile is less predictable of CVD risk and statins lose benefit with advancing CKD. This study aims to detect changes in cholesterol transport gene expression and to determine if such changes adversely affect macrophage lipid handling in CKD leading to atheromatous foam cell formation.

Methods: THP-1 human macrophages (10^6/ml) were incubated for 18h-24h with plasma from 10 CKD patients not on dialysis and non-renal transplant or 10 healthy control (HC) subjects. Post-incubation, mRNA was isolated and reverse transcribed to cDNA, and subjected to quantitative real-time PCR using specific primers for ATP binding cassette transporter (ABC)A1 (cholesterol efflux protein) and CD36, (a scavenger receptor with the capacity to endocytose oxidized LDL). Foam cell quantification using Dil-acetylated-LDL with VectaShield mounting medium was used on 5 samples from each group.

Results: PCR analysis showed that ABCA1 mRNA was reduced by 28±5% ($p<0.0001$) while CD36 mRNA was decreased by 35±6% ($p<0.0001$) in macrophages exposed to CKD plasma as compared to HC. Increase in foam cell accumulation in macrophages exposed to CKD plasma by 36±11% as calculated by total fluorescence per cell corrected for total nuclei in frame ($p<0.01$).

Conclusions: A different mechanism of lipid dysregulation in CKD based on impaired efflux, through proatherogenic suppression of ABCA1, differs from our finding in autoimmune rheumatic diseases where, in addition to lowering of ABCA1, augmentation of CD36 influx was observed. In CKD, oxidized lipid uptake appears less dependent on macrophage CD36. Statins reduce lipid influx via down regulation of CD36 but low CD36 expression in CKD would limit its benefit from this mechanism. These changes to ABCA1 and CD36 may explain the pathogenesis of elevated CVD risk accompanied by reduced statin efficacy in advanced CKD. Defining lipid handling changes in CKD could lead to novel, targeted CVD treatments in the CKD population.

Funding: Private Foundation Support

TH-PO359

Atorvastatin Decreases Vascular Wall Inflammation following Arteriovenous Fistula Creation in a Murine Model
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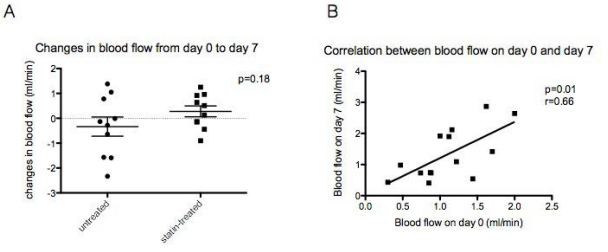
Background: The most common cause of AVF failure is inflammation-driven neointimal hyperplasia and thrombosis. Statins have well-recognized anti-inflammatory and anti-thrombotic properties. Here, we investigated whether statin therapy can improve murine AVF patency, and assessed the anti-inflammatory effects using in vivo nanoparticle-based fluorescence molecular imaging.

Methods: AVFs were created using internal jugular vein and carotid artery (n=20). AVF blood flow was measured 15 minutes post-surgery. On day 6, an inflammatory cell targeted fluorescent nanoparticle, CLIO-VT680 (10mg/kg) was administered. 24 hours later, *in vivo* epifluorescence imaging was performed to visualize inflammatory response of the mobilized vein. In the statin treated group, 1.14mg/kg atorvastatin was administered daily. Changes in blood flows (BF) were compared in both statin treated (SG) and untreated control group (CG).

Results: AVF BFs on day 0 and day 7 were similar between the SG and CG ($p>0.05$). The day 7 adventitial AVF inflammation signal (CLIO-VT680) assessed by in vivo epifluorescence imaging was significantly lower in the SG compared to the CG (6.3±0.98 vs 3.4±0.2, $p=0.002$). There was a nonsigificant trend to increased BFs from day 0 to day 7 in the SG compared to the CG (0.28 vs -0.33 ml/min, $p=0.18$).



The day 7 AVF BF strongly correlated with the day 0 BF ($r=0.66$, $p=0.01$).

Conclusions: Oral statin therapy decreases adventitial inflammation in experimental AVF as assessed by in vivo nanoparticle-based molecular imaging. There was a trend to improve AVF blood flow with statin therapy. Further studies are indicated to determine if statin therapy can improve AVF patency and maturation.

TH-PO360

Impact of HIV Infection on Arteriovenous Fistula Outcomes: A Retrospective Analysis
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Background: Multiple conditions have been associated to the elevated AVF failure rates. One of the influenced factors but less studied is the effect of the immunosuppression on the AVF vascular wall. In AVF, immunosuppression has been related with higher failure rates of newly created AVF in animal models.

Methods: This retrospective study assessed for the impact of HIV infection on one-stage and two-stage hemodialysis AVF outcomes. The study included 494 patients (HIV=42 patients) who underwent an AVF creation at the University of Miami/Jackson Memorial Hospital from 2008 to 2014. The effects of HIV on primary failure were determined using multivariate logistic regressions and Cox proportional hazard models adjusted for 10 clinical and demographic covariates.

Results: A positive predictors of primary failure are HIV infection ($p=0.004$) and previous AVF ($p=0.002$), but HIV does not correlate with primary patency after excluding primary failure cases. We could not find a correlation with any of the T-cell subsets counts (CD3, CD4, or CD8). In HIV patients a prior dialysis catheter is the only clinical factor that predisposes for AVF primary failure ($p=0.012$).

Conclusions: Our results suggest that immunosuppression might play a role in AVF outcomes. HIV infection show increased rate of AVF failure but this is not explained by the T-cell subsets counts and should be a different immunological relationship between AVF failure and vascular remodeling.

TH-PO361

Pro- and Anti-Inflammatory Factors and Vascular Stiffness in Chronic Hemodialysis Patients Botond Csiky,[1,2] Attila Peti,[5] Orsolya Lakatos,[4] Endre Sulyok.[3] *[1]FMC Dialysis Center Pecs, Pecs, Hungary; [2]Dept of Nephrology, Univ Medical School of Pecs, Pecs, Hungary; [3]Faculty of Health Sciences, Univ of Pécs, Pecs, Hungary; [4]Univ Medical School of Pecs, Pecs; [5]Siofok Hospital, Hungary.*

Background: In this cross-sectional study we addressed the accelerated arteriosclerosis in patients with chronic renal failure (CRF) on hemodialysis (HD) by measuring arterial stiffness parameters and attempted to relate them to pro-inflammatory and protective factors.

Methods: 96 consecutive patients receiving regular HD were included in the study. 20 adult patients without major renal, cardiovascular or metabolic morbidities served as controls. Arterial stiffness parameters (carotid-femoral pulse wave velocity – PWV, aortic augmentation index) were measured by using applanation tonometry (SphygmoCor, AtCor Medical,Sidney). In addition to routine laboratory tests 25(OH)vitamin D_3 (vitamin D_3) and hsCRP were quantified by immunometric assay; whereas fetuin-A, α-Klotho, TNF-α and TGF-β1 were determined by ELISA using commercially available kits (IBL International GmbH, Hamburg and BioVendol Laboratory Med. Inc Brno).

Results: Pro-inflammatory biomarkers (hsCRP, TNF-α and TGF-β1) were markedly elevated ($p<0.01$), while anti-inflammatory factors (fetuin-A: $p<0.05$, α-Klotho: $p<0.01$, vitamin D_3: $p<0.01$) significantly depressed in CRF patients on HD when compared to control patients. PWV was significantly affected only by total cholesterol, fetuin-A and dialysis time. Multiple linear regression analyses revealed that several clinical and laboratory parameters were associated with pro-and anti-inflammatory biomarkers rather than arterial stiffness.

Conclusions: Our results provide additional information on the pathomechanism of accelerated atherosclerosis in patients with CRF but failed to document direct influence of pro- and anti-inflammatory biomarkers studied on the complex interplay between uremic milieu and vascular health.

TH-PO362

Morphological and Immunohistochemical Characterization of Thrombotic Microangiopathy (TMA) in Native and Transplanted Kidney Biopsies: A Multicenter Study Jessica Schmitz,[1] Wei Dai,[1] Abedalrazag Ahmad Khalifa,[1] Jan Menne,[2] Ulrich Kunzendorf,[3] Oliver Witzke,[4] Hermann G. Haller,[2] Hans Heinrich Kreipe,[1] Jan H. Braesen.[1] *[1]Inst for Pathology, Hannover Medical School, Hannover, Germany; [2]Nephrology, Hannover Medical School, Hannover, Germany; [3]Nephrology, Univ Clinic Schleswig-Holstein, Campus Kiel, Kiel, Germany; [4]Nephrology, Univ Clinic Essen, Essen, Germany.*

Background: Thrombotic microangiopathy (TMA) is defined as microvascular endothelial injury and thrombosis, thrombocytopenia and MAHA, often affecting the kidney. Correct diagnosis of TMA in kidney biopsies is demanding since TMA may manifest without thrombi.

Methods: Using routine paraffin sections, accepted morphological criteria were analysed in TMA cases from the archives of the Insitute for Pathology at Hannover Medical School in 163 kidney biopsies from the last three years.

Results: Patient (female 45%) age ranged from 4 to 81 (mean 47) years. 45% of TMA cases occured in kidney transplants (KTx), 53% of these revealed rejection (cellular 7%, humoral 34%, mixed 12%). Thrombi were identified in 71% of KTx TMA cases (glomerular 41%, arteriolar 40%, arteries 25%) compared to 67% of native kidneys (glomerular 38%, arteriolar 53%, arteries 41%). Most useful histological TMA criteria were fragmented red blood cells (glomerular 65%, arterioles/arteries 67%), fibrillar appearance of mesangium (66%), endothelial swelling (glomeruli 68%, arterioles 67%), thickened capillary walls (66%), collapse of capillary tuft (92%) and arterial intimal mucoid edema (arteries 78%, arterioles 47%). Grouping of well-characterized patients regarding the underlying cause for the TMA showed differences between morphological criteria comparing genetically verified atypical HUS (more arteriolar/hilar involvement), humoral transplant rejection and medication induced injury (e.g. gemcitabine, more glomerular and overall thrombi). Stainings using antibodies for thrombomodulin, heparanase-2, CD34 and lectin stains for evaluation of the glycocalyx do not seem to mirror the morphological differences so far.

Conclusions: One third of TMA cases do not display thrombi in kidney biopsies. Certain morphological criteria vary in their diagnostic value and differ between causes of TMA.

TH-PO363

Matrix Metalloproteinase-10 in Glomeruli of Aldosterone-Infused Systemic and Podocyte-Specific Guanylyl Cyclase-A Knockout Mice Keisuke Osaki,[1] Yukiko Kato,[1] Naohiro Toda,[1] Akira Ishii,[1] Kiyoshi Mori,[2] Moin Saleem,[3] Taiji Matsusaka,[4] Masashi Mukoyama,[5] Motoko Yanagita,[1] Hideki Yokoi.[1] *[1]Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; [2]School of Pharmaceutical Sciences, Univ of Shizuoka, Shizuoka, Japan; [3]Academic and Children's Renal Unit, Univ of Bristol, United Kingdom; [4]Dept of Molecular Life Sciences, Tokai Univ School of Medicine, Kanagawa, Japan; [5]Dept of Nephrology, Kumamoto Univ Graduate School of Medical sciences, Kumamoto, Japan.*

Background: Natriuretic peptide receptor/guanylyl cyclase-A (GC-A) signaling exerts renoprotective effects by eliciting natriuresis and reducing blood pressure. We previously reported that high salt-fed systemic GC-A knockout mice with aldosterone, uninephrectomy and high salt showed accelerated hypertension and severe glomerular injury with massive albuminuria. However, genes involved in glomerular injury are elusive.

Methods: By using microarray analysis, we compared gene expression in the glomeruli of systemic GC-A knockout mice and wild-type mice with aldosterone. Furthermore, we constructed podocyte- specific GC-A KO mice to examine the role of GC-A in podocytes, and analyzed gene expression in systemic and podocyte-specific GC-A knockout mice.

Results: We identified 85 upregulated and 48 downregulated genes in GC-A knockout mice by more than 8-fold compared with wild-type mice. One of upregulated genes in GC-A knockout mice was matrix metalloproteinase-10 (MMP-10). Podocyte-specific GC-A KO mice with aldosterone exhibited albuminuria by 13-fold, mesangial expansion and footprocess effacement compared to control mice with aldosterone. We confirmed that the expression of MMP-10 from the glomeruli in systemic and podocyte-specific GC-A knockout mice was 200 and 3 times higher than that from control mice by real-time PCR, respectively. Podocyte-specific GC-A KO mice with aldosterone exhibited albuminuria, mesangial expansion and footprocess effacement. *In vitro*, the expression of MMP-10 was increased in podocytes as well as mesangial cells with TNF-α.

Conclusions: These results suggest that glomerular MMP-10 is increased in aldosterone-infused GC-A KO mice, and could play a role on inflammation during glomerular injury.

Funding: Government Support - Non-U.S.

TH-PO364

Gender-Dependent Hypertension-Induced Kidney Injury in Cystathionine γ Lyase Knock Out Mice; Amelioration by Sodium Hydrosulfide Hak Joo Lee,[1,2] Denis Feliers,[1] Jeffrey L. Barnes,[1] Goutam Ghosh-Choudhury,[1,2] Rui Wang,[3] Balakuntalam S. Kasinath.[1,2] *[1]Medicine, Univ of Texas Health Science Center, San Antonio, TX; [2]Medicine, South Texas Veterans Health Care System, San Antonio, TX; [3]Lakehead Univ, Thunder Bay, ON, Canada.*

Background: Hydrogen sulfide (H2S) is constitutively synthesized in the kidney by cystathionine γ lyase (CSE) and cystathionine β synthase (CBS). Although CSE knock out (KO) mice develop hypertension (HT) (Yang G et al, Science, 2008), whether they develop kidney injury is not known.

Methods: Male and female 2.5 to 4.5- month old wild type (WT) and CSE KO mice were randomized to receive water alone or 30 umoles/L of sodium hydrosulfide (NaHS, a source of hydrogen sulfide) in drinking water for 12 weeks (n=4-6 mice in each group).

Results: Compared to WT mice, male CSEKO mice had significantly higher blood pressure and albuminuria. NaHS robustly reduced the blood pressure and albuminuria in male CSEKO mice to WT levels (Systolic BP: WT water 114±19, WT NaHS 121±12, KO water 141±9, KO NaHS 122±8, $p<0.05$ ANOVA). Similar trends were seen in female CSEKO mice. However, the renal cortical expression of TGFβ, phospho-Smad3, collagen Iα2 and laminin was increased in male but not female CSEKO mice; NaHS restored these changes to normal. Renal cortical renin-angiotensin system assays in male CSEKO vs. WT mice showed higher Ang II, Ang III, AT1 receptor and low ACE2 levels; NaHS restored ACE2 to normal without affecting other parameters. There were no changes in renal cortical contents of renin, ACE, AT2, and Mas. Blood glucose and serum cystatin C levels were unchanged in CSEKO mice vs. WT mice. At the beginning of the study, both male and female CSE KO mice were smaller than the respective WT mice but equalled WT mice weight by the end of the study. In WT mice NaHS did not affect blood pressure, albuminuria, and the above parameters.

Conclusions: Our data show that male CSEKO mice are more susceptible to HT associated renal injury than female CSEKO mice. HT in male CSEKO mice is associated with complex changes in renal parenchymal renin-angiotensin system. Administration of H2S ameliorates HT and associated renal injury suggesting exploration of H2S as a treatment tool in HT.

Funding: Other NIH Support - NIA, VA Support

TH-PO365

Sustained Reduction in Blood Pressure and Improvement in Kidney Function in Hypertensive Sheep with Chronic Kidney Disease following Radio-Frequency Catheter-Based Renal Denervation Reetu R. Singh,[1] Lindsea C. Booth,[2] Karen M. Moritz,[3] Kate M. Denton.[1] *[1]Monash Univ, Clayton, VIC, Australia; [2]Florey Inst of Neuroscience and Mental Health, Parkville, VIC, Australia; [3]School of Biomedical Sciences, The Univ of Queensland, St Lucia, VIC, Australia.*

Background: Clinical trials investigating the effectiveness of radio-frequency catheter-based renal denervation (cDNX) in reducing blood pressure in hypertensive patients have yielded conflicting results. Additionally, the long-term efficacy of the procedure is unclear. The present study examined the consequences of cDNX on basal mean arterial pressure (MAP) and renal function at 2, 5 and 11 months following cDNX procedure in sheep with hypertension and chronic kidney disease (CKD).

Methods: Sheep with established hypertension and CKD (H-CKD) with an appropriate control group were used. At 10 months of age, some animals underwent cDNX (H-CKD-cDNX (*N*=7); control-cDNX (*N*=8)) while the remaining underwent sham procedure (H-CKD-intact (*N*=7); control-intact (*N*=6)). At 2, 5 and 11 months MAP was assessed continuously over 72 hours in unanesthetised sheep and glomerular filtration rate (GFR) was measured via clearance of ^{51}Chromium-EDTA.

Results: Following cDNX MAP in H-CKD sheep was significantly reduced at 2 months (~6mmHg, P<0.001), 5 months (~5mmHg, P<0.01) and at 11 months (~6mmHg, P<0.001) compared to MAP prior to cDNX. GFR was unchanged at 2 months post-procedure but was significantly increased in H-CKD sheep at 5 months (P<0.01) and at 11 months (P<0.001) compared to their pre-cDNX GFR.

Conclusions: In sheep with hypertension and CKD, cDNX caused a sustained reduction in blood pressure from 2-11 months post procedure and caused an increase in GFR from 5-11 months post procedure. These findings are interesting because in normotensive healthy sheep, at 5 and 11 months post-cDNX, both structural and functional reinnervation has been demonstrated. The sustained reduction in blood pressure and improvement in renal function in the present study suggests the rate and degree of reinnervation may be dissimilar in sheep with hypertension and CKD compared to normotensive.

Funding: Government Support - Non-U.S.

TH-PO366

Role of Adenosine A1 Receptor in Renal Afferent Arteriolar Constriction Induced by Hyperuricemia Lin Liu,[1] Xiaoyan Peng,[1] Qian Huang,[2] Jinling Hao,[1] Liang Zhao,[2] Xuewang Li,[1] En Yin Lai,[2] Limeng Chen.[1] *[1]Nephrology, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, China; [2]Physiology, Zhejiang Univ School of Medicine, Hangzhou, Zhejiang, China.*

Background: Hyperuricemia is known as an independent risk factor of hypertension with prominent cortical vasoconstriction and renin activation. Adenosine and A_1 adenosine receptor (A_1AR) play an important role in regulating the constriction of afferent arterioles (AAs), known as a part of tubuloglomerular feedback. However, there is no direct pathogenic proof of AAs constriction induced by uric acid and the role of A_1AR has not been studied yet.

Methods: We investigated the effects of A_1AR in AAs remodeling during hypertension induced by mild hyperuricemia in mice model. Renal arteriolopathy was evaluated by α-SMA staining. The protein expression of adenosine receptors in mice kidney was detected. The direct role of A_1AR in the AAs constriction induced by uric acid was observed by microperfusion technique and the diameter of AAs was monitored.

Results: Hyperuricemia induced by oxonic acid(OA) gavage effectively increased systemic systematic blood pressure in WT mice, associated with an increase in total medial area of the renal arteriolar wall and up-regulated A_1AR protein expression in renal tissues(1.50±0.10 vs 1.00±0.15, *P*=0.020). Hypertension and preglomerular arteriolopathy were abolished in A_1AR deficient mice. A_{2b}AR, another receptor of adenosine expressed on AAs and in charge of AA dilation, was obviously increased under hyperuricemia condition (1.12±0.02 vs 1.0±0.04, *P*=0.006) in A1AR$^{-/-}$ mice. AAs constriction was dose dependently increased by uric acid, when the concentration of uric acid increased from 10^{-7}mol/L to 10^{-3}mol/L, the AA luminal diameter diminished from (10.03±1.85)μm to (8.49±1.69)μm *(P*=0.005, paired t test). This constriction effect was abolished in $A_1AR^{-/-}$ mice(the average AA diameter increased from 10.46±1.00μm to 12.81±1.23μm, *P*<0.001), suggesting that uric acid induced hypertension possibly via directly activating AAs constriction.

Conclusions: Adenosine A_1 Receptor played an important role in renal afferent arteriolar constriction and remodeling induced by mild hyperuricemia.

Funding: Government Support - Non-U.S.

TH-PO367

Renal Blood Flow Measurements Using Invasive Flow Probe Measurements in Humans Can Identify Subjects with Poor Autoregulation Branko Braam,[1] Alexander Kiepas,[1,4] Nick Mitrou,[2] William A. Cupples,[3] Daniel H. Kim.[1] *[1]Medicine/Nephrology, Univ of Alberta, Edmonton, AB; [2]Western Univ, London, ON; [3]Physiology and Kinesiology, Simon Fraser Univ, Burnaby, BC; [4]McGill, Montreal, QB, Canada.*

Background: Autoregulation of renal blood flow (RBF) is well established in animals and is regarded important to stabilize renal function when BP fluctuates preventing functional/structural impairment during low BP, but also to protect the glomerulus from transmission of high pressures to the glomerulus. This study, in humans, tested whether renal autoregulation exists and can fail in humans, and whether imprints of myogenic response (MR) and tubuloglomerular feedback (TGF) can be detected in the pressure-flow relationship.

Methods: In 15 subjects who were undergoing cardiac catheterization, we also assessed RBF at 50 Hz using a Doppler-based flow velocity measurement by introducing a FloWire (Volcano) catheter into the renal artery for 5-10 minutes and using renal artery diameter. Renal artery pressure (RAP) was measured in the abdominal aorta at the origin of the renal artery. The BP/RBF relationship was analyzed using moving 10s windows for autoregulation efficiency and with time series analysis to investigate myogenic response.

Results: Of the 15 (1F/14M) recordings 14 could be analyzed. Average MAP was 80+8 mmHg, RBF 463+208 ml/min, and slope of 10s windows with a significant change in MAP 5 ml/min/mmHg. When divided into better and poorer autoregulation, RBF was significantly higher in the group with worse autoregulation. MR and TGF signatures could be identified in the Gain, Coherence and Phase plots.

Conclusions: The use of this newly developed method to assess autoregulation efficiency established by MR revealed good efficiency among half of the individuals. In summary, this approach makes it possible to investigate RBF dynamics, MR and TGF and efficiency of autoregulation in humans. Further studies are being undertaken to refine the analytical methodology for these human samples and to compare patients with and without heart failure with respect to RBF dynamics. In the future, this methodology may provide a more physiological parameter to assess diagnosis, prognosis and therapeutics in patients with heart or circulatory failure.

TH-PO368

Deletion of Endothelial Mineralocorticoid Receptors Confers Protection Toward Altered Contractility in Renal Vessels during Endothelial Dysfunction Henrik Dimke,[1] Sidsel Brandt Laursen,[1] Stine Louise Høyer Finsen,[1] Susan E. Quaggin,[2] Pernille B. Hansen.[1] *[1]Dept of Cardiovascular and Renal Research, Univ of Southern Denmark, Odense, Denmark; [2]Feinberg Cardiovascular Research Inst and Div of Nephrology and Hypertension, Northwestern Univ, Chicago, IL.*

Background: Aldosterone blockade confers substantial cardiovascular protection. The effects of aldosterone on mineralocorticoid receptors (MR) expressed in endothelial cells (EC) within the renal vasculature have not been delineated. We hypothethized that lack of MR in EC may be protective in renal vasculature in models of hypertension and endothelial dysfunction.

Methods: To examine the role of the MR in EC we utilized transgenic Tie2-Cre mice to ablate the MR gene (EC-MR). Blood pressure, heart rate and PAH clearance were measured using indwelling catheters in conscious mice. The role of the MR in EC on constriction and relaxation was investigated in the renal artery and in perfused afferent arterioles. Urinary sodium excretion was determined by use of metabolic cages after 4 weeks of AngII infusion.

Results: EC-MR transgenics had markedly decreased MR expression in isolated aortic endothelial cells as compared to littermates (WT). Baseline as well as the rise in blood pressure and renal plasma flow following one week of AngII infusion was similar between WT and EC-MR. No differences in constriction and relaxation was observed in isolated renal arteries between groups during baseline. Endothelial dysfunction, as evidenced by decreased acetylcholine-induced relaxation was evident in both genotypes after 4 weeks of AngII infusion. However, increased contractility of renal arteries was seen only in WT, but not EC-MR mice after infusion. The constriction of afferent arterioles from untreated mice was not different. No differences were found between the groups with respect to urinary and fractional excretion of sodium after 4 weeks on AngII infusion.

Conclusions: Deletion of the MR in EC does not confer protection towards the development of AngII-induced hypertension and endothelial dysfunction in renal arteries. However, loss of MR in EC prevents an augmented contractile response to constrictors under these conditions.

Funding: Private Foundation Support

TH-PO369

Anti-Hypertensive Effect of Thiazides Shifts from Salt Excretion to Vasorelaxation during Salt Restriction or Volume Depletion Saeed Alshahrani,[1] Kamyar A. Zahedi,[1] Min Jiang,[2] Michelle L. Nieman,[3] Sharon L. Barone,[1] John N. Lorenz,[3] Jack Rubinstein,[2] Manoocher Soleimani.[1] *[1]Divs of Nephrology, Univ of Cincinnati; [2]Cardiology, Univ of Cincinnati; [3]Cellular and Molecular Physiology, Univ of Cincinnati.*

Background: Thiazide derivatives, including hydrochlorothiazide (HCTZ), are specific inhibitors of the $Na^+.Cl^-$ Co-transporter (NCC), and the most commonly used diuretic to treat mild hypertension. Both renal (natriuretis) and extra renal (vasorelaxation) mechanisms have been proposed as major mediators of blood pressure reduction by HCTZ but the circumstances under which the renal or extra renal mechanism predominates remain unknown.

Methods: Systemic blood pressure was monitored by intra-arterial catheter and computerized tail cuff in transgenic mice lacking NCC under varying conditions. Pendrin KO or pendrin/NCC double KO (dKO) mice were used to ascertain the compensatory role of pendrin in salt reabsorption in response to HCTZ.

Results: Pendrin KO mice were the only group which showed enhanced salt excretion in response to HCTZ, with salt excretion increasing by ~30% in pendrin KO vs. WT mice (p<0.05). In mice lacking NCC, HCTZ significantly reduced the systemic blood pressure only during salt restriction and without enhancing salt excretion. In volume depleted but not in volume resuscitated NCC/pendrin dKO mice, HCTZ caused dramatic reduction in systemic blood pressure from 72.13± 5.1 at baseline to 51.06 ± 6.6 mm Hg in dKO mice

within 20 minutes of HCTZ administration (p<0.01 vs. baseline) with no significant effect in WT mice (p>0.5 vs. baseline) or in salt resuscitated NCC/pendrin dKO mice. There was no enhancement in salt excretion and no reduction in cardiac output in pendrin/NCC dKO mice in response to HCTZ. The antihypertensive effects of HCTZ were abrogated in the presence of paxilline, a specific blocker of BK channel, which is upregulated in arterial vasculature of volume depleted mutant mice.

Conclusions: Thiazides reduce blood pressure predominantly via vasorelaxation during salt restriction/volume depletion; whereas, they enhance salt excretion during salt replete state and specifically in conditions associated with pendrin inactivation.

Funding: VA Support

TH-PO370

The Metabolic Syndrome Does Not Affect Development of Collateral Circulation in the Post-Stenotic Swine Kidney

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Background: Development of collateral circulation around a stenotic renal artery contributes to maintenance of renal blood flow (RBF) in the ischemic kidney. Stenotic kidney RBF is elevated in the metabolic syndrome (MetS) compared to lean pigs, but the underlying mechanism is unclear. We hypothesized that MetS increased collateral circulation around renal artery stenosis (RAS).

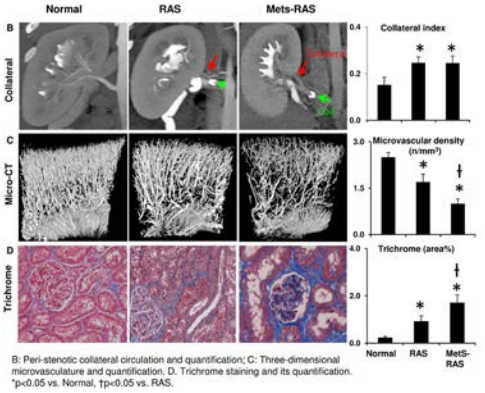
Methods: Unilateral RAS was induced using a coil [figure1B] in 14 domestic pigs after 6 weeks of either an atherogenic (high-fat/fructose, MetS-RAS) or standard diet, which then continued for 10 more weeks. Pigs on standard diet served as controls (n=7 each group). At completion of diet, RBF, glomerular filtration rate (GFR), and the peri-stenotic collateral index (CI) were assessed in vivo using multi-detector computed tomography (CT). CI was assessed as the fractional vascular volume in the zone encompassing visually discernible collaterals around the stenotic segment of the renal artery. The intrarenal microcirculation was examined ex vivo by micro-CT by the spatial density of microvessels, and renal fibrosis by trichrome staining.

Results: MetS-RAS developed obesity, dyslipidemia, and insulin resistance [figure1A]. RBF and GFR were decreased in RAS, but not in MetS-RAS, whereas their peri-stenotic CI's were similar [figure1B]. Conversely, intra-renal microvascular loss and fibrosis were greater in MetS-RAS [figure1C-D].

A

	Normal	RAS	MetS-RAS
MAP (mmHg)	89.6±2.1	97.2±2.0*	129.6±9.1*†
Total cholesterol (mg/dl)	103±34	102±27	377.7±84.6*
HOMA-IR (μU/ml×mg/dl)	0.6±0.1	0.8±0.1	1.9±0.1*†
Renal blood flow (ml/min)	676.9±34.6	544.6±42.7*	648.6±10.9†
Glomerular filtration rate (ml/min)	97.9±5.3	85.8±6.2*	95.2±3.4
Degree of stenosis (%)	-	64.8±3.8	65.0±5.0

MAP: mean arterial pressure; HOMA-IR: homeostasis model assessment insulin resistance.
*p<0.05 vs. Normal, †p<0.05 vs. RAS.



B: Peri-stenotic collateral circulation and quantification; C: Three-dimensional microvasculature and quantification. D. Trichrome staining and its quantification.
*p<0.05 vs. Normal, †p<0.05 vs. RAS.

Conclusions: The unaltered collateral vessel formation in the stenotic MetS compared to lean kidneys argues against a major contribution of the collateral circulation to preservation of RBF, which might be secondary to hemodynamic factors in MetS-RAS. Nevertheless, despite preserved RBF, the post-stenotic kidney shows microvascular loss, possibly due to MetS-induced fibrosis.

TH-PO371

Renal Nerves Mediate Increased Renal Vascular Resistance in Response to Moderate but Not Severe Elevation of Renal Venous Pressure in Rats

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Background: Heart failure (HF) often coincides with renal dysfunction, leading to significant and unexplained mortality, thus emphasizing the intricate connection between cardiac and renal systems. HF-induced elevation of central venous pressure translates to increased renal venous pressure (RVP) which may, in turn, impair renal function. We hypothesized that increases in RVP lead to increased renal vascular resistance (RVR) modulated by renal nerves. **Objectives:** (1) Determine the impact of selective RVP increase (10 or 20 mmHg) on renal hemodynamics, (2) Elucidate the contribution of renal nerves.

Methods: Blood pressure and RVP were assessed in anesthetized rats (300-400g, n=38). FITC-inulin was infused i.v. and urine collected to assess GFR; renal arterial blood flow (RBF) was directly measured. Rats were intact or subjected to bilateral renal denervation (RD). Following baseline measurements, RVP was selectively increased to either 10 or 20 mmHg by partial occlusion of the left renal vein for 120 min or not manipulated (time controls).

Results: Moderate elevation of RVP (1.1±0.3 to 11.3±0.4 mmHg, n=10) decreased RBF in intact rats with a concomitant increase in RVR (p<0.001, n=5). RD did not prevent a fall in RBF, but completely abolished the RVR increase (p<0.05, n=5). GFR remained unaltered in each group. Augmented RVP elevation (0.5±0.1 to 20.1±0.2 mmHg, n=12) similarly decreased RBF and increased RVR in intact rats (p<0.05, n=8), however, this was not prevented by RD (p<0.001, n=4). GFR dropped in both intact (1.2±0.1 to 0.3±0.1 mL/min, p<0.001) and RD (1.4±0.1 to 0.1±0.07 mL/min, p<0.001) rats.

Conclusions: Elevated RVP directly modulates renal hemodynamics, inducing significant reduction of RBF and GFR as well as a sustained increase in RVR, which appears to be differentially mediated by renal nerves at moderate and high levels of RVP.

SH and XH equally contributed to this work.

Funding: Private Foundation Support

TH-PO372

Transglutaminase Is a Critical Link between Inflammation and Hypertension

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Background: The pathogenesis of essential hypertension is multifactorial with different underlying mechanisms contributing to disease. We have recently shown that TNF superfamily member 14, LIGHT (also known as TNFSF14), induces hypertension when injected into mice. Research reported here was undertaken to examine the role of transglutaminase (TGase) in LIGHT induced hypertension.

Methods: Six to eight mice for each group were infused with LIGHT by minipump. Recombinant mouse LIGHT (R&D Systems, Minneapolis) was delivered at a rate of 4ng/day into mice for 14-days. Cystamine treated mice were provided drinking water containing 0.9 g/L cystamine dihydrochloride throughout the 14 days. Control mice were infused with saline. We collected urine and measured blood pressure at 0,3,7,10,14 days. After treatment for 14-days, mice were sacrificed.

Results: Initial experiments showed that plasma and kidney TGase activity was induced by LIGHT infusion and was accompanied with hypertension and renal impairment. The increase in renal TGase activity corresponded to an increase in RNA for the tissue Tgase isoform, termed TG2. Pharmacologically we showed that LIGHT-induced hypertension and renal impairment did not occur in the presence of cystamine, a well-known competitive inhibitor of TGase activity. Genetically we showed that LIGHT-mediated induction of TGase, along with hypertension and renal impairment, was dependent on IL-6 and endothelial HIF-1α. We also demonstrated that IL-6, endothelial HIF-1α and TGase are required for LIGHT induced production of angiotensin receptor agonistic autoantibodies, AT_1AA.

Conclusions: Thus, LIGHT induced hypertension, renal impairment and the production of AT_1-AA require TGase, most likely the TG2 isoform. Our findings establish TGase as a critical link between inflammation, hypertension and autoimmunity.

TH-PO373

Renal Cortex and Medulla Oxygenation during Chronic Angiotensin II Infusion in Conscious Rats

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Background: Angiotensin II (AngII) infusion persistently increases renal vascular resistance. We previously found reduction in renal cortical oxygenation during acute infusions of AngII in conscious rats [EDTA 2014]. Experiments under anaesthesia suggested impaired renal oxygen delivery. Here we characterize chronic effects of AngII infusion on tissue oxygen levels of kidney cortex and medulla in conscious rats using telemetric pO_2 recording.

Methods: Telemetric oxygen-sensitive carbon paste electrodes were implanted in Sprague-Dawley rats (250-300 g), either in renal cortex (n=7) or medulla (n=7). In vivo hyperoxia/hypoxia inhalation was performed weekly to test signal responsiveness. After recovery and baseline oxygen level assessment, 300ng/kg/min AngII was infused for 2 weeks by s.c. osmotic minipumps. Losartan (300mg/L) was added to drinking water for 2 days. Blood pressure was monitored by telemetry in a separate group (n=5).

Results: Hyperoxia/hypoxia confirmed sensitivity for reproducibly detecting changes in tissue oxygen throughout the experiment. Upon hyperoxia, oxygen increased more in cortex than in medulla (peak change relative to baseline at 100% oxygen was 297±56% in cortex vs. 131±5% in medulla). There was sustained increase in blood pressure during AngII infusion (from 95±2 to 168±12mmHg, P<0.01). Renal oxygen decreased transiently during the first 20 hours of AngII infusion in both cortex and medulla. Losartan increased oxygen levels during the first 8 hours (peak change compared to 12 hours before losartan was 121±19% in cortex and 125±20% in medulla, P≤0.05).

Conclusions: Our data suggest that less oxygen reaches medulla than cortex during hyperoxia, possibly due to countercurrent vasa recta that enable oxygen shunting. Chronic AngII exposure at levels that induce hypertension only causes transient hypoxia in both cortex and medulla. This suggests renal adaptation to hypoxia either by altered metabolic demand due to decreased blood flow or increased efficiency of oxygen consumption.

Funding: Government Support - Non-U.S.

TH-PO374

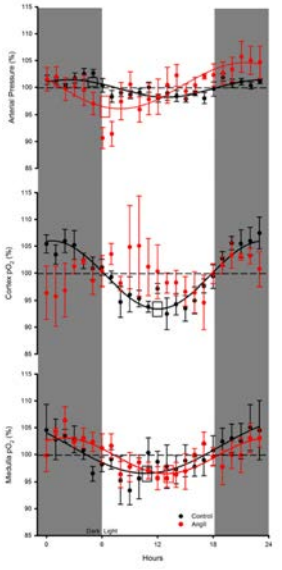
Circadian Rhytm in Kidney Tissue Oxygenation Tonja Emans,[1,2] Jaap A. Joles,[2] C.T.P. (Paul) Krediet.[1] *[1]Internal Medicine-Nephrology, AMC-UvA, Amsterdam, Netherlands; [2]Nephrology & Hypertension, UMC Utrecht, Netherlands.*

Background: Blood pressure, renal hemodynamics, electrolyte and water excretion all display diurnal oscillation. Disturbance of the renal circadian clock is associated with hypertension. Kidney oxygenation is dependent on oxygen delivery and consumption that in turn are regulated by renal hemodynamics and metabolism. We hypothesized that i) kidney oxygenation also demonstrates 24h periodicity, and ii) this periodicity is disturbed during angiotensin (Ang)II infusion.

Methods: Telemetric oxygen-sensitive carbon paste electrodes were implanted in Sprague-Dawley rats (250-300g), either in renal medulla (n=7) or cortex (n=7). Rats were housed in a 12h light-dark cycle. Arterial pressure (MAP) was monitored by telemetry in a separate group (n=5). After 2 weeks of stabilization and recovery, hypertension was induced by s.c. osmotic minipumps containing 300ng/kg/min AngII. Both at baseline and during AngII 5 consecutive days were analysed for periodicity. The first 3 days of AngII were not analyzed.

Results: MAP was 97±2 mmHg during active dark phase and 94±2 mmHg during daytime (P<0.01). During the dark oxygen levels increased to 106±2% in cortex and 104±4% in medulla (vs. baseline; P≤0.05). During the light oxygen levels decreased to 95±2% in cortex and 98±3% in medulla. Data was analysed for rhythmicity by curve fitting and 95% confidence intervals (rectangles in figure). During AngII rhythmicity for oxygenation was lost in cortex but not in medulla. There was a shift in MAP pattern.

Conclusions: We detected significant 24h periodicity in cortex and medulla oxygen based on curve fitting. Possibly oxygen levels in the kidney follow renal blood flow, which determines oxygen delivery and peaks in the active phase (at night) and troughs during the resting phase [Pons *et al.* AJP 1996;271:R1002]. Periodicity in cortex oxygen was disturbed by AngII, possibly by persistent vasoconstriction.



Funding: Government Support - Non-U.S.

TH-PO375

The Ablation of Dendritic Cells Prevents Hypertension and Enhances Natriuresis in Angiotensin II and High-Salt Diet Treated Mice Patricio A. Araos,[1] Daniel E. Hevia,[1] Carolina E. Prado,[2] Rodrigo Pacheco,[2] Luis F. Michea.[1] *[1]Millennium Inst on Immunology and Immunotherapy, ICBM Facultad de Medicina, Univ of Chile, Santiago, Chile; [2]Laboratory of Neuroimmunology, Fundación Ciencia & Vida, Santiago, Chile.*

Background: Angiotensin II (AngII) and high salt diet (HS) cause hypertension, endothelial dysfunction and the upregulation of renal sodium transporters. Our previous studies showed that the ablation of Dendritic Cells (DCs) in mice prevented hypertension and the increased expression of renal sodium transporters. In the present study we evaluated if the ablation of DCs modified natriuresis and arterial function in AngII+HS treated mice.

Methods: We studied wild type (WT) mice and CD11c.DOG transgenic mice (CD11c) for the selective elimination of DCs by Diphteria Toxin (DT) injection. WT and CD11c mice were divided into 3 groups: AngII+HS (AngII=1.042 µg/Kg/min+1% NaCl in drinking water), AngII+HS+DT (DT=8ng/g) and control. Blood pressure (BP) and urinary sodium excretion was analyzed. At days 4 and 14, we made saline challenge test (injection of isotonic saline; 10% of BW) and measured 4h natriuresis. We obtained aortic rings at day 14 for vascular reactivity and endothelial function studies.

Results: WT mice of AngII+HS and AngII+HS+DT groups showed similar increase of SBP. However, the injection of DT prevented the increase of SBP in CD11c mice. Telemetric studies confirmed high BP of AngII+HS CD11c mice (PAM=144±21 mmHg; SBP=160±26 mmHg, day14) that was prevented by the ablation of DCs (PAM=92.7±20 mmHg and SBP=104±26 mmHg). The AngII+HS treatment increased 24h natriuresis (19.4±7.6 µEq/g BW); the ablation of DCs further increased natriuresis (30±7.9 µEq/g BW; n=5; P<0.05) in CD11c mice. Natriuresis after saline challenge test in AngII+HS mice was similar in WT and CD11c mice at day 4. However, the DT injection in CD11c mice increased natriuresis in 27% compared to the other AngII+HS groups (P<0.05). Aortic rings showed similar vascular reactivity and endothelial function in all AngII+HS groups.

Conclusions: The results suggest that DCs modulate tubular sodium reabsorption in response to AngII and high salt diet. FONDECYT1130550, IMII P09-016-F, BECA CONICYT 21130482.

Funding: Government Support - Non-U.S.

TH-PO376

Central Nervous System Expression of Epithelial Sodium Channels and Regulatory Proteins in Secondary Hypertension following Renal Artery Stenosis Md. Shahrier Amin,[1] Mazen Osman,[2] Karen R. Lien,[2] Zeng Hu,[2] Sonu Kashyap,[2] Joseph P. Grande.[1,2] *[1]Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; [2]Mayo Foundation for Medical Research, Mayo Clinic, Rochester, MN.*

Background: Central pathways involving epithelial sodium channels (ENaC) contribute to sympathetic hyperactivity in salt sensitive hypertension. Whether or not these pathways are involved in the pathogenesis of secondary hypertension due to renal artery stenosis (RAS) has not been studied.

Methods: We studied protein distribution by immunohistochemistry of ENaC α, ENaC β, ENaC γ, mineralocorticoid receptor (MR) and serum and glucocorticoid regulated kinase-1 (SGK1), in brain areas involved in sodium homeostasis and regulation of BP in C57BL6 mice with unilateral RAS (n=9) compared to sham controls (n=5) at 4 weeks. RAS was achieved by placement of a 0.2 mm polytetrafluoroethylene cuff on the right renal artery.

Results: Unilateral RAS for 4 weeks was associated with decreased kidney weight (32±14 g) and global atrophy (88±21%) in the stenotic kidney vs non-stenotic kidney (184±20 g, no atrophy), and a modest increase in BP (124±9 mm Hg vs 90±15 mm Hg at baseline). Increased cytoplasmic abundance of all three ENaC sub-units was noted in the sub-fornical organ, supra-optic nucleus, para-ventricular nucleus and hippocampus, compared to other brain areas. RAS did not cause a significant change in staining intensity or distribution in these areas. However, increased apical staining in microvilli was noted for ENaCγ only in the choroid plexus. Staining for MR was mostly nuclear and cytoplasmic, and was not affected by RAS. Strong cytoplasmic immunostaining for SGK1 was noted in the magnocellular neurons, which also remained unaffected by RAS.

Conclusions: We noted increased staining for ENaCγ in the apical membrane and microvilli of the choroid plexus epithelia following unilateral RAS. Redistributed ENaCγ may contribute to formation of functionally active channels and act as a compensatory mechanism to reabsorb Na from the cerebrospinal fluid. No changes in protein expression in the hypothalamic nuclei, supports the observations that central MR-ENaC regulated pathways are primarily involved in salt sensitive hypertension.

Funding: Private Foundation Support, Clinical Revenue Support

TH-PO377

Dietary Potassium Regulates Renal Kallikrein, Renin and Cyclooxygenase-2: Morphological Evidence Carlos P. Vio,[1] Natalia A. Mendez,[1,2] Daniela P. Salas,[1] Jessica Diaz-Elizondo,[1] Mariana Labarca,[1] Carlos Cespedes.[1] *[1]Center for Aging and Regeneration, Dpt Physiology, Pontificia Univ Catolica de Chile, Santiago, Chile; [2]Inst of Anatomy, Histology, Pathology, Univ Austral de Chile, Valdivia, Chile.*

Background: The importance of dietary potassium in health and disease is underscored compared with that placed on dietary sodium. Much effort has been placed on reduction of sodium intake and less on the adequate dietary potassium, although natural food contains 10-15 times more potassium than sodium. The benefits of a potassium-rich diet are known, and recent evidence showed that high potassium diet dephosphorylate NCC resulting in acute natriuresis. With the hypothesis that dietary potassium regulates renal sodium excretory hormonal systems at long-term, we studied the effect of high potassium diet on kallikrein (Kall), renin and cyclooxygenase-2 (COX-2).

Methods: SD male rats on a normal sodium diet received normal potassium (0.9%, NK) or high potassium diet (3%, HK) for 4 weeks. Urine was collected in metabolic cages for measurement of electrolytes and enzyme activities. Renal tissue was used to analyze protein (Western blot) and mRNA (RT-qPCR) levels, and immunohistochemistry for morphometric analysis.

Results: Kall was restricted to connecting tubule cells, HK increased the Kall positive cell size and immunostaining area; cells were hypertrophied with increased Golgi and secretory-like vesicles. Cell changes were associated with increased enzyme activity (p<0.005), increased protein (p<0.05) and mRNA levels (p<0.01). Renin staining was restricted to granular cells of the afferent arteriole; a HK diet decreased the number of renin positive cells and renin mRNA levels (p<0.01). COX-2 containing cells were restricted to a subset of thick ascending limb segment and in response to HK decreased number of COX-2 cells was observed with decreased protein (p<0.01) and mRNA levels (p<0.05).

Conclusions: The increased renal kallikrein and decreased renin are consistent with the their contribution to the natriuretic and renoprotective effect of potassium. Downregulation of COX-2 could be compensatory and requires further study.

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Funding: Government Support - Non-U.S.

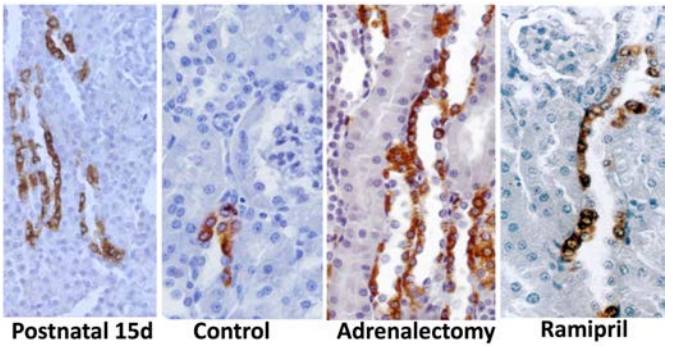
TH-PO378

Cyclooxygenase-2 Increases Its Expression by Recruitment of Neighboring Epithelial Cells from the Thick Ascending Limb of Henle Carlos P. Vio,[1] Natalia A. Mendez,[1,2] Carlos Cespedes.[1] *[1]Center for Aging and Regeneration, Dept Physiology, Pontificia Univ Catolica de Chile, Santiago, Chile; [2]Inst Anatomy, Histology and Pathology, Univ Austral de Chile, Valdivia, Chile.*

Background: Cyclooxygenase-2 (COX-2) is an enzyme that contributes to regulation of renal function via local prostaglandins. We described its origin in a subset of cells from the thick ascending limb of Henle (TALc). COX-2 is regulated in physiological conditions by dietary sodium, glucocorticoids, postnatal development and a negative feedback loop mediated by PGE_2 EP3 receptor. COX-2 increases its expression along the axis of the TAL segment and we hypothesize that this follows a recruitment pattern.

Methods: We used renal tissue from a wide variety of conditions, some are new experiments such as SD adult rats with adrenalectomy (ADX), or treated with coxibs (rofecoxib), or with ACEi (ramipril), or AT1 blockers (ARBs, losartan), or EP3 antagonist (L-798106). Other tissue was obtained from our collection of stored tissue: microdissected nephrons from treated rats, or early postnatal ages (5 to 15 days). The tissue was stained by immunohistochemistry, the levels of the enzyme quantified by its protein by Western blot and mRNA by RT-qPCR.

Results: A wide variety of stimuli produced the same pattern of recruitment of epithelial cells from TAL, with highest levels during early postnatal age, lowest levels in adult, and increased in ADX, ACEi, ARBs or EP3 antagonist. This axial recruitment was confirmed in microdissected nephrons.



Conclusions: Regardless of the stimuli, when COX-2 increases, a recruitment phenomenon was observed. The recruitment phenomenon is rare, and the most studied is a similar recruitment observed with renin expression in the afferent arteriole. Both COX-2 and renin recruitment share similarities like regulation by sodium, postnatal development, ACEi and ARBs. Funding Fondecyt 1130741, CONICYT PIA/Basal PFB12, SQM.

Funding: Government Support - Non-U.S.

TH-PO379

TLR4/NFkB Inhibition Strongly Attenuated Renal and Vascular Injury in the Chronic NO Synthase Inhibition/Salt Overload Model Fernanda F.F. Zambom,[1] Karin C. Oliveira,[1] Victor F. Avila,[1] Camilla Fanelli,[1] Simone C.A. Arias,[1] Flavia G. Machado,[2] Claudia R. Sena,[1] Vivian L. Viana,[1] Denise M. Malheiros,[1] Niels O.S. Camara,[1] Roberto Zatz,[1] Clarice K. Fujihara.[1] *[1]Univ of Sao Paulo, Brazil; [2]Washington Univ.*

Background: Chronic NO inhibition by Nω-nitroarginine methylester (NAME) combined with salt overload (HS) leads to severe hypertension (HT), albuminuria (ALB) and renal/vascular injury. The mechanisms of inflammation and tissue injury in this model remain poorly understood. We investigated the role of innate immunity in HS+NAME and the possible salutary effects of inhibiting NFκB with pyrrolidine dithiocarbamate (PDTC).

Methods: Male Munich-Wistar rats received oral NAME, 32 mg/Kg/d, and HS (N=11), or HS+NAME+PDTC, 60 mg/kg/d (N=13). Rats given HS only were controls (N=12). After 4 wk, we assessed tail-cuff pressure (TCP, mmHg), ALB (mg/d), glomerulosclerosis (GS, %), glomerular ischemia (GI, %), arteriolar onion skin lesions (OSL, %), interstitial α-actin, collagen 1 (COLL1, %), AngII+ cells and macrophages (MΦ), cells/mm^2. Renal content of IL1β (pg/mg), caspase-1 (Casp1), TLR4 and nuclear p65 (NFκB) was also measured (x HS).

Results:

	HS	HS+NAME	HS+NAME+PDTC
TCP	149±2	209±4[a]	174±4[ab]
ALB	9±3	147±12[a]	37±8[ab]
GS%	0.2±0.1	4.1±1.0[a]	0.7±0.3[b]
GI%	0.6±0.5	11.6±1.9[a]	2.6±1.1[b]
OSL%	1±1	23±3[a]	6±2[b]
COLL1	1±1	3±1[a]	2±1[ab]
MΦint	23±2	131±7[a]	34±6[b]
AngII	2±1	13±1[a]	3±1[b]
α-actin	0.7±0.2	10±1[a]	2±1[b]
IL1β	1.5±0.2	4±1[a]	2±1[b]
Casp1	1.0±0.2	1.6±0.3	1.8±0.5
TLR4	1.0±0.1	2.6±0.4[a]	1.3±0.2[b]
p65	1.0±0.1	2.9±0.3[a]	1.4±0.3[b]
Mean±SE;[a]p<0.05 vs HS, [b]p<0.05 vs HS+NAME			

Expectedly, HS+NAME promoted severe HT, ALB and renal/vascular injury/inflammation. Renal IL1β was increased along with activation of the TLR4/NFκB pathway. PDTC normalized renal IL1β and TLR4, reversed NFκB activation, prevented inflammation and strongly attenuated HT, ALB and renal injury.

Conclusions: Activation of the TLR4/NFκB pathway may promote, and its inhibition may reverse, renal injury in the chronic NOS inhibition model. The participation of other aspects of innate immunity, such as the Casp1/NLRP3 pathway, cannot be excluded. FAPESP/CNPq.

TH-PO380

The Effects of Pitavastatin on Renal Nitric Oxide System in Spontaneously Hypertensive Rats and Wistar-Kyoto Rats Gaizun Hu, Osamu Ito, Masahiro Kohzuki. *Internal Medicine and Rehabilitation, Tohoku Univ Graduate School of Medicine, Sendai, Miyagi, Japan.*

Background: Clinical trials have demonstrated renoprotective effects of atorvastatin (ATV) and pitavastatin (PTV), which belong to the strong statins, are more potent than other statins. We reported previously that ATV attenuated the development of hypertension in SHR with increasing the endothelial and neuronal nitric oxide synthases (eNOS, nNOS) expressions in the kidney, inhibited the eNOS phosphorylation at serine1177 and did not affect expressions in Wistar-Kyoto rats (WKY) . To clarify the mechanisms of antihypertensive and renoprotective effects of PTV, the present study examined the effects of PTV on blood pressure and NO system in the kidney of SHR and WKY.

Methods: Five-week-old, male SHR and WKY were given orally PTV (2mg/kg•day^{-1}) or vehicle for 8 weeks. The renal eNOS, nNOS expressions and eNOS phosphorylation were examined by westernblot.

Results: PTV attenuated the hypertension (220 ± 8 vs. 177± 4 mmHg) and albuminuria(684 ± 66 vs. 398 ± 42 mg/day) without changing plasma total cholesterol or creatinine, but did not change the parameters in WKY. PTV tended to increase NO_x concentration in plasma both in SHR and WKY and significantly increased urinary NO_x excretion in WKY. PTV increased the renal eNOS and nNOS expressions in the medulla of SHR (eNOS; by 182% and 186%, nNOS; by 315% and 194%), PTV increased the renal eNOS and nNOS expressions in the cortex and inner medulla of WKY (eNOS by 181% and 45%, nNOS by 45% and 125%). PTV significantly stimulated the eNOS phosphorylation at serine1177 in the inner medulla (98%) and inhibited the eNOS phosphorylation at threonine495 in the medulla of SHR (50% and 58%). PTV also enhanced the eNOS phosphorylation at serine1177 in the medulla (306% and 158%) and inhibited eNOS phosphorylation at threonine495 in inner medulla of WKY (39%).

Conclusions: PTV attenuates the development of hypertension and albuminuria in SHR. PTV increases the expressions, and activates the eNOS phosphorylation in the kidney of both in hypertensive and normotensive rats. The antihypertensive and renoprotective effects of PTV may be mediated in part by an upregulation of NO system in the kidney.

Funding: Pharmaceutical Company Support - Kowa Pharmaceutical Company, Government Support - Non-U.S.

TH-PO381

Role of Angiotensin II Type 1b (AT1b) in Renal Injury in the DOCA-Salt Hypertension Model Using AT1a Deficient Mice Mikako Hisamichi,[1] Atsuko Ikemori,[1,2] Takeshi Sugaya,[1] Daisuke Ichikawa,[1] Kenjiro Kimura,[3] Yugo Shibagaki.[1] *[1]The Div of Nephrology and Hypertension, Dept of Internal Medicine, St. Marianna Univ School of Medicine, Kawasaki City, Japan; [2]Dept of Anatomy, St. Marianna Univ School of Medicine, Kawasaki City, Japan; [3]JCHO Tokyo Takanawa Hospital, Tokyo, Japan.*

Background: Angiotensin II (Ang II) type 1 (AT1) receptors exist as two isoforms, designated AT1a and AT1b, in rodents. Although AT1a receptors play a major role in myogenic vasoconstriction of afferent arterioles for renal autoregulation and are the murine homologue of the single human AT1 receptor, AT1b receptors were reported to be more related to myogenic response in vascular smooth muscle than AT1a receptors. The aim of this study is to reveal the role of the AT1b receptor on myogenic vasoconstriction in pressure-dependent renal injury.

Methods: Female AT1a deficient($AT1a^{-/-}$) mice were subjected to left nephrectomy and were divided into three groups; the DOCA group received systemic DOCA ($75\mu g/kg^{-1}.min^{-1}$) using tablets and were provided with drinking water containing 1% NaCl for 28 days. We used losartan as a blocker of all AT1 receptors. The DOCA+losartan group was given an oral dose of 25mg/kg/day in addition to injections of DOCA and NaCl, while the control mice underwent sham operations and were provided with only tap water.

Results: Systolic blood pressure was significantly increased on day 28 in the DOCA group, but was not reduced by the losartan treatment. Expansion of the mesangial matrix and increase in urinary albumin induced by DOCA-salt tend to be slightly prevented by the losartan treatment. Both the glomerular size and the score for glomerular sclerosis induced by DOCA-salt were not aggravated by losartan. These results suggested that blocking the AT1b receptor in addition to the AT1a receptor did not increase vulnerability to pressure-dependent glomerular injury.

Conclusions: The AT1b receptor might not contribute to myogenic vasoconstriction of afferent arterioles in the DOCA-salt hypertension model using AT1a deficient mice.

TH-PO383

Renal Afferent Peptidergic Neurons – What Are Primary Stimuli? Tilmann Ditting,[1] Kristina Rodionova,[1] Sonja Loosen,[1] Christian Ott,[1] Roland E. Schmieder,[1] Kerstin U. Amann,[2] Roland Veelken.[1] *[1]Medical Dept 4, Univ of Erlangen, Erlangen, Bavaria, Germany; [2]Nephropathology, Univ of Erlangen, Erlangen, Bavaria, Germany.*

Background: Renal afferent nerves comprise a complicated neuro-paracrine regulatory system influencing the sympathetic nervous system. We tested the hypothesis that the activity of renal afferent neuronal units is primarily altered by inflammatory processes in cardiovascular disease.

Methods: In rats, hypertension was induced by unilateral clipping of one renal artery (2K1Cl model), normotensive renal inflammation (anti Thy-1) by i.v. injection of 1.75 mg/kg BW Thy-1 antibody . Retrograde labelling (DiI) identified renal afferent neurons in the dorsal root ganglion (DRG) (Th11-L2). Patch clamp recordings, i.e. current clamp allowed to characterize neurons as highly active or "tonic" with sustained action potential (AP) firing versus low active or "phasic" (<5 Aps) upon current injections. Electrophysiological parameters and AP properties were determined in all experimental groups, proteinuria and renal morphology for all kidneys.

Results: In renovascular hypertension (mean arterial pressure: 173+12 mmHg) only neurons with projections to the clipped kidneys showed a significant decrease in tonic firing (30.6% [23/75]), the non-clipped kidney showed an unaffected proportion of tonically firing neurons (67.5% [50/74], $p<0.05$). In nephritis, neurons with a tonic, more active response pattern decreased significantly (43,4% vs. 64,8%, $p<0.05$) compared to controls. There was no increase in blood pressure (BP) in nephritic animals. Rats with nephritis exhibited albuminuria (61±6 µg/24h), infiltration of macrophages in the interstitium (26 ± 4 cells/high-power field) and glomeruli (3.7±0.6 cells/glomerular cross-section). In 2K1Cl hypertension, renal inflammation occurred mainly in the glomeruli and interstitium of the nonstenotic kidneys, in clipped kidneys signs of inflammation were signifcantly less.

Conclusions: Inflammation (and hypertension) may play less important roles for the decreased activity pattern of afferent renal neurons in cardiovascular disease. Rather altered perfusion occurring in a clipped kidney with renal stenosis and likely also present in nephritis might be of importance.

Funding: Other NIH Support - Deutsche Forschungsgemenschaft

TH-PO384

Febuxostat Suppresses High Salt-Induced Hypertension and Renal Damages in Dahl Salt-Sensitive Rats Takahiro Miura, Akihiro Sakuyama, Masahiro Kohzuki, Osamu Ito. *Dept of Internal Medicine & Rehabilitation Science, Tohoku Univ Graduate School of Medicine, Sendai, Miyagi, Japan.*

Background: Several clinical studies reported that febuxostat (Fx), a xanthine oxidase (XO) inhibitor, has anti-hypertensive and renal protective effects. However, their mechanisms are not elucidated. We studied whether Fx affects the blood pressure and renal damages in Dahl salt-sensitive (Dahl-S) rats fed a high-salt diet (HS).

Methods: Eight-week-old, male Dahl-S rats were divided into three groups, normal salt diet (0.6% NaCl) group, HS (8% NaCl) group and HS+Fx (3 mg/kg/day, po) group. Every 2 weeks, 24 hours urine sample was collected, and the systolic blood pressure (SBP) was monitored by the tail-cuff method. After 8 weeks, the kidney was removed for XO activity measurement, Western blot analysis, and histologic analysis.

Results: HS intake significantly increased the SBP, urinary protein (UP), plasma creatinine (Cr), uric acid (UA) and urinary H_2O_2 excretion. Fx significantly improved the HS intake-induced hypertension, renal dysfunction and oxidative stress (SBP 209±4 vs.174±6 mmHg, UP 324.5±40.3 vs.152.4±20.9 mg/day, Cr 0.41±0.03 vs.0.29±0.01 mg/dl, UA 1.67±0.21 vs.0.53±0.06 mg/dl, urinary H_2O_2 483.8±47.4 vs.339.6±27.8 nmol/day, $P<0.01$ respectively, HS group vs.HS+Fx group). HS intake increased the XO activity and expression in the renal cortex, outer medulla, andproximal tubules, but not in the medullary thick ascending limbs. Immunohistochemical analysis showed that HS intake increased the XO expression in the proximal tubules and outer medullary interstitium. HS intake significantly increased index of glomerular sclerosis (IGS), desmin-positive area of glomeruli, relative interstitial volume (RIV) and ED-1 infiltration, and Fx significantly suppressed the HS intake-induced renal damages.

Conclusions: Fx suppresses the HS intake-induced hypertension and renal damages in Dahl-S rats. Fx may have anti-hypertensive and renal protective effects in patients with salt-sensitive hypertension.

Funding: Pharmaceutical Company Support - Teijin Limited, Government Support - Non-U.S.

TH-PO385

Fetal Programming of Renal Function and Blood Pressure by Maternal Circadian Disruption Natalia A. Mendez,[1,2] Karina Vergara,[1] Carlos Spichiger,[1] Diego Halabi,[1] Carlos P. Vio,[2] Hans Richter,[1] Claudia Torres-Farfan.[1] *[1]Anatomy, Histology and Pathology, Univ Austral de Chile, Valdivia, Chile; [2]Center for Aging and Regeneration, Dept Physiology, Pontificia Univ Catolica de Chile, Santiago, Chile.*

Background: A potential harmful condition for fetal development is the alteration of the maternal circadian system a novel determinant for fetal programming related to modern 24/7 society. We have demonstrated that gestational chronodisruption (maternal exposure to constant light) affects fetal growth with consequences in adult offspring (endocrine, metabolic and cognitive function). Currently, a number of studies in fetal programming describe hypertension and renal diseases as key targets linked to fetal programming of adult disease, however, the consequences of gestational chronodisruption on blood pressure (BP) control and renal function remain unknown.

Methods: Pregnant rats were housed under chronic rotation of photoperiod (CPS) during gestation until delivery. We studied in males CPS **(CPS)** and control males, gestated in standard photoperiod (1) heart rate (HR), temperature and activity by telemetry (2) gene expression in the kidney and circadian rhythms of hormones (3) BP by tail cuff method, and its response to 4%NaCl as well renal expression of kallikrein.

Results: We found that animals gestated in CPS condition had an increase in the variation of heart rate (measured as standard deviation-SD) during day and night, and that the acrophase of HR was advanced in almost one hour versus control. CPS group display changes in corticosterone, aldosterone and melatonin rhythms and effects on expression of *Sgk1*, *NHE3* and *αENaC* in kidney. Both groups showed circadian rhythms of BP, however adult CPS displayed larger amplitude of the rhythm during night, and responded to 4%NaCl with a significant increase of BP. Decreased protein expression of renal kallikrein was observed in adult CPS in basal condition and after 4%NaCl, relative to control rats.

Conclusions: Our findings show that gestational circadian disruption affects renal function at different levels, including transporters, vasoactive enzymes and blood pressure control.

Funding: Anillo ACT 1116, Fondecyt 1150069, DID-UACh, Chile, CONICYT PIA/Basal PFB12.

Funding: Government Support - Non-U.S.

TH-PO386

Catechol-O-Methyltransferase Deficiency Leads to Hypersensitivity on the Pressor Response against Angiotensin II Norikazu Ueki,[1,2] Satoru Takeda,[1] Daisuke Koya,[2,3] Keizo Kanasaki.[2,3] *[1]Obstetrics and Gynecology, Juntendo Univ, Tokyo, Japan; [2]Diabetology and Endocrinology, Kanazawa Medical Univ, Japan; [3]Div of Anticipatory Molecular Food Science and Technology, Medical Research Inst, Kanazawa Medical Univ, Japan.*

Background: Women with preeclampsia (PE) exhibit hypersensitivity on the pressor response against angiotensin II (AngII). Catechol-O-methyltransferase (COMT) metabolizes 2-hydroxyestradiol (2-OHE2) into 2-methoxyestradiol (2-ME) and COMT deficiency has shown to be associated with PE. We have hypothesized that COMT deficiency is reasonable to explain the molecular mechanisms of the hypersensitivity on the pressor response against AngII.

Methods: We utilized C57BL/6 male mice for all experiments. Mice were subjected to COMT inhibitor (COMTi: 25 mg/kg/day) or olive oil (Control) for 4 weeks, with or without low-dose AngII infusion (ANGII: 70ng/kg/min) for last 3 weeks. The AngII-infused mice were treated with 2-ME (10 ng/day), 2-OHE2 (10 ng/day), or vehicle for last 1 week. We obtained following 6 experimental groups; Control, ANGII, COMTi, COMTi+ANGII, COMTi+ANGII+2-ME, and COMTi+ANGII+2-OHE2. Also we performed similar experiments utilizing in vivo administration of siRNA (20 nmol/week) of COMT instead of COMTi.

Results: NeitherANGII nor COMTi alone exhibited significant alteration in blood pressure compared with Control. When compared to ANGII or COMTi alone, COMTi+ANGII displayed significantly higher blood pressure, increased albuminuria and glomerular endotheliosis; 2-ME normalized such physiological and pathological alterations. 2-OHE2 did nothing in all parameters. Similar phenotypes were observed in COMT siRNA treated mice. In human aortic smooth muscle cells, AngII (100nM) significantly increased AngII receptor type 1 (AT1R) mRNA and protein levels; 2-ME (500nM) suppressed either basal or AngII-induced AT1R levels.

Conclusions: Deficiency in COMT and 2-ME are associated with the hypersensitivity on the pressor response against AngII infusion. Similar mechanisms could be relevant to pregnant status and PE.

TH-PO387

Cyclosporin A Differentially Induces Activation of Renal Salt Transporters in the Distal Nephron Katharina Ilse Blankenstein,[1] Aljona Borschewski,[1] Kerim Mutig,[1] David H. Ellison,[2] Sebastian Bachmann.[1] *[1]Inst für Vegetative Anatomie, Charité Universitätsmedizin, Berlin, Germany; [2]Div of Nephrology & Hypertension, Oregon Health & Science Univ, Portland, OR.*

Background: The calcineurin inhibitor cyclosporin A (CsA) is broadly used for immunosuppression but may cause severe side effects including hypertension and electrolyte imbalance. Mechanisms of CsA-induced hypertension are complex and include renal

effects on salt transporters of the distal nephron. This study was designed to investigate the impact of local and systemic calcineurin inhibition on the function of renal cation-chloride cotransporters, NKCC2 of thick ascending limb and NCC of distal convoluted tubule.

Methods: Normal Wistar rats, vasopressin (AVP)-deficient Brattleboro rats or cultured distal convoluted tubule (DCT) cells (mpkDCT4) were treated with CsA at short (30 mg/kg for 4h) or long term (14 days). Urine was collected in metabolic cages. NKCC2, NCC and their activating kinases (WNK1, WNK4, and SPAK) were evaluated by quantitative PCR, immunoblotting, immunofluorescence and morphological analysis.

Results: Short term CsA administration to Wistar rats induced posttranslational activation of NCC and NKCC2 by increasing their phosphorylation (+ 200 % and + 500 %; $p<0.05$) and surface expression. Activating SPAK phosphorylation was augmented as well (+ 100 %; $p<0.01$). After 14 d of CsA, the diuretic responses to furosemide was higher than in controls (+ 100 %; $p<0.05$) and sodium excretion was diminished (- 20 %; $p<0.05$). CsA (4h) augmented SPAK and NCC phosphorylation in cultured mpkDCT4 cells as well. In the absence of AVP, CsA increased phosphorylation of SPAK and NCC but not NKCC2 in Brattleboro rats, suggesting that AVP is required for the activation of NKCC2 but not NCC in this setting.

Conclusions: Our data suggest that CsA augments the function of NKCC2 and NCC via posttranslational regulatory mechanisms. In contrast to NCC, however, NKCC2 requires baseline stimulation by AVP.

TH-PO388

Comparative Distribution and Localization of Renal Outer Medullary Potassium Channel in Rat, Dog, Rhesus Monkey, and Human Kidney Yonghua Zhu, Yan Cui, Emanuel Zycband, Yan Ni, Maya Dajee, Kathleen A. Sullivan. *Cardiometabolic Disease, Merck Research Laboratories, Kenilworth, NJ.*

Background: The renal outer medullary potassium channel (ROMK) mediates potassium recycling and facilitates sodium reabsorption in renal tubule. Accumulated evidence supports the promise of ROMK inhibitors as a novel target in the treatment of hypertension and heart failure. We set out to explore the distribution and localization of ROMK protein in the kidney of different species in order to facilitate preclinical animal model design and mechanism of action studies, and to ensure the translatability of data from bench to bedside.

Methods: Immunohistochemistry (IHC) allows the localization of proteins to specific regions of the nephron. Using a specific antibody (R80, provided by Welling PA & Wade JB) against rat ROMK and antibodies against Tamm-Horsfall Glycoprotein, a thick ascending limb (TAL) marker, and against Aquaporin 2, a collecting duct (CD) marker, IHCs were performed on normal kidney from rat, beagle dog, rhesus monkey, and human.

Results: Our IHC study revealed that ROMK is conservatively expressed on the apical membrane of tubular epithelial cells of TAL and macula densa (MD) across the four species. However, there are interspecies differences in ROMK expression in CD. In CD of rat and human kidney, ROMK positive stain was found on the apical membrane of cortical CD and medullary CD, consistent with published reports. On the contrary, ROMK positive stain in dog kidney was undetectable in cortical CD and relatively weak in medullary CD. In Rhesus kidney, the expression pattern of ROMK is similar to that of dog kidney.

Conclusions: This study provides comprehensive data demonstrating the localization of ROMK in kidney tissue originating from four different species. Our data revealed that ROMK is primarily expressed in the epithelial cells of TAL and MD and exhibits interspecies expression variability in the collecting ducts. In conclusion, these data suggest a molecular basis for potential species difference in the transporter handing of potassium to further the field's understanding of therapeutic benefit of ROMK inhibitors.

Funding: Pharmaceutical Company Support - Merck & Co., Inc.

TH-PO389

Most SUCNR1 Missense Variants Demonstrate Impaired Activity; Implications for Disease Susceptibility? Claudia Carmone, Peter M.T. Deen. *Physiology, Radboud UMC, Nijmegen, Netherlands.*

Background: The succinate receptor 1 (SUCNR1) is activated by succinate, a mitochondrial metabolite released from cells under metabolic or oxidative stress. In the kidney, the SUCNR1 is expressed in the macula densa cells and yields reduced renin and renal sodium uptake in unstressed mice. In type-1 diabetic (T1DM) mice, with elevated urinary succinate levels due to metabolic stress, the SUCNR1 was essential for T1DM-related renin release and hypertension, but a role for SUCNR1 in human diseases has not been reported yet. Database analysis, however, revealed many missense variants in the human SUCNR1 gene. Here, we tested the functionality of 18 of these.

Methods: Mutations were introduced in the hSUCNR1-mCherry construct. SUCNR1 variant functionality, expression and subcellular localization were tested in transiently-transfected HEK293 and stably-transfected MDCK cells using Ca2+ imaging, immunoblotting (IB) and immunocytochemistry (ICC), respectively.

Results: L26F, I32T, T42A, G47S, T75I, D92Y, I118T, K125R, R129Q, T166I, D174N, A211V, R252Q, R255T, I273L, R281Q, R281W, and Y295C variants were introduced. After succinate stimulation, Ca2+ imaging in HEK293 revealed 9 variants as functional as wild-type (wt). IB analysis revealed that only I32T and wt had similar banding patterns. When expressed at physiological levels in MDCK, the functionality, expression and plasma membrane localization of only I32T was similar to wt. All other variants showed weak IB signals and a different pattern from wt, dispersed subcellular staining and no Ca2+ imaging signal when stimulated with succinate.

Conclusions: Our data reveal that, except for I32T which is like wt, all other 17 missense single nucleotide polymorphisms lead to non-functional, misfolded and endoplasmic reticulum-retained SUCNR1 proteins. If occurring in homozygosity or compound heterozygosity in humans, these mutants are expected to cause hypotension and to prevent development of hypertension in T1DM, and possibly T2DM, variants.

Funding: Private Foundation Support

TH-PO390

Response of Renal Podocytes to High Hydrostatic Pressure: Pathophysiologic Cascade in a Model of Malignant Hypertension Ramzia Abu Hamad,[1] Moshe Stark,[1] Yafit Hachmo,[1] Fadia Hassan,[1] Keren Doenyas-Barak,[1,2] Shai Efrati.[1,2] *[1]Research & Development Unit, Assaf-Harofeh Medical Center; [2]Nephrology Div, Assaf-Harofeh Medical Center.*

Background: Renal injuries induced by increased intraglomerular pressure coincide with podocyte detachment from the glomerular basement membrane. We investigated the pathophysiologic cascade responsible forpodocyte detachment and the cascade's relationship with mesangial cells.

Methods: Rat renal mesangium and podocytes were exposed to high hydrostatic pressure for 1h to simulate malignant hypertension. In some cultures, podocytes were placed in milieu of mesangial cells pre-exposed to pressure, or treated with excessive angiotensin-II, TGF-β1 or the blockers. The resultant detachment, apoptosis and podocyte expression of adhesion proteins, podocin and integrin-β1, were evaluated.

Results: Pressure resulted in increased angiotensin-II production. Via AT1 receptors, this reduced the expression of podocin (54.3±6.06 vs. 84.8±15.6, $p< 0.05$) and integrin-β1 (27±11.3 vs. 55.8±10.5, $p< 0.05$), and culminated in detachment of viable and apoptotic podocytes. Mesangial cells, pre-exposed to pressure, resulted in a greater increase in angiotensin II production than podocytes exposed to pressure (2999.5 ±580 vs. 367±14.1, $p< 0.05$pg/ml). The massively increased concentration of angiotensin by mesangium, together with increased TGF-β1 production (20.5±4.5 vs. 84±30, $p< 0.05$), resulted in increased apoptosis, and considerable detachment of non-viable apoptotic podocytes, with no change in adhesion protein expression.

Conclusions: Malignant hypertension induces podocyte detachment by autocrine and paracrine effects. In direct response to pressure, podocytes increase angiotensin-II production. This leads, via AT1 receptors, to structural changes in the manifestation of adhesion proteins, culminating in detachment of viable podocytes.Further, the adjunct mesangial cellsrespond to pressure by increasing angiotensin-II and TGF-β_1 production, leading to massive apoptosis and detachment of non-viable podocytes.

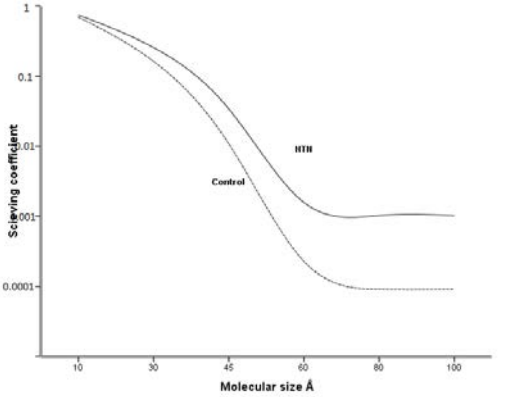
TH-PO391

Functional Alterations in the Glomerular Filtration Barrier in Rats Infused with Angiotensin II Omran Bakoush,[1] Charu Sharma,[1] Nima Nalin,[1] Subramanian Dhanasekaran,[2] Abderrahim Nemmar.[3] *[1]Internal Medicine, College of Medicine and Health Sciences, United Arab Emirates Univ, Al Ain, AbuDhabi, United Arab Emirates; [2]Pharmacology and Therapeutics, College of Medicine and Health Sciences, United Arab Emirates Univ, Al Ain, AbuDhabi, United Arab Emirates; [3]Physiology, College of Medicine and Health Sciences, United Arab Emirates Univ, Al Ain, AbuDhabi, United Arab Emirates.*

Background: Chronic infusion of angiotensin II leads to progressive hypertension and podocyte injury, however, the effect of chronic angiotensin infusion on the glomerular perm-selectivity have been less well characterized. In this study we evaluated the changes in the function of the glomerular filtration barrier caused by chronic angiotensin II infusion.

Methods: Male Wistar rats (n = 5) were fitted with an osmotic minipump and angiotensin II was infused for 7 days at 200 ng/kg/min. The glomerular sieving coefficient was measured for polydisperse inert ficoll molecules with a radius of 10-90 Å. Ficoll is a neutral polysaccharide that is not significantly reabsorbed by proximal tubules, which enables its use for determination of the filtrate-to-plasma concentration ratios for a broad spectrum of molecular radii (10–90 Å).

Results: The glomerular sieving coefficient for Ficoll was significantly increased in rats following chronic angiotensin II infusion compared to control animals. The sieving coefficient increased 1.6 fold for ficoll-20 Å, two-fold for ficoll-35 Å, six-fold to ficoll-50 Å, and ten-fold for ficoll-70 Å.



According to the two-pore theory, these changes are compatible with an increase in the number of large pores and shunts in the glomerular filtration barrier.

Conclusions: Angiotensin II infusion severely impairs the glomerular perm-selectivity to cause a ten-fold increase in the urinary leakage of large molecular weight molecules in the size range of IgG and IgM proteins.

Funding: Government Support - Non-U.S.

TH-PO392

Effect of Diet-Induced Vitamin D Deficiency on Renal Sodium Transporter Expression, Intrarenal RAS and Oxidative Stress Weverton M. Luchi,[1,2] Renato Crajoinas,[1] Antonio C. Seguro,[1] Adriana C.C. Girardi.[1] *[1]Nephrology, Medical School Univ of São Paulo; [2]Federal Univ of Espírito Santo, Brazil.*

Background: Vitamin D Deficiency(VDD) has been linked to hypertension in experimental and clinical studies. Thus, we aimed to test the hypothesis that high blood pressure in VDD rats is associated with altered expression of sodium transporters along the nephron.

Methods: Wistar rats were fed for 30 days with a vitamin D-free(VDD_{30}) or standard diet(controls). Blood Pressure(BP) was measured by tail cuff plethysmography. The expression of sodium transporters and intrarenal Renin-Angiotensin System(RAS) components were evaluated by immunoblotting. Serum concentration of vitamin D and urinary excretion of angiotensinogen(AGT) were determined by ELISA. Intrarenal redox status were analysed by the ratio of thiobarbituric acid reactive substances and glutathione levels(TBARS/GSH).

Results: Compared to controls, VDD_{30} rats had lower serum levels of 25(OH)D(48.0±2.5 vs. 4.2±1.0 ng/mL, p<0.01) and higher BP(153±2 vs. 119±3mmHg, p<0.01). Urinary flow and sodium excretion were not affected by VDD, but it slightly reduced GFR. VDD_{30} rats exhibited higher expression of NKCC2 in medulla(147±12 vs.100±10%, p<0.05) and cortex(157±12 vs.100±10%, p<0.05). No significant changes were observed in cortical levels of NHE3, NCC, NCC phosphorylated at Thr 53 and in cortical and medullary α, β and γ ENaC subunits between groups. However, the levels of NHE3 phosphorylated at Ser 552 were higher in cortex of VDD_{30} rats(200±12 vs.100±11%, p<0.01). Renin expression was only markedly elevated in the medulla of the VDD_{30} rats(207±28 vs.100±25%,p<0.05). Higher expression of cortical AGT(160±18 vs.100±19%,p<0.05) and urinary AGT/Cr ratio(0.35±0.08 vs.0.12±0.01ng/mg,p<0.05) were found in VDD_{30} rats. Angiotensin II concentration was higher in cortex(1.22±0.04 vs.0.60±0.07,p<0.01) and medulla(2.32±0.15 vs.1.55±0.10ng/g,p<0.01) of the VDD_{30}. Also, VDD_{30} rats showed higher TBARS/GSH ratio in cortex(11.5±0.9 vs.1.8±0.4,p<0.01) and medulla(6.9±0.5 vs.3.2±0.3,p<0.01).

Conclusions: These data suggest that VDD leads to altered renal sodium handling and high BP by upregulating NKCC2 coupled with intrarenal RAS activation and oxidative stress. CNPq

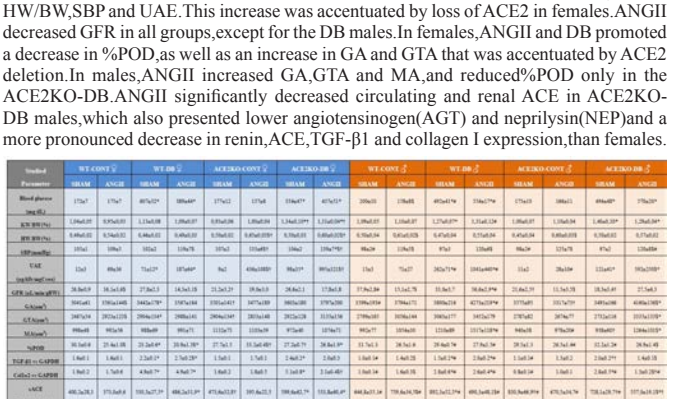
TH-PO393

Sexual Dimorphism in the Diabetic Kidney in Response to ACE2 Down-Regulation and ANGII Infusion Sergi Clotet-Freixas,[1] Maria Jose Soler,[1] Vanesa Palau,[1] Lidia Anguiano,[1] Marta Rebull,[1] Javier Gimeno,[2] Julio Pascual,[1] Marta Riera.[1] *[1]Nephrology, Hospital del Mar-Inst Hospital del Mar d'Investigacions Mèdiques, Barcelona, Spain; [2]Pathology, Hospital del Mar-Inst Hospital del Mar d'Investigacions Mèdiques, Barcelona, Spain.*

Background: Loss of ACE2 exacerbates hypertension in ANGII-infused male mice. Sex influence on the effects of ACE2 deletion in diabetic(DB)mice with ANGII-induced hypertension has not been studied.

Methods: We evaluated wild-type(WT)and ACE2KO streptozotocin(STZ)-induced female and male mice.At week8 of follow-up,minipumps for ANGII infusion were implanted.Kidney/body weight(KW/BW),heart/body weight(HW/BW),systolic blood pressure(SBP),urinary albumin excretion(UAE),GFR,glomerular area(GA),glomerular tuft area(GTA),mesangial area(MA),podocyte number(%POD),circulating(c)and renal(r)ACE activity,and renal mRNA levels of TGF-β1,collagen I,and RAS components were studied.

Results: ACE2KO-DB females showed increased KW/BW than WT.ANGII augmented HW/BW,SBP and UAE.This increase was accentuated by loss of ACE2 in females.ANGII decreased GFR in all groups,except for the DB males.In females,ANGII and DB promoted a decrease in %POD,as well as an increase in GA and GTA that was accentuated by ACE2 deletion.In males,ANGII increased GA,GTA and MA,and reduced%POD only in the ACE2KO-DB.ANGII significantly decreased circulating and renal ACE in ACE2KO-DB males,which also presented lower angiotensinogen(AGT) and neprilysin(NEP)and a more pronounced decrease in renin,ACE,TGF-β1 and collagen I expression,than females.



$ P<0.05 vs SHAM; * P<0.05 vs CONT; † P<0.05 vs WT; # P<0.05 vs FEMALE

Conclusions: Our results suggest a sexual dimorphism in relation to the role of ACE2 in diabetic and hypertensive kidney disease.Loss of ACE2 exacerbated ANGII-induced hypertension,albuminuria and cardiac,renal and glomerular hypertrophy in diabetic females(hemodynamic effect).In diabetic males,ANGII promoted mesangial expansion and podocyte loss in the context of ACE2 deficiency(tissue effect).

TH-PO394

Role of Innate Immunity in a Model of Malignant Hypertensive Nephrosclerosis Victor F. Avila, Orestes Foresto-Neto, Simone C.A. Arias, Camilla Fanelli, Lisienny C.T. Rempel, Mariliza V. Rodrigues, Claudia R. Sena, Vivian L. Viana, Denise M. Malheiros, Jose E. Krieger, Niels O.S. Camara, Roberto Zatz, Clarice K. Fujihara. *Univ of Sao Paulo, Brazil.*

Background: NFkB inhibition by PDTC during rat lactation ($PDTC_{lac}$) promotes moderate hypertension (HT) with no apparent renal injury. With salt overload (HS) and uninephrectomy (UNx), severe HT, glomerulosclerosis (GS), onion-skin renal arteriolar lesions (OSL) and NFκB activation develop. We further investigated the role of innate immunity (InIm) in this model.

Methods: Male newborn rat pups received PDTC or no treatment (C) for 20 d, underwent UNx at 10 wks of age, and were divided in: **C**, standard diet (NS); **$PDTC_{lac}$**, NS; **$PDTC_{lac}$+HS**, HS. After 3 mo, we assessed tail-cuff pressure (TCP, mmHg), GS index (GSI), %OSL, interstitial (I) collagen 1 (%COLL) and macrophages (MØ, cells/mm^2) and, by IHC, TLR4, Caspase1 (Casp1) or IL1β in glomeruli (G, %area) and I (cells/mm^2), as well as the renal content of IL1β, Casp1, TLR4 and nuclear p65.

Results:

	C	$PDTC_{lac}$	$PDTC_{lac}$+HS
TCP	145±2	167±3[a]	193±4[ab]
GSI	3±1	2±1	38±10[ab]
%OSL	0±0	1±1	17±5[ab]
%COLL	3±1	3±1	8±1[ab]
MØ	33±3	35±4	146±23[ab]
Casp1, G	0.7±0.1	1.2±0.2[a]	2.9±0.5[ab]
Casp1, I	3±1	5±1	12±2[ab]
IL1β, G	1.0±0.1	1.4±0.2	2.6±0.4[ab]
IL1β, I	3±1	4±1	8±1[ab]
TLR4, G	0.2±0.1	0.2±0.1	1.0±0.2[ab]
TLR4, I	0.3±0.1	0.6±0.2	2.9±0.6[ab]
p65	1.0±0.1	1.7±0.4	2.6±0.5[a]

Mean±SE, [a]p<0.05 vs C, [b]p<0.05 vs $PDTC_{lac}$.

Even without renal injury, Casp1 was upregulated in $PDTC_{lac}$, whereas TCP correlated with MØ and IL1β, suggesting incipient InIm activation. Expectedly, HS enhanced HT, renal injury/inflammation and the renal content of IL1β, TLR4 and p65 (p<0.05). Casp1 was prominent in OSL. MØ (both G and I) correlated with the respective Casp1, IL1β and TLR4 expressions, suggesting both inflammasome and TLR4/NFkB activation.

Conclusions: InIm is activated early in $PDTC_{lac}$, perhaps reflecting incipient vascular injury. HS enhances InIm, aggravating HT and renal/vascular injury. InIm may be an important mediator of renal injury by HT. FAPESP/CNPq.

Funding: Government Support - Non-U.S.

TH-PO395

Bimodal Action of Intrarenal Afferent Stimulation by Bradykinin on RSNA: Tonic Inhibition after Short Excitation Martin Hindermann,[1] Tilmann Ditting,[1] Kristina Rodionova,[1] Sonja Loosen,[1] Christian Ott,[1] Roland E. Schmieder,[1] Kerstin U. Amann,[2] Roland Veelken.[1] *[1]Dept of Nephrology and Hypertension, Friedrich-Alexander-Univ, Erlangen, Germany; [2]Dept of Nephropthology, Friedrich-Alexander-Univ, Erlangen, Germany.*

Background: Renal afferent nerves (RANs) play an important role in the modulation of renal sympathetic nerve activity (RSNA). We recently reported tonic sympatho-inhibitory action due to intrarenal afferent nerve stimulation by the TRPV1 agonist capsaicin. However, some studies indicate sympatho-excitatory RANs, stimulated by Bradykinin (BK). Since BK is known to augment TRPV1 effects we hypothesized that intrarenally applied BK would rather inhibit than excite RSNA.

Methods: 3 groups of anesthetized rats (n=8, each) were equipped with arterial and venous catheters for blood pressure (BP) and heart rate (HR) recording and drug application; left sided renal arterial catheter for intrarenal administration (IRA) of Bradykinin (BK; group 1) or the TRPV1 agonist capsaicin (CAP, pos. control; group 2) to stimulate RANs (CAP 3.3, 6.6, 10 and $33*10^{-7}$M, 10µl each; BK $10*10^{-6}$M, 20µl and BK $10*10^{-5}$ M; 2.5, 5, 10µl at 30, 45, 60, 75min). Normal saline (IRA NS) served as neg. control (group 3); right sided electrode for RSNA recording; After 105min the NK_1-receptor blocker RP67580 ($10*10^{-3}$M, 15µl).

Results: IRA BK and IRA CAP decreased RSNA from 4.2±0.8 to 1.3±0.2µV*sec (BK, *P*<0.01) and 3,6±0,5 to 0.9±0.2µV*sec (CAP, *P*<0.01) while maximum inhibition was reached within 70 minutes. IRA NS had no effect. Tonically suppressed RSNA (CAP & BK group) was transiently but completely unmasked by systemic (IV) administration of the NK_1-blocker (1.6±0.5 to 8.6±2.9µV*sec; *P*<0.01 (BK); 1.0±0.2 to 6.1±1.5µV*sec; *P*<0,01 (CAP)). IRA BK was associated with short lived (1-2 sec) increases of RSNA (up to 13.3±2.4µV*sec; *P*<0.01).

Conclusions: The effect of intrarenal BK was similar to CAP. Thus, the net effect of intrarenal stimulation of RANs by BK is sympatho-inhibitory in nature. The similarity of NK_1-blocker effects indicates a common final pathway of intrarenal afferent stimulation. However, the nature of the short-lived BK induced RSNA increase remains unclear. Nociceptive effects or differential central processing are possible.

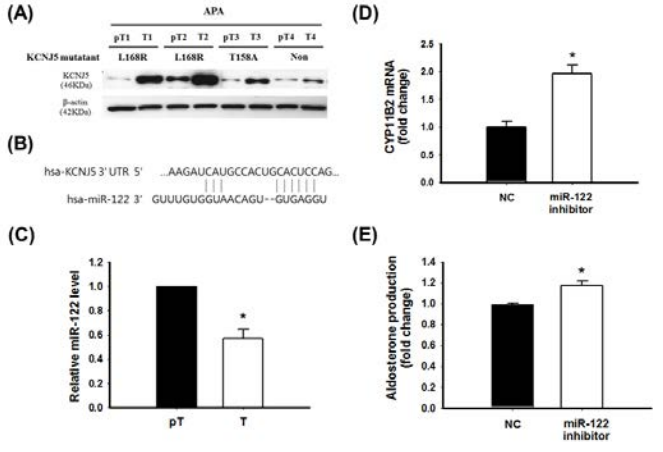
TH-PO396

MicroRNA-122 Regulates Aldosterone Production by Targeting KCNJ5 in Aldosterone-Producing Adenomas Kang-Yung Peng, Vincent Wu. *Dept of Internal Medicine, National Taiwan Univ, Taipei, Taiwan.*

Background: It has been identified that 40%–60% of aldosterone-producing adenoma (APA) patients carry somatic mutations in *KCNJ5* gene. Theses *KCNJ5* mutations lead to reduced K^+/Na^+ channel selectivity *in vitro* and result in increased calcium influx and expression of genes promoting aldosterone synthesis. In this study, we investigate the role of miR-122 in the pathogenesis of APA through targeting *KCNJ5*.

Methods: The expression level of miR-122 in APA and cultured adrenal cells were validated by using quantitative reverse transcriptase polymerase chain reaction (qPCR). Radioimmunoassay (RIA) was used to measure the aldosterone concentration in the culture supernatants. Liposome-mediated transfection of miR-122 inhibitor was constructed into HAC15 human adrenocortical cells. The expression of KCNJ5 was assessed by immunoblotting and qPCR.

Results: Our data showed that KCNJ5 protein was upregulated in APAs compared with peri-tumor tissue. Besides, the upregulated ratio of KCNJ5in APAs tissues than their conterpart with *KCNJ5* mutations were much higher than APA tissues without *KCNJ5* mutations. miR-122 was chosen based on its possible functions, and target prediction by multiple algorithms. The expression of miR-122 was down-regulated in APA when compared to the adjacent non-tumor tissues (p= 0.0207). In cultured HAC15 cells, miR-122 inhibitor augmented aldosterone synthase (CYP11B2) and promoted aldosterone production.



Conclusions: Our findings suggest that miR-122 may mediate some of hyperaldosterone in aldosteronism, in part via regulating KCNJ5 expression. The novel results add another dimension to accumulating evidence regarding further development of new therapies and diagnosis in APA.

Funding: Government Support - Non-U.S.

TH-PO397

Trend Toward Lower Exosomal Thiazide-Sensitive NaCl Co-Transporter Expression after Renal Denervation in Resistant Hypertensive Humans Olivier Bonny,[1,2] Candice Stoudmann,[2] Fanny Durussel,[2] Marc P. Maillard,[1] Johannes Loffing,[3] Grégoire Wuerzner.[1] *[1]Service of Nephrology, Lausanne Univ Hospital, Lausanne, Switzerland; [2]Dept of Pharmacology and Toxicology, Univ of Lausanne, Lausanne, Switzerland; [3]Inst of Anatomy, Univ of Zurich, Zurich, Switzerland.*

Background: The renal sympathetic nervous system is implicated in most forms of hypertension. It has recently been shown in animals that norepinephrine activates the thiazide-sensitive NaCl cotransporter (NCC), which participates to sodium retention in the distal part of the nephron (DCT). However, no data are available in humans. Now, we used human urinary exosomes from timed urine collection before and after renal denervation (RDN) and investigated the acute effect of renal denervation on NCC abundance and phosphorylation.

Methods: Baseline 24 hours blood pressure and sodium excretion were measured before RDN. Timed urines were collected the morning before and the morning after renal denervation. Exosomes were freshly isolated by ultracentrifugation and stored at -80°C. NCC abundance and phosphorylation were analyzed by Western blot. Detection of TSG101 was used to confirm exosome quality and equality of loading.

Results: Thirteen patients (7 women/6 men) with proven resistant hypertension and an estimated GFR ≥ 30 ml/min/1.73m^2 were included in the study. Mean age was 58.2±7.6 years, mean body mass index was 32.9±4.5 Kg/m^2, mean daytime systolic and diastolic blood pressure were respectively 146±17 mmHg and 87.6±12.3 mmHg. In the isolated urinary exosomes, the levels of total and phosphorylated NCC normalized to TSG101 varied considerably at baseline (pre-denervation), but showed a trend towards lower expression levels post-denervation, but without reaching significance though.

Conclusions: Thus, RDN may reduce total NCC abundance and phosphorylation and urinary exosome analysis may represent a mean to monitor the acute effects of RDN. Additional studies are necessary to confirm these initial observations and to assess the long term effects of RDN on renal NCC and possibly other renal transport proteins involved in blood pressure control.

Funding: Government Support - Non-U.S.

TH-PO398

A Novel Chronic Kidney Disease Mouse Model with Hypertension Jin Wei,[1] Jie Zhang,[1] Gensheng Zhang,[1] Shaohui Wang,[1] Lei Wang,[1] Jacentha Lynn Buggs,[2] Ruisheng Liu.[1] *[1]Molecular Pharmacology & Physiology, Univ of South Florida, Tampa, FL; [2]Tampa General Hospital.*

Background: Chronic kidney disease (CKD) affects 26 million American adults and may eventually develop into end-stage renal disease. Hypertension is a leading cause and a common consequence of CKD. Subtotal nephrectomy is a widely used low-nephron CKD model. This model creates hypertension in rats, however, the mouse model exhibits strain-dependent outcomes following subtotal nephrectomy. In particular, C57BL/6 mice are normotensive. The goal of the present study is to create a new CKD model with low nephron numbers and hypertension in C57BL/6 mice.

Methods: The reduction of renal mass was performed by ligating either upper (LU) or lower (LL) branches of the renal artery in the left kidney plus a nephrectomy (UX) of the right kidney. The mean arterial pressure was measured with a telemetry system and glomerular filtration rate (GFR) was measured in conscious mice.

Results: Eight weeks after surgery, there was no significant difference in body weight among LU, LL and control mice. The left kidney weight decreased by 22.7% in LU group (184.3±12.9 mg), and by 22.1% in LL group (185.7±13.2 mg) compared with control mice (238.4±19.1 mg) (n=4/group, p< 0.05 vs control). Both LU and LL mice had a significant decrease in GFR (LU: 128.41±21.47 µl/min and LL: 144.71±23.92 µl/min) compared with the control mice (193.76±13.94 µl/min). Plasma creatinine increased from 0.08±0.01 to 0.18±0.02 mg/dl in LU group; from 0.09±0.01 to 0.17±0.03 mg/dl in LL group; and from 0.08±0.03 to 0.11±0.02 in controls (n=4/group, p<0.05 vs control). The MAP increased and remained elevated at 131.5±12.7 mmHg in LU and 126.8±11.4 mmHg in LL mice. The MAP in control mice did not change (n=3/group, p<0.05 vs control). Proteinuria increased from 2.7±0.3 to 8.1±3.4 mg/24 h in LU; from 2.3±0.9 to 6.7±3.1 mg/24 h in LL mice; and from 2.5±0.9 to 2.7±0.7 in control mice (n=4/group, p<0.05 vs control). Glomerular injury score was 1.4±0.4 in LU mice, 1.2±0.5 in LL mice, and 0.2±0.1 in controls.

Conclusions: In summary, we developed a new CKD model with low-nephron and hypertension by a combination of ligation in renal artery branch and UX in C57BL/6 mice.

Funding: NIDDK Support

TH-PO399

Screening for HLA Linear Epitopes Using Personalized Peptide Array: A Feasibility Study of Alloantibody Specificity in Transplantation Jing Jin, Pan Liu, Tomokazu Souma, Andrew Z. Wei. *Dept of Medicine - Nephrology, Northwestern Univ, Chicago, IL.*

Background: HLA molecules are highly polymorphic cell receptors, posing a major obstacle to the success of organ transplantation. The allorecognition of mismatched donor HLA directly contributes to chronic rejection. DNA typing for HLA is widely used in the clinic and one of the most important challenges is to determine which mismatched transplants will fare well and which should be avoided. Therefore it is desirable to specify antibody reactivity to individual mismatched epitopes.

Methods: We use peptide antigens of donor sequences to probe for antisera specificity in kidney transplant subjects. A large custom panel of 15-residue HLA peptides was synthesized in an array format following one of the two designs: a standard array of a fixed panel of peptides or personalized arrays. The standard array contains 420 peptides derived from a predetermined set of HLA-DQ allelic antigens. The personalized arrays that each includes donor-derived peptides of HLA-A,B,C,DQ and DR sequences were separately synthesized for individual transplant subjects. These arrays were used to probe pre- and post-transplant patients' sera for alloantibodies against the peptide antigens.

Results: The array method detected distinct antiserum patterns among transplant subjects and revealed epitope-levels of specificity largely in accordance with the Luminex single-antigen results. Collective mapping of alloantibody epitopes in five kidney transplant patients revealed a highly antigenic "hotspot" of reactive epitopes in HLA-DQB1 across individual patients and their allelic variants, provided donor-recipient mismatch(es) present within this ~15 amino acid segment.

Conclusions: The peptide arrays robustly detected *de novo* antibodies following transplantation, directly revealing epitope-levels of antibody specificity associated with HLA mismatches. The array method also showed superior sensitivity to the Luminex single-antigen assay. Collectively, our pilot study proved the feasibility of personalized design to achieve high-resolution detections of linear HLA epitopes associated with distinct donor-recipient mismatches.

Funding: Private Foundation Support

TH-PO400

Anti-Fibrotic MicroRNA Strategies in a Mouse Model of Chronic Renal Allograft Dysfunction Celina Schauerte,[1] Song Rong,[2] Michael Mengel,[3] Hermann G. Haller,[2] Thomas Thum,[1] Johan Lorenzen.[1,2] *[1]Inst of Molecular and Translational Therapeutic Strategies (IMTTS), Hannover Medical School, Germany; [2]Dept of Nephrology & Hypertension, Hannover Medical School, Germany; [3]Dept of Laboratory Medicine & Pathology, Univ of Alberta, Canada.*

Background: Pro-fibrotic microRNA-21 (miR-21) is upregulated in chronic allograft dysfunction (CAD), which is characterized by fibrotic remodeling, renal injury and chronic inflammation. This study investigates miR-21 inhibition as a therapeutic approach in an evaluated murine model of CAD.

Methods: Allogenic kidney transplantation (KTx) was performed from male C57BL/6 into female Balb/c. Recipients were treated at day -1 and day 7 either with LNA-scr (control) or LNA-21 (inhibitor of miR-21) (20mg/kg BW, i.p.). Kidneys were analyzed 6 weeks after KTx, e.g. by qRT-PCR, PAS-, Picrosirius Red- and immunostaining. *In vitro* analyses were performed in renal fibroblasts (NRK49F) and macrophages (RAW264.7).

Results: We determined via qRT-PCR increased expression of fibrosis (αSMA, Col1, Col3, FSP-1) and inflammation (IL-6) markers in KTx kidneys which were rescued by miR-21 inhibition. Moreover, Picrosirius Red staining and BANFF scoring (ci and ct) revealed significantly less fibrosis and injury development due to miR-21 inhibition. Besides, allografts of LNA-21 treated mice showed less infiltrated T-cells (CD3) and macrophages (F4/80) visualized by immunostaining. *In vitro* we found LPS-activated macrophages to produce and secrete high levels of IL-6. IL-6 activates the transcription factor STAT3, which has a putative binding site in the miR-21 promoter. We hypothesize, that infiltrating macrophages produce IL-6 which affects resident renal cells causing fibrosis and injury progress. Co-culture assays confirmed a crosstalk between macrophages and renal fibroblasts with increased expression levels of miR-21, primary miR-21, IL-6 and CTGF in fibroblasts. Similar results were observed due to IL-6 treatment of fibroblasts. Furthermore, EMSA verified IL-6-mediated activation of STAT3 in fibroblasts.

Conclusions: MiR-21 antagonism could reduce allograft rejection due to less inflammation and fibrosis and suggests a new essentially needed anti-fibrotic treatment strategy against CAD.

TH-PO401

Role of Brain-Derived Neurotrophic Factor in Chronic Cyclosporine Nephropathy Long Ye Zhang, Shang Guo Piao, Ji Zhe Jin, Can Li. *Nephrology, YanBian Univ Hospital, YanJi, JiLin, China.*

Background: Increasing evidence suggests that Brain-derived neurotrophic factor (BDNF) induces a variety of psychiatric and neurological disorders. However, the role of BDNF in the kidney has yet to be determined. The present study examined the expression of BDNF and tropomyosin-related kinase (Trk) receptors in the kidney in a rat model of chronic cyclosporine A (CsA) nephropathy.

Methods: SD rats were maintained on a low-salt diet and treated daily for four weeks with vehicle or CsA. Basic parameters, histology (tubulointerstitial fibrosis and apoptosis), concentration of the oxidative stress marker 8-OHdG, and expression of BDNF and Trk receptors (TrkB and TrkC) were compared between groups. The effect of vasopressin infusion on the urine-concentrating ability was examined by measuring the expression of AQP-2 and BDNF and urine profiles in normal and CsA-treated rats.

Results: Compared with the vehicle-treated rats, rats given CsA showed renal insufficiency,increased urine volume and number of apoptotic cells, decreased urinary osmolality, and tubulointerstitial fibrosis. Immunohistochemistry showed that BDNF and Trk receptors TrkB and TrkC were constitutively expressed in the collecting duct of thecortex and medulla in vehicle-treated kidneys. This was confirmed by double immunofluorescent stainingfor Na-K-ATPase-α1, AQP-1, and AQP-2. By contrast, the expression of these factors decreased significantly in kidneys from CsA-treated rats. Donwregulation of BDNF and Trk receptors was accompanied by increase in urine volume and decrease in urine osmolality. These changes were reversed by exogenous infusion of vasopressin (all $p<0.05$), whereas AQP-2 expression was unchanged. The number of apoptotic cells correlated closely with BDNF protein expression ($r = 0.-866$, $p<0.001$) and urinary 8-OHdG excretion ($r = 0.884$, $p< 0.001$).

Conclusions: Our findings strongly suggest that long-term CsA treatment suppresses renal BDNF and Trk receptor expressionand thatthese changes are associated with impairment of the urine-concentrating ability in chronic CsA nephropathy. Renal tubular cell apoptosis at least partially accounts for the CsA-induced decrease in BDNF expression.

Funding: Other NIH Support - National Natural Science Foundation of China, Other U.S. Government Support, Clinical Revenue Support

TH-PO402

Quantitative Proteomic Analysis of the Calcineurin Inhibitors-Induced Nephrotoxicity Using the iTRAQ Approach Bastien Burat,[1] Julien Gonzalez,[1] Emilie Pinault,[2] Pierre Marquet,[1] Marie Essig.[1] *[1]UMR INSERM 850, Univ of Limoges, Limoges, France; [2]SCRABL, Univ of Limoges, Limoges, France.*

Background: In solid organ transplantation, Calcineurin Inhibitors (CNI), Cyclosporine A (CsA) and Tacrolimus (Tac), are the backbones of immunosuppressive drugs given to counteract allograft rejection. However, their great efficacy is undermined by their deleterious side effects such as nephrotoxicity whose mechanisms remain widely unknown. Despite their calcineurin similar target, Tac and CsA seem to have each specific nephrotoxicity, which would be of utmost interest to decipher to design new immunosuppressive drugs without such toxicity.

Methods: This study used the untargeted iTRAQ approach, allowing relative proteomic quantitation, to decipher specific modifications of proximal tubular cells induced by CsA or Tac or VIVIT, a specific NFAT pathway inhibitor. LLC PK-1 cells were exposed for 24 hours to CsA (5µM), Tac (0,05µM) or VIVIT (5µM). After cell lysis and trypsin digestion, peptidic samples from the different conditions were labelled with isobaric tags and analyzed by tandem mass spectrometry. Bioinformatic analysis was done through a custom-made and personalized process from the source material to the final bioinformatics steps.

Results: 131 proteins have been identified mainly from the following pathways: protein synthesis and maturation, cytoskeleton organization, metabolism or cell cycle . A third of the proteins were not altered by CNI or VIVIT; 15 proteins were equally overexpressed/repressed by CsA, Tac or VIVIT; most of the proteins were impacted in a Calcineurin-independent CNI-specific way. Na/K-ATPase α-1 subunit, Polypyrimidine Tract-Binding Protein-1 (PTBP-1), High Mobility Group protein B1 (HMGB1), Cofilin and Thymosin β10 were among the most CsA-sensitive. CsA seems to set up new actin cytoskeleton dynamics through RhoGTPases pathways and Calcium-dependent signaling.

Conclusions: Through iTRAQ technology, we demonstrated that each CNI altered the phenotype of tubular proximal cells in a unique and specific way. This bias-free approach is the first step to design new immunosuppressive drugs able to inhibit calcineurin activity without the current CNI nephrotoxic side effects.

Funding: Government Support - Non-U.S.

TH-PO403

Evaluation of CCR6 Expression on T Cells from Monkeys Tolerant of Kidney Allografts Achieved via Mixed Hematopoietic Chimerism Ruichao Yu, Gilles Benichou, Joren Madsen. *Center for Transplantation Sciences, Massachusetts General Hospital, Boston, MA.*

Background: Chemokine receptor 6 (CCR6), which is constitutively expressed by immature dendritic cells (DCs) and by T cells, regulates the migration and recruitment of DCs and T cells during inflammation and immunological responses. CCR6 is expressed by both T helper 17 cells (Th17) and regulatory T cells (Tregs), as well as by T cells with a dual Th17/Tregs phenotype. Tregs co-expressing FoxP3 and IL-17 retain their suppressive function in humans and mice. It is, however, unclear whether $FoxP3^+IL\text{-}17^+$ T cells represent a transitional stage in regulatory T cell differentiation or they display stable suppressive functions in non-human primates (NHPs).

Methods: Mononuclear cells were isolated from the peripheral blood of cynomolgus monkeys (PBMCs). First, the expression of CCR6 on $CD4^+FoxP3^+$ Tregs was compared among tolerant and rejecting animals using flow cytometry. Second, cytokine IL-17 secretion was measured after polyclonal activation of PBMCs by anti-CD3/CD28 Ab-coated beads. Next, we compared CCR6 expression of dual Tregs/Th17 cells isolated from the PBMCs of 1) naïve monkeys, 2) monkeys undergoing rejection of kidney allografts and, 3) monkeys which had been rendered tolerant of kidney allografts following donor mixed hematopoietic chimerism induction (consisting of leukodepletion, costimulation blockade and donor bone marrow transplantation) and short term immunosuppression.

Results: Naive monkey PBMCs expressed CCR6 on Th17 and Tregs, as well as on $FoxP3^+IL\text{-}17^+$ T cells. CCR6 expression was higher on Tregs as compared to T effector cells. After polyclonal activation, the expression of CCR6 was much higher among dual $FoxP3^+IL\text{-}17^+$ T cells (but not Th17 and Tregs) of tolerant monkeys as compared to rejecting animals.

Conclusions: Our data indicate that expression of CCR6 on dual Th17/Tregs is associated with tolerance induction/maintenance of kidney allografts in NHPs treated with our mixed chimerism procedure via regulating the migration and recruitment of T cells.

Funding: Other NIH Support - NIH; NIAID, Government Support - Non-U.S.

TH-PO404

Targeting Histone Deacetylase in Renal Tubular Epithelial Cells Reduces T Cell-Mediated Inflammatory Responses Byeongwoo Kim, Sunwoo Kang, Tae Hee Kim, Yeong Hoon Kim. *Div of Nephrology, Dept of Internal Medicine, Inje Univ Busan Paik Hospital, Busan, Republic of Korea.*

Background: More studies are focusing on renal tubular epithelial cells (RTECs) as a new target to restore inflammatory environment as clarifying their immune regulatory function. Here, we investigated whether histone deacetylases (HDACs) are activated in RTECs during T cell-mediated inflammation and their blockade is able to reducethe inflammatory responses.

Methods: Human renal proximal tubular epithelial cell line HK-2 was cultured in the presenceor absence of recombinant IFN-γ (200 U/ml) plus TNF-a(5 ng/ml). The HDAC activity was determined on the expression levels of acetylated H3 and a-tubulin by immune blot assay. To determine the functional activity of HDAC inhibitor SB939, we analyzed the immune stimulatory phenotype of HK-2 cells such as class II MHC molecule, CD80, CD86, and CD40 by flow cytometry. In addition, the culture supernatants were used for measuring cytokines and chemokines by ELISA assay.

Results: We found that HDAC activity was markedly increased in HK-2 cells by treatment of IFN-γ/TNF-a within 12h. Treatment of pan-HDAC inhibitor SB939 in HK-2 cells completely prevented HDAC activity increased by IFN-γ treatment. SB939 treatment predominantly inhibited up-regulating CD40 expression but not MHC class II, CD80, and CD86. In addition, MCP-1 was significantly inhibited more than IL-6 and TNF-a by SB939 treatment.

Conclusions: Our results demonstrate that 1) HDAC activity is increased in RTECs in response to IFN-γ, 2) which further facilitates T cell-mediated inflammatory responses through CD40 and MCP-1. Therefore, our study suggests that HDAC inhibitor has a therapeutic potential for the treatment of acute renal inflammatory diseases such as allograft rejection in transplantation.

Funding: Clinical Revenue Support

TH-PO405

High Dose Belatacept Is Diabetogenic and Toxic to Pancreatic Islet Cells Long Jin, Jian Jin, Chul Woo Yang. *Convergent Research Consortium for Immunologic Disease, Seoul St. Mary's Hospital, The Catholic Univ of Korea, Seoul, Korea.*

Background: Belatacept is a promising immunosuppressant for replacing calcineurin inhibitors in kidney transplantation, but its side effect is not fully studied. We evaluated whether belatacept is diabetogenic at therapeutic dose.

Methods: Three doses of belatacept (1,2, 4mg/kg) were chosen based on previous animal studies that 2 mg/kg of belatacept is effective in preventing acute rejection in rats. Belatacept was administered intravenously via tail vein on a weekly basis for 4 weeks in rats, and VH group rats received a saline via tail vein injection on the weekly basis for 4 weeks. Body weight, urine volume, and water intake were measured daily before sacrifice. The diabetogenicity of belatacept was evaluated by intraperitoneal glucose tolerance test (IPGTT) and area under the curve for glucose (AUCg) calculated by trapezoidal estimation. Pancreatic beta cells were isolated from experiment animals then AO/PI staining, which was explained viability of islet cells and glucose-stimulated insulin secretion (GSIS) were performed in isolated beta cells.

Results: After four weeks, there is no significant difference in body weight, water intake and 24hr-urine volume between control and belatacept-treated groups. Belatacept 1mg/kg and 2mg/kg treatment increased AUCg from the values obtained during the IPGTT, which was not statically significant. However, received 4mg/kg of belatacept group showed significantly increased blood glucose level at 30 min compared with VH group. Consistently, AO/PI staining showed PI-positive cell death were increased in belatacept 1mg/kg and 2mg/kg treatment groups. However, only treatment with belatacept 4mg/kg significantly increased PI-positive cell death compared with VH group. GSIS also showed a high dose of belatacept significantly decreased insulin secretion.

Conclusions: Our preliminary study clearly defines that belatacept (therapeutic dose) increased blood glucose level gradually and diabetogenic at the high dose. Further evaluation is needed to confirm diabetogenicity of belatacept in clinical practice.

Funding: Clinical Revenue Support

TH-PO406

Addition of a DPP-IV Inhibitor to Metformin Decreases Sirolimus-Induced Oxidative Stress and Improves Mitochondrial Respiration in Pancreatic Islet Cells Long Jin, Jian Jin, Chul Woo Yang. *Convergent Research Consortium for Immunologic Disease, Seoul St. Mary's Hospital, The Catholic Univ of Korea, Seoul, Korea.*

Background: The guideline for the management of new-onset diabetes after transplantation recommends metformin (MET) as a first-line drug, and the addition of a second-line drug is needed to better control of hyperglycemia. We tested the effect of the addition of a DPP-IV inhibitor to MET on sirolimus (SRL)-induced diabetes mellitus (DM).

Methods: Male Sprague-Dawley rats were treated initially with SRL for 3 weeks and then started to treat with DPP-IV inhibitor (LC15-0444) and/or MET for further 3 weeks. The effect of combined treatment of LC15-0444 and MET was evaluated by pancreatic islet function. The influence of oxidative stress and apoptotic cell death was evaluated by serum and pancreas tissue. An in vitro study was also performed by INS-1 cells. Pancreas beta cell death and production of ROS were evaluated by INS-1 cells. At the subcellular level, mitochondrial respiration was also evaluated in INS-1 cells.

Results: In an animal model of SRL-induced DM, MET treatment improved pancreatic islet function and attenuated oxidative stress and apoptotic cell death. The addition of a DPP-IV inhibitor to MET improved these parameters more than MET alone. An in vitro study showed that SRL treatment increased pancreas beta cell death and production of ROS, and pretreatment of ROS inhibitor or p38MAPK inhibitor effectively decreased SRL-induced islet cell death. Exendin-4 (EXD), a substrate of DPP-IV, or MET significantly improved cell viability and decreased ROS production compared with SRL treatment, and combined treatment with the two drugs improved both parameters. At the subcellular level, impaired mitochondrial respiration by SRL was partially improved by MET or EXD, and much improved further after addition of EXD to MET.

Conclusions: Our data suggest that addition of a DPP-IV inhibitor to MET decreases SRL-induced oxidative stress and improves mitochondrial respiration. This finding provides a rationale for the combined use of a DPP-IV inhibitor and MET in treating SRL-induced DM.

Funding: Clinical Revenue Support

TH-PO407

Regulation of IFNγ Production by IL-10 May Predict Functional Outcome in Chronic Antibody-Mediated Rejection Hatty A.A. Douthwaite, Hannah E. Wilkinson, The Dorling Group. *MRC Centre for Transplantation, King's College London, London, United Kingdom.*

Background: Kidney transplants do not last for the natural lifespan of most recipients. The single biggest cause of renal allograft failure is chronic rejection (CR). Surprisingly little is known about the mechanisms that underpin CR. HLA antibodies are important but multiple lines of evidence suggest that it is the cognate interactions between donor-specific CD4+ T and B lymphocytes that underpin CR. Th1 effector CD4+ T cells, which produce interferon-gamma (IFNγ), mediate chronic rejection. Regulation of Th1 cells by IL-10 is essential, as unchecked IFNγ production results in severe tissue damage and death. We demonstrate that ELISPOT patterns (detecting indirect CD4+-T cell alloresponses) are significantly associated with functional outcome after renal transplantation.

Methods: PBMCs were analysed by ELISPOT assay & Flow Cytometry from two patient cohorts undergoing renal transplant biopsy (PROTOCOL: 19 patients & FOR CAUSE: 46 patients) at baseline and 9-12 months later.

Results: IFNγ production that is dependent on donor alloantigen presentation by B cells ("Bdep" pattern) is correlated with kidney transplant dysfunction. Where IFNγ production becomes detectable after B cell (CD19+) depletion ("Breg" pattern); these patients have a better outcome. In these Breg samples we also found associations with IL- 10 cytokine production after polyclonal stimulation. These independent associations were found to be significant at two separate time points in both cohorts.

Conclusions: These data establish the utility of this ELISPOT assay and suggest that mechanisms that regulate IFNγ production appear to be critical determinants of transplant success. Moreover the significant associations with regulatory cytokine IL-10 give support to further investigation of the contribution of the Th1 lifecycle in CR.

Funding: Other NIH Support - NIHR, MRC

TH-PO408

Effect of Sodium Glucose Transporter 2 Inhibitor on Tacrolimus Induced Diabetes Mellitus Jian Jin, Long Jin, Sun Woo Lim, Chul Woo Yang. *The Catholic Univ of Korea.*

Background: Empagliflozin (Em) is an inhibitor of sodium glucose transporter and is recommended in type 2 diabetic patients. But, its effect on tacrolimus (TAC) - induced diabetes mellitus (DM) is undetermined.

Methods: Experimental model of Tac-induced DM in rats was induced by treating TAC (1.5mg/kg) subcutaneously for 3 weeks, and two doses of Em (5 and 10mg/kg) was injected for additional 3 weeks. Control rats were treated with Em only. Body weight, urine volume and water intake were measured every week. The effect of Em on TAC-induced DM was evaluated by assessing intraperitoneal glucose tolerance test (IPGTT), serum insulin level, glucose stimulated insulin secretion (GSIS), and pancreatic islet size. The effect of Em on kidney function was evaluated by assessing serum creatinine (Scr), creatinine clearance (Ccr), urine glucose excretion, urine albumin excretion and kidney tubulointerstitial fibrosis. In addition, we measured the expression of SGLT2, oxidative stress and apoptosis in each group.

Results: TAC treatment decreased delta body weight, increased urine volume and water intake compared with controls. TAC caused elevated IPGTT level, reduced serum and GSIS and pancreatic islet size compared to controls. But, Em treatment reduced blood glucose level, increased plasma insulin level, and recovered pancreatic islet size compared to the TAC group in a dose-dependent manner. Em treatment decreased SGLT2 expression in a dose-dependent manner. TAC impaired renal function, increased urine glucose and albumin excretion, and increased renal tissue fibrosis. But, Em treatment improved these parameters. In addition, Em treatment reduced oxidative stress and apoptosis caused by TAC.

Conclusions: Em is effective in control TAC-induced hyperglycemia and renal dysfunction. This finding provides clinical usefulness of Empa in renal transplant patients with TAC-induced DM.

Funding: Clinical Revenue Support

TH-PO409

Genes Causing Post-Transplant Lymphoproliferative Disease Philip Webster, Joanna Dawes, Katalin Takacs, Hamlata Dewchand, Barbara Iadarola, Anthony Uren. *MRC Clinical Sciences Centre, Imperial College London, United Kingdom.*

Background: Post-transplant lymphoproliferative disease (PTLD) is an important complication after renal transplantation. The anti-apoptotic BCL2 is frequently overexpressed in Non-Hodgkin's Lymphoma, and the limited genetic profiling of PTLD shows overexpression in these tumours. Epstein Barr Virus drives PTLD via oncoproteins that alter gene expression, including upregulating *MYC* and *BCL2*, and downregulating *p53*, thus creating an aberrantly expanding B cell population. BCL2 inhibitors have demonstrated some success in treating lymphoma, and in treating autoimmune disease and preventing transplant rejection in mice, however limited efficacy means there is a requirement for additional therapeutic targets.

Methods: We performed a retroviral insertional mutagenesis screen using Moloney murine leukaemia virus in *Vav-BCL2* C57BL/6 mice as our lymphoma model, with Next-Generation Sequencing to identify mutations that cooperate with BCL2. To validate candidate genes, we created a model of PTLD by overexpressing *Myc* in splenic B cells from *Vav-BCL2 p53*$^{+/-}$ C57BL/6 mice by retroviral transduction. Candidate genes are cotransduced and these cells are injected via tail vein into immunodeficient NOD scid gamma mice or irradiated C57BL/6 mice which are monitored for lymphoma.

Results: The screen identified 3,000 clonal and 700,000 subclonal mutations. Many genes were mutated more frequently in *Vav-BCL 2* mice than controls, including genes already implicated in PTLD e.g. *Bcl6a* and *Pax5* (2-tailed Fisher's exact p=0.0028 and 0.0224 respectively) and also lymphoma drivers novel to PTLD e.g. *Ebf1* and *Ikzf3* (2-tailed Fisher's exact p<0.0001 for both). In the validation model, mice developed lymphoma from 30 days and latency was modified by altering expression of candidate genes.

Conclusions: We have identified new *BCL2* cooperating mutations for further study in PTLD. We have developed a new model of PTLD to validate candidate genes, with disease generated in an immunodeficient state comparable to renal transplant. This furthers insight into disease mechanism, and identifies putative therapeutic targets, with implications that may extend to treating autoimmune disease and preventing transplant rejection.

Funding: Government Support - Non-U.S.

TH-PO410

Long Term Renal Allograft Survival and Inhibitory KIR Receptors Raj K. Sharma, Swayam Prakash, Suraksha Agarwal. *Nephrology, Sanjay Gandhi Post Graduate Inst of Medical Sciences, Lucknow, UP, India.*

Background: NK cell is regulated by KIR like inhibitory and activating cell surface receptors. We evaluated allelic diversity of KIR3DL1/3DS1 and effect of its HLA-Bw4 ligand affinity on long term transplant outcome.

Methods: KIR3DL1/3DS1 allelic diversity was examined in 100 renal transplant cases and 100 controls. All samples were positive for KIR3DL1 or/and KIR3DS1 and possessed HLA-Bw4 ligand. PCR-SSP was used to determine incidence of KIR3DL1/3DS1 genes and sequence based typing method evaluated the pattern of KIR3DL1/3DS1 allele distribution. HLA class-I genotyping was performed using PCR-SSP kits. Quantification of KIR3DL1/3DS1 mRNA expression was done by $2^{-\Delta\Delta Ct}$ algorithm with GAPDH as the housekeeping gene.

Results: We observed presence of 84 KIR3DL1/3DS1 alleles in the north Indian cases and controls. 6 inhibitory KIR3DL1 alleles and 4 activating KIR3DS1 alleles with incidence > 1% were noted. For KIR3DL1*0010101, no-risk (OR=0.37, p=0.0072) association was observed with increased mRNA expression among ABMR (Fold change=1.48±0.32, p=0.031), and antibody mediated chronic rejection (Fold change=1.12±0.15, p=0.042) cases. Risk was found for KIR3DS1*049N (OR=5.16, $p \leq 0.0001$) and KIR3DS1*01301 (OR=4.27, $p \leq 0.0001$). Both KIR3DS1*049N and KIR3DS1*01301 showed a decreased mRNA level. Looking at the ligand affinity, 3DS1*01301/HLA-Bw4+ (OR=2.12, p=0.0120) and 3DS1*049N/HLA-Bw4+ (OR=3.42, p=0.0051) combinations showed susceptibility. Kaplan-Meier survival analysis performed on a 15 year follow-up data revealed highest overall survival of 11 years for KIR3DL1*0010101-HLA-Bw4 (cumulative survival=63%). Less prolonged survival of 10 years for 3DS1*01301/HLA-Bw4+ (cumulative survival=36%) and 8 years for 3DS1*049N/HLA-Bw4+ (cumulative survival=18%) combinations. Inhibitory signal transmitted by KIR3DL1 induces the ITIM motifs giving rise to inhibitory signaling in KIR positive cells. Inhibition leads to higher T cell response due to protection of T cell from activation induced death.

Conclusions: Survival of renal allograft depends on presence of inhibitory KIR receptors. Suppressing KIR3DS1 like activating NK cell surface receptors may improve long term survival of kidney allografts.

TH-PO411

ATG Induction Is Associated with Increased De Novo Donor Specific Antibodies (d-DSA) in Living Related Transplantation Raj K. Sharma, Sonia Mehrotra, Mahabaleshwar Mayya, Amit Gupta, Narayan Prasad, Dharmendra Bhadauria, Anupama Kaul. *Nephrology, Sanjay Gandhi Post Graduate Inst of Medical Sciences, Lucknow, UP, India.*

Background: Post transplant DSA monitoring needs to be correlated with clinical outcome of renal transplant in patients receiving induction with ATG or Basiliximab.

Methods: Present study is comparison of two methods (single antigen bead (SAB) assay and solid phase cross match luminex assay using donor lysate), their sensitivity and specificity.121 living donor kidney transplant recipients were prospectively evaluated after transplantation for development of de-novo DSA against Class I and Class II HLA. All recipients were complement dependant cytotoxicity (CDC) cross match negative at time of kidney transplant. 87 recipients (72%) were given induction with either Basiliximab (62) or ATG (25) at time of kidney transplant.

Results: 26 recipients (21.4%) out of 121 developed dn-DSA within 1 to 3 months post-transplant by lysate based cross match. Of patients who were dn-DSA+ive, 11 were given Basiliximab and 9 got ATG induction. Sixteen out of 26 dn-DSA positive recipients (61%) developed only Class II DSA and seven patients (27%) developed only Class I DSA positivity; while in three patients (12%), both Class I and Class II dn-DSA developed. Eight recipients(31%) developed AR in positive group; 6 (75%) of these patients with AR had evidence of antibody mediated rejection (ABMR) with glomerulitis (5 C4d–ve, one C4d +ve), while 2 patients (25%) had T cell mediated AR. In the DSA negative group (78.5%): 18 recipients out of 95 (19%) developed AR. 22 (18.2%) recipients out of 121 were positive for dn-DSA by SAB assay and 99 (81.8%) were negative. On comparison of these two methods; the sensitivity of lysate assay was 100% (95% confidence interval 84.56 % to 100%) and specificity was 95.96% (95% confidence interval 89.98% to 98.89%) against SAB assay.There was increased dn-DSA development with ATG induction (36%) as compared to Basiliximab (17.7%) and no induction (17.6%).

Conclusions: Development of de-novo DSA was associated with more AR and ABMR. Lysate based solid phase cross match which is cheaper than SAB assay can be useful for post-transplant DSA monitoring.

TH-PO412

Effect of Inflammation on Intracellular Concentration of Tacrolimus Eunjin Bae,[1] Seung Seok Han,[2] Yon Su Kim.[2] *[1]Internal Medicine, Gyeongsang National Univ Changwon Hospital, Republic of Korea; [2]Internal Medicine, Seoul National Univ College of Medicine, Republic of Korea.*

Background: Calcineurin inhibitors improved the prognosis of transplant recipients. CNI is the substrate of ABCB1, which transports drugs from the intracellular to the extracellular domain. ABCB1 expression and function are controlled by CD44. We evaluated the effect of inflammation on intracellular concentration of tacrolimus (TAC), and its associations between ABCB1 and CD44.

Methods: We enrolled 9 kidney recipients with AR between 2015 and 2016. We measured both whole blood and intracellular concentration of TAC (BC-TAC and IC-TAC) in patients with AR and stable status. IC-TAC were measured using LC-MS/MS. The TAC ratio was defined as the ratio between IC-TAC and BC-TAC. Jurkat T cell line was treated with TAC by dose dependent manners for 21 hours and stimulated with PMA/ionomycin for 3hours. IL-2, 8 and IFN production were measured by RT-PCR. Furthermore, we analyzed the expression of CD44+and ABCB1+cells by FACS to examine the change of IC-TAC respect to treated TAC level and stimulation.

Results: In human data, only one person's TAC-ratio was lower at the time of AR than that of stable status. The other patients' TAC-ratio were higher at inflammatory status (infection: n=3, rejection: n=5) than stable status. The person who had lower level of TAC-ratio at the time of AR experienced recurrent inflammatory conditions, pneumonia and AR, during 1month. Other patients did not experience an inflammatory conditions at least 6 months before this event. In vitro data, the levels of IC-TAC increase proportionally with the levels of treated TAC in Jurkat T cells. After stimulation, the proportion of T cells producing IFN-γ, IL-2 and 8 was higher in the 0, 2.5 ng/ml TAC treated groups than the 5ng/ml TAC treated group. In addition, the levels of IC-TAC were decreased after stimulation. Under the same conditions, the frequency of CD44+ABCB1+cells were increased with TAC treatment and stimulation in FACS.

Conclusions: This study supports a hypothesis that chronic or recurrent inflammation such as rejection, infection, can decrease the IC-TAC level. This could be explained by drug efflux function of CD44+ABCB1+ cells.

TH-PO413

The Effects of Coenzyme Q10 in Sirolimus-Induced Pancreatic Islet Injury In O. Sun,[1] Kwang Young Lee,[1] Chul Woo Yang.[2] *[1]Internal Medicine, Presbyterian Medical Center, Jeonju, Republic of Korea; [2]Internal Medicine, Seoul St. Mary's Hospital, Seoul, Republic of Korea.*

Background: This study was performed to investigate the effect of addition of coenzyme Q_{10} (CoQ_{10}) to metformin (MET) on sirolimus (SRL)-induced diabetes mellitus (DM).

Methods: Animal model of SRL-induced DM was induced with daily treatment of SRL (0.3 mg/kg, s.c.) for 28 days, and CoQ_{10} (20mg/kg, p.o.)or metformin (250mg/kg, p.o.) was treatment alone or combination for 14 days. The effect of MET and CoQ_{10} on SRL-induced DM was evaluated by assessing by measuring of pancreatic islet function (blood glucose level and insulin secretion) and oxidative stress and apoptosis.

Results: SRL treatment induced pancreatic islet dysfunction and islet morphology with a higher level of 8-hydroxy-2'-deoxyguanosine (8-OHdG), the number of apoptotic death and depletion of the level of manganese superoxide dismutase. MET and MET + MET and CoQ_{10}

decreased blood glucose level and increased plasma insulin level significantly. These improvements were accompanied by a reduction in oxidative stress and apoptosis and were more prominent MET and CoQ_{10} than MET alone. At the subcellular level, shrunken mitochondria in the islet cells of SRL-treated rats was restored by the addition of CoQ_{10} to MET.

Conclusions: Combined use of MET and CoQ_{10} had more protective effect against SRL-induced pancreatic injury than MET alone therapy.

TH-PO414

Hypercapnic Acidosis Attenuates Ischemia-Reperfusion Injury Associated Acute Kidney Injury in Rats Ming-Tso Yan,[1] Chih-Jen Cheng,[1,2] Shih-Hua P. Lin.[1,2] *[1]Cathay General Hospital; [2]National Defense Medical Center; [3]Tri-Service General Hospital.*

Background: Hypercapnic acidosis (HCA) preconditioning was suggested to attenuate ischemia-reperfusion (IR) injury of brain and lung, and underlying mechanism is uncertain. No study has assessed renoprotective effect of HCA preconditioning on renal IR injury. Here we investigate the effect and mechanism of HCA preconditioning on renal IR injury in rats.

Methods: Adult Sprague-Dawley rats are randomly exposed to humidified gas containing either FiCO2 of 5% or room air only for 30 minutes before sham operation or clamping renal artery for 30 minutes. Three or 24 hours reperfusion followed. Urine, blood and kidney tissue were obtained for biochemistry and histology. Protein level was determined by immunoblot.

Results: Histologically, less IR-related tubulointerstitial injury, leukocyte infiltration and tubular cell apoptosis were disclosed after HCA preconditioning. Functionally, HCA preconditioning preserved renal function after IR injury, reflected by better concentrating ability as well as low serum creatinine and urea nitrogen. Circulating TNF-α, interleukin (IL)-1β and IL-6 levels in response to IR is suppressed significantly in HCA group. HCA preconditioning demonstrated anti-apoptotic effect by downregulating TRAF6-ASK1-p38/JNK pathway and reducing the cleavage of caspase 3 and PARP. HCA also suppressed NF-κB pathway to achieve anti-inflammatory effect and enhanced anti-stress ability by raising expression of heat shock protein 70 and heme oxygenase-1.

Conclusions: These results suggest that protective effect of HCA preconditioning on renal IR injury may be mediated by complex mechanisms including anti-apoptosis, anti-inflammation and anti-stress.

TH-PO415

Development of Experimental Model of Renal Thrombotic Microangiopathy in Rat Allogeneic Bone Marrow Transplantation Takafumi Kanemitsu, Yusuke Okabayashi, Michiko Aoki, Yusuke Kajimoto, Kiyotaka Nagahama, Akira Shimizu. *The Dept of Analytic Human Pathology, Nippon Medical School, Bunkyo, Tokyo, Japan.*

Background: The thrombotic microangiopathy (TMA) after bone marrow transplantation (BMT) is a severe complication that carries a high risk of renal dysfunction. In TMA after BMT, total body irradiation, use of immunosuppressants, and chronic graft-versus-host-disease (GVHD) have been proposed as risk factors in inducing endothelial cell injuries and causing TMA. The skin, gut and liver are well-known primary target sites in GVHD. In our previous study, the kidney was a primary target organ of acute GVHD after BMT. In TMA after BMT, the involvement of the kidney is not well-understood. We are focusing on the pathogenesis of TMA after BMT affecting the kidney.

Methods: We induced TMA in irradiated BN rat by transplanting BM cells from allogeneic Lewis rats without immunosuppression. For chimerism analysis, FCM was performed. We examined the clinical and pathological characteristics of TMA in several organs including kidney at 9 months after BMT.

Results: Almost all blood cells were replaced by the donor cells. Mild to moderate GVHD in the skin, gut and liver was developed at 9 months after BMT. The serum creatinine levels were mildly increased. Renal pathology at 9 months after BMT showed the increase number of collapsed and sclerotic glomeruli with endothelial cell injuries in all rats. In addition, in half of the rats, renal TMA developed, that were characterized by the glomeruli with mesangiolysis, double contour of the GBM with widening of subendothelial spaces, and fibrin thrombi formation in some glomerular capillaries. Exudative lesions in small arteries were also seen. These renal findings were quite similar to renal TMA after BMT in humans. RT-PCR showed that mRNA levels of Th2 cytokines are strongly expressed than Th1 cytokines in glomeruli.

Conclusions: We have developed the animal models of renal TMA after BMT in rats. In this model, renal TMA is accompanied with mild to moderate GVHD in the skin, gut, and liver. These findings may be indicated that renal TMA after BMT is one of the findings of chronic GVHD in the kidney. Further studies are also needed to assess the mechanism of TMA after BMT.

TH-PO416

Drug Repurposing: In Vitro Validation of In Silico Predicted Transcriptomic Changes in Primary Human Mesangial Cells Induced by Calcineurin Inhibitor FK 506 Constantin Aschauer,[1] Andreas Heinzel,[2] Judith Sunzenauer,[1] Paul Perco,[2] Rainer Oberbauer.[1] *[1]Dept of Nephrology, Medical Univ of Vienna, Vienna, Austria; [2]Emergentec Biodevelopment GmbH, Vienna, Austria.*

Background: Network based drug repurposing is an emerging area in systems pharmacology utilizing Omics-derived network-based models of disease pathophysiology and drug mechanism of action(MoA) in order to identify new indications for established drugs. The calcineurin-inhibitor FK 506 shows potential positive effects in a set of diseases outside the area of transplantation.

Methods: A FK 506 MoA molecular model was constructed using two published transcriptomics datasets and a set of molecular features affected by FK 506 based on a literature mining approach. This model was screened against an in-silico library of ~2000 phenotype molecular models. We set up an in-vitro experiment studying the effect of FK 506 on mesangial cells as diabetic nephropathy (DN) was among the hit phenotypes. Primary human mesangial cells were cultured in 6 well plates and treated for 24h with 1 µM FK 506 and changes in gene expression were analyzed using Affymetrix microarrays.

Results: A set of 222 transcripts mapping to 204 unique protein coding genes were found deregulated. Pathway enrichment analysis identified the TGF-β signaling pathway (p-value: 0.0210) and a set of cell adhesion molecules (p-value: 0.0217) as relevant. Although TGFB1 was upregulated (1.32 fold), also one major inhibitor of the TGFB signaling cascade, SMAD7, was upregulated (1.31 fold). Other drug targets in the context of diabetes and DN as JAK2 (0.81 fold) and DPP4 (0.76 fold) were downregulated. On the other hand, NOX4 and EDN1 were both significantly upregulated being detrimental for DN.

Conclusions: Our in-silico drug screening approach identified DN as one of the key hit candidates showing interference on a molecular level with FK 506. In an in-vitro experiment we could validate the effect of FK 506 on TGFB signaling as well as other drug targets currently being addressed in clinical practice or trials. A set of predictive markers might guide on the use of FK 506 in DN thus identifying those patients potentially benefitting from a low-dose tacrolimus therapy.

Funding: Government Support - Non-U.S.

TH-PO417

Allogeneic Neo-Islets, Composed of Equal Numbers of Mesenchymal Stem and Islet Cells, Are Immune Protected and Cure Auto-Immune Type 1 Diabetes Mellitus in NOD Mice Christof Westenfelder,[1,2] Anna Gooch,[2] Jon D. Ahlstrom,[2] Zhuma Hu,[2] Ping Zhang.[2] *[1]Medicine, Nephrology, Univ of Utah and VA Medical Centers; SCT, LLC, Salt Lake City, UT; [2]Medicine, VA Medical Center and SCT, LLC, Salt Lake City, UT.*

Background: Globally, individuals with autoimmune Type 1 Diabetes mellitus (T1DM) continue to depend for survival on insulin injections. While pancreas and intrahepatic pancreatic islet transplants can produce insulin-independence and ameliorate serious complications, both therapies depend on potentially toxic anti-rejection drugs. Furthermore, the scarcity of pancreas donors, islet transplant failures, and the inability to adequately culture expand insulin-producing β-cells significantly limit the general availability of such and other cell-based interventions. Encapsulation of islets to protect them from allo- and auto-immune destruction has shown both promise and failures, and there remains a critical need for curative therapies of T1DM.

Methods: Here we tested the hypothesis that the need for anti-rejection drugs or encapsulation devices, the shortage of pancreas donors can be overcome by harnessing the robust immune-modulating and complex trophic activities of Mesenchymal Stem Cells (MSCs). This was investigated with *ex vivo* generated islet-sized "Neo-Islets" (NIs) in which culture-expanded islet cells, via Epithelial-Mesenchymal-Transition (EMT), were aggregated in cell clusters with equal numbers of MSCs.

Results: The minimally invasive intraperitoneal administration of allogeneic NIs durably normalized blood glucose levels in Non-obese Diabetic (NOD) mice with auto-immune T1DM, a model of human T1DM. This was achieved, without anti-rejection drugs, by the spontaneous engraftment of NIs in the animals' omenta, redifferentiation of NI-intrinsic islet cells that physiologically secrete insulin into the hepatic portal vein, and omental and splenic upregulation of Tregs.

Conclusions: NIs, as engineered here, provide a novel therapy that, we posit, has significant translational relevance to clinical T1DM.

Funding: Pharmaceutical Company Support - SCT, LLC, Private Foundation Support

TH-PO418

Arctigenin Attenuates Podocyte Injury in Diabetic Kidney through Activation of PP2A Yifei Zhong,[1] Ruijie Liu,[2] Xueling Li,[1] Kyung (Kim) Lee,[2] John C. He.[2] *[1]Dept of Nephrology, Longhua Hospital, Shanghai Univ of Traditional Chinese Medicine, Shanghai, China; [2]Div of Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Arctigenin (ATG) is a major extract of Fructus Arctii which has been commonly used alone or in combination with other Chinese herbal Medicines to treat patients with diabetic kidney disease (DKD). However, it remains unknown whether ATG alone has renal protective effects for DKD.

Methods: To determine this, we treated streptozotocin (STZ)-induced diabetic $eNOS^{-/-}$ mice with either ATG or vehicle from 10 weeks post-STZ injection to 18 weeks. To understand the mechanism, we performed RNA sequencing of glomeruli from these mice. To explore the mechanism of ATG action in podocytes, we used *drug affinity responsive target stability* (*DARTS*) method combined with mass spectrometry analysis to identify ATG-bound proteins.

Results: We found that ATG markedly attenuated proteinuria, glomerular hypertrophy, mesangial expansion, foot process effacement and podocyte loss in diabetic mice as compared to those treated with vehicle. RNA sequencing of glomeruli revealed that ATG significantly affects cell cytoskeleton, cell migration, oxidative stress and inflammatory pathways in diabetic glomeruli. We confirmed that ATG reduced lamellipodia, inhibited migration, and attenuated superoxide production and pro-inflammatory gene expression in cultured podocytes. We identified that protein phosphatase 2A (PP2A) is an ATG-bound protein. The interaction between ATG and PP2A was also confirmed by structural analysis. Interestingly, ATG-PP2A interaction led to increased PP2A activity, suggesting that ATG is a natural agonist for PP2A. We demonstrated that ATG was able to reduce MAPK and p65 phosphorylation to have anti-inflammatory effects in cultured podocytes through enhanced PP2A activity. ATG also regulated RACK1 to inhibit podocyte migration through increased PP2A activity.

Conclusions: In conclusion, we demonstrated a renal protective effect of ATG in DKD and its novel mechanism of action in podocytes.

Funding: NIDDK Support

TH-PO419

Hormone-Like Function of Coagulation Protease Rescue Defective Insulin Signaling in the Kidney Sanchita Ghosh,[1] Madhusudhan Thati,[2] Moh'd Mohanad Ahmad Al-Dabet,[3] Jayakumar Manoharan,[4] Andi Marquardt,[5] Berend Heinrich Isermann.[6] *[1]IKCP, Otto-von-Guericke Univ, Magdeburg, Germany; [2]Thrombosis and Hemostasis, Univ Medical Center Mainz, Mainz, Germany; [3]IKCP, Otto-von-Guericke Univ, Magdeburg, Germany; [4]IKCP, Otto-von-Guericke Univ, Magdeburg, Germany; [5]IKCP, Otto-von-Guericke Univ, Magdeburg, Germany; [6]IKCP, Otto-von-Guericke Univ, Magdeburg, Germany.*

Background: Impaired insulin signaling in the kidney contributes to the progressive failure in glomerular filtration, the loss of the specialized glomerular epithelial cells (podocytes), and subsequent proteinuria in diabetic kidney disease (DKD).

Methods: We recently established that the coagulation protease activated protein C (aPC) protects mice from diabetic nephropathy, but the intracellular signaling mechanism remains unknown.Here we show that the aPC rescues defective insulin signaling by activating the unfolded protein response (UPR) arm of the multistep ER-stress response in podocytes. Analogous to insulin, physiological levels of aPC regulate homeostatic-UPR in podocytes by maintaining nuclear levels of sXBP1 while downregulating the transcription factors responsible for the maladaptive ER-stress response (ATF6 and CHOP). This cytoprotective mechanism of nuclear translocation of sXBP1 occurs via the interaction with regulatory subunits of PI3Kinase (p85α and p85β).

Results: Type I diabetic mice with podocyte specific deletion of the insulin receptor ($INSR^{\Delta Pod}$) develop enhanced albuminuria, glomerular basement membrane (GBM) thickening and podocyte foot process effacement compared to the wild type $INSR^{\Delta Pod}$ mice. Transgenic overexpression of protein C or treatment with aPC, protects the $INSR^{\Delta Pod}$ mice from DKD by restoring the nuclear sXBP1 and attenuating maladaptive ER-stress response.

Conclusions: Taken together, due to signaling redundancy aPC efficiently alleviates defective INSR signaling in podocytes, suggesting that aPC or its receptors could prove to be an excellent therapeutic adjunct for DKD.

Funding: Government Support - Non-U.S.

TH-PO420

Podocyte Specific Knockout (KO) of COX2 Exacerbates Kidney Disease in Diabetic Akita Mice Liming Wang,[1] Yonggang Sha,[1] Jingyi Bai,[1] William Eisner,[1] Anne Buckley,[2] Robert F. Spurney.[1] *[1]Medicine, Duke Univ and Durham VA Medical Centers, Durham, NC; [2]Pathology, Duke Univ Medical Center, Durham, NC.*

Background: Induction of COX2 expression in podocytes has been implicated in promoting podocyte injury in diabetic kidney disease (DKD).

Methods: To investigate the role of COX2 in DKD, we deleted COX2 specifically in podocytes in a mouse model of type 1 diabetes mellitus (male 129/SvEv Akita mice) by expressing Cre recombinase under the regulation of the podocyte specific podocin promoter.

Results: Wild type (WT) Akita mice and podocyte specific knockout (KO) Akita mice had similar levels of hyperglycemia at 8, 12, 16 and 20 weeks of age as well as similar levels of systemic blood pressure at 12 and 20 weeks of age. Albuminuria was significantly increased in both groups of Akita mice compared to non-diabetic controls at the 16- and 20-week time points. The increase in albuminuria was significantly greater in KO Akita mice compared to WT Akita mice at 16 weeks of age (138 ± 12 [WT Akita] vs 300 ± 48 [KO Akita] ug/24H; P<0.05) and at 20 weeks of age (158 ± 25 [WT Akita] vs 305 ± 50 [KO Akita] ug/24H; P<0.05). At the 20-week time point, mesangial expansion was significantly increased in both groups of diabetic mice compared to non-diabetic controls; but the degree of mesangial expansion was similar in WT and KO Akita mice. Tubular dilation and casts as well as tubulointerstitial inflammation and fibrosis were not significantly different in either group of diabetic mice compared to non-diabetic controls. Because systemic KO of COX2 causes developmental defects of the kidney, we also examined kidneys from non-diabetic WT mice and non-diabetic KO mice for abnormalities. There were no differences detected in kidney weights, kidney histology or glomerular ultrastructure between WT and KO groups.

Conclusions: These data suggest that deletion of COX2 specifically in podocytes has adverse effects on DKD in Akita mice. Some basal level of podocyte COX2 expression may be necessary to protect podocytes from injury in diabetes.

Funding: NIDDK Support, VA Support, Private Foundation Support

TH-PO421

Paricalcitol Prevents Glucose Induced-Podocyte Injury by Inhibiting Wnt/β-Catenin Pathway Xuan Xiong, Shi Xiao Zhong. *Dept of Nephrology, Guangzhou Red Cross Hospital, Jinan Univ, Guangzhou, Guangdong, China.*

Background: Diabetic nephropathy (DN) is one of the most important causes of end-stage renal disease and Wnt/β-catenin pathway is highly activited in diabetes.Paricalcitol has been reported to prevented podocyte demage, but its role in diabetic nephropathy remain unknow. This study was designed to investigate whether Paricalcitol could ameliorate high glucose induced podocyte injury and the underlying mechanisms.

Methods: The podocytes were cultured under different conditions for 24h, which were divided into 6 groups of normal glucose control(NG), mannitol Group(MG),high glucose group(HG), Paricalcitol group(PG),losartan group(LG) and Paricalcitol+LiCL group(PLG). Cell proliferation was detected by methyl thiazolyl tetrazolium(MTT). The podocyte injury induced by high glucose and the effect of Paricalcitol on it were evaluated by measuring the nephrin,wt1,Tgf-beta,Col IV,VDR and β-catenin expression.The wnts mRNA expression and Apoptosis rate of the podocytes were detected using reverse transcription PCR and flow cytometry, respectively. The nuclear translocation of VDR and β-catenin were evaluated too.β-catenin agonists (LiCL) were used to analyze the role of this pathway.

Results: The podocyte injury induced by HG was characterized by upregulated tgf-β and Col IV expression; increasing Apoptosis rate;with downregulated expressions of both wt1 and nephrin, which paralleled the increasing wnts mRNA expression and β-catenin nuclear translocation.Our data demonstrated that paricalcitol preserved the expression of nephrin,wt1,reduced the expression of tgf-βand Col IV,prevented apotosis in podocyte. It promoted VDR nuclear translocation and blocked β-catenin nuclear translocation.The expression of wnt4,wnt10a,wnt10b were inhibited at RNA level.We found that paricalcitol protect podocytes from high glucose by surpressing wnt pathway.LiCL,as a WNT/β-catenin Signaling pathway agonist, could abolish the effects of paricalcitol.

Conclusions: The results suggests that Paricalcitol attenuates high glucose-induced podocyte injury in vitro partly through inhibiting the wnt/β-catenin pathway.

TH-PO422

RTN1A Induces Podocytes Injury through Increased ER Stress and Is Ameliorated by Tauroursodeoxycholic Acid in Diabetic Nephropathy Ying Fan,[1] Jing Zhang,[1] Wenzhen Xiao,[2] Jiejun Wen,[1] Kyung (Kim) Lee,[2] Zhengzhe Li,[2] Li He,[1] John C. He,[2] Niansong Wang.[1] *[1]Dept of Nephrology, Shanghai Jiao Tong Univ Affiliated Sixth People's Hospital, Shanghai, China; [2]Dept of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Diabetic nephropathy (DN) remains the leading cause of chronic kidney disease (CKD) in most countries. Podocyte injury contributes to the progression of DN. Our previous studies reported a critical role of reticulon (RTN) 1A in mediating endoplasmic reticulum (ER) stress in kidney tubular cells and contributed to the progression of CKD. However, how ER stress mediates podocyte injury in DN remains largely unknown.

Methods: In the present study, we explored the role of ER stress in vivo using an accelerated murine model of advanced diabetic nephropathy, which is db/db mouse with early uninephrectomy. We also assessed the role of RTN1A in mediating ER stress in podocyte injury *in vitro*.

Results: We found that the expression of RTN1A and ER stress markers was upregulated in the kidney of diabetic mice. Administration of tauroursodeoxycholic acid (TUDCA), an inhibitor of ER stress, suppressed RTN1A and ER stress marker expression, attenuated kidney injury, preserved glomeruli function and protected podocytes from apoptosis in uninephrectomized db/db mice. *In vitro*, overexpression of RTN1A in human podocytes induced ER stress and cell apoptosis, whereas knockdown of RTN1A attenuated human serum albumin-induced podocyte ER stress and apoptosis. Interestingly, overexpression of RTN1A induced CHOP expression while knockdown of CHOP expression led a suppression of RTN1A expression, suggesting a positive feedback loop between RTN1A and CHOP to enhance the ER stress signaling.

Conclusions: In conclusion, ER stress is a key event for podocyte injury in DN. RTN1A might be a crucial mediator of ER stress in podocytes, probably through a positive feedback loop between RTN1A and CHOP.

Funding: Government Support - Non-U.S.

TH-PO423

Huangkui Capsule Protects against Podocyte Injury in Diabetic Nephropathy via Regulating Insulin Resistance and IRS1/PI3K/Akt2 Signaling Pathway, Compared with Rosiglitazone Wei Wu, Yigang Wan. *Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing Univ Medical School.*

Background: Huangkui capsule (HKC) has been applied extensively for treatment of proteinuria in patients with early diabetic nephropathy (DN) in China. However, its mechanism is fully unclear. In the process of early DN, insulin resistance (IR) and low activation of IRS1/PI3K/Akt2 signaling pathway in kidneys lead to podocyte lesion, which further results in proteinuria. This study thereby aimed to investigate effects and mechanisms in vivo of HKC on podocyte damage, compared withrosiglitazone (ROS)as an insulin sensitizer in clinic, by regulating IR and IRS1/PI3K/Akt2 signaling activity.

Methods: Rats were randomly divided into 5 groups, sham-operated group, vehicle-given group, low dose of HKC-treated group, high dose of HKC-treated group and ROS-treated group. HKC, ROS and saline were daily administrated for 8 weeks after the induction of DN by streptozotocin (STZ)with unilateral nephrectomy. Albuminuria, biochemicalindicators, IR-related markers (HOMA-IR), podocyte form, glomerular pathological changes, as well as the key protein expressions inIRS1/PI3K/Akt2 signaling pathway and podocyte structural molecules in kidneys including nephrin, podocin, CD2AP and neph1 were examined,respectively.

Results: The results showed that, urinary albumin, HOMA-IR, foot process effacement, glomerularsclerosis and the decreased protein expressions of p-IRS1, p-PI3K, p-Akt2, nephrin and podocin in the DN model rats were ameliorated in different extent in the HKC and ROS treated groups, especially in the high dose of HKC-treated group. More notably, HKC synchronously up-regulated IRS1/PI3K/Akt2 signaling activity and nephrin protein expression, whereas, ROS only increased nephrin and podocin protein expressions in kidneys.

Conclusions: In conclusion, by DN model rats, we demonstrated that IRcontributes topodocyte damage and IRS1/PI3K/Akt2 signaling activity inhibition. HKC, as a natural regulator in vivo, can improve IR-related podocyte injury via up-regulating the protein expressions of p-IRS1, p-PI3K, p-Akt2 and nephrin, which is different from ROS.

Funding: Government Support - Non-U.S.

TH-PO424

Dysregulation of LDL Receptor by Cyclooxygenase-2 Contributes to Podocyte Injury in Streptozotocin Induced Diabetic Rats Liang Liu, Kun Ling Ma, Yang Zhang, Gui Hua Wang, Zebo Hu. *Inst of Nephrology, Southeast Univ, Nan Jing City, JIang Su Province, China.*

Background: Podocyte injury and resulting microalbuminuria are early hallmarks of diabetic nephropathy(DN). Lipid disorder play crucial roles in podocyte injury of DN. This study was designed to investigate whether cyclooxygenase-2 (COX-2)is involved in podocyte injury by disrupting the low-density lipoprotein receptor (LDLr) pathway.

Methods: Eight-week old male *Sprague-Dawley* rats were treated for 12 weeks by dividing into three groups: nondiabetic rats (control), streptozotocin-induced diabetic rats (DM), and diabetic rats treated with Aspirin (DM+ Aspirin). The ratio of urinary microalbumin to creatinine (ACR) was detected by enzyme-linked immunosorbent assay. Intracellular lipid accumulation was evaluated by Oil Red O staining, Filipin staining, and a free cholesterol quantitative assay. The glomerular podocyte injury and the expression of molecules related with LDLr pathway was evaluated by, immunohistochemical staining, immunofluorescent staining, and Western Blot.

Results: There were increased levels of plasma lipid, serum creatinine, and urinary ACR in diabetic rats compared with control rats. Moreover, there was significant mesangial matrix expansion, basement membrane thickening, podocyte foot process effacement and phenotypic alteration in the diabetic rats. Additionally, lipid accumulation in the kidneys of diabetic rats was increased, due to increased protein expressions of LDLr, sterol regulatory element–binding protein (SREBP), cleavage activating protein (SCAP), and SREBP-2. The podocytes in kidneys of diabetic rats underwent epithelial-mesenchymal transition, which was closely associated with the increased expression of LDLr pathway components and subsequent cholesterol accumulation. Interestingly, COX-2 protein expression in kidneys

of diabetic ratswas markedly increased and closely correlated with increased LDLr protein expression, compared with the controls. However, these change was significantly inhibited by a nonselective inhibitor of COX-2, Aspirin.

Conclusions: Dysregulation of LDLr pathway contributes to podocyte injury in diabetic nephropathy, which might be mediated through the increased COX-2 expression.

TH-PO425

Multiglycoside of *Tripterygium wilfordii* Hook.f. Attenuates Podocyte Damage in Diabetic Nephropathy Rats via Regulating mTORC1 Signaling Pathways, Compared with Rapamycin Ge Shi,[1] Yigang Wan.[2] *[1]Nanjing Univ of Chinese Medicine; [2]Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing Univ Medical School.*

Background: Multiglycoside of *Tripterygium wilfordii* Hook.f. (GTW) has been applied extensively for treating podocyte injury in patients with early diabetic nephropathy (DN) in China. Activation of mTORC1 plays a critical role in podocyte damage under hyperglycemia, which can be realized by the combined actions of Akt activation and AMPK inhibition. This study thus aimed to investigate effects and mechanisms in vivo of GTW on podocyte lesion, compared with rapamycin (RAPA) as an mTORC1 inhibitor, by regulatingAkt/mTORC1 or AMPK/mTORC1 signaling activities.

Methods: Rats were randomly divided into 4 groups, the sham-operated group, the GTW-treated group, the vehicle-given group and the RAPA-treated group, and sacrificed at week 8 after theinduction of DN by 2 consecutive intraperitoneal injections of streptozotocin (STZ) with an interval of 1 week following unilateral nephrectomy. Daily oraladministration of GTW, RAPA and saline were started after the second injection of STZ until sacrifice.

Results: The results indicated that, after p-Akt was up-regulated and p-AMPK was down-regulated respectively, mTORC1signaling pathways wereconcurrentlyactivated in kidneys of the DN model rats. GTW, similar to RAPA, markedly regulated the protein expressions of p-Akt, p-AMPK, p-mTOR and p-p70S6 kinase in kidneys, and ameliorated albuminuria, foot process effacement, podocyte loss and glomerularsclerosis. In addition, the recuperative protein expressive levels of podocin and CD2AP and the rasied protein combinative levels between nephrin and neph1 in kidneys in the GTW-treated group were also observed, while RAPA only up-regulated the protein expression of podocin and the protein combinative levels between nephrin and neph1 in kidneys.

Conclusions: In summary, using the DN model rats, we clarified that GTW, as a natural regulator in vivo, effectively attenuates podocyte damage by the potential mechanisms involving the repair of podocyte structural molecules and the regulation of Akt/mTORC1 and AMPK/mTORC1 signaling activities.

Funding: Government Support - Non-U.S.

TH-PO426

TRIM72-Containing Microvesicles Protect Podocyte in Diabetic Nephropathy via TWIST Pu Duann,[1] Haichang Li,[4] Elias A. Lianos,[3] Pei-Hui Lin.[2] *[1]Medicine, OSU Wexner Medical Center, Columbus, OH; [2]Surgery, OSU Wexner Medical Center, Columbus, OH; [3]Medicine/ Nephrology Div, Rutgers RWJ Medical School, New Brunswick, NJ; [4]DHLRI, OSU Wexner Medical Center, Columbus, OH.*

Background: Glomerulonephropathy is the major kidney complication in diabetes. GBM thickening caused by disrupted ECM homeostasis, is a prominent feature in DN with the disrupted regulation with Type IV collagen, the main structural component of GBM. We previously reported a glocose intolerance phenotype with a TRIM72-null transgenic mice, which show proteinuriua and DN feature with reduce glucose uptake in podocyte. We also observed deliver TRIM72 by microvesicles reduced proteinuria and attenuate DN features. Apply TRIM-72 containing microvesicles on cultured podocytes, we observed cytoproting effects yet with unclear mechanism.

Methods: TRIM72(+)-microvesciles, isolated by ultracentrifuge, were applied on cultured podocytes, pulsed with normal- or high- glucose media. Effects on genes with TGF-β1 signal pathway, stress responsive cytokines or proinflammatory genes were assessed by Q-PCR and western blot analysis. Mic-tagged TRIM 72 and FLAG-tagged TWIST1 were co-transfected to HEP293 to verify immunoprecipitation. Contribution of individual genes, e.g. TWIST, was validated by mutant or knockdown by siRNA.

Results: TRIM72-null mice showing DN feature with thickened GBM and proteinuria. TRIM72 containing microvessicles attenuate proteinuria and partially rescue DN phenotype. TRIM72 co-precipitated with wild type- but not mutant TWIST lacking binding motif. Cultured podocyte treated with TRIM72-containg microvessicle displayed a altered expression pattern on genes including TGF b1, Smad2/3, but not COL4A. When TWIST knocking down by siRNA, TRIM72 lost its gene modulation effect.

Conclusions: We have shown that TRIM72-containing microvessicles modulate TGF-β signal pathway via TWIST. Though the synthesis COL4A was not directly altered, TGFb1 Smad2/3 are cleared changed. TRIM72-containing microvesicle are a powerful vehicle, readily uptake by cultured podocyte and modulate disease related genes. These findings suggest pharmacological targeting to ECM homeostasis against diabetic nephropathy.

Funding: Other NIH Support - GID, Private Foundation Support

TH-PO427

Pigment Epithelium Derived Factor (PEDF) Is Protective for Podocytes, and Global Genetic Ablation Exacerbates Glomerular Lesions in Mice with STZ-Induced Diabetes Minghao Ye, Olga V. Volpert, Jan A. Wysocki, Daniel Batlle. *Div of Nephrology and Dept of Urology, Northwestern Univ, Feinberg School of Medicine, Chicago, IL.*

Background: Pigment Epithelium Derived Factor (PEDF) encoded by *SERPINF1* gene is a multifunctional protein that has anti-angiogenic and cytoprotective activities. It has been reported that PEDF protein levels are reduced in the kidneys of rodents with experimentally induced diabetes and 44mer PEPF fragment may be renoprotective. We used SERPINF1 KO mice to examine the impact of global PEDF deficiency on kidney pathology and tested a short PEDF fragment for protective effects in cultured podocytes.

Methods: The potential protective effects of a novel PEDF peptide PMD-427 was tested in cultured podocytes exposed to high glucose or genotoxic stress (cisplatin, CPT). Podocyte apoptosis was measured by TUNEL assay and ROS levels were assessed using DHFR fluorescent dye. Metabolic activity was evaluated in cells exposed to control vehicle and PMD-427 using Seahorse analyzer in the presence of free log-chain fatty acids (Palmitate).

Results: Twelve weeks after diabetes induction by STZ, *SERPINF1* KO mice showed a significant increase in mesangial matrix (2.8±0.14 vs. 1.2±0.14 arbitrary units, $p<0.01$) and ~ 20% decrease in podocyte counts (8.2±0.0.4 vs. 9.7±0.2 podocytes/glomerulus, $p<0.01$) compared to the WT controls. In vitro, PMD-427 decreased apoptosis of cultured podocytes by 72±17% in hyperglycemic conditions and by 30±9% when exposed to CPT. The decreased apoptosis was associated with 70-90% decrease in ROS production. A significant 1.7 fold increase in fatty acid oxidation was also observed.

Conclusions: Global PEDF deficiency results in worsening of glomerular lesions in the STZ-induced mouse model of diabetes A short fragment of PEDF derived from its active epitope has a marked protective effect in vitro. This peptide attenuates ROS, and increases fatty acid oxidation in podocytes and may have therapeutic potential for diabetic kidney disease.

TH-PO428

Mitochondrial Dynamic Alterations Mediated by P66Shc Signaling Promotes Diabetes-Induced Tubular Cell Injury and Apoptosis Ming Zhan,[1] Yashpal S. Kanwar,[2] Lin Sun.[3] *[1]Medicine, Ningbo First Hospital, Zhejiang Univ, China; [2]Pathology, Northwestern Univ; [3]Medicine, Second Xiangya Hospital, Central South Univ, China.*

Background: Renal tubular injury is an early characteristic of diabetic nephropathy (DN), mitochondrial damage and the adaptor protein p66Shc-mediated oxidative stress are both critical during diabetic tubular cell injury and death, their correlation is unclear.

Methods: We investigate mitochondrial morphological changes in renal tissues from DN and MCD patients, and explore the involvement of p66Shc-mediated mitochondrial pathway in high glucose (HG)-induced mitochondrial dynamic alterations and cell apoptosis in human renal tubular cells.

Results: Elongated mitochondria became fragmented in renal tubules of patients with DN, compared with the control group. The levels of mitochondrial shaping proteins Drp1 and Fis1 were increased and Mfn1 decreased in DN tissues, these changes were accompanied with the elevation of p66Shc level and oxidative stress. In HK-2 cells, alterations in mitochondrial dynamics and its related protein levels was observed under HG ambience, together with upregulation of p66Shc and phosphorylated p66Shc at Ser36. Notably, siRNA knockdown of p66Shc alleviated HG-induced mitochondrial fragmentation, down-regulated Fis1 but increased Mfn1 expression under HG, and reduced the protein interactions between Mfn1 and proapoptotic protein Bak, resulting in decreased mitochondrial $\Delta\Psi$, mROS production and apoptosis. Oppositely, over-expression of p66Shc could exacerbate HG-induced mitochondrial fragmentation and apoptosis, whereas transfection with dominant-negative Ser36 p66Shc mutant in HK-2 has marginal similar effects.

Conclusions: Clinical evidence of mitochondrial fragmentation in human diabetic nephropathy was presented in our study. P66Shc activation and phosphorylation mediated mitochondrial dynamic alterations through regulating mitochondrial shaping proteins, and leading to tubular oxidative injury and apoptosis via p66Shc/Mfn1/Bak pathway under HG ambience.

Funding: Government Support - Non-U.S.

TH-PO429

Human Kidney Biopsies Gene Expression Reveals Changes in Mitochondrial and Lipid Metabolic Pathways in Obesity-Related Glomerulopathy Michal Herman-Edelstein,[1] Talia R. Weinstein,[1] Vivette D. D'Agati,[3] Avry Chagnac,[1] Moshe Levi.[2] *[1]Nephrology, Rabin -Felsenstein, Israel; [2]Colorado, Denver; [3]Columbia, New-York.*

Background: Obesity-related glomerulopathy (ORG) is an emerging complication of the obesity epidemic. However, pathways through which obesity may cause renal injury are not well understood. Potential mechanisms include metabolic maladaptive pathways, lipid accumulation, podocyte hypertrophy and dysfunction, adipokine dysregulation, oxidative and inflammatory stress.

Methods: To obtain insight into molecular mechanisms underlying obesity-induced kidney injury we studied metabolic target gene expression in amplified mRNA of laser captured microdissection (LCM) isolated glomeruli and tubules. We studied FFPE renal biopsies of patients with clinical and pathological established obesity- related

glomerulopathy (ORG), compared to normal kidneys. We also investigated lipid content and markers of podocyte injury and hypertrophy (Immunohistochemistry analysis of GLEPP1/WT1).

Results: ORG manifests a benign course with slow eGFR deterioration compare to DN. Glomerular surface area was markedly enlarged in ORG and was accompanied by significant decreases in the podocyte marker and genes with only limited compensatory podocyte hypertrophy. There was marked lipid accumulation in both glomeruli and tubules. The most prominent difference in lipid metabolism gene expression was down-regulation of fatty acid β oxidation genes in both glomerular and tubulointerstitial fractions, possibly secondary to reduced transcription of nuclear genes involved in mitochondrial respiration (PGC1α) and decreased expression of adiponectin receptors 1 and 2. Furthermore, increases were observed in genes contributing to cholesterol and triglyceride uptake (CD36) and decreases in cholesterol efflux (ABCA1) with a parallel decrease of liver X receptor alpha (LXRα) and an increase in sterol-regulatory element binding protein-2 (SREBP-2) mRNA content, mainly in the tubular fraction.

Conclusions: The major finding of this study is that lower expression of the mitochondrial respiratory pathway and defective regulation of lipid metabolism pathways involved in obesity- induced kidney injury.

Funding: NIDDK Support

TH-PO430

PGC1 α, Increases HO-1 Gene Expression Resulting in the Restoration of Mitochondrial Mfn1/2 Signaling and Prevention of Obesity-Induced Hypertension via Recruitment of Renal NaCl Co-Transporter

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Background: Elevated blood pressure (BP) was frequently observed in subjects with midlife weight gains and in obese mice. Elevation of mitochondrial dysfunction is associated with obesity induced BP elevation. Previously we and others have shown that an EET agonist (EET-A), reduced adiposity and ROS resulting in normalization of BP by unknown mechanisms. We hypothesized that EET-A may attenuate BP in mice fed high caloric intake diets by NCC Channel by recruiting PGC1a-HO-1 that resulted in restoring mitochondrial function and fusion.

Methods: C57/B16 mice at the age of 5 wks., fed a HF diet that for 24 wks. when all mice had established pre-diabetic stage (12-wks), EET-A was administered intraperitoneally, 1.5 mg/100g BW. (Blood was collected, glucose and visceral fat and renal tissues were harvested, HO-1, NKCC2, ENaC, NCC, insulin receptors, PGC1a Mito-fusion protein markers and VO_2 consumption were determined in group: A) Control, B) HF, C) HF-EET-A and D) EET-A-Ln-PGC1α (sh).

Results: Renal PGC1a, HO-1, pAMPK, and mitochondrial fusion protein Mfn 1/2, and Opa1 were decreased in obese mice and restored by EET-A treatment. VO_2 consumption were impaired in control obese mice compared to mice treated with either EET-agonists or vehicle solution $p<0.05$. A HF diet increased levels of NaCl co-transporter (NCC) but not type 2 Na-K-Cl co-transporter (NKCC2) or epithelial Na channel-alpha subunit ENaC while treatment with EET-A decreased NCC expression ($p<0.05$) that was associated with normalization of BP. Electron transport and mitochondrial citrate carrier ($p<0.05$) were lowered in mice fed a HF diet compared to EET-A.

Conclusions: EET-A restores cortical NCC channel function is associated with recruitment of PGC1α HO-1, mitochondrial Mfn1/2 and Opa1, mitochondrial function that is associated with normalization of BP. Pharmacological targeting mitochondrial fusion protein and increase of HO-1-derived antioxidant activity via increase bilirubin and CO may be a promising therapy in prevention of renal function and amelioration of hypertension.

Funding: Other NIH Support - National Institutes of Health grants HL-34300 (NGA)

TH-PO431

Acute Mitochondrial Response to High Glucose Exposure in Primary Renal Cells Studied with Super Resolution Microscopy

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Background: Hyperglycemia is a major cause of diabetic complications. Many aspects of mitochondrial dysfunction are reported in studies of experimental diabetic nephropathy. Yet, little is known about the immediate mitochondrial response to high glucose (HG) in primary renal cells.

Methods: Acute response of primary renal cells, proximal tubule cells (RPTC), mesangial cells (MC) and podocytes, to HG (15-20mM) exposure was studied with immunocytochemistry, TUNEL stain, Stimulated Emission Depletion (STED) and Stochastic Optical Reconstruction (STORM) microscopy.

Results: First we compared the 8 h response to HG in RPTC and MC, which express both Glut transporters and SGLT 2 or 1 respectively, and in podocytes which only express Glut transporters. We observed significant increase in apoptotic index in RPTC and MC but not in podocytes, associated with an increased expression of apoptotic factor Bax and decreased expression of anti-apoptotic factor Bcl-xL. Next we used STED to visualize initiation of apoptosis in RPTC exposed to HG. In control cells, Bax in inactive form was found in cytoplasm, while Bcl-xl was found on mitochondria. After 6 h of HG, clusters of active Bax was found on mitochondria, while Bcl-xl remained on mitochondria. STORM revealed progressive co-localization between Bax and the voltage–dependent anion channels (VDAC) in approximately 10% of cells. Bax-VDAC interaction permitted an uncontrolled mitochondrial calcium influx, marking the point of no return in the apoptotic process. Previously we have described how ouabain/Na,K-ATPase signaling exerts an anti-apoptotic effect. Here we show that this signal halts initiation of the apoptotic process.

Conclusions: We conclude that exposure to glucose in concentrations not uncommon in poorly controlled diabetes promptly initiates an apoptotic process in SGLT expressing renal cells and would require preventive anti-apoptotic treatment.

Funding: Private Foundation Support

TH-PO432

Apoptosis Signal-Regulating Kinase 1 (ASK1) Pathway Activation in Diabetic Kidney Disease (DKD) Patients and db/db eNOS-/- Mice

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Background: ASK1 is a serine/threonine kinase activated by pathological oxidative stress that drives renal inflammation, apoptosis, and fibrosis via the downstream MAPK kinases p38 and c-Jun N terminal kinase (JNK). GS-4997 is a selective ASK1 inhibitor in clinical development for the treatment of DKD. We quantified p38 activation (p-p38) in kidney biopsies from patients with DKD and renal ASK1 activation (p-ASK1) and p-p38 levels in the db/db eNOS$^{-/-}$ model of DKD. A selective ASK1 inhibitor was used to determine the role of ASK1 in p38 activation and progressive GFR decline in db/db eNOS$^{-/-}$ mice.

Methods: p-p38 levels in renal biopsy tissue from patients with DKD (n=10) and healthy subjects (n=7) were determined by IHC. Slide images were analyzed with Definiens Developer XD and expressed as an H-Score that quantifies intensity and distribution. Masson's trichrome, PAS, and H&E stains were done to assess fibrosis and morphology. 10 week old db/db eNOS$^{-/-}$ mice were treated with a structural analog of GS-4997 (GS-444217) or vehicle for 8 weeks (n=8-10). Endpoints included p-p38 and p-ASK1 in kidney lysates, histology, and GFR by inulin-FITC clearance.

Results: Compared to normal subjects, p-p38 levels were significantly elevated in DKD biopsies (144 ± 49 vs 15 ± 9 H-Score, $p<0.00001$). In glomeruli with mild to severe mesangial expansion, p-p38 expression was prominent and localized to mesangial cells, podocytes, and parietal epithelial cells. Tubule epithelium and areas of interstitial fibrosis/inflammation also had prominent p-p38. p-p38 staining was similarly distributed in kidneys of db/db eNOS$^{-/-}$ mice. Treatment of db/db eNOS$^{-/-}$ mice with an ASK1 inhibitor suppressed p-ASK1 by 80% ($p<0.05$) and p-p38 by 84% ($p<0.0005$), and decreased albuminuria, glomerulosclerosis, and GFR decline (365± 31 vs 212± 21 ml/min, $p=0.0007$) compared to vehicle.

Conclusions: p-p38 is elevated in the glomerulus and tubulointerstitium of patients with DKD. A selective ASK1 inhibitor strongly suppresses p-ASK1 and p-p38 levels and halts GFR decline in db/db eNOS$^{-/-}$ mice.

Funding: Pharmaceutical Company Support - Gilead Sciences, Inc.

TH-PO433

Involvement of Endoplasmic Reticulum Stress, Autophagy, and Apoptosis in Advanced Glycation End Products-Induced Glomerular Mesangial Cell Injury

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Background: Advanced glycation end-products (AGEs)-induced mesangial cell death is one of major causes of glomerulosclerosis in diabetic nephropathy. Both endoplasmic reticulum (ER) stress and autophagy are adaptive responses in cells under environmental stress and participate in the renal diseases. The role of ER stress and autophagy in AGEs-induced mesangial cell death is still unclear. Here, we investigated the effect and mechanism of AGEs on glomerular mesangial cells.

Methods: Mouse mesangial cells (MMCs) were obtained from Food Industry Research and Development Institute. MMCs were treated with AGEs to evaluate the cell viability by MTT assay and flow cytometry. The protein expressions were measured by Western blot assay. Furthermore, MMCs were treated with 3-Methyladenine (3MA), siATG5 and 4-phenylbutyric acid (4PBA) to study the influence of autophagy and ER stress.

Results: AGEs dose-dependently decreased mesangial cell viability and induced MMCs apoptosis. AGEs also induced ER stress signals (GRP78, IRE1α, eIF2α, ATF4, and CHOP) in a time- and dose-dependent manner. Inhibition of ER stress with 4PBA significantly inhibited the activation of eIF2α and CHOP signals and reversed AGEs-induced apoptosis. AGEs also significantly activated LC3 cleavage, decreased p62 expression, and increased Atg5 expression in a time- and dose-dependent manner, which indicated the autophagy induction in mesangial cells. Inhibition of autophagy by Atg5 siRNA transfection aggravated AGEs-induced MMCs apoptosis. Moreover, ER stress inhibition by 4PBA significantly reversed AGEs-induced autophagy, but autophagy inhibition (Atg5 siRNA) did not influence the AGEs-induced ER stress-related signals activation. These results suggest that AGEs induce MMCs apoptosis via an ER stress-triggered signaling pathway. The Atg5-dependent autophagy plays a protective role in AGEs-induced MMCs apoptosis.

Conclusions: ER stress is capable of interfering with the function of autophagy, which may offer a new strategy against AGEs toxicity in the diabetic kidney.

Funding: Government Support - Non-U.S.

TH-PO434

Modification of Renal Macrophage Signaling via MCP-1 Inhibition Reduces Albuminuria in Diabetic Nephropathy in Mice Daphne Thomas-Ijpelaar,[1] Margien G.S. Boels,[1] Angela Koudijs,[1] Cristina Avramut,[1] Wendy Sol,[1] Gangqi Wang,[1] Annemarie Van Oeveren-Rietdijk,[1] Anton Jan Van Zonneveld,[1] Hetty C. de Boer,[1] Johan Van der Vlag,[2] Cees van Kooten,[1] Dirk Eulberg,[3] Bernard van den Berg,[1] Ton J. Rabelink.[1] *[1]LUMC, Netherlands; [2]RadboudUMC, Netherlands; [3]NOXXON Pharma AG, Germany.*

Background: Recently, inhibition of the pro-inflammatory chemokine monocyte-chemotactic protein 1 (MCP-1) with Emapticap was found to reduce albuminuria in patients with type 2 diabetic nephropathy (DN). MCP-1 regulates inflammatory cell recruitment and differentiation of macrophages. Pro-inflammatory macrophages express cathepsin L (CTSL), which activates heparanase (HPSE), thereby degrading heparan sulphates, one of the components of the glomerular endothelial glycocalyx (GEG). Presence of GEG is essential to prevent albuminuria. Therefore, we hypothesized that MCP-1 inhibition reduces albuminuria via influencing macrophage function, resulting in reduced HPSE activity and restoration of GEG.

Methods: DN was induced in 6 weeks old ApoE-KO mice with STZ (5x 60mg/kg) and a high cholesterol diet (0.15%). At week 18 mice were treated for 4 weeks with mouse specific MCP-1 inhibitor mNOX-E36 (20mg/kg, s.c.) or control Spiegelmer. Cationic ferritin (CF) binding to the GEG was imaged using transmission electron microscopy. Glomeruli were analysed for F4/80, CTSL and HPSE protein expression. Macrophages were isolated from the kidney with FACS and *ex vivo* cytokine production was measured.

Results: Treatment with mNOX-E36 attenuated albuminuria, without changes in blood glucose and blood pressure. This was accompanied by reduced CTSL and HPSE expression and increased binding of CF to the GEG. The number of glomerular macrophages did not change upon treatment. However, functional *ex vivo* analysis showed a reduced LPS-induced IL-6/IL-10 ratio, demonstrating an anti-inflammatory phenotype.

Conclusions: MCP-1 inhibition by mNOX-E36 decreases albuminuria in diabetic apoE-KO mice. The accompanied anti-inflammatory phenotype of macrophages and GEG restoration, suggest that MCP-1 inhibition attenuates albuminuria in DN by restoration of the GEG via polarization of renal macrophages.

Funding: Other NIH Support - Dutch Kidney Foundation

TH-PO435

The Role and Mechanism of Alternatively Activated Macrophage in Renal Fibrosis of Diabetic Mice Ning Su, Jiang Zongpei. *Dept of Nephrology, The Six Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong Province, China.*

Background: The effect and mechanisms of alternatively activated macrophage (M2) on renal fibrosis in diabetic mice has not been elucidated.

Methods: M2 macrophages(F4/80+CD206 double positive cells) and the accumulation of fibronectin in the kidney were observed in diabetic C57BL/6J mice after eight weeks of diabetic mellitus with intraperitoneal injection of streptozocin. Liposome-encapsulated clodronate (LC, the specific scavenger of macrophages) was used to treat the diabetic mice by intraperitoneal injection (10μl/1g bodyweight) twice one week from the third to the eighth week to investigate the effect of M2 on renal fibrosis. Furthermore, Raw 264.7 cells were induced to M2 phenotype with high ambient glucose(30mmol/L) and TGF-β1(5ng/ml). The special inhibitor of Smad2(SB431542) and Erk(U016) were used to investigate the mechanism involved in the process of M2 differentiation.

Results: M2 macrophages in kidney were eliminated and the accumulation of fibronectin was improved in those diabetic mice treated with LC. Furthermore, the activation of Smad2 and Erk were all involved in the transformation of M2 macrophage, and not only the inhibitor of Smad2 but also Erk partially inhibited the process of M2 macrophage. However, no crosstalk between the Smad2 and Erk signal pathway was found in this process.

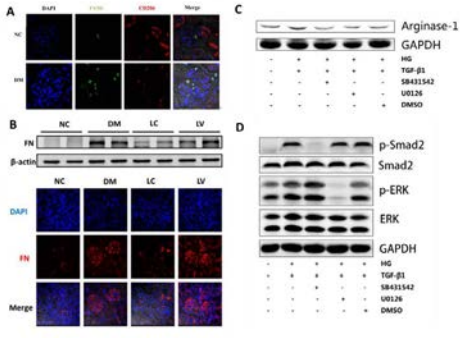

Figure1: A. M2 macrophage emerged in the kidney of diabetic mice after eight weeks of diabetic mellitus with intraperitoneal injection of streptozocin. B：LC (the specific scavenger of macrophages) was used to treat the diabetic mice by intraperitoneal injection (10μl/1g bodyweight) twice one week from the third to the eighth week. As a result, the accumulation of fibronectin were improved in those treated with LC. C: Not only the block of Smad2(with the inhibitor SB431542) but also Erk（with the inhibitor U0126）partially inhibit the transformation of M2 macrophage stimulated by high ambient glucose(30mmol/L D-glucose) and TGF-β1(5ng/ml), however. D:No crosstalk between the Smad2 and Erk signal pathway was found in this process. Abbreviations: NC: normal control group. DM: diabetic mice. FN: fibronectin. LC: Liposome-encapsulated clodronate. LV: Liposome-encapsulated vehicle(PBS). HG: high ambient glucose.

Conclusions: M2 macrophages aggravate the renal fibrosis of diabetic mice, and the Smad2 and Erk signal pathways independently involve in the transformation of M2 phenotype.

TH-PO436

De-Nitrosylation of Laminin 521 in Diabetic Nodular Glomerulosclerosis Alda Tufro, Qi Li, Pablo A. Ortiz-Pineda. *Pediatrics/Nephrology, Yale Univ, New Haven, CT.*

Background: We showed that glomerular basement membrane laminin 521 is nitrosylated in normal glomeruli. Laminin S-nitrosylation, a reversible post-translational modification controlled by nitric oxide availability and by VEGF-A in mouse kidneys and podocytes. Laminin 521 is increased in glomerular nodules observed in experimental diabetic nephropathy (DN) and likely involved in the pathogenesis of nodular glomerulosclerosis. We examined α5 and β2 laminin S-nitrosylation function in podocytes and DN.

Methods: We assessed S-nitrosylation (SNO) of α5-and β2-laminin using dual immunohistochemistry, biotin switch assay and proximity link assay in tissue and cultured cells. Kidneys from normoglycemic and T1D mice with mild DN and advanced DN were compared. SNO-α5-laminin and SNO-β2-laminin, secretion of each laminin chain, and cell migration were evaluated in human podocytes exposed to medium with normal glucose, high glucose, or mannitol.

Results: We determined that α5- and β2-laminin are S-nitrosylated in kidneys from non-diabetic mice and from mice with mild DN, whereas SNO-α5-laminin and SNO-β2-laminin decrease dramatically in advanced DN, inversely correlating with glomerular nodules. Podocytes cultured in normal glucose or mannitol medium express abundant SNO-α5-laminin and SNO-β2-laminin, while podocytes exposed to high glucose showed minimal SNO-α5-laminin and SNO-β2-laminin, as assessed by 3 independent methods. This SNO-α5-laminin and SNO-β2-laminin decrease was associated with several fold increase in α5- and β2-laminin secretion to the medium, which was abolished by nitric oxide (NO) donors. Wound assays showed that podocyte migration is impaired when α5-laminin and β2-laminin is de-nitrosylated by high glucose, and that NO donors rescue this migration defect.

Conclusions: De-nitrosylation of α5-laminin and β2-laminin leads to increased laminin secretion by podocytes, impairs their migration and contributes to development of glomerular nodules in advanced diabetic nephropathy. Nitric oxide donors reverse the podocyte increased α5-laminin and β2-laminin secretion and migration defect induced by high glucose. The inherent S-nitrosylation reversibility implies that this pathogenic mechanism may be a therapeutic target in DN.

Funding: NIDDK Support

TH-PO437

Periostin-Binding DNA Aptamer Attenuates Diabetic Nephropathy-Induced Renal Fibrosis Seonghun Kim,[1] Jae Eun Um,[1] Hae-Ryong Yun,[2] Boyoung Nam,[1] Seung Hyeok Han.[1,2] *[1]Dept of Internal Medicine, College of Medicine, Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ, Seoul, Korea; [2]Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.*

Background: Diabetic nephropathy is the major cause of chronic kidney disease, and is associated with progressive renal fibrosis. Recently, accumulation of periostin, an extracellular matrix, was shown to be implicated with renal fibrosis. Aptamers, a novel oligonucleotide which binds to specific target molecules, have been proved to have higher binding affinity without developing the common side effects of antibodies. In addition, the costs of aptamer productions are cheaper than small molecules making them a promising pharmaceutical candidate. This study was aimed to examine the therapeutic role of periostin-binding DNA aptamers (PA) on renal fibrosis under diabetic conditions.

Methods: *In vitro*, immortalized mouse distal convoluted tubule cells (mDCTs) were exposed to TGF-β1 (5 ng/ml) to induce fibrosis with or without PA (100nmol/l). *In vivo*, C57BL/6 mice were intraperitoneally injected with saline (C group, N=16) or streptozocin (50mg/kg/d) (DM group, N=16). Eight mice from each group were treated with PA (500μg/kg/d). mRNA and protein expressions of periostin, fibronectin, collagentype I (col-I) in mDCTs and mouse kidney were examined by real-time polymerase chain reaction and western blot analysis, respectively. Immunohistochemistry (IHC) was conducted with renal tissues.

Results: *In vitro*, TGF-β1 treatment significantly up-regulated periostin, fibronectin and col-I. PA treatment significantly ameliorated the TGF-β1 induced fibronectin and col-I expressions ($P < 0.05$). *In vivo*, fibronectin and col-I was significantly up-regulated in kidney samples of diabetic mice ($P < 0.05$). IHC staining revealed that the number of fibronectin and col-I (+) cells were significantly higher in diabetic mice ($P < 0.05$). These increases were clearly ameliorated by PA treatment ($P < 0.05$).

Conclusions: These findings suggest that inhibition of periostin using a DNA aptamer could be a potential therapeutic strategy against renal fibrosis in diabetic nephropathy.

TH-PO438

Susceptibility of Renal Fibrosis in Early Diabetes Shuqin Mei,[1,2] Qingqing Wei,[2] Man J. Livingston,[2] Changlin Mei,[1] Zheng Dong.[2] *[1]Shanghai Changzheng Hospital, Shanghai, China; [2]Augusta Univ, Augusta, GA; [3]Augusta Univ, Augusta, GA; [4]Shanghai Changzheng Hospital, Shanghai, China; [5]Augusta Univ, Augusta, GA.*

Background: The diabetic complication in kidneys is traditionally characterized as pathological alterations in glomeruli. However, tubulo-interstitial fibrosis (TIF) frequently occurs earlier than glomerular pathology in diabetic kidney disease (DKD). It is largely unclear how TIF is induced in DKD. We hypothesize in diabetes, renal tubulo-interstitium is predisposed to fibrogenesis and, upon stress, is highly sensitive to the development of TIF. To test this possibility, we examined renal fibrosis induced by unilateral ureteral obstruction (UUO) in diabetic models.

Methods: Two diabetic mouse models were tested: (1) Akita model. C57BL/6-*Ins*^{Akita}/J (Akita) mice were monitored to reach diabetic hyperglycemia at ~6-7 weeks of age and then were subjected to UUO along with matched wild-type littermate mice. The mice were sacrificed 7 and 14 days later for analysis. (2) STZ model. Mice were injected with 50mg/kg body-weight of STZ for 5 consecutive days at the age of 4 weeks. After verification of hyperglycemia 2-3 weeks, the mice were subjected to UUO for 7 or 14 days. For tissue analysis, Masson staining was used to detect collagen deposition and TUNEL staining was used to examine kidney injury. Fibrotic proteins were analyzed by immunoblotting. For in vitro study, mouse tubular BUMPT cells were incubated with high or normal glucose media under hypoxia for 48, 72, and 96h to examine pro-fibrotic changes.

Results: UUO induced higher fibronectin and α-SMA expression after 7and 14 days in Akita and STZ-induced diabetic mice than non-diabetic mice. Consistently, Masson staining showed more collagen deposition in Akita and STZ-induced mice. TUNEL staining also showed more apoptosis after UUO in Akita and STZ-induced mice. In cultured BUMPT cells, hypoxia induced fibronectin accumulation, which was significantly higher in high glucose cells than normal glucose group.

Conclusions: The results suggest that diabetes sensitize kidney tissues and renal tubular cells to fibrogenesis. Hyperglycemia exposure appears to contribute to this sensitivity.

TH-PO439

Aerobic Exercise(EXE) Reduce Proteinuria, Fibrosis and Renal Inflammatory Factors, in Diabetic Rats Rodolfo Rosseto Rampaso, Rafael DaSilva Luiz, Kleiton Augusto Santos Silva, Luciana Jorge, Edson Andrade Pessoa, Mario Luis Ribeiro Cesaretti, Nestor Schor. *Nephrology Div, Escola Paulista de Medicina/UNIFESP, São Paulo, Brazil.*

Background: We evaluated the role of EXE in controlling the progression of diabetic nephropathy as proteinuria, fibrosis, inflammatory factors, and thus, its possible renoprotective effects.

Methods: Wistar rats divided into 4 groups (n=8): Sedentary controls (SED), Diabetes+Sedentary (DM-SED), Diabetes+Exercise (DM-EXE) and Exercise+Controls (EXE). DM was induced with streptozotocin, 50mg/kg i.v. EXE was done on treadmill 60min/day/5 days/week/8 weeks. Weekly it was determined the Maximal Exercise Test(MEtest). Fibrosis,Glycemia 24h post training(glycemiapt), creatinine clearance/BW(CrCl/BW), mean arterial pressure(MAP), proteinuria(uProt), renal inflammatory factors were measured.

Results:

	SED	DM-SED	DM-EXE	EXE
uProt(mg/24h)	17±0.9	46±2.1 *#&	18±0.7	16±1.0
IL6(pg/ml)	541±98	993±40*#&	768±74*&	391±22
IL10(pg/ml)	545±86	876±34*#&	654±31*&	453±28
TNF-alpha(pg/ml)	3.1±0.4	5.2±0.8*#&	4.1±0.2*&	2.3±0.5
Fibrosis(m^2)	5.9±0.9	11.4±1.8*#&	8.4±2.1*	7.5±1.3
CrCL/(ml/min/BW)	5.6±0.7	5.0±0.4	4.2±0.4	4.2±0.3
glycemiapt(mg/dl)	103±2	551±7*&	491±5*&	87±2
MAP(mmHg)	122±1.9	134±1.8*#&	122±1.4	121±2.1
Weight(g)	455±6.0	236±14.4*#&	324±9.3*&	387±8.7
MEtest(m/min)	23.2±0.5#&	19.5±0.6*#&	35.1±1.0	37.5±0.6

***vs SED;#vs DM-EXE;&vs EXE P<0.05**.

Conclusions: Reductions in glycemia, fibrosis and MAP comparing DM-EXEvsDM-SED. The DM-EXE controlled weight loss(40%) compared to DM-SED, but did not prevent alteration in the CrCl/BW. However the effect of the EXE was strikingly observed in the reduction in both, mean uProt excretion(60%and25%) and in inflammatory factors comparing DM-SEDvsDM-EXE. Therefore preliminary data suggest that EXE can reduce proteinuria, renal fibrosis and inflammatory factors in diabetic animals and consequently diminish potential effects caused by diabetic and potentially could reduce the progression to renal failure.

TH-PO440

Enhanced Expression of Two Isoforms of Matrix Metalloproteinase-2 in Diabetic Nephropathy Sang Heon Song,[1] Eun Young Seong,[1] Dong Won Lee,[1] Soo Bong Lee,[1] Ihm Soo Kwak,[1] David H. Lovett.[2] *[1]Internal Medicine, Pusan National Univ School of Medicine, Busan, Korea; [2]Internal Medicine, Univ of California San Francisco, San Francisco, CA.*

Background: We recently reported on the enhanced expression of two isoforms of matrix metalloproteinase-2 (MMP-2) in human renal transplantation delayed graft function. These consist of the conventional secreted full length MMP-2 isoform (FL-MMP-2) and a novel intracellular **N**-**T**erminal **T**runcated isoform (NTT-MMP-2) generated by oxidative stress-mediated activation of an alternate promoter in the MMP-2 first intron. This generates an intracellular, enzymatically active MMP-2 isoform that induces mitochondrial injury. Here, we evaluated the effect of hyperglycemia and diabetes mellitus on the in vitro and in vivo expression of the MMP-2 isoforms.

Methods: We quantified the abundance of the FL-MMP-2 and NTT-MMP-2 transcripts by qPCR in HK2 cells cultured with high glucose or 4-hydroxy-2-hexenal (HHE) and tested the NF-κB inhibitor pyrrolidine dithiocarbamate (PDTC). The streptozotocin (STZ) murine model and renal biopsies of human diabetic nephropathy were used in this study.

Results: Both isoforms of MMP-2 in HK2 cells were upregulated by high glucose and HHE stimulation. PDTC treatment did not suppress high glucose FL-MMP-2 expression, but potently inhibited NTT-MMP-2 expression. In STZ mice, renal cortical expression of the isoforms was increased (FL-MMP-2, 1.8-fold vs. NTT-MMP-2, over 7-fold). Isoform-specific immunohistochemical staining revealed low levels of the FL-MMP-2 isoform in controls, while NTT-MMP-2 was not detected. There was a modest increase in diffuse epithelial cell staining for FL-MMP-2 in STZ mice. In contrast, NTT-MMP-2 was intensely expressed in a basolateral pattern. FL-MMP-2 and NTT-MMP-2 transcript expression were both significantly elevated in renal biopsies of human diabetic nephropathy (12-fold and 3-fold, respectively). NTT-MMP-2 expression correlated with tubular atrophy.

Conclusions: The expression of FL-MMP-2 and NTT-MMP-2 is enhanced by hyperglycemia, oxidative stress and in experimental and human diabetes. Selective MMP-2 isoform inhibition could offer a novel approach for the treatment of diabetic renal disease.

TH-PO441

Treatment with a Novel Phosphodiesterase-4 Inhibitor Reduces Diabetic Kidney Disease in eNOS -/- db/db Mice Hongyu Zhang,[1] Jharna Saha,[1] Takanori Matsuo,[2] Masatoshi Hazama,[2] Frank C. Brosius.[1] *[1]Univ of Michigan; [2]Takeda Pharmaceutical Company.*

Background: Phosphodiesterase 4 (PDE4) isoforms are expressed in immune, other nonrenal cells and in tubular epithelia in the kidney. Inhibition of PDE4 can reduce inflammation in multiple conditions. However, little is known about PDE4 effects in the pathogenesis of diabetic kidney disease (DKD). Recent findings suggest that PDE4 inhibitors may ameliorate DKD both by lowering blood glucose levels and perhaps by other mechanisms. Therefore, we determined whether a novel specific PDE4 inhibitor (PDE4I) ameliorated the DKD phenotype and compared it to combined losartan/lisinopril treatment in a type 2 diabetic model, the C57BLKS eNOS -/- db/db mouse.

Methods: db/db and db/+ eNOS -/- mice were bred in our animal facility. Mice received either the PDE4 inhibitor (3 or 10mg/kg), losartan/lisinopril (30mg/kg and 20mg/kg, respectively) or equal volume of vehicle (0.5% methylcellulose) daily by gavage between 18 and 25 wks of age (n = 8/group). Urine, blood samples and kidney tissues were obtained from each animal at 26 wks.

Results: At 26 wks all groups of diabetic mice had elevated blood sugar and glycosylated hemoglobin values which were reduced by 10mg/kg PDE4I but not by 3mg/kg PDE4I when compared to vehicle-treated db/db eNOS -/- mice. Albuminuria, mesangial matrix and tubulointerstitial fibrosis were increased and podocyte density was reduced (all $p < 0.05$) in all groups of db/db mice. All these changes were improved significantly ($p < 0.05$) and to a similar extent by treatment with 3mg/kg PDE4I or losartan/lisinopril.

Conclusions: Seven week treatment with a PDE4I in a robust model of DKD, at a dose that did not reduce hyperglycemia, ameliorated the functional and pathologic features of DKD to an extent similar to that achieved with ACE inhibitor/ARB therapy. Therefore, PDE4I therapy could be a treatment for patients with DKD.

Funding: Pharmaceutical Company Support - Takeda Pharmaceutical Company

TH-PO442

Novel and Selective Phosphodiesterase Type 4 Inhibitor Ameliorates Albuminuria in Mouse Model of Diabetic Nephropathy Mitsugi Ookawara, Yasunori Nio, Midori Yamasaki, Kanako Kuniyeda, Guido Stefan Hanauer, Masatoshi Hazama, Takanori Matsuo. *Takeda Pharmaceutical Company Ltd, Fujisawa, Kanagawa, Japan.*

Background: Diabetic nephropathy (DN) is one of the major microvascular complications in patients with diabetes mellitus (DM), and leads to chronic kidney diseases and end-stage renal failure. Phosphodiesterase (PDE) 4 is an enzyme class that selectively hydrolyzes cAMP and activates various cellular events such as inflammatory and fibrotic response. A recent clinical study demonstrated that roflumilast, a PDE4 inhibitor (PDE4i), improved glycemic control in T2DM patients (Wouters et al. 2012). Based on these unique mechanisms of action, our novel and selective PDE4i is expected to show a protective effect in DN.

Methods: Male uninephrectomized *db/db* mice (UNx-*db/db*) and KKA^y mice were used as DN mice models. After 8-week repeated dose, glycosylated hemoglobin (GHb), plasma

glucose (PG) and urinary albumin/creatinine ratio (UACR) were measured. In vitro study, anti-fibrotic effect of the PDE4i on transforming growth factor (TGF)-β-induced mRNA expression was evaluated using NRK-52E, rat tubular epithelial cell line.

Results: In vitro studies, PDE4i increased intracellular cAMP level and suppressed TGF-β-induced mRNA expression of pro-fibrotic markers in a concentration dependent manner in NRK-52E. Before start of the treatment in in-vivo studies, UNx-*db/db* mice and KKA^{y} mice showed marked hyperglycemia and albuminuria. Treatment with PDE4i for 8 weeks improved glycemic control and increase of UACR in UNx-*db/db* mice. Significant suppressive effect on UACR was observed at lower dose than that of glucose-lowering activity, thus suggesting that inhibitory effect on UACR is, at least in part, achieved by direct effect on kidney cells. Treatment with the compound for 8 weeks also significantly inhibited the increase of UACR in KKA^{y} mice, which is another mouse model of DN with intact leptin axis.

Conclusions: Selective PDE4i can ameliorate albuminuria in vivo in addition to improving the glycemic control and inhibit fibrotic response in vitro. This indicates that PDE4i could be a novel therapeutic option with multiple mechanisms of action for the treatment of DN.

TH-PO443

Vasopressin Plays a Role in Fructose-Induced Metabolic Disease through the Vasopressin 1b Receptor Thomas Jensen,[1] Ana Andres-Hernando,[2] Miguel A. Lanaspa,[2] Carlos Alberto Roncal-Jimenez,[2] Richard J. Johnson.[2] *[1]Dept of Medicine, Div of Endocrinology, Univ of Colorado, Aurora, CO; [2]Dept of Medicine, Div of Nephrology, Univ of Colorado, Aurora, CO.*

Background: Elevated vasopressin (AVP), besides its role in urinary concentration has recently been implicated in metabolic syndrome and diabetes. We hypothesize that AVP plays a role in fructose induced metabolic disease through the AVP 1b (V1b) receptor.

Methods: We exposed V1b Receptor KO Mice, V1a Receptor KO Mice, and Wild Type Mice to 30 weeks of either water or 15% Fructose water on normal chow. We did hepatic H&E and oil red O staining, analyzed hepatic triglycerides, uric acid, and cholesterol, and serum cholesterol, triglycerides, uric acid, and glucose by Alera ACE. We did ELISA to analyze serum insulin, copeptin, glucagon, and leptin, and hepatic beat hydroxybutyrate. We did western blot to analyze hepatic KHK, GLut5, hypothalamic KHK, and adipose tissue pAkt and Akt. We did PCR for hypothalamic mRNA of AVP. We obtained serum copeptin from KHK A/C KO, KHK A KO and WT on similar 30 week diet as the first group.

Results: V1b Receptor KO mice on fructose had significant less weight gain, hepatic triglycerides, elevations in liver enzymes, elevations in insulin and insulin resistance as well as elevations in leptin and food consumption as compared to Wild Type on fructose. V1a Receptor KO mice had greater weight gain and with trends toward higher insulin, insulin resistance, and leptin while it had similar elevations in liver enzymes and hepatic triglycerides. KHK levels did not differ in V1bKO and WT on fructose nor Glut5 suggesting intact fructose metabolism. We show that V1bKO and WT on high fructose diet have elevated copeptin levels despite V1bKO being protected from weight gain, hepatic steatosis, insulin resistance, and hyperleptinemia. Meanwhile KHK A/C, but not KHK A were protected from elevations in copeptin in the setting of fructose, thus showing the role KHK C isoform has in the AVP system.

Conclusions: Fructose mediates AVP release, and AVP through the V1b plays a role in the development of fructose-induced weight gain, hepatic steatosis, insulin resistance, and hyperleptinemia.

Funding: NIDDK Support

TH-PO444

Inhibition of LPA Receptor 1 Protects against Development of DN Ming-Zhi Zhang,[1] Brian Murphy,[2] Robert Kaltenbach,[3] Peter T. Cheng,[3] Bradley Zinker,[2] Raymond C. Harris.[1] *[1]Medicine, Vanderbilt Univ, Nashville, TN; [2]Fibrosis Discovery Biology, Bristol-Myers Squibb, NJ; [3]Fibrosis Discovery Chemistry, Bristol-Myers Squibb, NJ.*

Background: Lysophosphatidic acid (LPA) acts through LPA receptors (LPARs). The role of LPA in development of diabetic nephropathy (DN) has not been previously studied. BMS002 is a novel, relatively selective LPAR1 antagonist. We examined whether BMS002 affected development of DN in a type II diabetes model of progressive nephropathy and GFR decline.

Methods: eNOS$^{-/-}$ *db/db* mice received vehicle or BMS002 (20 mg/kg/day) or as a positive control, losartan and enalapril, from 8 to 20 weeks of age. GFR was measured before and at the end of 12 weeks of treatment.

Results: At 20 weeks of age, LPAR1 inhibition with BMS002 led to a marked reduction in albuminuria (ACR: 771 ± 98 vs. 1799 ± 230 μg/mg, $P < 0.0005$, n = 10), similar to that seen with the positive control (586 ± 87 μg/mg). BMS002 protected against progression of DN, as indicated by reduced histological glomerular injury and decreased pro-fibrotic and fibrotic components including fibronectin, α-SMA, CTGF, collagen I, and TGF-β. BMS002 also inhibited renal macrophage infiltration and oxidative stress. Although GFR markedly decreased in the vehicle group from 8 to 20 weeks of age (0.223 ± 0.014 vs. 0.159 ± 0.019 ml/min/mouse, $P = 0.017$, n = 10), BMS002 prevented this reduction (0.243 ± 0.020 vs. 0.258 ± 0.022, $P = 0.636$, n = 10), and the change from week 8 baseline to week 20 was significantly different between vehicle and BMS002 ($P<0.05$).BMS002 also slowed podocyte loss (podocytes/glomerulus: 8 weeks: 18.11 ± 0.31, n = 4; 20 weeks: vehicle: 8.57 ± 0.256, n = 7; BMS002: 14.51 ± 0.30, $P < 0.0001$ vs. vehicle group, n = 8). Immunofluorescent staining determined that LPAR1 was expressed in podocytes and its expression in podocytes increased in diabetic mice.

Conclusions: These studies indicate that BMS002 protects against GFR decline and attenuates development of DN through multiple mechanisms, including protection against podocyte loss and inhibition of TGF-β-mediated fibrosis, macrophage infiltration, and oxidative stress, suggesting that LPAR1 is a potential therapeutic target for the treatment of DN.

Funding: Pharmaceutical Company Support - BMS

TH-PO445

Incretin Effect Is Reduced in End-Stage Renal Disease Morten Buus Jørgensen,[1] Thomas Idorn,[1] Casper Rydahl,[2] Henrik Post Hansen,[2] Iain B. Bressendorff,[3] Lisbet Brandi,[3] Gerrit van Hall,[4] Jens Juul Holst,[5] Filip K. Knop,[5,6] Mads Hornum,[1] Bo Feldt-Rasmussen.[1] *[1]Dept of Nephrology, Rigshospitalet, Denmark; [2]Dept of Nephrology, Herlev Hospital, Denmark; [3]Dept of Cardiology, Nephrology and Endocrinology, North Zealand Hospital, Denmark; [4]CMCF, Rigshospitalet, Denmark; [5]The NNF Center for Basic Metabolic Research, Univ of Copenhagen, Denmark; [6]Center for Diabetes Research, Gentofte Hospital, Denmark.*

Background: Incretin hormone inactivity plays a pivotal role in the pathogenesis of postprandial hyperglycemia including impaired glucose tolerance (IGT) and diabetes. We hypothesized that uremia cause a (diabetes independent) reduced insulin secretion due to an impaired incretin effect which could contribute to the high incidence of IGT and diabetes observed in end-stage renal disease.

Methods: 12 chronic hemodialysis patients (ESRD) and 12 age, weight and height-matched healthy controls (CTRL), all with normal glucose tolerance, were included. On three separate days, a 2h euglycemic clamp followed by a 2h hyperglycemic (3 mM above fasting level) clamp was performed with concomitant (double-blinded) infusion of GLP-1 (1 pmol/kg/min), GIP (2 pmol/kg/min) or placebo. A 30% lower infusion rate was used in the ESRD group (derived from previous kinetic studies) to obtain comparable plasma concentrations.

Results: 22 patients and 14 controls were screened. Six patients had IGT and three diabetes, all diagnosed from postprandial (2h) plasma glucose levels. One withdrew consent. Two controls had elevated creatinine levels whereas one also had IGT. Glucose levels where comparable on all three examination days. The ratio of insulin during hyperglycemia and euglycemia on the placebo day was also comparable (ESRD: 3.1 [2.5 – 3.8] CTRL: 3.4 [2.9 – 3.9], NS). The relative effect of GLP-1 versus the placebo day tended to be lower during euglycemia in ESRD (26 [-18 – 53]%, NS) and was significantly reduced during hyperglycemia (50 [8 – 72]%, P=0.03). The relative effect of GIP during euglycemia tended to be lower in ESRD (23 [-5 - 43]%, NS) and was significantly reduced during hyperglycemia (34 [13 – 50]%, P=0.005).

Conclusions: The incretin effect is reduced in end-stage renal disease which could contribute to the high prevalence of postprandial hyperglycemia.

Funding: Private Foundation Support

TH-PO446

The DPP-4 Inhibitor Linagliptin Reduces Albuminuria Independently of Blood Glucose Levels Atsushi Uchida, Minoru Satoh, Tamaki Sasaki, Naoki Kashihara. *Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Okayama, Japan.*

Background: In diabetes, both high glucose and albuminuria are becoming a theranostic factor of nephropathy. A previous study showed that a dipeptidyl peptidase (DPP)-4 inhibitor has an antioxidant effect in addition to its hypoglycemic effect. We assumed that endothelial damage due to oxidative stress was the cause of albuminuria. Thus, we tested whether a DPP-4 inhibitor, linagliptin, suppresses albuminuria via the antioxidant effect at an early stage of diabetes.

Methods: Male C57BL/6 control (wild-type; WT) mice and Akita mice were used. The mice were subdivided into 4 groups: (1) control, (2) WT+ linagliptin, (3) Akita, and (4) Akita+ linagliptin. Linagliptin was administered daily for 8 weeks. To visualize glomerular filtration, the two-photon laser microscopic in vivo imaging method was used. Glomerular morphological changes, glomerular oxidative stress, and urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) excretion were examined.

Results: The DPP-4 inhibitor did not cause any changes in body weight, urine volume, and blood pressure. With respect to renal function, there were no differences among all the groups. Blood glucose, HbA1c level, and albuminuria increased significantly in Akita mice. Administration of linagliptin did not reduce blood glucose and HbA1c level but reduced albuminuria significantly. In the Akita group, the size of glomeruli increased, the mesangial area was expanded, and the glomerular endothelial surface layer was lost compared with the control group. These changes were attenuated in the Akita+ linagliptin group. Excretion of urinary 8-OHdG, which is an oxidative-stress marker was suppressed by linagliptin. In the WT glomeruli, 70-kDa dextran did not leak from glomerular capillaries. However, the 70-kDa dextran leaked into the Bowman space in the Akita group. This leakage was attenuated by linagliptin.

Conclusions: We showed that a DPP-4 inhibitor has a protective effect on endothelial cells and reduces albuminuria by suppressing oxidative stress. These effects were independent of blood glucose. These data suggest that administration of a DPP-4 inhibitor starting at an early stage of diabetes can suppress the onset and progression of nephropathy.

TH-PO447

Renoprotective Effects of Dipeptidyl Peptidase Type 4 Inhibitor Linagliptin in Glucagon Like Peptide 1 Receptor Knockout Mice with 5/6 Nephrectomy

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Background: Dipeptidyl peptidase (DPP)-4 inhibitors were reported to have beneficial effects in experimental chronic kidney disease (CKD) models. The underlying mechanisms are not completely understood. Many studies suggested that these renoprotective effects are mediated via the glucagon like peptide-1 (GLP-1)/GLP-1 receptor pathway. To challenge this hypothesis we investigated the renal effects of the DPP-4 inhibitor linagliptin (LIN) in delaying CKD progression in GLP-1 receptor knockout (GLP-1r$^{-/-}$) mice with 5/6 nephrectomy (5/6 Nx).

Methods: The mice were allocated to the following groups: sham + placebo (PBO); 5/6 Nx + PBO; 5/6 Nx + LIN; sham + GLP-1r$^{-/-}$ + PBO; 5/6 Nx + GLP-1r$^{-/-}$ + PBO and 5/6 Nx + GLP-1r$^{-/-}$ + LIN and the treatment period was 12 weeks.

Results: LIN treatment led to a significant decrease in plasma DPP-4 activity and a significant substantial increase of plasma active GLP-1, which was more pronounced in GLP-1r$^{-/-}$ mice than wild-type mice. Moreover, 5/6 nephrectomy caused the development of renal interstitial fibrosis and glomerulosclerosis and increased plasma cystatin C levels in wild-type and GLP-1r$^{-/-}$ mice and these effects were counteracted by LIN treatment. In addition, proteins were separated from kidney tissues and subjected to liquid chromatography-matrix-assisted laser desorption ionization mass spectrometry (LC-MALDI-MS). After mass spectrometry-data acquisition, spectra were analyzed and 298 signals were differentially regulated among the groups, with 150 signals specific to LIN treatment. The identification of the amino acid sequences of the peptides corresponding to these signals, by means of tandem mass spectrometry, is currently going on.

Conclusions: The beneficial renal effects of LIN in mice with 5/6 nephrectomy cannot solely be attributed to the GLP-1/GLP-1 receptor pathway,highlighting the importance of other signaling pathways influenced by DPP-4 inhibition.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

TH-PO448

Insulin Inhibits Nuclear Factor Erythroid 2-Related Factor 2 Gene Expression and Prevents Hypertension and Kidney Injury in Type 1 Diabetes

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Background: We hypothesized that insulin regulates nuclear factor erythroid 2-related factor 2 (*Nrf2*) gene expression via heterogeneous nuclear ribonucleoprotein F (hnRNP F) and hnRNP K, preventing Nrf2-stimulation of angiotensinogen (*Agt*) gene expression, hypertension and renal injury in Type 1 diabetic Akita mice.

Methods: Male Akita mice and non-Akita littermates (at week 12) were treated +/- insulin implants and euthanized at week 16. Hyperinsulinemic-euglycemic clamp was performed on adult wild-type mice. Effects of insulin on blood glucose, systolic blood pressure, renal proximal tubular cell (RPTC) gene expression and tubulointerstitial fibrosis were assessed. *In vitro* studies used rat immortalized PTCs (IRPTCs) stably transfected with *Nrf2*, *Agt*, *hnRNP F* or *hnRNP K* gene promoter.

Results: Insulin normalized hyperglycemia, inhibited renal *Nrf2* and *Agt* gene expression, up-regulated hnRNP F/K expression, and prevented hypertension and renal injury in Akita mice. *In vitro*, insulin inhibited *Nrf2* gene promoter activity via a specific DNA responsive element that binds hnRNP F/K, and averted Nrf2-stimulation of *Agt* gene expression via p44/42 mitogen-activated protein kinase signaling. Transient transfection of IRPTCs with *hnRNP F* and/or *hnRNP K* siRNA abolished insulin down-regulation of *Nrf2* gene expression. Furthermore, transient transfection of IRPTCs with *hnRNP F* and/or *hnRNP K* cDNA effectively blocked Nrf2 stimulation of *Agt* gene transcription. In hyperinsulinemic-euglycemic mice, renal *Nrf2* and *Agt* expression was lower, whereas *hnRNP F/K* expression was higher than in saline-infused mice.

Conclusions: We conclude that insulin prevented hypertension and nephropathy in diabetes, at least in part, via suppression of *Nrf2* transcription and consequently Nrf2-stimulation of renal *Agt* expression through enhancing hnRNP F/K expression.

Funding: Government Support - Non-U.S.

TH-PO449

Novel sGC Stimulator IW-1701 Prevents the Progression of Diabetic Nephropathy when Administered in Combination with Enalapril in the ZSF1 Rat Model

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Background: In diabetic nephropathy, elevated reactive oxygen species and reduced nitric oxide (NO) availability contribute to endothelial dysfunction and disease progression. Soluble guanylate cyclase (sGC) stimulators enhance NO signaling and increase the formation of cyclic guanosine monophosphate. Previous studies have shown the capacity of sGC stimulators to lower blood pressure and exert anti-inflammatory, antifibrotic and positive metabolic effects. This study assessed the effects of IW-1701, a novel sGC stimulator in clinical development, in the ZSF1 model of diabetic nephropathy.

Methods: Male ZSF1 rats were implanted with radiotelemetry transmitters (abdominal aorta) for continuous blood pressure recording. After recovery, rats received either plain or enalapril (3 mg/kg) in water for 10 days then 10 weeks of enalapril or enalapril + IW-1701 (10 or 30 mg/kg/d)in chow (n=8/group). Plasma and urine were collected during the study.

Results: After the initial 10 days, treatment with enalapril-only reduced mean arterial pressure (MAP) by 5+/-1 mmHg compared with untreated rats; this effect was sustained (8+/- 1 mmHg) through week 10 . Enalapril + IW-1701(10 and 30 mg/kg) reduced MAP by 13+/- 1 and 15 +/- 1 mmHg respectively ($p<0.05$ vs enalapril-only treatment). Kidney and liver hypertrophy were reduced in rats receiving enalapril + IW-1701 30 mg/kg/d. This dose combination also reduced fasted blood glucose, total cholesterol and triglycerides by ≥40% compared to untreated rats. Urinary protein creatinine ratio (UPCR) increased to 27.5+/- 3 by day 10 and to 51+/- 3 by week 10. Enalapril-only treatment reduced UPCR by 33% compared to untreated control. Enalapril + IW-1701 reduced UPCR by 54 and 90% at the 10 and 30 mg/kg/d doses, respectively.

Conclusions: IW-1701 in combination with enalapril demonstrated efficacy reducing blood pressure and proteinuria in the ZSF1 rats. This preclinical study suggests the sGC stimulator IW-1701 could be beneficial in preventing the progression of diabetic nephropathy when added to the standard of care.

Funding: Pharmaceutical Company Support - Ironwood Pharmaceuticals Inc

TH-PO450

Prolyl Hydroxylase Inhibitor Decreases Albuminuria and Improves Glucose and Lipid Metabolism in a Mouse Model of Type 2 Diabetes

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Background: Although prolyl hydroxylase (PHD) inhibition was reported to have beneficial effects in several kidney disease (especially acute kidney injury) models, the effect of long-term PHD inhibition on diabetic kidney disease remains unclear. We examined the effect of a specific PHD inhibitor, JTZ-951 (Japan Tobacco Inc., Japan), in a mouse model of type 2 diabetes.

Methods: Four-week-old male BTBR ob/ob mice were divided into the vehicle and JTZ-951 groups. JTZ-951 (0.005%; in feed) was administered from 4 weeks of age until euthanasia (at 22 weeks).

Results: During the study period, body weight and blood glucose level tended to be lower in the JTZ-951 group (HbA1c: 8.9±0.3 vs 8.2±0.2%) with comparable feed intake between the groups. JTZ-951 caused transient and mild polycythemia with an increase in plasma erythropoietin level (9.3±3.7 vs 21.0±2.4 mIU/mL) but did not affect plasma VEGF levels. PHD inhibition significantly decreased urinary albumin at 16 and 22 weeks (4.8±0.7 vs 1.9±0.4 and 5.9±1.3 vs 2.3±0.5 mg/mgCr, respectively). At euthanasia, GFR and kidney weight were comparable between the groups while PHD inhibition significantly decreased the epididymal white adipose tissue weight (1980±110 vs 1315±88 mg), total cholesterol (260±26 vs 164±19 mg/dL) and plasma insulin (6.0±1.0 vs 2.8±0.5 ng/mL) levels and increased plasma adiponectin levels (9.8±0.5 vs 15.8±1.4 ng/mL). Histological studies showed the glomerular tuft area, mesangial expansion, podocyte density, peritubular/glomerular capillary density, interstitial fibrosis, and macrophage infiltration were unaffected by PHD inhibition.

Conclusions: Long-term administration of JTZ-951 decreased urinary albumin levels and improved glucose/lipid metabolism without significant adverse effects in a mouse model of type 2 diabetes, indicating that PHD inhibition has potential as a novel therapeutic target in diabetic kidney disease.

Funding: Government Support - Non-U.S.

TH-PO451

Oral Treatment with PBI-4050, a Novel Anti-Diabetic and Anti-Fibrotic Compound, Reduces Renal and White Adipose Tissue Fibrosis in ob/ob Mice

Lyne Gagnon, Marie-Pier Cloutier, Alexandre Laverdure, Jonathan Richard, Liette Gervais, Alexandra Felton, Pierre Laurin, Brigitte Grouix. *ProMetic BioSciences Inc., Laval, QC, Canada.*

Background: PBI-4050 is a first-in-class novel orally active compound which displays anti-inflammatory/antifibrotic activities via a novel mechanism of action. PBI-4050 also displays metabolic properties by reducing blood glucose level. In healthy volunteers, PBI-4050 was found to be safe and well tolerated up to 2400 mg without any significant adverse effects (SAEs). Similarly, PBI-4050 was well tolerated in chronic kidney disease (CKD) patients with no SAEs observed at 800 mg. PBI-4050 is presently in Clinical Phase II in diabetes (T2D) associated with metabolic syndrome. Preliminary data from this open-labeled phase showed that PBI-4050 significantly reduced glycated hemoglobin (HbA1c, -0.7), and biomarkers (IL-18, resistin, and pentraxin-3) from the first 12 enrolled patients. This study examined the effect of PBI-4050 in leptin-deficient ob/ob mice, a model of type 2 diabetes with renal fibrosis.

Methods: ob/ob mice (6 weeks old) were treated with vehicle or PBI-4050 (100 and 200 mg/kg, oral once a day) from day 1 through 105. Blood glucose, pro-inflammatory/fibrotic gene expression in kidney and white adipose tissue, as well as kidney histology were examined.

Results: In oral glucose tolerance test, PBI-4050 slightly improved glucose metabolism. Collagen type IV and VI gene expression was significantly reduced in white adipose tissue of PBI-4050 treated animals compared to control ob/ob mice. Further characterization of the activity of PBI-4050 in ob/ob mice by quantitative RT-PCR analysis of pro-fibrotic markers demonstrated that PBI-4050 reduced α-SMA, fibronectin, CTGF, MRC-1, MCP-1 and MMP-2 expression in kidney. Furthermore, histomorphometry analysis was performed on kidneys and PBI-4050 was shown to reduce collagen deposition in glomeruli as determined by Picro Sirius staining.

Conclusions: Taken together, these results suggest that PBI-4050 offers the potential as a novel therapy for diabetes, diabetic nephropathy, and pro-inflammatory /pro-fibrotic markers in kidney and white adipose tissue.

TH-PO452

PBI-4050 Protects against Renal Fibrosis and Improves Pancreatic Function in High Fat Diet db/db Mouse Model Lyne Gagnon, Martin Leduc, Mikaël Tremblay, Liette Gervais, François Sarra-Bournet, Alexandra Felton, Marie-Pier Cloutier, Kathy Hince, Pierre Laurin, Brigitte Grouix. *ProMetic BioSciences Inc., Laval, QC, Canada.*

Background: PBI-4050, a novel first-in-class orally active compound which is currently in a phase II clinical trial, significantly reduced glycated hemoglobin (HbA1c) after 12 weeks of treatment in patients with type 2 diabetes and metabolic syndrome with elevated HbA1c despite anti-hyperglycemic treatment. In the present study, we examined whether PBI-4050 affected high fat diet (HFD)-induced triglycerides, insulin and adiponectin levels and the development of renal fibrosis induced by HFD in db/db mice.

Methods: db/db mice were fed with a HFD and received vehicle (water) or PBI-4050 (200 mg/kg/day) by daily gastric gavage from 6 to 21 weeks of age.

Results: High fat diet induced an increase in triglycerides and a decrease in adiponectin levels in serum which were significantly improved by PBI-4050 treatment. PBI-4050 increased serum insulin which correlated with the improvement of β-cell function observed by immunohistochemistry analysis. Kidney function was also improved by PBI-4050 treatment as shown by a decrease in hyperfiltration measured by inulin clearance. Furthermore, expression of IL-6, Collagen I, CTGF, MCP-1, and iNOS in kidney were downregulated by PBI-4050 treatment.

Conclusions: These studies suggest that PBI-4050 improves insulin production and β-cell function and survival, and prevents renal fibrosis in association with regulation of pro-fibrotic biomarkers in HFD obese db/db mice.

TH-PO453

Oral Treatment with PBI-4547, a Novel Anti-Diabetic and Anti-Fibrotic Compound, Reduces Blood Glucose and Renal Fibrosis in ob/ob Mice Brigitte Grouix, Marie-Pier Cloutier, Alexandra Felton, Jonathan Richard, Alexandre Laverdure, Liette Gervais, Pierre Laurin, Lyne Gagnon. *ProMetic BioSciences Inc., Laval, QC, Canada.*

Background: Type II diabetes is a major health problem worldwide. Adiponectin has been shown to play important roles in the regulation of energy homeostasis and insulin sensitivity, and its low level is predictive of future development of diabetes. PBI-4547 is an orally active compound that displays anti-fibrotic activities via a novel mechanism of action. This study examined the effect of PBI-4547 in leptin-deficient ob/ob mice, a model of type 2 diabetes with renal fibrosis.

Methods: ob/ob mice (6 weeks old) were treated with vehicle or PBI-4547 (10 and 50 mg/kg, oral once a day) from day 1 through 105. Blood glucose, white adipose tissue (WAT) histology, kidney pro-inflammatory/fibrotic gene expression, as well as serum adiponectin levels were examined.

Results: In oral glucose tolerance test, PBI-4547 increased glucose metabolism. Serum cholesterol and triglyceride levels were also reduced by PBI-4547. Serum level of adiponectin was reduced in ob/ob non-treated mice and strongly increased in PBI-4547-treated mice. Histomorphometry analysis performed on WAT indicated that PBI-4547 treatment reduced fibrosis, inflammatory cell infiltration and adipocyte size. Further characterization of the activity of PBI-4547 by quantitative RT-PCR analysis of pro-fibrotic markers in the kidney demonstrated that PBI-4547 reduced α-SMA, fibronectin, CTGF, MRC-1, MCP-1 and MMP-2 expression. Moreover, PBI-4547 reduced collagen deposition in glomeruli as determined by Picro Sirius staining.

Conclusions: Taken together, these results suggest that PBI-4547 offers the potential as a novel therapy for diabetes, diabetic nephropathy, and obesity by reducing blood glucose levels, reducing pro-inflammatory and pro-fibrotic markers in kidney, and by increasing serum adiponectin to regulate energy homeostasis.

TH-PO454

Effects of LCZ696 on Blood Pressure and Renal Injury in Type 2 Diabetic OLETF Rats with Overt Proteinuria Akira Nishiyama,[1] Yoshio Konishi,[2] Takashi Morikawa,[2] Daisuke Nakano,[1] Masahito Imanishi.[2] *[1]Dept of Pharamacology, Kagawa Univ Medical School, Japan; [2]Dept of Nephrology and Hypertension, Osaka City General Hospital, Japan.*

Background: In the present study, we aimed to examine the effect of LCZ696, an angiotensin receptor-neprilysin inhibitor, on blood pressure and renal injury in type 2 diabetic Otsuka-Long-Evans-Tokushima-Fatty (OLETF) rats with overt proteinuria.

Methods: In OLETF rats, vehicle (n=10), valsartan (30 mg/kg/day, n=10), LCZ606 (68 mg/kg/day, n=9) or valsartan plus hydralazine (3 mg/day, n=10) was treated from 56 to 80 weeks of age.

Results: At baseline (56-week-old), diabetic OLETF rats showed hypertension, overt proteinuria, glomerular injury (glomerular PAS positive area) and tubulointerstitial fibrosis (Sirius Red-positive area). At 80-week-old, vehicle-treated OLETF rats showed developed hypertension and proteinuria, severe glomerular injury and tubulointerstitial fibrosis, and increases in plasma BUN and creatine levels. Treatment with LCZ696 or valsartan plus hydralazine similarly caused greater blood pressure reduction than valsartan. On the other hand, LCZ696 caused greater attenuation of developments of proteinuria, glomerular injury and tubulointerstitial fibrosis than valsartan or valsartan plus hydralazine. LCZ696 also prevented the increases in plasma BUN and creatine levels.

Conclusions: These data suggest that LCZ696 elicits a reno-protective effect in type 2 diabetes with hypertension and nephrotic-range proteinuria.

Funding: Government Support - Non-U.S.

TH-PO455

Multi-Glycoside of *Tripterygium wilfordii* Hook. F. Alleviates Glomerulosclerosis in the Diabetic Nephropathy Model Rats via Inhibiting Microinflammation and IL-6/JAK2/STAT3 Signaling Activity Jingjing Yang,[1] Yigang Wan.[2] *[1]Dept of Graduate School, Nanjing Univ of Chinese Medicine, Nanjing, China; [2]Dept of Traditional Chinese Medicine, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing Univ Medical School, Nanjing, China.*

Background: Multi-glycoside of *Tripterygium wilfordii* Hook. f. (GTW), an extractedphyto medicine has been proved clinically effective in improving microinflammation in early diabetic nephropathy (DN) patients in China.However, the therapeutic mechanisms involved in vivo remain unclear.In the process of early DN, microinflammation and the activation of IL-6/JAK2/STAT3are the important mechanisms by which hyperglycemia contributes to glomerulosclerosis (GS).Therefore, this study aimed toexamine the ameliorative effects of GTW on GS, then to clarify its anti-microinflammatory mechanisms by inhibiting IL-6/JAK2/STAT3 signaling activities in kidneys.

Methods: All rats were divided into 4 groups, the Sham group, the Sham+GTW group, the Vehicle group and the GTW group. The suitable dose of GTW and vehiclewere daily administrated for 8 weeks after the induction of DN by unilateral nephrectomy combined with streptozotocin (STZ)intraperitoneal injections.

Results: The results showed that, GTWimprovedthe DN model rats' general condition and biochemical parameters, but did not lower blood glucose; GTW attenuated GS and suppressed glomerular microinflammation including the infiltration of macrophage in glomeruli and the protein overexpressions of IL-6, TNF-α and TGF-β1 in kidneys; GTW inhibited the protein overexpressions of p-JAK2 and p-STAT3 in kidneys, as well as other classical inflammatory signaling molecules including p-p38MAPK and NF-κB.

Conclusions: In conclusion, using the modified DN model rats, we expounded that GTW, as a natural regulator in vivo, alleviates GS without lowering hyperglycemia in the DN model rats, by way of anti-microinflammation including reducing macrophage infiltration in glomeruli, suppressing TNF-α and TGF-β1 overexpressions in kidneys and inhibiting IL-6/JAK2/STAT3 signaling activity. This study may provide the first evidence in vivo that GTW directly contributes to the prevention of DN via an anti-microinflammatory action.

Funding: Government Support - Non-U.S.

TH-PO456

Treatment with Sodium Acetate Reduces Diabetic Kidney Injury in Mice Xiaochen Chen,[1] Steven J. Chadban,[1,2] Jin Ma,[1] Tony King-Tak Kwan,[1] Huiling Wu.[1,2] *[1]Kidney Node Laboratory, The Charles Perkins Centre, Univ of Sydney, Australia; [2]Renal Medicine, Royal Prince Alfred Hospital, Australia.*

Background: Short-chain fatty acids (SCFAs) are derived from the fermentation of dietary fibre by the intestinal microbiota and exert profound effects on immune responses and inflammation. SCFAs delivered by diet or intraperitoneal (ip) injection have been found to attenuate the development of autoimmune and inflammatory diseases. Here we test the hypothesis that the administration of SCFA will attenuate kidney injury in streptozotocin (STZ)-induced diabetic nephropathy (DN).

Methods: DN was induced in C57BL/6 mice by STZ. Two weeks after STZ injection, both diabetic and non-diabetic mice received daily intraperitoneal injections of either sodium acetate (SA), 200mg/kg i.p./animal or saline for 6 weeks and were then switched to oral sodium acetate 150mM in their drinking water for the duration of the study. Samples were collected at 12 weeks post-induction of diabetes.

Results: Diabetic mice that received SA or saline remained similarly hyperglycaemic. SA-treated diabetic mice exhibited reduced albuminuria compared to control diabetic mice (ACR 161±46 versus 333±248, $p<0.05$). SA-treated diabetic mice demonstrated improvement in histological parameters compared to control diabetic mice, including glomerular hypertrophy (glomerular volume: $15.8\pm1.1\times10^4$ versus $20.6\pm4.4\times10^4\mu m^3$, $p<0.01$), glomerular hypercellularity (25±2 versus 29±3 cells/glomerulus, $p<0.01$), podocyte injury (16±1 versus 13±1 $WT1^+$ podocytes/glomerulus, $p<0.01$) and interstitial macrophage accumulation (13±3 versus 18±6 $CD68^+$ cells/field, $p<0.01$). mRNA expression of cytokines(IL6&TGF-β),chemokine(CCL2) and pro-fibrotic(fibronectin) genes in the kidney were attenuated in diabetic mice treated with SA versus control diabetic mice ($p<0.05$).

Conclusions: Treatment with sodium acetate provided partial protection against the development of diabetic nephropathy in mice with STZ-induced diabetes. Dietary manipulation of the microbiome warrants further exploration in the prevention and management of diabetic nephropathy.

TH-PO457

Novel Immunomodulatory Cytokine Offers Multi-Pronged Protection from Type-2 Diabetic Nephropathy (T2DN) Rahul Sharma,[1] Marta Stremska,[1] Saleh Mohammad,[1] Poonam R. Sharma,[2] Mark D. Okusa.[1] *[1]Div of Nephrology, Dept of Medicine, Univ of Virginia, Charlottesville, VA; [2]Dept of Biomedical Engineering, Univ of Virginia, Charlottesville, VA.*

Background: While inflammation contributes to T2DN pathogenesis, regulatory T cells (Treg) are protective. We developed a novel cytokine (IL233) bearing IL-2 and IL-33 activities in a single molecule. IL233 promotes Treg and protects mice from acute kidney injury and lupus glomerulonephritis (Sharma R et al, Kidney week 2015). We investigated whether IL233 will enhance Treg, inhibit inflammation and protect from T2DN.

Methods: Male BTBR.Cg-*Lep*^{ob} (Ob) mice were treated with saline or IL233 (3pmoles/g/d) for 5 days at 4-5 weeks or 10-12 weeks of age. Body weight, fasting blood glucose, glucose tolerance, kidney function (urinary albumin creatinine ratio, ACR; mean±SEM) were analyzed. Spleen, kidneys and visceral fat were analyzed by flow cytometry and histology at necropsy.

Results: Compared to controls, treatment of 4-5wk old Ob mice with IL233 induced a 2x increase in Treg as measured in the blood, which persisted for > 4 months in lymphoid organs (1.5x) and adipose tissue (2.3x) upon necropsy. IL233 treated Ob mice had lower proteinuria (ACR: 29±4 mg/g at necropsy) than controls (ACR: 133±35 mg/g). IL233-treatment also inhibited diabetes (lower blood glucose and normalization of glucose tolerance) and obesity (lower body and adipose tissue weights) in the Ob mice. Kidney histology of control Ob mice showed leukocytic infiltration and mesangial expansion, which was inhibited in the IL233 treated mice. IL233 treatment of the 10-12 weeks old Ob mice also resulted in lower proteinuria (2.4x higher ACR in controls over IL233-treated). This was accompanied with lower blood glucose starting two weeks post treatment and persisting until the end of study, when the control mice had to be euthanized. Along with increasing Treg, IL233 also enhanced Treg's ability to produce IL-10.

Conclusions: The novel cytokine IL233 containing the activities of IL-2 and IL-33 bears therapeutic potential as it protects genetically obese mice from T2DN, by regulating multiple contributors of pathogenesis, namely inflammation, obesity and diabetes.

Funding: NIDDK Support, Pharmaceutical Company Support - University of Virginia - AstraZeneca Research Alliance

TH-PO458

Identifying Novel Therapies in Diabetic Kidney Disease Mark Nguyen,[1] Minnie Sarwal.[2] *[1]Dept of Nephrology, Univ of California San Francisco, San Francisco, CA; [2]Dept of Surgery, Univ of California San Francisco, San Francisco, CA.*

Background: The development and progression of diabetic kidney disease (DKD) is thought to involve a combination of hemodynamic, metabolic, ischemic, and inflammatory factors; however, the exact mechanism remains to be elucidated. Given the pro-inflammatory component of DKD, gene expression of leukocytes is thought to provide additional insight into the disease. Here we describe microarray analysis of peripheral blood mononuclear cells (PBMCs) in diabetic patients with varying levels of albuminuria. The findings were compared against publicly available gene expression data from human diabetic kidney biopsies.

Methods: Microarray experiments were performed on PBMCs isolated from a cohort (Cohort I) of 33 healthy and diabetic patients (10 healthy controls, 11 normoalbuminuria, 7 microalbuminuria, and 5 macroalbuminuria). Gene expression across different levels of albuminuria were measured and ranked. From an independent cohort (Cohort II) of publicly available microarray experiments, a total of 67 microarray experiments (25 with DKD and 42 control) of kidney glomeruli were analyzed utilizing expression genome-wide association study. Immunohistochemistry (IHC) on tissue was done to validate protein expression.

Results: In Cohort I, there were 859 genes significant ($p < 0.05$) for increasing expression with higher levels of albuminuria. The meta-analysis of Cohort II, revealed 326 significant up regulated genes. There were 28 genes with increased expression in PBMCs and glomeruli with hypergeometric enrichment p value of 5E-04. From the list of candidate genes, we identified genes such as tumor necrosis factor and toll like receptor which have been previously described in the literature as playing a role in DKD progression thereby providing some validation to this methodology. Two targets, CCR1 and FcER1, were identified as potential mediators of disease progression. Protein expression was validated with IHC.

Conclusions: We described a novel study involving high throughput data to discover a number of candidate genes that may play a critical role in the development and progression of DKD in the hopes it will lead to novel therapies.

Funding: Other NIH Support - Institution T32

TH-PO459

High-Fat Diet-Fed Medaka Model for Human Diabetic Nephropathy and Hyperglycemia Tomoko Obara. *Cell Biology, Univ of Oklahoma Health Sciences of Center, Oklahoma City, OK.*

Background: Chronic hyperglycemia promotes diabetic nephropathy, leading to chronic kidney diseases (CKD) associated with nephron loss. CKD requires dialysis or kidney transplantation for survival. There is a critical need for new therapeutic approaches to preserve kidney function using suitable animal models that mimic the human pathology of diabetic nephropathy and hyperglycemia. Due to the polygenic origin of diabetes, therapeutic approaches must target multiple signaling pathways. The membrane metallo-endopeptidase (MME) activates peptide hormones and generates bioactive peptides distributed throughout the body. *MME* knockout mice developed dyslipidemia and hyperglycemia, however its renal effects are poorly understood. Mechanisms of renal effects of MME in diabetic nephropathy and hyperglycemia remain unexplored.

Methods: We established a high-fat diet (HFD)-fed medaka model that mimics human diabetic nephropathy and hyperglycemia. By using this model, we performed shotgun proteomics, western blot, and subcellular immunohistochemical analysis and discovered MME down-regulation in the kidney. We applied genetics to confirm the MME involvement in diabetic nephropathy and hyperglycemia in medaka and mouse models. Furthermore, we confirmed the relevant role of MME in diabetic human kidney specimens. Finally, we evaluated whether this model can be used for drug screening.

Results: We demonstrated that 1) MME is down-regulated in HFD-fed medaka kidney by shotgun HPLC-ESI-MS/MS, western blot, and subcellular immunohistochemical analysis, 2) *MME* knockdown in medaka and mouse adults resulted in diabetic nephropathy and hyperglycemia, 3) MME protein subcellular downregulation is confirmed in the glomeruli specimens from human patients with diabetes, 4) treatment with Telmisartan, omega-3-PUFAs, and metformin prevented diabetic nephropathy and hyperglycemia induced by HFD-fed medaka.

Conclusions: These data implicate that our new animal models will highlight novel therapeutic targets suitable for preventing diabetic nephropathy and resulted in decreased kidney function in response to hyperglycemia. In summary, these discoveries will lead to identification of highly specific therapeutic targets against human CKD.

Funding: Private Foundation Support

TH-PO460

Lacking Fructokinase-A Exacerbates Renal Injury in Streptozotocin-Induced Diabetic Mice Tomohito Doke,[1] Takuji Ishimoto,[1] Takahiro Hayasaki,[1] Miguel A. Lanaspa,[2] Richard J. Johnson,[2] Seiichi Matsuo,[1] Shoichi Maruyama.[1] *[1]Dept of Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Aichi, Japan; [2]Renal Diseases and Hypertension, Univ of Colorado Denver, Aurora, CO.*

Background: Ketohexokinase (KHK), a primary enzyme for fructose, exists as two isoforms, KHK-C and KHK-A. We have reported that endogenous fructose and its metabolism produced by polyol pathway activation in diabetes may have a deleterious role in the pathogenesis of diabetic nephropathy using mice lacking both isoform KHK-A and KHK-C. KHK-C has higher affinity for fructose compared to KHK-A. Although both isoforms express in proximal tubule, the role of KHK-A is not yet elucidated. The aim of this study is to determine the role of KHK-A in the development of diabetic nephropathy in mice.

Methods: Male wild-type mice, KHK-A knockout mice, and KHK-A/C knockout mice (lacking both isoforms) were used. Diabetes was induced with intraperitoneal injections of streptozotocin (50 mg/kg/day, 5 days). Body weight, blood glucose were measured regularly. At 18 weeks, urine and blood samples and kidney tissues were collected. Kidney injuries were assessed for proteinuria, urinary NGAL, serum creatinine, and histology. Gene and protein expressions related to inflammation, hypoxia, oxidative stress, and polyol pathway enzymes were analyzed.

Results: The level of blood glucose was similar among three genotypes during study period. However, diabetic KHK-A knockout mice showed significant increase of urinary NGAL, renal dysfunction, glomerular hypertrophy, and tubular injuries accompanied by increased HIF1α expression, inflammatory cytokines and macrophage infiltration (F4/80 staining) compared to diabetic KHK-A/C knockout mice. While diabetic wild type mice also showed increase of urinary NGAL, the degree of renal injury, inflammation, hypoxia and oxidative stress was significantly less than diabetic KHK-A knockout mice.

Conclusions: Kidney injury in streptozotocin-induced diabetes was exacerbated in mice lacking KHK-A, but is prevented in mice lacking both isoforms, KHK-C and KHK-A. These results suggest that KHK-A has an important role in attenuation of endogenous fructose-related kidney injury in diabetic mice.

TH-PO461

Inhibition of YAP Activity Ameliorates Diabetic Nephropathy Jianchun Chen, Ming-Zhi Zhang, Raymond C. Harris. *Medicine, Vanderbilt Univ, Nashville, TN.*

Background: Yes-associated protein (YAP) is a transcriptional regulator modulated by the Hippo signaling pathway. The Hippo/YAP signaling pathway controls the balance of cell proliferation, cell differentiation and cell death to define organ size, as well as to mediate fibrotic injury. Activation of YAP leads to nuclear translocation and interaction with the TEA domain (TEAD) family of transcription factors. The current studies investigated the effect of pharmacologic inactivation of YAP-TEAD interactions on development of diabetic nephropathy (DN).

Methods: We utilized a model of accelerated DN (STZ-eNOS-/-). Diabetic mice were treated for 20 weeks with vehicle or verteporfin (100 mg/kg, every other day), a porphyrin derivative that is used clinically as a photosensitizer for neovascular macular degeneration and that inhibits YAP-TEAD interactions.

Results: At 20 weeks of diabetes, verteporfin significantly decreased albuminuria (ACR: 232.7 ± 40.3 vs. 365.0 ± 31.8 μg/mg, $P < 0.05$, $n = 7$) and glomerulosclerosis index (0.74 ± 0.03 vs. 0.96 ± 0.06, $P< 0.01$, $n = 7$). It also decreased podocyte loss (15.83 ± 0.40 vs. 12.54 ± 0.60 podocytes/glomerulus, $P < 0.005$, $n = 7$) as well as decreasing kidney macrophage infiltration and increasing M2 markers including arginase 1 and YM-1. Immunoblotting showed that DN increased expression of the YAP-TEAD target genes CTGF and amphiregulin, which were inhibited by verteporfin. Immunostaining demonstrated higher CTGF expression in podocytes from vehicle-treated mice than in verteporfin-treated mice. Immunoblotting also indicated that verteporfin inhibited expression levels of markers of dedifferentiation and fibrosis, including TGF-ß, p-SMAD-2, a-SMA, snail-1, Kim-1, vimentin and collagen I.

Conclusions: Inhibition of YAP-TEAD activation ameliorates injury in a model of experimental diabetic nephropathy, suggesting an important role for this pathway in development of diabetic kidney injury and indicating that it may be a target for therapeutic intervention.

Funding: NIDDK Support, VA Support

TH-PO462

p66Shc Knockout Prevents Development of Diabetic Nephropathy in Streptozotocin-Treated Dahl Salt-Sensitive Rats Bradley S. Miller, Shoshana R. Blumenthal, Kevin D. Wright, Andrey Sorokin. *Medicine, Medical College of Wisconsin, Milwaukee, WI.*

Background: One of the main pathophysiological mechanisms, which are responsible for the kidney damage associated with diabetic nephropathy (DN), is the generation of reactive oxygen species (ROS) by mitochondrial electron transport system. The purpose of this study was to test whether adaptor protein p66Shc, a redox protein capable of promoting of mitochondrial ROS generation, is the cause of renal damage in streptozotocin-treated Dahl Salt-Sensitive (SS) rats.

Methods: p66Shc rat knockout and rats with a knock-in Ser36Ala substitution in p66Shc were generated using engineered Zinc Finger Nucleases (ZFN) and, in case of knock-in, also a template plasmid containing the desired mutation. Diabetes was induced in the SS control and mutant rats by an injection of streptozotocin (STZ). Hyperglycemia, excessive urination, body weight, albuminuria and display of renal pathologies, typical for patients with DN, was evaluated for the time period of twelve weeks after treatment.

Results: Following STZ injection SS rats develop hyperglycemia, excessive urination, albuminuria and other renal pathologies which accompany the progression of DN in patients. Both, p66Shc knockout and introduction of the mutation into p66Shc mutant, which incapacitated its translocation to mitochondria, prevented the development of DN in our rat model.

Conclusions: Adaptor protein p66Shc plays the principal role in the progression of DN in a STZ-triggered rat model of diabetes. The Ser36Ala substitution in p66Shc, which disables the phosphorylation-mediated mitochondrial translocation of p66Shc, is sufficient to prevent increase of albuminuria after treatment with STZ. Thus, the rat experimental model of DN provides novel opportunities for identification of new molecular targets and confirmation of previously identified molecules for therapeutic intervention in DN. The inhibiting of mitochondrial translocation of p66Shc could be considered as an efficient therapeutic strategy to combat DN.

Funding: NIDDK Support

TH-PO463

Role of P2Y2 Receptor in Adipogenesis and Metabolism Yue Zhang,[1] Carolyn M. Ecelbarger,[2] Christa E. Müller,[3] Anna U. Brandes,[1] Tao Liu,[1] Lisa Lesniewski,[1] Bellamkonda K. Kishore.[1] *[1]Univ of Utah & VA Medical Center, Salt Lake City, UT; [2]Georgetown Univ, Washington, DC; [3]Univ of Bonn, Bonn, Germany.*

Background: Previously we reported that genetic deletion of $P2Y_2$ receptor (R) confers significant resistance to the development of high-fat diet (HFD)-induced obesity, without reducing the food intake or causing steatorrhea. To understand the mechanisms involved in this protection, we investigated adipogenesis, lipid tolerance, energy metabolism and browning of white fat in $P2Y_2$-R knockout (KO) and wild type (WT) mice.

Methods: Preadipocytes from KO or WT mice were induced to mature in vitro in the absence or presence of AR-C 118925 to block $P2Y_2$-R. Intraperitoneal lipid tolerance test (LTT) was conducted in KO and WT mice. Metabolic Phenotype of KO and WT mice was determined in CLAMS Metabolic Cages. Browning of white fat was induced in vivo by injecting CL316,243 (β_3-adrenergic agonist) for 6 days or in vitro by adding rosiglitazone (PPARγ agonist) to the culture medium. UCP1 mRNA expression was used as an index of browning.

Results: When induced in vitro, preadipocytes derived from KO mice did not mature as robustly as those from WT mice, as assessed by the accumulation of lipid droplets (oil red staining). Blockade of $P2Y_2$-R in preadipocytes derived from WT mice prevented their maturation in a dose-dependent manner. Under basal conditions KO mice had significantly higher serum triglycerides and showed impaired lipid tolerance as compared to WT mice. Metabolic phenotyping revealed significantly increased VO_2 and energy production and decreased RER (respiratory exchange ratio) in KO mice vs. WT mice. When browning was induced, UCP1 expression was significantly higher in the inguinal fat of KO mice or adipocytes derived from KO mice vs. WT mice.

Conclusions: These results suggest that $P2Y_2$-R plays a significant role in the development of diet-induced obesity by promoting maturation of adipocytes, altering adipocyte lipid metabolism, and by negatively impacting browning of fat and thereby energy metabolism. Thus, targeting $P2Y_2$-R may be a viable strategy to prevent or treat diet-induced obesity.

Funding: NIDDK Support, VA Support

TH-PO464

Longitudinal Characterization of Glomerular Filtration Rate of the Naïve ZSF1 Rat Robin E. Haimbach, Li-Jun Ma, Maarten Hoek, Shirly Pinto, Xiaoyan Zhou. *Dept of Cardiometabolic Diseases, Merck & Co., Inc., Kenilworth, NJ.*

Background: The obese ZSF1 rat exhibits many features of metabolic syndrome in humans and is widely used as a translational model of diabetic nephropathy. However, the glomerular filtration rate (GFR) changes over time have not been fully characterized. Therefore, we evaluated FITC-sinistrin as a method to determine GFR and to characterize changes in GFR in ZSF1 rats with disease progression.

Methods: Male lean and obese ZSF1 rats were used for GFR measurements every 1-5 weeks from the age of 5 to 50 weeks old. GFR was measured using the plasma disappearance curve of the transcutaneous fluorescence of FITC-sinistrin excited and detected by a skin mounted detector (Mannheim Pharma & Diagnostics). In order to determine the robustness of FITC-sinistrin GFR measurement, additional groups of aged male ZSF1 rats (43-48 weeks old) were studied to compare the sensitivity and variability of FITC-sinistrin GFR with that of estimated GFR by creatinine clearance.

Results: Between 5 and 11 weeks of age, significant kidney hyperfiltration occurred ranging from a 22-45% increase compared to the lean ZSF1 control. After 15 weeks of age, we observed a progressive decrease in GFR until week 25 in both obese and lean rats. After week 25, the obese ZSF1 showed an increased rate of decline in kidney function compared to the lean ZSF1. Between 45-50 weeks, the ZSF1 obese rat displayed a sustained GFR decrease of ~50% compared to the lean. GFR values were replicated in three cohorts for the respective age groups of lean and obese rats. FITC-sinistrin GFR compared to creatinine clearance provides a 1.8-3.3x greater effect size that provides a more sensitive method to detect changes in GFR.

Conclusions: Data from these studies show that FITC-sinistrin GFR measurement is a more robust measurement of GFR than creatinine clearance in the ZSF1 rat. Consistent with the classical manifestation of early stage human diabetic nephropathy, the hyperfiltration phase of diabetic nephropathy in the male ZSF1 rat occurs at an early age (5-11 weeks old), with the obese ZSF1 GFR decline outpacing the lean ZSF1 GFR decline after 25 weeks of age.

Funding: Pharmaceutical Company Support - Merck & Co., Inc.

TH-PO465

A New Model for Diabetic Nephropathy: A Hypoxia-Induced Antioxidant Metallothionein-3 BACTG Mice Yumi Takiyama,[1] Ryoichi Bessho,[1] Takahiko Nakagawa,[2] Masakazu Haneda.[1] *[1]Dept of Medicine, Asahikawa Medical Univ, Asahikawa, Hokkaido, Japan; [2]Industry-Academia-Goverment Collaboration Promotion Center, Nara Medical Univ, Nara, Japan.*

Background: Metallothionein (MT) is a cysteine-rich protein with low molecular weight, and an antioxidant against the toxicity of metals, ischemia, and ROS. MT3 is one of the four MTs, which is originally cloned as a neuronal growth inhibitory factor from brain and is decreased in Alzheimer's brain. We have recently found that MT3 is a target for Hypoxia Inducible Factor-1 and MT3 protein expression is increased in tubular cells in diabetic nephropathy (DN). In addition, we found four putative hypoxia response elements containing the consensus sequence (A/G) CGTG within the human MT3 gene, not in mouse. The purpose of this present study was to reveal the pathophysiologic potential of MT3 in DN.

Methods: In this study, we generated transgenic mice, harboring a 40-kb bacterial artificial chromosome (BAC) expressing human MT3 mRNA and protein to generate humanized BAC transgenic mice (MT3 BACTG). By inducing hypoxic condition in vivo, we used streptozotocin-induced diabetic or aged MT3 BACTG mice.

Results: Aged transgenic mice which overexpress MT3 in renal tubules showed the nodular glomerulosclerosis like Kimmelstiel-Wilson lesion, capsular drop and doughnut lesions without hyperglycemia. The glomerular nodule in transgenic mice was negative for phosphotungstic acid-hematoxilin stain. Electron microscopy showed no electron dense deposits in mesangial lesion with thickening of the glomerular basement membranes and podocyte process effacement.Intriguingly, endothelial cell marker CD31 staining showed peritubular capillary dilatation accompanied with the swelling endothelial cells which caused narrowing capillary lumen. Multiple low-dose streptozotocin injections induced moderate hyperglycemia, histological mesangial expansion and an accumulation of hyaline material in collapsing glomerular segments without glomerular hypertrophy.

Conclusions: Overexpressed MT3 in tubular cells in BACTG mice complicates peritubular capillary, which could retrogradely cause glomerular hypertension, leading to the glomerular lesion. Humanized MT3 BACTG mice propose a new model for the study of DN.

Funding: Government Support - Non-U.S.

TH-PO466

Myostatin, a New Mediator of Inflammation and Tissue Injury in Diabetic Nephropathy (DN) Giacomo Garibotto, Daniela Verzola, Samantha Milanesi, Francesca Ansaldo, Francesca Viazzi, Annalisa Carta, Daniela Picciotto, Francesca Costigliolo, Chiara Barisione. *DIMI, Genoa Univ and IRCCS AOU San Martino-IST, Genoa, Italy.*

Background: Myostatin (MSTN), a structurally-related member of the TGFβ superfamily, acts as negative regulator of tissue growth and promotes fibrosis/atrophy. Although initially described as a negative regulator of muscle growth, MSTN has been found in other tissues, including the kidney in pigs. In humans, MSTN participates to the

body response to hyperglycemia. However, there is no information regarding MSTN in the normal kidney and in patients with DN. The aim of this study was to evaluate the role of MSTN in the normal kidney and in DN.

Methods: MSTN and Activin Receptor 2B (rtPCR and immunohistochemistry) were evaluated in microdissected tubuli and glomeruli from normal kidneys (n=10) (C) and DN (n=15, proteinuria 2 g/d, eGFR 45+2 ml/min). Moreover, MSTN regulation in response to diabetic milieu was studied in proximal human tubule (HK-2) cells.

Results: In the normal kidney MSTN mRNA was faintly expressed both in the tubular and glomerular compartments. In DN, MSTN mRNA and protein were 5-6 folds overexpressed with respect to C ($p<0.05$-0.001) in the tubular compartment, and even more (~40 folds, $p<0.05$), in the glomeruli. Glomerular MSTN was localized in podocytes and mesangial cells. Tubular cells, interstitium and mainly CD45+ cells infiltrates were highly MSTN positive. Activin Receptor 2B protein expression was localized in glomeruli, tubuli and interstitial cells both in C and DN kidneys. However, Activin Receptor 2B was downregulated in all compartments in DN. In HK-2 cells, high glucose, glycated serum and glycated albumin upregulated both MSTN mRNA and protein (by ~6 and ~2 folds respectively $p<0.05$-0.01). When MSTN was added to HK-2 cultures (48 hours) cell division was slowed and MCP1 and RANTES mRNAs expression rose ($p<0.01$).

Conclusions: Our data indicate that MSTN is expressed in the human kidney and overexpressed in DN. Diabetic milieu induces MSTN in PTECs. In vitro, MSTN slows cell proliferation and induces inflammatory changes. The above reported data suggest that MSTN could be a new mediator of inflammation and injury in DN.

TH-PO467

High Intensity Interval Training (HIIT) Prevent Proteinuria on STZ Diabetic Rats Natália Lopes Reinecke, Rafael DaSilva Luiz, Rodolfo Rosseto Rampaso, Waldemar S. Almeida, Nestor Schor. *Medicine/Nephrology, UNIFESP, São Paulo, São Paulo, Brazil.*

Background: The benefits of physical exercise on Diabetes are already well known, however, the insertion of these patients on a regular physical training program is still a challenge, given that 'lack of time' remains one of the most commonly cited barriers to regular exercise participation. HIIT, which involves repeated bursts of vigorous exercise interspersed with periods of rest, has been demonstrate to have potential cardio metabolic benefits in Diabetic or pre-diabetic subjects, even requiring a lower commitment time than the current recommendation of exercise for this population. However, the effects of HIIT on renal function of diabetic rats have yet no been studied. The aim of this study was to examine the effects of low-volume HIIT on renal function and physical capacity in STZ Diabetic rats.

Methods: Wistar rats were submitted to HIIT following a protocol: 10 bursts of 1 minute(90% of maximal effort test) intersected with 10 periods of low intensity walking(50% of maximal effort test), 3days/wk, 8wk total. Diabetes was induced by a single injection(50mg/kg i.v.). Animals were divided into three groups 6 to 8 animals/group: Sedentary Control(SC), Sedentary Diabetic(SD) and Diabetic HIIT(DHIIT).

Results: HIIT improved the exercise capacity as shown by the higher maximal velocity reached in the exercise test (37±1.55vs25.2±2.7m/min, DHIITvsSD,$p<0.001$). HIIT also prevented the increased proteinuria caused by Diabetes in comparison to SD(9.9±6vs19.6±1.9mg/dL/24h, $p<0.05$,respectively) with no difference between DHIITvsSC(9.9±6vs9.0±2.3). The urinary volume(67.2±19.3vs95.4±13.8mL/24h,$p<0.05$), the water ingestion(93.4±24.5vs124.2±22.1mL/24h,$p<0.05$), and the loss on muscular weight(1.00±0.19vs0.73±0.22g Tibial muscle,$p<0.05$) were also attenuated by exercise in HIIT group when compared to SD group.

Conclusions: Results of this study demonstrate that HIIT can improve exercise capacity, prevent the lower glomerular function(showed by the proteinuria) and attenuate other diabetic symptoms as polyuria, polydipsia and sarcopenia. These data suggests that HIIT can be a time-efficient strategy to a non-pharmacological treatment to minimize Diabetes complications.

Funding: Government Support - Non-U.S.

TH-PO468

Bias and Imprecision in Net Acid Excretion Predictions Lynda A. Frassetto,[1] Tanushree Banerjee.[1] *[1]UCSF; [2]Sunshine U.*

Background: Diets contribute to the body's net acid or base load. Several equations using diet cation, anion and protein content have been developed to help estimate whether specific foods would be acid or base containing and tested against the current gold standard, 24 hour net acid excretion(NAE), since measuring NAE requires a research lab. NAE has also been shown to correlate with urinary sulfate, organic acid and ion markers (UPRAL). How well equations or UPRAL predict any one individual's actual NAE has not been evaluated.

Methods: Retrospective analyses of studies where NAE and UPRAL were reported for same participant following both an acid and alkali dietary consumption were included. They also contained individual dietary data pertinent to estimating net endogenous acid production (NEAP). Estimate NEAP according to Frassetto (F), Remer/Manz (R), and Lemann (L) were computed in their usual manner. Bland-Altman technique was used to compute the accuracy and precision of the NEAP equations to NAE during the acid-forming and alkali consumption diets. All statistical analyses were completed using XLStat.

Results: The equations were too imprecise to NAE for any individual, although the accuracy of NEAP-R at a group level was reasonable for the acid-forming diets. Similar results for UPRAL vs NAE was noted, with agreement between the two techniques for the alkaline diets. See Table 1.

		Typical acid forming diets			Alkali supplementation		
	n	Bias	95% CI for the bias	Limits of agreement	Bias	95% CI for the bias	Limits of agreement
$NEAP_R$ vs NAE(mEq/d)	40	-0.7	-7.5, 5.9	-41.7, 40.2	-6.6	-13.1, -0.02	-46.8, 33.6
$NEAP_F$ vs NAE (mEq/d)	55	11.3	5.2, 17.4	-32.9, 55.5	35.1	25.7, 44.5	-32.8, 103.1
$NEAP_L$ vs NAE(mEq/d)	53	6.3	0.5, 12.2	-35.3, 47.9	19.4	11.1, 27.8	-39.8, 78.7
UPRAL vs NAE (mEq/d)	17	5.6	0.02, 11.1	-15.6, 26.7	0.93	-8.5, 10.4	-35.1, 37.0

Conclusions: Both dietary NEAP estimates and UPRAL are more precise for group as opposed to individual NAE estimates, and results differ depending on the diet acid or base load. Researchers may wish to collect both NEAP as well as UPRAL data when doing dietary acid experiments.

Funding: Clinical Revenue Support

TH-PO469

Genotype, Phenotype Correlations in Distal Renal Tubular Acidosis Benjamin A. Oliveira, Marilina Antonelou, Stephen B. Walsh, Detlef Bockenhauer, Robert Kleta, Robert J. Unwin. *Dept Renal Medicine, Univ College London, London, United Kingdom.*

Background: Distal renal tubular acidosis (dRTA) is characterized by an inability of α-intercalated cells in the distal nephron to secrete H^+ ions. Mutations leading to dRTA have been found in the anion-exchanger 1 (AE1), and vH^+ATPase subunits. AE1 mutations may be autosomal dominant or recessive, and dRTA has been described in compound heterozygotes who are also have the AE1 red cell disorder Southeast Asian Ovalocytosis (SAO). We sought to compare biochemical and hematological data among different genetic groups.

Methods: We compared patients with mutations in AE1 or vH^+ATPase subunits at our institution. Phenotypic data was collected including baseline electrolytes, hematological results, and urine tests.

Results: Tenty-six patients had a gene mutation known to cause dRTA; 5 were due to vH^+ATPase subunit mutations, 19 were due to AD AE1 mutations and 2 were AE1 compound heterozygotes for dRTA and SAO causing mutations ('dRTA/SAO group'). We found that serum bicarbonate was significantly lower in the dRTA/SAO group: 17 versus 23.5 and 22.4 mmol/L in the vH^+ATPase subunit and AD AE1 groups respectively ($P = 0.02$). There was a trend towards both AE1 groups having a lower citrate excretion than the vH^+ATPase subunit group; 0.12 versus 2.16 mmol/24h ($p=0.053$). The dRTA/SAO group had a hemoglobin of 111g/l which was significantly lower than the other two groups; 128 and 140 g/l ($p = 0.034$). The serum creatinine in the vH^+ATPase group was 73 µmol/L, which was significantly lower than the SAO and the AD AE1 groups; 124 and 112, respectively ($p =0.04$).

Conclusions: The lower hemoglobin seen in the dRTA/SAO group may reflect sub-clinical hemolysis known to occur in this group. Both the AE1 groups together had significantly worse GFR than the vH^+ATPase group; the trend towards lower serum bicarbonate and lower citrate excretion also suggests a more severe systemic acidosis. Acidosis may be both a factor contributing to deteriorating GFR, or a consequence. It has been suggested that vH^+ATPase subunit mutations cause a more severe phenotype than AE1 mutations; these data suggest that this might not always be the case and further work is required to elucidate this.

TH-PO470

Association of Serum Bicarbonate Levels with a Novel Marker of Serum Calcification Propensity Jessica B. Kendrick,[1,2] Emily Decker,[1] Andreas Pasch,[3] Zhiying You,[1] Michel Chonchol.[1] *[1]Univ of Colorado Denver; [2]Denver Health & Hospital; [3]Univ of Bern.*

Background: Acid retention in patients with chronic kidney disease (CKD) results in increased production of angiotensin II, aldosterone and endothelin-1, all of which can directly and indirectly induce vascular calcification. However, the relationship between serum bicarbonate levels and vascular calcification has not been examined. We evaluated the association between serum bicarbonate levels with a novel test that measures the overall calcification propensity of serum, T_{50}, in patients with CKD stage 3-4.

Methods: We measured serum bicarbonate levels and serum T_{50} levels in 128 patients with CKD stage 3-4. T_{50} measures the transformation time of amorphous calcium phosphate-containing primary calciprotein particles (CPP) to crystalline hydroxyapatite-containing secondary CPP. A higher T_{50} represents lower calcification propensity. Serum T_{50} was measured using a Nephelostart nephelometer (BMG Labtech, Offenburg, Germany). Multiple linear regression was used to examine the association between serum bicarbonate levels and T_{50}.

Results: The mean (SD) age and eGFR was 58.1 ± 12.4 years and 33.1 ± 10.2 ml/min/1.73m^2, respectively. Mean (SD) serum bicarbonate and T_{50} levels were 22.9 ± 2.9 mEq/L and 223.4 ± 46.8 min, respectively. Higher serum bicarbonate was associated with higher T_{50} (Table).

Serum Bicarbonate (mEq/L)	Serum T_{50} (minutes) β* (95% CI) *Adjusted for age, gender, race
< 21	-38.4 (-57.8 to -19.1)
21-23	-35.2 (-54.0 to -16.3)
>23	1.0 (REF)
per 1 mEq/L increase	5.18 (2.43 to 7.93)

Conclusions: Higher bicarbonate levels are associated with less overall serum calcification propensity in CKD stage 3-4, suggesting a beneficial role of alkali therapy on calcification in CKD.

Funding: NIDDK Support

TH-PO471

Acute Regulated Expression of Pendrin in Human Urinary Exosomes (UEs)

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Background: Regulation of pendrin upon chronic acid-base changes has been well studied in the rodent kidney. However, impact of acute acid-base changes on pendrin expression and subcellular localization is unknown. Furthermore, there is a paucity of data on the regulation of pendrin in the human kidney. Here we studied effect of acute acidosis, alkalosis or sodium chloride loading in humans on pendrin expression in urinary exosomes (UEs).

Methods: After acute acid NH_4Cl (100 mg/kg) or equimolar alkali NaHCO3 (157 mg/kg) or NaCl (110 mg/kg) loading in fasting individuals, urinary exosomes were isolated from hourly collected spot urine samples. Pendrin and the housekeeping UE protein alix were detected by immunoblotting. UE pendrin expression was normalized to alix expression.

Results: Acute NH_4Cl loading (n=8) elicited a systemic acidosis with a drop in urinary pH and an increase of urinary NH_4 excretion. Nadir urinary pH was achieved 5 hrs after NH_4Cl loading. UE pendrin expression was first significantly reduced after 3 hrs, lowest UE pendrin levels were observed after 4 hrs. In contrast, after acute equimolar $NaHCO_3$ loading (n=8), urinary and blood pH rose rapidly and urinary NH_4 excretion decreased. Densitometric analysis of immunoblots revealed rapid upregulation of UE pendrin expression already after 1 hr of $NaHCO_3$ loading. However, UE pendrin levels returned to baseline after 2 hrs. To analyze the effect of acute NaCl loading, we administered an oral equimolar amount of NaCl to healthy individuals (n=7). Urinary Na and Cl excretion increased significantly and rapidly after NaCl loading. Urinary pH, blood pH and urinary ammonia were unaltered throughout the experiment. Compared to baseline levels, UE pendrin abundance fell and was significantly lower at 3 hrs after NaCl loading.

Conclusions: Acute acid, alkali or chloride loading significantly alter UE pendrin expression in human UE within a few hours.

Funding: Government Support - Non-U.S.

TH-PO472

Urinary Exosomes Analysis of Renal Tubular Transporters in Patients with Acute and Chronic Hypokalemia

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Background: Urinary exosomes contain membrane and cytosolic proteins from each renal epithelial cell type and has been used as an index of renal tubular transporter expression in primary aldosteronism or renal tubular disorders. Urinary exosome analysis of renal sodium (Na^+) and potassium (K^+) associated transporters in hypokalemia patients has not been studied.We aim to evaluate renal $Na^+$and K^+ transporters expression in patients with acute and chronic hypokalemia.

Methods: We have collected timely spot urine from 19 hypokalemia patients includingthyrotoxic periodic paralysis with acute hypokalemia (TPP, n=6), Gitelman syndrome with chronic hypokalemia (GS, n=13) and healthy control (n=6). Urinary exosomes were further isolated by ultracentrifugation method. Membrane transporters proteins abundance including NCC, pNCC, NHE3, NKCC2, *CLCNK*β,ENaCβ, ROMK, and Maxi-K were analyzed by immunoblotting and another urinary exosome maker CD9 used as internal control.

Results: Mean plasma K^+ concentration was 2.4±0.3 mmol/L in TPP patients with acute hypokalemia and 2.5±0.4 mmol/L in GS. In TPP patients, only NHE3 abundance (intensity 0.36±0.04 vs. 1.08±0.29,p<0.05) and ROMK (intensity 1.39±0.11 vs. 2.58±0.20, p<0.01) in parallel to urinary K^+ excretion (K^+/Creatinine ratio, 0.11±0.01 mmol/L/mg/dl) were significantly decreased in acute phase and increased in recovery phase. In GS patients, NCC and pNCC abundance significantly decreased corresponding to NCC mutation compared to healthy control. Na^+ associated transporters abundance of NHE3 and ENaCβ significantly increased while K^+ associated transporters abundance of ROMK and Maxi-K significantly increased.

Conclusions: Urine exosomics could evaluate the renal Na^+ and K^+ transporters expression in hypokalemia. Acute hypokalemia may not affect expression in distal Na^+ transporters but affect ROMK, not Maxi-K, in response to hypokalemia. Chronic hypokalemia with NCC defect could activate upstream NHE3 and downstream ENaCβ with concomitant increased ROMK and Maxi-K expression in response to flow.

TH-PO473

Identification of a CACNA1S-Specific Missense Mutation in a Three Generation Pedigree with Hypokalemic Periodic Paralysis

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Background: Hypokalemia is an electrolyte imbalance that is not only common, but can also be debilitating and life-threatening to a patient if not addressed appropriately. Mechanisms that may lead to hypokalemia include decreased intake, increased losses via sweat, urine or the GI tract, and disproportionate translocation into cells. A rather rare cause (~1:100,000) of recurrent, modest to severe hypokalemia with accompanying muscle weakness is a neuromuscular disorder known as hypokalemic periodic paralysis (HypoPP). HypoPP is related to a skeletal muscle channelopathy of either the voltage-activated sodium channel $Na_v1.4$, encoded by SCN4A, or the L-type calcium channel $Ca_v1.1$, encoded by CACNA1S. We suspected the disease in an otherwise healthy 26-year-old male carpenter with no family history of hereditary disorders, who presented to the emergency room with flaccid quadriparesis and a serum potassium of 2.3 mmol/L.

Methods: We extracted the patient's genomic DNA and designed primers to specifically amplify and study the S4 voltage-sensor domains of $Na_v1.4$ and $Ca_v1.1$. DNA from HeLa cells was used as control template.

Results: Sequencing and alignment identified a heterozygous single nucleotide exchange (G to A) at position 1583 of the CACNA1S gene (chromosome 1q31-32), predicting an amino acid switch at position 528 from highly conserved arginine to histidine (R528H). To test the hypothesis of a de-novo mutation in this index case, we obtained and analyzed the DNA from the patient's first and second degree relatives. Interestingly, we found the same pathological single nucleotide polymorphism (SNP) in the patient's mother and maternal grandmother, although they have never had symptoms characteristic of HypoPP including sudden onset of profound muscle weakness or hypokalemia.

Conclusions: In conclusion, we have identified a new pedigree with autosomal-dominantly inherited HypoPP in central Germany. The possibility of missing or incomplete clinical manifestation of HypoPP has to be considered. The causal relationship between gender and HypoPP penetrance remains unclear and needs further investigation.

Funding: Government Support - Non-U.S.

TH-PO474

Association of Potassium Values with Mortality: Data from a Metropolitan Safety-Net Hospital

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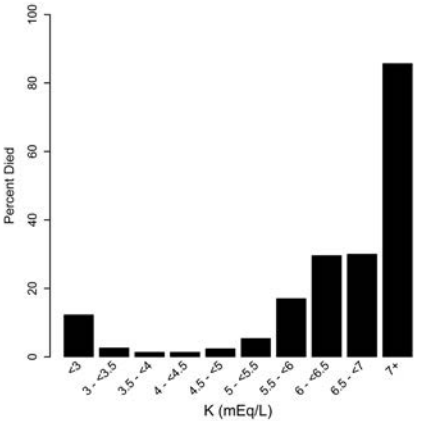
Background: Extremes of serum potassium (K) levels have been associated with adverse outcomes. We examined the association between K values with mortality in patients hospitalized at a metropolitan safety-net hospital.

Methods: We obtained K values for all patients hospitalized over a 1-yr period (July 2014-June 2015) and analyzed the association between K level, and variability, with in-hospital mortality. We also assessed the % of patients with K > 5.0 overall and by comorbidity: Diabetes Mellitus (DM), Chronic Kidney Disease (CKD), and Congestive Heart Failure (CHF).

Results: 17,317 hospitalizations with K values were included. The mean age was 50.2 yrs, 57.3% of patients were male, 47.7% white, 33.7% black; for comorbidities, 25.9% had DM, 14.1% CKD, and 6.2% CHF. The distribution of K <3.5, 3.5-<5, 5-<6, and 6+, was 7.9%, 88.7%, 3.1%, 0.3%, respectively. There was a U-shaped relationship between K and mortality, with the lowest risk between 3.5 and 5.0 mEg/L (see figure). The % of patients with K > 5.0 for patients with DM was 4.0%, CKD 6.4%, CHF 6.0%, compared to 0.9% among patients without any of the three comorbidities (all p < 0.001). For the association between K standard deviation (for each increase of 0.1) and in-hospital mortality, the odds ratio was 1.19 (p < 0.001).



Conclusions: Although both low and high K values were associated with an increased risk of mortality, risk of death increased once potassium exceeded 5.5 mEq/L and increased markedly thereafter. Increasing variability in K was also associated with mortality. The comorbid conditions of DM, CKD, and CHF are all associated with increased serum K levels. More intense efforts targeted to prevent severe hyperkalemia in pts with DM, CKD, and CHF may be warranted.

TH-PO475

Serum Potassium and the Risk of Adverse Outcomes: A CKD Prognosis Consortium Meta-Analysis Csaba P. Kovesdy, Kunihiro Matsushita, Yingying Sang, Juan Jesus Carrero, Gabriel Chodick, Takeshi Hasegawa, Atsushi Hirayama, Areef Ishani, Gijs W.D. Landman, Adeera Levin, Rupert Major, Dorothea Nitsch, David C. Wheeler, Josef Coresh, Stein I. Hallan, Varda Shalev, Morgan Grams. *CKD Prognosis Consortium.*

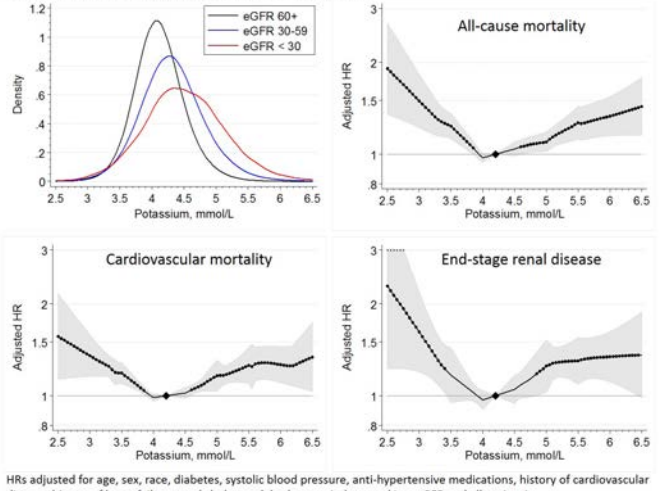
Background: Potassium levels outside the normal range may be dangerous. We evaluate the continuous relationship between potassium and all-cause mortality, cardiovascular mortality, and end-stage renal disease in 21 international cohorts.

Methods: We used Cox regression followed by random-effects meta-analysis to assess the relationship between baseline potassium (spline term with knots at 3.5, 4, 4.5, 5, and 5.5 mmol/L) and adverse outcomes, adjusted for age, sex, race, diabetes, systolic blood pressure, anti-hypertensive medications, cardiovascular disease, heart failure, total cholesterol, body-mass index, smoking, eGFR and albuminuria. We tested for effect modification by levels of eGFR (60+, 30-59, and <30 ml/min/1.73 m^2).

Results: There were 418,999 participants with both eGFR and albuminuria across 11 general population, 2 high cardiovascular risk, and 8 CKD cohorts followed for an average of 5 years. Mean baseline potassium was 4.2 mmol/L. Average age was 55 years, 54% were female, and 4% were black. Average eGFR was 83 ml/min/1.73 m^2, 19% had albuminuria, and 44% were on antihypertensive medications. The relationship between potassium and all-cause mortality demonstrated higher risk outside of the 3.5-5 mmol/L range (**Figure**). Compared to a reference of 4.2 mmol/L, the adjusted hazard ratio for all-cause mortality was 1.27 (95% CI: 1.12-1.45) at 5.5 mmol/L and 1.36 (95% CI: 1.17- 1.57) at 3.2 mmol/L. Risk relationships were similar for cardiovascular mortality and end-stage renal disease. Associations were similar but slightly attenuated in persons with lower eGFR.

Conclusions: Potassium levels both above and below the normal range are associated with adverse outcomes across a range of eGFR.

Distribution of potassium and adjusted hazard ratios (HRs) for all-cause mortality, cardiovascular mortality, and end-stage renal disease



HRs adjusted for age, sex, race, diabetes, systolic blood pressure, anti-hypertensive medications, history of cardiovascular disease, history of heart failure, total cholesterol, body-mass index, smoking, eGFR and albuminuria

Funding: NIDDK Support, VA Support, Pharmaceutical Company Support - The CKD Prognosis Consortium is supported in part by the National Kidney Foundation (whose funding sources include Relypsa)

TH-PO476

Hypothermia Induced Hypokalemia and Recovery during Rewarming: Risk for Hyperkalemia Khaled Boobes, Daniel Batlle, Tanya Tocharoen Tang, Robert M. Rosa. *Nephology, Northwestern Univ, Chicago, IL.*

Background: Induced hypothermia is a commonly recommended intervention to improve neurological outcome in patients who have survived prolonged cardiac resuscitation. Different degrees of hypothermia are currently used (91.4-96.8°F). Hypothermia, however, can produce hypokalemia and can be associated with rebound hyperkalemia during the rewarming phase.

Methods: We obtained retrospective data on 74 patients who underwent hypothermia after cardiac arrest of whom 64 developed hypokalemia (range 1.9-3.5 mEq/dl). We then excluded for this analysis who did not survive the rewarming phase.

Results: Hyperkalemia (defined as K >5.0 mEq/dL) developed in 47 out of the 74 patients. Of those, 18 had a K ≥ 6.0 mEq/dL and 5 had K > 7.0 mEq/dL.

A striking correlation was observed during the rewarming phase between the rising K and the rising temperature.

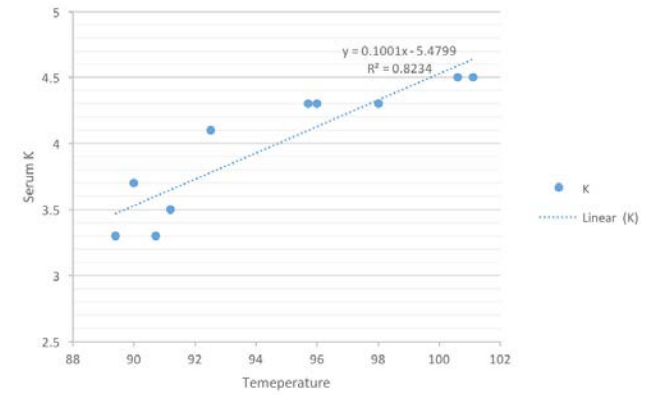


Figure 1 (representative patient)

In 5 patients we calculated the slope of K as a function of temperature, which revealed a linear relationship.

Table 1. Correlation coefficient calculated from the slope of K and Temperature during rewarming. Patients also received variable amounts of K supplementation.

Patients	R^2
1	0.894
2	0.823
3	0.846
4	0.564
5	0.569

Conclusions: Marked hypothermia produces hypokalemia due to a shift in the distribution of K between extracellular and intracellular compartments possibly by slowing down cellular K exit via K+ channels. The increase in K and the linear relationship between K and temperature during rewarming suggests the dominance of the K+ channels (exit pathway) over the Na,K-ATPase (entry pathway) by reactivation of temperature dependent K+ channels. The hyperkalemia encountered suggests that K+ supplementation should be minimized during rewarming.

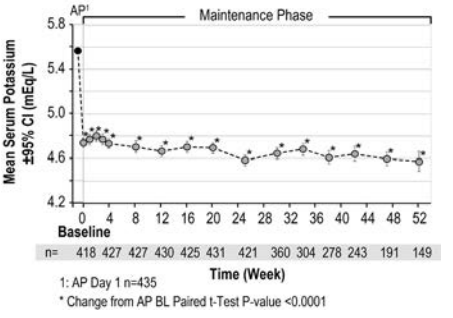
TH-PO477

Long-Term Sodium Zirconium Cyclosilicate Treatment in Patients with Hyperkalemia: Interim Analysis of an Open-Label Phase 3 Study Bruce S. Spinowitz,[1] James A. Tumlin,[2] Edgar V. Lerma,[3] Wajeh Y. Qunibi,[4] Bhupinder Singh,[5] Jose A. Menoyo,[5] Philip T. Lavin,[6] Henrik S. Rasmussen,[5] Steven Fishbane.[7] *[1]New York Presbyterian, Queens and Weill Medical College of Cornell Univ; [2]Univ of Tennessee College of Medicine; [3]Univ of Illinois at Chicago College of Medicine, Advocate Christ Medical Center; [4]Univ of Texas Health Science Center at San Antonio; [5]ZS Pharma; [6]Boston Biostatistics Research Foundation; [7]Hofstra Northwell Health School of Medicine.*

Background: Sodium zirconium cyclosilicate (ZS-9) is a non-absorbed, selective cation trap that binds potassium (K^+) throughout the GI tract.

Methods: This ongoing, open-label, single-arm Phase 3 trial enrolled adult patients (pts; N=751) with hyperkalemia (HK; K^+ ≥5.1 mEq/L). Pts received ZS-9 10g TID for 24–72 h (induction phase). Pts who achieved normokalemia (K^+ 3.5–5.0 mEq/L) received ZS-9 5g/d for ≤12 mo (maintenance phase).

Results: As of Dec 7, 2015, 751 pts were enrolled and 436 pts had completed 6 mo of treatment; 64.6% were on RAASi and 34.4% had heart failure. During the induction phase, 99.3% of pts achieved normokalemia and mean K^+ declined from 5.6 mEq/L at baseline to 4.7 mEq/L at maintenance phase start. Mean K^+ for all pts was 4.7 mEq/L during the maintenance phase. Among pts treated for ≥6 mo (n=436; figure), mean K^+ was 4.7 mEq/L and 89% of pts had mean K^+ ≤5.1 mEq/L over mo 3–12; results were similar for pts treated for ≥9 mo (n=287). The most common AEs across all treated pts were constipation (5.0%), peripheral edema (7.6%), and worsening hypertension (HTN; 8.2%); rates did not increase over time with increasing duration of exposure to ZS-9. No pts discontinued study drug due to edema or HTN. **Figure. Mean K^+ in Pts Treated ≥6 Mo (n=436)**.



Conclusions: These initial findings indicate that normokalemia was maintained with daily ZS-9 dosing in pts treated for ≥6 mo. Safety data is presented from all treated pts through Dec 7, 2015.

Funding: Pharmaceutical Company Support - ZS Pharma

TH-PO478

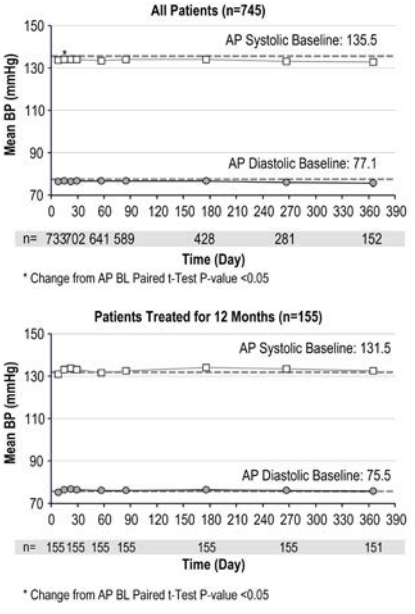
Effect of Sodium Zirconium Cyclosilicate Treatment for Hyperkalemia on Blood Pressure in a Long-Term Open-Label Phase 3 Study

Pablo E. Pergola,[1] Bruce S. Spinowitz,[2] Peter A. McCullough,[3] Bhupinder Singh,[4] Jose A. Menoyo,[4] Philip T. Lavin,[5] Henrik S. Rasmussen,[4] Steven Fishbane.[6] *[1]Renal Associates PA, San Antonio, TX; [2]New York Presbyterian, Queens and Weill Medical College of Cornell Univ, Flushing, NY; [3]Baylor Univ Medical Center, Dallas, TX; [4]ZS Pharma, San Mateo, CA; [5]Boston Biostatistics Research Foundation, Framingham, MA; [6]Hofstra Northwell Health School of Medicine, Great Neck, NY.*

Background: Sodium zirconium cyclosilicate (ZS-9) is a non-absorbed, selective cation trap that binds potassium (K^+) in exchange for H^+ and Na^+ throughout the GI tract. This interim analysis assessed the effects of ZS-9 on blood pressure (BP) in a 12-month study in patients (pts) with hyperkalemia (HK).

Methods: This ongoing, open-label, single-arm Phase 3 trial enrolled adult patients (pts; N=751) with HK (K^+ ≥5.1 mEq/L). Pts received ZS-9 10g TID for 24–72 h (induction phase). Pts who achieved normokalemia (K^+ 3.5–5.0 mEq/L) received ZS-9 5g daily for ≤12 mo (maintenance phase).

Results: As of Dec 7, 2015, 751 pts were enrolled; 82.6% with hypertension (HTN), 34.4% with heart failure and 64.6% on RAASi. During the induction phase, 99.3% of pts achieved normokalemia and mean K^+ declined from 5.6 mEq/L at baseline to 4.7 mEq/L at start of maintenance phase. There were no clinically meaningful changes in mean systolic and diastolic BP nor in related variables like body weight over time for all treated patients and those who completed 12 mo of treatment (n=155; figure). The most common AEs were constipation (5.0%), peripheral edema (7.6%), and worsening HTN (8.2%); rates did not increase over time with increasing duration of exposure to ZS-9. No pts discontinued study drug due to edema or HTN. **Figure. Mean BP Over Time**



Conclusions: These initial findings indicate no clinically meaningful changes in BP were observed with daily ZS-9 treatment of HK. Safety data is presented from all treated pts through Dec 7, 2015.

Funding: Pharmaceutical Company Support - ZS Pharma

TH-PO479

Aldosterone, Renin and Blood Pressure during Patiromer Treatment of Hyperkalemia in CKD

Matthew R. Weir,[1] David M. Spiegel,[2] Daniel J. Wilson,[2] Wade Benton,[2] Jinwei Yuan,[2] Coleman Gross.[2] *[1]Univ of Maryland School of Medicine; [2]Relypsa, Inc.*

Background: Patiromer, a non-absorbed K-binding polymer, reduced serum K (sK) in CKD patients (pts) with hyperkalemia (HK), all on renin-angiotensin-aldosterone system (RAAS) inhibitors at baseline (BL), in the Phase 3 OPAL-HK study. Blood pressure (BP) and aldosterone (ALD) reductions occurred during OPAL-HK. Patiromer may also bind sodium (Na) in the GI tract. We explored patiromer effects on BP in pts with low plasma renin activity (PRA) and low ALD.

Methods: This was a post-hoc analysis (N=243) from the 4-week (Wk) initial treatment phase of OPAL-HK (NCT01810939). Starting patiromer doses were 8.4 and 16.8 g/d based on BL sK (5.1-<5.5 and ≥5.5-<6.5 mEq/L, respectively [local lab]). We identified 2 levels of low PRA low ALD at BL depending on sK (≥5.1 or ≥5.5 mEq/L [central lab]), reflecting diminished RAAS activity: ALD<5 ng/dL, PRA<1 µg/L/h, sK≥5.1 mEq/L (LRA1) and ALD<10 ng/dL, PRA<2 µg/L/h, sK≥5.5 mEq/L (LRA2). Change in sK, ALD, PRA and BP at Wk 4 was analyzed for pts with and without LRA1 or LRA2. Data are mean±SD.

Results: Of 243 pts with BL sK≥5.1 mEq/L, 24 had LRA1; of 151 pts with BL sK≥5.5 mEq/L, 44 had LRA2. sK and BP decreased similarly in all groups (Table). ALD did not decrease in LRA1 and LRA2 but did decrease in other groups. Baseline SBP and DBP were higher in LRA1 (p= NS/p<0.01) and LRA2 (p=0.04/p<0.001) by unpaired t-test compared to pts without LRA1 or LRA2, respectively. PRA increased in LRA1 and LRA2 only.

Conclusions: Patiromer reduced sK in HK pts with CKD regardless of BL ALD level. ALD decreased in pts without diminished RAAS activity. LRA1 and LRA2 had higher BL BP and patiromer did not decrease ALD but modestly increased PRA. This may reflect mild volume expansion in LRA1 and LRA2 that improved with patiromer treatment. BP reduction was observed in all groups possibly due to both aldosterone reduction and decreased Na absorption.

		Pts with BL sK≥5.1 mEq/L (n=243)		Pts with BL sK≥5.5 mEq/L (n=151)	
		LRA1 (n=24)	No LRA1 (n=219)	LRA2 (n=44)	No LRA2 (n=107)
eGFR	BL	37.5±14.7	35.2±16.4	40.3±15.6	33.8±16.7
K	BL	5.6±0.3	5.6±0.5	5.7±0.3	5.8±0.4
mEq/L	Chg Wk 4	-1.3±0.5*	-1.0±0.7*	-1.4±0.5*	-1.2±0.7*
ALD	BL	3.4±0.9	12.8±8	5.4±2.5	14.8±13.4
ng/dL	Chg Wk 4	1.0±3.3	-2.7±9.8*	0.1±3.9	-5.1±11.2*
PRA	BL	0.4±0.3	10.2±12.4	0.6±0.5	11.1±12.2
µg/L/h	Chg Wk 4	1.9±4.5¶	-0.5±10.6	2.1±4.1†	0.1±10.8
SBP	BL	145.7±18.6	140.8±16.9	145.9±16.5	139.8±16.8
mmHg	Chg Wk 4	-7.8±16.3‡	-5.5±17.2*	-6.2±20.4§	-6.0±15.8*
DBP	BL	85.1±11.5	78.0±10.6	84.1±11.4	76.6±10.5
mmHg	Chg Wk 4	-7.6±9.9†	-3.5±11.3*	-7.0±13.2†	-3.4±11.3†

*p<0.001,†p<0.01, ‡p=0.05, §p=0.07, ¶p=0.08 for change (Chg) from baseline (BL) to Wk 4 by paired t-test.

TH-PO480

Evaluation of Potential Pharmacodynamic Interactions with Antihypertensive Drugs Given Concomitantly with Patiromer: Pooled Analysis of Phase 2/3 Clinical Trials

Matthew R. Weir,[1] Martha Mayo,[2] Dahlia Garza,[2] Natalie Panov,[2] Lilla S. Simon,[2] Charles Du Mond,[2] Lance Berman,[2] George L. Bakris.[3] *[1]Univ of Maryland School of Medicine, Baltimore, MD; [2]Relypsa, Inc., Redwood City, CA; [3]Univ of Chicago Medicine, Chicago, IL.*

Background: Patiromer is a sodium-free, non-absorbed potassium binder approved for the treatment of hyperkalemia (HK). In *in vitro* studies, patiromer was shown to bind about half of the oral medications tested. Recent studies in healthy volunteers indicate that there may be a much lower potential for pharmacokinetic interactions with patiromer. We retrospectively evaluated the potential for adverse pharmacodynamic (PD) effects on 3 antihypertensive drugs that showed *in vitro* binding and were most frequently used in patiromer clinical trials.

Methods: Safety data were pooled from 4 patiromer trials, (2 HK treatment studies in CKD patients and 2 HK prevention studies in HF). Patiromer was initiated at total daily doses of 8.4-33.6 g (divided BID). In patients on stable doses of oral antihypertensive drugs (AHDs) of interest at baseline (amlodipine [AM], furosemide [FUR], and metoprolol [MP]), objective measures of PD effects, ie changes in systolic and diastolic blood pressure (SBP/DBP), and AHD dose increases, were evaluated during the first 4 weeks after patiromer initiation.

Results: Overall 666 patients were treated with patiromer in the clinical trials; hypertension was present in 97.3%. Of these, 512 were receiving oral AHDs of interest at baseline: AM (n=227), FUR (n=227) and MP (n=58). Mean ± SD SBP at baseline, at week 4 and change from baseline to week 4 are shown (Table). An oral AHD dose increase was required in 1 patient each in the AM and MP groups and in 5 patients in the FUR group.

Conclusions: No evidence of adverse systematic BP effects of oral AHDs were observed after the initiation of patiromer in clinical trials for the prevention or treatment of hyperkalemia.

Blood Pressure	Statistics/Parameter	Amlodipine	Furosemide	Metoprolol
	Baseline:			
	N	227	227	58
SBP (mm Hg)	Mean (SD)	146.3 (15.4)	143.1 (17.9)	146.4 (20.3)
DBP (mm Hg)	Mean (SD)	80.1 (11.2)	80.9 (11.8)	81.5 (9.9)
	Week 4:			
	N	202	203	45
SBP (mm Hg)	Mean (SD)	140.6 (16.9)	135.6 (17.9)	135.8 (18.9)
DBP (mm Hg)	Mean (SD)	76.6 (11.8)	75.7 (11.5)	75.9 (10.2)
	Change from Baseline to Week 4			
	N	202	203	45
SBP (mm Hg)	Mean (SD)	-5.4 (17.7)	-7.1 (17.8)	-9.8 (18.4)
DBP (mm Hg)	Mean (SD)	-3.6 (11.8)	-5.6 (12.1)	-5.8 (10.3)

Funding: Pharmaceutical Company Support - Relypsa, Inc.

TH-PO481

Profound Hypokalemia and Generalized Paralysis following the Chronic Ingestion of Large Amounts of Ibuprofen Opeyemi Oladele, Paul Zamudio, Nand K. Wadhwa, Edward P. Nord, Rajeev B. Patel, Wilfred Lieberthal. *Medicine, Stony Brook Medicine, Stony Brook, NY.*

Background: The effects of an acute overdose with the non-steroidal anti-inflammatory drug (NSAID) Ibuoprofen are well described, and include oliguric AKI, alterations in mental state, metabolic acidosis and gastrointestinal bleeding. However, the effects of the chronic ingestion of large amounts of Ibupfrofen are rarely documented.

Results: CASE REPORT: A 48 year old male complained of progressive muscle weakness for 10 days prior to presentation. He was taking 10-12 tablets (600mg/tablet) of Ibuprofen every 4-6 hours almost daily for about one year for back pain. He was fully oriented with normal vital signs. The only notable finding on exam was profound weakness and an inability to lift his extremities or sit up. Laboratory data on admission: Serum electrolytes: BUN 68mg/dL, creatinine 3.84 mg/dL, sodium 123 mmol/L, potassium < 1.5 mmol/L, chloride 78 mmol/L, bicarbonate 7 mmol/L (anion gap 38 mmol/L). Calcium 8.1 mg/dL, phosphorus 5.4 mg/dL, magnesium 2.7 mg/dL. Plasma beta-hydroxybutrate 0.6 mmol/L. L-lactate 2.4 mmol/L. D-lactic acid undetectable. Toxicology screen negative. Urine electrolytes: pH 5.5, sodium 80 mmol/L, potassium 118 mmol/L and chloride 56 mmol/L. The patient was given potassium intravenously (IV) and orally. When his potassium exceeded 2.0 mmol/L, an IV infusion of sodium bicarbonate was started. Two days after admission the BUN was 45 mg/dL and creatinine 3.1 mg/dL. The serum sodium was 141 mmol/L, the bicarbonate 20mmol/L and the anion gap 16 mmol/L. When the patient was seen in renal clinic 2 months later after discharge his BUN was 31 mg/dL, his creatinine 2.6 mg/dL and his electrolytes were normal.

Conclusions: There are sparse reports of Ibufrofen abuse causing profound hypokalemia with a non-anion gap acidosis and a urine pH >6.0, suggesting a form of renal tubular acidosis. By contrast, the severe life threatening hypokalemia and metabolic acidosis in this case, was associated with a large anion gap of undetermined cause and a urine pH of 5.5. To the best of our knowledge, no cases of Ibuprofen abuse with these electrolyte abnormalities have been described previously.

TH-PO482

Dietary Salt Induces Catabolism in Humans Kento Kitada,[1] Natalia Rakova,[2] Steffen Daub,[1] Tetyana Pedchenko,[1] Yahua Zhang,[1] Friedrich C. Luft,[1,2] Jens Titze.[1] *[1]Div of Clinical Pharmacology, Vanderbilt Univ Medical Center, Nashville, TN; [2]Experimental and Clinical Research Center, Charité Medical Faculty and the Max- Delbrueck Center for Molecular Medicine, Berlin, Germany.*

Background: The concept that increasing salt intake elevates fluid intake and urine volume originates from short-term experiments in humans exposed to extremes in salt intake. In the first ultra-long term sodium and water balance study performed in man, we tested the hypothesis that increasing salt intake by only 6 g/day induces similar changes in water balance.

Methods: We performed two separate balance studies of 105 and 205 days in 10 healthy male subjects simulating a space flight to Mars. We exposed our subjects to 3 salt intake levels (12 g/day, 9 g/day and 6 g/day) and monitored their daily water intake and urine volume. We studied the effect of increasing salt intake on water balance, urine osmolyte elimination and free water excretion and their relation to glucocorticoid excretion.

Results: Elevated salt intake and sodium excretion increased urine volume, but surprisingly decreased water intake in all 10 subjects. High salt intake suppressed aldosterone levels, but increased glucocorticoid levels. This salt-driven increase in glucocorticoid excretion predisposed our subjects to increased urine volume with low urine osmolality despite reduced fluid intake, indicating a catabolic state with increased free water production and excretion. This salt-induced catabolic state was characterized by increased sodium concentration and reduced urea concentration in the urine.

Conclusions: The seemingly paradoxical decrease in fluid intake during high dietary salt consumption can be explained by a glucocorticoid-driven catabolic endogenous water production. Dietary salt is excreted by a urine concentration mechanism. Catabolic urea production and accumulation of urea osmolytes in the renal medulla may provide the necessary driving force for water reabsorption when sodium is concentrated into the urine.

Funding: Other NIH Support - RO1 HL118579-01, Government Support - Non-U.S.

TH-PO483

High Salt Intake Induces Muscle Wasting via Catabolic Urea Formation in Mice Kento Kitada,[1] Steffen Daub,[1] Yahua Zhang,[1] Janet D. Klein,[2] Daisuke Nakano,[3] Tetyana Pedchenko,[1] Akira Nishiyama,[3] Friedrich C. Luft,[1] Jeff M. Sands,[2] Jens Titze.[1] *[1]Div of Clinical Pharmacology, Vanderbilt Univ Medical Center, Nashville, TN; [2]Renal Div, Dept of Medicine, and Dept of Physiology, Emory Univ, Atlanta, GA; [3]Dept of Pharmacology, Kagawa Univ, Kagawa, Japan.*

Background: In the first ultra-long term salt and water balance study performed in man, we found that high salt intake induced a catabolic state with increased metabolic water formation that accompanied the excretion of dietary salt by renal concentration. We hypothesized that salt induces energy-intense urea generation, which is accumulated in the renal medulla and provides with the osmotic driving force necessary to concentrate the urine and excrete dietary salt without osmotic diuresis.

Methods: We fed male mice (C57/B6) a low-salt diet (<0.1%NaCl) with tap water (LSD) or a high-salt diet (4%NaCl) with 0.9% saline to drink (HSD) for 4 consecutive weeks, followed by 2 weeks of pair-feeding to match energy intake in both groups. We studied the effects of high-salt intake on osmolyte and water balance and urea generation.

Results: HSD increased urea content and urea transporter expression in the renal medulla, resulting in reduced urea osmolyte excretion. Retaining urea osmolytes, HSD mice preserved their urine concentration ability despite excess Na and Cl osmolyte excretion, thereby preventing osmotic diuresis. HSD induced arginase-driven urea production in liver and skeletal muscle, but not in the kidney. Metabolomic analysis revealed corticosterone-driven free amino acid wasting in muscle to provide liver with nitrogen for urea generation. The energy-intense nature of urea osmolyte generation resulted in a catabolic state with exploitation of stored energy fuels and ketogenesis.

Conclusions: Na metabolism cannot be understood without investigation of urea metabolism. The biological pattern of dietary salt excretion includes urea osmolyte generation and accumulation in the kidney to concentrate the urine and prevent salt-driven water loss by osmotic diuresis. The resulting reprioritization of energy metabolism for energy-intensive urea production may explain muscle wasting in patients with Na overload.

Funding: Other NIH Support - RO1 HL118579-01

TH-PO484

The Relationship of Tissue Sodium Concentration to Cardiovascular Indices in Advanced Chronic Kidney Disease Nicos Mitsides,[1] Damien J. Mchugh,[2] Jane Alderdice,[1] Paul E. Brenchley,[1] Geoff J.M. Parker,[2] Sandip Mitra.[1] *[1]Manchester Academic Health Science Centre; [2]Centre for Imaging Sciences of the Univ of Manchester.*

Background: Body sodium (Na) balance is considered to be an important determinant of cardiovascular (CV) risk. Chronic kidney disease (CKD) is considered to be a salt sensitive state. However the role of Na tissue accumulation in influencing CV parameters in CKD has not been investigated.

Methods: The relationship of tissue Na concentration to CV indices was investigated using a 3T Magnetic Resonance (MR) scanner & a dual-tuned $^{1}H/^{23}Na$ coil. We acquired ^{23}NaMR images of the lower legs of 6 healthy volunteers (HV) and 7 CKD stage 5 patients (eGFR<15 ml/min, not yet on dialysis) and calculated Na concentration in the muscle and subcutaneous (SC) tissue using calibration saline phantoms placed under the leg. Participants underwent simultaneous assessment of their CV status using pulse wave velocity (PwV), 24hr ambulatory Blood Pressure monitoring (ABPM), skin auto-fluorescence & sublingual dark field capillaroscopy.

Results: The MR derived Na concentrations (mmol/l) for CKD participants were higher than HV. This difference was more pronounced in the SC tissue (CKD 26.3±9.4, HV 18.1±3.5, $p<0.05$) than in the muscle (CKD 24.3±4.0, HV 22.6±3.0, $p=0.19$). The mean ABPM measurements (mmHg) for the entire cohort was systolic (127±12.5), diastolic (79.9±8.6) and mean arterial pressure (MAP) (95.8±9.6). Muscle Na concentration showed a positive correlation with ABPM derived systolic ($p=0.02$), diastolic ($p=0.02$) and MAP ($p=0.02$). Both Na concentration for muscle and SC tissue correlated with capillaroscopy measured markers of endothelial glycocalyx damage with the former exhibiting a positive association with the thickness of the Perfused Boundary Region of large size capillaries ($p=0.02$) and the latter with Red Cell width ($p<0.01$).

Conclusions: Our results indicate that CKD leads to higher tissue accumulation of salt. Both SC and muscle Na concentrations are linked to microvascular injury and the muscle Na accumulation is closely linked to hypertension.

Funding: Clinical Revenue Support

TH-PO485

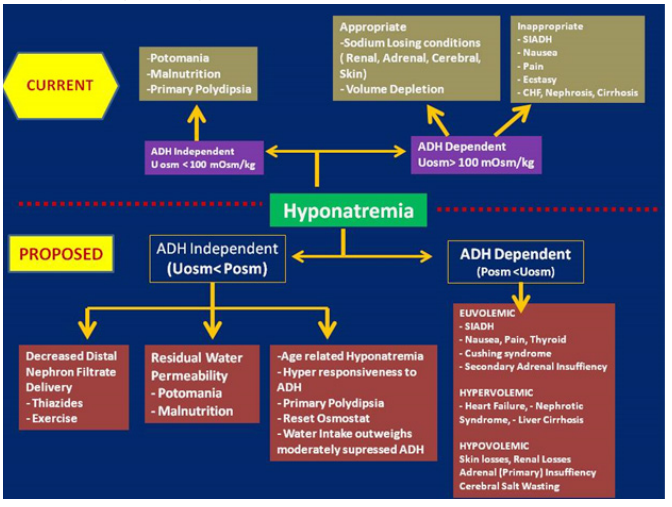
Syndrome of Inappropriate ADH versus Reset Osmostat: Blind Spots in Classification and Evaluation of Hyponatremia Hormaz Dara Dastoor,[1] Chandra Mauli Jha,[2] Ken J. Donaldson,[3] Thalakunte Muniraju,[3] Samra Abouchacra,[1] Hatem Mohyeldin Ebeid.[4] *[1]Div of Nephrology, Rahba Hospital- Johns Hopkins International, Abu Dhabi, United Arab Emirates; [2]Div of Nephrology, Burjeel Hospital, Abu Dhabi, United Arab Emirates; [3]Div of Nephrology, Dumfries and Galloway Royal Infirmary, Dumfries, United Kingdom; [4]Div of Nephrology, Al Noor Hospital, Abu Dhabi, United Arab Emirates.*

Background: We present a case diagnosed as SIADH on the basis of current classification of Hypotonic Hyponatremia. However, further evaluation including measurement of Vasopressin levels revealed the diagnosis as Reset Osmostat. A careful review reveals that present diagnostic algorithm of hypotonic hyponatremia has a tendency to over diagnose SIADH and it is long overdue to reclassify Hyponatremic Hyponatremia.

Methods: Case A 72-year-old lady presented with nausea and euvolemic hyponatremia with Plasma Sodium 121 mmol/l, urine osmolality 162 mOsm/kg. On the basis of prevalent diagnostic algorithm she was diagnosed to have SIADH and Fluid restriction raised her P_{Na+} to 130 mmol/l. However measured ADH levels at time of admission was found to be < 0.1 pg/ml (normal 0.7- 3.8 pg/ml) suggesting near absence of ADH. The patient had either Reset Osmostat or Age related inability to excrete Free Water with Primary Polydipsia.

Results: We find the current t diagnostic algorithm of hyponatremia leads to a false over diagnosis of SIADH.

Conclusions: Using a diagnostic approach of combining the pathophysiology of hyponatremia and measurement of Urine Osmolarity, we have been able to accurately diagnose pathologies which have been mistakenly labelled as SIADH. These include Residual Water Permeability, Reset Osmostat and Age related Hyponatremia. and Diagnosis of SIADH in euvolemic hyponatremic patients with urinary Na <100 mOsm/L appears to be faulty causing over diagnosis of SIADH.



TH-PO486

Is the Fall in Serum [Na] in Response to a Rise in Serum Glucose ([Glu]) Affected by Prevailing [Glu]? Philip Goldwasser,[1] Andrea Roche-Recinos,[2] Robert H. Barth.[1] *[1]Medicine, VA NY Harbor Heathcare System, Brooklyn, NY; [2]Medicine, SUNY Downstate, Brooklyn, NY.*

Background: [Na] falls (ΔNa) as [Glu] rises (ΔGlu), but the slope of this effect (ΔNa/ΔGlu) may vary. Theory predicts the slope should shallow as [Glu] increases (Robin '79; Moran '85), but one *post hoc* study found it to steepen when [Glu] exceeded 400 mg/dL (Hillier '99). Changes in total protein (TP), hemoglobin (Hb) and bicarbonate (tCO_2)—which often accompany ΔGlu—cause bias in [Na] measured by either the indirect (diluted) method (iNa), in chemistry (chem) panels, or the direct method (dNa), in gas panels. Prior estimates of ΔNa/ΔGlu didn't account for these biases. We recently derived linear corrections for them in 772 paired chem and gas panels, obtained up to 19 min. apart (median: 4 min.), retrospectively collected from our critical care units [NDT '15; ASN Nov '15].

Methods: To test whether [Glu] itself influences ΔNa/ΔGlu, we classified each pair, by the mean of its chem and gas [Glu], into one of 4 subgroups: [A] ≤100 mg/dL; [B] 101-200; [C] 201-300; [D] >300. Next, defining ΔGlu as chem [Glu] - gas [Glu] and ΔNa as iNa - dNa, we estimated the effect on ΔNa of ΔGlu by regression, adjusting for TP, Hb, and tCO_2, in the subgroups and the entire cohort. Data on changes in the balance of Na, K and water were unavailable.

Results: In the entire cohort, mean [Glu] ranged from 40 to 1043 mg/dL, and ΔGlu from -189 to 164; ΔNa was -2.4 ± 0.4 [SE] mEq/L per 100 mg/dL of ΔGlu ($p< 10^{-8}$). The subgroup slopes varied from -1.4 to -5.1, but pairwise comparison of the 4 slopes yielded only one difference of even borderline significance (C vs D: p=.05, unadjusted for multiple comparisons).

Group	N	[Glu] mean±SE	Slope [95%CI]	p
A	124	87±1	-5.1 [-9.0 to -1.2]	.01
B	504	136±1	-2.0 [-3.2 to -0.8]	.001
C	96	243±3	-1.4 [-2.9 to +0.05]	<.06
D	48	472±26	-3.6 [-5.0 to -2.3]	10^{-5}

Conclusions: Mean ΔNa/ΔGlu varied markedly, but not significantly, according to prevailing [Glu], in an analysis that accounted for assay bias, but not for water and salt balance. While the results don't exclude an effect of prevailing [Glu] on the slope, they are consistent with no interaction at all.

Funding: VA Support

TH-PO487

Hyponatremia in the Emergency Department, Role of Prescription Medications Gudrun Sigurdardottir,[1] Petur S. Gunnarsson,[1,2] Anna Ingibjörg Gunnarsdóttir,[1,2] Elin Ingibjorg Jacobsen,[1] Runolfur Palsson,[1,2] Olafur S. Indridason.[2] *[1]Univ of Iceland; [2]Landspitali - the National Univ Hospital of Iceland, Reykajvik, Iceland.*

Background: Commonly prescribed medications have been associated with development of hyponatremia. We examined the frequency of hyponatremia, defined as serum sodium (SNa) ≤135 mmol/L in patients visiting a University Hospital emergency department (ED) and its relationship to medication use.

Methods: This was a retrospective study of all patients >18 years, who visited the ED in 2014. SNa levels and other clinical data were obtained from the electronic medical records. Information on drug dispensing for subjects with hyponatremia and matched controls drawn from ED patients with normal SNa levels, was obtained from the National Pharmaceuticals Database of the Directorate of Health. Patients were matched on age, sex, creatinine and diagnoses of hypertension, diabetes, coronary artery disease, COPD, malignancy and psychiatric disorders. Kaplan-Meier method was used for survival analysis and the log-rank test to compare groups.

Results: In total, 40,365 individuals had 58,137 ED visits. SNa was measured at 26,474 visits of 19,159 patients, with hyponatremia present at 2,287 (3.9%) visits of 1,785 (4.4%) patients, of whom 62.5% were women. Frequency of hyponatremia increased with age and was 12.8% in patients >70 years. Compared with the control group, more patients with hyponatremia had filled a prescription for thiazides (25.6% vs 19.6%, p<0.001), amiloride (11,0% vs 7.4%, p<0.001), aldosterone antagonists (8.7% vs 5.5%, p<0.001), proton pump inhibitors (42.1% vs 36.9%, p<0.001), carboxamide anti-epileptics (2.7% vs 0.8%, p<0.001), ACE inhibitors (16.9% vs 14.0%, p=0.04) and tricyclic antidepressants (6.2% vs 4.8%, p=0.048). No difference was observed for SSRI (21.7% vs 21.3%, p=0.74) or SNRI (13.3 vs 13.8%, p=0.86). One-year survival was 78.3% (95% CI, 76.3-80.2%) in the hyponatremia patients compared with 84.6% (95% CI, 82.9-86.4%) in the control group (p<0.001).

Conclusions: Hyponatremia is common in the ED, especially among older individuals and is associated with increased mortality. Thiazides, aldosterone antagonists and proton pump inhibitors are likely causative agents in many patients.

TH-PO488

Severe Hyponatremia in the Hospital Setting: Incidence, Etiology and Outcome Arni H. Geirsson,[1] Runolfur Palsson,[1,2] Kristinn Sigvaldason,[1,2] Olafur S. Indridason.[1] *[1]Landspitali - The National Univ Hospital of Iceland; [2]Univ of Iceland, Reykjavik, Iceland.*

Background: Severe hyponatremia can be a devastating disorder and its management is frequently very challenging. The aim of this study was to investigate the incidence, etiology and outcome of severe hyponatremia, defined as serum sodium (SNa) <120 mmol/L, in a metropolitan area.

Methods: This was a retrospective study that included all patients >18 years of age with SNa <120 mmol/L at the University Hospital in Reykjavik, in 2005-2014. Patients were identified in the electronic database of the Department of Clinical Biochemistry and clinical data were extracted from medical records. Incidence was calculated per hospital admission and per 100,000 population of the greater Reykjavik area. Changes in incidence were evaluated by poisson regression.

Results: A total of 590 patients suffered 619 episodes of severe hyponatremia. Median age was 74 (range, 23-98) years and 76% were females. The average annual incidence was 2.49/1000 admissions, increasing from 1.69/1000 to 2.59/1000 over the study period (p=0.007). The average population incidence was 41.6/100,000/year, without a significant change during the study period (p=0.59). The etiology of severe hyponatremia was considered to be SIAD in 205 cases (33.1%), volume depletion in 153 (24.7%) and a thiazide diuretic in 141 patients (22.8%), 113 (80.1%) of whom were women. Intensive care was required in 102 cases (16.5%). Eighty patients (12.9%) had acute hyponatremia and 24 (3.9%) received emergency treatment with 3% saline. The in-hospital mortality was 9%. Five patients experienced neurologic complications following correction of SNa. Thirteen patients (2.1%) had SNa <105 mmol/L, of whom 2 died and 5 could not be dischargeddirectly to their home.

Conclusions: The frequency of severe hyponatremia is increasing in hospitalized patients and most commonly occurs in females and older individuals. Intensive care management is often needed and the mortality rate is substantial. Since thiazide diuretics are a common cause of severe hyponatremia, a more cautious use of these agents is warranted in patients at increased risk, such as elderly women.

TH-PO489

The Association between Serum Sodium Levels at Hospital Admission and Outcomes among 2.7 Million Hospitalized Patients Saleem M. Al Mawed,[1] Matthew Sandoval,[2] Maria-Eleni Roumelioti,[1] V. Shane Pankratz,[1] Mark L. Unruh.[1] *[1]Div of Nephrology, Univ of New Mexico Health Sciences Center, Albuquerque, NM; [2]CTSC, Univ of New Mexico, Albuquerque, NM.*

Background: Hyponatremia is the most common electrolyte disturbance in hospitalized patients. While studies have addressed its association with selected outcomes, few included a large cohort of hospitalized patients. In this study we examined the association of serum sodium at hospital admission with subsequent outcomes.

Methods: We extracted data from the Cerner Health Facts database. We included the index hospital admission defined by the first inpatient encounter of any patient between 2000 and 2014 that met the following inclusion criteria: age ≥ 18 years and serum sodium levels drawn during 24 hours before admission. ICD-9 codes were used to identify the comorbidities. Logistic regression models were used in the analysis.

Results: 2.7 million patients were included in this analysis. 14.7% of patients had serum sodium (Na) <135 mEq/L. The prevalence of Na <135 mEq/L increased with age. Adjusting for age, sex, and race, patients with diabetes mellitus, end stage renal disease, cirrhosis, lung cancer, adrenal insufficiency, and HIV were associated with a higher likelihood of Na <135 mEq/L. After adjusting for age, sex, race, and the Deyo Charlson Comorbidity Index, a serum Na across a range of 115 to <135 had a higher likelihood of in-hospital mortality compared to Na of 140 to <145 mEq/L (p<0.001). Similar trends were observed between Na and discharge to hospice while inverse relationship was observed between Na and discharge to home (figure1).

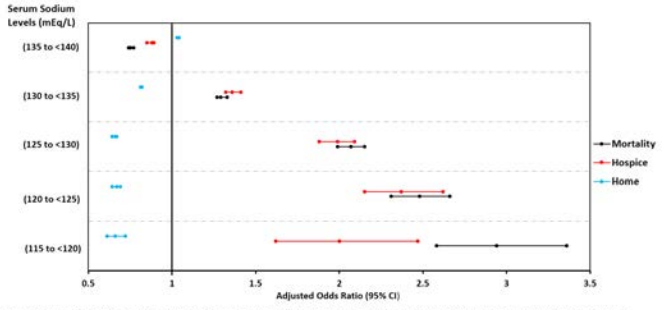


Figure 1: Forest plot of the odds ratios (95% confidence intervals (CI)) for in-hospital mortality, discharge to hospice, or discharge to home associated with different intervals of serum sodium levels (mEq/L) at hospital admission. Serum sodium levels of (140 to <145 mEq/L) served as referent. The odds ratios were derived from logistic regression models adjusted for age, sex, race, and Deyo Charlson Comorbidity Index.

Conclusions: Hyponatremia (Na <135 mEq/L) is common in patients who present to the hospital and is independently associated with outcomes such as in-hospital mortality and discharge to hospice. More research is needed to study other outcomes associated with hyponatremia.

Funding: Other NIH Support - Clinical and Translational Science Center (CTSC) Award

TH-PO490

Association of Hyponatremia with Impaired Cognition Kristen L. Nowak,[1] Eric Orwoll,[2] Joachim H. Ix,[3] Zhiying You,[1] Michel Chonchol.[1] *[1]Univ of Colorado Anschutz Medical Campus; [2]Oregon Health and Science Univ; [3]Univ of California San Diego.*

Background: Hyponatremia is a common finding in older adults and is linked to attention deficits, gait disturbances, and risk of falls. However, the association of hyponatremia with cognition in older adults is currently unknown. We hypothesized that hyponatremia would be associated with cognitive impairment and risk of cognitive decline in asymptomatic, community-dwelling older men.

Methods: 5,376 men aged > 65 years who were enrolled in the Osteoporotic Fractures in Men (MrOS) study were included in this analysis. Multivariable logistic regression was used to examine the association between baseline serum sodium levels and the odds of both prevalent cognitive impairment (cross-sectional analysis; modified mini-mental status [3MS] score <80 or Trail Making Test Part B score >1.5 S.D. above the mean [>223.4 sec]) and decline incident cognitive impairment (prospective analysis [n=3,667]: follow-up 3MS score of <80 or decline of >5 points, or change in Trails B time >1 S.D. above mean change in completion time [>45.1 sec]).

Results: Mean age was 74±6 years with a mean serum sodium level of 141±3 mmol/L. After adjustment demographics, education, co-morbid conditions, smoking, alcohol, body-mass index, estimated glomerular filtration rate, physical activity, and quality of life measures, serum sodium was associated with prevalent cognitive impairment (quartile 1 [126-140 mmol] vs. quartile 4 [143-153 mmol] OR: 1.49, 95% CI: 1.15-1.92). For incident cognitive impairment (median follow-up of 4.6 years), quartile 3 (142-143 mmol) was associated with lower odds of cognitive impairment vs. quartile 4 (143-153 mmol; adjusted OR: 0.77, 95% CI: 0.61-0.96), with no difference in quartile 1 (126-140 mmol) vs. quartile 4 (adjusted OR: 0.95, 95% CI: 0.77-1.18).

Conclusions: In asymptomatic, community-dwelling older men, hyponatremia was associated with prevalent but not incident cognitive impairment.

Funding: Other NIH Support - NIA and NIAMS

TH-PO491

Postoperative Hyponatremia in Urologic Surgery Is Associated with Poor Survival and Long-Term Renal Outcome Sehoon Park,[1] Jung Nam An,[2] Jung Pyo Lee,[2] Dong Ki Kim,[1] Kwon Wook Joo,[1] Yon Su Kim,[1] Chun Soo Lim.[2] *[1]Dept of Internal Medicine, Seoul National Univ Hospital, Seoul, Korea; [2]Dept of Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Korea.*

Background: Although in-hospital hyponatremia is a well-known factor for adverse clinical outcomes, the impact of postoperative hyponatremia in urology remains unclear.

Methods: We examined the incidence, risk factors, and outcomes of postoperative hyponatremia in urologic surgery. Patients with events of postoperative sodium level lower than 135 mEq/L within 7 days after surgery were included in our study group, and the others in the control group. Primary outcomes were postoperative all-cause mortality and end-stage renal disease (ESRD) progression, defined by the start of dialysis or newly diagnosed stage 5 chronic kidney disease (eGFR < 15ml/min/1.73m^2). The secondary outcome was the worsening of the long-term renal outcome, including ESRD progression and serum creatinine doubling/eGFR halving from baseline, occurring 1 month or more after surgery.

Results: The medical records of 9,449 cases of bladder, prostate, ureter, and kidney surgery were collected. Incidence of postoperative hyponatremia was 16.5% (1,562/9,449). Postoperative hyponatremia mostly developed in patients with high-risk perioperative characteristics. Moreover, postoperative hyponatremia was related to both mortality (adjusted HR 1.46, 95% CI 1.02-2.11, $P = 0.04$) and ESRD progression (adjusted HR 1.31, 95% CI 1.07-1.62, $P = 0.008$). The secondary outcome was also related to the electrolyte imbalance in prostate (adjusted HR 1.78, 95% CI 1.21-2.62, $P = 0.003$), ureter (adjusted HR 1.83, 95% CI 1.07-3.13, $P = 0.03$), and kidney (adjusted HR 1.22, 95% CI 1.01-1.49, $P = 0.04$) surgery. However, this relationship was not observed in bladder surgery cases (adjusted HR 1.09, 95% CI 0.83-1.45, $P = 0.54$).

Conclusions: Postoperative hyponatremia was a common electrolyte imbalance after urologic surgery, especially in patients with high-risk perioperative status. Postoperative hyponatremia was an important predictor of both mortality and adverse renal outcome in major urologic operations.

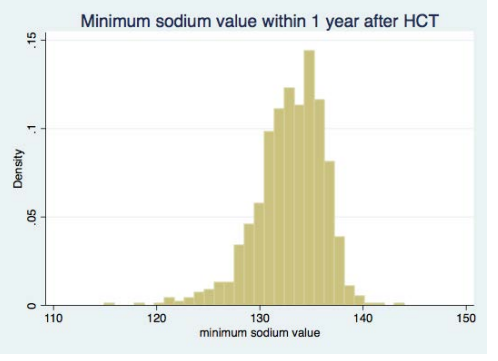
TH-PO492

Hyponatremia Is Common among Patients Receiving Stem Cell Transplant and Is an Independent Predictor of Mortality Jaya Kala, Amit Lahoti. *Nephrology, Univ of Texas MD Anderson Cancer Center, Houston, TX.*

Background: Electrolyte disturbances are common among patients who undergo hematopoietic cell transplant (HCT). Hyponatremia is frequently diagnosed in this population. However, there have been few studies published to date examining the incidence and prognostic effect of hyponatremia in patients receiving HCT.

Methods: We retrospectively analyzed the records of 1041 patients who underwent hematopoietic cell transplant (HCT) at our institution from Jan 2004 through Dec 2006. A Cox Proportional Hazards Model was used to examine the effect of hyponatremia on mortality. Hyponatremia was defined as a level less than or equal to 135 meq/L. The minimum sodium level obtained within 1 year after transplant was included in the analysis. Other covariates included age, gender, race, HTN, diabetes, CMV status, prior HCT, transplant type, sepsis, acute kidney injury, acute GVHD, and maximum bilirubin.

Results: The majority of patients (76%) developed hyponatremia within 1 year of HCT. Minimum sodium values were 131-135, 126-130, and <=125 meq/L in 57%, 15.8%, and 2.8% of patients, respectively. The hazard ratios for mortality were 1.9, 2.9, and 3.1 (p<.001 for all categories), respectively. When analyzed as a continuous variable, we found a 9% decrease in mortality per 1 meq/L rise in sodium level. Other variables associated with mortality included acute kidney injury, acute GVHD, and allogeneic transplant (HR 1.9, 3, and 2.9, respectively).



Conclusions: We found that a majority of our patients developed some degree of hyponatremia after HCT, and even mild decreases in serum sodium (131-135 meq/L) are associated with a significantly increased risk of mortality in a multivariate model. Whether correction of hyponatremia after transplant improves survival is of interest.

TH-PO493

Hyponatremia in Cancer Patients Treated with Immune Checkpoints' Inhibitors: Is Adrenal Impairment the Cause? Laura Cosmai,[1] Wanda Liguigli,[2] Camillo Porta,[3] Maurizio Gallieni,[4] Marina Foramitti,[1] Fabio Malberti.[1] *[1]Nephrology, Istituti Ospitalieri, Cremona, Italy; [2]Oncology, Istituti Ospitalieri, Cremona, Italy; [3]Oncology, IRCCS San Matteo Univ Hospital Foundation, Pavia, Italy; [4]Nephrology, San Carlo Borromeo Hospital, Milan, Italy; [5]Nephrology, Istituti Ospitalieri, Cremona, Italy; [6]Nephrology, Istituti Ospitalieri, Cremona, Italy.*

Background: Immune checkpoints' inhibitors such as Ipilimumab and Nivolumab are more and more commonly used to treat patients (pts) with different solid cancers (e.g. melanoma, lung cancer and kidney cancer).

Methods: We have observed 7 pts who developed hyponatremia during treatment with Ipilimumab + Nivolumab (within a randomized phase III trial conducted in metastatic kidney cancer, n = 6) or Ipilimumab monotherapy (for melanoma, n = 1).

Results: Of the 7 pts observed, 1 had a grade 4, 3 a grade 2, and 2 a grade 1 hyponatremia. The patient with grade IV was hospitalized (seriuos adverse event was reported) and treated with 40 mEq sodium i.v. supplementation over 24 hours for 4 days, before complete resolution; of the other 3 pts with a grade 2 hyponatremia, 2 received 20 mEq sodium i.v. supplementation over 24 hours for 1 to 2 days, and 1 was treated with steroids (methylprednisolone 32 mg i.v.) for 2 days. All events resolved, but in 5 out of 7 cases, hyponatremia relapsed at the following administrations (never worst than grade 1); the only patients treated with steroids had a complete and long lasting resolution of his hyponatremia.

Conclusions: Hyponatremia is a relatively frequent event during treatment with immune checkpoints' inhibitors; its pathogenesis is unknown, but a drug-induced adrenal impairment/inflammation could be postulated and the efficacy of steroids in one of our cases do support this hypothesis.

TH-PO494

Predictors of Rapid Correction of Hyponatremia Caused by the Syndrome of Inappropriate Secretion of Antidiuretic Hormone during Treatment with Tolvaptan Jesse H. Morris,[1] Rachel E. Crawford,[2] Denise O. Kelley,[3] Nicole Bohm,[4] Bhavna Bhasin,[1] Paul Nietert,[5] Juan Carlos Q. Velez.[1] *[1]Div of Nephrology, Dept of Medicine, Medical Univ of South Carolina; [2]Dept of Pharmacy, Wake Forest Baptist Medical Center; [3]Dept of Pharmacy, UF Health Jacksonville; [4]Dept of Clinical Pharmacy and Outcomes Sciences, Medical Univ of South Carolina; [5]Dept of Public Health Sciences, Medical Univ of South Carolina.*

Background: Tolvaptan can correct hyponatremia caused by SIADH rapidly, thus carrying a risk for central pontine demyelination. We hypothesized that clinical and/or lab parameters predict the likelihood of rapid correction of SIADH-induced hyponatremia during treatment with tolvaptan.

Methods: Data were extracted from hyponatremic [serum sodium (sNa) ≤ 130 mmol/L] adults with SIADH treated with tolvaptan (1st dose 15 mg) at 3 university hospitals between 2010 and 2015. Those who also received po/i.v. sodium or demeclocycline were excluded. The ability of baseline parameters to predict the change in sNa was assessed by Spearman correlations and a multivariate linear mixed model.

Results: A total of 22 patients entered the analyses. Mean baseline sNa was 121.2 mmol/L and the mean rise in sNa over the first 24 hrs was 8.4 mmol/L. Correction of sNa > 12 or > 8 mmol/L/24 hrs occurred in 27% and 36% of the cases, respectively. Change in sNa over 24 hrs significantly correlated with baseline sNa (r=-0.75, p=0.0001), blood urea nitrogen (BUN) (r=-0.76, p=0.0001) and eGFR (r=0.58, p=0.01), but not with other parameters. A model incorporating time and baseline sNa (p<0.0001) explained 64% of the variation in 24 hr sNa. When baseline BUN was added to the model, it explained 75% of the variation in 24 hr sNa, although its effect did not reach significance (p=0.10). Four out of 4 patients with baseline sNa <120 mmol/L and BUN < 7 mg/dL corrected their sNa > 12 mmol/L/24 hrs (mean rise in sNa: 17.8 mmol/L/24 hrs).

Conclusions: Lower baseline sNa is significantly predictive of the magnitude of response to tolvaptan therapy for SIADH, and a lower baseline BUN may also be predictive. We advise caution when dosing tolvaptan in patients with particularly low sNa (< 120 mmol/L) and low BUN (< 7 mg/dL).

TH-PO495

Use of Salt Tablets in the Treatment of Mild-to-Moderate Hyponatremia due to Syndrome of Inappropriate Antidiuresis Ittikorn Spanuchart,[1] Thomas Aldan,[1] Hideaki Watanabe,[1] Dominic Chow,[1,2] Roland C.K. Ng.[1,2] *[1]Univ of Hawaii Internal Medicine Residency Program; [2]Univ of Hawaii John A. Burns School of Medicine.*

Background: Hyponatremia is the most common electrolyte disorder with significant morbidity and mortality. However, the effectiveness of salt tablets in treating this disorder has never been systematically examined. In this retrospective cohort study, we examined the effectiveness of salt tablet treatment in correcting mild-to-moderate hyponatremia.

Methods: Eighty-three patients with hyponatremia on fluid restriction, and laboratory values of urine osmolality >100 mosm/kg and urine sodium >30 mEq/L, who did not correct with normal saline infusion, were studied. Patients who had received salt tablets and fluid restriction were compared with those on fluid restriction alone. The primary outcome was the change in serum sodium at 48 hours.

Results: There were 41 patients in the non-salt treated group (NS) and 42 patients in the salt-treated group (S).The median serum sodium before treatment was (NS) 129 mEq/L (IQR: 125-131.5) and (S) 124 mEq/L (IQR121-129). The S patients tended to be older (p=0.019), female (p=0.049), lower weight (p=0.039), and have lower initial serum sodium (p=0.005). The serum sodium after 48 hours of treatment increased significantly more with salt tablets (S) than with fluid restriction (NS) alone (p=0.014). The change in serum sodium remained significant with S even after adjustment for age, gender, weight and initial serum sodium. The length of stay was longer in the S group (p=0.006). When the analysis was confined to more refractory patients (urine osmolality >500 mosm/kg), S (8 patients) and NS (5 patients), treatment with salt tablets resulted in a significant increase in serum sodium (p=0.004) compared with fluid restriction alone. Adverse effects such as congestive heart failure and severe hypertension were not different in the two groups.

Conclusions: Use of salt tablets in the treatment of mild-to-moderate hyponatremia due to syndrome of inappropriate antidiuresis is effective. Further studies of a prospective, randomized nature should be done to confirm these data.

TH-PO496

Salt Taste Thresholds and Salt Preference in Patients with Chronic Kidney Disease According to Stage: A Cross-Sectional Study Jae Wan Jeon, Hyosang Kim, Soon Bae Kim. *Internal Medicin, Nephrology, Asan Medical Center, Seoul, Republic of Korea.*

Background: Increased salt thresholds may affect the adequate control of oral salt intake and subsequent high blood pressure. This study was performed to evaluate the differences in salt taste thresholds among normal controls and non-dialysis chronic kidney disease (CKD) patients according to the stage and to evaluate the relationship between salt taste thresholds or salt preference and the mean spot urine sodium.

Methods: This cross-sectional study enrolled 436 patients with nondialysis CKD who visited Asan Medical Center (Seoul, Korea) more than three times and underwent spot urine sodium measurement at each clinic visit. We averaged the three most recent spot urine sodium concentrations and used this "mean spot urine sodium" value to estimate sodium intake. In addition, 74 normal controls were enrolled and their one-time spot urine sodium was measured. We evaluated the detection and recognition thresholds, salt preference, and salt usage behavior (via questionnaire) in CKD patients and normal controls.

Results: The detection thresholds of the stage 3a, 3b, 4 and 5 CKD patients and the recognition thresholds of the stage 3a and 3b CKD patients were higher than those of normal controls. The salt preference of the stage 5 patients and the salt usage behavior scores of the stage 4 and 5 patients were lower than those of normal controls. Estimated glomerular filtration rate (eGFR), salt usage behavior, and salt preference significantly correlated with the mean spot urine sodium in CKD patients. Age, sex, the detection and recognition thresholds, and serum zinc did not show a relationship with the mean spot urine sodium. Multiple regression analysis showed that eGFR, salt preference, and salt usage behavior score independently correlated with the mean spot urine sodium.

Conclusions: The detection and recognition thresholds are increased and salt preference and the salt usage behavior score are decreased in CKD patients. eGFR, salt preference, and the salt usage behavior score are independent predictors of the mean spot urine sodium in CKD patients. However, detection and recognition thresholds are not associated with the mean spot urine sodium in CKD patients.

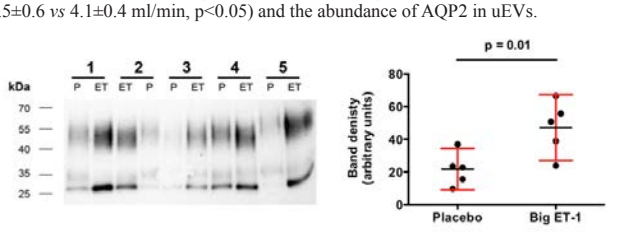
TH-PO497

Endothelin Induces Aquauresis in Man via an AQP2-Independent Mechanism Robert W. Hunter. *Centre for Cardiovascular Science, Univ of Edinburgh, United Kingdom.*

Background: Endothelin-1 (ET-1) receptor antagonists show promise in the treatment of diabetic nephropathy. Their use is complicated by salt / water retention. Whereas in animal models ET_B receptors cause natriuresis and aquauresis, with collecting duct ET_B inhibiting the activation of AQP2 channels, the pathogenesis of fluid retention with ET antagonists in man is not known. We aimed to determine the effect of ET-1 on water transport in the human collecting duct.

Methods: We conducted a 2-phase randomised, double-blind, placebo-controlled crossover study in 10 healthy volunteers. After sodium restriction, subjects received either intravenous placebo or the inactive ET-1 precursor, big ET-1, in an escalating dose (up to 300pmol/min). We prepared urinary extracellular vesicles (uEVs) by ultracentrifugation and analyzed them by immunoblot using antisera to AQP2 (Millipore).

Results: Big ET-1 infusion increased plasma concentration and urinary excretion of ET-1. Fractional excretion of ET-1 rose from 0.6 to 2.4% and urine ET-1/creat from 0.05 to 0.20pg/μmol. Big ET-1 caused a fall in heart rate (~8 beats/min) but no change in other measures of systemic hemodynamics or in GFR. Fractional excretion of sodium increased by ~0.5%. There was no change in urine flow rate. Big ET1 increased free water clearance (5.5±0.6 *vs* 4.1±0.4 ml/min, p<0.05) and the abundance of AQP2 in uEVs.



Conclusions: In man, ET-1 increased AQP2 excretion in uEVs (a proxy for AQP2 density in the collecting duct apical membrane). ET-1 stimulates pituitary AVP release, a

potential cause of increased AQP2 expression. However there was an apparent paradoxical increase in free water clearance. Thus the mechanism responsible for aquauresis was independent of any effect of ET-1 on AQP2. Further exploration of this mechanism will help manage the fluid retention associated with ET antagonists, a prerequisite for their use in the therapy of diabetic nephropathy.

Funding: Private Foundation Support

TH-PO498

Tolvaptan Increases Renal Water and Sodium Excretion More Than Furosemide in Patients with Congestive Heart Failure Complicated by Advanced Chronic Kidney Disease Naoto Tominaga,[1] Keisuke Kida,[2] Takayuki Inomata,[3] Naoki Sato,[4] Tohru Izumi,[5] Yoshihiro J. Akashi,[2] Yugo Shibagaki.[1] *[1]Div of Nephrology and Hypertension, St. Marianna Univ, Japan; [2]Div of Cardiology, St. Marianna Univ; [3]Dept of Cardio-angiology, Kitasato Univ; [4]Cardiology and Intensive Care Unit, Nippon Medical School Musashi-Kosugi Hospital; [5]Div of Cardiology, Niigata Minami Hospital.*

Background: Tolvaptan (TLV) is known to increase electrolyte-free water clearance. However, TLV actions on renal electrolytes including urine sodium (uNa) excretion and its consequences are less well understood in congestive heart failure (CHF) patients with CKD. This subanalysis investigated the effect of add-on TLV compared to furosemide (FUR) on both free water and electrolyte clearance in patients with CHF complicated by advanced CKD.

Methods: The Kanagawa Aquaresis Investigators Trial of TLV on HF Patients with Renal Impairment was a multicenter, open-labeled, randomized, and controlled prospective clinical study. Eighty-one Japanese patients with congestive HF and residual signs of congestion despite oral FUR treatment (≥40 mg/day) were recruited. They were randomly assigned to a 7-day treatment with either add-on ≤40 mg/day FUR or ≤15 mg/day TLV. However, 31 patients dropped out during the study and 16 patients had missing data resulting in 17 patients in each group. Free water and electrolyte excretion were compared before and after therapy between the two groups.

Results: As expected, free water clearance was significantly higher in the add-on TLV group than in the add-on FUR group (0.25±0.07 vs. -0.01±0.04 mL/min, P=0.001). However, electrolyte clearance was also higher in the add-on TLV group than in the add-on FUR group (0.06±0.06 vs. -0.08±0.07 mL/min, P=0.185). This was mainly because ΔuNa excretion was significantly higher in the add-on TLV group than in the add-on FUR group (13.8±10.9 vs. -16.2±12.0 mEq/day, P=0.040), since ΔuK excretion was significantly lower in the add-on TLV group than in the add-on FUR group (-6.7±2.4 vs. 0.8±1.2 mEq/day, P=0.014).

Conclusions: Add-on TLV may have an effect to increase both renal water and Na excretion in CHF patients with advanced CKD to a greater degree than add-on FUR.

TH-PO499

Urea for SIADH: The First U.S. Long Term Results Gregory Lee Braden, Michael H. O'Shea, Daniel L. Landry. *Nephrology Div, Baystate Medical Center/Tufts Medical School, Springfield, MA.*

Background: Urea has been used in Europe for >35 years to treat SIADH but it is not available in the U.S. Also, the long term effects of Urea on uric acid(UA) handling in SIADH have not been defined. We obtained Urea USP from MEDISCA, a compounding company with U.S. distributors. The Urea is made by Merck in Germany and costs a patient(pt) $30/mo. We studied Urea in 6 female pts with only Medicare plan D for meds, ages 66-91 with SIADH (4 lung cancer, 1 idiopathic & 1 psych meds) who failed 1000 ml/d fluid restriction, demeclocycline(DMC) [3 nausea, 1 aki & 6 unaffordable at $600-900/mo] or tolvaptan(TOL) unaffordable at >$700/mo.

Methods: We measured serum(S) sodium (Na), BUN, creatinine, UA, plasma(P) Osm, Urine Osm, fractional excretion(FE)Na, & FE UA before Urea , & 7 d, 30 d & 180 d after starting Urea 10 -15 grams twice daily. Fluid was restricted to 1500 ml daily for 1 week then liberalized to ad lib.

Results: Results are expressed as X+SEM:

	Before Urea	7d	30d	180d	p
S Na (mEq/L)	126+1	132+1	135+1	136+1	.0007
P Osm (mOsm/kg)	266+3	278+1	289+3	287+3	.0044
S UA (mg/dL)	2.7+0.4	3.8+0.2	4.8+0.5	4.7+0.4	.0092
FE UA (%)	16.8+1	12.1+0.5	8.1+0.4	8.1+0.5	.0017

S Na was near normal after 7 d and thereafter remained normal for 180d. BUN increased from 13.8+2.6 mg/dl to 27.2+3.7 after 7d, to 39.3+6 after 30d & to 36.5+5 after 180 d confirming the pts took Urea (.0084). The S UA was normal after 7d & remained normal at 180 days(p=.0092). The FE uric acid was elevated,>12%, before Urea but was normal thereafter(p=.0017). No patient had polyuria or any reaction to Urea except for it being distasteful . Their were no differences in urine Osm ,urine Na, FE Na or serum creatinine.

Conclusions: Indeed, pharmaceutical grade Urea USP is available in the US & all Baystate Medical Center pharmacies stock it. Urea is a safe, effective, inexpensive alternative therapy for pts with SIADH intolerant to DMC or who can't afford DMC or TOL. Similar to successful fluid restriction in SIADH, Urea normalizes S UA & FE UA as the S Na reaches normal levels.

TH-PO500

A Gain of Function NKCC2 Mutation in a Patient with Chronic Cyclic Edema Minhtri K. Nguyen,[1] Alejandro Rodriguez-Gama,[2] Erika Moreno,[2] Theresa L. Nilson,[1] Gerardo Gamba,[2] Ira Kurtz.[1] *[1]David Geffen School of Medicine, UCLA, Los Angeles, CA; [2]Molecular Physiology Unit, INCMNSZ-IIB-UNAM, Mexico City, Mexico.*

Background: We report a 20 y.o. female with a complex medical history significant for chronic cyclic edema, who has a homozygous R116H substitution in the *SLC12A1* gene. The patient was normotensive without any electrolyte or metabolic acid-base abnormalities. Urine studies showed significantly reduced 24 hr excretion of Na^+, K^+, Cl^-, Ca^{2+}, and Mg^{2+} consistent with increased NKCC2 activity: Na^+ 63 meq, K^+ 24 meq, Cl^- 44 meq, Ca^{2+} 22 mg, Mg^{2+} undetectable, creatinine 710 mg (weight 50 kg). The patient's cyclic edema was completely prevented by treatment with 20 mg of Lasix.

Methods: Expression/phosphorylation of NKCC2 was assessed by Western blot in proteins extracted from transiently transfected HEK-293 cells with wild-type and mutant NKCC2-R116H that were exposed to control and different osmolar conditions.

Results: Basal phosphorylation was similar between wild-type and NKCC2-R116H. However, following exposure to low chloride stress for 10, 20 and 30 min (known to activate NKCC2), the mutant transporter was phosphorylated significantly more rapidly than the wild-type transporter. In separate experiments, the rate of dephosphorylation was monitored following cell swelling (known to inhibit NKCC2). The phosphorylation of NKCC2 at 10, 20 and 30 min decreased from 1.0 ± 0.01 (arbitrary units) at basal state to 0.74 ± 0.06, 0.6 ± 0.1, and 0.5 ± 0.07 respectively, while in mutant NKCC2-R116H at the same time points the decrease in phosphorylation was significantly less: 1.0 ± 0.01 to 0.95 ± 0.03, 0.83 ± 0.05, and 0.8 ± 0.09 respectively.

Conclusions: The NKCC2 dephosphorylation is precluded by the R116H mutation. Since phosphorylation of NKCC2 stimulates its transport activity, the R116H mutation in our patient appears to represent the first gain of function NKCC2 mutation ever reported.

Funding: Private Foundation Support

TH-PO501

Gender Difference in Thiazide Sensitive Na-Cl Cotransporter Activity and Expression in Wild Type and Angiotensin II Type 1a Receptor (AT1a) Deficient Mice Jing Li,[1] Ryo Hatano,[1] Lei Yang,[2] Shuhua Xu,[1] Alan Mark Weinstein,[2] Lawrence G. Palmer,[2] Tong Wang.[1] *[1]C. & M. Physiology, Yale Univ, School of Medicine, New Haven, CT; [2]Physiology and Biophysics, Weill Medical College of Cornell Univ, New York, NY.*

Background: Thiazide sensitive Na-Cl cotransporter (NCC) mediates the majority of NaCl absorption in the distal tubule. Alteration of NCC directly affects salt and water balance and blood pressure. We studied gender differences in NCC activity and expression in WT and AT_{1a} receptor knockout (KO) mice.

Methods: Renal clearance experiments were performed on both male and female WT and KO mice. Urine volume (UV), GFR, absolute (ENa) and fractional (FNa) Na excretion were measured and compared at peak changes after a bolus iv injection of hydrochlorothiazide (HCTZ; 30mg/kg). NCC mRNA expression was examined by Q-PCR; total NCC (tNCC) and phosphorylated NCC (pNCC) were examined by Western-blotting. In WT mice, HCTZ produced greater diuretic and natriuretic effects in females, compared to males.

Results: The fractional increases of UV, ENa and FENa by HCTZ were 8.3- vs. 5.3-fold; 13.3- vs. 6.7- fold and 9.4-vs. 4.9-fold in female, compared with male, respectively (n=6, $P<0.05$). In contrast, there was no gender difference in $AT_{1a}^{-/-}$ mice, since HCTZ produced stronger diuretic and natriuretic effects on male $AT_{1a}^{-/-}$ than the WT, and female WT and KO mice had the same effect. The fractional increases of UV, ENa and FENa by HCTZ were 8.9- vs. 6.3-fold; 10.5- vs. 15.1- fold, and 7.8- vs. 13.7-fold in female compared with male respectively ($P>0.05$). NCC mRNA expression was 39% and 48% higher in female, both WT and KO, mice compared to the male mice (n=4, $p<0.05$). Total NCC and pNCC expression was 36% and 34% higher in female WT compared to the male, consistent with the larger response to HCTZ. tNCC increased by 30% in both male and female KO, but pNCC was not significantly different from WT.

Conclusions: We conclude that in WT higher NCC expression in females correlates with activity; the gender-specific difference in activity is absent in $AT_{1a}^{-/-}$ mice. The findings are consistent with less reliance on the renin-angiotensin system for BP maintenance in females.

Funding: NIDDK Support

TH-PO502

Impaired Renal Electrolyte Reabsorption in Moesin-Deficient Mice Kotoku Kawaguchi, Ryo Hatano, Shinji Asano. *College of Pharmaceutical Sciences, Ritsumeikan Univ, Kusatu, Shiga, Japan.*

Background: ERM (ezrin, radixin, and moesin) proteins have important roles in organizing membrane domains through their ability to cross-link transmembrane proteins and actin cytoskeleton. Previously, we have reported that ezrin plays important roles in the regulation of membrane localizations of Na^+ dependent phosphate transporter (NaPi2a) and scaffolding protein NHERF1 in the proximal tubules. However, physiological roles of radixin and moesin in the kidney still remain unclear. In the present study, we have investigated the physiological functions of radixin and moesin in the kidney using knockout mice.

Methods: To investigate the renal functions in male radixin (*Rdx*$^{-/-}$) and moesin (*Msn*$^{-/y}$) knockout mice, these mice were housed in metabolic cages. After acclimation for 7 days, daily urine volume and water intake were measured. Spot urine was collected

for the measurement of urinary excretion of electrolytes. These mice were sacrificed to obtain plasma and renal tissue after experiments. Glomerular filtration rate (GFR), absolute (ENa, EK), and fractional excretion (FENa, FEK) were measured. Brush border membrane vesicles (BBMVs) were prepared from renal cortex of these mice to compare the membrane localizations of transmembrane proteins in proximal tubules. Subcellular localization of associated proteins was examined by immunofluorescent analysis.

Results: *Msn*$^{-/y}$ mice showed significant increase in the absolute (ENa) and fractional (FENa) Na^+ excretion, although there was no apparent abnormality in the solute reabsorption in *Rdx*$^{-/-}$ mice. Expression levels of Na^+ transporters as NaPi2a and Na^+/H^+ exchanger 3 (NHE3) located in proximal tubules were unaltered in BBMVs from both Rdx$^{-/-}$ and Msn$^{-/y}$ mice compared to WT mice, suggesting that proximal tubular Na^+ reabsorption is not impaired. Immunofluorescent analysis exhibited the colocalization of moesin and NKCC2 in the apical membrane of thick ascending limb of Henle (TAL). Moesin is also co-immunoprecipitated with NKCC2 using renal medulla.

Conclusions: Our results suggest that moesin, but not radixin, plays an important role in the regulation of sodium reabsorption in the TAL, possibly due to the regulation of membrane localizations of NKCC2.

TH-PO503

Urokinase-Type Plasminogen Activator Is Not Required for Edema Formation in Experimental Nephrotic Syndrome Ferruh Artunc, Bernhard Bohnert, Matthias Woern, Sophie Daiminger. *Internal Medicine, Div of Nephrology, Univ Hospital, Tuebingen, Germany.*

Background: Edema formation in nephrotic syndrome is thought to arise from activation of the epithelial sodium channel (ENaC) by the serine protease plasmin after conversion of aberrantly filtered plasminogen by tubular urokinase-type plasminogen activator (uPA). Inhibition of uPA might prevent plasmin generation and subsequent edema formation.

Methods: We investigated the effects of inhibiting of uPA in a model of experimental nephrotic syndrome using a pharmacological approach with amiloride in wild-type mice or in mice with genetic uPA deficiency (uPA$^{-/-}$ mice). Proteinuria was induced by a single injection of doxorubicin (14.5 µg/g). Urinary uPA and plasmin activity was measured using chromogenic substrates, conversion of plasminogen to plasmin was analyzed with western blot (WB).

Results: Amiloride inhibited urinary uPa activity of control mice with an IC50 of 6 µM (95%CI 4;9). In amiloride-treated wild-typ mice (10 µg/g i.p., once daily) weight gain was almost completely prevented after onset of proteinuria (+6±1% , n=6 vs. +20±2% in vehicle-treated mice, n=8; p=0.001). Urinary amiloride concentration reached up to 362 µM 4 h after injection and fell to zero after 24h. Urinary uPa and plasmin activity was significantly reduced by amiloride (p=0.04); WB showed absent plasminogen conversion in amilorid-treated mice. In uPA$^{-/-}$ - mice, there was no urinary uPA activity detectable under control conditions. After induction of proteinuria the increase in urinary plasmin activity was completely absent in uPA$^{-/-}$ - mice and WB showed only a single plasminogen band. However, uPA$^{-/-}$ - mice were not protected from weight gain (+21±1%, n=7 vs. +20±1%, n=7; p=0.85) and sodium retention (minimal urinary sodium concentration 8±3 vs. 11±9mM, p=0.72) compared to uPA$^{+/+}$ - mice.

Conclusions: uPA is responsible for conversion of aberrantly filtered plasminogen to plasmin in the tubulus lumen. This is however not essential for edema formation in experimental nephrotic syndrome.

TH-PO504

Extending the Use of Bioimpedance Spectroscopy and Body Composition Modelling for Assessment of Fluid Status to Children Indranil Dasgupta,[1] Elizabeth J. Lindley,[2] Peter Wabel.[3] *[1]Heartlands Hospital, United Kingdom; [2]Leeds Teaching Hospitals, United Kingdom; [3]Fresenius Medical Care, Germany.*

Background: Bioimpedance spectroscopy (BIS) together with a whole-body model to distinguish excess fluid from the hydration of major body tissues provides an objective assessment of fluid status. This technology is integrated into the Body Composition Monitor (BCM,Fresenius AG, Bad Homburg) and has been well validated in adults. The aims were (a) to assess the agreement between total body water (TBW) measured using BIS and a gold standard technique; (b) to compare the estimated hydration of lean tissue (LT) in children and adults; (c) to look for systematic deviation from zero in the measured excess fluid in healthy children.

Methods: TBW_D2O was determined from the decline in the concentration of deuterium in urine samples, collected for 5 days following a drink containing 7% D_2O. dilution. The hydration of LT was estimated by extrapolating a plot of TBW/weight vs. %fat measured with DEXA to 0% body fat. TBW_BCM and excess fluid was determined from a standard wrist-to-ankle BCM measurement. The agreement between TBW_D2O and TBW_BCM was analysed using Bland-Altman method.

Results: 61 healthy children between 6 and 14 years (32 male, median age 10.3) completed the study, 5 children aged 2 to 5 years were recruited for aim (c) only. 60 children provided sufficient urine samples for analysis. The BMI correction to fluid volumes determined from BIS was not appropriate for children, but there was good agreement between the uncorrected TBW_BCM and TBW_D2O with a bias of +0.6 L (95% limits of -2.0 to +3.2 L). The estimated water content of lean tissue of 70.4% (95% CL 68.0-72.7%) was consistent with the 70.3 ± 0.9% estimate for adults. The median absolute excess fluid volume was +100 mL (IQR -140 to +480 mL). The median excess fluid normalised to body weight was +0.48% (IQR -0.51% to + 1.45%). There was no correlation between age and either absolute or normalised excess fluid in this group of healthy children.

Conclusions: Although BCM data should be used with caution in patients that differ significantly from the population used to develop the models, these results suggest that the device can be used in children.

TH-PO505

Exploring the Effect of Tacrolimus on the Renal Kinome: Identification of Novel Phosphoproteins Felice K.Y. Leung,[1,2] Benedetta Lombardi,[1] Mark Desmond Crawford,[1] Anselm A. Zdebik,[1,2] Jasminka Godovac Zimmermann,[1] Joanne Marks,[1,2] Stephen B. Walsh.[1] *[1]Centre for Nephrology, UCL, London, United Kingdom; [2]Dept of Neuroscience, Physiology and Pharmacology, UCL, United Kingdom.*

Background: Tacrolimus is a calcineurin inhibitor (CNI), and the main immunosuppressant used in organ transplantation. However, it causes complications such as hypertension, acidosis, hyperkalaemia, diabetes mellitus and hypercalciuria, mimicking the metabolic syndrome, which may be mediated by altered renal tubular transport mechanisms.

Methods: Male C57BL/6J mice, 6-8 weeks of age, were administrated vehicle or tacrolimus (2mg/kg/day/ I.P) for two weeks. At the end of the treatment period they were euthanized by cervical dislocation, under Schedule 1, and the kidneys were removed. The cytoplasmic and membrane fraction of the renal cortices were separated by centrifugation. The proteins were reduced, alkylated and digested by trypsin. Peptides were then labelled with isobaric Tandem Mass Tags, followed by TiO_2 phosphopeptide enrichment. Vehicle and tacrolimus treated samples were combined and injected into the liquid chromatography-mass spectrometry (LC-MS/MS) for analysis.

Results: Several hypertension-related phosphopeptides were identified in this study. The thiazide-sensitive sodium-chloride cotransporter (NCC) had significantly increased phosphorylation at T122 (+13.32%) and S124 (+12.09%); a novel phosphosite- S127 was also identified with increased phosphorylation (+17.74%), and the coexpression of pS124 and pS127 showed enhanced phosphorylation (+20.71%) after tacrolimus treatment. Other phosphopeptides identified included regulatory factors involved in tacrolimus induced hypertension. Angiotensin-converting enzyme had increased phosphorylation at S1305 (+23.89%). Sodium-hydrogen exchanger regulatory factor 1 (12.18-25.61%) had increased phosphorylation at a number of phosphosites.

Conclusions: The data suggests that the effects of calcineurin inhibition on renal electrolyte transport and their potential regulators are complex, profound and may relate to adverse effects of CNIs. Further investigation of the role of these novel candidates in the effects of CNIs is warranted.

TH-PO506

The Effect of Tacrolimus on Distal Renal Calcium Transporter Expression Felice K.Y. Leung,[1,2] Joanne Marks,[1,2] Stephen B. Walsh.[1] *[1]Centre for Nephrology, UCL, United Kingdom; [2]Dept of Neuroscience, Physiology and Pharmacology, UCL, United Kingdom.*

Background: Tacrolimus (FK506) is an immunosuppressant widely used in transplant medicine to prevent rejection. Hypercalciuria, hypertension, hyperkalaemia, metabolic acidosis and diabetes mellitus are common side effects of tacrolimus; the effect of tacrolimus on calcium handling in the distal nephron is unclear.

Methods: This study investigated the effect of tacrolimus on the renal mRNA and protein expression of calcium-transport proteins: the apical transient receptor potential cation channel-V (TRPV5) and basolateral plasma membrane Ca^{2+} ATPase (PMCA) and basolateral sodium-calcium exchanger (NCX1). Regulatory proteins including: cytosolic Ca^{2+}-binding protein calbindin-D (D28k), calcineurin and calnexin were also investigated. Male C57BL/6J mice of 6-8 weeks age were treated with vehicle or tacrolimus (2mg/kg/day/I.P) for 2 weeks. Quantification of mRNA expression was determined by qPCR and protein levels were quantified by Western blotting. Values are presented as mean fold changes relative to controls ± S.E.M.; statistical significance was calculated using unpaired t-test.

Results: FK506 significantly increased renal mRNA expression of TRPV5 (1.48±0.11, $p<0.01$); mRNA expression of the other transport-proteins: PMCA1, PMCA4 and NCX1, was not significantly different. FK506 significantly decreased mRNA expression of D28k (0.60±0.10, $p<0.05$), but changes in calcineurin was not observed. Furthermore, FK506 caused no change in the protein abundance of TRPV5 but significantly increased the protein levels of PMCA (3.02±0.24, $p<0.0001$) and NCX1 (2.76±0.27, $p<0.001$). Although the protein abundance of the regulatory proteins: D28k and Canx, showed no significant difference after FK506 treatment, a decreasing trend post-FK506 treatment was observed in D28k.

Conclusions: These data are not compatible with FK506 induced hypercalciuria arising from altered calcium transporter levels in the distal convoluted tubule. The increase in the protein abundance of PMCA and NCX1 may be due to the removal of the inhibitory effect of calcineurin and dysregulated protein kinase C signalling.

TH-PO507

The Effect of Sodium Nitrite Infusion on Renal Variables, Brachial and Central Blood Pressure during Enzyme Inhibition by Allopurinol, Enalapril or Acetazolamide in Healthy Subjects: A Randomized, Double-Blinded, Placebo-Controlled, Cross-Over Study Jeppe B. Rosenbaek, Erling B. Pedersen, Jesper N. Bech. *Univ Clinic in Nephrology and Hypertension, Dept of Medical Research, Regional Hospital West Jutland and Aarhus Univ, Denmark.*

Background: Sodium nitrite ($NaNO_2$) causes vasodilation, presumably by enzymatic conversion to nitric oxide (NO). Several enzymes with nitrite reducing capabilities have been discovered in vitro, but their relative importance in vivo has not been investigated. We aimed to examine the effects of $NaNO_2$ on hemodynamics, fractional sodium excretion (FE_{Na}), free water clearance (C_{H2O}) and GFR, following pre-inhibition of xanthine oxidase, angiotensin-converting enzyme and carbonic anhydrase.

Methods: In a double-blinded, placebo-controlled, cross-over study, 16 healthy subjects were treated, in a randomized order, with placebo, allopurinol 150 mg twice daily (x 2), enalapril 5 mg x 2, or acetazolamide 250 mg x 2. After four days of treatment and standardized diet the subjects were examined at our lab. During administration of 240 mg $NaNO_2$/kg/hour for two hours, we measured brachial and central blood pressure (BP), plasma and urine osmolality, GFR by Cr-EDTA clearance, FE_{Na} and urinary excretion rate (UER) of cyclic guanosine monophosphate (cGMP) and nitrite and nitrate (NO_x). Subjects were supine and orally water-loaded throughout the examination day.

Results: After 90-120 min of $NaNO_2$ infusion we observed an increase in FE_{Na}, heart rate, UER of NO_x, and a decrease in C_{H2O}, UER of cGMP, and brachial systolic BP irrespective of pretreatment. We observed a consistent trend towards a reduction in central systolic BP, which was only significant after allopurinol. An increase in GFR was only observed after placebo.

Conclusions: This study shows a BP lowering and natriuretic effect of $NaNO_2$ regardless of preceding enzyme inhibition. GFR was increased by $NaNO_2$ infusion, when no enzymes where inhibited. The decrease in UER of cGMP indicates little or no conversion of nitrite to NO, thus the effect of $NaNO_2$ does not seem to be mediated by NO generation.

Funding: Government Support - Non-U.S.

TH-PO508

Generation of p62/SQSTM1 (p62) KO Cell Lines Using CRISPR/Cas9 -The Role of p62 on WNK1 Regulation by Changes of Extracellular Potassium Concentration- Yutaro Mori,[1,2] Shintaro Mandai,[1] Takayasu Mori,[1] Eisei Sohara,[1] Tatemitsu Rai,[1] Shinichi Uchida.[1] *[1]Dept of Nephrology, Graduate Schools of Medical and Dental Sciences, Tokyo Medical and Dental Univ, Tokyo, Japan; [2]Div of Nephrology, Tsuchiura Kyodo General Hospital, Tsuchiura, Ibaraki, Japan.*

Background: We reported that KLHL3 binds to WNK4 and Cullin3 (CUL3) and ubiquitinate WNK4 and that the impaired WNK4 ubiquitination and degradation cause human hypertensive disease through the activation of WNK-OSR1/SPAK-NCC cascade. We also discovered that p62/SQSTM1 (p62), an autophagic adaptor protein, binds to WNK4-KLHL3 complex and is degraded together by selective autophagy. However, the physiological role of autophagic degradation of WNKs remained to be determined. Here, we generated p62 knockout (KO) cell lines by using CRISPR/Cas9 system and investigated the physiological role of selective autophagy in WNKs degradation.

Methods: We generated p62 KO HEK293T cell lines by using CRISPR/Cas9 system and analyzed them by western blotting. We exposed wild-type and p62 KO cells to different potassium concentration medium and examined WNK protein levels. We also performed siRNA knockdown (KD) experiments of p62 using COS7 cells and performed similar experiments.

Results: We designed the guide RNA targeting the exon 3 of p62 gene. We transfected HEK293T cells with the guide RNA expression vector and Cas9 vector. By single colony isolation after transfection, some hetero or homo KO cell lines were obtained. We confirmed that expressed WNK4 and KLHL3 protein level was dramatically increased in p62 KO cells. In wild-type HEK293T and COS7 cells, exposure to low potassium medium increased WNK1 expression, and high potassium medium decreased. However, in p62 KO and KD cells, WNK1 changes were partially canceled compared with wild-type.

Conclusions: We succeeded the generation of p62 KO cell lines. We confirmed that p62 degraded WNK4-KLHL3 complex by selective autophagy. Furthermore, this degradation system may regulate WNKs expression under changes of extracellular potassium concentration.

TH-PO509

Three-Layered Proteomic Analysis of MAGED2 Signaling Markus M. Rinschen,[1] Malte P. Bartram,[1] Thomas Benzing,[1] Robert A. Fenton,[2] Martin Kömhoff,[3] Bodo B. Beck.[4] *[1]Internal Medicine, Univ Hospital Cologne, Cologne, Germany; [2]Dept Biomedicine, Aarhus Univ, Aarhus, Denmark; [3]Univ Children's Hospital, Philipps Univ Marburg, Germany; [4]Human Genetics, Univ Hospital Cologne, Cologne, Germany.*

Background: Loss of function mutations in the X-chromosomal MAGED2 gene were recently discovered as a novel cause for X-linked antenatal Bartter's syndrome and polyhydramnios. The antenatal Bartter's syndrome was severe but completely resolved within a few weeks after birth. Staining of a fetal kidney from a patient with a truncating mutation in *MAGED2* revealed decreased total and apical abundance of NKCC2 and NCC. Cell culture studies demonstrated impaired maturation of the NKCC2 and NCC protein in the absence of MAGED2.

Methods: To investigate the function of MAGED2 in an unbiased manner, we performed a three-layered proteomic analysis. First, we analyzed the interactome of native MAGED2 in HEK293T cells. We also analyzed the interactome of wildtype (WT) and mutant (R446C)-MAGED2 when overexpressed in HEK 293T cells. Finally, we analyzed the effect of MAGED2 knockdown on the proteome and phosphoproteome.

Results: We performed an initial interactomic analysis of MAGED2 natively expressed in HEK293T cells using two different antibodies. We found that MAGED2 interacts with the nucleolar proteins NAP1L1, NAP1L2, and the stimulatory G-protein Gsalpha (gene symbol: GNAS). Next, we expressed tagged WT- and R446C-MAGED2 in HEK293T cells. The R446C mutant was less stable as compared to the WT MAGED2. In interactomic analysis, both WT- and R446C-MAGED2 were found to interact with NAP1L1 and NAP1L2. MAGED2 WT, but not R446C-MAGED2 interacted with GNAS and Hsp40. Cell culture studies confirmed the involvement of MAGED2 in controlling G-protein coupled receptor signaling. Proteomic and phosphoproteomic analyses of cells with MAGED2 knockdown demonstrated that several candidate proteins and substrates are controlled by MAGED2.

Conclusions: Our analyses suggest that MAGED2 could be a modulator of GNAS function. During renal development, sensitivity of adenylate cyclase increases. To understand the transient phenotype, the role of MAGED2 in controlling cAMP signaling in the distal nephron needs to be elucidated in greater detail.

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TH-PO510

Free Vitamin D May Be Altered during Chronic Kidney Disease Anaïs Bouchara, Marie-Christine Carlier, Laetitia Koppe, Mathilde Nouvier, Maurice Laville, Bertille Pommier, Denis Fouque, Solenne Pelletier. *Univ de Lyon, Lyon, France.*

Background: Most chronic kidney disease (CKD) patients suffer from 25OH vitamin D (25OHvitD) deficiency, which might contribute to adverse health outcomes. Because vitamin D binding is altered during CKD, it has been proposed that serum free 25OHvitD better reflects vitamin D metabolism than total 25OHvitD. We aim to evaluate whether serum free 25OHvitD varies regarding the different stages of CKD, in comparison with total 25OHvitD.

Methods: We prospectively assessed 34 CKD patients during a glomerular filtration rate measurement (GFR) by inulin clearance. We measured serum free 25OHvitD by ELISA (DiaSource, Leuven, Belgium) and total 25OHvitD by immunoluminometry (DiaSorin, Italy).

Results: Patients were aged 54.7 ±13.6 yr, 44% were males. Mean GFR was 59 ±26 ml/min/1.73m^2, serum total 25OHvitD was 59.9 ±27.5 ng/ml and serum free 25OHvitD 5.45 ±1.96 pg/ml. We found a strong association between free 25OHvitD and total 25OHvitD ($r=0.88$, $p<0.001$). There was no correlation between free 25OHvitD and GFRwhereas total 25OHvitD significantly declined with GFR decrease($r=-0.34$, $p=0.048$). Of interest, the ratio free/total 25OHvitD strongly decreased with the decline of kidney function ($r=0.55$ $p<0.001$).We did not find any relationship between free 25OHvitD nor total 25OHvitD and measures of mineral metabolism.

Conclusions: This pilot study suggests that vitamin D bioavailability may be reduced in advanced CKD. The serum level of total 25OHvitD may indeed mask low free 25OHvitD and inadequate correction of vitamin D deficiency. Free 25OHvitD may represent a new target for treatment adaptation.

TH-PO511

Effect of Vitamin D Therapy on CKD-MBD Biomarkers in CKD: A Post Hoc Analysis of the PACE Study Stuart M. Sprague,[1] Ying Zhou,[1] Mark D. Faber,[2] Daniel W. Coyne.[3] *[1]NorthShore Univ HS-Univ of Chicago; [2]Henry Ford Hosp; [3]Washington Univ.*

Background: PACE, a 24 week randomized study comparing calcitriol (Calci) and paricalcitol (Pari) in CKD stage 3 & 4. Both Calci and Pari similarly decreased PTH, with minimal effects on Ca and Phos. Few studies have evaluated the effect of VDRA therapy on other mineral biomarkers in CKD. Therefore, a *post hoc* analysis of biomarkers was performed in a subgroup of subjects at baseline and week 24.

Methods: PACE, an open label, active comparator, multi-center, parallel group, phase 4 study of Pari vs Calci for suppression of PTH in CKD stages 3 & 4. Of the 110 original subjects, serum was available for 76 (38 in each group) for analysis of FGF23, sclerostin, bone specific alkaline phosphatase (BSAP), tartrate resistant acid phosphatase (TRAP), osteocalcin (OC), and 1,25 vitamin D (1,25D). The effect of therapy on their serum levels were analyzed.

Results:

	Calci		Pari		Calci vs Pari	
	Mean Change (SE)	p	Mean Change (SE)	p	Mean Diff (SE)	p
Ca (mg/dL)	0.34±0.07	<0.001	0.36±0.0.07	<0.001	-0.02±0.10	NS
PTH* (pg/mL)	-0.68±0.07	<0.001	-0.84±0.07	<0.001	0.16±0.10	NS
1,25D (pg/mL)	4.95±5.39	0.416	21.84±6.20	0.0014	-16.90±8.63	0.059
FGF23 (RU/mL)	184.4±45.2	0.001	190.8±44.4	<0.001	-6.4±63.4	NS
BSAP (µg/L)	-3.69±0.96	0.0007	-2.96±0.97	0.006	-0.74±1.36	NS
TRAP (ng/mL)	-1.08±0.20	<0.001	-0.73±0.20	0.0007	-0.35±0.29	NS
OC (ng/mL)	-16.40±8.95	0.078	-17.38±9.70	0.085	0.98±13.20	NS
Sclerostin (pg/mL)	88.2±31.5	0.008	152.38±33.15	<0.001	-64.20±45.77	NS

*Log transformed

Conclusions: Calci and Pari had comparable actions on biomarkers of bone activity, including significant increases in Ca, FGF23, and sclerostin, with significant suppression of bone turnover markers PTH, TRAP, BSAP, and a trend toward reducing OC. Pari, but not Calci, significantly increased 1,25D. Except for the difference between Calci and Pari on 1,25D, there was no differential effects on multiple biomarkers of these agents in a 6-month prospective clinical trial treating SHPT in patients with CKD.

Funding: Pharmaceutical Company Support - AbbVie

TH-PO512

Modified-Release Calcifediol Is Effective in African-American and Non-African-American Patients with Stage 3-4 CKD, Secondary Hyperparathyroidism and Vitamin D Insufficiency

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Background: Current treatments for vitamin D insufficiency (VDI) and related secondary hyperparathyroidism (SHPT) in stage 3 or 4 CKD are ineffective, a particular concern with African-American (AA) CKD patients who have lower serum total 25-hydroxyvitamin D (25D) and higher PTH levels than non-AA patients. In the present studies, the effectiveness of oral modified-release calcifediol (MRC) for treating VDI and SHPT was evaluated in AA versus non-AA subjects.

Methods: Two identical, randomized, double-blind, placebo-controlled trials were conducted in 429 subjects (138 AA, 291 non-AA) with stage 3 or 4 CKD, SHPT (>85 pg/mL) and VDI (25D of 10-29 ng/mL) and the data were pooled. Subjects were randomized 2:1 to receive MRC or placebo for 26 weeks. MRC dosing started at 30 µg/d and was increased after 12 weeks to 60 µg/d, as needed, to lower plasma iPTH. Changes in plasma iPTH, serum total 25D, total 1,25-dihydroxyvitamin D (1,25D), calcium (Ca) and phosphorus (P) were compared within AA and non-AA subjects using the per-protocol population.

Results: MRC increased mean serum 25D from 18.7 to 66.3 ng/mL in AA subjects, and from 20.3 to 69.6 ng/mL in non-AA subjects ($p < 0.001$); levels in placebo-treated subjects declined slightly. MRC reduced mean plasma iPTH by 15.7% (from 153 to 129 pg/mL) in AA subjects, and by 25.2% (139 to 104 pg/mL) in non-AA subjects ($p < 0.05$ for both relative to placebo). Mean iPTH in placebo-treated AA and non-AA subjects increased 4% and 10%, respectively. MRC increased mean serum 1,25D levels by 16 pg/mL in AA subjects and 11 pg/mL in non-AA subjects versus 5 pg/mL with placebo. Adverse event rates were similar between treatment groups within AA and non-AA subjects. Changes in serum Ca and P with MRC were similar in AA and non-AA subjects, and were slightly greater (~0.1 mg/dL) than with placebo.

Conclusions: MRC was effective for correcting VDI and reducing iPTH in both AA and non-AA subjects with stage 3 or 4 CKD.

Funding: Pharmaceutical Company Support - OPKO Health

TH-PO513

Cholecalciferol Supplementation and MBD-Related Parameters in Hemodialysis Patients - A Randomized Controlled Trial

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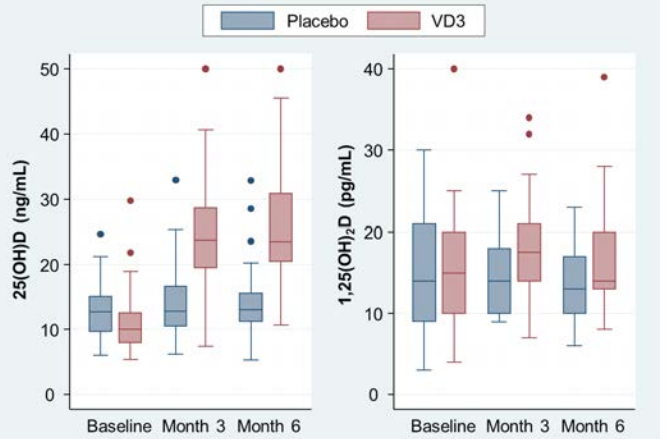
Background: A previous study demonstrated that ergocalciferol supplementation showed no effects on CKD-MBD related parameters in maintenance hemodialysis (MHD) patients. However, still scarce data exist regarding the effect of cholecalciferol (VD_3) and the impact of administration interval in this population.

Methods: This is a post-hoc analysis of a double-blind RCT of VD_3 supplementation in MHD patients. Patients were randomly assigned to either thrice-weekly (TW) 3,000 IU VD_3, once-monthly (OM) VD_3 (equivalent to 9,000 IU/week), TW placebo, or OM placebo. Based on the intention-to-treat principle, we compared VD_3 vs. placebo by using *a priori* defined generalized linear model with baseline adjustment ignoring the administration intervals. We also examined the differences between TW- vs. OM-VD_3.

Results: Out of 96 participants, 3 and 4 dropped out until Month 3 and between Month 3 and Month 6, respectively. Median (IQR) serum 25(OH)D levels at baseline and Month 6 were 13 (10–15) and 13 (11–16) ng/mL in the placebo, 10 (8–13) and 24 (21–31) ng/mL in the VD_3 group, respectively. After baseline adjustment, no significant differences were observed in serum levels of calcium, phosphorus, or intact PTH between the placebo vs. VD_3 groups. However, the VD_3 group showed 1.2 (95%CI, 1.1–1.4) times higher serum $1,25(OH)_2D$ levels at both Month 3 and 6. Their vitamin D receptor activator (VDRA) doses were more frequently reduced overtime than the placebo group (P=0.055 and 0.023 at Month 3 and 6, respectively). Any of those indices did not show differences between TW- and OM-VD_3.



Conclusions: Both TW- and OM-VD_3 supplementation are effective in increasing serum $1,25(OH)_2D$ levels and hence, reduces VDRA doses without affecting serum levels of calcium, phosphorus, and PTH in MHD patients.

Funding: Pharmaceutical Company Support - Molecular Physiological Chemistry Laboratory, Inc., Private Foundation Support

TH-PO514

Impact of Genetic Variants in DBP, CYP2R1, CYP24A1, and VDR on Serum 25-Hydroxyvitamin D Levels and Cholecalciferol Supplementation in Hemodialysis Patients

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Background: Genetic variants in vitamin D-related genes have been linked to serum 25(OH)D levels and the effect of cholecalciferol (VD_3) supplementation. However, it still remains unclear whether these findings can be extrapolated to hemodialysis population where vitamin D deficiency is frequently observed.

Methods: This is a post-hoc analysis of a double-blind RCT of VD_3 supplementation in MHD patients. A total of 96 patients were randomly assigned to either thrice-weekly 3,000 IU VD_3, monthly VD_3 (equivalent to 9,000 IU/week), thrice-weekly placebo, or monthly placebo. Of those, 89 (93%) provided informed consent to this gene study. We put each genetic variant in DBP (*rs7041*, *rs12512631*, and *rs2282679*), CYP2R1 (*rs10741657* and *rs2060793*), CYP24A1 (*rs2209314*), and VDR (*rs11568820*) into multivariate linear regression model with adjustment for age, sex, and season of blood draw ignoring the administration intervals.

Results: Baseline serum 25(OH)D levels were median 11 (8–14) ng/mL. The T allele at *rs11568820* was associated with 1.12 (95%CI, 1.01–1.24) times higher serum 25(OH) D levels per allele while alleles in the other candidate variants did not show significant association. Median (IQR) change in serum 25(OH)D levels was 2.0 (-1.0–5.1) ng/mL in the placebo and 13.5 (8.4–18.8) ng/mL in the VD_3 group at Month 3, and none of genetic variants did not significantly modify the effect of VD_3 on serum 25(OH)D levels.

Conclusions: Patients with the T allele at *rs11568820* had slightly lower serum 25(OH)D levels but the effect of VD_3 supplementation was not modified by these genetic variants in MHD patients.

Funding: Pharmaceutical Company Support - Molecular Physiological Chemistry Laboratory, Inc., Private Foundation Support

TH-PO515

Baseline 25-Hydroxyvitamin D Level and the Anti-Albuminuric Response to Vitamin D Receptor Activation in Patients with Chronic Kidney Disease

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Background: Vitamin D receptor activators (VDRA) reduce albuminuria beyond RAAS-blockade; it is unclear whether this effect is similar among vitamin D sufficient and deficient individuals. We studied whether baseline 25(OH) vitamin D status determines the anti-albuminuric response to VDRA treatment.

Methods: We performed a posthoc analysis of the VIRTUE trial (NTR2898); a double-blind, randomized, cross-over trial including patients with stage 1-3 CKD (eGFR 67±22) and albuminuria >300 mg/day. Patients received ramipril (10 mg/d) plus four 8-wk study periods in a random order: regular (RS, 200 mmol/d Na^+) or low-sodium (LS, 50 mmol/d) diet combined with VDRA (paricalcitol, 2 µg/day, PARI) or placebo (PLAC). Plasma 25(OH)D levels were measured with LC-MS/MS. Analyses were limited to patients with >95% compliance to PARI (N=34). Albuminuria is shown as geometric mean [95% CI]; 25(OH)D as mean±SD.

Results: Plasma 25(OH)D was 21.2±9.1 ng/mL during RS+PLAC and did not change between study periods (P_{ANOVA}=0.29). 25(OH)D level was <20 ng/mL in 48% and 20-30 ng/mL in 39% of patients. Paricalcitol reduced residual albuminuria beyond the effect of sodium restriction (RS+PLAC: 1004 [716-1407]; LS+PLAC 804 [489-1,321], LS+PARI 690 [417-1,143] mg/24h; P=0.04 vs LS+PLAC, P<0.001 vs RS+PLAC). There was no association between baseline 25(OH)D and the anti-albuminuric effect of PARI during RS (*r -0.08,* P= 0.31) or LS (*r* -0.10, P=0.52). Findings were similar in regression models adjusted for baseline albuminuria and $eGFR_{CKD\text{-}Epi}$ (RS: st.b -0.22, P=0.25, LS: st b 0.11, P=0.63).

Conclusions: The anti-albuminuric response to VDRA is independent of baseline 25(OH)D levels, suggesting that VDRA therapy should not be restricted to vitamin D-deficient patients.

Funding: Government Support - Non-U.S.

TH-PO516

Effect of Vitamin D Receptor Activation and Sodium Restriction on Calcification Propensity and Fibroblast Growth Factor 23: The Virtue-CKD Trial Maarten A. de Jong,[1] Charlotte A. Keyzer,[1] Fenna van Breda,[2] Marc G. Vervloet,[2] Gerjan Navis,[1] Stephan J.L. Bakker,[1] Harry Van Goor,[3] Andreas Pasch,[4] Martin H. De Borst.[1] *[1]Div of Nephrology, UMCG, Groningen, Netherlands; [2]Dept of Nephrology, VuMC, Amsterdam, Netherlands; [3]Dept of Pathology, UMCG, Groningen, Netherlands; [4]Div of Nephrology, Inselspital, Bern, Switzerland.*

Background: Vitamin D receptor activators (VDRA) reduce albuminuria but also increase FGF23 levels and vascular calcification. To address whether these effects are linked, we studied the effect of VDRA on FGF23 and calcification propensity in relation to its efficacy (i.e. albuminuria reduction).

Methods: This is a posthoc analysis of a double-blind, randomized, cross-over trial (NTR2898) in patients with stage 1-3 CKD (eGFR 67±22) and albuminuria >300 mg/d, treated with ramipril (10 mg/d) throughout plus four 8-wk study periods: VDRA (paricalcitol, 2 µg/day, PARI) or placebo (PLAC) combined with a regular (RS, 200 mmol/d Na^+) or low-sodium (LS, 50 mmol/d) diet. Patients ≥95% VDRA compliant were analyzed (N=34). C-terminal FGF23 was measured by ELISA, calcification propensity by calciprotein particle maturation time (T_{50}). Effects were assessed with linear mixed models and Pearson's r. Data is shown as geometric mean[95%CI].

Results: During RS, PARI didn't reduce albuminuria (1082[666;1756]mg/d) vs. PLAC (1177[715;1939]mg/d), but increased FGF23 (113[79;137] to 140[104;185]RU/mL, P=0.001) and reduced T_{50} (388[355;420] to 332[300;366]min, P<0.01). During LS, PARI reduced albuminuria (804[489;1321] to 690[417;1143]mg/d, P=0.04), while FGF23 levels increased from 111[96;128] to 141[121;165]RU/mL (P=0.001) and T_{50} remained similar (354[321;387] vs. 354[323;385]min). Changes in FGF23 and T_{50} were not associated with albuminuria reduction during RS (r=-0.11, P=0.5 and r=0.08, P=0.6, respectively) or LS (r=-0.08, P=0.6 and r=0.16, P=0.4).

Conclusions: VDRA treatment increased plasma FGF23 levels and calcification propensity (i.e. reduced T_{50}). Notably, the changes in FGF23 and T_{50} weren't associated with albuminuria reduction. This intra-individual discordance suggests distinct mechanisms for the beneficial (anti-albuminuric) and adverse (FGF23/T_{50}) effects of VDRA treatment, and suggests potential for personalized medicine.

Funding: Government Support - Non-U.S.

TH-PO517

FGF23 and Inflammatory Markers Blood Levels Decrease with Paricalcitol and Atorvastatin Combined Treatment in Hemodialysis Patients with Tunneled Central Vascular Catheters: The SENPARIC Study (NCT 1820767) Ricardo Mouzo,[1] Valter Ruggiero Lombardi,[2] Jose Carlos Diez Baylon,[3] Herless Rodrigo Avellaneda Campos,[1] Fernando Simal,[1] Jose Paniagua De la Riva,[1] Ana Tierra,[1] Jorge Estifan Kasabji,[4] Carmen Perez Nieto.[1] *[1]Nephrology, Hospital El Bierzo, Ponferrada, Leon, Spain; [2]Laboratory, CODEBI, A Coruña, Spain; [3]Hemodialysis Unit, PONFEDIAL, Ponferrada, Leon, Spain; [4]Nephrology, Hospital El Bierzo, Leon, Spain.*

Background: The aim of the current study was to evaluate the effect of different oral treatments, paricalcitol (P), paricalcitol plus atorvastatin (P+A), and atorvastatin (A) alone on FGF23 and pro-inflammatory cytokines/oxidative stress blood markers.

Methods: Thirty patients (age 71 ±16) in Hemodialysis (HD) treatment 3 times per week for 48 ± 64 months were randomized to a 12 weeks period study. Group 1 (n=10) was treated with P; Group 2 (n=11) was treated with P+A; Group 3 (n=9) received A alone. Blood samples were collected two weeks before treatment (T-2), at baseline (T0), 6 weeks (T6) and 12 weeks after treatment (T12) and 2 weeks post treatment (T14). FGF-23, COX-2, iNOS and PEG-2 serum levels were analyzed by ELISA. CD3, CD4, CD8, CD19, CD25, CD56, CD69 and CD95 lymphocytes markers and serum levels of IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-1β, TNF-α ,TNF-β and IFN-γ were analyzed by flow cytometry.

Results: Treatment with P+A significantly reduced FGF23 (T0 vs T12: p=0.044) and the expression of CD25, CD56, CD25/CD56 and CD69 compared with P and A alone. A diminution in IFN-γ, IL-1β, IL-2 and IL-5 was also noted, mainly in Groups 1 and 2, as well as in COX-2 p<0.012 (T0 vs T12).

Conclusions: It is well known that the administration of vitamin D analogues to HD patients is associated with improved survival despite an increase of FGF23 serum levels. This apparent paradox is not observed in our CT where the combined treatment with P+A to HD patients reduces FGF23 levels and elicits an early and significant decrease of inflammation and oxidative stress. These results could be of interest in the approach to atherosclerotic disease in HD patients.

Funding: Pharmaceutical Company Support - Abbvie

TH-PO518

Let-7 and microRNA-148 Regulate Parathyroid Hormone Levels in Secondary Hyperparathyroidism Iddo Z. Ben-Dov, Vitali Shilo, Irit Mor Yosef Levi, Gilad Wasserman, Tally Naveh-Many. *Nephrology, Hadassah Hebrew Univ Medical Center, Jerusalem, Israel.*

Background: Secondary hyperparathyroidism (SHP) commonly complicates chronic kidney disease (CKD) and associates with morbidity and mortality. MicroRNA (miRNA) are small RNAs that regulate gene expression. Parathyroid specific deletion of *Dicer* that mediates the final step of miRNA maturation showed that miRNA are essential for the increase in serum PTH during both acute and chronic hypocalcemia, uremia and the hyperplastic process in SHP.

Methods: We profiled miRNA in parathyroids from SHP models and CKD patients by miRNA deep-sequencing. We demonstrated the function of specific miRNA using antagonizing oligonucleotides *in vivo* in normal and CKD rats and *in vitro* in parathyroid organ cultures.

Results: miRNA deep-sequencing showed that human, rat and mouse parathyroids share similar profiles. Parathyroids from SHP and normal rats segregated based on their miRNA expression profiles, and a similar finding was observed in humans. We identified specific parathyroid miRNAs that were dysregulated in experimental SHP, including miR-29, miR-21, miR-148, miR-30 and miR-141 (up-regulated) and miR-10, miR-125 and miR-25 (down-regulated). Importantly, inhibition of the parathyroid abundant let-7 family increased PTH secretion in normal and CKD rats, as well as in parathyroid organ cultures. Conversely, inhibition of the up-regulated miR-148 family prevented the increase in serum PTH in CKD rats and decreased secreted PTH in parathyroid cultures.

Conclusions: The evolutionary conservation of abundant miRNA and their regulation in SHP indicates their importance for parathyroid function and the development of SHP. Specifically, let-7 and miR-148 antagonism modified PTH secretion *in vivo* and *in vitro*, implying roles for these miRNA in SHP. Our studies show that let-7 members restrict PTH secretion, while miR-148 members promote secretion. In CKD, the expression of parathyroid let-7 and the increase in miR-148 members would contribute to the development of SHP. Our findings suggest a role for miRNA in parathyroid physiology and disease. They may be utilized for therapeutic interventions aimed at altering PTH expression in diseases such as osteoporosis and SHP.

TH-PO519

The Down-Regulated Vitamin D Receptor Involves in the Parathyroid Glands Hyperplasia via Nuclear Factor-κB Pathway Activation Sen Kan, Qian Zhang, Minmin Zhang, Jing Chen. *Div of Nephrology, Huashan Hospital, Fudan Univ, Shanghai, China.*

Background: Vitamin D receptor (VDR) plays a key role in the parathyroid gland (PG) hyperplasia of secondary hyperparathyroidism (SHPT). However, the mechanism is still unclear. The study aimed to explore the role of nuclear factor-kappa B (NF-κB) pathway in parathyroid hyperplasia, and the correlation between VDR and NF-κB pathway in growth of parathyroid.

Methods: Parathyroid gland samples obtained from hemodialysis patients who accepted the parathyroidectomy surgery were divided into diffuse hyperplasia and nodular hyperplasia according to the H.E staining.Sham-operated rats were fed with the normal diet. 5/6-nephrectomized rats were fed with a high phosphate diet and treated with NF-κB inhibitor PDTC or calcitriol. Rats were sacrificed to collect the blood and parathyroid samples after 3 months. The expressions of PCNA, VDR and activation of NF-κB pathway in PGs were determined by immunohistochemistry and Western Blot.

Results: The activation of NF-κB pathway was significantly increased in nodular hyperplasia PGs than diffuse PGs in SHPT patients (P<0.05), the activated NF-κB p65 positive cell were (32.2±5.9)% and (59.5±5.9)% respectively. 5/6-nephrectomy rats fed with a high-phosphate diet had markedly higher serum PTH levels and larger PGs than sham-operated rats. The PCNA level and activation of NF-κB pathway in PGs were higher compared with the control rats (P<0.05), the VDR level was decreased significantly (P<0.05). NF-κB inhibitor and calcitriol attenuated the enlargement of PGs in uremic rats (P<0.05). Besides, the notably reduced serum PTH, down-regulated expression of PCNA and activation of NF-κB pathway were detected in the rats treated with NF-κB inhibitor or calcitriol compared with the 5/6-nephrectomy rats fed with a high-phosphate diet (P<0.05). The expression of VDR was markedly up-regulated by calcitriol (P<0.05).

Conclusions: Our study demonstrated that NF-κB pathway is involved in the growth of parathyroid gland. VDR deficiency might play an important role in the parathyroid hyperplasia through the activation of NF-κB pathway.

Funding: Government Support - Non-U.S.

TH-PO520

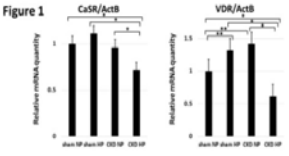
Hypermethylation of the CaSR and VDR Genes in the Parathyroid Glands in Chronic Kidney Disease Rats with High Phosphate Diet

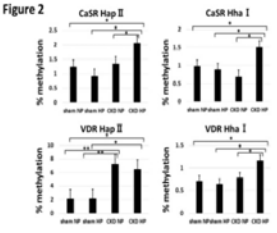
Taketo Uchiyama, Sahoko Kamejima, Ichiro Ohkido, Takashi Yokoo. *Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Minato-ku, Tokyo, Japan.*

Background: Chronic kidney disease (CKD) disrupts mineral homeostasis and its representative pathosis is defined as secondary hyperparathyroidism (SHPT). SHPT occurs during the early course of progressive renal insufficiency, and is associated with mortality and cardiovascular events. SHPT causes reduction of calcium-sensing receptor (CaSR) and vitamin D receptor (VDR) in the parathyroid glands during CKD. However, the precise mechanism of *CaSR* and *VDR* reduction is largely unknown.

Methods: CKD was induced through two-step 5/6 nephrectomy, then CKD rats and sham-operated rats were maintained for 8 weeks on diets containing 0.7% phosphorus (normal phosphate) or 1.2% phosphorus (high phosphate). In gene expression analysis taqman probes were used for quantitative real-time polymerase chain reaction. CaSR and VDR protein expressions were analyzed using immunohistochemistry. DNA methylation analysis was performed using a restriction digestion and quantitative PCR.

Results: CaSR and VDR mRNA were reduced only in CKD rats fed the high phosphorus diets (CKD HP), then CaSR and VDR immunohistochemical expressions were compatible with gene expression assay. SHPT was observed only in CKD HP rats. Furthermore CKD HP rats showed the hypermethylation in *CaSR* and *VDR* genes; however, the percentage methylation of both genes was low.





Conclusions: Although *CaSR* and *VDR* hypermethylation was demonstrated in PTGs of CKD HP rats, the extent of hypermethylation was insufficient to support the relevance between hypermethylation and down-regulation of gene expression because of the low percentage of methylation. Consequently, our data suggest that mechanisms, other than DNA hypermethylation, were responsible for the reduction in mRNA and protein levels of *CaSR* and *VDR* in PTGs of CKD HP rats.

TH-PO521

Intact Parathyroid Hormone Is Associated with Increased Risk of Death but Not Fragility Fracture in Patients with Chronic Kidney Disease

Alex R. Chang,[1] Amanda Young,[1] Ion D. Bucaloiu,[1] James E. Hartle,[1] Morgan Grams.[2] *[1]Geisinger Health System; [2]Johns Hopkins Univ.*

Background: Patients with chronic kidney disease (CKD) are at increased risk for secondary hyperparathyroidism and fragility fractures. Little is known about the relationship between intact parathyroid hormone (iPTH) and adverse outcomes in CKD patients.

Methods: We evaluated the association between iPTH with risk of incident fragility fracture (vertebral, hip, wrist, humerus) and death in 4737 patients in the Geisinger Health System who had estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^{2}and no history of end-stage renal disease. Analyses were adjusted for demographics, smoking status, eGFR, albuminuria, renal risk factors, and medications that affect bone.

Results: Median values (interquartile range) of eGFR and iPTH were 40.8 (30.0-50.2) ml/min/1.73m^2 and 59 (38-94) pg/ml, respectively. The prevalence of iPTH >= 130 pg/ml (twice the upper limit of normal range) was 4.3%, 7.8%, 28.8%, and 62.7% in patients with eGFR 45-59, 30-44, 15-29, and <15 ml/min/1.73m^2. Over a median of 5.6 (4.0-7.8) years of follow-up, 708 (15.0%) patients experienced an incident fragility fracture. Compared to iPTH in the normal range (15-65 pg/ml), elevated iPTH >= 130 pg/ml was not associated with increased risk of fragility fracture (aHR 1.10 (95% CI: 0.84-1.43; p=0.5), but was associated with a 35% increased risk of death (aHR 1.35, 95% CI: 1.15-1.58, p=<0.001). Low PTH <15 pg/ml was not significantly associated with incident fragility fracture (aHR 1.35, 95% CI: 0.90-2.02; p=0.1) or mortality (aHR 1.18, 95% CI: 0.86-1.62; p=0.3). Results for fragility fracture were similar in analyses accounting for competing risk of death.

Conclusions: Elevated iPTH levels are associated with increased risk of death but not fragility fracture in CKD patients. Additional strategies beyond controlling PTH levels are needed to improve bone health.

Table 1. Adjusted* Hazard Ratios of Fragility Fracture and Mortality by Intact PTH Category

Intact PTH Category	Fragility Fracture			Mortality		
	IR (per 1000 PY)	aHR (95% CI)	P Value	IR (per 1000 PY)	aHR (95% CI)	P Value
<15 pg/ml (n=124)	31.2	1.35 (0.90-2.02)	0.2	45.1	1.18 (0.86-1.62)	0.3
15-65 pg/ml (n=2502)	25.8	REF		36.0	REF	
65-130 pg/ml (n=1492)	24.9	0.98 (0.82-1.68)	0.8	55.3	1.11 (0.98-1.25)	0.1
≥ 130 pg/ml (n=619)	23.6	1.10 (0.84-1.43)	0.5	82.5	1.35 (1.15-1.58)	<0.001

Abbreviations: IR (incidence rate), PY (person-years), aHR (adjusted hazard ratio)
*Adjusted for age, sex, race, smoking status, eGFR, albuminuria, blood pressure, body mass index, cardiovascular disease, medications affecting the bone (corticosteroids, diuretics, anti-psychotics, estrogens, testosterone, calcium, vitamin D, and calcimimetics)

Funding: NIDDK Support

TH-PO522

Parathyroidectomy Effects on Bone Mineralization in Patients with Chronic Kidney Disease and Secondary Hyperparathyroidism

Geovanna Oliveira Pires,[1] André L. Teixeira,[1] Ivone Braga de Oliveira,[1] Melissa Fernanda Pinheiro Santos,[1] Luciene dos Reis,[1] Wagner Dominguez,[1] Aluizio B. Carvalho,[2] Rosa M.A. Moyses,[1,3] Vanda Jorgetti.[1] *[1]Nephrology Div, Univ of Sao Paulo, São Paulo, SP, Brazil; [2]Nephrology Div, Federal Univ of Sao Paulo, São Paulo, SP, Brazil; [3]Medicine Master Degree Program, Univ Nove de Julho (UNINOVE), São Paulo, SP, Brazil.*

Background: Secondary hyperparathyroidism (SHPT) is a complication of chronic kidney disease (CKD) which compromises skeletal integrity, since excessive parathyroid hormone (PTH) increases remodeling, especially resorption, and decreases bone mineral density, increasing the risk of fractures. Patients with SHPT undergoing parathyroidectomy (PTX) go from a very high PTH condition to another where hormone levels drop dramatically. The effects of PTX in bone tissue are poorly studied, especially in osteocyte-expressed proteins, such as fibroblast growth factor-23 (FGF23), dentin matrix protein 1 (DMP1), matrix extracellular phosphoglycoprotein (MEPE), sclerostin, receptor activator of nuclear factor-κB ligand (RANKL) and osteoprotegerin (OPG), which regulate remodeling and especially bone mineralization. Studies that evaluated bone biopsies (BB) after PTX showed low remodeling and impaired bone mineralization. The aim of this study is to characterize bone expression of FGF23, DMP1, MEPE, sclerostin, RANKL and OPG and analyze their correlations with histomorphometric analysis results of BBs of patients with SHPT pre and post PTX.

Methods: We studied 10 patients with SHPT undergoing pre bone biopsy and at 6 to 12 months after PTX. We assessed histomorphometry and osteocyte-expressed proteins by immunohistochemistry.

Results: After PTX, there was significant increase in sclerostin expression 3.91 ± 2.76 vs10.3 ± 1.34 % / p=0.013) and of OPG [0.88 (0.17-3.03) vs 1.91 (0.53-16.13) % / p=0.002]. Percentage change of MEPE was inversely correlated with the time interval for mineralization (MLT) (r= -0.62 / p=0.05) and directly with bone formation rate (BFR / BS) (r= 0.73 / p=0.02). After PTX, six patients showed worsen mineralization and significant increase in OPG expression [1.1 (0.8-3.0) vs 2.3 (1.2-10.7) % / p=0.03].

Conclusions: Significant changes in expression of bone proteins (sclerostin, OPG and MEPE) that can potentially compromise mineralization were observed after PTX.

TH-PO523

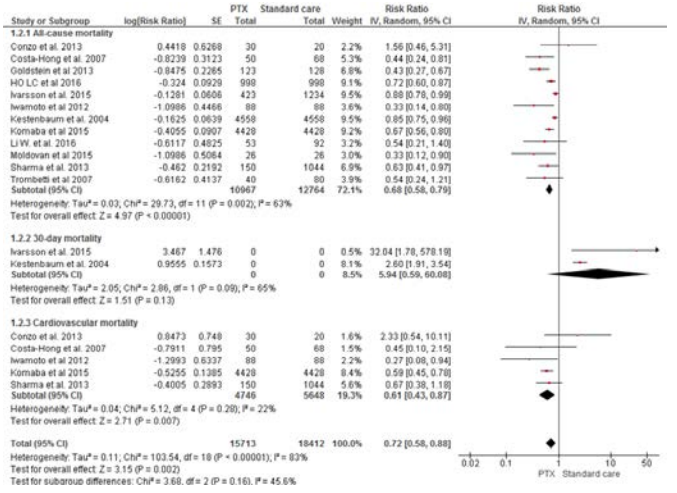
Surgical Parathyroidectomy Confers a Survival Advantage in Chronic Kidney Disease Patients - Results of the Largest Meta-Analysis

David Goldsmith,[1] Mugurel Apetrii,[2] Dimitrie Cristian Siriopol,[2] Ionut Nistor,[2] Dragos Scripcariu,[2] Adrian Covic.[2] *[1]Guy's and St. Thomas' Hospitals, London, United Kingdom; [2]Parhon Hospital, Iasi, Romania.*

Background: Secondary hyperparathyroidism (SHPT) leads to progressive enlargement of parathyroid glands, and increasingly "autonomous" parathormone (PTH) secretion. Vitamin-D therapy is the usual treatment, but if refractory, patients have traditionally then had surgical parathyroidectomy (SPTX). We aimed to assess the impact of PTX in SHPT patients.

Methods: A systematic review and meta-analysis was conducted on observational and randomized controlled trials (RCTs) in adults with CKD/ESRD that evaluated the role of PTX in determining clinical outcomes. We studied CKD/ESRD patients who had undergone parathyroid surgery. The surgery itself could be (1) total parathyroidectomy without auto transplantation, (2) total parathyroidectomy with auto transplantation, or, (3) subtotal parathyroidectomy.

Results: 12 cohort observational studies, comprising 23,731 participants were included in the final analysis. The follow-up period varied between 12 and 360 months. Compared with standard treatment, parathyroidectomy significantly decreased all-cause mortality (RR 0.68 [95% CI, 0.58 to 0.78], p<0.001) in ESRD patients with biochemical and / or clinical evidence of SHPT . PTX had also a positive effect on decreasing CV mortality (RR 0.61 [95% CI, 0.43 to 0.87], p<0.01) in 5 observational studies that included almost 10,000 patients.



Conclusions: This is the largest and most comprehensive meta-analysis of SPTX reported to date. We show that a there is clinically significant beneficial effect of PTX on all-cause and CV mortality in CKD patients with SHPT. The immediate need now is for a well-conducted,independent RCT comparing surgical PTX with cinacalcet therapy examining mortality, major morbidity, to mental and physical health, quality of life, and pharmaco-economics.

TH-PO524

Downregulation of ABCG2, a Urate Exporter, by Parathyroid Hormone Enhances Urate Accumulation in Secondary Hyperparathyroidism Hiroshi Watanabe,[1] Ryusei Sugimoto,[1] Motoko Tanaka,[2] Hirotaka Komaba,[3] Masafumi Fukagawa,[3] Toru Maruyama.[1] *[1]Dept of Biopharmaceutics, Graduate School of Pharmaceutical Sciences, Kumamoto Univ, Kumamoto, Japan; [2]Dept of Nephrology, Akebono Clinic, Kumamoto, Japan; [3]Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Japan.*

Background: Hyperuricemia occurs with increasing frequency among patients with hyperparathyroidism. However, the molecular mechanism by which serum parathyroid hormone (PTH) regulates serum urate levels remains unknown.

Methods: Secondary hyperparathyroidism (SHPT) model rats were created by feeding a high phosphorus diet (Ca 0.6%, P 1.2%) to the 5/6 renal nephrectomy rats. In vitro experiments were performed to investigate the effect of PTH on ABCG2 expression in Caco-2 cells. A total of 17 patients in stable medical condition with SHPT were enrolled in this study.

Results: We show that, in rats with SHPT, serum urate levels are increased and urate excretion in the intestine and kidney is decreased, presumably due to the downreguration of the intestinal and renal membrane expression of a urate exporter ABCG2. These effects were prevented by the administration of the calcimimetic PTH suppressor, cinacalcet, indicating that PTH downregulates ABCG2 expression. In Caco-2 cells, the plasma membrane expression of ABCG2 was directly downregulated by PTH (1-34) and its mRNA level remained unchanged, but an inactive PTH derivative (13-34) had no effect, suggesting a posttranscriptional regulatory system acting through the PTH receptor. Additional clinical studies showed, as observed in an animal study, that treatment with cinacalcet resulted in significant reductions in serum urate levels together with decreases in PTH levels in SHPT patients who were undergoing dialysis.

Conclusions: PTH downregulates ABCG2 expression on plasma membrane, and thereby suppresses intestinal and renal urate excretion, and that the effects of PTH can be prevented by a cinacalcet treatment.

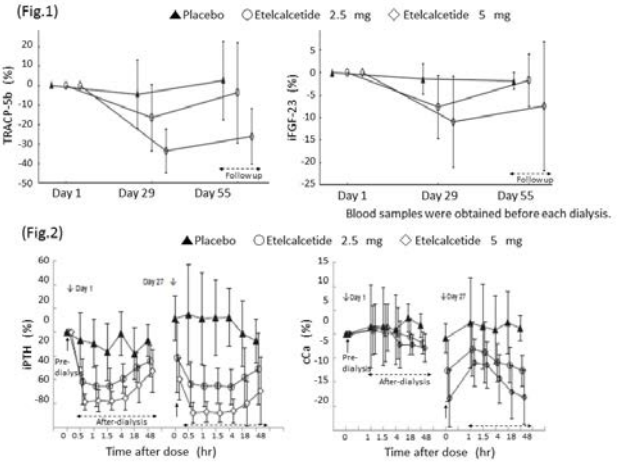
TH-PO525

Etelcalcetide (ONO-5163/AMG 416) Influences Bone Metabolism and Exhibits Stable Pharmacodynamics Keitaro Yokoyama,[1] Masafumi Fukagawa,[2] Takashi Shigematsu,[3] Takashi Akiba,[4] Akifumi Fujii,[5] Motoi Odani,[5] Tadao Akizawa.[6] *[1]The Jikei Univ; [2]Tokai Univ; [3]Wakayama Medical Univ; [4]Sekikawa Hospital; [5]Ono Pharmaceutical Co., Ltd.; [6]Showa Univ, Japan.*

Background: Etelcalcetide, a novel intravenous calcimimetic, lowers PTH and is expected to affect bone metabolism and lower Ca. It is important to clarify the pharmacodynamic parameters for a multiple-dose of etelcalcetide to appropriately assess its efficacy and safety. This study was conducted to investigate the time-course changes and daily fluctuations in pharmacodynamic parameters after multiple-dose administration of etelcalcetide three times/week for 4 weeks in Japanese patients with secondary hyperparathyroidism on hemodialysis.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. In two cohorts (2.5 or 5 mg), 11 patients each were randomized to etelcalcetide or placebo at an 8:3 ratio.

Results: Etelcalcetide dose-dependently decreased the levels of TRACP-5b and intact FGF-23 after multiple dosing (Fig 1). However, the daily fluctuations of intact PTH and corrected Ca after the multiple dosing did not vary largely compared with the levels after the initial dose (Fig 2).



Conclusions: If unstable fluctuations of pharmacodynamic parameters are observed, the timing for assessment of efficacy and safety needs to be considered. Although etelcalcetide influenced bone metabolism, marked daily fluctuations of pharmacodynamic parameters did not occur. Therefore, it may not be necessary to consider the timing for its assessment.

TH-PO526

Etelcalcetide (ONO-5163, AMG 416), an Intravenously Available Agonist of the Calcium-Sensing Receptor, Effectively Controls Plasma Parathyroid Hormone Levels in a Rat Chronic Renal Insufficient Model with Secondary Hyperparathyroidism Masakazu Konno, Kazutsune Harada. *ONO Pharmaceutical Co., Ltd., Osaka, Japan.*

Background: Secondary hyperparathyroidism (SHPT) is a complication of chronic kidney disease and end stage renal disease that results in defective Ca and P homeostasis, thereby persistently elevated levels of parathyroid hormone (PTH) in blood caused by the ongoing release of excess amounts of PTH from enlarged parathyroid glands. Currently, we have developed the first intravenously available CaSR agonist etelcalcetide (ONO-5163 or AMG 416). The objectives of these studies were to elucidate *in vitro* pharmacological profile and *in vivo* PTH lowering activity of etelcalcetide in rat 5/6 nephrectomized (5/6 Nx) model of chronic renal insufficiency with SHPT.

Methods: To determine *in vitro* activity, cells stably expressing human CaSR and parent cells were treated with etelcalcetide, and the intracellular Ca concentration was measured using Fura-2-AM dye. Also, the primary cultured rat parathyroid cells were treated for 24 hours with etelcalcetide, and the PTH concentrations in culture supernatant were measured.To determine *in vivo* activity, nine-week-old male 5/6 Nx rats were fed a special diet (1.0% phosphate) to induce SHPT. Following 3 weeks on the special diet, 5/6 Nx rats were intravenously single injected with etelcalcetide (0.3, 1, 3 mg/kg). Blood were sampled predose and at 1, 6, 24, 48 hours after dosing and the plasma PTH and the serum Ca were measured.

Results: *In vitro*, etelcalcetide increased the intracellular Ca concentration in cells stably expressing human CaSR with EC_{50} of 0.53 µmol/L. No signaling activity was observed in parent cells. Etelcalcetide also suppressed PTH secretion from the primary cultured rat parathyroid cells with EC_{50} of 0.36 µmol/L. Furthermore, *in vivo*, etelcalcetide dose-dependently suppressed circulating levels of plasma PTH and subsequently serum Ca in rat 5/6 Nx with SHPT. Reductions of PTH and Ca were reversible.

Conclusions: We have identified etelcalcetide as a novel calcimimetics with a potent PTH lowering efficacy via CaSR-agonistic activity. Etelcalcetide will provide a new therapeutic option for the SHPT patients that may improve compliance and pill burden.

TH-PO527

Interim Analysis of a Multicenter Single-Arm Extension Study to Describe the Long-Term Safety of Etelcalcetide (AMG 416) in the Treatment of Secondary Hyperparathyroidism in Subjects with Chronic Kidney Disease on Hemodialysis Kevin J. Martin,[1] Geoffrey A. Block,[2] Sunfa Cheng,[3] Botond Csiky,[4] Hongjie Deng,[3] K. Adu Ntoso,[5] Rainer Oberbauer,[6] Mariano Rodriguez,[7] Dennis L. Ross,[8] Glenn Matthew Chertow.[9] *[1]St. Louis Univ SOM, St. Louis, MO; [2]Denver Neph, Denver, CO; [3]Amgen; [4]FMC Hungary, Budapest, Hungary; [5]Penn Neph Assoc, Philadelphia, PA; [6]Med Univ of Vienna, Vienna, Austria; [7]Univ of Cordoba, Cordoba, Spain; [8]KS Neph Physicians, Wichita, KS; [9]Stanford SOM, Palo Alto, CA.*

Background: Etelcalcetide is a novel IV calcimimetic shown to decrease parathyroid hormone (PTH) in 3 26-week (wk) phase 3 (P3) trials, with sustained efficacy in a 52-wk open label extension (OLE) trial. This follow-on OLE further characterizes the long-term safety of etelcalcetide.

Methods: Subjects (subj) enrolled from previous OLEs stayed on the same dose; subj from the P3 trial of etelcalcetide vs cinacalcet had a 4 wk washout. Etelcalcetide was titrated by 2.5mg or 5mg to a max of 15mg, at a frequency based on the site's standard of care to achieve PTH ≥2x to ≤9x the upper limit of normal (ULN). Primary endpoint was subj incidence of adverse events (AEs). Secondary endpoints were (1) PTH ≥2x to ≤9x the ULN and (2) phosphorus (P) ≤ULN at months (M) 6, 12, 18.

Results: 902 subj enrolled; mean time on drug was 391 days. Mean dose/session at M6, M12, M18 was 5.1, 5.3, and 5.0 mg. 82% and 41% had AEs and serious AEs (SAEs), respectively. 4% had AEs that led to stopping drug. Most common AE (>10%) was blood Ca decreased (decr) (25%); most common SAEs (≥2%) were pneumonia (4%) and sepsis (2%). Most common AEs leading to stopping drug were blood Ca decr, nausea, vomiting-4 subj each. The secondary endpoints and additional analyses results are:

	M6	M12	M18
PTH≥2x and ≤9x ULN	515/767 (67%)	434/591 (72%)	93/133 (70%)
P ≤ULN	288/739 (39%)	197/533 (37%)	43/122 (35%)
PTH ≥2x and ≤9x ULN AND P ≥3.5 and ≤5.5 mg/dL	211/716 (30%)	194/520 (37%)	34/110 (31%)
PTH ≥2x and ≤9x ULN, P ≥3.5 and ≤5.5 mg/dL, normal corrected Ca	151/701 (22%)	154/516 (30%)	26/109 (24%)

Conclusions: (1) No new safety findings with additional long-term treatment; (2) using real-world PTH targets achieved sustained reductions in PTH and P.

Funding: Pharmaceutical Company Support - Amgen

TH-PO528

The Evaluation of the Safety and Efficacy with Etelcalceide (ONO-5163/AMG 416: A Novel Intravenous Calcimimetic) on Secondary Hyperparathyroidism (SHPT) for 52 Weeks in Japanese Hemodialysis Patients Takashi Shigematsu,[1] Masafumi Fukagawa,[2] Keitaro Yokoyama,[3] Takashi Akiba,[4] Akifumi Fujii,[5] Hiroe Tani,[5] Motoi Odani,[6] Tadao Akizawa.[7] *[1]Div of Nephrology, Dept of Internal Medicine, Wakayama Medical Univ, Wakayama, Japan; [2]Dept of Nephrology, Endocrinology and Metabolism, Tokai Univ, School of Medicine, Isehara, Japan; [3]Dept of Nephrology and Hypertension, Jikei Univ, School of Medicine, Tokyo, Japan; [4]Dept of Nephrology, Sekikawa-kai, Sekikawa Hospital, Tokyo, Japan; [5]Clinical Development, Ono Pharmaceutical Co., Ltd., Osaka, Japan; [6]Data Science, Ono Pharmaceutical Co., Ltd., Osaka, Japan; [7]Dept of Nephrology, Showa Univ, School of Medicine, Tokyo, Japan.*

Background: Etelcalcetide had decreased serum intact PTH (iPTH) in Japanese HD patients with SHPT for a 12-week. We designed the 52-week, phase III, multicenter, open-label, single-arm study to evaluate the long-term safety and efficacy of etelcalcetide.

Methods: We prescribed etelcalcetide intravenously at 3 times/week for 52 weeks on all HD subjects with the both of serum iPTH >240 pg/mL and corrected calcium (cCa) level ≥8.4 mg/dL. The initial dose was 5 mg, followed by individual adjustment to dose of 2.5–15 mg to achieve Japanese serum iPTH target of 60–240 pg/mL.

Results: 191 subjects were enrolled, of whom 83.8% completed the 52-week treatment. The 96.8% and 14.7% of subjects experienced AEs and serious AEs, respectively. The 7.4% had AEs that led to stopping etelcalcetide. Vomiting, nausea, and symptomatic hypocalcaemia were observed in 9.5%, 4.7%, and 1.1%, respectively. The serum iPTH were achieved as 60–240 pg/mL in 87.5%. The 90.6% subjects can achieve the 30% or more reductions in iPTH. The serum cCa, phosphorus, and intact fibroblast growth factor-23 were also decreased rapidly and subsequently maintained.

Conclusions: Etelcalcetide is an effective intravenous therapy on SHPT with no new safety findings for the long-term 52-week treatment compared to the results in the previous shorter study.

Funding: Pharmaceutical Company Support - Ono Pharmaceutical Co., Ltd.

TH-PO529

Treatment with Cinacalcet Reduces Oxidative Stress in Hemodialysis Patients with Secondary Hyperparathyroidism Marcin Adamczak,[1] Piotr Kuczera,[1] Grzegorz Machnik,[2] Boguslaw Okopien,[2] Andrzej Wiecek.[1] *[1]Dept of Nephrology, Transplantation and Internal Medicine, Medical Univ of Silesia, Katowice, Poland; [2]Dept of Internal Medicine and Clinical Pharmacology, Medical Univ of Silesia, Katowice, Poland.*

Background: It is known well that oxidative stress is one of the factors contributing to the increased mortality in patients with chronic kidney disease (CKD). Cinacalcet is used in the treatment of secondary hyperparathyroidism (sHPT) in patients with CKD. The purpose of this prospective clinical study was to assess the influence of treatment with cinacalcet on the oxidative stress in patients on hemodialysis with sHPT.

Methods: In 58 hemodialysed patients with sHPT plasma Advanced Oxygenation Protein Products (AOPP) and total antioxidant capacity – ImAnOx (TAS/TAC) and serum PTH, calcium and phosphate concentrations were assessed before the first dose of cinacalcet and after 6 months of treatment. A log transformation was used to normalize the distribution of PTH, AOPP and ImAnOx concentrations, thus these results are presented as geometric means with 95% CI. Paired t-test was then used to assess the variables change over time. Correlation coefficients were calculated using Spearman's rank correlation.

Results: Serum PTH concentration decreased significantly from 895 (748-1070) pg/ml to 384 (289-510) pg/ml and plasma AOPP concentration decreased significantly from 152 (126-185) µmol/l to 49 (43-57) µmol/l after 6 months of treatment; p<0.0001. Plasma antioxidant capacity (ImAnOx) significantly increased from 260 (251-270) µmol/l to 272 (264-280) µmol/l; p=0.047. After 6 months of treatment a significant, positive correlation as found between ImAnOx and the dose of cinacalcet (r=0,30; p=0.02). Also the change of plasma ImAnOx during treatment with cinacalcet significantly correlated with the dose of cinacalcet r=0.35; p=0.01. No significant correlations were found between plasma AOPP concentration or ImAnOx and PTH, nor their changes in time.

Conclusions: 1. 6-month treatment with cinacalcet reduces oxidative stress in maintenance hemodialysis patients with sHPT 2. This beneficial effect seems to be related rather to the direct action of cinacalcet than to the decrease of serum PTH concentration.

Funding: Government Support - Non-U.S.

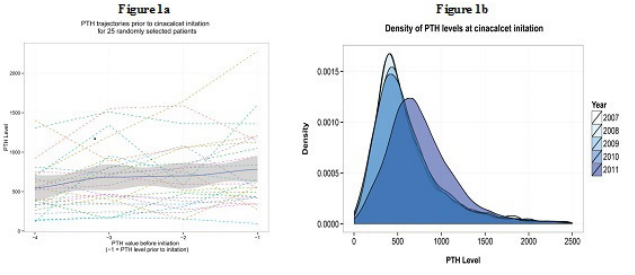
TH-PO530

Cinacalcet Initiation at Varying Parathyroid Hormone (PTH) Levels Paul Dluzniewski,[1] M. Alan Brookhart,[2] Diane Reams,[2] Kerry Cooper,[1] Abhijit V. Kshirsagar,[2] Brian D. Bradbury.[1] *[1]Amgen Inc., Thousand Oaks, CA; [2]Univ of North Carolina, Chapel Hill, NC.*

Background: Despite evidence of the effectiveness of cinacalcet in managing secondary hyperparathyroidism (SHPT) related biochemistries, PTH levels are increasing over time, possibly due to delays in treatment initiation. We sought to describe real-world PTH levels and trajectories leading up to cinacalcet initiation.

Methods: Using patient-level data from a large dialysis provider merged with data from the USRDS, we identified adult new users of cinacalcet (2007-2011) from Part D prescription claims. We estimated the mean ± standard deviation of PTH levels (same assay throughout follow-up period) and the distribution across PTH categories: 150-300, 301-600, 601-900, and > 900 pg/mL. We also assessed PTH trajectories in the 12 months prior to cinacalcet initiation.

Results: We identified 21,786 patients who initiated cinacalcet during our study period. Overall, PTH levels increased steadily in the 12 months leading up to initiation of cinacalcet. We observed varying patterns of increasing versus decreasing PTH levels prior to the initiation of cinacalcet (Figure 1a). We also observed substantial variability in PTH levels at the time of cinacalcet initiation (Figure 1b).



Conclusions: In clinical practice, the PTH level motivating initiation of cinacalcet therapy is frequently higher than recommended targets, including levels above 1000 pg/mL. Future research is needed to understand the impact of delaying calcimimetic treatment.

Funding: Pharmaceutical Company Support - Amgen Inc.

TH-PO531

Disparate Actions of Paricalcitol and Cinacalcet on Parathyroid Oxyphil Cell Content in Patients with Chronic Kidney Disease Cynthia S. Ritter, Brent W. Miller, Alex J. Brown, Eduardo Slatopolsky. *Div of Nephrology, Washington Univ School of Medicine, St. Louis, MO.*

Background: Parathyroid (PT) oxyphil cell content increases in patients with uremia. This increase is even more enhanced in patients receiving treatment with the calcimimetic cinacalcet and/or calcitriol for hyperparathyroidism (HPT). Previously, we reported that oxyphil cells have significantly more calcium-sensing receptor (CaSR) than chief cells, supporting the hypothesis that the CaSR and, likewise, calcimimetics are involved in the transdifferentiation of a chief-to-oxyphil cell type. Here, we compared the effect of the vitamin D analog paricalcitol (which is less calcemic than calcitriol) and cinacalcet on the oxyphil content in uremic patients to investigate further the genesis of oxyphil cells.

Methods: We analyzed archived H&E-stained sections of PT tissue from 28 CKD patients who underwent parathyroidectomy (PTX) for secondary HPT. Patients received the following treatment for HPT prior to PTX: no treatment (n=7), cinacalcet (n=8), paricalcitol (n=8), and cinacalcet+paricalcitol (n=5). Tissue from 4 "normal" subjects was examined. Each tissue section was digitally captured in its entirety using serial images (200x) and analyzed using Image-Pro Plus software. Oxyphilic areas were circumscribed, the area calculated and reported as % of the total area of tissue for each patient.

Results: The % PT oxyphil content was as follows (avg±sem): no treatment, 5.3 ± 1.25%; cinacalcet, 27.9 ± 4.79% (p≤0.001 vs no treatment); paricalcitol, 6.9 ± 1.81% (p≤0.001 vs cinacalcet); cinacalcet+paricalcitol, 12.7 ± 7.10%; normal subjects, 1.03 ± 1.03%.

Conclusions: Unlike cinacalcet, treatment of patients with paricalcitol does not stimulate genesis of oxyphil cells. Because the function of the oxyphil cell is not known, the question remains as to whether the genesis of oxyphil cells is favorable or unfavorable to the patient. Nevertheless, the finding that two conventional treatments for HPT have disparate effects on parathyroid composition, and perhaps function, is provocative and may be useful when evaluating future drugs for HPT.

Funding: Pharmaceutical Company Support - Abbott Laboratories

TH-PO532

Calcium Sensing Receptor Genotype and Response to Cinacalcet Sharon M. Moe,[1] Brian S. Decker,[1] Leah Wetherill,[1] Dongibng Lai,[1] Safa Abdalla,[2] Jin Long,[2] Matteo Vatta,[1] Tatiana Foroud,[1] Glenn Matthew Chertow.[2] [1]*Indiana Univ, Indpls, IN;* [2]*Stanford, Stanford, CA.*

Background: The calcimimetic cinacalcet is a calcium sensing receptor (CASR) allosteric activator, and thus polymorphisms in *CASR* may alter the drugs therapeutic response. Genetic mutations in *CASR* are known to lead to diseases of mineral metabolism. We tested the hypothesis that single nucleotide polymorphisms (SNPs) in *CASR* alters the biochemical response to cinacalcet.

Methods: We analyzed DNA samples in the EVOLVE trial (EValuation Of Cinacalcet Hydrochloride (HCl) Therapy to Lower CardioVascular Events (EVOLVE), a randomized trial comparing cinacalcet to placebo on a background of usual care (calcitriol or analogues and binders). 49% of subjects in EVOLVE consented to DNA collection, and 1,852 samples were of initial adequate quality to be genotyped for 18 known *CASR* polymorphisms. All SNPs were in Hardy-Weinberg equilibrium in the European American (EA, N=1,086) and African American (AA, N=413) samples; these groups were assessed separately. The association of SNPs with baseline and change from 0 to 20 weeks in calcium, phosphorus, PTH and FGF23 was determined using PLINK.

Results: There was modest association of baseline PTH and bone alkaline phosphatase levels with *CASR* SNPs in the EA population (all $p<0.04$), but not in the AA population. In contrast, there was a modest association of baseline calcium, and FGF23 levels with *CASR* SNPs (all $p<0.03$) in the AA, but not in the EA, sample. The only *CASR* SNP that showed association with percent reduction in PTH after adjustment for significant covariates was rs1393199 in the EA sample ($p = 0.042$). Among placebo-treated patients, those with genotype CC for rs1393199 had higher percent change in PTH relative to individuals with AA genotype. Cinacalcet-treated patients had approximately equal percent change in PTH, irrespective of genotype.

Conclusions: SNPs in *CASR* are only modestly associated with baseline CKD-MBD laboratory tests with different clinical phenotypes in EA and AA groups. Only one SNP was associated with change in PTH at 20 weeks in the EA population. This association was not seen in patients treated with cinacalcet.

Funding: NIDDK Support, Pharmaceutical Company Support - Amgen

TH-PO533

Oral Calcitriol and Outcomes in Hemodialysis Patients Lin Ma,[1] Ravi I. Thadhani,[2] Norma J. Ofsthun,[1] Amanda Stennett,[1] Jeffrey L. Hymes,[1] Franklin W. Maddux.[1] [1]*Fresenius Medical Care North America, Waltham, MA;* [2]*Massachusetts General Hospital, Boston, MA.*

Background: A large clinical pilot began at Fresenius Medical Care North America (FMCNA) in December of 2013 to examine the feasibility of administering oral calcitriol (OC) rather than intravenous Vitamin D (IVD) for in-center hemodialysis (IHD) patients. We conducted a matched case-control study to compare the survival and hospitalization risks associated with OC and IVD treatments.

Methods: 6,613 cases (OC) and 13,226 matched controls (IVD) were selected from IHD patients who started OC or received only IVD between December 1, 2013 and June 30, 2014. Cases and controls were 1:2 matched on propensity score of index date, age, sex, white (Y/N), hispanic (Y/N), incident patient (Y/N), HD catheter (Y/N), diabetes (Y/N), the most recent albumin at baseline. The index date was set to the date of starting OC or a random date within the study period for those patients receiving IVD. Kaplan-Meier and multivariable Cox proportional hazards models were used to examine all-cause mortality and hospitalization risks in the first year.

Results: For cases, the mean age was 61.6 years; 57.1% were male; 42.5% were white; 38.4% were black; 19.1% were of other racial ancestry; 10.9% were incident patients; 25.6% had an HD catheter; 64.4% were diabetic. Cases and matched controls were not significantly different on these matching factors. Compared with IVD, crude mortality rate for OC was 23.9% lower (12.8% vs. 16.9%) and hospitalization risk was 5.2% lower (54.4% vs. 57.4%) at 1 year. Hazard ratios (HRs) of 1-year death: unadjusted was 0.73 (95%CI: 0.68, 0.79); case-mix adjusted was 0.73 (95%CI: 0.67, 0.79); case-mix and lab adjusted was 0.71 (95%CI: 0.66, 0.77). HRs of hospitalization: unadjusted was 0.90 (95%CI: 0.87, 0.94); case-mix adjusted was 0.92 (95%CI: 0.89, 0.96); case-mix and lab adjusted was 0.91 (95%CI: 0.87, 0.95), all $p<0.0001$. The mean serum calcium and median iPTH were in the normal range for 12 months before and after the index date.

Conclusions: Hospitalization and mortality outcomes were not worse in the oral calcitriol group at 1 year, and may have been slightly better. Follow-up laboratory results were comparable and remained within the KDIGO guidelines.

TH-PO534

IL-6 Acts on Bone to Increase FGF23 Expression in Acute and Chronic Kidney Failure and In Vitro Ronen Levi,[1] Karina Durlacher,[1] Alia Hassan,[1] Jonathan H. Axelrod,[2] Justin Silver,[1] Tally Naveh-Many.[1] [1]*Nephrology, Hadassah Hebrew Univ Medical Center, Jerusalem, Israel;* [2]*Gene Therapy, Hadassah Hebrew Univ Medical Center, Jerusalem, Israel.*

Background: Acute kidney injury (AKI) is a common complication in hospitalized patients. The development and pathogenesis of the high serum FGF23 levels in AKI patients and in experimental models is unclear. We show a central role of cytokines and specifically IL-6 in the high levels of FGF23 in acute and chronic kidney failure.

Methods: We induced AKI in mice by a single ip injection of folic acid. Dexamethasone (DEX) was injected 1 h prior to folic acid. Chronic uremia was induced in control and *IL-6* knock-out mice by an adenine high phosphorus diet given for 3 w. FGF23 mRNA levels were analyzed by qRT-PCR in calvarial tissue, UMR106 cells and neonatal calvarial organ cultures.

Results: In mice with folic acid induced AKI, serum FGF23 levels increased 5-fold at 6 h. Serum levels of several cytokines were increased at 3 h. Serum IL-6 levels rose from 64 ± 15 to 8608 ± 2250 pg/ml, $p= 0.01$. DEX, that decreased serum IL-6, prevented the increase in serum FGF23 at 6 h after folic acid. Calvarial FGF23 mRNA levels increased 11-fold in mice treated with folic acid compared to controls, but only 4-fold in mice treated with DEX before AKI induction. IL-6 receptor/IL-6 fusion protein (Hyper-IL-6) increased FGF23 mRNA levels in calvarial cultures (11 -fold at 6 h) and in osteoblast like UMR106 cells, demonstrating a direct effect of IL-6 to increase FGF23 expression. Uremic *IL-6* knock-out mice had an impaired increase in serum FGF23 and calvarial FGF23 mRNA levels in adenine high phosphorus induced chronic kidney failure, compared to the marked increases in uremic wild type mice, indicating that IL-6 is also necessary for the increased FGF23 of prolonged uremia.

Conclusions: Serum IL-6 levels increase in folic acid induced AKI and this precedes the increase in FGF23. DEX prevents the increase in FGF23 expression in AKI. Hyper-IL-6 acts directly on bone cells to increase FGF23. IL-6 is essential for the increased FGF23 serum and mRNA levels in chronic kidney failure. Therefore, IL-6 is an important mediator of the high levels of FGF23 in both acute and chronic uremia.

TH-PO535

WNK Pathway Regulates Osteoblastic FGF23 Secretion Olena Andrukhova,[1] Sibel Ada,[1] Yeliz Toluay,[1] Dario Alessi,[2] Reinhold Erben.[1] [1]*Dept of Biomedical Sciences, Univ of Veterinary Medicine Vienna, Vienna, Austria;* [2]*MRC Protein Phosphorylation & Ubiquitylation Unit, Univ of Dundee, Dundee, United Kingdom.*

Background: With-no-lysine kinases (WNK) are key regulators of intracellular trafficking of ion transporters such as the Na-Cl cotransporter (NCC) in the kidney. Chronic activation of the WNK signaling pathway by activation of the renin–angiotensin–aldosterone system (RAAS) or by genetic defects leads to increased renal sodium reabsorption, and hypertension. We previously reported that FGF23 signaling activates WNK4 and that FGF23 and aldosterone signaling interact in the kidney.

Methods: To better understand the mechanisms underlying this crosstalk,we used kelch-like 3 (KLHL3R528H/+) knock-in Mutant mice in which lack of the KLHL3-mediated degradation of WNKs results in a constantly activated WNK signaling pathway. In patients, this loss-of-function mutation in the RING ligase family member KLHL3 leads to pseudohypoaldosteronism type II (PHAII).

Results: As expected, KLHL3R528H/+ mutants exhibited a PHAII-like phenotype with hyperkalemia, hypernatremia and increased phosphorylation of NCC in the kidney. Surprisingly, KLHL3R528H/+ mutants also showed increased serum levels of Fgf23 and increased abundance of total and phosphorylated WNK1 and NCC protein in bone. Isolated primary osteoblasts from KLHL3R528H/+ mutants secreted increased amounts of Fgf23 in the medium as compared to wild-type (WT) cells, indicating that activation of WNK signaling in osteoblasts results in a cell autonomous increase in Fgf23 secretion. Treatment of mutant osteoblasts with the WNK pathway inhibitor closantel (0.3 μM) normalized the enhanced secretion and mRNA expression of Fgf23. To confirm the involvement of WNK in the physiological regulation of Fgf23 secretion, we treated WT osteoblasts with aldosterone (10 ng/ml) alone or in combination with closantel. Aldosterone increased WNK phosphorylation in WT osteoblasts, demonstrating that aldosterone activates WNK signaling in osteoblasts. However, the aldosterone-induced increase in Fgf23 mRNA and protein expression was abrogated by co-treatment with closantel.

Conclusions: Taken together, we identified WNK signaling as a novel regulator of Fgf23 secretion in osteoblasts.

TH-PO536

Klotho Does Not Have FGF23 Independent Functions in Mineral Homeostasis Olena Andrukhova, Jessica Bayer, Ute Zeitz, Reinhold Erben. *Dept of Biomedical Sciences, Univ of Veterinary Medicine Vienna, Vienna, Austria.*

Background: Fibroblast growth factor-23 (FGF23) is a bone-derived hormone regulating vitamin D production and mineral homeostasis by signaling through a FGF receptor/αKlotho (Klotho) complex. Whether Klotho has FGF23-independent effects on mineral homeostasis is a controversial issue.

Methods: Here, we aimed to shed more light on this controversy by comparing male and female triple knockout mice with simultaneous deficiency in *Fgf23* and *Klotho* and a nonfunctioning vitamin D receptor (VDR) (*Fgf23*/*Klotho*/VDR) with double (*Fgf23*/VDR and *Klotho*/VDR) and single *Fgf23*, *Klotho* and VDR mutants. Ablation of vitamin D signaling is known to rescue the severe phenotype of *Fgf23*and *Klotho* single mutants. To prevent hypocalcemia in VDR mutants, all mice were kept on a rescue diet enriched with calcium, phosphate and lactose.

Results: As expected, 4-wk-old *Fgf23* and *Klotho* knockout mice were hypercalcemic and hyperphosphatemic, whereas VDR, *Fgf23*/VDR and *Klotho*/VDR mice on rescue diet were normocalcemic and normophosphatemic. Mineral homeostasis did not differ between 4-wk-old triple *Fgf23*/*Klotho*/VDR and double *Fgf23*/VDR or *Klotho*/VDR knockout mice. Three-mo-old male and female *Fgf23*/VDR and *Klotho*/VDR compound mutants were characterized by hyperphosphatemia, hypocalcemia, increased serum PTH as well as renal Ca and sodium (Na) wasting. Notably, 3-mo-old *Fgf23*/*Klotho*/VDR triple knockouts were indistinguishable from double *Fgf23*/VDR and *Klotho*/VDR compound mutants in terms of body weight, serum Ca, serum Pi, serum Na, serum PTH as well as urinary Ca and Na excretion. Protein expression analysis revealed increased membrane abundance of

the Na-P-cotransporter NaPi-2a, and decreased expression of the Na- and Ca-transporting molecules NCC and TRPV5 in kidneys of *Fgf23/Klotho*/VDR, *Fgf23*/VDR, and *Klotho*/VDR mice, relative to WT and VDR mice, but no differences between triple and double knockouts. Similarly, bone mineral density remained unchanged in 4-wk-old and 3-mo-old *Fgf23/Klotho*/VDR mice compared with *Fgf23*/VDR and *Klotho*/VDR mice.

Conclusions: In conclusion, our data suggest that the main physiological function of Klotho for mineral homeostasis *in vivo* is its role as co-receptor for Fgf23 signaling.

TH-PO537

Excessive FGF23 Drives Progression of Chronic Kidney Disease in Mice via Partially Klotho-Independent Activation of WNK Signaling Olena Andrukhova,[1] Svetlana Slavic,[1] Jessica Bayer,[1] Reinhold Erben.[1] *[1]Dept of Biomedical Sciences, Univ of Veterinary Medicine Vienna, Vienna, Austria; [2]MRC Protein Phosphorylation & Ubiquitylation Unit, Univ of Dundee, Dundee, United Kingdom.*

Background: It is currently unclear whether elevated circulating fibroblast growth factor-23 (FGF23) causes maladaptive pathological effects in chronic kidney disease (CKD). Here, we analyzed the role of Fgf23 and its co-receptor Klotho in the pathogenesis of CKD in mice by a dual approach, using genetic loss-of-function together with pharmacological inhibition models.

Methods: CKD was induced by 5/6 nephrectomy in 3-month-old wild-type (WT) mice, vitamin D receptor (VDR) mutant mice, *Fgf23*$^{-/-}$/VDR$^{\Delta/\Delta}$ (Fgf23/VDR), and *Klotho*$^{-/-}$/VDR$^{\Delta/\Delta}$ (Klotho/VDR) compound mutant mice. All mice were kept lifelong on a rescue diet enriched with calcium, phosphorus, and lactose to prevent secondary hyperparathyroidism in VDR mutant mice. Sham-operated (SHAM) mice served as controls. In addition, SHAM and CKD WT, VDR, and Klotho/VDR mice were treated with low dose anti-FGF23 antibody (anti-FGF23Ab, 50 µg per mouse, two times per week) over 8 weeks.

Results: In our *in vivo* models, we found that high circulating concentrations of intact Fgf23 activate Klotho dependent and independent with-no-lysine kinase (WNK) signaling pathways in the kidney, contributing to volume overload, hypertension, hypercalcemia, cardiac dysfunction, and vascular calcification in CKD mice. Using Western blotting analysis as well as 2-photon microscopy of live 200-µm-thick renal slices prepared from WT and Klotho/VDR mice and treated with recombinant FGF23, we uncovered a novel Klotho-independent FGF23 action in the kidney, leading to FGF receptor 3/4- and WNK1/4-mediated stimulation of distal renal tubular Ca^{2+} and Na^{+} uptake.

Conclusions: In conclusion, our study identified excessive Fgf23 signaling as a major disease-modulating factor in CKD progression, promoting vascular calcification and volume overload.

TH-PO538

Oral Sodium Ferrous Citrate (Fe^{2}) Reduces the Serum Fibroblast Growth Factor 23 Levels of Maintenance Hemodialysis Patients to the Same Extent as Ferric Citrate Hydrate (Fe^{3}) Sonoo Mizuiri,[1] Yoshiko Nishizawa,[1] Kazuomi Yamashita,[1] Shigehiro Doi,[2] Takao Masaki,[2] Kenichiro Shigemoto.[1] *[1]Ichiyokai Harada Hospital; [2]Hiroshima Univ Hospital.*

Background: Iron deficiency stimulates FGF23 transcription. It was reported that ferric citrate hydrate (Fe^{3}) reduces the serum FGF23 levels of iron-deficient chronic kidney disease (CKD) and hemodialysis (HD) patients. However, ferric citrate hydrate is an iron-based phosphate binder and might reduce serum FGF23 levels via actions other than increasing iron stores. This study aimed to determine whether oral ferrous (Fe^{2}) iron reduces the serum FGF23 levels of iron-deficient maintenance HD (MHD) patients.

Methods: Thirty-one MHD patients with iron deficiency were enrolled in this study. The exclusion criteria included the use of intravenous or oral iron or iron-based phosphate binders within 8 weeks. The patients' iron stores and their serum FGF23, phosphate, calcium (Ca), intact parathyroid hormone (iPTH), albumin, and C-reactive protein (CRP) levels were examined at the baseline and after 3 months' treatment with sodium ferrous citrate.

Results: The patients' transferrin saturation values (13.8±0.8 vs. 38.8±4.4%, P<0.0001) and serum iron (37.4±2.3 vs. 94.6±11.3 µg/dl, P<0.0001) and ferritin levels (37.6±4.4 vs. 87.0±16.3 ng/ml, P<0.01) were significantly increased after 3 months' treatment, as were their serum albumin levels (P<0.05). Conversely, their serum intact FGF23 (iFGF23) (4157±1107 vs. 3045±736 pg/ml, P<0.05), C-terminal FGF23 (cFGF23) (643±127 vs. 506±129 pg/ml, P<0.05), and CRP (P<0.05) levels were significantly reduced after 3 months' treatment. No such changes in the patients' serum iFGF23:cFGF23 ratios or serum phosphate, Ca, or iPTH levels were detected. Multivariate analysis of variance showed that the changes in the subjects' serum iFGF23 and cFGF23 levels induced by sodium ferrous citrate supplementation were attributable to changes in their serum ferritin levels (p<0.05).

Conclusions: Short-term oral iron supplementation with sodium ferrous citrate (Fe^{2}) replenished the iron stores and reduced the serum iFGF23 and cFGF23 levels of iron-deficient MHD patients, and these changes occurred without variations in the patients' serum phosphate, Ca, or iPTH levels.

Funding: Private Foundation Support

TH-PO539

Iron Therapy and Fibroblast Growth Factor-23 in Hemodialysis: A Randomized Controlled Trial Matthew A. Roberts,[1] Louis L. Huang,[1] Darren H.K. Lee,[1] Robert J. Macginley,[1] Stefanie Troster,[1] Annette B. Kent,[1] Sukhvinder Singh Bansal,[2] Iain C. Macdougall,[3] Lawrence P. McMahon.[1] *[1]Eastern Health Clinical School, Monash Univ, Australia; [2]Inst of Pharmaceutical Science, King's College, United Kingdom; [3]Renal Medicine, King's College, United Kingdom.*

Background: Intravenous (IV) iron increases serum levels of intact fibroblast growth factor-23 (iFGF23) and decreases its c-terminal cleavage product (cFGF23) in iron-deficient people with normal renal function. We hypothesized that IV iron modulates levels of iFGF23 and cFGF23 in hemodialysis patients, with different effects according to formulation.

Methods: Prevalent hemodialysis patients requiring protocol IV iron were randomized to a single 200mg dose of IV ferric carboxymaltose (FCM) or iron sucrose (IS). The primary outcome, change in iFGF23 and cFGF23 from pre- (Day 0) to post-infusion (Day 2), used the Wilcoxon rank sum test. Serum hepcidin, ferritin and PO_4 were also measured. Linear mixed models with an interaction term for treatment and time evaluated between-group effects.

Results: In the FCM group (n=22), median (IQR) values of ferritin, hepcidin and cFGF23 increased but iFGF23 and PO_4 reduced; in the IS group (n=20), ferritin and hepcidin changed (Table). The between-group difference was only significant for serum hepcidin (p for interaction=0.03), with a greater increase in the FCM Group.

	IS (n=20)			FCM (n=22)		
	Day 0	Day 2	P	Day 0	Day 2	P
iFGF23, pg/mL	381 (245-1,526)	378 (235-1,584)	0.77	843 (313-1,922)	576 (356-1,296)	0.046
cFGF23, RU/mL	710 (448-1,548)	646 (307-1,576)	0.23	704 (475-1,204)	813 (267-1,156)	0.036
Ferritin, µg/L	191 (77-237)	370 (218-475)	<0.001	198 (129-276)	327 (281-472)	<0.001
Hepcidin, ng/mL	3.4 (2.7-8.8)	12.2 (7.3-19.2)	<0.001	7.8 (2.7-12.6)	21.4 (13.9-26.2)	<0.001
PO_4, mmol/L	1.29 (1.11-1.65)	1.34 (1.08-1.54)	0.089	1.53 (1.14-1.71)	1.37 (1.05-1.67)	0.030

Conclusions: Hemodialysis patients given protocol IV FCM demonstrated a fall in iFGF23 and rise in cFGF23, changes not evident with IS. This suggests a differential effect of IV iron according to formulation, and different effects to people with normal renal function.

Funding: Pharmaceutical Company Support - Partial financial support for this investigator-initiated study was provided by Vifor Pharma Australia through an unrestricted grant

TH-PO540

Ferritin and Erythropoetin Are Main Determinants of Fibroblast Growth Factor 23 in Renal Transplant Recipients Michele F. Eisenga, Martin H. De Borst, Marco van Londen, Stephan J.L. Bakker, Carlo A. Gaillard. *Nephrology, UMC Groningen, Groningen, Netherlands.*

Background: Fibroblast growth factor 23 (FGF23) regulates phosphate and vitamin D homeostasis. In renal transplant recipients (RTR), an elevated level of FGF23 is an independent risk factor for mortality and allograft loss. To date, the interplay between FGF23, iron metabolism and red blood cell dynamics has not been fully evaluated.

Methods: Plasma C-terminal FGF23 was measured with enzyme-linked immunosorbent assay in stored plasma samples. Statistical analyses were performed using univariable linear regression followed by stepwise backward linear regression.

Results: We included 593 stable RTR (age 52±12 years; 53% males at 8.0±6.4 years after Tx). Median [IQR] FGF23 was 140 (95-219) RU/ml, ferritin was 160 (81-287) µg/l, EPO was 17.4 (12.0-24.5) U/L, and mean eGFR was 47±16 ml/min/1.73m2. In univariable and multivariable analysis, eGFR (ß=-0.39, p<0.001), phosphate (ß=0.23, p<0.001), EPO (ß=0.22, p=<0.001), ferritin (ß=-0.16, p<0.001), CRP (ß=0.13, p<0.001), and PTH (ß=0.12, p<0.001) (total model R^2=0.44) were identified as independent determinants of FGF23 (Table 1). Moreover, a significant interaction between EPO and hemoglobin on FGF-23 was noted (p=0.02).

Conclusions: We identified serum ferritin and EPO levels as major, potentially modifiable independent determinants of serum FGF23, alongside of the known association with phosphate homeostasis. EPO was positively associated with FGF23 independent of kidney function suggesting that anemia and/or EPO resistance may play a role in the association. Furthermore, since iron status and FGF23 are inversely associated, correction of iron deficiency may be a promising target to reduce FGF23 levels in an attempt to improve outcome.

Parameter	Univariable analysis		Multivariable analysis	
	std. ß	p-value	std. ß	p-value
Age	0.09	0.02		
eGFR	-0.54	<0.001	-0.39	<0.001
Calcium	0.04	0.33		
Phosphate	0.39	<0.001	0.23	<0.001
PTH	0.19	<0.001	0.12	<0.001
25(OH) Vitamin D	0.04	0.44		
Hemoglobin	-0.14	0.001		
Ferritin	-0.11	0.008	-0.16	<0.001
EPO	0.32	<0.001	0.22	<0.001
CRP	0.23	<0.001	0.13	<0.001

TH-PO541

Fibroblast Growth Factor 23 Associates with Resistance to Erythropoietin-Stimulating Agents in Maintenance Hemodialysis Patients Naoto Hamano,[1] Hirotaka Komaba,[1,2] Takehiko Wada,[1] Takatoshi Kakuta,[1] Masafumi Fukagawa.[1] *[1]Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Japan; [2]The Inst of Medical Sciences, Tokai Univ, Isehara, Japan.*

Background: A recent experimental study has shown that fibroblast growth factor 23 (FGF23) inhibits erythropoiesis through suppression of erythropoietin production and downregulation of its receptor. However, it is unknown whether high levels of FGF23 affect renal anemia in hemodialysis patients.

Methods: To assess the relationship between resistance to erythropoiesis stimulating agents (ESA) and FGF23 levels, we used baseline data from the Tokai Dialysis Cohort Study, a prospective observational study of 654 hemodialysis patients. Erythropoietin resistance index (ERI), calculated as the weight-adjusted dose of ESA divided by the hemoglobin level, was used as an index of resistance to ESA. We defined top quartile of ERI as the ESA resistant group. Serum FGF23 levels were determined using a chemiluminescence immunoassay (Kyowa Medex Co., Ltd., Tokyo, Japan) that exclusively detects the full-length FGF23 peptide.

Results: A total of 458 patients were receiving ESA at baseline and were included in the analysis. The median ERI was 6.9 IU/kg/wk/g/dl (IQR 3.9-11.4 IU/kg/wk/g/dl) and the median FGF23 was 1,955 pg/ml (IQR 572-5,263 pg/ml). Multivariate logistic regression analysis identified body mass index, serum albumin, transferrin saturation, and FGF23 (OR 1.65, 95%CI 1.01-2.71 per 10-fold increase in FGF23) as independent risk factors for ESA resistance.

Conclusions: Our findings suggest that elevated FGF23 contributes to ESA resistance in patients undergoing hemodialysis. Future research should focus on whether FGF23-lowering treatment improves control of renal anemia in end-stage renal disease.

TH-PO542

Effect of Iron Deficient Diet on Fetuin A and FGF23 Regulation of Adriamycin-Induced CKD Model Mouse Masanori Takaiwa,[1] Kosei Hasegawa,[2] Takayuki Miyai.[2] *[1]Dept of Pediatrics, Matsuyama Red Cross Hospital, Matsuyama, Ehime, Japan; [2]Dept of Pediatrics, Okayama Univ Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.*

Background: FGF23 is involved in the pathogenesis of CKD-MBD and cardiovascular disease in CKD. Deficiency of Fetuin A (Fet-A) is associated with increased arterial calcification and mortality in CKD. Fetuin-mineral complex, calciprotein particles (CPP), is increased in CKD and reflects extraosseous calcification stress. Previously, we produced an early CKD model mouse by adriamycin (ADR) treatment. Using this model, we observed that Fe deficiency enhanced the FGF23 elevation. In this study we examined the effect of Fe deprivation on FGF23, Fet-A and CPP of this model.

Methods: Upon making 6 groups (2% Fe and 2% Fe-CKD –fed a 2% Fe diet; 0.6% Fe and 0.6% Fe-CKD - fed a 0.6% Fe diet; 0.02% Fe and 0.02% Fe-CKD - fed a 0.02% Fe diet), 10-week-old male C57BL/6J mice were administered either ADR (2%-Fe-CKD, 0.6%-Fe-CKD and 0.02%-Fe-CKD) or serine every 7 days, and were sacrificed on day 28. Data were expressed as the mean±SEM. A value of $p<0.05$ was considered significant.

Results: The kidneys of ADR treated animals were smaller in size ($p<0.01$). There was no difference in Ca. Pi and PTH among all groups. In the 0.02% Fe-CKD, intact FGF23 (670.7±134.4 pg/ml) and a ratio between the intact FGF23 and C-terminal FGF23 (Int/C-FGF23 ratio) were higher than the other groups ($p<0.01$). Serum Fet-A is lower in the 0.02% Fe-CKD (55.0±2.0 ng/ml) than the 0.6% Fe (125.1±18.8 ng/ml) and all other groups ($p<0.05$). Fet-A mRNA of the 0.02% Fe-CKD was suppressed compared with the other ADR treated groups ($p<0.05$). The circulating CPP was elevated in the 0.02% Fe-CKD ($p<0.05$).

Conclusions: In this study, the increased intact FGF23 and Int/C-FGF23 ratio of the 0.02% Fe-CKD suggested that the FGF23 elevation was enhanced by the Fe deficiency. Significantly, the 0.02% Fe-CKD showed decreased Fet-A expression associated with increased CPP. Hence, it was suggested that Fe deprivation during the early CKD might accelerate CKD-MBD progression and strengthen the ectopic mineralization stress via inducing aberrant FGF23 proteolysis and Fet-A deficiency.

Funding: Private Foundation Support

TH-PO543

Elevations in FGF23 Precede Abrogation of Either Phosphate or Iron Homeostasis in a Mouse Model of Renal Insufficiency Jackie A. Fretz,[1] Tracy Nelson,[1] Xiuqi Li,[2] Karin Finberg.[2] *[1]Orthopaedics and Rehabilitation, Yale School of Medicine, New Haven, CT; [2]Pathology, Yale School of Medicine, New Haven, CT.*

Background: Phosphate and iron metabolism are linked intimately through the phosphatonin FGF23. Iron status is inversely correlated to the level of circulating FGF23, and improvement in iron status within individual patients correlates with a decrease in FGF23. Development of anemia during chronic kidney disease is a multifactoral process, but the exact mechanisms driving its development during the early stages of renal function decline are still not completely understood.

Methods: To better understand the events regulating the early dysfunction of iron bioavailability, phosphate balance and FGF23 we employed targeted deletion of the transcription factor Early B cell Factor 1 (Ebf1) from the kidney stromal progenitors (using Foxd1-cre). This results in a developmental abrogation of outer cortex development, and animals present with *glomerulosclerosis*, phosphate wasting, elevations in FGF23, and anemia. We profiled the sequential presentation of indicators of renal dysfunction (NGAL, albuminuria, hematuria, TGFβ), phosphate imbalance (PTH, $1,25(OH)_2D_3$, serum phosphate, phosphaturia), and regulators of iron bioavailability and transport (hepcidin, transferrin, erythrocyte counts, Epo, and splenic erythropoiesis) to understand the events that initiate and drive abrogation of the phosphate, iron, FGF23 regulatory axis.

Results: Elevated intact FGF23 coincides with the earliest indicators of renal dysfunction (elevated NGAL), and precede changes in urinary phosphate wasting or changes in iron homeostasis. Histological abnormalities are apparent at postnatal day 14, but proteinuria is not apparent until day 24, with splenomegaly at day 28. Serum Epo was normal until disease was well established, at 1 month, but was preceded by transferrin loss in the urine (day 20).

Conclusions: Elevated FGF23 has been shown to negatively regulate erythropoiesis. We conclude that it is primary elevations in FGF23 that drive the subsequent perturbations of phosphate and iron homeostasis in this model, and not a primary Epo-insufficiency generated by the actions of Ebf1 within the renal stroma.

Funding: NIDDK Support

TH-PO544

Klotho Modulates FGF23-Mediated NO Synthesis and Oxidative Stress in Human Coronary Artery Endothelial Cells Maren Leifheit-Nestler, Beatrice Richter, Jacqueline Haller, Dieter Haffner. *Dept of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany.*

Background: Endothelial dysfunction (ED) characterized by an imbalance of NO bioavailability and ROS formation is an early hallmark of CKD, a state of Klotho deficiency and excess of FGF23. Both dysregulations were shown to be associated with oxidative stress and ED. Klotho possesses antioxidative properties and increases resistance to oxidative stress but direct vascular effects of FGF23 remain largely elusive. We assess the effects of FGF23 in relation to Klotho on NO synthesis and ROS formation and detoxification in human coronary artery endothelial cells (HCAEC).

Methods: HCAEC were pre-treated with pan-FGF receptor (FGFR) or Akt inhibitor and anti-Klotho neutralizing antibody followed by stimulation with 10,000 pg/mL FGF23, resembling those found in moderate stages of CKD. Cells were investigated for FGFRs, membrane-bound and soluble Klotho, intracellular NO synthesis cascade, and ROS formation by qPCR, immunoblotting, and flow cytometry.

Results: Membrane-bound Klotho is expressed in HCAEC, and FGF23 increases the expression of the Klotho shedding protease ADAM17, and consequently the secretion of soluble Klotho. FGF23 stimulates NO release via FGFR/Akt-dependent activation of endothelial NO synthase (eNOS). Both FGFR-dependent ROS formation via NADPH oxidase 2 (Nox2) and ROS degradation via superoxide dismutase 2 (SOD2) and catalase (CAT) are stimulated by FGF23. Pre-incubation with Klotho inhibitor blunts the FGF23-stimulated Akt-eNOS activation and NO synthesis, decreases ROS degradation by blocking SOD2 and CAT enzymes, whereas FGF23-stimulated ROS synthesis via Nox2 is unaffected, resulting in low NO bioavailability and increased oxidative stress.

Conclusions: Our data indicate that in the presence of Klotho, FGF23 induces NO release in HCAEC and its stimulating effects on ROS production are counterbalanced by increased ROS degradation. In states of Klotho deficiency, e.g. CKD, FGF23-mediated NO synthesis is blunted and ROS formation overrules ROS degradation. Thus, FGF23 excess may primarily promote oxidative stress and consequently endothelial dysfunction.

TH-PO545

Soluble Klotho and Mortality in Maintenance Hemodialysis Patients Hisae Tanaka,[1] Hirotaka Komaba,[1,2] Takao Suga,[3] Takehiko Wada,[1] Takatoshi Kakuta,[1] Masafumi Fukagawa.[1] *[1]Div of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Japan; [2]The Inst of Medical Sciences, Tokai Univ, Isehara, Japan; [3]Medical Corporation Showakai, Tokyo, Japan.*

Background: Klotho is a transmembrane protein that functions as a co-receptor for fibroblast growth factor 23 (FGF23). Klotho also exists as a soluble circulating protein, and recent experimental data demonstrated that soluble Klotho has multiple beneficial functions including renoprotection, prevention of vascular calcification, and inhibition of cardiac hypertrophy. However, it is unknown whether soluble Klotho levels are associated with risk of death in patients on hemodialysis.

Methods: We conducted a prospective cohort study of 654 maintenance hemodialysis patients (the Tokai Dialysis Cohort Study). The primary exposure variable was the baseline soluble Klotho level. The primary outcome was 3-year, all-cause mortality. Soluble Klotho levels and full-length FGF23 levels were measured using a sandwich ELISA kit (Immuno-Biological Laboratories, Co., Ltd, Gunma, Japan) and a chemiluminescence immunoassay (Kyowa Medex Co., Ltd., Tokyo, Japan), respectively.

Results: At study enrolment, the mean (±SD) soluble Klotho level was 377± 231 pg/ml and the median (IQR) FGF23 level was 1,878 (571-4,932) pg/ml. Higher levels of soluble Klothocorrelated with longer dialysis duration, higher hemoglobin, higher creatinine, and lower total cholesterol; there was no correlation with serum calcium, phosphorus, parathyroid hormone, or FGF23. In univariate analysis, soluble Klotho levels were not significantly associated with risk of mortality. This result was unchanged after multivariable adjustment.

Conclusions: Soluble Klotho levels were not related to parameters of bone mineral metabolism and did not predict mortality in patients undergoing hemodialysis. Further research is required to determine whether soluble Klotho plays a role in bone disease and vascular calcification in end-stage renal disease.

Funding: Government Support - Non-U.S.

TH-PO546

Klotho and Inflammation in Early Stages of Chronic Kidney Disease

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Background: One of the major functions of Klotho is its role as an obligatory co-receptor for FGF23 signaling. The effect of Klotho/FGF23 system is opposite to vitamin D. Reduced expression of Klotho may contribute to a number of complications of chronic kidney disease. Similarly inflammation is also well-known risk factor of progression and complications of CKD. The aim of the study was to asses Klotho status in patients in early stages of chronic kidney disease in correlation to inflammation.

Methods: 89 patients with CKD stage 2-3 according to KDIGO were enrolled to the study and divided into two groups – with and without subclinical inflammation according to hsCRP measurements. Serum creatinine was obtained using standard laboratory methods in certified local central laboratory. Commercially available kits were used to measure FGF23, Klotho, hsCRP, IL-6, GDF15, and vitamin D. Analyses of the correlation of each parameter were performed using Pearson or Spearman correlation coefficients.

Results: Klotho concentration was significantly lower in patients with inflammation defined as elevated hsCRP > 10 mg/dl (p=0.01). Klotho was significantly correlated with vitamin D in all patients, however in patients with inflammation this correlation was stronger ($r = 0.49$, $p<0.05$). Similarly we observed significant correlation between Klotho and GDF-15, especially marked in patients with inflammation($r = - 0.4$, $p<0.05$). No statistically significant correlations between Klotho and FGF23 as well as inflammatory parameters such as hsCRP and IL-6 have been observed. In multiple regression analysis vitamin D and GDF-15 were found to be predictors of Klotho.

Conclusions: Lower Klotho concentrations are connected with subclinical inflammation in patients with early stages of chronic kidney disease. As Klotho is linked to life expectancy, inflammation may also contribute to shortened survival in CKD.

TH-PO547

The Metabolic Bone Disease Associated with the Hyp Mutation Is Independent of Osteoblastic HIF1α Expression

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Background: Fibroblast growth factor-23 (FGF23) is a hormone controlling key responses to systemic phosphate increases through its actions on the kidney. FGF23 also positively responds to iron deficiency anemia and hypoxia in rodents and humans and is responsible for late-onset ADHR. The disorder X-linked hypophosphatemia (XLH) is characterized by elevated FGF23 and an intrinsic bone mineralization defect. Further, the *Hyp* mouse model of XLH has disturbed osteoblast to osteocyte differentiation with altered expression of FGF23. Since Hypoxia inducible factor-1a (HIF1a) has been implicated in FGF23 production and is important for bone cell differentiation, the goals of this study were to determine whether HIF1a activation under normal iron conditions could influence FGF23, and to test the role of HIF1a on the *Hyp* endocrine and skeletal disease *in vivo*.

Methods: Treating primary cultures of osteoblasts/osteocytes and UMR-106 cells with HIF1a activator, AG490. Generation of *Hyp* mice bred onto the HIF1a/Osteocalcin-Cre background.

Results: Treatment of primary bone cultures and UMR-106 cells with the AG490 resulted in HIF1a stabilization and increased FGF23 mRNA (50-100 fold; $p<0.01$-0.001). Since FGF23 is elevated in the *Hyp* mouse, we sought to determine whether a bone-specific HIF1a deletion would correct FGF23 production and the *Hyp* disease phenotype. Although HIF1a effects on bone could be detected, the cross of *Hyp-HIF1a-OCN* had no effect on the metabolic bone disease associated with the *Hyp* mutation.

Conclusions: In summary, FGF23 can be driven by ectopic HIF1a activation under normal iron conditions *in vitro*, but factors independent of HIF1a activity after mature osteoblast formation are likely responsible for the elevated FGF23 in *Hyp* mice *in vivo*. Clinically, these findings suggest that although iron therapy holds promise for ADHR, patients with XLH would likely benefit from other treatment approaches.

Funding: Private Foundation Support

TH-PO548

KRN23, a Fully Human Monoclonal Antibody to FGF23, Reverses Renal Phosphate Wasting and Improves Rickets in Children with X-Linked Hypophosphatemia

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Background: In patients with X-linked hypophosphatemia (XLH), high circulating FGF23 impairs renal phosphate (Pi) reabsorption and $1,25(OH)_2D$ production, resulting in hypophosphatemia, defective bone mineralization, and rickets. Conventional treatment with oral Pi and active vitamin D fails to restore Pi homeostasis and often leads to nephrocalcinosis and hyperparathyroidism.

Methods: In a phase 2 study, we administered KRN23, which binds and inhibits the renal actions of FGF23, to children (ages 5-12 years, ≤Tanner 2) with XLH, either biweekly (Q2W) or monthly (Q4W) by subcutaneous injection. KRN23 doses were titrated to achieve age-appropriate serum Pi concentrations, which were measured biweekly.

Results: At enrollment, 35 of the first 36 participants had received conventional treatment for a mean of 6.6 years. After 40 weeks of KRN23 treatment, renal TmP/GFR, serum Pi, and $1,25(OH)_2D$ increased significantly, and alkaline phosphatase decreased. Increases in serum Pi were more stable and sustained with Q2W dosing. In this interim analysis, increases in $1,25(OH)_2D$ did not impact serum or urinary calcium, PTH, or nephrocalcinosis. Radiographic findings of rickets improved substantially in most patients, with greater improvements in the subset with higher-severity rickets at baseline.

Mean (SD)		Baseline	Week 38	Week 40
Serum Pi (mg/dL)	Q2W	2.5 (0.4)	3.2 (0.4)*	3.2 (0.4)*
	Q4W	2.3 (0.3)	3.4 (0.4)*	2.8 (0.3)*
TmP/GFR (mg/dL)	Q2W	2.3 (0.5)	3.1 (0.6)*	3.2 (0.6)*
	Q4W	2.0 (0.4)	3.4 (0.4)*	2.6 (0.3)*
Serum $1,25(OH)_2D$ (pg/mL)	Q2W	40 (23)	69 (12)*	69 (16)*
	Q4W	41 (17)	83 (21)*	61 (17)*
Serum Calcium (mg/dL)	Q2W	9.8 (0.3)	9.8 (0.3)	9.6 (0.2)*
	Q4W	9.8 (0.5)	9.8 (0.4)	9.7 (0.4)
2-hr Urine Calcium/Creatinine Ratio (mg/mg)	Q2W	0.12 (0.08)	0.08 (0.04)	0.10 (0.09)
	Q4W	0.16 (0.10)	0.08 (0.05)*	0.13 (0.11)
Serum Alkaline Phosphatase (U/L)	Q2W	454 (109)		388 (95)*
	Q4W	443 (111)		415 (112)
		Baseline	**Week 36**	
Serum iPTH (pg/mL)	Q2W	48 (34)	48 (19)	
	Q4W	41 (24)	50 (23)	

* P<0.05 vs baseline values, by paired analysis. N=18 participants in each dosing schedule arm. In the Q4W dosing group, Week 38 is the midpoint of a dosing interval; Weeks 36 and 40 are the ends of the dosing intervals.

Conclusions: These data provide evidence that by binding and inhibiting excess FGF23, KRN23 improves the impairments in renal Pi reabsorption and $1,25(OH)_2D$ production in XLH and consequently, improves rickets, without adversely affecting calcium metabolism.

Funding: Pharmaceutical Company Support - Ultragenyx Pharmaceutical, Inc.

TH-PO549

High Serum Levels of Fibroblast Growth Factor 23 Are Associated with Decreased Renal Blood Flow in Early Autosomal Dominant Polycystic Kidney Disease

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Background: Previous studies have reported a 4-fold elevation in circulating fibroblast growth factor 23 (FGF23) levels in early autosomal dominant polycystic kidney disease (ADPKD) when compared to other etiologies of chronic kidney disease (CKD). FGF23 levels have been associated with impaired vasoreactivity in CKD. We tested the hypothesis that higher serum FGF23 is a risk factor for a decrease in renal blood flow (RBF) in early ADPKD.

Methods: Intact FGF23 (iFGF23) serum levels (Kainos)were measured in 343 hypertensive ADPKD patients who participated in the HALT-PKD trial study A. Participants were randomized to standard or low blood pressure control and to either lisinopril plus telmisartan or lisinopril plus placebo, with evaluation of RBF by abdominal magnetic resonance imaging at baseline, 24, 48, and 60 months. The study population was divided into tertiles of iFGF23. We used mixed effect models to examine the associations between tertiles of iFGF23 with repeated measures of RBF during the course of the study.

Results: At baseline, participants mean age, CKD-EPI-eGFR and RBF were 37 ± 9 years, 88 ± 16 ml/min/1.73m^2, 606 ± 205 ml/min/1.73m^2, respectively. The median (IQR) iFGF23 was 40.5 (33-55) pg/mL. After adjustment for age, gender, race, randomization group, body mass index, systolic blood pressure, eGFR, urine albumin excretion, serum calcium, and phosphate, the highest iFGF23 tertile was associated with greater RBF decline (β: -42.76, [95% CI -2.38 to -83.14]; $p < 0.03$) compared with the lowest iFGF23 tertile. Similarly, when evaluated as a continuous variable, higher levels of iFGF23 were associated with a lower RBF (β: -35.88, [95% CI -2.23 to -69.53]; p=0.03 per natural log unit increase).

Conclusions: High serum iFGF23 levels are associated with a lower RBF over time in patients with early ADPKD. Further studies are required to determine the mechanisms underlying these relationships and to test whether interventions that reduce FGF23 levels might be renoprotective in early ADPKD.

Funding: NIDDK Support

TH-PO550

FGF23 Can Predict the Worsening of Cognitive Impairment in Dialysis Patients? Valentina Corradi,[1,2] Fiorenza Ferrari,[2] Sara Samoni,[2] Roberto Zambianchi,[2] Ilaria Santolin,[3] Elisabetta Galloni,[3] Massimo de Cal,[1,2] Elisa Scalzotto,[2] Carlotta Caprara,[2] Ornella Gambero,[3] Lucia Meligrana,[3] Mariangela Mettifogo,[1,2] Alessandra Brendolan,[1,2] Federico Nalesso,[1,2] Carlo Crepaldi,[1,2] Francesco Perini,[3] Claudio Ronco.[1,2] *[1]Nephrology, San Bortolo Hospital; [2]IRRIV, San Bortolo Hospital; [3]Neurology, San Bortolo Hospital.*

Background: Cognitive impairment (CI) in patients with chronic kidney disease (CKD) patients on dialysis is common and shows a prevalence on the rise. Especially cognitive performance was significantly associated with eGFR in all domains except language. Several studies showed the uremia-related factors for cognitive impairment in CKD-stage V but its development remain unclear. Recently FGF23 was associated with worse performance on a composite memory score. FGF-23 levels in hemodialysis patients may contribute to cognitive impairment. The aim of our study was to determine if the FGF23 could predict the worsening of cognitive impairment.

Methods: We performed a prospectively study (baseline, T0 and after 1year, T1) in chronic dialysis (HD and PD). The assessment of cognitive status was performed through two psychometric tests: Mini-Mental State Exam (MMSE) and Montreal Cognitive Assessment (MoCA). The C-terminal FGF23 (cFGF23) levels were determined in plasma by ELISA (Immutopics, Inc.San Clemente, CA) as RU/ml. Statistical analysis was performed by R Core Team (2016).

Results: Baseline, we enrolled 133 pts, 58 HD and 75PD (mean age 64,09±13,65 yrs; 71% M; median dialysis time: 2,79 (1,38-6,03) years). The median cFGF-23 level baseline was 1493 (927-4035) RU/mL. The cognitive assessment of pts are shown in table 1.

variable	T0 (133)	T1 (104)	*p* value
MMSE	27.49 (24.40-28.48)	27.70 (26.30-28.48)	NS
MoCA (ES)	23,33 (20,63-25,71)	23,37 (20,07-26,11)	0.056

The linear regression model showed for all increase of 100 RU/ml of cFGF23 a decrease of MoCA ES of 0.003 unit from T0 to T1.

Conclusions: FGF-23 levels seems to be associated with worse performance of executive function of dialysis pts. High level of FGF-23 levels in dialysis patients could be contribute to cognitive impairment. Further studies are needed to confirm our data and to investigate the impact of different dialysis modalities on CI.

TH-PO551

Genetic Background Influences Cardiac Phenotype in Murine Chronic Kidney Disease Samantha Neuburg, Lixin Qi, Connor Francis, Xueyan Wang, Corey Dussold, Valentin David, Myles S. Wolf, Aline Martin. *Div of Nephrology and Hypertension, Northwestern Univ - Feinberg School of Medicine, Chicago, IL.*

Background: An increased levelof fibroblast growth factor (FGF)-23 is the earliest detectable sign of disordered mineral metabolism in chronic kidney disease (CKD), and a powerful risk factor for left ventricular hypertrophy (LVH), heart failure and death. Experimental models of CKD with elevated FGF23 and LVH are needed. We hypothesized that slower rates of CKD progression in the Col4a3^{KO} mouse model of CKD would increase exposure to elevated FGF23 and promote development of LVH.

Methods: We backcrossed 129X1/SvJ-Col4a3^{KO} with C57Bl6/J mice and generated Col4a3^{KO} and WT on a mixed background with either 25% C57Bl6/J (***129***) or 94% C57Bl6/J (***Bl6***) genomes. We compared overall survival and assessed renal function, FGF23 levels and cardiac morphology by echocardiography in WT controls and Col4a3^{KO} with advanced CKD: at 10 weeks in the ***129***, 20 weeks in the ***Bl6*** mice.

Results: ***Bl6-***Col4a3^{KO} lived significantly longer than ***129-***Col4a3^{KO} (22±1 vs. 11±1 weeks; p<0.05). 10 week-old ***129-***Col4a3^{KO} showed impaired renal function (BUN: 100±12 vs. 21±1 mg/dL), hyperphosphatemia (9.6±0.6 vs. 6.1±0.4 mg/dL) and a 10-fold increase in serum FGF23 levels (p<0.05 vs. WT for each). At 20 weeks, ***Bl6-***Col4a3^{KO} showed similarly impaired renal function (BUN: 78±17 vs. 25±2 mg/dL), hyperphosphatemia (7.9±0.4 vs. 6.2±0.3 mg/dL) and a 10-fold increase in FGF23 levels (p<0.05 vs. WT for each), indicating comparable severity of CKD to the 10-week ***129-***Col4a3^{KO}. Whereas ***129-***Col4a3^{KO} did not show significant cardiac alterations (LV Mass: 102±15 vs. 104±4 mg; NS vs. WT), ***Bl6-***Col4a3^{KO} demonstrated LVH (LV Mass: 132±3 vs. 96±5 mg; p<0.05 vs. WT).

Conclusions: The genetic background of the Col4a3^{KO} mouse influences its rate of CKD progression, cardiac phenotype and survival. Slower CKD progression and longer survival are associated with development of LVH in ***Bl6-***Col4a3^{KO}, which can serve as a novel model of cardiorenal disease. Whether LVH is mediated, in part, by longer exposure of ***Bl6-***Col4a3^{KO} mice to elevated FGF23 levels requires further study.

Funding: NIDDK Support

TH-PO552

Increase in Cardiac Expression of Fibroblast Growth Factor 23 (FGF23) in Two Mouse Models of Chronic Kidney Disease Dorothy Daniel,[1] Emily M. Adamic,[2] Jason R. Stubbs,[3] Chad D. Touchberry,[2] Michael J. Wacker.[1] *[1]Univ of Missouri-Kansas City School of Medicine, Kansas City, MO; [2]Health and Sport Sciences, Univ of Memphis, Memphis, TN; [3]Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS.*

Background: FGF23 is a hormone released from osteocytes in response to elevated serum phosphate and acts to decrease phosphate reabsorption. FGF23 serum levels rise with the progression of chronic kidney disease (CKD) and are associated with cardiovascular disease and mortality. While bone release of FGF23 is known to increase during CKD, it has not been fully elucidated if the heart directly contributes to FGF23 expression and if it is increased during CKD. To test this hypothesis, we utilized two mouse models of CKD: *Col4a3* null (Alport syndrome) and adenine diet (chronic tubulointerstitial nephritis). Both mouse models have progressive renal dysfunction as evidenced by elevated BUN, creatinine, phosphate, and FGF23 serum levels. Our aim was to measure changes in expression of FGF23 in the hearts of *Col4a3* null and adenine-fed mice and also determine if exercise would prevent these changes.

Methods: *Col4a3* null and wild-type (WT) mice were sacrificed at 10 weeks. For the adenine model, CD1 mice were fed 0.2% adenine daily for 12 weeks and a subset of these mice were exercised on a treadmill daily. Hearts were removed and real time RT-PCR was used to measure expression of FGF23. Analysis was performed using the 2^ddct method.

Results: Basal cardiac FGF23 expression was low in *Col4a3* WT and control diet mice, with an average delta CT of 16.9 in relation to β-actin expression. Cardiac FGF23 expression was increased 3.2 fold in *Col4a3* null mice (p<0.05; n=5) and increased 3.0 fold in adenine-fed mice (p<0.05; n=6) compared to control mice. Exercise did not improve kidney function in adenine-fed mice and FGF23 expression was elevated 3.2 fold (p<0.05; n=5).

Conclusions: FGF23 expression was increased in the hearts of CKD mice indicating that FGF23 may have paracrine effects on cardiac remodeling during CKD and could prove to be an important therapeutic target. This particular exercise regimen did not abate FGF23 expression and may be adverse for CKD disease.

Funding: Private Foundation Support

TH-PO553

Correlation of Fibroblast Growth Factor Receptor and Fibroblast Growth Factor 23 Expression with Cardiac Structure and Function in Failing Human Hearts Morgan E. Marcuccilli,[1] Angela K. Peter,[1] Suneet Nitin Purohit,[1] Amrut V. Ambardekar,[1] Rahul Kakkar,[2] Leslie A. Leinwand,[1] Michel Chonchol.[1] *[1]Univ of Colorado; [2]Corvidia.*

Background: Experimental studies have demonstrated that fibroblast growth factor 23 (FGF23) promotes left ventricular hypertrophy by activating fibroblast growth factor receptors 4 (FGFR4). However, FGF23 can signal through multiple FGF receptors (FGFRs), and the relationship between FGF23 and FGFRs expression with echocardiographic measures of cardiac structure and function in humans with end stage heart failure is unknown.

Methods: We conducted a retrospective study in patients with normal kidney function and end-stage heart failure from either ischemic cardiomyopathy (n=10), ischemic cardiomyopathy treated with a left ventricle assisted device (n=10), hypertrophic cardiomyopathy (n=10) or non-ischemic or hyperthrophic cardiomyopathy with concentric left ventricular hypertrophy (LVH). Left ventricular tissue was collected and flash frozen at the time of heart transplant. FGFR 1-4 and FGF23 expression was evaluated using quantitative real-time PCR. Linear regression models were used to examine the association between FGFRs and FGF23 expression with echocardiographic parameters.

Results: Median (IQR) age was 53 (47-61) years, and 77% were male. The median (IQR) ejection fraction (EF), left ventricular internal diameter in systole (LVIDs) and diastole (LVIDd), systolic and diastolic volumes were 23 (15-30)%, 5.3 (4.3-6.3) cm, 5.8 (5.1-7.2) cm, 110 (70-187) ml and 155 (107-236) ml, respectively. After adjusting for age, gender, race and cardiac pathology, only FGFR3 and FGFR4 were associated with LVIDs [β(SE): - 0.70 ± 0.33; p=0.04 and β SE): -0.77±0.32; p=0.02, respectively] and systolic LV volume [β(SE): -46.25±19.47; p=0.02 and β SE): -51.49±17.64; p=0.0008, respectively]. FGF23 was strongly associated with fractional shortening (β(SE): 3.03±0.78; p=0.0005). Higher FGFR1, 3 and 4 expression were all associated with higher EF (P < 0.004 for all).

Conclusions: FGFR3, FGFR4 and FGF23 correlate with echocardiographic parameters of cardiac structure and function in end stage heart failure. Further studies should explore the possible mechanistic role of FGFR 3 and 4 in advanced cardiomyopathy.

Funding: NIDDK Support, Pharmaceutical Company Support - Astrazeneca

TH-PO554

FGF23 Is Not Predictive of Functional Cardiovascular Reserve in Advanced CKD Kenneth Lim,[1] Stephen M.S. Ting,[2] Dihua Xu,[1] Sahir Kalim,[1] David H. Ellison,[3] Ravi I. Thadhani,[1] Daniel Zehnder,[4] Thomas F. Hiemstra.[5] *[1]Div of Nephrology, Massachusetts General Hospital, Boston, MA; [2]Dept of Medicine, Heart of England NHS Foundation Trust, United Kingdom; [3]Div of Nephrology & Hypertension, Oregon Health and Science Univ, Portland, OR; [4]Div of Metabolic & Vascular Health, Warwick Medical School, United Kingdom; [5]School of Clinical Medicine, Univ of Cambridge, United Kingdom.*

Background: Chronic kidney disease (CKD) patients exhibit impaired functional cardiovascular reserve with reduced peak exercise oxygen consumption (VO_2max), a predictor of survival. In CKD, bone derived FGF23 is elevated and has been implicated in the development of cardiovascular disease. We sought to determine whether FGF23 is a predictor of VO_2max in CKD.

Methods: In this cross-sectional study, we enrolled 171 CKD stage V patients and 88 controls with essential hypertension: age 46.7±14.3 vs. 53.2±8.1years (p<0.001), male 60.2% vs. 48.9%, MAP of 98±13.4 vs 104.2±9.5mmHg (p<0.001). VO_2max was determined by cardio-pulmonary exercise test (CPET) and left ventricular mass index (LVMI) by 2D echocardiogram.

Results: CKD patients had higher FGF23 levels (2845.4 pg/ml, IQR 595.9-10947 vs 41.7pg/ml, IQR 35-51.7, p<0.001), higher LVMI (110±36.5 g/m^2 vs 87.6±16.9, p <0.001), and markedly reduced VO_2max (19.8±12.1 vs 24.8±23.4 ml/min/kg, p<0.001). Univariate regression showed that lnFGF23 was not associated with VO2max (p = 0.05), but was associated with LVMI (p < 0.05) in CKD; lnFGF23 were neither associated with VO2max or LVMI in controls. In a multivariate regression model for CKD: lnFGF23 was not associated with VO_2max (β=-.018, p=0.08), but positively associated with age (p<0.0001), HR (p<0.0001) and LVMI (p=0.002). In control: lnFGF23 was also not associated with VO_2max (β=-.07, p=0.4), but positively associated with HR (p<0.0001) and LVMI (p<0.0001) but not with age (p=0.6).

Conclusions: As previously observed, this study describes an association between FGF23 and LVMI in both CKD and essential hypertension. However, FGF23 did not predict cardiovascular reserve in the context of hypertension alone or CKD and hypertension.

Funding: Private Foundation Support

TH-PO555

Fibroblast Growth Factor 23 Is Not Associated with Incident Acute Kidney Injury among HALT PKD Study B Participants Anna Jeanette Jovanovich,[1,2] Zhiying You,[2] Berenice Y. Gitomer,[2] Myles S. Wolf,[3] Michel Chonchol.[2] *[1]Denver VA Medical Center; [2]Univ of Colorado Denver; [3]Northwestern Univ.*

Background: Fibroblast growth factor 23 (FGF23) levels are elevated in acute kidney injury (AKI) independent of other bone mineral metabolism parameters. Furthermore, higher pre-operative FGF23 levels predict more severe AKI and greater need for renal replacement therapy among patients undergoing cardiopulmonary bypass surgery. To further evaluate the relationship between AKI and FGF23, we investigated the association of baseline serum FGF23 levels and AKI among patients with autosomal dominant polycystic kidney disease (ADPKD).

Methods: We measured intact FGF23 levels (Kainos) in stored baseline serum samples in the HALT PKD Study B, which evaluated the efficacy of renin-angiotensin-aldosterone system (RAAS) blockade on the progression renal disease among participants with ADPKD and GFR 25-60 mL/min/1.73 m^2. Participants were randomized to either single agent (lisinopril + placebo) or dual agent (lisinopril + telmisartan) RAAS blockade. Goal blood pressure was 110-130/80 mmHg. We used logistic regression analysis to evaluate the association of baseline FGF23 levels and incident AKI (increase in serum creatinine >0.3 mg/dL).

Results: A total of 437 participants were included in these analyses. Mean age was 49±8 years, 51% were female, mean CKD-EPI eGFR was 48±12 mL/min/1.73 m^2, and median serum intact FGF23 was 67 [49-90] pg/mL. Incident AKI occurred in 48 participants over 5-8 years of follow-up. In the unadjusted model, higher FGF23 was associated with 2-fold greater odds of incident AKI (odds ratio [OR] 2.1; 95% CI, 1.1-4.0). However, after full adjustment for demographic and clinical factors as well as treatment group, the magnitude of the association was somewhat attenuated and no longer significant (OR 1.8; 95% CI, 0.8-3.7).

Conclusions: Baseline serum FGF23 levels were not significantly associated with incident AKI among participants with ADPKD and stage III-IV chronic kidney disease. However, the number of incident AKI cases was small and the magnitude of the association was only slightly attenuated after full adjustment.

Funding: VA Support

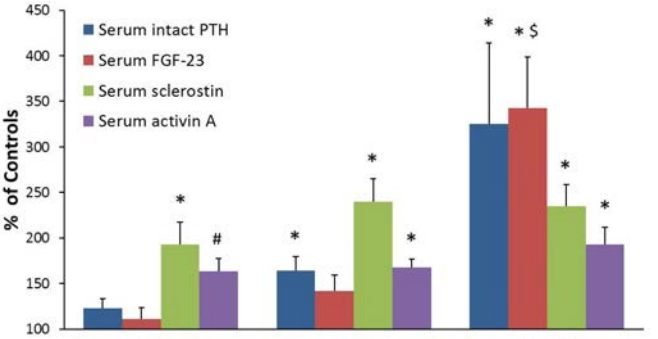
TH-PO556

Activin A and Sclerostin in Blood Increase before PTH and FGF-23 in CKD Stages 2 to 5 Florence Lima, Marie-Claude M. Faugere, Hanna W. Mawad, Amr El-Husseini Mohamed, Hartmut H. Malluche. *Div of Nephrology, Bone & Mineral Metabolism, Univ of Kentucky, Lexington, KY.*

Background: Renal osteodystrophy (ROD) develops in early stages of chronic kidney disease (CKD) and progresses during loss of kidney function. Serum levels of intact parathyroid hormone (iPTH) have been used as the primary indicator of bone abnormalities in ROD. There are other markers that may be useful for assessment of ROD in patients with various stages of CKD. This study evaluated changes in blood levels of iPTH, fibroblast growth factor 23 (FGF-23), bone-specific alkaline phosphatase (BSAP), tartrate resistant acid phosphatase 5b (TRAP-5b), sclerostin, activin A, Dickkopf-1 (DKK1), a-Klotho and cathepsin K in patients with CKD stages 2 to 5.

Methods: These biochemical parameters were measured in 71 subjects with CKD stages 2 to 5. There were 18 patients with CKD-2, 37 patients with CKD-3 and 16 patients with CKD-4 or 5 (not on dialysis). Serum levels of FGF-23, BSAP, TRAP-5b, sclerostin, activin A, DKK1, a-Klotho and cathepsin K were measured by ELISA and iPTH by chemiluminescent immunoassay (DiaSorin).

Results: In CKD-2, only serum activin A and sclerostin were significantly higher compared to normal controls. In CKD-3, activin A, sclerostin and iPTH were higher while in CKD-4/5, activin A, sclerostin, iPTH and FGF-23 were higher (Fig). DKK1 was not significantly higher compared to controls in CKD-2 and -3 but significantly lower in CKD-4/5 (P<0.05). BSAP, TRAP-5b, a-Klotho and cathepsin K were not different from normal controls at any stages of CKD.



# P < 0.05 versus controls. * P < 0.01 versus controls. $ P < 0.01 versus CKD-2 and CKD-3

Conclusions: The data show elevated blood levels of activin A and sclerostin as early as CKD-2 preceding elevated levels of iPTH and FGF-23. The pathogenic and diagnostic relevance of these findings awaits further studies. Activin A and sclerostin blood levels may be of interest as new biomarkers for ROD early in the course of loss of kidney function.

Funding: NIDDK Support, Private Foundation Support

TH-PO557

Changes in Markers of Mineral Metabolism following Living Kidney Donation Sven-Jean Tan,[1,2] Timothy D. Hewitson, Peter D. Hughes,[1,2] Stephen G. Holt,[1,2] Nigel David Toussaint.[1,2] *[1]Nephrology, The Royal Melbourne Hospital, Parkville, Victoria, Australia; [2]Medicine (RMH), The Univ of Melbourne, Parkville, Victoria, Australia; [3]The Royal Melbourne Hospital.*

Background: Aim: To evaluate the effect of nephrectomy on markers of mineral metabolism in living kidney donors (LKD) compared to healthy volunteers (HV) over 12 months. **Background:** LKDs experience reduction in kidney function however serum phosphate (sPi) levels are lower when compared to eGFR-matched CKD patients. Mineral metabolism adaptations that occur in LKDs have not been adequately investigated.

Methods: Twenty-one adult LKDs and twenty HVs were evaluated with respect to renal function and mineral metabolism parameters, including sPi, intact parathyroid hormone (PTH), fibroblast growth factor-23 (FGF23), soluble Klotho (sKl) and urinary phosphate, prior to donation (T_0), 1-month (T_1), 6-months (T_6) and 12-months (T_{12}) post kidney donation/baseline. Statistical analyses were conducted on normalised variables and changes were assessed using two-way ANOVA.

Results: Mean (±SD) age of LKDs and HVs were 54.1 ± 14.7 and 52.6 ± 8.0 years respectively. There were no baseline clinical or biochemical differences between LKDs and HVs. At T_1, mean (±SD) serum creatinine (sCr) increased from 75 ± 12 to 114 ± 22 umol/L, with FGF23 elevation (52 ± 15 to 70 ± 19 pg/mL) and sKl reduction (564 (469-662) to 424 (375-523) pg/mL), all p<0.001. Changes were sustained at T_{12}. Following donation, LKDs consistently demonstrated lower sPi compared with T_0 (1.08 ± 0.15 mmol/L) though maximal sPi change was detected at T_6 (0.89 ± 0.17 mmol/L), p<0.001. Other markers of mineral metabolism were unchanged in LKDs. There were no differences in parameters over 12 months in HVs.

Conclusions: Prospective evaluation of mineral metabolism parameters in LKDs provides valuable insight into compensatory mechanisms following reduction in kidney function. Further reduction of sPi at T_6 despite early alterations in FGF23 and sKl suggest adaptation of mineral metabolism continues long-term in LKDs.

Funding: Government Support - Non-U.S.

TH-PO558

FGF23 Initially Plays a Important Role on Phosphate Homeostasis in Chronic Kidney Disease Takaaki Kimura,[1] Kazuhiro Shiizaki,[2] Makoto Kuro-o,[2] Takashi Yagisawa.[1] *[1]Div of Renal Surgery and Transplantation, Dept of Urology, Jichi Medical Univ, Shimotsuke-City, Tochigi, Japan; [2]Div of Anti-Aging Medicine, Center for Molecular Medicine, Jichi Medical Univ, Shimotsuke-City, Tochigi, Japan.*

Background: It has been well known that phosphate homeostasis is regulated by the increased level of fractional excretion of phosphorus (FEP), which is the ratio of clearance of phosphorus and creatinine, exerted by both fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) as the phosphaturic hormones, so serum phosphate level is kept within the normal range until the end stage of chronic kidney disease (CKD). However, the precise mechanism and the induction point of such kind of compensatory mechanism for the phosphate homeostasis in CKD have not been recognized. We evaluated the phosphate homeostasis in the artificial CKD model, which is the patients undergone a nephrectomy (Nx) as the kidney donors.

Methods: Twenty-one kidney donors were included and the estimated glomerular filtration rate (eGFR), the amount of urine phosphorus excretion per day, FEP, serum FGF23, Vitamin D (1,25(OH)2D), and PTH levels were measured. These data were collected one month before and six months after Nx.

Results: The eGFR after Nx was significantly decreased from 74.0±15.4 mL/min/1.73m2 to 47.0±10.7 mL/min/1.73m2 ($p < 0.05$). The levels of FGF23 before and after Nx were 43.9pg/mL (IR: 35.7-48.0) and 62.0pg/mL (IR: 54.0-71.0), respectively ($p < 0.05$). FEP was significantly increased from 12.2% (IR: 9.7-15.1) to 20.6%(IR: 17.7-23.2) ($p < 0.05$) and 1,25(OH)2D was significantly decreased from 58.6pg/mL (IR: 50.1-66.9) to 52.7pg/mL (IR: 43.8-56.6) ($p < 0.05$). All of these changes were inducted at about 60.0 mL/min/1.73m2 of eGFR in the biphasic linear shape regression line fitted eGFR and FEP, FGF23 or 1,25(OH)2D levels. However, the amounts of urine excretion of phosphorus and serum PTH level did not change significantly (1.0g/day (IR:0.8-1.3) to 0.9g/day (IR:0.8-1.3) and 41pg/mL (IR: 33-53) to 47pg/mL (IR:34-61), respectively).

Conclusions: The compensatory mechanism for the phosphate homeostasis is induced at CKD stage 3 and the major contributing factor is FGF23 but not PTH.

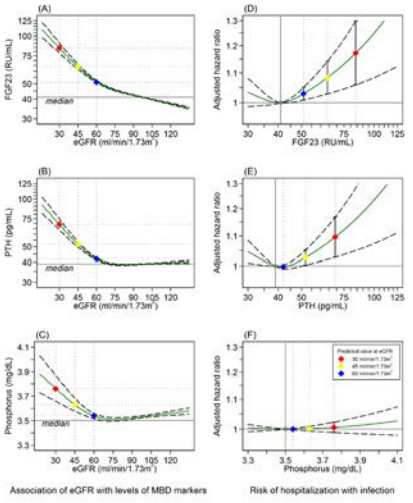
TH-PO559

Mineral and Bone Disease Markers and Risk for Hospitalization with Infection: Atherosclerosis Risk in Communities (ARIC) Study Junichi Ishigami,[1] Bernard G. Jaar,[1] Morgan Grams,[1] Csaba P. Kovesdy,[2] Josef Coresh,[1] Pamela L. Lutsey,[3] Kunihiro Matsushita.[1] *[1]Johns Hopkins Univ; [2]Univ of Tennessee; [3]Univ of Minnesota.*

Background: Elevated levels of mineral and bone disease (MBD) markers interfere with innate and adaptive immunity and thus may explain increased risk of infection in CKD patients.

Methods: Using 12,724 participants from the ARIC study (baseline during 1990-1992 and follow-up through 2013), we first assessed the cross-sectional association of serum fibroblast growth factor 23 (FGF23), parathyroid hormone (PTH), and phosphorus with eGFR; and then evaluated their longitudinal contributions to the risk for hospitalization with infection with restricted cubic spline terms.

Results: The mean age was 56.8 years, with 56% women and 25% black. At baseline, all the MBD markers were higher when eGFR was <60 ml/min/1.73m^2, and the slope for FGF23 was significantly positive across levels of eGFR (**Figure A-C**). During a median follow-up of 19.2 years, there were 5,753 hospitalizations with infection (IR, 28.2 per 1,000 person-years). Higher FGF23 and higher PTH, but not phosphorus, were associated with risk for hospitalization with infection in Cox analysis adjusting for potential confounders including eGFR (**Figure D-F**). Of note, while PTH started to be significantly associated with infection risk at around values corresponding to eGFR 45 ml/min/1.73m^2 (i.e., predicted value of PTH at eGFR 45 ml/min/1.73m^2) (yellow diamond in **Figure E**), FGF23 showed significant association even at a value corresponding to eGFR 60 ml/min/1.73m^2 (blue diamond in **Figure D**).



Conclusions: Higher levels of MBD markers were associated with low eGFR, and higher levels of FGF23 and PTH were associated with risk for hospitalization with infection beyond eGFR. FGF23 appeared to be a particularly important predictor of infection risk even at early stages of CKD.

Funding: Other NIH Support - NHLBI

TH-PO560

Fibroblast Growth Factor 23 and Risk of Incident Coronary Heart Disease Bhupesh Panwar,[1] Suzanne E. Judd,[1] Virginia J. Howard,[1] Virginia G. Wadley,[1] Nancy Jenny,[2] Monika M. Safford,[3] Orlando M. Gutierrez.[1] *[1]Univ of Alabama at Birmingham; [2]Univ of Vermont; [3]Weill Cornell Medicine.*

Background: Higher fibroblast growth factor 23 (FGF23) is associated with higher risk of heart failure and stroke. The associations of FGF23 with coronary heart disease (CHD) risk have been less consistent, perhaps due to the relatively few events in prior studies.

Methods: We examined the association of plasma FGF23 with incident CHD in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a cohort of black and white adults ≥45 years of age. Using a case-cohort design, FGF23 was measured in 829 participants who developed incident CHD (cases) and in 812 participants randomly selected from the REGARDS cohort (comparison sub-cohort).

Results: In Cox regression models adjusted for demographic factors and established CHD risk factors FGF23 was associated with increased risk of CHD (Table 1). Sex modified the association of FGF23 with CHD (p-interaction 0.07) such that among men, higher FGF23 concentrations were associated with increased risk of incident CHD in the fully adjusted model, whereas no statistically significant association of FGF23 with risk of CHD was found among women. **Table 1.** HRs (95% CI) of incident CHD by quartiles of fibroblast growth factor 23 (FGF23) overall and stratified by sex.

	FGF23 Quartile 1 (< 53 RU/ml)	FGF23 Quartile 2 (53 - 70 RU/ml)	FGF23 Quartile 3 (70.5-100 RU/ml)	FGF23 Quartile 4 (> 100 RU/ml)
Overall				
Events	122	183	208	316
Model*	ref	1.69 (1.14,2.49)	1.47 (0.97,2.25)	2.29 (1.47,3.55)
Men				
Events	80	133	129	162
Model*	ref	2.11 (1.31,3.40)	1.75 (1.04,2.94)	2.87 (1.59,5.16)
Women				
Events	42	50	79	154
Model*	ref	0.96 (0.51,1.78)	0.95 (0.49,1.86)	1.41 (0.79,2.51)

* Fully adjusted model: adjusted for demographic, clinical, and laboratory variables including estimated glomerular filtration rate and natural log-transformed albumin to creatinine ratio.

Conclusions: The association of higher FGF23 with higher CHD risk differs by sex, with the magnitude and strength of this association being greater in men than women.

Funding: Other NIH Support - National Institute of Neurological Disorders and Stroke (NINDS)

TH-PO561

Fibroblast Growth Factor 23 Induced Left Ventricular Hypertrophy Is Reversible Alexander Grabner, Christopher Yanucil, Karla J. Schramm, Brian A. Czaya, Christian Faul. *Dept of Nephrology, Univ of Miami, Miami, FL.*

Background: Left ventricular hypertrophy (LVH) is a common feature of cardiovascular injury in chronic kidney disease (CKD). Serum levels of fibroblast growth factor (FGF) 23 continuously rise as patients progress to renal failure. We have previously shown that FGF23 can activate FGF receptor (FGFR) 4 and the PLCγ/calcineurin/NFAT pathway in cardiac myocytes and cause hypertrophy. Administration of a FGFR4 blocking antibody (anti-FGFR4) in the 5/6 nephrectomy model of CKD immediately after surgery protects rats from developing LVH. Furthermore, we could show that established LVH in rats 2 weeks after surgery is reversible and treatable with a pan-FGFR blocker. The aim of the current study is to investigate if FGF23 induced hypertrophy is reversible.

Methods: Isolated neonatal rat ventricular myocytes (NRVMs) were treated with FGF23 and anti-FGFR4. To study the reversibility of FGF23-mediated cardiac hypertrophy in vivo, we elevated serum FGF23 levels in wild type mice by administration of a high phosphate (2%) diet for 3 months, followed by 3 months of regular chow. Control animals remained on high phosphate diet, or were fed regular chow for 6 months.

Results: Cultured NRVM recovered within 24 hours from cellular hypertrophy upon removal of FGF23. In the presence of FGF23, co-treatment with anti-FGFR4 reversed established hypertrophy in NRVM. Serum levels of phosphate as well as FGF23 were elevated in mice on high phosphate diet when compared to control mice on normal chow. Animals on high phosphate developed LVH as evident by significantly increased LV wall thickness and myocyte cross sectional area. When wild type mice were switch from high phosphate to normal diet, the LVH phenotype resolved within 3 months and cardiac parameters were comparable to those of mice that constantly received regular chow.

Conclusions: These findings indicate that cardiac hypertrophy caused by FGF23 elevation is reversible when FGF23 levels are normalized. Hence, we propose that FGF23-induced LVH in CKD is treatable, and that the FGF23/FGFR4 signaling mechanism in the heart provides novel options for pharmacological interventions, including FGFR4 blockade.

Funding: Other NIH Support - NHLBI, Pharmaceutical Company Support - U3Pharma

TH-PO562

Intravenous Calcium Loading Increases Fibroblast Growth Factor 23 in Normal and Uremic Rats Yasuto Shikida,[1] Masahide Mizobuchi,[1] Takashi Inoue,[1] Toma Hamada,[1] Hiroaki Ogata,[2] Fumihiko Koiwa,[3] Takanori Shibata.[1] *[1]Div of Nephrology, Dept of Medicine, Showa Univ School of Medicine, Tokyo, Japan; [2]Dept of Internal Medicine, Showa Univ Northern Yokohama Hospital, Yokohama, Kanagawa, Japan; [3]Div of Nephrology, Dept of Medicine, Showa Univ Fujigaoka Hospital, Yokohama, Kanagawa, Japan.*

Background: The mechanisms underlying the stimulation of FGF23 remain to be investigated. We studied the effect of intravenous calcium (Ca) loading on FGF23 levels in normal and 5/6 nephrectomized uremic rats.

Methods: Normal SD rats were fed a standard diet for 8 weeks and then divided into 2 groups: 1) with the standard diet (Normal-control), and 2) with intravenous calcium (20 µl/hr with 50% of $CaCl_2$ solution) infusion using a microinfusion pump (Normal-IV). Blood and urine were collected at day 1 and 7 and the kidneys were obtained at day 7 after the interventions. 5/6-nephrectomized uremic rats with the same protocol were also examined (Nx-control group and Nx-IV group).

Results: Serum creatinine and phosphorus levels were comparable throughout the period between Normal-control (Cre: 0.26±0.01 mg/dl, P: 6.1±0.2 mg/dl) and Normal-IV rats (Cre: 0.26±0.03 mg/dl, P: 6.0±0.2 mg/dl). Ionized Ca levels in blood and urinary Ca excretion at day 7 were significantly higher in Normal-IV (iCa: 1.6±0.02 mmol/l, urinary Ca: 11.0±3.5 mg/day) than those in Normal-control (iCa: 1.3±0.02 mmol/l, urinary Ca: 0.7±0.1 mg/day, $p<0.05$ respectively). FGF23 levels at day 7 in Normal-IV (1992±485 pg/ml) were significantly higher than those in Normal-control (431±22 pg/ml, $p<0.05$). Noteworthy finding was that urinary phosphate excretion at day 7 in Normal-IV (2.7±19.5 mg/day) was significantly suppressed compared with Normal-control (19.5±1.2 pg/ml) despite of FGF23 elevation. Renal Klotho mRNA expression in Normal-IV was prominently lower than that in Normal-control. These changes in the parameters were augmented in uremic rats.

Conclusions: These results suggest that intravenous Ca loading increases FGF23 in normal and uremic rats, however renal phosphate excretion was abolished suggesting that the bioactivity of FGF23 was inhibited. Decrease in renal Klotho expression might have some roles in this pathological process.

TH-PO563

Effects of Ferric Citrate Administration in a Murine Model of CKD Connor Francis, Samantha Neuburg, Lixin Qi, Xueyan Wang, Corey Dussold, Aline Martin, Myles S. Wolf, Valentin David. *Div of Nephrology and Hypertension, Dept of Medicine, and Center for Translational Metabolism and Health, Inst for Public Health and Medicine, Northwestern Univ-Feinberg School of Medicine, Chicago, IL.*

Background: Elevated levels of fibroblast growth factor 23 (FGF23) are strongly associated with cardiovascular disease, mortality and progression of chronic kidney disease (CKD). Hyperphosphatemia and iron deficiency are powerful stimuli of FGF23 production. This suggests that reducing dietary phosphate intake or absorption and increasing serum iron may lower FGF23 levels and improve clinical outcomes in CKD.

Methods: We investigated the effects of ferric citrate, which simultaneously corrects iron deficiency while also binding phosphate. We fed 4 week-old wild-type (WT) mice and Col4a3^{ko} mice (CKD), a mouse model of progressive CKD, a control diet or 5% ferric citrate-enriched diet (FC) for 6 weeks.

Results: At 10 weeks, CKD mice fed the control diet displayed a decline in renal function as shown by a 7-fold increase in BUN and a 9-fold increase in urinary albumin compared to WT in association with a marked increase in serum levels of FGF23 compared to WT (both total FGF23 [tFGF23], which detects intact and C-terminal: 11426 ± 2623 vs. 433 ± 32 pg/mL; and intact FGF23 [iFGF23]: 7312 ± 1749 vs. 207 ± 57 pg/mL; $p<0.05$ for each). Six weeks of FC significantly increased serum iron levels in both WT and CKD mice by 1.5-fold compared to mice of the same genotype fed the control diet. No other changes were observed in WT mice in response to FC. In CKD mice, 6 weeks of FC reduced serum phosphate and dramatically reduced tFGF23 by 6-fold and iFGF23 by 3-fold ($p<0.05$ for each vs. control diet). In addition, FC decreased BUN (33±8 vs. 158±24 mg/dL, $p<0.05$ vs. control diet) and 24h urine albumin (101±69 vs. 586±91 µg, $p<0.05$ vs. control diet).

Conclusions: FC administration to CKD mice reduced the magnitude of FGF23 elevation and slowed CKD progression. Further studies are needed to test whether FC might mitigate cardiac injury and improve clinical outcomes in CKD.

Funding: Pharmaceutical Company Support - Keryx Biopharmaceuticals

TH-PO564

Characteristics of Responders and Non-Responders to Phosphate Binder Therapy: A Post Hoc Analysis of a Phase 3 Study Jürgen Floege,[1] Stuart M. Sprague,[2] Anjay Rastogi,[3] Markus Ketteler,[4] Adrian Covic,[5] Sebastian Walpen,[6] Viatcheslav Rakov,[6] Sylvain Larroque,[6] Pablo E. Pergola.[7] *[1]RWTH Univ Hospital Aachen, Germany; [2]NorthShore Univ Health System, Chicago; [3]Univ of California; [4]Coburg Clinic and KfH-Dialysis Center, Germany; [5]'Gr. T. Popa' Univ of Medicine and Pharmacy, Romania; [6]Vifor Pharma, Switzerland; [7]Renal Associates PA, San Antonio, TX.*

Background: *Post hoc* analysis of a 52-wk Phase 3 study to evaluate predictors of treatment response to the iron-based phosphate binder sucroferric oxyhydroxide (SFOH) or sevelamer carbonate (SEV) in dialysis patients.

Methods: Overall, 1059 patients were randomized to SFOH (1.0–3.0 g/day; n=710) or SEV (2.4–14.4 g/day; n=349) for 12 wks' dose titration then 12 wks' maintenance. Eligible patients enrolled in a 28-wk extension study. Out of 497 patients who completed the 52-wk study, 302 responded to either SFOH or SEV (i.e. achieved serum phosphorus levels of ≤5.5 mg/dL at wk 52) and 195 patients did not respond. Differences in baseline characteristics and serum levels of CKD-MBD indices between these 2 subgroups were analyzed.

Results: Comparison of baseline characteristics showed that responders were older than non-responders ($p=0.005$). Baseline serum phosphorus levels were significantly lower in responders vs non-responders ($p<0.001$) (Table). Reductions in serum phosphorus levels during the study were greater in responders vs non-responders ($p<0.001$). Serum iPTH levels decreased in responders but increased in non-responders during the 52-wk study ($p<0.001$). FGF-23 decreased to a greater extent among responders vs non-responders after 24 and 52 wks ($p\leq0.017$).

Table: Baseline values and mean changes in serum phosphorus, iPTH and FGF23 in responders and non-responders

Parameter, Mean (SD)	Time point	Responders to SFOH or SEV (N=302)	Non-responders to SFOH or SEV (N=195)	P-value responder vs non-responder
Serum phosphorus, mg/dL	BL	7.30 (1.48)	7.85 (2.01)	<0.001
	ΔWeek 24	–2.44 (1.70)	–2.13 (2.28)	<0.001
	ΔWeek 52	–2.89 (1.62)	–0.99 (2.23)	<0.001
iPTH, pg/mL	BL	423.3 (282.5)	419.2 (287.1)	0.874
	ΔWeek 24	–51.0 (246.9)	–32.6 (237.1)	0.435
	ΔWeek 52	–28.6 (299.2)	102.7 (356.7)	<0.001
FGF23 (SD), µg/l	BL	98.4 (201.3)	110.4 (204.2)	0.532
	ΔWeek 24	–41.5 (187.9)	–20.0 (199.6)	0.017
	ΔWeek 52	–76.3 (185.2)	–51.5 (273.5)	0.011

Mean (standard deviation) serum levels. BL, baseline; iPTH, intact parathyroid hormone; FGF23, fibroblast growth factor receptor-23; SD, standard deviation; SEV, sevelamer carbonate; SFOH, sucroferric oxyhydroxide

Conclusions: Age and baseline serum phosphorus levels appeared to be predictive of treatment responses to SFOH or SEV. Greater reductions in serum phosphorus were associated with more pronounced decreases in serum iPTH and FGF-23, although the impact of concomitant medications should also be considered.

TH-PO565

Effect of Non-Calcium Phosphate Binders on CKD-MBD Indices in Dialysis Patients: A Post Hoc Analysis of a Phase 3 Study Markus Ketteler,[1] Stuart M. Sprague,[2] Adrian Covic,[3] Anjay Rastogi,[4] Bruce S. Spinowitz,[5] Sylvain Larroque,[6] Viatcheslav Rakov,[6] Sebastian Walpen,[6] Jürgen Floege.[7] *[1]Coburg Clinic and KfH-Dialysis Center, Germany; [2]NorthShore Univ Health System, Chicago; [3]'Gr. T. Popa' Univ of Medicine and Pharmacy, Romania; [4]Univ of California; [5]New York Hospital Queens; [6]Vifor Pharma, Switzerland; [7]RWTH Univ Hospital Aachen, Germany.*

Background: *Post hoc* analysis of a 52-wk Phase 3 study evaluated the impact of serum phosphorus control on CKD-MBD indices among dialysis patients treated with the iron-based phosphate binder sucroferric oxyhydroxide (SFOH) or sevelamer carbonate (SEV).

Methods: 1059 patients were randomized 2:1 to SFOH (1.0–3.0 g/day; n=710) or SEV (2.4–14.4 g/day; n=349) for 12 wks' dose titration plus 12 wks' maintenance. Eligible patients enrolled in a 28-wk extension. Since SFOH and SEV had a comparable phosphorus-lowering effect during the 52-wk study and a similar impact on CKD-MBD indices, treatment groups were pooled for this analysis.

Results: Table displays changes in CKD-MBD indices. Serum phosphorus control was maintained throughout the study. Significant decreases in serum FGF-23 were observed over 52 wks. Serum iPTH decreased after 24 wks, but returned to near baseline levels by wk 52. Only minimal changes in serum calcium were observed over 1 year. Of the bone resorption markers, TRAP5b decreased significantly over 1 year, whereas CTX levels initially increased, returning to baseline levels by wk 52. Serum levels of the bone formation markers BSAP and OST increased during the study.

Table: Mean (SD) change from baseline in levels of serum markers of CKD-MBD (Completers; N=549).

Marker	Baseline	Δ Week 24	Δ Week 52 endpoint§
Phosphorus (mg/dL)	7.5 (1.7)	–2.3 (1.9)*	–2.1 (2.1)*
FGF-23 (µg/L)	100.7 (198.6)	–29.7 (188.9)*	–65.6 (219.6)*
iPTH (pg/mL)	420.3 (280.4)	–43.6 (242.3)*	23.1 (330.4)
Ca^{2+} (mg/dL)	8.8 (0.7)	0.1 (0.7)*	0.2 (0.8)*
TRAP5b (U/L)†	5.0 (2.4)	–1.1 (2.6)*	–1.1 (2.9)*
CTX (ng/mL)†	3.1 (2.3)	3.1 (4.1)*	–0.2 (2.7)
BSAP (ng/mL)‡	15.5 (12.7)	3.7 (12.8)*	1.0 (13.6)
OST (ng/mL)‡	14.3 (16.0)	1.8 (17.0)*	10.3 (25.4)*

*Significant change from baseline ($p<0.05$); †markers of bone resorption; ‡markers of bone formation; §with last observation carried forward.

BSAP, bone-specific alkaline phosphatase; Ca^{2+}, calcium; CKD-MBD, chronic kidney disease-mineral bone disorder; CTX, carboxy-terminal collagen crosslinks; FGF-23, fibroblast growth factor 23; iPTH, intact parathyroid hormone; OST, osteocalcin; SD, standard deviation; TRAP5b, tartrate-resistant acid phosphatase 5b

Conclusions: One year of treatment with SFOH or SEV was associated with significant reductions in serum FGF-23; this may be of clinical benefit in CKD patients. The observed trend toward increased levels of bone formation markers indicates a beneficial effect of phosphate-binder therapy for the activation of bone metabolism; however, the potential impact of concomitant medications needs further evaluation.

TH-PO566

Phosphocalcic Markers and Calcification Propensity for Assessment of Interstitial Fibrosis and Vascular Lesions in Kidney Allograft Recipients

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Background: Renal interstitial fibrosis (IF) and arterial lesions predict loss of function in CKD. Currently, IF and arterial lesions are evaluated invasively through routine kidney biopsies but with many limitations. Noninvasive estimation of IF and vascular lesions are currently not available.

Methods: In this retrospective study, we analyzed the associations and predictive values of phosphocalcic markers and T_{50} with chronic histological changes in 129 Kidney allograft recipients. We hypothesized that phosphate, calcium, vitamin D (25D), PTH, T_{50}, Klotho and FGF23 level may be useful markers of IF and chronic vascular lesion.

Results: PTH, T_{50} and 25D levels were independently associated to IF. PTH elevation was associated with increasing IF severity (r=0.29, p=0.001) while T_{50} (r=-0.20, p=0.025) and 25D (r=-0.23, p=0.009) were protective. On the contrary, FGF23 (r=0.18, p=0.045) and Klotho (r=-0.18, p=0.045) correlated only modestly with IF whereas calcium and phosphate were not associated with IF. PTH, 25D and T_{50} were predictors of extensive fibrosis (>40%)(Figure 1B), whereas PTH and FGF23 were modestly predictive of low fibrosis (<20%)(Figure 1A). T_{50} was the only marker associated with chronic vascular lesions assessed by the Banff score. T_{50} decreased with increasing arterial lesions (r=-0.21, p=0.038). The discriminative performance of T_{50} in predicting significant vascular lesions was modest (Figure 1C).

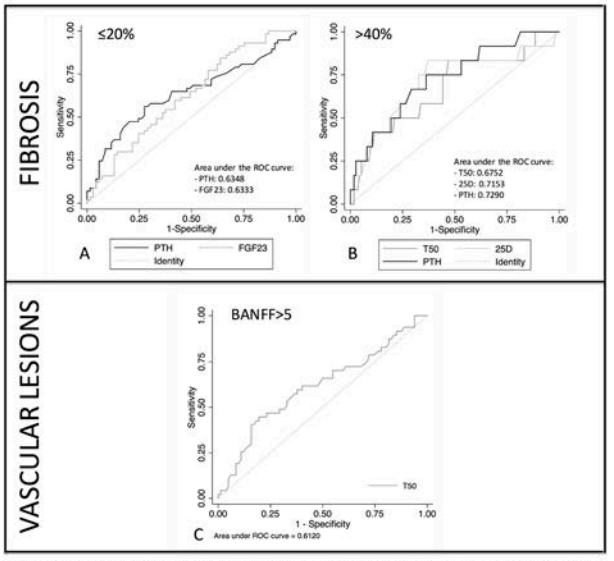

Figure 1: A: ROC curves of PTH and FGF23 in predicting fibrosis ≤20%; **B**: ROC curves of T50, 25D and PTH in predicting fibrosis >40%; **C**: Vascular lesions estimated by BANFF: ROC curve of T_{50} in predicting significant vascular lesions (BANFF cv+ah+aah >5).

As 25D and T_{50} are markers that are negatively associated with fibrosis we used the opposite values of those markers. FGF23 and PTH values were logarithmically transformed on a natural logarithm due to abnormal distribution. 25D: 25-hydroxyvitamin D; FGF23: Fibroblast growth factor 23; PTH: parathyroid hormone; ROC: Receiver Operating Characteristic; T_{50}: Calcification propensity.

Conclusions: In summary, we demonstrate that PTH, 25D and T_{50} may be useful in the noninvasive assessment of IF and vascular lesions in kidney allograft recipients. FGF23 and Klotho are in contrast of lower value in this context.

Funding: Government Support - Non-U.S.

TH-PO567

Mineral Metabolites and Ambulatory Blood Pressure: Results from the African American Study of Kidney Disease and Hypertension (AASK)

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Background: Higher serum phosphorus (P_i) and P_i regulatory hormones [fibroblast growth factor 23 (FGF-23), parathyroid hormone (PTH)] associate with higher risk of cardiovascular disease (CVD) including left ventricular hypertrophy, stroke, and heart failure. While these outcomes are highly BP dependent, it is unknown if P_i, FGF-23, and PTH associate with adverse 24h ambulatory BP (ABP) profiles as a possible mechanism.

Methods: P_i, intact FGF-23, PTH, and ABP were measured at baseline in African Americans with CKD in the AASK Cohort Study. Participants were treated to contemporary BP goals with preference for an ACE inhibitor or ARB. We modeled the association of each mineral metabolite (MM) with mean 24h systolic BP (SBP) and diastolic BP (DBP), and with blunted nocturnal dipping (<10% drop in both SBP and DBP).

Results: In 396 participants with complete data, mean eGFR was 42.6 ± 19.4 mL/min/1.73m^2, mean P_i was 3.59 ± 0.77 mg/dL, median FGF-23 was 45.4 pg/mL (IQR 32.3-75.3 pg/mL), and median PTH was 41.9 pg/mL (IQR 27.5-67.5 pg/mL). Mean SBP and DBP were 136.5 ± 17.0 and 80.5 ± 10.5 mmHg respectively, and 79% had blunted nocturnal dipping. We saw no consistent association between any MM and mean SBP or DBP (p>0.05 for all). In unadjusted models, higher P_i associated with lower risk of blunted nocturnal dipping, but we saw no linear trend on full adjustment (p=0.08). CKD severity did not modify any relationships between MMs and ABP (p-interaction>0.05 for all).

Association Between Mineral Metabolites and 24h Ambulatory BP Patterns.

	Difference in Mean SBP (95% CI)		Difference in Mean DBP (95% CI)		Blunted Nocturnal Dipping OR (95% CI)	
	Unadjusted	Adjusted[1]	Unadjusted	Adjusted[1]	Unadjusted	Adjusted[1]
Per 1 mg/dL increase in P_i	-1.17 (-3.35, +1.01)	-1.93 (-4.34, +0.48)	-0.45 (-1.80, +0.90)	-0.22 (-1.73, +1.28)	0.71 (0.52, 0.96)	0.72 (0.49, 1.05)
Per FGF-23 doubling[2]	+0.78 (-0.53, +2.10)	+0.09 (-1.43, +1.62)	+0.48 (-0.33, +1.29)	+0.21 (-0.74, +1.16)	0.92 (0.76, 1.11)	0.83 (0.64, 1.05)
Per PTH doubling[2]	+0.68 (-0.83, +2.19)	-0.41 (-2.18, +1.36)	+0.48 (-0.45, +1.41)	+0.50 (-0.60, +1.60)	0.87 (0.70, 1.08)	0.77 (0.58, 1.03)

[1] Adjusted for age, gender, income, smoking, alcohol, eGFR, albuminuria, number of anti-hypertensive medications, and 24h urine sodium and urea nitrogen.
[2] Determined by use of FGF-23 and PTH values transformed to log base 2 values.

Conclusions: With CKD and well-treated BP, higher MM levels do not associate with adverse ABP profiles in African Americans. Whether previously documented MM associations with CVD are independent of ABP or mitigated by aggressive BP control remains to be determined.

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TH-PO568

Impact of Residual Kidney Function on the Association between Parameters of Mineral Bone Disorder and Mortality in Hemodialysis Patients

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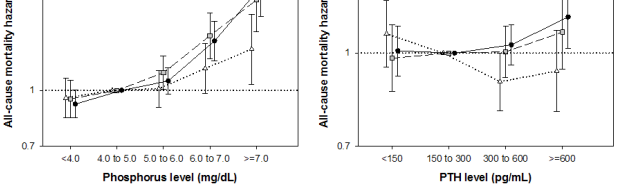
Background: The relationship between mineral and bone disorders (MBD) and survival has not yet been studied in hemodialysis patients according to their residual kidney function (RKF). We hypothesized that RKF modifies the association between MBD parameters and mortality.

Methods: The associations of serum phosphorus, uncorrected and albumin-corrected calcium, intact parathyroid hormone (PTH) and alkaline phosphatase (ALP) with all-cause mortality were examined across three strata of baseline residual renal urea clearance (CLurea) using Cox models with adjustment for clinical characteristics and laboratory measurements in 35,114 incident hemodialysis patients treated in a large dialysis organization in the U.S. between 2007 and 2011.

Results: There was an incremental mortality risk across higher serum phosphorus concentrations, which was pronounced among patients with higher CLurea (Pinteraction=0.001). Lower intact PTH were associated with higher mortality among patients with low CLurea (i.e., <1.5 mL/min/1.73m^2; Ptrend=0.02) while higher concentrations showed a trend toward higher mortality risk among patients with high CLurea (i.e., ≥3.0 mL/min/1.73m^2; Ptrend=0.09)(Pinteraction=0.002). CLurea did not modify the associations of uncorrected total calcium, corrected total calcium, and ALP with all-cause death (Pinteraction=0.8, 0.4, 0.14 respectively); higher concentrations of these markers were linearly associated with higher mortality risk across all CLurea strata.



Conclusions: RKF modified the association of serum phosphorus and intact PTH with mortality. RKF levels should be accounted for in better risk assessment of serum phosphorus and intact PTH. Additional studies are needed to better understand the mechanism behind these associations.

Funding: NIDDK Support

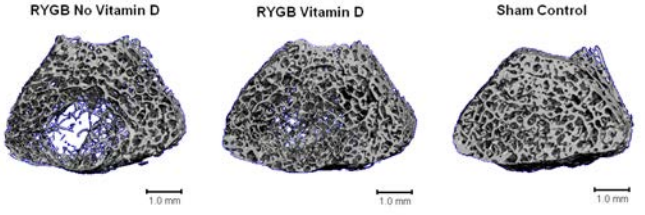
TH-PO569

Vitamin D Supplementation Does Not Improve Gastric Bypass-Related Bone Resorption Benjamin Canales,[1] Shahab Bozorgmehri,[1] Anne Schafer,[2] Thomas Carpenter.[3] *[1]Urology, Univ of Florida, Gainesville, FL; [2]Medicine, San Francisco Veterans Affairs Medical Center, San Francisco, CA; [3]Medicine, Yale Univ, New Haven, CT.*

Background: Roux-en-Y gastric bypass (RYGB)-associated bone resorption is believed to be driven by vitamin D deficiency (VDD) and secondary hyperparathyroidism. However, in humans, bone turnover markers (BTM) remain elevated despite adequate vitamin D supplementation (VDS) and PTH correction. We sought to determine additional drivers of bone resorption in a diet-induced obese (DIO) RYGB model.

Methods: Forty DIO female rats were randomized to sham or RYGB surgery. Post-operatively they were placed on 10% fat/1% calcium diet and assigned to RYGB VDD (n=10), RYGB VDS (n=10), sham pair-fed (n=10) or ad lib (n=10) groups. Calciotropic hormones, serum gut hormones, sex hormones, BTM, and urinary calcium/creatinine (UCC) were measured baseline and q4 weeks until week 12 euthanasia. Femurs were analyzed using micro-computed tomography (uCT) and 3 point bending test (BT).

Results: Compared to controls, RYGB animals had lower body weight, UCC, insulin, C-peptide, leptin, and progesterone levels along with higher GLP-1 and PYY hormones. RYGB VDS rats had higher 25-hydroxyvitamin D and lower parathyroid hormone levels than their VDD counterparts, reflecting vitamin D repletion. Despite VDS, both RYGB groups had elevated 1,25-dihydroxyvitamin, coupled increases in BTMs, more brittle bone by BT, and uCT skeletal findings of reduced trabecular bone volume and thickness (figure 1) and reduced cortical volume and thickness versus controls.



Conclusions: In our DIO model, RYGB-related bone resorption and calcium gut absorption occur independent of vitamin D status. Gut and sex hormones, particularly PYY and progesterone, may play a role in bone mass differences. Further mechanistic research to explore these differences may identify targets for RYGB bone loss prevention.

Funding: NIDDK Support

TH-PO570

MEMO1 Deletion in Mice Causes a Mineral Disorder Resembling Hypophosphatasia Matthias B. Moor,[1] Suresh Krishna Ramakrishnan,[1] Barbara Haenzi,[2] Willy Hofstetter,[3] Olivier Bonny.[1,4] *[1]Dept of Pharmacology and Toxicology, Univ of Lausanne, Lausanne, Switzerland; [2]Cambridge Centre for Brain Repair, Dept of Clinical Neuroscience, Univ of Cambridge, Cambridge, England, United Kingdom; [3]Dept of Clinical Research, Univ of Bern, Bern, Switzerland; [4]Service of Nephrology, Lausanne Univ Hospital, Lausanne, Switzerland.*

Background: Hypophosphatasia is a bone mineralization disorder generally caused by mutations in the gene coding for tissue-nonspecific alkaline phosphatase (ALPL). Mediator of ErbB2-driven Cell Motility 1 (Memo) is a redox protein and an intracellular signaling modulator of growth factors. We previously showed that renal FGF23-induced signaling requires Memo. Now, we report that Memo deficiency in mice causes a disease resembling hypophosphatasia.

Methods: Exon 2 of the *MEMO1* gene was deleted in Memo fl/fl mice using a tamoxifen-inducible Cre recombinase to obtain conditional knockout (cKO) mice. Littermates without Cre served as controls. Bones were studied by micro-computed tomography and histomorphometry. Serum, tissue and urinary chemistry were analyzed. Primary bone cell cultures were isolated and cultured for functional and metabolic studies.

Results: Memo cKO mice developed empty distal femoral metaphysis with severely disturbed trabecular structure and mineral apposition. The mice displayed higher serum calcium levels, hypercalciuria, and increased urinary inorganic pyrophosphate excretion. Serum and bone tissue ALP activities were decreased in cKO, and intracellular redox state in Memo null bone tissue was altered. Native PAGE and thiol conjugation studies revealed no differences in bone ALP protein between genotypes, but bone tissue from Memo cKO animals revealed a diminished ALP stability. Primary cultured osteoclasts and osteoblasts from Memo control and cKO animals were of comparable cellular function, but Memo null osteoblasts revealed an altered metabolic profile.

Conclusions: Memo deletion leads to a mineral disorder that may constitute a novel secondary form of hypophosphatasia associated with distinct metabolic changes in the bone.

Funding: Private Foundation Support

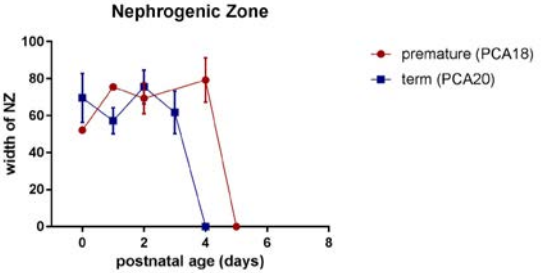
TH-PO571

Early Cessation of Nephrogenesis in Mouse Model of Prematurity Jennifer R. Charlton, Valeria M. Pearl, Hiwot M. Abate, Jennifer M. Laws, Maria Luisa S. Sequeira Lopez. *Univ of Virginia.*

Background: Premature neonates are at risk of developing chronic kidney disease (CKD). Human nephrogenesis is completed by 36 weeks gestation, whereas in rodents nephrogenesis continues until a postnatal age (PNA) of 4 days. Completion of nephrogenesis is dependent on self-renewing cells in the nephrogenic zone (NZ), but their fate following premature birth is unknown. Using a mouse model of prematurity which develops CKD as an adult, we hypothesize that NZ depletion is determined by PNA not postconceptional age.

Methods: CD-1 dams underwent C-section at post-conception age (PCA) 18 days. The term group delivered at PCA20. All pups were fostered. Pups were euthanized in the first week of life or as adults. In the pups, NZ was measured on midsagittal kidney sections, apoptosis by TUNEL+ cells and proximal tubular (PT) fraction by lotus lectin. In the adults, glomerular area and PT fraction were measured.

Results: Both body (BW) and kidney weights (KW) were smaller in the premature group as compared in the term group on PNA 2 and 4 days (n=5/grp). The NZ of the premature mouse kidney persisted at PNA 4, but was depleted by PNA 5, truncating nephrogenesis by one day in prematurely born mice.



There was no difference in the PT fraction or apoptosis on the day prior to the end of nephrogenesis between the premature and term pup groups. The premature adult female kidneys weighed more than term female kidneys (diff: 43.3 mg, 95%CI (10.1 to 76.6), p=0.02) with a higher PT fraction in the adult premature group (diff: 6%, p=0.02). There was no difference in BW, glomerular area or serum creatinine between the premature and term adult groups (n=3/grp).

Conclusions: Prematurely born mice have a shorter duration of nephrogenesis which was associated with heavier kidneys and a larger PT contribution in the adults. This model of prematurity may provide insights into the connections between human prematurity and CKD.

Funding: NIDDK Support

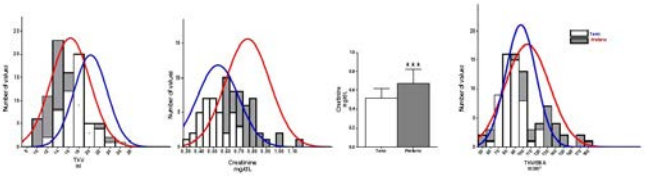
TH-PO572

Assessment of Total Kidney Volume at Birth as a Surrogate of Nephron Mass Marissa J. Defreitas,[1] Wacharee Seeherunvong,[1] Chryso P. Katsoufis,[1] Teresa C. Cano,[1] Marta G. Galarza,[2] Salih Y. Yasin,[3] Gaston E. Zilleruelo,[1] Carolyn L. Abitbol.[1] *[1]Pediatric Nephrology, Univ of Miami/Holtz Children's Hospital, Miami, FL; [2]Neonatology, Univ of Miami/Holtz Children's Hospital, Miami, FL; [3]OB/GYN, Univ of Miami/Holtz Children's Hospital, Miami, FL.*

Background: An individual's "nephron endowment" has implications for lifelong renal health and is determined by the intrauterine environment and gestational age (GA). Hence, preterm birth or low birth weight may predispose to kidney disease in later life. Our objective was to determine if neonatal total kidney volume (TKV) indexed to body surface area (BSA) would reveal an advantage of nephron mass across GA groups and to provide baseline normative data to be followed prospectively relative to kidney function.

Methods: A cross-sectional cohort of 140 healthy newborns, 84 preterm (PT; ≤37 weeks GA) and 56 term (T; >37 weeks GA), was enrolled at birth for evaluation of kidney size and function. Infants with congenital anomalies, acute kidney injury by KDIGO modified criteria, ≤24 weeks GA, and ≤500 g were excluded. TKV was determined by renal ultrasound and reported in milliliters (ml) indexed to body size parameters. Kidney function was assessed by serum creatinine (Scr) and Cystatin C (CysC).

Results: TKV correlates closely with kidney function in the neonate. TKV/BSA (ml/m^2) is independent of GA. Average Scr ± SD for the entire cohort was 0.6±0.2, while T-Scr was 0.5±0.1 compared to PT-Scr of 0.7±0.2 mg/dl (p<0.001). Similarly, CysC distinguished T from PT infants (1.3±0.2 vs 1.5±0.2 mg/L; p<0.001).



Conclusions: TKV/BSA offers an assessment of nephron mass that is independent of gestational age providing a simple and non-invasive measure of renal adaptation potentially across a lifespan.

Funding: Private Foundation Support

TH-PO573

The Endocytic Role of OCRL and INPP5b in Mouse Proximal Tubulopathy

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Background: Human mutations in inositol polyphosphate 5-phosphatase, *Ocrl* (Occulocerebrorenal Syndrome of Lowe) has been demonstrated to cause proximal tubulopathy in Lowe Syndrome (LS) patients. In-vitro cell culture work suggests the role of Ocrl in the uncoating of clathrin coated pits and actin regulation. Yet, the in-vivo mechanisms on how the loss of function of OCRL results in Fanconi's Syndrome remains unclear.

Methods: Genetic ablation of *Ocrl* doesn't recapitulate the human phenotype in mice models suggesting that an OCRL paralog, *Inpp5b* may compensate for the lack of OCRL. Therefore doxycycline (Dox) induced renal tubule specific *Inpp5b* knockout mice on an underlying *Ocrl* KO background (*Ocrl*$^{-/-}$, *Pax8*^{rtTa}, *TetO-Cre Inpp5b*$^{fl/fl}$ (DKO)) were generated. To assess endocytosis in-vivo, fluorescently tagged lactoglobulin, dextran, or horseradish peroxidase (HRP) was injected in control, *Ocrl* KO, and DKO mice.

Results: DKO mice exhibited robust low molecular weight proteinuria, phosphaturia (control:6.70 (Urine phosphate/urine creatinine ratio)) vs DKO:16.30, 3 months after Dox induction), glucosuria, and acidemia which mimics what has been observed in LS patients. DKO mice displayed massive reduction in endocytic uptake of lactoglobulin, dextran, and HRP in the proximal tubules. To further elucidate how marked inhibition of endocytosis would impact NaPi2a function, we examined NaPi2a trafficking in-vivo. DKO mice showed a marked delay in NaPi2a internalization after PTH injection. DKO mice also displayed elevated plasma and urine PTH. Lastly, after 8 months following Dox induction, the mutant mice develop kidney failure and fibrosis.

Conclusions: We have generated a genetic mouse model of LS developing a proximal tubulopathy and have revealed that loss of Ocrl and Inpp5b function in-vivo results in significant defects in clathrin mediated endocytosis suggesting that this fundamental process likely contributes to the kidney manifestations observed in LS.

TH-PO574

AT2R Deficiency Induces Podocyte Apoptosis and Epithelial Mesenchymal Transformation via Ectopic Hedgehog Interacting Protein Gene Expression

Min-Chun Liao,[1] Xin-Ping Zhao,[1] Shiao-Ying Chang,[1] Chao-Sheng Lo,[1] Isabelle Chenier,[1] Julie R. Ingelfinger,[2] John S.D. Chan,[1] Shao-Ling Zhang.[1] *[1]CRCHUM, Univ of Montreal, Montreal, QC, Canada; [2]Pediatr Nephrol Unit, Mass. Gen. Hosp., Boston, MA.*

Background: Angiotensin type 2 receptor (AT_2R) deficient mice (AT_2RKO) exhibit a spectrum of congenital abnormalities of the kidney and urinary tract (CAKUT); however, the mechanisms by which these abnormalities occur are poorly understood. We aimed to study whether AT_2R deficiency impairs glomerulogenesis via podocyte apoptosis and/or epithelial mesenchymal transformation (EMT) and also to elucidate the underlying mechanisms *in vivo* and *in vitro*.

Methods: Embryonic kidneys of nephrin-cyan fluorescent protein (CFP)-transgenic (Tg) (Nephrin-CFP-Tg) and Nephrin/AT_2RKO mice were used to assess glomerulogenesis; kidneys from neonate to 3 weeks old of suckling pups --both wild-type (WT) and AT_2RKO mice were used to evaluate mature podocyte morphology/function. Immortalized mouse podocytes (mPODs) were employed for *in vitro* studies.

Results: AT_2R deficiency resulted in diminished glomerulogenesis in E15 embryos, but had no impact on actual nephron numbers in neonates. Pups lacking AT_2R displayed features of renal dysplasia—e.g., lower glomerular tuft volume and podocyte number, and retarded podocyte maturation, as revealed by podocyte markers (Wilms tumor-1 (WT-1), p57, nephrin and synaptopodin). *In vivo* and *in vitro* studies, demonstrated that loss of AT_2R was associated with significantly elevated oxidative stress and increased ectopic hedgehog interacting protein (*Hhip*) gene expression in podocytes, which in turn, led to podocyte apoptosis. Concomitantly, the increased Hhip expression enabled interaction with TGFβ1 RI/II, targeting TGFβ1-Smad2/3 cascades to trigger epithelial-mesenchymal transition (EMT) in podocytes.

Conclusions: Loss of AT_2R is associated with podocyte apoptosis and EMT, and the underlying mechanism appears to be mediated, at least in part, via augmented ectopic Hhip expression.

Funding: Government Support - Non-U.S.

TH-PO575

Caspase-3 Mediates Inhibition of Ureteric Branching and Nephrogenesis by Maternal Nutrient Restriction in Mice

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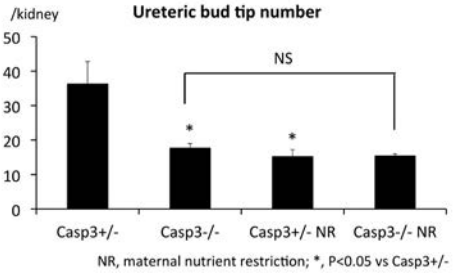
Background: We reported that maternal nutrient restriction (NR) inhibits ureteric branching, nephrogenesis, and caspase-3 (Casp3) activity in rats (Pediatr Res, 2015). Ureteric branching and nephron number are reduced in homozygous caspase-3-deficient mice (Casp3-/-) compared with heterozygous (Casp3+/-) and wild type mice (WT), probably due to Casp3's action to enhance migration of ureteric bud cells (ASN 2011, 2012). We now examined the role of Casp3 in reduced ureteric branching and nephrogenesis by NR in mice.

Methods: Pregnant C57BL/6J mice were subjected to 50% food restriction throughout pregnancy. Female Casp3 (+/-) or Casp3 (-/-) were mated with Casp3 (-/-) or Casp3 (+/-), respectively. Ureteric buds were visualized by pancytokeratin staining. Glomerular density was determined on HE sections. Glomerular number was counted by acid maceration.

Results: In WT, NR significantly reduced fetal body weight (156±4 vs 167±5 mg) and ureteric tip number (15.9±0.8 vs 36.9±2.4/kidney) at embryonic day 13 (E13). Glomerular number counted at 7 weeks was decreased in NR by 20% ($P<0.05$). At E13, body weight of Casp3-/- was not different vs Casp3+/- (131±10 vs 139±18 mg, n=5-6), but ureteric tip number was significantly reduced.



NR, maternal nutrient restriction; *, P<0.05 vs Casp3+/-

NR significantly decreased ureteric branching of Casp3+/- without affecting body weight (124±10 vs 139±18). In contrast, NR had no effect on body weight or ureteric tip number of Casp3-/-. Under NR conditions, there was no difference in glomerular density between Casp3+/- and Casp3-/- at E15 and E16.

Conclusions: NR reduces ureteric branching and nephrogenesis in WT and Casp3+/- mice. In contrast, NR had no effect in Casp3-/- suggesting that Casp3 mediates inhibition of ureteric branching and nephrogenesis by NR.

Funding: Government Support - Non-U.S.

TH-PO576

Aggravated Unilateral Ureteral Obstruction-Induced Renal Injury in Rat Offspring with Maternal Nutrient Restriction Is via Decreased Renal Nitric Oxide Production

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Background: Maternal nutrient restriction (NR) not only reduces nephron number but may also affect tubules, interstitium, capillary density, and endothelial function. We reported that NR aggravates tubular necrosis and interstitial fibrosis after unilateral ureteral obstruction (UUO) without affecting peritubular capillary density (ASN 2015). Increased or decreased nitric oxide (NO) has been shown to alleviate or aggravate UUO-induced renal injury, respectively. We examined whether aggravated UUO-induced renal injury in NR is due to decreased renal NO production and if so investigated the mechanism.

Methods: Six-week-old offspring from rats given food ad libitum (CON, n=7) and those subjected to 50% food restriction throughout pregnancy (NR, n=11) were subjected to left UUO. Body weight, blood pressure (BP), blood urea nitrogen (BUN) were examined before and after UUO. Urine from the left kidney were collected at the time of sacrifice. Urine NO was measured by ELIZA. Kidneys were stained with HE and Masson trichrome for the quantification of collagen. Expression of eNOS was assessed by immunoblot.

Results: Before UUO, body weight was significantly lower (131±6 vs 163±8 g) and BP was significantly higher in NR than CON (104±3 vs 94±6 mmHg). After UUO, there was no difference in body weight between CON and NR (153±8 vs 177±15 g). Systolic BP increased significantly in NR (118±5) but not in CON (105±7 mmHg). BUN also did not change in CON (20.5±0.7 to 23.1±2.8) but increased significantly in NR (16.8±1.1 to 20.7±1.4 mg/dl) after UUO. Tubular necrosis was more extensive and the collagen area ratio of the obstructed kidney was significantly greater in NR compared with that in CON (5.4±2.3 vs 2.6±0.3%). Urine NO of the obstructed kidneys was significantly decreased in NR compared with that in CON (57±14 vs 586±238 nmol/mg Cr). eNOS expression of the obstructed kidney was increased vs contralateral kidneys in both CON and NR, but the extent was less in NR.

Conclusions: Decreased renal NO production in NR may explain more severe UUO-induced renal injury.

Funding: Government Support - Non-U.S.

TH-PO577

Uroplakins Play a Protective Role during Obstructive Nephropathy

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Background: Studies involving the *mgb*$^{-/-}$ mouse model of congenital obstructive nephropathy indicate an adaptive role for the renal urothelium during the development of progressive hydronephrosis. Specifically, uroplakin transcripts and protein expression were significantly increased, as well as the Krt14 progenitor cell marker. Recently, the tetraspanin uroplakin, *Upk1b*, has been implicated in urothelial plaque formation and stabilization of renal urothelium. We hypothesize that urothelial remodeling and increased urothelial plaque formation during congenital obstructive nephropathy is a protective measure against the development and progression of hydronephrosis.

Methods: To test our hypothesis, we destabilized the urothelial plaque through genetic ablation of *Upk1b* in *mgb*$^{-/-}$ mice and quantitated hydronephrosis using ultrasound. Biochemical and immunhistochemical techniques were used to characterize uroplakin, Krt14, Krt5, and Ki67 expression patterns in renal urothelium.

Results: Loss of *Upk1b* caused destabilization of the urothelial plaque in *mgb*$^{-/-}$ mice, increased proliferation, increased urothelial cell layers and expression of Krt14 and Krt5 basal urothelial cells. Electron microscopy and a FITC-dextran permeability assay identified defects in the urine permeability barrier in the absence of *Upk1b*. Compound homozygotes (*Mgb*$^{-/-}$;*Upk1b*$^{RFP/RFP}$) develop worse, bilateral hydronephrosis at an earlier age than either mouse strain alone (*Mgb*$^{-/-}$ - unilateral, moderate; *Upk1b*$^{RFP/RFP}$ - bilateral, moderate), and often die prematurely suggesting the loss of the urothelial plaque leads to earlier and faster disease progression.

Conclusions: To our knowledge, we provide the first evidence that remodeling of the renal urothelial plaque functions to protect the kidney in the context of congenital obstruction in a mouse model. The clinical significance of this finding remains to be fully evaluated in children with similar defects, such as ureteropelvic junction obstruction.

Funding: NIDDK Support

TH-PO578

Conditional Ablation of Urothelial Cells for Identification of Context Specific Roles during Renal Disease Ashley R. Jackson,[1] Christina B. Ching,[1,2] Birong Li,[1] Kirk M. McHugh,[1,4] Brian Becknell.[1,3] *[1]Center for Clinical and Translational Research, Nationwide Children's Hospital Research Inst; [2]Urology Div, Nationwide Children's Hospital; [3]Nephrology Section, Nationwide Children's Hospital; [4]Dept of Anatomy, Ohio State Univ.*

Background: Urothelium serves vitals roles in establishing a urine permeability barrier, in part through the elaboration of uroplakin (Upk) plaques. *Upk1b* deficiency leads to hydronephrosis, urothelial dysplasia, and altered infectious susceptibility. To better understand the role of Upk+ cells in renal disease, we adapted a technique to ablate Upk+ cells in an inducible manner. Here we provide the first report of genetic ablation of Upk2+ urothelial cells in the renal pelvis and urothelium.

Methods: The *Upk2-iCre* mouse was used to drive Cre/LoxP dependent expression of a tdTomato reporter (Ai14) or a floxed HBEGF (Diphtheria Toxin Receptor; DTR) in a tamoxifen (TM)-dependent manner. Five daily doses of 75 mg/kg body weight TM were IP injected into six week old *Upk2-iCre*$^{+}$*;Ai14*$^{+}$ and *Upk2-iCre*$^{-}$*;Ai14*$^{+}$ mice. Organs were harvested at 1 week. Adult *Upk2-iCre*$^{+}$*;ROSA*^{iDTR}and *Upk2-iCre*$^{-}$*;ROSA*^{iDTR} mice were Cre activated as above followed by a single IP dose of 0.25mg/kg or 0.5mg/kg body weight diphtheria toxin (DT). Mice were euthanized 24 hours after DT administration and cellular ablation was analyzed by routine histology and dual immunofluorescent labeling.

Results: Cre-recombinase specificity in Upk2(+) cells was confirmed in *Upk2-iCre*$^{+}$*;Ai14*$^{+}$ mice by anti-RFP detection. Multiple layers of bladder, ureter and renal pelvis urothelium were RFP+,whereas isolated RFP+ cells were identified in the renothelium. In *Upk2-iCre*$^{+}$*;ROSA*^{iDTR} but not *Upk2-iCre-;Rosa*^{iDTR}, Upk(+) cells were absent following DT treatment. While Krt14(+) and Krt5(+) basal urothelial cell populations remained in *Upk2-iCre*$^{+}$*;ROSA*^{iDTR}, bladder, ureter, renal pelvis and renothelium each revealed loss of Upk-expressing cells.

Conclusions: Temporally controlled, cell specific ablation of Upk+ cells can be achieved using the *Upk2-iCre* and *Rosa*^{iDTR} mice. This technique will be utilized to determine the impact of urothelial destabilization on renal injury in the settings of pyelonephritis and obstructive nephropathy.

Funding: NIDDK Support

TH-PO579

Morphologic Basis for Urothelial Remodeling during Obstructive Nephropathy Rachel Millner,[1] Ashley R. Jackson,[2] Kirk M. McHugh,[2,3] Christina B. Ching,[2,4] Brian Becknell.[1,2] *[1]Nephrology Section, Nationwide Children's Hospital; [2]Center for Clinical and Translational Research, Nationwide Children's Hospital; [3]Dept of Anatomy, Ohio State Univ; [4]Urology Div, Nationwide Children's Hospital.*

Background: Ureteropelvic junction obstruction (UPJO) is the most common cause of pediatric obstructive nephropathy. The urothelium establishes the urine permeability barrier and protects obstructed renal parenchyma. Here, we investigated the morphologic basis for pelvic urothelial remodeling during UPJO.

Methods: Resected tissues were obtained with informed consent from 15 patients undergoing pyeloplasty. Adult male FVB/N mice underwent unilateral ureteral obstruction or sham operation, followed by euthanasia at post-operative days 1, 3, 7, or 14. Sections from UPJ, proximal renal pelvis, and distal ureter were subject to histologic stains and immunofluorescence microscopy using urothelial markers (CK5, CK14, UPK3A) and proliferation antigens (Ki67, PCNA).

Results: In UPJO cases, urothelial thickening occurs in the proximal pelvis, with loss of structural integrity compared to distal ureter. Obstructed UPJ and renal pelvis exhibit absent or patchy UPK3A staining, whereas UPK3A is distributed uniformly at the apical surface of the urothelium in distal ureteral segments. CK5 and CK14, proteins typically expressed by basal progenitor cells, localize diffusely throughout the obstructed renal pelvis and UPJ, extending into the apical layer. Widespread urothelial expression of cell proliferation antigens Ki67 and PCNA occurs in CK5+ and CK14+ cells. In mice, UPJO leads to loss of mucosal integrity and expansion of CK5 and CK14 throughout the renal pelvis, with increased urothelial cell thickness and proliferative index.

Conclusions: This study provides a morphologic basis for urothelial remodeling during UPJO, characterized by exfoliation of UPK3A+ apical cells, disrupted urothelial barrier function, and proliferation of CK5+ and CK14+ progenitors. While urothelial remodeling may initially occur as a physiologic response to urine back-pressure, this may prove maladaptive and contribute directly to renal pathology in obstructive nephropathy. Further studies are warranted to test this hypothesis directly.

Funding: NIDDK Support

TH-PO580

Structural Variants Analysis in Patients with Posterior Urethral Valves Valentina Capone,[1] Miguel Verbitsky,[1] David Fasel,[1] Rik Westland,[2] Monica Bodria,[7] Friedhelm Hildebrandt,[3] Asaf Vivante,[3] Francesco SCOLARI,[4] Marijan Saraga,[5] Velibor Tasic,[6] Krzysztof Kiryluk,[1] Gian Marco Ghiggeri,[7] Simone Sanna-Cherchi.[1] *[1]Colmbia Univ, NY; [2]VU Univ Med Center, Amsterdam; [3]Harvard Medical School, Boston; [4]Div of Nephrology, Brescia; [5]Deptartment of Pediatrics, Univ of Split, Split; [6]Univ Children's Hospital, Skopje; [7]Gaslini Inst, Genoa.*

Background: PUV is among the most severe non-malignant urologic diseases, but its etiology is mostly unknown. Despite its rarity, PUV accounts for almost 20% of pediatric end-stage renal disease (ESRD). We hypothesize a genetic background of PUV based on its presence in genetically determined syndromes (i.e. Townes-Brocks and Down syndrome). No mutations associated to isolated PUV have been identified so far, providing a unique opportunity for gene discovery. Given the rarity of familial forms and its high mortality and morbidity, *de novo* dominant mutations are the most likely variant explaining PUV.

Methods: We performed genome-wide CNV analysis in 152 patients with PUV: 137 were genotyped using high-density SNP microarrays and 15 were subjected to WGS. QC of DNA microarrays data and CNV analysis were performed with PLINK and PennCNV software. Analysis of WGS data was performed using Genome STRiP and Delly v0.59. Structural variants were annotated with UCSC RefGene and RefExon, 1000 Genome data, an in-house list of 220 known genomic disorders and 21,575 controls.

Results: We identified structural variants diagnostic for 21 known genomic syndromes (7 deletions and 14 duplications) in 18/152 patients (12%), compared to 98/21,575 controls (0.45%; p-value<$2.2x10^{-16}$, OR=29.4). Duplications were found at loci usually deleted in patients with kidney malformations.

Conclusions: Our data indicate that PUV patients are enriched in genomic imbalances with a high burden of structural variants diagnostic for known genomic syndromes. The presence of heterozygous CNVs supports our model of dominant deleterious mutations with large effect size. Among the 5 patients with parental data, 3 CNVs were de novo and 2 inherited from the maternal side, which supports our hypothesis that PUV can be likely determined by de novo or by maternally inherited mutations, since the phenotype is not expressed in females.

Funding: NIDDK Support, Private Foundation Support

TH-PO581

Novel Biomarkers of Obstructive Uropathy: Urinary Antimicrobial Peptides Brian Becknell,[1,2] Janae Preece,[3] Sudipti Gupta,[1] Rachel Millner,[2] Christina B. Ching.[1,3] *[1]Center for Clinical and Translational Research, Research Inst at Nationwide Children's Hospital; [2]Nephrology Section, Nationwide Children's Hospital; [3]Urology Div, Nationwide Children's Hospital.*

Background: Epithelial antimicrobial peptides (AMPs) are well defined in urinary tract infection due to their bactericidal and bacteriostatic activity. Their role in obstructive nephropathy, however, is less well known. We evaluated urinary AMP expression in anatomic and functional urinary tract obstruction.

Methods: With IRB approval, urine was collected from 3 pediatric populations: 1) Obstructed group: patients undergoing surgical intervention for ureteropelvic or ureterovesical junction obstruction; 2) Neurogenic group: patients with known spinal cord abnormality (i.e. myelomeningocele); 3) Control group: children in a general nephrology clinic without obstruction, neurologic lesion, or UTI. Patients with augmentation cystoplasty were excluded. ELISAs were run to detect beta defensin 1 (BD-1), human alpha defensin 5 (HD-5), HIP/PAP, LL-37, and NGAL, and normalized to urine creatinine. Results were analyzed with Mann-Whitney U test. A p-value of <0.05 was considered significant.

Results: 21 obstructed, 12 neurogenic, and 17 controls samples were obtained. The mean (median, range) age of obstructed, neurogenic, and control patients were: 5.4 years (4.3 years; 3.6 months-18.4 years), 5.7 years (4.6 years; 3.6 months-15.8 years), 12.9 years (13.3 years; 7-18 years). Males represented 76%, 58%, and 65% of the samples, respectively. All AMPs were significantly higher in obstructed and neurogenic patients as compared to controls: BD-1 (p<0.0001 and p=0.0006), HD-5 (p<0.0001 and p=0.0013), HIP/PAP (p<0.0001 and p=0.0004), NGAL (p=0.0046 and p=0.0416), and LL-37 (p<0.0001 and p=0.0005). BD-1 levels were significantly higher in neurogenic versus obstructed patients (p=0.0401).

Conclusions: AMPs may serve as biomarkers of obstructive uropathy, whether from anatomic obstruction or functional obstruction due to a neurologic lesion. Expression in non-infectious urinary tract conditions suggests alternative biological roles for AMPs as damage-associated molecular patterns and/or mediators of epithelial regeneration.

TH-PO582

Essential Roles for IL-6/Stat3 Signaling in Antimicrobial Gene Expression during Experimental Urinary Tract Infection Birong Li,[1] Sudipti Gupta,[1] Nicholas Ryan Mayne,[4] Christina B. Ching,[1,2] Brian Becknell.[1,3] *[1]Center for Clinical and Translational Research, The Research Inst at Nationwide Children's Hospital; [2]Urology Div, Nationwide Children's Hospital; [3]Nephrology Section, Nationwide Children's Hospital; [4]Nationwide Children's Hospital.*

Background: Host factors required for antimicrobial peptide (AMP) expression during urinary tract infection (UTI) are incompletely understood. Interleukin-6 (IL-6) levels increase during UTI, but the mechanisms whereby IL-6 promotes host immunity remain unclear. We hypothesized that IL-6 signals through the signal transducer and activator of transcription (Stat3), to drive AMP expression in infected urothelium.

Methods: We performed experimental UTI by transurethral inoculation of uropathogenic *Escherichia coli* (UPEC) in IL-6 knockout versus wild-type mice, as well as mice treated with IL-6 neutralizing antibody or isotype control. We determined the role of bacterial endotoxin signaling in Stat3 Tyr705 phosphorylation through *Tlr4* hypomorphic mice. We measured Stat3 activation based on Tyr705 phosphorylation in infected urinary tracts and primary human urothelial cells by immunoblotting. We localized pStat3 Tyr705 in experimentally infected urothelium by immunofluorescence. We measured mRNA expression of Stat3 target genes including AMPs by quantitative RT-PCR.

Results: UPEC inoculation leads to brisk Stat3 Tyr705 phosphorylation in bladder and renal urothelium in a Tlr4-dependent manner. IL-6 neutralization or gene ablation significantly reduces urothelial pStat3 Tyr705 levels. Conversely, administration of recombinant IL-6 leads to Stat3 Tyr705 phosphorylation in murine and human urothelium. We globally identify transcriptional targets of IL-6/pStat3 Tyr705 signaling in UPEC infected urothelium and demonstrate that IL-6 knockout mice exhibit significantly impaired expression of the AMPs *Reg3g* and *Reg3b* following experimental UTI.

Conclusions: IL-6/pStat3 Tyr705 signaling drives a conserved transcriptional program of AMP expression in UPEC infected urothelium. Deficiencies in IL-6/pStat3 Tyr705 activation may explain infection predisposition in certain patients with UTI. Conversely, local pharmacologic activation of pStat3 Tyr705 through IL-6 may promote mucosal immunity in individuals with recurrent UTI.

Funding: NIDDK Support

TH-PO583

Urinary YKL-40 as a Candidate Biomarker for Febrile Urinary Tract Infection in Young Children Jin-Soon Suh,[1] Byoung-Soo Cho.[2] *[1]Dept of Pediatrics, College of Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea; [2]Director of MIRAE-iNG Kidney Center, MIRAE-iNG Kidney Center.*

Background: YKL-40 is regarded as a site-specific inflammatory marker. We sought to evaluate the association of YKL-40 with urinary tract infection (UTI) in febrile children.

Methods: We enrolled 44 children aged from 0 to 24 months with febrile UTI and 35 controls who were matched for age and sex, but had other causes of fever. An enzyme-linked immunosorbent assay was used to determine the level of YKL-40 in urine collected from each child.

Results: The ratio of urinary YKL-40/creatinine (Cr) was higher in the children with UTI than in the controls (P<0.001). The area under a receiver-operator characteristic curve for detecting UTI was 0.88 for urinary YKL-40/Cr, 0.86 for pyuria, and 0.71 for positive nitrite on urinalysis. We applied a cutoff value of 125.23 pg/mg to urinary YKL-40/Cr for detecting UTI. Eight of nine children in the control group with pyuria had urinary YKL-40/Cr levels lower than 125.23 pg/mg, and the one child in the UTI group without pyuria or positive nitrite had a urinary YKL-40/Cr level greater than 125.23 pg/mg.

Conclusions: Determining the levels of urinary YKL-40/Cr, may help identify true UTI in febrile young children, especially when they have pyuria, but not nitrite.

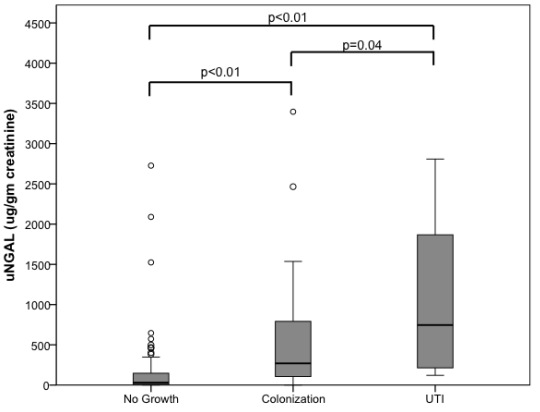
TH-PO584

Urine NGAL in Distinguishes Urinary Tract Infection from Colonization in Children on Clean Intermittent Catheterization Catherine Forster, Elizabeth C. Jackson, Stuart Goldstein. *Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

Background: Children with neurogenic bladders who require clean intermittent catheterization (CIC) frequently have bacteriuria, although distinguishing between urinary tract infection (UTI) and colonization (UTC) in this population can be difficult. Urinary neutrophil gelatinase-associated lipocalin concentrations [uNGAL] are increased in UTIs. We hypothesize that [uNGAL] will be higher in UTI compared to UTC and negative cultures.

Methods: Urine samples were obtained from children requiring CIC who had a urine culture sent for clinical care. Urine cultures were grouped as no growth, UTC, or UTI based on opinion of the managing clinician who did not know the [uNGAL]. Cultures with growth of mixed organisms or fungi, and from patients with concern for acute kidney injury were excluded. [uNGAL] was measured by ELISA, and [urine creatinine] by assay. Normally distributed continuous variables were compared by ANOVA and t-test; non-normally distributed variables were compared by Mann-Whitney U. Categorical variables were compared by chi-square.

Results: 171 cultures from 157 patients were included(no growth=80, UTC=77, UTI=14). Patients with no growth were younger than those with UTI (9.4±6.5 vs 14.7±6.7 years, p=0.02). There were more females in the UTC group compared to no growth (64.9% vs 38.8%, p<0.01). There was no difference in etiology of neurogenic bladder between groups. Median [uNGAL/Cr] was higher in the UTI group (746.1[205.7, 1914.3] µg/gm cr) compared to all groups (no growth, 30.3[8.9, 148.5](p=<0.01); UTC, 269.6 [105.7, 796.6](p=0.036)).



The AUC for NGAL for UTI was 0.79, 95% CI(0.69 -0.89).

Conclusions: [uNGAL] is elevated in children who require CIC who have UTI compared to negative cultures and UTC. uNGAL levels will provide actionable data to inform treatment decisions about UTIs in this unique population.

Funding: Other NIH Support - NRSA T32 General Pediatrics Training Grant

TH-PO585

Usefulness of Plasma NGAL as a Marker to Predict Renal Parenchymal Involvement in Infants with Febrile UTI Eun Mi Yang. *Dept of Pediatrics, Chonnam National Univ Hospital, Gwang-ju, Korea.*

Background: Accurate detection of renal parenchymal involvement in febrile urinary tract infections (UTI) is important, especially in infants. The aim of this study was to evaluate the predictive accuracy of plasma neutrophil gelatinase-associated lipocalin (NGAL) for biomarker of renal parenchymal involvement in infants with acute febrile UTI.

Methods: A total of 61 infants, who were admitted with febrile urinary tract infection, were enrolled in this study. Enrolled patients were divided into the cortical defect group (n = 40) and non-cortical defect group (n = 21), according to the result of renal scan.

Results: The patients' mean age was 4.4 ± 3.2 months. There were no significant differences between two groups in respect of age, gender, and fever duration. In cortical defect group, the white blood cell count and C-reactive protein levels were significantly higher than non-cortical defect group, respectively (11.7 ± 5.1 vs. 21.0 ± 19.5 10^3/mm^3, P < 0.001; 2,2 ± 1,3 vs. 5.5 ± 4.5 mg/dL, P = 0.001). Plasma NGAL also significantly increased in cortical defect group than non-cortical group (119 ± 135 vs. 677 ± 1951 ng/mL, P = 0.013). The most optimal cut-off value of plasma NGAL for predicting renal parenchymal involvement was defined as 230 ng/mL in the receiver operating characteristics curve analysis (sensitivity, 67.5%; specificity, 71.4%; AUC, 0.696; P = 0.006).

Conclusions: Plasma NGAL is significantly higher in cortical defect group. Although not a standalone test, plasma NGAL could be used for early detection renal parenchymal involvement in infants with acute febrile UTI.

TH-PO586

Use of Urine Sodium to Creatinine Ratio Multiplying by the Estimated Urine Creatinine for Prediction Urine Sodium in Pediatric Hypercalciuria Eun Mi Yang. *Dept of Pediatrics, Chonnam National Univ Hospital, Gwang-ju, Korea.*

Background: Elevated sodium excretion in urine resulting from excessive sodium intake can lead to hypercalciuria and contribute to the formation of urinary stones. The spot urine sodium to potassium ratio (Na/K) is a convenient method to estimate sodium excretion. The aim of this study was to evaluate the accuracy of predicting 24-hour urine sodium using spot urine sample in pediatric hypercalciuria.

Methods: This study included 58 children with hypercalciuria. The 24-hr urine creatinine level was estimated with the use of three existing equations: one equation for adult (Cockcroft-Gault formula) and two equations for children (Ghazali-Barratt and Hellerstein equation). The correlation was evaluated between spot urine samples, such as Na/K, urine sodium to creatinine ratio (Na/Cr), and corrected Na/Cr by 24-hour creatinine excretion, and 24-hour urine sodium.

Results: The patients' mean age was 8.5 years, 30 patients presented hypernatriuria (52%). There was a no significant correlation among Na/K, Na/Cr and 24-hour urinary sodium excretion. A moderate correlation was found between corrected Na/Cr by 24-hour creatinine excretion and 24-hour urine sodium (r = 0.387, P = 0.003). After estimating the 24-hr urine sodium levels by using the estimated urine creatinine, the correlation coefficients between the estimated and measured 24-hr urine sodium levels were 0.335, 0.372, and 0.351, respectively (All P < 0.05).

Conclusions: The corrected Na/Cr by 24-hour creatinine excretion improved the prediction of estimating 24-hour urine sodium. And spot Na/Cr multiplying by the estimated urine creatinine is not inferior to that of the corrected Na/Cr by measured 24-hour creatinine. The spot Na/Cr multiplying by the estimated urine creatinine can be used to predict 24-hour urine sodium in pediatric hypercalciuria.

TH-PO587

Inflammation Drives Renal Scarring in Experimental Reflux Nephropathy
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Background: Children with vesicoureteral reflux can develop renal scars after pyelonephritis, and this reflux nephropathy is associated with hypertension, proteinuria, and renal insufficiency. Limited knowledge of histopathology, immune cell recruitment and gene expression changes during pyelonephritis restricts the development of therapies to prevent acquired renal scarring. Here, we address this knowledge gap using inbred, immunocompetent mice with vesicoureteral reflux.

Methods: Female C3H/HeOuJ mice with 100% vesicoureteral reflux were transurethrally inoculated with uropathogenic *Escherichia coli* (UPEC) strain CFT073. Kidneys were analyzed by histopathology and flow cytometry. Pyelonephritis transcriptomes were evaluated by RNAseq and pathway analysis.

Results: Transurethral inoculation of UPEC leads to renal mucosal injury, tubulointerstitial nephritis, and cortical fibrosis. Fibrosis correlates most significantly with inflammation 7 and 28 days post infection. Flow cytometry identifies recruitment of neutrophils and inflammatory macrophages to infected kidneys, in proportion to renal bacterial burden. Transcriptome analysis reveals molecular signatures associated with renal ischemia-reperfusion injury, immune cell chemotaxis, and antimicrobial peptide production.

Conclusions: This murine model recapitulates the cardinal histopathologic features observed in humans with acquired renal scarring following pyelonephritis. The integration of histopathology, flow cytometry, and transcriptome data begins, for the first time, to define potential mechanisms of tissue injury during pyelonephritis in the context of an intact immune response. The relationship between inflammatory cell recruitment and fibrosis supports the hypothesis that acquired renal scarring arises as a consequence of excessive host inflammation and suggests that immunomodulatory therapies should be investigated to reduce renal scarring in patients with pyelonephritis.

Funding: NIDDK Support

TH-PO588

The Childhood Nephrotic Syndrome Observational Study: A Midwest Pediatric Nephrology Consortium Study
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Background: Childhood nephrotic syndrome (NS) is one of the most common pediatric glomerular disorders. Modern, large-scale natural history studies are lacking.

Methods: The Childhood NS Observational Study (CNOS) is a prospective, longitudinal study of children 1-18 yrs with incident NS. Children w/ secondary NS are excluded. Data are collected at presentation, 3 mo, and yearly. Two sample t-tests were used for continuous values and Fisher's exact tests for categorical values.

Results: 126 children from 10 sites had 3-month data. Prior to diagnosis, children had an avg (range) of 1.1 (0-6) primary care visits and 0.8 (0-3) ER visits with NS symptoms. 62.7% were hospitalized at dx. 84% of children were treated with a standard 12 week steroid course.

Demographic and clinical information at presentation (N)	Steroid-sensitive (N=96; 76%)	Steroid-resistant (N=30; 24%)	P-value
Age			0.003
≤ 6 years (72)	86%	14%	
> 6 years (54)	63%	37%	
Sex			0.67
Male (80)	78%	22%	
Female (46)	74%	26%	
Race/ethnicity			0.24
Caucasian, non-Hispanic (60)	78%	22%	
Black, non-Hispanic (37)	65%	35%	
Hispanic (14)	79%	21%	
Asian (8)	100%	0	
Mixed Race (2)	100%	0	
Gestational age			0.50
<37 weeks (13)	85%	15%	
≥37 weeks (80)	73%	27%	
Systolic HTN			0.18
yes (56)	71%	29%	
no (53)	83%	17%	
eGFR (ml/min/1.73m^2, mean, SD)	142.5 (81.6)	97.6 (26.8)	<0.001
Urine blood			0.43
Negative (46)	80%	20%	
Trace (14)	64%	36%	
Positive (60)	78%	22%	

Conclusions: Children w/ NS have high healthcare utilization around the time of dx. Children w/ steroid resistant NS are older and have lower eGFR at presentation. The CNOS registry will provide a framework for future observational and interventional studies in pediatric NS.

Funding: Private Foundation Support

TH-PO589

Race and Growth Velocity in Children with Nephrotic Syndrome: A Midwest Pediatric Nephrology Consortium Report
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Background: Delayed linear growth occurs in a subset of children with nephrotic syndrome (NS), but the cause is incompletely understood. An association between race and growth has been reported in children with CKD, but it is unknown whether race affects growth in children with NS.

Methods: Growth velocity of children enrolled in the multicenter prospective Childhood Nephrotic Syndrome Observational Study was assessed as the difference between height z-scores at enrollment and 1 year follow-up. Children were enrolled at the time of initial diagnosis. Race and other variables were compared between children with growth velocity below vs. above the cohort median (S - "slow" growth group vs. F - "fast" growth group, respectively), using the two-sample t-test and chi-square test. The paired t-test was used to compare height z-scores between enrollment and 1 year follow-up.

Results: Growth data were available for 71 children (54% Caucasian, 26% Black, 11% Hispanic). Height z-score was 0.07±1.49 at enrollment and 0.11±1.17 at 1 year (p=0.90). Racial distribution was significantly different between the S vs. F groups (p=0.009): non-Hispanic Blacks were more prevalent in the S and Hispanics in the F groups; the prevalence of Caucasians was not different between the groups. Gender, birthweight, gestational age and type of health insurance were not different between the groups. There was a trend toward higher prevalence of steroid-responders in the F group (p=0.06).

Conclusions: Despite steroid exposure, height z-score did not change 1 year after diagnosis in this contemporary cohort of children with NS. However, growth rates were slower in Blacks and faster in Hispanics. Further analyses are ongoing to determine whether the effect of race on growth is mediated by steroid responsiveness and development of CKD.

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TH-PO590

Vincristine Is Effective in Some Children with Challenging Nephrotic Syndrome
Vladimir Belostotsky, Steven Arora. *Pediatrics, McMaster Children's Hospital, Hamilton, ON, Canada.*

Background: Vincristine was proven to be effective in some children with Nephrotic Syndrome (NS) who had Frequently Relapsing (FRNS), Steroid Dependent (SDNS) or Steroid Resistant (SRNS) disease. Clinical trials were suggested in late 1990s to early 2000s, but never happened due to development of other therapeutic agents including Calcineurin Inhibitors (CNIs) such as tacrolimus (Tac), ciclosporin (CsA); MMF and rituximab (Rit). Aim: To review Vincristine use in our institution in complex cases of nephrotic syndrome where treatments with Steroids (S), CNIs, MMF were unsuccessful in inducing remission (Rem) (patients 1,3,4,5,6) or maintaining low frequency of relapses (patient 2).

Methods: Records of 6 children who received Vincristine for NS over last 5 years were reviewed.

Results: Vincristine was given at the dose of 1.5 mg/m^2 (max 2 mg) IV weekly for 4 doses. If successful in inducing remission then it was continued, otherwise it was stopped. Findings are summarized in table 1.

Diagnosis (D)	Biopsy	Age of D	Age now	Previous treatments and duration in months	Response to V	N of doses/ year	Current state
FRNS, SDNS then SRNS	FSGS, C1Q	2	12	S, pulsed S, CsA	yes	37/2012	Stable Rem on CsA
FRNS, SDNS	Minimal Change	2	12	S, cyclophosphamide, MMF, CsA	yes	38/2013	Stable Rem on CsA
FRNS, SDNS then SRNS	FSGS	4	11	S, pulsed S, CsA, MMF + Tac	no	4/2011	Rem after Rit+S
FRNS, SDNS then SRNS	FSGS	9	20	S, CsA, Tac, MMF	no	4/2012	Adult services
SRNS	FSGS	10	12	S, pulsed S, CsA, MMF + CsA, Plasma exchange	no	4/2015	Nephrotic on MMF
FRNS, SDNS then SRNS	Minimal Change	7	11	S, pulsed S, Tac	yes	6/2016	Rem, V ongoing

Conclusions: We found Vincristine to be effective in half of our small group of children with challenging course of NS which was resistant to CNIs and MMF. CsA seems to work better to maintain remission after treatment with Vincristine.

TH-PO591

COQ6 Mutations in Children with Steroid-Resistant Focal Segmental Glomerulosclerosis and Sensorineural Hearing Loss Eujin Park,[1] Yo Han Ahn,[2] Hee Gyung Kang,[1,3] Kee Hwan Yoo,[4] Young Seo Park,[5] IL-Soo Ha,[1] Hae Il Cheong.[1,3] *[1]Dept of Pediatrics, Seoul National Univ Children's Hospital, Seoul, Republic of Korea; [2]Dept of Pediatrics, Hallym Univ Kangnam Sacred Heart Hospital, Seoul, Republic of Korea; [3]Research Coordination Center for Rare Diseases, Seoul National Univ Hospital, Seoul, Republic of Korea; [4]Dept of Pediatrics, Korea Univ Guro Hospital, Seoul, Republic of Korea; [5]Dept of Pediatrics, Asan Medical Center, Univ of Ulsan College of Medicine, Seoul, Republic of Korea.*

Background: The phenotypic combination of steroid-resistant focal segmental glomerulosclerosis (SR-FSGS) and sensorineural hearing loss (SNHL) has been reported mainly in patients with mitochondrial cytopathies, including primary coenzyme Q10 (CoQ10) deficiency.

Methods: In this study of ten children with SR-FSGS and SNHL, we identified six patients with CoQ10 deficiency caused by biallelic COQ6mutations. We performed genotype and phenotype analyses of these six patients.

Results: The median age at the onset of nephrotic syndrome was 29 months (range 15–47 months). All patients progressed to end-stage renal disease within the median duration of 13 months (range 1–27 months) after onset. Kidney biopsies revealed FSGS with variable degrees of glomerular sclerosis, and abnormal mitochondrial proliferation in podocytes was a constant finding. None of the five patients who underwent kidney transplantation developed recurrence of FSGS.

Conclusions: Primary CoQ10 deficiency due to COQ6 mutations should be considered in children presenting with both SR-FSGS and SNHL. The condition is treatable when CoQ10 supplementation beginning in the early stage; therefore, early diagnosis of COQ6 mutations is essential. We recommend early kidney biopsy because detection of abnormal mitochondrial proliferation in podocytes might provide a means to earlier diagnosis.

TH-PO592

ADCK4-Associated Focal Segmental Glomerulosclerosis in Children Eujin Park,[1] Hee Gyung Kang,[1,2] Young Seo Park,[3] IL-Soo Ha,[1] Hae Il Cheong.[1,2] *[1]Dept of Pediatrics, Seoul National Univ Children's Hospital, Seoul, Republic of Korea; [2]Research Coordination Center for Rare Diseases, Seoul National Univ Hospital, Seoul, Republic of Korea; [3]Dept of Pediatrics, Asan Medical Center, Univ of Ulsan College of Medicine, Seoul, Republic of Korea.*

Background: ADCK4 is one of the novel genes causing autosomal-recessive steroid-resistant nephrotic syndrome (SRNS). ADCK4 interacts with components of the CoQ10 biosynthesis pathway. ADCK4 mutations usually manifest as isolated adolescent-onset focal segmental glomerulosclerosis (FSGS).

Methods: Here we tried to figure out the incidence of ADCK4 mutations in our Korean pediatric cohort of SRNS as well as phenotype analyses of the patients with ADCK4 mutations.

Results: The incidence of ADCK4-associated FSGS was 7.5% (4/53) of 5-year-old or older children with multidrug-resistant FSGS. Two additional patients were included for the phenotype analyses; one detected by family screening and the other with cyclosporine-responsive FSGS and medullary nephrocalcinosis. All six patients presented with incidentally found proteinuria. The median age at the onset was 110 months (range, 60–153 months), and five patients progressed to ESRD within a median duration of 46 months (range, 36–79 months) after the onset. Kidney biopsy revealed FSGS in all the patients (n=5), including a not-otherwise-specified (NOS) variant in three patients and a collapsing variant in two patients. Abnormal mitochondrial proliferation was detected in podocytes as well as in renal tubular epithelial cells. Interestingly, all patients accompanied bilateral medullary nephrocalcinosis of various degrees. None of the patients had neurologic or other extrarenal manifestation.

Conclusions: ADCK4 mutations should be considered in older children presenting with SR-FSGS. An early diagnosis of ADCK4mutations is essential because the condition is treatable when CoQ10 supplementation is started at the early stage. Abnormal mitochondrial proliferation in the kidney biopsy and accompanying medullary nephrocalcinosis may be useful diagnostic clues.

TH-PO593

Injuries of Glomerular Capillaries and Basement Membrane May Be Involved in Renal Dysfunction in Thin Basement Membrane Disease Yusuke Kajimoto, Takafumi Kanemitsu, Michiko Aoki, Yusuke Okabayashi, Shinya Nagasaka, Dedong Kang, Akira Shimizu, Kiyotaka Nagahama. *Analytic Human Pathology, Nippon Medical School, Bunkyo-ku, Tokyo, Japan.*

Background: Thin basement membrane disease (TBMD) is diagnosed by diffuse reduction of the thickness of glomerular basement membrane (GBM) in electron microscopy (EM), and characterized clinically by benign familial hematuria. However, some cases progress to end-stage renal disease. In the present study, we performed the clinico-pathological analyses of TBMD, especially focusing on glomerular capillary injuries, including morphological and qualitative alterations of GBM and glomerular capillaries, and correlated with clinical findings.

Methods: In our department, 27 renal biopsy cases of TBMD was identified in 1395 renal biopsy cases. We investigated clinical characteristics using clinical records. We also examined pathological characteristics using light microscopy and EM, immunostaining for CD34, which can detect glomerular capillaries, immunostaining for α5 (IV) chains of type IV collagen, which is one of the main component of GBM, and low-vacuum scanning electron microscopy (LV-SEM), which allows detailedthree-dimensional observation of GBM surface.

Results: In our cases, 26 cases (96.3%) had hematuria, 21 cases (77.8%) had proteinuria. In 6 cases, the eGFR declined in G3a to G4 in clinical CKD stage. In image analysis for CD34 immunostaining using a computer, narrowed glomerular capillaries significantly increased with accumulation of glomerular extracellular matrix (ECM) that may be associated with renal dysfunctions, compared with controls. In immunofluorescence, α5 (IV) expression was significantly reduced in the GBM with partial enhancement of α2 (IV). In LV-SEM observations, thinning and flattering of GBM was noted with multiple small holes and coarse manufactures in the surface of GBM.

Conclusions: In TBMD, narrowing glomerular capillaries with alterations of GBM developed with increased glomerular ECM, which may be associated with urinary abnormalities and renal dysfunctions. Injuries of glomerular capillaries and GBM may be developed in TBMD, and be associated with urinary abnormalities and renal dysfunction.

TH-PO594

Eculizumab Use in Pediatric Practice: Dosing and Renal Outcomes - A Collaboration of the Midwest Pediatric Nephrology Consortium (MWPNC) Keia Sanderson,[1] Melissa A. Muff-Luett,[2] Ashley K. Sherman,[3] Yi Cai,[5] Stefan Kiessling,[7] Mahmoud Kallash,[6] Yosuke Miyashita,[8] Abiodun A. Omoloja,[9] Sheena Sharma,[10] Cheryl L. Tran,[11] Donald J. Weaver,[12] Scott E. Wenderfer,[13] Robert Woroniecki,[14] Nianzhou Xiao,[15] Asif Mansuri,[16] Tracy E. Hunley,[17] Rima S. Zahr,[18] Rachel M. Engen,[19] Meredith Seamon,[20] Sarah J. Kizilbash,[21] Erica Winnicki,[22] Tarak Srivastava,[3] Carla M. Nester.[4] *[1]Univ of North Carolina Kidney Center; [2]Univ of Nebraska Medical Center; [3]Children's Mercy Hospitals and Clinics; [4]Univ of Iowa Hospital; [5]Helen De Vos Children's Hospital; [6]Women and Children's Hospital of Buffalo; [7]Kentucky Children's Hospital; [8]Children's Hospital of Pittsburg of UPMC; [9]Dayton Children's Hospital; [10]Children's Hospital of Philadelphia; [11]Mayo Clinic; [12]Carolinas Medical Center; [13]Texas Children's Hospital; [14]SUNY Stony Brook; [15]Children's Hospital of Richmond; [16]Univ of Texas Southwestern; [17]Children's Hospital at Vanderbilt; [18]Emory; [19]Seattle Children's Hospital; [20]Utah; [21]Minnesota; [22]UC Davis.*

Background: Eculizumab is approved for treatment of atypical hemolytic uremic syndrome (aHUS) but is also being used "off-label" to treat disorders with presumed complement dysregulation. The aim of the study was to characterize the use and outcomes in children treated with Eculizumab according to diagnosis.

Methods: We performed a retrospective chart review of 152 patients ≤25 years of age, treated with eculizumab at 21 centers within the MWPNC.

Results: Eculizumab was used for "off-label" diagnoses in 44.1%. 31% received non-standard dosing. The reasons for alternative dosing included critical illness (15.2%), physician preference (15.2%) and other (47.8%). 46.5% of children remained on therapy at study end.

Primary Diagnosis		At Initiation	6 months*	12 months*	Most Recent Value**
aHUS	eGFR (n) # on RRT UPC (n)	42.1 (34) 43 9.2 (21)	108 (32) 5 0.5 (24)	101.8 (24) 3 2.2 (15)	110.6 (51) 8 2.0 (36)
ST-HUS	eGFR (n) # on RRT UPC (n)	21.6 (2) 15	98.1 (2) 1	115.2 (1) 0	89.1 (15) 3 0.5 (5)
Other Infectious HUS	eGFR (n) # on RRT UPC (n)	24 (3) 2 12 (2)			133.1 (4) 0 0.9 (4)
Other TMA	eGFR (n) # on RRT UPC (n)	67.5 (9) 3 6.9 (7)	53.5 (2) 2 1.5 (2)	1	100.9 (7) 4 2.7 (8)
C3GN	eGFR (n) # on RRT UPC (n)	61.6 (7) 0 11.6 (7)	57.8 (2) 1 9.5 (5)	23.6 (1) 0 1.1 (1)	105.7 (2) 2 4.0 (8)
DDD	eGFR (n) # on RRT UPC (n)	63.8 (2) 3 1.3 (1)	86.5 (5) 1 2.5 (3)	92.5 (2) 1 1.3 (2)	98.7 (3) 1 1.6 (3)
Antibody Mediated Rejection	eGFR (n) # on RRT UPC (n)	84.1 (6) 1	69 (3) 0	62.1 (2) 0	68.7 (6) 2

x̄ eGFR (n)=patients used to calculate x̄ eGFR
*Children excluded from eGFR calculations if they were off eculizumab therapy, on dialysis or following renal transplant
** Children excluded from eGFR calculations if they were on dialysis or following renal transplant

# on RRT = # of patients on RRT at each time point
UPC= x̄ urine protein to creatinine ratio in mg/mg (n)=patients used to calculate x̄ UPC

Conclusions: This large pediatric cohort shows 44% of current eculizumab use in children is for "off-label" indications. Renal outcomes for these "off-label" indications show no clear trend as compared to the aHUS patients.

TH-PO595

Efficacy of Cyclosporine A for Severe Henoch-Schönlein Purpura Nephritis in Children Takahisa Kimata, Jiro Kino, Sohsaku Yamanouchi, Chikushi Suruda, Shoji Tsuji, Kazunari Kaneko. *Pediatrics, Kansai Medical Univ, Hirakata-shi, Osaka, Japan.*

Background: Though the treatment for severe Henoch-Schönlein purpura nephritis (HSPN) is not established. While methylprednisolone and urokinase pulse therapy (MUPT) or intensive multiple-drug therapy including steroid (MDT) have been reported to be effective in some patients with HSPN of poor prognosis, others do not respond to these therapies. Recently, cyclosporin A (CsA) has been postulated to be effective for children with severe HSPN. Our aim was to assess the efficacy of CsA as the rescue therapy for steroid-resistant HSPN or the first line treatment for severe HSPN.

Methods: 9 children with severe HSPN (5 boys, median age 7.3: range 4-13 years) were enrolled. Severe HSPN was defined as both the histological severity of grade III-V and the clinical severity showing nephrotic range proteinuria. 4 patients allocated for the rescue therapy (G-I) received MUPT or MDT initially without success and were switched to CsA administration. Their median protein-to-creatinine (PC) ratios at the time of CsA initiation was 10.3 g/gCr. 5 patients allocated for the first line treatment (G-II) did not receive any steroid before the administration of CsA. Their median PC ratios at the time of CsA initiation was 16.1 g/gCr. CsA dosage ranged from 2.5 to 4 mg/kg per day. All patients in both groups received an angiotensin-converting enzyme inhibitor before CsA initiation. This study was approved by the ethical committee of Kansai Medical University.

Results: We excluded 1 patient in G-II from the study, as she developed hypertension after initiation of CsA. Except for this patient, other 8 patients responded well to CsA: proteinuria disappeared in all with the median period after CsA commencement of 4.7 months in G-I and 6.0 months in G-II: The total period of pharmacological treatment in G-II was shorter than that in G-I (10.6 vs 6.0 months, P=0.08). There were no significant differences in age, gender and the dose of CsA between the groups. Adverse events (anemia) were observed in two patients.

Conclusions: CsA is effective to reduce the amount of proteinuria not only as the rescue therapy for steroid-resistant HSPN but also as the first line treatment for severe HSPN.

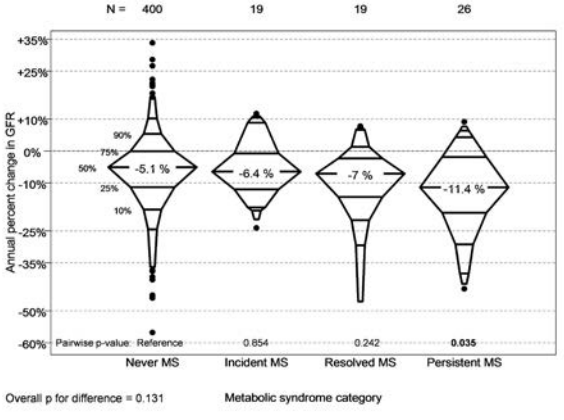
TH-PO596

Metabolic Syndrome and Associated Longitudinal Changes in Kidney Function in Children with CKD Shwetal P. Lalan,[1] Derek Ng,[2] Fernanda Kupferman,[1] Susan L. Furth,[5] Bradley Warady,[4] Mark Mitsnefes.[3] *[1]Brookdale Univ Hospital Center; [2]Johns Hopkins Bloomberg School of Public Health; [3]Cincinnati Children's Hospital; [4]Children's Mercy Hospital; [5]The Children's Hospital of Philadelphia.*

Background: While individual CV risk factors are frequent in children with CKD, incidence of metabolic syndrome (MS) and its effect on CKD progression are not well known. The goal of this study was to describe prevalence of MS and associated longitudinal changes in renal function in children in the CKiD study.

Methods: MS was defined as presence of obesity (BMI >90th percentile) and at least 2 of the 4 comorbidities: high triglycerides (TG)(> 200 mg/dl), low HDL cholesterol (<40mg/dl), hypertension (HT)SBP/DBP >95th percentile, diagnosis or use of antiHT therapy) and hyperglycemia (>100mg/dl). Subjects were classified as never MS, incident MS, resolved MS and persistent MS with annual eGFR change. Wilcoxon rank sum tests compared the distributions of annual percent change in GFR by MS classification, overall and pairwise with never MS as the reference group.

Results: Of 706 children, 64 (9%) had MS at the baseline. The majority had high TG levels (83%) and HT (78%), hyperglycemia occurred in 31%. 71% of those with MS had 3 and 30% had 4 components of MS. Of those without MS at baseline, 43% had HT, 38% had high TG and 12% had hyperglycemia. Among those free of MS, 96% continued to be free (never MS) and 5% developed incident MS. Of the 64 with baseline MS, 42% did not have MS after 2 years (resolved MS) and 58% continued to have MS (persistent MS). Children with and without MS had similar eGFR at baseline. The decline in eGFR per year was faster in children with persistent MS, -11.4% compared to never MS, -5.1% (p=0.04).



Conclusions: Persistent MS was associated with accelerated eGFR decline, preventing or treating these comorbidities, particularly obesity, may slow the progression of CKD.

TH-PO597

The Excretory Activity of the Kidneys in Children Treated for Overweight or Obesity Tomasz Jerzy Irzyniec,[1,2] Anita Kocieba-Laciak,[3] Izabela Maciejewska-Paszek.[1] *[1]Dept of Health Promotion and Community Nursing, Faculty of Health Sciences, Medical Univ of Silesia, Katowice, Poland; [2]Dept Nephrology/ENDO, MSWiA Hospital, Katowice, Poland; [3]Medical Univ of Silesia, Katowice, Poland.*

Background: Children with excess weight usually exhibit enhanced kidney perfusion resulting in glomerular hyperfiltration. Unfortunately, there are no noninvasive methods to precisely evaluate GFR in children. A useful method of GFR estimation in obese children is the calculation of eGFR according to the Bouvet formula. The aim of the study was to evaluate the influence of excess weight and successful weight reduction on the excretory activity of the kidneys in overweight or obese children.

Methods: Creatinine (Cr) and cystatin C (cyC) concentrations were determined and eGFR was calculated using the Bouvet formula in a group of 95 children (9-13y.), of whom 62 were overweight and 33 obese.The results were compared to the values, which could be found in the population of Polish children (PC) with BMI at the 50th percentile (BMI 17.5±0,8kg/m^2, Cr 0.6±0.2mg/dL, cyC 0.54±0.1 mg/L, eGFR 53.1±4.3ml/min). The results obtained before and after a 6-month weight reduction period in 23 patients, who demonstrated BMI reduction of over 5% were also analyzed.

Results: Children with excess weight had higher cyC and eGFR compared to PC. Despite of the different BMI (30±4 vs 24.5±2kg/m2), CyC and eGFR were only slightly higher in obese compared to overweight children (1.21±0.5 vs 1.14±0.4 mg/L - ns and 100.7±29.7 vs 90.8±25 ml/min, p=0.08). In contrast to overweight, in obese children, after a 6-month weight reduction program, the decreases in cystatin C level (1.3±0.8 vs 0.8±0.4 mg/l, p<0.02) and eGFR (107.6±46.5 vs 79.3±29.2 ml/min, p<0.01) were significant. Further calculations revealed that the decrease in cystatin C level (p<0.04) and eGFR (p<0.04) was only significant in male obese patients.

Conclusions: 1. Excess weight in children causes glomerular hyperfiltration. 2. Due to reduced glomerular hyperfiltration, weight loss has a beneficial effect on the excretory activity of the kidneys, in obese children. 3. Following weight reduction, a significant decrease in cystatin C level and eGFR value occurs but only in obese boys.

TH-PO598

Identification and Staging of Blood Pressure Using the STOP Intervention in Pediatric Nephrology Ambulatory Care Hailey Woollen, Donald J. Weaver, Charles P. McKay, Susan F. Massengill. *Pediatric Nephrology, Levine Children's Hospital, Charlotte, NC.*

Background: Prior studies in pediatric patients with chronic kidney disease (CKD) have shown an association with declining kidney function and hypertension (HTN), yet uncontrolled HTN persists in children with CKD. The goal of the STOP (**S**urveillance, **T**arget, **O**utpatient, blood **P**ressure) study is to increase the recognition, diagnosis, and control of hypertension in pediatric CKD patients through a simple practice-based intervention.

Methods: In a pediatric nephrology CKD practice, ambulatory BPs were measured, classified and labeled as optimal (<75%, green), pre-hypertensive (76-89%, yellow) and hypertensive (>90%, red) according to age, height and sex specific percentiles. Color-coded cards were placed on encounter documents for provider use during the visit. Assessment of provider actions related to BP were collected by chart review and classified as repeated measure, further evaluation, medication change or none.

Results: 47 patients, mean age 11, range 2-19 years, were analyzed. 32 (68%) had glomerular CKD, 8 (17%) had HTN and 6 (13%) were on anti-HTN therapy prior to baseline. At baseline, initial BP class was 21 (45%) Green, 15 (32%) Yellow and 11 (23%) Red. Final BP class was 33 (70%) Green, 10 (21%) Yellow and 4 (9%) Red. 44 (94%) had repeat measures, 4 (9%) had re-evaluation and 2 (4%) had medication adjustment.

Conclusions: Repeat BP measurement was common regardless of initial BP classification. One third of patients were either pre-hypertensive or hypertensive at the final reading but only 13% had an intervention of additional evaluation or therapy change. The remaining 17% forms an at-risk group for practice improvement. The study is ongoing and will address the blood pressure control outcome in an expanding cohort of children with CKD.

TH-PO599

Ambulatory Blood Pressure Tracking in Pediatric Kidney Transplant Recipients Gilad Hamdani,[1] Edward Nehus,[1] Coral D. Hanevold,[2] Judith Sebestyen VanSickle,[3] Scott E. Wenderfer,[4] David K. Hooper,[1] Bradley Warady,[3] Mark Mitsnefes.[1] *[1]Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [2]Pediatric Nephrology, Seattle Children's Hospital, Seattle, WA; [3]Pediatric Nephrology, Children's Mercy Hospital, Kansas City, MO; [4]Pediatric Renal Section, Texas Children's Hospital, Houston, TX.*

Background: Hypertension (HTN) is common after kidney transplantation, and is associated with adverse outcomes. We aimed to assess blood pressure (BP) control by using ambulatory BP monitoring (ABPM) in pediatric and young adult kidney transplant recipients.

Methods: A retrospective chart review of all kidney transplant recipients in 4 pediatric centers with at least two ABPMs during the follow up post transplantation. Casual HTN was defined as systolic/diastolic BP ≥95th%tile or ≥130/90. Abnormal ABPM was defined as 24H-BP load ≥25%.

Results: One hundred and twenty four patients (median age 17y, 40% young adults, 69% male) were included in the study. Median time between first and last ABPM was 2 years. More patients were taking BP medications at last follow up (79% vs. 71%, p=0.01); 47% had normal first ABPM and 62% had normal last ABPM (p=0.01). At initial ABPM, 36% and 17% of patients were classified as having masked and sustained HTN, respectively, compared with 31% and 7% at last ABPM. The proportion of controlled HTN (normal BP on hypertensives) increased from 27% to 42%, whereas uncontrolled HTN decreased from 41% to 32% (table). Proportion of patients with masked HTN not on hypertensives decreased from 11% to 4%.

BP Status according to initial and last ABPM (n=124)								
	Off BP medications				On BP medications			
	Normal BP	White Coat HTN	Masked HTN	Sustained HTN	Controlled HTN	White Coat HTN	Masked HTN	Sustained HTN
Initial ABPM	17 (14%)	4 (3%)	14 (11%)	1 (1%)	33 (27%)	4 (3%)	31 (25%)	20 (16%)
Last ABPM	19 (15%)	0	5 (4%)	3 (2%)	52 (42%)	6 (5%)	33 (27%)	6 (5%)

Conclusions: Using ABPM to monitor BP, we observed improvement in BP control in pediatric and young adult kidney transplant recipients during follow up.

TH-PO600

Left Ventricular Hypertrophy in Pediatric Hypertension and Obesity: A Systematic Review of Echocardiographic Studies Iwona Dziewa, Haseena Sahib, Katarina Supe-Markovina, Robert Woroniecki. *Pediatrics and Pediatric Nephrology, Stony Brook Children's Hospital, Stony Brook, NY.*

Background: Left ventricular hypertrophy (LVH) is an important end point of hypertension (HTN), and/or obesity-associated cardiovascular disease. However, there are multiple definitions of LVH in children, and it is unclear how those definitions affect LVH prevalence. Our objective was to perform a systematic review of literature to report LVH prevalence as determined by echocardiography (ECHO) in children with HTN and/or obesity, and to examine how various definitions affect LVH prevalence.

Methods: PubMed search was performed in accordance with the PRISMA statement. We used terms: left ventricular hypertrophy, LVH, LVMI, obesity, hypertension, echocardiogram, ECHO, cardiac hypertrophy, obesity, cardiomyopathy, and limited search to infants, children and adolescents. Full text articles published in English from 01/01/2000 to 05/31/2016 were included. Subjects with kidney transplantation or chronic kidney disease were excluded. We examined effect of 4 definitions on LVH, based on left ventricular mass index (LVMI): (A) LVMI> 51 g/m$^{2.7}$, (B) LVMI >38.6 g/m$^{2.7}$(Daniels *et al.*), (C) LVMI> the 95th-tile LMS reference (Foster *et al.*), and (D) LVMI >95th-tile for gender and chronological age (Khoury *et al)*.

Results: Our search yielded 111 articles, and 13 studies that met all inclusion/exclusion criteria were included in the final analysis. There were 1613 subjects, 13.9±1.9 years old, 56.1% males, with body mass index (BMI) 27.4±5.1, 44.9% were obese. 7/13 (53.8%) studies reported Caucasian race: 215/754 subjects (28%), and 4/13 (30.8%) studies, African-American race: 421/545 subjects (77.2%). LVMI was significantly and positively correlated with systolic blood pressure (SBP) parameters in 4/13, and with BMI in 3/13 studies. LVH data is presented in the Table:

Definition	LVH prevalence (%)	95%CI
A	25.3	22.2-28.4
B	37.5	34.6-40.4
C	14.8	7.9-21.7
D	25.0	15.0-35.0
Overall	25.6	23.7-27.5

Conclusions: LVH prevalence determined by ECHO is variable. LVMI/LVH are associated with SBP/BMI. More precise indexing of left ventricular mass is required in the management of childhood HTN/obesity.

TH-PO601

Left-Ventricular Hypertrophy and Associated Factors in Children with Chronic Kidney Disease: Results from the KoreaN Cohort Study for Outcomes in Patients with Pediatric Chronic Kidney Disease (KNOW-Ped CKD) Heeyeon Cho,[1] Kyoung Hee Han,[7] Seong Heon Kim,[4] Hee Sun Baek,[2] Min Hyun Cho,[2] Jae Il Shin,[6] Joo Hoon Lee,[3] Young Seo Park,[3] Hyun-Jin Choi,[5] Hee Gyung Kang,[5] IL-Soo Ha,[5] Hae Il Cheong.[5] *[1]Pediatrics, Samsung Medical Center, Seoul, Korea; [2]Pediatrics, Kyungpook National Univ Children's Hospital, Daegu, Korea; [3]Pediatrics, Asan Medical Center, Seoul, Korea; [4]Pediatrics, Pusan National Univ Hospital, Pusan, Korea; [5]Pediatrics, Seoul National Univ Children's Hospital, Seoul, Korea; [6]Pediatrics, Severance Hospital, Seoul, Korea; [7]Pediatrics, Jeju National Univ Hospital, Jeju, Korea.*

Background: Children with chronic kidney disease (CKD) has been known to be a high risk group of cardiovascular disease, and left-ventricular hypertrophy (LVH) is an early marker of cardiovascular disease. We assessed the prevalence and contributing factors of LVH in pediatric CKD patients.

Methods: We conducted a cross-sectional study using baseline data from the KoreaN cohort study for Outcome in patients With Pediatric Chronic Kidney Disease (KNOW-Ped CKD), a nationwide, prospective, and observational cohort study of pediatric CKD. Univariate and multiple logistic regression analysis were performed to evaluate the association of variables with LVH. LVH in children has been widely defined as a left ventricular mass index (LVMI) > 95th percentile. However, LVMI increases with decreasing height in young children, and we used a novel method of expressing left ventricular mass relative to body size in children. The patients with left ventricular mass above the 95th percentile for height (z score>1.64) were classified as having LVH.

Results: Total 381 children with CKD were enrolled, and the mean age was 9.93±5.45 years. Thirty patients (9.1 %) were diagnosed with LVH. Univariate logistic regression revealed positive association between LVH and primary disease (glomerulonephritis), body mass index, and systolic hypertension. Primary disease of glomerulonephritis and systolic hypertension were independently associated with LVH in multivariate logistic regression (p=0.0055, p<0.001).

Conclusions: The results of this study suggest that the history of glomerulonephritis and systolic hypertension might predispose to increased LVMI in pediatric patients with CKD.

Funding: Government Support - Non-U.S.

TH-PO602

Carotid Intima Media Thickness in Children with Chronic Kidney Disease Abdullahi Mudi,[1,2] Zaiboonisa Holland,[3] Caroline Dickens,[4] Daynia Ballot,[1] Cecil S. Levy.[1] *[1]Dept of Paediatrics and Child Health, Univ of the Witwatersrand and Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; [2]Dept of Paediatrics, Bayero Univ, Kano, Nigeria; [3]Dept of Radiology, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; [4]Dept of Medicine, Univ of the Witwatersrand, Johannesburg, South Africa.*

Background: Cardiovascular disease (CVD) is a common complication of chronic kidney disease (CKD). In children with CKD, CVD may manifest as early changes in arterial thickness and or stiffness. We aimed to determine the correlates of carotid intima media thickness (cIMT) in children with CKD.

Methods: Seventy-one children with CKD stage 1–5 had a physical examination, routine follow up blood tests and a Carotid Doppler ultrasound to determine the average cIMT.

Results: The mean age of the children was 11.1y ± 3.4, with 46/71 males and 25/71 females and a mean cIMT of 0.504mm ± 0.062. There were 43/71 pre-dialysis CKD patients and 28/71 on chronic dialysis. The mean cIMT and mean arterial pressure(MAP) were greater in patients on dialysis (0.530mm ± 0.067 and 92.00mmHg ± 2.67) when compared to the pre-dialysis CKD patients (0.488mm ± 0.054 and 80.44mmHg ± 2.54), and there was a significant difference between the means (p=0.005 and 0.004). There was a significant positive correlation of cIMT with MAP, blood urea, alkaline phosphatase and PTH levels (p<0.05). There was also a significant negative correlation of cIMT with haemoglobin levels (p<0.05). Duration on dialysis also showed a positive correlation with cIMT. After adjusting for the various correlates in a multivariate regression model, only MAP had a significant association with cIMT (p=0.023).

	cIMT r (p value)
Age (yr) n=71	0.069 (0.567)
Duration on dialysis (months) n=28	0.459 (0.014)
MAP (mmHg) n=71	0.261 (0.028)
Hb (g/dl) n=71	-0.405 (0.001)
Urea (mmol/l) n=71	0.242 (0.042)
Ca (mmol/l) n=71	-0.201 (0.093)
Alkaline Phosphatase (U/l) n=71	0.256 (0.031)
PTH (pmol/l) n=71	0.357 (0.002)
Ferritin (ug/l) n=71	0.220 (0.065)
Urine protein/creatinine (g/mmol) n=47	0.242 (0.101)

Conclusions: MAP is an independent correlate of cIMT in both pre dialysis and dialysis CKD children.

TH-PO603

Circulating Mid-Region Pro-Adrenomedullin Is Associated with Abnormal Aortic Pulse Wave Velocity in Pediatric Chronic Kidney Disease Isaac Liu,[1] Qiao-Zhi Chee,[1] Mya Than,[1] Lingli Gong,[2] Josephine Berboso Lunaria,[2] Teng Hiang Heng,[1] Chloe Chan,[1] Yew Weng Perry Lau,[1] Wee Song Yeo,[1] Lieng H. Ling,[2] Mark Richards,[2] Yiong Huak Chan,[3] Kar Hui Ng,[1] Hui Kim Yap.[1] *[1]Shaw-NKF-NUH Children's Kidney Center, KTP-Univ Children's Medical Inst, National Univ Health System, Singapore; [2]Cardiovascular Research Inst, National Univ Health System, Singapore; [3]Biostatistics Unit, Yong Loo Lin School of Medicine, National Univ of Singapore, Singapore.*

Background: Children with chronic kidney disease (CKD) are at risk of early arteriopathy and aortic pulse wave velocity (PWV) is a predictor of cardiovascular mortality. This study examined its association with circulating biomarkers such as mid-region pro-adrenomedullin (MR-proADM).

Methods: Cross-sectional analysis of baseline parameters was carried out in a cohort of 67 (39 male) consecutive patients (mean age 14.2±6.3 years) with CKD stage 2–5D (mean duration of disease 10.6±6.4 years). Aortic PWV was measured by B-mode ultrasound. MR-proADM, N-terminal pro-B-type natriuretic peptide (NT-proBNP), asymmetric dimethylarginine (ADMA), and high-sensitivity C-reactive protein were measured along with routine biochemical parameters including hemoglobin, uric acid, calcium, and phosphate. Univariate and multivariate logistic regression was performed to examine associations between abnormal PWV (>2 SD for height) and biomarkers with performance of ROC analysis.

Results: Thirteen (19.4%) patients had abnormally increased PWV. On univariate analysis, phosphate (OR 3.17; 95%CI 1.01–9.98; p=0.048) and MR-proADM (OR 2.50; 95%CI 1.30–4.82; p=0.006) were significantly associated with abnormal PWV. On multivariate logistic regression, MR-proADM remained independently associated with abnormal PWV (OR_{adj} 4.37; 95%CI 1.18–16.19; p=0.027). MR-proADM discriminated normal from elevated PWV by ROC analysis (AUC=0.75; 95% CI 0.60–0.90; p=0.005). MR-proADM >1.44 nmol/L, had 85% sensitivity and 67% specificity for detection of elevated PWV.

Conclusions: MR-proADM is an independent identifier of abnormally increased aortic PWV, and may be useful for predicting arteriopathy in children with CKD.

Funding: Government Support - Non-U.S.

TH-PO604

Improving Blood Pressure Control in a Pediatric Chronic Kidney Disease Population

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Background: Intensive blood pressure (BP) control can slow pediatric chronic kidney disease (CKD) progression, yet many have untreated or uncontrolled BP. We wished to understand how system-level interventions would improve systolic BP (SBP) control.

Methods: We developed an EMR CKD registry, pre-visit planning, and patient care tools that displayed the 3 previous clinic SBP and achievement of CKD care goals. The registry was queried monthly for the last clinic SBP%. Using cross-sectional analysis or statistical process control (SPC), we assessed 1) 5 "perfect BP measurement" elements 2) anti-hypertensive therapy in pts with SBP > 75%, & 3) controlled clinic SBP to < 90%, 75%, or 50%. Results were limited to CKD stage 2-4 pts between 2-18 yrs of age.

Results: 494 visits occurred in 119 patients (57% male, avg 1.9 visits/pt/yr) during the study. CKD etiology was non-glomerular (57%), glomerular (11%), or unknown/undocumented (32%) in origin. The median creatinine (Schwartz)-based eGFR was 56 ml/min/1.73 m2; 85 (71%) had a cystatin C eGFR > 45 ml/min. 34 (29%) were overweight; 22 (19%) were obese (BMI > 85% vs 95% for age & gender, respectively). "Perfect BP measurement" was documented 81% of the time. There was no significant increase in anti-hypertensive med Rx in pts with SBP > 75% (from 61% to 71%; p=0.34). Pts prescribed BP medications (n=70) had similar CKD severity compared to untreated patients. Median cycle time between current & previous SBP reading was prolonged overall (9.3 m), with no difference between treated and untreated pts (8.9 vs 10.1 m; p=0.33). From 2/2014 to 4/2016, we observed improvement in SBP control to < 75% (56% to 72%; p=0.03); there was no change in SBP control to < 90% (80 vs 85%) or < 50% (33% vs 39%).

Conclusions: System-level interventions led to improved SBP control to < 75% in a pediatric CKD population. Further interventions to optimize medication dosing, reduce cycle time in those with elevated SBP, and recognize & mitigate barriers to adherence are all hypothesized to improve BP control in this population.

TH-PO605

Genomic Imbalances in Children with Chronic Kidney Disease

Beata S. Lipska-Zietkiewicz,[1] Magdalena Koczkowska,[1] Elke Wuehl,[2] Craig S. Wong,[3] Anette Melk,[4] Uwe Querfeld,[5] Franz S. Schaefer.[2] *[1]Medical Univ of Gdansk, Poland; [2]Univ of Heidelberg, Germany; [3]Univ of New Mexico; [4]Hannover Medical School, Germany; [5]Charite Berlin, Germany.*

Background: Chromosomal microarrays are routinely utilized for genetic testing of developmental delay/intellectual disability, autism spectrum disorders or multiple congenital anomalies. Here, we studied the prevalence of DNA copy number variations (CNVs) in a large cohort of European and Turkish children presenting with chronic kidney disease.

Methods: 998 consecutive patients enrolled in the ESCAPE and 4C studies were genotyped at ~2.4 millionsingle-nucleotide polymorphism (SNP) markers using the Illumina Infinium 2.5M microarray. Data was interpreted in accordance to ACMG Practice Guidelines using the Nexus Copy Number software. Filtering criteria included the size of imbalance, overlap with known benign CNVs, gene content, and verification against Decipher and ISCA databases.

Results: Three out of forty patients with clinically suspected syndromic disease were molecularly confirmed. Among 958 children without overt syndromic features, 39 (4.1%) were classified as having a definite pathogenic genomic aberration, and another 11 as having a likely pathogenic CNV. Definite diagnoses were made in 4.4% of individuals with CAKUT, 4.1% of patients with a glomerulopathy and 2.9% of those with a tubulointerstitial disorder. The most frequent imbalances were 17q12 deletions encompassing the *HNF1B locus* (n=9), 1q21.1 deletions including the *CHD1L* gene (n=7) and rearrangements at 22q11.2 (n=5). Small, including single gene, rearrangements were reported for *CTNS, EYA1, HNF1B, PKD1, TSC2, FAM58A, BMP2* and *TFAP2A loci*.

Conclusions: The detection of a genomic imbalance allowed for reverse phenotyping in most cases, resulting in clinical interventions such as evaluation for extra-renal involvement and multidisciplinary care. Genomic disorders account for a small but significant portion of children with CKD and their diagnosis has important implications for genetic counseling and clinical management.

Funding: NIDDK Support

TH-PO606

Office Blood Pressure Has Similar Associations with ESRD and Death as 24 Hour Ambulatory Blood Pressure in Hypertensive CKD

Elaine Ku,[1] Charles E. McCulloch,[1] Francis B. Gabbai,[2] Joachim H. Ix,[2] Chi-Yuan Hsu.[1] *[1]UCSF; [2]UCSD.*

Background: Although ambulatory blood pressure monitoring (ABPM) is considered the best method of assessing blood pressure, few studies have performed comparisons of the ability of ABPM vs. office blood pressures (BPs) to discriminate risk of adverse outcomes in patients with CKD.

Methods: In the African American Study of Kidney Disease Cohort (AASK) study (N=527), we compared office vs. ABPM BPs in their prediction and discrimination of risk for two outcomes: i) concurrent left ventricular hypertrophy (N=285) by echocardiography and ii) subsequent ESRD or death (N=267). Unadjusted models were used to compare the association between these outcomes and i) one office systolic (SBP) or diastolic (DBP) reading vs. ii) mean 24 hour SBP or DBP ABPM readings taken concurrently. C-statistics were determined for all models, and net reclassification indices (NRI) determined in models where ABPM was added to office BPs.

Results: For all outcomes, c-statistics were similar for models with office vs. ABPM BPs, and differences in the c-statistics did not achieve statistical significance for either SBP or DBP (all p>0.05). There was no improvement in NRIs when ABPM BPs were added to office BPs (all p>0.05).

	Odds ratio for LVH for every 10 mm Hg higher BP (95% CI)	**C-statistic for LVH** (95% CI)	**Hazard ratio for ESRD or death with every 10 mm Hg higher BP** (95% CI)	**C-statistic for ESRD or death** (95% CI)
Office SBP	1.10 (1.01-1.20)	0.56 (0.51-0.61)	1.12 (1.06-1.19)	0.57 (0.52-0.59)
Mean 24 hour SBP	1.14 (1.03-1.27)	0.56 (0.52-0.62)	1.19 (1.11-1.28)	0.57 (0.53-0.61)
Office DBP	1.03 (0.89-1.20)	0.52 (0.47-0.56)	1.17 (1.05-1.30)	0.54 (0.50-0.57)
Mean 24 hour DBP	1.06 (0.90-1.25)	0.52 (0.47-0.57)	1.20 (1.07-1.35)	0.55 (0.51-0.58)

Conclusions: A single office BP measurement taken in a standardized, protocol-driven setting in AASK is not inferior to ABPM in the discrimination of BP-related adverse outcomes. Overall, the discrimination of the risk for outcomes by office or ABPM BPs was poor. Future studies may need to consider the discriminatory performance of ABPM vs. office BPs when comparing their informative value.

TH-PO607

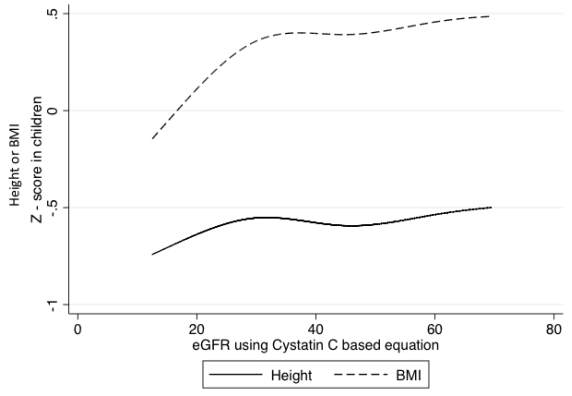
BMI and Height Trajectory with Declines in Kidney Function in Children with CKD

Elaine Ku,[1] Charles E. McCulloch,[1] Joel D. Kopple,[2] Mark Mitsnefes,[3] Kirsten L. Johansen.[1] *[1]UCSF; [2]Harbor-UCLA; [3]Univ of Cincinnati.*

Background: Protein-energy wasting and short stature are associated with poorer prognosis for children with CKD. However, few studies have rigorously described the relationship between CKD progression and longitudinal weight or height changes. We examined weight (assessed by changes in body mass index [BMI]) and height trajectory with declines in renal function over time in children in the Chronic Kidney Disease in Children (CKiD) cohort study.

Methods: We included 836 participants with CKD for longitudinal analysis. Weight, height, and serum cystatin C were measured annually. All BMI and height values were converted into age and sex standardized z-scores using Center for Disease Control normative standards. We used segmented, mixed effects regression for modeling the repeated measures of BMI z-score and linear mixed models for modeling height z-scores as a function of estimated GFR (using the 2012 Schwartz equation).

Results: Mean BMI z-score was 0.46, and mean height z-score was -0.55 at baseline. During mean follow-up of 3.1 years, BMI z-score was stable until eGFR of approximately 30 mL/min/1.73m^2. When eGFR dropped below 30 mL/min/1.73 m^2, a 0.3 (95% CI 0.2, 0.4) decline in BMI z-score was noted with each 10 mL/min/1.73 m^2 decline in eGFR. The associations between eGFR and BMI z-score trajectory before and after an eGFR of 30 mL/min/1.73 m^2 were statistically significantly different (p<0.001). In contrast, for height, there was a continuous and linear 0.01 decrease in height z-score with every 10 mL/min/1.73 m^2 decline in eGFR.



Conclusions: In children with CKD, steeper declines in BMI mostly occur when eGFR is ≤30 mL/min/1.73 m^2, whereas height exhibited a continuous and linear decline with advancing CKD. Further research is needed to determine whether earlier interventions to prevent weight loss and improve height accrual with advancing stages of CKD will improve outcomes.

Funding: Other NIH Support - NHLBI

TH-PO608

Disparities in Transplant Access Partially Mediate Higher Risk of Mortality in Black versus White Children with ESRD Elaine Ku, Charles E. McCulloch, Barbara A. Grimes, Kirsten L. Johansen. *UCSF.*

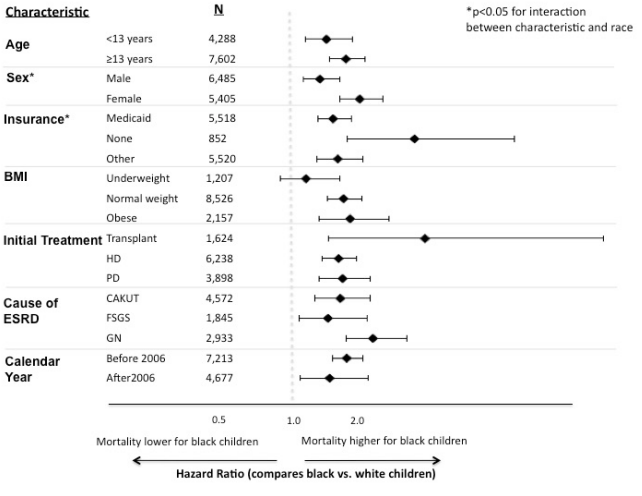
Background: Although black race is associated with worse health outcomes in the general population, observational studies have reported that black adults receiving dialysis have paradoxically better survival than their white counterparts. Whether this racial "survival paradox" exists in children with ESRD is unclear. Our objective was to compare the mortality risk among black versus white children treated with renal replacement therapy.

Methods: Retrospective analysis of mortality risk in black (N=8,782) or white (N=3,108) children who developed ESRD between 1995-2011 and were followed through 2012 in the national ESRD registry (US Renal Data System) using Cox models.

Results: During median follow-up of 7.1 years, 8,791 transplants and 1,579 deaths occurred. Risk of death was 1.58 times higher in black vs. white children (95% CI 1.42-1.76).

Overall cohort (N=11,890)	Hazard ratio (95% CI)	P-value
Unadjusted model	1.86 (1.68-2.05)	<0.001
Adjusted model*	1.58 (1.42-1.76)	<0.001
Adjusted model with transplant as time dependent covariate*	1.21 (1.08-1.34)	0.001
*Adjusted for co-variates listed in Figure		

The higher risk of death in black (vs. white) children did not differ significantly by age category, body mass index, initial treatment modality, cause of ESRD, or calendar period (all p>0.05 for interaction), but did differ by sex (p=0.003) and insurance status (p=0.04) such that the disparity was more pronounced among girls and children without insurance.



Adjustment for transplant as a time dependent covariate attenuated, but did not abolish, the higher risk of death in black children (HR 1.21 [95% CI 1.08-1.34]).

Conclusions: We did not find evidence of a racial survival paradox in children treated with dialysis. Instead black children had higher mortality than white children, which was explained, in part, by differences in access to transplantation.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-PO609

Chronic Kidney Disease in Rural Indigenous Children: The FINISHED Screen/Triage/Treat Program Allison Dart,[1] Barry Ad Lavallee,[2] Caroline D. Chartrand,[2] Lorraine L. Mcleod,[2] Thomas W. Ferguson,[3] Navdeep Tangri,[3] Audrey Gordon,[3] Tom D. Blydt-Hansen,[4] Claudio Rigatto,[3] Paul Komenda.[3] *[1]Children's' Hospital Research Inst of Manitoba, Univ of Manitoba Max Rady College of Medicine, Winnipeg, MB, Canada; [2]Diabetes Integration Project, Winnipeg, MB, Canada; [3]Internal Medicine, Univ of Manitoba Max Rady College of Medicine, Winnipeg, MB, Canada; [4]Pediatrics, Univ of British Columbia, Vancouver, BC, Canada.*

Background: Indigenous populations have high rates of chronic kidney disease (CKD), and progression to kidney failure on average 10 years prior to other ethnic groups. Burden of early disease in children is a key knowledge gap with important implications for prevention and treatment strategies. We sought to evaluate the prevalence of CKD and associated risk factors in youth from rural Indigenous communities.

Methods: The First Nations Community Based Screening to Improve Kidney Health and Prevent Dialysis (FINISHED) project actively screened 11 rural First Nation communities in Manitoba, Canada. Body mass index (BMI), blood pressure, urine albumin-to-creatinine ratios (ACR), estimated GFR's (eGFR) and hemoglobin A1c's (A1c) were evaluated. CKD was defined by eGFR <90ml/min/1.73m2 and/or ACR >3mg/mmol.

Results: 353 Indigenous youth 10-17 years were recruited after community and school engagement. The median age was 12 years (IQR 10 – 13) and 55% were female. Fifteen percent of youth were identified with CKD. Fifty-five percent were overweight/obese, 5.4% had hypertension and 11.9% had pre-hypertension. Diabetes was identified in 1.4%, and 1.4% had pre-diabetes with A1c's between 6.1 and 6.49%. Although 31.8% of the overweight/obese group had hypertension or CKD, 54.7% of the group with CKD had no other risk factors.

Conclusions: CKD and associated risk factors are highly prevalent in rural Indigenous children. This study highlights the need to evaluate the efficacy of screening and intervention strategies in Indigenous children to slow the progression of kidney failure and address this critical population health issue.

Funding: Government Support - Non-U.S.

TH-PO610

Systemic Anticoagulation with Enoxaparin in Children with End Stage Renal Disease Receiving Hemodialysis or Peritoneal Dialysis Sun-Young Ahn,[1] Asha Moudgil,[1] Kirtida Mistry,[1] Yaser A. Diab.[2] *[1]Nephrology, Children's National Health System, Washington, DC; [2]Hematology, Children's National Health System, Washington, DC.*

Background: Due to predictable pharmacokinetics (PK) and anticoagulation response, enoxaparin is the preferred anticoagulant in children. However, enoxaparin is renally cleared and bioaccumulation over time leading to over-anticoagulation and increased bleeding risk is a concern in End Stage Renal Disease (ESRD). The effect of Hemodialysis (HD)/Peritoneal Dialysis (PD) on enoxaparin PK is not clearly understood and there are no reports on the safety and efficacy of enoxaparin in pediatric dialysis patients. We report our center's experience with a recently implemented protocol for enoxaparin anticoagulation in children with ESRD receiving HD or PD.

Methods: Enoxaparin was initiated at an age- and weight-based dose administered at half the standard frequency (once daily) after HD or PD. Peak and trough anti-Factor Xa (anti-FXa) levels were monitored closely and dose and/or frequency were adjusted to achieve target peak anti-FXa levels and maintain trough anti-FXa ≤0.3 U/mL. We retrospectively reviewed the records of patients on dialysis who received enoxaparin for treatment or prevention of thromboembolism according to this protocol.

Results: 9 patients (3 males, median age 4 years) with ESRD on HD(5) or PD(4) received 10 enoxaparin courses (5 therapeutic, 5 prophylactic) per our protocol. 8 patients had at least 2 thrombophilic risk factors, with factor VIII elevation being the most common risk factor (63%). At the time of this study, the median duration of anticoagulation was 4.5 months (1-32) with 5 patients still receiving enoxaparin. Bioaccumulation was observed in 3 patients receiving daily therapeutic enoxaparin (2 PD, 1 HD) which resolved after adjusting the dose frequency to every other day. There were no anticoagulation failures or bleeding complications.

Conclusions: Enoxaparin is a feasible option for systemic anticoagulation in children on HD or PD but requires close laboratory monitoring to ensure safe and optimal anticoagulation. Larger studies are needed to clarify safety and efficacy of our protocol.

TH-PO611

Assessment of the Long-Term Safety and Efficacy of Multiple Doses of C.E.R.A. (Continuous Erythropoietin Receptor Activator – Methoxy Polyethylene Glycol-Epoetin β) for Maintenance Treatment of Anemia in Pediatric Patients with Chronic Kidney Disease (CKD) on Hemodialysis (HD) (NH19707, NCT00717366) Michel Fischbach,[1] Elke Wuehl,[2] Sylvie C. Meyer Reigner,[3] Zoe Morgan,[3] Franz S. Schaefer.[2] *[1]Univ Hospital Strasbourg, CHU HautePierre, Strasbourg, France; [2]Heidelberg Univ Hospital, Heidelberg, Germany; [3]F. Hoffman-La Roche Ltd, Basel, Switzerland.*

Background: The objective of this study was to document the long-term safety and efficacy of C.E.R.A. administration in pediatric patients with anemia associated with CKD.

Methods: This open-label multicenter study included a 2-week screening period, 16-week dose-titration period, and 4-week evaluation period. Stable patients (hemoglobin

[Hb] within ± 1 g/dL of baseline and between 10 and 12 g/dL) could enter a 1-year optional safety extension. Patients aged 6–17 years on HD with stable chronic renal anemia were given C.E.R.A. every 4 weeks at a starting dose determined by previous epoetin alfa/beta or darbepoetin dosing. Two conversion factors were tested sequentially. In the optimum dose group the starting dose was 4 µg for each weekly dose of 125 IU epoetin alfa/beta or 0.55 µg darbepoetin.

Results: 64 patients were enrolled, including 48 in the optimum dose group, and 47 finished the core phase. 37 entered the safety extension and 17 completed 73 weeks of treatment. Most withdrawals were due to renal transplantation. In the optimum dose group (mean age 13 years), median doses at the point the patient exited the study were 2.51 and 2.36 µg/kg/4 weeks for 6–11 and 12–17 year olds, respectively. Hb concentrations over time in response to adjusted doses of C.E.R.A. were stable. 70% of patients overall had an Hb value within 10–12 g/dL at the point they exited the study and 62% were within ± 1 g/dL of baseline. The overall pattern of reported adverse events was similar to that observed in studies in adult patients. No new safety signal was detected.

Conclusions: C.E.R.A. was efficacious in maintaining stable Hb levels in pediatric patients on HD with stable anemia of CKD when switched from maintenance treatment with epoetin alfa/beta or darbepoetin. Safety was consistent with the known safety profile for C.E.R.A. in adults.

Funding: Pharmaceutical Company Support - F Hoffman-La Roche Ltd

TH-PO612

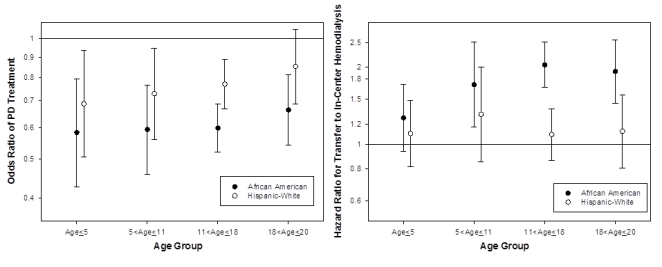
Racial/Ethnic Disparities in Use of Peritoneal Dialysis and Transfer to In-Center Hemodialysis among Pediatric Patients

Melissa Soohoo,[1] Elani Streja,[1] Matthew B. Rivara,[2] Scott V. Adams,[2] Connie Rhee,[1] Keith C. Norris,[3] Kamyar Kalantar-Zadeh,[1] Rajnish Mehrotra.[2] *[1]UC Irvine; [2]Univ of Wash.; [3]UCLA.*

Background: Racial/ethnic disparities exist in adult end-stage renal disease(ESRD) patients, showing that minorities are less likely to utilize peritoneal dialysis(PD) and African-Americans are more likely to transfer off of PD, compared to whites. PD is increasingly used for treating ESRD; however, racial/ethnic differences in utilization and outcomes among pediatric PD patients remain understudied.

Methods: We used logistic regression to examine the odds of PD use according to race/ethnicity among 14,109 pediatric(age<20 years) patients who initiated dialysis between 2000-2013 and treated for at least 60 days during follow-up, according to USRDS records. Among 6,551 pediatric PD patients, we used competing risk regression to examine the association of race/ethnicity with mortality, transplantation and transfer to in-center hemodialysis. Models were stratified by age at ESRD incidence and adjusted for cause of ESRD, demographics and socioeconomic factors.

Results: Among pediatric patients, African-Americans <20 years old and Hispanic whites ≤18 years old were less likely to use PD, compared to whites. The cohort treated with PD was comprised of 48% whites, 25% African-Americans and 27% Hispanic whites. We did not observe significant racial/ethnic survival differences while using PD. However, African-Americans and Hispanic whites had a lower risk of receiving a kidney transplant while on PD compared to whites. Finally across strata of age, African-American patients ≥5 years old had a higher risk of transferring to in-center hemodialysis(ref:whites).



Conclusions: Racial/ethnic and age disparities are present in the utilization of PD as well as transplantation and transfer to in-center hemodialysis among pediatric PD patients. Additional studies are needed to better understand the reasons for these differences.

Funding: NIDDK Support

TH-PO613

Peritoneal Expression of Antimicrobial Ribonucleases in Pediatric Patients Undergoing Chronic Peritoneal Dialysis

Neha Dhingra,[1] Rose M. Ayoob,[1] Brian Becknell.[1,2] *[1]Nephrology Section, Nationwide Children's Hospital; [2]Center for Clinical and Translational Research, Nationwide Children's Hospital.*

Background: Peritoneal dialysis (PD) is the most common dialysis modality for children with End Stage Renal Disease (ESRD). PD catheter-related infections cause significant morbidity and mortality in children. Antimicrobial peptides serve critical roles in epithelial defense throughout the body, but their roles in the peritoneum are mostly unexplored. The Ribonuclease (RNase) A superfamily encodes multiple AMPs with potent microbicidal activity against pathogens implicated in peritonitis. We hypothesize that antimicrobial RNases are present in the peritoneum of children undergoing PD.

Methods: With institutional review board approval, we recruited 7 patients from our dialysis unit aged 3-21 years on chronic continuous cycling PD (CCPD). Up to 200 ml of PD effluent was collected from each patient, prior to starting nightly PD. Viable cells were isolated by centrifugation, and subject to protein extraction. Antimicrobial RNases and the Ribonuclease Inhibitor (RNH1) were detected by immunoblotting. RNase activity was measured by tRNA hydrolysis. Since these patients underwent omentectomy at the time of PD catheter placement, we localized RNases in omentum by immunostaining.

Results: RNase activity was detectable in PD effluents, which expressed RNase3, RNase6, and RNase7 proteins by immunoblotting. When effluents were subject to centrifugation, the RNase3, RNase6, and RNH1 proteins were detectable in the leukocyte-rich cellular sediment. Within omentum, RNase3 and RNase6 localized to neutrophils and mononuclear leukocytes, whereas RNase7 localized to mesothelium.

Conclusions: Leukocytes and mesothelial cells collaborate to release antimicrobial RNase3, RNase6, and RNase7 into human peritoneal fluid in the absence of peritonitis. This process is likely under tight regulation by RNH1, to prevent RNase cytotoxicity. These findings have important ramifications for our understanding of mechanisms governing sterility within the peritoneal space. Strategies aimed at enhancing antimicrobial RNase levels and activity may reduce the incidence and severity of infectious peritonitis in ESRD patients.

TH-PO614

Hemodialysis in Neonates and Infants: A Systematic Review

Prashanth Vijayaraghavan,[1] Mohit Gupta,[2] Ramya Vajapey,[3] Jessica Darusz,[4] Siddharth Sethi,[5] Gaurav Kapur,[6] Rupesh Raina,[2] Vinod Krishnappa.[1] *[1]Akron Nephrology Associates, Akron, OH; [2]Internal Medicine, Akron General Medical Center, Akron, OH; [3]Northeast Ohio Medical Univ, Rootstown, OH; [4]Akron Nephrology Associates, Parma, OH; [5]Kidney and Urology Inst, Medanta, India; [6]Children's Hospital of Michigan.*

Background: Hemodialysis (HD) in neonates and infants is difficult to implement and maintain due to a lack of machines adapted to neonatal blood flow volumes. Subsequent issues include hemodynamic instability and difficult vascular access. Hence, peritoneal dialysis is preferred in neonates and infants. The purpose of this study was to systematically review HD and discuss innovations in HD for neonates and infants.

Methods: PubMed was searched for "hemodialysis", along with the Medical Subject Heading term, "infant". 1,310 potential matches were returned, of which 9 studies met inclusion and exclusion criteria. Pooled descriptive statistics were calculated, weighted according to the number of subjects in each study. Data regarding patient characteristics, hemodialysis indications, parameters, and patient outcomes was recorded.

Results: The total number of subjects across the nine selected studies was 104, with a mean age of 3.1 months (range: 2 days to 12 months). Among all subjects there was a 62% survival rate. Indications for HD included inborn errors of metabolism, acute kidney injury, and renal dysplasias. The most common complications were catheter dysfunction, hypotension, and anemia.

Total Patients	Average Age	Survival Rate	Transplant Rate	Common Causes for HD	Type of HD
104	3.1 months	62%	33%	Inborn errors of Metabolism (42%)	Acute (36.5%)
				Acute Kidney Injury (32%)	Chronic (63.5%)
				Renal Dysplasia (17%)	

Conclusions: Indications for hemodialysis included acute renal failure, primary intrinsic renovascular disorders, inborn errors of metabolism, and intoxications. Hemodialysis techniques used for neonates and infants included blood priming of extracorporeal circuits, minimizing extracorporeal circuit volumes and use of smaller catheters. This paper concludes with a discussion of techniques that are best suited for neonates and infants.

TH-PO615

Pediatric Intradialytic Hypotension: A Systematic Review

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Background: Intradialytic hypotension (IDH) is commonly encountered in pediatric patients that receive hemodialysis (HD) sessions lasting 4 hours. The purpose of this study was to systematically review publications discussing IDH in pediatric patients and preventive measures taken in the particular patient population.

Methods: PubMed/MEDLINE was searched for the terms "hemodialysis" and "hypotension", with the word "peritoneal" excluded. The Medical Subject Heading (MeSH) terms included hypotension, infant, child, or adolescent, again with the word "peritoneum" excluded. 183 potential matches were returned, of which 11 met inclusion and exclusion criteria.

Results: The total number of subjects across the ten selected studies was 148 with ages ranging from 2 days – 18 years old, patient weight ranged from 3.2 kg to 61.4 kg. Non-invasive blood monitoring (NIVM) was implemented with HD in 65% of patients. Ultrafiltration (UF) strategies were not uniform across all studies. UF either remained constant throughout study duration or UF profiles were implemented based on changes observed in dry weight. Similar to UF, sodium levels were not synonymous across studies and either remained constant or sodium ramping in linear and/or stepwise fashion was observed. Although not reported in all studies, percent frequency of hypotensive events ranged from 19.6% - 75%, with lower percentages observed in patients who received NIVM during HD.

Conclusions: Among studies reviewed, use of NIVM was helpful in achieving appropriate dry weight as well as predicting and preventing intradialytic hypotension. Although such findings appear significant, studies reviewed had small patient populations and relatively short study durations. Hence, future studies involving larger study populations and NIVM utilization with the goal of reducing episodes of intradialytic hypotension will be necessary in determining the effectiveness of this approach in HD therapy in pediatric patients.

TH-PO616

Interinstitutional Cooperation Program in Pediatric Kidney Transplantation and the Impact on Transplantation Count Maria Goretti M.G. Penido, Marcelo S. Tavares, Carolina Moura Diniz Ferreira Leite, Mariana G. Penido de Paula, Felipe B.P. De Caux. *Pediatric Nephrology Unit, Santa Casa de Belo Horizonte, Belo Horizonte, MG, Brazil.*

Background: Kidney transplantation is the preferred treatment for the end stage of chronic renal disease in children and adolescents. The aim of this study was to evaluate an interinstitutional cooperation program between an experienced pediatric transplantation center and a developing center in other state, 600 km apart, and the count of kidney transplantation surgeries performed during the 3-year duration of the cooperation.

Methods: The cooperation consisted of short periods of fellowship (max 1 month) of pediatric nephrology residents, nurse and 2 physicians (one ped-nephrologist and 1 surgeon), along a 3-year period, as well as weekly teleconferences for case discussions once a week. The yearly count of pediatric kidney transplants (p-KT) in the developing center along the period was compared to the national mean as well to the state's mean.

Results: Since 2011, thirty pediatric patients were transplanted, 1 in 2011, 1 in 2012, 8 in 2013, 8 in 2014 and 12 in 2015. The interinstitutional program was held between 2012 and 2014. In comparison to the national count of p-KT, the developing center was responsible for 0.34% (2011), 0.26% (2012), 2.59% (2013), 2.29% (2014) and 3.79% (2015) of all p-KT. The analysis of the p-KT performed within the state showed that the developing center had a progressive participation on this procedure: 5% (2011), 3.2% (2012), 34.7% (2013), 36.3% (2014) and 46.15% (2015). However, there was a fall on the total count of p-KT during the period until 2014, but rose in 2015: 20 (2011), 31 (2012), 23 (2013), 22 (2014) and 26 (2015).

Conclusions: The results reflect a successful case of interinstitutional cooperation program that was valid for the development of a p-KT center, with progressive results. Investments in educational campaigns, targeting specifically the medical community as well the general public may allow an even higher increase of p-KT counts in the coming years. The model may be valid for localities with same goal of increasing the number of kidney transplantations.

TH-PO617

Latin America Pediatric Urolithiasis Register: Preliminary Report Maria Goretti M.G. Penido, Michelle M. Lopez, Nilzete Liberato Bresolin, Laura Alconcher, Mary Velasco, Stella M. Dieguez, Ana Paula Spizzirri, Jose Maria Ojeda, Judith Exantus, Morgana De Moro, Marcela Thiemi Korogi, María A. Colina. *Latin America Pediatric Urolithiasis Register - Multicentric Study.*

Background: Considering the socioeconomic and geographic variables, the objective of this study was to outline an epidemiological profile of primary pediatric urolithiasis in Latin America.

Methods: This is an observational, descriptive and retrospective study of pediatric patients with confirmed urolithiasis from Pediatric Nephrology Centers of Latin American from December of 1995 to December of 2015. Data were collected from medical records and placed at a database created online. The study was approved by each institutional review board.

Results: Of the 512 patients (58%M) all had normal serum creatinine, electrolytes and minerals. Urolithiasis was diagnosed by ultrasound in 80% of cases and by computerized tomography in 20%. Median age at diagnosis was 8,0 years (4,9-11,0). Microscopic or gross hematuria (36%), as well as flank or abdominal pain (58%) were the most common clinical presentations. Family history of kidney stones was positive in half of the cases (51%). The most common metabolic urinary abnormalities were idiopathic hypercalciuria (63%) and idiopathic hypocitraturia (52%), alone or in combination with other abnormalities. 22% of the patients had urine flow less than 1.0 ml/kg/hour, 30% had hyperuricosuria and 11% had mild idiopathic absorptive hyperoxaluria. Twenty-five patients had cystinuria (5%) and in 20% no metabolic abnormalities were found. The majority of kidney stones were unilateral (76%) and most of the patients had from 1 to 4 stones (80%).

Conclusions: Despite some differences between the populations, the leading causes of primary pediatric urolithiasis in Latin America were idiopathic hypercalciuria, followed by idiopathic hypocitraturia and "oliguria". The male-female ratio was almost equal, with a slight predominance of males. The diagnosis was done by ultrasound in the majority of the cases and hematúria associated to abdominal or flank pain was the most common clinical presentation. The finding of near similarity between the populations studied calls for combined efforts in addressing these challenging matters.

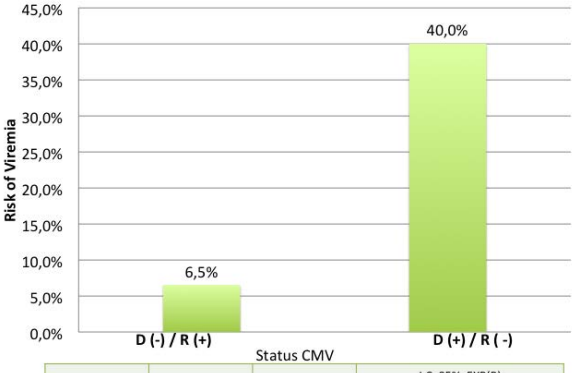
TH-PO618

Incidence and Clinical Impact of Cytomegalovirus in Pediatric Kidney Transplantation: Ten Years of Experience in a Single Center Liliana Rubio. *Pediatric Nephrology, Hospital Univ San Vicente Fundación, Medellin, Antioquia, Colombia.*

Background: Cytomegalovirus is opportunistic agent after transplantation, pediatric recipients are more likely to be CMV seronegative 62.7%. This study evaluated incidence CMV infection/disease and risk factors after transplantation and usefulness of prophylaxis with valganciclovir.

Methods: 56 pts. 1 to 15 yrs underwent transplantation, during 10 yrs. Pre transplantation test was done for CMV status using enzyme-linked assay for IgG antibodies. D+/R+,D+/R-,D-/R+ received prophylaxis, IV ganciclovir (5mg/Kg/BID) was given at 55% of the pts for two weeks, mean dose was 175,2 mg/day during 9,8 days followed by valganciclovir once a day at 100 % of pts. The dose was (mg)= 7 x surface area (m2) x creatinine clearance (mL/min per 1,73 m2). The mean daily dose of valganciclovir was 501mg/day for 125 days.

Results: CMV Serostatus: R+/D-n=4,R+/D+n=42,R-/D+n=10. Seven pts (12,5%) had CMV viremia, one patient had detectable CMV viremia before prophylaxis began, remaining 6 were positive after prophylaxis ended. The development of viremia was 54 days, the number of transplant with viremia positive was 5 in 100 days and 1 after 200 days. CMV disease occurred in 10,7% all received 100 days prophylaxis. The univariated analysis shows that the highest risk group of CMV viremia was D+/R- with 40 % of cases and that D+/R- increases 9.5 times the risk of CMV infection. (p= 0.01).



	Value p	OR	I.C. 95% EXP(B)	
			Low	High
Donor	0,010	9,556	1,705	53,550

Younger age of recipient was associated with higher incidence of infection, 7 yrs vs 10.5 yrs in the CMV-negative infection.

Conclusions: Kidney transplants recipients at highest risk for CMV viremia are those without preexistent CMV specific immunity. The main strategy against CMV in pediatric renal transplantation is universal prophylaxis with valganciclovir. Extending prophylaxis to 6 months in high-risk kidney transplantation is a recommendation that appears to provide a significant benefit.

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TH-PO619

PH1 Mutation p.Gly170Arg+ Urine Proteomics Ellen Brooks,[1,2] Dawn S. Milliner,[3] Bernd Hoppe,[4] Eduardo C. Salido,[5] Heather Price,[2] Craig B. Langman.[1,2] *[1]Feinberg School of Medicine, Pediatrics, Northwestern U, Chicago, IL; [2]Kidney Diseases, Ann & Robert H Lurie Children's Hosp of Chicago, Chicago, IL; [3]Nephrology, Mayo Clinic, Rochester, MN; [4]Pediatric Nephrology, U Hospital Cologne, Cologne, Germany; [5]Centre for Biomedical Research on Rare Diseases, U of La Laguna, Hosp U de Canarias, Tenerife, Canary Islands, Spain.*

Background: Primary hyperoxaluria type 1 (PH1) is a rare disorder with>100 mutations (m) in the liver peroxisomal alanine:glyoxylate aminotransferase (AGXT) gene that leads to hepatic oxalate (Ox) overproduction. Except for the homozygous (HOM) or heterozygous (HET) p.Gly170Arg AGXTm, limited genotype-phenotype correlation exists. Daily pyridoxine (Vit B_6) therapy may reduce or normalize urine (Ur) Ox in Gly170Arg$^+$patients.

Methods: Targeted multiplexed proteomic immunoassays of 24 hr. Ur (Myriad Rules Based Medicine, Austin TX) were used to compare HOM or HET Gly170Arg$^+$ patients (n=26) vs. Gly170Arg$^-$ (n=21). For this cross-sectional study, we hypothesized Vit B_6 treated Gly170Arg$^+$patients would exhibit uniformly protective proteomic patterns vs. Gly170Arg$^-$.

Results: Ur endothelin 1 (ET1) and IL17E were lower (p=0.04;0.03), while MMP9 and MIF1 were higher (p=0.002;0.03) in Gly170Arg$^+$. Trends were seen in Gly170Arg$^+$ for higher MIP1β, MCP4, and MMP7 (p=0.052-0.055). The table below includes other group differences

Group Differences (Md, IQR).			
Data	**Gly170Arg$^+$**	**GLy170Arg$^-$**	**p**
On Vit B_6 Rx (%)	96	62	-
Vit B_6 Dose (mg/day)	400 (300,475)	300 (250,525)	0.78
UrOx (mmol/L/1.73m^2)	0.82 (0.5,1.2)	1.3 (0.9,2.2)	0.008
Ur Calcium (mg/kg/d)	1.17 (0.6,2.5)	1.02 (0.7,1.6)	0.86
eGFR (ml/min/1.73m^2)	84.2 (57,104)	66.0 (54,93)	0.44

Conclusions: PH1 Gly170Arg$^+$ patients on Vit B_6 had lower UrOx and downregulated inflammatory and fibrotic factors, ET1 and IL17E but upregulated MIF1 and MMP9. No differences in oxidative stress and calcification inhibition or calcification promotion markers were seen between the groups. Vit B_6 therapy for Gly170Arg m$^+$ or $^-$ may not offer consistent suppression of extracellular matrix breakdown, macrophage accumulation and fibrosis despite lowering UrOx. B_6 compliance monitoring with targeted Ur proteomics should be considered.

Funding: NIDDK Support

TH-PO620

Genetic Determinants of Uremic Toxins in Hispanic Children: The Viva La Familia Study V. Saroja Voruganti,[1] Geetha Chittoor,[1] Katie A. Meyer,[1] Karin Haack,[2] Sandra L. Laston,[3] Nitesh R. Mehta,[4] Shelley A. Cole,[2] Anthony Gean Comuzzie,[2] Nancy F. Butte.[4] *[1]Univ of North Carolina at Chapel Hill; [2]Texas Biomedical Research Inst; [3]Univ of Texas Rio Grande Valley; [4]Baylor College of Medicine.*

Background: Uremic toxins are organic compounds, which in excess concentrations negatively impact biologic functions. Uremic toxins have been linked to oxidative stress, endothelial dysfunction, increased risk for chronic kidney disease and acute kidney injury, and cardiovascular events and mortality. Adult studies showing environmental and genetic factors affecting uremic toxins cannot be extrapolated to children. Thus, our aim was to identify genetic determinants of 11 serum uremic toxins (low molecular weight molecules: creatine, creatinine, uric acid, xanthine, hypoxanthine, asymmetric dimethylarginine, uridine, and protein-bound molecules: p-cresol sulfate, indole acetate, kynurenine, kynurenate) in 686 Hispanic children.

Methods: Uremic toxins were measured by untargeted metabolomics profiling. A genome-wide association analysis was conducted using a measured genotype approach accounting for kinships.

Results: All uremic toxins were significantly heritable (h^2 = 0.2-0.9, $p < 0.005$). There was a strong association of serum uric acid with variants in uric acid transporter (*SLC2A9*), as previously reported. Of the 10 remaining uremic toxins, a strong association was observed between asymmetric dimethylarginine and rs13406433 of echinoderm microtubule associated protein like 6 (*EML6*)($p = 4.3 \times 10^{-8}$), and suggestive associations were observed between creatine and rs11711956 of calcium voltage-gated channel auxilliary subunit alpha2delta3 (*CACNA2D3*) and rs6593900 of ATPase plasma membrane Ca2+ transporting 4 (*ATP2B4*), indole acetate and rs17182135 of *LOC105378145*, uridine and rs11965452, rs28570682, rs3757328, rs9261261, rs6917477 of zinc ribbon domain containing 1 antisense, pseudogene (*ZNRD1-AS1*) and p-cresol sulfate and rs1078317 of *LOC105378909* ($p < 9 \times 10^{-7}$). The frequency of the minor allele and the effect sizes ranged from 1 - 47% and 2-5%, respectively.

Conclusions: In summary, we demonstrate significant genetic influence on uremic toxins in Hispanic children.

Funding: NIDDK Support

TH-PO621

A CE-MS Pipeline for Long Term Comparable Assessment of the Urinary Metabolome Panagiotis Moulos,[1,2] Valerie Brunchault,[1] Benjamin Breuil,[1] Franck Boizard,[1] Julie Klein,[1] Stephane Decramer,[3] Jean-Loup Bascands,[1] Joost Schanstra,[1] Benedicte Buffin-Meyer.[1] *[1]INSERM U1048/I2MC, Toulouse, France; [2]HybridStat Predictive Analytics, Athens, Greece; [3]CHU Toulouse, Hôpital des Enfants, Toulouse, France.*

Background: 'Urinary omics' strategies are promising tools of high relevance in the clinical setting as they have already led to the design of multimarker protein-based models for the diagnosis of complex diseases. Compared to proteins, metabolites are in the closest biological proximity to the phenotype and can thereby provide functional signatures of pathological states. However, although the field of metabolomics has advanced significantly in the past years, there has been little progress in the discovery of clinically useful urinary metabolite biomarkers.

Methods: Most metabolomics studies use NMR spectroscopy and LC-MS. In contrast, capillary electrophoresis coupled to mass spectrometry (CE-MS) has been rarely used for metabolome analysis due to issues related to stable coupling of CE to MS instrument and limited loading capacity of CE columns. Here, we report an optimized CE-MS setup and data analysis pipeline that allows comparing the metabolite content in urine samples.

Results: A novel normalization procedure using endogenous stable urinary metabolites was developed based on the combined metabolome of 75 different urine samples from healthy and disease individuals. Using this normalization method, the CE-MS platform displayed high performance in terms of long-term stability as it allowed comparison of the same sample analyzed nearly 130 times over a range of 4 years. Next we evaluated the clinical utility of the CE-MS pipeline for the discovery of urinary biomarkers for diagnosis of obstructive nephropathy in infants. We compared the urine metabolome of 34 newborns with ureteropelvic junction (UPJ) obstruction and 15 healthy newborns. This led to the identification of 32 differentially excreted metabolites. Combination of the 32 compounds in a SVM classifier predicted with 88% sensitivity and 86% specificity (AUC 0.90) UPJ obstruction in a separate validation cohort of 24 individuals.

Conclusions: This proof-of-concept study demonstrates the feasibility to use CE-MS as a tool for identification of clinically relevant urinary metabolites.

TH-PO622

Newly-Identified Symptoms of Left Renal Vein Entrapment Syndrome Mimicking Orthostatic Disturbance Tomoki Miyazawa, Keisuke Sugimoto, Kohei Miyazaki, Hidehiko Yanagida, Mitsuru Okada, Tsukasa Takemura. *Pediatrics, Kindai Univ Faculty of Medicine, Osakasayama, Osaka, Japan.*

Background: In addition to the urinary abnormalities, symptoms of left renal vein entrapment between the aorta and superior mesenteric artery (left renal vein entrapment syndrome, LRVES) may include abdominal and flank pain as well as chronic fatigue. We investigated various LRVES symptoms in this study.

Methods: In 53 pediatric LRVES patients treated at our department, 22 had a score of 5 points or higher on orthostasis. Initial evaluation of LRVES by abdominal ultrasonography showed a stenotic-to-prestenotic vein diameter ratio of 0.2 or less. Definitive diagnosis was made by computed tomography and magnetic resonance angiography. Cortisol, catecholamine (CA), and brain natriuretic peptide (BNP) were also measured.

Results: The frequency of LRVES was 2.5 times higher in girls than in boys. Low or very low body mass indexes were seen in both sexes. The most common initial finding was urine abnormalities, followed by dizziness and malaise. In 6 patients, orthostasis precluded school attendance. 10 patients had orthostasis scores above 12. Patients unable to attend school had either low levels of plasma or urinary cortisol. Midodrine significantly decreased orthostasis scores. Some patients required treatment with fludrocortisone. Plasma CA, renin, and BNP levels were all normal.

Conclusions: Locally excessive venous pressure may cause reversible adrenal dysfunction with transitory Addisonian symptoms. Children with cryptogenic malaise or severe orthostasis should be evaluated for LRVES.

TH-PO623

The Relationship of Kidney Disease Knowledge with Self-Management and Healthcare Transition Readiness Maria E. Ferris,[1] Meaghan Nazareth,[1] Julie A. Wright Nunes,[2] Karina Javalkar,[1] Alex Phillips,[1] Sarah Elizabeth Cohen,[1] Jessica Cuttance,[1] Miranda A.l. van Tilburg,[1] Stephen R. Hooper,[1] Keisha L. Gibson,[1] Dorey A. Glenn,[1] Keia Sanderson,[1] Eniko Rak.[1] *[1]UNC Chapel Hill, Chapel Hill, NC; [2]Univ of Michigan, Ann Arbor, MI.*

Background: Successful transition from pediatric to adult-focused services requires knowledge and effective self-management of the chronic kidney disease (CKD).

Methods: English speaking adolescents and young adults (AYA) who attended the UNC Kidney Center clinic in 2015 completed the Kidney Knowledge Survey (KiKS) and the TRxANSITION Scale. Regression was used to explore this relationship while controlling for percentage of life with the disease, sex, race, and insurance.

Results: 155 AYA aged 10-20 years old completed the surveys (mean age 15.79 ± 2.34). Participants were 50.3% females, 36.8% white, 34.2% African American, 53.5% private insurance and 32.9% public insurance. All AYA had been diagnosed with CKD stages 1 to 5. The model as a whole predicted healthcare transition readiness ($F_{6,118}$=4.654, p=0.000). This significance was related to kidney disease knowledge (β=0.340, p=0.000) and percentage of life with the disease (β=-0.216, p=0.013). Race, sex, and insurance were not significant. Correlations of the 10 TRxANSITION Scale domains with the KiKS Score were performed, and Type of illness (r=0.366, p=0.000), $R_{x=\text{prescriptions}}$ (r=0.313, p=0.000), Issues of Reproduction (r=0.250, p=0.003), and Insurance (r=0.276, p=0.001) demonstrated significant, positive correlations.

Conclusions: Participants who had a great understanding of kidney disease knowledge were better prepared to transition to adult care. Increased kidney disease knowledge may also relate to increased knowledge in specific domains of transition readiness, although this relationship must be further explored. In turn, percentage of life with the disease was negatively related to transition readiness. Increase in percent of life with the disease is associated with a decrease in transition readiness.

Funding: Private Foundation Support

TH-PO624

All You Need Is Love: A Low Literacy Curriculum for CKD Education and Self-Management Meaghan Nazareth, Jordan Richards, Jessica Cuttance, Karina Javalkar, Alex Phillips, Sarah Elizabeth Cohen, Eniko Rak, Miranda A.l. van Tilburg, Stephen R. Hooper, Brian H. Pitts, Maria E. Ferris. *UNC Chapel Hill, Chapel Hill, NC.*

Background: To successfully manage chronic kidney disease (CKD), patients need to be able to understand their condition. The efficacy of a low-literacy curriculum developed with interdisciplinary input needs to be assessed.

Methods: The ALL YOU NEED IS LOVE Curriculum provides CKD education, self-management tips, and mindfulness in 6 weeks. A graded intervention was deployed in two groups of adolescents and young adults (AYA). One group received CKD education and self-management and the second group received the same information enhanced with mindfulness activities. Mindfulness provides training in self-acceptance and coping, buffering stress resulting from having a chronic health condition as it integrates openness and present-moment awareness. English speaking AYAs (aged 12-29) with CKD stages

1-5 at pediatric and adult clinics of the UNC Kidney Center, received a booklet and a MP3 player. The outcome was change in the STARx Questionnaire (Ferris 2015), a self-management and transition readiness tool with a best score of 90. Paired t-tests were used to determine significance of changes in transition readiness.

Results: 20 AYA in pediatric and adult clinics have completed the study. Among the pediatric patients, 24% have an ADHD or ADD diagnosis, and 40% have an Individualized Education Plan or 504 plan at school. Mean STARx Questionnaire scores significantly improved, with a greater increase in those with the additional mindfulness intervention (Table 1).

Conclusions: Initial results suggest that this low-literacy curriculum is having a positive impact on knowledge and self-management of CKD among AYAs with this condition. Further exploration is ongoing.

	Mean Baseline STARx Score	Mean Follow-Up STARx Score	p-value
All Participants (n=20)	75.10±12.68	78.70±10.30	0.03
Pediatric Participants (n=16)	72.00±12.08	76.69±10.24	0.02
Adult Participants (n=4)	87.25±6.40	86.75±6.40	0.82
CKD Education + Self-Management (n=10)	75.50±16.43	78.70±13.33	0.20
CKD Education + Self-Management + Mindfulness	74.60±8.31	78.70±6.82	.09

Funding: Private Foundation Support

TH-PO625

Parent-Child Kidney Disease Knowledge Concordance Jordan Richards,[1] Meaghan Nazareth,[1] Julie A. Wright Nunes,[2] Karina Javalkar,[1] Alex Phillips,[1] Sarah Elizabeth Cohen,[1] Jessica Cuttance,[1] Miranda A.l. van Tilburg,[1] Eniko Rak,[1] Stephen R. Hooper,[1] Maggwa Dwayne Shaun Ndugga,[1] Maria E. Ferris.[1] *[1]UNC Chapel Hill, Chapel Hill, NC; [2]Univ of Michigan, Ann Arbor, MI.*

Background: Parents must help manage their children's chronic kidney disease (CKD). It is not clear how much disease-specific knowledge parents have and how concordant it is to their children's knowledge. It is also not clear how this knowledge relates to health care transition readiness.

Methods: English speaking adolescents and young adults (AYA) at the UNC Kidney Center and their parents completed an abridged form of the Kidney Knowledge Survey (KiKS) (max score 100%) as well as the TR$_x$ANSITION Scale (best score is 10). AYA and their parents reported demographic information including AYA age, age at diagnosis, sex, race, and insurance status. Linear regression was used examine the relationship between the parent kidney knowledge score and youth transition scale score total while controlling for percentage of life with the disease, sex, insurance, and race. Pearson's correlation was used to examine parent-AYA KiKS and TR$_x$ANSITION Scale concordance.

Results: 41 parent-AYA dyads completed the surveys. AYA's characteristics included females (68.3%); mean age 15.05 ± 1.89 (range 12-19); mean age at diagnosis 7.71 ± 6.26; private insurance (49%) and Caucasians (49%). The majority of parent participants were mothers (92.7%). The mean parent KiKS score was 70.2% ± 12.9% (range 40 – 100%). The mean AYA KiKS score was 60.7% ± 15.6% (range from 13.3 – 86.7%). Mean parental TR$_x$ANSITION Scale score was 8.1 ± 0.9, and mean AYA TR$_x$ANSITION Scale score was 6.6 ± 1.5. The model was not significant. Correlation between parent and AYA transition scales was significant (r=0.413, p=0.008), while correlation between parent and youth kidney knowledge was not significant.

Conclusions: Parents have lower than expected disease knowledge and transition preparation. Parents with more disease-specific knowledge are likely better prepared to educate AYA about their disease. We identified opportunity for parents to pass their knowledge on to children to further support future self-management and transition to adult care.

Funding: Private Foundation Support

TH-PO626

The Prognostic Value of the Furosemide Stress Test in Predicting Delayed Graft Function following Deceased Donor Kidney Transplantation Blaithin A. McMahon,[1] Edward S. Kraus,[1] Tessa Kimberly Novick,[1] Steven Menez,[1] Sami Alasfar,[1] Niraj Desai,[1] Lakhmir S. Chawla,[3] Jay L. Koyner.[2] *[1]Johns Hopkins Univ School of Medicine, Johns Hopkins Univ, Baltimore, MD; [2]Dept of Medicine, Univ of Chicago, Chicago, IL; [3]Dept of Medicine, The George Washington Univ, San Diego, CA.*

Background: The Furosemide Stress Tess (FST) is a novel dynamic assessment of tubular function that has been shown in preliminary studies to predict patients who will progress to advanced stage Acute Kidney Injury, including those who receive dialysis.The aim of this study is to investigate if the urinary response to a single intraoperative dose of furosemide predicts delayed graft function (DGF) in patients undergoing deceased donor kidney transplant (DDKT).

Methods: This is a single center retrospective cohort analysis of 300 patients undergoing kidney transplantation (KT) at Johns Hopkins Hospital from January 2012 to October 2015. All patients undergoing KT received a single 100mg dose of intraoperative furosemide monitoring UO at 2 and 6 hr post furosemide administration.We utilized the 2 and 6 hour post FST urine output along with multiple logistical regression analysis and area under the receiver operator curves (AUC) to determine DGF (defined as receipt of RRT within 7 days of transplantation).

Results: In multivariate analysis, the FST predicted the need for dialysis after adjusting for donor age, donor race, recipient weight, cold ischemic time, pre-transplantation baseline urinary flow rates (classified as oliguria versus non oliguria),and donor serum creatinine. The AUC for prediction of DGF based on a UO of <150mls at 2 hours and 6 hours was 0.84 and 0.86, respectively.The median length of hospital stay among FST responders (>600mls at 6 hours) was 8 days compared to 12 days in non FST responders (<600mls at 6 hours). There was no significant difference in the prevalence of hypotension and hypokalemia (within 24 hours), as well as graft loss and death in those patients who were FST responders compared to those who were not (median follow up 1.69 years).

Conclusions: The FST is a predictor of DGF post DDKT and has the potential to identify patients requiring RRT early after KT.

TH-PO627

A Sensitive Urinary Furosemide HPLC Assay to Complement the Furosemide Stress Test Jonathan Street,[1] Erik H. Koritzinsky,[1] Lakhmir S. Chawla,[2] Peter S.T. Yuen,[1] Robert A. Star.[1] *[1]NIDDK, Bethesda, MD; [2]VA, Washington, DC.*

Background: The furosemide stress test has been reported as a functional biomarker with good performance in predicting adverse outcomes after AKI. Furosemide binds and inhibits NKCC2, causing a diuresis that can be easily measured. To reach the NKCC2 on the apical surface of the thick ascending limb furosemide must be actively secreted by the proximal tubule. We hypothesized that the excretion of furosemide may provide additional information beyond the urine volume. To investigate this we developed a sensitive assay for urinary furosemide.

Methods: We used a reverse phase HPLC separation with detection by absorbance at 335 nm to sensitively detect furosemide. A 5 µl sample of urine is mixed with 100 µl acetonitrile, centrifuged to pellet precipitated proteins, and the supernatant dried. The HPLC assay utilizes a 50 mm PRP-C18 column with a 10 min isocratic elution using 70% 20 mM potassium phosphate pH 4.5 / 30% acetonitrile as the mobile phase. The dried samples are resuspended in mobile phase prior to injection.

Results: The furosemide assay was linear from 0.5 to 500 ng/µl, with R^2=0.999. The protocol used had a coefficient of variation of 6%. Furosemide standard was spiked into urine and samples stored for 0, 4 and 24 hours at room temperature. There was no degradation with storage over this period (100% recovery). Furosemide was also stable over multiple freeze-thaw cycles with no change observed between 1 and 4 cycles. The assay was robust in the presence of albumin with no change in stability or variability.

Conclusions: Furosemide assay is sensitive, reproducible, and robust. Furosemide is stable in urine over both prolonged storage and multiple freeze-thaw cycles. The protocol is able to accurately measure furosemide concentration in 5 microliters of urine over ranges expected in both human and rodent studies.

Funding: NIDDK Support

TH-PO628

Furosemide Stress Test, Renal Angina Index, or Urinary Sediment: Which I Should Use to Predict Acute Kidney Injury? Rolando Claure-Del Granado, Daniela Torrico-Guillen, Ivan Chavez-Mostajo, Marcelo Coca-Villarroel, Alex J. Arauco-Meneses, Lety Castro-Cossio. *Hospital Obrero #2 - CNS, Cochabamba, Bolivia.*

Background: In recent years several approaches for identifying patients at risk of AKI were used; among them 2 have been of increasing interest: the furosemide stress test (FST) and the renal angina index (RAI). We recently used Perazella et al urinary sediment score (USS) to predict subsequent development of clinical AKI. All of these approaches aim to identify patients at risk for subsequent AKI. We assessed the performance of these 3 different approaches to identify patients at risk of AKI in an ongoing cohort of adult critically ill patients.

Methods: We analyzed data from 30 hospitalized patients admitted to a Medical ICU. We measured serum creatinine (sCr) every 24 h for 7 consecutive days following ICU admission, and urinary volume was assessed hourly each 24 h. At admission (day 0), **RAI** was calculated using the following formula: **Risk level** (presence of sepsis, use of vasopressors, use of invasive mechanical ventilation, and presence of DM) ***x*** **Injury level** (changes in eGFR); we evaluate **USS**; and we applied the **FST** at day 0 (as describe by Chawla et. al. Crit Care 2013; 17(5):R207). We assessed the performance of these 3 tests to predict the subsequent development of AKI using KDIGO sCr and urinary volume criteria.

Results: Of the 30 patients included in this study, 4 (13.3%) patients met the primary end point of AKI (sCr KDIGO criteria). The performance of **RAI**, **FST** and **USS** are shown on table 1.

Performance of the different tests and scores	Furosemide stress test	Renal angina index	Urinary sediment score
Sensitivity (%)	75	100	100
Specificity (%)	100	100	92
PPV (%)	100	100	67
NPV (%)	96	100	100
ROC-AUC (*p* value)	0.990 (0.002)	1.00 (0.002)	0.981 (0.002)

Of note, we consider a cut-off point of <600 cc of urine at 2 h for **FST** since none of the patients who developed AKI had <200 cc of urine as the original cut-off proposed value.

Conclusions: The RAI, FST and USS have robust predictive capacity to identify critically ill patients at high risk of developing AKI before a rise in sCr occurs. These preliminary data of our ongoing study warrants future studies to validate these findings.

TH-PO629

Subclinical Acute Kidney Injury Is an Early Stage of Acute Kidney Injury Rolando Claure-Del Granado,[1] Vania Cecilia Prudencio Ribera,[1] Ravindra L. Mehta.[2] *[1]Medicine, Hospital Obrero #2 - CNS, Cochabamba, Bolivia; [2]Medicine, Univ of California San Diego, CA.*

Background: A recent ADQI consensus on AKI biomarkers has suggested that novel biomarkers (NGAL, KIM-1, and IGFBP-7) can identify kidney damage prior serum creatinine (sCr) elevations. Combining damage and functional markers can thus permit recognition of an early stage of AKI termed **subclinical AKI** (S-AKI). We tested the hypothesis that a panel of damage biomarkers could detect ***S-AKI*** and would predict the subsequent development of **clinical AKI** (C-AKI).

Methods: We included 50 consecutive patients admitted to a Medical ICU. Daily sCr, urine albumin (uAlb) and urine β2–Microglobulin (uβ2-M) levels were measured each 24 h for 7 consecutive days; we evaluated urine sediment (USS) and assigned a score using Perazella et. al. criteria. We define ***S-AKI*** if any of the following criteria was reached in the absence of sCr elevations: new onset of uAlb ≥15 mg/L, or uβ2-M ≥3.2 mg/L, or USS ≥2. ***C-AKI*** was defined by KDIGO sCr criteria. We analyzed the predictive value of each of these biomarkers for the subsequent development of ***C-AKI*** as well to predict survival.

Results: Of the 50 patients, 11(22%) did not develop AKI while 39(78%) developed ***S-AKI***. Of the 39 patients with ***S-AKI,*** 26(67%) progressed to ***C-AKI*** while 13(33%) did not. The predictive value of uAlb, uβ2-M and USS at 24 and 48 h are show in table 1.

Predictive value of the different biomarkers	ROC-AUC (95% CI)	*p* value
Urinary Albumin (≥15 mg/L) 24 h 48 h	 0.753 (0.612-0.894) 0.707 (0.555-0.859)	 0.02 0.01
ß$_2$ Microglobulin (≥2.5 mg/L) 24 h 48 h	 0.770 (0.624-0.916) 0.703 (0.545-0.861)	 0.01 0.14
Urinary Sediment Score (≥ 2) 24 h 48 h	 0.818 (0.638-0.998) 0.773 (0.580-0.965)	 0.001 0.006

28-day mortality did not differ between patients with ***S-AKI*** who didn't developed ***C-AKI*** and patients with ***S-AKI*** who developed ***C-AKI***.

Conclusions: Our data shows high incidence of ***S-AKI*** that progressed to ***C-AKI***. These findings support the ADQI recommendations to consider ***S-AKI*** based on positive damage biomarkers alone as an early phase of AKI. Identification of ***S-AKI*** would potentially allow earlier intervention with preventive and treatment strategies to reverse kidney injury and improve recovery.

TH-PO630

Clinically Relevant Furosemide Stress Test Is Predictive for AKI Progression in ICU Patients with Elevated Plasma NGAL Level Ryo Matsuura,[1] Yohei Komaru,[1] Yoshihisa Miyamoto,[3] Teruhiko Yoshida,[1] Kohei Yoshimoto,[2] Rei Isshiki,[1] Kengo Mayumi,[1] Tetsushi Yamashita,[1] Yoshifumi Hamasaki,[3] Masaomi Nangaku,[1,3] Eisei Noiri,[1] Kent Doi.[2] *[1]Dept of Nephrology and Endocrinology, The Univ of Tokyo Hospital, Tokyo, Japan; [2]Dept of Emergency and Critical Care Medicine, The Univ of Tokyo Hospital, Tokyo, Japan; [3]Dept of Dialysis and Apheresis, The Univ of Tokyo Hospital, Tokyo, Japan.*

Background: Furosemide stress test (FST), which evaluates urine output after furosemide administration, has been suggested for predicting progression of severe AKI. Although the standardized dose (1 mg/kg) is required in FST, different doses are used to see urine output responsive to furosemide in the clinical. In addition, biomarker information is expected to improve prediction performance of FST.

Methods: We evaluated retrospectively plasma NGAL and furosemide response (FR), defined as urine output measured for 2 hours after injection, for stratifying the risk of AKI progression in our ICU. Furosemide dose was determined by clinical judgement based on the severity of illness including renal and cardiac function.

Results: 95 ICU patients were analyzed in this study. 18 patients developed AKI stage 3 within one week (19%). ROC analysis showed the AUC and cutoff values as follows; plasma NGAL 0.80 [0.67-0.88], 142 ng/ml and FR 0.87 [0.73-0.94], 3.9 ml/mg-furosemide. Only one patient with lower NGAL level (< 142 ng/ml) progressed to AKI stage 3. FR provides the AUC of 0.84 [0.67-0.94] for prediction of the development to AKI stage 3 even in the patients with higher NGAL (>142 ng/ml). With the cutoff value of 3.9 ml/furosemide dose (mg), 13 NGAL-high patients with FR negative developed AKI stage 3 (86.7%), while four FR positive patients developed to AKI stage 3 (11%) with the odds ratio of 52 (8.5-319.5) (p<0.01).

Conclusions: Although different doses of furosemide were administered, FR showed good performances for predicting AKI progression even in high plasma NGAL patients. This suggests combination of FR and biomarkers can stratify the risk in AKI progression in the clinical settings.

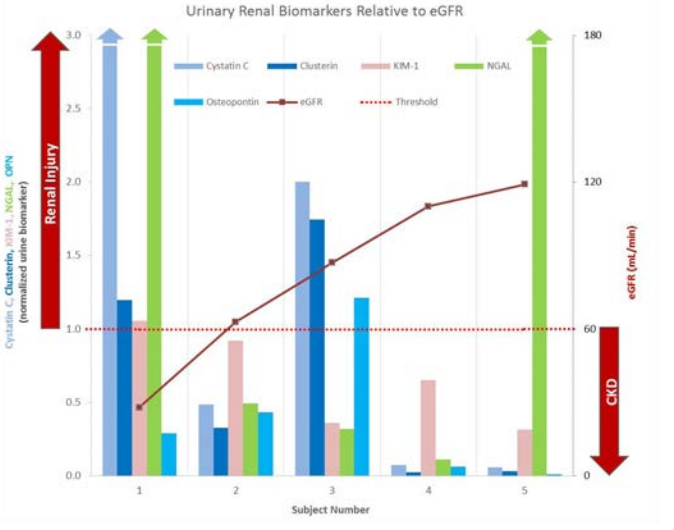
TH-PO631

Monitoring and Diagnosing Acute Kidney Injury Using Biochip Array Technology Candace M. Adamo,[1] Amar Sethi,[1] Eibhlin M. Mccole,[2] Marie Mcgarvey,[2] Ciaran Richardson,[2] Peter Fitzgerald,[3] John Lamont,[3] Timothy H. Carlson.[1] *[1]Pacific Biomarkers, Seattle, WA; [2]Randox Teoranta, Dungloe, Co. Donegal, Ireland; [3]Randox Laboratories, Crumlin, Co. Antrim, United Kingdom.*

Background: The risk of acute kidney injury (AKI) is currently assessed by serum creatinine and clinical representation using the KDIGO classification. Recent efforts have identified several novel biomarkers that are more specific and sensitive in the monitoring and diagnosis of AKI.

Methods: The collective response in 20 subjects of five urinary biomarkers (KIM-1, cystatin C, NGAL, osteopontin (OPN) and clusterin) were measured by ELISA and by a newly developed multiplexed biochip array (Randox Evidence Investigator™).

Results: Correlation coefficients (r^2) between the two methods were above ≥0.98 for all biomarkers except for clusterin (r^2=0.80), with a slope between 0.86 – 1.43, indicating excellent agreement. Preliminary comparison of sensitivity (NGAL=0.78 ng/mL; KIM-1=15.61 pg/mL) and dynamic range (data not shown) between the two methods showed equal or better performance. Multiplexing suggests improved AKI detection as subject 3 with normal eGFR had 3 of 5 biomarkers elevated, indicating renal injury; subject 1 with CKD and eGFR <60 mL/min had biomarker elevations in 4 of 5 tested. The biomarker profiles for the remaining subjects at risk for AKI differed, indicating reduced renal function may be better captured by several biomarkers, as each biomarker reflects different mechanisms that lead to the same injury outcomes (representative data shown below).



Conclusions: These results suggest the potential of this novel multiplex AKI panel to become a robust and cost-effective tool for monitoring renal injury, which is tested from a smaller sample volume with faster turn-around time and without compromising sensitivity or dynamic range.

TH-PO632

Evaluating Renal Injury and Function in Marathon Runners Using Injury and Repair Biomarkers Sherry Mansour,[1] Gagan Verma,[1] Rachel W. Pata,[2] Thomas Martin,[2] Chirag R. Parikh.[1] *[1]PATR, Yale Univ; [2]Quinnipiac Univ.*

Background: There is growing interest in the effects of strenuous activity on renal function, in light of the recent kidney disease epidemic among Mesoamerican sugarcane workers. Marathon running serves as a model of extreme activity and heat stress. This prospective study evaluated renal function of runners during the 2015 Hartford Marathon using conventional and novel renal biomarkers.

Methods: We enrolled 22 runners and collected samples 24 hours pre-marathon (Day 0), immediately after marathon (Day 1) and 24 hours post-marathon (Day 2). Six injury biomarkers: IL-6, IL-8, IL-18, kidney injury molecule-1, neutrophil gelatinase-associated lipocalin and tumor necrosis factor alpha, and two repair biomarkers: YKL-40 and monocyte chemoattractant protein-1 (MCP-1) were measured. Serum creatinine, creatine phosphokinase (CPK), urine microalbumin and urine microscopy were also evaluated. We assessed changes in biomarker levels, AKI (stage I or higher by AKIN criteria) and urine microscopy score ≥ 2 (strong predictor of ATN).

Results: The mean age of runners was 44 years old and 41% were males. 27% used NSAIDs pre-race. Serum creatinine was elevated on Day 1 versus Day 0 (1.33 mg/dL vs 0.85 mg/dL, p<0.01). Urine microalbumin was elevated on Day 1 versus Day 0 (6.46 mg/dL vs 0.57 mg/dL, p<0.01). On Day 2 creatinine and microalbumin levels started decreasing. 82% of runners developed AKI and 73% had a positive microscopy score. Serum CPK increased from Day 0 to Day 1 and continued to rise on Day 2 (110.32 U/l vs 299.86 U/l vs 769.19 U/l respectively, p <0.01). Urine biomarkers of injury were significantly elevated on Day 1 versus Day 0 and all biomarkers except IL-8 and TNF-α remained significantly elevated on Day 2 versus Day 0. Repair biomarkers were significantly elevated on Day 1 versus Day 0 but only MCP-1 remained significantly elevated on Day 2 versus Day 0.

Conclusions: Marathon runners developed AKI and urine sediments predictive of ATN. A rise in injury and repair biomarkers further indicated structural damage. These changes in renal function of runners may elucidate mechanisms of nephropathy in Mesoamerican sugarcane workers. Our results should be validated in larger cohorts.

Funding: Other NIH Support - T-32 grant

TH-PO633

Back to Basics: Is Urinary Sediment Earlier Marker Than Urinary NGAL or KIM-1 for Diagnosis of AKI after Open Heart Surgery? Salah S. Naga. *Nephrology, Alexandria Faculty of Medicine, Alexandria, Egypt.*

Background: AKI is common after open heart surgery (CPB). Several biomarkers have been used including urinary NGAL and KIM-1 for the early diagnosis of AKI. This study was carried out to evaluate the role of urinary sediment scoring (USS) in comparison to NGAL and KIM-1 in the early detection of AKI after CPB.

Methods: This prospective cohort study was carried out on 45 adult patients of both sexes with a Cleveland score (CCS) (0-5) and scheduled for CPB surgery in Alexandria Main University Hospital. The renal function of the patients was assessed before and every day after surgery.Fresh urine samples were taken from every patient and centrifuged for microscopic examination of the urinary sediments and for measurement of NGAL and KIM-1 before, 2, 6, 12 and 24 hours after CPB.

Results: Eleven patients developed AKI. Patients with AKI had a higher CPB and cross clamp times (90+/-16.2 in comparison to 60.9+/-8.1 minutes in the non-AKI patients). Serum creatinine started to be significantly higher in the AKI group from the second postoperative day with a mean value of 1.56+/-0.28 mg/dl compared to a mean value of 0.85+/-0.14mg/dl in the non AKI group. Urine sediment score (USS) 1 and 2 were higher in the AKI group 2 hours after CPB and till the end of the first day with area under the curve (AUC) average of (0.865). Urinary NGAL significantly increased in the AKI group 2 and 6 hours after CPB with corresponding AUC of (0.710 and 0.700). Urinary KIM-1 was higher in the AKI group 12 and 24 after CPB with AUC of 0.725 and 0.703, respectively. Combination of USS, NGAL and KIM-1 gives an AUC of 0.906 in predicting AKI. Multivariable binary logistic regression analysis revealed that the most powerful independent predictors of AKI were USS 24 hours (RR 4.752) and urinary NGAL 6 hours (RR 1.020) after CPB.

Conclusions: Urinary microscopic examination to detect urinary sediments, which is often neglected, was found to have a higher sensitivity and specificity for early detection of AKI in comparison to the novel biomarkers NGAL and KIM-1. They can also be used in combination to improve their performance.

TH-PO634

Urinary Biomarkers at the Time of AKI Diagnosis as Predictors of Progression of AKI among Patients with Acute Cardiorenal Syndrome Xiaobing Yang, Fan Fan Hou. *Renal Div, Nanfang Hospital, Southern Medical Univ, Guangzhou, China.*

Background: A major challenge in early treatment of acute cardiorenal syndrome (CRS) is the lack of predictor for progressionof AKI. Weaim to investigate the utility of urinary angiotensinogen and other renal injury biomarkers in predicting AKI progression inCRS.

Methods: In this prospective, multicenter study, we screened 732 adults who admitted for acute decompensated heart failurefrom September 2011 to December 2014, and evaluated whether renal injury biomarkers measured attime of AKI diagnosis can predict worsening of AKI. In 213 patients who developed KDIGO stage 1 or 2 AKI,six renal injury biomarkers, including urinary angiotensinogen (uAGT), urinary and plasma neutrophil gelatinase-associated lipocalin (NGAL), urinary IL-18 (uIL-18), urinary kidney injury molecule-1 (uKIM-1), and urinary albumin to creatinine ratio (UACR), were measured at time of AKI diagnosis. The primary outcome was AKI progression defined by worsening of AKI stage (50 patients). The secondary outcome was AKI progression with subsequent death (18 patients).

Results: After multivariable adjustment, the highest tertile of three urinary biomarkers remained associated with AKI progression compared with the lowest tertile: uAGT (OR, 10.8; 95%CI, 3.4-34.7), uNGAL (OR, 4.7; 95%CI, 1.7-13.4) and uIL-18 (OR, 3.6; 95%CI, 1.4-9.5). Urinary AGT was the best predictor for both primary and secondary outcomes with AUC of 0.78 and 0.85. These three biomarkers improved risk reclassification compared with the clinical model alone, with uAGT performing the best(category-free net reclassification improvement for primary and secondary outcomes of 0.76 (95%CI, 0.46-1.06) and 0.93 (95%CI, 0.50-1.36), P<0.001). Excellent performance of uAGT was further confirmed with bootstrap internal validation.

Conclusions: Urinary AGT, uNGAL and uIL-18 measured at time of AKI diagnosis improved risk stratification and identified CRS patients at highest risk of adverse outcomes.

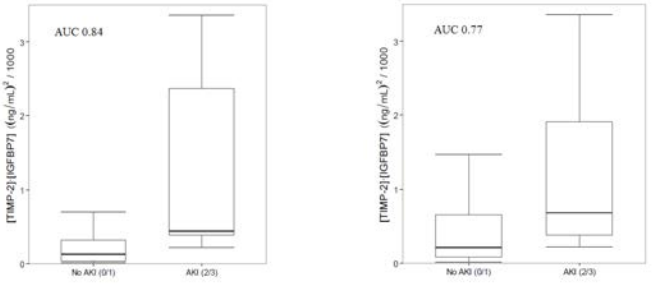
TH-PO635

Urinary [TIMP-2]·[IGFBP7] for Risk Prediction of Acute Kidney Injury in Decompensated Heart Failure Moritz Schanz,[1] Jing Shi,[2] Christoph Wasser,[1] Mark Dominik Alscher,[1] Martin Kimmel.[1] *[1]General Internal Medicine and Nephrology, Robert-Bosch Hospital, Stuttgart, Germany; [2]Walker Bioscience, Carlsbad, CA.*

Background: Acute decompensated heart failure (ADHF) is a common reason for hospitalization and the risk of acute kidney injury (AKI) is high. Early detection of patients at risk for cardiorenal syndrome is important. We tested urinary [TIMP-2]·[IGFBP7], a new FDA-cleared test to assess AKI risk, in a cohort of hospitalized ADHF patients.

Methods: 400 patients were enrolled in the ED at Robert-Bosch-Hospital, Stuttgart, Germany. Urinary [TIMP-2]·[IGFBP7] was analyzed in samples collected at enrollment, after 6 hours, and the following mornings over up to 7 days. We examined the predictive ability of urinary [TIMP-2]·[IGFBP7] for development of AKI stage 2 or 3 within 24 hours of sample collection in patients with ADHF. Operating characteristics were determined for the previously validated [TIMP-2]·[IGFBP7] cutoffs of 0.3 and 2.0. [TIMP-2]·[IGFBP7] results are reported in units of $(ng/mL)^2/1000$.

Results: Eleven (27.5%) of the 40 ADHF patients met the AKI stage 2-3 endpoint within 7 days. [TIMP-2]·[IGFBP7] discriminated for risk of AKI stage 2-3 with an AUC (95% confidence interval) of 0.84 (0.72-0.95) for initial presentation (within 24 hours) and 0.77 (0.65-0.88) for samples collected within 7 days.



At the 0.3 cutoff for [TIMP-2]·[IGFBP7], the sensitivity was 86% and the specificity was 71% for prediction of AKI stage 2-3 and at the 2.0 cutoff, the sensitivity was 43% and the specificity was 95% for samples collected within 24 hours of enrollment. Kaplan-Meier curves showed a trend (p=0.09) for decreased survival over one year in patients who reached AKI stage 2 or 3 within 7 days compared with those who did not.

Conclusions: In conclusion, urinary [TIMP-2]·[IGFBP7] predicts moderate-to-severe AKI in patients with ADHF.

Funding: Pharmaceutical Company Support - Astute Medical, San Diego, USA, Private Foundation Support

TH-PO636

Urinary [TIMP-2]·[IGFBP7] in Platin-Induced Renal Injury Moritz Schanz, Martin Kimmel, Mark Dominik Alscher. *General Internal Medicine and Nephrology, Robert-Bosch Hospital, Stuttgart, Germany.*

Background: Platin-based chemotherapy is a potent antineoplastic agent, but cisplatin nephrotoxicity is a limiting side effect. Identifying those patients who are at risk for developing platin-induced renal injury is an important issue. We tested urinary [TIMP-2]·[IGFBP7], a new FDA-cleared test to assess AKI risk, in a cohort of patients with malignant disease receiving platin-based chemotherapy (PBC).

Methods: 58 patients were enrolled in this study. N=32 patients had available both, urinary [TIMP-2]·[IGFBP7] prior to PBC application and subsequent serum creatinine values for detecting AKI within 72 hours. Urinary [TIMP-2]·[IGFBP7] was collected on the same day prior to PBC application and the earliest available specimen after chemotherapy administration. We examined the predictive ability of [TIMP-2]·[IGFBP7] for development of KDIGO stage 1-3 within 72 hours after administration of chemotherapy in 32 patients with malignant disease. Operating characteristics were determined for the previously validated [TIMP-2]·[IGFBP7] cutoff of 0.3. [TIMP-2]·[IGFBP7] results are reported in units of $(ng/mL)^2/1000$.

Results: Four (12.5%) patients developed AKI stage 1-3 within 72 hours. Primary disease was in n=13 (40.6%) lymphoma and in n=19 (40.6%) solid tumors. Eight patients (25.0%) received carboplatin, n=24 (75.0%) cisplatin. [TIMP-2]·[IGFBP7] discriminated for risk of AKI stage 1-3 with an AUC (95% CI) of 0.86 (0.73-0.98). At the 0.3 cutoff for [TIMP-2]·[IGFBP7], the sensitivity was 75% and the specificity was 82% for prediction of AKI stage 1-3.

Sensitivity	Specificity	NPV	PPV	AUC
0.75 (0.19 – 0.99)	0.82 (0.63 - 0.94)	0.96 (0.79 – 1.00)	0.38 (0.09 - 0.76)	0.86 (0.73-0.98)

Comparing urinary [TIMP-2]·[IGFBP7] values prior to and after PBC application, a significant decrease of urinary [TIMP-2]·[IGFBP7] was remarkable (p=0.026).

Conclusions: Urinary [TIMP-2]·[IGFBP7] prior to PBC identifies patients who are at risk for developing platin-induced acute kidney injury. Because of a significant decrease of urinary [TIMP-2]·[IGFBP7] after PBC application (p=0.026), presumably due to prehydration, specimens gathered prior to chemotherapy seem to be more eligible for risk prediction of AKI.

Funding: Pharmaceutical Company Support - Astute Medical, San Diego, USA, Private Foundation Support

TH-PO637

Cost-Effectiveness of NephroCheck® for Acute Kidney Injury in Critical Care Andrew J.P. Lewington,[1,2] Alison F. Smith,[2,3] David M. Meads,[3] Michelle Hutchinson,[3] Elizabeth D. Mitchell,[3] Judy M. Wright,[3] David Allan Cairns,[3] Michael P. Messenger,[1,2] Rebecca L. Kift,[1,2] Claire Louise Corps,[1,2] Patrick Hamilton,[4] Aleksandra Sobota,[3] Peter S. Hall.[2,5] *[1]Leeds Teaching Hospitals Trust, United Kingdom; [2]NIHR Diagnostic Evidence Cooperative Leeds, United Kingdom; [3]Univ of Leeds, United Kingdom; [4]Univ of Manchester, United Kingdom; [5]Univ of Edinburgh, United Kingdom.*

Background: Early diagnosis of acute kidney injury (AKI) in the Intensive Care Unit (ICU) may improve patient outcomes. The Nephrocheck® test (ASTUTE Medical, San Diego, CA) has gained FDA approval, but there is currently a lack of evidence on its cost-effectiveness. We therefore conducted a cost-utility analysis of NephroCheck® vs. standard care (daily serum creatinine and urine testing) from a UK NHS perspective.

Methods: All patients (AKI KDIGO stage≤1) were assumed to be tested on ICU admission. True Positive [TP], True Negative [TN], False Positive [FP] and False Negative [FN] cohorts were created using results from a systematic review and meta-analysis (sensitivity 0.91; specificity 0.49). A probabilistic lifetime Markov model was constructed and used daily cycles (day 0-90) to capture ICU KDIGO AKI stages, and annual cycles thereafter to capture long-term Chronic Kidney Disease (CKD) and mortality. TPs were assumed to have reduced risks (RR=0.78) of AKI progression due to early intervention; no harm was assumed for FP/FN results. In the absence of a published price for Nephrocheck® a range of values were tested.

Results: Nephrocheck® produced an average of 0.06 (95% CI:-0.21 to 0.37) extra QALYs at an additional cost of £154 (-1222 to 1554) to £332 (-1046 to 1731), assuming per-test costs of £10 [US$14] to £200 [$287] respectively. Incremental Cost-Effectiveness Ratios (ICERs) ranged from £2,420 [$3477] to £5,225 [$7507] per QALY. The test had a 65-68% and 68-69% probability of being cost-effective at willingness-to-pay per QALY thresholds of £20,000 [$28700] and £50,000 [$71800]. Results were sensitive to parameters including the AKI incidence and impact of early treatment.

Conclusions: These results can be considered sufficient justification for further research. The cost-effectiveness of Nephrocheck® compared to other market competitors should now be evaluated.

Funding: Government Support - Non-U.S.

TH-PO638

Comparison of NephroCheck(R) and Neutrophil Gelatinase-Associated Lipocalin for Risk Prediction in Combat Casualties Ian J. Stewart,[1] Jonathan Sosnov,[2] Kevin Chung,[3] Javance Tercero,[3] Elizabeth H. Babcock.[3] *[1]David Grant Medical Center, Travis AFB, CA; [2]San Antonio Military Medical Center, Fort Sam Houston, TX; [3]United States Army Inst of Surgical Research, Fort Sam Houston, Texas.*

Background: The NephroCheck®, which measures the product of tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7), has been shown to predict the subsequent development of AKI. We have previously shown that other novel urinary biomarkers for AKI, such as neutrophil gelatinase-associated lipocalin (NGAL), are associated with poor outcomes in a homogenous population of casualties from the war in Afghanistan. We hypothesized that the NephroCheck® would also predict poor outcomes in this patient population.

Methods: We conducted a prospective, observational study in a combat support hospital in Afghanistan. Patients that were US military members that suffered traumatic injury and were admitted to the intensive care unit (ICU) were included for analysis. Urine was collected at the time of admission to the ICU, frozen and shipped back to the US for later analysis. The combined outcome was defined by either death or the need for renal replacement therapy.

Results: Eighty seven patients were included in our study. Of these, 12 either died or required renal replacement therapy. Median admission product of TIMP-2 and IGFBP7 was higher in patients that subsequently developed the outcome (0.35, IQR 0.07-0.98) compared to those that did not (0.11, IQR 0.06-0.26), but this difference was not statistically significant (p=0.1). The area under the curve (AUC) for predicting the combined outcome was 0.65 and did not reach statistical significance (p=0.19). This stands in contrast to our prior our prior work examining urinary NGAL, which demonstrated an AUC of 0.82 (p<0.001).

Conclusions: In a group of young, critically injured military members, NephroCheck® did not significantly predict the combined endpoint of death or the need for renal replacement therapy. While the NephroCheck® has shown great promise for diagnosing AKI early, our work suggests that other urinary biomarkers, such as NGAL, may be superior at predicting other outcomes.

Funding: Other U.S. Government Support

TH-PO639

Urinary Biomarker TIMP-2 Predicts Adverse Outcomes in Patients with Acute Kidney Injury Sung Yoon Lim, Jihyun Yang, Young Ju Na, Myung-Gyu Kim, Sang-Kyung Jo, Won-Yong Cho. *Korea Univ Anam Hospital, Korea.*

Background: Several recent studies have shown that insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP2) is a promising biomarker for the early detection of acute kidney injury (AKI), but the role of IGFBP7 and TIMP2 in predicting adverse clinical outcomes has not been well addressed. The purpose of this study was to evaluate the usefulness of urine IGFBP7 and TIMP2 as outcome predictor in patients with AKI.

Methods: This was a prospective cohort study enrolling established AKI patients. Urinary biomarkers, including IGFBP7, TIMP2 and NGAL were determined on admission and discharge from hospital. The primary clinical outcome variables were renal replacement therapy (RRT), renal recovery and in-hospital mortality.

Results: We prospectively enrolled 253 patients with AKI. Initial plasma creatinine concentrations and urinary biomarkers at AKI diagnosis were significantly higher in the RRT group than in the non-RRT group (Creatinine 5.17±3.59 vs 2.98±1.60 mg/dL; NGAL 2035.44±2431.73 vs 880.54±1413.68; IGFBP7 47.67±46.44 vs 33.23±44.55; TIMP2 24.27±45.60 vs 9.58±14.48 ng/mg creatinine, P<0.05). For predicting RRT requirement, increased plasma creatinine and TIMP2 was independently associated with greater odds of RRT in multiple logistic regression analysis. (odds ratio 1.77, P= 0.048; 48.30, P= 0.04, respectively) However, plasma creatinine and urinary biomarkers did not show statistically significant difference and could not predict recovery and the death in this study.

Conclusions: This prospective observational study could suggest that Urinary TIMP2 might be served as a strong predictor for the need for the renal replacement therapy early in the course of AKI.

Funding: Private Foundation Support

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Value of Urinary Neutrophil Gelatinase Associated Lipocalin for Differential Diagnosis of Acute Kidney Injury in Decompensated Cirrhosis Sonia Rodriguez, Rossana O. Olmedo Ocampo, Barbara Vazquez-Cantu, Jose Antonio Nino-Cruz, Juan Antonio Ortega-Trejo, Rosalba Pérez-Villalva, Ricardo Correa-Rotter, Norma Bobadilla, Juan Carlos Ramirez-Sandoval. *Inst Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico.*

Background: Early measurement of uNGAL could be useful for differential diagnosis of acute kidney injury (AKI) causes in patients with cirrhosis.

Methods: Observational cohort of patients with decompensated cirrhosis and AKI admitted to the Emergency Room. AKI was defined as an increase in SCr≥0.3 mg/dl from baseline; uNGAL was measured by ELISA in urine obtained at:(1) admission and diagnosis of AKI and (2) after 8-12 hours of volume expansion. We excluded patients with shock, massive bleeding, post-obstructive AKI, kidney transplant, and baseline sCr>2.5 mg/dL.

Results: We evaluated 65 patients (mean age: 59±14 years, female: 55% [n=33], sepsis: 57% [n=37]) of which we prospectively collected 130 urine specimens. All patients were initially treated with intravenous albumin and withdrawal of diuretics. A low initial uNGAL level predicted pre-renal AKI, with an area under the receiver operating characteristic curve (AUC-ROC) of 0.76 (95% confidence interval[CI]: 0.62-0.91, p:0.002). The 2nd uNGAL measurement, after 8-12 hours of treatment, had an AUC-ROC of 0.88 (95%CI: 0.77-0.99, p<0.001). At a cutoff concentration of 64 ng/mg uCr, the second measurement of uNGAL diagnosed pre-renal AKI with sensitivity of 93% and specificityof 81%. uNGAL was superior to predict full response to volume expansion (return to SCr baseline ±0.2mg/dL) compared with the initial Na fractional excretion or degree of AKI. We did not find differences in uNGAL levels between hepatorenal syndrome and intrinsic-AKI. uNGAL levels were positively associated with sepsis severityand MELD score (p<0.001).

Conclusions: Early uNGAL determination in patients with decompensated cirrhosis and AKI is useful to diagnose pre-renal AKI, even before diuretic withdrawal and plasma volume expansion with IV albumin for 2 days, and may avoid delay of effective treatment for other causes of non pre-renal AKI such as hepatorenal syndrome or intrinsic-AKI. uNGAL did not differentiate between hepatorrenal syndrome and intrinsic-AKI.

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The Clinical Value of Urinary Neutrophil Gelatinase-Associated Lipocalin (uNGAL) for the Diagnosis of Acute Kidney Injury during Hospitalization for Acute Heart Failure: Primary Findings of the Acute Kidney Injury N-gal Evaluation of Symptomatic Heart Failure Study (AKINESIS) Patrick T. Murray,[1] Alan S. Maisel.[3,4] *[1]School of Medicine, Univ College Dublin, Dublin, Ireland; [2]Dept of Cardiology, Univ Medical Center Groningen, Groningen, Netherlands; [3]Div of Cardiovascular Medicine, Veterans Affairs Medical Center, San DIego, CA; [4]Div of Cardiovascular Medicine, Univ of California San Diego, San Diego, CA.*

Background: Acute Kidney Injury (AKI) often occurs during acute heart failure (AHF) and can portend adverse outcomes; therefore, early identification may help mitigate risk. Urinary Neutrophil Gelatinase-Associated Lipocalin (uNGAL) is a novel renal biomarker that may predict AKI in certain disorders, but its value in AHF is unknown. Our objective was to determine whether uNGAL is superior to plasma creatinine (PCr) for prediction and/or prognosis of AKI in hospitalized patients with AHF.

Methods: A multicenter, prospective cohort study enrolling patients presenting with AHF requiring IV diuretics. The primary outcome was whether uNGAL could predict the development of AKI, defined as a sustained increase in PCr of ≥0.5 mg/dL or ≥50% above first value or initiation of acute renal replacement therapy (RRT), within the first five days of hospitalization. The main secondary outcome was in-hospital adverse events.

Results: 927 subjects (age 68.5 years, 62% men) were enrolled. The primary outcome occurred in 72 subjects (7.8%). First PCr was more predictive of the primary outcome than either the first or peak uNGAL values (AUCs 0.623, 0.593, and 0.567, respectively). First PCr was similarly more predictive of RRT within the first five days of hospitalization than

either first or peak uNGAL values (AUCs 0.88, 0.795, and 0.724, respectively). There were 235 in-hospital adverse events in 144 subjects. The first PCr was a better predictor of this composite outcome than either first or peak uNGAL (0.687, 0.648, and 0.604, respectively).

Conclusions: Urine NGAL was not superior to plasma creatinine for the prediction of AKI or adverse in-hospital outcomes in patients hospitalized with AHF. The use of uNGAL to diagnose AKI in AHF cannot be recommended at this time.

Funding: Pharmaceutical Company Support - Abbott Labs; Alere

TH-PO642

No Evidence of Chloride Nephrotoxicity Using Urinary Excretion of NGAL as Biomarker between 155 mmolar Chloride Infusion with 98 mmolar Chloride in Patients Undergoing Primary Uncemented Hip Replacement

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Background: The use of fluids containing high amounts of chloride (Cl) reduced the need for renal-replacement-therapy. Animal studies showed that Cl reduced renal blood flow. Thus, Cl might cause acute ischemic kidney injury. The purpose of the study was to measure whether chloride induced kidney damage in a clinical study using urinary excretion rate of neutrophil gelatinase associated lipocalin (u-NGAL) as biomarker for nephrotoxicity.

Methods: In a randomized, double-blinded, placebo-controlled study of patients undergoing primary uncemented hip replacement, thirty eight-were randomized to receive either isotonic saline (155 mmolar chloride) or plasma-lyte (98 mmolar chloride) 15ml/kg during the first hour and 5ml/kg the following two hours after start of surgery. Urine was collected in four periods: Period 1: 24 hours before surgery, Period 2: 4 hours from the start of surgery, Period 3: from end of period 2 to 7.30 the next day and Period 4: 24 hours 10-12 days later. In addition, spot urine samples were collected before surgery and before discharge. Blood was collected before surgery and at the end of period 2 and period 3. We measured urinary u-NGAL and plasma concentrations of chloride (p-Cl) and creatinine (p-Crea).

Results: U-NGAL (median values) was the same in the saline group and the plasma-lyte group in all four periods. Period 1: 15.92 (plasma-lyte)/15.60 (saline) ng/min (p=0.54); Period 2: 22.51/9.88 ng/min (p=0.68); Period 3: 10.95/6.44 ng/min (p=0.05); Period 4: 4.05/2.04 ng/min (p=0.05). In the saline group p-Cl (mean value) 110.5 mmol/l was significantly higher than in the plasma-lyte group 107.9 mmol/l (p = 0.004). P-Crea was the same in both groups.

Conclusions: No evidence of nephrotoxicity was detected between infusions of high and low concentrations of chloride in a clinical trial using urinary excretion of NGAL as marker of kidney damage.

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

TH-PO643

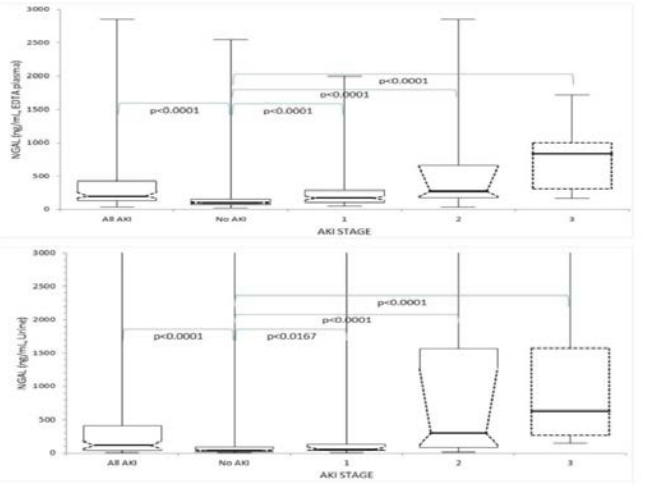
Neutrophil Gelatinase-Associated Lipocalin (NGAL) Correlates to AKI Stage in ICU Patients

Ladan Golestaneh,[1] A. Osama Gaber,[2] Sahir Kalim,[3] Peter A. McCullough,[5] Michael J. Germain.[4] *[1]Medicine, Albert Einstein College of Medicine, Bronx, NY; [2]Medicine, Houston Methodist Hospital, Houston, TX; [3]Medicine, Massachusetts General Hospital, Boston, MA; [4]Medicine, Baystate Medical Center, Springfield, MA; [5]Medicine, Baylor Univ Medical Center, Dallas, TX.*

Background: Acute kidney injury (AKI) is a commonly encountered complication in ICU patients and associated with poor outcomes. The diagnosis is based on serum creatinine (sCr) elevations compared to a poorly defined baseline. NGAL is a marker of AKI that has been shown to increase early in urine and plasma of different patient populations with AKI. We evaluated the ability of NGAL to detect AKI in a heterogenous ICU cohort.

Methods: Four sites participated in this study and recruited a total of 245 ICU patients. Blood and urine samples were taken daily and stored. Concentrations were determined with the NGAL Test (BioPorto) in batched samples by a central laboratory. Three clinicians adjudicated each patient case according to KDIGO guidelines and also determined the AKI stage once present. The clinical reviewers were blinded to the NGAL results.

Results: There was a statistically significant relationship between NGAL level and stage of AKI. For the subjects classified as not having AKI, median NGAL was 97 ng/mL, in EDTA plasma and 33 ng/mL in urine . For the subjects classified as having any stage of AKI, median plasma NGAL level was 197 ng/mL i and 116 ng/mL in urine. The median plasma NGAL levels for AKI- stage 1: 170 ng/mL and 53 ng/mL in urine: AKI-stage 2: plasma 274 ng/mL and urine300 ng/mL in U; AKI- stage 3: plasma 838 ng/mL and urine629 ng/mL in U.



Conclusions: NGAL is progressively increased in a graded fashion with ascending stages of AKI. These data suggest NGAL is a useful, objective tool, not only to identify patients with AKI but to also gauge the severity of their AKI.

TH-PO644

Impacts of Serial Plasma Neutrophil Gelatinase-Associated Lipocalin Measurement as Biomarker for Diagnosis and Prognosis in Acute Kidney Injury Patients of Emergency Room

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Background: Acute kidney injury (AKI) is a common and serious condition, the diagnosis of which currently depend on functional markers such as serum creatinine measurement. Neutrophil gelatinase-associated lipocalin (NGAL) appears to be a promising novel biomarker for the early diagnosis of AKI patients and a wide range in its predictive value has been reported. The aim of this study was to evaluate the predictive value of serum NGAL and serial measurement in patients with established AKI in emergency room.

Methods: Serum NGAL was measured in 701 patient at admission and 24hr later. Patients were divided four groups; group 1 includes patients with normal renal function, group 2 includes patients with AKIN stage 1, group 3 includes patients with AKIN stage 2, group 4 includes patients with AKIN stage 3. Serum NGAL was measured by ELISA at admission. We studied possible relationship between serum NGAL, estimated glomerular filtration rate (eGFR), and mortality in patient with AKI.

Results: Serum NGAL levels were significantly higher in AKI patient than in healthy control (452.19 ± 471.57 ng/mL vs. 183.12 ± 259.46 ng/mL, $p < 0.001$). The serum NGAL level showed a significant inversed correlation with GFR (r=0.164, p=0.018). The discriminatory ability of NGAL for AKI also increased with increasing AKIN stage. (AKIN1 56.0 (52.0-548.0), AKIN2 159.0 (77.5-425.5), AKIN3 503.5 (88.0-1300), $p < 0.001$).

Conclusions: From this results, we concluded that serum NGAL is a reliable marker of renal function in AKI patient. Serial NGAL measurement has impacts for diagnosis and prognosis, but monitoring protocols are needed for early detection and management of AKI patients.

TH-PO645

Urinary Angiogenin Reflects the Magnitude of Kidney Injury at the Infra-Histological Level

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Background: The ribonuclease angiogenin is secreted by renal epithelial cells upon activation of the IRE1a-sXBP1 axis, and is instrumental to the adaptation to acute kidney injury. It is unknown whether the amount of angiogenin in urines of individuals with a kidney injury reflects the magnitude of the lesions, and is predictive of the risk of organ failure.

Methods: To address this question, we explored individuals referred for a kidney injury and determined the biochemical characteristics of urinary angiogenin, as well as its diagnostic and prognostic values.

Results: In a cohort of 242 kidney transplant recipients with an acute allograft dysfunction, higher urinary angiogenin levels at the time of the biopsy were associated with a worse renal function and higher proteinuria, but did not correlate with histological lesions, as defined in the Banff classification. The risk of graft failure of kidney transplant recipients with urinary angiogenin amounts in the highest 50% was 3.59 times as high (95% confidence interval, 1.12-15.94) as that in the lowest 50%. We demonstrate that in the early post transplantation period, angiogenin is produced in large amounts in response to ischemia/reperfusion injury and acts as a paracrine mediator produced by renal epithelial cells under ER stress and primes non-stressed renal epithelial cells to activate the Integrated Stress Response pathway (PERK/eIF2a/ATF4), thereby promoting cell preconditioning. After 3 months, angiogenin is produced following the activation of sXBP1, as a consequence of smoldering immune infiltration (angiogenin levels are associated with interstitial inflammation scores, and sXBP1 is expressed by immune cells, including dendritic cells and B cells) and of non-immune insults associated with the activation of the IRE1a-sXBP1 axis.

Conclusions: The prognostic value of urinary angiogenin is related to the magnitude of renal injury, and angiogenin is not instrumental in the process of kidney allograft damage. Urinary angiogenin is a non-invasive indicator of the extent of tissue damage independent of the histological lesions, and a risk predictor of kidney allograft failure.

TH-PO646

The Role of Urine NGAL for Early Detection of Colistin-Induced AKI: A Randomized Controlled Trial Sadudee Peerapornratana, Nattachai Srisawat. *Div of Nephrology, Dept of Medicine, Chulalongkorn Univ, Bangkok, Thailand.*

Background: Colistin-induced acute kidney injury (AKI) are common cause of hospital acquired AKI. Neutrophil gelatinase-associated lipocalin (NGAL) is a promising biomarker for early detection of AKI which have been validated in various settings except in this specific setting. The aim of this study was to validate the role of serial urine NGAL measurement in improvement the detection of colistin-induced AKI.

Methods: We conducted a randomized controlled trial at King Chulalongkorn Memorial Hospital, Bangkok, Thailand during June 2015 and January 2016. Adult patients treated by colistin were randomized into two groups, using urinary NGAL or serum creatinine for AKI monitoring on day 1, 2, 3, 5, 7, 14 and 28. We also notified the primary physician when urinary NGAL >400 mcg/L in NGAL monitoring group or when achieving KDIGO stage I criteria in creatinine monitoring group. The primary outcomes was median time to AKI detection after colistin initiation.

Results: Thirty one patients were enrolled into the study. The mean age of patients were comparable in both group. Baseline glomerular filtration rate were 121.5±54.1 and 73.7±52.7 ml/min/1.73 m^2 in NGAL and creatinine monitoring group, respectively (P = 0.02). The overall incidence of colistin-induced AKI within 28 days was 70.9%. The median times to AKI detection were 1 and 5 days in NGAL monitoring and creatinine monitoring group, respectively (P = 0.001). There were no significant difference in renal replacement therapy and 28-day mortality.

Conclusions: Urinary NGAL monitoring could detect colistin-induced AKI more earlier than routine serum creatinine monitoring. The further study in larger population is still warrant.

Funding: Government Support - Non-U.S.

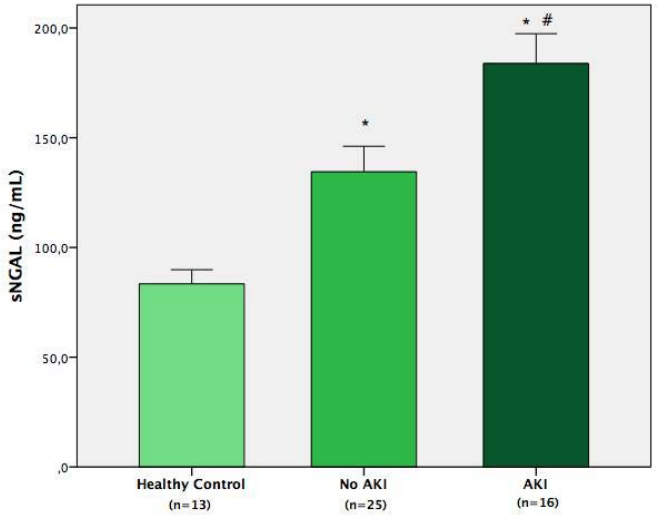
TH-PO647

Serum Neutrophil Gelatinase-Associated Lipocalin Levels Predict Acute Kidney Injury in Visceral Leishmaniasis Gdayllon C. Meneses,[1] Elizabeth F. Daher,[1] Geraldo B. Silva Junior,[2] Gabriela F. Bezerra,[1] Alexandre B. Liborio,[2] Alice M.C. Martins.[1] *[1]Federal Univ of Ceara; [2]Univ of Fortaleza, Brazil.*

Background: Acute Kidney Injury (AKI) can be found in a significant proportion of patients with Visceral Leishmaniasis (VL). The aim of this study is to investigate the role of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in the diagnosis of AKI in VL patients before specific treatment.

Methods: This is a prospective study with 41 patients with confirmed diagnosis of VL. This study was conducted in the Sao Jose hospital, a reference hospital of infectious disease in the state of Ceara, Brazil. At admission and before specific treatment for VL, blood and urine samples were collected. A control group was included with 13 healthy people. AKI was defined according to theKDIGO criteria. NGAL was measured in blood (sNGAL) and urine (uNGAL) through sandwich ELISA assay (R&D systems Inc). Urine biomarkers were expressed as ratios to urinary creatinine concentration (mg/g-Cr).

Results: Patients' average age was 45±19 years and 88% were male. In comparison with healthy controls, VL patients presented higher sNGAL and uNGAL levels than controls (sNGAL: 153±61 vs. 83±23ng/ml, p<0.001; uNGAL: 12±5.9 vs. 7.9±6.9ng/ml, p=0.03).



During hospital stay, 88% of VL patients received amphotericin B, and 16 (39%) developed AKI. sNGAL presented moderate to strong correlation with GFR, serum creatinine and urea in VL patients. Moreover, in logistic regression analysis, sNGAL was an independent risk factor for AKI. sNGAL was an important predictor of AKI in VL patients (AUC: 0.771; 95% CI 0.624-0.918, p=0.004).

Conclusions: VL patients presented high frequency of AKI during hospital stay. For the first time, serum NGAL levels on admission was evidenced to be a useful tool for assessing AKI risk among VL patients, even before specific treatment initiation.

TH-PO648

Copper-Zinc Superoxide Dismutase Is a Novel Prognostic Biomarker of Acute Kidney Injury following Cardiothoracic Surgery Joseph H. Holthoff,[1] Nithin Karakala,[1] Christian Herzog,[1] Joseph Alge,[2] John M. Arthur.[1] *[1]Internal Medicine - Div of Nephrology, Univ of Arkansas for Medical Sciences, Little Rock, AR; [2]Internal Medicine - Div of Nephrology, Medical Univ of South Carolina, Charleston, SC.*

Background: Acute kidney injury (AKI) remains a significant cause of morbidity and mortality, and approximately 20% of patients who undergo cardiothoracic surgery will develop AKI. The identification and prognosis of AKI, as well as the translation of preclinical therapeutic options has been impeded by the lack of a detectable biomarkers during AKI. Copper-Zinc superoxide dismutase (CuZn SOD) is an endogenous antioxidant protein which serves to neutralize superoxide radicals. Previous proteomics studies in our lab detected increased CuZn SOD in urine from patients who developed AKI after cardiothoracic surgery, as well as mice with ischemia-reperfusion injury and rat glycerol models of AKI. Thus, CuZn SOD offers a promising option as a novel biomarker for AKI.

Methods: Urine samples were obtained from 37 patients who developed stage 1 AKI within 48 hours of cardiothoracic surgery. Urine samples were diluted at 1:20 with phosphate-buffered saline (PBS), and urinary CuZn SOD was quantified by ELISA. Data were analyzed and a receiver operating characteristic curve (ROC) was constructed using Graphpad Prism 7.0.

Results: We found a significant increase in CuZn SOD concentration in the urine of patients that developed Stage 3 AKI, required renal replacement therapy (RRT), or died within 30 days when compared to patients who had a maximum increase in serum creatinine corresponding to stage 1-2 AKI. Urine CuZn SOD concentration was able to predict the combined outcome of stage 3 AKI, RRT, and mortality with an area under the ROC curve of 0.75 (95% C.I. = 0.59-0.91, p = 0.017).

Conclusions: This study demonstrates the potential for CuZn SOD to serve as a novel prognostic biomarker for AKI.

Funding: NIDDK Support

TH-PO649

Plasma Uric Acid and Development of Acute Kidney Injury in the Critically Ill Anand Srivastava, David E. Leaf, Venkata Sabbisetti, Sushrut S. Waikar. *Renal Div, Brigham & Women's Hospital, Boston, MA.*

Background: Elevations in plasma uric acid (PUA) may lead to acute kidney injury (AKI) through multiple mechanisms: tubular injury, mitochondrial dysfunction, endothelial dysfunction, oxidative stress, and intra-renal inflammation. The association between PUA levels and incident AKI in critically ill patients has not been rigorously evaluated.

Methods: We measured PUA levels in blood samples obtained within the first 24 hours of ICU admission in 117 critically ill patients without AKI. We fit multivariable logistic regression models to test the association between PUA levels and the primary end point of incident AKI, defined by the KDIGO criteria. Secondary end points were severe AKI (KDIGO stage 2 or 3) and the composite end point of renal replacement therapy (RRT) or in-hospital mortality.

Results: Mean age was 62.2 ± 14.4 years, 90.6% were white, 62.4% were female, and mean estimated glomerular filtration rate (eGFR) was 87.7 ± 21.4 ml/min/m^2. Mean ± SD PUA levels were 4.6 ± 2.0 mg/dl and were inversely correlated with eGFR (r = -0.30, p=0.0009). Patients who developed AKI had higher PUA levels and lower eGFR at enrollment than those who did not develop AKI (Table):

	Incident AKI	No Incident AKI	p-value
PUA, mg/dl	5.6±2.3	4.2±1.7	0.0008
Age, years	62.7±12.2	62.0±15.3	0.83
Female	40.6%	36.5%	0.68
Caucasian	87.5%	91.8%	0.48
eGFR, ml/min/m^2	75.1±23.5	92.4±18.7	<0.0001
APACHE II	14 [11-17]	14 [10-17]	0.61
*Data presented are Mean ± SD or Median [Interquartile range]			

After adjusting for age, sex, race, eGFR, and APACHE II score, PUA levels remained significantly associated with incident AKI (odds ratio 1.29, 95% confidence interval 1.02 to 1.64) and severe AKI (odds ratio 1.39, 95% confidence interval 1.01 to 1.90), but not the composite end point of RRT/mortality.

Conclusions: Higher PUA levels are associated with an increased risk for the development AKI in critically ill patients admitted to the ICU, independent of confounding factors including enrollment eGFR and severity of disease. These results are consistent with a pathogenic role for uric acid in the development of AKI.

Funding: NIDDK Support

TH-PO650

Platelet Aggregability as a Predictor of Acute Kidney Injury and Cardiovascular Events in Vascular Surgeries Mauricio Teixeira,[1] Daniela Calderaro,[2] Etienne Macedo.[1,3] *[1]USP; [2]INCOR; [3]UCSD.*

Background: Platelet aggregation is one theory that can explain the AKI process after the reperfusion is obtained in the ischemic model. In the population with arterial illness, this process may play a role in acute ischemic events like AKI and Cardiovascular Events (CvEv). Evaluation of platelet aggregability is used to study perioperative cardiovascular risk. The purpose of this study is to evaluate if the platelet aggregation could be a marker to predict AKI and CvEv in patients submitted to vascular surgeries.

Methods: Analysis of a prospective cohort of patients submitted to a major vascular surgery from whom the platelet aggregation test was performed. The extent of aggregation assesses the amount of platelet aggregates after the exposure to some agonists. The arachidoniac acid (AA) is the most important agonist in the present study because every patient was under chronic use of aspirin. This medicine inhibits platelet aggregation by blocking cyclooxygenase. This is a validated tool for the measure of aspirin response. Severity of AKI was stratified by the KDIGO classification using the first creatinine before the surgery.

Results: A total of 185 patients were analyzed. The main vasculopathy was in the aorta, 36,2%. We had 70 (37,8%) patients with AKI and 42 (22,7%) CvEv. There was a significant association between higher platelet response to AA and AKI. The mean of resistance in the no AKI group was 5,06Ω (n=115) and in the AKI group was 6,92Ω, p = 0,037. We could demonstrate that the response to AA increases with the severity of AKI: 5,88Ω in the KDIGO 1 group (n = 45), 10,5Ω KDIGO 2 group (n = 9) and 7,8Ω in the KDIGO 3 group (n = 16), p = 0,022. There was also association between platelet aggregation and CvEv: 5,3 Ω no CvEv and 7,4 Ω in the CvEv group, p = 0,04. We also had an association between AKI and CvEv: 57% of the CvEv were in the AKI group, p=0,003.

Conclusions: Platelet aggregation may play a critical role in the pathophysiology of AKI and of CvEv. This can be one of the common pathways that predisposes some patients to develop ischemic events. In our cohort we showed that there was an association between platelet aggregation and AKI and also an association between AKI and CvEv.

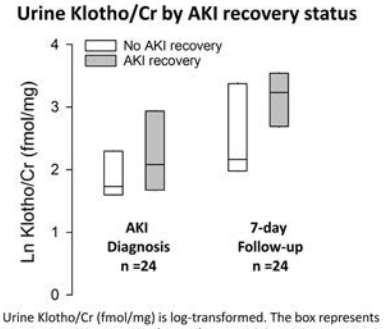
TH-PO651

Urine Klotho Is a Potential Marker of AKI Recovery in the Intensive Care Unit Javier A. Neyra, Xilong Li, Federica Mescia, Victor E. Prado, Johanne Virginia Pastor, Beverley Adams-Huet, Ming Chang Hu, Robert D. Toto, Orson W. Moe. *UT Southwestern, Dallas, TX.*

Background: AKI carries increased risk for subsequent CKD. Klotho deficiency has been observed in AKI and low Klotho post-AKI is associated with progression to CKD in rodents. We aim to characterize post-AKI urine Klotho trajectories in ICU patients with and without 7-day AKI recovery.

Methods: We conducted a prospective study of 54 AKI patients and 52 controls without AKI in the ICU setting. We excluded patients with baseline eGFR<60 or kidney transplant. Urine samples were obtained within 24h of AKI diagnosis (KDIGO stage ≥2) and within 48h of ICU admission in frequency-matched controls (by baseline eGFR and age). Renal recovery was defined as the ratio of follow-up serum creatinine (SCr)/baseline SCr ≤1.5. Urine Klotho was measured by immunoprecipitation-immunoblot. Nonparametric tests were used for comparisons.

Results: Mean (SD) age was 57 (16) years, 57% were men and 70% white. Patients with AKI had higher critical illness scores than controls without AKI. Most AKI cases (76%) were attributed to ATN and/or sepsis. A total of 24 (44%) patients died and 18 (33%) required RRT in the AKI group. Urine Klotho adjusted by urine creatinine (uKlotho/Cr) was significantly lower in AKI cases than in controls, median 7 [IQR 5–10] vs 28 [11–59] fmol/mg, $p<0.001$. Furthermore, uKlotho/Cr significantly increased with time in patients that exhibited AKI recovery (n=8, Δ+266%, $p=0.02$) but not in those that did not (n=16,Δ+31%, $p=0.10$), between-group $p=0.03$, median follow-up 6 (3-7) days.



Urine Klotho/Cr (fmol/mg) is log-transformed. The box represents the interquartile range (25th to 75th percentile) and the horizontal line represents the median.

Conclusions: Urine klotho is significantly lower in patients with AKI when compared to ICU controls without AKI. Urine Klotho significantly recovered only in patients that exhibited 7-day AKI recovery. Urine Klotho may be a prognostic marker of AKI recovery in the ICU.

Funding: Other NIH Support - P30 DK079328-06; UL1 TR001105

TH-PO652

Proteomic Approaches to Identify Differentially Expressed Proteins in Cardiac Surgery Associated Acute Kidney Injury Ravi C. Dwivedi,[1] Mario Navarrete,[1] Nora Choi,[1,3,4] Vic Spicer,[1] Peyman Ezzati,[1] Claudio Rigatto,[2] Rakesh C. Arora,[4] Oleg Krokhin,[1] Julie Ho,[1,2,3] John A. Wilkins.[1,3] *[1]Manitoba Centre for Proteomics & Systems Biology, Health Sciences Centre, Univ of Manitoba; [2]Dept of Internal Medicine, Section of Nephrology, Univ of Manitoba; [3]Dept of Immunology, Univ of Manitoba; [4]Cardiac Sciences Program, St. Boniface Hospital, Winnipeg.*

Background: Acute kidney injury (AKI) after cardiopulmonary bypass (CPB) is an important cause of morbidity and mortality. Mass-spectrometry (MS)-based proteomics may allow us to improve our understanding of ischemia-reperfusion injury (IRI) and identify 'at-risk' individuals. The goal was to perform an in-depth proteomic analysis of patients undergoing CPB.

Methods: A nested case-control cohort (5 AKI & 5 non-AKI patients) from a prospective cohort of 306 adult CPB patients was evaluated at: baseline, start CPB, 1hr CPB, arrival to ICU, POD day 1 and 3-5. Pooled urines were processed using modified Filter Assisted Sample Preparation, separated and analyzed by 2D-LC-MS/MS for protein identification and to generate an ion library. A label-free approach was applied for protein quantitation. Protein identification accuracy was increased by analyzing the same samples with SWATH-MS (Sequential Window Acquisition of All Theoretical Fragment ion spectra Mass-Spectrometry). Protein relative abundance was compared in AKI vs non-AKI using both 2D-LC-MS/MS and SWATH.

Results: Using a high-content MS approach we confidently identified 2,061 proteins (≥2 peptides, log(e)≤-3) across all time-points. For more complete comparison we used SWATH-MS to provide quantitative data on 826 proteins, which demonstrated some overlap with the 2D-LC-MS/MS data. Differential analysis detected 10 decreased and 11 increased proteins in AKI vs non-AKI patients, based on normalized Z-scores >1 across all time-points. Urinary MMP9 was validated as decreased in AKI versus non-AKI pooled urines using ELISA.

Conclusions: This study provides high quality protein quantitation in AKI vs non-AKI patients throughout IRI. The differential proteomic changes identified may provide insight into the pathophysiology of IRI and potential novel biomarker identification.

Funding: Government Support - Non-U.S.

TH-PO653

Low Regulatory T Cell Abundance before Cardiac Surgery Is Associated with Increased Risk of AKI: A Pilot Study Gilbert R. Kinsey,[1] Jennie Z. Ma,[2] John Kern,[3] Mark D. Okusa,[1] Charles H. Brooks,[1] Sandra Burks,[3] Ashley Craddock,[3] Adrienne Lynne Stimson,[3] Victoria L. Yu,[1] Brian K. Stevens.[1] *[1]Div of Nephrology and Center for Immunity, Inflammation and Regenerative Medicine, Univ of Virginia; [2]Public Health Sciences, Univ of Virginia; [3]Surgery, Univ of Virginia.*

Background: Patients who undergo cardiac surgery (CS) are at high risk of developing post-surgical acute kidney injury (AKI). The pathogenesis of AKI involves inflammation, nephrotoxins and ischemia-reperfusion injury (IRI). Preclinical studies have demonstrated regulatory T cells (Tregs) protect the kidney from inflammation and dysfunction induced by IRI and nephrotoxins. We hypothesized that patients with low circulating Treg numbers at the time of surgery would be at increased risk of developing AKI in the post-surgical period.

Methods: Circulating Treg number was determined by flow cytometry of blood from 45 adult CS patients on the morning of surgery, prior to initiating cardiopulmonary bypass, and again 24h after surgery. Occurrence of AKI was determined using KDIGO Stage II creatinine and urine output criteria over the first 48h after CS.

Results: The number of circulating Tregs ($CD4^{+}CD127^{low/-}CD25^{high}$) per ml of blood, prior to CS, was variable with a range of 7,100 to 84,000. Patients were split into low, medium and high tertiles based on Treg number and the rate of AKI compared between groups. Stage II AKI occurred in 60, 13, and 20% of patients in these groups, respectively. After adjusting for the effect of pre-existing CKD and advanced age in logistic regression, the odds ratio for developing AKI in the low Tregs group vs. high group was 7.0 (95% CI: 1.2-41.5), and there was no significant difference between middle and high groups. In 36/45 patients the circulating number of Tregs was decreased by an average of 30% after CS (P<0.01).

Conclusions: These results demonstrate that patients in this pilot study with low circulating Tregs, prior to CS, developed AKI at a higher rate than patients with middle or high levels of Tregs. Along with preclinical studies, this suggests strategies to boost Tregs prior to CS, in patients with low circulating Tregs, may reduce the risk of post-surgical AKI in these patients.

Funding: NIDDK Support

TH-PO654

Urinary Excretion of Active Serine Hydrolases in Cardiac-Surgery Associated Acute Kidney Injury Mario Navarrete,[1] Julie Ho,[1,2,3] Ravi C. Dwivedi,[1] Nora Choi,[1,3] Peyman Ezzati,[1] Oleg Krokhin,[1] Vic Spicer,[1] Rakesh C. Arora,[4] Claudio Rigatto,[2] John A. Wilkins.[1] *[1]Manitoba Centre for Proteomics & Systems Biology, Health Science Centre, Univ of Manitoba, Winnipeg, MB, Canada; [2]Internal Medicine, Section of Nephrology, Univ of Manitoba, Winnipeg, MB, Canada; [3]Immunology, Univ of Manitoba, Winnipeg, MB, Canada; [4]Cardiac Science Program, St. Boniface Hospital, Winnipeg, MB, Canada.*

Background: Changes in enzyme activity are physiologically relevant and may be independent of enzyme quantity. Activity-based protein profiling (ABPP) is a proteomic approach to assess the functional status of enzymes. ABPP may offer insight into ischemia-reperfusion injury (IRI) and identify novel acute kidney injury (AKI) markers following cardiopulmonary bypass (CPB). The goal was to characterize urine serine hydrolase activity and composition throughout IRI.

Methods: A nested case-control cohort (8 AKI & 8 non-AKI patients) from a prospective cohort of 306 adult cardiac surgery patients was evaluated at: baseline, start CPB, 1hr CPB, arrival to ICU, POD 1 and 3-5. ABPP was visualized by SDS-PAGE and protein by Coomassie. Serine hydrolase composition was determined by MS/MS. Active serine hydrolases were affinity purified and identified on MS/MS.

Results: Serine hydrolase activity remained stable throughout IRI in non-AKI. AKI urines demonstrated early differential intraoperative serine hydrolase activity that was independent of protein quantity.

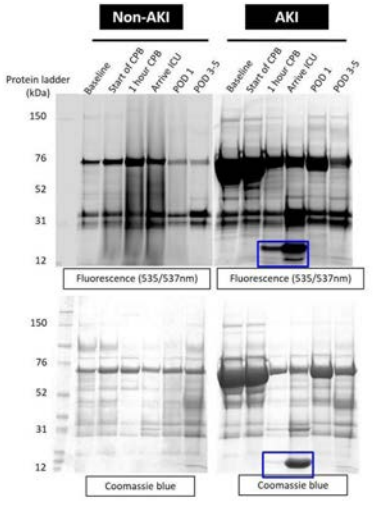


Figure 1. Serine hydrolase ABPP demonstrates early enzyme activity, independent of protein concentration, that differs between AKI versus non-AKI patients

AKI urines had 53 serine hydrolases on compositional analysis, whereas 31 were identified in their active state. Quantitative assays confirm differential enzyme activity between AKI and non-AKI.

Conclusions: We demonstrated novel serine hydrolase activity and confirmed differential enzyme activity in AKI vs. non-AKI patients. These findings have implications in understanding the serine hydrolase response to IRI and may be a potential early intraoperative marker of AKI.

Funding: Government Support - Non-U.S.

TH-PO655

Latent Class Analysis Identifies AKI Sub-Phenotypes with Differing Biomarker Profiles of Endothelial Dysfunction and Relation to Risk of Death and Need for Renal Replacement Therapy Pavan K. Bhatraju,[1] Cassianne Robinson-Cohen,[2] Jonathan Himmelfarb,[2] Mark M. Wurfel.[1] *[1]Pulmonary and Critical Care, Univ of Washington, Seattle, WA; [2]Kidney Research Inst, Univ of Washington, Seattle, WA.*

Background: The heterogeneity of acute kidney injury (AKI) may limit identification of patients at highest risk of poor outcomes. Latent class analysis (LCA) is a statistical modeling technique to identify unobserved sub-groups using observed clinical and biologic patient characteristics. We hypothesized that LCA would identify AKI sub-phenotypes with differing biomarker profiles and associations with outcomes.

Methods: We applied LCA to 806 ICU subjects with AKI (change in serum creatinine of 0.3 mg/dl, <72 hours of ICU admit) from a cohort of patients with systemic inflammatory response syndrome. Subjects were equally split into discovery and validation sets. In the discovery group the LCA included 25 biological and clinical variables measured on day 1 of study enrollment. We then tested the association of sub-phenotypes with 28 day mortality, incident RRT and identified sub-phenotype predictors using Akaike information criterion (AIC). Predictors were then tested in the validation set for associations with outcomes.

Results: A two-class model was the best fit in the derivation set ($p < .001$). Sub-phenotype 2 was characterized by higher biomarker levels of inflammation and endothelial dysfunction, higher use of vasopressors and higher levels of serum creatinine compared to sub-phenotype 1. There were higher rates of hospital mortality (25% vs 8% $p < .001$) and use of RRT (19% vs 4% $p < .001$) in sub-phenotype 2. Angiopoietin 2 (ang-2) had the lowest AIC. In the validation cohort ang-2 identified similar sub-phenotypes with sub-phenotype 2 having higher mortality (29% vs 8%) and RRT (18% vs 5%) compared to sub-phenotype 1, $p < .001$.

Conclusions: LCA identified two sub-phenotypes among critically ill patients with AKI, one of which is characterized by endothelial dysfunction and worse clinical outcomes. This AKI sub-phenotype may identify a more biologically homogeneous group at high-risk for poor outcomes.

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TH-PO656

Soluble FAS and Soluble Tumor Necrosis Factor I, Biomarkers of Apoptosis and Inflammation, Are Differentially Associated with a Non-Resolving AKI Sub-Phentoype Pavan K. Bhatraju,[1] Cassianne Robinson-Cohen,[2] Jonathan Himmelfarb,[2] Mark M. Wurfel.[1] *[1]Pulmonary and Critical Care, Univ of Washington, Seattle, WA; [2]Kidney Research Inst, Univ of Washington, Seattle, WA.*

Background: Acute kidney injury (AKI) is a heterogeneous syndrome involving the interplay of apoptosis, inflammation and endothelial dysfunction. This heterogeneity limits the ability of biomarker analysis to identify potentially targetable pathways in disease development. We hypothesize that the trajectory of serum creatinine (resolving and non-resolving) in the first 72 hours of ICU admission will identify AKI sub-phenotypes with different levels of plasma biomarkers.

Methods: Among 1255 subjects with systemic inflammatory response syndrome and admitted to the ICU at Harborview Medical Center, we evaluated a panel of biomarkers of apoptosis, inflammation and endothelial dysfunction, from plasma obtained within 24 hours of admission: soluble tumor necrosis factor receptor 1 (sTNFR-I), soluble FAS (sFAS), interleukin 6, 8, 17, angiopoietin 1, angiopoietin 2 and soluble vascular cell adhesion molecule 1 (sVCAM-1). We examined associations of biomarkers with subsequent AKI sub-phenotypes using relative risk regression.

Results: During the first 72 hours of ICU admission, 816 (65%)subjects developed AKI. Of these 480 (59%) had a resolving sub-phenotype and 336 (41%) had a non-resolving sub-phenotype. The hospital mortality rate of subjects with no AKI was 4%, resolving sub-phenotype was 10% and a non-resolving sub-phenotype was 23%. Plasma sFAS, sTNFR-1 and sVCAM-1 concentrations were independently associated with a non-resolving sub-phenotype compared to resolving after adjustment for age, body mass index, diabetes and apache III scores ($p < .001$). Notably, after adjustment for endothelial dysfunction (sVCAM-1), a doubling of sFAS and sTNFR-1 remained strongly associated with a non-resolving sub-phenotype (RR 1.25 (95% CI 1.11, 1.42, $p<.001$)) and (RR 1.20 (95% CI 1.09, 1.33, $p<.001$)), respectively.

Conclusions: This work suggests research identifying modifiable targets in the sFAS and sTNFR-1 pathways may allow the prevention and treatment of a severe sub-phenotype of AKI.

Funding: Other NIH Support - R01-HL-089807 from the National Institutes of Health and the Heart Lung and Blood Institute

TH-PO657

Serum Cystatin C Predicts Renal Recovery Earlier Than Serum Creatinine among Hospitalized Patients with Acute Kidney Injury Kamel A. Gharaibeh, Abdurrahman M. Hamadah, John C. Lieske, Ziad El-Zoghby, Nelson Leung. *Nephrology, Mayo Clinic, Rochester, MN.*

Background: Limited evidence suggests serum cystatin C (cysC) peaks earlier than serum creatinine (sCr) during the course of acute kidney injury (AKI). Earlier identification of AKI recovery could support less intensive resource utilization and earlier hospital discharge. We conducted an observational pilot study to determine the relative time course of sCr and cysC change in hospitalized patients with AKI in a tertiary medical center.

Methods: Hospitalized patients with AKI at our institution between May 2015 and May 2016 who had serial sCr and cysC levels measured during their hospitalizations were identified. AKI was defined based on the Acute Kidney Injury Network criteria. Demographic data, baseline creatinine, cause of AKI, and other significant comorbidities were collected by medical record review.

Results: Overall, 63 patients were identified. Mean age was 58.7 ± 13.9 years, 62% were men, 95% were white, and median BMI was 27.8 kg/m^2. Baseline median sCr was 1.05 (IQR 0.8-1.3), 13% had a kidney transplant and 37% had received corticosteroids. Co-morbidities included malignancy (38%), diabetes (33%), thyroid disorder (16%) and heart failure (19%). The majority of cases were AKI stage III (61%) with 22 patients (35%) requiring dialysis. The cause of AKI was ATN in 71% of patients. CysC peaked before sCr in 68% of patients (6% 3 days, 16% 2 days, 46% 1 day sooner), on the same day in 24%, and in 5 patients (8%) cysC peaked after SCr. Overall cysC peaked a mean of 0.92 days prior to sCr (95% CI 0.65-1.18; $p<0.001$). Exploratory analyses did not reveal effects of patient co-morbidities on the timing of peak cysC compared to sCr. Lower baseline eGFR predicted earlier recovery by cysC ($P=0.035$). Overall cysC performed equally well or better than sCr in 92% of patients in this study for monitoring recovery from AKI.

Conclusions: This study suggests cysC peaks earlier than sCr in the majority of hospitalized AKI patients. These findings have significant clinical implications for managing AKI with the potential for shortening hospital stay and reducing costs. A large prospective study is warranted to confirm these findings.

TH-PO658

Temporal Profiling Refines the Prognostic Value of Acute Kidney Injury Urinary Biomarkers Margaret Rachel Ninemire,[1] Shina Menon,[2] Erin K. Stenson,[3] Stuart Goldstein,[4] Rajit K. Basu.[3,4] *[1]Pediatrics, Cincinnati Children's Hospital; [2]Pediatric Nephrology, Seattle Children's Hospital; [3]Pediatric Critical Care, Cincinnati Children's Hospital; [4]Center for Acute Care Nephrology, Cincinnati Children's Hospital.*

Background: Acute kidney injury (AKI) is common in critically ill children with sepsis, and persistent AKI (pAKI) is associated with poor clinical outcomes. Novel urinary biomarkers used for AKI prediction have been studied in many populations. However, these studies generally only compare individual biomarkers measured at a single time point. Analysis of biomarker measurement trends over time to predict pAKI is not well described.

Methods: We conducted a single center, prospective study of children admitted to the intensive care unit (ICU) with multiple urinary biomarker levels (neutrophil gelatinase associated lipocalin (uNGAL) and kidney injury molecule-1 (uKIM-1)) in the first 36 hours to test the hypothesis that predictive performance of pAKI by changes in biomarkers was superior versus changes in serum creatinine (SCr). Stage 2-3 KDIGO SCr criteria 72 hours after admission defined pAKI.

Results: 173 pts (51% male, median age 6.7 yrs), including 42 with sepsis (24%) and 31 with pAKI (18%) were studied. Combination of a persistent elevation in uNGAL (>150 on days 1 and 2) and an increasing uKIM-1 (rising value from day 1 to 2) increased the likelihood of pAKI nearly 2-fold compared to doubling of SCr from baseline. When stratified by sepsis, the positive likelihood of pAKI predicted by the biomarker changes in combination remained statistically significant versus the changes in SCr.

Patients	↑ uNGAL	↑ uKIM-1	↑uNGAL ↑uKIM-1	↑2-3x SCr
All	2.6 (1.6-4.2)	1.4 (1.1-1.9)	4.6 (2.3-9.2)	2.8 (1.1-7.4)
No Sepsis	2.5 (1.3-4.9)	1.4 (0.9-2.0)	4.2 (1.6-10.7)	1.7 (0.2-15.8)
Sepsis	2.3 (1.3-4.0)	1.6 (1.0-2.7)	3.3 (1.4-7.7)	2.2 (0.8-5.6)

↑ = Multiple, Sequential Elevation

Conclusions: Together, how urinary biomarkers change over time may provide added insight for AKI prediction compared to single measurements and refine AKI stratification compared to current clinical standards. Further studies are needed to validate these findings.

TH-PO659

Biomarkers at Discontinuation of Renal Replacement Therapy Predict 90-Day Clinical Outcomes in Critically Ill Patients with Acute Kidney Injury Tingting Yang, Baihai Su. *Dept of Nephrology, West China Hospital, Sichuan Univ, Chengdu, Sichuan, China.*

Background: There is no consensus on the specific indications of weaning renal replacement therapy (RRT) in acute kidney injury (AKI).This study aimed to explore the prognostic value of several biomarkers at discontinuation of RRT for 90-day outcomes and find potential indicators for discontinuation of RRT.

Methods: We prospectively enrolled 102 patients with AKI who require RRT from intensive care unit (ICU). Serum osteopontin (sOPN), serum interleukin-6 (sIL-6), serum Cystatin C (sCysC), sIL-18, serum neutrophil gelatinase-associated lipocalin (sNGAL) and urinary NGAL (uNGAL) and uIL-18 were measured at discontinuation of RRT. Patients were followed-up till 90 days for survival and renal recovery. Multivariate logistic regression and ROC analysis were performed to assess the predictive value of each biomarker for prognosis.

Results: Patients who survived had lower levels of all serum and urinary biomarkers. Serum OPN was an independent predictor of 90d mortality (OR, 1.029; 95% CI, 1.013-1.047; p=0.001).Lower sOPN and sIL-6 were associated with greater odds of 90d survival (area under the ROC curve (AUC), 0.812 and 0.741). Lower sCysC was associated with greater odds of 90d renal recovery (AUC, 0.743). The AUC reached best when combining biomarkers with conventional indicators at discontinuation of RRT (0.881 for predicting survival and 0.923 for predicting renal recovery).

Conclusions: Serum and urinary biomarkers at discontinuation of RRT can be predictive for 90d survival and renal recovery in critically ill AKI patients. Serum OPN, IL6 and CysC are promising indicators for discontinuation of RRT.

Funding: Government Support - Non-U.S.

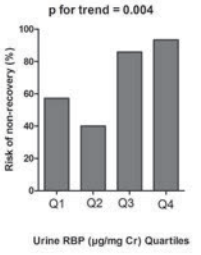
TH-PO660

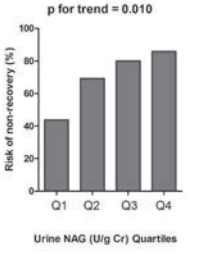
Urinary Retinol-Binding Protein as a Risk Factor of Poor Prognosis in Acute-on-Chronic Renal injury Yanhong Yuan, Shan Mou. *Dept of Nephrology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong Univ, Shanghai, China.*

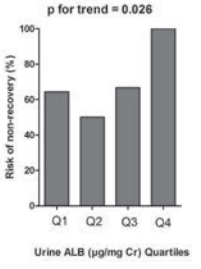
Background: Acute-on-chronic renal injury was commonly seen in clinical practice. This study tested whether urinary biomarkers could be used as a noninvasive prognostic marker in acute-on-chronic renal injury patients.

Methods: 108 adult patients with pre-existing chronic kidney disease presenting with acute-on-chronic renal injury were included. Urinary retinol-binding protein , N-Acetyl-b-D-Glucosaminidase and albumin was quantified.

Results: Reversibility of renal function was achieved in 43 patients of the included patients.The levels of urinary retinol-binding protein, N-Acetyl-b-D-Glucosaminidase and albumin for non-recovery acute-on-chronic renal injury patients were much higher than recovery patients. Quartiles of retinol-binding protein, urinary N-Acetyl-b-D-Glucosaminidase and albumin had a graded relationship with the risk for un-recovery AKI.







And the urinary retinol-binding protein was an independent risk factor for outcome of acute-on-chronic renal injury patients by multivariate logistic regression analysis

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)	1.026	1.001-1.051	0.038			0.172
baseline Scr (µmol/L)	1.007	1.001-1.013	0.016			0.068
Scr at AKI (µmol/L)	1.006	1.002-1.010	0.007			0.062
uRBP (µg/mg Cr)	1.175	1.046-1.320	0.007	1.162	1.036-1.303	0.010
uNAG (U/g Cr)	1.0112	0.999-1.026	0.06			0.377
uALB (µg/mg Cr)	1.000	1.000-1.001	0.046			0.29

Conclusions: In patients with acute-on-chronic renal injury, quantification of urinary retinol-binding protein may be developed as a non-invasive tool for predicting outcome of acute-on-chronic renal injury patients.

TH-PO661

Five-Year Kidney Injury Biomarkers after Pediatric Acute Kidney Injury Jason Henry Greenberg,[1] Prasad Devarajan,[2] Heather Thiessen Philbrook,[1] Catherine Krawczeski,[3] Simon Li,[4] Amit X. Garg,[5] Steven G. Coca,[6] Chirag R. Parikh,[1] Michael Zappitelli.[7] *[1]Program of Applied Translational Research, Yale Univ, CT; [2]Pediatrics, Cincinnati Childrens, OH; [3]Pediatrics, Stanford Univ, CA; [4]Pediatrics, Maria Fareri Childrens, NY; [5]Medicine, Western Univ, London; [6]Medicine, Mount Sinai, NY; [7]Pediatrics, McGill Univ, Montreal.*

Background: We recently determined that pediatric AKI after cardiac surgery (CS) is not associated with an increased risk of CKD at 5 years of follow-up. We evaluated if at 5 years after CS, there was evidence of subclinical kidney injury, measured by renal injury biomarkers, in patients with *vs.* without AKI.

Methods: The Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) long-term study is a 3 center prospective cohort study of children 1 month to

18 years old who underwent cardiopulmonary bypass for CS and survived hospitalization. At 5 years post-CS, we measured urine interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), monocyte chemoattractant protein-1 (MCP-1), and YKL-40 to evaluate for subclinical chronic renal injury. Biomarker levels were compared between patients with AKI (≥50% or ≥0.3 mg/dL serum creatinine rise) *vs.* without.

Results: 305 study subjects survived hospitalization: 4 (1.3%) died after discharge; 110 (42%) participated in the 5 year follow-up (median 5.4 years follow-up). Mean age at follow-up was 8.7 years; 52% were male. 49/110 (45%) had AKI. At 5 years, there was no significant difference in any of the biomarker concentrations between AKI groups (see Table).

Conclusions: Post-operative pediatric AKI is not associated with elevation of kidney injury biomarkers 5 years after CS. This may either represent a lack of chronic renal injury after pediatric AKI, that longer follow-up is needed to determine long-term AKI renal damage, or that our studied biomarkers are inadequate for evaluating subclinical chronic renal injury.

Table. Five-year biomarker results by AKI status

	AKI N=49	No AKI N=61	P value
Urine IL-18 (pg/mL)	16.57 [9.53, 24.25]	13.94 [7.92, 21.79]	0.26
Urine KIM-1 (pg/mL)	366.07 [157.56, 656.82]	336.34 [175.81, 525.38]	0.40
Urine MCP-1 (pg/mL)	103.44 [45.27,169.38]	116.4 [47.43,167.25]	0.83
Urine YKL-40 (pg/mL)	344.54 [184.23, 645.88]	330.11 [149.55, 614.82]	0.58
Values are expressed as median [interquartile range].			

Funding: NIDDK Support

TH-PO662

Proteinuria Is an Independent Predictor for Acute Kidney Injury following Coronary Artery Bypass Grafting Kevin D. Hageman,[1] Alice M. Lee,[1] Joseph A. Forgione,[1] Injoon Lee,[1] Roja Chimakurthi,[2] Rodrigo Aguilar Campos,[1] Wen Shen,[2] Jaeil Ahn.[3] *[1]Dept of Medicine, Georgetown Univ Hospital, Washington, DC; [2]Dept of Nephrology and Hypertension, Georgetown Univ Hospital, Washington, DC; [3]Dept of Biostatistics, Georgetown Univ, Washington, DC.*

Background: Acute kidney injury (AKI), a common postoperative complication of CABG, is associated with increased morbidity and mortality. Proteinuria is a promising biomarker of early AKI. Understanding if preoperative proteinuria predicts AKI post-CABG may help us optimize treatment and minimize the risk of AKI.

Methods: A retrospective cohort study was conducted on patients undergoing first-time CABG between 2004-2014 with a preoperative urine study. Patients with age <18, eGFR of <30, history of RRT and combined cardiac surgery were excluded. A total of 557 patients were included. AKI diagnosis was based on SCr 48 hours after CABG, and was defined by AKIN criteria. Logistic regression was used to analyze the associations between proteinuria and AKI, AKI requiring RRT, and in-hospital mortality. The association models were further adjusted for confounding variables (age, race, gender, HTN, DM, CVA/TIA, CHF, anemia, CVA/TIA, PVD, smoking) known to correlate with AKI.

Results: The incidence of AKI in patients with preoperative proteinuria is higher than that without proteinuria [39.9% vs 18.9%, OR 2.85, 95% CI (1.95- 4.20), p < 0.001). Compared with no proteinuria, mild proteinuria increased the risk of AKI 2.13 times [95% CI (1.95, 4.20)], moderate proteinuria 3.58 times [95% CI (1.70, 7.49)] and severe proteinuria was associated with a 5.97 fold higher risk of AKI [95% CI (3.09, 11.75)]. After adjusting for covariates, proteinuria was still strongly associated with higher AKI incidence (OR 2.44, 95% CI (1.58- 3.79)). The incidence of AKI requiring RRT was higher in patients with proteinuria compared to patients without proteinuria, however, the difference is not statistically significant due to rare cases of AKI requiring RRT (2.8% vs 2.5%).

Conclusions: Preoperative proteinuria was strongly associated with post-CABG AKI before and after adjustment of covariates. The incidence of AKI increased along with the severity of proteinuria.

Funding: Private Foundation Support

TH-PO663

Prognosis Prediction by Biomarkers on Dialysis-Requiring Severe Acute Kidney Injury Tetsushi Yamashita, Eisei Noiri, Kengo Mayumi, Ryo Matsuura, Masaomi Nangaku, Kent Doi. *The Univ of Tokyo, Tokyo, Japan.*

Background: Many biomarkers have been developed mainly for early detection of AKI. Another challenge is prediction of mortality and renal recovery. It is clinically important to predict these outcomes of severe AKI patients requiring renal replacement therapy. This study was conducted to evaluate the performance of biomarkers measured at CRRT initiation for severe AKI.

Methods: This study enrolled 98 AKI patients who needed CRRT in the adult mixed ICU of The University of Tokyo Hospital from October 2013 to March 2015 by consecutive sampling. Blood biomarkers of NGAL, NT-proBNP, Cystatin C, and HMGB-1 and urine biomarkers of L-FABP, NAG, α1- microglobulin and TIMP-2 were measured at CRRT initiation. We evaluated whether these biomarkers could predict mortality and renal recovery by receiver operating characteristic (ROC) analysis. We also evaluated whether the addition of biomarkers to a clinical model, which consisted of age and SOFA score, is helpful to predict mortality and renal recovery using category-free net reclassification improvement (cfNRI) and integrated discrimination improvement (IDI).

Results: In-hospital mortality was 46% in this cohort and only urine L-FABP was significantly higher in the non-survivors than the survivors. ROC analysis showed the AUC-ROC of 0.64 [0.52-0.75]. The cfNRI demonstrated addition of L-FABP to the clinical model improved mortality prediction. Thirty-nine patients (40%) showed renal recovery, which was defined as being alive and independent from dialysis on discharge with a less than 50% decrease in eGFR. Only plasma NGAL was significantly lower in these patients than the others. The AUC-ROC of plasma NGAL for renal recovery prediction was 0.71 [0.60 - 0.81]. The cfNRI and IDI demonstrated addition of NGAL to the clinical model showed significant improvement of renal recovery prediction.

Conclusions: Urine L-FABP and plasma NGAL measured at CRRT initiation could predict mortality and renal recovery, respectively. Even in the most severe AKI, which requires RRT, L-FABP and NGAL have potential to predict hard outcomes.

Funding: Government Support - Non-U.S.

TH-PO664

Urinary Hepcidin-25 Is Elevated after Cardiac Surgery in Non-AKI versus AKI Patients Nora Choi,[1,2] Claudio Rigatto,[3] Brett M. Hiebert,[4] Ang Gao,[2] Simon Christie,[4] Michael Zappitelli,[5] Rakesh C. Arora,[4] Julie Ho.[1,2,3] *[1]Immunology, Univ of Manitoba, Winnipeg, MB, Canada; [2]Manitoba Centre for Proteomics & Systems Biology, Univ of Manitoba, Winnipeg, MB, Canada; [3]Internal Medicine, Univ of Manitoba, Winnipeg, MB, Canada; [4]Cardiac Sciences Program, St. Boniface Hospital, Winnipeg, MB, Canada; [5]Pediatric Nephrology, McGill Univ, Montréal, QC, Canada.*

Background: Acute kidney injury (AKI) following cardiac surgery results in increased morbidity and mortality. Using proteomic techniques, we previously identified urine hepcidin-25 as a predictor for AKI avoidance. The goal of this study was to independently validate urine hepcidin-25 as an early AKI marker in a prospective observational cohort of cardiopulmonary bypass (CPB).

Methods: Serial urines were collected at baseline, start CPB, 1hr CPB, arrival to ICU, post-operative day (POD) 1 and 3-5. Urine hepcidin-25 was evaluated with ELISA in a nested case-controlled cohort of AKI vs. non-AKI (n=42) across 6 time points and at POD1 in the full cohort (n=306). AKI was defined using KDIGO (creatinine >50% or 26.5μmol/L/48hrs). Stepwise logistic regression was performed using significant univariate predictors of AKI.

Results: Peak hepcidin-25 levels were confirmed at POD1 in AKI and non-AKI patients. Univariate predictors of AKI were hepdicin-25, age, baseline eGFR & creatinine, diabetes (DM), congestive heart failure and THAKAR & EUROscore II. Urine hepcidin-25 was an independent predictor for AKI avoidance on multivariate analysis. The combined model with eGFR, DM and hepcidin-25 had an AUC 0.815.

Table 1.Urine hepcidin-25 is an independent predictor for avoidance of AKI after cardiac surgery

Variable	Odds Ratio	95% CI	p-value
eGFR (mL/min/1.72 m^2) – Per Unit	0.96	0.95 – 0.98	<0.01
Diabetes mellitus	3.08	1.47 – 6.45	<0.01
Average Hepcidin-25 Concentration (ng/ml) – Per 1000 Units	**0.67**	**0.50 – 0.95**	**0.02**

Final multivariable logistic regression model developed using stepwise selection method. Missing covariate values estimated via multiple imputation. **Area Under the ROC Curve = 0.815 (0.746 – 0.884)** Hosmer-Lemeshow P-Value = 0.90

Conclusions: We validated urine hepcidin-25 as an AKI avoidance marker in an independent cardiac surgery cohort. Urine hepcidin-25 may be renoprotective by sequestering iron in renal tubular epithelial cells.

Funding: Other NIH Support - CIHR

TH-PO665

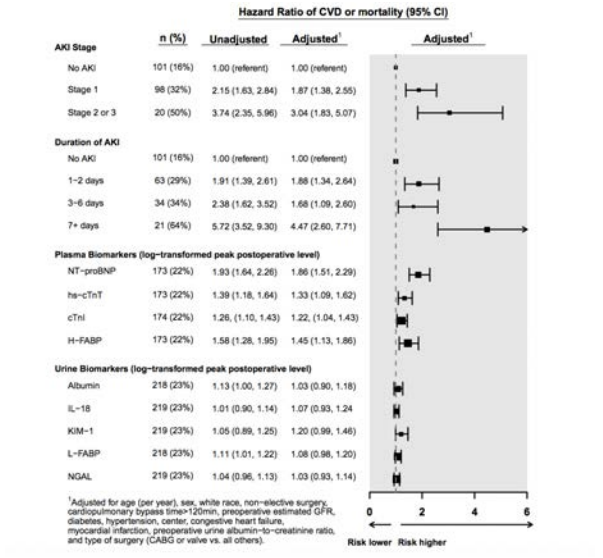
Association between Different Measures of Kidney Injury and Long-Term Risk of Cardiovascular Events and Mortality after Cardiac Surgery Chirag R. Parikh, Jeremy Puthumana, Amit X. Garg, Heather Thiessen Philbrook, Eric McArthur, Jay L. Koyner, Michael Shlipak, Steven G. Coca. *TRIBE-AKI Consortium.*

Background: Acute kidney injury (AKI) has been associated with cardiovascular disease (CVD) in observational studies. However, it remains unclear whether kidney injury is causally linked to CVD or whether the observed association between AKI and CVD is simply reflective of changes in renal perfusion due to underlying cardiac and hemodynamic dysfunction.

Methods: In a prospective multicenter study, we examined 968 adults who underwent cardiac surgery in the TRIBE-AKI cohort. On postoperative days 1-3, we measured the following urine biomarkers of renal injury: IL-18, NGAL, KIM-1, L-FABP, and albumin. In addition, we measured the following plasma biomarkers of cardiac injury: NT-proBNP, hs-cTnT, cTnI, and H-FABP. AKI was defined as a ≥50% or 0.3 mg/dL increase in serum creatinine, within 7 days of surgery. CVD and death were ascertained using administrative linkages with national datasets during a median follow-up of 3.8 (3.1-4.6) years.

Results: During follow-up, 136 (14.1%) patients experienced CV events and 83 (8.6%) patients died. We found that the magnitude and duration of postoperative creatinine-based AKI were strongly associated with CVD and mortality **(Figure)**. However, peak postoperative elevations in urinary kidney injury biomarkers were not significantly associated with risk for future CV events and mortality **(Figure)**. Instead, elevations in four cardiac injury biomarkers, independent of kidney injury, strongly associated with future CV events and mortality **(Figure)**.

Conclusions: These results suggest that creatinine-based AKI may be a surrogate for an inability of the kidneys of some patients to compensate to cardiovascular stress or injury, rather than an independent pathway for adverse cardiovascular outcomes.



Funding: Other NIH Support - R01-HL085757

TH-PO666

Serum and Urinary Hepcidin, but Not Free Iron as Protective and Inverse Biomarkers of CI-AKI in Patients Undergoing Percutaneous Coronary Interventions-PCI Jacek S. Malyszko,[1] Hanna Gajewska,[2] Ewa Koc-Zorawska,[3] Jolanta Malyszko,[2] Slawomir Dobrzycki.[2] *[1]1st Dept Nephrol, Medical Univ, Bialystok, Poland; [2]Dept Invasive Cardiology, Medical Univ, Bialystok; [3]2nd Dept Nephrol, Medical Univ, Bialystok.*

Background: Contrast-induced acute kidney injury (CI-AKI) is a common and potentially serious complication of percutaneous coronary interventions-PCI. Hepcidin, a peptide hormone that regulates iron homeostasis.Iron is supposed to be crucial in cell regeneration. We tested the hypothesis whether serum hepcidin could represent an early protective biomarker of CI-AKI in 80 patients with normal serum creatinine undergoing PCI. We also assessed serum and urinary NGAL, cystatin C, in these patients as well as LPI (labile plasma iron) and e eLPI(NTBI-non transferrin bound iron).

Methods: Serum and urinary hepcidin as well as NGAL, cystatin C, were evaluated before, and after 2, 4, 8, 24 and 48 hours after PCI using commercially available kits. LPI and e eLPI were assessed by Aferrix, Israel. Serum creatinine was assessed before, 24 and 48 hours after PCI.

Results: We found a significant rise in serum hepcidin as early as after 4 hours when compared to the baseline values. It was also significantly higher 8 and 24 hours after PCI. Serum NGAL increased after 2, 4 and 8 hours, and in urinary NGAL after 4,8 and 24 hours after PCI. We found a significant rise in serum NGAL after 2, 4 and 8 hours, and in urinary NGAL and IL-18 after 4, 8&24 hours after PCI. Serum cystatin C increased significantly 8 hours, reaching peak 24 hours after PCI and then decreased after 48 hours. In all the patients both LPI and eLPI When contrast nephropathy was defined as an increase in serum creatinine by >25% of the baseline level 48 hours after PCI, the prevalence of CI-AKI was 4/26. Urine hepcidin were significantly lower 8 and 24 hours after PCI in patients with CI-AKI, while serum and urine NGAL were significantly higher in patients with CI-AKI. Hepcidin correlated negatively with NGAL ($r=-0.42$, $p<0.05$).

Conclusions: Our findings suggest that serum hepcidin might be an early predictive biomarker of ruling out CI-AKI after PCI, thereby contributing to early patient risk stratification. Free iron does not appear to be involved in CI-AKI.

Funding: Government Support - Non-U.S.

TH-PO667

Multi Center ICU Study Finds NGAL Increases Rate of AKI Detection Sahir Kalim,[1] A. Osama Gaber,[2] Ladan Golestaneh,[3] Michael J. Germain,[4] Peter A. McCullough.[5] *[1]Massachusetts General Hospital, Boston, MA; [2]Houston Methodist Hospital, Houston, TX; [3]Montefiore Medical Center, Bronx, NY; [4]Baystate Medical Center, Springfield, MA; [5]Baylor Univ Medical Center, Dallas, TX.*

Background: Acute kidney injury (AKI) is a severe and frequently encountered complication in ICU patients. AKI is often under diagnosed and detected late in the ICU because the diagnosis is based on elevations in serum creatinine (sCr), a relatively late marker of AKI. Neutrophil gelatinase-associated lipocalin (NGAL) is a biomarker indicating tubular damage that has been shown to rise early and dramatically in both urine and plasma during AKI. We examined the sensitivity of NGAL as a test for AKI, as compared to a clinical diagnosis using creatinine and the KDIGO guideline recommended criteria.

Methods: A total of 245 patients admitted to the ICU from four sites were enrolled. Blood and urine samples were taken daily and stored. NGAL concentrations were determined using the NGAL Test (BioPorto) in batch samples at a central laboratory with a cutoff value of 250 ng/mL. Retrospectively, a team of three clinicians, blinded to the NGAL results, adjudicated each patient case as having or not having AKI according to KDIGO guidelines.

Results: In this study, only 17 patients were chart diagnosed as having AKI. In contrast, NGAL identified AKI in a total of 56 patients, which represents an increase of 329% using a single cutoff of 250 ng/mL. Of those above this cutoff, there was 70% rate of confirmation of the diagnosis of AKI by the adjudicators.

Conclusions: The incorporation of serial NGAL measurements is a simple approach for increasing the rate and speed of AKI detection in an ICU population. Use of a structural kidney biomarker (NGAL) enhances the detection of AKI in combination with a functional biomarker (sCr).

Funding: Pharmaceutical Company Support - BioPorto

TH-PO668

Urinary UDP-Glucose as a Biomarker of Acute Kidney Injury in ICU Patients Rachel Nager Liberman,[1] Andrew S. Allegretti,[1] Juliana Sesma,[2] Leileata M. Russo,[1] Eduardo R. Lazarowski,[2] Sahir Kalim,[1] Dennis Brown,[1] Sushrut S. Waikar,[3] Ravi I. Thadhani,[1] Sylvie Breton.[1] *[1]Massachussetts General Hospital, Boston, MA; [2]UNC Chapel HIll, Chapel Hill, NC; [3]Brigham and Women's Hospital, Boston, MA.*

Background: Acute Kidney Injury (AKI) in Intensive Care Unit (ICU) patients is common and complicates up to two thirds of cases. A rise in serum creatinine is the current diagnostic standard for AKI, but serum creatinine is a relatively late marker. We have recently identified UDP-glucose (UDP-G) to be a mediator of sterile inflammation in the kidney, through its action on the P2Y14 receptor. Injured cells release UDP-G that activates P2Y14 receptors oriented on the luminal side of intercalated cells (ICs). ICs subsequently secrete inflammatory chemokines, which results in pathological inflammatory cell recruitment into the renal medulla. Because AKI is often associated with uncontrolled inflammation, we investigated whether urinary UDP-G is an early biomarker of AKI in patients admitted into the ICU.

Methods: A prospective, longitudinal cohort study was performed using urine collected from 41 patients with 108 urine samples. Urine was collected daily from patients admitted through the ICU for up to 8 days. UDP-G concentration was measured by a radiometric assay. The association between urinary UDP-G and AKI status - as defined by AKIN criteria or ICU team clinical diagnosis - was measured by ROC-AUC analysis.

Results: UDP-G concentrations increased with AKIN stage of AKI ($P < 0.0001$). At a cutoff value of 40 nM urinary UDP-G to predict AKI, the ROC-AUC was 0.94 (sens. = 0.88, spec. = 0.86) when AKI was defined by the ICU team, and 0.80 (sens. = 0.59, spec. = 0.80) when AKI was defined by AKIN criteria. UDP-G levels were elevated up to 48 hours before an AKI-related change in serum creatinine occurred.

Conclusions: UDP-G is a promising biomarker of AKI due to its high sensitivity and specificity as a predictor of subsequent AKI. Furthermore, as UDP-G plays a functional role in the development of renal inflammation, pharmacological inhibition of the P2Y14 receptor may be a potential therapeutic target to prevent/mitigate AKI.

TH-PO669

Microparticles and Kidney Injury in Stroke Begoña Campos, Charuhas V. Thakar, Anthony C. Leonard. *IM Div of Kidney CARE, Univ of Cincinnati, Cincinnati, OH.*

Background: Acute kidney injury (AKI) affects 1-in-3 hospitalizations, and is more common in setting of other vital organ injury. Recent evidence demonstrates that in response to stress or injury cells release phenotypically distinct micro particles (MP's), which can be both markers or mediators of disease. The *objective* of this study was to evaluate type and quantity of MP's in setting of kidney injury (KI) and stroke.

Methods: In a prospectively collected biological repository of 38 eligible stroke subjects (14 ischemic and 24 hemorrhagic) and 37 controls. Demographic, comorbid and laboratory variables were collected at the time of admission. Kidney injury (KI) was defined as either admission creatinine > 1.2 mg/dl or development of AKI. Comparisons were made across Group I (Stroke) (Ia = no KI; Ib = KI) and Group II (no Stroke) (IIa = no KI; IIb = KI) Flow Cytometric analysis measured MPs in plasma for CD146 (endothelial cells), CD10 and CD13 (renal proximal tubular epithelial/RPTE markers). FlowJo software evaluated MP's, and levels were expressed as 10^7 and compared by Wilcoxon test (two-sided p-values).

Results: For Group I and II, CD146 MP's were 48.8 vs 39.3 ($p = 0.0026$); where as CD 10 MP's were 8.4 vs 15.4 ($p = 0.001$); and CD13 MP's were 19.4 vs 20.6 ($p = 0.21$) For Group II, RPTE MP's were higher in IIb vs IIa: CD 10 levels were 22.5 vs 14.0 ($p = 0.048$), and CD 13 were 23.4 vs 19.9 ($p = 0.023$). Within Group I, RTPE MP's and endothelial MP's were not different by KI status. When KI status was compared across Groups I and II (Ib vs IIb), CD146 levels were 50.0 vs 36.9 ($p = 0.002$); CD 10 were 8.9 vs 22.5 ($p = 0.0274$); CD 13 were 19.3 vs 23.4 ($p = 0.013$).

Conclusions: We confirm that endothelial MP's are increased in Stroke. In non Stroke patients, RPTE MP's are higher associated with KI; however this difference is not significant in Stroke subjects. Interestingly, when KI status was compared across Stroke vs Controls, RPTE MP's were significantly decreased in Stroke patients. This suggests an interplay between up-regulation of endothelial MP's and down regulation of RPTE MP's in the setting of dual organ injury. This is one of the first study to detect RPTE MP's in plasma of patients with vital organ dysfunction.

Funding: Clinical Revenue Support

TH-PO670

Extracellular Histones in Relation to Organ Dysfunction and Inflammation during Kidney-Lung Crosstalk Xin Wan, Yasser M.Z. Gendoo, Changchun Cao. *Dept of Nephrology, Nanjing First Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Mortality rates due to kidney-lung crosstalk have remained high despite advances in the management of AKI and ARDS. The inflammatory mediators believed to be responsible for this are yet unidentified. Extracellular histones are known to exacerbate inflammation and tissue injury. Here we investigate whether there is a clinical correlation between blood histone concentrations, kidney function, and lung function during AKI and ARDS.

Methods: In a prospective cohort, blood samples were collected from 54 patients upon admission to our hospital who were diagnosed with AKI, ARDS, community acquired pneumonia, or a combination of these. Serum histone concentrations were measured by ELISA and plotted against PaO_2/FiO_2, eGFR, neutrophils, and CRP. Pearson correlation test was performed and $p < 0.05$ was considered significant.

Results: The scatter-graphs show histone concentrations against the four parameters. In the overall sample population, histone concentrations were significantly correlated with PaO_2/FiO_2 ($P=0.0017, R^2=0.1652$); change of eGFR from baseline ($P<0.0001, R^2=0.3107$); neutrophil counts ($P=0.0174, R^2=0.1021$) and CRP ($P=0.0004, R^2=0.2207$). However, when patients were divided according to diagnosis, there was no significant correlation between these same parameters.

Conclusions: When viewed in light of the adverse effects of extracellular histones, the correlations reported in this study strongly suggest that extracellular histones may be potential mediators of kidney-lung crosstalk. Additional research is necessary to reveal the mechanisms of their involvement and whether they participate in or are merely a consequence of injury. Further endeavours to understand the pathophysiology of crosstalk will likely lead to improved treatment strategies and outcomes.

Funding: Government Support - Non-U.S.

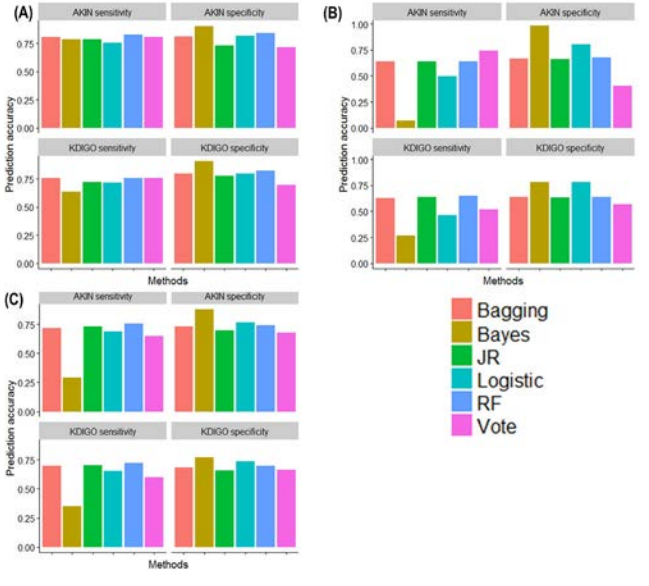
TH-PO671

Prediction Model for Postoperative Acute Kidney Injury after Noncardiac Major Surgery Using Machine Learning Seokwoo Park, Dong Ki Kim, Kwon Wook Joo, Yon Su Kim, Hajeong Lee. *Internal Medicine, Seoul National Univ of College of Medicine, Seoul, Korea.*

Background: Prediction for postoperative AKI can be helpful to identify high risk patients and elicit early intervention. In this study, we incorporated several pre- and intraoperative factors to build a prediction model for postoperative AKI using various machine learning methods.

Methods: We included adult (age ≥ 18 years) patients who received noncardiac major (duration>1 hour) surgery in Seoul National University Hospital from 2004 to 2013. Patients with baseline creatinine (Cr) over 4 mg/dl or maintenance renal replacement therapy (RRT) were excluded. AKI was diagnosed according to both KDIGO and AKIN criteria based on Cr measurements and initiation of RRT within 14 days after surgery. Variables used include age, sex, department, BMI, BP, comorbidities, medication, ASA class, anesthesia type, emergency, laboratory measurements, surgery duration and intraoperative BP measurements. We developed prediction models using Bagging, Naïve Bayes (Bayes), JRip (JR), logistic regression (Logistic), random forest (RF), and voted perception (VP) method, and calculated sensitivities and specificities of each method using 10-fold cross-validation.

Results: Among a total of 58,919 cases, 4,092 (6.95%) and 3,347 (5.68%) AKI were identified by KDIGO and AKIN, respectively. Prediction accuracy using preoperative (A), intraoperative (B), pre- and intraoperative variables (C) were demonstrated in Figure1.



RF method using all variables among the classifiers showed the highest sensitivity for AKI

	All	GS	OS	OG	UR	NS
AKIN	74.3	79.2	71.7	82.7	67.2	56.8
KDIGO	71.3	75.4	69.1	75.5	72.7	60.4

Conclusions: AKI prediction using pre- and intraoperative variables by machine learning algorithms showed fairly acceptable sensitivity and specificity. Further efforts are needed until clinical implication of machine learning algorithms.

TH-PO672

More Accurate AKI Diagnosis by Incorporating Urinary Biomarkers with No Reference Serum Creatinine Value Rei Isshiki,[1] Maki Sumida,[1] Yoshifumi Hamasaki,[1] Masaomi Nangaku,[1] Eisei Noiri,[1] Kent Doi.[2] *[1]Nephrology and Endocrinology, Univ Hospital, Univ of Tokyo, Tokyo, Japan; [2]Emergency and Critical Care Medicine, Univ Hospital, Univ of Tokyo, Tokyo, Japan.*

Background: The KDIGO guideline defines AKI based on relative changes in serum creatinine from baseline values, which is sometimes unavailable. This study was aimed to evaluate whether urinary biomarkers is useful to reduce misclassification rates of AKI compared with employing estimated serum creatinine value calculated by MDRD formula assuming a GFR of 75 ml/min/1.73m^2 (e-sCr).

Methods: We conducted a prospective observational study that included adult ICU patients with known baseline serum creatinine values. Misclassification rate of AKI was calculated when using e-sCr instead of available baseline values. A predictive model incorporating urinary biomarkers (NGAL and L-FABP) using decision tree analysis was developed for reducing AKI misclassification.

Results: Of 135 patients, 44 patients (32.6%) had developed AKI at ICU admission. When using e-sCr, 28 patients were misclassified as AKI (false positive rate 30.8%) and 4 patients were misclassified as non-AKI (false negative rate 9.1%) The total number of misclassification was 32 in all the enrolled patients (23.7%). Levels of urinary NGAL were significantly higher in the true AKI patients compared with the patients who were misclassified as AKI (839.8 vs 161.6 ng/ml; p=0.0047), however urinary L-FABP level showed no significant difference. Urinary NGAL alone showed a similar misclassification rate (22.9%) with the Youden-index cut-off value of 430 ng/ml. Decision tree analysis incorporating absolute serum creatinine values and urinary NGAL at ICU admission revealed that the misclassification rate was decreased to 17.7%. The area under the curve (AUC) for this developed decision tree analysis model was 0.87 (95%CI, 0.80-0.92), whereas the model using e-sCr alone showed a significantly lower AUC value (0.80 [0.73-0.86]; p=0.0002).

Conclusions: Even when no baseline serum creatinine value is available, urinary NGAL in addition to the absolute serum creatinine value at ICU admission can show more accurate AKI diagnosis compared with back calculation of baseline serum creatinine by MDRD formula.

TH-PO673

Severe Acute Kidney Injury in Hospitalized Patients Can Be Predicted from the Emergency Department: A Feasibility Study Holly R. Hanson, Michael Adam Carlisle, Rachel S. Bensman, Terri Byczkowski, Stuart Goldstein, Rajit K. Basu. *Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

Background: Early recognition of patients at risk of acute kidney injury (AKI) may expedite supportive and preventive care. We previously derived and validated an AKI risk stratification methodology, renal angina, for prediction of severe AKI in patients three days after admission to the intensive care unit (ICU). Use of renal angina applies context to patients, optimizing the predictive performance of biomarkers for subsequent AKI. AKI risk stratification in the emergency department (ED) has not been well described.

Methods: We conducted a prospective, single-center observational study in a tertiary pediatric ED to derive and validate a modified "acute" RAI (aRAI) for the prediction of severe AKI (SCr KDIGO Stage 2 or 3) at 48-72 after hospitalization. The aRAI was determined at the time of disposition from the ED.

Risk Strata Score		
Characteristic	**Risk**	**Score**
ED Concern for Sepsis or Shock	Moderate	1
History of Transplant and/or active Oncologic Disease	High	3
>40 mL/kg intravenous fluid and/or ED Intubation	Very High	5
Injury Score		
Change from Baseline Creatinine		**Score**
< 1.5x		1
≥ 1.5x to <2x		2
≥ 2x to <3x		4
≥ 3x		8
aRAI = Risk Strata Score x Injury Score **aRAI ≥ 8 fulfills renal angina**		

Results: 118 children were enrolled (48% male, mean age 7.8 ± 6.4 years). 11% were RAI positive for renal angina in the ED, 16% were admitted to the ICU, and 66% remained hospitalized after 48 hours (ICU or ward). The rates of severe AKI at 48 and 72 hours were 8.0% and 7.7%. The aRAI demonstrated a positive predictive value of 0.29 (0.05, 0.70) and negative predictive value of 0.97 (0.82, 0.99) with an AUC of 0.76 (0.43, 1.00) for severe AKI.

Conclusions: Our pilot study demonstrates a sensitive screening tool for stratification of patients by risk for AKI from presentation in the ED, the earliest time possible for intervention. Biomarker incorporation into the aRAI model is anticipated to augment the post-test probability of AKI and creates a model useful for testing of strategies targeted at mitigating further renal insult.

Funding: Private Foundation Support

TH-PO674

Secretory Function in Acute Kidney Injury Frank J. O Brien, Scott M. Sutherland, Natalie Plummer, Timothy W. Meyer, Tammy L. Sirich. *VA Palo Alto HCS and Stanford Univ.*

Background: Impairment of renal function in acute kidney injury (AKI) is routinely evaluated by measurement of ureaN (UN) and creatinine (Cr) which are markers largely of tubular reabsorption and glomerular filtration. Tubular secretory function in AKI has much less often been assessed.

Methods: Plasma levels for the normally secreted solutes indoxyl sulfate (IS) and phenylacetylglutamine (PAG) were measured along with levels of UN and Cr in 6 AKI and 25 maintenance hemodialysis (HD) subjects. Solute clearances were also measured in the AKI subjects and 9 normal (NL) subjects.

Results: (mean±stdev; *p<0.05 AKI vs NL; **p<0.05 AKI vs HD):

	Fractional clearance (k_{solute}/k_{Cr})		Plasma levels (mg/dl)		Concentration ratio HD/AKI
	AKI	NL	AKI	HD	
IS	0.8 ± 0.7	0.4 ± 0.1	0.19 ± 0.18	2.9 ± 1.1	16**
PAG	2.9 ± 0.7	2.7 ± 0.5	0.22 ± 0.17	5.2 ± 2.5	23**
UN	0.3 ± 0.1	0.5 ± 0.1*	81 ± 14	65 ± 25	0.8
Cr	-	-	2.3 ± 0.5	10.8 ± 3.3	4.8**

Clearances relative to the Cr clearance (fractional clearance; k_{solute}/k_{Cr}) were well preserved for the secreted solutes in AKI. In contrast, the fractional clearance of UN was significantly reduced. As a result, the UN level in AKI was elevated to a similar degree as in HD. In contrast, the levels for the secreted solutes were significantly higher in HD than AKI subjects because hemodialysis does not replicate secretory function.

Conclusions: Secretory function is well preserved in AKI. Further studies of secreted solutes may enhance our ability to assess renal function in AKI and to determine the timing of dialysis initiation.

Funding: NIDDK Support, VA Support

TH-PO675

Predictive Value of Cystatin C-Based eGFR for Successful Weaning from Continuous Renal Replacement Therapy: A Prospective Observational Study Chang Seong Kim,[1] Tae Ryom Oh,[1] Ha Yeon Kim,[1] Yong Un Kang,[1] Eun Hui Bae,[1] Seong Kwon Ma,[1] Jong Un Lee,[2] Soo Wan Kim.[1] *[1]Dept of Internal Medicine, Chonnam National Univ Hospital, Gwangju, Republic of Korea; [2]Dept of Physiology, Chonnam National Univ Medical School, Gwangju, Republic of Korea.*

Background: Continuous renal replacement therapy (CRRT) is the mainstay of treatment for critically ill patients with acute kidney injury. The aim of our study is to identify whether biomarkers or factors of renal function can predict successful weaning from CRRT.

Methods: We conducted a prospective observational study of 110 patients who had received CRRT and were weaned from it after renal recovery. Successful weaning from CRRT was defined as elimination of the requirement for RRT for at least 14 days after cessation of CRRT, whereas redialysis within 14 days was defined as restart-RRT. Serum levels of cystatin C (CysC), neutrophil gelatinase-associated lipocalin (NGAL), and conventional biomarkers of renal function were checked at the time of cessation of CRRT.

Results: Of the 110 patients we evaluated, 89 patients (80.9%) were successfully weaned from CRRT while 21 (19.1%) patients were not. Setting of CRRT and simplified acute physiology score III did not differ significantly between both groups. Serum CysC levels were lower and urine output was higher in the success group compared with the restart-RRT group at the time of cessation of CRRT (CysC: 1.70 ± 0.68 mg/L vs. 2.47 ± 0.93 mg/L, $P < 0.001$; urine output: 2.03 ± 2.10 mL/h/kg vs. 1.02 ± 0.93 mL/h/kg, $P = 0.016$). Multivariable logistic regression showed that CysC-based estimated glomerular filtration rate (eGFR) was an independent predictor for successful weaning from CRRT (OR, 1.25; 95% CI, 1.04-1.51; $P = 0.016$) while NGAL and urine output were not associated with successful weaning from CRRT. The area under the receiver operating characteristic curve of CysC-based eGFR, which predicts successful weaning from CRRT, was 0.75 (95% CI, 0.63–0.86); sensitivity and specificity were 65.2% and 76.2%, respectively, at a cutoff of 32.9 mL/min/1.73 m^2.

Conclusions: Cystatin C-based eGFR at the time of cessation of CRRT is a good predictor of successful weaning from CRRT in critically ill patients with actue kidney injury.

TH-PO676

Pregnancy Related Acute Kidney Injury: A Single Center Experience Umesha Lingaraj. *Nephrology, Inst of Nephrourology, Bangalore, Karnataka, India.*

Background: Pregnancy Related Acute Kidney Injury (PRAKI) may comprise up to 25% of the referrals to dialysis centers in developing countries and is associated with substantial maternal and fetal mortality.

Methods: We conducted a prospective cross sectional observational study to evaluate the etiological factors and final outcome of AKI with special reference to pregnancy related acute kidney injury. AKI was diagnosed as per AKIN (Acute Kidney Injury Network) criteria.

Results: In this prospective study between February 2012 to February 2016, total of 624 patients were studied among them 460 were admitted with medical causes (73.7%), 124 with obstetrical causes (19.8%) and 40 (6.4%) with surgical causes. The mean age among PRAKI was 21±4 (17-36) years and duration of hospital stay was 9.41±7.3 days. Etiological factors include puerperal sepsis in 65(52.41%), pregnancy induced hypertension in 30(24.1%), 12(9.67%) patients had postpartum hemorrhage, 7(5.64%) antepartum hemorrhage, postpartum hemolytic uremic syndrome in 3 patients (2.41%) and miscellaneous causes was seen 7(5.6%). Renal biopsy was performed if a patient was oliguric or dialysis dependent at the end of 3 weeks. Biopsy was done on 22 patients and 6 of them had patchy cortical necrosis, 11 patients showed acute tubular necrosis, two with features of acute interstitial nephritis and three patients had thrombotic microangiopathy. Out of 124 patients 101(81.45%) patients recovered from acute kidney injury, 4(3.22%) patient remained on dialysis and 2(1.61%) patient had partial recovery from renal failure. Seventeen patients died with mortality rate of 13.70%. Out of these 9 patients died within 48 hours of admission. Sepsis, multiorgan dysfunction, coagulation abnormalities and retained products of conception were factors associated with mortality.

Conclusions: Pregnancy related acute kidney injury was comprising about 19.8% of the patients. Puerperal sepsis is the most frequent etiological factor and accounted for a majority of maternal mortality.

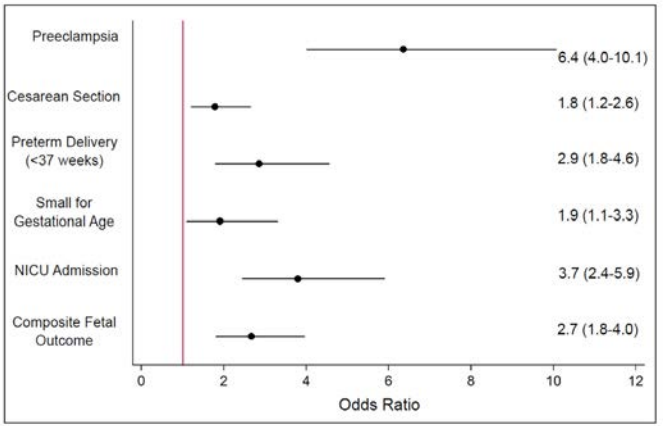
TH-PO677

Pregnancy Outcomes following Clinical Recovery from Acute Kidney Injury in Young Women Jessica Sheehan Tangren,[1] Camille Elise Powe,[1] Elizabeth D. Ankers,[1] Jeffrey Ecker,[1] Kate Bramham,[2] Michelle A. Hladunewich,[3] S. Ananth Karumanchi,[4] Ravi I. Thadhani.[1] *[1]Massachusetts General Hospital, Boston, MA; [2]King's College London, London, United Kingdom; [3]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [4]Beth Israel Deaconess Medical Center, Boston, MA.*

Background: Acute kidney injury (AKI) is a risk factor for future morbidity and mortality but the effect of clinically recovered AKI on future pregnancy outcomes is unknown. Our objective was to assess if a previous episode of AKI with subsequent recovery of renal function is associated with adverse pregnancy outcomes, including preeclampsia.

Methods: We conducted a retrospective cohort study of women who delivered infants between 1998 to 2008 at the Massachusetts General Hospital. Pregnancy outcomes in women with recovered AKI (r-AKI) without a history of chronic kidney disease (n=105) were compared to outcomes in women without kidney disease (n=24,640). AKI was defined as a rise in serum creatinine to 1.5 fold above baseline with subsequent clinical recovery (eGFR > 90) prior to conception.

Results: Pre-pregnancy serum creatinine measurements in women with r-AKI were 0.70±0.20 mg/dl vs 0.69±0.10 mg/dl in controls. Women with r-AKI had an increased rate of preeclampsia (23% vs 4%, p<0.001). Infants of women with r-AKI were born earlier (37.6±3.6 vs 39.2±2.2 weeks, p<0.001), with increased rates of small for gestational age births (15% vs 8%, p=0.03). After multivariate adjustment including age, race, parity, obesity, hypertension and diabetes, r-AKI remained associated with increased odds of adverse maternal-fetal outcomes.



Conclusions: An episode of AKI, despite return to normal renal function prior to pregnancy, is associated with adverse pregnancy outcomes. This describes a new group of women at high risk for preeclampsia and preterm delivery. This finding may help explain disparate rates of preeclampsia across the globe.

Funding: NIDDK Support

TH-PO678

Outpatient Acute Kidney Injury Increases Risk of Chronic Kidney Disease and Mortality Regardless of Recovery Daniel P. Murphy,[1] Max Leither,[1] Scott Reule,[1] Areef Ishani,[2] Robert N. Foley,[1] Paul E. Drawz.[1] *[1]Div of Renal Diseases and Hypetension, Univ of Minnesota, Minneapolis, MN; [2]Div of Nephrology, Minneapolis VA Medical Center, Minneapolis, MN.*

Background: Hospital acquired acute kidney injury (AKI) is common and is a risk factor for all-cause mortality and chronic kidney disease. The epidemiology and outcomes of patients with outpatient AKI are poorly characterized, particularly those whose creatinine returns to baseline.

Methods: Patients with at least two primary care visits within the Fairview Health Service's electronic health record were included in this retrospective study. During an 18 month exposure period beginning with the second primary care visit, patients were categorized into five groups (no creatinine measurement, no AKI, AKI with recovery, AKI without recovery, and AKI without a repeat creatinine). AKI was defined by a 50% increase in creatinine compared to the average of the last three outpatient creatinine values between 30 and 365 days prior. Recovery was defined by any subsequent creatinine less than or equal to 110% of baseline creatinine. Mortality, obtained by Minnesota death certificate records, and a creatinine value >3 mg/dL at last follow-up were co-primary outcomes.

Results: There were 1.77 million patients in the electronic health record and 464,474 that visited primary care at least twice. Of these, 55.3% had no creatinine measured, 43.2% had no AKI, 0.4% had AKI without recovery, 0.8% had AKI with recovery, and 0.3% had AKI without a repeat creatinine. Patients with AKI were more likely to have a final creatinine >3 mg/dL and were more likely to die during follow-up.

	No Cr	No AKI	AKI with recovery	AKI without recovery	AKI with no repeat Cr
Count	256,908	200,674	3,653	1,929	1,279
Age (std dev)	35.9 (15.3)	51.4 (17.6)	62.8 (17.5)	62.9 (17.1)	57.5 (19.2)
Female	58.6%	54.5%	58.3%	57.3%	59.3%
Last Cr >3 mg/dL	0.2%	0.7%	6.4%	12.6%	5.3%
Mortality	0.7%	4.1%	20.6%	20.2%	15.6%

Conclusions: Outpatient AKI is associated with a significantly increased risk of development of chronic kidney disease and mortality regardless of whether creatinine returns to baseline.

TH-PO679

Hospital Readmissions after an Acute Kidney Injury Hospitalization Samuel A. Silver,[1] Ziv Harel,[1,2] Eric McArthur,[2] Danielle Marie Nash,[2] Rey R. Acedillo,[3] Abhijat Kitchlu,[1] Amit X. Garg,[2,3] Glenn Matthew Chertow,[4] Chaim Bell,[2,5] Ron Wald.[1,2] *[1]Nephrology, Univ of Toronto, Toronto, ON, Canada; [2]Inst for Clinical Evaluative Sciences, Toronto, ON, Canada; [3]Nephrology, London Health Sciences Centre, London, ON, Canada; [4]Nephrology, Stanford Univ School of Medicine, Palo Alto, CA; [5]Medicine, Mount Sinai Hospital, Toronto, ON, Canada.*

Background: The risk of hospital readmission in acute kidney injury (AKI) survivors is not well understood. We sought to estimate the rate of hospital use and identify the determinants of 30-day readmission after a hospitalization complicated by AKI.

Methods: We conducted a retrospective population-based study of all patients who survived a hospitalization complicated by AKI from 2003-2013 in Ontario, Canada. The primary outcome was 30-day hospital readmission. We used a propensity score model to match patients with and without AKI during the index hospitalization. We derived subdistribution hazard ratios and 95% confidence intervals from Cox proportional hazards models stratified on the matched sets with death as a competing risk. We used similar models to identify predictors of 30-day readmission in the entire cohort.

Results: We identified 156,690 patients who were discharged from hospital after an episode of AKI, of whom 27,457 (18%) were readmitted to hospital, 15,988 (10%) visited the emergency department (ED), and 7480 (5%) died without incurring a hospitalization or ED visit. We successfully matched 111,778 patients with AKI 1:1 to patients without AKI. The risk of 30-day readmission was higher in AKI survivors than patients without AKI (adjusted hazard ratio [aHR] 1.53 [95% CI 1.50-1.57]). The factors most strongly associated with 30-day rehospitalization were the number of hospitalizations in the preceding year (aHR 1.63 per 5 visits, 95% CI 1.51-1.76) and inpatient chemotherapy (aHR 1.49, 95% CI 1.36-1.63).

Conclusions: Patients who survive a hospitalization complicated by AKI are at high risk for readmission in the subsequent 30 days. Better strategies are needed to identify and care for AKI survivors in the community.

Funding: Government Support - Non-U.S.

TH-PO680

Acute Kidney Injury Recovery at 90 Days and Subsequent CKD in Critically Ill Sepsis Survivors Javier A. Neyra,[1] Xilong Li,[1] Beverley Adams-Huet,[1] Jerry Yee,[2] Orson W. Moe,[1] Robert D. Toto.[1] *[1]UT Southwestern, Dallas, TX; [2]Henry Ford Hospital, Detroit, MI.*

Background: AKI is a frequent complication of sepsis and is associated with increased risk for subsequent CKD. The purpose of this study was to investigate whether incomplete AKI recovery at 90 days post-discharge increases the risk of CKD in sepsis survivors.

Methods: Single-center, retrospective cohort study of adults admitted to the ICU with a diagnosis of severe sepsis/septic shock. Subjects with pre-admission eGFR <15 or receiving chronic RRT were excluded. AKI during ICU stay was diagnosed based on KDIGO serum creatinine (SCr)-criteria in reference to a baseline SCr within 3 months before admission. AKI recovery was determined by the ratio of 90-day SCr/baseline SCr in RRT-free survivors: <1.1 indicated complete recovery, ≥1.1 to <1.5 incomplete (mild) recovery and ≥1.5 incomplete (severe) recovery. Incident or progressive CKD post-AKI was adjudicated based on relative and/or absolute eGFR changes during the follow-up period.

Results: Of 6290 patients included in the study, 3642 (58%) suffered from AKI and 741 (12%) required acute RRT. The 90-day mortality rate was 26%. Among survivors, we identified 1249 patients who suffered from AKI, were RRT-free, and had available follow-up data. CKD occurred in 319 of the 1249 patients: 54% of those with incomplete (severe) recovery, 29% of those with incomplete (mild) recovery and 13% of those with complete recovery; median follow-up 2.5 years. 90-day AKI recovery status was an independent predictor of CKD: adjusted HR 4.7, 95% CI 3.5–6.3 for incomplete (severe) vs. complete recovery; 2.3, 1.7–3.1 for incomplete (mild) vs complete recovery; and 2.1, 1.6–2.8 for incomplete (severe) vs incomplete (mild) recovery. Other predictors of post-AKI CKD were older age, black race, anemia, and higher admission SOFA score.

Conclusions: Incomplete AKI recovery within 90 days following hospital discharge is a strong and independent predictor of CKD in sepsis survivors. The timely evaluation of AKI recovery may serve to risk-stratify sepsis survivors and implement more vigilant surveillance for CKD in this susceptible population.

Funding: Other NIH Support - P30 DK079328-06; UL1 TR001105

TH-PO681

Impact of CKD on Adverse Outcomes in Critically Ill Septic Patients with and without AKI Federica Mescia, Xilong Li, Beverley Adams-Huet, Robert D. Toto, Orson W. Moe, Javier A. Neyra. *UT Southwestern, Dallas, TX.*

Background: AKI is a common condition in the ICU associated with substantial morbidity and mortality, including CKD post-AKI. Similarly, CKD increases the risk of AKI, severe infections and death. The coexistence of CKD and AKI is frequently encountered in critically ill septic patients, but how their interplay affects clinical outcomes is not well elucidated.

Methods: Single-center, retrospective cohort study of adults admitted to the ICU with a diagnosis of severe sepsis or septic shock. Subjects were classified into 6 subgroups (2x3 matrix) according to pre-admission eGFR and AKI status during ICU stay: MDRD-eGFR <60 (CKD) vs ≥60 (no-CKD) and KDIGO serum creatinine (SCr)-criteria (no-AKI, AKI stage 1, AKI stage ≥2), respectively. Outcomes were 90-day mortality and a composite of CKD (incident CKD =eGFR <60 and ≥25% reduction from baseline; progressive CKD =eGFR <15 or ≥50% reduction from baseline), dialysis and death.

Results: 2632 patients were included and classified as no-CKD/no-AKI (22.7%); no-CKD/AKI1 (13.8%); no-CKD/AKI≥2 (17.5%); CKD/no-AKI (20.4%); CKD/AKI1 (13.8%) or CKD/AKI≥2 (11.8%). Overall 90-day mortality rate was 26.7% and CKD/dialysis/death occurred in 19.1% over a median follow-up of 18 months. Multivariable Cox regression hazard models included relevant demographic and clinical parameters.

Subgroup	Adjusted HR (95% CI) 90-day mortality	Adjusted HR (95% CI) CKD/dialysis/death
no-CKD/no-AKI	Reference	Reference
no-CKD/AKI1	1.50 (1.13 – 1.98)	1.91 (1.26 – 2.91)
no-CKD/AKI≥2	2.44 (1.92 – 3.11)	2.56 (1.72 – 3.83)
CKD/no-AKI	1.07 (0.82 – 1.41)	1.23 (0.80 – 1.90)
CKD/AKI1	1.19 (0.89 – 1.60)	1.14 (0.71 – 1.84)
CKD/AKI≥2	2.22 (1.70 – 2.89)	2.63 (1.73 – 4.00)

Conclusions: Stage 1 AKI on CKD was not independently associated with an increased risk of adverse outcomes in critically ill septic patients. However, AKI stage ≥2 on CKD and any level of AKI in no-CKD patients were strongly and independently associated with adverse outcomes. Stage 1 AKI on CKD may represent a distinct AKI phenotype with more pre-renal cases or less severe *de novo* intrinsic damage.

Funding: Other NIH Support - UL1 TR001105; P30 DK079328-06

TH-PO682

Inhibition of IRAK4-Mediated Innate Immune Responses Is Protective in Acute Kidney Injury Irina Alexandra Leaf, Bryce Gordon Johnson, Ivan G. Gomez, Jeremy Stuart Duffield. *Duffield Lab, Biogen, Cambridge, MA.*

Background: Fibrotic diseases can affect all tissues and organs and lead to over 40% of natural deaths. We analyzed pathways enriched in human kidney biopsies and found that innate immune signaling is strongly associated with disease progression. Cell-specific profiling of injured kidneys show that pericytes are the major contributors of pro-inflammatory cytokines and chemokines. While in a healthy state these cells support

homeostasis, in injury, they become activated and differentiate into myofibroblasts depositing pathogenic extracellular matrix, a hallmark of fibrosis. Previous work had highlighted the role of innate immune signaling in kidney injury and MyD88 knockout mice were protected. Surprisingly, neither macrophage- nor epithelial cell-specific deletion of MyD88 contributed to this protective phenotype. Here we show that pericyte-specific ablation of MyD88 significantly attenuates tissue injury and fibrosis.

Further mechanistic studies show that in culture, pericytes respond to the TLR ligands and endogenous injured kidney DAMPs by secreting pro-inflammatory cytokines and chemokines in a TLR2/4-, MyD88- and IRAK4-dependent manner. Injury DAMPs are sufficient to prime and activate NLRP3 inflammasome leading to secretion of IL-1b. Additionally, pericytes respond to IL-1b in a MyD88- and IRAK4-dependent manner and provide an autocrine loop amplifying inflammation. Unexpectedly, TLR2/4, MyD88 and IRAK4 also control TGFb- or injury DAMPs-induced pericyte migration and myofibroblast differentiation. This mechanism is conserved, and human pericytes also activate inflammatory and fibrotic responses that require MYD88 and IRAK4.

Inhibition of IRAK4, a downstream kinase in TLR/MyD88 signaling, by a novel potent, highly selective small molecule BIIB-IRAK4i is highly protective in ischemia reperfusion injury and significantly reducing.

TH-PO683

Prediction of Death and Renal Replacement Therapy in Hospitalised Patients with Acute Kidney Injury Vishal Nangalia,[1] Alistair Connell,[1] Simon T. Brown,[1] Anne B. Dawnay,[2] Zudin Puthucheary,[1] David Barber,[1] Chris Laing,[1] Geraint Rees,[1] Hugh E. Montgomery.[1] *[1]UCL, London, United Kingdom; [2]UCLH NHS Trust, London, United Kingdom.*

Background: Acute kidney injury (AKI) is reported to be common and associated with poor outcomes including death and need for renal replacement therapy (D-RRT). In 2015, The English National Health Service (NHSE) mandated that all hospitals implement an Kidney Disease: Improving Global Outcomes (KDIGO)-based algorithm (NHSE-algorithm) to detect and stage (for severity/risk) AKI. In the largest AKI study ever, we characterised AKI prevalence and progression, explored weaknesses in the NHSE-algorithm, and determined whether machine learning (ML) methodologies might better determine risk.

Methods: Demographics, blood results, diagnoses, and procedure codes from 14 NHSE Hospital Trusts (2005-2015) were collated. Admissions were grouped by co-morbidities/ NHSE-algorithm-trigger-route, and D-RRT rates related to first (AKI_{first}) and maximum (AKI_{max}) AKI stage. A 'gradient-boosting-machine' ML model used data up to AKI_{first} to predict D-RRT using positive predictive value thresholds 1:2(ML50), 1:3(ML33) and 1:4(ML25).

Results: Of 1•9 million admissions, 170,596 (8•7%) developed AKI. Stage advanced from AKI_{first} in 23,226(13•6%). D-RRT affected 64,296 (3•3%, death 56,076 (2•8%) without AKI, but 21% of AKI cases, incidence rising with stage for both AKI_{max} (stage 1: 13•2%, 2: 27•3%, 3: 42•4%) and AKI_{first} (18•7%, 25•5%, 32•8% for AKI1-2 respectively). D-RRT rate also varied with the NHSE-algorithm-trigger-route by which an AKI stage was reached- from 12•7-16•6% in stage 1 and 3:38•6-45•9% (stage 3). Plotted against maximum Creatinine and ratio of Creatinine:Baseline Creatinine, D-RRT rates vary from 5-50% and 0•5-70% for AKI_{max} stages 1 and 3 respectively. The ML-model's AUROC was 85•3%, with ML50 (D-RRT=50%) and ML33 (D-RRT=33•3%) achieving sensitivities of 71•6 and 94•6% respectively.

Conclusions: AKI is prevalent and associated with increased morbidity and mortality. AKI stage poorly predicts individual risk, and machine learning models perform better.

Funding: Government Support - Non-U.S.

TH-PO684

Recognition and Management of Acute Kidney Injury in Children Around the World: The ISN 0by25 Global Snapshot Study Etienne Macedo,[1] Jorge Cerda,[2] Michael V. Rocco,[3] Ravindra L. Mehta.[1,4] *[1]Univ California San Diego; [2]Albany Medical College; [3]Wake Forest Univ; [4]On Behalf of the ISN 0by25 AKI investigators.*

Background: In low and middle-income countries, there is a lack of reliable data on the epidemiology of childhood acute kidney injury (AKI). The recently completed Global Snapshot, a study carried out by the International Society of Nephrology "*0 by 25*" AKI initiative, was an observational, cross-sectional analysis designed to evaluate AKI around the world.

Methods: A web based survey tool was used to prospectively obtain data from individual clinicians about pts who had AKI based on KDIGO criteria. Countries were defined by gross national income per capita (GNI): Low and lower middle income (LLMIC), upper middle income (UMIC) and high income (HIC). Need for dialysis, mortality, and renal recovery were assessed at 7 days after AKI diagnosis or at hospital discharge, whichever came first.

Results: 92 physicians from 41 countries collected data on 354 pediatric pts with AKI. The median (interquartile) age in years was 0.4 (0.03, 6.0) in HIC, 8 (2,16.5) in UMIC and 4 (0.3),13.5) in LLMIC. HIC children were much younger and developed post surgical AKI more commonly. Factors associated with AKI were dehydration (32.5%), hypotension (32%), infection (29%), and nephrotoxin exposure (20%). The percentage of pts dialyzed were 10.5% in HIC; 40.3% in UMIC; and 26.5% in LLMIC. Initiation of dialysis was much later in LLMIC than in other country categories. Dialysis was indicated but not used in 7 (9.2%) of LLMIC, 6 (14.0%) of UMIC and 2 (1.3%) of HIC patients ($P < 0.0001$). Overall mortality was lower in HIC countries (1.2%) compared to UMIC (12.5%) and LLMIC countries (19.6%) ($p < 0.0001$) . Community-acquired AKI-associated mortality was 7 times higher in LLMIC than HIC. Complete recovery from AKI at 7 days of observation was seen in 37%, partial recovery in 34% and none in 17%; status was unknown in 12%. AKI recovery was more often complete in LLMIC (44, 40.7%) than in HIC (63, 36.2%) or UMIC (21, 29.2%).

Conclusions: In resource-limited countries, pediatric AKI is associated with higher morbidity and mortality than in higher income countries, possibly related to late referral and limited resources.

Funding: Private Foundation Support

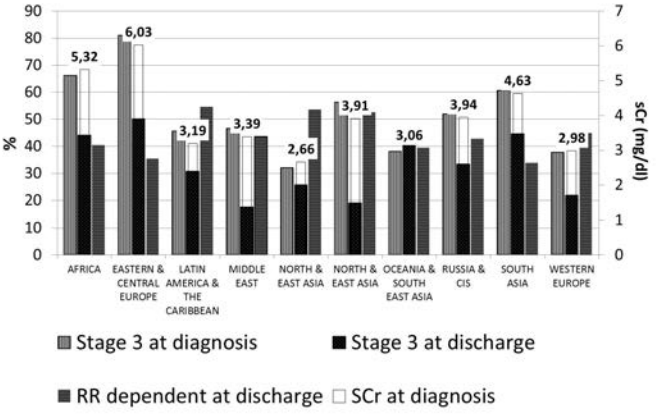
TH-PO685

International Society of Nephrology 0by25 AKI Global Snapshot: Regional Analysis of Adult Patients Etienne Macedo,[1] Michael V. Rocco,[2] Ravindra L. Mehta.[1,3] *[1]Univ California San Diego; [2]Wake Forest; [3]On Behalf of the ISN 0by25 Investigators.*

Background: The ISN 0by25 AKI Global Snapshot Project (GSP) was designed to determine the spectrum of AKI pts seen in health care facilities throughout the world.

Methods: A web based survey tool was used to obtain data from individual clinicians about pts with AKI based on KDIGO criteria. Countries were grouped into three categories based on gross national income per capita (GNI): High income with GNI > US$12476, low and lower middle income with GNI < US$4035, and upper middle income with GNI between levels 1 & 3.

Results: Of the 3664 adults AKI pts included in the analysis 305 (1091) were from North and East Asia, followed by Latin America and Caribbean (516, 14%) and Africa (507, 14%). Almost all centers from North and East Asia were located in cities with more than 1.5 million people and were from HIC and UMIC. African and Caribbean centers were more often located at smaller cities. While most pts in North and East Asia developed AKI in the hospital (689, 63%), about half the pts from Latin America and Caribbean (284, 55%) and the majority from Africa (430, 85%) developed AKI in the community. The creatinine level at both diagnosis and discharge, the severity of AKI at diagnosis and the need for renal replacement therapy varied by region.



In Eastern & Central Europe (68, 81%) and Africa (306, 66%), most pts were at AKI stage 3 at diagnosis, while in North & East Asia about half the pts (521, 51%) were at AKI stage 1 at diagnosis. The frequency of chronic kidney disease (CKD) was low, ranging from 1.6% in LLMIC countries of Latin American and the Caribbean to 10% in North America. The exception was Russia & Commenwealth Independent States, with 20% of pts with CKD.

Conclusions: There is wide variability in the incidence and severity of AKI by geographic region.

Funding: Private Foundation Support

TH-PO686

Characteristics and Outcomes of Adults Discharged Home from the Emergency Department with Acute Kidney Injury Rey R. Acedillo,[1,2] Ron Wald,[3,6] Eric McArthur,[4] Danielle Marie Nash,[4] Samuel A. Silver,[3] Matthew T. James,[5] Michael J. Schull,[6] Edward D. Siew,[7] Michael Edwin Matheny,[8] Andrew A. House,[1] Neil S. Klar,[2] Amit X. Garg.[1,2,4] *[1]Nephrology, London Health Sciences Centre, London, ON, Canada; [2]Epidemiology and Biostatistics, Western Univ, London, ON, Canada; [3]Nephology, St. Michael's Hospital, Toronto, ON, Canada; [4]Inst for Clinical Evaluative Sciences, London, ON, Canada; [5]Nephology, Foothills Hospital, Calgary, AB, Canada; [6]Inst for Clinical Evaluative Sciences, Toronto, ON, Canada; [7]Nephrology, Vanderbilt School of Medicine, Nashville, TN; [8]Veteran Affairs, Vanderbilt Univ Medical Center, Nashville, TN.*

Background: Adults discharged home from an emergency department (ED) with acute kidney injury (AKI) are not well described and may have poor outcomes.

Methods: We conducted a population-based retrospective cohort study in Ontario, Canada from 2003 to 2012 of 6,346 adults discharged from the ED with AKI. We used serum creatinine-based KDIGO criteria to define AKI. We assessed the 30-day risk of all-cause mortality and receipt of acute dialysis after ED discharge. To compare outcomes, we used propensity score methods to match 4,379 of these adults to 4,379 adults hospitalized with similar AKI stage (subpopulation 1). We assessed whether the association between

ED discharge versus hospitalization and mortality was modified by AKI stage. We also matched 6,188 of these adults to 6,188 adults discharged home from the ED without AKI (subpopulation 2).

Results: The mean age was 69 years, 4.6% had stage 2 AKI, and 0.7% had stage 3 AKI. Within 30 days of ED discharge, 2.3% (stage 2 AKI: 5.3%, stage 3 AKI: 15.9%) died, and 0.3% received acute dialysis. In subpopulation 1, an ED discharge versus hospitalization was associated with lower mortality (3.0% vs. 11.9%, RR: 0.25, 95% CI: 0.21-0.30). The difference in mortality was attenuated in adults with stage 3 AKI (15.9% vs. 15.9%, RR: 1.00, 95% CI: 0.38-2.64). In subpopulation 2, an ED discharge with AKI versus without AKI was associated with higher mortality (2.2% vs. 1.4%, RR: 1.56, 95% CI: 1.20-2.04).

Conclusions: Adults discharged from the ED with stage 2 and 3 AKI are at risk of poor 30-day outcomes. A better understanding of AKI care among this population is warranted.

TH-PO687

Acute Kidney Injury Related to Renal Colic: A Neglected Condition? Gabriela Ottati, Carolina Gelber, Andres Urrestarazu, Ricardo Silvariño, Alejandro Ferreiro, Oscar A. Noboa. *Centro de Nefrologia, Hospital de Clinicas, Facultad de Medicina, Univ de la Republica, Montevideo, Uruguay.*

Background: Kidney stone formation is highly prevalent with rates of up to 14.8%. Acute kidney injury during episodes of renal colic are frequently overlooked. The aim of this study is to determine the frequency of acute kidney injury (AKI) during acute episodes of renal colic (RC) of kidney stone etiology at the Emergency Department (ED) and its contributing factors.

Methods: This was a prospective, observational, single-center study. All patients assisted at the ED with a diagnosis of RC of renal stone etiology were prospective included. Clinical and analytical data were recorded. All patients were evaluated with abdominal echography at admission. AKI was defined according to AKIN criteria. Informed consent was collected and the Hospital Ethics Committee approved the study protocol. Exclusion criteria: patients with lumbar-abdominal pain of etiologies other than kidney stones. Cases with incomplete data at admission or evolution were also excluded.

Results: Data were obtained from 34 patients, 25 (73.5 %) male. Median age was 38.5 years (age range between 18-80). Previous history of RC was present in 21/34 (61.8 %). Hematuria in urinalysis was present in 19/34 (55.8 %). AKI was diagnosed in 11/34 (32.3 %) patients. In 10/11 (91 %) AKI was stage 1. Mean creatinine at recovery was 0.87 ± 0.28 mg% vs creatinine at diagnosis 1.18± 0.43 ($p<0.05$) The mean estimated glomerular filtration rate decrease was 42 ± 23, 44 ml/min, and 1 case was stage 3 AKI. The average time to complete glomerular filtration recovery was 15 days. Significant association was observed between the use of nonsteroidal antinflammatory (NSAIDs) drugs and development of AKI during the episode. AKI was associated to unilateral obstructive stones in 10/11 patients. None required renal replacement therapy.

Conclusions: AKI was frequent among those patients who consulted for RC in the ED (32.3%). NSAIDs consumption was significantly related with AKI development. Kidney stone obstruction was unilateral except for one patient that presented bilateral involvement.

TH-PO688

Long-Term Outcomes and Associated Risk Factors of Post-Hospitalization Dialysis-Dependent AKI (PHD-AKI) Ajay Singh Rathore,[1] Jennie Z. Ma,[2] Wenjun Xin,[2] Emaad M. Abdel-Rahman.[1] *[1]Nephrology, Univ of Virginia, Charlottesville, VA; [2]Public Health Sciences, Univ of Virginia, Charlottesville, VA.*

Background: CMS has reversed its clarification allowing AKI patients to be dialyzed at outpatient ESRD facilities starting 2017.Data assessing long-term outcomes and predictors of PHD-AKI are needed to adopt guidelines ensuring adequate management of these patients in the outpatient settings. We aimed to assess long-term outcomes and associated risk factors in patients with PHD-AKI.

Methods: Patients discharged from UVA between 4/13/2012 and 12/25/2013 with PHD-AKI, and who were alive 90 post hospital discharge (PHD) were prospectively followed for outcomes. The effects of baseline demographics and co-morbidities on the outcomes were assessed in a logistic regression.

Results: From 91 patients followed, 52 were declared ESRD (group 1) and 39 were dialysis-independent (group 2) at 90 days PHD. Outcome and follow up period is shown in table. At the end of the study 32/91 (35.2%) were dialysis-independent (3 from group 1 and 29 from group 2).Mortality was much higher in group 1 than group 2. After adjusting for demographics and co-morbidities, the odds ratio (OR) for mortality for both groups was 4.2 and 3.4 for being declared ESRD and requiring CRRT, respectively. Group 1 patients OR for mortality were 3.99 for CRRT and 3.55 for hypotension. Group 2 patients OR for composite outcome (ESRD and death) was 11.5 for GFR<45 ml/min. Other demographics or co-morbidities were not significant to predict long-term outcomes.

Outcome Status	Group 1 (n=52) N(%)	Group 1 (n=52) Follow up Time (Days)	Group 2 (n=39) N(%)	Group 2 (n=39) Follow up Time (Days)
ESRD	24 (46.1%)	1151.1 (538-1391)	7 (17.9%)	445 (35-900)
Recovered	3 (5.7%)	28.7 (13-53)	29 (74.4%)	1220 (916-1394)
Death	25 (48.1%)	431.7 (7-1219)	3 (7.7%)	402.7 (84-580)

Conclusions: Sustaining long-term dialysis-independence in patients with PHD-AKI is significant. Recovery, though minimal, is still possible in patients who remained dialysis dependent 90 days PHD. Baseline renal function and hemodynamic changes during hospitalization are predictors of long-term outcomes. Meticulous follow up of PHD-AKI patients in the outpatient dialysis facilities is crucial.

TH-PO689

Preoperative Echocardiography Predicts Acute Kidney Injury and Long-Term Mortality in Coronary Artery Bypass Grafting Seung Seok Han,[1] Seokwoo Park,[1] Dong Ki Kim,[1] Sejoong Kim,[1,2] Ho Jun Chin,[1,2] Ki Young Na.[1,2] *[1]Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea; [2]Internal Medicine, Seoul National Univ Bundang Hospital, Gyeonggi-do, Korea.*

Background: Acute kidney injury (AKI) is a common complication in patients undergoing coronary artery bypass grafting (CABG), which is associated with significant morbidity and mortality. This study identified echocardiographic predictors of AKI and determined whether these predictors were related to long-term mortality in CABG.

Methods: This retrospective cohort study included 1,300 patients who underwent echocardiography before CABG at two tertiary referral centers from 2004 to 2010. The best echocardiographic predictor of AKI was determined using multivariate and stepwise selection methods. Subsequently, patients were followed for 72 ± 28.8 months (maximum 11 years) for tracing all-cause mortality. Based on these information, we measured the adjusted odds ratio (OR) and hazard ratio (HR) for AKI and all-cause mortality, respectively, according to the chosen echocardiographic parameter.

Results: E/e' was the best predictor of AKI among echocardiographic parameters [figure 1]. The high E/e' group (>15) exhibited a higher OR for AKI [2.2 (1.51–3.27)] than the low E/e' group (<8). The high E/e' group required a longer hospital stay [16 days (12–23 days)] than the low E/e' group [14 days (11–17 days)]. There were 272 deaths (20.9%) during the following period. The high E/e' group exhibited a higher HR for mortality [1.9 (1.34–2.76)] than the low E/e' group, and this difference remained significant, regardless of the occurrence of AKI and the size of the ejection fraction volume.

Conclusions: E/e' in preoperative echocardiography is the best predictor of AKI and long-term mortality in patients undergoing CABG.

TH-PO690

Preoperative C-Reactive Protein Predicts Acute Kidney Injury and Long-Term Mortality after Coronary Artery Bypass Grafting Seung Seok Han,[1] Dong Ki Kim,[1] Sejoong Kim,[1,2] Ho Jun Chin,[1,2] Ki Young Na.[1,2] *[1]Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea; [2]Internal Medicine, Seoul National Univ Bundang Hospital, Gyeonggi-do, Korea.*

Background: Precise prediction of post-surgical acute kidney injury (AKI) is an important concern in patients with coronary artery bypass grafting (CABG) regarding high morbidity and mortality of AKI. The present study addressed whether preoperative C-reactive protein (CRP) is predictive of AKI and long-term mortality in CABG.

Methods: This retrospective cohort study included 1,700 patients whose high-sensitivity CRPs were measured before CABG at two tertiary referral centers from 2004 to 2010. The odds ratios (ORs) and hazard ratios (HRs) for AKI and all-cause mortality were estimated according to the tertiles of CRP levels after adjustment of multiple covariates. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated to determine whether the addition of CRP to risk model for AKI improves prediction.

Results: The prevalence of AKI was higher in the 3rd tertile group (42.4%) than in the 1st tertile group (25.7%). The corresponding OR of AKI and *P* values were 1.90 (1.44–2.52) and <0.001, respectively. Compared with the reference risk model, the addition of CRP improved the predictability with 0.107 of NRI (*P*=0.037) and 0.005 of IDI (*P*=0.007). During the median duration of 89 months (maximum 12 years), 491 deaths (28.9%) were observed. The 3rd tertile group exhibited a higher HR for mortality [1.64 (1.29–2.08)] than the 1st tertile group. This predictability for mortality remained consistent irrespective of the presence of sepsis or AKI.

Conclusions: Preoperative CRP may be needed to predict post-surgical AKI and mortality in patients undergoing CABG.

TH-PO691

Cardiovascular Mortality after Major Surgery in Elderly Negiin Pourafshar, Tezcan Ozrazgat-Baslanti, Anis Davoudi, Parisa Rashidi, Mark S. Segal, Azra Bihorac. *Univ of Florida, Gainesville, FL.*

Background: In the developed world, the increase in life expectancy with the resultant increase in the age of the population has led to a rise in multiple age-associated disorders. Among all the diseases in elderly, acute kidney injury (AKI) appears to have among the highest incidences and is a major risk factor for end stage renal disease (ESRD). The aim of this study is to determine the long-term cardiovascular-specific mortality in elderly patients with AKI or chronic kidney disease (CKD) after major surgery.

Methods: In a single-center cohort of 16,655 elderly (≥65 years-old) surgical patients undergoing major inpatient surgery, long-term cardiovascular-specific mortality was modeled using a multivariable subdistributional hazards model while treating any other cause of death as a competing risk. Preexisting CKD, ESRD and postoperative AKI were the main independent predictors and each model was adjusted for preoperative demographic and clinical variables.

Results: Prior to the admission, 3% and 12% of the cohort had preexisting ESRD and CKD not requiring renal replacement therapy, respectively. During hospitalization, 47% developed AKI. Among the 7768 deaths reported, the main causes of death were cardiovascular disease (32%) and cancer (31%). Adjusted cardiovascular mortality estimates for patients with no kidney disease, AKI without CKD, CKD without AKI, AKI with CKD, and ESRD at 10 years were 12.2%, 19.4%, 18.4%, 29.7%, and 45.8%, respectively. Adjusted hazard ratios (95% CIs) for cardiovascular mortality were significantly elevated among

patients with AKI without CKD (1.69 95% CI 1.52-1.87), CKD without AKI (1.59 95% CI 1.25-2.01), AKI with CKD (2.83 95% CI 2.47-3.24) and ESRD (5.21 95% CI 4.32-6.27), compared to patients with no kidney disease.

Conclusions: Perioperative AKI is common in elderly patients undergoing major surgery and is associated with a high risk for future cardiovascular-specific mortality. These findings emphasize the importance of preoperative and postoperative risk stratification for kidney disease and the application of strategies to prevent perioperative AKI.

TH-PO692

Development of Hypertension after Acute Kidney Injury in the Pediatric Intensive Care Unit

Erin Hessey, Ana Palijan, Michael Pizzi, Radu Alexandru Paun, Michael Zappitelli. *McGill U, QC, Canada.*

Background: Acute kidney injury (AKI) in the pediatric intensive care unit (PICU) is common and associated with poor hospital outcomes. Long-term renal effects of PICU-AKI, like microalbuminuria (MA) and hypertension (HTN), are not well understood. We will determine the prevalence of MA and HTN in children admitted to the PICU 5-10 years ago.

Methods: Design & population: Ongoing longitudinal follow-up study of children (<18 years old) admitted to the Montreal Children's Hospital PICU between 2005-2010. Patients in the neonatal ICU or with pre-PICU renal disease excluded. Study visit: Occur 5-10 years after PICU admission. We collect medical histories, anthropometric measures, 3 office BP measures, first morning urine for MA determination and 24-hour ambulatory BP monitoring (ABPM) for HTN determination. Exposure: KDIGO serum creatinine (SCr) AKI staging. Outcomes: MA defined by KDIGO (albumin/creatinine>30 mg/g). HTN defined by the 2014 American Heart Association guidelines (figure 1). Analysis: The prevalence of HTN and MA was calculated, ABPM HTN phenotypes were detailed. Univariate AKI *vs.* non-AKI comparisons were made using χ^2 tests.

Classification	Casual BP	Mean Ambulatory SBP and/or DBP (day, night, or 24hr)	SBP and/or DBP load (%) (day, night, or 24hr)
Normal BP	<90th %tile	<95th %tile	<25
White coat HTN	≥95th %tile	<95th %tile	<25
Prehypertension	≥90th %tile or >120/80mmHg	<95th %tile	≥25
Masked hypertension	<95th %tile	>95th %tile	≥25
Ambulatory HTN	>95th %tile	>95th %tile	≥25-50
Severe ambulatory HTN	>95th %tile	>95th %tile	>50
Other:			
Non-BP dipping	([mean daytime BP] – [mean nighttime BP])/mean daytime BP x 100 <10%		

Figure 1: American Heart Association staging of Ambulatory BP in children. The casual BP, mean ambulatory BP, and BP load must meet the criteria to be classified as hypertensive.
Casual BP values based on National High BP Education Program Task Force normative data.
ABP and BP load values based on the American Heart Associations normative data.
%tile = percentile; *BP* = blood pressure; *SBP* = systolic blood pressure; *DBP* = diastolic blood pressure; *HTN* = hypertension; *Load* = percentage of readings over the 95th percentile

Results: Study visits have been performed on 101 patients (male 51%, mean age±SD=11.0±4.8 years), 32/75 (42.7%) had past PICU-AKI (n=26 no SCr in PICU). 93 patients attempted the 24-hour ABPM, and 89 (96%) were successful. Of these, 11 (12.4%) had HTN (10 masked HTN, 1 ambulatory HTN), 4 (4.5%) had prehypertension, 1 (1.1%) had white coat HTN, and 34/68 (50%) had non-BP dipping. 5/29 (17%) of AKI patients had HTN *vs*. 5/38 (15%) non-AKI patients (p=0.6). MA was present in 9/100 (9%) patients with urine samples analyzed (AKI: 3.1% vs. no AKI: 11.6%, p=0.2).

Conclusions: HTN and non-BP dipping prevalence are high in children with past PICU admission. Future work must elucidate the risk factors for HTN to provide an evidence base for post-PICU follow-up guidelines.

TH-PO693

Acute Kidney Injury Is Associated with Long-Term Renal Outcomes Using Administrative Data in Children

Erin Hessey,[1] Sylvie Perreault,[2] Louise Roy,[2] Rami Ali,[1] Marc Dorais,[3] Philippe Jouvet,[2] Jacques R. Lacroix,[2] Genevieve Morissette,[2] Veronique Phan,[2] Nikki J. Rink,[1] Michael Zappitelli.[1] *[1]McGill U; [2]U de Montreal; [3]StatScience Inc., QC, Canada.*

Background: Acute kidney injury (AKI) may be a risk factor for long-term chronic kidney disease (CKD) or hypertension (HTN). Provincial administrative health data (PAHD), using International Classification of Disease codes (ICD-9/ICD-10), is a rich resource to study long-term AKI outcomes in adults, but has been poorly explored in child AKI research. We will develop a child CKD and HTN definition using PAHD and evaluate association between intensive care unit (ICU) AKI and 5-year post-discharge CKD and HTN.

Methods: Chart data from a retrospective ICU cohort (2 Montreal pediatric ICUs, 2003-2005 [n=2499]; no health care number, ICU deaths, pre-existing CKD excluded) was merged with Quebec 5-year post-ICU PAHD. Several CKD and HTN PAHD algorithms were developed (literature review, expert opinion), tested, and discussed, followed by final algorithm selection (figure 1). Exposure: KDIGO serum creatinine AKI. Outcomes: 5-year post-ICU CKD, HTN, per PAHD. Analysis: univariate AKI *vs.* non-AKI comparisons (χ^2 tests).

Results: Cohort: n=2404, 56% male, mean ± SD age=6.0 ± 5.7 years, PRISM (mortality) score=10.1 ± 7.5, 467/1934 (24.2%) ICU-AKI. 3 HTN and 17 CKD algorithms were evaluated (high sensitivity vs. specificity). The selected CKD algorithm combines the high specificity diagnostic and procedural codes, medications, and nephrology visits (figure 1). The HTN algorithm combines outpatient diagnostic codes and medications (figure 1). We found that 8.6% developed CKD (AKI: 17.6%, non-AKI: 6%, p<0.0001); 9.7% developed HTN 5 years post-ICU (AKI: 21.2%, non-AKI: 7.5%, p<0.0001).

Conclusions: Pediatric ICU-AKI is associated with 5-year post-ICU PAHD-defined CKD and HTN. Research should evaluate validity of child PAHD-defined CKD and HTN.

Figure 1: Proposed CKD definition: one or more diagnostic codes, **OR** CKD medication prescription, **OR** fulfill nephrology visit criteria.
Proposed hypertension algorithm: one or more outpatient hypertension diagnostic codes **OR** prescription for anti-hypertensive medication.

CKD ALGORITHM

Inpatient or outpatient diagnostic (ICD9 or ICD10)/procedural codes (CCP or CCI)			Medications	Nephrology visits
Description	**ICD-9**	**ICD-10**	• Erythropoietin • Activated Vitamin D • Potassium-removing agents • Phosphate binding agents	Two or more outpatient nephrology visits in a 16 month time period.
CKD	585	N18.x		
Unspecified renal failure	586	N19		
Proteinuria	791.0	R80		
Kidney transplant	V42.0, 996.8, 590.8	Z94.0, T86.100, T86.101, N16.5		
Description	**CCP**	**CCI**		
Dialysis related	5127, 5142, 5129, 660	1KY76LA, 1KY80LA, 1KG76MZXXA, 1KG76MZXXN, 1SY55LAFT		
Transplant related	6751, 6759, 6483	1PC83LA, 1PC85LAXXU, 1PC85LAXXX, 1OK85TNXXX, 1OK85XTXXX, 1OK85XUXXX, 1OK85XVXXX		
Outpatient diagnostic (ICD-9 or ICD-10)/procedural codes (CCP or CCI) only				
Description	**ICD-9**	**ICD-10**		
Dialysis related	V45.1, V53.9, V56.0, V56.8, 996.1, E87.02, E87.12, E87.22, E87.91	Z99.2, Z49.0, Z49.1, Z49.2, T82.4, V60.2, Y61.2, Y62.2, Y84.1		
Description	**CCP**	**CCI**		
Dialysis related	6698, 5195, 0789, 6693	1PZ21HPD4, 1PZ21HQBR, 7SC59QD, 1OT53DATS, 1OT53HATS, 1OT53LATS		

HYPERTENSION ALGORITHM

Outpatient diagnostic codes (ICD-9 or ICD-10)			Medications	Nephrology visits
Description	**ICD-9**	**ICD-10**	Diuretics • Loop Diuretics • Thiazide Diuretics • Thiazide-like Diuretics • Miscellaneous Diuretics Beta-Blockers Calcium Channel Blockers Angiotensin-Converting Enzyme (ACE) Inhibitors Angiotensin II Receptor Blockers (ARBs) Alpha-Adrenergic Blockers Renin Inhibitors	N/A
Primary Hypertension	401.x	I10.x		
Hypertensive heart disease	402.9	I11		
Hypertensive nephropathy	403.9	I12		
Hypertensive cardionephropathy	404.9	I13		
Secondary Hypertension	405.x	I15.x		

ICD = International Classification of Diseases; *CCP* = Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; *CCI* = Canadian Classification of Health Interventions; *CKD* = Chronic Kidney Disease

TH-PO694

Evaluation of Height-Dependent and Height-Independent Methods of Estimating Baseline Serum Creatinine in Critically Ill Children

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Background: Baseline serum creatinine (bSCr) is required for diagnosing acute kidney injury (AKI). In children, measured bSCr is often missing. The alternative, estimating bSCr with height-based glomerular filtration rate (GFR) equations, is not always feasible. We will evaluate the accuracy of back-calculating bSCr (estimated bSCr) from height-dependent and height-independent GFR equations.

Methods: Retrospective intensive care unit (ICU) cohort (two Montreal pediatric ICUs, 2003-2005[n=2499]; excluded: no health care number, baseline renal disease). Patients with a measured bSCr, height, and ICU SCr (n=538) included. Height-dependent GFR: CKiD equation and age-based GFR norms. Height-independent method: Hoste et al equation and age-based GFR norms. Analysed bias, accuracy, and precision of estimated bSCr methods relative to measured bSCr. Calculated agreement of AKI ascertainment using measured and estimated bSCr. Performed multivariate analyses to assess the impact of estimated bSCr on AKI-outcome associations.

Results: Figure 1 shows results. Both methods slightly underestimated bSCr, had good accuracy (~30% of estimated bSCr ± 10% measured bSCr), but poor precision (wide 95% limits of agreement). Agreement of AKI defined by estimated *vs.* measured bSCr was >80% (κ>0.5). AKI was associated with longer ICU stay and mechanical ventilation, but not ICU mortality (after adjustment), by measured and estimated bSCr methods.

Figure 1: Performance of estimated bSCr methods compared to measured bSCr (n=538).

	Measured bSCr	Height-dependent	Height-independent
Mean bias, SD (95% CI) [µmol/l]	Ref	-3.4 ± 13.5 (-4.5 – -2.2)	-2.5 ± 13.5 (-3.6 – -1.4)
Mean percent bias, SD (95% CI) [%]	Ref	2.0 ± 38.0 (-1.3 – 5.2)	3.2 ± 39.5 (-0.2 – 6.5)
95% limits of agreement of percent bias [%]	Ref	-72.5 to 76.5	-74.2 to 80.6
% within ± 30% of measured bSCr	Ref	73%	72%
% within ± 10% of measured bSCr	Ref	30%	29%
Agreement - AKI (Yes/No)	Ref	82%	81%
Kappa statistic - AKI classification	Ref	0.53	0.52
Length of stay (by AKI yes/no), adjusted HR (95% CI)	0.6 (0.4-0.7)*	0.7 (0.5-0.9)*	0.7 (0.6-0.9)*
Days of mechanical ventilation (by AKI yes/no), adjusted HR (95% CI)	0.6 (0.4-0.8)*	0.6 (0.5-0.8)*	0.6 (0.5-0.8)*
Mortality (by AKI yes/no), adjusted OR (95% CI)	3.5 (1.2-9.8)*	2.2 (0.8-6.3)	1.8 (0.6-5.3)

*P<0.05

SD = standard deviation; *CI* = confidence interval; *AKI* = acute kidney injury; *HR* = hazard ratio; *OR* = odds ratio; *bSCr* = baseline serum creatinine

Conclusions: The height-dependent and height-independent formulas perform similarly for bSCr estimation. When bSCr and height are missing, AKI can be defined using bSCr estimated by a height-independent method.

TH-PO695

Neonatal Acute Kidney Injury: A Survey of Neonatologists and Nephrologists' Perceptions to Diagnosis and Follow-Up Jennifer R. Charlton,[1] Cherry Mammen,[2] Ronnie Guillet,[3] Katja M. Gist,[9] Mina Hanna,[4] Ahmad I. El Samra,[5] David T. Selewski,[7] David J. Askenazi,[8] Alison Kent.[6] *[1]Univ of Virginia; [2]Univ of British Columbia and BC Children's Hospital; [3]Univ of Rochester; [4]Univ of Kentucky; [5]Franciscan St. Elizabeth Health; [6]Canberra and Australian National Univ; [7]Univ of Michigan; [8]Univ of Alabama at Birmingham; [9]Children's Hospital Colorado.*

Background: Neonatal acute kidney injury (nAKI) is associated with increased morbidity and mortality. However, it is unclear if neonatologists and nephrologists diagnose, treat and follow up nAKI in similar ways. The aim of this study was to assess the knowledge and management of nAKI by surveying neonatologists and pediatric nephrologists.

Methods: An electronic survey containing both general questions and case-based scenarios was developed and distributed to neonatologists and pediatric nephrologists in Australia, New Zealand, Canada, USA and India on behalf of the Neonatal Kidney Collaborative (NKC).

Results: Of the 375 completed surveys 244 were returned by neonatologists (65%) and 131 by nephrologists (35%). The majority of neonatologists (60%) were unaware of the categorical definitions of nAKI. Nephrologist were more likely to recognize stage 1 AKI (80%, Neo: 60%). In the case-based scenarios, nephrologists were more likely to believe that neonates with stage 1 and 2 AKI were at risk of later chronic kidney disease (CKD). The majority of respondents (neonatologists: 92%; nephrologists: 86%) reported renal assessments were not included in their program's growth and development follow-up.

Conclusions: Pediatric nephrologists who participated in this case-based survey were more likely than neonatologists to recognize nAKI and consider it risk for the development of CKD. There is minimal renal follow-up of neonates at risk of CKD, an area for quality improvement projects.

TH-PO696

Pediatric Acute Kidney Injury after Cardiac Surgery - Incidence and Outcomes Garima Aggarwal. *Nephrology, Amrita Inst of Medical Sciences, Kochi, Kerala, India.*

Background: The aim of this study is to know the incidence of Acute Kidney Injury (AKI) in the immediate postoperative period following pediatric cardiac surgeries.To study the effect of AKI on adverse outcomes –death, mechanical ventilation and length of hospital stay, length of stay in pediatric Intensive Care Unit (PICU) and to identify the perioperative risk factors associated with AKI.

Methods: Children undergoing heart surgery in a tertiary hospital in Kerala were studied. After receiving institutional research ethics board approval, 180 consecutive children, age<18 years who underwent any type of cardiac surgery and admitted to the PICU were prospectively studied till length of hospital stay. Patients with diagnosed underlying kidney disease were excluded. Preoperative, intraoperative and postoperative possible risk factors for AKI and their relationship with adverse patient outcomes were assessed. To test the statistical significance of the association of AKI versus non AKI with different categorical variables chi squared test was applied and 21 variables were identified. Multivariate stepwise backward conditional logistic regression analysis was applied to identify significantly contributing variables with respect to presence or absence of post operative AKI.

Results: The prevalence of Acute Kidney Injury (AKI) was 32.8% in our study population. Fifty nine (developed AKI according to the pRIFLE criteria, with 12 (20.3 %), two (3.4 %), and forty five (76.3%) patients classified in the R, I, and F groups, respectively. Neonatal age group, weight ≤ 5 kg, pre operative AKI, intra operative mean arterial pressure on Cardio Pulmonary Bypass (CPB) ≤40mmHg, use of albumin during CPB, inotrope requirement for more than 48hours in the post operative period and post operative albumin use were all associated with high incidence of AKI on multivariate analysis (p=<0.05). Patients with AKI had longer duration of mechanical ventilation and longer duration of hospital stay (p=<0.05).

Conclusions: AKI is common in the postoperative period in children following cardiac surgery and is associated with adverse clinical outcomes.

TH-PO697

AKI Outcomes in Young Adults Emily Lauren Joyce,[1] Dana Y. Fuhrman,[1,2] Priyanka Priyanka,[2] John A. Kellum.[2] *[1]Dept of Pediatrics, Div of Nephrology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA; [2]Critical Care Medicine, CRISMA Center, Univ of Pittsburgh School of Medicine, UPMC, Pittsburgh, PA.*

Background: Acute kidney injury (AKI) is associated with adverse outcomes including increased healthcare costs, morbidity and mortality. Outcomes of AKI in critically ill young adults have not been well described, and this is a unique population given that mortality is less confounded by chronic disease. The goal of this project was to assess outcomes in critically ill young adults who developed AKI.

Methods: Data was obtained from the HiDenIC database which contains > 45,000 critically ill patient records from UPMC. The cohort was divided into four age strata: young adults ages 16-25 and ages 26-35, 36-45, and 46-55. Descriptive outcomes are provided and multivariable logistic regression was used to analyze mortality.

Results: A total of 8270 critically ill adults developed AKI across all age groups, with 862 young adults. The incidence of AKI in young adults was 39.8%, and is associated with poor outcomes including prolonged hospital and ICU length of stay, and 10.4% one-year mortality. One third of the mortality occurred after hospital discharge. See table 1 for outcomes of patients with AKI stratified by age. AKI, APACHE 3 score, multiple comorbidities and vasopressor use are strong predictors of ICU, hospital, 90-day and 1-year mortality in young adults.

Outcome	Age 16-25	Age 26-35	Age 36-45	Age 46-55
Need for RRT, N (%)	46 (5.3)	77 (7)	172 (7.9)	345 (8.4)
No recovery from RRT at 90 days, N (%)	22 (47.8)	37 (48.1)	92 (53.5)	229 (66.4)
ICU length of stay (days), Mean (SD)	9.6 (10.7)	10.3 (15.1)	8.7 (11.6)	8.8 (66.4)
Hospital length of stay (days), Mean (SD)	20.1 (22.2)	21.7 (25.4)	19.5 (24.1)	19.5 (24.2)
ICU Mortality, N (%)	51 (5.9)	80 (7.3)	245 (11.2)	486 (11.8)
Hospital Mortality, N (%)	64 (7.4)	107 (9.7)	319 (14.6)	674 (16.4)
Mortality at 90 days, N (%)	67 (7.8)	123 (11.2)	390 (17.8)	860 (20.9)
Mortality at 1 year, N (%)	90 (10.4)	180 (16.4)	498 (22.8)	1145 (27.8)

Conclusions: Critically ill young adults have a high incidence of AKI with significant associated mortality.

Funding: NIDDK Support

TH-PO698

The Prognostic Importance of Duration of Acute Kidney Injury with Mortality: A Systematic Review and Meta-Analysis Swati Mehta,[1] Achint Patel,[1] Kinsuk Chauhan,[1] Shanti N. Patel,[3] Rachel Pinotti,[1] Girish N. Nadkarni,[1] Chirag R. Parikh,[2] Steven G. Coca.[1] *[1]Nephrology, Icahn school of medicine at Mount Sinai, NYC, NY; [2]Nephrology, Yale Univ school of medicine, New Haven, CT; [3]Internal Medicine, Maimonides Medical Center, Brooklyn, NY.*

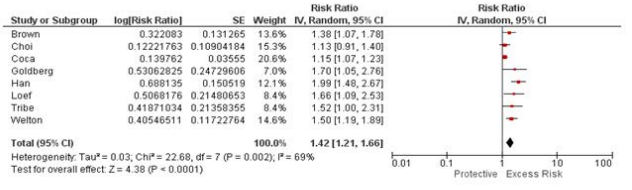
Background: Staging of AKI is based on the magnitude of peak rise in serum creatinine and does not explicitly consider the duration of AKI. We sought to determine the independent association of duration of AKI with long-Term mortality.

Methods: We performed a systematic review and meta-analysis of studies that examined the relationship between duration of AKI and long-term mortality. Medline, Embase, Cochrane library, web of science and CINAHL were searched through December 2015. Duration of AKI was categorized as "short" for AKI ≤ 2 days, medium" for durations 3-6 days, and "long" for ≥ 7 days or "non-recovered." Pooled adjusted risk ratios for duration of AKI were estimated with inverse variance method using RevMan5.3.

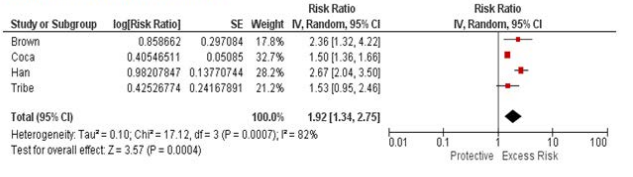
Results: Of 6209 initially identified studies, 8 were included for full review. These 8 studies were comprised of 65,080 patients with a median follow-up time of 6.4 years. The overall incidence of AKI was 21.2%, with 58% short, 18.4% medium, and 21.7% long duration. The pooled RRs demonstrated a dose response relationship with highest risk for long-duration AKI. There was considerable heterogeneity across pooled studies.

Forest plots for risk of long term mortality by duration of AKI

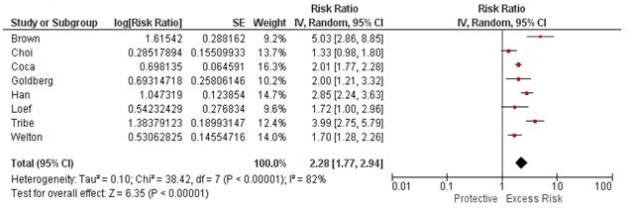
A. Short duration vs no AKI



B. Medium duration vs no AKI



C. Long duration vs no AKI



Conclusions: Duration of AKI was independently associated with long-term mortality in a graded manner. Duration of AKI should be incorporated into risk-models for long-term mortality post-AKI and possibly in staging systems for AKI.

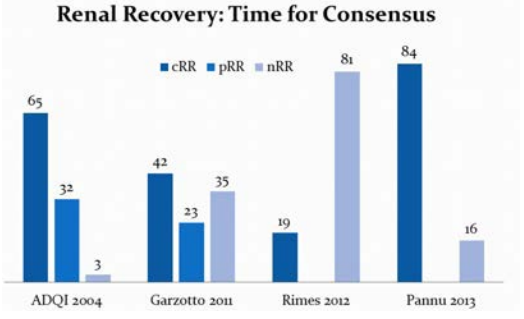
TH-PO699

Renal Recovery: Time for Consensus Maria Isabel Acosta-Ochoa, Alicia Mendiluce. *Nephrology, Hospital Clínico Univ, Valladolid, Spain.*

Background: AKI is a global public health problem, which increases mortality and bears long term consequences. We can find several definitions of renal recovery (complete cRR), partial RR (pRR) and no RR (nRR). Our aim was to compare some currently used criteria by means of rates of RR, and to describe the differences between them.

Methods: Retrospective study of hospitalized patients with diagnosis of AKI, we excluded patients who died during the index hospitalization. We tested four RR criteria: **ADQI 2004:** cRR discharge SCr <1.5x baCr, pRR >1.5x and nRR HD persistence; **Garzotto, et al. 2011** (cRR discharge SCr <1.2x baCr, pRR 1.21-1.49x and nRR >1.5x or HD persistence; **Rimes et al. 2012** (cRR return to baEGFR, nRR any alteration of EGFR; **Pannu et al. 2013** nRR, doubling baCr, and plotted the results.

Results: 342 patients were included, mean age 71.7±14, 64% males, 40% diabetes, 85% hypertension, and 53% CKD, mean Charlson Index 4±2.4, KDIGO Stage 1 (29%), 2 (13%), 3 (58%), need for HD 13%, persistence in HD 3%. We found rates of RR: **ADQI** cRR 65%, pRR 32%, nRR 3% (persistence in HD); **Garzotto:** cRR 42%, pRR23%, nRR 32% + 3% HD persistence; **Rimes:** cRR 19%, nRR 81%; **Pannu**: nRR 13%. Comparison of RR rates in figure 1.



Conclusions: We found a wide variability in renal recovery rates depending on the used author's criteria. Renal recovery after AKI lacks of standard definition and absence of unified criteria (complete, partial, and no recovery, Cr based, eEGFR based, HD dependence or not, and including vs. excluding in-hospital mortality). A consensus definition would contribute to the unification of study designs, results interpretation, refining the quest for risk and protective factors, and as public health tool in order for planning nephrology consultation needs and hemodialysis resources.

TH-PO700

Acute Kidney Injury Followed by Complete Recovery Is Associated with Higher Infection Risk Anna Jeanette Jovanovich,[1,2] Zhiying You,[2] Kyle Hiroyasu,[3] Benjamin Griffin,[2] John R. Holmen,[3] Sarah Faubel,[1,2] Michel Chonchol.[2] *[1]Denver VA Medical Center; [2]Univ of Colorado Denver; [3]Intermountain Healthcare.*

Background: Acute kidney injury (AKI) affects myriad organ systems including the immune system. Immune cells are altered in animal and human AKI. Sepsis may develop after AKI among hospitalized patients, and those with AKI requiring dialysis have a higher risk of sepsis after discharge compared to controls. We aim to determine the risk of infection in the year following a non-infectious hospital admission complicated by AKI with complete recovery in a well-matched cohort of cases and controls.

Methods: We identified 886 AKI cases (AKI Network definition) with complete kidney function recovery at the time of discharge, defined as serum creatinine <1.10 times the pre-admit baseline value, during a non-infectious hospital admission between January 1, 1999 and December 31, 2009 from an integrated health care delivery system. We matched 886 controls (no AKI during index admission) based on a propensity score including: age, sex, race, prior inpatient visits, coronary artery disease, congestive heart failure, chronic pulmonary disease, hypertension, diabetes, and admission day. The primary outcome was incident infection, defined by ICD-9 codes, during the 12 months following discharge.

Results: Baseline characteristics among the cases and controls were similar: age 62±16 years, 45% female, 94% white, serum creatinine 0.9±2 mg/dL. During the 12 months after discharge, 342 cases and controls developed infection. Post-discharge infection was more common among cases compared to controls. In the periods between 30, 60, 90, and 365 days after discharge, infection developed in 90, 53, 44, and 133 cases compared to 29, 27, 21 and 65 controls, respectively. These events correspond to greater than 2-fold higher odds of infection among cases compared to matched controls (odds ratio 2.6 [95% CI, 2.0 – 3.3]; p <0.0001).

Conclusions: Among patients from an integrated health care delivery system, non-infectious AKI followed by complete recovery was associated with an increased risk of infection in the year after discharge. These data support long-term immune dysfunction after AKI.

Funding: VA Support

TH-PO701

Risk Factors for Hospital Readmission and New-Onset CKD and Prevalence of Nephrology Follow-Up Care following AKI Grace M. Choong,[1] Mark D. Faber,[2] Denise White Perkins,[2,3] Lois Lamerato.[3] *[1]Wayne State Univ School of Medicine, Detroit, MI; [2]Henry Ford Hospital, Detroit, MI; [3]Henry Ford Health System, Detroit, MI.*

Background: Many studies report the incidence and hospital-associated mortality of acute kidney injury (AKI) but less is known about follow-up care and longer term outcomes in this population. PURPOSE: to identify risk factors for hospital readmission and new-onset CKD, and to characterize follow up care, in hospitalized patients with AKI.

Methods: Retrospective, univariate analysis of individuals with AKI as defined by ICD-9 codes, hospitalized at 1 of 4 HFHS hospitals in 2012-2014. To enhance completeness of follow-up only patients enrolled in Health Alliance Plan of Michigan (HAP) for 6 months before and after AKI were followed. HAP is a managed care plan and subsidiary of HFHS. Individuals were 18-90 years old and excluded if they died during the index event. Subjects were followed for subsequent admissions and other aspects of care for 6 months after discharge.

Results: The study population (n=4002) had a mean age of 72.6, was predominantly male (52.5%) and non-African American (NAA) (57%). 17.7% of patients were readmitted within 30 days. Age, gender and race did not predict readmission. Readmission risk was increased by concurrent diabetes (DM), congestive heart failure (CHF), cancer, liver disease or preexisting CKD, whereas sepsis, COPD and peripheral vascular disease did not. 32.8% of individuals had CKD prior to the AKI event, while 20.6% developed CKD after the AKI. Being AA or <65 years old predicted new-onset CKD, as did having DM or CHF. Diagnoses of sepsis or hypertension were associated with a decreased risk of CKD. Despite having had AKI, only 10.6% of patients saw a nephrologist within 6 months of discharge.

Conclusions: Substantial opportunity exists to improve post discharge care of patients following hospitalization with AKI. Better understanding of risk profiles for readmission may help reduce the high and costly readmission rate. More importantly, deficient nephrology care following AKI discharge may place patients at risk for poor outcomes by denying patients the benefits of comprehensive multidisciplinary nephrology outpatient care.

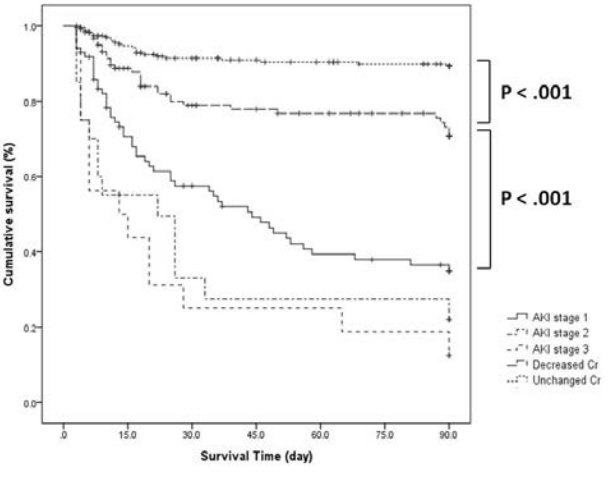
TH-PO702

Decrease in Serum Creatinine after ICU Admission Is Associated with Increased Mortality Hye Ran Kang, Sinae Lee, Jin Seok Jeon, Hyunjin Noh, Dong-Cheol Han, Soon Hyo Kwon. *Div of Nephrology, Soonchunhyang Univ Hospital, Seoul, Republic of Korea.*

Background: The elevation of serum creatinine (SCr), acute kidney injury (AKI), is associated with an increase of mortality in critically ill patients. However, it is uncertain whether decrease of SCr in intensive care unit (ICU) has an effect on outcome.

Methods: In a retrospective study, we enrolled 486 patients who admitted to an urban tertiary ICU from Jan 2014 to Dec 2014. The effect of change in SCr after ICU admission on 90 days mortality was analyzed. Patients were classified into 3 groups based on change in SCr after ICU admission: unchanged Cr group (ΔCr < 0.3mg/dL within the prior 7 days), decreased Cr group (ΔCrea ≤ -0.3 mg/dL within the prior 7 days) and increased Cr group meeting the KDIGO AKI definition.

Results: SCr decreased in 123 (25.3%) patients after ICU admission. AKI developed in 125 (24.4%) patients. The overall 90-day mortality rate was 29.0%. In a Kaplan-Meyer analysis, the mortality in the AKI group was higher than that of other groups (p<0.001). Patients with decrement in SCr showed the higher mortality rate compared to those with unchanged SCr (p<0.001).



The Cox analysis showed that decrease (HR; 3.56, 95% CI; 1.59-7.97, p=0.002) and increase in SCr were independent risk factors for death (AKI stage 1, HR; 9.35, 95% CI; 4.18-20.9, p<0.001: AKI stage 2, HR; 11.82, 95% CI; 3.85-36.28, p<0.001: AKI stage 3, HR; 17.41, CI; 5.50-55.04, p<0.001, respectively) comparing unchanged SCr group.

Conclusions: Not only increment in SCr, but also decrement in SCr was associated with mortality in critically ill patients.

TH-PO703

Evaluation of Absolute Serum Creatinine Changes in Characterizing Stages for Cirrhosis-AKI and Its Association with Long-Term Outcomes
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Background: Acute kidney injury (AKI) in cirrhotic patients is associated with worse outcomes. To date, there is no uniformity as to the classification for cirrhosis-AKI. We aimed to evaluate absolute serum creatinine (sCr) changes ('Delta-sCr') for characterizing stages of AKI, and its impacts onlong-term outcomes in cirrhotic patients, compared with the KDIGO criteria.

Methods: We conducted a retrospective analysis of 333 hospitalized cirrhotic patients from January 2013 through December 2014. We defined AKI stages using: 1) KDIGO criteria, and 2) the Delta-sCr, defined by the difference between the baseline and the peak sCr value during hospitalization.The Delta-sCr cut-points were defined as follows: Stage 0, sCr increase <0.3 mg/dl, Stage I, 0.3–0.7mg/dl, Stage II, 0.7–1.2 mg/dl and Stage III, ≥1.2 mg/dl. The end point was the hazard of death or readmission in one year.

Results: The 1-year mortality in cirrhotic patients with AKI was 36.67%. Multivariate analysis and Cox hazard analysis both showed that Delta-sCr was significantly associated with readmission(OR=1.008; p=0.006) and 1-year mortality (HR=1.009; p=0.000) . ROC analysis demonstrated that the Delta-sCr staging for AKI was more accurate than KDIGO staging in predicting 1-year mortality (AUC=0.825 vs 0.803; p=0.23). Though it did not achieve statistical significance, the values of specificity and positive likely radio were both higher when classifying AKI stage III. And the Delta-sCr staging also modestly improved reclassification (C-index increased from 0.6699 to 0.6803; NRI= 22.9%, p=0.04).

Conclusions: The Delta-sCr is associated with the 1-year readmission and mortality. And the Delta-sCr staging may optimize the discrimination of risk prediction, especially when classifying AKI stage III.

Funding: Government Support - Non-U.S.

TH-PO704

Acute Kidney Injury and Its Prognosis in Patients with Decompensated Cirrhosis
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Background: Acute kidney injury (AKI) occurs frequently in patients with cirrhosis. However, studies are limited on the impact of AKI on the mortality of patients with decompensated cirrhosis.

Methods: The present prospective observational study included subjects ≥ 18 years of age with cirrhosis and AKI. Patients were recruited from January 2015 to December 2015 and were followed for 90 days. Cases with Chronic kidney disease, on renal replacement therapy at the time of admission, pregnant and lactating mothers, liver transplant candidates and those with diabetes mellitus were excluded. Outcome was mortality at end of the study. Acute kidney injury network criteria were used to diagnose AKI. Hepato-renal syndrome (HRS) was diagnosed based on the 2007 Ascites Club Criteria. MELD score was used to predict severity of cirrhosis.

Results: Total 207 patients were admitted with cirrhosis and 56 patients (27%) had AKI. Mean age (yrs) was 52.12± 8.31. Mean serum creatinine(mg/dl) at admission and 48 hrs after admission was 1.84 ± 0.96 and 3.67 ± 1.29. Mean MELD score was 30.60 ± 6.47. Of the 56, patients with pre-renal azotomia(PRA) were 25 (44.64%), 15(26.78%) had acute tubular necrosis (ATN), patients with HRS were 13(23.21%) and 3 patients had other etio logies(Membranoproliferative glomerulonephritis, IgA nephropathy and acute interstitial nephritis). Fifteen patients (26.78%) died at the end of follow up. On univariate analysis, MELD score (p-0.0001), serum sodium (p-0.014), AKIN stage (0.002), serum creatinine at admission and after 48 hrs of admission (p-0.0001 and 0.0001), urine output(p-0.0001), dialysis requirement(0.007), systolic blood pressure (p-0.016) were associated with mortality. Patients with HRS had significantly high mortality when compared with PRA and ATN (p-0.004). However on multivariate analysis, only MELD score (OR- 1.308, 95% CI- 1.031-1.660) and serum sodium (OR-11.89, 95% CI-0.94-149.71) were independent predictors of mortality.

Conclusions: PRA is the most common form of AKI in patients with decompensated cirrhosis. Patients with HRS had significantly high mortality when compared with ATN and PRA. MELD score and serum sodium were independent predictors of mortality.

TH-PO705

The Study of Risk Factors for Acute Kidney Injury in 424 Patients with Decompensated Cirrhosis
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Background: Acute kidney Injury(AKI) is a common complication with significant morbidity and mortality in decompensated cirrhotic patients. The aims of this study are to investigate and analyze the risk factors for AKI in these patients.

Methods: Relevant clinical data of 424 patients with decompensated cirrhosis was collected from Ningbo No.2 Hospital between January 2012 and December 2014, patients were divided into AKI group and non-AKI group according to the KDIGO criteria. Risk factors for AKI were analyzed by univariate and multivariate analysis methods.

Results: The incidence of AKI in decompensated cirrhosis is 17.7%, There were 47 men and 28 women, with a mean age of 63.04±10.21 years. The mean course of cirrhosis is 6.75±5.83 years and the average days of hospitalization were 19.20±13.90 days. The multivariate Logistic analysis showed the development of AKI in decompensated cirrhosis was correlated with increasing age(OR=1.068, P=0.003), infection(OR=8.119, P<0.001), decreasing eGFR(OR=0.919, P<0.001), ascites(OR=5.389, P<0.001),use of ACEI/ ARB(OR=7.675, P =0.028).

Conclusions: The incidence of AKI in patients with decompensated cirrhosis is high, increasing age, infection, decreasing eGFR, ascites and using of ACEI/ARB were independently associated with the development of AKI in decompensated cirrhosis.

Funding: Government Support - Non-U.S.

TH-PO706

Cholemic Nephropathy in Patients with End-Stage Liver Disease with AKI: A Postmortem Kidney Biopsy Study
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Background: Acute kidney injury (AKI) occurs frequently in patients with end-stage liver disease (ESLD) and portends a poor prognosis. Cholemic nephropathy (CN) is a pathological diagnosis observed in kidney biopsy of patients with jaundice and characterized by predominantly tubular epithelial injury together with intraluminal bile cast formation. Role of CN in pathogenesis of AKI is unknown. Aim of the study was to study the frequency and predictors of CN on postmortem renal biopsy among ESLD patients admitted with AKI. **Material and Methods**: We prospectively studied the post-mortem kidney biopsies of 154 ESLD patients with AKI who died between March 2012 - September 2015. Biopsies were processed and subjected to light microscopy and immunofluorescence. Bile casts were identified by light microscopy and confirmed using Fouchet's stain. We studied and divided the all biopsies into two groups Group 1 with acute tubular necrosis (ATN) and Group 2 with Cholemic Nephropathy (CN) **Results:**Of the 127 renal biopsies analyzed, 70 (55.1%) & 57(44.8%) were in group 1 and group 2 respectively. All baseline characteristics are shown on given table.

	ATN (n=70)	Cholemic (n=57)	p value
Age(yrs)	50.73 ± 11.730	43.23±12.237	.001
***Blood Urea(mg/dl)**	42 (4.10-379)	78 (8.20-352.10)	0.21
***Serum Creatinine(mg/dl)**	1.27 (0.20-7.70)	1.58 (0.23-9.65)	0.18
***Serum Bilirubin Direct(mg/dL)**	2.65(0.20-19.10)	16.27 (0.20-45.80)	**.0001**
***Serum Bilirubin Indirect(mg/dL)**	3.2 (0.60-14.80)	8.9 (0.37-42.40)	**.0001**

On multivariate analysis the predictors was total bilirubin with OR= 1.10, 95%CI (1.059-1.152, p<0.001) cut off value was 11.5 with senstivitiy and specificity as 75 and 77 respectively. Conclusions: A high clinical index of suspicion of Cholemic nephropathy should be kept in all patients who have high serum bilirubin and it was found to be a significant predictor of cholemic nephropathy on multivariate analysis.

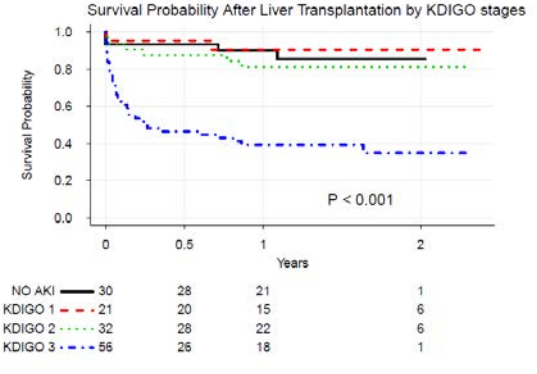
TH-PO707

Acute Kidney Injury and Long-Term Mortality after Orthotopic Liver Transplantation
Bernardo V. Reichert,[1] Ramaiane Aparecida Bridi,[1] Nzuzi Érika Mfinda,[1] Camila Eleuterio Rodrigues,[1] Igor Lepski Calil,[2] Luiz M. Malbouisson,[3] Luiz D´albuquerque,[2] Lucia Andrade,[1] Victor F. Seabra.[1,4] *[1]Nephrology; [2]Hepatology; [3]Intensive Care Unit, Univ of Sao Paulo School of Medicine; [4]Albert Einstein Hospital.*

Background: There is limited data on the association of Acute Kidney Injury (AKI) and long-term mortality after liver transplantation.

Methods: We examined the association of AKI and perioperative characteristics with long-term mortality in cases of orthotopic liver transplantation using cox proportional hazards analyses.

Results: 139 participants were enrolled for this analysis. Mean age was 55 years, 67% were men, and mean MELD-Na score was 19.6. The participants were followed for mean of 391 days [interquartile range (IQR) 97 to 610 days). The overall mortality was 33%. The figure shows the Kaplan Meier curve of probability of survival and KDIGO stages:



In unadjusted analysis, KDIGO stage 3 AKI was associated with a 6.67-fold higher risk for mortality (P <0.001; 95% confidence interval, 2.36 to 18.82) and a 6.15-fold higher risk for mortality after adjustment for other covariates (P <0.01; 95% confidence interval, 1.83 to 20.74).

Conclusions: KDIGO stage 3 is associated with long-term mortality after liver transplantation. Larger studies are needed to confirm these findings. This study was supported by FAPESP.

Funding: Government Support - Non-U.S.

TH-PO708

Association of Perioperative Characteristics and Acute Kidney Injury with In-Hospital Mortality after Orthotopic Liver Transplantation

Bernardo V. Reichert,[1] Ramaiane Aparecida Bridi,[1] Nzuzi Érika Mfinda,[1] Camila Eleuterio Rodrigues,[1] Igor Lepski Calil,[2] Luiz M. Malbouisson,[3] Luiz D´albuquerque,[2] Lucia Andrade,[1] Victor F. Seabra.[1,4] *[1]Nephrology; [2]Hepatology; [3]Intensive Care Unit, Univ of Sao Paulo School of Medicine, Brazil; [4]Albert Einstein Hospital.*

Background: There is limited data on the association of Acute Kidney Injury (AKI) and other perioperative characteristics with mortality in patients undergoing liver transplantation.

Methods: We examined the association of AKI and perioperative characteristics with in-hospital mortality in cases of orthotopic liver transplantation using logistic regression analyses.

Results: 139 participants were enrolled for this analysis. Mean age was 55 years, 67% were men, and mean MELD-Na score was 19.6. The overall mortality was 22%, the incidence of AKI was 78%, and 49% required renal replacement therapy. In univariate analysis, KDIGO stage 3 AKI was associated with higher risk of in-hospital mortality when compared with subjects without AKI (odds ratio [OR], 10.50; 95% confidence interval [CI], 2.78 to 69.03). Pre-operative (MELD-Na score, total bilirubin, serum bicarbonate levels and fulminant hepatitis) and intra-operative (number of packed red blood cells and fresh frozen plasma transfusions and prolonged anesthesia time) variables were also associated with in-hospital mortality. In multivariate analysis, the association of KDIGO stage 3 AKI and higher in-hospital mortality persisted after adjustment for other variables (OR, 13.65; 95% CI, 2.16 to 279.86). In the final model, the presence of fulminant hepatitis (OR, 8.22) and duration of anesthesia (OR, 1.32; per hour increase) were also associated with higher in-hospital mortality.

Conclusions: AKI predicts in-hospital mortality after liver transplantation. Larger studies are needed to confirm these findings. Supported by FAPESP.

Funding: Government Support - Non-U.S.

TH-PO709

Prediction of Mortality or the Need for Continued Renal Replacement Therapy following Acute Kidney Injury Requiring Dialysis

V. Shane Pankratz, Christos Argyropoulos, Orrin Myers, Mark L. Unruh. *Univ of New Mexico, Albuquerque, NM.*

Background: Managing the care of patients with acute kidney injury (AKI) remains inadequately defined. The availability of tools that simultaneously assess the probability of both mortality and continued need for renal replacement therapy (RRT) may enhance the decision making process for clinicians caring for such severely ill patients.

Methods: Using data from the VA/NIH Acute Renal Failure Trial Network, we developed a regression model that simultaneously evaluated the risk of death or continued RRT at multiple time points (28 days, 60 days, and 1 year post randomization) using the lasso shrinkage estimator on an extensive collection of data available at baseline evaluation from patients with AKI. This model was used to compute a score, which was categorized to place patients at low or high risk for each of the separate time-dependent outcomes. These scores were evaluated to assess their ability to classify patients into risk groups for the various time-dependent outcomes.

Results: The risk scores estimated for each of the time-dependent outcomes had areas under the ROC curve of roughly 0.77 for mortality risk at each of the three time points, and areas under the ROC curve of roughly 0.66 for the continued need for RRT at day 28 and day 60. The model did not identify any covariates to be associated with one-year mortality. Of those in the low risk group for all 3 mortality time outcomes, 41% were deceased at one year, while of those in the high risk group for all 3, 82% were deceased. Of those in the low risk group for the two RRT time outcomes, only 7.5% remained on RRT, and of those in the high risk group 17% still required RRT.

Conclusions: Simultaneously considering the risks for multiple outcomes at multiple future time points has the potential for being a useful tool for evaluating the ultimate status of a patient. This, in turn, has important implications for the care plans that will be implemented for the management of patients with AKI.

Funding: Pharmaceutical Company Support - Dialysis Clinic Inc. (DCI)

TH-PO710

Follow-Up to 3 Years after an Episode of Hospital Acquired Acute Kidney Injury

Anna Saurina, Irati Tapia, Monica Pou, Vicents Esteve, Veronica Duarte, Fatima Moreno, Miquel Fulquet, Jose Ibeas, Manel Ramírez de Arellano. *Nephrology, Consorci Sanitari de Terrassa, Terrassa, Barcelona, Spain.*

Background: Hospital Acquired Acute kidney Injury (HAAKI) influences in morbidity, mortality, length of hospital stay and costs. There are not enough studies of long-term monitoring.

Methods: Retrospective single-center study in two phases: Phase 1: analysis of episodes of HAAKI detected during 18 months. Phase 2: follow up at 3 years after the HAAKI. Iatrogenic HAAKI: AKI-related to medical intervention.

Results: Phase 1: 373 HAAKI. Age: 76±14. 62.5% male. Baseline creatinine: 109±30.4 µmol/L and baseline GFR(CKD-EPI): 56.3±21.6ml/min. Average recovery time: 7 days (0-60). Early recovery (1-3 d: 29 %), medium (4-9 d: 42.9 %) and late (≥10 d: 20.6%). Iatrogenic in 40.2%. At discharge: Creatinine: 125.32±57.37 µmol/L and GFR: 46.82±20.17 ml/min. 19.33% with GFR<30 ml/min. At 3 years: 167 were exitus: (E= 44.8 %), 147 alive (A= 39.4 %) and 59 had no follow-up (15.8 %). 32.2 % with GRF<30 ml/min and 2.74 % require RRT. The age of A at HAAKI was significantly lower than that in E (71.46 vs 79.86;p=0.000). The length of hospital stay: A=16 days (1-97) and E=18 days (1-128) (p=ns). Iatrogenic was observed in 42.2 % of A and 42.5 % of E (p=ns). GRF at follow up: A: 50.63 ml/min and E: 35.58 ml/min (p=0.000). Compared to baseline GFR a significant decrease of GFR at follow up was observed in A (57.47 vs 50.63 ml/min; p=0.000) and in E (52.16 vs 35.58 ml/min; p=0.005). There were also significant differences between GRF al the discharge compared to GFR at follow up in E (40.03±17.46 ml/min; p=0.000) but not in A (49.97±20.11 ml/min; p=0.811). Trend to worsening GFR (although not significant) in longer recovery time in A (p=0.869) and E (p=0.871). Patients A with iatrogenic HAAKI presented worse GFR al follow up than those without iatrogenic (p=0.02). These differences were not observed in E (p=0.556).

Conclusions: - Exitus were associated with elderly and lower baseline GFR and at discharge. - A non-significant trend to further deterioration of the RF is observed in longer recovery time. - The presence of iatrogenic is associated to worsening GFR at follow up in survivors at 3 years of follow up.

TH-PO711

Nutritional Factors Associated to Survival in Acute Kidney Injury Patients in a Tertiary Health Care Hospital

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Background: Malnutrition in hospitalized patients is associated with poor clinical outcomes.There is little evidence of KDIGO guidelines on nutritional management in AKI patients and outcomes in the hospital setting. We evaluated the impact of nutritional factors on survival on hospitalized patients.

Methods: 87 AKI patients admitted to the Hospital Civil de Guadalajara Fray Antonio Alcalde were included. Each patient had a clinical and biochemical evaluation; nutritional status was assessed by SGA, anthropometric data and 24-hour dietary recall.

Results:

Variable	Survivors n=55	Non-survivors n=32
Age (y)	51±16	56±18
Male, (%)	37(67)	25(78)
Surgical cases, (%)	20(36)	9(28)
AKI KDIGO stage, (%)*	13(24)	0
1	19(34)	11(34)
2	23(42)	21(66)
3	13(23)	21(66)
Dialysis, (%)*	10(18)	13(41)
Mechanical ventilation, (%)*	50(90)	24(75)
Non-oliguric, (%)*	6(10)	14(43)
Fasting, (%)*	37(67)	10(31)
Oral nutrition, (%)*	9(16)	4(12)
Enteral nutrition, (%)	3(5)	4(12)
Parenteral nutrition, (%)	12,8±8,6	15,1±10,7
Energy intake (kcal/kg)	0,48±0,38	0,56±0,45
Protein intake (g/kg)	26,4±6,3	25,7±6,2
BMI (kg/m^2)	25(46)	32(47)
Malnutrition SGA, (%)		

*p <0.05

Age [OR 1.032 (95% CI 1-1.06) p=<0.05], AKI KDIGO 3 [OR 3.04 (95% CI 1.37-6.77) p=0.006] and fasting [OR 7.04 (95% CI 2.12-23.29) p=0.001], increase the risk of death.

Conclusions: We conluded that fasting was associated with increased hospital mortality in patients with AKI. Aditionally a high proportion of malnutrition and poor nutrient intake was found.

TH-PO712

Effects of Acute Kidney Injury Duration on Outcomes in Critically Ill Patients

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Background: Acute kidney injury (AKI) is a common and serious illness. Duration of AKI has been recognized as an important risk factor for adverse long-term outcomes, but less is known about the impact of AKI duration on mortality and other organ functions in critically ill patients.

Methods: We analyzed data from the NHLBI ARDS Network's "Statins for Acutely Injured Lungs from Sepsis" (SAILS), a multicenter trial of ICU patients with sepsis-associated ARDS. Patients who developed AKI over the first 5 days of enrollment were identified using the KDIGO creatinine criteria. AKI duration was defined using the number

of consecutive days at which the KDIGO creatinine criteria were fulfilled, and categorized into four groups: transient(duration 1-2days),medium(3-7days),persistent(≥7days), or death during AKI. Mann-Whitney test and Chi-square test were used to evaluate differences between the groups.

Results: Among the 249 SAILS participants who developed AKI during the first 5 days of enrollment, 77 had transient AKI, 47 had medium-duration AKI, 87 had persistent AKI, and 38 patients died while still suffering from AKI. There were no significant differences between the transient and medium-duration AKI groups in 30-day mortality, cardiovascular failure free days or ventilator free days. Patients with persistent AKI had significantly lower lengths of cardiovascular failure free days and ventilator free days.

	Transient AKI, n=77	Medium AKI, n=47	P (trans vs medium)	Persistent AKI, n=87	P (persistent, trans,medium)
Free of cardiovascular failure to day 7(mean±SD)	4.7±2.3	4.8±2.2	0.96	3.4±2.5	<0.001
Ventilator free days to day 28(mean±SD)	17.7±10.7	17.5±10.7	0.94	13.3±10.1	<0.001
30-Day Mortality	18.2%	14.9%	0.82	18.4%	0.86

Conclusions: In critically ill patients with sepsis-associated ARDS and AKI, patients with transient AKI did not have better outcomes compared to those with AKI lasting up to 7 days. Persistent AKI lasting ≥7 days was associated with worse outcomes, emphasizing the importance of developing interventions that shorten the length of renal injury to improve patient outcomes.

Funding: Other NIH Support - NHLBI

TH-PO713

Model Establishing and Factor Analysis: An Insight into the Prediction of Acute Kidney Injury after Heart Surgery in China

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Background: Acute kidney injury is a common complication after cardiac surgery, known as cardiac surgery associated-acute kidney injury (CSA-AKI). This study aimed at exploring the prediction of different stages of CSA-AKI and making further efforts into factor analysis in China.

Methods: Five years of retrospective data (2008-2012, n=2811) were collected in the Division of Thoracic and Cardiovascular Surgery, Nanjing First Hospital. Variables presenting for injury and improvement of kidney function were developed to evaluate the influence of different factors. The method of Logistic Regression was applied to establish three preliminary models for predicting different stages of CSA-AKI, and with both Logistic Regression and non-parametric statistical analysis were used to analysis different factors.

Results: Among 2811 patients included in the study, incidence of CSA-AKI was 35.1%, in which the morality rate was 2.4%, double of the all-cause mortality (1.2%). Regression models for CSA-AKI from stage 1 to stage 3 showed differences in accuracy of prediction (the AUC of ROC curve: 0.676 vs. 0.759 vs. 0.813). Covariates selected in different models varied without clear evidence of stage-dependence. Factors showed significance(P<0.05) in both methods include male, age, hypertension, diabetes mellitus, insulin controlled diabetes, preoperative renal function, diagnosed chronic kidney diseases, preoperative hemoglobin, erythrocytes transfusion, duration of mechanical ventilation, ejection fraction(EF), body mass index (BMI) and surgical manner. While emergency surgery and aortic aneurysm only showed statistical significance in non-parametric test. The rank sum of factors suggested that abnormal BMI, lower preoperative hemoglobin (<130g/L in male, <120g/L in female) and lower EF (<50%) may increase the risk of postoperative AKI and lower the postoperative renal benefits.

Conclusions: The existing models for prediction may have defects in factor classification and severity evaluation; adjustment of BMI, EF and hemoglobin before elective surgery may lower the incidence of CSA-AKI and improve the prognosis.

Funding: Government Support - Non-U.S.

TH-PO714

Risk Prediction Model for Kidney Injury in Two Stage Revision Arthroplasty with Antibiotic Loaded Spacers for Prosthetic Joint Infections

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Background: Two-stage revision arthroplasty using antibiotic loaded spacers (ALS) is the preferred surgical treatment for prosthetic joint infections (PJI). Acute Kidney Injury (AKI) is increasingly being identified as a known complication of this procedure. We propose a risk prediction model to predict the incidence of Kidney Injury (KI) in patients undergoing this procedure along with its validation.

Methods: Between August 2007 and December 2012 we identified all patients who underwent two-stage revision arthroplasty using antibiotic loaded spacers (Cases, N=71) and aseptic revision arthroplasty (Controls, N=110) at a single referral center. Kidney injury was defined as AKI based on KDIGO definition or >50% increase in baseline creatinine during the course of spacer implantation. We compared the two groups using univariate and multivariate analysis to identify pre-operative and peri-operative risk factors for kidney injury. Coefficients from this analysis were used to formulate the prediction model which was validated in patients with the same eligibility criteria who underwent above mentioned procedures from January 2013 to December 2015.

Results: The incidence of kidney injury according to our definition was higher in cases as compared to controls [42.3% vs 24.5%, OR 2.25 95% CI (1.18 – 4.27) p = 0.01]. Risk factors for KI on unadjusted analysis included baseline CKD, HTN, ACE inhibitor use and systemic vancomycin use. The most important baseline risk factors after multivariable adjustment that contributed to the predicted risk score included CKD (OR 2.37; 95% CI 1.17-4.82), and was compounded by spacer implantation (OR 2.25; 95% CI 1.18-4.27).

Conclusions: Kidney injury including AKI in the post-operative period as well as late kidney injury during the course of spacer implantation is significantly associated with two stage arthroplasty with ALS for PJI. The proposed risk prediction model can be used to better identify the patients at higher risk of nephrotoxic complications of the procedure.

TH-PO715

Risk Factor of Development of Acute Kidney Injury in Orthopedic Surgery

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Background: Postoperative acute kidney injury (AKI) is major concern to surgeons, which leads the increasing postoperative morbidity and mortality. Perioperative risk factors of AKI are well known such as underlying chronic kidney disease, exposure of iodine contrast and low hemoglobin in bypass cardiac surgery. However, there is little known about development of postoperative AKI after orthopedic surgery.

Methods: Patients underwent total hip or knee replacement surgery were enrolled from January 2011 to December 2015 in this retrospective study. A number of variables was assessed such as age, gender, preoperative glomerular filtration rate, drugs (NSAIDs, ACE inhibitor or ARB, statins), albumin, hemoglobin, type of anesthesia, amount of bleeding and infused fluid, presence of diabetes, hypertension, contrast use and chronic kidney disease (CKD). AKI was defined when postoperative creatinine increased more than or equal to 0.3 mg/dL and CKD was defined when glomerular filtration rate was under 60 ml/min/1.73m^2 by CKD-EPI equation.

Results: Overall, AKI was developed in 13 among 351 cases (3.7%). Among the examined variables, presence of hypertension (11 out of 193 cases), CKD (9 out of 66 cases), low level of albumin (3.3 g/dL vs. 3.6 g/dL), hemoglobin (11.3 g/dL vs. 12.4 g/dL) and total CO_2 (24.27 mmol/L vs. 26.53 mmol/L) content were related to AKI significantly. In subgroup analysis with CKD group, AKI was developed in 8 out of 63 cases. Low albumin (3.3 g/dL vs. 3.6 g/dL) and hemoglobin (10.58 g/dL vs. 11.7 g/dL) were related risk factor in CKD patients. Use of crystalloid fluid only or combined with colloid fluid did not have any significant meanings. Among perioperative crystalloid fluid, 2 AKI case in 5 unbalanced fluid (40%) and 6 AKI cases in 58 balanced fluid (10%) were developed.

Conclusions: We should monitor the renal function closely after orthopedic surgery if the patients have hypertension, CKD and low level of albumin, hemoglobin and total CO_2 content. The correction of albumin and hemoglobin level is needed before orthopedic surgery in CKD patients. In addition, use of balanced fluid is helpful to prevent AKI in CKD patients if there are no electrolyte abnormalities.

TH-PO716

Beta-Blocker Use and Clinical Outcome in Patients with Acute Renal Injure Requiring Dialysis

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Background: Beta-blocker users have survival benefits in cardiovascular mortality, but its long-term effect in patients with acute renal injure (AKI) requiring dialysis is unknown.

Methods: This study was a perspective cohort study. We used National Health Insurance database in Taiwan from 2000 to 2014 to collect 13,889 patients with acute renal injure requiring dialysis. The inclusion criteria were as follows: first, they had hypertension and used anti-hypertensive drugs; second, they did not have any further dialysis recode within 1 year after the first dialysis commencement as recognized to be the AKI case.

Results: There were 6,262 beta-blocker users and 7,636 beta-blocker nonusers identified; of whom 2,200 and 3,045 died in 5 years, respectively. The 5 years mortality in beta-blocker users and nonusers were 124.1 and 146.3 case per 1,000 person-years, respectively. In Cox's proportional hazard model, after adjusting for age, gender, nephrologist care, myocardial infarction, stroke, diabetes mellitus (DM), chronic obstructive pulmonary disease, cancer, anti-hypertensive drugs used, oral antidiabetic drugs used, insulin, DM duration, statin, chronic kidney (CKD) stage, sepsis, heart failure, cardiovascular surgery, pesticide or metal poisoning, the hospital setting (treated as a cluster unit), and development of long-term dialysis (time dependent-variable), the mortality risk in beta-blocker users was 0.88 (95% confident interval: 0.83 and 0.93, p value < 0.001). In addition to the all-cause mortality, the beta-blocker users also had lower mortality risk in cardiovascular, DM and end-stage renal disease mortality. In subgroup analyses, the results in most subgroups were similar to the main results except those younger than 40, cancer patients, those with stage 5 CKD and those who developed sepsis induced AKI.

Conclusions: We conclude that for the hypertensive patients who develop AKI requiring dialysis, beta-blockers may be a preferred choice to prevent premature mortality.

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TH-PO717

Akute Kidney Injury after Cardiac Arrest Is Associated with Neurological Outcome and Mortality, an Observational Follow-Up of 10 Years Natalie M. Otto, Ralf Schindler, Anne C. Krueger, Andreas Kahl, Christian Storm. *Dept of Nephrology, Charité, Berlin, Germany.*

Background: Acute kidney Injury(AKI) is associated with early and long-term patient morbidity and mortality. In ICU patients, AKI is associated with a decrease in survival. AKI is considered a surrogate maker for illness severity and a consequence of the underlying disease. We evaluated the prevalence of AKI in cardiac arrest patients in association to their neurological outcome (according to the Cerebral Performance Categories Scale =CPC), their disease severity (APACHE Score) and hypoxia level (NSE) after administering therapeutic target temperature management at 33°C for 24hours.

Methods: Observational single center study between 2006 und 2013 in a cardiac arrest center in Berlin, Germany. All out and in hospital cardiac arrest (OHCA / IHCA) patients were included in our study. AKI was defined by the KDIGO guidelines. Main outcome was the assessment of good (CPC Scale 1-2) vs poor (CPC Scale 3-5) neurological outcome and its association with disease severity by APACHE Score, NSE levels as marker of hypoxia and AKI vs non AKI as an independent risk factor. Long term monitoring of up to 120 months assessing mortality was performed.

Results: A total of 497 patients after cardiac arrest were evaluated. Their CPC Scale obtained at discharge from ICU. 242 patients had good neurological(CPC 1-2) vs. 255 with a poor neurological outcome (CPC 3-5). The CPC 1-2 group had a NSE-level at day 3 of 18.5 vs 62.3 mg/l in the poor outcome group ($p<0.01$). The APACHE Score was similar in both groups (27.6 vs 27.9). In the CPC 1-2 group only 16.5% had an AKI vs 41.2% in the CPC 3-5 group ($p<0.001$). Patients with AKI and a poor neurological outcome had a mean survival of 0.04 years compared to patients with good neurological outcome and no AKI with a mean survival of 8.5 years.

Conclusions: AKI is a prevalent issue in critically ill patients such as survivors of cardiac arrest with long-term health issues. In addition to surviving cardiac arrest, the neurological long-term outcome remains a crucial subject. AKI is associated with mortality but also with poor neurological outcome after surviving cardiac arrest. New strategies may be needed to address this issue.

TH-PO718

Acute Kidney Injury in Asphyxiated Neonates Treated with Therapeutic Hypothermia Mariko Sawada. *Pediatrics, Kurashiki Central Hospital, Kurashiki, Okayama, Japan.*

Background: Multi-organ failure increases morbidity and mortality rates in severely asphyxiated neonates. Acute kidney injury (AKI) is one of the most severe complications in these patients, which can affect their short-term survival. In this study, we investigated the incidence and the outcomes of AKI in asphyxiated neonates treated with therapeutic hypothermia.

Methods: We retrospectively reviewed 105 cases of neonates who experienced perinatal asphyxia and treated with therapeutic hypothermia in a single neonatal intensive care unit (NICU) between June 2000 and June 2015. We used the proposed neonatal AKI definitions to classify and to establish the stage of AKI. We investigated the incidence of AKI, dialysis, mortality, and prolonged renal insufficiency.

Results: AKI occurred in 33 of 105 severely asphyxiated neonates (31.4%), and oliguric AKI was present in 57.6% of patients. Four patients (12.1%) received continuous hemodiafiltration. Overall mortality rate was 4.8%, and was much higher in those with AKI than in those without AKI (15.2% vs 0%). The mortality rate was 50% in neonates requiring dialysis. The mortality rate was 26.3% in neonates with oliguric AKI compared to 0% in those with non-oliguric AKI. Percent fluid overload was higher in the group of neonates who died than in those alive ($15.4 \pm 8.1\%$ vs $7.5 \pm 5.1\%$; $p<0.05$). The peak value of serum creatinine level was 1.7 ± 0.7 mg/dL in the former group and 2.0 ± 0.9 mg/dL in the group of neonates who died. No asphyxiated neonate developed persistent kidney dysfunction.

Conclusions: The incidence of AKI in asphyxiated neonates treated with therapeutic hypothermia was lower than previously reported. The mortality rate of neonates with AKI remains high, especially in those requiring dialysis. Oliguric AKI and higher fluid overload are associated with increased mortality rates.

TH-PO719

Impact of Therapeutic Hypothermia on Kidney Function Post Cardiac Arrest Tahir Muhammad Abdullah Khan, Armaghan Soomro, Raja Asif Masood, Shimshon Wiesel, Abdul H. Siddiqui, Anna S. Gutman, Suzanne E. El Sayegh. *IM, SIUH, Staten Island (SI), NY; Nephrology, SIUH, SI, NY.*

Background: Mortality in cardiac arrest patients remain high with limited consensus on medical management following return of spontaneous circulation (ROSC). Therapeutic hypothermia post cardiac arrest leads to better neurological outcomes however its effect on kidney function is uncertain. To better assess this, we trended serum creatinine, to determine acute kidney injury (AKI) following initiation of therapeutic hypothermia at our hospital.

Methods: A retrospective inpatient data review was conducted in patients who achieved ROSC following cardiac arrest. Patients were divided into two cohorts i.e. hypothermia and normothermia. AKI was diagnosed as per AKIN criteria. Patients who had coma prior to arrest &/or were on dialysis were excluded. Eligible patients' serum creatinine and urine output was recorded at different stages post cardiac arrest. Baseline variables in both cohorts were adjusted and multivariate regression analysis was conducted.

Results: A total of 96 patients (hypothermia n= 53, normothermia n= 43) were studied. Baseline mean serum creatinine levels in both cohorts were similar. At 24 hours after ROSC, mean serum creatinine in normothermia cohort was greater than in hypothermia cohort however was not statistically significant (2.13 vs. 1.97, p value= 0.466). Net difference of mean serum creatinine from baseline was increased more in normothermia cohort (+0.29 mg/dl, p value = 0.002), median length of stay (LOS) in normothermia group was also longer than in hypothermia group (20 vs. 7 days, p value < 0.001). Both results were statistically significant. Mortality in hypothermia group was 2.5 times higher than in normothermia group (80.4 % vs. 33.3 %, p value < 0.001).

Conclusions: Therapeutic hypothermia may have a renoprotective role in cardiac arrest patients and this may predict reduced hospital stay. Absence of AKI however may not predict improved mortality outcomes in post cardiac arrest patients treated by Hypothermia protocol.

TH-PO720

Genetic Factors of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Has an Impact on the Development of AKI Yasunori Iwata, Kengo Furuichi, Yasuyuki Shinozaki, Tadashi Toyama, Akihiro Sagara, Shinji Kitajima, Yasutaka Kamikawa, Shinji Kitajima, Norihiko Sakai, Takashi Wada. *Nephrology, Kanazawa Univ.*

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) causes hospital and community acquired infection. Development of acute kidney injury (AKI) increases mortality during MRSA infection. While underlying condition of the patient are associated with the progression of infection, it is unclear whether bacterial factor, especially genetic character could contribute to the disease pathogenesis in MRSA infection. We hypothesized that whole genome analysis could reveal the key gene loci and/or gene mutation, those have the impacts on the clinical manifestation, including acute kidney injury in MRSA infection.

Methods: Whole genome sequence (WGS) of MRSA from 96 cultured samples with clinical information were analyzed with next generation sequencer. Then, we evaluated the association of clinical manifestation in MRSA infection with genomic information.

Results: WGS revealed gene mutations, those were correlated with clinical manifestation of MRSA infection. The mutation on *staphylocoagulase* locus showed the highest correlation. Among the top 50 mutations, 22 mutations were on the adhesion and biofilm related loci. Interestingly, all of the strains, those were positive for both collagen adhesion gene (*cna*)locus and SNP in *staphylocoagulase* locus, caused blood stream infection (BSI). The strains also cause AKI during BSI. Logistic regression analysis also showed the high odds ratio for AKI in the strains.

Conclusions: The cluster, that was positive for *cna* locus and SNP in *staphylocoagulase* locus showed high frequency for BSI of MRSA and high risk for AKI. These findings suggest that bacterial genotype might affect the clinical character on MRSA infection.

Funding: Government Support - Non-U.S.

TH-PO721

Use of Life-Sustaining Interventions among Patients with Acute Kidney Injury Who Received Palliative Care Services prior to Death Kelly Chong, Cristian George Bologa, Herbert T. Davis, V. Shane Pankratz, David N. van der Goes, Mark L. Unruh. *Internal Medicine, Univ of New Mexico, Albuquerque, NM.*

Background: Acute Kidney Injury (AKI) is a common and serious complication of hospitalized patients without specific therapies. AKI patients requiring dialysis with unclear life expectancy and goals of care may benefit from palliative care. Palliative care (PC), focused on relief of suffering, has been shown to have many benefits, including increased patient and family satisfaction, honoring patient preferences for treatment intensity, and cost savings. Although overall use of PC is growing, little is known about PC use in the AKI patient population. In this study, we describe the use of PC among AKI patients who died during hospitalization, focusing on their use of life-sustaining interventions (LSI).

Methods: We extracted data from Cerner's Health Facts database between 2000 and 2014. We analyzed the first inpatient encounter of adult AKI patients who died during that hospitalization. We compared patient and hospital characteristics, and use of LSIs between patients who received PC with those who did not.

Results: Of 4,600 adult AKI patients who died during hospitalization, 1,089 (24%) received inpatient PC services. Mean age is slightly older for patients who received PC (75 vs. 74 years old). Among the >=90 years of age group, greater proportion of patients received PC ($p<0.0001$). PC use is significantly greater among teaching and larger hospitals, and hospital in the Northwest, West, and Midwest regions. Mean hospital length of stay is 8.9 days for the PC group compared the non-PC group (8.2 days). In the PC group, significantly less CPR, mechanical ventilation, and dialysis were used prior to death. There was no significant difference in the use of enteral feeding support between the two groups.

Conclusions: Our study reveals use of life-sustaining interventions was uniformly lower in the AKI population receiving palliative care services, except for use of feeding tube. The variations found in this study can help us gain greater understanding of providing PC to the right patients at the right time.

Funding: Pharmaceutical Company Support - Dialysis Clinic Inc (DCI)

TH-PO722

The KDIGO Criteria Are Superior Predictors of Mortality after Non-Cardiac Major Surgery Compared to AKIN Criteria Seokwoo Park, Dong Ki Kim, Kwon Wook Joo, Yon Su Kim, Hajeong Lee. *Internal Medicine, Seoul National Univ of College of Medicine, Seoul, Korea.*

Background: Postoperative acute kidney injury (AKI) is a serious adverse event which leads to higher mortality. Although several studies have been published on the subject, heterogeneous definitions of AKI in each study makes it difficult to synthesize study results. We evaluated which is superior between the Kidney Disease: Improving Global Outcomes criteria (KDIGO) and Acute Kidney Injury Network criteria (AKIN) in predicting patient outcomes after non-cardiac surgery.

Methods: We included adult patients who received non-cardiac major surgery (duration>1 hour) in Seoul National University Hospital from 2004 to 2013. AKI was diagnosed according to both KDIGO and AKIN criteria based on Cr measurements and initiation of RRT within 14 days after surgery. Positive predictive value (PPV) and negative predictive value (NPV) for in-hospital, 30-day, and 90-day mortality were compared using generalized score statistics. Discirimination ability was evaluated by c-statistics.

Results: Among a total of 58,919 cases, 4,092 (6.95%) and 3,347 (5.68%) were identified to be AKI by KDIGO and AKIN, respectively. KDIGO showed significantly lower PPV and higher NPV for in-hospital, 30-day, and 90-day mortality than AKIN

	PPV			NPV		
	KDIGO	AKIN	p-value	KDIGO	AKIN	p-value
In-hospital (%)	4.2	4.8	.002	99.9	99.8	<.001
90-day (%)	6.1	6.6	.006	99.2	99.2	<.001
1-year (%)	14.3	15.1	.007	96.3	96.2	<.001

The differences between C-statistics of KDIGO and AKIN were statistically significant in all 3 clinical outcomes, namely in-hospital (0.82 vs. 0.80; p=.002), 90-day (0.80 vs. 0.77; p<.001) and 1-year (0.66 vs. 0.64; p<.001) mortality.

Conclusions: KDIGO may be more useful for discriminating postoperative mortality than AKIN demonstrated by higher C-statistics. Also, considering prevalence of postoperative AKI and clinical relevance, superiority in sensitivity and discrimination power obtained by KDIGO compared to AKIN can outweigh inferiority in specificity. Implementing KDIGO criteria for defining postoperative AKI in non-cardiac surgery could prevent confusion in communication and help interpretating future studies in this field.

TH-PO723

Risk of ESRD Higher with Lower Adherence of DASH Diet in African Americans with Moderate CKD Tanushree Banerjee,[1] Deidra C. Crews,[2] Meda E. Pavkov,[3] Nilka Rios Burrows,[3] Jennifer L. Bragg-Gresham,[4] Rajiv Saran,[4] Neil R. Powe.[1] *[1]UCSF; [2]JHU; [3]CDC; [4]UM.*

Background: Dietary modifications play an important role in management of patients with CKD and ESRD. Few studies have examined the association of adherence to a DASH-type diet with risk of CKD progression among adults with moderate CKD from different race and ethnic backgrounds.

Methods: Among a cohort of 293 non-Hispanic black (NHBs) and 664 non-Hispanic white (NHWs) adults with moderate CKD (eGFR 30-59 ml/min) and with hypertension enrolled in NHANES III (1988-1994), we used 24-hour dietary recall data to determine adherence score to a DASH-type diet. Adherence was defined as score ≥4.5 out of a possible score of 9. Development of ESRD was ascertained over follow-up via linkage with USRDS. We used the Fine-Gray competing risks method separately in the NHB and NHW model for testing our hypothesis that greater DASH diet adherence would be independently associated with lower risk of ESRD.

Results: DASH diet adherence was greater among NHWs (22.3%) vs NHBs (16.1%), p value<0.05. Median DASH score in NHBs was 2.5 (Q1-Q3: 1.5-4) while in NHWs it was 3.5 (2-4). Total of 178 (18.6%) participants –103 NHB and 75 NHW--developed ESRD during a median of 11.2 years. Table shows the relative hazard of developing ESRD for race-specific models based on quintiles of DASH score. Lower scores (lower quintiles) indicate less adherence to the DASH diet

	RH (95% CI)			
	Unadjusted		Fully-Adjusted*	
DASH score (Quintiles)	NHBs	NHWs	NHBs	NHWs
1	2.9 (1.2-5.2)	2.9 (1.9-4.5)	2.5(1.1-3.5)	1.1 (0.6-1.7)
2	4.2 (2.4-6.1)	1.8 (1.0-3.2)	2.7 (1.5-4.7)	1.6 (0.9-2.8)
3	3.9 (2.0-5.8)	0.9 (0.6-1.9)	2.5 (1.3-3.9)	0.8 (0.4-1.5)
4	2.5 (0.7-4.2)	1.8 (1.2-2.9)	1.8 (0.5-2.5)	1.0 (0.6-2.0)
5	1.0 (Ref.)			

*Adjusted for age, sex, physical activity, diabetes, eGFR, and albuminuria. p trend = 0.02 for NHBs and 0.68 for NHWs.

Conclusions: Among adults with moderate CKD and hypertension, low adherence to a DASH-type diet was associated with higher risk of ESRD only among NHBs. Diet modification may be a potential target for intervention to prevent or delay progression in NHBs with CKD.

TH-PO724

Comparison of Accuracy between Pre- and Post-HD Values of Nutritonal Factors for Prediction of Mortality in Hemodialysis Patients Yoshihiko Kanno,[1] Eiichiro Kanda.[2] *[1]Tokyo Medical Univ, Japan; [2]Tokyo Kyosai Hospital.*

Background: To assess the nutritional status of patients receiving hemodialysis (HD), regularly measured pre-HD laboratory data are often used. However it has been included the problem whether the most diluted value would be appropriate to evaluate. We compared the pre-and post HD laboratory data to investigate their value to predict mortality.

Methods: 104289 maintenance hemodialysis (HD) patients (males 61.2%) were enrolled as subjects in this analysis as part of a prospective cohort study of the Japanese Society for Dialysis Therapy. The outcome events were one- and five-year mortalities. Their laboratory data included pre- and post-HD values of nutritional factors such as body mass index (BMI), and serum albumin, creatinine, and urea nitrogen levels. We compared the accuracy between pre- and post-HD values for the prediction of one- or five-year mortality using receiver operating characteristic (ROC) curves by the bootstrap resampling method.

Results: Mean age±standard deviation was 65.47±12.18 years; vintage, 8.62±7.05 years. The number of patients who died in one year was 6868 (6.6%); that in five years, 33188 (31.8%). The highest area under the ROC curve (AUCs) for the prediction of one-year mortality was post-HD serum albumin level [0.733 (95% CI 0.720, 0.746)]; and that of five-year mortality, pre-HD serum creatinine leve [0.702 (95% CI 0.699, 0.706)]. The AUCs showed that pre-HD BMI, serum creatinine and urea nitrogen levels were more accurate than post-HD values (each p<0.001). Although no statistical difference was observed between the AUCs of pre- and post-HD values of serum albumin levels for predicting one-year mortality (p=0.142), the post-HD serum albumin level was more accurate than the pre-HD level for predicting five-year mortality (p<0.0001). Stratifiction analysis based on gender, age, and diabetes mellitus as a cause of end-stage renal disease showed similar trends, that is, pre-HD BMI, and serum creatinine and urea nitrogen levels were more accurate than post-HD values.

Conclusions: Pre-HD values of nutritional factors, except serum albumin levels, were more accurate than post-HD values for predicting mortality in HD patients.

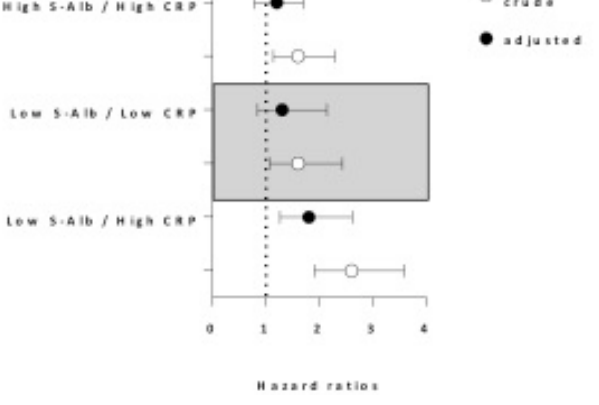
TH-PO725

Inflammatory Status Markedly Affects Ability of Serum Albumin to Predict Outcome in Chronic Kidney Disease Filipa Caeiro Alves,[1,2] Jia Sun,[2] Abdul Rashid Tony Qureshi,[2] Sunna Snaedal,[2,3] Peter F. Barany,[2] Olof Heimburger,[2] Bengt Lindholm,[2] Peter Stenvinkel.[2] *[1]Nephrology, Hospital Espírito Santo, Évora, Portugal; [2]Renal Medicine and Baxter Novum, CLINTEC, Karolinska Inst, Stockholm, Sweden; [3]Nephrology, Landspitali Univ Hospital, Reykjavik, Iceland.*

Background: The mortality predictive value of low serum albumin in patients (pts) with chronic kidney disease (CKD) is partly linked to its association with systemic inflammation but it is not clear to what extent its predictive strength depends on concomitant systemic inflammation. Here we addressed this question in pts with CKD stage 3-5.

Methods: Serum albumin (S-Alb), inflammatory status (high-sensitive C-reactive protein, CRP), cardiovascular disease (CVD) and nutritional status were assessed at baseline in 854 pts comprising: 97 pts with CKD stages 3-4 (median S-Alb 37g/L, median CRP 2.7mg/L), 523 pts with CKD stage 5 (median S-Alb 33g/L, median CRP 4.8 mg/L), 178 prevalent HD (median S-Alb 34g/L, median, CRP 6.8mg/L), and 56 prevalent PD pts (median S-Alb 31g/L, median CRP 4.4mg/L). Pts were divided into four groups according to median levels of CRP and S-Alb in each cohort: Group 1 (n=298) - High S-Alb/Low CRP; Group 2 (n=211) - High S-Alb/High CRP; Group 3 (n=218) - Low S-Alb/Low CRP; Group 4 (n=218) - Low S-Alb/High CRP. Survival over 60 months was analyzed.

Results: In Cox analysis, Group 4 (Low S-Alb/High CRP) had increased mortality risk (adjusted HR (95%CI): 1.8 (1.26 - 2.61); p<0.01), whereas the augmented risks for Groups 2 and 3 in univariate analyses were lost after adjustments for age, sex, CVD, diabetes, smoking, handgrip strength, CKD stage and renal replacement therapy.



Conclusions: Mortality risk is increased in CKD pts with low S-Alb and high CRP but not in pts with low S-Alb and low CRP or high CRP and high S-Alb, suggesting that inflammatory status should be taken into account when using S-Alb to predict outcomes in CKD patients.

Funding: Pharmaceutical Company Support - Baxter Healthcare, Government Support - Non-U.S.

TH-PO726

Net Endogenous Acid Production, an Index of Dietary Acid Load, Is Associated with the Progression of CKD Koji Toba,[1] Michihiro Hosojima,[2] Shoji Kuwahara,[3] Ryohei Kaseda,[1] Tomomichi Iida,[1] Sawako Goto,[1] Naohito Tanabe,[4] Yoshiki Suzuki,[5] Ichiei Narita,[1] Akihiko Saito.[3] *[1]Div of Clinical Nephrology and Rheumatology, Niigata Univ, Niigata, Japan; [2]Dept of Clinical Nutrition Science, Niigata Univ, Niigata, Japan; [3]Dept of Applied Molecular Medicine, Niigata Univ, Niigata, Japan; [4]Health and Nutrition, Univ of Niigata Prefecture, Niigata, Japan; [5]Health Administration Center, Niigata Univ, Niigata, Japan.*

Background: Recent studies have suggested that metabolic acidosis mediates the progression of CKD. Dietary acid load, a potential cause of metabolic acidosis, might be associated with CKD progression, although few studies have analyzed this. Here, we investigated the association of dietary acid load with CKD progression by evaluating the net endogenous acid production (NEAP), an index of the dietary acid load, and reviewing clinical records of CKD patients.

Methods: Subjects of this study were 96 outpatients with CKD (61 patients with diabetes; average eGFR, 53.0±18.1 mL/min/1.73 m^2) at Niigata University Hospital. We estimated their intake of foods and nutrients from the results of a self-administered dietary history questionnaire (DHQ) completed in 2011. We estimated NEAP using the following formula: NEAP (mEq/day)=54.5 (protein [g/day])/(potassium [mEq/day])-10.2 (Scialla, JJ. et al. Clin J Am Soc Nephrol 2011). Progression of CKD was assessed by comparing eGFR between 2008 and 2014.

Results: Average NEAP was 50.0±18.1 (mEq/day). Urinary pH was significantly lower in patients with higher NEAP (n=46) than in those with lower NEAP (n=50). Higher NEAP was significantly associated with intake of more meat and less vegetables, fruit, and potassium. Protein intake was not significantly associated with NEAP. Reduction of eGFR from 2008 to 2014 was significantly greater in patients with higher NEAP than in those with lower NEAP (-8.9 vs. -2.5 mL/min/1.73 m^2, p=0.038).

Conclusions: Higher NEAP could be a risk factor for CKD progression. Further studies are warranted to evaluate the protective effects of dietary acid control on CKD progression.

Funding: Government Support - Non-U.S.

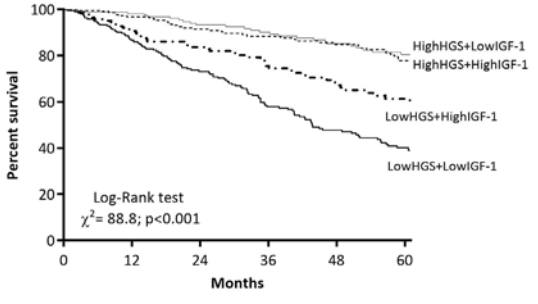
TH-PO727

Muscle Strength Interaction with Insulin-Like Growth Factor-1 (IGF-1) Influences Survival in Chronic Kidney Disease (CKD) Chen Zhimin,[1,2] Erik Nilsson,[2] Jia Sun,[2] Bengt Lindholm,[2] Olof Heimburger,[2] Peter F. Barany,[2] Peter Stenvinkel,[2] Abdul Rashid Tony Qureshi.[2] *[1]Kidney Disease Center, 1st Affiliated Hospital College of Medicine, Zhejiang Univ, Hangzhou, China; [2]Renal Medicine and Baxter Novum, CLINTEC, Karolinska Inst, Stockholm, Sweden.*

Background: CKD patients (pts) display resistance to IGF-1. Hand-grip muscle strength (HGS) is a reliable and easy-to-perform nutritional parameter. Both low IGF-1 and low HGS predict mortality. We hypothesized that concomitant presence of both conditions increases mortality risk in CKD.

Methods: IGF-1, HGS and other nutritional and inflammatory markers were measured in 724 pts (median age 58 years; 62% males) with different stages of CKD. Pts were stratified into 4 groups according to median levels of HGS and IGF-1 and all-cause mortality over 60 months was analyzed.

Results: Pts with low IGF-1 (<median) and low HGS (<median) were older and had elevated levels of high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6) and tumor necrosis factor (TNF) and worse survival in Kaplan-Meier analysis, see Fig 1. Multivariable logistic regression analysis adjusted for age, gender, diabetes, cardiovascular disease (CVD), HGS, subjective global assessment (SGA), albumin, smoking and hsCRP, revealed that independent predictors of lower IGF-1 were age, diabetes and low HGS. In receiver-operating characteristics curve (ROC) analysis, lower IGF-1 associated with higher mortality only in low HGS group. In Cox proportional hazards analysis, across the four HGS-IGF-1 categories, the group with low IGF-1 and low HGS had highest mortality after adjustments for age, gender, diabetes, CVD, SGA, smoking, hsCRP and albumin.



Conclusions: CKD pts with concomitant low IGF-1 and low HGS have increased mortality risk suggesting that the association of IGF-1 with mortality in CKD pts depends on nutritional status.

Funding: Pharmaceutical Company Support - Baxter Healthcare, Government Support - Non-U.S.

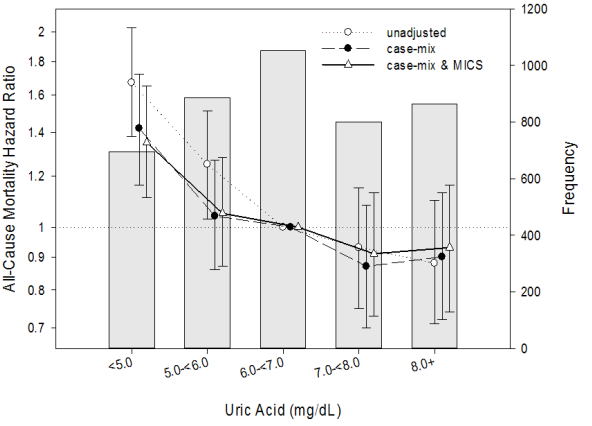
TH-PO728

Serum Uric Acid Level and Mortality in Hemodialysis Patients Christina Park, Yoshitsugu Obi, Elani Streja, Melissa Soohoo, Kamyar Kalantar-Zadeh. *UC Irvine.*

Background: Elevated uric acid concentrations are associated with cardiovascular events and mortality in the general population. However, there are scarce data regarding the mortality risk associated with hyperuricemia in the hemodialysis (HD) population.

Methods: We retrospectively examined a subcohort of 4,298 HD patients whose first serum uric acid measurements were obtained during treatment in a large dialysis organization from 2007-2011. Patients were grouped into 5 uric acid categories. Using Cox proportional hazards model, we explored the association between serum uric acid levels and time to all-cause death from first uric acid measurement with adjustments for case-mix variables (demographics, comorbidities, and spKt/V) and laboratory markers of malnutrition and inflammation (MICS).

Results: Mean age was 63±15 years and 39% were women. Mean uric acid level was 6.6±1.8 mg/dL. There was a trend toward lower mortality risk across higher uric acid levels irrespective of the adjustment models (P_{trend} <0.001); the highest category (≥8.0 mg/dL) showed non-significant lower mortality risk while the lowest category (<5.0 mg/dL) was significantly associated with higher mortality compared to the middle category (6.0-<7.0 mg/dL); case-mix adjusted HRs were 1.42 (95% CI, 1.16-1.72) and 0.90 (95% CI, 0.72-1.13), respectively. These findings were consistent across subgroups of age, gender, race, diabetes, albumin, and body mass index ($P_{interaction}$>0.1). However, mortality risk associated with low uric acid levels (<5.0 mg/dl) were significant among patients with low nPCR (<0.9 g/kg/day) but not among those with high nPCR (≥0.9 g/kg/day) ($P_{interaction}$=0.001).



Conclusions: Among HD patients, hyperuricemia may be a marker of better nutritional status, and were paradoxically related to lower all-cause mortality risk in contrast to those in the general population. Future studies are needed to investigate the mechanism behind this association.

Funding: NIDDK Support

TH-PO729

The Effect of Extended Duration Nocturnal Hemodialysis on the Human Metabolome Sahir Kalim,[1] Ron Wald,[2] Dihua Xu,[1] Anders H. Berg,[3] Eugene P. Rhee,[1] Jeffrey Perl.[2] *[1]Massachusetts General Hospital, Boston, MA; [2]St. Michael's Hospital, Toronto, ON; [3]Beth Israel Deaconess Medical Center, Boston, MA.*

Background: Human metabolite profiling has been increasingly used to describe the small molecule disarray that arises in ESRD and several specific "uremic solutes" have been associated with adverse clinical outcomes including mortality in ESRD. In-center extended duration nocturnal hemodialysis (INHD) has been credited with a variety of clinical benefits but the impact of INHD on metabolite profiles remains unclear.

Methods: We conducted a prospective, multi-center parallel arm observational study of 53 prevalent conventional HD patients (CHD, 4 h/session, 3x/week) of whom 33 converted to INHD (7-8 h/session, 3 x/week) while 20 remained on CHD (controls). In both groups, we applied liquid chromatography-mass spectrometry based metabolite profiling at baseline and at 1-year. We examined longitudinal changes in metabolites among those who remained on CHD as compared to those who converted to INHD using Wilcoxon tests with significance thresholds adjusted for multiple comparisons using a false discovery rate correction (FDR).

Results: Among 164 polar metabolites examined, none significantly differed from baseline to study end in the control group. 27 metabolites differed in the INHD group, the majority of which actually increased with INHD (including several amino acids, including all three branched chain amino acids; all FDR adjusted P<0.05) suggesting the observed changes were not a direct effect of additional solute clearance. By contrast, several

established uremic solutes including p-cresol sulfate, indoxyl sulfate, trimethylamine N-oxide, and symmetric- and asymmetric-dimethylarginine did not change with extended duration INHD (all adjusted P>0.05).

Conclusions: INHD significantly alters metabolite profiles, however this may be a secondary effect of other metabolic and nutritional changes and not directly related to increased solute clearance. No change in several uremic solutes measured by our platform was observed.

Funding: NIDDK Support

TH-PO730

Fibroblast Growth Factor 21, a Novel Hormone, Is Associated with Lipid Metabolism and Renal Function in Nondialyzed Chronic Kidney Disease Patients Joao Victor Salgado, Maria Dalboni, Aluizio B. Carvalho, Maria Eugenia F. Canziani. *Discipline of Nephrology, Federal Univ of Sao Paulo, Sao Paulo, Brazil.*

Background: Fibroblast growth factor 21 (FGF-21), a member of the endocrine FGF subfamily, is secreted mainly by the liver with critical role in glucose and lipid homeostasis. High FGF-21 levels are associated with metabolic disorders and predict kidney disease progression in patients with type 2 diabetes. However, it is still unclear what factors are truly affecting FGF-21 levels in CKD patients.

Methods: This study is *post hoc* analysis which included ninety five CKD patients stage 2-5 (age ≥ 18 and <70 yrs). Serum concentrations of total FGF-21 were quantified by enzyme-linked immunosorbent assay.

Results: Circulating FGF-21 did not change significantly with regards to age, gender and diabetes mellitus, but was different between CKD stages (2-5) (p=0.023) with highest values detectable in stage 5. Serum FGF-21 values correlated negatively with glomerular filtration rate based on the CKD-EPI equation (r=-0.28; p=0.007) and positively with serum creatinine (r=0.29; p=0.006), proteinuria (r=0.21; p=0.046), fasting glucose (r=0.21; p=0.047), triglycerides (r=0.36; p<0.001) and alkaline phosphatase levels (r=0.25; p=0.018). Multiple linear regression analysis revealed that triglycerides (β coefficient 0.395; p<0.001), GFR (β coefficient -0.309; p=0.001) and alkaline phosphatase (β coefficient 0.215; p=0.016) remained independently associated with circulating FGF-21 levels after adjustment for age, gender, BMI, and diabetes mellitus.

Conclusions: Circulating FGF-21 levels increase with CKD progression and appear to be associated with lipid rather than glucose metabolism.

Funding: Government Support - Non-U.S.

TH-PO731

Total Energy Expenditure as Estimated by Activity Trackers and Its Relationship to Hemodialysis Adequacy Schantel Williams,[1] Maggie Han,[1] Anna Meyring-Wosten,[1] Xiaoling Ye,[1] Marcee Bonner,[3] Candace Young,[3] Daniel Marsh,[3] Peter Kotanko.[1,2] *[1]Research, Renal Research Inst, New York, NY; [2]Nephrology, Icahn School of Medicine, New York, NY; [3]Research, Renal Associates Baton Rouge, Baton Rouge, LA.*

Background: While Kt/V_{urea} and urea reduction ratio (URR) are widely used indicators of hemodialysis (HD) adequacy, their conceptual flaws have been recognized. This method of evaluating adequacy may put those with low body mass index (BMI) at risk of under-dialysis. Metabolic rate, not V_{urea}, has an impact on toxin generation. Consequently, it is proposed that total energy expenditure (TEE) and metabolic rate may be more appropriate factors in determining HD dose adequacy (Singer, *AJKD* 2000). To do this, TEE needs to be measured routinely. Using activity trackers, clinically acceptable TEE can now be obtained (Murakami et al *JAMA* 2016). The aim of this study is to determine if a correlation between TEE and Kt/V exists.

Methods: Chronic HD patients wore the Fitbit® Flex™, a commercially available activity tracker, for 5 weeks. TEE, expressed in average daily calories burned, was obtained. Equilibrated Kt/V_{urea} was taken from monthly HD lab reports. Using linear regression, the relationship between TEE and eKt/V was assessed. Confounding factors, e.g. gender and BMI, were adjusted for.

Results: 44 patients, with an average age of 53.8± 11.3 years, BMI of 28.3±7.37 kg/m^2, 50% male and 75% Black were enrolled. Mean TEE was 2221± 457kcal. eKt/V_{urea} & TEE were not correlated in unadjusted (R^2 0.0149) nor adjusted (R^2 0.0153) analysis.

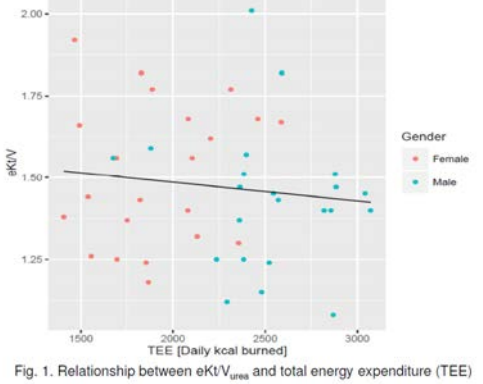


Fig. 1. Relationship between eKt/V_{urea} and total energy expenditure (TEE)

eKt/V_{urea} and TEE were not correlated in unadjusted (R^2 0.0149) nor adjusted (R^2 0.0153) analysis.

Conclusions: TEE is not related to eKt/V_{urea} and not reflected in the current assessment of HD adequacy. This may be a flaw as TEE is a proxy of determining metabolic toxin production compared to V_{urea} (Sridharan, *Hemodialysis Int'l* 2013). It is important to consider TEE when determining HD adequacy. Studies should further explore the relationship of TEE with generation of toxins. Eventually, TEE may be considered for HD dose prescription.

TH-PO732

Protein Intake Is Inversely Associated with Renal Function in Class III and IV CKD: The PROGREDIR Study Alisson Diego Machado,[1] Fernanda Silva Nogueira dos Anjos,[1] Maria Alice Muniz Domingos,[1] Maria del Carmen B. Molina,[2] Dirce Marchioni,[3] Paulo Lotufo,[4] Isabela M. Bensenor,[4] Silvia M. Titan.[1] *[1]Nephrology Div, School of Medicine, Sao Paulo Univ, Sao Paulo, Brazil; [2]Nutrition Dept, Federal Univ of Espirito Santo, Vitória, Espírito Santo, Brazil; [3]Nutrition Dept, School of Public Health, Sao Paulo Univ, Sao Paulo, Brazil; [4]Epidemiological and Clinical Research Center, Univ Hospital, Sao Paulo Univ, Sao Paulo, Brazil.*

Background: Benefits of protein restriction in CKD are still controversial. In addition, phosphorus intake could be a major confounding variable in that relation.

Methods: We evaluated the association between protein intake and baseline renal function in 454 class III and IV CKD patients (Progredir Study). A validated food frequency questionnaire was apllied and nutrient intake was estimated using USDA Database, with adjustment for energy. Models on the association between protein intake (g/kg) and renal function were built, adjusting for cardiovascular risk factors and phosphorus intake deattenuated of protein intake. Lastly, we compared participants reporting <0,8 g/kg/d of protein intake with those >0,8g/kg/d, after matching for age, sex and BMI.

Results: Tertiles of protein intake were associated to female sex, HDL, and inversely related to waist circumference (WC), BMI, hemoglobin, HOMA, alcohol, and eGFR. In linear regression, protein intake was related to log eGFR [B=-0.20 (-0.32- -0.07), p=0.002], BMI, WC and DBP. After adjustments for age, sex, hypertension, diabetes, dyslipidemia, alcohol, caloric and phosphorus intake, protein intake remained significantly associated with eGFR [B=-0.16 (-0.30 - -0.02), p=0.03]. Only 44 (9,7%) participants reported an intake of protein <0,8 g/kg/d, the KDOQI guideline. When we compared participants reporting <0,8 g/kg/d with those reporting >0,8g/kg/d after matching for age, sex and BMI, those >0,8g/kg/d presented a lower eGFR [B-4.22 (-8.18- -0.27), p=0.03], even after adjustments [B-3.93 (-8.17- -0.03), p=0.04].

Conclusions: In this cross-sectional study, higher protein intake was significantly associated with a lower eGFR, independently of phosphorus intake and other confounding variables.

Funding: Government Support - Non-U.S.

TH-PO733

The Relative Contribution of Lean and Fat Body Mass on Response to Erythropoiesis Stimulating Agents in Hemodialysis Patients Lucia Del Vecchio,[1] Valeria Aicardi,[2] Selena Longhi,[1] Vincenzo La Milia,[1] Giuseppe Pontoriero.[1] *[1]Nephrology and Dialysis, A Manzoni Hospital ASST Lecco, Lecco, Italy; [2]Nephrology and Dialysis, Clinica INDISA, Santiago del Chile, Chile.*

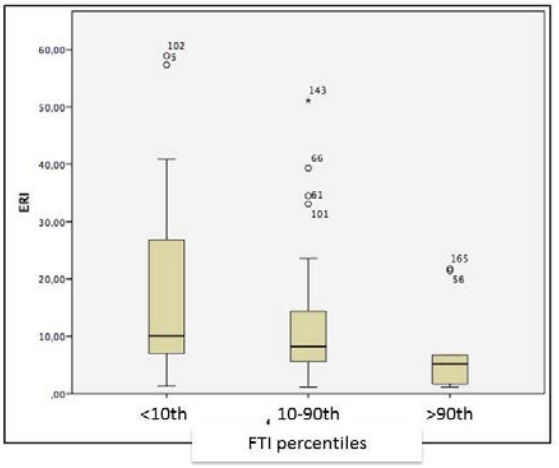
Background: High-dose ESA are associated with malnutrition and inflammation; little is known about ESA response according to lean and fat body composition.

Methods: 90 prevalent hemodialysis patients (M/F: 53/37, mean age 68.88 ± 14.01 years) on ESA therapy underwent nutritional assessment by Body Composition Monitoring. Hyporesponse to ESA defined as ERI>14.8, >75th percentile). Considering that LTI and FTI values vary according to age and gender, we analyzed the data according to Lean Tissue Index (LTI) and Fat Tissue Index (FTI) percentiles relative to an age- and sex-matched healthy population.

Results: Twenty (22%) and 19 (21%) patients had LTI and FTI values below the 10th percentile, respectively.

	ERI ≤ 14.8	**ERI > 14.8**	**P value**
BMI (Kg/m^2)	27.26 ± 4.45	25.78 ± 3.08	NS
Serum albumin (g/dl)	3.65 ± 0.51	3.13 ± 0.59	0.002
Muscular brachial area (cm^2)	55.97 ± 12.30	48.84 ± 15.74	0.078
Fat brachial area (cm^2)	20.40 ± 13.98	18.34 ± 13.41	NS
LTI (Kg/m^2)	13.16 ± 2.99	13.10 ± 2.45	NS
FTI (Kg/m^2)	13.15 ± 4.53	11.14 ± 3.59	NS

Table 1 shows main data for ERI category. Ferritin levels and TSAT were not significantly different. FTI values were inversely related to lnERI (r2= 0.094, beta -0.30, p=0.005). Patients with FTI values below the 10th percentile had higher ERI compared to the 10-90th and > 90th percentile (19.23 18.05, 11.6 ± 9.84 and 7.44 ± 7.69, respectively; p= 0.025).



The difference in mean ERI among LTI percentile categories had opposite trend (9.04 ± 7.74, 12.45 ± 11.04 and 19.63 ± 19.71 for < 10th, 10- 90th and > 90th percentile; p= 0.072).

Conclusions: In hemodialysis patients ESA hyporesponse is mainly associated with decreased fat body mass.

TH-PO734

Association of Ascorbic Acid Supplementation with Plasma Ascorbic Acid and Oxalate Levels in Prevalent Hemodialysis Patients William D. Sirover,[1] Yuguan Liu,[2] Amanda Logan,[4] Krystal Hunter,[4] Craig B. Langman,[3] Lawrence S. Weisberg,[1] Garry J. Handelman.[2] *[1]Nephrology, CMSRU, Camden, NJ; [2]Nutrition, UMASS, Lowell, Lowell, MA; [3]Nephrology, Feinberg School of Medicine, Chicago, IL; [4]Cooper Research Inst, Cooper Univ Hospital, Camden, NJ.*

Background: Ascorbic acid (AA) facilitates erythropoiesis and a plasma AA concentration (p[AA]) of at least 70 µM may be necessary to reduce erythropoiesis-stimulating agent resistance. Hemodialysis (HD) patients are commonly prescribed or take AA supplementation. Oxalate (Ox), an AA-metabolite, is excreted in the urine and is also removed during HD. Ox accumulation may limit AA use as an anemia adjuvant. When the plasma Ox concentration (p[Ox]) reaches 30 µM, Ox may deposit pathologically in organs. Plasma AA levels of 70-100 µM are not associated with p[Ox] surpassing this 30 µM threshold. We examined further the efficacy and safety of escalating degrees of AA supplementation.

Methods: In 2011, we surveyed outpatients on HD regarding AA supplement use. Pre-HD p[AA] and p[Ox] were measured in 197 patients. Moderate AA supplementation was defined as an oral AA dose of up to 120 mg/day.

Results: Median p[AA] and mean p[Ox] showed a significant positive association with escalation of AA dose (Figures 1 and 2).

	0 mg AA/ day	50-75 mg AA/ day	100-120 mg AA/day	≥150 mg AA/ day	*P*-value
AA dose (mg/ day)	0	60 (IQR 60-60)	100 (IQR 100-100)	560 (IQR 530-600)	<0.001
Albumin (gm/ dL)	3.9±0.4	4±0.4	3.9±0.3	3.9±0.4	0.74
spKt/V	1.73	1.77	1.76	1.6	0.38

Figure 1

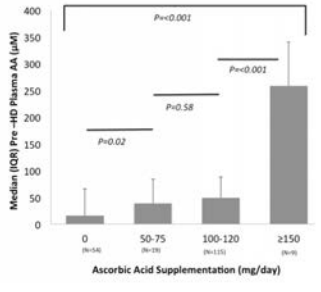
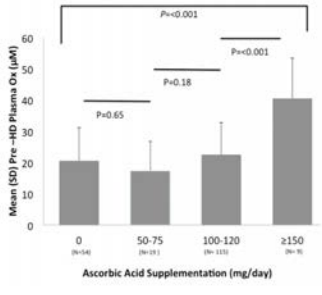


Figure 2



Conclusions: Moderate AA supplementation was not linked with p[Ox] surpassing 30 µM. However, this degree of supplementation was associated with a p[AA] below 70 µM. Prospective studies are needed to determine an AA dose that maintains p[AA] between 70-100 µM and, for now, HD patients should avoid an AA dose that exceeds 120 mg/day.

Funding: Private Foundation Support

TH-PO735

Muscle Mass Assessment by Computed Tomography at Lumbar Vertebra: Agreement with Surrogate Methods in Chronic Kidney Disease Patients Juliana Giglio,[1] Maria A. Kamimura,[2] Antonio C. Cordeiro,[3] André Valente Bichels,[2] Nivaldo Pinho,[4] Nilian Souza,[1,4] Carla Maria Avesani.[1] *[1]Rio de Janeiro State Univ, Brazil; [2]Federal Univ of Sao Paulo, Brazil; [3]Dante Pazzanese Inst of Cardiology, Brazil; [4]National Inst of Cancer, Brazil.*

Background: The assessment of muscle mass by computed tomography (CT) has been suggested as the preferred method for analyzing skeletal muscle mass (SMM). We wish to evaluate the agreement of SMM assessed by CT at L3 with surrogates of muscle mass in chronic kidney disease (CKD) patients.

Methods: This is an ongoing study including 30 nondialyzed CKD patients (age: 59 ±9 years; 56% men; glomerular filtration rate: 12 (9 - 28) mL/min/1.73 m^2; median and interquartile range). SMM was evaluated by CT at the third lumbar vertebra for analysis of total muscle cross-sectional area (cm^2), trough the following muscles quantification: rectus abdominus, abdominal (lateral and oblique), psoas, and paraspinal (quadratus lumborum, erector spinae) using Slice-O-Matic software (v.4.3; Tomovision, Canada). Lean body mass by bioelectrical impedance (LBM-BIA) and anthropometry (skinfold thicknesses) (LBM-ANT); SMM calculated from Janssen and Baumgartner equation and midarm muscle circumference (MAMC) were selected as surrogates of muscle mass. Low muscle mass was defined as the lower P50th according to gender for each method.

Results: The kappa coefficients and sensitivity between SMM assessed by CT and surrogates (table 1) showed that the highest kappa coefficients for low muscle mass was observed for MAMC, followed by SMM-Baumgartner and LBM-ANT. The univariate association with SMM assessed by CT on the other hand were stronger for SMM-Baumgartner and LBM-ANT.

	Kappa (r;*p*)	Sensitivity (%)	Especificity (%)	Univariate association (r; *p*)
CT *vs* LBM-BIA	0.40 (0.03)	69	71	0.71 (<0.01)
CT *vs* LBM-ANT	0.46 (0.01)	75	71	0.74 (<0.01)
CT *vs* SMM Janssen	0.34 (0.06)	63	71	0.62 (<0.01)
CT *vs* SMM Baumgartner	0.46 (0.01)	75	71	0.81 (<0.01)
CT vs MAMC	0.60 (<0.01)	81	79	0.53 (<0.01)

Conclusions: Our preliminary analyzes showed that the assessment of low muscle mass in CKD patients by CT at L3 showed the best agreement with MAMC, SMM-Baumgartner and LBM-ANT.

TH-PO736

Altered Metabolism of Serum Manganese Is Associated with Low Levels of Hemoglobin in the Patients with Chronic Kidney Disease Minyoung Kim, Eun Sil Koh, Hyung Wook Kim, Seok Joon Shin, Sungjin Chung. *Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.*

Background: Manganese (Mn) is one of the essential minerals which is likely to be deficient in malnutrition. Given that malnutrition is a major issue in chronic kidney disease(CKD), Mn could be inadequate to maintain physiologic balance in CKD patients. Several reports highlighted that serum Mn level was higher in the patients with anemia. Although anemia is common manifestation of chronic kidney disease, it has been barely established whether serum Mn level have some effect on anemia in CKD patients. The purpose of this study is to analyze the relationship between serum Mn level and anemia in the patients with CKD.

Methods: This study was a cross-sectional study based on the patients with CKD. Total 300 patients with CKD were included in single center from 2014 to 2016. They were divided into two groups by serum manganese level, 8.0 ug/L, according to the reference range of the hospital laboratory policy.

Results: The median value of serum Mn and eGFR of all participants were 8.0 ug/L (interquartile range: 4.9 to 11.5 ug/L) and 12.5 ml/min 1.73 m^2 (interquartile range: 7.18 to 25.1 ml/min 1.73 m^2), respectively. The higher Mn group showed higher hemoglobin (Hb) level (11.3 ± 2.1 *vs.* 9.5 ± 1.8 g/dL ; $p < 0.001$) and higher eGFR (21.1 ± 16.8 vs. 15.71 ± 12.7 ml/min 1.73 m^2; $p < 0.001$), compared with the lower Mn group. Serum Mn level showed the significant correlation with Hb level and eGFR (r=0.474, $p < 0.001$; 0.142, p=0.014, respectively). A multivariate logistic regression analysis adjusted for age, gender, body mass index and eGFR was performed; the odds ratio was 0.173 (95% CI: 0.090 to 0.334, p<0.001) for anemia (Hb < 11.5 mg/dl), when comparing the higher Mn group with the lower Mn group.

Conclusions: In the CKD patients, higher Mn level might have positive association with hemoglobin level. Although the specific mechanism is not known yet, the role of serum Mn level may be important especially in CKD patients with an aspect of anemia management.

TH-PO737

Fetuin-A and Calciprotein Particles Profiles in Patients on Peritoneal Dialysis
Thalita Moura Santos Braga, Erica Adelina Guimarães, Rodrigo Souza Adao, Wagner Dominguez, Fabiana Graciolli, Hugo Abensur, Rosilene M. Elias, Rosa M.A. Moyses. *Nephrology, Faculty of Medicine, Univ of São Paulo, São Paulo, Brazil.*

Background: Fetuin-A is an inhibitor of mineralization that complexes with mineral apatite precursors generating high molecular weight fetuin-A-containing calciprotein particles (CPP), which are associated with aortic stiffness and all-cause mortality. CKD patients usually have low fetuin-A and high CPP, although data in peritoneal dialysis (PD) patients are scarce.

Methods: Dialysate and serum fetuin-A levels were measured in 13 patients on PD. CPP were obtained of the supernatant after high-speed centrifugation samples in both serum and dialysate. The patients were submitted to peritoneal equilibrium test (PET) and nutritional status evaluation by bioimpedance analysis.

Results: Patients aged 43 ± 15 years (69.2% women), were on PD for a median time of 23 (4-70) months. Nine patients (69.2%) were well nourished/mild nutritional risk and 8 (61.5%) patients were classified as high/high average (H/HA) transporters. Fetuin-A was 352 ± 61g/L and CPP was 29.8 ± 11.8µg/mL. The serum CPP was higher in H/HA than in low/low average transporters (34.1 ± 10.7% *vs.* 13.1 ± 1.9%, p=0.034) and correlated with dialysis vintage (r=0.579, p=0.030). The dialysate loss of fetuin-A correlated with the loss of albumin (r=0.967, p=0.0001), glucose absorption (r=0.626, p=0.022), muscle mass (r=0.620, p=0.042), cell mass (r=0.627, p=0.039), bone mass (r=0.791, p=0.004), and the percentage of fat body (r=-0.624, p=0.040).

Conclusions: The CPP appears to be higher in patients longer on PD, especially in those with H/HA transporters characteristic. Muscle reserves and nutrition status may influence this exchange.

Funding: Government Support - Non-U.S.

TH-PO738

Fibroblast Growth Factor21 Is Increased in CKD Patients and React with Protein Restriction
Mio Matsuura, Hirofumi Nishikawa, Natsuki Maeda, Tatsuki Matsumoto, Yoshiko Shimamura, Kosuke Inoue, Yoshinori Taniguchi, Taro Horino, Yoshio Terada. *Endcrinology, Matabolism and Nephrology, Kochi Medical School, Japan.*

Background: Fibroblast growth factor21 (FGF21) is known to play a role in glucose and lipid metabolism. Recent report showed that FGF21 expression is increased in response to starvation and ketogenic diets. However, detailed mechanism and significance of FGF21 has not been elucidated in CKD. CKD patients are taking a protein-restricted diet as the treatment. This study was designed to investigate the regulation of FGF21 of CKD patients with low-protein diet and elucidate relation FGF21 and nutritional parameters and CKD-MBD biomarkers.

Methods: We made a continuously survey of CKD patient characteristics and outcomes in Kochi prefecture (Western area of Japan) for 24 months. Patients of CKD (total N=442) were enrolled. Serum sample were collected and measured FGF21 by using an ELISA kits. In addition, serum creatinine, hemoglobin, albumin, calcium, phosphate, NTproBNP and FGF23 were measured. Therapeutic effect of the low-protein diet is determined in the BUN / Creatinine ratio. This study was approved by Kochi Medical School review board. All patients provided written informed consent.

Results: The serum level of FGF21 was negatively correlated to BUN/Creatinine ration (P<0.0001: r=-0.319). Furthermore, albumin level was negatively correlated (P<0.001: r=-0.171). FGF21 is increased in response to the protein restriction. The serum level of FGF21 elevated significantly according to the progression of CKD stage. The serum level of FGF21 was positively correlated to NTproBNP (P<0.0001: r=0.249).

Conclusions: In CKD patients, the serum level of FGF21 were increased according to CKD stages and response to the protein restriction. Our date indicate that FGF21 may play a role in CKD pathogenesis, especially in nutritional aspect.

TH-PO739

Obesity and Immunosuppressive Therapy Effects on Glucose Intolerance in Allogeneic Kidney Transplant Patients
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Background: The population of kidney transplant patients receiving immunosuppressive treatment is particularly susceptible to glucose intolerance, and development of post-transplant diabetes in the future.

Methods: The study covered 152 patients with a functioning kidney transplant more than 6 months after the procedure (Ktx): 81 women and 71 men. The average patient age was 47.8±11.6 years. The patients received immunosuppressive dual therapy (steroids, ICN) or triple therapy (steroids, calcineurin inhibitor, proliferation inhibitor). Their body composition was assessed using the bioimpendance method (BIA) and anthropometric measurements. Nutritional status and obesity type were determined with the Waist-to-Height Ratio (WHtR) and the Waist-to-Hip Ratio (WHR). Glucose intolerance was evaluated by several measurements of fasting blood glucose levels, and its association with a specific type of obesity and glomerular filtration rate (eGFR) calculated with the MDRD formula was analysed. Patients with diabetes diagnosed before the kidney transplant procedure were excluded from the study.

Results: Glucose intolerance was diagnosed in 56% of subjects, and obesity was found in 48% of patients with hyperglycaemia and 20% of patients with correct glucose levels. The subjects with an android body type were more susceptible to glucose intolerance compared with those with the gynoid body type (p=0.004). Increased glucose blood levels were significantly correlated to cyclosporin A and tacrolimus levels (p<0.05). Furthermore, the patients with an android body type had lower eGFR compared with people with the correct body weight (p=0.004).

Conclusions: One of the basic directions for management of kidney transplant patients with glucose intolerance accompanied by abdominal obesity is reduction of their body weight combined with physical activity adapted to patients' current physical fitness. Treatment with calcinerin inhibitors (IC), particularly tacrolimus, may be a predictor for diabetes in transplant patients; therefore they should be regularly monitored.

Funding: Private Foundation Support

TH-PO740

Obesity Paradox in Hemodialysis: Could Omega 3 Be the Link?
Ana Rita Mateus Martins,[1,2] Inês Filipa Moreira,[1] Ana Sofia Ferreira,[1] Iolanda Nunes Godinho,[1] Teresa Adragao,[2] Andre L. Weigert.[1,2] *[1]Davita Obidos, Davita Portugal, Portugal; [2]Nephrology Dept, Hospital Santa Cruz, Lisbon, Portugal.*

Background: In advanced chronic kidney disease (CKD), obesity is paradoxically linked with greater survival. The potential mechanisms underlying the "obesity paradox" in CKD are still not well known. Omega3 intake has been linked to many beneficial impacts in cardiovascular (CV) health, affecting lipid profile, insulin resistance, platelet aggregation. Therefore, we postulate that patients (pts) who consume large amounts of fish may have more favorable CV status.

Methods: Observational study in 155 prevalent Portuguese HD pts. We obtained baseline demographic data, blood biochemistry, comorbidities and daily diet. In order to evaluate omega 3 incorporation in red blood cell (RBC) membranes, we used frozen RBC for FAME (fatty acid methyl esters) and obtained the percentage of eicosapentaenoic (EPA) and docosahexaenoic (DHA) in total FAME.

Results: In our cohort 79 were male, mean age was 67 years, 39% had diabetes (DM) and average time on HD was 73 months. Body index mass (BIM) was 26±4.6 kg/m^2. The follow up period time was 21 months and there were 71 CV events and 52 hospitalizations. BIM was associated with RBC omega3 incorporation (*Pearson*; p=0,045). Higher BIM was associated with a lower number of CV events (*Pearson*; p=0,038) and with lower hospitalization time (*Pearson*: p=0,04). In a multivariate analysis (linear regression), a higher EPA+DHA RBC incorporation was associated with a higher BIM and albumin, in a model adjusted to time on dialysis and age (Exp(B) 0.088; p=0.05; IC 95% 0.002 to 0.177). Larger hospitalization time was correlated with lower EPA+DHA RBC incorporation (linear regression: Exp(B)-5.7; p=0.023; IC 95% -10.52 to -0.91), in a model adjusted to DM and age. In a binary regression, CV event were associated with EPA+DHA RBC incorporation (Exp(B) – 1,56; p=0.05; IC 95% -2,36 to 0.98), in a model adjusted to age, time on HD and DM.

Conclusions: There appears to be a consistent association between obesity and an higher omega3 incorporation with better clinical outcomes in our cohort of HD pts. This fact may suggest a possible explanation for the reverse obesity epidemiology in advanced CKD.

Funding: Private Foundation Support

TH-PO741

Serum Tatal Ghrelin Maybe a Biomarker for Mortality in Hemodialysis Patients
Jie Ma, Yang Yu, Xuemei Li. *Nephrology Dept, Peking Union Medical College Hospital.*

Background: Ghrelin is involved in the pathogenesis of protein-energy wasting (PEW), inflammation, and cardiovascular complications in end-stage renal disease (ESRD). Plasma ghrelin may prove to be a powerful biomarker of mortality in hemodialysis patients. The objective of this study was determined the correlation between serum ghrelin and mortality in dialysis patients.

Methods: We prospectively followed a cohort of 119 maintenance hemodialysis patients for 30 months in Peking Union Medical College Hospital dialysis center. We assessed the impact of the serum total ghrelin and free ghrelin levels on the cumulative survival rates according to the cox-regression method in the dialysis patients.

Results: A total of 119 cases were enrolled this study, male 59, female 60, age 19-90years, mean age 59.3years, with duration of dialysis for10-95 months. The mean serum total ghrelin level was detectable in all patients was 1200.11±750.19pg/mL (median 971.52pg/mL). The mean serum free ghrelin level was 122.98±75.17pg/mL (median 109.31pg/mL). Total ghrelin was significantly associated with dialysis patient mortality(P=0.032), but free ghrelin not(P=0.061).

Conclusions: Ghrelin has significant regulatory roles in energy homeostasis, systemic inflammation, and the cardiovascular system. From our study,serum total ghrelin was significantly associated with dialysis patient mortality, we considered that serum total ghrelin maybe a meaningful biomarker of mortality in dialysis patients.

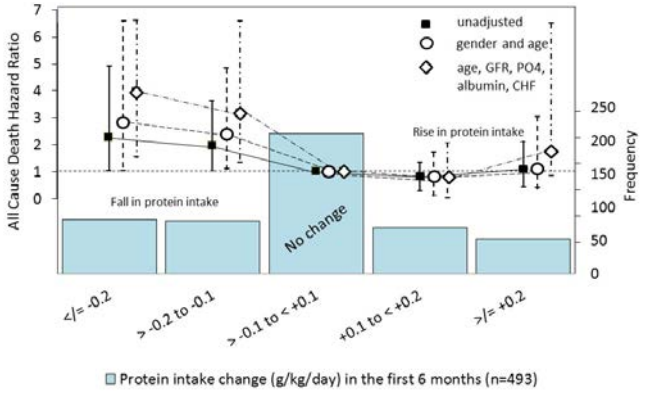
TH-PO742

Restriction of Protein Intake in Non-Dialysis Chronic Kidney Disease Patients May Be Not Beneficial when a Renal Dietitian Is Not Available Pablo Molina,[1] Sandra Beltrán,[1] Jose Roldan Iborra,[2] Marco Montomoli,[1] Belen Vizcaino,[1] Veronica Escudero,[1] Cristina Castro,[1] Jonay Pantoja Perez,[1] Ana Avila,[1] Julia Kanter,[1] Luis M. Pallardo,[1] Jose L. Gorriz.[1] *[1]Nephrology, Dr Peset Univ Hospital, Spain; [2]Dietetic Unit, Alcer Turia, Spain.*

Background: Due to safety concerns, CKD patients who are on a low-protein diet (LPD: 0.60–0.80 g/kg/d), should be carefully monitored. However, few patients receive dietary counseling before dialysis, and whether LPD without dietitian counseling is beneficial or risky remains unknown. We tested the hypothesis that LPD when an onsite renal dietitian is not available is independently associated with poor outcomes in CKD population.

Methods: The relation between dietary protein intake (DPI) and its change during the first 6 months, and mortality and kidney progression were examined in a 3-year cohort of 493 clinically stable patients with CKD stages 4-5 with a baseline DPI≥0.60 g/kg/d, using multivariate Cox models. General advice was given regarding reducing DPI, but a dietician did not routinely assess the patients. DPI was estimated by using 24-h urea nitrogen according to Maroni's formula.

Results: At baseline, the mean DPI was 0.89±0.20 g/kg/d. After a median follow-up of 31 months, there were 72 deaths and 151 required dialysis. The best survival was associated with DPI>1.0 g/kg/d, whereas DPI between 0.6 to 0.8 g/kg/d was associated with greater mortality. A decrease in DPI during the first 6 months was associated with greater death risks in the subsequent 30 months, whereas an increase in DPI tended to correlate with better survival. DPI did not predict renal progression.



Conclusions: LPD or decrease in DPI over time was associated with increased risk for death in ND-CKD patients in which counseling with a renal dietitian was not available, with no benefits on kidney progression. These results reinforce the need for predialysis dietitian care, especially when LPD is prescribed.

Funding: Private Foundation Support

TH-PO743

α Ketoanalogues of Amino Acids in Patients with Chronic Kidney Disease: Experience of a Nutritional Care Center Rocio Urbina, Silvia Moran, Julia Nava, Verónica Figueroa, Rafael Montufar. *Centro de Atención Nutricional, Fresenius Kabi México, Ciudad de México, Distrito Federal, Mexico.*

Background: A low protein diet (LPD) supplemented with alpha keto analogues of amino acids (AKAAA) has a metabolic stabilizing effect, which prolongs the pre-dialysis stage and improves the quality of life.

Methods: The effects of LPD supplemented with AKAAA (sLPD) were assessed the body composition and renal function stage in patients in the stages 3,4 and 5 of chronic kidney disease. This was a retrospective, longitudinal study at the Fresenius Kabi Mexico's Nutritional Care Center (NCC); records were reviewed with AKAAA treatment periods >6 months (1 tablet per 5 to 7 kg), LPD (0.5 to 0.6 g/kg of ideal body weight). The variables measured were; anthropometry, body composition, dynamometry, blood pressure, laboratory test and creatinine clearance at 30,60 and 180 days. The information was captured and evaluated by personnel unrelated to the NCC , the software SPSS version 20 was used in the statistics evaluation.

Results: 210 cases were included; the mean age was 63.5 years, 119 male patients and 91 female patients. A cut-off data was performed after 6 months of sLPD treatment, the results were 39 patients in stage 3, 105 patients in stage 4 and 66 patients in stage 5; body weight, fat mass and fat-free mass decreased significantly; an increase in muscle strength was observed; serum albumin and total protein did not change. Blood pressure showed no difference; urea, creatinine and creatinine clearance, show a decrease levels showed significant decreases (p<0.0001) ; measures of uric acid and Ca/P declined during the study.

Conclusions: Supplemented with nutritional therapy AKAAA, allowed address metabolic abnormalities of uric acid, calcium, phosphorus, glucose, cholesterol and triglycerides. No alterations were observed in nutritional status according to anthropometric and biochemical parameters. It is proposed that this procedure may be a link in the model of comprehensive care of patients with CKD.

Funding: Pharmaceutical Company Support - Fresenius Kabi

TH-PO744

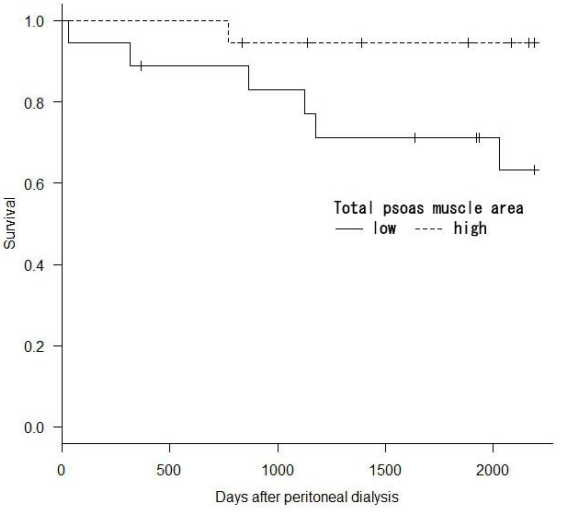
Psoas Muscle Area Predicts Mortality among Incident Peritoneal Dialysis Patients Yu Honda, Nanae Matsuo, Yukio Maruyama, Emi Kimoto, Yasuyuki Nakada, Masatsugu Nakao, Yudo Tanno, Ichiro Ohkido, Keitaro Yokoyama, Takashi Yokoo. *Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan.*

Background: Cardiovascular disease (CVD) is common among chronic kidney disease (CKD) patients. Malnutrition, inflammation and atherosclerosis (MIA) syndrome was reported as one of the mechanisms of a high prevalence of CVD in this population. Since it was also associated with mortality, to assess the risk of MIA syndrome is an important issue in CKD patients. Body composition, especially estimated muscle mass, has been recognized as a useful nutritional marker. Total psoas muscle area (PMA) measured by computed tomography (CT) scan is one of the methods to estimate muscle mass. Although its usefulness already has been reported among non-renal patients, studies conducted in dialysis patients are limited. The aim of this study was to evaluate whether PMA at the start of peritoneal dialysis (PD) was associated with clinical parameters and mortality.

Methods: This study included 36 male patients (59±11 years, diabetes 36%) who initiated PD between 2007 and 2008. We evaluated the associations between PMA at the third lumbar vertebra (L3) level measured by CT scan and clinical parameters. We divided the patients into two groups based on the median PMA at the L3 level and compared each cumulative survival rates using Kaplan-Meier method.

Results: The mean PMA at the L3 level was 18.41 cm^2. PMA at the L3 level was inversely correlated with serum albumin (rho=-0.352, P<0.05) and positively with body weight (rho=0.514, P<0.01) and body mass index (rho=0.454, P<0.05). 6-year cumulative survival rates were significantly lower in the low PMA group than in the high PMA group (P<0.05).

Conclusions: PMA at the L3 level was related to mortality. We suggest that PMA assessed on CT is the useful parameter of body composition among incident PD patients.



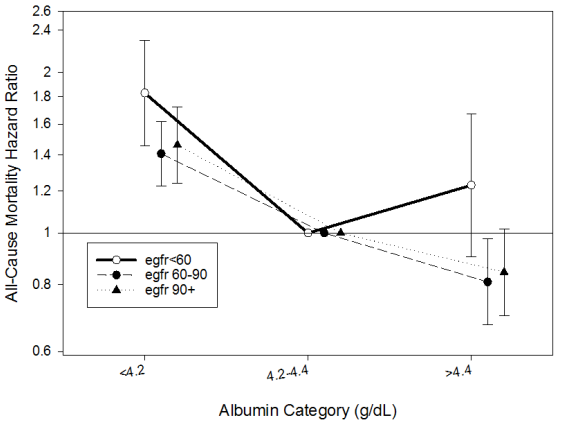
TH-PO745

Serum Albumin Concentration, Estimated Glomerular Filtration Rate, and Survival among 1999-2010 NHANES Participants Amanda R. Tortorici,[1] Elani Streja,[1] Melissa Soohoo,[1] Daniel L. Gillen,[1] Connie Rhee,[1] Keith C. Norris,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]UCLA.*

Background: As a potential strong predictor of longevity in the general population and in those with chronic kidney disease, we sought to examine whether higher serum albumin (Alb) levels are associated with greater survival in the nationally representative NHANES cohort.

Methods: We identified 31,274 participants from the 1999-2010 continuous NHANES survey who had available Alb measurements and laboratory values for calculation of eGFR, as well as survival data. Follow up time began the date after Alb measurement until December 31, 2011. We analyzed the association of Alb (<4.2, 4.2-<4.4 and ≥4.4 g/dL) with mortality across strata of eGFR (<60, 60-<90, and ≥90 ml/min/1.73m^2) using Cox proportional hazards models adjusted for age, sex, race, and education.

Results: The mean±SD age of the cohort was 48±20 years, among whom 52% were female, 20% were African-American, 22% were Mexican-American, and 7% were other Hispanic American. Across all eGFR strata, participants with Alb levels <4.2 g/dL (n=11,384 people) had higher mortality rates compared to the reference group (Alb 4.2-<4.4 g/dL, n=10,793 people). In contrast, participants with Alb levels >4.4 g/dL (n=9097) and eGFR 60-90 ml/min/1.73m^2 (n=1,911) experienced lower rates. See figure for adjusted hazard ratios.



Conclusions: Among 1999-2010 continuous NHANES participants, lower Alb levels were associated with 40% to 80% greater mortality risk irrespective of the eGFR values.

Funding: NIDDK Support

TH-PO746

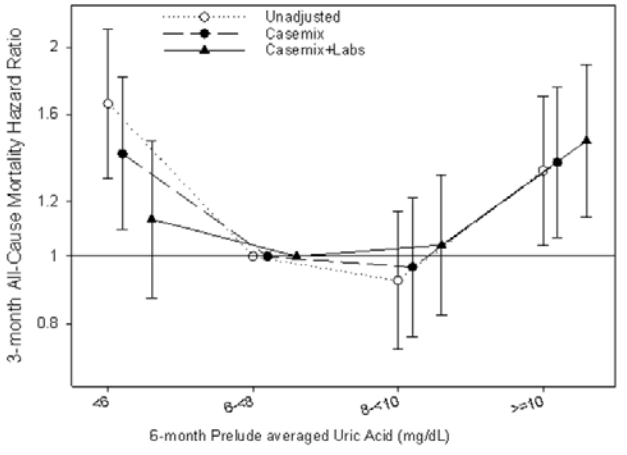
Association of Pre-ESRD Uric Acid with Post-ESRD Mortality: A Transition of Care in CKD Study

Vanessa A. Ravel,[1] Connie Rhee,[1] Elani Streja,[1] Yoshitsugu Obi,[1] Jason Chou,[1] Melissa Soohoo,[1] Daniel L. Gillen,[1] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Univ of Tenn.*

Background: Although uric acid is commonly elevated in chronic kidney disease (CKD) patients, it has only recently been posited as a possible risk factor contributing to the progression of CKD. To date, most studies have focused on linking pre-ESRD uric acid to adverse pre-ESRD outcomes. We sought to examine the association between pre-ESRD serum uric acid and post-ESRD mortality among US veterans.

Methods: From a cohort of US veterans who transitioned to dialysis between 10/2007-09/2011, we identified 6,086 patients with a pre-dialysis uric acid measurement in the 6 months before transitioning to ESRD. We examined pre-ESRD uric acid as a predictor of all-cause mortality within the first 3 months post-transition using Cox proportional hazards models adjusted for case-mix covariates, BMI at prior to initiation and additional adjustments for laboratory values and eGFR (both 6-month averaged and last available before dialysis initiation).

Results: The mean age of the cohort was 67±11years old and included 2% females, 71% diabetics, and 34% African Americans. The 6-month prelude uric acid average was 8.07 ± 2.03 mg/dL. Overall, 9.3% of patients died during the first 3 months on dialysis. 6-month prelude uric acid exhibited a U-shaped association with 3-month post-ESRD all-cause mortality. Compared to the reference (6-<8 mg/dL), patients with uric acid level ≥10 mg/dL have the highest early mortality across all levels of adjustment.



Conclusions: Both low and very high serum uric acid (<6 and ≥10 mg/dL, respectively) during the prelude period to ESRD are associated with higher early all-cause mortality in US veterans. Whether this U-shaped association calls for changes to therapeutic paradigms regarding pre-ESRD hypo- and hyperuricemia warrants further studies.

Funding: NIDDK Support

TH-PO747

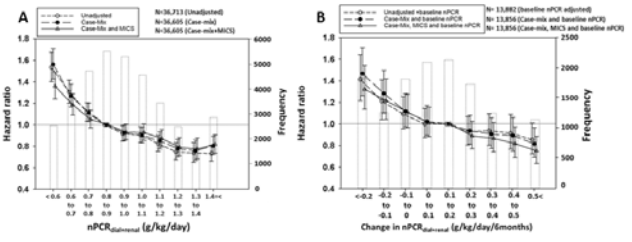
Associations of Dietary Protein Intake with Mortality in Incident Hemodialysis Patients: Using Normalized Protein Catabolic Rate Accounting for Residual Kidney Function

Rieko Eriguchi, Yoshitsugu Obi, Elani Streja, Connie Rhee, Melissa Soohoo, Kamyar Kalantar-Zadeh. *UC Irvine.*

Background: There are inconsistent reports on the association of normalized protein catabolic rate (nPCR), an index of dietary protein intake, with mortality among hemodialysis patients. This discrepancy may be partly due to not accounting for residual renal urea clearance (CLurea) among hemodialysis patients when evaluating nPCR.

Methods: Among 36,713 incident hemodialysis (HD) patients in a large dialysis organization from 1/2007 to 12/2011, we examined baseline and change in nPCR during the first 6 months of dialysis accounting for residual kidney function. Cox proportional hazard models with adjustment for case-mix covariates and markers of the malnutrition-inflammation cachexia syndrome (MICS) were used to examine associations of these nPCR markers with mortality.

Results: Patients were 62±15years old, 37% female, 28% African-American, and 47% diabetics. At baseline, median (IQR) of nPCR with CLurea was 0.94 (0.77, 1.14) g/kg/day. In the fully adjusted model, baseline nPCR< 0.7 g/kg/day was significantly associated with higher mortality, and nPCR > 1.1 g/kg/day was significantly associated with better survival compared to the reference (0.8-0.9 g/kg/day). Finally, a decrease in nPCR < 0.1 g/kg/day was associated with higher mortality whereas an increase in nPCR> 0.5 g/kg/day was associated with better survival.



Conclusions: Among incident HD patients, patients with low nPCR accounting for CLurea , and those who decreased in nPCR over the first 6 months of HD had a higher risk of death. Additional studies are needed to investigate the differences in mortality risk prediction for nPCR with and without factoring CLurea.

Funding: NIDDK Support

TH-PO748

Metabolites Associated with Dietary Protein Intake in the Modification of Diet in Renal Disease (MDRD) Study

Casey Rebholz,[1] Morgan Grams,[1] Lawrence J. Appel,[1] Mark J. Sarnak,[2] Lesley Inker,[2] Andrew S. Levey,[2] Josef Coresh,[1] David Graham.[1] *[1]Johns Hopkins Univ; [2]Tufts Medical Center.*

Background: Dietary protein intake leads to production of a range of known and unknown metabolic effects of possible relevance to CKD symptoms and progression. Discovering metabolic consequences of diets with lower vs. higher protein intake could elucidate new pathways of protein metabolism in CKD patients.

Methods: Metabolites were measured by Metabolon (HD4 untargeted platform) using gas-chromatography-mass spectrometry and liquid chromatography-mass spectrometry in serum specimens from the 12 month follow-up visit in the MDRD study for 470 participants in study A (GFR 25-55 mL/min/1.73 m^2) and 196 participants in study B (GFR 13-24 mL/min/1.73 m^2). We used multivariable linear regression to test for differences in log-transformed metabolites (outcome) by to dietary protein intervention groups (exposure). Statistical significance was assessed at the Bonferroni-corrected threshold: $0.05/1{,}194=4.2*10^{-5}$.

Results: A total of 1,194 known and unknown metabolites were detected. After adjusting for age, sex, race, GFR, cause of kidney disease, and blood pressure intervention, 137 metabolites (86 known from 27 distinct pathways including 10 amino acid pathways and 51 unknown) were significantly different among participants randomized to the low protein diet vs. moderate protein diet in study A. Among participants randomized to the very low protein diet vs. low protein diet, 29 metabolites (20 known from 8 distinct pathways including 5 amino acid pathways and 9 unknown) were significantly different in study B.

Table. Selection[1] of Known Metabolites Associated with Dietary Protein Intake in the MDRD Study

Comparison	Metabolite	Pathway	β coefficient[2]	P-value
Study A[3]: Low Protein Diet vs. Moderate Protein Diet	tiglylcarnitine	leucine, isoleucine, and valine metabolism	-0.6	$<1.0*10^{-40}$
	1-(1-enyl-palmitoyl)-2-arachidonoyl-GPE (P-16:0/20:4)	plasmalogen	-0.4	$1.8*10^{-20}$
	6-hydroxyindole sulfate	chemical	-0.4	$2.2*10^{-13}$
	guanidinosuccinate	guanidino and acetamido metabolism	-0.8	$2.4*10^{-13}$
	indolin-2-one	food component/plant	-0.4	$9.2*10^{-11}$
Study B[4]: Very Low Protein Diet vs. Low Protein Diet	3-hydroxy-2-ethylpropionate	leucine, isoleucine, and valine metabolism	1.6	$<1.0*10^{-40}$
	creatine	creatine metabolism	-0.4	$2.1*10^{-9}$
	1-(1-enyl-palmitoyl)-2-arachidonoyl-GPC (P-16:0/20:4)	plasmalogen	-0.2	$2.6*10^{-9}$
	sulfate	chemical	-0.1	$6.3*10^{-6}$

[1] Selection of 5 known metabolites representing distinct pathways was based on statistical significance for each comparison.
[2] β coefficient represents the adjusted effect of lower vs. higher randomized protein diet on metabolite concentration.
[3] Study A: low protein diet (0.58 g/kg/day) vs. moderate protein diet (1.3 g/kg/day)
[4] Study B: very low protein diet (0.28 g/kg/day + 4-9 mg/kg/day of an essential ketoacid supplement) vs. low protein diet

Conclusions: Among CKD patients, an untargeted metabolomic platform identified multiple pathways and metabolites affected by randomized groups of dietary protein consumption. Further research is necessary to characterize unknown compounds and evaluate the ability of these metabolites to predict CKD progression.

Funding: NIDDK Support

TH-PO749

Dietary Modifications for Adults with Chronic Kidney Disease: Meta-Analysis of Randomized Trials Suetonia Palmer,[1] Katrina L. Campbell,[2] Jonathan C. Craig,[3] David W. Johnson,[2] Marinella Ruospo,[4] Allison Tong,[3] Giovanni F.M. Strippoli.[3,4,5] *[1]Univ of Otago Christchurch; [2]Univ of Queensland; [3]Univ of Sydney; [4]Diaverum; [5]Univ of Bari.*

Background: Dietary changes are routinely recommended in patients with CKD on the basis of randomized evidence in the general population and non-randomized studies in CKD that suggest healthy eating patterns may prevent cardiovascular events (CVEs) and mortality. Patients with CKD have prioritized dietary interventions as an important treatment uncertainty. This systematic review aimed to assess the benefits of dietary modification in patients with CKD.

Methods: Meta-analysis of randomized clinical trials (RCTs) of any dietary modification in adults with CKD was conducted. Electronic databases were searched in January 2016 without language restriction. Evidence quality was assessed using GRADE.

Results: The meta-analysis included 10 RCTs (874 patients) of dietary counseling, Mediterranean diet, low-carbohydrate, polyphenol-enriched diet, or increased fruit and vegetable intake for 12 months on average. Evidence quality was very low. Dietary counseling significantly lowered diastolic blood pressure (-8.6 mmHg, CI -13.3 to -3.98) but not systolic blood pressure (-6.73, CI -16.9 to 3.44). A Mediterranean diet lowered serum LDL cholesterol levels by 1.00 mmol/l (95% CI -1.56 to -0.44) and increased serum albumin levels by 0.60 g/l (CI 0.11-1.09). Increased fruit and vegetable intake lowered systolic blood pressure by 7.10 mmHg (CI -9.60 to -4.60), while effects on diastolic blood pressure were not available. A carbohydrate-restricted diet with higher olive oil intake and lower red meat content reduced risk of serum creatinine doubling (RR 0.53, CI 0.33-0.86). Quality of life outcomes were sparse. Dietary modification had uncertain effects on ESKD, CVEs, and mortality.

Conclusions: Dietary interventions in adults with CKD have potentially beneficial effects on chronic disease risk factors including serum cholesterol, blood pressure, and serum albumin levels, but have uncertain effects on patient-level outcomes such as CVEs, ESKD, mortality, and quality of life.

TH-PO750

Reproducibility of a Test-Battery for Physical Performance and Protein-Energy Wasting in Hemodialysis Patients Manouk Dam,[1] Peter Jm Weijs,[1] Caroline Douma,[2] Brigit C. van Jaarsveld.[3] *[1]Nutrition and Dietetics, VU Univ Medical Center, Amsterdam, Netherlands; [2]Nephrology, Spaarne Gasthuis, Hoofddorp, Netherlands; [3]Nephrology, VU Univ Medical Center, Amsterdam, Netherlands.*

Background: The assessment of physical performance (PP) and protein-energy wasting (PEW) is hampered by large variability and controversy between researchers about which tests to use. Combining different tests is advocated, but variation in test outcomes has not been studied. We studied reproducibility of a test-battery for PP and PEW in HD pts.

Methods: Two measurements with 1-2 month interval, without interventions in-between, were performed by one investigator in 33 HD pts (2-4x/wk, 3-5 hr). PP was measured by the short physical performance battery (SPPB: gait speed, chair rises, balance), 6-min walk test, handgrip strength and 7-day physical activity monitor (PAM). PEW was measured by the visual analogue scale for appetite (VAS), subjective global assessment (SGA), mid-upper arm muscle circumference (MUAMC), fat free and fat mass measured with bio-electrical impedance. Reproducibility was assessed by paired t-tests and intraclass correlation coefficients.

Results: No differences were found between the 1st and 2nd measurement, apart from a slight increase in the SPPB:

Variables	1st measurement (mean±SD)	2nd measurement (mean±SD)	*P*	ICC*
SPPB (ranking 1-12)	8.2±2.6	9.4±1.7	<0.05	0.79
6-minute walk test (m)	350.2±138.0	351.8±116.0	NS	0.93
Handgrip strength (kg)	27.4±9.9	26.5±10.2	NS	0.96
PAM activity score	14.2±4.4	13.3±5.3	NS	0.47
VAS appetite (cm)	7.6±2.1	7.4±2.2	NS	0.43
SGA (score 1-7)	5.7±0.8	5.7±0.7	NS	0.81
MUAMC (cm)	25.1±5.0	25.5±3.7	NS	0.77
Fat free mass (kg)	36.1±8.4	36.9±8.2	NS	0.81
Fat mass (kg)	31.4±14.4	33.3±13.9	NS	0.83

*ICC:<0.40 poor, 0.40-0.59 fair, 0.60-0.75 good and ≥0.75 excellent correlation.

Conclusions: The proposed test-battery to assess PP and PEW in HD pts through a diversity of parameters shows excellent reproducibility of most components. SPPB revealed a possible learning effect, necessitating a second measurement of SPPB in order to avoid overestimation of the effect on physical performance.

Funding: Pharmaceutical Company Support - Baxter Global

TH-PO751

Prediction of LBM Using One Day Urinary Creatinine Excretion and Creatinine Clearance Rate in Non-Dialysis CKD Patients Tomohito Matsunaga. *Kidney Center, Eijinkai Hospital, Osaki, Miyagi, Japan.*

Background: The assessment of Lean body mass (LBM) is quite important to monitor the nutrition status of CKD patients. And it is well known that one day urinary creatinine excretion (UCE) reflects LBM (muscle mass) strongly. The purpose of this study is to predict LBM using one day urinary creatinine excretion and creatinine clearance rate in non-dialysis CKD patients.

Methods: UCE were measured by one day urinary collection in 35 non-dialysis CKD3-5 patients (27 males, 8 females; mean age 68.4±7.7 years; 12 DM patients). Ccr was calculated by UCE and Serum Creatinine, not collected body surface area. LBM was measured using BIA (Inbody 3.0).

Results: The mean levels of UCE, Ccr and BH (Body Height) were 0.969±0.215 g/day, 27.62±16.27 ml/min and 1.62±0.08m. LBM (45.54±7.55kg) was correlated with UCE and BH ($r=0.802$ $p<0.01$ and $r=0.903$ $p<0.01$, respectively) not correlated with Ccr. Multiple linear regression analysis showed that LBM was correlated with UCE, BH and Ccr ($r=0.960$ $p<0.01$). The obtained equation of regression was as follows: estimated LBM = 17.00 x UCE + 52.77 x BH – 0.09 x Ccr – 53.95. Estimated LBM was significantly correlated with measured by BIA ($r^2=0.922$, $p<0.01$).

Conclusions: These findings suggest that LBM can be predicted using UCE, BH and Ccr in non-dialysis CKD patient.

TH-PO752

Acute Effects of Nutritional Supplementation during Hemodialysis on Hemodynamics and Symptoms Brandon Kistler,[1,2] Annabel Biruete,[2] Jin Hee Jeong,[2] Peter J. Fitschen,[2] Kevin Heffernan,[3] Karen Chapman-Novakofski,[2] Talat Alp Ikizler,[4] Ken Wilund.[2] *[1]Ball State Univ, Muncie, IN; [2]Univ of Illinois, Urbana, IL; [3]Syracuse Univ, Syracuse, NY; [4]Vanderbilt Univ, Nashville, TN.*

Background: Due to the potential for hemodynamic instability following eating during hemodialysis (HD), many clinics have restricted food in favor of oral nutritional supplements (ONS). However, the effect of ONS on treatment hemodynamics has not been examined.

Methods: 11 HD patients (47±13 years, 73% male, 64% African American) underwent resting measures of cardiac function (ejection fraction, EF) and vascular structure (carotid intima-media thickness) via ultrasound, vascular function (aortic pulse wave velocity, PWV and augmentation index, AIx) via tonometry, blood pressure (BP), and autonomic function (heart rate variability, HRV and baroreceptor sensitivity, BRS) via plethysmography, followed by standard HD treatment with and without ONS (Nepro, Abbott). Beat-to-beat hemodynamics, gastrointestinal (GI) symptoms, and efficiency were measured throughout each treatment. The delta BP (lowest BP after ONS – Pre-ONS BP) was correlated with descriptive variables.

Results: There was no interaction between sessions for any hemodynamic measure ($p>0.05$ for all), but cardiac output ($p=0.04$) and heart rate ($p=0.05$) were higher throughout the ONS session. GI symptoms (Reflux, Abdominal Pain, Indigestion, Constipation, Diarrhea) and the reduction ratio of β2-microglobulin (ONS, 37.89 ± 15.63% vs. HD, 48.97 ± 18.62%) were not significantly different between ONS and HD ($p>0.05$ for all). Aortic PWV (9.0±1.1 m/s), AIx (21.1±10.9%), albumin (4.06±0.35 g/dL), IMT (0.62±0.13mm), EF (61.1±15.6%), and ultrafiltration (8.8±2.2 ml/kg/min) were not associated with delta BP following ONS. However, BRS (Down-Down, 9.30±7.08 ms/mmHg) was correlated with the change in systolic BP and mean BP ($r=.79$ and .71, respectively; $p<.05$).

Conclusions: We found minimal hemodynamic alterations, but no significant changes in GI symptoms or efficiency in response to a renal specific ONS during HD. Measures of autonomic function were associated with the maximum change in BP following ONS and should be a future target of research.

Funding: Private Foundation Support

TH-PO753

Short-Term Potato Intake and Endothelial Function Lea Borgi, John P. Forman. *Medicine, Renal Div, Brigham and Women's Hospital, Boston, MA.*

Background: Recently, potatoes have been reintroduced into food packages for the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), and restrictions on potatoes from school lunches have been lifted. In their report, the Institute of Medicine stated that evidence for adverse health effects of potatoes is lacking. However, we published that increasing consumption of boiled, baked or mashed potatoes was independently associated with an increased risk of developing hypertension in three large prospective cohort studies of US women and men. The mechanisms underlying this association are still unclear. We hypothesized that the association of potatoes with hypertension may be mediated by endothelial dysfunction.

Methods: We performed a cross-sectional analysis using data obtained from the NIH-funded ongoing Modifiable Effectors of Renin System Activation Treatment Evaluation (MODERATE) trial. Dietary information and endothelial-dependent vasodilation (EDV, a measure of endothelial function using brachial artery ultrasound) were ascertained at baseline. We used multivariable linear regression to analyze the independent association of self-reported potato intake and EDV while controlling for multiple potential confounders.

Results: By the end of the trial, 209 participants underwent brachial artery ultrasound and reported potato intake over the previous day preceding EDV measurements. Compared with participants with no intake of potatoes, those who consumed one or more servings the day before had significantly worse endothelial function after adjusting for potential confounders (difference in EDV = -1.7%, p-value=0.01). By comparison, every 10 year increase in age was associated with a 1.2% lower EDV, indicating the important magnitude of the association between potatoes and EDV.

Conclusions: We found that short-term potato intake was associated with substantially worse endothelial function. These results support the hypothesis that endothelial dysfunction may be a potential mechanism underlying the association of potatoes with hypertension.

TH-PO754

Use of a Smartphone Application to Provide Dietary Feedback in Hemodialysis Patients - A Pilot Study Brendan T. Bowman, Mitchell H. Rosner, Elaine T. Mccall, Lesley Mcphatter. *Div of Nephrology, Univ of Virginia, Charlottesville, VA.*

Background: Hemodialysis (HD) patients are required to follow strict dietary regimens with limited phosphorus and potassium intake. Despite this, 40% of HD patients have phosphorous levels above current recommendations. The purpose of this study was to assess HD patients' ability to integrate mobile technology into nutrition self-care. We developed a smartphone app to provide phosphorous and potassium content reports to HD patients based on a photographic meal log.

Methods: We recruited 16 HD patients for a 90 day trial. Patients were asked to submit, via app, photos of all meals/snacks, a brief description, and number of binders taken. Photos were graded by the unit dietitian and a score report was provided to the patient within 48 hours. Weekly and monthly summary reports were also available and the app was integrated into care rounds. We collected demographic info, a pre & post nutrition survey, laboratory data, and app usage statistics.

Results: The app was loaded on 13 Android and iOS devices with three patients withdrawing prior to start. A total of 1022 meal photos were submitted with an avg of 79 per patient (0.87 reports/day/patient). Reporting compliance averaged 17% overall. Patients used the app an average of 58 days over the course of the trial. Lab review showed no definite trends overall. Among the six highest frequency users (> 50 photos submitted); however, four had significantly decreased phos levels compared to the preceding 90 days. The other two patients had decreased phos levels over the 90 days, though not to pre-trial levels. Potassium levels were unchanged.

Conclusions: This is the first trial of a smartphone based meal log and diet counseling app in HD patients. We believe this pilot demonstrates HD patients can integrate mobile apps into their nutrition counseling. The majority of patients submitted a significant number of meal photos over a sustained time period. Though lab data did not change overall, several patients showed > 10% improvement in phos, including the majority of the frequent use group.

Funding: Private Foundation Support

TH-PO755

ACF-TEI, a Novel Oral Uremic Toxin Adsorbent, Has Potent Adsorption Profiles and Reduces Serum Indoxyl Sulfate in Rodent Models of Chronic Kidney Disease Hiroshi Shimoyama, Yasumi Nishiwaki, Yoshimasa Takahashi, Tsunefumi Kobayashi. *Pharmaceutical Development Research Laboratories, TEIJIN Inst for Bio-Medical Research, TEIJIN Pharma Ltd., Tokyo, Japan.*

Background: Uremic toxins such as indoxyl sulfate (IS) accumulate in the blood of patients with impaired renal function. Since several observation studies have demonstrated a link between serum uremic toxin levels and clinical outcomes, they have much attention as key factors in the progression of chronic kidney diseases (CKDs) and cardiovascular diseases. Spherical activated carbon (AST-120) adsorbs uremic toxins secreted or produced in the intestinal tract and excretes them out of the body with feces. These functions are effective in improving symptoms of uremia and delaying the introduction of dialysis treatment for CKD patients. However, the oral adsorbents comprising AST-120 have insufficient adsorption performance and need to be taken at high daily doses. To improve their compliance and efficacy, we focused on active carbon fiber (ACF) and have identified a novel and potent oral uremic toxin adsorbent, ACF-TEI. In this study, we examined ACF-TEI *in vitro* adsorption profiles and *in vivo* effects on reducing serum IS.

Methods: As for the *in vitro* adsorption profiles of ACF-TEI, we examined the adsorption of indole, the precursor of IS in the intestinal tract, and digestive enzymes. To evaluate the *in vivo* effects, we orally administered ACF-TEI in normal mice and CKD model (bilateral nephrectomized and renal artery ligated) rats, and measured serum IS concentrations.

Results: Compared with AST-120, ACF-TEI showed more potent capacity and speed in adsorbing indole, whereas it had a low capacity to adsorb digestive enzymes to the same extent. In normal mice, ACF-TEI showed a higher effect of reducing serum IS than that of AST-120. Moreover, administered in CKD rats, ACF-TEI dose-dependently reduced the serum IS at lower doses than those of AST-120.

Conclusions: The adsorption capacity and efficiency of ACF-TEI were superior to AST-120. In addition, it was confirmed that ACF-TEI reduced the serum IS concentrations at lower doses than those of AST-120 in the CKD models. Thus, ACF-TEI is expected to show more beneficial effects than AST-120 in clinical.

TH-PO756

Folic Acid Supplementation Reduces the Concentrations of Uric Acid in Hypertensive Adults: A Predefined Sub-Study of the CSPPT Xianhui Qin,[1] Youbao Li,[1] Binyan Wang,[1] Genfu Tang,[2] Mingli He,[3] Delu Yin,[3] Yong Huo,[4] Xin Xu,[1] Fan Fan Hou.[1] *[1]Nanfang Hospital, Southern Medical Univ; National Clinical Research Center for Kidney Disease; [2]Anhui Medical Univ; [3]First People's Hospital, Lianyungang; [4]Peking Univ First Hospital.*

Background: We aimed to test the efficacy of folic acid therapy on reducing UA concentrations in a predefined sub-study of the China Stroke Primary Prevention Trial(CSPPT).

Methods: Eligible CSPPT patients, recruited from 20 communities in China, were randomly assigned to a double-blind daily treatment with a single tablet containing 10mg enalapril and 0.8mg folic acid(n=7685) or 10mg enalapril alone (n=7679).The main outcome was change in UA concentrations, defined as the UA level at the exit visit minus that at baseline. Secondary outcomes included:(1)controlled hyperuricemia; and (2)new-onset hyperuricemia in patients with normal baseline UA concentrations(<357μmol/L). Hyperuricemia was defined as a UA concentration≥417μmol/L in men or ≥357μmol/L in women. Controlled hyperuricemia was defined as a UA concentration<357μmol/L after treatment.

Results: Mean baseline UA were 293.9μmol/L. After a median treatment duration of 4.4 years, folic acid therapy significantly reduced the UA concentrations by a mean of 4.0μmol/L(95% CI:1.6-6.5,P<0.001). Moreover, folic acid therapy resulted in a significant increase in the adjusted odds of controlled hyperuricemia (30.3% vs 25.6%; OR:1.30;95%CI:1.00-1.68;P=0.046), and a significant decrease in the adjusted odds of new-onset hyperuricemia(15.0% vs 16.3%;0.88;0.78-0.99;P=0.040). More importantly, the largest reduction in UA concentrations was observed in the highest category of baseline homocysteine(Hcy) levels(P for interaction=0.020). Furthermore, there was a significantly negative association between Hcy reduction(Hcy at baseline minus that at the exit visit) and change in UA concentrations. After further adjustment for the reduction of Hcy, the effect of folic acid therapy on the reduction of UA was attenuated and insignificant (1.3μmol/L; -0.8, 3.5;P=0.219).

Conclusions: Folic acid supplementation can significantly reduce UA concentrations among hypertensive adults. The reduction of Hcy may be an important pathway to reduce UA concentrations.

Funding: Government Support - Non-U.S.

TH-PO757

Folic Acid Supplementation Reduces the Risk of Mortality Associated with Heavy Proteinuria: Findings from a Randomized Trial Youbao Li,[1] Xianhui Qin,[1] Binyan Wang,[1] Yong Huo,[2] Fan Fan Hou,[1] Xin Xu.[1] *[1]Nanfang Hospital, Southern Medical Univ; National Clinical Research Center for Kidney Disease; [2]Peking Univ First Hospital.*

Background: We aimed to evaluate whether baseline proteinuria and eGFR levels can modify the efficacy of folic acid supplementation on the risk of all-cause mortality in the China Stroke Primary Prevention Trial (CSPPT).

Methods: A total of 20,702 hypertensive patients without a history of major cardiovascular diseases were randomly assigned to double-blind daily treatment with a single tablet daily containing 10mg enalapril and 0.8mg folic acid (n=10,348) or 10mg enalapril alone (n=10,354).

Results: During median treatment duration of 4.5 years, in the enalapril alone group, both heavy proteinuria (versus normal, 10.8% *vs*. 2.7%; HR=3.30; 95%CI:2.10-5.18) and lower eGFR levels (<60 versus ≥90 mL/min/1.73m^2, 13.0% versus. 2.2%; 1.93; 1.19-3.12) were significantly associated with increased risk of all-cause mortality. Folic acid supplementation significantly reduced the risk of all-cause mortality in patients with heavy proteinuria(6.4% in the enalapril-folic acid versus 10.8% in the enalapril alone group, HR=0.49; 95%CI:0.26-0.94), but not in those with normal or mild proteinuria (2.8% versus. 2.9%,0.99;0.84-1.17; P for interaction=0.040).

	no. of events /no. of participants(%)				
	Enalapril	Enalapril-folic acid	HR (95%CI)	P Value	P for interaction
Overall	296/9675(3.1)	279/9674(2.9)	0.94(0.80-1.11)	0.486	
Proteinuria					
Heavy	24/223(10.8)	16/249(6.4)	0.49(0.26-0.94)	0.031	ref
Normal or mild	272/9452(2.9)	263/9425(2.8)	0.99(0.84-1.17)	0.908	0.040

However, eGFR levels did significantly modify the effect of folic acid supplementation in reducing the risk of all-cause mortality(P for interaction=0.228).

Conclusions: Among hypertensive patients without a history of major cardiovascular diseases, folic acid supplementation could reduce the mortality risk associated with heavy proteinuria.

Funding: Government Support - Non-U.S.

TH-PO758

Administration of IL-1ra Does Not Affect Carbamylation Load in Hemodialysis Patients

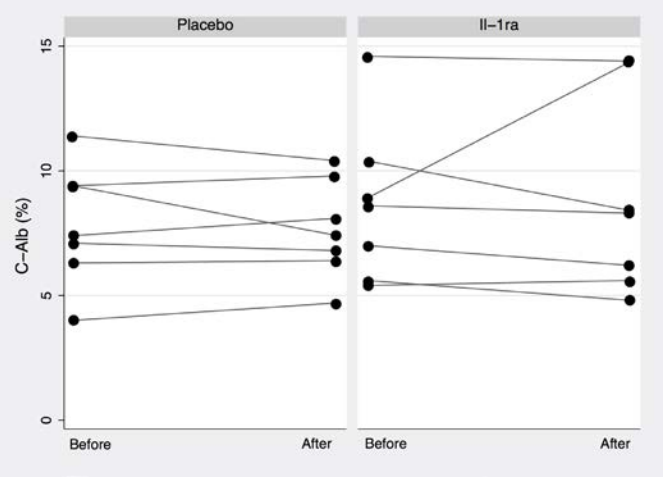
Charbel C. Khoury,[1] Adriana Hung,[2] Dihua Xu,[1] Eugene P. Rhee,[1] Talat Alp Ikizler,[2] Sahir Kalim.[1] *[1]Renal Div, Mass General Hospital; [2]Renal Div, Vanderbilt Univ Medical Center.*

Background: Protein carbamylation is strongly associated with cardiovascular complications in kidney disease and is a predictor of mortality in ESRD. This post-translational protein modification is largely driven by the nonenzymatic binding of isocyanate derived from urea. Recent reports also suggest inflammation as an alternative driver of carbamyaltion via myeloperoxidase-mediated catabolism of thiocyanate. We set out to determine whether anti-inflammatory therapy using an interleukin 1 receptor antagonist (IL-1ra) altered carbamylation burden as measured by carbamylated albumin (C-Alb) levels in ESRD patients.

Methods: This was a pilot randomized placebo-controlled trial of the administration of IL-1ra in chronically inflamed hemodialysis patients. 22 patients were randomly assigned to receive 100 mg of IL-1ra or placebo (1:1) for 4 weeks, and 14 completed the trial. The primary outcome was percent change in C-Alb and the secondary outcomes were changes in uremic metabolites captured by a metabolomics platform.

Results: The mean C-Alb change was not significantly different between the IL-1ra and placebo groups using ANCOVA models (p=0.89). This is despite a significant reduction in hsCRP and IL-6 in the IL-1ra arm. Furthermore there were no significant trends in several established uremic solutes including p-cresol sulfate, indoxyl sulfate, trimethylamine-N-oxide, symmetric- and asymmetric dimethylarginine, kynurenine and kynurenic acid.

Pre- and post-study levels of C-Alb(%) in individual study subjects



Conclusions: Administration of the immunosuppressant IL-1ra did not affect carbamylation load or levels of several uremic solutes despite significant decrease in inflammatory markers. In ESRD, inflammation may have a limited role in protein carbamylation burden. Further studies of longer duration and larger sample size are needed to confirm these findings.

TH-PO759

Effect of Diet Modification from 65% Animal-Based Protein to 70% Plant-Based Protein on Trimethylamine N-oxide (TMAO) Levels in Subjects with Stage 3-4 CKD

Catherine K. Yeung,[1,2] Jonathan Himmelfarb,[2] Sharon M. Moe,[3] Ranjani N. Moorthi.[3] *[1]Dept of Pharmacy, Univ of Washington, Seattle, WA; [2]Kidney Research Inst, Univ of Washington, Seattle, WA; [3]Div of Nephrology, Indiana Univ School of Medicine, Indianapolis, IN.*

Background: Elevated levels of circulating pro-atherogenic uremic solutes, particularly trimethylamine N-oxide (TMAO), have been implicated in cardiovascular disease development in patients with chronic kidney disease (CKD). TMAO and precursor choline are generated from dietary phosphatidylcholine which is abundant in animal-derived high-fat foods.

Methods: We conducted a dietary intervention study in 13 subjects with stage 3-4 CKD (median GFR=26 (IQR 14.7) ml/min/1.73m^2). Protein in the baseline diet was 65% animal-based. During the 4-week study, subjects consumed a diet with 70% of dietary protein from plants and 30% protein from animals (meat, dairy, eggs), provided by the Indiana Clinical Research Institute. Plasma samples at baseline (week 0), and at 2 and 4 weeks on the study diet were analyzed for levels of TMAO and choline.

Results: Mean concentrations of both choline and TMAO trended down following diet modification; however these changes did not reach statistical significance. Concentrations of choline at 0, 2, and 4 weeks were 2.7±1.3 µg/mL, 2.5±1.4 µg/mL, and 2.2±0.6 µg/mL (p=0.22). Concentrations of TMAO at 0, 2, and 4 weeks were 2.8±3.7 µg/mL, 1.5±1.0 µg/mL, and 1.7±0.9 µg/mL (p=0.29).

Conclusions: The results of this small pilot study in patients with CKD suggest that diet modification with 70% of dietary protein from plant sources may reduce systemic concentrations of TMAO, which may be associated with increased cardiovascular risk. A larger study is warranted in order to determine if modest dietary modification can reduce TMAO concentrations in this population or if non-dietary sources of TMAO in uremia or decreased clearance prevail regardless of diet.

Funding: NIDDK Support, Other NIH Support - NCATS KL2 TR000421, Private Foundation Support

TH-PO760

Implementation of a Motivational Interviewing Program to Improve Patient Engagement within a Large Dialysis Organization

Deborah A. Benner,[1] Susan W. Butterworth,[2] Sharon Brandl,[1] Jane J. Wheeler,[1] Becky Brosch.[1] *[1]DaVita Inc, Denver, CO; [2]Q-consult LLC, St. Petersburg, FL.*

Background: Engaging Patients In their Care (EPIC) is a program within a large dialysis organization (LDO) that provides training in patient-centered motivational interviewing (MI) techniques to dietitians, with the goal of fostering improved patient engagement. A small-scale pilot of the program demonstrated improvements in dietitians' proficiency in MI techniques and measurable improvements in measures of patients' phosphorus control following program completion. However, the complexity of the skill-set and the commitment level needed to build and maintain proficiency in MI are significant and we sought to assess whether the program could be successfully implemented on a larger scale across the LDO.

Methods: The EPIC program was launched LDO-wide in 2015, reaching over 1800 dietitians. Program participation involved attendance at a 1-day intensive MI training session and recorded skill-building sessions were conducted with MI experts before and after training completion. Certified MI experts used a validated, standardized assessment system to objectively measure dietitians' proficiency in MI techniques of partnering, evoking, expressing empathy, guiding, supporting activation, reflection, and strategically responding to change talk. Total MI Scores (a combination of 7 global scores) at baseline and after program completion were compared using paired-samples t-tests.

Results: Among dietitians who have completed the MI training workshop and all skill-building sessions to date (N = 639), total MI scores were significantly higher following program completion compared to baseline. Mean total MI scores were 4.35 [SD, 0.84] at baseline and 6.39 [SD, 1.01] after program completion; ($t = -10.12$, $P < 0.001$; Wilcoxon Signed-Rank test $z = -5.240$, $P < 0.001$).

Conclusions: Our findings demonstrate that a complex MI-based program can be implemented effectively across an LDO, with participating dietitians achieving levels of MI proficiency similar to those observed in the program pilot. Analyses to evaluate the impact of LDO-wide program implementation on patient engagement and clinical outcomes are ongoing.

Funding: Pharmaceutical Company Support - DaVita Inc

TH-PO761

Impact of Low-Protein Diet on Protein-Energy Wasting in Diabetic CKD Patients

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Background: Nutritional impact of low-protein diet (LPD) in diabetics with CKD (DM) is uncertain. We evaluated the effects of LPD supplemented with ketoacids on protein-energy wasting (PEW) in DM with moderate to advanced CKD.

Methods: 81 DM and 116 controls (CON) with CKD stages 3/5 were prescribed a LPD (0.5-0.6 g protein/kg/d), normal-high energy (30-35 kcal/kg/d) supplemented with ketoacids (Ketosteril®, 1 tab/5-7 kg/d) for at least 6 months. Metabolic status, nutrition and body composition were evaluated.

Results: DM and CON were comparable for gender (Male 59 vs 55%), age (66±9 vs 63±18 y) and renal function (eGFR 23±13 vs 24±13 mL/'). Serum urea (0/6 mo: DM 131±58 to 105±49 mg/dl, p<.05; CON 115±52 to 88±36, p<.05) and phosphate (0/6 mo: DM 4.5±1.3 to 4.1±1.2 mg/dl, p=.07; CON 4.3±1.0 to 3.7±0.8, p<.05) reduced; fasting glucose declined in DM (0/6 mo: 122±54 to 103±29 mg/dl, p<.05) without changes in insulin dose. These effects were maintained after 3 years. Serum albumin did not change in short (DM 3.7±0.6 to 3.8±0.4 mg/dl; CON 4.0±0.6 to 4.0±0.4) and long-term. Body weight (BW) (DM 68.9±14.3 kg; CON 66.6±15.1) soon declined (6 mo: DM to 65.1±12.1 kg, p<.05; CON to 64.1±15.1, p<.05) and then remained stable for 3 years. BW decline was associated with reduction of body water (-1 Lt, p<.05), fat mass (FM; -1 kg, p<.05) at 6 months; after 3 years FM was reduced (-2 kg, p<.05). Low BMI (<23 kg/m^2) and albumin (< 3.8 g/dl) were present in 30% patients at baseline and did not change during the study; cholesterol (<100 mg/dl) was always normal in all patients; low FM (<10%) prevalence raised (0/3 y: DM 14 to 60 %, p<.05; CON, 5 to 39, p<.05). Muscle strength (DM 20.8±7.9 kg; CON 25.0±7.8) did not changed at 6 month and 3 year time.

Conclusions: In DM with moderate to advanced CKD a low protein ketodiet while allowing adequate metabolic control, causes sudden BW decline which remains stable thereafter; muscle mass and muscle fitness remain stable too, while fat mass declines. No differences vs. non-diabetic CKD controls are observed.

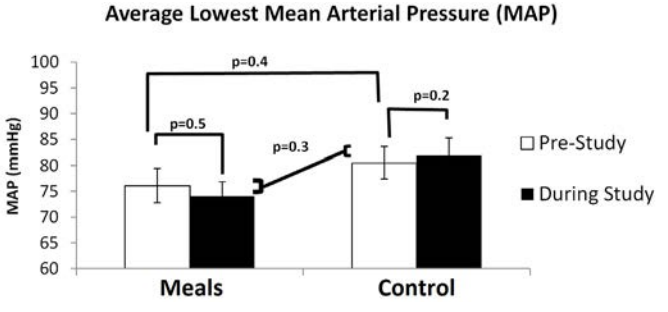
TH-PO762

Effect of High Protein Meals during Hemodialysis on Intradialytic Hypotension Mun Sun Choi,[1] Amy Wright,[1] Ranjani N. Moorthi,[2] Sharon M. Moe,[2] Kathleen M. Hill Gallant.[1] *[1]Nutrition Science, Purdue Univ, W. Lafayette, IN; [2]Nephrology, Indiana Univ School of Medicine, Indpls, IN.*

Background: High protein (PRO) meals during hemodialysis (HD) may help prevent PRO-energy wasting. However, eating during HD is often discouraged in US dialysis centers due to possible adverse events, particularly postprandial hypotension. The aim of this pilot study was to determine the effects of high PRO meals during HD on symptomatic intradialytic hypotension (SH).

Methods: 18 HD patients (N=9/group) were recruited from 2 shifts (~10AM-2PM, MWF&TTS) at 1 dialysis center for a 9-wk, non-randomized, parallel arm study. Patients received meals with 30g PRO & KDOQI guidelines for Na, K, P, & fluid, or a control social interaction at each session. Blood pressure data were collected 2mo pre-study and during study. Differences within groups for 2mo pre-study vs during study were determined by Wilcoxon signed-rank/paired t-test, and between group differences were determined by Wilcoxon rank-sum/unpaired t-test.

Results: Patients were 62±16y old, 55% female, and had dialyzed for 3.4±2.6y. In the meal group, there were 4 SH in 3 patients over 25 dialysis sessions pre-study and 12 SH in 4 patients over 25 dialysis sessions during study; in controls, there was 1 SH in 1 patient pre-study and 5 SH in 4 patients during study. Change between pre-study and during study SH was not significant for either group, both p>0.2. Average lowest MAP was not different, Fig. When asked "How interested would you be in receiving nutritious meals during dialysis?", 70% of patients responded ≥4 (5-pt scale, 5=very interested; p=NS between groups).



Conclusions: These pilot data suggest that meals during HD do not increase the frequency of SH, and patients generally have positive attitudes towards receiving meals. Larger, long-term studies are needed to confirm these results along with effects on nutritional and clinical outcomes.

Funding: NIDDK Support, Other NIH Support - UL1TR001108

TH-PO763

Effect of Low Phosphate Diet Education and Phosphate Binder Education among Maintenance Hemodialysis Patients: A Randomized Controlled Trial Eunsoo Lim, Yujeong Kim, Gyu Tae Shin, Heungsoo Kim, Inwhee Park, Jong Cheol Jeong. *Dept of Nephrology, Ajou Univ Hospital, Suwon, Kyeonggi, Korea.*

Background: Among dialysis patients, hyperphosphatemia is associated with hyperparathyroidism, mineral bone disorder and increased incidence of cardiovascular diseases. Thus, dietary education and proper intake of phosphate binder is essential.

Methods: We randomized 70 patients into education group(n=48) and control group(n=22). Phosphate binder intake education was given by pharmacists, and nutritional consultation by dietitians. Drug compliance was assessed by Morisky Medication Adherence Scales-4(MMAS-4) and bioequivalent dosage of prescribed phosphate binder. The patients' knowledge of when to take phosphate binder was assessed by questionnaire and nutritional status by using Patient-Generated Subjective Global Assessment(PG-SGA).

Results: Baseline characteristics of two groups were similar. Primary goal was the proportion of patients who reached calcium-phosphorus product lower than 55. Among education group, 36(75%) patients achieved primary goal, compared to the 16(72.7%) of control group(*P*=0.430). The improvement of MMAS-8 score were not different between education and control group(for short term,0.26±1.12 vs 0.02±1.30,education vs. control,*P*=0.445. for long term,0.11±1.17 vs 0.30±1.29,*P*=0.555).Education non-significantly increased patients' knowledge of when to take phosphate binder(22.9% vs. 3.5%,education vs. control,*P*=0.347), and it didn't affect the amount of dietary phosphate intake per body weight(-1.18±3.54 vs. -0.88±2.04 mg/kg,education vs. control,*P*=0.851). However, it decreased dietary phosphate to protein ratio(-0.64±2.04 vs. 0.65±3.55,education vs. control,*P*=0.193). Education on phosphate restriction did not affect the PG-SGA(0.17±4.58 vs. -0.86±3.86,education vs. control,*P*=0.363), nor dietary protein intake(-0.03±0.33 vs. -0.09±0.18,education vs. control,*P*=0.569).

Conclusions: Education didn't affect the calcium phosphate product compared with control group. However, education corrected timing of phosphate binder intake and lowered dietary phosphate to protein ratio, although it wasn't statistically significant. These findings imply the importance of educational effort.

TH-PO764

Effects of Probiotic Supplementation on Trimethylamine-N-Oxide Plasma Levels in Chronic Kidney Disease Patients Denise Mafra,[1] Natalia Alvarenga Borges,[1] Cristiane Moraes,[1] Milena Barcza Stockler-Pinto,[1] Peter Bergman,[2] Peter Stenvinkel.[2] *[1]Federal Univ Fluminense, Brazil; [2]Karolinska Inst, Sweden.*

Background: Components present in the diet can be metabolized by gut microbiota to produce metabolites like trimethylamine-N-oxide (TMAO) that play a role in cardiovascular disease in CKD patients. The objective of this study was evaluate the effects of probiotic supplementation on TMAO plasma levels in hemodialysis patients.

Methods: A randomized, double-blind trial was performed in 21 HD patients [54.8 ± 10.4 years old, 9 men, BMI 26.1 ±4.8 kg/m^2, dialysis vintage 68.5 (34.2 – 120.7) months]. Ten patients were randomly allocated to the placebo group and 11 to the probiotic group (3 capsules, with 90 billion of colony forming units per day of S. *thermophilus*, L. *acidophilus*, and B. *longum*). Plasma TMAO, choline, and betaine levels were measured at baseline and after 3 months with LC-MS/MS.

Results: The averageof TMAO, choline, and betaine plasma levels did not change after supplementation.

	Placebo Group (N= 10)		***Probiotic Group (N=11)***	
	Baseline	***Post***	***Baseline***	***Post***
Uremic toxins				
TMAO (ng/µl)	8.8 ± 4.6	6.2 ±1.9	7.4 ± 4.4	7.2 ± 4.7
Choline (ng/µl)	10.0 ±1.8	9.8 ±2.2[a]	11.4 ±2.4	12.6 ±2.7
Betaine (ng/µl)	4.3 ±2.0	4.1 ±1.6	4.5 ± 1.6	5.4 ±1.7
Biochemical parameters				
CRP (mg/dL)	3.8 (1.2 – 9.5)	2.7 (1.3 – 7.0)	3.7 (1.6 – 6.7)	5.7 (2.6 – 12.3)
Urea (mg/dL)	159.7 ± 55.3	168.3 ± 29.8	156.0± 39.0	164.4± 53.2
Hematocrite (%)	34.8 ± 5.4	33.0 ± 5.5	33,7 ±2.8	31.4 ±3.1[a]
Hemoglobin (g/dL)	11.2 ± 1.6	11.0 ± 1.6	10.9 ±1.4	10.4 ±1.7

The % of changes in the plasma levels of betaine and choline were higher in probiotic group when compared to placebo [choline - probiotic group: 2.6% (- 9.5 – 46.0) *vs* placebo group: -10.0 % (-18.7 – -0.4), p=0.03; betaine - probiotic group: 37.2% (-14.3 – 80.9) vs placebo group: 1.1% (-16.0 – 19.1), p=0.04.].

Conclusions: Short-term probiotic supplementation does not appear to influence TMAO, choline, and betaine levels in HD patients.

TH-PO765

Prediction of Fractures among Older Kidney Transplant Recipients Mara McAdams-DeMarco, Sunjae Bae, Dorry L. Segev. *Johns Hopkins.*

Background: Kidney transplantation is a growing treatment option for older adults with ESRD. Fracture risk is elevated in ESRD patients who undergo KT compared to waitlist candidates. While previous studies have identified risk factors for fractures after KT, we sought to create a post-KT fracture prediction model based on pre-transplant factors.

Methods: We studied older (aged >=55) KT recipients who were Medicare Primary (between 1/1/99-12/31/11) using SRTR data linked to Medicare claims. We estimated the cumulative incidence of a fracture (based on claims) using the Kaplan-Meier method. We developed a prediction model based on recipient, transplant and donor factors known prior to KT for the post-KT incidence of fracture using an AIC-based selection method for the Cox proportional hazards model.

Results: Using national data on 41,145 older KT recipients, we estimated the post-KT cumulative incidence of fractures to be 7.9% at 5 years and 17.4% at 10 years. We identified recipient, donor and transplant factors as predictors of post-KT fractures (C-statistic=0.65).

Predictor	HR (95% CI)	p-value
Age (5 year change)	1.18 (1.14-1.23)	<0.001
Female	1.54 (1.41-1.68)	<0.001
White Race	1.81 (1.65-1.98)	<0.001
Diabetes	2.21 (2.02-2.42)	<0.001
BMI (kg/m^2)		
<18.5	1.88 (1.35-2.63)	<0.001
25-30	1.35 (1.19-1.49)	<0.001
30-25	1.12 (1.01-1.25)	0.03
>35	Reference	
Year of KT (1 year change)	0.96 (0.95-0.98)	<0.001
Donor type		
Live	Reference	
Deceased Standard Criteria	1.12 (1.01-1.25)	0.04
ECD	1.26 (1.11-1.43)	<0.001
DCD	1.21 (0.97-1.50)	0.09
Peak PRA<80	1.14 (0.97-1.32)	0.10

Conclusions: The cumulative incidence of fractures increases to 17.4% 10 years after KT for older recipients. Recipient, donor and transplant factors obtained prior to KT can be used to predict which older recipients are at risk of post-KT fracture.

Funding: Other NIH Support - NIA, Private Foundation Support

TH-PO766

A Prospective, Randomized, Controlled Study of Cholecalciferol Supplementation in Kidney Transplant Recipients - Preliminary Results at 30 Months Cristina Jorge,[1] Teresa Adragao,[1] Patrícia Matias,[1] Margarida Bruges,[1] Rita Birne,[1] Ivo Laranjinha,[1] Jorge Azinheira,[2] Maria João Andrade,[3] Andre L. Weigert,[1] Domingos Machado.[1] *[1]Nephrology, CHLO - HSC; [2]Clinical Pathology, CHLO - HSFX; [3]Cardiology, CHLO - HSC, Portugal.*

Background: The benefits of nutritional vitD supplementation in KTR are not well defined.

Methods: We prospectively followed a group of KTR randomly allocated to receive cholecalciferol (4000 IU/day: GD, n=73) or no therapy (GC, n=68). Comparison was performed with the T test, Mann Whitney U or chi-square test; survival was analyzed through Kaplan-Meier test.

Results: The 2 groups were similar in gender (male: 57,4% vs 56,2%), age distribution (mean 51 vs 52 years), dialysis vintage (mean 46 vs 53 months(m)), cold ischemia time (average 18h17min vs 18h43min), PRA (0% of median in 2 groups), time since KT (median 46 vs. 48,5 m) and major comorbidities, respectively in GD vs. GC. Basal calcidiol levels were similar in both groups (18,7 vs. 19,1 ng/ml) and so were eGFR (EPI) (67,4 vs 63,3 mL/min/1.73 m2), Hb (12, 8 vs 13 g/dl), CRP (0,5 vs. 0,61mg/dl), iPTH (107 vs 119 pg/ml), alkaline phosphatase (72 vs 77 U/L), phosphate (P) (3.7 vs. 3.5 mg/dl) or magnesium (1.7 vs. 1.8 mg/dl) levels. However, basal serum calcium (9,8 vs. 10,2 mg/dl) was significantly lower in GD. We found a significant increase in the levels of calcidiol (ng/ml) at 6m (39,7 vs. 22,1), 12m (40,7 vs 22,1), 18m (40,6 vs 22,7), 24m (42,1 vs 22,2) and at 30m (43,5 vs 21,1), with no significant increase of calcemia, but with significant reduction in iPTH (pg/ml) at 6m (81 vs. 112), 12m (87 vs 103), 24m (76 vs 97,5) and at 30m (64,2 vs 98,6) in GD versus GC. There were no differences between the 2 groups in the evolution of excretion fraction of Ca, P, or Mg, in the urine protein/creatinine ratio, pulse pressure, left ventricular mass índex or hospitalizations. Treatment with antihypertensives (including ACEI or ARBs), active vitD or cinacalcet was similar between the 2 groups. There were no differences in graft or patient survival.

Conclusions: The dose of 4000 IU/day of cholecalciferol was safe and allowed to rise calcidiol levels of GD and reduce iPTH at 6,12, 24 and 30 months compared with the control group, without other significant results so far.

TH-PO767

FGF23/Klotho System and Vitamin D Receptor Activation in Kidney Transplant Recipients Javier Donate,[1] Fernando Henríquez-Palop,[2] Ernesto Martín,[1] Nayra Pérez-Delgado,[1] Anabel Rodriguez,[1] Carlos Marín,[1] Mercedes Muros de Fuentes,[1] Carmen Mora,[1] Juan F. Navarro-Gonzalez.[1] *[1]Univ Hospital Nuestra Señora de Candelaria (Santa Cruz de Tenerife); [2]Univ Hospital Dr. Negrin (Las Palmas de Gran Canaria).*

Background: Recent studies have demonstrated the usefulness of paricalcitol for the treatment of secondary hyperparathyroidism (SHPT) in kidney transplant recipients, also suggesting beneficial pleiotropic effects. The aim of this study was to analyze the influence of selective activation of the vitamin D receptor (VDR) on the FGF-23/KLOTHO system.

Methods: Twenty-nine renal transplant patients with iPTH >100 pg/mL were treated with oral paricalcitol (1 µg/day) for 3 months. A group of 8 patients matched for age, sex and renal function with iPTH <100 pg/mL was included as controls. Serum concentrations of FGF-23 and KLOTHO were measured by ELISA, and gene expression levels of KLOTHO (KL) were analyzed in peripheral blood mononuclear cells (PBMCs) as reflect of renal expression levels. Promoter methylation of KL was also studied.

Results: iPTH decreased in paricalcitol-treated patients (p<0.0001). Serum FGF-23 enhanced (p<0.01), whereas KLOTHO concentrations showed a trend to increase (p=0.067). KLOTHO gene expression in PBMCs increased by 45.7% in paricalcitol-treated patients (p<0.01), without change in controls. Paricalcitol administration resulted in a median percent decrease of 56% in methylated DNA levels of KLOTHO promoter (p<0.001). The ratio of un-methylated/methylated KLOTHO promoter DNA did not change in controls, but it increased by 177% in paricalcitol-treated subjects (p<0.0001). The increase in the un-methylated/methylated KLOTHO promoter ratio was independently associated with the change in serum KLOTHO (r=0.55, p<0.01) and mRNA expression levels (r = 0.40, p<0.05).

Conclusions: Paricalcitol induces an increase in KLOTHO gene expression and serum Klotho concentrations, which is significant and independently associated with a rise in the ratio of un-methylated/methylated KLOTHO promoter DNA. Long-term studies are needed to assess whether this effect may translate into beneficial clinical effects.

Funding: Government Support - Non-U.S.

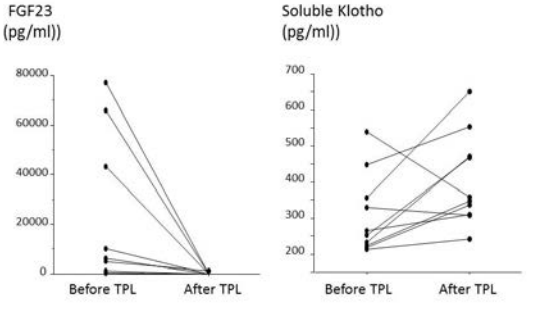
TH-PO768

Serum Levels of Soluble Klotho and Fibroblast Growth Factor-23 Changes after Renal Transplantation Yukiko Hasuike, Kosuke Mizusaki, Yuki Morikami, Yasuyuki Nagasawa, Takeshi Nakanishi. *Div Kidney and Dialysis, Dept Internal Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan.*

Background: Data on serum soluble Klotho levels in chronic kidney disease after renal transplantation (TPL) are contradictory. The effects of renal TPL on serum levels of soluble Klotho and fibroblast growth factor (FGF)-23 in the recipients after TPL were investigated.

Methods: Ten renal transplant recipients underwent serum soluble Klotho (ELISA, IBL Co.,), FGF-23 (ELISA, Kinos Co.,), and 25-OH vitamin D level measurements before TPL and 1-year after TPL were examined. Correlations between serum soluble Klotho and FGF-23, vitamin D, and the other factors were also investigated.

Results: Mean age of 41.8±15.9 years. After TPL, serum level of soluble Klotho was significantly higher and FGF-23 was significantly lower than before TPL (p = 0.0469, p = 0.0051, respectively).



Vitamin D levels were not different between before and after of TPL. Serum level of soluble Klotho after TPL had a significant negative correlation with age (r = -0.721, p = 0.0187) while FGF-23 nor 25-OH vitamin D were not.

Conclusions: Serum level of soluble Klotho after TPL was associated with age. Further studies are needed to define a change of soluble Klotho level in renal TPL recipients.

TH-PO769

Urinary Calcium Excretion and Risk of Graft Failure and Mortality in Renal Transplant Recipients Jacob M. Taylor, Lyanne M. Kieneker, Else van den Berg, Martin H. De Borst, Stefan P. Berger, Jan-Stephan Sanders, Ron T. Gansevoort, Stephan J.L. Bakker. *Internal Medicine, Univ of Groningen, UMCG, Groningen, Netherlands.*

Background: Calcium and vitamin D supplementation are often prescribed to help improve bone health in renal transplant recipients (RTRs). However, high levels of urinary calcium excretion (UCaE) have been shown to increase the risk for nephrolithiasis and nephrocalcinosis. Furthermore, calcium supplements may increase the risk for cardiovascular disease. Therefore, we investigated whether high UCaE increases the risk of graft failure and mortality in a cohort of RTRs.

Methods: Urine samples were collected in a single-center, longitudinal cohort of 691 RTRs with a functioning graft for at least one year (baseline). UCa concentration was performed on a 24-hour specimen at baseline by indirect potentiometry. UCaE was measured as a continuous variable and grouped according to event-based tertiles of UCaE. UCaE was compared to graft failure (defined as restarting dialysis or re-transplantation) and mortality during follow-up.

Results: Baseline median UCaE was 95 mg/24h (interquartile range [IQR]: 46-156 mg/24h), similar between males and females. A total of 44 events of graft failure and 81 events of mortality were identified in the cohort during a median follow-up of 3.13 years (IQR: 2.66-3.87 years). After multivariable adjustment, no association was observed between UCaE and risk of graft failure during follow-up (HR: 0.88 [0.61-1.29], p=0.52, for every 1 log unit increase in UCaE). Surprisingly, an inverse association between UCaE and mortality was present (HR: 0.68 [0.53-0.88], p=0.003), with the highest risk in the tertile of subjects with the lowest UCaE. When further adjusting for other dietary factors associated with poor nutrition, a trend remained (HR: 0.79 [0.59-1.07], p=0.13), although formal statistical significance was lost.

Conclusions: High UCaE was not associated with an increased risk of graft failure or mortality in RTRs. These data do not provide evidence that calcium supplementation is harmful in RTRs.

Funding: Private Foundation Support

TH-PO770

Direct-Acting Antivirals for the Treatment of Hepatitis C Virus Infection in Kidney Transplant Recipients: A Multicenter Study
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Background: HCV is a relevant negative prognosis factor for graft and transplant recipient survival.New direct-acting antivirals(DAA)allow us to solve this problem in an effective way.It is crucial to know their real impact in our daily practice.

Methods: Observational,retrospective and prospective study.We analyze treatment results with DAA,in kidney transplant(KT)recipients from 15 hospitals,regarding effectiveness,tolerance and impact on immunosuppression and renal function-proteinuria in a short-medium term.

Results: Until March 2016,119 KT recipients were included(9combined liver-kidney transplants).69.7%male;average age 54.2±9yo;KT length 11.4±10years. More than 50%showed stage 3-4 chronic kidney disease.Immunosuppressive therapies:tacrolimus(70%) or cyclosporine(18%)with MMF(76%).Predominant genotype was 1b(68.1%),1a(13.8%),3(7.8 %),4(6%) and 2(4.3%);51% had grade 3-4 of fibrosis,17%portal hypertension.The main DAA used was sofosbuvir(91%)combined with ledipasvir(55%),simeprevir(14%)or daclatasvir(13%);in 9 cases(7%)the combination of paritaprevir-ritonavir-ombitasvir-dasabuvir(3D)was employed;18% were treated with Ribavirin as coadjuvant.Side effects were limited,23.5 %,and without relevance,except for anemia caused by Ribavirin.2 patients interrupted the treatment,due to neurotoxicity caused by the interaction between 3D and tacrolimus and anemia caused by Ribavirin(both had virological response).All the patients that completed the treatment(94)are alive and show virological response in 95.6% of cases.Liver function analysis improved:74%normal vs 21%before the treatment(p<0.001).Renal function and proteinuria did not change significantly.Tacrolimus level at the end was lower with respect to the beginning(5.8±2.1 vs 7.4±1.8ng/ml,p=0.03),in spite of a slight increase in the dose(2.6 vs 2.3mg/day p=0.17).

Conclusions: DAA are highly effective in KT patients,with good tolerance,making it possible to solve the problem and having a good chance to improve the prognosis in our patients.The use of DAA in these patients requires special control and coordination with hepatologists,especially when 3D or Ribavirin is used.

TH-PO771

The Combination of Sofosbuvir Ribavirin and Interferon for Hepatitis C Virus Treatment Increases Access to Kidney Transplantation
Himanshu V. Patel, Vivek Balkrishna Kute, Minaxi Patel, Pankaj R. Shah. *Nephrology and Transplant, IKDRCITS, Ahmedabad, India.*

Background: HCV-infected renal transplant recipients have worse patient and allograft survival after transplantation compared with non-infected renal transplant recipients. However, HCV-infected patients have a lower mortality following transplantation compared with mortality on dialysis. HCV infection is not considered a contraindication to transplantation. The current AASLD and ISDA HCV guidelines state that Sofosbuvir -containing regimens can be considered for patients with CrCl < 30 mL/ min with expert consultation, as efficacy and safety data are not yet available.

Methods: We used in 22 ESRD patients (19 males and 3 females) on dialysis a combination of Sofosbuvir (400mg alternate day), Injection PEG-INF 2a 135 mcg subcutaneous once a week and ribavirin (200Mg once a day) for 12 weeks.

Results: Mean baseline HCV-RNA (QUANTITATIVE) was 409523.6 copies/ml. All patients has HCV genotype 1. HCVRNA by reverse transcription polymerase chain reaction (RT-PCR) was less than detected in 4, 8 and 12 weeks in 81.8 %(n=18), 90.9%(n=20) and 100% (n=22). All the patients had stable hemoglobin with optimization of iron, erythropoietin and anemia therapy. Blood transfusion was given in 3 patients. There have been no serious adverse events reported and no treatment-related discontinuations thus far. 8 Patients underwent kidney transplantation when HCV RNA was negative and post –transplant they were continued on combination of Sofosbuvir , and ribavirin (200Mg once a day) to complete therapy. There was no interaction with levels of tacrolimus and immune injury. There was no reactivation of HCV after completion of therapy after transplantation.

Conclusions: combination of Sofosbuvir , Injection PEG-INF 2a 135 and ribavirin for 12 weeks is safe and effective for treatment of HCV infection in CKD patients on dialysis however, frequent monitoring is warranted for patients with severe renal impairment. The combination of Sofosbuvir and ribavirin is safe and effective after kidney transplantation. Final results from this study will need to be confirmed before further recommendations can be made.

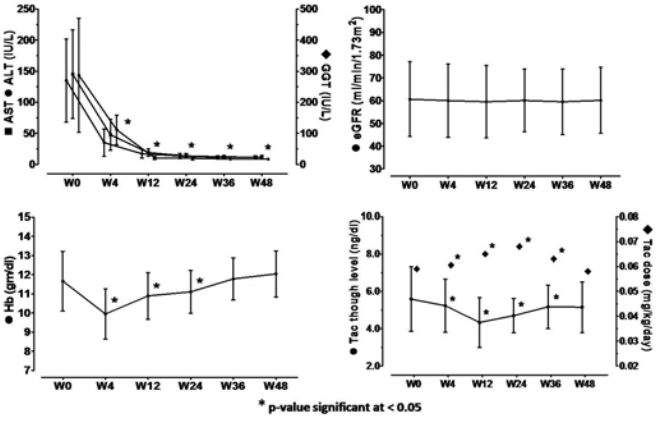
TH-PO772

Direct Acting Anti-Viral Agents in Post Renal Transplant Hepatitis C Virus infection: Efficacy and Safety
Narayan Prasad, Manas Ranjan Patel, Akhilesh Jaiswal, Dharmendra Bhadauria, Raj K. Sharma, Amit Gupta. *Dept of Nephrology, SGPGIMS, Lucknow, India.*

Background: Hepatitis C (HCV) infection in renal allograft recipient is associated with increased morbidity and mortality. Direct acting antiviral agents (DAAs) are highly effective in HCV infected liver transplant patients; however there is paucity of data on use of DDAs in renal transplant. We aimed to study the efficacy and safety of sofosbuvir based regimens to treat HCV in renal allograft recipients.

Methods: All HCV infected renal allograft recipients (n=68, 5.4%) between January 2005 to December 2015 (n=1254) were screened for HCV virus replication by PCR. Of them 28 showed active HCV replication (range 96425-24175475copies logsIU/mL) and 22 (14 genotype3;6 genotype1 and one each 2 and 4) were included in the study after exclusion of 6 patients(3 with eGFR < 30ml/min/1.73m^2, 1 with hepatic decompensation and 2 for no consent).

Results: 14 patients completed 24 weeks of treatment with dual drug (sofosbuvir and ribavirin; genotype 3, n=10; genotype 1, n=2; genotype 2, n=1; and genotype 4, n=1). Subsequently with availability newer DAAs, either daclatasvir (genotype 3, n=4 and genotype 1, n=1)or ledipasvir (genotype 1, n=3) was added to above regimen in eight patients (i.e. triple drug for a minimum of 12 weeks).A virological response with undetectable virus (i.e. Rapid 92%, End therapy 100%, and sustained VR12 of 100% and 24 of 100%) was seen in all patients.The changes in liver enzymes AST,ALT and GGT; hemoglobin, trough tacrolimus, and eGFR changes on follow up is shown in figure 1.



The treatment was well tolerated except fall in Hb and one required blood transfusion and 3 required EPO. Tacrolimus dose was increased in 10 and decreased in 2 to achieve required trough level. All had sustained remission at end of one year followup.

Conclusions: DDAs are safe and effective therapy for treatment of replicating HCV post kidney transplantation.

Funding: Government Support - Non-U.S.

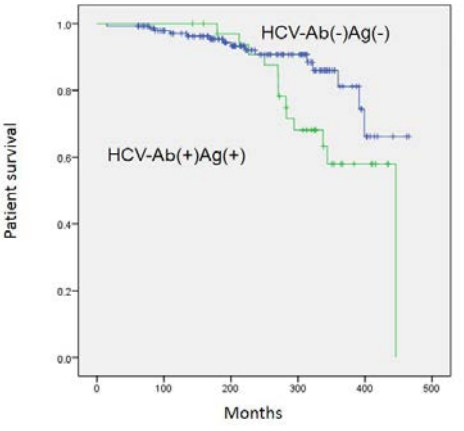
TH-PO773

The Long-Term Outcome of Hepatitis C Viral Core Antigen-Positive Japanese Renal Allograft Recipients
Kazuaki Okino, Yuki Okushi, Kiyotaka Mukai, Keiji Fujimoto, Hiroki Adachi, Hideki Yamaya, Hitoshi Yokoyama. *Nephrology, Kanazawa Medical Univ School of Medicine, Kanazawa, Ishikawa, Japan.*

Background: The impact of hepatitis C virus (HCV) infection on patient survival after renal transplantation was controversial.

Methods: To clarify the long-term outcome of Japanese renal allograft recipients with HCV infection, we studied 187 cases (118 males, 69 females; 155 living-donor cases, 32 cadaveric-donor cases; mean follow-up period 249 months ranging from 0 to 466 months) who underwent the first renal transplantation in Kanazawa Medical University since 1974.

Results: In this cohort, 35 cases (18.7%) were HCV core antigen-positive, and 13 out of them (37%) were dead by liver cirrhosis (4 cases), hepatocellular carcinoma (1 case), and infections complicated with chronic hepatitis (6 cases) in chronic phase, and fibrosing cholestatic hepatitis due to HCV (1 case) after surgery. On the other hand, only 15 out of 146 (10%) recipients were lost in HCV- both core antigen and antibody negative group. The patient survival rate was significantly lower in HCV core antigen-positive group by Kaplan-Meier life table method (Log Rank test, Kay-square 4.242, p=0.039). Survival rate of HCV core antigen-positive recipients decreased rapidly 240 months after renal transplantation.



In addition, HCV core antigen-positive was a most important independent risk factor for survival times after renal transplantation by Cox proportional hazard model (Wald 6.254, p=0.012) as compared with age, gender, type of donors, serum creatinine levels on renal transplantation one year later, and Immunosuppressive therapy.

Conclusions: Continuous HCV infection was a harmful risk factor for the patient survival, especially 20 years after renal transplantation.

TH-PO774

Transplanting Hepatitis C Virus Infected Kidneys into Hepatitis C Positive Recipients in the Direct Acting Antiviral Agents Era
Juan E. Kusnir, Adriana Dejman, Kalyan Bhamidimarri, Fernando E. Pedraza, Marco A. LadinoAvellaneda, David Roth. *Medicine/Nephrology, Univ of Miami/VAMC, Miami, FL.*

Background: The availability of direct acting antivirals (DAAs) has changed the treatment of hepatitis C virus (HCV) infection. The decision to treat a HCV positive patient before or after transplant has important ramifications for patients in the deceased donor waiting list. Effective treatment can now be administered in the post-transplant period allowing for HCV infected kidneys to be allocated to HCV infected recipients. Potential benefits include significant decrease in waiting list time translating into long term benefits of decreased time on hemodialysis. Yet many questions regarding the treatment, adverse effects and potential complications remain unknown.

Methods: In this observational study of 21 HCV positive patients receiving a HCV positive kidney allograft, we reviewed the outcomes of post-transplant HCV treatment with DAAs during the 12 week treatment period. The 21 patients received induction with thymoglobulin and basiliximab, and maintenance immunosuppression with tacrolimus and mycophenolate mofetil. All patients started DAAs 60-90 days after transplant and were on Sofosbuvir with the following combinations: 13 patients on ledipasvir and ribavirin, 5 patients on ledipasvir, 1 patient on daclatasvir, 1 patient on simeprevir and 1 patient on ribavirin.

Results: The mean time on the list for these patients was 116 days. All patients that completed the prescribed DAA therapy achieved a sustained virologic response at 12 weeks (SVR12). Four patients were complicated by antibody mediated rejection while on therapy. Tacrolimus dose adjustments were required in 10 patients to maintain therapeutic levels. The response to DAA therapy was similar to that reported in the general population.

Conclusions: Accepting a kidney from a HCV positive donor dramatically reduces wait time for kidney transplantation. Complications including allograft rejection and variable tacrolimus levels will require closer monitoring of these patients and more intense immunosuppression dose adjustments. Further research into this unique population is needed to obtain better understanding and thus optimize patient care.

TH-PO775

Treatment of Hepatitis C in Kidney Transplant Recipients with Directly Acting Antiviral Agents
Michelle Lubetzky, Maria Ajaimy, Layla Kamal, Maria Coco, Enver Akalin, Graciela De Boccardo. *Montefiore Transplant Center, Albert Einstein College of Medicine, Bronx, NY.*

Background: With the development of new all oral, interferon-free directly acting antiviral (DAA) medications, treatment of Hepatitis C infection (HCV) in renal transplant recipients is possible, but limited data exists on its safety and efficacy.

Methods: We performed a retrospective cohort analysis of patients transplanted at our center with HCV who have been started on DAAs. Primary endpoints included sustained virologic response (SVR) as defined as negative viral load at 12 weeks post completion of therapy and allograft function.

Results: A total of 31 patients met inclusion criteria. The most commonly used regimen was sofosbuvir and ledipasvir (n=21). Upon completion of therapy, 100% had undetectable viral load. Of the 23 patients with at least 12 weeks of follow up after completion of therapy 95.7% achieved SVR. Both graft and patient survival at most recent follow up was 100%, although 2 patients now have GFR <20 ml/min/BSA. A total of 6/31 (19.3%) patients had worsening proteinuria during or shortly after therapy. Patients with more than 500mg/g of proteinuria were significantly more likely to develop worsening proteinuria than those without proteinuria at the start of therapy (p<0.001).

Conclusions: Our data demonstrates that DAAs are effective in treating HCV in patients after kidney transplantation. Patients with proteinuria and/or decreased GFR should be monitored closely.

	Prior to Therapy	After Therapy	P value
Creatinine mg/dl	1.3 ± 0.4	1.4 ± 0.5	0.25
GFR (MDRD) ml/ min/BSA	64.2±16.5	58.9±17.5	0.22
Proteinuria mg/g	0.66 ± 1.2	1.1 ± 2.0	0.10
Class I PRA	19.8 ±30.5	14.3 ± 27.5	0.45
Class II PRA	31.3±37.6	17.7 ± 34.4	0.13
AST	52.7 ±51.5	21.5±10.9	0.002
Platelets	197.8 ±75.0	216.5±73.7	0.5
Viral load	8450646.32 ±18282133.63	0	<0.001
Tacrolimus level ng/mL	6.2±1.7	6.2±2.5 (done 4-8 weeks after starting therapy)	P=0.9

TH-PO776

Sofosbuvir Based Therapy for HCV Infection in Post Renal Transplant Recipients
Vivek Pathak. *Nephrology, Kovai Medical Center and Hospital, Coimbatore, Tamil-Nadu, India.*

Background: The purpose of this study was to assess the efficacy and safety of an interferon free Sofosbuvir therapy to treat HCV infection in kidney transplant recipients .

Methods: We used sofosbuvir based therapy in 33 post transplant patients. Treatment was given for 24 weeks. Sofosbuvir and Ribavarin were given for 10, Sofosbuvir and Ledipasvir for 18 and Sofosbuvir and Daclatasavir for 3 patients.24 were suffering from genotype 1 , 07 were suffering from genotype 3 and 02 were suffering from genotype 4 infection. The median time between transplant and the start of anti HCV therapy was 60 months. They all received steroid free immunosuppression based on Tacrolimus and MMF.

Results: All the patients became negative for HCV RNA and those who were tested 12 weeks after cessation of therapy remained negative .Only one patient with genotype 1 had relapsed after stopping the treatment and he also responded well to Sofosbuvir and Ledipasvir combination. HCV infection causes significant post kidney transplant effects like new onset diabtes mellitus, Cryoglobulinaemia, chronic liver disease and infection related deaths. Sofosbuvir based therapy was found to be safe and no interaction was noted with Tacrolimus.There was no acute rejection or graft loss during the treatment. One patient required increase in Tacrolimus dose following remission of HCV infection. Mean SGPT was 74 IU/ml before and 20 IU/ml after therapy. There were 5 new onset diabetes mellitus in this group and 4 improved subsequently and anti diabetic agents were discontinued.Two patients with cirrhosis and ascites showed reversal and ascites disappeared and fibroscan became normal.There were no adverse side effects with this drug except fall in haemoglobin in those who received Ribavarin. One patient developed fungal brain abcess during the tratment but responded well to surgical drainage and Amphotericin.

Conclusions: Sofosbuvir based therapy induced remmission in 100% patients, reversed diabtes in 4 out of 5 patients and chronic liver disease with ascites in 2 patients without putting the graft at any risk. We will reduce the treatment duration to 3 months now.

TH-PO777

Short Term Effects of Hepatitis C Virus Clearance Using Direct Acting Antivirals on Markers of Glomerular Damage in Kidney Transplant Patients
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Background: Hepatitis C Virus (HCV) is an independent risk factor for chronic kidney disease progression, end stage renal disease, and poorer kidney graft survival. The role of HCV clearance in long-term kidney graft survival is unknown. In this study, we examined the short-term impact of direct acting antivirals (DAAs) on markers of glomerular damage in kidney allografts.

Methods: We conducted a retrospective study of kidney transplant patients with chronic HCV infection seen at the University of Alabama at Birmingham 1917 Viral Hepatitis Clinic between January 2013 and June 2016. Of the 23 patients identified, 16 had received DAA treatment. Two patients who had achieved HCV cure were excluded due to 1) antibody mediated rejection related to low levels of immunosuppression post HCV treatment; and 2) self-limited, unexplained proteinuria post HCV treatment. Glomerular damage was assessed using serial protein/creatinine (P/C) ratios measured pre- and post- treatment.

Results: The median age of the 14 patients included was 59 years (Q1=57, Q3=64). Of these patients, 64% were African American, 36% were white, and 64% were male. Post-treatment P/C ratios (median 0.107, Q1=0.081, Q3=0.151) were significantly lower (p=0.001) than the pre-treatment ratios (median=0.176, Q1=0.165, Q3=0.385). P/C ratios decreased in 12 out of 14 patients (86%) with an absolute median decrease of 0.118 (median percent decrease=50%).

Conclusions: In this preliminary study, there was a significant trend of decrease in P/C ratios associated with HCV clearance. These results suggest a promising role for DAAs and viral clearance in improving short-term kidney graft survival. In the future, larger cohort studies will be needed to assess the long-term benefits of DAAs in this population of HCV-infected patients.

Funding: NIDDK Support, Other NIH Support - This work was funded in part by the UAB-UCSD O'Brien Core Center for Acute Kidney Injury Research (NIH P30-DK079337); UAB Medical Student Summer Research Program

TH-PO778

Effectiveness of Direct-Acting Antivirals in Hepatitis C Infected Post-Kidney Transplant Recipients
Michelle T. Martin, Darby Rosenfeld, Grace E. Go, Todd Lee, Maya Campara, Ignatius Yun-Sang Tang. *Univ of Illinois at Chicago.*

Background: The American Association for the Study of Liver Diseases guidelines recommend the use of specific regimens for liver transplant recipients with hepatitis C virus (HCV), but do not address the treatment of HCV infected recipients of kidney alone, liver/kidney, or kidney/pancreas transplants. The objective of this study was to gain knowledge on HCV treatment response in kidney transplant recipients (KTRs).

Methods: This was a retrospective, single-center analysis of KTRs who started HCV treatment between January 1, 2014 and February 3, 2016. Electronic medical records of

patients taking direct acting antiviral (DAA) regimens of sofosbuvir + ribavirin, sofosbuvir + simeprevir, or ledipasvir/sofosbuvir + ribavirin were reviewed for demographics and laboratory values. The primary endpoint was the sustained virologic response (SVR) at 12 weeks after treatment completion.

Results: Thirty KTR patients were treated for HCV; 9 were excluded: 4 had not yet reached 12 weeks after treatment, and 5 were lost to follow-up due to transfer of care. The remaining 21 patients had a mean age of 58.3±7.3 years; 17(81%) were male, 13(62%) Black, 11(52%) cirrhotic, 12(57%) had genotype 1a, 8(38%) had 1b, and 1(5%) had 1e/1g. There were 5(24%) liver/kidney, 13(62%) kidney alone, and 3(14%) kidney/pancreas transplant patients. Eighteen (86%) patients received tacrolimus, 13(62%) had diabetes, and 13(62%) had a BMI <30 kg/m^2. During HCV treatment, immunosuppression dosage did not change for 15(71%) patients, it was increased for 2 patients, decreased for 3 patients, and changed in both directions for 1 patient. Twenty of 21 patients (95%) achieved SVR. No difference in SVR rate was found in treatment naïve or experienced (100% vs 86%, p=0.33), cirrhotic or non-cirrhotic (89% vs. 100%, p=0.429), or non-obese or obese (100% vs. 88%, p=0.99) patients. The SVR did not differ by regimen, genotype, gender, ethnicity, age, diabetes, or insurance (p>0.05).

Conclusions: DAA regimens were highly effective in KTRs. SVR did not differ by treatment or demographics; comparison across groups was limited due to small numbers. Immunosuppressive levels should be monitored closely with HCV treatment.

TH-PO779

Hepatitis B Virus(HBV) Re-Activation in HBsAg- and HBsAb-Negative and HBcAb-Positive (sAg-sAb-cAb+) Kidney Transplantation(KT) Recipients

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Background: According to the Korean Dialysis Registry, 5.0% of hemodialysis patients were positive for HBV. Patients who received immunosuppressive treatment commonly face the risk of HBV reactivation. sAg-sAb-cAb+ can be interpreted as low-level hepatitis B carrier or hepatitis B in remote past. European Association for the Study of the Liver Clinical Practice Guideline recommended that HBsAg-negative, anti-HBc positive patients with undetectable serum HBV DNA and regardless of anti-HBs status who receive chemotherapy and/or immunosuppression should be followed carefully by means of ALT and HBV DNA testing. However, evidences supporting these recommendations are scarce. This study was performed to evaluate the incidence of HBV reactivation in sAg-sAb-cAb+ KT recipient.

Methods: From February 1997 to March 2015, 178 sAg-sAb-cAb+ patients (M:F 130:48, 47.7+10.9 years) received KT. Forty seven patients had diabetic nephropathy. Median duration of follow-up was 83 (6~226) months. We checked liver function test (LFT) on every visit. HBsAg was rechecked in 101 patients (reason for recheck: 17 with abnormal LFT, 84 routine check) during the follow-up period.

Results: HBV reactivation was found in 6 (3.4%, 5 with abnormal LFT, 1 routine check, M:F 4:2, 50.0+7.3 years) at median 72 (8~121) months. One patient died of hepatic failure, two showed persistence of HBV DNA and three experienced HBsAg seroclearance with antiviral therapy. LFT of the 5 survivors were all normal at the final visit. Biopsy-proven acute rejection was found in 36 and Rituximab was used in 15. Fifty patients received transfusion. Eighteen patients died and graft failure was reported in 26 patients. HBV reactivation was not associated with presence of diabetic nephropathy, acute rejection, use of Rituximab, transfusion, donor HBV markers, graft failure or death.

Conclusions: We recommend LFT on every visit and HBsAg in every year in sAg-sAb-cAb+ KT recipients, however, not regular HBV DNA titer because of low incidence and high cost.

TH-PO780

Kinetics of Cytomegalovirus Viral Load in Kidney Transplant Recipients Receiving Everolimus or Mycophenolate Sodium and No Pharmacological Prophylaxis

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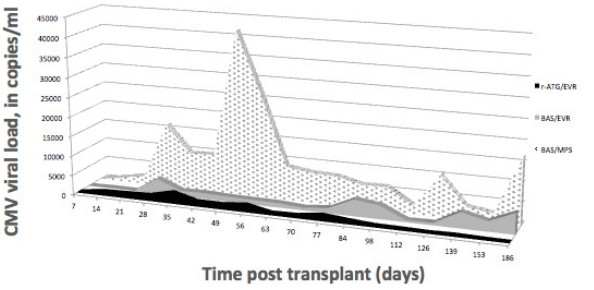
Background: Cytomegalovirus (CMV) infection is associated with morbidity and mortality after transplantation. Studies have shown that the use of mammalian target of rapamycin inhibitors are associated with lower rates of CMV infection.

Methods: The purpose is to investigate the **kinetics of CMV viral load** in kidney transplant recipients receiving tacrolimus (TAC) + everolimus (EVR) or mycophenolate sodium (MPS) and no CMV pharmacological prophylaxis. This is a comparative analysis of a **prospective**, single-center trial, in which **288** kidney transplanted patients were **randomized** to receive a single 3mg/kg dose of antithymocyte globulin, TAC, EVR and prednisone (r-ATG/EVR, n=85); basiliximab, TAC, EVR and prednisone (BAS/EVR, n=102); or BAS, TAC, MPS and prednisone (BAS/MPS, n=101). They were monitored with weekly pp65 antigenemia. CMV infection/disease were treated with intravenous ganciclovir. In a blinded fashion, samples were collected for **quantitative nucleic acid testing** (QNAT, in-house method).

Results: The incidence of first CMV infection/disease was 4.7, 10.8 and 37.6% in r-ATG/EVR, BAS/EVR and BAS/MPS (p<0.001) and the mean viral load in was 828, 1878 and 10.123 copies/ml, respectively.



Although r-ATG/EVR group had the same proportion of patients with at least one positive QNAT as BAS/MPS group (75.3 vs. 73.3%, p<0.01), the mean viral load was significantly lower in both everolimus groups (r-ATG/EVR vs. BAS/EVR, p=0.326; r-ATG/EVR and BAS/EVR vs. BAS/MPS, p<0.01).

Conclusions: The use of EVR was associated with lower incidence of CMV infection/disease and lower viral load compared to MPS. The use of r-ATG induction may have contributed to a higher proportion of patients with one episode of viremia, although its effect on vital replication was transient and mild.

Funding: Private Foundation Support

TH-PO781

Adenovirus Nephritis in Kidney Transplant Recipients: Clinicopathologic Features and Correlation

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Background: Adenoviruses (AdV) are increasingly being recognized as emerging pathogens and causes of substantial morbidity in stem cell and solid-organ transplant recipients. AdV are double-stranded DNA viruses that have a reported prevalence of infection during the 1st year after kidney transplantation of 11% by urine culture and 6.5% by serum PCR. In kidney transplant recipients, certain clinical and histologic features should raise concern for adenovirus nephritis (ADN). Here we report 9 renal biopsies with ADN from seven kidney transplant recipients.

Methods: A retrospective search to identify cases of ADN in renal transplant recipients was performed.

Results: Nine biopsy reports were identified (2009-2016) from among seven patients. The median time from transplant to development of ADN was 52 days (range: 13-1,414 days). Clinically, macrohematuria was observed in 71% (5/7) of the patients, microscopic hematuria in all patients (n=7) and significant proteinuria in all patients (n=7). Serum creatinine increased by a median of 56.5% from baseline (range: 26.3%-190%). Histologically, interstitial inflammation was present in 100% (9/9), granulomas were identified in 44% (4/9), tubular epithelial necrosis was present in 78% (7/9), nuclear inclusions were seen in 22% (2/9), and obliterative tubulitis was present in 56% (5/9). Immunostaining for adenovirus showed tubular epithelial cell reactivity in 100% (9/9).

Conclusions: Granulomas and inclusions are not identified consistently and thus make the diagnosis of ADN versus acute cellular rejection difficult. Immunostaining for adenovirus is the most important diagnostic tool when clear-cut histological features of ADN are not present on the biopsy sample. Overall, a strong emphasis on the clinical presentation should be used to help with the diagnosis. Based on this review, we advocate for adenovirus immunostaining on any renal biopsy when a patient presents (especially within 1 year from time of transplant) with gross or microscopic hematuria, and histological findings of intense interstitial inflammation, obliterative tubulitis, or granulomatous inflammation.

TH-PO782

Incidence of Infection following Rituximab Use in Kidney Transplant Recipients

Lana Wong, Michael G. Ison, Chad Richardson, Aneesha A. Shetty. *Northwestern Memorial Hospital, Chicago, IL.*

Background: Rituximab is used off-label in solid organ transplant for desensitization and treatment of antibody-mediated rejection (AMR). It targets CD20 and results in B cell depletion. Although it may be beneficial in preventing or fighting rejection, it may be associated with unfavorable infectious outcomes. The purpose of this study was to evaluate the incidence of infection in kidney transplant recipients who received rituximab for desensitization or AMR treatment.

Methods: This was a single-center, retrospective analysis of living and deceased donor kidney transplant recipients at Northwestern Memorial Hospital from January 1, 2007 to October 1, 2015. The following were inclusion criteria: alemtuzumab induction; age 18 years or older; receipt of at least one dose of rituximab. Patients were excluded for: previous transplant; simultaneous organ transplants; rituximab for an oncologic indication; history of human immunodeficiency virus. The primary efficacy endpoint was incidence of infection over 1 year following first dose of rituximab. Secondary endpoints were patient and graft survival 1 year following first dose of rituximab.

Results: Of the 145 subjects included, 114 (79%) received rituximab for desensitization and 31 (21%) for treatment of AMR. Overall, there were 34 cases of fungal and viral infections. The primary endpoint is shown in table 1. Five patients had death-censored graft failure and 8 patients died within the study period, 2 which were attributed to sepsis. A sub-analysis comparing those who received rituximab for desensitization versus AMR revealed no significant difference in incidence of infection, patient survival or graft survival.

Incidence of Infection (n=145)	
Number of patients with infection, n (%)	27 (19.0%)
Incidence of viral infection CMV Viremia, n (%) BK Viremia, n (%)	 15 (10%) 17 (12%)
Incidence of fungal infection	2 (1.4%)
Overall cases of infection	34

Conclusions: Approximately 19% of patients receiving rituximab experienced a fungal or viral infection. Graft failure occurred in 3% and death occurred in 6% of patients. There were no significant differences in outcomes for patients receiving rituximab for desensitization or AMR.

TH-PO783

Post-Transplant Anemia in Kidney Transplant Recipients: Prevalence, Risk Factors, and Outcomes Venkat Sainaresh Vellanki, Pei Xuan Chen, Olusegun Famure, Yanhong Li, Joseph Kim. *Div of Nephrology and the Kidney Transplant Program, Toronto General Hospital, Univ Health Network, Univ of Toronto, Toronto, ON, Canada.*

Background: This study aims to evaluate the association between post-transplant anemia (PTA) and adverse outcomes such as cardiovascular diseases (CVDs) and total graft failure (i.e., return to chronic dialysis, preemptive re-transplant, or death with graft function) in kidney transplant recipients (KTRs).

Methods: This cohort study examined all KTRs at Toronto General Hospital from 1-Jan-2000 to 31-Dec-2013 with the development of PTA, defined as a hemoglobin level of < 11.0 g/dL. The main study endpoints were cardiovascular events and total graft failure. The study baseline was set at 3-months after transplantation. Time-fixed and time-dependent multivariable Cox proportional hazards models were used to assess the independent association of PTA with the study endpoints.

Results: A total of 1,175 (61.7% male) KTRs were included in the study. The prevalence of anemia at three-months post-transplant was 53.7%. In the time-fixed model, PTA at baseline was not associated with cardiovascular events while there was increased risk of total graft failure (HR 1.50 [95% CI: 1.10, 2.06]). In the time-dependent model, PTA was significantly associated with both cardiovascular events (HR 2.13 [95% CI: 1.51, 3.00]) and total graft failure (HR 4.39 [95% CI: 3.18, 6.03]).

Conclusions: PTA is a significant independent risk factor for cardiovascular events and total graft failure in KTRs, particularly in statistical models that properly account for the time-dependent nature of anemia.

TH-PO784

Clinical Characteristics of Parvovirus B19 Infection in Kidney Transplant Patients Chung Hee Baek, Hyosang Kim, Su-Kil Park. *Div of Nephrology, Dept of Internal Medicine, Asan Medical Center.*

Background: Parvovirus B19 is a small, nonenveloped, single-stranded DNA virus with special affinity for the erythroid progenitor cells of the bone marrow. The first case of parvovirus B19 infection(PVI) in kidney a transplant(KT) recipient was reported in 1986. Since then, the data about risk factors and specific clinical characteristics of PVI are still insufficient.

Methods: We identified PVI among all 4,392 KT recipients by parvovirus B19 polymerase chain reaction(PCR) from January 1990 to April 2016, and the clinical characteristics of patients with positive results were compared with those of age and sex-matched patients with negative results by PCR.

Results: Total 39 KT recipients showed positive parvovirus B19 PCR, and they were compared with age and sex-matched 78 patients among 563 KT recipients showed negative PCR results. The 89.7% of positive parvovirus B19 PCR was reported within the first year of KT. Bone marrow biopsies were performed in 13 patients with compatible bone marrow changes of parvovirus infection and positive parvovirus B19 PCR in bone marrow specimens. The 74.4% of patients with positive parvovirus B19 PCR were treated with intravenous immunoglobulin, and all patients were recovered from anemia. In multivariate analysis, parvovirus B19 PCR performed within 1 year of KT [relative risk(RR) 17.139, 95% confidence interval(CI) 3.989-73.641, P<0.001], deceased donor KT (RR 6.896, 95% CI 1.625–29.261, P=0.009) and hemoglobin level at the time of PCR (RR 0.438, 95% CI 0.295–0.649, P<0.001) were significantly related with positive parvovirus B19 PCR. Pancytopenia showed a trend of relation (RR 4.756, 95% CI 0.932–24.257, P=0.061). In addition, the use of tacrolimus showed a significant relationship with PVI in univariate analysis (RR 4.270, 95% CI 1.889–9.651, P<0.001), but the significance was lost in multivariate analysis. Graft survival of two groups were not different during follow up period of 111.68±54.54 months (P=0.685 by log rank test).

Conclusions: The related factors of positive parvovirus B19 PCR might be useful for suspicion and early detection of parvovirus B19 infection. Further studies are necessary to elucidate the characteristics of parvovirus B19 infection in KT.

TH-PO785

Pure Red Cell Aplasia Related to Human Parvovirus B19 Infection in Kidney Transplant Recipients: A Single Center Experience Yan Jiang, Zhechi He, Rending Wang, Jingyi Zhou, Jianghua Chen. *The First Affiliated Hospital of Zhejiang Univ, Zhejiang Univ, Hangzhou, Zhejiang Province, China.*

Background: To investigate the incidence, clinical manifestation, diagnosis and treatment of pure red cell aplasia (PRCA) related to human parvovirusB19 (HPV-B19) infection in kidney transplant recipients.

Methods: This is a retrospective cohort study of all patients who underwent kidney transplantation between January 2010 and December 2014 at kidney disease center, the first afflicted hospital of Zhejiang university. PRCA is defined by the absence of mature erythroid precursors in the bone marrow with normal white blood cell and platelet count (or deep reticulocytopeniain peripheral blood in the absence of other possible causes).We used standard real-time polymerase chain reaction (PCR) amplification to detect HPV B19 in serum sample. The clinical data of HPV-B19 PRCA patients were collected and analyzed retrospective.

Results: In the past 5 years, of 813 kidney transplant recipients, 26(3.2%) were diagnosed with HPV-B19 PRCA at a median of 46 days(range, 21days-2years) posttransplantaion. All 26 patients had severe anemia with the mean lowest hemoglobin count of 58.3±10.1 g/L.6 patients (23.1%) experienced graft dysfunction (creatitine elevation) at HPV-B19 PRCA diagnosis. 25 of 26 patients received intravenous immunoglobulin (IVIG) treatment after diagnosis. Transient serum creatinine elevating during IVIG treatment was observed in 23.1% patients.MMF was discontinued in 20(77%) patients to reduce the degree of immunosuppression. 88.3% of patients were switched from FK to CSA.Scarnet sodium was used in 5 patients as antiviral regimen (combination with IVIG in 4 patients and used alone in 1 patients).For these 25 patients who received IVIG-based comprehensive treatment, 19(80%) patients achieved long term remission after first course of IVIG treatment. 7 patients experienced HPV B19 PRCA relapse and responded well to additional IVIG courses with or withoutscarnet sodium. All 26 patients are alive with functional graft kidney at the end of follow up.

Conclusions: HPV-B19 PRCA is a rare but significant disease after kidney transplantation. Treatment with IVIG is effective in most cases.

Funding: Clinical Revenue Support

TH-PO786

Metabolic Acidosis and Outcome in Patients Long Term after Kidney Transplantation Marcin Adamczak, Damian Gojowy, Katarzyna Skiba, Magdalena Bartmanska, Aureliusz Kolonko, Andrzej Wiecek. *Dept of Nephrology, Transplantation and Internal Medicine, Medical Univ of Silesia, Katowice, Poland.*

Background: Metabolic acidosis (MA) frequently occurs in patients after kidney transplantation (KTx). Results of both experimental and clinical studies suggest that MA may contribute to faster progression of native kidney disease. It is unknown however whether or not such relationship occurs also in KTx patients. The aim of this clinical, single center, retrospective, observational study was to examine the relationship between MA and both mortality and renal outcomes in patients after KTx.

Methods: Four hundred eighty six (290 male; 196 female) patients aged 48 ± 12 years at least one year after KTx were analyzed. Blood HCO_3^- were measured and subsequently patients were observed during 3 years. MA was defined as the blood HCO_3^- concentration less than 22 mmol/L. The endpoints in survival curves analysis were death and initiation of dialysis therapy. In patients who did not reach above mentioned endpoints the difference between final (after 3 years follow-up) and initial eGFR was calculated (according to the MDRD formula). Relative risks (RR) were presented with 95% CI.

Results: MA was diagnosed in 57 (12%) patients being long term after KTx. In patients with MA the risks of death and initiation of dialysis therapy were significantly higher than in patients without MA [RR=4.11 (1,58-10,67), p=0.0038 and RR=3.58 (3,58-6,32), p<0.001; respectively]. In KTx patients with MA who did not reach above mentioned outcomes blood bicarbonate concentration at baseline correlated positively with change of eGFR values (R=0.48, p=0.002, n=36). Such correlation was not found in patients without MA (n=386).

Conclusions: 1. MA increases mortality and worsens graft survival in patients after KTx. 2. The intensity of MA is associated with faster progression of kidney dysfunction in KTx patients.

Funding: Government Support - Non-U.S.

TH-PO787

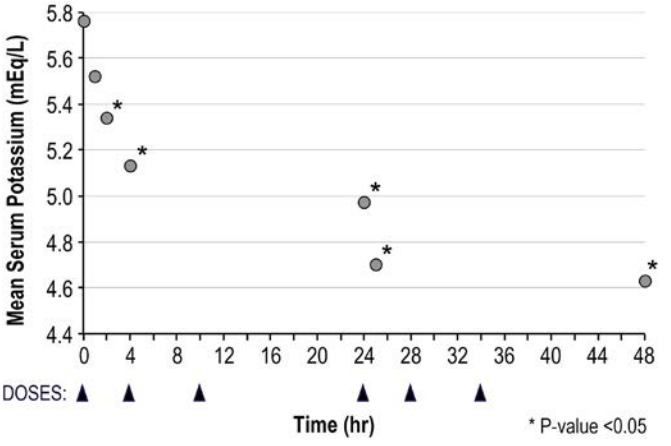
Sodium Zirconium Cyclosilicate Treatment of Hyperkalemia in CKD Patients with a Solid Organ Transplant: Data from Two Trials Mohamed A. El-Shahawy,[1] Edgar V. Lerma,[2] Wajeh Y. Qunibi,[3] Bhupinder Singh,[4] Jose A. Menoyo,[4] Henrik S. Rasmussen.[4] *[1]Academic Medical Research Inst, Los Angeles, CA; [2]Univ of Illinois at Chicago College of Medicine, Advocate Christ Medical Center, Oak Lawn, IL; [3]Univ of Texas Health Science Center at San Antonio, San Antonio, TX; [4]ZS Pharma, San Mateo, CA.*

Background: Sodium zirconium cyclosilicate (ZS-9) is a non-absorbed, selective cation trap that binds potassium (K^+) throughout the GI tract. The effects of ZS-9 in patients (pts) with a solid organ transplant have not been previously reported. This subgroup post-hoc analysis assessed the effects of ZS-9 in transplant pts with hyperkalemia (HK).

Methods: Data were pooled from two completed phase 3 prospective, randomized, placebo-controlled trials: ZS-003 and HARMONIZE. Both trials had an induction phase, where pts received 10g ZS-9 TID for 48h, and a maintenance phase.

Results: In the ZS-003 and HARMONIZE studies, 9 CKD pts had previously undergone solid organ transplants (5 kidney, 3 liver, 1 dual kidney/liver) and were receiving various immunosuppressive therapies including calcineurin inhibitors, antiproliferative agents and corticosteroids; 4 pts had heart failure and diabetes, and 5 were on RAASi therapy. Mean serum K^+ declined from 5.76 mEq/L at baseline to 4.63 mEq/L at 48h in these pts (figure); 67% and 100% of pts achieved normal serum K^+ by 24h and 48h, respectively. Median time to serum K^+ normalization was 4.0 h. None of the transplant pts experienced an adverse event (AE) during the induction phase. In the overall pt population who received 10g ZS-9 during the induction phase (n=401), the most common AEs were GI disorders (3.7%).

Figure. Mean Serum K^+ Over Time in Transplant Pts.



Conclusions: ZS-9 appeared to restore K^+ to the normal range in transplant pts with HK; the response to ZS-9 in these pts appeared to be similar to that observed in the general pt population in the trials.

Funding: Pharmaceutical Company Support - ZS Pharma

TH-PO788

Effect of Renal Transplantation on Carotid Intimal Medial Thickness and Left Ventricular Mass Index-A Longitudinal Study Sandeep Mahajan, Sucheta Yadav, Yogesh Kumar Chhabra. *Nephrology, A.I.I.M.S, Delhi, India.*

Background: Various nontraditional risk factors (NTRFs) and increased left ventricular mass index (LVMI) have been implicated for high cardiovascular (CV) mortality in CKD. Renal transplantation (RT) by correcting uremic milieu improves most NTRFs, however CV mortality remains high post RT. This has been scarcely evaluated but could be due to exacerbation of traditional & NTRFs by drugs or legacy effect of previous CKD related risk factors. Carotid intimal medial thickness (CIMT) is established marker of structural atherosclerosis & has been shown to decrease after correction of risk factors in some clinical scenarios. Only a few small, mostly pediatric studies have longitudinally assessed CIMT & LVMI post RT with inconsistent results. We for first time have prospectively looked at both CIMT & LVMI in adult CKD 5D patients just prior & at 1year post RT.

Methods: 131 consecutive, eligible & consenting adults undergoing live RT were enrolled from March 2014-15, of which 31 couldn't complete 1-year follow-up. All investigations, CIMT & LVMI assessments were done at baseline (≤1 week prior to RT) & 1-year post RT. Patients with established coronary & valvular heart disease were excluded.

Results: In study population 85.5% subjects were male, mean age was 31.8±10.7 years & median dialysis vintage was 227 days. Basic disease was unclassified in 72.5% & 6.1% were diabetic. All were on 3-drug immunosuppression of mycophenolate mofetyl, steroids & calcineurin inhibitors (94.6% Tacrolimus, 4.6% Cyclosporine). Mean Serum creatinine was 1.4±0.6 mg% at 1 year.Mean CIMT (mm) & LVMI (g/m^2)at baseline & after 1 year post RT were0.51±0.1 & 0.49±0.1 (p=0.75) & 203±48.3 & 173.1±44.7 (p<0.001) respectively. CIMT correlated significantly only with age, BMI & LVMI (p<0.001), while LVMI was significantly increased only in pateints with history of hypertension & those on >2 anti-hypertensive drugs (p<0.01).

Conclusions: In younger, low risk population we document no significant change in CIMT at 1 year post RT, while LVMI decreased by 14.7%. Further studies including more diabetic & elderly patients with longer follow up are therefore warranted.

Funding: Government Support - Non-U.S.

TH-PO789

Incidence and Characteristics of Kidney Stones in Kidney Transplant Recipients: A Meta-Analysis Wisit Cheungpasitporn, Charat Thongprayoon, Michael A. Mao, Wonngarm Kittanamongkolchai, Tsering Dhondup, Stephen B. Erickson. *Nephrology and Hypertension, Mayo Clinic, Rochester, MN.*

Background: The incidence and characteristics of kidney stones in kidney transplant recipients are not well studied. The objective of this meta-analysis was to evaluate the incidence and types of kidney stones after kidney transplantation.

Methods: A literature search was performed using MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews from the inception of the databases through March 2016. Studies assessing the incidence of kidney stones in kidney transplant recipients were included. We used a random-effects model to estimate the incidence of kidney stones.

Results: Eighteen studies with 61,785 kidney transplant patients were included in the analyses to assess the incidence of kidney stones after kidney transplantation. The estimated incidence of kidney stones was 0.9% (95% CI, 0.6%–1.4%). The mean duration to diagnosis of kidney stones after kidney transplantation was 28 ± 22 months. The mean age of patients with kidney stones was 42 ± 8 years. Within reported studies, approximately 50% of kidney transplant recipients with kidney stones were males. 62% of kidney stones were calcium based stones (34% mixed CaOx/CaP, 18%CaOx and 10%CaP), followed by struvite stones (22%) and uric acid stones (16%).

Conclusions: The estimated incidence of kidney stones in patients after kidney transplantation is 0.9%. Although calcium based stones are the most common kidney stones after transplantation, struvite stones (also known as "infection stones") are not uncommon in kidney transplant recipients. These findingsmay impact the prevention and clinical management of kidney stones after kidney transplantation.

TH-PO790

Association between Cardio-Ankle Vascular Index, Carotid IMT and Level of FGF-21 in Renal Transplant Patients Thananda Trakarnvanich,[1] Yingchia Wang.[2] [1]*Renal Unit, Dept of Medicine, Faculty of Medicine, Vajira Hospital, Navamindradhiraj Univ, Bangkok, Thailand;* [2]*Renal Unit, Dept of Medicine, Renal Unit, Dept of Medicine, Navamindradhiraj Univ, Bangkok, Thailand.*

Background: Cardiovascular disease is the major cause of death in patients with CKD, even after renal transplantation. The major risk factor is arterial stiffness. The cardio-ankle vascular index (CAVI) was developed as an indicator of arterial wall stiffness . Fibroblast growth factor 21 (FGF-21) is a metabolic regulator and elevated FGF-21 levels have been reported in coronary heart disease and carotid artery plaque. We aimed to study the association of CAVI with FGF-21 and their relation to carotid media thickness and various parameters that can contribute to cardiovascular disease.

Methods: A total of 90 participants who underwent renal transplant were included in the study. The following measurements were done and laboratory data collected: CAVI, echocardiogram, homocysteine, hs-CRP, carotid IMT, FGF-21, medication after renal transplantation, and incidence of cardiovascular disease.

Results: The average CAVI score was 7.51±1.69. The CAVI values had a positive correlation with carotid IMT and a negative correlation with hemoglobin (r=0.214, P=0.000 and r=-0.219, P=0.044, respectively). No association was observed between CAVI and FGF-21 . FGF-21 had a positive correlation with hs-CRP, urine protein excretion, triglyceride, and a negative correlation with renal function. The average carotid IMT score in this study was 0.57±0.18. Patients with age above 60, low cholesterol and HDL, and high BMI had significantly higher carotid IMT values.

Conclusions: CAVI values after renal transplantation were within normal range and showed an association with carotid IMT. Despite the negative association with FGF-21 in this study, FGF-21 still had a positive correlation with hs-CRP, lipid profile and urinary protein excretion. This indicates that renal transplantation patients had improved arterial stiffness but still had risk factors of CVD. Close monitoring for cardiac events and risk factor modification are highly recommended even after successful renal transplantation.

Funding: Government Support - Non-U.S.

TH-PO791

High-Molecular-Weight Adiponectin Inhibits the Progression of Vascular Calcification in Japanese Renal Allograft Recipients Hiroki Adachi, Yuki Matsui, Norifumi Hayashi, Keiji Fujimoto, Hideki Yamaya, Hitoshi Yokoyama. *Nephrology, Kanazawa Medical Univ, Uchinada, Ishikawa, Japan.*

Background: Adiponectin has antiatherogenic effects and prevents the development and recurrence of cardiovascular events. However, few long-term studies have been conducted on changes in serum adiponectin levels and arterial calcification in renal allograft recipients.

Methods: The effects of serum ADPN fractions on renal functions and serum lipid markers were examined in 51 Japanese patients. The calcification of abdominal aorta was examined by CT scan based on aortic calcification index(ACI) and aortic calcification area index(ACAI), in order to reveal the relationship in the rate of change between arterial calcification and serum high- and low-molecular weight (HMW-/LMW-)ADPN fractions during 8 years. Furthermore, factors influencing vascular calcification such as age were also examined.

Results: The rates of change of ACI and ACAI at the abdominal aorta were grouped into quartiles for comparison with the alteration of ADPN fractions for 8 years. As a result, the rate of change of ACI and ACAI were much lower in the highly HMW-ADPN elevated group of (p<0.01). In the multiple regression analysis, an advanced age at transplantation increased the rate of changes in ACI, while the increased the rate of changes in HMW-ADPN concentrations decreased it. In addition, an advanced age at transplantation and a history of cardiovascular complications increased the rate of changes in ACAI, while both the increase of HMW-ADPN concentrations and the improvement of eGFR decreased it. In this notion, eGFR was negatively correlated with HMW-/LMW-ADPNconcentrations (r=-0.300, p=0.033 and r=-0.380, p=0.006, respectively). BMI was positively correlated with the LDL-C/HDL-C ratio and negatively correlated with the HDL-C values (r=0.412, p=0.003 and r=-0.379, p=0.006, respectively). In a multiple regression analysis, the increased rate of changes in HDL-C was a significant factor improving the HMW-ADPN concentrations.

Conclusions: The increase of HMW-ADPN associated with HDL-C may inhibit the progression of vascular calcification at the abdominal aortaeven in Japanese renal allograft recipients during 8 years follow-up.

TH-PO792

Improvement of Arterial Stiffness Parameters after Kidney Transplantation: A Systematic Review and Meta-Analysis Aboubacar Sidibé, Catherine Fortier, Marie-Pier Desjardins, Fabrice Mac-Way, Sacha A. De Serres, Mohsen Agharazii. *Social and Preventive Medicine, Medicine, Research Center of CHU de Québec, Hôtel-Dieu de Québec Hospital, Nephrology Div, Laval Univ, Medicine, Quebec City, QC, Canada.*

Background: Chronic kidney disease is associated with increased arterial stiffness. Correction of the uremic milieu by kidney transplantation (KTx) may improve arterial stiffness. However, the results from clinical studies are not uniformly convincing. The objective of the present study is to measure the impact of KTx on the reduction of arterial stiffness.

Methods: Observational studies and randomized controlled trials with measurements of pulse wave velocity (PWV) were extracted from MEDLINE, EMBASE, COCHRANE LIBRARY, and Web of Science from their inception to January 2016. Two reviewers independently identified eligible studies comparing PWV pre to post KTx and extracted data including population characteristics, interventions and outcomes.

Results: 13 studies met our inclusion criteria. 11 Studies (408 renal transplants) have been included in meta-analysis. There was a standard mean change of PWV by -0.45 (95% CI: - 0.68; -0.20, I^2=58%) post-KTx. Both studies using aortic PWV (5 studies, 160 patients) and those using brachial-ankle PWV (3 studies, 151 patients), showed a significant decrease of PWV by -1.58 m/s (95% CI: -2.97; - 0.19, I^2= 87%) and -1.21 m/s (95% CI: - 1.89 ; – 0.54, I^2=0 %) post-KTx, respectively. Analysis of central pulse pressure and augmentation index pressure showed significant reduction post-KTx by -4.77 (95% CI: -9.19; -0.35, I2=55%) and -11.59 (95% CI:-15.64; -7.53, I2=43%), respectively. Only two studies have reported adjusted parameters for mean arterial pressure.

Conclusions: There is a significant reduction in PWV, central pulse pressure and augmentation index after KTx. Heterogeneity among studies are moderate. Further analysis is required to examine the importance of changes in different vascular beds taking into account changes in blood pressure.

TH-PO793

Clinical Outcome of Aortic Arch Calcification in Kidney Transplant Recipients – Single Center Study Yaerim Kim, Woo Yeong Park, Seong Sik Kang, Sang Mok Yeo, Kyubok Jin, Sung Bae Park, Seungyeup Han. *Internal Medicine, Keimyung Univ School of Medicine, Keimyung Univ Kidney Inst, Daegu, Korea.*

Background: Cardiovascular disease is one of the most important causes of death in kidney transplant recipients (KTR) s. Aortic calcification is a major risk factor for cardiovascular disease and associated with coronary artery disease in KTRs. The aim of this study was to evaluate the prevalence and clinical outcome of aortic arch calcification in KTRs.

Methods: We retrospectively evaluated the aortic arch calcification (AoAC) in KTRs who received kidney transplantation (KT) from 2000 to 2010, using chest radiography. AoAC was semiquantitatively estimated by calculating calcification score. The association of clinical and biochemical parameters were evaluated.

Results: A total of 258 patients were enrolled in this study and their mean age was 40.7 year-old, male: female was 135:123, diabetes was 24.4% and deceased donor KT was 36.8%. Fifty-three (20.5%) patients had AoAC at the time of transplantation and pretransplant AoAC score was 0.8 ± 2.0. Pretransplant AoAC was significantly correlated with age, serum calcium level at the transplantation and deceased donor KT. The proportion of KTRs with AoAC gradually increased to 23.3%, 26.4%, and 28.7% at 1, 3 and 5 years after transplantation, respectively. AoAC score also gradually increased to 1.0 ± 2.3, 1.2 ± 2.8 and 1.6 ± 3.1 at 1, 3 and 5 years after transplantation. During the mean follow-up duration of 101.9 months, 33 patients (12.8%) lost their grafts. Five-year graft survival rates were 97.5% in no AoAC group and 95.7% in AoAC group, but there was no statistical significance between two groups. Five-year patient survival rates were 98.0% in no AoAC group and 93.8% in AoAC group, and there was statistical significance between two groups (p=0.004).

Conclusions: AoAC is an independent predictor of poor cardiovascular outcome of KTRs. Age, pretransplant serum calcium and deceased donor KT were significantly correlated with AoAC. Regular follow-up by chest radiography could be a simple and useful method to screen the cardiovascular mortality.

TH-PO794

Endovascular Management of Transplant Renal Artery Stenosis: A Safe and Effective Treatment Ana Karoline Nobrega Cavalcanti,[1] Bento C. Santos,[1,2] Marcelino Souza Durao,[1,2] Eduardo J. Tonato,[1] Marisa Petrucelli Doher,[1] Felipe Nasser,[1] Breno Boueri Affonso,[1] Leonardo Guedes Moreira Valle,[1] Nadia Guimaraes- Souza,[1] Alvaro Pacheco-Silva.[1,2] *[1]Nephrology, Hospital Israelita Albert Einstein, São Paulo, SP, Brazil; [2]Nephrology, Univ Federal de São Paulo, São Paulo, SP, Brazil.*

Background: Transplant Renal Artery Stenosis (TRAS) is a low incidence complication, but if untreated, can lead to graft failure, refractory hypertension (HT) and reduced life expectancy. Primary stent implantation is a well-tolerated technique for TRAS treatment.

Methods: The aim of this study was to assess the safety and efficiency of TRAS endovascular therapy. The primary end point was graft survival. The secondary end points were serum creatinine level, blood pressure evolution, and the number of antihypertensive drugs (AHD) pre- and post-procedure. We performed a retrospective single-institutional review of all cases of TRAS from January 2011 to Abril 2016.

Results: From 519 renal transplant, 26 percutaneous procedures have been performed on 24 patients (68% men, 88% with HT, mean age 50 y). The median time to presentation was 169 days. Stenting was performed in all patients with 100% technical and clinical success. The major indications were acute graft dysfunction (54%) and poor function (25%); in addition to two cases of HT and three cases of delayed graft function (DGF). During a mean follow-up of 23 months, a reduction in SCr (Pre-procedure 3.05mg /dL x 30 days 1.73mg /dL x 60 days 1.62mg /dL p <0.001) with 92% graft survival was shown. We found that recovering of renal function before 30 days was an independent predictor of graft survival. All DGF patients left hemodialysis after procedure. When HT was the indication for the procedure improved blood pressure parameters and reduction in the number of AHD, was also observed in other patients (2.09x 1,50 p = 0.008). In 2 cases restenosis was observed requiring new treatment. 2 patients died from unrelated causes to the procedure.

Conclusions: The endovascular management with stent placement of TRAS is safe and presents a high rate of clinical success with low morbidity. Its impact on SCr is significant in our experience, being an effective procedure for restoring and maintaining the graft function.

TH-PO795

Detection of Silent Myocardial Ischaemia Using Radionuclide Imaging and Long-Term Outcomes after Kidney Transplantation Sanmay Low,[1] Horng-Ruey Chua,[2] Raymond C.C. Wong,[3] Angeline Goh,[1] Yue-Harn Ng,[2] Boon Wee Teo,[2] Anantharaman Vathsala.[1] *[1]National Univ Centre for Organ Transplantation, National Univ Hospital, Singapore; [2]Div of Nephrology, National Univ Hospital, Singapore; [3]Dept of Cardiology, National Univ Heart Centre, Singapore.*

Background: Silent myocardial ischemia (SMI) may predict major adverse cardiac events (MACE) which increase graft loss and mortality in kidney transplant recipients (KTRs). We aim to examine the incidence of SMI using myocardial perfusion imaging (MPI) and its association with long-term outcomes in KTRs.

Methods: Retrospective cohort study of KTRs *without* pre-transplant coronary artery disease, who underwent *post-transplant* MPI for SMI detection, defined by moderate-severe myocardial perfusion defects or post-stress cardiac ejection fraction <50%. Primary outcome (composite of all-cause mortality, graft loss, MACE) was examined over minimum 5 years post-transplantation.

Results: 135 KTRs underwent 226 MPIs post-transplant with 1.5 (1.1–2.6) years to first scan. 91 patients had two serial MPIs, with scan interval of 2.2 (2.0–2.5) years. Follow-up was 10 (7.4–12.7) years. 32% of overall total cohort and 84% of subgroup with two MPIs were diabetic. 86% of diabetics had NODAT. 110 (81%) had normal MPIs, 11 (8%) had mild perfusion defects, and 14 (10%) had SMI, of which 3 SMI were detected only on second scan. Correspondingly, primary outcome was met in 6%, 27%, 43% (p=0.04), and MACE occurred in 7%, 0%, 21% (p=0.11), respectively. Total 26 patients met the primary outcome over 4.8 (2.6–7.3) years, including 11 with MACE. On multivariate analysis, SMI (p=0.04), higher LDL (p=0.006) and proteinuria >0.3g/day (p=0.02) predicted earlier onset of primary outcome, while only SMI predicted MACE (p=0.007). Serial MPIs to detect SMI increased the positive predictive value for MACE from 17% to 25%, and correspondingly 50% to 38% for primary outcome. Absence of SMI had negative predictive value of 93% for MACE and 83% for primary outcome.

Conclusions: SMI outperforms conventional risk factors in predicting mortality, graft loss, and MACE in KTRs, with good negative but poor positive predictive value for adverse outcomes, the latter even with serial screenings.

TH-PO796

The Nocturnal BP Profile and Sleep Disordered Breathing (SDB) in Renal Transplant Patients Francesca Mallamaci, Rocco Tripepi, Daniela Leonardis, Maria Carmela Versace, Pasquale Fabio Provenzano, Angela Mafrica, Claudia Torino, Graziella D'arrigo, Giovanni Tripepi, Carmine Zoccali. *CNR-IFC, Reggio Calabria, Reggio Calabria, Italy.*

Background: Nocturnal hypertension and the non-dipping BP profile in renal transplant patients capture exposure to vascular barotrauma which is not apparent when BP is measured in the office or when the average 24h ABPM is considered (Transplantation 2015). However, risk factors for the altered nocturnal BP profile in renal transplant patients are still largely undefined.

Methods: We sought to identify the correlates of BP during night (average nocturnal BP) and of the night/day ratio, an indicator of the extent of nocturnal dipping, in 215 renal transplant patients. 24h ABPM and polysomnography recordings were performed in all patients alongside with Framingham risk factors and CKD-specific risk factors (including phosphate, the eGFR, proteinuria and CRP).

Results: In polysomnographic studies 56 patients (17%) had mild to moderate SDB [Apnea Hypopnea Index, (AHI) >5 episodes/hour <15 episodes/hour] and 19 (9%) had severe SDB (AHI >15 episodes/hour). Night-time systolic BP (r=0.19, P=0.005) and the night/day SBP ratio (r=0.18, P=0.01) were linearly related with AHI and to weaker extent with average 24h SBP and DBP (both r=0.14, P=0.04). Furthermore, high AHI associated also with older age, male gender, BMI, diabetes, high phosphate and C-Reactive Protein and CV comorbidities. In multiple regression analyses adjusting for these parameters as well as for average day-time SBP, Hb, and proteinuria, AHI remained related with average night-time SBP (beta=0.10, P=0.02) and with the night/day SBP ratio (beta=0.17, P=0.02). Of note, in these multiple regression analyses, the AHI ranked as the strongest correlate of BP during night time and of the night /day systolic BP ratio.

Conclusions: Sleep disordered breathing, as measured by the AHI, is the most powerful correlate of the altered nocturnal BP profile in renal transplant patients. Since sleep disordered breathing is highly prevalent in dialysis patients and in part regresses after renal transplantation, these associations suggests that persistence of this disturbance is a major player for the excessive nocturnal BP burden in transplant patients.

Funding: Government Support - Non-U.S.

TH-PO797

Post-Transplant Hypertension: A Potential Role of Genetic Kidney Disease

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Background: Genetic factor plays a role in hypertension(HTN). Kidney transplantation from non-hypertensive donors may improve post-transplant HTN.

Methods: A total of 103 kidney transplantations were reviewed. There were 32 living-donor renal transplant(LDRT; 15 living-related and 17 living-unrelated) and 12 deceased donor renal transplant(DDRT) recipients, who received paired deceased donor kidneys (derived from the same donor transplanted to different recipients) leading to 5 "mate" recipient pairs.

Results: Of 44 recipients, mean age was 53.3 yrs old(21.4-79.5) and 57% were female. Mean duration of follow-up was 7.93 mo(0.6-16.3). Mean serum creatinine(SCr) was 1.4+/-0.1(LDRT 1.23±0.05 vs. DDRT 1.95±0.29,p=0.0006). Up to 93% of recipients had pre-transplant HTN, and 45% became non-hypertensive post-transplant(SBP≤140, DBP≤90, or on ≤2 BP agents regardless SBP or DBP). Mean post-transplant SBP was lower than mean pre-transplant SBP but not statistically significant(132±2.63 vs. 135±2.42,p=0.3526) as same as DBP(77±1.74 vs. 80±2.13,p=0.2406). Among 13 LRRT recipients with pretransplant HTN, 5 patients were non-hypertensive post-transplant; whereas 16 of 29(55%) recipients of unrelated recipients (LURT+DDRT) became non-hypertensive(Figure1A). Among 11 DDRT recipients with pretransplant HTN, only 4 patients(2 mate pairs) had the same post-transplant BP outcomes(Figure1B). Pretransplant BP, the number of BP medications, and normotensive kidneys were not determinants of post-transplant HTN in a logistic regression model.

Conclusions: Pre-transplant HTN may be resolved post-transplantation. Since the prevalence of post-transplant HTN trends to be lower in recipients receiving kidneys from unrelated donors (LURT+DDRT) compared to those recipient of LRRT, genetic factors may play an important role in pathogenesis of post-transplant HTN.

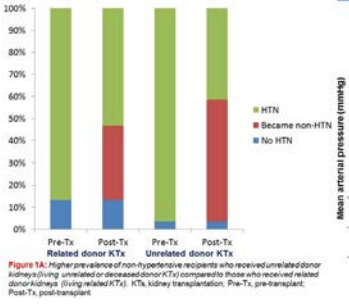

Figure 1A: Higher prevalence of non-hypertensive recipients who received unrelated donor kidneys (living unrelated or deceased donor KTx) compared to those who received related donor kidneys (living related KTx). KTx, kidney transplantation; Pre-Tx, pre-transplant; Post-Tx, post-transplant

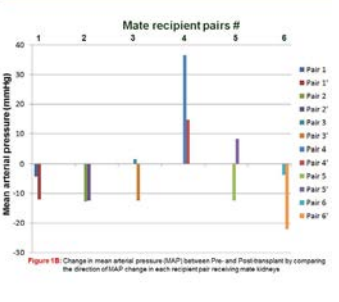

Figure 1B: Change in mean arterial pressure (MAP) between Pre- and Post-transplant by comparing the direction of MAP change in each recipient pair receiving mate kidneys

TH-PO798

Renal Artery Angioplasty Improves Short-Term Blood Pressure and Renal Allograft Function in Transplant Renal Artery Stenosis

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Background: Similar to non-kidney transplant patients, the favorable outcomes of renal artery angioplasty±stenting on blood pressure(BP) control and renal function are unclear. We aim to describe these outcomes after this procedure and identify risk factors of transplant renal artery stenosis(TRAS).

Methods: An 8-year-search of medical records(2008-2015) yielded 1,919 kidney transplant recipients in whom angiography-proven TRAS was diagnosed in 19. Each of the 19 patients was individually matched to 3 subjects without TRAS based on age, gender, diabetes, and year of kidney transplantation.

Results: The TRAS group had a mean age of 50.3 years old and was 63% diabetic, 84% male, and 42% white. About 1/3 of the patients had HTN as the cause of ESRD. Median time to TRAS onset after transplant was 3.4 months(0.4-63.2), and median duration of follow-up after diagnosed TRAS was 2.16 years(0.36-6.35). SBP and serum creatinine(SCr), but not DBP were lower after transplant renal artery angioplasty±stenting (1-mo post- minus pre-angiographic differences: mean SBP 19.4±29.5 mmHg(-55 to 65,p=0.01), median SCr 0.16(-1.42 to 9.57,p=0.008), and mean DBP of 6.7±14.4 mmHg(-12 to 35,p=0.06). Median duration of follow-up from transplantation to the time when the most recent SCr were measured were 2.8 and 2.5 years in TRAS and control groups, respectively. In TRAS group, graft survival was 95% and all patients survived; whereas, graft and patient survival in control group were 93% and 91%, respectively. Compared to non-TRAS patients, history of BK viuria(OR 2.1,p=0.19) may increase the risk of TRAS; however, neither history of CMV viremia nor other potential risk factors (serum Ca, PO_4, PTH, vitamin D or donor age) was a statistically significant risk factor in a univariate conditional logistic regression.

Conclusions: Although limited to short-term follow-up, renal artery angioplasty±stenting improved BP and renal allograft function in TRAS patients. In addition, graft and patient survival do not appear lower than in non-TRAS patients. Potential risk factors of TRAS are still unclear given the small number of TRAS patients.

TH-PO799

Renal and Obstetrical Outcomes of Pregnancy in Kidney Transplant under Calcineurin Inhibitors

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Background: The management of calcineurin inhibitors (CNI) in renal transplant patients during pregnancy is not clearly codified. Their per-partum CNI levels physiologically decrease leading to a frequent adjustment of dose, although without evidence of a concomitant decline of the therapeutic efficiency. We here report the features of pregnancies during which CNI doses were unchanged.

Methods: This retrospective study identified 34 pregnancies with unchanged dose of CNI in 27 renal transplant patients in a French single-center from 1987 to 2014. We studied their nephrologic, obstetrical characteristics and outcome.

Results: The mean age at pregnancy was 28.5 (±4.7). The creatinine level was lower than 1.5 mg/dL in 23 patients before pregnancy (mean:1.28mg/dl±0.16). Immunosuppression regimen included tacrolimus or cyclosporine in 12 and 22 pregnancies, respectively. Mean residual levels decreased 48% for tacrolimus and 55% for cyclosporine (nadir: 30 weeks of amenorrhea, WA). Gestational hypertension occurred in 13 (38%) patients, complicated with pre-eclampsia in 6 of them. Prematurity was 44% (mean birth term: 35.5±3.7 WA) and 15 infants (47%) had a hypotrophy (mean birth weight: 2247±925 grams). HLA alloimmunization were identified in 6 patients (23%) at one year postpartum, including donor specific anti-HLA antibodies in 1 case. None acute rejection was reported and 8 patients (30%) developed a graft dysfunction within 2 years postpartum, related to immunological process, CNI toxicity or unidentified cause in 2, 2 and 4 cases respectively.

Conclusions: The no-adaptation of CNI dose according to their residual does not seems to induce more immunological complications or a poorer renal outcome. This can be explaining by the fact that circulating free drug is increased during pregnancy due to hypoalbuminemia. Considering the small size of our sample, more studies are nevertheless necessary to confirm these results.

TH-PO800

A Trial-Based Algorithm for Insulin Pump Therapy in Hyperglycemic Patients Early after Kidney Transplantation

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Background: Correction of early postoperative hyperglycemia prevented posttransplantation diabetes mellitus in our previous proof-of-concept clinical trial. We hypothesized that insulin pump therapy with maximal dosing during the afternoon, in consequence of the morning administration of glucocorticoids, would further flatten the daily glucose profiles in comparison with insulin isophane.

Methods: In our multicentre study of insulin isophane versus standard of care (NCT01683331), we added a third treatment arm at a single center (NCT01680185), employing continuous subcutaneous short-acting insulin infusion therapy (CSII, Medtronic) in 24 previously non-diabetic kidney transplant recipients who had developed pre-supper glucose ≥140mg/dL.

Results: The final insulin lispro dose after up-titration of each patient was 9.6±6.0IU daily on average ± standard deviation, compared to 17.0±11.4IU overall in the previous insulin isophane group. The insulin algorithm below shows, 75.4% of the total daily dose were administered from 11am-7pm.

Hour	% of total daily insulin lispro dose [avg ± stdev]
10pm-11pm	0.4±0.3%
11pm-12am	0.3±0.1%
12am-1am	0.3±0.1%
1am-2am	0.3±0.1%
2am-3am	0.3±0.1%
3am-4am	0.4±0.1%
4am-5am	0.4±0.2%
5am-6am	0.5±0.4%
6am-7am	1.1±0.9%
7am-8am	2.0±1.7%
8am-9am	3.1±3.1%
9am-10am	3.1±1.9%
10am-11am	4.2±2.1%
11am-12pm	5.9±2.0%
12pm-1pm	8.2±2.3%
1pm-2pm	9.3±2.4%
2pm-3pm	11.7±2.9%
3pm-4pm	12.1±2.2%
4pm-5pm	11.6±2.8%
5pm-6pm	9.5±2.9%
6pm-7pm	7.1±3.4%
7pm-8pm	4.5±2.5%
8pm-9pm	2.5±1.8%
9pm-10pm	1.0±1.0%

Hypoglycemia ≥52mg/dL was observed twice. Glucose profiles in CSII patients were flatter than in the previous insulin isophane study group, and lower overall; the greatest daily decrease in glucose occured fasting.

Conclusions: The first algorithm for CSII therapy against early postoperative hyperglycemia in previously non-diabetic kidney transplant recipients was safe, employed less insulin, but provided better efficacy than previous insulin isophane treatment.

Funding: Pharmaceutical Company Support - Astellas Pharma, Private Foundation Support, Government Support - Non-U.S.

TH-PO801

B-trace Protein as Predictor of Cardiovascular Risk in Patients with Renal Transplantation Carola-Ellen Ruiner, Roxana Werberich, Louisa Werberich, Miranda Leunga Mbouamba, Rainer Woitas. *Nephrology, Bonn Univ Hospital, Bonn, Germany.*

Background: ß-trace protein (BTP) is an alternative marker for renal function. Furthermore, it has been suggested as predictor of mortality and coronary artery disease (CAD). We determined the prognostic value of BTP for cardiovascular risk and major adverse cardiac events (MACE) in patients following kidney transplantation.

Methods: The cohort consisted of 585 consecutive patients that were kidney transplanted between March 1996 and May 2015. MACE was defined as either myocardial infarction (ST-segment elevation (STEMI) or non ST-segment elevation (NSTEMI)), stroke, intervention requiring CAD or death for cardiovascular reason. Blood samples were drawn prior to the kidney transplantation. BTP was measured by routine methods. Median observation time was 2.6 years. Data were analyzed by Mann-Whitney *U* tests, Kaplan-Meier survival and Cox regression analyses.

Results: MACE occurred in 17 % of kidney transplant recipients on average after (mean ± SD) 5.1 ± 4.4 years. Incidence of MACE in the first year following kidney transplant was highest (0.088%). Most frequently patients suffered from NSTEMI (11.7%), followed by STEMI (1.9%) and CAD (1.6%). Only 0.6 % patients died due to cardiovascular reasons. BTP was significantly higher in patients with MACE compared to the other recipients ((mean ± SD) 14.4 ± 5.7 vs 11.2 ± 5.2, p<0.001). BTP was a predictor of MACE in univariate analysis (HR 1.08, 95% Cl 1.03-1.12, p<0.01). Serum BTP was divided into quartiles: Recipients with preoperative BTP ranging from 14.8 to 32 mg/l (4th quartile, mean ± SD 19.2 ± 3.9 mg/l) had an average time to event of 7 years (95% Cl 6.1-8.3), while patients with BTP ranging from 11.2 to 14.7 mg/l (3rd quartile, mean ± SD 12.7 ± 1 mg/l) showed a mean time to event of 10 years (95% Cl 8.9-11.3) (p<0.05). BTP remained an independent risk factor (HR 1.11, 95% Cl 1.06-1.16, p<0.001) after adjustment for potential cofounders' creatinine, c-reactive protein, gender and nicotine dependence.

Conclusions: Within the first year of kidney transplantation the incidence of MACE was the highest. BTP may be used to assess renal function, but also to predict cardiovascular risk in in kidney transplant recipients' patients.

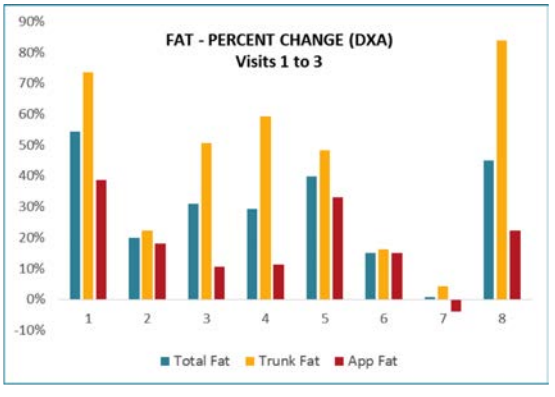
TH-PO802

Adverse Weight Gain after Kidney Transplantation Biruh Workeneh,[1] Ahmed Osama Gaber,[2] William E. Mitch.[1] *[1]Medicine/Nephrology, Baylor College of Medicine, Houston, TX; [2]Surgery, Houston Methodist Hospital, Houston, TX.*

Background: Among the most serious complications to these patients are adverse weight gain and the development of diabetes, commonly termed New-Onset Diabetes After Transplantation (NODAT) with consequent CV mortalityHowever, there no consensus about the cause of post-transplant weight gain and the metabolic determinants of body composition change.

Methods: Our aims were to determine the nature of the weight gain after Tx (i.e., relative changes in fat vs. muscle vs. fluid volume) using DXA and total body potassium and nitrogen counters, and to determine effect on insulin sensitivity. We enrolled 22 subjects who have had pre-transplant and 3mo characterization and 8 subjects who have completed the protocol.

Results:



The cumulative weight gain after after 1 year in 8 subjects was 6.8kg p<0.01. Fig 1 shows changes in body fat in 8 subjects who completed 1 year of follow-up and all but one had a significant increase in fat mass. The fat gain is primarily in the trunk (android fat distribution) than in the appendages, which has been linked to poorer cardiovascular outcomes. Insulin sensitivity quantified by Matstuda index show statistical and clinically significant worsening of insulin resistance. Changes in muscle mass does not contribute substantially to the gain of weight.

Conclusions: The results of this study will permit us to elucidate the complex metabolic underpinnings of excessive weight gain and insulin resistance that occurs frequently in kidney transplant patients and to potentially identify those at risk for adverse weight gain and develop effective interventions.

Funding: Private Foundation Support

TH-PO803

Prolonged Fluoroquinolone Prophylaxis to Prevent BK Viremia in Kidney Transplant Recipients Marie Jacobs, Jaclyn Daigneault, Margaret V. Thomas, Kerry Crisalli, David Wojciechowski. *Massachusetts General Hospital.*

Background: Prophylaxis regimens for renal transplant recipients have successfully lowered the early incidence of infections such as CMV. However, 1 and 3 month courses of fluoroquinolone prophylaxis have not proven decisively successful for BK virus, despite positive in vitro evidence. It is possible that the prophylaxis duration was too short.

Methods: We retrospectively evaluated the 1 year incidence of BK viremia in a cohort of patients transplanted from 7/1/2004 to 6/30/2014 who received 6 months of ciprofloxacin or levofloxacin post kidney transplant due to a sulfa allergy (n=10) compared to a no prophylaxis cohort transplanted from 7/1/2012 to 6/30/2014 (n=69). Inclusion criteria included BK viremia screening performed at least once in months 1-6 and months 7-11, and at one year post-transplant. We compared patient and transplant demographics and immunosuppression regimens between the groups. The primary outcome was the 1 year incidence of BK viremia.

Results: The groups did not differ significantly in demographic or transplant variables or immunosuppression regimens.

	Prophylaxis (n=10)	No Prophylaxis (n=69)	P Value
Mean age, years	53.8	54.8	0.77
Male, n	4	50	0.065
Live donor, n	5	24	0.48
rATG induction, n	8	64	0.19
Mean tacrolimus trough (ng/mL)			
6 mos	7.29	6.09	0.067
12 mos	6.23	6.51	0.67
Mean MMF dose (mg)			
6 mos	1312.5	1350	0.79
12 mos	1250	1218.3	0.82
Mean prednisone dose (mg)			
6 mos	5.75	5.46	0.76
12 mos	5	5.04	0.89

The incidence of BK viremia at one year was 10% and 24.6% in the prophylaxis and no prophylaxis group, respectively (p=0.44). There were no cases of BK virus associated nephropathy in either group. Three cases of acute rejection developed in the no prophylaxis group, while none developed in the prophylaxis group (p=1.00).

Conclusions: A 6 month course of fluoroquinolone prophylaxis resulted in a numerically lower incidence of BK viremia. Our data suggest that there may be a benefit of this strategy which warrants evaluation in a larger cohort of patients. The safety of this strategy must also be assessed.

Funding: Clinical Revenue Support

TH-PO804

Low Level Serum BK Viremia Is Not Associated with Increased Risk of Rejections, Infections or Poor Graft Survival Amber Hertz-Tang,[1] Brad C. Astor,[2] Maha A. Mohamed,[2] Didier A. Mandelbrot,[2] Arjang Djamali,[2] Sandesh Parajuli.[2] *[1]Internal Medicine, Univ of Wisconsin, Madison, WI; [2]Nephrology, Univ of Wisconsin, Madison, WI.*

Background: BK virus infection is considered to be a risk factor for additional infections, increased risk of rejections and graft failure. There is limited data about association of low level BK viremia and graft outcomes.

Methods: This is a retrospective study among kidney transplant recipients (KTR) at our institution transplanted between 2006 and 2013. Serum BK polymerase chain reaction (PCR) is monitored every 2 weeks for first 3 months then every month from month 3-6 and then monthly from 6-12 months post-transplant. BK level is also checked prior to allograft biopsy. Patients were divided into three groups based on their BK level during the first year post transplant: no detectable BK level (G1), low level BK (G2)(< 1000 copies/ml) and high level of BK (G3) (> 1000 copies/ml).A level of 1000 was chosen, as this is a generally accepted cutoff for adjusting immunosuppression at our institution.Results were adjusted for donor and recipient age, gender, and race, as well as, live vs. deceased donor, HLA mismatch, CMV status, cause of ESRD, prior transplant, induction, and DGF.

Results: There were a total of 1126 KTR, 841 were in G1, 51 in G2 and 234 in G3. Comparing between G1 and G2, there were no statistically significant differences in donor or recipient age, gender, race, or type of transplants. Incidence of rejections, CMV disease, rate of graft loss and mortality were also not significantly different. Comparing between G2 and G3, G3 had significantly higher rate of infections (p= 0.004). The majority of infections were urinary tract infections. G3 had a higher trend toward increased rate of death and graft failure though not statistically significant.

Conclusions: Low level BK itself does not increase the risk of rejections, infections or graft loss compared to no detectable BK level and may predict lower rate of any infection compared to a high level BK.

TH-PO805

Prevalence of BK Nephropathy Post Allogeneic Stem Cell Transplant: Autopsy Evidence Ala Abudayyeh,[1] Rima N. Pai,[1] Ankita Tandon,[2] Miao Zhang,[1] Asha S. Multani,[1] William F. Glass.[2] *[1]The Univ of Texas MD Anderson Cancer Center; [2]The Univ of Texas Medical School at Houston.*

Background: BK virus (BKV) is known to be causally related to chronic kidney disease (CKD) in renal transplant recipients. In hematopoietic stem cell transplant (HSCT) recipients, BKV is associated with hemorrhagic cystitis. The relationship between BKV and CKD in HSCT recipients, however, is not as well established. We chose to investigate the prevalence of BKV in kidneys obtained at autopsy of patients that have undergone HSCT.

Methods: We retrospectively for patients that who had undergone a HSCT and had an autopsy performed between 2004 and 2014. Formalin fixed paraffin embedded kidney tissue blocks from these patients were analyzed by light microscopy and anti-SV40 immunohistochemistry (IHC) for detection of BKV. Cases were considered positive for BKV if moderate-to-strong staining was present in nuclei of renal tubular epithelial cells with appropriate controls and semi-quantitated based on percentage of total tubular epithelial cells affected (<25% vs. >25%). Additional clinicopathologic parameters were collected. To overcome the nonspecific staining using IHC due to autolysis in autopsy tissue we performed In situ hybridization using a BK Biotin-labeled DNA probe.

Results: A total of 46 patients were included in the study. **Sixteen patients (35%) had positive SV40 staining in ≥ 25% of tubular epithelial cells.** In situ hybridization using a BK Biotin-labeled DNA probe further confirmed the prevelance of BK in the kidney.

Conclusions: We have demonstrated tissue evidence of the prevalence of BKV in renal tissue of stem cell transplant patients. The results of this study will help shed more light on the role of BK post SCT and progression to CKD. Further research in looking in to immune predictors of the infection and a grading system to guide early intervention would be needed to improve SCT renal outcomes.

TH-PO806

Serum Levels of Uric Acid and Progression of Arteriolar Hyalinosis after Kidney Transplantation Yasuyuki Nakada,[1] Izumi Yamamoto,[1] Mayuko Kawabe,[1] Takafumi Yamakawa,[1] Haruki Katsumata,[1] Ai Katsuma,[1] Akimitsu Kobayashi,[1] Yudo Tanno,[1] Ichiro Ohkido,[1] Hiroyasu Yamamoto,[1] Masayoshi Okumi,[2] Hideki Ishida,[2] Takashi Yokoo,[1] Kazunari Tanabe.[2] *[1]Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan; [2]Dept of Urology, Tokyo Women's Medical Univ, Tokyo, Japan.*

Background: Arteriolar hyalinosis (AH) of the kidney is considered to be strongly associated with progression of chronic kidney disease (CKD). Aging, hypertension, and diabetes mellitus generally exacerbate the extent of AH in the native kidney. In addition, in allograft kidney, nephrotoxicity attributable to the calcineurin inhibitor (CNI) can also develop, increasing the severity of AH progression. In recent years, it has often been claimed that hyperuricemia induces AH progression and accelerates the nephrotoxicity caused by CNI. We postulated that, over time, the uric acid (UA) burden in allograft kidney recipients could influence AH progression and interstitial fibrosis/tubular atrophy (IF/TA).

Methods: We evaluated 126 recipients who received kidney transplants from January 2005 to December 2009 at the Department of Urology, Tokyo Women's Medical University. Patients with diabetes mellitus were excluded. Progression of AH and IF/TA were considered present if the Banff scores increased by two or more. To evaluate factors associated with such pathological progression, we subjected clinical parameters (age, gender, blood pressure, serum CNI concentration, baseline UA in serum[s-UA]) and the UA burden over time (the average annual level of s-UA) to logistic regression modeling.

Results: The baseline s-UA was correlated with progression of IF/TA ($p = 0.03$) but not AH ($p = 0.86$). However, the UA burden over time was associated with progression of both AH ($p = 0.03$) and IF/TA ($p < 0.01$). Of other clinical parameters, donor age was strongly associated with AH progression ($p < 0.01$).

Conclusions: Although IF/TA progression was correlated with the UA burden over the whole course of disease, the UA burden over time, but not the baseline value, induced AH progression in transplanted kidney. Therefore, we suggest that monitoring s-UA after transplantation is important to prevent AH and IF/TA progression.

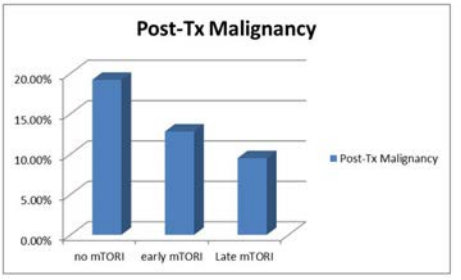
TH-PO807

The Mammalian Target of Rapamycin Inhibitors and Post-Transplant Malignancy in Kidney Transplantation Lee-Moay Lim,[1] Hung-Tien Kuo.[1,2] *[1]Div of Nephrology, Dept of Internal Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung, Taiwan; [2]Faculty of Renal Care, College of Medicine, Kaohsiung Medical Univ, Kaohsiung, Taiwan.*

Background: Improving long-term graft and patient survival is a major challenge in kidney transplantation due to prolonged immunosuppression significantly increases the risk of malignancy, contributing to the overall morbidity and mortality. The aim of our study was to investigate the association of Mammalian Target of Rapamycin Inhibitors (mTORI) usage (early and late) with major transplant outcomes and post-transplant malignancy in kidney transplant recipients from a medical center in Taiwan.

Methods: A total of 201 adult kidney transplant recipients surviving with a functioning graft> 3 months were included. The mean follow-up days were 2368. mTORi users were categorized into early and late users at the cut-off of 6 months duration after transplantation. Odds ratios for malignancy were examined using multivariate logistic regression analysis while hazard ratios for clinical outcomes were analyzed using multivariate Cox regression analysis.

Results: The major causes of death in our cohort were cardiovascular disease, malignancy and infection. Urinary tract urothelial carcinoma (UTUC) and hepatoma comprised the major malignancy after transplantation. After adjusting for confounding factors, mTORi users has lower risk of post-transplant malignancy (adjusted OR=0.28, P=0.04).



	Reference	Adjusted OR	P-value
mTORI (n=123)	No mTORI	0.28 (0.08-0.96)	0.04
Early mTORI (n=39)	No mTORI	0.64 (0.18-2.24)	0.49
Late mTORI (n=84)	No mTORI	0.35 (0.11-1.09)	0.07

Early mTORI users have better overall graft survival (adjusted HR=0.73, P=0.52) and patient survival(adjusted HR=0.95, P=0.95) when compared to late users and non-users.

Conclusions: In our renal transplant recipients, the leading causes of death were cardiovascular disease, infection, and malignancy. The most common post-transplant malignancy were UTUC and hepatoma. The usage of mTORI was associated with a decreased risk of post-transplant malignancy.

TH-PO808

Chemoprevention of Cutaneous Squamous Cell Carcinoma (cSCC) in Long Term Renal Transplant Recipients (LRTR): A Case-Controlled Analysis Rachel Hung,[1,2] Rakesh Anand,[2] Mary Wain,[3] Antonia Cronin.[2] *[1]Renal, UCL Centre of Nephrology, Royal Free Hospital, London, United Kingdom; [2]Renal, MRC Centre of Transplantation, Guy's and St. Thomas' Hospital, London, United Kingdom; [3]Dermatology, Guy's and St. Thomas' Hospital, London, United Kingdom.*

Background: Organ transplant recipients are up to 200 times more likely to develop cSCCs than age-matched general populations. Development of NMSC in LRTR is affected by Fitzpatrick skin type, ultra-violet light exposure, and the type and duration of immunosuppression. Systemic retinoids have shown promising preventative effects against the development of cSCC, however this is associated with adverse side effects including liver dysfunction, dyslipidaemia, and use in renal impairment is cautioned.

Methods: We collected retrospective data from our cohort (n=469) of LRTR (>7 years) attending our annual review clinic, of which 108 patients had been diagnosed with NMSC. We identified patients (n=12) on treatment with the acitretin and matched them to an equal number of controls by age, total years from transplant and Fitzpatrick skin type. We compared GFR, liver function and lipid profile at 1 year pre, and 1, 3 and 5 years post commencing acitretin and the total number of cSCCs pre and post acitretin.

Results: Serum total cholesterol and LDL were significantly lower (p=0.007 and p=0.012 respectively) in patients prescribed acitretin at 5 years post treatment compared with baseline measurements. There were no other statistically significant differences in lipid profile, GFR or LFTs at baseline parameters and at 1, 3 and 5 years after starting treatment within cases or comparing cases and controls. After starting acitretin treatment the median number of new cSCCs per patient was 2 (0 - 4) which was significantly lower than the median number prior to treatment of 6 (3-10) p=0.005.

Conclusions: Acitretin usage did not adversely affect renal transplant function,liver function or lipid profiles when compared with baseline or matched untreated controls,and showed a statistically significant reduction in total number of new cSCCs during 5-year follow-up. Acitretin can be considered as a safe and effective chemoprevention agent in selected LRTR with multiple SCCs who are under regular dermatology surveillance.

TH-PO809

The Incidence of Non-Melanoma Skin Cancers in Renal Transplant Recipients - Polish Centre Experience Alicja Debska-Slizien,[1] Beata Imko-Walczuk,[2] Maria Luiza Piesiakow,[1] Slawomir Lizakowski,[1] Boleslaw Rutkowski.[1] *[1]Dept of Nephrology, Transplantology and Internal Diseases, Medical Univ of Gdansk, Gdansk, Poland; [2]Dermatology Dept, Copernicus Hospital in Gdansk, Gdansk, Poland.*

Background: Non-melanoma skin cancers (NMSCs), especially squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), are the most frequent malignant neoplasms in renal transplant recipients (RTRs). SCC, due to its unusual and aggressive

clinical course in RTRs, is a diagnostic and therapeutic challenge. The aim of the study was to assess the incidence of NMSCs in Polish population of RTRs and propose methods of prevention and early diagnosis.

Methods: We included prospectively and retrospectively 77 patients with NMSCs in a group of 813 RTRs, who were patients of Nephrology, Transplantology and Internal Diseases Department of Medical University of Gdansk in years 1980-2015. Majority of study group (92.2%) underwent a single transplantation (Tx) and the mean time of observation was 12.5±5.8 years. The most frequently treatment scheme was MMF (mycophenolate mofetil)- CsA (cyclosporine A)-GS (glucocorticosteroids) 33,8%, MMF-TAC (tacrolimus)-GS - 22,1%.

Results: In 77 patients, 139 NMSCs were diagnosed. It shows more than 253-times higher risk of NMSCs development in Polish RTRs ($p<0.000001$). The median time since the Tx to cancer diagnosis was 75.5(3.0-227.0) months for BCC and 80,0(31.0-358)months for SCC. Furthermore a single lesion was diagnoses in 61.0% patients, whereas the others presented a multifocal cancers. 73,7% SCC were noticed in RTRs who received CsA as a immunosuppressive treatment and 73,3% BCC were diagnosed in patients using MMF in treatment scheme.

Conclusions: The incidence rate of skin cancer in Polish RTRS population is more than 250 times higher compared with the immunocompetent individuals (ICIs). The SCC to BCC ratio increases from 0,2:1 in general population to 0,73: 1 in our study group. Skin cancers in RTRs very often develop multicentrically.

TH-PO810

The New Method of Vesico-Ureteric Reflux Prophylactic in Kidney Transplant Recipients: Randomised Clinical Study Aleh Kalachyk, Alexei Narbin, Alexej Shkutov, Maria Kozlova. *National Center for Nephrology, Minsk, Belarus.*

Background: Vesico-ureteric reflux (VUR) is a common complication in renal transplant recipients. VUR is associated with increased risk of UTI and graft loss. The objectives of that study were to determine the incidence and risk factors of VUR, to create and prove the efficacy of new method of VUR prophylactic in kidney transplant recipients.

Methods: We conducted case-control survey of 68 patients to detect the risk factors for VUR in renal allograft. Voiding cystograms were performed to find the reflux. We checked the association of VUR with recipient's gender, age, type and duration of dialysis, residual urine volume output, cold ischemia time, ureteric stent placement, kidney function and infections. The new method of antireflux defense consists of the ureteroneocystostomy by Starzl with JJ stent placement followed by the simultaneously stent removal and endovesical submucosal injection of bulking substance on POD 30. To prove the efficacy of the new antireflux defense method we conducted a prospective, randomized clinical study. Kidney transplantation with Lich-Gregoir ureteroneocystostomy was performed in the control group. 36 kidney graft recipients were randomized in two groups. The voiding cystography was performed on POD 60 to compare the VUR rates in both groups.

Results: The cumulative incidence of VUR was found as 45/68 (66,2%). The statistically significant risk factor for VUR was residual urine volume output (50 (0-200) versus 250 (0-850)cc, p=0,006).ROC-analysis showed cut-off value 200 cc (AUC 0,71, p=0,0018). This volume was established as the cut off for the inclusion criteria for patients in control and study groups. The groups were similar in gender, age, type and duration of dialysis, residual renal function, and HLA mismatches. The incidence of VUR in the study group was found as 5/18 (28%), and it was 13/18 (72%), p=0, 0184 in the control group.

Conclusions: We found that residual renal output 200 cc is a significant risk factor of VUR in kidney transplant recipients. The Starzl ureteroneocystostomy with ureteric stenting and delayed endovesical antireflux bulking substance injection is a new effective method of VUR prophylactic in the high VUR risk kidney recipients.

TH-PO811

Urinary Tract Infections in the First Year Post Kidney Transplantation Prasanti Kotagiri,[1] Jessica Ryan,[2] Nigel David Toussaint.[1,3] *[1]Royal Melbourne Hospital, Parkville Australia; [2]Monash Health, Clayton, Australia; [3]Univ of Melbourne, Australia.*

Background: Urinary tract infections (UTI) are the commonest infectious complication in kidney transplant recipients (KTRs). Effects on graft function are unclear. No recommendations exist regarding treatment of asymptomatic bacteriuria but concern that immunosuppression and denervation of the graft masks symptoms often prompts treatment. We aimed to identify potential risk factors for UTIs, microbiological profile and role of treatment of asymptomatic bacteriuria, and effects on graft outcomes.

Methods: Retrospective analysis of UTIs in KTRs transplanted between Jan 2012 and Dec 2013 in two Australian tertiary transplant centres where patients are routinely commenced on prophylactic sulfamethoxazole/trimethoprim. Clinical and microbiological data was analysed for the first year following transplantation.

Results: 276 KTRs were evaluated, 67% male, mean age of 51yrs. 158 recipients (57%) had no bacteriuria in the first year post-transplant, 75 (27%) had only asymptomatic bacteriuria, 21 (8%) had symptomatic UTIs and 22 (8%) with UTIs developed either pyelonephritis or urosepsis. Most frequent pathogens identified were Enterococcus Faecalis and Escherichia Coli, and 36% were multi-drug resistant. Female gender was a risk factor for infection (p=0.002) and presence of a ureteric JJ stent significantly increased the risk of asymptomatic bacteriuria and symptomatic UTIs (p=0.003). Diabetes, age and prior transplantation did not increase risk. Presence of infection was not associated with increased rejection or adverse longer-term outcomes with similar renal function at 12 months. For all episodes of bacteriuria in our cohort (n=420), cases of untreated asymptomatic bacteriuria (n=185) followed by symptomatic UTI with the same organism were significantly higher (p=0.002) compared to cases of treated asymptomatic bacteriuria (n=139).

Conclusions: Treatment of asymptomatic bacteriuria in the first year post-transplant may be beneficial to prevent subsequent episodes of symptomatic UTIs.

TH-PO812

Asymptomatic Bacteriuria in Renal Transplant Patients Anna Price, Lukas Foggensteiner. *Renal Dept, Queen Elizabeth Hospital Birmingham, Birmingham, West Midlands, United Kingdom.*

Background: Patients with renal transplant are vulnerable to post-operative infection, particularly urinary tract infection (UTI). UTIs are linked with acute cellular rejection, graft loss, sepsis and death. The management of asymptomatic bacteriuria (AB) however, remains a clinical conundrum in these patients. The risk of untreated AB vs. the risk of antimicrobial side effects or overuse is unclear.

Methods: Aims: 1. Quantify the frequency and nature of AB amongst renal transplant patients at our unit. 2. Determine our management of these cases and any adverse outcomes. Methods: Between 1st January 2013 and 31st December 2013 132 renal transplant patients with AB were identified and followed up for 12 months. Demographic data was collected from electronic patient records. The urinary pathogen, bacterial count and white blood cell count of each AB was recorded from microbiology records. Patient management, admissions and subsequent urine results were retrospectively reviewed.

Results: Of the 132 patients identified, 82 patients met inclusion criteria. There were more females (n=55) than males (n=27). The mean age was 50.8 yrs. (range 17.4-79yrs). All ABs had greater than 80 white blood cells (WBC) or 10^5 bacterial organisms. Most ABs were 'Heavy mixed growth' or E.coli. Only 14 patients had complete resolution, 56 patients had AB reoccurrence and 12 patients had persistent AB throughout follow up. Of the 82 patients, 27 were treated with antibiotics. There were no related deaths or episodes of acute rejection. Only 8 admissions to hospital were associated with AB during follow up (n=1 pyelonephritis, n=4 urosepsis, n=3 symptomatic UTI). All of these patients had previously received antibiotics for AB prior to the admission. A further 12 patients during follow up later developed symptomatic UTI not requiring hospital admission (8 of which were also previously treated for AB).

Conclusions: Asymptomatic bacteriuria led to few admissions and complications. Treating patients did not seem to prevent subsequent admissions. A high proportion of 'Heavy mixed growth' may indicate incorrect collection. Practice varies widely amongst clinicians but the vast majority of ABs are not being treated.

TH-PO813

High Incidence of Arterial and Venous Thrombosis in Patients with ANCA-Associated Vasculitis Amy Kang,[1] Marilina Antonelou,[1] Anisha Tanna,[2] Nishkantha Arulkumaran,[1] Frederick W.K. Tam,[2] Charles D. Pusey.[2] *[1]Imperial College Renal and Transplant Centre, Imperial College NHS Trust, London, United Kingdom; [2]Renal and Vascular Inflammation Section, Dept of Medicine, Imperial College London, London, United Kingdom.*

Background: A few previous studies have shown an association between AAV and cardiovascular disease (CVD) and venous thromboembolism (VTE), which may be mediated by inflammation or anti-plasminogen antibody. We aimed to determine the incidence and risk factors for arterial and venous thrombosis in ANCA-associated vasculitis (AAV).

Methods: This single-centre retrospective cohort study presents the incidence of arterial thrombosis (defined as coronary events and ischaemic stroke), VTE and all-cause mortality in people diagnosed with AAV between 2005 -2014. We collected patient baseline characteristics, risk factors for CVD and VTE, and events of CVD, VTE, AAV relapse and death.

Results: 204 patients with AAV were identified with a median follow-up of 5.3 [range: 0.08-10] years or total of 1088 person-years. The overall incidence was 2.76/100 person-years for CVD (1.65 for coronary events and 1.10 for ischaemic stroke) and 1.47/100 person-years for VTE (0.83 for DVT only and 0.64 for PE with or without DVT). Two coronary events were fatal. 71 percent of our cohort had renal involvement with a median creatinine of 117 (IQR 73-268)mmol/L. On multivariate analysis only prior ischaemic heart disease was a predictor of CV events. CVD (but not VTE) was an independent predictor of all-cause mortality. When we removed patients with prior CVD the incidence of CV events was still elevated at 2.32/ 100 person-years (1.26 for coronary events and 1.06 for ischaemic stroke). When we compared these results with reported rates for the UK population, the rates in AAV patients were 17 times higher for coronary events, 10 times higher for incident stroke and 20 times higher for VTE.

Conclusions: Patients with AAV have a high incidence of arterial and venous thrombosis. These results may aid in the development of protocols to minimise thrombotic risk and improve prognosis for patients with AAV.

TH-PO814

Risk Factors of Severe Infections following Rituximab in ANCA-Associated Vasculitis Andreas Kronbichler,[1,2] Julia Kerschbaum,[2] Federico Alberici,[1,3] Rachel B. Jones,[1] David R.W. Jayne.[1] *[1]Addenbrooke's Hospital, Univ of Cambridge, Vasculitis and Lupus Clinic, Cambridge, United Kingdom; [2]Internal Medicine IV (Nephrology and Hypertension), Medical Univ Innsbruck, Innsbruck, Austria; [3]Renal Medicine and Vasculitis, San Carlo Borromeo Hospital, Milan, Italy.*

Background: Severe infections potentially leading to hospitalization are frequently observed in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). The aim of our study was to investigate potential risk factors having an impact on severe infections following rituximab treatment.

Methods: Both univariate and multivariate logistic regression analyses were performed, using as the outcome of interest the occurrence of at least one life-threatening or severe infection. Nominal variables were compared using the chi-square test (or Fisher's exact test when appropriate), and metric variables were compared using the Mann-Whitney U. All variables showing univariate association with the dependent variable with a p-value less than 0.100 were entered into a multivariate logistic regression model.

Results: Study population consisted of 134 patients diagnosed with GPA, 28 with MPA and 30 with EGPA. 23% had a life-threatening or severe infection during 24 months of follow-up. Univariate analysis showed that lung involvement (OR 2.1; p=0.032), and especially endobronchial involvement (OR 3.824; p<0.001), COPD (OR 10.357; p=0.045), diabetes (OR 2.941; p=0.034), rituximab as a first line treatment (versus maintenance, OR 3.615; p=0.034), whereas higher levels of lymphocytes (OR 0.524; p=0.023 per unit increase) and the use of co-trimoxazole as an antibiotic prophylactic treatment (PR 0.406; p=0.04) were associated with a lower risk. Multivariate anaylsis showed that prophylactic antibiotic treatment with co-trimoxazole significantly reduced the risk of severe infections (adjusted OR 0.171; p=0.016).

Conclusions: This is the first study assessing risk factors of severe infections following rituximab treatment for AAV. Co-trimoxazole significantly reduced the risk for severe/life-threatening infections in patients with AAV. Further studies are clearly necessary to recommend antibiotic prophylaxis with co-trimoxazole in AAV.

TH-PO815

ANCA-Associated Glomerulonephritis in the Elderly - Predictors of Outcome Martin Russwurm,[1] Hermann-Josef Groene,[2] Ivica Grgic,[1] Joachim Hoyer.[1] *[1]Dept of Internal Medicine and Nephrology, Philipps Univ, Marburg, Germany; [2]Dept of Cellular and Molecular Pathology, German Cancer Research Center, Heidelberg, Germany.*

Background: ANCA-associated Vasculitis (AAV) is the most frequent reason for biopsy proven acute kidney injury (AKI) in the elderly, however clinical data regarding outcome after standardized immunosuppression (IS) remain scarce.

Methods: All patients (pts.) >65yrs admitted to the University Hospital Marburg (Germany) undergoing a renal biopsy between 2003 and '15 were screened for AAV defined as positive serum ANCA, AKI, histomorphologically proven necrotizing GN and were enrolled in this retrospective study. Pts were observed for a period of 1-12yrs. Clinical history, histological findings and serological data were assessed. Student's t-test and Wilcoxon's rank sum test were used, where appropriate. A linear regression model was performed for analysis of predictors of renal outcome.

Results: From a total of 678 pts. 163 were older than 65yrs. In this group, AAV was the most frequent biopsy-proven cause of AKI (24.5%). In those 40 pts., median age was 76yrs and median follow-up time was 723 days (IQR 598 to 730). Nearly all pts. received standard IS (CYC, prednisolone) adjusted to GFR, age and body weight. Pts. who presented with a serum creatinine (SC) >5,0mg/dL (n=16; 40%) and/or required RRT (n=14; 35%) were additionally treated with plasma exchange (PE). Pt. survival rate after one and two years was 90% and 87.5%, respectively. Complete (SC <1.5mg/dL) and partial (SC <3mg/dl) remission was achieved in 27.5% and 55%, respectively. Mean SC decrease was 3.7 to 1.7mg/dL in pts that did not receive RRT (p<0.0001), 4.7 to 2.0mg/dL in pts that did receive RRT and recovered (p=0.012), and 5.4 to 2.0mg/dL in pts treated with PE (p=0.003). Dialysis dependency rate was 17.5% one year after diagnosis, while none of the others progressed to ESRD. Predictors of renal outcome were SC at diagnosis (p=0.001) and number of necrotic (p=0.02) and unaffected glomeruli (p=0.048).

Conclusions: Our data show that elderly pts. with AAV may also benefit from guideline-directed therapy inducing a high rate of remission.

Funding: Clinical Revenue Support

TH-PO816

Valaciclovir to Prevent Cytomegalovirus Mediated Adverse Modulation of the Immune System in ANca Associated VAScultis (CANVAS): Results of a Randomised Controlled Clinical Trial Dimitrios Chanouzas, Michael Sagmeister, Lovesh Dyall, Charles Ferro, Paul Moss, Matthew David Morgan, Lorraine Harper. *Univ of Birmingham, United Kingdom.*

Background: CD4+CD28- T-cell expansion in patients with ANCA-associated vasculitis (AAV) is associated with increased risk of infection, cardiovascular disease (CVD) and mortality. In a linked study submitted for ASN 2016 we have shown that CD4+CD28- cells in AAV are a Cytomegalovirus (CMV) specific proinflammatory subset associated with increased arterial stiffness, a surrogate marker of CVD. We undertook a proof of concept open label randomised controlled clinical trial to determine whether controlling subclinical CMV reactivation using valaciclovir can reduce expansion of CD4+CD28- cells in patients with AAV.

Methods: 38 CMV seropositive AAV patients in remission were randomised 1:1 to 6 months valaciclovir (2g QDS; eGFR adjusted) or no additional treatment (NCT01633476). CMV reactivation (primary outcome) was assessed by quantitative plasma and urine PCR. Change in CD4+CD28- T cells was assessed by whole blood surface staining flow cytometry at baseline, 6 months and 6 months after the end of treatment.

Results: No CMV reactivation was detected in valaciclovir treated patients whereas reactivation was detected in four control patients (21.1%) (p=0.037). After 6 months valaciclovir treatment there was a significant reduction in both the mean percentage of CD4+CD28- cells (mean reduction 23% (95% confidence interval (CI) 3-39%; p=0.039) and the absolute count of CD4+CD28- cells (mean reduction 27% (95%CI 7-42%); p=0.013) whereas no significant change was seen in the control group (mean change -5% (95%CI -18% to +11%; p=0.449) and -7% (95%CI -25% to +16%; p=0.523) respectively). The reduction in CD4+CD28- cells in the valaciclovir treated group persisted 6 months after cessation of treatment. Valaciclovir was well tolerated. None of the patients had clinical CMV reactivation.

Conclusions: Blocking subclinical CMV reactivation led to a persistent reduction in CD4+CD28- cells suggesting CMV causes the expansion of this cytotoxic T-cell subset and offering novel therapeutic opportunities in AAV to reduce the risk of infection, CVD and mortality.

TH-PO817

High Incidence of ANCA-Associated Vasculitis after the Great East Japan Earthquake Yoichi Takeuchi, Ayako Saito, Tasuku Nagasawa. *Nephrology, Red Cross Ishinomaki Hospital, Ishinomaki, Miyagi, Japan.*

Background: ANCA-associated vasculitis including microscopic polyangiitis (MPA) is triggered by silica exposure. After the Great East Japan earthquake on March 11 in 2011, tsunami waves produced a huge volume of silica-containing sludge. We aimed to determine if the incidence of the MPA increased following the serious disaster.

Methods: This is an observational retrospective population-based study in a single institute. Forty-three consecutive patients were selected through the CHCC2012 criteria for the MPA from 2007 to 2015. We fitted the Poisson regression model to the incidence with the annual population of the medical district. The participants were selected during 3-year period from before (13 people) to after the disaster (20 people). The differences between the groups were analyzed by using Fisher's exact test and the Mann-Whitney *U* test. Overall survival was calculated according to the Kaplan-Meier method. All statistical data were analyzed by using EZR.

Results: The incidence of MPA per million increased after the disaster (λ= 17.4 [95%CI: 7.66 - 39.6] before the disaster and λ= 33.1 [95% CI: 17.7 - 61.7] after the disaster, P = 0.044). High Birmingham Activity Score was associated with a high incidence of MPA after the disaster (16.0 [12.0 - 18.0] before the disaster and 18.0 [16.0 - 22.0] after the disaster, P = 0.019). The overall survival of the patients with MPA declined after the disaster (P = 0.029 by log rank test).

Conclusions: The incidence of MPA increased after the Great East Japan earthquake. The patients enrolled after the disaster had severe symptoms and a high mortality rate.

TH-PO818

Restablishment of Immune Tolerance in ANCA-Associated Vasculitis: A Cohort with Both Sustained Undetectable Antibody, and Disease Free Remission Thomas Oates,[1] Fernanda Florez-Barros,[1] Sarah Katrina Todd,[1] Coen A. Stegeman,[2] Peter Heeringa,[2] Abraham Rutgers,[2] Min Chen,[3] Jan-Stephan Sanders,[2] Alan D. Salama.[1] *[1]UCL Centre for Nephrology; [2]Univ of Groningen, Netherlands; [3]Peking Univ First Hospital, China.*

Background: ANCA associated vasculitis (AAV) is associated with disease relapse in up to 50% of patients despite immunosuppression (IS). We studied patients who became persistently ANCA negative off IS without relapse to define a tolerant phenotype.

Methods: Patients at 3 centres were identified who became ANCA negative and were off IS therapy for 2 years or more. Clinical, and laboratory data were analysed. A subset of tolerant patients were compared to other remission patients and healthy controls.

Results: 35 tolerant patients were identified. Baseline characteristics are in Table 1.

Variable	**Number**
Age (years, median (range))	59 (14-74)
Female/Male	22/13
MPO/PR3/neither	17/17/1
UK/China/Netherlands	7/11/17
System	**MPO/PR3 (%)**
Renal	82/59
Lung	47/56
ENT	29/61
Eyes	6/33
Musculoskeletal	18/17

Induction regimens included steroids (97% patients) and cyclophosphamide (88%). During maintenance, 67% received azathioprine. All patients became ANCA negative and ceased IS. Median time to ANCA -ve was 5.5 months (mo) and was similar in cANCA (3mo) and pANCA (8mo; P=0.59). The cohort proportion who were ANCA -ve at 6mo was similar to patients analysed in the IMPROVE trial (P=0.67). Median time to stop therapy was 30.5mo and did not differ according to ANCA type (P=0.60). Median duration of ANCA -ve follow-up is 61mo with median duration off IS of 46mo. Analysis of PBMC in a subset of tolerant patients (n=4) demonstrated significantly higher proportion of CD24CD38+ regulatory B cells compared to non-tolerant remission patients (n=33; p=0.002)and similar levels to healthy controls (n=9). Proportions of regulatory T cells did not differ significantly. Analysis of leukocyte subsets is ongoing and may provide insight into cellular mechanisms underlying restoration of tolerance.

Conclusions: AAV patients who remain persistently ANCA -ve off IS are uncommon, are clinically similar to other remission patients, but display different molecular phenotypes.

Funding: Government Support - Non-U.S.

TH-PO819

Risk Factors of Treatment-Related Diabetes Mellitus in ANCA Vasculitis Patrick H. Nachman, Yichun Hu, Caroline J. Poulton, William Franklin Pendergraft, Ronald J. Falk, Susan L. Hogan. *UNC Kidney Center, Univ of North Carolina, Chapel Hill, NC.*

Background: Diabetes mellitus (DM) is a complication of glucocorticoid treatment which affects a third of patients with ANCA-vasculitis (ANCA-V). We describe the time course and complications of treatment-related DM and identify the independent risk factors in a large cohort of patients with ANCA-V.

Methods: Patients with ANCA-V and no prior history of DM were selected from the Glomerular Disease Collaborative Network. The association of induction IV methylprednisolone (MP) with DM was evaluated as a categorical (exposure vs no) and as continuous variable of cumulative dose. Several multivariable proportional hazard models were explored to identify independent risk factors of DM [results reported as hazards ratios (HR) with 95% confidence intervals (CI) and p-values].

Results: 454 patients were identified (median age 59 years (IQR 45, 70), 55% MPO-ANCA positive). Median follow up was 2.8 years (IQR 1.2, 6.2). 155 (34%) developed DM in a median of 0.69 months (IQR 0.07, 4.05). DM was associated with a higher frequency of severe infections. By multivariable analysis, exposure to, cumulative dose of MP, PR3-ANCA, and the combination of family history of DM *and* BMI $\geq$ 26.5 kg/m^2 were associated with an increased risk of DM. ENT disease was associated with a decreased risk.

Variable	HR (95% CI)	P value
Age (per year)	1.02(1.00,1.03)	0.012
Female Sex	1.45(0.90,2.34)	0.125
MP (exposure vs no)	1.75(1.08,2.84)	0.024
MP (cumulative dose, per g)	1.24(1.05,1.47)	0.012
No Family Hx & BMI $\geq$ 26.5*	1.59(0.88,2.88)	0.126
Family Hx & BMI < 26.5*	1.88(0.85,4.18)	0.118
Family Hx & BMI $\geq$ 26.5*	2.70(1.45,5.02)	0.002
PR3- vs MPO-ANCA	1.78(1.10,2.88)	0.019
ENT (vs no)	0.50(0.30,0.85)	0.01

*vs No Family Hx & BMI < 26.5.

Conclusions: In addition to combined obesity and family history, treatment-related DM in ANCA-V is independently associated with PR3-ANCA and exposure to induction MP. The relative benefits and risks of IV MP in treating ANCA-V are not well established. Our results support using IV MP sparingly in patients at risk of DM.

Funding: NIDDK Support

TH-PO820

Immunoglobulin Levels and Infection Risk with Rituximab Induction for ANCA Associated Vasculitis Shivani Shah, Keiko I. Greenberg, Duvuru Geetha. *Johns Hopkins Univ.*

Background: Rituximab (RTX), a B cell depleting anti-CD20 monoclonal antibody, is approved for treatment of ANCA associated vasculitis (AAV). Low immunoglobulin (Ig) levels have been observed surrounding RTX treatment. The association between the degree of Ig deficiency and infection risk is unclear in AAV patients.

Methods: AAV patients treated with RTX for remission induction in a single center (2005 to 2015) with serum Ig measurements were included. Patient characteristics, serum Ig levels, and occurrence of infections were collected retrospectively. Logistic regression models were adjusted for age at RTX administration and race.

Results: Our cohort of 28 patients had a median age of 65 years; 23 were women; 15 had GPA; and 13 were PR3 ANCA positive. Ten received concomitant cyclophosphamide. Mean IgG, IgM and IgA levels were 569.8mg/dL, 47.8mg/dL, and 123.1mg/dL, respectively. Twenty one patients had low serum IgG levels (<750 mg/dL) following RTX treatment. Over 2.4 years of follow up, 5 individuals developed infections requiring hospitalization (3 bacterial pneumonia, 1 PJP pneumonia, and 1 C. difficile colitis). IgG level $\leq$375mg/dL was associated with higher odds of infection requiring hospitalization compared to IgG level >375mg/dL (odds ratio 26.7, 95% CI: 1.6-452, p=0.023). Similarly, low IgM and IgA levels were also associated with infection.

Number of Infections Requiring Hospitalization (%)	IgG Level			p-value*
	$\geq$750 mg/dL (n=7)	376-749 mg/dL (n=14)	0-375 mg/dL (n=7)	
	1 (14%)	0 (0%)	4 (57%)	0.005
	IgM Level			
	$\geq$46 mg/dL (n=13)	24-45 mg/dL (n=5)	0-23 mg/dL (n=10)	0.093
	1 (8%)	0 (0%)	4 (40%)	
	IgA Level			
	$\geq$82 mg/dL (n=16)	41-81 mg/dL (n=9)	0-41 mg/dL (n=3)	0.004
	1 (6%)	1 (11%)	3 (100%)	

Conclusions: Lower Ig levels were associated with increased odds of infection requiring hospitalization in this cohort. Further investigation is warranted given our study is limited by small sample size, concomitant cyclophosphamide use, and variable timing of Ig measurement.

TH-PO821

Efficacy and Safety of Rituximab in Patients with ANCA Associated Vasculitis and Renal Disease in Clinical Practice Panagiota E. Giannou,[1] Konstantinos Thomas,[2] Aglaia Chalkia,[1] Aikaterini Damianaki,[1] Dimitrios Vassilopoulos,[2] Dimitrios Petras.[1] *[1]Nephrology Dept, Hippokration General Hospital, Athens, Greece; [2]Clinical Immunology-Rheumatology Unit, 2nd Dept of Internal Medicine and Laboratory, Univ of Athens, School of Medicine, Hippokration General Hospital, Athens, Greece.*

Background: Rituximab (RTX), a monoclonal antibody against CD20 is a recently approved therapeutic agent for ANCA-associated vasculitis (AAV). Our study aimed to evaluate the efficacy and safety of administration of RTX in patients with AAV and renal involvement in daily clinical practice.

Methods: Fourteen patients (57.1% males with a mean age of 59.8 years) with Granulomatosis with polyangiitis (GPA- n=8) and Microscopic polyangiitis (MPA- n=6) treated with RTX in our center, between the period of 2011 and 2015, were included. All patients had generalized disease (100%) and were followed for a mean period of 24.7 months. During follow up, disease activity, according to Birmingham Vasculitis Activity Score/WG (BVAS/WG) and adverse effects were recorded.

Results: Eight (57.1%) patients were treated with RTX due to resistant or relapsing disease and 6 (42.8%) received RTX as initial treatment. At 6 months, 71% of patients (10/14) responded to therapy. One patient (7.1%) who had not responded at 6 months, showed complete response at 9 months. Two of 14 (14.2%) patients did not respond to therapy and enrolled in hemodialysis program, possibly due to the chronicity on renal biopsy at the time of diagnosis (>50% global glomerulosclerosis). Overall during treatment, a statistically significant improvement in disease activity was observed (BVAS/WG before RTX: 5.7, 6 months: 1.3, 12 months: 1.1, p=0.01). Among responded patients (n=11), 1 (9%) demonstrated 2 relapses during follow up (one minor and one major). One patient with GPA-associated fulminant pulmonary-renal syndrome died from septic shock one month after RTX administration in combination with cyclophosphamide while in clinical remission from his AAV. No other serious infections or allergic reactions were noticed during the follow up period.

Conclusions: These real life data confirm the excellent efficacy and safety of RTX in patients with newly diagnosed or relapsing AAV.

TH-PO822

Increased Prevalence of Thyroid Disease in Patients with ANCA Associated Vasculitis Maria Prendecki,[1] Leire Martin,[1] Anisha Tanna,[1] Marilina Antonelou,[2] Charles D. Pusey.[1] *[1]Section of Renal and Vascular Inflammation, Imperial College, London; [2]UCL Centre for Nephrology, Royal Free Hospital, London.*

Background: In addition to the known association between different auto-immune diseases, ANCA associated vasculitis (AAV) has previously been associated with thyroid disease possibly due to use of anti-thyroid medications which can induce ANCA. In our clinical practice we have noted a higher prevalence of thyroid disease than would be expected in the general population.

Methods: We identified 279 patients with AAV, diagnosed between 1991 and 2014. Patients were excluded if they were diagnosed prior to 1990 or if insufficient clinical information was available. Data were collected retrospectively on ANCA type, features of vasculitis, history of thyroid disease and treatment.

Results: Thyroid disease was identified in 60 of 279 patients (21.5%); 44 patients had hypothyroidism and 5 patients hyperthyroidism. Three of the hyperthyroid patients developed subsequent hypothyroidism following treatment. Five patients had subclinical hypothyroidism and 5 had subclinical hyperthyroidism. Three patients had goitre and 2 had thyroid nodules. Forty-three patients received treatment with thyroxine, 3 patients received radio-iodine followed by thyroxine, and only 2 patients were treated with propylthiouracil. There were more female patients in the group with thyroid disease than those with AAV and no thyroid disease (73.3% vs. 45.2% female, p=0.0002 chi-squared) and patients were more likely to have anti-MPO antibodies than anti-PR3 antibodies (56.7% vs. 30.5%, p=0.0016). A greater proportion of patients with thyroid disease had evidence of renal involvement as part of their vasculitis (95% vs. 81.7%, p=0.02).

Conclusions: Our data shows a prevalence of thyroid disease of 21.5% and prevalence of hypothyroidism of 15.4% in our group of patients with AAV. This compares to a population prevalence in the UK for hypothyroidism of around 2% for females and <0.1% for males. In view of this association we suggest that patients diagnosed with AAV should be tested for thyroid disease.

TH-PO823

Myeloperoxidase Antibody Positivity in Patients without Primary Systemic Vasculitis Marilina Antonelou,[1] Lara Perea-Ortega,[2] Sally Hamour,[1] Alan D. Salama.[1] *[1]Centre for Nephrology, Univ College London; [2]Hospital General de Fuerteventura.*

Background: The combination of a pANCA immunofluorescence pattern with antibodies specific for myeloperoxidase (MPO) has been reported to have 99% specificity for the diagnosis of ANCA associated vasculitis(AAV). However, increased testing for MPO-ANCA in unselected populations can reduce the specificity for diagnosing vasculitis. The aim of this study was to gain an understanding of the frequency and associations of MPO-ANCA positivity in patients without primary AAV using current detection methods.

Methods: Retrospective review of all patients identified as MPO-ANCA positive, as determined by Luminex testing in our laboratory over a 4 year period. Case notes and laboratory results were reviewed subsequently to establish if they had a diagnosis of AAV or alternate diagnoses.

Results: Two hundred and eight patients were positive for MPO-ANCA, of whom 121(58.2%) had primary AAV. Seventy nine(37.9%) patients were anti-MPO positive without AAV. Clinical associations included other autoimmune disorders (69.6%), infections (8.9%), malignancy (5.1%) and other miscellaneous conditions(16.4%). The median(IQR) MPO-ANCA titre in this group was 16(12-30)U/ml vs 66(24-100)U/ml in the group with primary AAV ($p<0.001$). Thirty eight(48%) patients without known AAV had renal impairment defined as eGFR<60ml/min and/or uPCR ≥100. Twenty two of these patients had a kidney biopsy that ruled out the diagnosis of primary AAV. The characteristics of the 16 patients that were not biopsied are shown in Table 1.

n=16	
Age, mean(SD)	70(16)
MPO-ANCA titre, U/ml, median (IQR)	13(11-37)
eGFR/ml/min, mean(SD)	49.4(26.1)
Other antibodies	11(69%)
Clinical associations Infection/TB Autoimmunity **No association found**	 1 11 4

Conclusions: In patients with MPO-ANCA positivity, 37.9% showed a variety of underlying non-vasculitic conditions, much higher than that reported for PR3-ANCA, in which 9.7% of patients did not have AAV(1). As detectable antibodies may predate the onset of disease, unexplained ANCA findings require long-term follow up and often warrant tissue diagnosis.

1.McAdoo *et al*. J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis. 2012 Oct;18(7):336–40.

TH-PO824

Therapeutic Effect of Plasma Exchange in the Treatment of Severe Renal Damage in Anti-Neutrophil Cytoplasm Antibody Associated Vasculitis

Liping Wang. *Div of Nephrology, Fuzhou Dongfang Hospital, Fuzhou, Fujian, China.*

Background: Anti-neutrophil cytoplasm antibody-associated vasculitis (AAV) is associated with high rates of mortality due to uncontrolled disease and treatment toxicity. Small randomized trials suggest adjunctive plasma exchange(PE) may improve disease control.

Methods: ALL AAV patients presenting between 2011 and 2013 were retrospectively analyzed.The patients were divided into two groups according to the presence of PE or not. The two groups in age, sex, BVAS, serum creatinine and the level of ANCA have no statistical difference ($P > 0.05$).Patients were treated with corticosteroids, and intravenous CYP. Rate of dialysis independence at1 , 3 months and compared with theoutcome of the two groups.

Results: Forty-six patients were included. The two groups in age, sex, BVAS, serum creatinine and the level of ANCA have no statistical difference ($P > 0.05$). PE group had 23 cases ,in PE group,the level of ANCA were from[(169.1±69.8)to(92.9 ±61.8)RU/ml,P<0.05],serum creatinine from [(580.7±206.1) to (405.7±191.1)umol/L, P<0.05];In control group,the level of ANCA from[(170.6±72.4) to (105.64±62.26) RU/ml,P<0.05],serum creatinine from [(678.7±372.04)to (392.26±187.03)umol/L,P <0.05]. In PE group, 5 patients(21.7%) died at a month; 4 patients(17.2%) died in control group. 7 patients with dialysis at a month in PE group, 3 (42.9%) were dialysis independent at a month 5 patients with dialysis in the control group , 1 (20%) was dialysis independent at a month. At 3 months, 8(34.7%) patients were were dialysis independent in PE group; 3 (13%) patients were dialysis independent in control group. Follow up (21.3±8) months,no statistical difference of survival rates was found between two groups .

Conclusions: PE combined corticosteroids and intravenous CYP could effectively reduce the level of ANCA and improve renal function,rate of dialysis independence at 3 months was higher than control group. but the long-term survival In PE group was no difference from the control group.

Funding: Government Support - Non-U.S.

TH-PO825

Prevalence of Immunofluorescent Deposits in ANCA Associated Vasculitis: How "Pauci" Is "Pauci-Immune"?

Layla Alharbi, Lonnie Pyne, Michael Walsh. *McMaster Univ.*

Background: ANCA associated vasculitis is classically associated with a necrotizing, crescentic glomerulonephritis with a lack of immune deposits on immunofluorescent microscopy. We studied the prevalence and characteristics of immunofluorescent deposits in a cohort of patients with known ANCA associated vasculitis.

Methods: We performed a retrospective, single centre cohort study in Hamilton, Canada. We identified patients with a clinical diagnosis of granulomatosis with polyangiitis or microscopic polyangiitis and a renal biopsy. Biopsy records were reviewed for reports of the type, location and intensity of immune deposits on immunofluorescence. Patient characteristics were extracted from clinical charts with a standardized case report form. Biopsy and clinical characteristics were summarized using descriptive statistics. We used multivariable logistic regression to determine if there was an association between immunofluorescent staining and age, sex, ANCA type or need for dialysis at time of biopsy.

Results: We identified 69 patients with ANCA associated vasculitis and a renal biopsy. The patients were a median of 62 (IQR 54 to 70) years old, 33 (48%) were male, 16 (23%) required dialysis at the time of biopsy, 22 (32%) were anti-PR3 positive, 46 (67%) were anti-MPO positive and 1 (1%) was positive for both. Twelve (17%) were reported as pauci immune, however, IgG was found reported as at least 1+ in 23 (33%) in the mesangium and 24 (35%) in the capillaries. IgM was reported in the mesangium of 27 (39%) and in the capillaries of 22 (32%) and IgA in the mesangium of 22 (32%) and in the capillaries of 21 (30%). C3 was reported in 26 (38%) in the mesangium and 28 (41%) in the capillaries. The majority (80%) of positive immunofluorescence was reported at 3+. Male sex was associated with a 3-fold increase in the odds of positive IgG immunofluorescence ($p=0.04$ for mesangial and 0.03 for capillary) but not with age, ANCA type or need for dialysis.

Conclusions: Although the glomerulonephritis in ANCA associated vasculitis is classically described as pauci-immune, 30-40% of patients have immunofluorescence staining, most often men.

TH-PO826

Distribution of Neutrophil Extracellular Traps in the Kidney Suffering from Myeloperoxidase-ANCA Associated Vasculitis with Peritubular Capillaritis

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Background: Neutrophil extracellular traps (NETs) have been shown to contribute to development of MPO-AAV. We previously reported that peritubular capillaritis (PTC) was accompanied by 55% of patients with myeloperoxidase-ANCA associated vasculitis (MPO-AAV). We hypothesized that NETs could be found around PTC as well as crescentic formation in MPO-AAV. The purpose of this study is to reveal the distribution of intrarenal NETs in MPO-AAV with PTC.

Methods: We evaluated the distribution of NETs by immunofluorescence in paraffin-embedded tissue sections of 24 patients with MPO-AAV diagnosed by kidney needle biopsies in Hamamatsu University Hospital from January 2011 to January 2016. PTC was defined by histological findings of inflammatory cells accumulated in the peritubular capillary in association with the disruption of the capillary wall that was stained by anti-CD34 antibody. NETs were identified by colocalization of DNA and citrullinated histone and MPO with confocal immunofluorescence microscopy.

Results: PTC was found in 11 of 24 patients with MPO-AAV. There were no significant difference in ages (70.0±17.1 vs 63.1±19.1), serum creatinine (1.62 ± 1.08 vs 2.15 ± 1.52 mg/dl), MPO-ANCA titers (156.5±108.8 vs 170.1±205.4 IU/ml) between MPO-AAV with and without PTC. NETs were seen more outside glomeruli especially in and/or around PTC and less within glomeruli in MPO-AAV with PTC than without PTC (extraglomerular NETs positive fields / total fields: 33.9 ± 20.3 % vs 13.7 ± 12.8 %, $p<0.05$, NETs positive glomeruli / total glomeruli : 12.7±13.1 vs 28.7±18.7, $p<0.05$). The detection rate of extraglomerular NETs were correlated with the level of urinary α1 microglobulin excretion.

Conclusions: NETs were found around not only crescent but also PTC in the kidney suffering from MPO-AAV with capillaritis, suggesting NETs might contribute to development of PTC.

TH-PO827

Long-Term Follow-Up of a Combined Rituximab and Low-Dose Cyclophosphamide Regimen for Remission Induction in Renal ANCA-Associated Vasculitis

Stephen Paul McAdoo,[1] Nicholas R. Medjeral-Thomas,[1] Anisha Tanna,[1] Megan Griffith,[1] Jeremy B. Levy,[1] H. Terence Cook,[1] Tom Cairns,[1] Alan D. Salama,[2] Charles D. Pusey.[1] *[1]Imperial College Kidney and Transplant Centre, United Kingdom; [2]Univ College Centre for Nephrology, United Kingdom.*

Background: We have previously reported prolonged relapse-free survival in a cohort of 23 patients with renal AAV, following remission-induction treatment with a rituximab-based, cyclophosphamide-sparing regimen. We now report long-term outcomes using this protocol in an extended cohort of 66 patients.

Methods: We report long-term follow-up of consecutive patients presenting with new or relapsing renal AAV at our centre since 2006, who were treated with our published regimen of oral steroids, rituximab and low-dose pulsed intravenous cyclophosphamide. Patients who presented with alveolar haemorrhage, renal-failure requiring dialysis, or other severe disease manifestations requiring addition of plasma exchange were not included. Maintenance therapy was commenced at 3 months with azathioprine of MMF.

Results: 66 patients are included in the current analysis. The median BVAS and creatinine at presentation was 19 and 205µmol/l respectively. The median dose of rituximab and cyclophosphamide was 2g and 3g respectively. All patients achieved B cell depletion, and 95% were in remission by 6 months. At last follow-up (median 5 years; range 1-10), renal and patient survival were 94% and 84% respectively. Ten patients (15%) experienced a major relapse during follow-up, at a median time of 39 months. All were ANCA positive and 90% B cell replete at relapse. 30% of patients had an infection requiring hospital admission. No unexpected adverse events were observed.

Conclusions: These findings confirm our previous observations that this regimen affords early disease control in renal AAV, and relapse rates that are favorable compared to published controlled studies. These observations are in keeping with long-term follow-up of the RAVE trial, where sustained remission was observed without maintenance therapy following rituximab treatment. We believe this combined regimen may provide the basis to further refine remission-induction protocols in AAV, potentially by allowing early withdrawal of corticosteroids.

Funding: Government Support - Non-U.S.

TH-PO828

A Steroid-Sparing Regimen for Remission Induction Therapy in Renal ANCA-Associated Vasculitis Stephen Paul McAdoo, Rachna Bedi, Megan Griffith, Tom Cairns, Charles D. Pusey. *Imperial College Kidney and Transplant Centre, United Kingdom.*

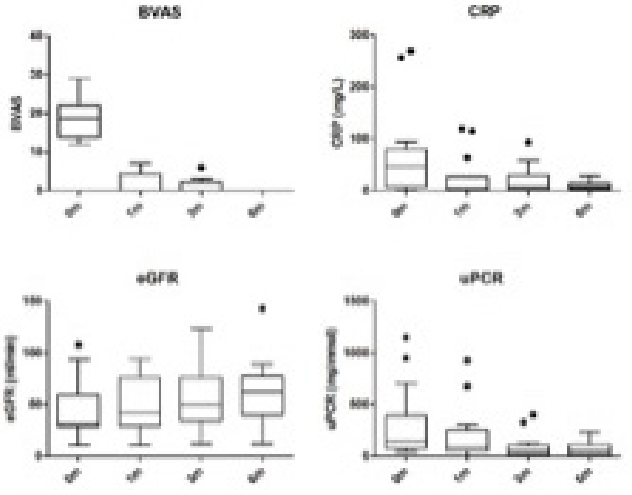
Background: The majority of early mortality in AAV is now attributed to infections, rather than active disease. Infection, along with cardiovascular disease, remains a common cause of long-term mortality. It is likely that corticosteroid exposure contributes to the risk of these adverse outcomes, and that steroid avoidance may improve outcomes in AAV.

Methods: This is a cohort study of a novel steroid-sparing regimen that has been in use for treatment of new or relapsing renal AAV at our centre since 2014 (Table 1).

Summary of the Induction Protocol		
Rituximab	1gx2	Wk 0,2
Cyclophosphamide	750mgx2; 500mgx4 pulses	Wk 0,2,4,6,8,10
iv Methylprednisolone	500mgx2	Wk 0,2
Oral Prednisolone	30mg daily	Wks 0-2 inclusive

Patients with significant alveolar hemorrhage or renal failure requiring dialysis were not included. Maintenance therapy commenced at 3 months with azathioprine or MMF.

Results: To date, 14 patients have completed at least 6 month follow-up. The median BVAS and creatinine at presentation were 17 and 180µmol/l, respectively. All patients achieved clinical remission by 6 months (Figure 1).



8 infections were seen in 6 patients, of which none were atypical. There were no new cases of diabetes and measurements of HbA1c did not change significantly (46 vs 42 mmol/mol pre- and post- treatment, respectively, p=0.23). No relapses have been observed at last follow-up 9.3 months (6.5-22).

Conclusions: Our data suggests that remission in AAV may be achieved with significantly lower corticosteroid doses than previously reported. This was not associated with early relapse, and may result in an improved adverse event profile. Controlled studies are required to establish if steroid avoidance using this, or similar, protocols will result in improved long-term outcomes in larger cohorts.

Funding: Government Support - Non-U.S.

TH-PO829

Clinical Features and Outcome of Elderly Patients with Anti-Neutrophil Cytoplasmic Autoantibody-Associated Vasculitis Eun Young Seong,[1] Harin Rhee,[1] Jong Man Park,[1] Sang Heon Song,[1] Il Young Kim,[2] Dong Won Lee,[2] Soo Bong Lee,[2] Ihm Soo Kwak.[1] *[1]Internal Medicine, Pusan National Univ Hospital, Busan, Republic of Korea; [2]Internal Medicine, Pusan National Univ Yangsan Hospital, Yangsan, Republic of Korea.*

Background: Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) is common in elderly population, but there is few data of clinical characteristics and outcome, especially in Asia. This study aimed to investigate demographic factors, treatment and outcome in patients aged ≥65 years with AAV in Korea.

Methods: We reviewed the medical records of 228 C-ANCA or P-ANCA positive patients in a university-affiliated nephrology center from 2005 to 2016. Patients classified as having secondary vasculitis, drug-induced vasculitis, eosinophilic granulomatosis with polyangiitis and polyarteritis nodosa were excluded. A total of 69 patients were included in this study.

Results: Twenty-eight patients (40.6%) were older than 65 years old (elderly group), and 41 patients (59.4%) were younger than 65 years old (younger group). Median age at diagnosis was 71.25±4.54 years in elderly group and 47.02±13.61 years in younger group. In elderly group, initial blood urea nitrogen level and C-reactive protein (CRP) were higher and initial estimated glomerular filtration rate (eGFR) was lower than younger group. Comorbidity score and organ involvement were not different between two groups. Median follow-up was 20.74 months. Overall survival was significantly lower in elderly group (75.0%) than younger group (7.1%) (p=0.024). Older age and higher serum creatinine level were associated with higher mortality. Renal survival was 50% in elderly group and 31.7% in younger group. High serum creatinine level at diagnosis was the only significant predictor of renal survival. Patients who were treated with standard immunosuppressive therapy had same survival and renal survival in elderly group.

Conclusions: AAV is a disease with substantial mortality and morbidity among elderly patients. This study showed that standard immunosuppressive therapy may not help improve the outcome in elderly AAV patients.

TH-PO830

Management and Outcome of Anti-Glomerular Basement Membrane (GBM) Disease: A Single Centre Retrospective Case Series Anna K. Forbes, David Makanjuola, Marie B. Condon, Bhrigu Raj Sood, Fiona E. Harris. *Renal Medicine, St. Helier Hospital, London, United Kingdom.*

Background: Anti-GBM disease is a rare autoimmune condition characterised by rapidly progressive glomerulonephritis and/or pulmonary haemorrhage. Data on optimal treatment and outcomes is limited and is mainly from uncontrolled studies, with plasma exchange, corticosteroids and oral cyclophosphamide (CyP) widely accepted as induction therapy. In our centre, we routinely use pulsed intravenous (i.v.) CyP in lieu of oral, thereby reducing total CyP dose. The role of maintenance immunosuppression is less clear; where this is used, Azathioprine is our first line therapy. We present retrospective data from a cohort of patients with anti-GBM disease.

Methods: Using our local database, we identified 29 patients with anti-GBM disease presenting over a 14 year period. Data were collected from paper and electronic medical records.

Results: 16 (55%) patients were dialysis dependent at presentation. In this group, patient and renal survival were 75% and 12.5% at 1 year and 62.5% and 6.25% at last follow up respectively. Of the 13 (45%) patients who were dialysis independent at presentation, patient and renal survival were 100% and 69% at 1 year and 100% and 61.5% at last follow up. This demonstrated a significant difference in renal survival at 1 year (p = 0.014) and at last follow up (p = 0.012). The mean duration of anti-GBM antibody (Ab) persistence was 135 days. In those patients receiving maintenance immunosuppression (n=13, 45%), the duration of Ab persistence was shorter at 96 days compared with 175 days in those not receiving maintenance therapy.

Conclusions: Our findings are consistent with published data on patient and renal survival. Our data suggest that pulsed i.v. CyP may be as effective as oral. This therapeutic strategy may reduce treatment related toxicity without affecting outcome. Furthermore, our data suggest that time to Ab negativity is shorter in those receiving maintenance immunosuppression, an important consideration in potential transplant recipients. A randomised controlled trial is necessary to validate these findings.

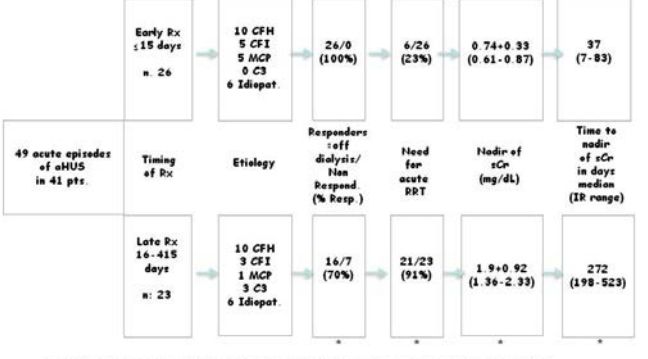
TH-PO831

Timing of Eculizumab Treatment and Renal Outcome in aHUS Gianluigi Ardissino, Francesca Tel, Donata Cresseri, Stefania Salardi, Sara Testa, Fabio Paglialonga, Michela Perrone, Martina Sgarbanti, Silvana Tedeschi, Florjan Mehmeti, Chiara Ferraris Fusarini, Piergiorgio Messa. *Fondazione IRCCS Ca' Granda Osp. Maggiore Policlinico, Milano, Italy.*

Background: Atypical HUS (aHUS) is a severe thrombotic microangiopathy (TMA). Eculizumab (ECU) is the frontline treatment (Rx) it is not always started early after diagnosis; late Rx may result in permanent renal renal damage.

Methods: We analyze the renal outcome of patients (Pts) treated at our Center for aHUS as to timing of ECU Rx. Since 2009, at least 49 acute episodes of aHUS in 41 Pts with ongoing TMA, were treated with ECU. The 17 Pts with bone marrow transplantation-related TMA, were excluded for the different pathogenesis and the systematically different(poor) response to ECU Rx.

Results: Twelve Pts were children,25 females,4 were kidney transplant recipients,median age was 29.3 years(IR 11.7-44.2),25 episodes had been treated with plasmaexchange(PEX) before ECU and 27 required RRT. In 26 events,ECU was started within 15 days of presentation(median2.5; IR1-6) while in the remaining 23, Rx was started at a median of 43 days (IR 30-165). Five events (19%) treated early, had also been exposed to PEX before ECU compared to 20(87%) in the late Rx group. Pts' carachteristics and their renal outcome according to timing of ECU Rx, are shown in the figure.



Legends: Rx: treatment; RRT: renal replacement therapy sCr: serum creatinine; *: p<0.01

The pt who started ECU as late as415 days(the latest)after disease presentation(CFH mutation)reached a nadir of sCr as low as .7 mg/dL.

Conclusions: Early Rx provides better renal outcome as to response rate, need for acute RRT, final renal function and time to reach the nadir of sCr. The better outcome turns into lower costs for the possibility of early discontinuation of ECU, for which a good residual renal function is essential. We stress that ECU Rx can be useful even if started late, we encourage to treat Pts as long as signs of ongoing TMA are present, regardless of disease duration.

TH-PO832

A Simple and Early Prognostic Index for STEC-HUS at Presentation
Gianluigi Ardissino, Francesca Tel, Sara Testa, Fabio Paglialonga, Michela Perrone, Dario Consonni. *Fondazione IRCCS Ca' Granda Osp. Maggiore Policlinico, Milano, Italy.*

Background: STEC-HUS is an unrare, severe acute thrombotic microangiopathy (TMA) burdened with life-threatening complications (Cs), high case-fatality rate and significant long term sequels. It is important, both for patient's (Pts) management and prognosis communication, to identify Pts at high risk for severe Cs, as early as possible in the course of the disease possibly through a simple and straightforward approach. It has been demonstrated that hemoconcentration at presentation of STEC-HUS is associated with worse short- and long-term outcome.

Methods: The very first laboratoy examination with signs of TMA of Pts referred to our Center during recent years, were analyzed in order to identify and develop a reliable, as well as easy to calculate (at bedside), index to predict Cs. The following outcomes were considered together: 1. death, 2. CNS involvement, 3. need for RRT, 4. long-term renal and systemic sequels. Receiver Opereiting Characteristic (ROC) and their area under the curve (AUC) for the continuous laboratory parameters hemoglobine (Hb), serum creatinine (sCr) and LDH at presentation, were calculated, alone and in combination, after univariate and multiple logistic regression models, on the dataset of 38 patients (20 Females) with documented STEC-HUS and with a mean age of 4.9 yrars (IR 1.5-7.1).

Results: Overall there were 25 Pts (65.8%) with the listed Cs. Hb level at presentation alone proved to be the best predictor of poor outcome (AUC: 0.751). The probability of Cs increased linearly with Hb level, from about 10% at Hb of 7 gr/dL to 50% at 12 and up to 70% when Hb was 14. Frequency of Cs was 9.1% when sCr was < 1 mg/dL and 38.9% when >1 mg/dL (AUC: 0.756). The AUC for Hb and sCr combined was 0.884 (CI 0.763-0.942).

Conclusions: We conclude that in STEC-HUS, Pts with higher Hb level (>11 gr/dL) and those with high sCr, although Hb is <11 gr/dL, at presentation should be carefully evaluated, monitored and managed accordingly for the very high risk of Cs most likely related to hidden hemoconcentration in ongoing TMA.

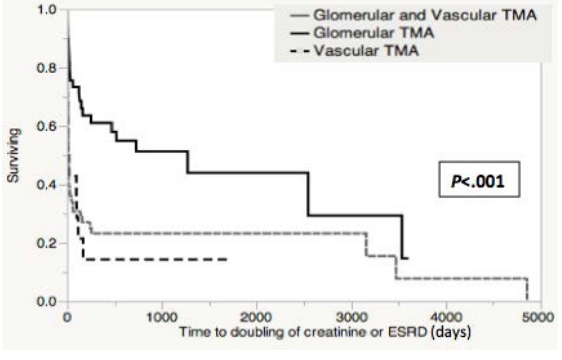
TH-PO833

Renal Thrombotic Microangiopathy in the Modern Era: A Report of 128 Cases from a Single Center
Gauri Bhutani,[1] Samar M. Said,[3] Nelson Leung,[2] Mary E. Fidler,[3] Mariam P. Alexander,[3] Lynn D. Cornell,[3] Samih H. Nasr.[3] *[1]Nephrology, Univ of Wisconsin, Madison; [2]Nephrology, Mayo Clinic; [3]Pathology, Mayo Clinic, Rochester.*

Background: Large modern series addressing renal thrombotic microangiopathy (TMA) are lacking. This study aimed to define current epidemiology, outcomes and clinicopathologic correlations in renal TMA.

Methods: We identified 128 patients with renal TMA by retrospective review of our pathology archives from 2000-14. Pathologic findings, clinical, treatment and outcome parameters were correlated. Statistical analysis employed Fisher's exact and Log Rank tests.

Results: Median age was 51 yrs (34-65); 55% were female and 84% Caucasian. Median serum creatinine (Cr) and proteinuria at renal biopsy (bx) were 2.9 mg/dL (1.8-4.2) and 2.0 g/day (0.8-4.5), respectively. The most common causes were autoimmune diseases (29%), hematologic clonal disorders (17%), drugs (13%), complement-mediated disorders (12%) and hypertension (10%). Evidence of microangiopathic hemolytic anemia (MAHA)-thrombocytopenia and peripheral schistocytes- was seen in 54% and 42%, respectively. Acute TMA on bx (fibrin thrombi and/or schistocytes) was noted in 59% and correlated with detectable MAHA (88% vs 54%, *P*<.001]. Median follow up was 752 days (169-1396) with 66% developing doubling of Cr/need for acute dialysis [median time: 13 days (4-59.5)], and 34% progressing to ESRD. TMA involved glomeruli alone, vessels and glomeruli, and vessels alone in 38%, 51%, and 11%, respectively. Vascular TMA was associated with autoimmune diseases (38% vs.16%, *P*=.01) and poor renal outcomes (Figure).



Conclusions: The epidemiology of renal TMA is evolving: autoimmune, hematologic clonal, complement-mediated disorders and drugs account for most cases. Systemic MAHA is not always present, emphasizing the importance of renal bx for diagnosis. Despite medical progress in TMA, renal prognosis remains poor, particularly with vascular involvement.

TH-PO834

Renal Prognosis of TKI Induced Thrombotic Microangiopathy, a Case Series
Keren Doenyas-Barak,[1] Avishay Sella,[2] Shai Efrati.[1] *[1]Nephrology and Hypertension, Asaf Harofeh Medical Center, Israel; [2]Oncology, Asaf Harofeh Medical Center.*

Background: Anti-VEGF tyrosine kinase inhibitors (TKIs) have substantially improved survival and quality of life of metastatic renal cell carcinoma (mRCC) patients. However, soon after the introduction of these drugs, data regarding their toxicity emerged. Renal toxicity, typically characterized by proteinuria, hypertension and renal failure, and pathologically by thrombotic microangiopathy, appears in up to 2% of patients. Most guidelines recommend withholding TKI use, but limited alternatives exist, and thus cautious continuation of TKIs may be desired. We report our three year experience treating patients with clinical TKI-induced thrombotic microangiopathy (TMA).

Methods: From the database of the nephro-oncologic clinic in Asaf Harofe Medical Center, baseline characteristics, renal progression and outcomes were extracted for Renal cell cancer patients treated with TKIs who developed proteinuria, renal failure and clinical signs of TMA.

Results: We allocated 7 patients. Their baseline characteristics included: proteinuria: 0.5 to 10.1gr (mean 5.13gr), creatinine of 1.58-4.06 mg/dl (mean 2.26mg/dl), hemoglobin of 8.4-13 mg% (mean 10.93 mg%) and platelet count of 90000-372000 (mean 193000).

TKI treatment was held in one patient due to decompensated malignant ascites, but resumed in 6 patients with mean follow-up of 22 months. Proteinuria was reduced in all patients with ACE inhibitors or ARBs treatment and tight blood pressure control.

During the follow up period creatinine blood levels were stable with mean change of 0.02mg/dl (-0.6 to +0.45mg/dl), compared to baseline. One patient with baseline creatinine of 4.06mg/dl had started dialysis simultaneously with axitinib readministration.

None of the patients developed grade III-IV anemia or thrombocytopeania, nor thrombo-embolic events.

Conclusions: TMA related to TKIs may present as an indolent disease. Careful follow up by an experienced nephrologist may enable continuation of TKI treatment.

TH-PO835

Atypical Hemolytic Uremic Syndrome: A Meta-Analysis of Case Reports
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Background: Atypical Hemolytic Uremic Syndrome is a life threatening thrombotic micro-angiopathy that affects the GI tract, Kidneys and the Central Nervous System. Recently, uncontrolled complement activation has been associated with aHUS. Different mutations have been linked with atypical HUS paving the way for targeted drug therapy. We will discuss the various mutations that are linked to atypical HUS, treatment modalities and their impact on prognosis.

Methods: A PubMed/Medline search for case studies including "atypical hemolytic uremic syndrome" was conducted between November 2000 and November 2015. Points reviewed were time to symptom resolution and mortality. Wilcoxon Rank Sum Test was used to compare time for symptom resolution, normalization of creatinine and platelets amongst treatment groups and mutation carriers.

Results: Between 2005 and 2015, 222 articles related to aHUS were reviewed. Patients between 2010 to 2015 had a higher severity of illness compared to the previous interval. The proportion of CFI and MCP mutations across the first 5 year interval was also higher. Use of Eculizumab has also increased from 7.5% to 48.6% over the last five years. Plasma Exchange therapy use was higher in patients with higher levels of Creatinine in comparison to those who didn't (p<0.001). Both Plasma Exchange and Eculizumab decreased mortality (p=1; p=0.25).

Conclusions: The incidence of aHUS has significantly increased over the past 5 years. Plasma exchange is the preferred modality with 65 % case studies using the same. Eculizumab was used in 35% of the case studies reviewed and was found to reduce mortality. Mutations associated with aHUS were CFH followed by MCP and CFI. Patients with CFH mutation were more likely to be involved in plasma exchange therapy. aHUS was a disease of exclusion but now has specific mutations and it's own treatment. With greater registry programs and clinical trials, we would have more clinical knowledge that would hopefully help us decrease the incidence of the disease.

TH-PO836

Renal Outcome in Primary Thrombotic Microangiopathies
Hassan A. Salameh, Jennifer C. Yui, Fernando C. Fervenza, Ronald Go, Jeffrey L. Winters, Nelson Leung. *Mayo Clinic, Rochester, MN.*

Background: Thrombotic microangiopathy (TMA) describes a pathological process of microvascular thrombosis, microangiopathic hemolytic anemia and consumptive thrombocytopenia leading to end-organ ischemia. Any organ can be involved but patients usually present with acute kidney injury (AKI) and/or cerebral dysfunction. Literature

suggests that hemolytic uremic syndrome induces more severe renal injury than thrombotic thrombocytopenic purpura (TTP) but this is not universally found. The aim of this study is to analyze the severity of AKI and clinical outcome of patients with renal TMA in a cohort of patients from a single center's experience.

Methods: Clinical and laboratory data of 126 patients diagnosed with TMA from 2000 to 2014 were retrospectively analyzed. Patients were followed for 1 year after diagnosis and renal outcomes at 3 months and 1 year were analyzed using serum Creatinine and GFR. 43 patients were excluded due to insufficient data or loss to follow-up.

Results: Patients were subcategorized into shiga toxin producing E. Coli hemolytic uremic syndrome (STEC-HUS), TTP or atypical hemolytic uremic syndrome (aHUS) and results are summarized in table 1. Primary TMA was associated with AKI in 80.7% of patients. Atypical HUS was associated with more severe AKI with 81.8% presenting with AKIN stage 3 compared to 38% of TTP patients. Long term outcome was worse for aHUS patients with 50% requiring dialysis at one year compared to 11.3% of TTP patients.

	STEC-HUS (6)		aHUS (11)		TTP (66)	
No AKI	**0**		**0**		**24.2%**	
Stage 1 AKI	**0**		**9.1%**		**24.2%**	
Stage 2 AKI	**16.7%**		**9.1%**		**13.6%**	
Stage 3 AKI	**83.3%**		**81.8%**		**38%**	
	3 months	**1 year**	**3 months**	**1 year**	**3 months**	**1 year**
GFR >60	**33.3%**	**66.6%**	**18.2%**	**12.5%**	**45.2%**	**45.3%**
GFR 30–59	**0**	**0**	**0**	**12.5%**	**27.4%**	**26.4%**
GFR 15–29	**33.3%**	**33.3%**	**36.4%**	**12.5%**	**4.8%**	**1.9%**
GFR <15	**0**	**0**	**9%**	**0**	**1.6%**	**0**
On Dialysis	**33.3%**	**0**	**36.4%**	**50%**	**11.3%**	**11.3%**
Mortality	**0**	**0**	**0**	**12.5%**	**9.7%**	**15.1%**

Conclusions: TMA imposes a large burden on renal health. In our center's experience aHUS had worse acute and long term renal outcomes when compared with TTP or STEC-HUS. However, the number of patients in both the STEC-HUS and aHUS were small in comparison to the TTP group.

TH-PO837

Hypertension-Associated Thrombotic Microangiopathy and Complement Dysregulation Sjoerd Timmermans,[1] Myrurgia Abdul-Hamid,[2] Jan Damoiseaux,[3] Pieter Van Paassen.[1] *[1]Nephrology and Clinical Immunology, Maastricht UMC, Netherlands; [2]Pathology, Maastricht UMC, Netherlands; [3]Central Diagnostic Laboratory, Maastricht UMC, Netherlands.*

Background: Renal thrombotic microangiopathy (TMA) can be both cause and consequence of severe hypertension, ultimately leading to renal failure. Underlying pathophysiological mechanisms differ among the diverse TMA syndromes with great impact on treatment options and prognosis. We hypothesized that dysregulation of the alternative pathway (AP) is a treatable, but often unrecognized cause of hypertension-associated TMA, particularly in patients without biochemical signs of TMA, and that the prognosis resembles atypical hemolytic uremic syndrome (aHUS).

Methods: Consecutive patients with hypertension-associated TMA, defined as severe hypertension (BP ≥180/120 mmHg) and biopsy-proven renal TMA, were screened for AP abnormalities, including genetic and serological testing. Renal biopsies were stained for complement components.

Results: Ten patients were identified, including 8 patients without biochemical signs of TMA. *C3* (*n*=3), *CFI* (*n*=1), *CD46* (*n*=1) and/or *CFH* (*n*=2) mutations either with or without Δ*CFHR1-CHFR3* (*n*=2) and/or at-risk *CFH* haplotypes (*n*=5) were found in 7 patients. C3c and C5b-9 deposits along the vasculature and glomerular capillary wall confirmed complement activation in vivo. Patients with genetic AP abnormalities invariably presented with end-stage renal disease (ESRD), while ESRD did not occur among patients without complement defects. Remarkably, disease recurrence developed in 4 out of 5 allografts (*n*=3), which was associated with graft loss; recurrence-free survival was achieved in a single patient who received eculizumab after transplantation, however.

Conclusions: AP abnormalities can be found in a subset of patients with hypertension-associated TMA even though biochemical signs of TMA are mostly absent. Renal survival is poor and TMA recurrence appeared common, indicating that these patients fall into the spectrum of aHUS. Genetic testing for AP abnormalities should therefore be performed in patients with hypertension-associated TMA, particularly in those not responding to treatment and/or prior to renal transplantation.

TH-PO838

Clinical Features of Primary Membranoproliferative Glomerulonephritis in Japan: An Analysis of the Japan Renal Biopsy Registry (J-RBR) Naoki Nakagawa,[1] Motoshi Hattori,[2] Michio Nagata,[3] Hitoshi Yokoyama.[4] *[1]Nephrology, Asahikawa Medical Univ, Japan; [2]Tokyo Women's Medical Univ; [3]Tsukuba Univ; [4]Kanazawa Medical Univ.*

Background: The clinical features of primary membranoproliferative glomerulonephritis (MPGN) in an adequate sample of patients has not been studied in detail. We therefore surveyed the features of primary MPGN based on data from the Japan Renal Biopsy Registry (J-RBR).

Methods: A cross-sectional survey of 332 patients with primary MPGN registered in the J-RBR between 2007 and 2015 was conducted. Clinical parameters of blood pressure (BP), and blood and urine laboratory findings at diagnosis were compared between children (< 20 years), adults (20-64 years) and elderly persons (≥ 65 years). Factors affecting declining renal function in adult and elderly patients were assessed using multiple regression analysis.

Results: Mean age was 51.6 ± 24.6 years, mean systolic BP 137.9 ± 22.4 mmHg, mean proteinuria 3.8 ± 3.4 g/day, mean serum albumin 2.97 ± 0.80 g/dL and mean eGFR 49.9 ± 26.1 ml/min/1.73m^2. The clinical features were significantly more severe in elderly patients, especially systolic BP (children, 112.8 ± 15.8; adult, 136.0 ± 18.1; elderly patients, 148.2 ± 20.3 mmHg; P<0.001), proteinuria (children, 1.8 ± 2.2; adult, 4.0 ± 3.2; elderly patients, 4.2 ± 3.6 g/day; P<0.001), low albumin levels (children, 3.5 ± 0.9; adults, 3.0 ± 0.8 g/day; elderly patients, 2.8 ± 0.7 g/dL; P<0.001), and low eGFR (adults, 59.6 ± 28.7; elderly patients, 40.2 ± 18.6 ml/min/1.73m^2; P<0.001). The rate of clinically classified nephrotic syndrome was significantly higher in adults (48.8%) and elderly patients (62.9%) than children patients (16.7%), whereas the rate of chronic glomerulonephritis was significantly higher in children (76.7%) than adults (46.5%) and elderly patients (29.4%). Multiple regression analysis revealed that high systolic BP and high proteinuria were independent factors associated with decreased eGFR in adult and elderly patients with primary MPGN.

Conclusions: In Japan, the clinical features of adults and elderly patients with primary MPGN were more severe than those of children. Further investigation is needed to explore the clinical outcomes in patients with primary MPGN.

Funding: Government Support - Non-U.S.

TH-PO839

Immune-Complex Mediated Membranoproliferative Glomerulonephritis: A New Approach to a Forgotten Entity Paola Rodríguez, Enrique Morales, Evangelina Merida, Eduardo Gutierrez-Martinez, Manuel Praga. *Nephrology, Hospital Univ 12 de Octubre, Madrid, Spain.*

Background: The better understanding of membranoproliferative glomerulonephritis (MPGN) based on immunofluorescence has changed its therapeutical approach. Idiopathic immune-complex mediated MPGN is a partially known entity. The aim of this study was to analyze the clinical presentation, treatment and outcome of this disease.

Methods: Retrospective review ofpatients diagnosed of idiopathic immune-complex mediated MPGN at our Nephrology Department from 1976 to 2015.

Results: Twenty-three patients (10%) of our 228 MPGN patients were labeled as idiopathic immune-complex mediated MPGN (56.5% males), with a mean age 41±25 (10-81) years. The mean follow-up was 215±203 (1-489) months. Acute kidney injury was present in 50% of the patients at time of diagnosis. The most common clinical presentation was nephrotic syndrome (60.8%) with a mean proteinuria of 4.2±3.1 (0.10-12.0) g/day. When we compared patients according the decade of diagnosis, patients diagnosed after 2003 (N=12) were older (55.8±29.8 vs 20.4±7.7 years, p < .001), with more severe kidney impairment (1.7±0.9 vs 0.9±0.4 mg/dl, p = .044), higher systolic blood pressure (BP) (152±26 vs 124±13 mmHg, p = 0.009), and proteinuria (4.8±3 vs 2.9±2.2 g/day, NS). Thirteen patients (52%) received immunosuppression (100% steroids, 90% mycophenolate mofetil and 42% Rituximab®) due to a more aggressive clinical presentation. Elderly patients (> 65 years, N=6) presented worse baseline SCr (2.5±0.8 vs 1.0±0.4 mg/dl, p < .005), higher systolic BP (168±7 vs 130±22 mmHg, p < .005), and proteinuria (6.2±4.1 vs 3.6±2.6 g/day, NS), and reached ESRD more frequently (66.7% vs 11.8%, p < .008) compared with young patients (N=17). Six patients (26%) progressed end stage renal disease (ESRD) in a mean time of 35.3±39.8 (2-84) months.

Conclusions: The clinical presentation of idiopathic immune-complex mediated MPGN has dramatically changed, affecting older patients with more severe renal impairment and poor response to immunosuppressive therapies. Further prospective studies are needed for a better knowledge of this entity.

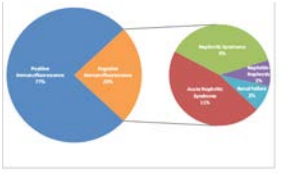
TH-PO840

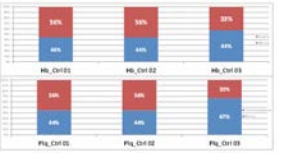
Membranoproliferative Glomerulonephritis and Negative Immunofluorescence: A Clinicopathological Study Luis A. Castillo,[1,2,3] Eduardo I. Navarro,[2] Gustavo Aroca Martinez,[2,3] Henry J. Gonzalez Torres.[2] *[1]Nephrology, Univ Cooperativa de Colombia, Santa Marta, Magdalena, Colombia; [2]Nephrology, Univ Simón Bolívar, Barranquilla, Atlantico, Colombia; [3]Nephrology, Clínica de la Costa, Barranquilla, Atlantico, Colombia.*

Background: Membranoproliferative GN (MPGN) represents a pattern of injury seen on light microscopy. Recent advances in understanding of the underlying pathobiology have led to a proposed classification scheme based on immunofluorescence findings. Given recent advances in our understanding of the role of the alternative pathway of complement in MPGN, a practical approach is to view MPGN as either immune complex– or complement-mediated. If neither of these causes is present (null complement and immune complex), then chronic thrombotic microangiopathy may be the cause of the MPGN.

Methods: Cross-sectional study. The data were extracted from NefroRed ©, a software platform that contains the socio-demographic, clinical and laboratory data of 1200 kidney biopsies. It was selected for the study those patients that showed the pattern of MPGN and negative immunofluorescence. Each biopsy was studied by light microscopy and immunofluorescence. Frequency tables and graphics were performed on relevant into R (figure 1).

Results: The average age of men was 33.8 years and for women was 33.6 years. The 1200 Biopsies showed 58 injuries MPGN (5%) of these 58 cases only 23% lesions showed negative immunofluorescence. The Acute Nephritic Syndrome was the most common clinical presentation (46%), Nephrotic Syndrome (38%), and Acute kidney Injury (8%) (figure 2).





Conclusions: 23% of patients with MPGN have negative immunofluorescence either immune complex o complement. The presence of anemia and thrombocytopenia in several patients during clinical evolution suggest the presence of a thrombotic microangiopathy. The most common clinical presentation was acute nephritic syndrome.

TH-PO841

Determinants of Long-Term Outcomes in Monoclonal Immunoglobulin Deposition Disease Florent Joly,[1] Camille Cohen,[2] Vincent Javaugue,[1] Bertrand Arnulf,[3] Mathilde Nouvier,[4] Vincent Audard,[5] Francois Provot,[6] Dominique Nochy,[7] Bertrand Knebelmann,[2] Arnaud Jaccard,[8] Jean-Paul Fermand,[3] Frank Bridoux.[1] *[1]CHU Poitiers; [2]Hôpital Necker, Paris; [3]Hôpital Saint Louis, Paris; [4]CHU Lyon; [5]Hopital Henri Mondor, Creteil; [6]CHU Lille; [7]HEGP Paris; [8]CHU Limoges, France.*

Background: Monoclonal immunoglobulin deposition disease (MIDD) is a rare complication of plasma cell disorders, defined by linear Congo red-negative deposits of monoclonal light chain (LCDD), heavy chain (HCDD) or both (LHCDD) along basement membranes. Treatment strategies and long-term outcomes are poorly defined.

Methods: We retrospectively reviewed 176 French patients (pts) with biopsy-proven LCDD (n=143), HCDD (n=18) and LHCDD (n=15). Renal response (defined by >50 % decrease in 24h-proteinuria without a >25 % decrease in eGFR) and patient survival were compared with hematological response after chemotherapy.

Results: Median age at diagnosis was 63 years. Renal involvement was constant, with median eGFR of 18 ml/min/1.73m², proteinuria of 1.8 g/d, microhematuria (68%) and hypertension (64%). 55 pts had extra-renal disease, with heart (n=18), peripheral nerve (n=18) or liver (n=8) involvement. Hematologic diagnosis was multiple myeloma in 42% and MGRS in 57%. Serum free light chain (FLC) ratio was abnormal in all 113 tested pts. Among 169 pts who received chemotherapy, based on bortezomib and/or alkylating agents, 60% achieved hematological response (HR), as defined by post-treatment dFLC <40 mg/L. Median overall survival in pts with and without HR was 169 months and 78 months (p=0.001), with a median renal survival of 216 months and 108 months, respectively (p=0.05). Median overall survival was 169 and 64 months in pts who achieved or not a renal response (p<0.001). Predictive factors of renal response were baseline eGFR >30 ml/min/1.73 m², post-treatment dFLC <40 mg/L, bortezomib-based therapy, and severity of renal interstitial fibrosis/vascular lesions.

Conclusions: Achievement of dFLC <40 mg/L translates into improved renal and patient survival in MIDD. Renal response is associated with higher patient survival. Due to their efficacy and good tolerance profile, bortezomib-based regimens should be considered as first-line therapy.

TH-PO842

Hereditary Aα Fibrinogen Amyloidosis: The French Cohort Marc Ulrich,[1] Lara Meyer,[2] Sophie Valleix,[3] Hélène François,[2] Laurence Vrigneaud.[1] *[1]Néphrologie, Dialyse et Médecine Interne, CH Valenciennes, Valenciennes, Nord, France; [2]Néphrologie et Transplantation, Hopital Kremlin Bicetre, Le Kremlin Bicetre, France; [3]Génétique Médicale, Hopital Necker Enfants Malades, Paris, France.*

Background: Aα-Fibrinogen amyloidosis (AFib) is the most frequent renal hereditary amyloidosis in Northern Europe characterized by rapidly progressive chronic kidney disease (CKD), high proteinuria and massive glomerular deposits.

Methods: French AFib patients were identified from a genetic registry (S. Valleix), complemented with a national call on members of the French nephrological society to report cases.

Results: Data were collected on 21 families: 30 patients with E526V mutation (n=22), R554L (n=2), Δ 517-522 (n=2) and not reported in the medical file (n=4). Mean age at presentation was 54.33 years. A family history of nephropathy was present in 10 cases, 7 of whom were amyloidosis. Four patients died, with a mean time from diagnosis of 109 months. Principal characteristics were rapidly progressive CKD with hypertension (63%) and proteinuria (4g/d), often nephrotic range (30%). Renal biopsy consistently showed massive glomerular amyloid deposits. Fibrinogen immune-staining was positive in 7 cases and negative in 8 cases. End-stage renal disease occurred in all symptomatic patients (mean time from diagnosis 29 months). Fourteen patients underwent transplantation, 11 renal and 3 hepato-renal grafts. There were 5 recurrences on isolated renal graft, leading to graft lost in 3 cases, in a mean time of 109.2 months.

Conclusions: This first French series confirms phenotypical and histological presentation of AFib, with a predominance of E526V variant and a poor renal prognosis. Extra-renal manifestations seem limited. Assessment of family is a key point and can lead to early diagnoses. The only certain diagnostic tool is genetic assessment, although the massive glomerular deposits and family history may lead to suspect an AFib. Renal graft survival is about 10 years in case of renal transplantation, whereas there is no recurrence in hepato-renal transplantation. Renal transplantation is the best choice in most cases. For the youngest patients hepato-renal transplantation affords the best long-term outcomes.

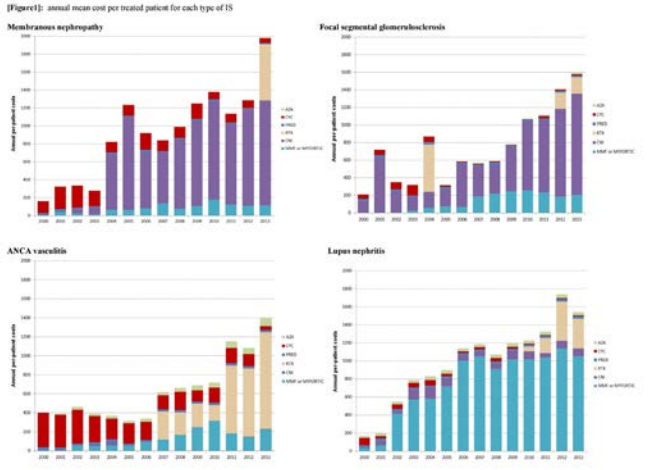
TH-PO843

The Population-Level Costs of Immunosuppression Treatment for Glomerulonephritis Are Increasing over Time Sean Barbour,[1,2] Clifford Lo,[1] Gabriela Espino-Hernandez,[1] John Feehally,[3] Sharareh Sajjadi,[2] Jagbir Gill.[1,2] *[1]BC Renal Agency, Canada; [2]Univ of BC, Canada; [3]LGH, Leicester, United Kingdom.*

Background: To date, there has been no assessment of the real-world cost of immunosuppression (IS) treatment for glomerulonephritis (GN). Given the chronic nature of GN, and advances in treatments that are more safe and effective, but also more expensive, the cost of treating GN is likely substantial. In renal transplant, the use of newer IS treatments resulted in a doubling of medication costs over time. We hypothesize a similar trend exists in GN as a result of a transition to newer more expensive therapies.

Methods: A population-level incident GN cohort (n=2983) was created by linking 3 provincial databases in British Columbia: pathology (includes all kidney biopsies), renal (includes clinical and laboratory characteristics) and PharmaNet (includes all medications with costs). This cohort captures the treatment costs of all GN patients in BC from 2000-2013.

Results: The annual IS treatment cost per patient increased 6.8x from $205 in 2000 to $1,394 in 2013 (p<0.001). The contribution of each medication to increasing costs over time varied by GN type.



Overall, the yearly cost of azathioprine per patient increased slightly ($12 to $32 p<0.001), whereas prednisone/cyclophosphamide decreased ($32-125 to $22 p=0.002 and <0.001). MMF, calcineurin inhibitors and rituximab had the largest cost increases ($0-26 to $417-455 each, p<0.001). In 2000, they constituted only 17.6% of costs; this increased to 94.5% in 2013 but was used to treat only 40.8% of patients.

Conclusions: We describe for the first time the real-world population-level cost of IS treatment for GN, and have demonstrated a striking increase in costs due to the use of newer/more expensive therapies. Our results suggest that efforts to improve cost-effectiveness will need to focus on the minority of patients treated with disproportionately expensive therapies.

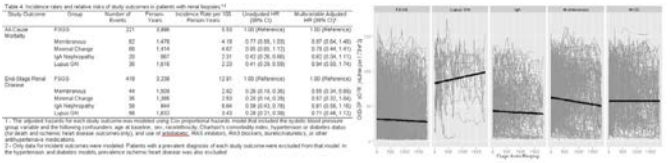
TH-PO844

Incident ESRD and eGFR Decline among the Most Common Glomerulopathies (GN): The Kaiser Permanente Southern California (KPSC) Cohort John J. Sim,[1] Michael Batech,[2] Teresa N. Harrison,[2] Sally F. Shaw,[2] Sejal Vora,[3] Aviv Hever.[1] *[1]Nephrology and Hypertension, Kaiser Permanente Los Angeles Medical Center; [2]Research & Evaluations, Kaiser Permanente Southern California; [3]Mallinckrodt Pharmaceuticals.*

Background: While GN is an important contributor to ESRD and morbidity/mortality outcomes, the clinical course is often variable among and within different GN. Within an integrated health system, we sought to evaluate and compare eGFR decline and incident ESRD rates in patients with focal nephrosclerosis (FSGS), membraneous GN (MGN), minimal change disease (MCD), IgA nephropathy (IGAN) and lupus nephritis (LN).

Methods: Retrospective longitudinal cohort study in the period 1/1/2000 through 12/31/2013 among patients within KPSC who had biopsy proven primary GN, were characterized and followed using serial laboratory measurements until they reached the outcome of ESRD (hemodialysis, peritoneal dialysis, transplant). All eGFR's measured at and subsequent to biopsy were used to evaluate trend of eGFR. Medications prescribed within 180 days of biopsy were extracted.

Results: Among 2226 GN patients (FSGS 46%, MGD15%, MCD12%, IGAN12%, LN15%) with mean follow up of 3.9yrs, 609 (27%) progressed to ESRD. Preemptive transplant occurred in 2.6%. Steroids (39.6%), calcineurin inhibitors (4.6%), MMF (3.3%) and alkylating agents (2.7%) were the most frequent initial treatments. FSGS had the highest ESRD incidence rate at 12.9 followed by IGAN 6.6, LN 3.4, MGN 2.9, and MCD 2.5 (per 100 person-yrs). LN was the only GN that had improvement in eGFR slope after biopsy whereas MGN had the steepest decline.



Conclusions: Among a large racially/ethnically diverse GN population within a routine treatment environment, FSGS patients had the highest rate of progression to ESRD, while MGN patients were observed to have the steepest decline and LN patients appeared to have the best treatment response based on eGFR trends.

Funding: Pharmaceutical Company Support - Mallinckrodt Pharmaceuticals

TH-PO845

Light Chain Amyloidosis and Light Chain Deposition Disease - Single Centre Treatment Results Elena Zakharova.[1,2] *[1]Nephrology, City Clinical Hospital n.a. S.P. Botkin, Moscow, Russian Federation; [2]Nephrology, State Univ of Medicine and Dentistry n.a. A.I. Evdokimov, Moscow, Russian Federation.*

Background: Treatment approaches to AL amyloidosis and Light Chain Deposition Disease (LCDD) evolved over last decades. In 2012-2013 the term "monoclonal gammopathy of renal significance" (MGRS) was introduced, and treatment strategies for MGRS recommended by International Kidney and Monoclonal Gammopathy Research Group.

Methods: We analysed retrospectively the data for patients with biopsy-proven AL amyloidosis and LCDD, treated with chemotherapy in 2001-2015. Study group of 49 patients was divided in 3 treatment subgroups: 1) oral melphalan-based regimens - 20 (40.8%); 2) high-dose melphalan/autologous stem cell transplantation (HDM/ASCT) - 7 (14.2%); 3) bortezomib-based regimens - 22 (44.8%).

Results: 26 (53%) males and 23 (47%) females, median age 59 [48; 64.5] years, median duration from the disease onset 12 [6; 24], median follow-up 12 [4; 29] months. Clinical presentation shown in Table.

Kidneys only pts n (%)	14 (28.5)
Kidneys and heart pts n (%)	11 (22.4)
Multiorgan involvement n (%)	24 (48.9)
Nephrotic syndrome pts n (%)	39 (79.5)
Median proteinuria g/L	5.0 [3.2; 6.7]
CKD stage 2-4 pts n (%)	23 (46.9)
Median serum creatinine μmol/L	121.5 [95.2; 176.7]
Nephrotic syndrome and CKD stage 2-4 pts n (%)	16 (32.6)

46.9% achieved haematological remission (HR), 36.7% - organ remission (OR). Rate of HR was significantly higher in the subgroup 2 compared to subgroups 1 and 3 (85.7% vs 40.0% and 40.9% respectively, p<0.05), OR rate did not differ between the subgroups. 5-year kidney survival was 73%, 100% and 70%, patient's survival - 32%, 33% and 70%, cumulative patient's and kidney survival - 14%, 33% and 14% in the subgroups 1, 2 and 3 respectively, all differences were not significant.

Conclusions: Majority of our patients presented with severe nephrotic syndrome, impaired kidney function and multiorgan damage. However, under chemotherapy about half of them achieved haematological remission, and more than one third - organ remission, with significantly better results after HDM/ASCT. 5-year cumulative patient's and kidney survival did not exeed 33% even in HDM/ASCT subgroup.

TH-PO846

Long Term Renal Outcomes and Clinical Associations of Scleroderma Renal Crisis: A Retrospective Case/Control Study Sarah M. Gordon, Dustin J. Little, Rodger S. Stitt, Wayne Bailey, Jess D. Edison, Stephen W. Olson. *Nephrology, Walter Reed National Military Medical Center, Bethesda, MD.*

Background: Scleroderma (SSc) has a heterogeneous clinical presentation with potential multisystem organ involvement and known associations with cancer and thyroid disease. Scleroderma renal crisis (SRC) is a severe complication of SSc. Few previous studies have compared SRC cases to SSc without SRC disease controls (SSc w/o SRC DC) and none have reported the long term renal outcomes for SRC patients not requiring renal replacement therapy (RRT) or characteristics at the time of SSc diagnosis that associate with future SRC.

Methods: 53 SRC cases and 204 SSc w/o SRC DC were identified, and comprehensive clinical and laboratory data was collected using the military electronic medical record. Comparisons were made between SRC cases and SSc w/o SRC DC for multiple clinical and laboratory findings both at SSc diagnosis and throughout disease progression. Fisher's Exact test and the student's t-test were used for statistical analysis.

Results: SRC cases that did not require chronic RRT experienced a similar mean change in GFR per year compared to SSc w/o SRC DC (+0.3 vs. -0.02 cc/min/yr, p=0.7). SRC patients had a higher incidence of proteinuria (75% vs. 6%, p<0.001), a higher median ESR (37 vs 12, p<0.001), and a lower hemoglobin (11.7 vs. 13.7, p<0.001) at initial SSc diagnosis than SSc w/o SRC DC. SRC cases had higher lifetime rate of cancer (21% vs. 7%, p<0.001), thyroid disease (38% vs. 14%, p<0.001), pulmonary hypertension (39% vs. 17%, P<0.001), pericarditis (23% vs. 6%), and anti-RNA polymerase III antibody (39% vs. 14%) than SSc w/o SRC DC.

Conclusions: SRC patients that do not require chronic RRT have stable long term renal function. Proteinuria, anemia, and elevated ESR at initial SSc diagnosis are associated with future SRC. SRC is specifically associated with cancer, thyroid disease, and pulmonary hypertension. Our retrospective findings could be utilized to develop a model to more accurately identify SSc patients at high risk for SRC. Patients with an SRC diagnosis may benefit from earlier and more aggressive screening for cancer and thyroid function. Prospective confirmation is required.

TH-PO847

The Diagnosis of Renal Amyloidosis Using Laser Microdissection and Liquid Chromatography–Mass Spectrometry Michiko Aoki, Dedong Kang, Ai Katsuma, Yusuke Okabayashi, Takafumi Kanemitsu, Yusuke Kajimoto, Kiyotaka Nagahama, Akira Shimizu. *Nippon Medical School, Bunkyo-ku, Tokyo, Japan.*

Background: In our department, renal amyloidosis of kidney biopsies have been diagnosed by congo-red stain, immunofluorescence (IF) for immunoglobulin light (L) and heavy (H) chains, immunostaining for amyloid A, transthyretin, and β2-microglobulin. Recently liquid chromatography tandem mass spectrometry (LCMS/MS) technique began to be performed to detect the amyloid precursor proteins.

Methods: We selected 18 cases of AL amyloidosis that were diagnosed by serum immunoelectrophoresis (SIEP) and biopsy samples with congo-red stain, IF, and immunostaining for amyloid A, from a series of renal biopsies in our department from 1999 to 2014. We examined the component proteins in deposited amyloid in formalin fixed paraffin embedded tissues using laser microdissection of glomeruli and LCMS/MS. These results were compared with the results of SIEP and findings of IF.

Results: In AL amyloidosis which was previously diagnosed using SIEP and biopsy samples with congo-red stain, IF, and immunostaining for amyloid A, LCMS/MS detected AL amyloidosis in 12/18 cases (66.7%), AHL amyloidosis in 5 /19 cases (27.8%), and AH amyloidosis in 1/18 cases (5.5%). In 5 cases (27.8%), monoclonal immunogloburin in serum could not detected by SIEP. Furthermore, in IF, all cases had irregular non-specific immunoglobulin L and H chains and complement components in our cases. LCMS/MS could detect the component proteins in amyloid deposition even in the cases that had less than 5% area of amyloid deposition in glomeruli.

Conclusions: In our cases, non-specific staining for immunoglobulin L and H chains was seen in AL amyloidosis. In addition, ALH and AH amyloidosis could not be diagnosed by SIEP and IF for immunoglobulin L and H chains. LCMS/MS is very helpful for diagnosis of amyloidosis, especially for AHL and AH amyloidosis.

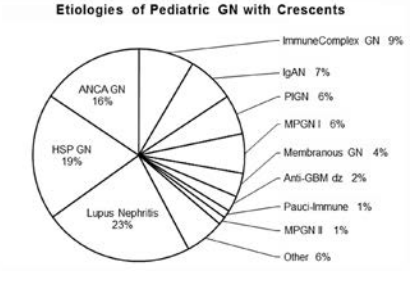
TH-PO848

Crescentic Glomerulonephritis in Children: A Midwest Pediatric Nephrology Consortium Study Joseph George Maliakkal,[1] Michelle N. Rheault,[3] Jason Misurac,[4] Joseph T. Flynn,[5] William E. Smoyer,[2] Scott E. Wenderfer,[1] Guillermo Hidalgo.[6] *[1]Pediatric Nephrology, Baylor College of Medicine, Houston, TX; [2]Nationwide Children's Hospital, Columbus, OH; [3]Univ Minnesota, Minneapolis, MN; [4]Univ Iowa, Iowa City, IA; [5]Seattle Children's Hospital, WA; [6]East Carolina Univ, Greenville, NC.*

Background: Crescents on kidney biopsy predict poor prognosis in acute glomerulonephritis (GN). The clinical presentation and etiology of crescentic GN in children have not been well studied for over 30 years.

Methods: Children <21 years old from 4 centers who presented after Jan. 2004 with >1 crescent on kidney biopsy were enrolled in a multi-center registry. Demographic, clinical, laboratory, and kidney biopsy findings were collected.

Results: The registry includes 83 patients (40% Hispanic, 36% Caucasian, 21% African American), with median age at presentation of 12 years (range 1-18). At presentation, 64% were hypertensive and 21% had pulmonary involvement. Estimated GFR was <60mL/min/1.73m2 in 58% of patients at time of biopsy. Median proportion of glomeruli with crescents was 16% (IQR 8-28%). Histological diagnoses are listed in the Figure.



Patients with anti-glomerular basement membrane (GBM) disease had the greatest proportion of crescents (66%). Renal replacement therapy (RRT) at presentation was required in 11% of all patients and in 50% of patients with anti-GBM disease. The proportion of crescents on biopsy was significantly higher in patients requiring RRT at presentation (58%) compared to those who did not (21%, p=0.002).

Conclusions: The prevalence of glomerular diseases in US children that manifest with crescentic glomeruli is changing. The proportion of crescents was associated with a need for RRT at presentation. Continued investigation of this cohort will improve our understanding of the presentation, optimal evaluation and management of pediatric patients with crescentic GN.

TH-PO849

Recruitment of Plasmacytoid Dendritic Cell to Renal Ectopic Germinal Center in Primary Sjögren Syndrome with Tubulointerstitial Injury

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Background: Renal involvement of Primary Sjögren syndrome (pSS) is predominated by tubulointerstitial injury (pSS-TIN). Large sample clinicopathological studies are sparse and mechanisms underlying renal damage remain to be elucidated. This study aimed to evaluate ectopic germinal center (EGC) formation, recruitment of pDC and mDC, and activation of B cell chemokine CXCR5 in pSS-TIN, and to analysis the factors affecting eGFR long term prognosis.

Methods: From 1993 to 2015, 64 pSS patients were diagnosed with tubulointerstitial lesions by renal biopsy in a single center of Beijing. EGC ($CD21^+$), pDC ($BDCA\text{-}2^+$), mDC ($DC\text{-}SIGN^+$) and CXCR5 were identified by immunohistochemistry staining. Peripheral pDC ($Lin\text{-}^-HLADR^+CD123^+$) and mDC ($Lin\text{-}^-HLADR^+CD11c^+$) were evaluated by flow cytometry.

Results: pSS-TIN patients were mostly middle-aged female. eGFR (56.3±29.5ml/min/1.73m^2) was independently correlated with age (R^2=0.102, 95%CI(-1.592, -0.357), p=0.003), glomerular sclerosis index (R^2=0.099, 95%CI(-77.261, -12.381), p=0.008) and tubulointerstitial leision (R^2=0.457, 95%CI(-20.780, -2.306), p=0.016). 15.6% had EGC in renal interstitium. Both pDC and mDC were detected in EGC, but only pDC had a higher prevalence (semiquantatively scoring 2.0±0.9 vs. 1.1±0.3, p=0.025) comparing to patients without EGC. Peripheral pDC decreased significantly in pSS with renal involvement than health control (0.01±0.00% vs. 0.07±0.05%, p=0.001). $CXCR5^+$ cell infiltration was more prominent in the presence of EGC and was mainly near the adjacent vessels. 93.8% received glucocorticoid and 45.3% received immunosuppresant treatment. Patients were followed up for median 38.0 monthes. eGFR improved from 56.3±29.5 to 72.3±26.7ml/min/1.73m^2 in 1 year and remained stable in the following 3 years. eGFR at renal biopsy is the sole risk factor affecting long term renal function (R^2=1.024, 95%CI(1.012, 1.036), p<0.001).

Conclusions: EGC were detected in renal interstitium of pSS-TIN, with pDC recruitment from peripheral blood and increased CXCR5 expression. It may participate in renal tubulointerstitial injury.

TH-PO850

Genetic Changes Predisposing to Complement Dysregulation and Infection May Play Role in a Case of Atypical Hemolytic Uremic Syndrome

Elena Volokhina,[1] Birendra Singh,[2] Martin Kömhoff,[3] Marcin Okroj,[4] Nicole Van De Kar,[1] Kristian Riesbeck,[2] Anna Blom,[2] Lambertus P.W.J. Van den Heuvel.[1,5] *[1]Radboud Univ Medical Center, Nijmegen, Netherlands; [2]Lund Univ, Malmo, Sweden; [3]Univ Medical Centre Groningen, Groningen, Netherlands; [4]Medical Univ of Gdansk, Gdansk, Poland; [5]Univ Hospitals Leuven, Leuven, Belgium.*

Background: Hemolytic uremic syndrome (HUS) is a major cause of renal failure in childhood. Most cases are caused by infection with Shiga-toxin producing *Escherichia coli* (STEC). In 5-10% of cases, HUS is not preceded by the STEC infection and is considered atypical (aHUS). These cases are strongly associated with genetic defects leading to dysregulation of the complement system. Often aHUS is triggered by a non-STEC infection, however, genetic predisposition to such infections in aHUS has not yet been sufficiently addressed. Here we present genetic analysis of a 2 months old patient with *Bordetella pertussis* infection, followed by aHUS.

Methods: DNA analysis was performed by Sanger sequencing, analysis of autoantibodies to CFH was performed by ELISA. Recombinant vitronectin variants were produced in HEK293T cells, purified and used in hemolytic assay with sheep erythrocytes and purified C5b-6, C7, C8 and C9 complement proteins.

Results: The patient carried a previously described p.Ala43Thr variant in thrombomodulin that alters complement regulation, but had no abnormalities in CFH, CFI, MCP, C3 and CFB or autoantibodies to CFH. In search of the new genes in etiology of aHUS, we screened the patient´s DNA for aberrations in complement inhibitor vitronectin and discovered a rare heterozygous variant p.Arg229Cys. Prediction software (SIFT, PolyPhen-2) indicated it as likely pathogenic. *In vitro* experiments using recombinant vitronectin variants have shown that this mutation enhances complement inhibition.

Conclusions: A rare vitronectin change could have contributed to the severe development of *B. pertussis* infection. Our work indicates that a genetic cause may contribute to aHUS not only by a well-known effect of complement dysregulation, but also by enhancing vulnerability to infections.

Funding: Government Support - Non-U.S.

TH-PO851

The CureGlomerulonephropathy (CureGN) Cohort Study: Enrollment Characteristics to Date

Laura H. Mariani, Andrew S. Bomback, Michelle A. Hladunewich, Michelle N. Rheault, Dana Rizk, Michael F. Flessner, Lisa M. Guay-Woodford. *On Behalf of the CureGN Consortium.*

Background: In minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), and IgA nephropathy (IgAN)/Henoch-Schonlein Purpura (HSP), challenges to studying underlying mechanisms, biomarkers and new therapies include the rarity of each diagnosis and slow progression, which together may require decades of follow-up to measure the effectiveness of interventions on ESKD or death.

Methods: CureGN is a 64-center prospective cohort study of children and adults with biopsy-proven MCD, FSGS, MN or IgAN/HSP. Target recruitment is 2,400 patients with first diagnostic kidney biopsy within 5 years of enrollment. Patients with ESKD, other organ transplant, or secondary causes of kidney disease (diabetes, lupus, HIV, active malignancy, hepatitis B or C) are excluded. Study visits occur 4 times in the first year and 3 times per year thereafter.

Results: As of May 2016, 1,223 (255 MCD, 306 FSGS, 221 MN, 441 IgAN including 87 with HSP) patients have been enrolled. 32% (n=396) are 'incident,' as defined by diagnostic biopsy within 6 months of enrollment. Median (IQR) of time since biopsy is 1.2 (0.3-2.8) yrs at enrollment. 36% are <18 years old (n=445 pediatric patients; 166 MCD, 107 FSGS, 17 MN, 155 IgAN/HSP). 41% are male, 13% Hispanic, 68% White/Caucasian, 15% Black, 7% Asian and 2% multi-race. 27% reported a family history of kidney disease. Table 1 provides an overview of medication exposure, enrollment kidney function and proteinuria by diagnosis.

TABLE 1	Overall* (n=930)	MCD (n=198)	FSGS (n=214)	MN (n=176)	IgAN** (n=342)	HSP (n=73)
% Exposed to immunosuppression prior to enrollment	74%	94%	71%	76%	62%	82%
% On immunosuppression at enrollment	52%	79%	55%	47%	39%	60%
eGFR*** (median [IQR], mL/min/1.73m2)	85 (47, 113)	114 (89, 136)	67 (36, 100)	66 (42, 95)	85 (44, 112)	108 (88, 119)
UPCR (median [IQR], mg/mg)	1.3 (0.2, 3.6)	0.5 (0.1, 4.4)	2.1 (0.6, 4.6)	2.6 (1.1, 5.3)	0.7 (0.2, 1.8)	0.6 (0.2, 2.2)

*Participants with completed enrollment visit
**Excludes IgAN with HSP
***CKD-Epi formula for participants ≥18yo; modified CKiD-Schwartz formula for <18yo

Conclusions: CureGN enrollment now exceeds 50% of target. Robust clinical data combined with serial biosamples from a diverse group of adults and children with MCD, FSGS, MN, and IgAN will be a valuable resource for researchers in glomerular disease and platform for ancillary studies.

Funding: NIDDK Support, Private Foundation Support

TH-PO852

Safety and Effectiveness of Restrictive Eculizumab Treatment in Atypical Hemolytic Uremic Syndrome

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Background: Atypical hemolytic uremic syndrome (aHUS) is a rare, but severe form of thrombotic microangiopathy, characterized by hemolytic anemia, thrombocytopenia, and acute renal failure, as a consequence of complement dysregulation. Atypical HUS has a poor outcome with mortality up to 10% and over 50% of patients developing end stage renal disease. Since the end of 2012, these outcomes have drastically improved with the introduction of eculizumab. The European Medicines Agency has approved eculizumab as lifelong treatment in aHUS patients. However, there is no hard evidence to support this advice. Historically, a substantial number of aHUS patients were weaned of plasma therapy, often without disease recurrence. Moreover, the long-term consequences of eculizumab treatment are unknown. Here we describe a case series of 16 aHUS patients treated with a restrictive treatment regimen of eculizumab.

Methods: All patients with aHUS who presented in the Radboudumc in the Netherlands, between 2012-2016, and who received eculizumab treatment, according local practice, are described. Clinical, diagnostic, genetic and follow up data were gathered and reviewed.

Results: Of the 16 patients (10 adults, 6 children) who presented with aHUS since 2012, 15 received restrictive eculizumab therapy. Therapy was either gradually withdrawn (n=4) or discontinued (n=11). Two patients, both known with factor H mutation, experienced recurrence of aHUS after therapy discontinuation. Due to close monitoring, recurrence was detected early, eculizumab was restarted, and no clinical sequela such as proteinuria or diminished kidney function were detected subsequently. In total, eculizumab could be safely discontinued in 9 patients of which 6 are event free for over a year now. With this strategy approximately €7.5 million has been saved.

Conclusions: A restrictive eculizumab regimen in aHUS is safe and effective. Future studies should focus on finding reliable predictors of disease recurrence.

TH-PO853

Investigating the Role of Connective Tissue Growth Factor (CTGF) Antagonism on Renal Outcomes in Cryoglobulinaemia

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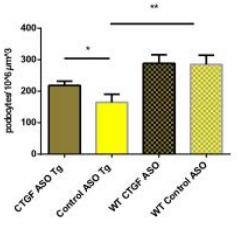
Background: Transgenic thymic stromal lymphopoeitin (TSLP Tg) mice develop membranoproliferative nephritis secondary to cryoglobulinaemia. We have shown high circulating levels of CTGF in these animals and attenuation of disease following use of CTGF antisense oligonucleotide(ASO) therapy in a pilot study. We now describe the impact of CTGF antagonism on renal parameters.

Methods: 32 TSLP Tg animals were treated with weekly ip CTGF or control ASO therapy (50mg/kg) for 10 weeks. Renal parameters were evaluated.

Results: Mice that received CTGF ASO had significantly lower proteinuria for the duration of therapy compared to control ASO ($p<0.001$). Glomerular mesangial expansion score was significantly reduced in CTGF ASO compared with control ASO treated (1.456 ±0.3105 vs 2.078 ±1.038, p=0.0159) Podocytes were identified by IHC for p57, and their density morphometrically quantitated



WT mice had preserved podocyte density that was unaffected by ASO therapy (CTGF ASO treated 288.3 +/- 67 vs control ASO treated 285+/- 73 podocytes/10^6 µm^3), while TSLP-Tg control ASO mice had significantly reduced podocyte density which was significantly ameliorated by CTGF ASO treatment (control ASO treated 164.8 +/- 57vs CTGF ASO treated 218 +/- 35 podocytes/10^6 µm^3). In addition, podocyte CTGF expression was significantly lower in CTGF ASO treated mice compared with untreated mice(proportion glomeruli with CTGF expression 0.3333 ± 0.5164 vs 0.8333 ± 0.4082, p=0.0462 respectively).

Conclusions: This study demonstrates that antagonism of CTGF leads to amelioration of glomerular injury and podocyte preservation in cryoglobulinaemic MPGN and may represent a future therapeutic target.

TH-PO854

Clinical and Histological Differences between PR3-ANCA and MPO-ANCA Vasculitis in a Spanish Cohort Montserrat M. Diaz Encarnacion,[1] Helena Marco,[2] Xavier Fulladosa,[3] Gema Fernandez Juarez,[4] Luis F. Quintana,[5] Manuel Praga,[6] Jose Ballarin.[7] *[1]Fundacio Puigvert, Barcelona; [2]H.U Germans Trias i Pujol, Barcelona; [3]H.U Bellvitge, Barcelona, Barcelona; [4]H.U Foundation Alcorcón, Alcorcon, Madrid; [5]HU Clínic, Barcelona; [6]H.U 12 Octubre, Madrid; [7]Fundacio Puigvert, Barcelona.*

Background: There are significant differences between patients with ANCA-PR3 and MPO, which have been reinforced by genetic studies in recent years. The aim of this study is to analyse demographics difference and prognostic values of ANCAS Serotypes in a Spanish cohort.

Methods: 304 patients with positive ANCA vasculitis diagnosed in 12 Spanish centers between 1978-2014. Clinical/laboratory variables, renal function, renal biopsy, presence of recurrences, severe infections, leukopenia and renal / patient survival are evaluated. Chi-square test, likelihood ratio test, Kruskal-Wallis test and the Kaplan-Meier curve when appropriate is used.

Results: 304 patients, 82% MPO ANCA-positive and 18% ANCA-PR3 positive patients were included. PR3 positive patients were younger ($p = 0.001$) and higher proportion of men ($p <0.001$) than MPO positive patients. PR3 patients had a higher number of affected organs ($p <0.001$), highlighting a greater involvement of lungs ($p <0.001$) and respiratory tract ($p <0.001$) compared MPO. No differences in initial mean creatinine levels between PR3 and MPO, although renal biopsy showed more active lesions in PR3 patients. There was no difference in the need for dialysis during follow-up (29% vs 34%, $p = 0.519$), although we observed a higher percentage of patients with GFR> 60 ml / min in PR3 patients (31.9% vs14.6% $p = 0.01$). PR3 patients had more relapses than MPO patients (36% VS19% $p = 0.014$). There were no differences in the presence of other complications or patient survival.

Conclusions: These results show that clinical presentation and histology class are different depending on ANCAS serotype. Also we have found a higher rate of relapse in patients PR3, This could have therapeutic implications, specially at the level of maintenance therapy.

TH-PO855

Long Term Outcomes of Kidney Transplantation in Patients with End Stage Renal Disease due to Pauci-Immune Glomerulonephritis Sophia Lionaki,[1] Konstantinos Panagiotellis,[1] Nikolaos Altanis,[1] Ilias Makropoulos,[1] George Liapis,[2] Georgios Zavos,[3] John N. Boletis.[1] *[1]Nephrology, Laiko Hospital, National & Kapodistrian Univ of Athens, Faculty of Medicine, Athens, Greece; [2]Pathology, Laiko Hospital, Athens, Greece; [3]Transplantation Unit, Laiko Hospital, Athens, Greece.*

Background: To evaluate the long term outcomes of kidney transplantation (KTx) in patients with end stage renal disease (ESRD) due to pauci-immune glomerulonephritis (PIGN), in comparison with patients with primary diseases (PD) of non-autoimmune nature.

Methods: We retrospectively studied all patients with ESRD due to PIGN, transplanted in our hospital between 1995-2014, with a follow up of 1 year post KTx or more. Demographics, clinical, and laboratory data were recorded. For comparisons reasons, a control group, consisted of patients with PD of non-autoimmune origin, matched for age, gender, donor source, and KTx date was selected.

Results: 21 patients with PIGN as PD were identified. Of these, 12(95.2%) were ANCA positive at PIGN diagnosis. 14(66.5%) had developed rapidly progressive disease at presentation. The baseline characteristics of the two groups were similar.

Parameter, (mean±sd) or %	Patients with PIGN N=21	Control group N=71	p-value
Donor age (years)	55.4(±14.25)	53.95(±16.6)	0.74
Time in dialysis (months)	78.3(±69.6)	57(±38.9)	0.08
Induction with anti-CD25	95.2	93	0.88
Maintained with a calcineurin inhibitor, mycophenolic acid and steroids	85.7	97.2	0.28
Follow up (fup) post KTx (months)	81.9(±55.6)	65.0(±27.3)	0.06
Ser.creatinine at end of follow up (mg/dl)	1.9(±1.4)	1.4(±0.7)	0.03
Acute rejection	10.5	15.7	0.7
Survival with functioning graft	90.5	97	0.24
Graft failure	9.5	1.5	0.14
Infection requiring hospitalization	95.2	51.5	0.0004

Serum creatinine and eGFR were lower in patients with PIGN compared to controls, but graft survival was similar between them.

Conclusions: Graft function of patients with ESRD due to PIGN, was inferior from that of patients with a PD of non-autoimmune origin at end of follow up, but this fact had no impact on graft survival. Infections requiring hospitalization were more frequent among patients with PIGN.

TH-PO856

Fast Development of Iron Deficient Anemia and Heart Failure in a Rat Model of CKD-MBD: A Suitable Model to Study the Cardiorenal Syndrome Anja Verhulst, Ellen Neven, Patrick C. D'Haese. *Pathophysiology, Univ of Antwerp, Antwerp, Belgium.*

Background: Cardiorenal syndrome (CRS) is an umbrella term covering disorders of the heart and the kidneys whereby dysfunction of the one organ may induce dysfunction of the other. Despite advances in treatment of both (chronic) kidney disease (CKD) and cardiovascular disease (CVD), CRS remains a major health problem. The current study aimed at optimizing an animal model mimicking CRS in order to allow experimental evaluation of new treatment strategies.

Methods: An adenine (0.25%) supplemented, high phosphate (P) diet was administrated to 56 male Wistar rats, which were sacrificed at different time-points: 3,4,5,6,7 and 8wks (n= 8 or 10/group) after start of adenine treatment. Control animals (n=4, standard diet) were sacrificed at 8wks. Blood samples were taken at 2,4,6 and 8wks. The following aspects of CRS where studied: CKD, mineral-bone disorder (MBD), CVD and (iron deficient) anemia. Hereto the following parameters were followed-up during the study: serum creatinine (crea), -Ca, -P, -FGF23, dynamic bone parameters, aortic Ca deposits, heart weight, serum NT-proANP, Hct, Hb, retyculocytes, spleen iron, serum hepcidin.

Results: Serum crea, P and FGF23 showed a statistically significant increase and –Ca a decrease after respectively 2,6, 4 and 2wks. These parameters became more severe during the course of the study and thus evidenced the development of a severe CKD and disturbed mineral balance. CKD-related complications developed from week 5 on; significantly increased bone turn over and aorta calcification (von Kossa positive staining). Moreover the animals promptly (wk2) developed a serious iron deficient anemia as evidenced by significantly steep decreases in Hct, Hb and reticulocyte levels and significant, steep increases in serum hepcidin and spleen iron. Finally the animals developed heart failure as demonstrated by significantly and steadily increasing heart weight (relative to whole body weight) and significantly increased NT-proANP levels.

Conclusions: The proposed animal model for the first time will allow to study CRS in all its aspects and will be useful to concomitantly evaluate effects of new treatment strategies on the various aspects of CRS.

Funding: Government Support - Non-U.S.

TH-PO857

Inadequate Vitamin D and Risk for Anemia in the CKiD Cohort Kathleen Elizabeth Altemose,[1] Juhi Kumar,[2] Anthony A. Portale,[3] Bradley Warady,[4] Susan L. Furth,[5] Jeffrey J. Fadrowski,[1] Meredith A. Atkinson.[1] *[1]Johns Hopkins Univ; [2]Weill Cornell Medical College; [3]Univ of California San Francisco; [4]Children's Mercy Hospital; [5]Children's Hospital of Philadelphia.*

Background: Inadequate 25-hydroxyvitamin D (25D) levels are common in children with chronic kidney disease (CKD), and are associated with increased risk for anemia in healthy children. This association has not been explored in children with CKD.

Methods: Cross-sectional analysis of 25D and hemoglobin (Hgb) in 580 children in the Chronic Kidney Disease in Children (CKiD) study. Anemia = Hgb < 5th%ile for age/sex. Inadequate 25D = 25D < 30 ng/ml. GFR measured via plasma disappearance of iohexol. Linear regression analyses examined the association between Hgb, risk for anemia and 25D level. Logistic regression analysis examined the association between risk for anemia and inadequate 25D. Models adjusted for race, BMI, GFR, treatment with iron or an ESA, and age/sex (linear models with Hgb only).

Results: Median (IQR) age of cohort was 11 (8,15) yrs, 63.1% male. Median 25D was 28.3 (19.8, 35.3) ng/ml with 57.6% inadequate.

Median (IQR) or %	25D <30 ng/ml (n=334)	25D Sufficient (n=246)	p-value
Age (yrs)	13 (9,15)	9 (6,13)	<0.001
Male	64.1	61.8	0.57
Race			<0.001
W	58.4	81.1	
B	23.7	3.7	
Other	18	14.2	
BMI (kg/m^2)	20.1 (16.7, 24.4)	17.2 (15.8, 19.3)	<0.001
GFR (ml/min/1.73m^2)	48.1 (28.9, 67.6)	43.1 (28.2, 62.9)	0.09
Hgb (g/dL)	12.7 (11.6, 13.7)	12.8 (11.9, 13.6)	0.37
Anemic	28.4	17.1	0.001
On ESA	9.9	10.6	0.79
On iron	23.4	30.1	0.07

In linear regression, each 1 ng/ml increase in 25D was associated with a 0.2 g/dl increase in Hgb (p=0.001) and decreased anemia risk (OR 0.97, 95% CI 0.95-0.99, p<0.01). Inadequate 25D was associated with twice the risk for anemia compared to subjects with 25D levels >= 30 ng/ml (OR 2.02, 95% CI 1.29-3.17, p<0.01). Further adjustment for ferritin/TSAT among 285 subjects with levels available showed the increased risk for anemia in those with inadequate 25D remained significant: OR 2.15, 95%CI 1.05-4.40, p=0.04.

Conclusions: Inadequate 25D is associated with increased risk for anemia in children with CKD, identifying it as a potentially modifiable risk factor for the anemia of CKD.

Funding: Other NIH Support - T32 grant

TH-PO858

Anemia Profiles by Chronic Kidney Disease Stage in a Large National Cohort of Patients Yue Jiao,[1] Dugan Maddux,[1] Marta Reviriego-Mendoza,[1] John W. Larkin,[1] Len A. Usvyat,[1] Tomislav Kovacevic,[2] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Vifor Fresenius Medical Care Renal Pharma, Zurich, Switzerland.*

Background: Profiles of anemia in the different stages of chronic kidney disease (CKD) have not been fully defined. We aimed to determine the levels of hemoglobin (Hgb) and ferritin (Fer) by CKD stage in a large national cohort of patients who did not require dialysis.

Methods: The Fresenius Medical Care CKD Data Registry was utilized to analyze data from 349,420 patients from 2013 to 2015. For CKD stage 3, 4, and 5 patients, we calculated the mean annual Hgb and Fer levels, as well as, the percent (%) of patients with Hgb <11g/dL, Hgb <12g/dL, Fer <100ng/mL, Fer <200ng/mL, Hgb <11g/dL & Fer <100ng/mL, Hgb <11g/dL & Fer <200ng/mL, Hgb <12g/dL & Fer <100ng/mL, and Hgb <12g/dL & Fer <200ng/mL.

Results: Overall, we observed that Hgb levels decrease, and Fer levels rise with advancing CKD. In CKD stage 5, 70% of patients exhibit Hgb levels are under 11g/dL, while 13% have Fer levels below 100ng/mL (Figure 1A). We also noted an inverse relationship between Hgb and Fer measurements; average Hgb levels decrease from 12.6 to 10.6g/dL as the patients' CKD stage progress from 3-5, while average Fer levels increase from about 200 to >400ng/mL from CKD stage 3 to 5 (Figure 1B).

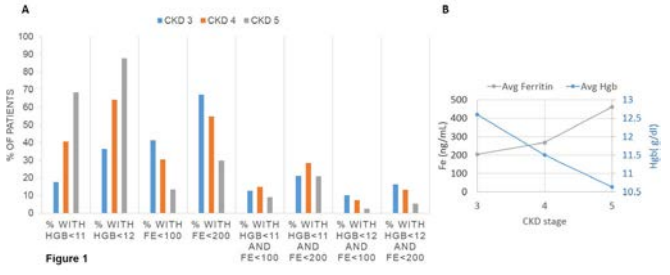


Figure 1

Conclusions: Our data shows a persistent decrease in Hgb levels with the progression to later stages of CKD in patients not on dialysis. Despite this, Fer levels increase with the advancement of CKD; this may be reflecting an increasing inflammatory status with the progression of CKD, or could be secondary to intravenous (IV) Fer regimens. Unfortunately, medication data was not readily available in this registry. Further investigations are needed to define the practice patterns for administration of ESA therapies and IV Fer therapies in pre-dialysis CKD stages 4 and 5.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-PO859

Association between 25-Hydroxyvitamin D Deficiency and Rapid Chronic Kidney Disease Progression Ha Yeon Kim,[1] Eun Hui Bae,[1] Seong Kwon Ma,[1] Kook-Hwan Oh,[2] Curie Ahn,[2] Soo Wan Kim.[1] *[1]Dept of Internal Medicine, Chonnam National Univ Medical School, Gwangju, Korea; [2]Dept of Internal Medicine, Seoul National Univ, Seoul, Korea.*

Background: 25-hydroxyvitamin D [25(OH)D] deficiency is highly prevalent in the chronic kidney disease (CKD) population, which is linked with cardiovascular events and mortality. Here we evaluated the relationship between 25(OH)D deficiency and the rapid declining in estimated glomerular filtration rate (eGFR) using KNOW-CKD cohort data.

Methods: In total, 1063 CKD patients were measured for the concentrations of 25(OH)D and creatinine with a follow-up of 4 years in a prospective multi-center cohort study of CKD patients in Korea. We divided the patients into two groups according to their serum 25(OH)D levels (deficiency group: 25(OH)D < 15 ng/ml, vs. non-deficiency group: 25(OH)D ≥ 15 ng/ml). Rapid progression was defined by the decline of eGFR over 5 ml/min/1.73m^2 per year (N=326) and as controls if decline of eGFR was under 1 ml/min/1.73m^2 per year (N=609).

Results: The average of decline in eGFR was 1.82 ml/min/1.73m^2 per year, maximum value of which was 53.8 ml/min/1.73m^2 per year. The mean of 25(OH)D was 16.8 ng/ml in the rapid progression groups, while that of the control group was 18.5 ng/ml. Univariate linear regression analysis showed that the rapid CKD decline was correlated with age, diabetes, serum albumin, 25(OH)D deficiency, cystatin C, and the albumin-to-creatinine ratio. Multiple analysis revealed that age, hypoalbuminemia, 25(OH)D deficiency, diabetes, and macroalbuminuria associated with rapid progression.

Conclusions: Vitamin D deficiency was associated with rapid eGFR decline in CKD patients. The results of this prospective cohort study suggest that vitamin D supplementation may significantly help the preservation of renal function in CKD patients.

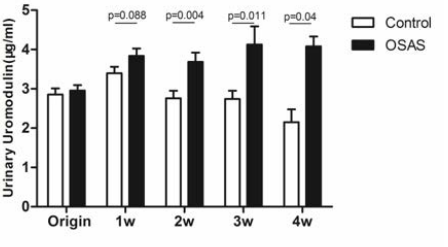
TH-PO860

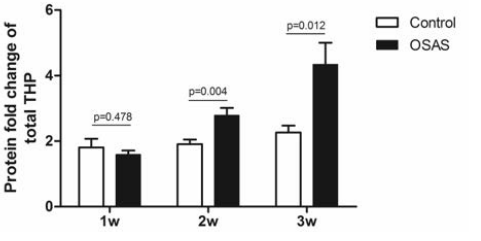
Uromodulin Mediated Hypoxia Induced Renal Injury Yaqin Wang, Kunjing Gong, Min Xia, Ying Liu, Yuqing Chen. *Dept of Nephrology, Peking Univ First Hospital, Beijing, China.*

Background: Increased urinary uromodulin level associated with high risk of CKD in general population. And excretion of uromudulin also increased in children with obstructive sleep apnea syndrome . Thus we hypothesized that uromodulin may be an earlier indicator of hypoxia injury to kidney and involved in the pathogenesis of hypoxia induced renal injury.

Methods: Totally eighty 12-week-old male SD rats were divided into OSAS and control groups. Rats in OSAS groups lived in a designed chamber, in which oxygen level changed from normal to low (10%) every 60 s for 8 h during daytime. We got 24-h urine and kidney tissue after 1, 2, 3 and 4 weeks. EM and LM were used to view structure of the rat kidney. Western blot was used to assay the expression of uromodulin. Rat urinary uromodulin level was determined using ELISA. We also use the cultured mIMCD3 to explore the regualtor of uromodulin under hypoxia.

Results: After 3-weeks of OSAS condition, no obvious injury was visualized under light microscope. However, we found more foot process fusion of podocytes, and more secondary lysosomes, vacuoles and mild swelling of mitochondria in tubular cells. We also identified an increased uromodulin secretion into urine and expression in tubuli after 1 week hypoxia in OSAS groups compared with controls.





In cultured mIMCD3 cells, the expression of uromodulin also started to increase after exposure of hypoxia condition for 6h, and continue to rise after 12h, 24h and 36h. HNF-1B is one of the transcription factors regulating UMOD transcription. Thus we inhibited HNF-1B expression of mIMCD3 cells with siRNA, but expression of uromodulin still increased under hypoxia condition.

Conclusions: Uromodulin increased earlier after kidney injury induced by hypoxia. Hnf-1b may not play a key role in hypoxia induced uromodulin expression.

Funding: Government Support - Non-U.S.

TH-PO861

Urinary miR-196a as a Risk Predictor for Progression to ESRD in Patients with FSGS Changming Zhang, Shao-Shan Liang, Shuiqin Cheng, Xia Wang, Cai-Hong Zeng, Chun-Xia Zheng, Zhihong Liu. *National Clinical Research Center of Kidney Diseases, Research Inst of Nephrology, Jinling Hospital, Nanjing, Jiangsu, China.*

Background: miR-196a is predominantly expressed in kidney and plays an important role in renal fibrosis, which is a factor for evaluating the prognosis of FSGS. Moreover, our previous study indicates correlation between urinary miR-196a and FSGS activity. In the present study, we attempted to investigate whether urinary miR-196a can serve as a predictor of disease progressionin patients with FSGS.

Methods: Urinary and plasma miR-196a were compared in patients with active FSGS (FSGS-A), FSGS in complete remission (FSGS-CR) and normal controls (NCs) using both testing set and validation set. Urinary miR-196a levels at the time of renal biopsy were also measured by qRT-PCR in 231 FSGS patients. The relationship between urinary miR-196a and the prognosis of FSGS was analyzed using Kaplan-Meier and Cox regression analysis.

Results: Urinary miR-196a levels were significantly increased in FSGS-A patients as compared with FSGS-CR patients and NCs in the testing set, as well as in the validation set. However, plasma miR-196a levels were similar among the three groups and there was no correlation between urinary and plasma miR-196a, suggesting that the change of urinary miR-196a was not due to the change of plasma miR-196a. Of the 231 patients, 43 patients developed ESRD during the follow-up period for at least 3 years. Urinary miR-196a levels were significantly higher in patients who progessed to ESRD than those with stable renal function. Urinary miR-196a at the time of renal biopsy was associated with proteinuria, eGFR, tubulointerstitial damage and the occurrence of ESRD. Kaplan-Meier analysis showed patients with higher urinary miR-196a levels had a worse renal outcome than those with lower urinary miR-196a levels. Multivariable Cox regression analysis additionally demonstrated urinary miR-196a was an independent risk factor for progression to ESRD.

Conclusions: Urinary miR-196a may serve as a potential biomarker for risk classification of FSGS patients, facilitating early identification of those who will subsequently develop ESRD.

TH-PO862

Urinary MicroRNAs as Biomarkers for Early Prediction of Radiation Nephropathy Sagar Bhayana, Feifei Song, Naduparambil K. Jacob. *Radiaton Oncology, The Ohio State Univ, Columbus, OH.*

Background: The risk of chronic kidney disease (CKD) is strongly associated with treatment associated late toxicities in cancer survivors. The early predictive biomarkers detecting kidney toxicity are still lacking. There has been heightened interest in the utility of extracellular miRNAs as minimally invasive biomarkers for early detection of a wide range of human pathologies. The goal of our study was to investigate miRNAs as potential early indicators of radiation induced kidney damage in rodents.

Methods: Three kinds of TBI regimen were used: 7.7 Gy (LD50 dose) for evaluation of time dependent changes, sublethal to lethal dose (2, 4, 6 & 8 Gy) for evaluation of dose response and a more complex fractionated regimen that was applied in clinic. Cell free miRNAs isolated from urine and serum were subjected to expression profiling using an amplification free hybridization based nCounter assay. Selected high counts miRNAs were further analyzed for their expression and localization by *in situ* hybridization.

Results: Over 40 miRNAs were detected in urine samples collected from mice and over 80 miRNAs were detectable in serum. Following acute single dose TBI, the expression of most microRNAs peaked at 6-8 hours post irradiation. Among them, miRNA-1224 and miRNA-714 were of particular interest because they also showed increase in their urinary levels in response to increase in doses (2, 4, 6, and 8 Gy) of TBI. Moreover, miRNA-1224 and miRNA-714 exhibited dose and time dependent changes following exposure to fractionated myeloablative regimen (6 x 2 Gy= 12 Gy). Specifically, the urinary miRNA-1224 and -714 were shown to be localized in the outer medulla by *in situ* hybridization, suggesting their proximal tubular origin.

Conclusions: Systematic profiling of cell-free urinary and serum miRNAs haveidentified biomarkers with potential to develop as biomarkers of toxicity response after TBI. In particular, our study demonstrated that outer medulla is the source of origin for molecules such as miRNA-1224 and miRNA-714 that exhibited clear dose response. Cell-free miRNAs detectable in urine and serum can serve as bioindicators of kidney toxicity in response to radiation and potential early predictors of late effects.

Funding: Other U.S. Government Support

TH-PO863

The Effect of Renin-Angiotensin-Aldosterone System Inhibitors on Clinical Outcomes in Severe Advanced Chronic Kidney Disease Yun Jung Oh,[1] Sun Moon Kim,[2] Su Mi Lee,[3] Ae Jin Kim,[4] Han Ro,[4] Jae Hyun Chang,[4] Hyun Hee Lee,[4] Wookyung Chung,[4] Ji Yong Jung.[4] *[1]Dept of Internal Medicine, Cheju Halla General Hospital, Jeju, Republic of Korea; [2]Dept of Internal Medicine, Chungbuk National Univ Hospital, Cheongju, Republic of Korea; [3]Dept of Internal Medicine, Dong-A Univ Hospital, Busan, Republic of Korea; [4]Dept of Internal Medicine, Gachon Univ Gil Medical Center, Incheon, Republic of Korea.*

Background: The renin-angiotensin-aldosterone system (RAAS) blockades have been considered to slow renal progression in chronic kidney disease (CKD) patients. However, whether the habitual use of RAAS inhibitors affects renal progression and outcomes in pre-dialysis advanced CKD patients remains uncertain.

Methods: From a total of 2,076 pre-dialysis patients with advanced CKD stage 4 or 5, RAAS blockade users were paired with non-users for analyses using inverse probability of treatment weighted (IPTW) and propensity score (PS) matching. The outcomes were renal death, all-cause mortality, hospitalization for hyperkalemia, and interactive factors for composite outcomes.

Results: RAAS blockades were prescribed for 1,236 (59.6%) patients with CKD stage 4 to 5. RAAS blockade users showed an increased risk of renal death in PS matching (HR, 1.381; 95% CI, 1.071-1.781; P =0.013), in agreement with the result of IPTW analysis (HR, 1.298; 95% CI, 1.123-1.500; P <0.001). The risk of composite outcomes (renal death, all-cause mortality and hospitalization for hyperkalemia) was higher in RAAS blockade users, but did not reach a statistically significant level (HR, 1.243; 95% CI, 0.996-1.550; P =0.054), in PS matched analysis level. However, the result of IPTW adjustment showed significant increased risk of composite outcomes (HR, 1.154; 95% CI, 1.016-1.310; P =0.027).

Conclusions: The use of RAAS blockades may hasten the onset of renal death without a benefit in all-cause mortality in pre-dialysis advanced CKD patients. Further studies were warranted to determine whether the withholding it may lead to better outcomes in this patients.

TH-PO864

Low Molecular Weight Serum Filtration Markers as Predictors of Acute Kidney Injury and CKD Progression in Adults with Chronic Kidney Disease Meredith C. Foster, Andrew S. Levey, Josef Coresh, Amanda Hyre Anderson, Jiang He, Edward J. Horwitz, Chi-Yuan Hsu, Amy B. Karger, Paul L. Kimmel, John W. Kusek, James P. Lash, Robert G. Nelson, Haochang Shou, Raymond R. Townsend, Vasan S. Ramachandran, Sushrut S. Waikar, Xiaoming Zhang, Lesley Inker. *CKD Biomarkers Consortium and the CRIC Study.*

Background: The low molecular weight (LMW) serum filtration markers β-trace protein (BTP) and β-2 microglobulin (B2M) are independently associated with ESRD in adults with chronic kidney disease but less is known about their associations with acute kidney injury (AKI) and CKD progression.

Methods: We studied participants in the Chronic Renal Insufficiency Cohort Study (N=3609, mean age 58 yrs, 45% women), a prospective cohort study of adults with CKD. Cox proportional hazards regression was used to evaluate associations of measured GFR (mGFR) and estimated GFR (eGFR) using CKD-EPI equations for creatinine, cystatin C, BTP, B2M (eGFRcr, eGFRcys, eGFRBTP, eGFRB2M) with subsequent AKI (first hospitalization with AKI ICD codes [584.x]) and CKD progression (30% decline in eGFRcr from baseline) during follow-up. Hazard ratios are presented for a 30mL/min/1.73m^2 lower baseline GFR. We used seemingly unrelated regression to compare the magnitude of associations to that observed for eGFRcr.

Results: Participants were followed a median of 6.7 yrs for AKI and 4.3 yrs for CKD progression (**Table**). For all measures lower GFR was associated with higher risks for AKI and CKD progression in MV adjusted models. For AKI, eGFRcys, eGFRBTP and eGFRB2M had stronger associations than eGFRcr, which persisted with mGFR adjustment. For CKD progression only eGFRBTP and eGFRB2M had stronger associations than eGFRcr, which persisted with mGFR adjustment.

Conclusions: Estimated GFR from serum LMW proteins are independently associated with increased risk of AKI and CKD progression in adults with moderate CKD, beyond that of eGFRcr or mGFR.

Table: Multivariable° adjusted associations for AKI and CKD progression. Hazard ratios (HR) are presented for a 30mL/min/1.73m^2 lower baseline mGFR or eGFR in each model.

Outcome: Acute Kidney Injury (905 events/3609 population at risk)				
	Multivariable° Adjusted		Multivariable° + mGFR Adjusted*	
Exposure	HR (95% CI)	p vs. eGFRcr §	HR (95% CI)	p vs. eGFRcr §
mGFR*	1.75 (1.38, 2.22)	0.09	-	-
eGFRcr	1.43 (1.21, 1.68)	-	0.71 (0.47, 1.08)	-
eGFRcys	1.90 (1.65, 2.19)	<0.001	1.68 (1.14, 2.46)	<0.001
eGFRBTP	1.78 (1.49, 2.12)	0.006	1.28 (0.87, 1.89)	0.02
eGFRB2M	2.56 (2.15, 3.05)	<0.001	2.41 (1.54, 3.79)	<0.001
Outcome: CKD Progression (1303 events/3389 population at risk)				
Exposure	HR (95% CI)	p vs. eGFRcr §	HR (95% CI)	p vs. eGFRcr §
mGFR*	1.95 (1.66, 2.28)	0.57	-	-
eGFRcr	1.89 (1.67, 2.14)	-	0.92 (0.68, 1.25)	-
eGFRcys	1.94 (1.74, 2.15)	0.33	1.28 (0.98, 1.69)	0.02
eGFRBTP	2.54 (2.20, 2.93)	<0.001	1.72 (1.27, 2.32)	0.001
eGFRB2M	2.64 (2.31, 3.01)	<0.001	2.06 (1.50, 2.82)	<0.001

°Multivariable models adjusted for baseline age, sex, race/ethnicity, HDL cholesterol, log(C-reactive protein), smoking status, cardiovascular disease, hypertension, diabetes, and log(urinary albumin to creatinine ratio)
* Analyses limited to the subset of CRIC participants with mGFR assessment (N=1328 with 300 events for AKI; N=1271 with 638 events for CKD progression).
§ P-value from seemingly unrelated regression.

Funding: NIDDK Support

TH-PO865

Proteinuria without Impairment in Kidney Function or Kidney Scarring Potentiates Atherosclerosis Yohei Tsuchida,[1] Jianyong Zhong,[1] Macrae F. Linton,[2] Agnes B. Fogo,[3] Haichun Yang,[3] Valentina Kon.[1] *[1]Pediatrics, Vanderbilt Univ Medical Center, Nashville, TN; [2]Medicine, Vanderbilt Univ Medical Center, Nashville, TN; [3]Pathology, Vanderbilt Univ Medical Center, Nashville, TN.*

Background: CKD is a well-established risk for cardiovascular disease (CVD) with an inverse relationship between degree of kidney impairment and CVD. This relationship may reflect accumulation in uremic toxins that activate proatherogenic pathways. CKD is often accompanied by proteinuria. We now examine if proteinuria without other renal functional impairment or renal structural injury impacts development of atherosclerosis.

Methods: NEP25 transgenic mice express the human CD25 receptor on podocytes and develop proteinuria when injected with LMB2 toxin. NEP25/ApoE-/- mice were generated by cross-breeding. NEP25/ApoE-/- female mice were injected with LMB2, and compared to littermates not receiving toxin. All mice were fed a high fat diet. Body weight, as an index of edema, and albuminuria, assessed as spot urine albumin:creatinine ratios (ACR) were assessed weekly until sacrifice 4 weeks later. BUN was assessed at sacrifice. Atherosclerosis was measured by Oil-Red-O staining of proximal aortae, and kidney morphology was assessed.

Results: NEP25/ApoE-/- mice had increased ACR after LMB2 toxin compared to control (289.6±125.1 vs 28.4±8.6ug/mg, $p<0.05$). Although ACR was persistently elevated in NEP25+/ApoE-/-, the mice had no change in body weight and BUN was unchanged in toxin-exposed vs control (24.0±9.3 vs, 24.9±1.8mg/dl). Renal light microscopic morphology remained normal. NEP25+/ApoE-/- with LMB2 toxin had significantly greater atherosclerotic area than control that did not receive LMB2 (416954.0±111754.5 vs 235807.1±39861.2um^2, $p<0.05$). The degree of elevation in ACR correlated with the magnitude of atherosclerotic plaque burden (R^2=0.7213).

Conclusions: In summary, even in the absence of changes in BUN or histological damage, proteinuria per se amplifies atherosclerosis and the degree of proteinuria correlates with extent of atherosclerotic plaques. Additional studies are needed to further clarify the atherogenic mechanisms augmented by disruption in the glomerular filtration barrier.

Funding: Other NIH Support - NHLBI

TH-PO866

Low-Grade Albuminuria Predicts Age-Related GFR Decline in the General Non-Diabetic Population Toralf Melsom, Marit D. Solbu, Jørgen Schei, Vidar T.N. Stefansson, Trond G. Jenssen, Bjorn Odvar Eriksen. *Metabolic and Renal Research Group, UiT The Arctic Univ of Norway, Tromso, Troms, Norway.*

Background: Rapid age-related loss of GFR is a risk factor for chronic kidney disease (CKD), cardiovascular disease and mortality. Albuminuria, defined as an albumin-creatinine-ratio (ACR) >3.0 mg/mmol, predicts steeper age-related GFR decline in the general population. However, whether an ACR level below this cut off also constitute a risk of GFR decline is unknown. We investigated this hypothesis in a general non-diabetic population.

Methods: In the Renal Iohexol-clearance Survey in Tromsø 6 (RENIS-T6) we measured GFR as iohexol-clearance in a representative sample of 1562 middle-aged persons from the general population without baseline diabetes, cardiovascular disease or albuminuria. A total of 1274 (82%) had a repeated GFR measurement after a median of 5.6 years in the RENIS-Follow-Up (FU). ACR was measured in urine samples collected on three separate days at baseline.

Results: The median (interquartile range) ACR at baseline was 0.2 (0.1 – 0.5) mg/mmol and the mean (standard deviation) GFR decline rate was 0.95 (2.23) mL/min/year. One standard deviation higher baseline log-transformed ACR was associated with a 1.85 (95% CI: 0.48 to 3.21) mL/min higher baseline GFR and a 0.15 (95% CI: 0.26 to 0.04) mL/min/year steeper GFR decline rate during follow up in a linear mixed model ($P < 0.01$). We adjusted for sex and baseline height, weight, blood pressure, fasting glucose, LDL-cholesterol, triglycerides, smoking and the use of antihypertensive medications. A similar association was found after excluding those with high normal ACR defined as ACR>1.1 mg/mmol (>10 mg/g).

Conclusions: We conclude that higher ACR levels within the normal range predict accelerated age-related GFR decline in the general non-diabetic population.

Funding: Pharmaceutical Company Support - Main funding from the Norhern Norway Health Autority; Additional funding from Boeheringer-Ingelheim, Government Support - Non-U.S.

TH-PO867

Renal Hyperfiltration Predicts a Steeper GFR Decline in the General Non-Diabetic Population Toralf Melsom, Jørgen Schei, Vidar T.N. Stefansson, Trond G. Jenssen, Marit D. Solbu, Bjorn Odvar Eriksen. *Metabolic and Renal Research Group, UiT The Arctic Univ of Norway, Tromso, Troms, Norway.*

Background: An abnormally elevated glomerular filtration rate (GFR), or hyperfiltration, has been proposed as a risk factor for subsequent GFR decline and chronic kidney disease (CKD) of different origins. Treatments that cause an initial drop in GFR, such as ACE-inhibitors in hypertension and sodium-glucose co-transport inhibitors in diabetes, have been associated with a slower GFR decline in the long term. We hypothesized that higher baseline GFR levels predict a steeper age-related GFR decline rate in the general non-diabetic population.

Methods: We measured GFR at baseline and follow-up in the Renal Iohexol Clearance Survey Follow-up (RENIS-FU). A total of 1594 middle-aged persons without diabetes or CKD were investigated at baseline and 1324 (83%) had a follow-up after 5.6 years. A random sample of 88 persons had a third GFR measurement within the RENIS-FU, which allowed us to use a linear mixed model to investigate the GFR decline rate. This method overcomes the problems of mathematical coupling and regression to the mean when investigating the relationship between initial value and change.

Results: Mean (SD) baseline GFR was 104.0 (20.1) mL/min and mean GFR decline rate was 0.95 (2.23) mL/min/year. Male sex, tobacco smoking, higher body weight, and higher fasting glucose were associated with a higher baseline GFR (a higher intercept), in multivariable adjusted linear mixed regressions with random intercept and slope ($p<0.001$). The correlation (95% CI) between the random intercept and the random slope was -0.32 (-0.40 to -0.23), demonstrating that high baseline GFR values were associated with a subsequent steeper GFR decline.

Conclusions: This study indicates that renal hyperfiltration is a risk factor for accelerated age-related GFR decline in the general population.

Funding: Pharmaceutical Company Support - Main funding from the Northern Norway Health Authority; additional grant from Boehringer-Ingelheim, Government Support - Non-U.S.

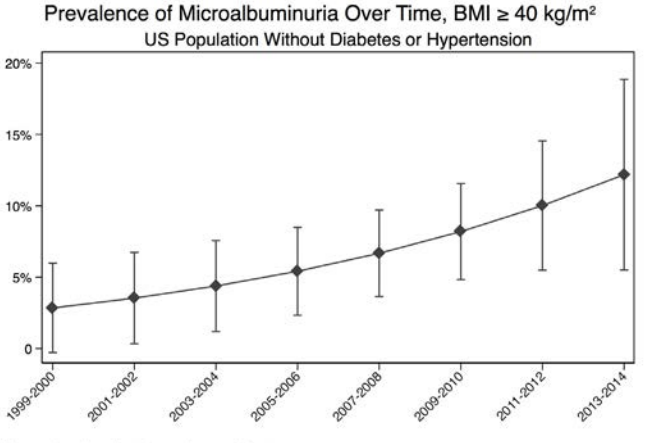
TH-PO868

Prevalence of Albuminuria among Obese U.S. Adults without Other Comorbid Conditions Meera Nair Harhay,[1] Andrew Stokes,[3] Eun Ji Kim,[3] Justin C. Brown,[2] Michael Oscar Harhay.[2] *[1]Medicine, Div of Nephrology and Hypertension, Drexel Univ College of Medicine, Philadelphia, PA; [2]Univ of Pennsylvania; [3]Boston Univ.*

Background: Obese individuals without evidence of obesity-related metabolic abnormalities may not be routinely screened for proteinuria. The prevalence of proteinuria among non-hypertensive and non-diabetic obese adults is unknown.

Methods: Our study sample was derived from the multi-ethnic, nationally representative sample of US adults (age>18 years) from eight waves (1999-2014) of the National Health and Nutrition Examination Surveys (NHANES). We included adults with estimated glomerular filtration rate>90 ml/min/1.73m^2, no history of diabetes or hypertension, glycated hemoglobin<6.5%, and blood pressure<140/90 mmHg. We estimated age- and gender-adjusted prevalence over time of microalbuminuria and macroalbuminuria (urine albumin:creatinine >30 and <300 mg/g, and >300 mg/g, respectively) in this subsample, by body mass index (BMI) category.

Results: 22,476 NHANES participants met inclusion criteria. From 1999-2014, the age-adjusted prevalence of obesity (BMI>30 and <40 kg/m^2) in this sample increased from 21% to 25% (p=0.02), and morbid obesity (BMI>40 kg/m^2) increased from 2.4% to 5.8% (p<0.001). The overall age- and gender-adjusted prevalence of microalbuminuria increased from 6.8% (95% CI: 5.3-8.1%) to 7.1% (6.0-8.2%), p=0.04 for trend. The overall prevalence of macroalbuminuria also rose over time, from 0.3% (0.1-0.6%) to 0.7% (0.5-1.0%), p=0.01 for trend. The age and gender-adjusted prevalence of microalbuminuria among morbidly obese participants increased from 2.7% (0.0-5.8%) in 1999-2000 to 11.6% (5.0-18.3%) in 2013-2014 (p interaction=0.08).



Conclusions: The prevalence of microalbuminuria has been increasing over time among morbidly obese US adults without evidence of other commonly assessed proteinuria risk factors.

Funding: NIDDK Support, Other NIH Support - Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (MNH, K23-DK105207), National Heart, Lung, and Blood Institute (MOH, F31-HL127947) and the National Cancer Institute (JCB, F31-CA192560, R21-CA182726) of the National Institutes of Health

TH-PO869

High-Normal Albuminuria Predicts the Incidence of Chronic Kidney Disease in a Nondiabetic Population Aki Sanada, Toshinori Ueno, Ayumu Nakashima, Shigehiro Doi, Takao Masaki. *Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan.*

Background: Microalbuminuria is considered to be one of the predictors of the incidence in decline of glomerular filtration rate (GFR). However, little is currently known about the relationship between high-normal albuminuria and chronic kidney disease (CKD) developing in the general population without diabetes mellitus.

Methods: A 10-year follow-up retrospective cohort study was preformed involving 1364 Japanese men (mean age, 44 years) who were free of CKD and diabetes mellitus. CKD was defined as an estimated GFR (eGFR) of <60 ml/min per 1.73 m2 or urine albumin to creatinine ratio (ACR) of ≥30 mg/g. Multivariate stepwise analysis was used to assess independent predictors of the baseline ACR. Logistic regression approaches were then used to assess determinants of the incidence of CKD. Receiver operator characteristics curve (ROC) analysis was used to determine the optimal cut-off value of the ACR as a predictor of incident CKD.

Results: At the baseline examination, eGFR, hypertension, age, body mass index, and the presence of hematuria were independently associated with the ACR. Among 1364 participants, 182 (13.3%) complied with our definition of incident CKD through 10 years of follow-up. The rate of decline in eGFR was higher with increasing quartiles of the ACR. Participants who had an ACR in the highest quartile (5.9 to 28.9 mg/g) were more likely to develop microalbuminuria (odds ratio 13.2, 95% CI 5.1 to 44.7) and CKD (odds ratio 3.7, 95% CI 2.3 to 6.0) than those who had an ACR in the lowest quartile (1.3 to 3.6 mg/g). These results were unchanged after adjustment for age, eGFR, hematuria, body mass index, and smoking status, as well as the presence of hypertension, hyperuricemia, and dyslipidemia. In ROC analysis, the area under the curve was 0.62 and an albuminuria level of 7.0 mg/g was decided as the cut-off value of incident CKD.

Conclusions: Our study shows that high-normal albuminuria is associated with incident CKD in the nondiabetic population.

TH-PO870

The Clinical Association among Urinary Albumin Excretion within Normal Range, Left Ventricular Diastolic Functional and Structural Change in General Korean Population Dong-Young Lee,[1] Hyun Sun Park.[1] *[1]Internal Medicine, VHS Medical Center, Seoul, Korea; [2]Total Healthcare Center, Kangbuk Samsung Hospital, Sungkyunkwan Univ, School of Medicine, Seoul, Korea.*

Background: Urine albumin creatinine ratio (UACR) is a reliable index of urinary albumin excretion and getting great attention on its association with cardiovascular disease. Nonetheless, the clinical association between UACR within normal range and subclinical left ventricular (LV) change was not clearly identified. Therefore, this study was designed to examining the clinical association between normal range of UACR and subclinical LV change.

Methods: A total of 31,334 apparently healthy Korean who received medical health check up including echocardiography in Kangbuk Samsung hospital were enrolled in this study. Study population was stratified by 3 groups according to their UACR (Tertile 1<3.17, Tertile 2: 3.17-4.95, Tertile 3≥4.95). The odd ratios (ORs) with 95 % confidence interval (CI) of abnormal LV relaxation, LV remodeling, and hypertrophy were compared among 3 groups using the multivariable logistic regression analysis. We also analyzed the adjusted mean value of parameter associated with LV diastolic function and structure.

Results: When tertile 1 group was set as reference, the adjusted ORs (95%CI) for abnormal LV relaxation showed proportional relationship with UACR levels within normal range [OR; 0.86 (95% CI 0.59 – 1.22) in underweight, 1.81 (95% CI 1.63 – 2.00) in overweight, 2.75 (95% CI 2.49 - 3.03) in obese, and 4.34 (95% CI 3.65 - 5.16) in severe obese]. Adjusted ORs for abnormal LV relaxation significantly increased with UACR levels. [tertile 2 (1.72; 1.15-3.08) and tertile 3 (2.18; 1.24-3.87)], even after adjusting for other covariates. Adjusted ORs for LV remodeling and hypertrophy were also significantly associated with UACR levels [tertile 2 (1.54; 0.93-2.16) and tertile 3 (1.94; 1.31-2.63)].

Conclusions: Elevated UACR, even within normal range, was significantly associated with the risk of LV diastolic functional and structural abnormality.

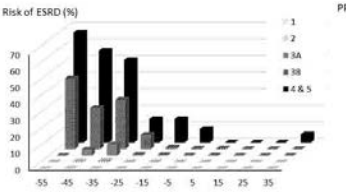
TH-PO871

Evaluation of Glomerular Filtration Rate Change as Surrogate Endpoint for End-Stage-Renal Disease Eiichiro Kanda,[1] Tomoko Usui,[2] Naoki Kashihara,[3] Chiho Iseki,[4] Kunitoshi Iseki,[4] Masaomi Nangaku.[2] *[1]Tokyo Kyosai Hospital; [2]The Univ of Tokyo; [3]Kawasaki Medical School; [4]Okinawa Heart and Renal Association, Tomishiro Center Hospital.*

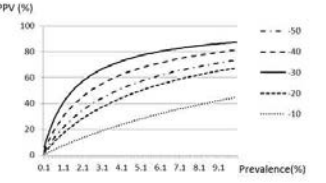
Background: Chronic kidney disease patients have high risks of death and end-stage renal disease (ESRD). Although more clinical studies are needed to improve their prognosis, good surrogate endpoints for ESRD have been required, because it takes a long time and involves large costs until true endpoints occur.

Methods: Subjects with data on serum creatinine level for a baseline period over 1 to 3 years were enrolled (n=69248) in this community-based prospective cohort study in Okinawa, Japan, and followed up for four years. The percent of estimated glomerular filtration rate (%eGFR) change converted into 2 years (%/2 years) was calculated on the basis of the baseline period.

Results: Among the subjects recruited, 15.81 % had low-eGFR (eGFR<60ml. min/1.72m^2), and 0.11 % developed ESRD. Subjects with a range of -40 ≤ %eGFR change < -30 %/2 years had the highest risks [high-eGFR (60ml.min/1.72m^2≤eGFR) group adjusted odds ratio (aOR), 12.8 (95 % confidence interval 3.4, 48.3); low-eGFR group, aOR 53.9 (13.3, 219.0)]. Cumulative population attributable risk percent showed that %eGFR change < -30 %/2 years contributed to the ESRD population. The positive predictive value for ESRD was highest at %eGFR change -30 %/2 years.



A Risk distribution of ESRD and CKD stage. The risk of ESRD sharply increases from %eGFR change -30 to -40 %/2 years.



B Positive predictive value of ESRD based on a cutoff value of % eGFR change. -30% was highest at %eGFR change -30 %/2 years.

The accuracy of prediction of ESRD based on %eGFR change [AUC 0.93 (0.89, 0.98)] was higher than those based on the change in eGFR slope [0.85 (0.80, 0.90)].

Conclusions: %eGFR change is associated with the risk of ESRD. %eGFR change -30%/2 years can be a surrogate endpoint for ESRD in the Japanese population.

TH-PO872

Performance of Creatinine-Based Equations to Assess Glomerular Filtration Rate Decline - The NephroTest Cohort Study Marieke H.C. Van Rijn,[1,2] Marie Metzger,[1] Jan A.J.G. van den Brand,[2] Martin Flamant,[3] Jean-Philippe Haymann,[4] Pascal Houillier,[5] Marc Froissart,[1] Benedicte Stengel.[1] *[1]Inserm U1018, France; [2]Radboud Univ Medical Center, Netherlands; [3]Bichat Hospital; [4]Tenon Hospital; [5]InsermU1138 & European G. Pompidou Hospital, France.*

Background: One point performance of creatinine-based estimated glomerular filtration rate(eGFR) equations has been extensively analyzed, but little is known on their ability to evaluate GFR trajectories. We studied the performance of the MDRD and CKD-EPI equations in estimating GFR decline over time.

Methods: We included 1955 stage 1 to 4 CKD adult patients who underwent up to 13 simultaneous IDMS-calibrated serum creatinine and GFR measurements (mGFR; ^{51}Cr-EDTA renal clearance). We estimated absolute and relative slopes for mGFR and both MDRD and CKD-EPI eGFR equations using linear mixed models. Performance was assessed by the bias and 95% limits of agreement (LoA) between mGFR and eGFR slopes, overall and by patient subgroups.

Results: Patients underwent a total of 5515 visits; 60% had at least two over a median 3.4-yr follow-up (IQR: 2.0-5.6). The bias for the absolute slope was close to zero for both equations.

	GFR at baseline (mL/min/1.73m^2)	Absolute GFR slope (mL/min/1.73m^2/year)			Relative GFR slope (% change per year)		
	mean (sd)	mean (sd)	Mean Bias	95% LoA	mean (sd)	Mean Bias	95% LoA
mGFR	44.0 (19.0)	-1.56 (0.90)			-4.33 (3.10)		
CKD-EPI eGFR	46.4 (22.2)	-1.52 (1.10)	-0.04 (0.86)	(-1.72, 1.64)	-3.74 (2.77)	-0.59 (1.82)	(-4.16, -0.67)
MDRD eGFR	44.5 (20.9)	-1.31 (1.04)	-0.25 (0.82)	(-1.87, 1.36)	-3.32 (2.65)	-1.01 (1.90)	(-4.72, 2.71)

Using relative slope yielded greater bias, which was stronger for the MDRD than the CKD-EPI equation. The LoA were wide for both absolute and relative slopes, indicating low precision. Performance of equations varied by subgroups defined by baseline GFR, age, gender and hypertension.

Conclusions: In CKD patients, both equations were very accurate in estimating the absolute GFR decline at the population level, but their precision was low, indicating large differences at the individual level. Patient and disease characteristics may impact equation longitudinal performance.

TH-PO873

Within-Person Variability of Albuminuria and Glomerular Filtration Markers in CKD Sushrut S. Waikar, Casey Rebholz, Chi-Yuan Hsu, Harold I. Feldman, Dawei Xie, Kathleen D. Liu, Lesley Inker, Theodore E. Mifflin, John H. Eckfeldt, Paul L. Kimmel, Vasan S. Ramachandran, Joseph V. Bonventre, Josef Coresh. *CKD Biomarkers Consortium, NIDDK.*

Background: We conducted a study to determine the short-term within-person variability and reference change values for albuminuria and four filtration markers used for GFR estimation in CKD.

Methods: We collected 3 repeat plasma samples and 5 urine samples (2 first morning and 3 random spot) from 49 patients with CKD over 1 month. Inclusion criteria were diagnosis of CKD; attendance at a nephrology clinic; and eGFR <60 ml/min/1.73 m^2 or

albumin:creatinine ratio (ACR) >100 mg/g. We measured albumin and creatinine in urine samples, and the filtration markers creatinine (SCr), cystatin C (CysC), β-trace protein (BTP), and β_2-microglobulin (B2M) in plasma samples, in single batches with blind split replicates to measure assay variability. Reference change values (RCV) at 95% confidence level were calculated from median values of within-person coefficient of variation (CV) from non-log transformed values.

Results: The distribution of CKD stages was 13% stage 5, 24% stage 4, 31% stage 3b, 20% stage 3a, 4% stage 2, and 2% stage 1; the distribution of albuminuria was 28% normo-, 28% micro-, and 43% macroalbuminuria. Analytic CVs for urine albumin, creatinine, and all four filtration markers were <2%. The Table shows medians, ranges, CV, and RCV for each analyte.

	ACR, mg/g		SCr, mg/dL	CysC, mg/dL	BTP, mg/L	B2M, mg/L
	First morning	Random				
Median conc. (range)	162 (0 - 3,557)	173 (0 - 4,006)	1.77 (0.62 - 9.41)	1.88 (0.82 - 4.39)	1.26 (0.28 - 4.91)	4.54 (1.62 - 15.54)
Median CV, % (range)	31.1 (0.2 - 95.1)	31.0 (13.6 - 76.8)	5.5 (0.8 - 69.3)	4.1 (0.4 - 52.2)	7.3 (1.1 - 49.4)	5.7 (0.2 - 54.9)
RCV, %	86	86	15	11	20	16

Conclusions: In CKD patients, albuminuria exhibits substantial within-person variability with RCVs exceeding 50%, which has been proposed in proteinuric kidney diseases as part of the definition for partial remission. The within-person variability of filtration markers in CKD appears comparable to reports in healthy individuals and does not exceed thresholds commonly used to define CKD progression.

Funding: NIDDK Support

TH-PO874

Screening for CKD Risk in the General Population in Belgium Using the QKidney®-2014 Risk Calculator Eric E. Gheuens, Koenraad Peter Bouman, Ronald Daelemans. *ZNA Kidney Clinic, Ziekenhuis Netwerk Antwerpen, Antwerpen, Belgium.*

Background: On World Kidney Day 2015 we launched the QKidney®-2014 risk calculator (www.qkidney.org) to screen for risk for developing chronic kidney disease (CKD) or end stage renal disease (ESRD) in the general population.

Methods: A webpage was created and launched on march 12th 2015, followed by a Facebook® advertising campaign in February 2016.

Results: In one year more than 60.000 records were created.

Characteristics of the population	Women	Men
n	31580	31085
Median age [IQR], years	52 [44, 60]	56 [45, 64]
BMI, Mean (SD)	26 (4,62)	26 (4,62)
Smoking status, n(%)		
Ex Smoker	1485 (4,70)	2058 (6,62)
Heavy Smoker	1147 (3,63)	1975 (6,35)
Light Smoker	1568 (4,97)	1399 (4,50)
Moderate Smoker	2948 (9,34)	2060 (6,63)
Non Smoker	24432 (77,37)	23593 (75,90)
Clinical conditions, n(%)		
Type 1 diabetes	331 (1,05)	795 (2,56)
Type 2 diabetes	1193 (3,78)	1859 (5,98)
Cardiovascular disease	1401 (4,44)	2623 (8,44)
Congestive heart failure	1217 (3,85)	1867 (6,01)
Peripheral vascular disease	1522 (4,82)	1654 (5,32)
Treated hypertension	7018 (22,22)	8635 (27,78)
Kidney stones	3381 (10,71)	4431 (14,25)
Family history of kidney disease	5308 (16,81)	3958 (12,73)

We included only complete records for our final analysis (21162 women, 21581 men). The 5-year risk score (mean [95%CI]) for CKD is 1,92 [1,83-2,02] for women, 4,39 [4,25-4,54] for men. For ESRD this is 0,75 [0,68-0,82] and 1,72 [1,60-1,84] respectively. 417 (1,97%) women and 1260 (5.84%) men have a slightly elevated risk for developing ESRD within 5 years (scores between 3-15). 171 (0.81%) women and 425 (1,97%) men have a high risk for developing ESRD within 5 years (scores >15).

Conclusions: The risk for developing CKD or ESRD is low in the general population. In our population the risk is higher for males than for females, explained by the higher age and presence of comorbidities. The use of the Qkidney risk calculator allows detection of high risk persons, eligible for screening.

TH-PO875

Hematuria as a Risk Factor for the Progression of Chronic Kidney Disease Paula Ferreira Orlandi,[1] Naohiko Fujii,[1] L. Lee Hamm,[3] James H. Sondheimer,[4] Chi-Yuan Hsu,[5] Michael J. Fischer,[2] Harold I. Feldman.[1] *[1]Center for Clinical Epidemiology and Biostatistics, Univ of Pennsylvania, Philadelphia, PA; [2]Renal Div, Univ of Illinois Hospital and Health Sciences Center, Chicago, IL; [3]School of Medicine, Tulane Univ School of Medicine, New Orleans, LA; [4]School of Medicine, Wayne State Univ, Detroit, MI; [5]School of Medicine, Univ of California, San Francisco, CA.*

Background: Hematuria from nephrogenic causes is associated with oxidative stress and inflammation, which may mediate further structural damage to the nephron. Despite its inexpensive and universally accessible assessment, hematuria has rarely been explored as a risk factor for CKD progression.

Methods: In the Chronic Renal Insufficiency Cohort (CRIC) Study, we evaluated the relationship of hematuria with CKD progression. Presence of hematuria was defined as a positive dipstick in one urinary sample during patient enrollment. All 3272 participants for whom hematuria was assessed were included. Hazards ratios for the development of ESRD over a median follow-up of 5 years were estimated for patients with and without hematuria. Analyses were stratified by eGFR (<30; 30-44.9; 45-59.9, >=60 ml/min/1.73m2), history of diabetes and proteinuria (<0.10; 0.10 -0.49; 0.50- 1.49; >=1.50g/dl).

Results: From all participants, 1145 (29%) presented hematuria at screening. Groups with and without hematuria differed on racial distribution (22% of Hispanics in the group with hematuria vs. 9.5% in the group without), proportion of diabetes (55.72% vs. 47.6%), eGFR (40.2 vs. 45.3 ml/min/1.73m2) and presence of proteinuria at baseline (34.8% vs. 8.5% presented at least 1.5g/day). For patients with diabetes, hematuria was associated with the development of ESRD within the first year (Hazard Ratio: 2.43; 95%CI: 1.18-5.00, p=0.016) and second year of follow-up (Hazard Ratio: 1.68; 95%CI: 1.11-2.54, p=0.013), and this relationship was attenuated over time.

Conclusions: In a large adult cohort with CKD, hematuria was associated with a significantly greater risk of CKD progression. These results suggest the potential role of hematuria as a predictor of CKD progression.

Funding: NIDDK Support

TH-PO876

The Chronic Kidney Disease Metabolome - Untargeted Metabolomics in Living Kidney Donors, Kidney Transplant Patients, Chronic Kidney Disease Patients and Various Dialysis Modalities Brad Urquhart,[1,2] Thomas Velenosi,[1] Benjamin Kervin Thomson,[2,3] Amit X. Garg,[2] Andrew A. House.[2] *[1]Physiology and Pharmacology, Western Univ; [2]Medicine, Div of Nephrology, Western Univ, London; [3]Medicine, Div of Nephrology, Queens Univ, Kingston, ON, Canada.*

Background: Although a number of studies have assessed metabolic changes in chronic kidney disease (CKD), this study aimed to evaluate overall metabolic changes in living kidney donors, CKD, transplant and various dialysis modalities as well as before and after dialysis using an untargeted metabolomics approach.

Methods: Plasma was collected from living kidney donors prior to and one year following kidney donation. Age-matched control plasma was collected in the same time frame. Dialysis patient plasma was collected prior to and immediately following dialysis for conventional dialysis (Conv. HD), nocturnal intermittent peritoneal dialysis (NIPD) and a number of home hemodialysis (Home HD) modalities including: frequent nocturnal (FN), short-hours daily (SHD), intermittent conventional (IC) and intermittent nocturnal (IN). Plasma from CKD and transplant patients was collected during routine follow-up appointments. Untargeted metabolomics analysis of plasma samples was performed using reverse phase (RPLC) and hydrophilic interaction liquid chromatography (HILIC) coupled to mass spectrometry.

Results: All pre-dialysis and CKD samples demonstrated more than 250 significantly different metabolites compared to control patients by both RPLC and HILIC analysis. Transplant samples resulted in less than 35 metabolites significantly different than controls in by RPLC and HILIC analysis. Principal component analysis demonstrated clustering of control, living donor and transplant patient samples compared to CKD and all dialysis modalities. When comparing pre and post dialysis samples, NIPD resulted in minimal metabolic changes. The largest change in metabolite levels during dialysis was seen in Home HD FN samples.

Conclusions: Plasma metabolic profiles of living kidney donors and kidney transplant patients were not distinguishable from controls by principal component analysis for both RPLC and HILIC data further supporting kidney transplant as ideal renal replacement therapy.

Funding: Government Support - Non-U.S.

TH-PO877

1,5-Anhydroglucitol Predicts CKD Progression in Macroalbuminuric Diabetic Kidney Disease: Results from Non-Targeted Metabolomics

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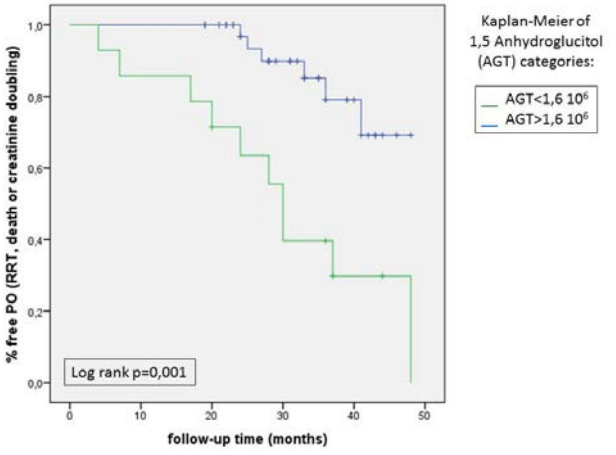
Background: In DKD, few biomarkers of disease progression are available, besides eGFR and albuminuria. Metabolomics is a new tool that allows exploration of novel biomarkers.

Methods: Non-targeted metabolomics was done on plasma of 56 DKD patients in Brazil. After a follow-up of 2.5y, the primary outcome (PO: dialysis need, doubling of serum creatinine, or death) occurred in 17 patients (30.3%). Samples were derivatized by methoximation and MSTFA, and analyzed by GC-MS Agilent 5977A/7890B. Data was processed using Agilent MassHunter with NIST 11 and Fiehn A.01.00 compound library. Metaboloanalyst 3.0 and SPSS 20.0 were used for analysis.

Results: After cleaning, 186 metabolites were left for analysis. Of those, 14 were associated with the PO (Mann-Whitney test). In Cox regression, only 1,5-anhydroglucitol (AGT) (HR 0.10; 95%CI 0.01-0.63, p=0.01), norvaline and L-aspartic acid where associated with the PO. After adjustments for baseline eGFR and glycated hemoglobin, AGT remained significantly and inversely associated with the PO (HR 0.05; 95%CI 0.01-0.33, p=0.002). A significant KM curve is shown in Figure 1.



Conclusions: Our results show that 1,5-anhydroglucitol, an inverse marker of hyperglycemia, is a significant predictor of CKD progression in DKD. Notably, a recent study highlighted AGT as a marker for new onset CKD among African Americans. Our findings extend this association to established DKD, in a racially diverse population.

Funding: Government Support - Non-U.S.

TH-PO878

Ceruloplasminuria Predicts Progression of CKD and Precedes the Development of Macroalbuminuria

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Background: We previously used a discovery proteomic analysis to identify ceruloplasmin (Cel) as a candidate marker to predict decline in renal function in diabetic patients. This is an initial validation study to determine if Cel predicts progression of CKD in diabetic patients.

Methods: We used 258 urine samples from the VA Diabetes Trial that were collected when patients had normo or microalbuminuria with normal serum creatinine (Cr). The median urine albumin to Cr ratio (ACR) was 11.5 mg/g. The primary outcome measure is a 50% rise in serum Cr from baseline during follow-up. Secondary outcomes are a 3.3% decline in eGFR per year and development of macroalbuminuria. Ceruloplasmin (Cel) was measured in urine samples collected as part of the VADT study using ELISA. Urine creatinine (Cr) was measured using a kinetic Jaffe assay. Results adjusted for treatment groups and use of ACE inhibitors.

Results: 13.4% of subjects had a 50% increase in serum Cr. As predicted from the discovery proteomic analysis, urine Cel concentration is associated with the risk of future decline of renal function in patients with normal renal function at baseline. For each 1 standard deviation increase in Cel, the odds ratio (OR) for a 50% increase in Cr is 1.33 (CI 1.01-1.75p=0.045, AUC 0.56). Standardizing Cel to urine Cr concentration using a Cel to Cr ratio (CCR) the OR for CCR is 1.51 (CI 1.14-1.99, p=0.004, AUC 0.61). For comparison the OR for ACR is 1.68 (CI 1.22-2.30, p=0.001, AUC 0.64). To examine whether the combination of ACR and CCR could improve prediction, we divided subjects into 4 groups based on the median splits of ACR and CCR and compared the risk of reaching the primary outcome in each of these groups to using the low ACR and low CCR group as the referent group. When compared to the referent group, all other categories had statistically significantly elevated risk. Subjects that had both high ACR and high CCR had the nominally highest risk.

Conclusions: Ceruloplasminuria can identify type 2 diabetic patients with an increased risk of loss of renal function. The combination of ACR and CCR may enhance prediction. Hence, CCR may be useful as a clinical predictor in combination with ACR.

TH-PO879

Urinary Activin A as a Valuable Biomarker Reflecting the Activity of Various Kidney Diseases

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Background: Activin A, a member of TGF-β superfamily, is known to regulate cell growth and differentiation in various tissues. It has been reported that activin A modulates ureteric bud branching in kidney development, inhibits tubular regeneration after renal ischemia, and acts as a potent inducer of renal fibrosis in rodents. However, the role of activin A in kidney diseases remains unknown in human. To address this issue, we analyzed renal biopsy specimens and urine from patients with various kidney diseases.

Methods: Patients with IgAN (n=81), lupus nephritis (n=80), ANCA-associated vasculitis (n=32), glomerulosclerosis (n=31), minimal change nephrotic syndrome (n=21), and others (n=147) who were treated in our department from 2011 and 2015 were included in this study. Urinary concentration of activin A, follistatin (activin antagonist), N-gal, KIM-1 and serum activin A were measured by ELISA. The localization of activin A in renal biopsy specimens was examined by immunostaining. Normal kidney specimens from patients who underwent nephrectomy were used as controls.

Results: Urinary activin A was almost undetectable in healthy volunteers (9.6 ± 2.3 ng/gCr), but was significantly increased in patients with acute kidney injury (257.9 ± 174.6), lupus nephritis type IV (51.7 ± 15.0), and ANCA-associated vasculitis (120.4 ± 38.7). Urinary activin A levels of these patients was rapidly decreased after the initiation of treatment. There was a significant correlation of urinary activin A level with urinary N-gal, KIM-1 and serum activin A. Urinary activin A level was negatively correlated with eGFR and hemoglobin. Activin A was localized in the cytoplasm of distal tubules of normal kidneys. In contrast, activin A was present not only in distal tubules, but also in the apical lumen of proximal tubules, infiltration macrophages, and vascular smooth muscle cells in patients with kidney diseases.

Conclusions: These data suggest that urinary activin A is a valuable biomarker reflecting the activity of various kidney diseases.

Funding: Pharmaceutical Company Support - Astellas Pharma Inc.

TH-PO880

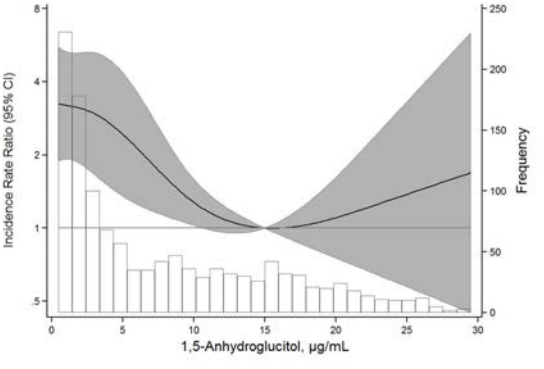
Serum Levels of 1,5-Anhydroglucitol and Risk of Incident End-Stage Renal Disease

Casey Rebholz,[1] Morgan Grams,[1] Yuan Chen,[2] Alden Lawrence Gross,[1] Yingying Sang,[1] Josef Coresh,[1] Elizabeth Selvin.[1] *[1]Johns Hopkins Univ; [2]Columbia Univ Mailman School of Public Health.*

Background: Low 1,5-anyhydroglucitol (1,5-AG) is a biomarker of hyperglycemic excursions that has recently been associated with early stages of kidney disease. However, it is unknown if low 1,5-AG levels can lead to more advanced stages of kidney disease independent of kidney function and glycemia (e.g., hemoglobin A1c).

Methods: Blood levels of 1,5-AG, other glycemic markers, and filtration markers were measured in 13,279 Atherosclerosis Risk in Communities (ARIC) Study participants. End-stage renal disease (ESRD) was defined as entry into the U.S. Renal Data System registry from baseline through 2011. Structural equation modelling was used to estimate the association between 1,5-AG and ESRD with latent variables for kidney function (creatinine, cystatin C, β_2-microglobulin) and glycemia (diabetes, fasting glucose, hemoglobin A1c, fructosamine, glycated albumin), and adjusting for demographics and established risk factors.

Results: During a median follow-up of 20 years, there were a total of 271 incident ESRD cases. After adjusting for age, sex, race, hypertension, body mass index, smoking status, and the latent variable for kidney function, the linear spline terms representing 1,5-AG levels <6 µg/mL (IRR: 0.80, 95% CI: 0.71-0.95) and 6-<10 µg/mL (IRR: 0.76, 95% CI: 0.66-0.87) were significantly associated with ESRD. After additionally adjusting for the glycemia latent variable, low levels of 1,5-AG (<6 µg/mL) were no longer significantly associated with ESRD (IRR: 0.92, 95% CI: 0.81-1.05).



Conclusions: Low levels of 1,5-AG are associated with higher risk of incident ESRD independent of baseline kidney function but not glycemia. 1,5-AG is a marker of hyperglycemia and glucose variability, an important metabolic pathway that accelerates progression to ESRD.

Funding: NIDDK Support, Other NIH Support - National Heart, Lung and Blood Institute

TH-PO881

Two Forms of Urinary Megalin Excretion Are Novel Predictors of the Progression of Early-Stage Diabetic Nephropathy in Type 2 Diabetes Mellitus

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Background: Megalin is an endocytic receptor at the apical membrane of proximal tubules. We established sandwich ELISA to measure urinary (u-) excretion of the ectodomain and full-length forms of megalin, A- and C-megalin, respectively. Here, we examined the significance of these markers to predict the progression of early-stage diabetic nephropathy.

Methods: We analyzed 175 cases with type 2 diabetes mellitus (T2DM) (103 men; median age 68 [IQR, 58–75] years) with a median observation period of 3.97 (2.10–4.12) years. Cases were selected according to the u-albumin/creatinine (Cr) ratio (ACR, mg/g) and eGFR (mL/min/1.73m^2). We evaluated u-A- and C-megalin in relation to the risks of eGFR reduction (≥20% of initial data) and the escalation of ACR stages (from normo- [ACR<30] to microalbuminuria [30≤ACR<300], or from micro- to macroalbuminuria [ACR≥300]),using Cox's proportional hazard analysis.

Results: U-A-megalin/Cr was found to be a predictor of the escalation of the ACR stage in 69 microalbuminuric cases with eGFR≥30 (HR, 9.71 [95% CI, 1.34–70.67]) and of eGFR reduction in 120 cases with eGFR≥ 60 (HR, 6.31 [95% CI, 1.48–26.82]), even after adjusting for sex, age, HbA1c, eGFR, body mass index, and u-markers including ACR, β_2-microglobulin/Cr, and NAG/Cr. U-C-megalin/Cr was also a predictor of the escalation of the ACR stage in 62 normoalbuminuric cases with eGFR≥60 (HR, 2.45 [95% CI, 1.02–5.86]).

Conclusions: A- and C-megalin are novel u-biomarkers, independent of albumin, β_2-microglobulin, and NAG, that can predict particularly the progression of diabetic nephropathy in T2DM at micro- and normoalbuminuric stages, respectively.

Funding: Pharmaceutical Company Support - Denka Co., Ltd., Government Support - Non-U.S.

TH-PO882

Effects of Oxidative Stress on the Relationship between Hyperuricemia and Intrarenal Arteriolar Lesions in Chronic Kidney Disease

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Background: We previously reported that hyperuricemia (HU) is related to intrarenal arteriolar lesions in patients with chronic kidney disease (CKD). Here we investigated whether oxidative stress affects this relationship.

Methods: After excluding patients with vasculitis, we recruited a total of 139 patients (mean age, 44 years; 55 females; 84 males) who had undergone renal biopsy at our department. Hyalinized intrarenal arteriolar lesions were semi-quantitatively evaluated (grades 0–3). Relative oxidative stress was calculated using the formula: reactive oxygen metabolites-derived compounds (d-ROMs) ÷ biological antioxidant potential (BAP) value × correction coefficient (5.8). A result of ≥1 indicated a state of increased oxidative stress (OS). Subjects were divided into four subgroups according to the presence or absence of HU and OS (HU-/OS-, HU+/OS-, HU-/OS+, and HU+/OS+), and arteriolar lesions were compared between each group.

Results: The highest mean hyalinization grade was found in the HU+/OS+ group; this grade and differed markedly from that found in the HU-/OS- group. However, only a relatively small difference was detected between the HU+/OS- and HU-/OS- groups. Multivariate analysis was also used to investigate factors that may be associated with severe arteriolar hyalinization (values above the median grade), including age, gender, systolic blood pressure, HbA1c level, and HU/OS subgroup. Results indicated that HU+/OS+ (Ref: HU-/OS-) was a significant factor (Odd's ratio: 3.7; 95% CI, 1.0–14.6) and that the HU+/OS+ group exhibited the lowest%FMD.

Conclusions: Results indicated that the relationship between HU and intrarenal arteriolar hyalinized lesions may become more prominent in CKD patients when OS increases and endothelial dysfunction occurs.

TH-PO883

Urinary Markers of Oxidative Stress Do Not Accelerate the Age-Related GFR Decline Rate in the General Non-Diabetic Population

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Background: Oxidative stress plays an important role in the pathogenic process of age-related chronic diseases. The urinary levels of 8-oxo-7, 8-dihydro-2'-deoxyguanosine (8-oxodG) and 8-oxo-7, 8-dihydroguanosine (8-oxoGuo) are well-established markers of oxidatively damaged DNA and RNA, and have been associated with chronic kidney disease (CKD) in animal studies and progression of diabetic nephropathy in humans. However, whether increased urinary levels of 8-oxodG and 8-oxoGuo predict an accelerated age-related GFR decline in the general population is unknown.

Methods: We measured GFR using iohexol clearance at baseline and follow-up in the Renal Iohexol Clearance Survey Follow-Up study (RENIS-FU). The cohort included 1,591 middle-aged subjects without diabetes, cardiovascular-, or kidney disease at baseline. After a median of 5.6 years, 1,298 subjects were included in the follow-up study. Baseline urinary levels of 8-oxodG and 8-oxoGuo were measured with LC-MS/MS.

Results: Mean (SD) annual GFR decline was -0.95 (2.23) mL/min/year. The median (IQR) urinary 8-oxodG/creatinine and 8-oxoGuo/creatinine ratios were 1.36 (1.04-1.74) and 3.45 (2.68-4.44) nmol/mmol, respectively. In multivariable adjusted mixed models, the log-transformed 8-oxodG/creatinine and 8-oxoGuo/creatinine were not associated with the GFR decline rate. When using 8-oxodG and 8-oxoGuo not corrected for urinary creatinine, one nmol/L higher concentration was associated with a slower GFR decline of 0.19 (95% CI: 0.03-0.35) and 0.16 (95% CI: 0.01-0.30) mL/min/year, respectively.

Conclusions: We found that the urinary concentrations of 8-oxodG and 8-oxoGuo predicted a slower GFR decline in a cohort representative of the general population. This does not support the hypothesis that oxidative stress plays an important role for an accelerated age-related GFR decline.

Funding: Pharmaceutical Company Support - Boehringer-Ingelheim, Government Support - Non-U.S.

TH-PO884

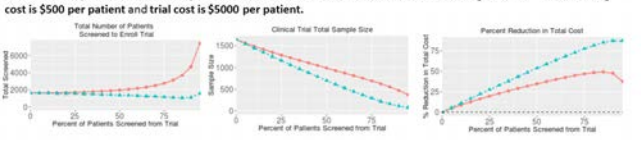
Evaluating Biomarkers for Prognostic Enrichment of Clinical Trials

Kathleen F. Kerr,[1] Jeremy Roth,[1] Kehao Zhu,[1] Allison Meisner,[1] Heather Thiessen Philbrook,[2] Francis Perry Wilson,[2] Steven G. Coca,[2] Chirag R. Parikh.[2] *[1]Biostatistics, Univ of Washington, Seattle, WA; [2]Yale Univ.*

Background: Although there is broad agreement that biomarkers should be evaluated with respect to their intended use, little has been written about how to evaluate a biomarker for prognostic enrichment of clinical trials.

Methods: For an intervention intended to reduce the occurrence of some unwanted clinical event, a prognostically enriched trial enrolls only patients at relatively higher risk of experiencing the event without the intervention. The rate of the unwanted event is higher in the "enriched" study population, which implies that a smaller sample size can be used in a clinical trial while maintaining adequate power to detect a treatment effect.

Results: We developed methods for evaluating biomarkers for prognostic enrichment of clinical trials. These methods are implemented in free software called BioPET (**Bio**marker **P**rognostic **E**nrichment **T**ool). A BioPET analysis evaluates a prognostic biomarker for its impact on clinical trial sample size, the total of trial patient costs and the costs of screening, and calendar time to enroll the trial. Depending on the performance of the biomarker and its cost to measure, the cost of a prognostic enrichment trial strategy can increase or decrease with the stringency of screening. Modestly performing biomarkers typically increase the calendar time to enroll a prognostically enriched trial, but high performing biomarkers will decrease the time. We demonstrate methods with examples in ESRD and ADPKD.



Conclusions: BioPET provides investigators with tools to assess biomarkers for prognostic enrichment. BioPET addresses several competing dimensions in trial design, including sample size, cost, time for enrollment, and ethical considerations. BioPET is available as a webtool and as a package for the R statistical platform, which has extended functionality.

Funding: NIDDK Support

TH-PO885

A Risk Scoring Model to Predict Progression of Renal Dysfunction in Patients with Chronic Kidney Disease Complicated with Contrast-Induced Nephropathy Seung Don Baek,[1] Mun Jang,[1] Wonhak Kim,[1] Eun Kyoung Lee,[2] Jai Won Chang.[1] *[1]Dept of Internal Medicine, Asan Medical Center, Seoul, Korea; [2]Dept of Internal Medicine, Dankook Univ College of Medicine, Cheonan-si, Korea.*

Background: The contrast-induced nephropathy (CIN) occurs more frequently in patients with lower estimated glomerular filtration rate (eGFR). Since CIN may be associated with the progression of chronic kidney disease (CKD), it would be important to predict the risk of irreversible renal damage prior to contrast-enhanced CT.

Methods: We retrospectively analyzed 18,278 enhanced CTs performed in 9,097 CKD patients with eGFR less than 60 mL/min/1.73 m^2 for at least 3 months, from January 2013 to December 2014. The progression of renal dysfunction was defined as reduction of eGFR >25%. We investigated 1-year renal outcomes in CKD patients complicated by CIN (increase ≥25% and/or ≥0.5 mg/dL in serum creatinine within 3 days after CT) and compared the outcomes between the progression and the non-progression groups. A risk score of 4, 5, 6, 7, or 7 was assigned to diabetes, baseline eGFR <45 mL/min/1.73 m^2, hypertension, repeated contrast exposure, and congestive heart failure, respectively.

Results: The overall occurrence of CIN was 5.8% (1,051/18,278) of all enhanced CTs performed, in 7.6% (689/9,097) of the total CKD patients. Among 689 patients, 465 were excluded due to follow-up loss or death. Among the remaining 224 patients, 70 (31.3%) patients had progression of renal dysfunction. The aggravation of azotemia compared with baseline serum creatinine level, was more severe in the progression group (1.84 ± 0.75 mg/dL *vs.* 2.46 ± 1.13 mg/dL, $p < 0.001$) than in the non-progression group (1.67 ± 0.60 *vs.* 1.69± 0.83, $p = 0.827$) at 1-month later after CIN. The risk scoring model demonstrated that the risk of progression of renal dysfunction increased with the sum of risk score in CKD patients complicated by CIN (*c* statistic = 0.735).

Conclusions: Although our risk scoring model needs to be validated in another population, our study suggested the possibility of predicting the risk of progression of renal dysfunction in CKD patients prior to contrast administration.

TH-PO886

Validation of a Systems Biology Derived Model to Predict Renal Disease Progression in Diabetes Mellitus Gert J. Mayer,[1] Hiddo Jan Lambers Heerspink,[2] Constantin Aschauer,[3] Judith Sunzenauer,[3] Georg Heinze,[4] Alexander Kainz,[3] Paul Perco,[5] Michelle Pena,[2] Peter Rossing,[6] Dick de Zeeuw,[2] Rainer Oberbauer.[3] *[1]Internal Medicine IV, Medical Univ Innsbruck, Innsbruck, Austria; [2]Dept of Clinical Pharmacy and Pharmacology, Univ Medical Center Groningen, Groningen, Netherlands; [3]Dept of Nephrology, Medical Univ of Vienna, Vienna, Austria; [4]Center for Medical Statistics, Informatics and Intelligent Systems (CeMSIIS), Section for Clinical Biometrics, Medical Univ of Vienna, Vienna, Austria; [5]Emergentec Biodevelopment, Vienna, Austria; [6]Steno Diabetes Center, Gentofte, Denmark.*

Background: Progression of renal function loss in diabetes mellitus (DKD) has a complex molecular pathophysiology. We aimed to identify a panel of biomarkers able to predict the individual eGFR decline using a systems biology derived model and validated the markers in a large sample of patients at various stages of DKD.

Methods: We used publicly available -omics data to develop a molecular process model of DKD and identified a representative parsimonious set of 9 biomarkers (CHI3L1, GH1, HGF, MMP2, MMP7, MMP8, MMP13, TIE2, TNFR1), which were measured in baseline plasma samples of 1765 patients recruited into two large clinical trials with baseline eGFRs of 87.2 (IQR 16.4) and 33.5 (9.5) ml/min/1.73m2 (DIRECT-2 and SUN Macro). The prediction of eGFR decline by biomarkers, clinical risk factors (including baseline eGFR and albuminuria) and both combined was evaluated by mixed linear regression models for longitudinal data.

Results: A combination of molecular and clinical predictors achieved an explained variability (R^2) of longitudinal eGFR values of 35 and 63% for patients with >60 and <60 ml/min/1.73m^2 respectively. The contribution to R^2 by molecular predictors was 15 and 34% for clinical predictors 20 and 29% respectively.

Conclusions: We conclude that a small set of plasma protein biomarkers identified by a systems biology approach enhances the prediction of renal function loss by standard clinical variables in patients with a wide range of baseline eGFR. Furthermore the biomarkers reflect a molecular model of DKD and thus might allow patient stratification based on pathophysiology providing an opportunity to apply targeted therapy.

Funding: Government Support - Non-U.S.

TH-PO887

Prediction of Six Months Progression to End Stage Renal Disease Hao Han,[1] Yuedong Wang,[2] Sheetal Chaudhuri,[1] Terry L. Ketchersid,[1] Dugan Maddux,[1] Sophia Rosen,[1] John W. Larkin,[1] Peter Kotanko,[3,4] Len A. Usvyat,[1] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Univ of California Santa Barbara, Santa Barbara, CA; [3]Renal Research Inst, New York, NY; [4]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: The progression of chronic kidney disease (CKD) to end stage renal disease (ESRD) is difficult to predict in routine management of patients (Pts). We aimed to understand the performance of four CKD progression predictive models using sensitivities and specificities.

Methods: We used data from 28,608 CKD Pts from 2000 to 2011 in the Fresenius Medical Care CKD Data Registry to construct two linear and spline models that utilize up to 6 months of historic estimated glomerular filtration rates (eGFRs) data, or logarithm of eGFRs (log-eGFRs), for prediction of CKD progression to ESRD. We excluded CKD stage 5 Pts and those with a kidney transplant. Prediction performance was assessed using alpha of 0.1 for sensitivities and specificities segregated by historical eGFR sample sizes (n) to identify adequate sample numbers for the models; groups are as follows: 5≤ n <10, 10≤ n <20, 20≤ n <30, 30≤ n <40, and n ≥40.

Results: The performance of the models is detailed in Figure 1. All models performed well for prediction with n <20 eGFR samples. For eGFR samples n ≥20, sensitivities and specificities were unreliable secondary to a limited Pts that progressed to ESRD.

Figure 1			sensitivities				specificities			
eGFR sample n	Pt number	Progressed to ESRD	Linear eGFR (95%CI)	Spline eGFR (95%CI)	Linear log-eGFR (95%CI)	Spline log-eGFR (95%CI)	Linear eGFR (95%CI)	Spline eGFR (95%CI)	Linear log-eGFR (95%CI)	Spline log-eGFR (95%CI)
5≤ n <10	3,254	73	0.897, (0.840 0.955)	0.832, (0.761,0.903)	0.877, (0.815,0.940)	0.755, (0.673,0.837)	0.683, (0.594,0.771)	0.704, (0.617,0.790)	0.788, (0.710,0.866)	0.785, (0.707,0.864)
10≤ n <20	1,309	42	0.857, (0.765,0.949)	0.804, (0.700,0.908)	0.732, (0.616,0.848)	0.786, (0.678,0.893)	0.759, (0.647,0.871)	0.733, (0.617,0.849)	0.843, (0.747,0.938)	0.830, (0.731,0.928)
20≤ n <30	192	8	0.545, (0.251,0.840)	.818, (0.590,1.00)	0.455, (0.160,0.749)	0.636, (0.352,0.921)	0.842, (0.626,1.00)	0.851, (0.641,1.00)	.911, (0.743,1.00)	0.901, (0.724,1.00)
30≤ n <40	45	2	0.667, (0.133,1.00)	0.667, (0.133,1.00)	0.667, (0.133,1.00)	0.667, (0.133,1.00)	0.615, (0.065,1.00)	0.654, (0.115,1.00)	.731, (0.229,1.00)	0.769, (0.292,1.00)
n ≥40	43	0	NA	NA	NA	NA	0.929, (0,1.00)	0.786, (0,1.00)	0.929, (0,1.00)	0.857, (0,1.00)

Conclusions: The four prediction models for determining six month risk for progression to ESRD were found to have good sensitivity and reasonable specificity. While our modeling efforts rely on historic eGFR values, other models, with similar c-statistics, use multiple factors to predict future eGFR.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-PO888

GDF-15 and Risk of Decline in Kidney Function in Patients with Chronic Kidney Disease Viji Nair,[1] Cassianne Robinson-Cohen,[2] Michelle R. Smith,[1] Keith A. Bellovich,[3] Zeenat Yousuf Bhat,[4] Maria Bobadilla,[5] Frank C. Brosius,[1] Ian H. De Boer,[2] Ivan Formentini,[5] Crystal A. Gadegbeku,[6] Debbie S. Gipson,[1] Jennifer Joyce Hawkins,[1] Jonathan Himmelfarb,[2] Bryan R. Kestenbaum,[2] Matthias Kretzler,[1] Maria Chiara Magnone,[5] Susan P. Steigerwalt,[1] Wenjun Ju,[1] Nisha Bansal.[2] *[1]UM; [2]UW; [3]St. John; [4]Wayne; [5]Roche Pharmaceutical; [6]TU.*

Background: Growth differentiation factor-15(GDF-15)is a novel biomarker of cardiac inflammation and remodeling.The association with progression of kidney disease is less certain and may identify a novel risk factor for loss of kidney function.In two prospective cohort studies of chronic kidney disease ,C-PROBE and SKS,we tested the association of circulating levels of GDF-15 with rapid decline in kidney function, and correlation with kidney tissue expression of GDF-15 mRNA.

Methods: We investigated the association of serum GDF-15 level with progression to a composite endpoint(ESRD or 30% reduction from baseline eGFR)using Cox models and continuous eGFR decline using GEE model in the C-PROBE (n=224) and SKS (n=297). We examined the correlation of intrarenal expression of *GDF-15* mRNA with the serum GDF-15 levels in matching samples (n=24,C-PROBE).

Results: 32% participants progressed to kidney disease,median F/U: 3.5yrs (C-PROBE)/4yrs(SKS).Higher GDF-15 concentration significantly associated with a greater risk of progression of kidney disease.Similarly, every doubling of GDF-15 associated with a 5.8%/year and 3.0%/year rapid decline in eGFR in C-Probe and SKS respectively (p<=0.01).

Figure1: Association of GDF-15 with progression to ESRD or loss of30% of eGFR

C-PROBE			SKS Study		
GDF-15 (pg/mL)	Events[$]	HR (95% CI)	GDF-15 (pg/mL)	Events[$]	HR (95% CI)
437 – 1307	08 (2.6)	1.0 (ref)	403 – 1636	15 (6.5)	1.0 (ref)
1307 –1938	13 (4.5)	2.24(0.90, 5.59)	1636 – 2338	17 (7.4)	0.76 (0.35,1.64)
1938 –2891	20 (7.2)	2.13(0.87, 5.18)	2338 – 3508	30 (13.5)	1.48 (0.68,3.21)
2891 – 8444	31 (11.1)	3.25(1.26, 8.36)*	3508 – 9549	33 (18.3)	2.56 (1.15,5.72)*

[$]Incidence Rate, per 100 person – years
Adjusted :CVD, diabetes, SBP, & anti-hypertensive medication. *pvalue <0.02

Circulating GDF-15 concentrations significantly correlated (p=<0.01) with intrarenal GDF15mRNA(r=0.54) and baseline eGFR(r=-0.57).

Conclusions: Elevated GDF-15 was associated with increased risk of rapid decline of eGFR in two independent CKD cohorts.There was a strong correlation of circulating GDF-15 with intrarenal tubulointerstitial *GDF15* mRNA.These data suggest that GDF-15 may be a novel mechanistic biomarker of CKD progression.

Funding: NIDDK Support, Other NIH Support - R03DK102452, Pharmaceutical Company Support - Roche Pharmaceutical

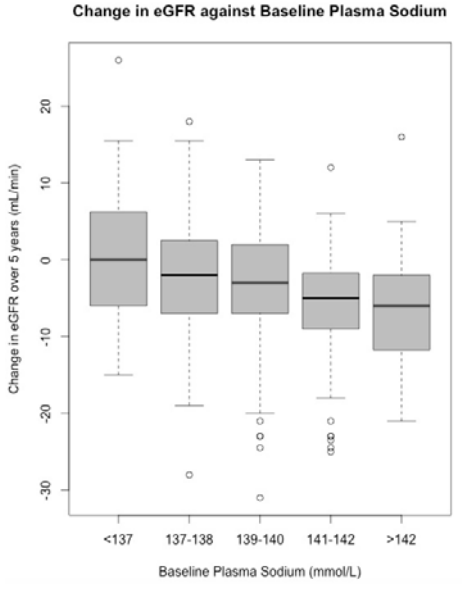
TH-PO889

Relationship between Plasma Sodium Concentration and Chronic Kidney Disease Progression Nicholas I. Cole,[1] Rebecca Suckling,[1] Feng J. He,[2] Pinnaduwage Vipula De Silva,[1] Pauline A. Swift.[1] *[1]South West Thames Renal Unit, St. Helier Hospital, London, United Kingdom; [2]Wolfson Inst of Preventative Medicine, Queen Mary Univ of London, London, United Kingdom.*

Background: Observational and experimental studies have demonstrated that small increases in plasma sodium concentration (PNa) are associated with increased blood pressure and changes to endothelial function. Increases in PNa may therefore contribute to the adverse renal and cardiovascular outcomes observed in those with chronic kidney disease (CKD).

Methods: This was a retrospective study of data collected between January 2009 and December 2014. We included patients known to our renal service with a minimum of three blood tests taken every two years and an estimated glomerular filtration rate (eGFR) of <60 mL/min at baseline. Exclusion criteria were renal replacement therapy, diabetes mellitus, heart failure, decompensated liver disease, and significant fluctuations in renal function.

Results: 7,063 blood results from 309 patients were included in the study. The mean PNa at baseline was 139.7 mmol/L (SD 2.0). We found no relationship between baseline PNa and eGFR, and no significant change in PNa occurred over time in those with progressive CKD. However, there was a significant correlation between baseline PNa and the change in eGFR over time (r = -0.2, P <0.001). After adjustment for age, gender, ethnicity, CKD stage and diagnosis, a 1 mmol increase in baseline PNa was associated with a 0.70 mL/min decrease in eGFR over 5 years (P < 0.001, 95% CI 0.29-1.12).



Conclusions: This study is the first to identify an association between PNa and the progression of CKD. Small increases in PNa, within the normal physiological range, were associated with a greater rate of eGFR decline during the study period. The cause of this association is uncertain but increased PNa may be associated with higher blood pressure, problems with salt and water regulation, and endothelial dysfunction.

TH-PO890

Serum Osmolarity Is an Independent Risk Factor for Chronic Kidney Disease; 5 Year Cohort Study in Japan Masanari Kuwabara,[1,2,3] Miguel A. Lanaspa,[1] Carlos Alberto Roncal-Jimenez,[1] Ana Andres-Hernando,[1] Tamara Milagres,[1] Thomas Jensen,[1] Richard J. Johnson.[1] *[1]Div of Renal Diseases and Hypertension, Univ of Colorado Denver, Aurora, CO; [2]Dept of Cardiology, Toranomon Hospital, Tokyo, Japan; [3]St. Luke's International Hospital, Tokyo, Japan.*

Background: Epidemics of chronic kidney disease (CKD) not due to diabetes or hypertension have been observed among individuals working in hot environments in several areas of the world. Experimental models have confirmed that recurrent heat stress and water restriction can lead to CKD, and the mechanism may be mediated by hyperosmolarity that activates pathways (vasopressin, aldose reductase-fructokinase) that can induce renal injury. Here we tested the hypothesis that elevated serum osmolarity may be an independent risk factor for the development of CKD.

Methods: This study was a large-scale, single-center, retrospective 5-year cohort study at St. Luke's International Hospital Center for Preventive Medicine, Tokyo, Japan, between 2004 and 2009. We analyzed 13,201 subjects who underwent annual medical examination at the hospital. Of those, 12,041 subjects were enrolled who were between 30 years and 85 years old in 2004 without diabetes mellitus and/or CKD. This analysis evaluated age, gender, body mass index, abdominal circumference, hypertension, dyslipidemia, hyperuricemia, and calculated serum osmolarity.

Results: After adjusted regression analysis, the risk factors for developing CKD were as follows: age [Odds Ratio (OR): 1.07 per 1 year increased, 95% confidence interval (CI): 1.06-1.08], body mass index (OR: 1.12 per 1 kg/m^2 increased, 95% CI: 1.08-1.16), abdominal circumference (OR: 0.96 per 1cm increased, 95% CI: 0.95-0.98), hyperuricemia (OR: 1.68, 95% CI: 1.44-1.95), and serum osmolarity (OR: 1.04 per 1 mOsm/L increased, 95% CI: 1.03-1.05). Compared with the lowest serum osmolarity quartile, the highest quartile had a higher adjusted OR for new onset CKD, being 1.52 fold (95% CI: 1.23-1.88) in men and 1.34 fold (95% CI: 1.04-1.72) in women.

Conclusions: Elevated serum osmolarity is a strong independent risk factor for development of CKD. This result indicates the importance of limitation of high salt diet and prevention of dehydration to prevent CKD.

Funding: Other NIH Support - NIH grant 1RO1DK109408-01A1, Private Foundation Support

TH-PO891

Anion Gap Associated with Risk of Progression to ESRD in Adults with Moderate CKD Tanushree Banerjee,[1] Deidra C. Crews,[2] Sharon Saydah,[4] Nilka Rios Burrows,[4] Brenda W. Gillespie,[3] Rajiv Saran,[3] Neil R. Powe.[1] *[1]Medicine, Univ of California, San Francisco; [2]Medicine, Johns Hopkins Univ; [3]Medicine, Univ of Michigan, Ann Arbor; [4]Centers for Disease Control and Prevention.*

Background: Anions that accumulate during the course of CKD, including unmeasured anions (e.g. p-cresol sulfate and indoxyl sulfate), may accelerate the progression of CKD. Whether undetermined anions, as indicated by the anion gap, are associated with risk of progression to ESRD in adults with moderate CKD has not been elucidated.

Methods: We analyzed data from 1,286 adults with moderate CKD (eGFR 30-59 ml/min/1.73 m^2) enrolled in National Health and Nutrition Examination Survey III (1988-1994). Anion gap was determined from laboratory tests (serum Na-(serum Cl +serum bicarbonate). The development of ESRD was ascertained over a median of 10.4 years of follow-up via linkage with USRDS. We used a proportional hazards regression model to test the association between anion gap and risk of ESRD after adjusting for demographics (age, gender, race/ethnicity), clinical factors (diabetes and hypertension), eGFR, and albuminuria.

Results: The mean baseline anion gap was 9.5 mEq/L. A significant elevation in the tertiles of anion gap was found with eGFR 45-59 ml/min/1.73 m^2 compared to eGFR 30-44 ml/min/1.73 m^2. Demographics and clinical factors of diabetes and hypertension did not differ by anion gap tertile (p>0.05). During the follow-up period, 16.7% developed ESRD. Compared to the lowest, the highest tertile of anion gap was associated with an increased risk of ESRD when adjusted for demographics, clinical factors, eGFR, and albuminuria (Relative hazard [95% CI]: 1.81 [1.01-3.08]). There was no significant risk of ESRD noted comparing the middle to the lowest tertile of anion gap (RH [95% CI]: 1.10 [0.52-2.04]).

Conclusions: In a nationally representative sample of adults with CKD, we observed that anion gap was independently associated with risk of ESRD. These data highlight the anion gap as a potential therapeutic target for slowing CKD progression.

TH-PO892

Association between Water Intake and Kidney Function: The Korea National Health and Nutrition Examination Survey Mina Yu. *Nephrology, Seoul Seonam Hospital, Seoul, Republic of Korea.*

Background: The effect of plain water intake on kidney function is not yet clear. Chronically low fluid intake may induced vasopressin up-regularion and increased GFR via tubuloglomerular feedback and hyperfiltration. However, some data reported that water intake may prevent GFR decline.

Methods: The population-based, cross-sectional study analyzed, total 37,753 participants from the Korea National Health and Nutrition Examination Survey conducted in 2008-2011. the water intake (cup=200 m/dayl) was estimated by asking the question " how much water do you usually cosume per day?". Dietary water intake (g/day) was estimated by 24hr dietary recall.The 24-hr urinary sodium values were estimated from sodium and creatinine values of random urine samples using Tanaka's equation. CKD was defined 4 groups as an GFR (GFR<30, 30=<GFR<60, 60=<GFR<90, GFR>=90). Data was splitted into ages by 10 years.

Results: Of 26,955 adults (range 19-96yrs), CKD defined (GFR<30: 56[0.2%],30<GFR<60:829[2.1%],60<GFR<90:8824[26.7%]. As ages urine specific gravity was significantly reduced (1.022 vs.1.202 vs. 1.019 vs.1.018 vs.1.017 vs. 1.016, 19 =<Age<30/30-39/40-49/50-59/60-69/70-96 (p<0.05)). The estimated amount of sodium excretion (mmol/d) increased to 60s decreased from 70s (18,426 vs. 19,317 vs. 19984 vs. 20847 vs. 21294 vs. 20476 (p<0.05)), showed a similar pattern is also sodium intake (g/d) estimated from food (4.876 vs. 5.414 vs. 5.513 vs. 5.197 vs, 4.547 vs. 3.603(p<0.05)). Fair water intake (cups/day) and total water intake from diet (g/day) were not differ between ages, In each ages group, average water consumption (cups/da) was decreased with decreased GFR, at 60s and 70s, low water intake is associated with low GFR group significantly. (60s; water intake 7.61vs. 5.57vs. 5.05 vs.5.53, 70s; 11.7 vs. 6.5vs. 4.2 vs.4.2 in GFR>90/60<GFR<90/30<GF=<60/GFR<30).

Conclusions: This result suggest that water intake associated with CKD significantly in elderly people.

TH-PO893

Effect of Homocysteine on Intestinal Permeability in Rats with Adenine-Induced Experimental Uremia Shanshan Liang, Hongli Jiang. *Dialysis Dept of Nephrology Hospital, First Affiliated Hospital of Medicine School, Xi'an Jiaotong Univ.*

Background: Previous studies have revealed increased levels of plasma and intestinal homocysteine(Hcy) in Chronic Kidney Disease (CKD). However, whether Hcy is involved in increased intestinal permeability and barrier dysfunction of CKD remains unclear. This study aimed to investigate the effect of Hcy on intestinal in rats with adenine-induced uremia and elucidate its possible mechanism.

Methods: SD rats were divided into four groups:normal, Hcy, adenine, adenine +Hcy. Experimental uremia was induced by adenine and Hcy were injected subcutaneously. The serum creatinine, urea nitrogen as well as the renal pathological tissue staining were tested to assess the model. The serum C-reactive protein, IL-6 and TNF-α, Hcy, endotoxin, intestinal epithelial permeability and intestinal tissues Hcy, SOD and MDA levels were assessed. The fibrosis releated protein of MMP-9,α-SMA and TGF-β were assessed by Western blot.

Results: The serum biochemical parameters and renal pathological show a success of animal model (Fig1). the serum inflammatory factors, endotoxin, Hcy ,endotoxin and intestinal permeability were shown in Figure 2, and intestinal tissue levels of Hcy ,SOD and MDA in Figure 3.The change of MMP-9,α-SMA and TGF-β protein abundance were shown in Figure 4.Compared with normal and adenine group, the serum inflammatory factors, endotoxin, Hcy and intestinal permeability, and intestinal tissue levels of Hcy and MDA were significantly higher, with the SOD activity markedly decreased in adenine+Hcy group. In adenine group and adenine+Hcy group , the protein expression were significantly increased than normal group.

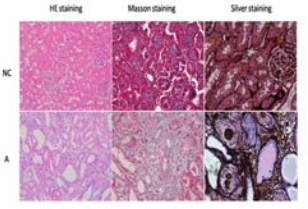


Figure 1 Renal pathological changes of group NC and group A by HE, Masson and Silver staining. (× 200)

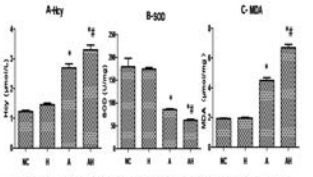


Figure 3 Levels of Hcy, SOD and MDA of each group. *P < 0.05 compared with group NC; #P < 0.05 compared with group A.

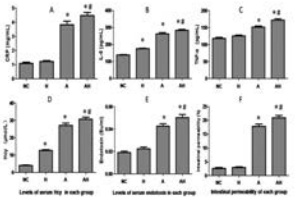


Figure 2 Levels of inflammatory biomarkers (IL- 6, CRP, and TNF-α), Hcy ,endotoxin, and intestinal permeability of each group. *P < 0.05 compared with group NC; #P < 0.05 compared with group A.

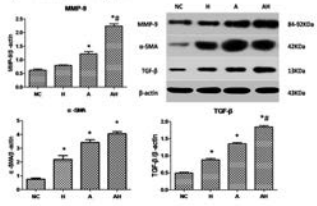


Figure 6 Relative protein expression levels of MMP-9, α-SMA and TGF-β in colonic tissue of each group, and were normalized to β-actin. * p < 0.05 vs. the NC group; # p < 0.05 vs. group A.

Conclusions: Hcy can increase intestinal permeability and aggravate inflammatory damage in adenine-induced uremia rats.The underlying mechanisms of which may be attributed to its effects of promoting the expression of fibrosis related factors.

Funding: Government Support - Non-U.S.

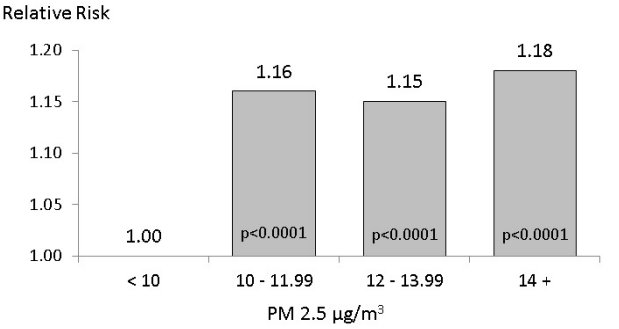
TH-PO894

County-Level Air Quality and the Incidence of ESRD in the U.S. Population Jennifer L. Bragg-Gresham, Patrick Albertus, Hal Morgenstern, Robert D. Brook, Peter X.K. Song, Rajiv Saran. *Univ of Michigan, Ann Arbor, MI.*

Background: Considerable geographic variation exists in the incidence of ESRD across the U.S. Higher rates have been noted along the Ohio and Mississippi river valleys and in more industrialized parts of the country. We explore the association between air quality and ESRD incidence by county in the US.

Methods: Using data on all incident cases of ESRD from the USRDS data base (2012-2014: n=338,042), the US Census (2013), and 2006 EPA air-quality data, we examined the association between a county-level measure of air pollution—particulate matter ≤2.5 μm (PM2.5), which includes toxic particulates, such as heavy metals—and the incidence of ESRD, for all U.S. counties with complete data (n=3,053). Poisson regression was used to estimate the relative risk of new cases of ESRD (per county population) by county PM2.5 level, adjusting for potential country-level confounders—mean age, proportion male, and proportion Black, Asian, and Native American.

Results: The crude incidence rate of ESRD ranged from 0 to 2,341 new cases per 1,000,000 population among counties (median =335) in the full sample and 69 to 1,581 (median=367) in a sample of counties with at least 10 new cases, after adjusting for age, sex, and race of the county. Treating PM2.5 level a continuous variable, the adjusted RR for an increase of 4 μg/m^3 was 1.10 (95% CI = 1.09-1.11; $p < 0.0001$). The results when categorizing PM2.5 by quartiles suggest a possible detrimental threshold effect at PM2.5 level of 10 μg/m^3, which is below the current EPA guideline of 12 μg/m^3.



Conclusions: We found that poorer air quality was associated with higher incidence rate of ESRD. However, the ecological design and lack of individual exposure data precludes causal inference. Future investigations should include measures of multiple air pollutants and individual exposure, as well as more extensive control of confounding.

Funding: NIDDK Support

TH-PO895

APOL1, Sickle Cell Trait (SCT), and Risk of Chronic Kidney Disease (CKD) in the Jackson Heart Study (JHS) Bessie A. Young,[1,2,3] Alex Reiner,[3] L. Ebony Boulware,[4] Neil R. Powe,[5] Bryan R. Kestenbaum,[2,3] Nora Franceschini,[7] Nisha Bansal,[2] Adolfo Correa,[6] Jonathan Himmelfarb,[2] Ronit Katz.[2] *[1]Hospital and Specialty Care, VA Puget Sound Health Care System, Seattle, WA; [2]Kidney Research Inst and Div of Nephrology, UW, Seattle, WA; [3]Epidemiology, UW, Seattle, WA; [4]Medicine, Duke, Surham, NC; [5]Medicine, UCSF, San Francisco, CA; [6]Medicine, UMC, Jackson, MS; [7]Epidemiology, UNC, Chapel Hill, NC.*

Background: *APOL1* high-risk variants and SCT have been shown to be associated with increased risk of CKD among African Americans (AA). Little is known regarding risk of development of CKD/ESRD among AA with one risk variant compared to none; or whether there is an association with SCT. We determined the association between *APOL1* risk variants, SCT, and development of CKD among AA. of JHS.

Methods: JHS is a prospective cohort study of 5306 AA. Participants were enrolled at baseline (2000-2004), and followed at exam 2 (2005-2008) and 3 (2009-2012). The primary outcomes of interest were incident CKD (eGFR <60ml/min/m^2), incident albuminuria (albumin to creatinine ratio (ACR) ≥ 30mg/g), incident ESRD or rapid kidney function decline (defined as ≥30% decline). Multivariable models (Cox, logistic, and linear) were adjusted for age, sex, diabetes (DM), hypertension (HTN), SCT, and ancestry informative markers.

Results: Baseline creatinine and genetic information on *APOL1* variants and/or SCT were available for 2300 AA. Of those, 41.3% had zero, 52.0% had one, and 6.7% had two *APOL1* variants; SCT was found in 8.5% (199/2299). Subjects with one (HR=1.41, 95% CI 1.00-1.99) and two (HR=1.97, 1.12-3.47) *APOL1* risk alleles had increased risk of incident ACR that remain significant after adjustment, while incident ESRD was significant for only those with two alleles (aOR 11.89, CI 2.10-67.45). Continuous decline in eGFR and rapid decline in eGFR>30% were significant for those with two but not one alleles.

Conclusions: Among AA, the presence of one or two *APOL1* risk alleles was associated with increased risk of incident ACR in a graded fashion. Those with two alleles also had increased risk of incident ESRD, continuous decline, and rapid decline of eGFR independent of DM, HTN or SCT.

Funding: NIDDK Support, VA Support

TH-PO896

Insulin Requirement Is a Risk Factor for End-Stage Renal Disease (ESRD) Independent of Hemoglobin (Hb) A1C Levels in Type 2 Diabetes Mellitus (T2DM) Rabia Nadeem Kiani,[1] R. E. Boucher,[1] Guo Wei,[1] Debra Lynn Simmons,[1] Linda F. Fried,[2] T. S. Bjordahl,[1] Tom Greene,[1] Srini Beddhu.[1] *[1]Univ of Utah, SLC, UT; [2]VA, Pittsburgh.*

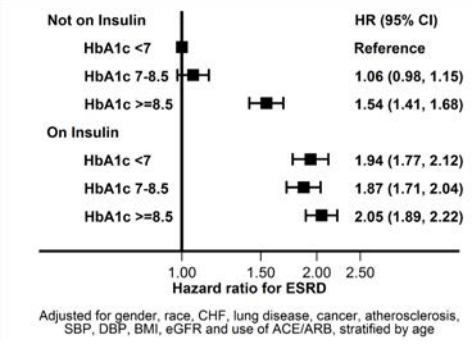
Background: As the need for insulin might be a reflection of insulin resistance, we hypothesized that independent of HbA1c levels, insulin use might be a risk factor for ESRD in T2DM.

Methods: In a cohort of 1,561,876 veterans with serum creatinine and serum HDL-cholesterol measured within 3 months of each other from Jan 1, 2000 to Dec 31, 2008, we analyzed 188,544 veterans with T2DM (defined by ICD9 codes). Data on filled medications were obtained from outpatient pharmacy database. Laboratory data were obtained from routine clinical labs. Follow-up was until 10/1/2011. ESRD data were obtained by linking to USRDS. Based on HbA1C levels and the use of insulin, 6 groups were defined. Using the HbA1c< 7 and no insulin as the reference group, the risk of ESRD in the other groups were examined in Cox regression models.

Results:

	Without insulin			With insulin		
HbA1c%	<7 N=81470	7-8.5 N=42782	>8.5 N=26184	<7 N=9292	7-8.5 N=12933	>8.5 N=15883
Age (yr)	67±11	66±11	61±11	66±11	66±10	60±11
Male(%)	97	98	97	98	98	97
AA(%)	15	16	24	19	18	28
SBP(mmHg)	140±21	142±21	142±21	141±22	141±22	141±22
DBP(mmHg)	75±12	77±12	80±12	73±13	74±13	78±13
Atherosclerosis(%)	40	40	30	48	49	40
CHF(%)	8.2	7.8	6.0	14.9	15.0	12.2
BMI(kg/m^2)	30.7±5.9	31.3±6.0	31.6±6.2	31.6±6.6	31.9±6.5	31.7±6.7
ACEI/ARB(%)	63.3	67.5	64.4	72.8	76.2	73.8
eGFR(ml/min/1.73m^2)	72±21	73±21	82±21	66±26	68±24	76±25

There were 5757 ESRD events over 1,463,762 years of follow-up.



Conclusions: A limitation is the lack of data on duration of T2DM. However, even in those with HbA1C < 7, need for insulin was associated with increased ESRD risk. Interventions that ↓ the need for insulin might ↓ the risk of ESRD in T2DM.

Funding: NIDDK Support, VA Support

TH-PO897

Deoxycholate, a Gut-Microbiome Derived Bile Acid Is Elevated in Patients with Diabetic Kidney Disease Adil Jadoon, Anna V. Mathew, Jaeman Byun, Farsad Afshinnia, Subramaniam Pennathur. *Div of Nephrology, Univ of Michigan, Ann Arbor, MI.*

Background: Diabetic Kidney Disease (DKD) is the most common cause of end stage renal disease in the United States but underlying mechanisms of DKD initiation and progression remain unclear. Bile acids are a diverse group of aliphatic compounds which modulate gene transcription and may play a critical role DKD as evidenced by recent murine studies. In this study, we sought to explore the association of plasma bile acid profiles in patients with DKD compared to those with non-diabetic kidney disease to identify potential mechanisms and markers of DKD development and progression.

Methods: Our study population consisted of 34 DKD and 34 subjects with non-diabetic CKD. Bile acids were extracted from fasting plasma from the study subjects and subjected to highly sensitive and specific liquid chromatography/mass spectrometry (LC/MS) to measure 25 primary and secondary bile acids .We then explored the differences in the bile acid profiles between the two study groups using logistic regression modeling in SPSS.

Results: Bile acid profiles were compared by t-test followed by multivariable logistic regression. Most bile acid levels were significantly higher in DKD subjects ($p<0.0001$). Multivariable logistic regression revealed deoxycholate to be the top differentially regulated compound that independently differentiated the two clinical groups after correction of confounding variables.

Conclusions: Deoxycholate is an unconjugated bile acid derived from metabolism of bile acids by the gut microbiota and thus not under the control of the biosynthetic machinery of the host. Our data concludes that bile acid levels in subjects with chronic kidney disease are much higher among those with DKD and Deoxycholate can precisely identify those with CKD due to diabetic nephropathy. This data also suggests a potential role for gut microbiota and altered bile acid metabolism in DKD which needs to be further evaluated in future mechanistic studies.

Funding: Other NIH Support - T32 grant

TH-PO898

Guanidinylations of Albumin Decreased Binding Capacity of Hydrophobic Metabolites Vera Jankowski, Joachim Jankowski. *Inst for Molecular Cardiovascular Research, Univ Hospital RWTH Aachen, Aachen, Germany.*

Background: Since post-translational modifications of proteins may have an impact on the pathogenesis of diseases like atherosclerosis, diabetes mellitus and chronic kidney disease (CKD), post-translational modifications are currently gaining increasing interest. In this study, a comprehensive method for analysis of these post-translational modifications is established for the clinical diagnostic routine.

Methods: Here, we analysed albumin –the most abundant plasma protein in human– isolated from CKD patients and healthy controls by chromatographic steps and identified by MALDI mass-spectrometry.

Results: Albumin isolated from plasma of CKD patients but not from healthy control subjects was specifically post-translationally modified by guanidylation of lysines. After identification of guanidylations as post-translational modifications of albumin isolated from CKD patients, these modifications were quantified by mass-spectrometry demonstrating a significant increase in the corresponding mass-signal intensities in CKD patients compared to healthy controls. The relative amount of guanidylation in CKD patients was determined as 63 ± 32 %. Subsequently, we characterized the pathophysiological impact of the post-translational guanidylation on the binding capacity of albumin for representative hydrophobic metabolic waste products. *In-vitro* guanidylation of albumin from healthy control subjects caused a decreased binding capacity of albumin in a time-dependent manner. Binding of indoxyl sulfate (protein bound fraction) decreased from 82 ± 1 % of non post-translationally modified albumin to 56 ± 1 % after *in-vitro* guanidylation ($p < 0.01$). Thus, *in-vitro* post-translational guanidylation of albumin had a direct effect on the binding capacity of hydrophobic metabolites like indoxyl sulfate and tryptophan.

Conclusions: We used a mass spectrometry-based method for the characterisation of post-translational modification and demonstrated the pathophysiological impact of a representative post-translational modification of plasma albumin. The data described in this study may help to elucidate the pathophysiological role of protein modifications.

TH-PO899

Reported Randomized Controlled Trial Results in Nephrology Are Fragile: An Analysis Using the Fragility Index Lani Shochet, Peter G. Kerr, Kevan Polkinghorne. *Dept of Nephrology, Monash Health, Clayton, Victoria, Australia.*

Background: The Fragility Index (FI) is a tool for testing the robustness of randomized controlled trial (RCT) results for dichotomous outcomes. It describes the minimum number of patients in whom changing an event status would alter a statistically significant result to a non-significant result.

Methods: A systematic literature search identifying all RCT in 5 nephrology (JASN, cJASN, AJKD, NDT and KI) and 5 general journals (NEJM, Lancet, BMJ, JAMA and Annals of Internal Medicine) from 2005-2014 was performed. RCT reporting at least one dichotomous positive outcome ($p<0.05$) were eligible for inclusion. FI was calculated using the Fischer exact test. FI, total event number and sample size were log transformed. Multiple linear regression were performed to assess factors independently associated with FI.

Results: 129 RCT were included (111 nephrology, 18 general). Six studies had a FI of zero and were excluded from further analysis. Of the remaining 123 studies, median sample size was 132 (range 22-11506) with 18 (range 0-1243) events in the intervention group. Median FI was 3 (range 1-166) indicating that in half of the studies the addition of 3 events to one of the treatment arms rendered the result non-significant. A doubling in total event number and sample size independently increased median FI by 30% and 16% respectively ($p<0.001$ and $p=0.009$). Compared to a reported p-value of >0.01-<0.05, those reporting 0.01-0.001 and <0.001 had a 74% ($p<0.001$) and 497% ($p<0.001$) increase in the median FI. After adjusting for event number, sample size and p-value, the median FI was 58% lower in general medical journals compared to renal journals ($p=0.007$). Finally, of the studies reporting loss to follow-up (n=106), 41% had a FI < total loss to follow-up indicating potential to change a trial result had all subjects been accounted for in the study.

Conclusions: Reported nephrology RCT results are fragile, with half of the studies' results susceptible to changes in small numbers of events. This study highlights the need for larger RCT with accurate accounting for loss to follow-up to adequately guide evidence-based practice.

TH-PO900

Scope and Consistency of Outcomes Reported in Randomized Trials Conducted in Children with Chronic Kidney Disease Camilla Sara Hanson,[1,2] Lauren Chong,[1,2] Benedicte Sautenet,[1,2] Allison Tong,[1,2] Jonathan C. Craig.[1,2] *[1]School of Public Health, The Univ of Sydney; [2]Centre for Kidney Research, The Children's Hospital at Westmead.*

Background: Randomized controlled trials (RCTs) have been conducted to improve outcomes in children with chronic kidney disease (CKD), but the outcomes reported may not be relevant to children, families or clinicians, and variability in outcome domains and measures make it impossible to assess the comparative effectiveness of interventions. We assessed the scope and consistency of outcomes reported in RCTs of interventions for children in any stage of CKD.

Methods: The Cochrane Renal Register of Controlled Trials was searched for all RCTs in children across all stages of CKD published before March 2016. The frequency of reporting of each outcome domain, and the measurement characteristics were evaluated.

Results: From the 205 trials, 99 different outcome domains were reported including 37 and 44 domains specific to transplantation and dialysis, respectively. Across all outcome domains, 50 (51%) were surrogate, 40 (40%) were clinical, and 9 (9%) were patient-reported. The median number of domains per trial was 15 (IQR 9-26). The five most commonly reported domains were: blood pressure (75 [37%] trials), medication use/duration (73 [36%] trials), relapse/remission (72 [35%]), kidney function (66 [32.2%]) and infection (61 [30%]). Mortality was reported in 28 (14%) trials. Cardiovascular disease and quality of life were reported very infrequently, in 8 (4%) and 2 (1%) trials, respectively. There was inconsistency of measures and time points used across all trials. Across the 99 domains, 1671 different measurements were reported. For blood pressure and medication use/duration, 76 and 54 measures were used across trials, respectively.

Conclusions: The outcomes reported in RCTs involving children with CKD primarily report surrogate outcomes, rather than clinical and patient-centered outcomes such as mortality, cardiovascular disease, quality of life and cognition. The multiplicity and heterogeneity of outcomes at all levels – domain, measurement, threshold, and time points - deters efforts to compare the effectiveness of interventions and use trial evidence in decision-making.

TH-PO901

Effects of Ferric Citrate (FC) in Adults with Non-Dialysis-Dependent Chronic Kidney Disease and Iron-Deficiency Anemia (IDA): Ph 3 Clinical Trial

Steven Fishbane,[1] Geoffrey A. Block,[4] Pablo E. Pergola,[5] Lisa Loram,[3] John F. Neylan,[3] Katrin Uhlig,[3] Glenn Matthew Chertow.[2] *[1]Hofstra Northwell Health, Great Neck, NY; [2]Stanford Univ, Palo Alto, CA; [3]Keryx Biopharmaceuticals, Boston, MA; [4]Denver Nephrologists PC, Denver, CO; [5]Renal Associates PA, San Antonio, TX.*

Background: Iron deficiency anemia is common and consequential in non-dialysis-dependent chronic kidney disease (NDD-CKD). Efficacy and tolerability of conventional oral iron supplements are mixed; intravenous (IV) iron administration is associated with finite but important risks.

Methods: 234 patients were randomized 1:1 to FC and Placebo (P) in a double blind clinical trial comparing the safety and efficacy in patients with NDD-CKD stages 3-5 and IDA. The starting dose of 3 tablets/day was increased every 4 weeks if hemoglobin (Hgb) was not >1g/dL above baseline. IV or oral iron, erythropoeisis stimulating agents, blood transfusions and other phosphate binders were not permitted during the trial. The primary endpoint was the proportion of patients who achieved ≥1.0 g/dL increase in Hgb at any time during a 16-week randomized period. Patients who completed the 16-week period were asked to participate in an 8-week open label extension period.

Results: Patients randomized to FC were significantly more likely to achieve the primary endpoint [52.1% (61/117) *vs* 19.1% (22/115), p<0.001]. All secondary endpoints also reached statistical significance, including the mean relative change in Hgb (0.84 g/dL, 95% confidence interval 0.58 to 1.10 g/dL, p<0.001) and the proportion of patients who achieved a sustained increase in Hgb [≥0.75 g/dL over any 4-week time period during the randomized trial period] [48.7% (57/117) *versus* 14.8% (17/115), p<0.001). Gastrointestinal disorders were the most commonly observed adverse events, with diarrhea reported in 24 (20.5%) and 19 (16.4%), nausea in 13 (11.1%) and 3 (2.6%) and constipation in 22 (18.8%) and 15 (12.9%) patients treated with FC and P, respectively. The rate of serious AEs was similar across groups (12 FC vs 11.2 % P) and no SAEs or deaths were related to study drug.

Conclusions: The study demonstrated that in patients with NDD-CKD, FC is well tolerated and may be an efficacious treatment for IDA.

Funding: Pharmaceutical Company Support - Keryx Biopharmaceuticals

TH-PO902

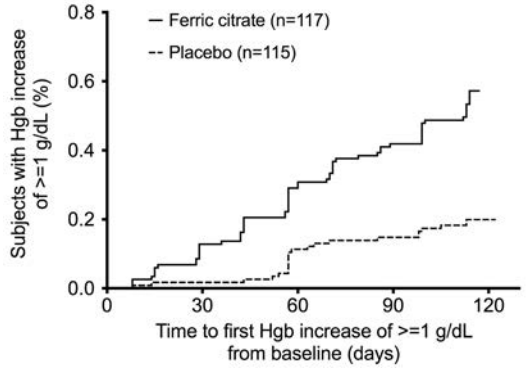
Hemoglobin Response to Ferric Citrate (FC) in Subjects with Non-Dialysis Dependent (NDD) Chronic Kidney Disease (CKD) and Iron Deficiency Anemia (IDA): Data from a Phase 3 Clinical Trial

Glenn Matthew Chertow,[1] Steven Fishbane,[2] Pablo E. Pergola,[3] Katrin Uhlig,[4] John F. Neylan,[4] Geoffrey A. Block.[5] *[1]Stanford Univ, Palo Alto, CA; [2]Hofstra Northwell Health, Great Neck, NY; [3]Renal Associates, San Antonio, TX; [4]Keryx Biopharmaceuticals, Boston, MA; [5]Denver Nephrologists, Denver, CO.*

Background: The hemoglobin (Hgb) response to Ferric Citrate (FC) in a Phase 3 clinical trial in subjects with NDD-CKD and IDA was further explored.

Methods: 234 subjects were randomized 1:1 to FC and placebo (P) in a 16 week Randomized treatment period. The dose of FC or placebo was started at 3 tablets/day and up-titrated if Hgb had not risen by >1 g/dL provided that the subject's increase in Hgb from baseline is ≤1.0 g/dL at any titration time point. The rate and durability of Hgb response and the effect of baseline Hgb is evaluated here.

Results: We have reported elsewhere a significant increase in Hgb from baseline to the end of 16 wk for FC compared to P (p<0.001) and that 52.1% of FC achieved ≥ 1 g/dL rise in Hgb (primary end point of the trial) compared to 19.1% in P (p<0.001). Time to first ≥1 g/dL rise in Hgb is shown in the Figure.



In the last 4 weeks of the trial, 33.3% of those on FC vs 6.1% on P achieved ≥0.75 g/dL increase from baseline in Hgb (p<0.001) suggesting that the increase in hemoglobin is durable. A logistic analysis to determine whether baseline hemoglobin (≤ 10.5 vs >10.5 g/dL) predicted the response of Hgb showed that the response to FC treatment was independent of baseline Hgb (p=0.768). Treatment failure was characterized as Hgb <9.0 g/dL for 2 visits in a row at least 7 days apart and occurred in less subjects in the FC group (4.3%) versus (8.7%) in the P group.

Conclusions: In patients with NDD-CKD and IDA, FC increased and maintained hemoglobin levels independent of baseline Hgb.

Funding: Pharmaceutical Company Support - Keryx Biopharmaceuticals

TH-PO903

Effects of Ferric Citrate on Parameters of Mineral and Bone Metabolism in Patients with Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) Treated for Iron Deficiency Anemia (IDA)

Geoffrey A. Block,[1] Steven Fishbane,[2] Pablo E. Pergola,[3] Katrin Uhlig,[4] John F. Neylan,[4] Glenn Matthew Chertow.[5] *[1]Denver Nephrology, Denver, CO; [2]Hofstra Northwell Health, Great Neck, NY; [3]Renal Associates, San Antonio, TX; [4]Keryx Biopharmaceuticals, Boston, MA; [5]Stanford Univ, Palo Alto, CA.*

Background: Ferric citrate (FC) is an approved iron-based phosphate binder. A recent Phase 3 Clinical trial was completed to evaluate the efficacy and safety of FC for the treatment for IDA in NDD-CKD. Here we evaluate the effect of FC on serum phosphate (Phos), intact parathyroid hormone (PTH) and fibroblast growth factor (FGF)-23 levels when FC dose was titrated to hemoglobin (Hgb).

Methods: 234 subjects randomized 1:1 to FC and Placebo (P) were included in a 16 week Randomized period followed by an 8 week Extension period. Subjects with serum Phos <3.5 mg/dL at screening were excluded. The starting dose of 3 tablets/day was increased at fixed intervals if Hgb at any time point had not increased by ≥1g/dl AND if serum Phos was > 2.5 mg/dL. Between-group changes in serum Phos, PTH, c-terminal and intact FGF-23 were evaluated from baseline to the end of 16 week using MMRM (parametric data) and Wilcoxin Rank-Sum test (non-parametric data).

Results: Data for serum Phos, PTH and FGF-23 are presented in the Table.

	FC (n=117)		P (n=115)		P-value
	BL	EOT	BL	EOT	
Serum Phosphate (mg/dL) mean ± SD	4.23±0.08	3.72±0.06	4.12±0.06	3.86±0.08	0.02
i-FGF23 (pg/mL) median [IR]	134 [90,233]	105 [67,180]	134 [83,202]	120 [82,213]	< 0.001
c-FGF23 (RU/mL) median [IR]	364 [198,601]	233 [137,397]	306 [177,484]	309 [186,503]	< 0.001
PTH (pg/mL) median [IR]	103 [67,171]	84 [58,173]	92 [62,168]	90 [62,148]	
BL- baseline, EOT, end of 16 week randomized period					

During the Randomized Period, 4 (3.4%) and 3 (2.6%) subjects on FC and P, respectively, had serum Phos <2.5 mg/dL.

Conclusions: In patients with NDD-CKD, FC given in doses to raise Hgb, reduced serum Phos, with infrequent excursions below normal. FC also lowered PTH, c-terminal and intact FGF23 levels.

Funding: Pharmaceutical Company Support - Keryx Biopharmaceuticals

TH-PO904

Predictors of Hemoglobin Response to Ferric Citrate in Patients with Non-Dialysis Dependent Chronic Kidney Disease and Iron Deficiency Anemia

Pablo E. Pergola,[1] Steven Fishbane,[2] Geoffrey A. Block,[3] John F. Neylan,[4] Katrin Uhlig,[4] Glenn Matthew Chertow.[5] *[1]Renal Associates PA, San Antonio, TX; [2]Hofstra Northwell Health, Great Neck, NY; [3]Denver Nephrologists, Denver, CO; [4]Keryx Biopharmaceuticals, Boston, MA; [5]Stanford Univ, Palo Alto, CA.*

Background: Ferric citrate (FC), an approved iron-based phosphate binder, raised hemoglobin (Hgb) in a phase 3 trial of iron deficiency anemia (IDA) in patients with Non-Dialysis Dependent CKD (NDD-CKD).We examined demographic and clinical factors and routinely available laboratory tests as determinants of hemoglobin (Hgb) response.

Methods: In the 16 week randomized period, 61/117 FC treated subjects had an increase in Hgb of ≥ 1g/dL at any point (defined as "responders"). We compared baseline characteristics and laboratory changes of responders and non-responders. Laboratory variables (Hgb, TSAT, ferritin, eGFR, phosphate, calcium, bicarbonate, PTH, and albumin) identified as candidate predictors of Hgb change in univariate analyses (with a p-value of ≤0.1) were entered into multivariable linear regression analysis. PTH was log transformed.

Results: Baseline demographic and clinical characteristics did not differ by responder status. In univariate analyses, TSAT, ferritin, eGFR, and phosphate were identified as candidate predictors of Hgb change. TSAT and eGFR combined provided the best fitting multivariate model. A 5% lower TSAT was associated with a 0.2 g/dL (95% confidence interval 0 to 0.35, p=0.029) greater increase in Hgb; a 10 ml/min/1.73 m2 higher eGFR with a 0.2 g/dL (0 to 0.35, p=0.036) greater increase in Hgb. Responders relative to non-responders experienced larger increases in TSAT (20% versus 11%, p=0.01) and ferritin (164 versus 117 ng/dL, p=0.045) during the trial.

Conclusions: Patients with NDD-CKD and IDA respond to FC with an increase in Hgb regardless of degree of iron deficiency and renal impairment. Patients with more pronounced iron deficiency (lower TSAT) and better kidney function (higher GFR) experience a more robust Hgb response to FC associated with repletion of iron stores, as reflected by greater increases in TSAT and ferritin among responders.

Funding: Pharmaceutical Company Support - Keryx Biopharmaceuticals

TH-PO905

Efficacy and Safety of Sevelamer Carbonate in Hyperphosphatemic Pediatric Patients with Chronic Kidney Disease Sahar A. Fathallah-Shaykh,[1] Mark R. Benfield,[2] Dorota Drozdz,[3] Joseph T. Flynn,[4] Randall Jenkins,[5] Katherine Wesseling-Perry,[6] Sarah J. Swartz,[7] Craig S. Wong,[8] Beverly Accomando,[9] Gerald F. Cox,[9] Bradley Warady.[10] *[1]U of Alabama at Birmingham, Birmingham, AL; [2]Pediatric Nephrology of Alabama, Birmingham, AL; [3]Dept of Pediatric Nephrology, JU MC, Krakow, Poland; [4]Seattle Children's Hosp, Seattle, WA; [5]Oregon Health & Science U, Portland, OR; [6]Children's Health Center, UCLA, Los Angeles, CA; [7]Texas Children's Hosp, Houston, TX; [8]U of New Mexico HSC, Albuquerque, NM; [9]Sanofi Genzyme, Cambridge, MA; [10]Children's Mercy Hosp, Kansas City, MO.*

Background: No currently marketed oral phosphate binders are FDA-approved for management of hyperphosphatemia in children with chronic kidney disease (CKD). This phase 2 study (NCT01574326) evaluated safety and efficacy of sevelamer carbonate (SC) in hyperphosphatemic pediatric patients with CKD before/on dialysis.

Methods: After 2–4 week screening/washout, children with serum phosphorus (SP) higher than age-appropriate levels were randomized to receive SC/placebo in 0.4–1.6 g doses based on body surface area for a 2-week fixed-dose period (FDP) followed by a 6-month single-arm open-label dose titration period (DTP). Primary efficacy endpoint: change in SP from baseline to end of FDP (ANCOVA); secondary efficacy endpoint: change in SP from baseline to end of DTP (descriptive statistics). Adverse events (AEs) were recorded.

Results: Of 101 patients enrolled at 29 centers, 66 completed the study (74% adolescents [mean age=14.1 years]; 77% on dialysis); renal transplant was the main reason for discontinuation. Mean overall baseline SP was 7.16 mg/dL. SC significantly reduced SP levels from baseline during FDP (–0.90 mg/dL,*P*=0.001) and DTP (–1.18 mg/dL,*P*<0.0001). SP became age-appropriate in 8% patients on SC during FDP and overall 27% patients at end of DTP. Safety/tolerability of SC was comparable to placebo during FDP; mild gastrointestinal AEs occurred in DTP. No clinically relevant changes occurred in vital signs and in calcium/bicarbonate levels.

Conclusions: Sevelamer carbonate lowered SP significantly in hyperphosphatemic children with CKD, with no significant safety issues identified.

Funding: Pharmaceutical Company Support - Sanofi Genzyme

TH-PO906

Low Rate of Early Response to Oral Iron in Patients with Non-Dialysis Dependent CKD (ND-CKD) Iain C. Macdougall,[1] Andreas H. Bock,[2] Fernando Carrera,[3] Kai-Uwe Eckardt,[4] Carlo A. Gaillard,[5] David B. Van Wyck,[6] Yvonne Meier,[7] Sylvain Larroque,[7] Simon D. Roger.[8] *[1]King's College Hospital, London, United Kingdom; [2]Kantonsspital Aarau, Aarau, Switzerland; [3]Eurodial, DaVita, Leiria, Portugal; [4]Uni. Erlangen-Nürnberg, Erlangen, Germany; [5]Uni. Medical Centre Groningen, Groningen, Netherlands; [6]DaVita Healthcare Partners Inc, Denver, CO; [7]Vifor Pharma, Glattbrugg, Switzerland; [8]Renal Research, Gosford, NSW, Australia.*

Background: Hematopoietic response rates to oral iron in ND-CKD are low. Understanding the likelihood of a subsequent response after initial non-response could guide decision-making.

Methods: *Post hoc,* 626 iron-deficient patients with ND-CKD and anemia, randomized (2:1:1) in the FIND-CKD trial to oral iron or IV ferric carboxymaltose (FCM, targeting higher or lower ferritin) were assessed for response (Hb increase ≥1 g/dL from baseline [BL]) during the first 8 weeks, when additional anemia therapy was permitted only for rescue. Patients without Hb data at BL and week 4 (W4) for the W4 analysis, or BL and weeks 4 and 8 for the week 8 (W8) analysis were excluded. Data from the FCM groups are shown for comparison.

Results: At week 4, the response rate was 22% with oral iron. BL Hb, ferritin and TSAT were higher in W4 non-responders vs responders (Table). With oral iron, only 11% of patients with no response at W4 responded by W8. Among W4 non-responders, 4.4% of patients received rescue therapy by W8 under oral iron.

Conclusions: Hematopoietic response to oral iron was achieved in ~20% of ND-CKD patients with anemia and iron deficiency by W4. Thereafter, ~10% of early non-responders responded by W8. Earlier intervention for non-response to oral iron may improve anemia management.

	Oral iron	High ferritin FCM	Low ferritin FCM
Hb response at W4, n (%)*	63/292 (22%)	61/149 (41%)	20/144 (14%)
Hb response at W8 in week 4 non-responders, n (%)*	20/180 (11%)	23/73 (32%)	17/104 (16%)
Baseline values:W4 responders vs non-responders			
Mean Hb, g/dL	9.9 vs 10.5	10.1 vs 10.5	9.8 vs 10.5
Mean ferritin,ug/L	37 vs 61	41 vs 65	37 vs 57
TSAT, %	12 vs 17	12 vs 19	15 vs 16

*Excluding patients with rescue therapy.

Funding: Pharmaceutical Company Support - This work was supported by Vifor Pharma Glattbrugg, Switzerland

TH-PO907

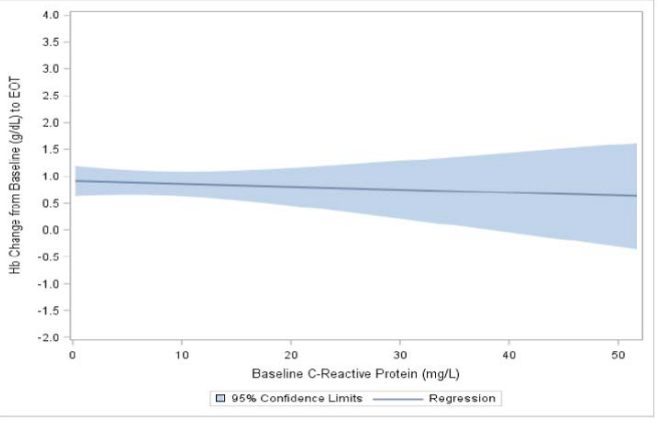
Efficacy and Dose Requirements of Vadadustat Are Independent of Systemic Inflammation and prior Erythropoiesis-Stimulating Agent (ESA) Dose in Patients with Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) Volker H. Haase,[1] Bruce S. Spinowitz,[2] Pablo E. Pergola,[3] Zeeshan Khawaja,[4] Jason Chan,[4] Qing Zuraw,[4] Bradley J. Maroni,[4] Ramin Farzaneh-Far.[4] *[1]Vanderbilt Univ, Nashville, TN; [2]New York Presbyterian Queens, Flushing, NY; [3]Renal Associates PA and Univ of Texas, San Antonio, TX; [4]Akebia Therapeutics, Inc., Cambridge, MA.*

Background: CKD is associated with systemic inflammation, which in turn is linked to worsening anemia and high ESA dose requirements. Vadadustat is a novel, once-daily, oral, hypoxia-inducible factor prolyl-hydroxylase inhibitor in development for the treatment of renal anemia.

Methods: A randomized, double-blind, placebo-controlled study was conducted to assess the hemoglobin (Hb) response to 20 weeks of vadadustat dosing in NDD-CKD patients with anemia. Patients were randomized (2:1) to receive vadadustat (n=138; 450mg QD) or placebo (n=72). A post-hoc analysis was performed to explore correlations between final vadadustat dose, mean change in Hb, markers of inflammation (hepcidin and C-reactive protein [CRP]), and weekly ESA dose prior to study entry.

Results: Baseline inflammatory markers and weekly ESA dose (prior to study entry) did not correlate with vadadustat dose at Week 20 (p=0.4). The magnitude of the mean increase in Hb (from baseline to Week 20) was independent of baseline hepcidin (p=0.6), ESA dose (p=0.9) and CRP (p=0.6; figure). In addition, vadadustat treatment maintained Hb within target range (p<0.0001 vs placebo), with few Hb excursions above 13g/dL (6/138; 4%).

Change in Hb from baseline to Week 20 (end-of-treatment) was independent of the baseline CRP levels



Conclusions: The Hb response and vadadustat dose requirement for correction and maintenance of Hb are independent of underlying systemic inflammation and baseline ESA dose in patients with NDD-CKD.

Funding: Pharmaceutical Company Support - Akebia Therapeutics, Inc.

TH-PO908

Daprodustat, a HIF-Prolyl-Hydroxylase Inhibitor, Increases and Maintains Hemoglobin over 24 Weeks in Anemic Chronic Kidney Disease Subjects Louis Holdstock,[1] Borut Cizman,[1] Amy M. Meadowcroft,[1] Nandita Biswas,[1] Delyth Jones,[1] Brendan M. Johnson,[2] John J. Lepore,[1] Sung Gyun Kim,[3] Alexander Ralph Cobitz.[1] *[1]GlaxoSmithKline; [2]Roivant Sciences; [3]Hallym Univ, South, Korea.*

Background: The efficacy and safety of daprodustat (GSK1278863) was evaluated in 252 chronic kidney disease (CKD) subjects over 24 weeks (w).

Methods: rhEPO-naïve subjects were randomized 3:1 and rhEPO-users 1:1 to daprodustat (1–4mg, based on starting hemoglobin [Hgb; g/dL] for rhEPO-naïve subjects; 2 mg for rhEPO-users) or control groups (CTRL; rhEPO per investigator discretion; 91% of rhEPO naive subjects and all rhEPO users received at least 1 rhEPO dose). For rhEPO-naïve subjects, entry Hgb was 8-10 (group [G] 1) or 8-11 (G2); for rhEPO-users, entry Hgb was 9-10.5 (G1) or 9-11.5 (G2). Study drug was titrated to maintain Hgb in a target range (TR) of 9–10.5 (G1) or 10–11.5 (G2).

Results: In rhEPO naïve subjects, mean Hgb increased from 9.6 to 10.2 (G1) and 10.1 to 11.0 (G2) in the daprodustat groups, and from 9.6 to 10.6 (G1) and 10.2 to 11.1 (G2) in CTRL. Median percent of time within Hgb target range was 81% for the combined daprodustat groups and 47% for combined CTRL. In rhEPO users, Hgb was maintained in both daprodustat groups, whereas Hgb in CTRL increased by 0.7 (G1) and 0.4 (G2). The median percent of time within Hgb target range was 94% for the combined daprodustat groups compared to 88% for the combined CTRL. In rhEPO naïve subjects, hepcidin decreased from baseline at 24 w by 19.3% in the daprodustat group and increased by 6.7% in CTRL. In rhEPO users, hepcidin decreased by 9.9% at 24 w in the daprodustat group, and by 17.1% in CTRL. Daprodustat did not effect plasma EPO or VEGF levels throughout the study. There were no differences between groups in blood pressure or eGFR. Daprodustat was well tolerated with an adverse event profile consistent with the CKD population.

Conclusions: In patients with CKD, daprodustat safely and effectively enabled rhEPO users to achieve target Hgb levels and maintained target Hgb levels in over a 24-w period. Daprodustat reduced hepcidin, and did not change plasma EPO or VEGF levels. These data support future long-term clinical studies of daprodustat to treat anemia of CKD.

Funding: Pharmaceutical Company Support - This study was funded by GlaxoSmithKline

TH-PO909

High versus Low Dose Erythropoiesis-Stimulating Agents in People with End-Stage Kidney Disease Treated with Hemodialysis (C.E. DOSE Trial): A Pragmatic, Multicenter, Randomized Controlled Trial

Valeria M. Saglimbene,[1,2] Suetonia Palmer,[3] Marinella Ruospo,[1,4] Gabrielle J. Williams,[2] Jonathan C. Craig,[2] Jorgen B.A. Hegbrant,[1] Giovanni F.M. Strippoli.[1,2,5] *[1]Diaverum Medical Scientific Office; [2]Univ of Sydney; [3]Univ of Otago Christchurch; [4]Amedeo Avogadro Univ of Eastern Piedmont; [5]Univ of Bari, on behalf of the C.E. DOSE Investigator.*

Background: The increased risks of death and adverse cardiovascular events with erythropoiesis-stimulating agent (ESA) therapy targeting a higher hemoglobin level in patients with ESKD are established, but it is unclear whether these adverse effects can be mitigated and quality of life benefits maintained when a fixed treatment dose approach is used.

Methods: The C.E. DOSE trial was a multicenter, pragmatic, non-blinded, randomized, controlled, parallel-group trial allocating 656 hemodialysis patients with anemia to receive either high dose (18,000 IU epoetin alfa or epoetin beta or 90 mcg darbepoetin alfa per week) or low dose (4000 IU epoetin alfa or epoetin beta or 20 mcg darbepoetin alfa per week) ESA. The primary outcome was a composite of death or a CV event (non-fatal myocardial infarction, non-fatal stroke, or hospitalization for acute coronary syndrome, transient ischemic attack, unplanned percutaneous coronary intervention or peripheral revascularization). ClinicalTrials.gov, number NCT00827021.

Results: High dose ESA did not increase the primary outcome by 12 months (55 [17%] *vs* 46 [14%] patients; hazard ratio [HR] 1.19, 95% CI 0.81–1.77), death (40 [12%] *vs* 35 [11%]; HR 1.21, 95% CI 0.77–1.91), or myocardial infarction (8 [2%] *vs* 4 [1%]; HR 1.78, 95% CI 0.52-6.08), and had no impact on HRQOL (mean difference in physical composite score at 12 months 1.70, 95% CI -0.95 to 4.35).

Conclusions: In this fixed-dose trial of ESA treatment for anemia in patients with ESKD, a high dose strategy had uncertain effects on mortality, CVEs, and health-related quality of life. Funding: Italian Medicines Agency.

TH-PO910

Efficacy of Add-On Tolvaptan in the Very Early Treatment Phase of Congestive Heart Failure Complicated by Advanced CKD

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Background: The aim of this subanalysis was to investigate the efficacy of add-on tolvaptan (TLV) in congestive heart failure (CHF) patients complicated by advanced CKD with or without hyponatremia (HN) in the very early treatment phase.

Methods: The Kanagawa Aquaresis Investigators Trial of TLV on HF Patients with Renal Impairment was a multicenter, open-labeled, randomized, and controlled prospective clinical study consisting of 81 Japanese patients with CHF and residual signs of congestion despite oral furosemide (FUR) treatment (≥40 mg/day). They were randomly assigned to 7-day treatment with either ≤15 mg/day of newly added TLV or ≤40 mg/day of increased FUR. A subanalysis was conducted for 73 patients, except those for whom some results were not available within 2 days from baseline (day 1). We classified these patients into two groups according to their serum sodium level (sNa): non-HN (sNa>135 mEq/L, n=58) and HN (sNa≤135 mEq/L, n=15). Subsequently, each group was stratified into two subgroups (increased FUR/added TLV, n=32/26 in non-HN group; n=5/10 in HN group), and the differences (Δ) of urine and serum parameters between day 1 and 3, were compared between the subgroups in each group.

Results: ΔUrine volume (UV) was greater in TLV subgroups than in FUR subgroups (472.3±158.2 vs 78.9±60.1 mL/day in non-HN group, P=0.024; 446.0±139.6vs 202.2±246.4 mL/day in HN group, P=0.426), and ΔuOsm was also greater in TLV subgroups (-100.2±25.3 vs -21.0±8.9 mOsm/kg in non-HN group, P<0.001; -96.5±15.9 vs -16.8±23.6 mOsm/kg in HN group, P=0.019). As a result, ΔsNa was greater in TLV subgroups (2.0±0.5 vs 0.1±0.3 mEq/L in non-HN group, P=0.003; 2.7±1.3 vs 0.7±0.5 mEq/L in HN group, P=0.154).

Conclusions: In this subanalysis, add-on TLV increased UV, decreased uOsm and improved sNa more than increased FUR in the very early treatment phase of CHF complicated by advanced CKD.

TH-PO911

NT-proBNP Levels Predict the Individual Drug Response to Aliskiren in Patients with Type 2 Diabetes at High Cardio-Renal Risk

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Background: The individual response to renin-angiotensin-system (RAS) intervention is blunted in the setting of volume overload. Diuretic treatment or low sodium diet is often required to enhance the response to RAS intervention. We investigated whether NT-proBNP, a biomarker of volume expansion, can be used to predict the individual response to aliskiren.

Methods: A post-hoc analysis was performed in the ALTITUDE trial, a double blind randomized controlled trial comparing the effect of aliskiren 300 mg/d vs. placebo on cardio-renal endpoints in 8561 patients with type 2 diabetes at cardio-renal risk. Data from 5081 patients with available NT-proBNP measurements were used. The primary endpoint was a composite of CV death, resuscitated sudden death, MI, stroke, hospitalization for heart failure, end-stage renal disease (ESRD), or doubling of serum creatinine. We investigated variation in the effect of aliskiren on the cardio-renal endpoint based on baseline tertiles of NT-proBNP in Cox proportional hazard regression models using an interaction term (treatment*NT-proBNP).

Results: Median NT-proBNP levels by tertiles were 50, 157, and 534 pg/ml, respectively. During a median follow-up of 2.5 years, 840 (16.4%) patients experienced a cardio-renal event. There was a statistically significant trend across NT-proBNP tertiles, with a lower risk of events in the aliskiren group, compared with placebo, in patients with a lower NT proBNP and the converse in patients with a higher NT proBNP (Table). Similar trends were observed for the cardiovascular and ESRD endpoints.

Conclusions: Elevated NT-proBNP levels, reflecting volume overload, predict a poor response to aliskiren in patients with type 2 diabetes at cardio-renal risk. These data highlight the importance of achieving adequate extracellular volume control by diuretic treatment or dietary sodium restriction.

Extracellular Volume	NT proBNP Tertiles	Hazard Ratio Cardio-Renal Endpoint	P trend
Low	≤ 94	0.80 (0.58 – 1.10)	
Mid	95 - 266	0.98 (0.76 – 1.26)	0.009
High	> 266	1.25 (1.04 – 1.51)	

Funding: Pharmaceutical Company Support - Novartis sponsored the ALTITUDE trial

TH-PO912

Effect of Direct Renin Inhibitor Aliskiren Compared with Angiotensin II Receptor Blockers on Clinic and Ambulatory Blood Pressure Profiles in Hypertensive Chronic Kidney Disease Patients

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Background: Increasing evidence indicates that appropriate control of blood pressure (BP) is critical in the management of hypertensive patients with chronic kidney disease (CKD). The direct renin inhibitor aliskiren (DRI) reportedly exert comparable BP lowering effects in hypertension. However, the clinical evidence of DRI in hypertensive patients with CKD is insufficient as compared to that of angiotensin II receptor blockers (ARBs). In the present study, we compared effects of DRI and ARBs on clinic and ambulatory BP profile in hypertensive patients with CKD.

Methods: Hypertensive patients with CKD who have already been treated with ARBs therapy were eligible for the study. After the 4-week run-in period, eligible patients were randomized either to DRI replacement group (DRI group) or control ARBs group (ARB group) during the 24-week active treatment period. Clinic BP and ambulatory BP profiles were evaluated at baseline and after the protocol therapy.

Results: 36 patients were enrolled and randomly assigned to DRI group (n=18) or ARB group (n=18). One patient in each group withdrew consent. The baseline clinic BP levels and the after-treatment/baseline (A/B) ratios of clinic BP levels, estimated after 24-week treatment period, were similar in both groups. However, with respect to the effects on ambulatory BP, the A/B ratios of the daytime and nighttime systolic BP in DRI group were significantly higher than those in ARB group (DRI vs ARB: daytime systolic BP, 0.99±0.11 vs 0.92±0.08, *P*=0.041; nighttime systolic BP, 1.03±0.12 vs 0.91±0.12, *P*=0.010). Concomitant anti-hypertensive medication was comparable in both groups during 24 weeks of treatment.

Conclusions: The results of the present study suggest that DRI therapy is not superior to ARB therapy in lowering ambulatory BP in hypertensive CKD patients, in spite of comparable clinic BP lowering effects.

TH-PO913

Effect of Spironolactone on Vascular Stiffness in Hemodialysis - A Randomized Crossover Study

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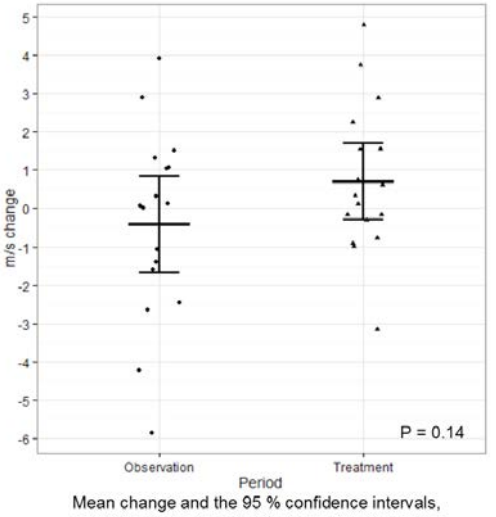
Background: Hemodialysis (HD) is associated with high cardiovascular mortality and increased vascular stiffness is a known risk factor for cardiovascular events. Spironolactone treatment is associated with improved survival in HD and in other populations vascular

stiffness has been reduced. This study investigates possible cardiovascular actions of spironolactone in HD and we hypothesized that spironolactone would affect vascular stiffness as measured by pulse-wave velocity (PWV) in HD.

Methods: This was a two center, open, randomized crossover study. Primary end-point was based on long-term ECG changes and the present sub-study represents a secondary hypothesis. Subjects on HD (n = 30) were randomly allocated using sealed envelopes into two study arms starting with either treatment with spironolactone 50 mg daily or observation for twelve weeks, then a six week wash-out period followed by cross-over for another twelve weeks. PWV was measured before and after treatment and observation, respectively. Difference in PWV change during the two periods was analyzed using confidence intervals (CI) and paired Student's t-test.

Results: Complete PWV data was available for 17 participants and included in the analysis. Mean PWV change was 0.71 (95 % CI: -0.28 – 1.71) m/s during treatment and -0.42 (-1.69 – 0.85) m/s during observation. The difference between periods was not statistically significant, p = 0.14. No adverse events were considered associated with the intervention.

Figure 1: Change in Pulse Wave Velocity



Mean change and the 95 % confidence intervals, calculated from the t-distributions. P-value for the difference between periods. n = 17.

Conclusions: PWV increased slightly after treatment with spironolactone but compared with the observation period the change was not statistically significant. Although this study has low power for detecting changes in PWV, results indicate that spironolactone does not have a clinically significant positive effect on vascular stiffness in HD.

Funding: Government Support - Non-U.S.

TH-PO914

Impact of Vitamin D on Cardiac Structure and Function in Chronic Kidney Disease: A Randomised Controlled Trial Debasish Banerjee,[1] Nihil Chitalia,[1] Kristel E. Medina-Rodríguez,[1] Laura E. Tooth,[1] Evan Appelbaum,[2] Ravi I. Thadhani,[2] Juan Carlos Kaski,[1] David Goldsmith.[3] *[1]St. Georges Univ of London; [2]Harvard Univ; [3]Guys Hospital.*

Background: CKD is associated with cardiac hypertrophy. We examined impact of oral cholecalciferol supplementation on cardiac structure and function, in a double-blind, placebo-controlled randomised trial.

Methods: After screening 84 stable, non-diabetes, CKD stage 3-4 patients on ACEi/ARB, with vitamin D concentrations <75 nmol/L, 48 patients with left ventricular [LV] mass in the upper tertile of normal range, were randomised to receive either 6 directly-observed doses of 100,000 units of cholecalciferol or matched placebo over 42 weeks. Cardiac MRI and echocardiography were performed at baseline and 52 weeks.

Results: The clinical characteristics were well matched at baseline between vitamin D and placebo groups as follows: age 52±12 vs 52±11 years (p=0.94); eGFR 35±11 vs. 34±11 (p=0.75); calcium 2.4±0.1 vs 2.4±0.1 (p=0.37); phosphate (1.1±0.2 vs 1.0±0.3; p=0.42). The vitamin D concentrations in the vitamin D and placebo groups; at baseline, 24 weeks and 52 weeks, were 43±18 vs. 43±20 [p=0.95], 77±14 vs. 49±27 [p<0.001], 78±24 vs. 43±21 nmol/L [p<0.001] respectively. The left ventricular mass by MRI scan at baseline and 52 weeks, in the vitamin D and placebo groups were 104±39 vs. 100±29 gm [p=0.97] and 108±39 vs. 96±27 gm [p=0.28]. At 52 weeks there were no difference in LV volumes, RV volumes and mass, RA area, LA area, Mitral valve E/A ratio, E/e' ratios at septum and lateral wall, pulmonary artery systolic pressure between the vitamin D and placebo groups [see table 1].

Conclusions: Cholecalciferol supplementation over 52 weeks increased vitamin D levels but did not have an impact on cardiac structure of function in stable, non-diabetic, CKD patients with low vitamin D.

Table 1: The outcome variables at 52 weeks

Outcome measures	Placebo	Vitamin D	p value
LV ED Mass (gm)	96±26	108±39	0.28
LV stroke volume (ml)	96±21	95±23	0.86
LV ED Volume (ml)	149±36	154±36	0.67
LV ES Volume (ml)	108±29	118±46	0.25
RV Stroke Volume (ml)	97±24	98±33	0.74
RV ED volume (ml)	161±43	162±39	0.92
RV ES Volume (ml)	66±26	64±15	0.69
RV ejection fraction (%)	59.9±7.0	59.8±8.6	0.97
RA Area (cm^2)	20±5	20±4	0.68
LA Area (cm^2)	21±3.7	22±3.7	0.63
MV e/a ratio	1.02±0.22	0.96±0.27	0.41
E/e' lateral wall	9.68±4.50	7.6±2.80	0.93
E/e' septum wall	10.8±3.1	9.9±3.2	0.92
PA systolic pressure (mmHg)	22.5±8.0	22.4±5.3	0.96

Legend: LV=left ventricle, RV=right ventricle, RA=right atrium, LA=left atrium, PA=pulmonary artery, ED=end diastolic, ES=end systolic, MV=mitral valve

TH-PO915

Prospective Trial of Exogenous Growth Hormone Administration on Circulating Concentrations of α-Klotho in Healthy and Chronic Kidney Disease Subjects Aaltje Ymkje Adema,[1] Camiel L.M. de Roij van Zuijdewijn,[1] Joost Hoenderop,[2] Martin H. De Borst,[3] Pieter M. Ter Wee,[1] Marc G. Vervloet.[1] *[1]Nephrology, VU Univ Medical Center, Amsterdam, Noord-Holland, Netherlands; [2]Physiology, Radboud Univ Medical Center, Nijmegen, Gelderland, Netherlands; [3]Internal Medicine, Div of Nephrology, Univ Medical Center Groningen, Groningen, Netherlands.*

Background: Chronic kidney disease (CKD) is characterized by a decline in soluble α-Klotho levels, which may play a role in adverse outcomes. Cross-sectional studies demonstrated that growth hormone (GH) and α-Klotho concentrations are associated.This work represents the first study reporting on the effect of exogenous GH administration on α-Klotho concentrations in patients with mild CKD and healthy subjects.

Methods: A prospective, single-center open label case-control pilot study was performed involving 8 patients with mild CKD and 8 healthy controls matched for age and sex. All participants received subcutaneous GH injections (Genotropin®, 20 mcg/kg/day) for 7 consecutive days. α-Klotho concentrations were measured at baseline, after 7 days of therapy and 1 week after discontinuation of the treatment.

Results: Three women and five men were included in both groups (mean age 46.9±12.9 and 44.5±11.4 years; eGFR 57±17 and 100±8 ml/min/1.73m^2 in CKD and healthy controls respectively). At baseline, α-Klotho concentrations were not significantly different between CKD-patients and controls (529±132 vs. 646±338 pg/mL, P=0.38). GH therapy successfully increased IGF-1 concentrations from 26.8±5.0 nmol/L to 61.7±17.7 nmol/L (P<0.001) in the pooled cohort, as well as in both groups (26.3±2.8 to 59.8±20.5 nmol/L (P=0.002) in CKD and 27.3±6.8 to 63.6±15.6 nmol/L (P=0.001) in healthy controls). However, α-Klotho concentrations did not increase significantly after GH, neither in the pooled cohort (588 ± 255 to 669 ± 286 pg/mL, P=0.10) nor in each treatment group (529±132 to 625±325 pg/mL (P=0.29) and 646±338 to 712±256 pg/mL (P=0.19) in CKD and healthy controls respectively).

Conclusions: Exogenous growth hormone therapy does not increase α-Klotho concentrations in patients with mild CKD or healthy controls.

Funding: Pharmaceutical Company Support - Pfizer provided the research product

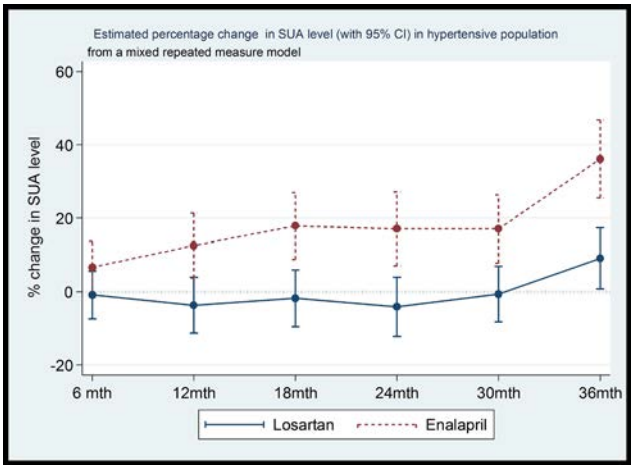
TH-PO916

Losartan Significantly Lowers Serum Uric Acid in Hypertensive Children with Proteinuria Charlotte Bryant,[1] Azita Rajai,[2] Ronald J. Hogg,[3] Nicholas J. Webb.[1] *[1]Royal Manchester Children's Hospital, United Kingdom; [2]Central Manchester Univ Hospital, United Kingdom; [3]Texas A&M Health Science Center College of Medicine.*

Background: Serum uric acid (SUA) has emerged as a potentially modifiable risk factor for the progression of chronic kidney disease (CKD). We have previously reported the results of a randomised controlled trial showing that losartan and enalapril are comparable in their efficacy and safety in reducing proteinuria in children with CKD (KI 2012;82:819).

Methods: In a post-hoc analysis of these patients, we determined the effect of losartan vs. enalapril on SUA over 36 months in 201 normotensive and 47 hypertensive children with CKD and examined the change in estimated glomerular filtration rate (eGFR).

Results: Despite no overall difference between the two treatment groups, change in SUA was significantly different between losartan and enalapril in the hypertensive population at 12 months (3.69% decrease [95% CI -3.93%, 11.31%]) vs. 12.57% increase [3.72%, 21.41%], p=0.007). This significant difference remained after 24 and 36 months of treatment.



This effect was not observed in normotensive patients. The change in SUA showed a statistically significant negative correlation with change in eGFR at each time point over 36 months p<0.001.

Conclusions: Compared to enalapril, losartan significantly lowers SUA in hypertensive children with CKD and this is correlated with change in eGFR. Studies are needed to evaluate whether changes in clinical practice, such as the preferential use of losartan over other antihypertensive agents, will slow progression in children with CKD.

TH-PO917

Impact of Baseline Renal Function on Efficacy and Safety of Febuxostat Extended and Immediate Release Formulation in Patients with Gout

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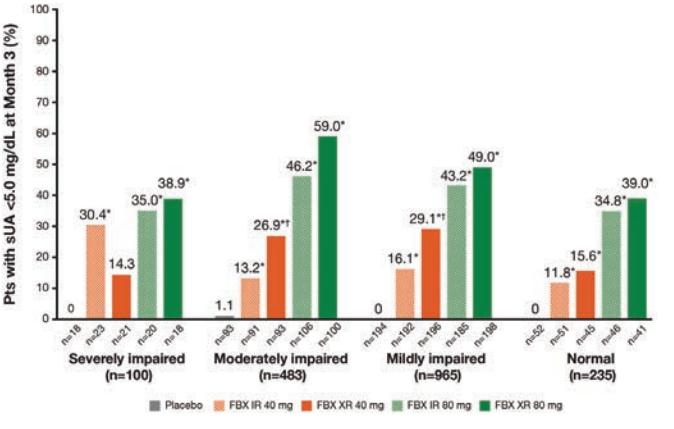
Background: Phase 1/2 data suggest that febuxostat (FBX) extended release (XR) may provide equal or better reduction in serum urate level (sUA), with reduced exposure vs currently marketed FBX immediate release (IR) in patients (pts) with gout. This Phase 3 study compared the efficacy and safety of XR vs IR in pts with gout stratified by baseline (BL) renal function.

Methods: In a multicenter, randomized, placebo-controlled, double-blind study, 1783 pts with gout (sUA ≥8.0 mg/dL; estimated glomerular filtration rate ≥15 mL/min; ≥1 gout flare within previous 12 months [mos]) received placebo or XR 40 mg, XR 80 mg, IR 40 mg, or IR 80 mg once daily for 3 mos; ≥30% of pts had moderate-to-severe BL renal impairment. The primary endpoint was the percentage of pts with sUA <5.0 mg/dL at 3 mos.

Results: In the primary analysis, more pts achieved sUA <5.0 mg/dL at 3 mos with XR 40 vs IR, p<0.001. Although the difference was not statistically significant after multiplicity adjustment, more XR 80-mg treated pts achieved the primary endpoint compared with IR 80 mg. By BL renal function, more pts with mild or moderate renal impairment achieved sUA <5 mg/dL with XR 40 mg vs IR (p<0.05); there was a non-statistically significant trend for XR 80 mg vs IR (**Figure**). Treatment-emergent adverse events were infrequent and did not differ among renal function subgroups.



*p<0.05 vs placebo; †p<0.05 vs equivalent dose IR formulation

Normal renal function = eGFR ≥90 mL/min; Mild renal impairment = eGFR ≥60 to 89 mL/min;
Moderate renal impairment = eGFR ≥30 to 59 mL/min; Severe renal impairment = eGFR ≥15 to 29 mL/min

eGFR = estimated glomerular filtration rate; FBX = febuxostat; IR = immediate release; pts = patients; sUA = serum urate; XR = extended release

Conclusions: More XR-treated pts achieved sUA targets of <5 mg/dL vs IR-treated pts with mild or moderate renal impairment. There were no meaningful differences in safety data for XR vs IR in pts with gout stratified by BL renal function. Both FBX formulations were efficacious in reducing sUA and well tolerated.

Funding: Pharmaceutical Company Support - Takeda

TH-PO918

The Comparison of Febuxostat and Allopurinol in Chronic Gout Patients with Chronic Kidney Disease, a Randomized Prospective Study

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Background: The aim of this 12-week, open-label, non-inferiority trial was to compare the safety and efficacy of febuxostat with allopurinol in treating chronic gout patients with chronic kidney disease (CKD).

Methods: Patients were randomized to febuxostat (n= 53; 40mg daily for the first 4 weeks, 80mg thereafter) or allopurinol (n=53; dose adjusted based on ones kidney function), and both groups were stratified by baseline serum uric acid (SUA) 10.0 mg/dL. SUA was checked for 4 times (week2, 4, 8, 12) The primary end point was the proportion of SUA below 6.0 mg/dL at the end of the study. The non-inferiority margin for the difference in rates *(of SUA below 6.0 mg/dL)* was defined as -15 %. Efficacy analyses were done both by intention-to-treat (ITT) and per protocol (PP).

Results: Uric acid control with febuxostat (n= 49, 94.2 %) was non-inferior to that achieved with allopurinol (n= 13, 26 %), difference 0.68 [97.5 % CI 0.54 to ∞]. The proportion of SUA below 6.0 mg/dL at week 2 was 57.69 % (febuxostat) and 12% (allopurinol), respectively. And the rate increased in both group to 94.23 % (febuxostat), 26 % (allopurinol) at week 12 (p<0.0001).

	Febuxostat (N=53)	Allopurinol (N=50)	P=value
ITT group			
Initial SUA < 10 mg/dL At week 12 SUA < 6.0 mg/dL, N (%)	31 (93.94)	10 (33.33)	< 0.0001
Initial SUA > 10 mg/dL At week 12 SUA < 6.0 mg/dL, N (%)	18 (94.74)	3 (15)	< 0.0001
PP group			
Initial SUA < 10 mg/dL At week 12 SUA < 6.0 mg/dL, N (%)	28 (100)	10 (38.46)	< 0.0001
Initial SUA > 10 mg/dL At week 12 SUA < 6.0 mg/dL, N (%)	17 (94.44)	15 (83.33)	< 0.0001

The difference rate of SUA compared with baseline SUA increased with time in febuxostat, but not in allopurinol (at week 12: -47.13±15.1 % vs -24.34±11.45 %, p<0.0001). The rate of GFR change or incidence of AKI had no difference in both group. Skin eruption was observed in 1 case with allopurinol, but was tolerable.

Conclusions: Febuxostat was as effective as allopurinol in reducing SUA in chronic gout patients with CKD, with a similar safety profile.

Funding: Pharmaceutical Company Support - SK Chemicals

TH-PO919

Orally Administered Complement 5a Receptor Inhibitor CCX168 Shows Ex Vivo Anti-Thrombogenic Activity in a Phase 2 Study in End-Stage Renal Disease Patients with Atypical Hemolytic Uremic Syndrome (ACCESS Study)

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Background: The primary objective of this study is to evaluate whether CCX168 treatment of patients with atypical hemolytic uremic syndrome (aHUS) dampens the ex vivo thrombogenic properties of the serum on cultured microvascular endothelial cells.

Methods: Up to 10 patients with aHUS on stable peritoneal or hemodialysis for ≥6 mo are dosed at 30 mg CCX168 b.i.d. for 2 wks. Blood samples are collected during the study for ex vivo thrombogenesis assay (Ruiz-Torres MP et al, Thromb Haemost 2005;93:443-52).

Results: Five patients with aHUS (CFH, C3, CFI mutations: n=1 each, no mutations: n=2) have been treated to date. Mean±SD age: 50.6±8.96, male 1, female 4; 2 on peritoneal and 3 on hemodialysis. All patients showed a decrease in thrombus size (mean -83%); 3 showed 100% inhibition of thrombus formation at Day 14; 2 showed >30% inhibition. When CCX168 treatment was stopped, the thrombogenic activity returned to baseline levels (see table).

Treatment Period (N=4)	Thrombus Size (pixel²) mean ± SEM
Baseline	8690 ± 4811
Day 2	12582 ± 3018
Day 14	3964 ± 3960 *
No Treatment Follow-up Period	
Day 16	4364 ± 2367
Day 21	9680 ± 4504
* P = 0.016 versus baseline for paired t test	

Not unexpectedly, serum C3, C4, and plasma C5b-9 levels were unchanged. Two patients had low platelet counts which increased on CCX168 (163 to 223/μL and 152 to 196/μL). One patient, with a high cardiovascular event risk because of diffuse coronary calcifications and several cardiovascular risk factors related to long history of uremia and

a previous failing kidney transplant had a serious adverse event during a peritoneal dialysis session on Day 4 of cardiac asystole resulting in death. This event was not considered related to CCX168 use.

Conclusions: CCX168 was effective in reducing aHUS-induced thrombus formation in an ex vivo thrombogenesis assay, with all 5 patients showing an inhibition and 3 of 5 patients showing a complete inhibition.

Funding: Pharmaceutical Company Support - ChemoCentryx, Inc.

TH-PO920

A Multi-Level Intervention among Low-Income Patients with Chronic Kidney Disease to Improve Blood Pressure Control: Kidney Awareness Registry and Education Pilot Trial

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Background: Low patient awareness and provider recognition of CKD can impede efforts to slow CKD progression and lead to adverse outcomes. A randomized control pilot trial entitled Kidney Awareness Registry and Education (KARE, NCT01530958) examined the impact of 1) a primary care CKD *Registry* with point-of-care provider notifications and quarterly feedback, 2) a patient-facing CKD *self-management support (CKD-SMS)* program, and 3) their combination, on systolic blood pressure (SBP) among low-income patients with CKD, eligible by eGFR or albuminuria, compared to a control group without either intervention.

Methods: Among patients with SBP recorded at baseline and 12 months (n=121/137), we examined the impact of each intervention (*Registry*, n=22; *CKD-SMS*, n=29; *Registry+CKD-SMS*, n=34) compared to usual care (n=36) on change in SBP using linear regression models adjusted for baseline SBP.

Results: KARE enrolled racially/ethnically diverse patients (7% White, 42% Black, 36% Hispanic, 15% Asian). Mean age was 56 years; 49% were male; 40% were non-English speaking. Mean eGFR was 47.6 (SD=9.5) ml/min/1.73m^2; mean baseline SBP was 130 (SD=21.8) mmHg. Compared to patients receiving usual care whose average SBP decrease was -0.24 mmHg, patients in the three intervention arms had larger non-statistically significant decreases in SBP (-3.6 for *Registry*; -3.1 for *CKD-SMS*; -2.8 for *Registry+CKD-SMS*). There was no evidence of effect modification by baseline SBP ($p_{interaction}$= 0.16), but decreases in SBP were non-statistically larger among patients with baseline SBP >140 mmHg (n=40) randomized to the intervention groups compared to usual care: -5.2 for usual care; -21.6 for *Registry*; -12.1 for *CKD-SMS*; -9.9 for *Registry+CKD-SMS*.

Conclusions: The KARE pilot study suggests that multi-level interventions can improve SBP among low-income patients with CKD. A trial with greater power comparing these interventions among patients with CKD and SBP >140 mmHg is warranted.

Funding: NIDDK Support

TH-PO921

Patient Navigators and Enhanced Personalized Health Records in Kidney Disease: A Randomized-Controlled Pragmatic Clinical Trial

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Background: Patient navigators have been shown to improve quality of care delivered to cancer patients; their impact on CKD care is unclear.We developed a CKD Patient Navigator program adapting the chronic care model and an electronic health record (EHR)-based enhanced personal health record (PHR) to disseminate CKD stage-specific goals of care and education. We report the results of a randomized clinical trial examining the clinical outcomes of a CKD Patient Navigator or enhanced PHR, and their combination compared to usual care among CKD Stage 3b/4 patients.

Methods: 209 patients with CKD from 6 outpatient clinics were randomized in a 2x2 factorial design. Primary outcome measure was the change in eGFR over a 2-year follow-up period. We also evaluated secondary outcome measures including: acquisition of appropriate laboratory measures, appropriate specialty referral and hospitalization rates. Outcomes were captured using EHR and telephone interviews without in-center visits.

Results: Median age of the study population was 68.5 years with 75% being Caucasians. Literacy score (STOFLA) was adequate in 97% of the study population. Prior to enrollment, 54% of patients were followed by nephrologists and 88% of them were on ACEI/ARBs. During 2-year follow-up, eGFR decline was similar across the four groups (p=0.81). Measurement of CKD-related laboratory data were not statistically significantly different between study groups. Further, referral for dialysis education and vascular access placement, emergency room visits and hospitalization rates were not statistically significantly different between the four study arms.

Conclusions: We successfully developed a patient navigator program and an enhanced PHR for CKD population.However, there were no differences in eGFR and quality care metrics between study groups in this randomized clinical trial. Longer follow up is needed to see a potential difference and additional analyses are needed to evaluate patient-specific benefits of the interventions.

Funding: NIDDK Support

TH-PO922

Efficacy and Safety on Traditional Chinese Medicine Niaoduqing Particles in Delaying Moderate/Severe Renal Dysfunction: A Randomized Controlled Trial

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Background: Traditional Chinese medicine Niaoduqing particles can delay renal dysfunction, but there is no high-quality evidence. The present study aimed to determine the efficacy and safety of Niaoduqing particles in delaying renal dysfunction.

Methods: The study was a prospective, randomized, double-blind, placebo-controlled, multi-centered clinical trial (Clinical Trial registration number: ChiCTR-TRC-12002448). 300 adult patients with estimated glomerular filtration rate (eGFR) 20~45 mL/min per 1.73 m^2 were enrolled form 22 hospitals in China.The test group was given 3 doses of 5g Niaoduqing particles during the day and 10g Niaoduqing particles before bedtime; the control group was given placebos with same mode. Primary efficacy indicators included comparing serum creatinine and eGFR values and the change of values before and after treatment between the two groups. Endpoint event was defined as doubling of creatinine and/or commencing renal dialysis.

Results: At the end of treatment, there was no significant difference (P>0.05) in serum creatinine and eGFR between the two groups. However, compared with baseline, the value change of serum creatinine after treatment was significantly different between the two groups (ΔScr median was 1.1 μmol/L in test group versus 11.7 μmol/L in control group, P=0.008); compared with baseline, the value change of eGFR after treatment was also significantly different between the two groups (ΔeGFR median was -0.2 mL/min/1.73m^2 in test group versus -2.21mL/min/1.73m^2 in control group). 6 patients in test group and 4 patients in control group had creatinine doubled, and 1 patient in test group and 2 patients in control group started renal dialysis. In terms of adverse events, there was no significant difference (P>0.05) between the two groups.

Conclusions: For the first time, this study has determined that Niaoduqing particles could effectively delay renal dysfunction in CKD3b-4 patients.

TH-PO923

Analysis of the Paediatric Investigation Plans (PIP) of the EMA in Nephrology

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Background: To assess the requirements of the European Medical Agency (EMA) for paediatric clinical trials in nephrology we assessed the decisions on PIPs, which are required to get approval for new drugs. Clinical trials are needed in order to base therapy on evidence, but the relevant population can be very small in paediatric nephrology.

Methods: All 20 decisions on PIPs published by the EMA for nephrology were included. Data are presented as proportions (categorical data) and median (range) (numerical data).

Results: 7 of the published decisions granted a full waiver (i.e., no pediatric studies required). For the remaining 13, a PIP was agreed. For 6 of those 13 PIPs, a partial waiver was granted for certain ages (0-6 months (2x), 0-5, 0-6, 0-8, 12-18 yrs. The PIPs require the conduct of 0 – 3 (median 1) quality studies, 0 – 2 (median 0) non-clinical studies, and 1 – 6 (median 3) clinical studies. As there are ca. 9 paediatric dialysis subjects per million of all paediatric subjects, roughly ca. 400 patients in EU. At least 4 PIPs require inclusion of paediatric dialysis subjects, requiring 14 clinical studies, i.e., ca. 14 subjects are available for each of those studies. There are no concessions in powering the studies, and therefore, the required numbers will be much higher than the available number of subjects in EU. The time between start of the procedure and the decision of the PdCo/EMA was 103 days (35 – 468 days). The time between the date of decision of the PdCO/EMA and the date of the required completion of the PIP ranged from 0.03 yrs – 13.47 yrs (median 4.84 yrs).

Conclusions: In summary, we show some imbalances: a) All partial waivers affected the lowest age groups. Although the youngest age groups need an evaluation of new substances most, the granted partial waivers indicate how difficult it is to conduct trials in this group. b) Only 4 of the 13 PIPs are concerned with frequent indications, while 9 of those aim at rare. For those 9, a median of 3 studies are required. It is unlikely that the required subjectss can realistically be recruited. c) The required studies make the timely conduct (median 4.84 yrs) and completion at the same time adult studies questionable, which could delay approval.

TH-PO924

Response to Vaccination against Hepatitis B and Antibody Evolution in 130 Hemodialysis Patients Followed during Six Years

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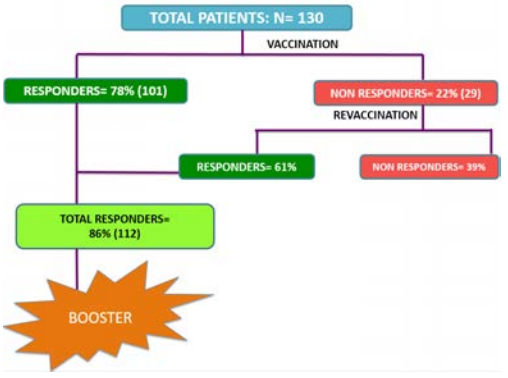
Background: Hemodialysis(HD) patients have a higher susceptibility to infections with Hepatitis B virus because of their advanced age,immunosuppressed state,increased transfusion requirements as well as because of the staff"s failure to strictly abide by published preventive universal precautions. This makes vaccine provided prevention particularly important in this population of patients.

Methods: In this manuscript we describe our observations in 130 HD patients-81 males (62%) and 49 females (38%) median age 53 years (range between 20-81 years), and median time on HD of 40 months (range 6-84 months). All patients were at onset AgHbs and anticore antigen negative. Vaccination was provided with double doses of

recombinant vaccine (Euvax-B) 40 ug IM deltoid muscle at 0, 30 and 180 days.Those who were classified as responders(anti Hbs antibody titer > 100 IU/ml) received an additional 40 ug booster annually.



Results: With this regimen, at the conclusion of the initial course of vaccination **78%** of the patients achieved an adequate level of antibody with a mean of **777** IU//ml. The response was highly heterogeneous, including the failure of **22%** following the first vaccination.This group underwent a second course of three double doses 40µg of vaccine on days 0-30 and 180. Following this,as many as 61% achieved adequate seroconversion, while the other 39% remained resistant.

Conclusions: Conclusion employing the approach described herein 86% of HD patients can attain adequate immunization against Hepatitis B virus.Increasing age is associated with decreased antibody response,but neither time on dialysis nor the underlying etiology of the renal disease significantly impacted the immunologic response.The persistence along the time of the immunization in normal range depend on the initial high answer to the vaccine.

Funding: Clinical Revenue Support

TH-PO925

Implementing Teaching Guidelines on Quality of Life and Adaptation on Hemodialysis Patients

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Background: Health Related Quality of life (HRQOL) of patients with End Stage Renal Disease (ESRD) is influenced by the disease itself and by the type of replacement therapy. Clinical practice guidelines were established to provide recommended ranges for parameters associated with management of ESRD patients. The aim of this study is to assess the QOL and adaptation in patients with ESRD on regular HD and to study the implantation of teaching of the European best practice guidelines on those types of patients.

Methods: Prospective study which was carried out on 95 patients. Two different tools were used in data collection to all subjects: Tool 1: Assessment sheet consists of four parts includes patients' socio demographic criteria, medical history, clinical data and laboratory investigations. Tool 2: QOL and adaptation assessment using Arabic form of SF-36 and brief cope.

Results: There were statistically significant improvement of HB, creatinine level, urea reduction ratio, phosphorus and albumin level after teaching of the guidelines. There were no statistically significant improvement of WBC, PLT, calcium level, kt/v and PTH level. There was statistically no-significant increased QOL in all domains after teaching of guidelines. There was sever decrease in all QOL domains . Median range of physical function was 54.50 (27.70 – 100) and mean limitation due to both physical health and emotional problems was 51.35 ± 21.08 and 51.40 ± 20.61 respectively. While mean energy feeling, Emotional wellbeing, Social functioning, Pain, General health were 48.91 ± 18.13, 49.56 ± 18.33, 43.83 ± 18.76, 58.20 ± 23.86 and 55.10 ± 18.89 in order.

Conclusions: : HRQOL is much lower in HD patients. The implementation of teaching guidelines has a positive effect on the studied patients' total knowledge and most of laboratory parameters while it has no significant effect on HRQOL for the studied patients regarding almost all domains. Continuous education should be provided by the healthcare team for HD patients.

Funding: Government Support - Non-U.S.

TH-PO926

A Quality Improvement Initiative Assessing Factors Improving Inadequate Hemodialysis in Hospitalized Patients

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Background: Hemodialysis (HD) adequacy is associated with a number of clinical outcomes, including hospitalizations and death. The adequacy of HD treatments in hospitalized patients is usually not measured and may not be achieved. This quality improvement (QI) study aimed to measure the adequacy of inpatient HD treatments and analyze the factors associated with improvement over time.

Methods: We performed a quality improvement initiative with retrospective cohort analysis of hospitalized patients undergoing HD in 2009, 2010 and 2015. The intervention was a comprehensive education initiative for nephrology fellows and attending physicians in prescribing adequate HD. The primary outcome was the frequency of adequate HD treatments defined as single pool Kt/V >1.2. Subsequently, we retrospectively compared factors affecting spKt/V to explain the observed improvement.

Results: Outside of the QI initiative, HD adequacy was not being routinely assessed throughout all time periods. The initial phases of the study in 2009 found only 44% of HD treatments were adequate with insignificant improvement in 2010. However, after initiation of a comprehensive education initiative, 94% of HD treatments were adequate in 2015 (P< 0.001 vs 2009) with mean spKt/V of 1.6±0.37 in 2015 compared to 1.1± 0.34 in 2009 (P<0.001). Retrospective analysis found no difference between 2009 and 2015 in patient size (81.87±28.05 Kg vs 73.46±19.68 Kg, P=0.13) or HD time (213.9±42.74 minutes vs 220.9±28.91 minutes, P= 0.47). A significant difference was observed in blood flow rates (344.4±39.66 ml/min vs 385.8±46.70 ml/min, P< 0.001) and in dialyzer size with only 13% of treatments in 2009 vs 75% in 2015 utilizing dialyzers with surface area ≥ 1.8 m^2 (P<0.001).

Conclusions: Inpatient HD adequacy was not being measured and initially found to be quite poor. Adequacy was improved by a focused QI program with more intensive training in HD prescriptions which lead to increased use of larger dialyzers and greater blood flow rates. To ensure that hospitalized patients receive adequate HD, measurements of adequacy should be undertaken to detect whether corrective action is necessary.

TH-PO927

The Association of Bilirubin and Mortality in Patients Underwent Regular Hemodialysis

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Background: Bilirubin has the effect of anti-oxidation and anti-inflammation, benefiting in cardiovascular events, which is very common in end stage renal disease patients (ESRD) underwent regular hemodialysis. However, the association between mortality and bilirubin level in ESRD patients was not clear.

Methods: A total 102,599 patients in TWRDS, a national-wide end state renal disease registration system in Taiwan were surveyed. After deleting 45865 patients with an abnormal higher bilirubin >1.2 mg/dl or extremely lower bilirubin level <0.1 mg/dl. Finally, 47560 patients were analyzed in this study. Multi-variates adjusted cox proportional analyses were used to find out the relationship between the bilirubin groups (low <0.3 mg/dL, reference 0.3-0.7 mg/dL, high >0.7 mg/dL) and mortality during a 8 years follow-up.

Results: There were no obvious demographic difference between the groups of bilirubin levels. In the contrary, higher bilirubin was correlated with higher all-cause mortality. The cox proportional hazard ratio for death in high bilirubin group was 1.15 times (95 % CI 1.09-1.22, p < 0.01) higher than the reference group (bilirubin between 0.3-0.7 mg/dL). Every 1mg/dl increase in bilirubin had a 1.39 times (95% CI 1.26-1.53, p <0.01) higher the mortality risk.

Conclusions: Surprisingly, this study revealed that bilirubin had a negative impact on mortality in HD patients. Further solid evaluations are warranted to support this point of view.

TH-PO928

The Association between Dialysis Session Time and the Risk for Hospitalization and Death in Maintenance Hemodialysis Patients

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Background: Recently, dialysis efficiency was dramatically improved by using super flux dialysis membrane. However, in the condition of the common use of high flux dialysis, it has not been well studied the relationship between treatment time and adverse events or survivals of maintenance hemodialysis (MHD).

Methods: Subject: 805 patients undergoing MHD. Study design period: prospective, observational multi-center study of 3 years. Measurement: We measured serum levels of urea nitrogen (UN), creatinine (Cr), β2microgroblin (MG), total protein, albumin, prealbumin, high sensitive C reactive protein (hCRP) every 3month. We also evaluated body mass index (BMI), and Kt/V. The associations between dialysis intensity and adverse events or death were investigated with the cox proportional hazards model for time-dependent variables.

Results: Although there was no significant correlation between pre-dialysis levels of β2MG or UN and adverse event or survival, high pre-dialysis Cr level was associated with lower risk of hospitalization (HR:0.89, P=0.003) and death (HR:0.71, P=0.002). Moreover, high Kt/V was also associated with lower risk for cerebrovascular and cardiovascular disease (CCVD) (HR:0.37, P=0.039) and hospitalization (HR:0.55, P=0.026). There was no significant difference in serum levels of prealbumin, albumin, Cr, Kt/V and hCRP levels among 3 groups of treatment time (<4hours(h), 4-5h, >5h). On the other hand, BMI in the patients treated with >5h was significantly (p=0.012) higher than those of patients treated with <4h. In time dependent cox hazard model, the risk of hospitalization (HR:0.43, P=0.001) and death (HR:0.49, P=0.013) of patients treated with 4-5h were significantly lower than that of patients treated with <4h. Moreover, the risk of death in patients treated with >5h was significantly (HR:0.45, P=0.024) lower than that of treated with <4h.

Conclusions: Higher Kt/V was associated with lower risk of CCVD and hospitalization of MHD patients, but not pre-dialysis level of β2MG levels. Shorter dialysis session time (<4 hr) was associated with higher risk of hospitalization or death than that of longer treatment time.

TH-PO929

Vegetarian Diets Reduce Advanced Glycosylation End Product Deposition in the Skin in Chronic Hemodialysis Patients Arkom Nongnuch,[1,2] Andrew Davenport.[2] *[1]Renal Unit, Dept of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol Univ, Bangkok, Thailand; [2]UCL Centre for Nephrology, Royal Free Hospital, Univ College London, London, United Kingdom.*

Background: Advanced glycosylation end products (AGEs), are protein-bound uremic toxins and associated with increased risk of developing cardiovascular disease and mortality in HD patients. As AGEs are deposited in the skin, they can be measured by skin autofluorescence (SAF). Vegetarian diets potentially reduce AGEs formation, thus we desired to determine whether vegetarian diets reduce AGEs deposition.

Methods: Prospective repeated measurements were made in 180 prevalent hemodialysis patients in North London between June 2012 and September 2013. Clinical data and serial laboratory data were collected and were analysed by linear mixed effects model.

Results: A total of 180 HD patients were studied. Sixty-six percent were male and 45% had diabetes. The mean increased in SAF after 12 months was 0.27 ± 0.12 AU. Univariate analysis showed age, history of diabetes, peripheral vascular disease, prescription of lanthanum carbonate (LC), clopidogrel, insulin, warfarin, elevated CRP, vitamin D and HbA1c were positively associated with an increased in SAF, whereas non-Caucasian ethnicity, urine output >250 ml/day, serum albumin and vegetarian diets reduced skin AGEs deposition. Multivariate analysis revealed the usage of warfarin, LC, insulin and age significantly associated with increased in SAF, whereas urine output > 250 ml/day and vegetarian diet were associated with attenuated accumulation in SAF.

	Univariate analysis		Multivariate analysis		
Factors	Coefficient	P value	Coefficient	Confidence interval	P value
lantanum	0.37	0.006	0.36	0.11 to 0.6	0.004
clopidogrel	0.29	0.046			
Insulin use	0.211	0.10	0.29	0.055 to 0.52	0.016
Diabetes	0.274	0.022			
History of PVD	0.311	0.073			
Chronological age	0.01	0.018	0.013	0.005 to 0.02	0.002
Vegetarian	-0.7	0.001	-0.59	-0.96 to -0.21	0.002
Ethnics					
Asians	-0.419	0.003			
African-carribeans	-0.756	0.001			
urine output > 250/d	-0.229	0.072	-0.258	-0.49 to -0.2	0.033
vit D level	0.0035	0.052			
CRP	0.002	0.062			
albumin	-0.0219	0.049			
HbA1C	0.005	0.005			
Warfarin	0.6	0.024	0.62	0.14 to 1.1	0.012

Conclusions: Vegetarian diets and residual renal function (RRF) lessen AGEs accumulation in HD patients. Strategies to preserve RRF with low AGEs diets may reduce AGEs deposition and potentially reduced CVD risk in HD patients.

Funding: Private Foundation Support

TH-PO930

Time-Varying Changes in Serum Albumin and Cytokines Predict HD Patient Mortality Paul L. Kimmel,[1] Kenneth J. Wilkins.[2] *[1]DHUHD, NIDDK NIH, Bethesda, MD; [2]Biostatistics Program, NIDDK NIH, Bethesda, MD.*

Background: High baseline circulating pro-inflammatory cytokine levels (CLs) are linked to ESRD hemodialysis (HD) patient (PT) mortality. Whether HD PT CLs are stable over time is unknown. Whether changes in CLs predict mortality, adjusting for known longitudinal predictors is unstudied.

Methods: We studied interleukin (IL)-1, IL-6 and Tumor-Necrosis Factor-α (TNF-α) CLs in 234 HD PTs (75 incident, 159 prevalent), followed a mean of 3.3 y with a median of 3 assessments at 3 centers in Washington, DC (total 763 person-y followup). CLs were skewed, ranging over 6 natural logs. Scatter plots revealed high and low groups for all cytokines at baseline. This ad hoc univariate grouping was assessed for each cytokine at baseline to have >90% accuracy by multivariate methods (K-means cluster, quadratic discriminant and principal components analyses). Groupings were then assessed for how well each predicted mortality using Cox models (adjusting for known time-varying predictors such as serum albumin [SAlb]), to compare the use of ad hoc high/low values, with log 4 as a threshold, as an alternative to clustering by baseline values or trajectories, with models using time-varying prediction by actual values.

Results: In the low IL-1 group (n=157), only 5% exhibited post-baseline values >4 log (54.6 pg/mL). In the high IL-1 group (n=77), only 13% exhibited values <4 log. A majority of CLs remained roughly constant over follow-up. 81% of variability is explained by individual mean CLs, with similar findings for IL-6 and TNF-α. Exceeding 4 logs of these levels predicted mortality using time-varying Cox models, even after adjusting for baseline CLs and trends in SAlb since the previous cytokine measure (HR, 95% CIs] IL-1: 3.3 [2.1, 5.3]; IL-6: 3.4 [2.2, 5.4]; TNF-α: 3.3 [2.1, 5.3]). No residual variation in events appears correlated with baseline CLs.

Conclusions: CLs exhibit limited variability over time in the majority of HD PTs. Longitudinal cytokine levels can be characterized as "high" or "low," according to baseline measurements with negligible misclassification, and predict mortality or survival. Such characterization will be useful in stratifying PTs for interventional trials.

Funding: NIDDK Support

TH-PO931

A Novel Risk Factor for Hospitalization in Patients with ESRD Buthayna A. Dinary,[1] Jasmine Harris,[2] Nivetha Subramanian,[2] Michael S. Simonson,[1] Sharmeela Saha.[1] *[1]Nephrology and Hypertension, Univ Hospitals Case Medical Center and Case Western Reserve Univ School of Medicine, Cleveland, OH; [2]Case Western Reserve Univ School of Medicine, Cleveland, OH.*

Background: In the US dialysis population, the overall hospitalization rate in 2012 was 1.73 per patient year. 35.2% of prevalent hemodialysis patients were readmitted within 30 days of discharge. These readmission rates are twice that of the general Medicare population. Cognitive impairment (CI) may be a contributor. There are currently no standardized screening guidelines for the end-stage renal disease (ESRD) population. Our aim is to identify modifiable risk factors for re-hospitalization in a hemodialysis-treated ESRD population at a tertiary-care center.

Methods: We conducted a retrospective cohort study of hemodialysis patients greater than 18 years of age years at UHCMC between January 2015 and November, 2015, and followed until December 31, 2015. The primary outcome was the number of any-cause hospitalizations following the index admission. We collected information regarding patient demographics, comorbidities, medications and Mini-Cog score. The Mini-Cog test was used to assess whether or not a patient suffered from CI.

Results: A cohort of index admissions (n=40) was analyzed for a primary outcome of any-cause hospitalization per person. The most common causes of hospitalization were hypertensive emergency, cardiovascular, infection, access related issue, and hypervolemia. Lower serum albumin levels and higher systolic blood pressure strongly predicted higher hospitalization rate in a multivariate linear regression model (P = 0.003) adjusted for age, female sex and black race. In addition, hospitalizations were 2.3-fold higher in hemodialysis patients with cognitive impairment (P = 0.019). Cognitive impairment predicted hospitalizations independent of age, sex, and black race.

Conclusions: Our findings suggest that ESRD patients with cognitive impairment are at higher risk for hospitalization. Mini-Cog performance is a novel marker of re-hospitalization risk. Future studies will assess whether identification of CI and use of alternative learners reduces hospitalizations in hemodialysis patients.

Funding: Other NIH Support - University Hospitals Quality Improvement

TH-PO932

Current Status of Hemodialysis in China, 2015 Xiang-Mei Chen, Ying Zheng. *Dept of Nephrology, Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Medical Quality Control Center for Kidney Diseases, MOH, Beijing.*

Background: In order to further understand the the current status of the patients of ESRD and hemodialysis in China, in May 2010, the first nationwide, web-based prospective renal data registration platform, the Chinese Renal Data System (CNRDS) was launched in China. The goal of the study was to determine the current status of hemodialysis in China by analyzed the data from CNRDS.

Methods: Data in CNDRS includes demographic, clinical, and laboratory data for dialysis cases. We analyzed the data from CNRDS by the end of 2014.

Results: There were 4089 domestic hemodialysis centers were registered by the end of 2015. On Dec. 31, 2015, 385055 prevalent cases were receiving hemodialysis therapy. Compared to 2014, the number increased by 45307 cases. The unadjusted prevalence (proportion) was 281.5 per million in the Chinese population. The number of incident cases receiving hemodialysis therapy in 2015 was 61790, which was the lowest since 2011. The unadjusted incidence rate was 45.2 per million/year. In the prevalent cases, 59.0% were male, the mean age and dialysis time was 55.7years and 46.7 months, respectively. Both of the age and dialysis time continue to increase since 2011. Though the proportion of glomerulonephritis declined to 54.2% in 2015, it was still the leading causes of ESRD who receiving hemodialysis therapy in prevalent cases. The proportion of diabetic nephropathy in incident cases was 21.2%, the number continues to rise. 13839 cases were died in 2015. 58.3% of them were male. The mean age and dialysis time was 62.7 years and 41.2 months, respectively. Both of the two number in mortality cases continue to increase since 2011. The main causes of death were cardiovascular events and stroke.

Conclusions: In recent years, the hemodialysis in China has made a great progress. As Chinese National Health and Family Planning Commission have enhanced the basic medical security system on hemodialysis, the population and prevalence of hemodialysis rose sharply during 2011-2015.

TH-PO933

Involuntary Discharges (IVDs): Analysis of Case Characteristics of End Stage Renal Disease (ESRD) Network 2 in New York before and after Bundled Payment Implementation by Centers for Medicare and Medicaid Services (CMS) Ranjeet Singh,[1] Brittany Kalosza,[1] Syeda Hussain,[2] Chaim Charytan,[2] George N. Coritsidis.[1] *[1]Nephrology, Elmhurst Medical Center, Elmhurst, NY; [2]Nephrology, New York-Presbytarian, Queens, NY.*

Background: Dialysis providers are authorized to involuntarily discharge patients under certain circumstances, as set forth in Medicare's Conditions of Coverage. We wanted to analyze how etiologies for the rate of IVDs have changed since the CMS prospective payment system for ESRD in 2011.

Methods: We collected IVD data reported to ESRD Network 2 from Jan-2007 to December-2015. Being the first year of the CMS changes 2011 data was excluded. Reasons for IVDs and patient characteristics were reviewed.

Results: 153 IVDs were identified. The number of IVDs increased following CMS bundled payment model from 66 patients (16.5 IVDs/year) to 87 patients (21.8 IVDs/year). Male patients had a significantly higher IVD rate before and after bundled payment. Rate of IVD of African Americans decreased after the CMS bundle (78.8 % vs 59.8 % respectively). The major reason for discharge continue to be behavioral issues (76.7%) followed by non-payment (19.3%).

Involuntary Discharge for Network 2	Total N = 153	2007-2010 43.14%(n=66)	2012-2015 56.86% (n=87)	p-value
Rate of IVD per Year		**16.5**	**21.8**	
Age	51.5	52.2	51.0	0.485
Sex, male, %(n)	71.2(109)	71.2(47)	71.3(62)	0.994
Race,%(n) Caucasian	30.1(46)	19.7(13)	38.0(33)	0.015
African American	68.0(104)	78.8(52)	59.8(52)	0.013
Asian	1.3 (2)	1.5(1)	1.2 (1)	0.382
Ethnicity, Latino %(n)	13.8 (21)	12.1(8)	15.1 (13)	0.596
Reason for Discharge,%(n)				
Behavioral	76.7(115)	81.0(51)	73.6(64)	0.291
Non-payment	19.3(29)	16.0(10)	21.9(19)	0.361
Non-Compliance	1.3 (2)	3.2 (2)	0.0	0.094

Conclusions: Analysis of data for NY reveal higher IVD rates after the bundled payment changes. IVD patients were younger than ESRD patients as a whole and IVD was predominantly due to behavioral issues. More Caucasians and fewer African Americans were IVDs after the CMS bundle, possibly indicating that racial disparities are equalizing.

TH-PO934

Intermediate Care Outcomes before and after Switching to Nocturnal In-Center Hemodialysis Adam S. Wilk,[1] Kristen Senetar,[1] Laura Plantinga,[1] Janice P. Lea.[2] *[1]Emory Univ; [2]Emory Dialysis Centers, Emory Healthcare.*

Background: Nocturnal dialysis (ND) can support longer sessions with lower ultrafiltration (UF) rates, compared to traditional (daytime) in-center hemodialysis. We compare dialysis care traits and intermediate health outcomes for ND patients before and after they initiate ND treatment.

Methods: Among patients undergoing hemodialysis at a medium-sized dialysis organization, we identified ND patients as those for whom at least 80% of dialysis sessions over a 3-month window (≥20 sessions) began at 6:30pm or later and lasted 5 hours or more. For these patients, we extracted dialysis treatment orders and session records, demographics, and other electronic health record data relevant for within 90 days of ND transition. We estimated session-level ordinary least squares regression models of key intermediate outcomes—session duration, UF rate, completed session rate (fraction with at least 90% of treatment order time), pre-session blood pressure (systolic [SBP] and diastolic [DBP]), and lowest recorded intradialytic SBP and DBP—to identify conditional effects of post-transition ND care status, clustering standard errors within patients.

Results: We identified 55 ND patients (3.9% of 1,420 patients in care), with 1,065 pre-transition sessions and 1,877 post-transition ND sessions. Relative to pre-transition sessions, post-transition ND sessions were 3.2 hours longer ($p<0.001$), had UF rates 4.9 ml/h/kg lower ($p<0.001$), and were completed equally often ($p=0.9$). Likewise, patients' SBP and DBP levels, both pre-session and lowest intradialytic, were not significantly different pre- vs post-transition, though we observed small but statistically significant declines over time across post-transition ND sessions in nearly all SBP and DBP outcomes.

Conclusions: ND treatment sessions were longer than pre-transition hemodialysis sessions and had lower UF rates, but ND did not affect patients' session completion rates or absolute SBP and DBP levels. For patients selecting into ND, the effect appears to be as intended.

TH-PO935

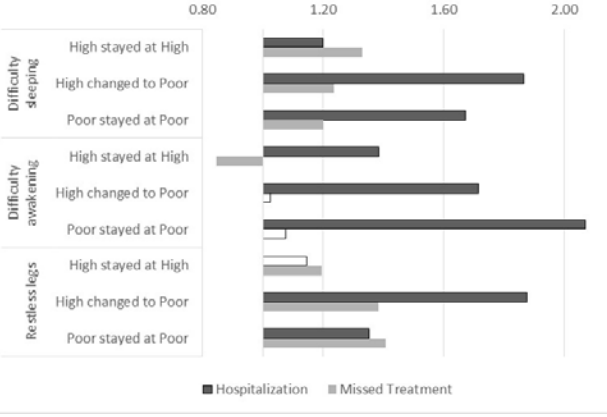
Improved Sleep Quality Is Associated with Reduced Hospitalization Rate and Increased Treatment Adherence in Hemodialysis Patients Nien-Chen Li, Felicia N. Speed, Marta Reviriego-Mendoza, John W. Larkin, Norma J. Ofsthun, Stephanie Johnstone, Franklin W. Maddux. *Fresenius Medical Care North America, Waltham, MA.*

Background: Patients (pts) with end-stage renal disease often suffer from sleep disorders. We investigated if a social worker (SW) quality improvement program effects sleep quality (SQ), and subsequently alters rates of hospitalizations and treatment adherence in a cohort of hemodialysis (HD) pts.

Methods: HD pts (869) enrolled in an 8-week SW program between 7/1/2013 and 2/28/2014 were provided a 5-item SQ questionnaire before and after the SW intervention. Using a factor analysis, 5 items were reduced to 3: difficulty sleeping, difficulty awakening, and restless legs during sleep. For each item, SQ was defined as "high" for scores better than the baseline median and "poor" otherwise. Hospitalization and missed treatment data were captured 1 year before and after intervention. Rate ratios (RR) in hospitalization and missed treatment, stratified by changes in SQ were analyzed using Poisson regression, offset with the length of exposure period and adjusted for baseline hospitalization or missed treatment count, age, gender, race, diabetes, coronary artery disease (CAD), and congestive heart failure (CHF).

Results: Pts had a mean age of 55.3 ± 14.1 years, 51.8% males, 69.7% white, and 58.6% with diabetes, 19.5% CAD, and 38.1% CHF. The impact of changes in SQ parameters on hospitalization and missed treatment rates are detailed in Figure 1. That is, in almost all cases, RR > 1 indicating higher risk in hospitalization and/or missed treatment when comparing with SQ improved from poor to high after intervention.

Figure 1. RR (Rate Ratio) in Hospitalization and Missed Treatment by Change in SQ Before and After Intervention (Ref: SQ changed from Poor to High, all RR are significant p<.05 unless no fills)



Conclusions: The findings suggest that the SW program was associated with improvements in SQ and, in turn, with reductions in hospitalization risk and better adherence to HD treatments. Implementing a strong QS program in HD clinics may improve HD pts' outcomes.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-PO936

Associations between Sleep Quality and Quality of Life, Stress, and Depressive Symptoms in Hemodialysis Patients Nien-Chen Li, Stephanie Johnstone, Felicia N. Speed, Marta Reviriego-Mendoza, John W. Larkin, Norma J. Ofsthun, Franklin W. Maddux. *Fresenius Medical Care North America, Waltham, MA.*

Background: We investigated if implementing a social worker (SW) quality improvement program resulted in better sleep quality (SQ) and thus, improved depressive symptoms, psychosocial stress, pain perception and Kidney Disease Quality of Life (KDQOL) scores in HD pts.

Methods: We analyzed data from 869 pts at Fresenius Medical Care North America enrolled into the 8-week SW program between 7/1/13 and 2/28/14. SQ was assessed before and after the SW program. The original SQ 5-item assessment was reduced to 3-items by way of factor analysis: difficulty sleeping, difficulty awakening and restless legs during sleep. We used the following questionnaires: the center for epidemiologic studies depression scale-10 (CESD-10), KDQOL, Psychosocial Stressor Screening tool, and Comfort Barriers Screening tool (pain items). Paired t-tests were used to compare means of Pt data before and after implementing the SW program. Regression analysis was used to assess associations of changes in questionnaire scores and SQ, adjusted for baseline score, age, gender, race, and diabetes, coronary artery disease (CAD), and congestive heart failure (CHF).

Results: Pts in the study had mean age of 55 ± 14 years, 52% males, 70% white, and 59% with diabetes, 20% CAD, and 38% CHF. Results show that SQ improved after SW intervention (all $p<0.05$). We found that: i) improvements in CESD, mental component score (MCS), burden of kidney disease, and stress indicators were significantly associated

with improvements in difficulty sleeping (all p<0.01), ii) improvements in CESD and heath symptoms and loss/grief stressors were associated with improvements in difficulty awakening (all p<0.01), and iii) improvements in CESD and financial/insurance and family/relationships stressors were associated with less restless legs during sleep (p<0.02).

Conclusions: Our study indicates that improvements in SQ are associated with improvements in depressive symptoms, psychosocial stress, MCS, and KDQOL measures in HD patients. SW interventions may aid in improving pts' SQ and, consequently, HD outcomes.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

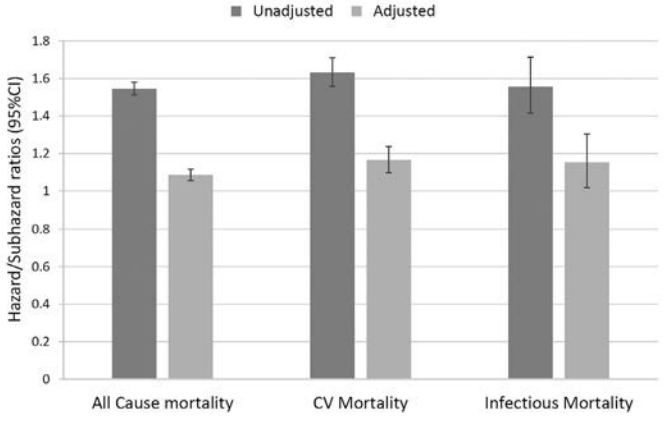
TH-PO937

Outcomes Associated with Inpatient versus Outpatient Hemodialysis Initiation in a Large Incident ESRD Cohort Faisal M. Arif,[1] Miklos Zsolt Molnar,[1] Keiichi Sumida,[1] Praveen Kumar Potukuchi,[1] Jun Ling Lu,[1] Geeta G. Gyamlani, Fatima Hassan,[1] Fridtjof Thomas,[1] Elani Streja,[2] Kamyar Kalantar-Zadeh,[2] Csaba P. Kovesdy.[1,3] *[1]Univ of Tennessee Health Science Center, Memphis, TN; [2]Univ of California, Irvine; [3]VA Medical Center, Memphis, TN.*

Background: The setting (Inpatient vs. Outpatient) of chronic HD initiation could be determined by medical (e.g. comorbidities) or other factors (e.g. no available mature vascular access). It is unclear if the setting of HD initiation is associated with mortality risk in the post-dialysis period.

Methods: We examined the association of inpatient (vs. outpatient) HD initiation with all-cause and cause-specific mortality in 48,261 US veterans transitioning to HD between 10/2007-09/2011. Associations were examined in Cox (all-cause mortality) and competing risk regression models (cause-specific mortality), adjusted for demographics, comorbidities, vascular access type, predialysis Nephrology care and medication use, and pre-ESRD eGFR and hemoglobin.

Results: 22,338 (46.3%) patients started HD as inpatients. Inpatient HD start was associated with older age, presence of a tunneled catheter, and more comorbidity. Higher hemoglobin, lower eGFR and predialysis use of active vitamin D were associated with outpatient HD start. 32,323 patients died over a median follow up time of 2.1 years (mortality rate, 95%CI: 290/1000 patient-years, 287-293). Inpatient vs. outpatient HD start was associated with significantly higher crude all-cause, CV and infectious mortality. These associations were substantially attenuated, but remained significant after multivariable adjustment (Figure).



Conclusions: Veterans who transitioned to HD in a hospital setting experienced significantly higher mortality following dialysis initiation. Better predialysis care may allow more patients to initiate HD as outpatient. Future studies are needed to examine the impact of this on mortality.

Funding: NIDDK Support, VA Support

TH-PO938

Outbreak of Gram Negative Bacilli Non Fermenters Associated to the Lack of Chlorine in Pre-Treated Water for Hemodialysis Cinthia Sobral Vieira, Claudio Stadnick, Ethel Ribas, Rozeli Biedrzycki, Andressa Kowal, Gisele Lobato, Gabriela Sobral Vieira. *Nephrology Unit, Hospital Ernesto Dornelles, Porto Alegre, RS, Brazil.*

Background: Bacteremia presented during dialysis can lead to harmful outcome to patients. Varied reasons are cited, long associated with the use of catheters. When in outbreak the whole process must be thoroughly analyzed. Our purpose is to report possible causes of bacteremia and the subsequent assessment of the outbreak occurred in a hemodialysis service.

Methods: Between March and April 2016, there were 20 cases of bacteremia in patients under hemodialysis therapy in a private hospital in South of Brasil The blood cultures showed Gram-negative bacilli non fermenters (GNBNF) commonly associated to water contamination. Physical-chemical, microbiological analyses of all materials used for hemodialysis were carried out including water. At the same time, sanitization, deodorization and exchange resins in water purification system were realized.

Results: 20/98 patients with bacteremia presented GNBNF. They were *Stenotrophomonas maltophilia, Burkholderia cepacia, Ralstonia mannitolilytica and Ralstonia pickettii*. Reverse osmose were used for water treatment and the dialyzers were manually reprocessed. The microbiological tests showed that the growth of colonies occurred after activated carbon. The potable water produced during the epidemic period, had chlorine concentrations below the desirable standards imposed by the guide of best practices in dialysis in Brasil which requires 0.5 mg/l maximum for chlorine. The chlorine free water was arriving very hot to the reverse osmose, suggesting that chlorine evaporated during passage through the external plumbing and favoring the bacterial growth. It was a very hot summer with long distance from the water tower to the reverse osmose suggesting a mixture with water from central boiler. Individualized plumbing (exclusively from public water system) and an extra 10.000 liters water tank were installed before water treatment room and no more cases were seen.

Conclusions: It is imperative to monitor all procedures involving the water used in the process of hemodialysis. Cases are avoided when the focus of the outbreak quickly and effectively is found.

Funding: Private Foundation Support

TH-PO939

Negative Correlation of Serum Adiponectin Level with Peripheral Artery Disease in Hemodialysis Patients Yu-Hsien Lai,[1] Bang-Gee Hsu.[2] *[1]Buddhist Tzu Chi General Hospital, Hualien, Taiwan; [2]Buddhist Tzu Chi General Hospital, Hualien, Taiwan.*

Background: Adiponectin is a fat-derived hormone produced and secretedexclusively by adipocytes that have anti-atherosclerotic effects. Peripheral arterial disease is associated with an increased risk of death in hemodialysis (HD) patients. The aim of this study was to evaluate the relationship between serum adiponectin levels and peripheral artery disease by ankle-brachial index (ABI) in HD patients.

Methods: Blood samples were obtained from 100 HD patients. The ABI values were measured using an ABI-form device (VaSera VS-1000). Serum adiponectin levels were measured using a commercial enzyme-linked immunosorbent assay kit. Left or right ABI values that were < 0.9 were included in the low ABI group.

Results: Among 100 HD recipients, 18 patients (18.0%) were in the low ABI group. Compared with patients in the normal ABI group, patients in the low ABI group had higher prevalence of diabetes (p = 0.043), older age (p = 0.027), and lower serum adiponectin level (p = 0.003). HD patients with diabetes mellitus (DM) had lower serum adiponectin level than non-DM HD patients (p = 0.016). According to multivariable forward stepwise linear regression analysisshowed that waist circumference (β: -0.216, p = 0.029), log transformed triglyceride (log-TG) (β: -0.230, p = 0.019), and log transformed C-reactive protein (log-CRP) (β: -0.241, p = 0.008) were the independent predictors of adiponectin level in HD patients, and multivariate logistic regression analysis, adiponectin (Odds ratio [OR]: 0.927, 95% confidence interval [CI]: 0.867-0.990, p = 0.025) and age (OR: 1.054, 95% CI: 1.002-1.109, p = 0.043) was the independent predictors of peripheral arterial disease in HD patients. The sensitivity, specificity, positive predictive value, negative predictive value, and area under the receiver-operating characteristic (ROC) curve predicting peripheral arterial disease in HD patients were 72.22%, 64.63%, 36.68%, 99.92%, and 0.691 (95% CI: 0.591-0.780, p = 0.008), and the adiponectin cut-off value was 43.27 μg/mL.

Conclusions: In this study, serum adiponectin level was proved to be involved in the pathogenetic process of peripheral arterial disease in HD patients.

TH-PO940

Impacts of Insurance Type on Hospitalization and Mortality Rates in Hemodialysis Patients Xiaoling Ye,[1] John W. Larkin,[2] Marta Reviriego-Mendoza,[2] Len A. Usvyat,[2] Peter Kotanko,[1,3] Franklin W. Maddux.[2] *[1]Renal Research Inst, New York, NY; [2]Fresenius Medical Care North America, Waltham, MA; [3]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Insurance types may be associated with outcomes in chronic hemodialysis (HD) patients (Pts). We compared outcomes in Pts who initiated and remained on HD with commercial insurance (COM) to matched Medicare fee-for-service Pts with comparable demographic and clinical parameters.

Methods: We analyzed data from 2008 to 2014 on 16,357 Pts at FMCNA who initiated and survived 6 months(mo) on HD with COM as primary coverage. Pts with Medicare primary coverage who survived 6mo on HD were identified using 1:1 nearest neighbor matching on logit of propensity score for race, gender, HD initiation year, and 15 comorbidities, as well as number of in-center treatments, hospitalization rate, adherence rate, treatment time, pre-HD SBP, IDWG, and Kt/V in first 6 mo of HD. We performed exact matching for: age, race, diabetes, % of treatments with catheter, mean albumin, and mean BMI during first 6mo of HD; Pts without an exact match were excluded. We compared 12mo hospitalization and mortality rates per patient year (ppy) in groups after first 6mo of HD.

Results: Data from a total of 3,280 HD Pts was analyzed (1,640 COM & Medicare Pts each). We found Pts starting the first 6mo of HD covered by COM had 0.45 (95 CI,0.44–0.46) less hospitalizations ppy, compared to matched Medicare Pts (p<0.001) [figure1]. Similarly, we observed 1.49 (95%CI,1.41-1.60) fewer deaths ppy for COM Pts versus Medicare patients (p<0.001).

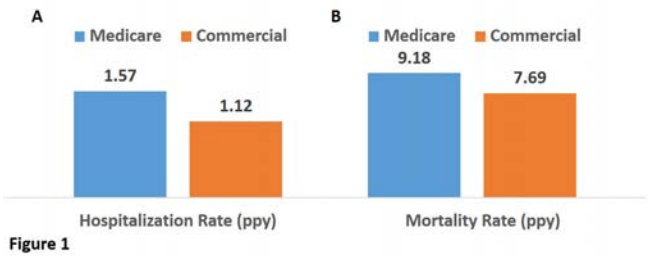


Figure 1

Conclusions: Our analysis suggests that Pts who initiate and remain on HD with COM may have lower hospitalization and mortality rates when compared to their Medicare peers. Further analyses are warranted to understand these differences in outcomes and whether patient characteristics or plan benefits are involved.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-PO941

Effect of Interdialytic Time on Outcomes in Chronic Hemodialysis Patients

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Background: Most chronic hemodialysis (HD) patients dialyze on MonWedFri or TueThuSat. Prior studies suggest that the risk of cardiovascular events (CVEs) is highest after the weekend, ie Mon and Tue, respectively. Since our Veterans Administration (VA) Hospital HD unit is closed on weekends, non-traditional HD schedules were created, ie 3-day weekends (compared to the usual 2-day weekend). We wondered if more frequent CVEs and greater mortality occurred after longer inter-HD time intervals.

Methods: We reviewed charts of all chronic HD patients since 2002, when the VA electronic medical record was initiated. Patients were placed on a HD schedule randomly. Those dialyzed for at least 3 months (4 - 144, median 21) without change in HD schedule were studied (n = 85). Those dialyzing on MonWedFri and MonTueFri (n = 29) constituted the short-weekend group (SWG), and those dialyzing on MonWedThu, MonTueThu, TueWedFri, and TueThuFri (n = 56) constituted the long-weekend group (LWG). Outcomes consisted of all-cause mortality, CVEs requiring hospital visits, and day in HD schedule when CVEs occurred: D-0, during and after HD; D-1, 1st day after last HD; D-2, 2nd day after last HD; D-3, 3rd day after last HD; D-4, 4th day after last HD.

Results: Demographics and co-morbidities of the 2 groups were similar, except for more coronary artery disease ($p < 0.03$) and higher serum phosphorus concentration ($p < 0.001$) in SWG. All-cause mortality was not different between groups, even after normalization for coronary artery disease and serum phosphorus level. For each group, we compared observed CVE rates to expected CVE rates (null hypothesis: CVEs were expected to occur at the same rate on D-0, D-1, D-2, D-3, and D-4). For D-0, we observed 56% more CVEs than expected in SWG, and we observed the expected rate of CVEs (-4%) in LWG. In SWG, we observed 52% fewer CVEs than expected on D-1, 22% fewer on D-2, and 340% more on D-3; in LWG, we observed 67% fewer CVEs than expected on D-1, 52% fewer on D-2, 227% more on D-3, and 352% more on D-4 (both $p < 0.05$ for trend).

Conclusions: In chronic HD patients, CVEs occur more frequently after longer inter-HD intervals.

Funding: Clinical Revenue Support

TH-PO942

Cytokine Removal by Different Dialysis Membranes

Markus Storr, Michael Hulko, Julia Gauss, Rose Speidel, Bernd Krause. *Dialyzer R&D, Gambro Dialysatoren GmbH (Part of Baxter International Inc.), Hechingen, Germany.*

Background: The purpose was to compare the removal efficiency of inflammatory and cell activating molecules by different types of dialysis membranes with a standardized in vitro test system.

Methods: Mini-dialyzers (membrane area 360 cm²) were prepared from commercial dialyzers Polyflux Revaclear (PR), Fresenius Cordiax (FC), highflux membranes with extended permeability (MCO1, MCO4) and HCO1100 (HCO). They were tested in an in vitro dialysis setup with 220 ml recirculating human serum on blood side (10 ml/min) and 220 ml recirculating bicarbonate dialysis fluid on dialysate side (25 ml/min) in countercurrent flow without net ultrafiltration at 37°C for 90 min. Serum solution was prepared from LPS activated whole blood as uniform solution divided into identical fractions. Samples were analyzed with an Interleukin-6 (IL6) ELISA kit. Dialysate samples were added to 3 different cell systems and cell activation was studied. Tubular epithelial cells (TEC) and normal human dermal fibroblasts (NHDF) were analyzed for IL6 generation; and human whole blood was FACS analyzed for CD11b expression on granulocytes.

Results: Serum IL6 decrease, IL6 recovery in dialysate and cell activation of TEC, NHDF and granulocytes by dialysate samples at 90 min are displayed in table below. IL6 starting concentration was 8667 pg/ml. Numbers are given as mean +/- standard deviation of 3 independent runs.

Membrane type	Serum IL6 decrease [pg/ml]	Dialysate IL6 recovery [pg/ml]	TEC IL6 [ng/10^6 cells]	NHDF IL6 [ng/10^6 cells]	CD11b on granulocytes [GeoMean signal]
PR	687 ± 310	399 ± 57	14 ± 0.6	643 ± 71	376 ± 16
FC	37 ± 107	190 ± 66	12 ± 0.8	584 ± 178	325 ± 18
MCO1	1047 ± 109	744 ± 111	20 ± 0.6	866 ± 115	417 ± 27
MCO4	1366 ± 371	1302 ± 136	28 ± 0.5	930 ± 41	496 ± 61
HCO	2175 ± 734	2075 ± 268	35 ± 3.6	831 ±18	651 ± 46
Dialysis fluid control	na	na	3 ± 0.1	1 ± 0.1	437

Conclusions: In a standardized test system different membranes were compared by their removal efficiency of specific pro-inflammatory mediators like IL6 and their general capacity to remove cell activating molecules measured by cell responses in 3 cell assays.

Funding: Pharmaceutical Company Support - Gambro Dialysatoren GmbH (part of Baxter International Inc.)

TH-PO943

MCO Dialyzer: Enhanced High-Flux Membrane with Expanded Toxin Removal

Markus Storr, Adriana Boschetti-de-Fierro, Manuel Voigt, Michael Hulko, Bernd Krause. *Research & Development, Gambro Dialysatoren GmbH, Hechingen, Germany.*

Background: MCO is a newly designed high-flux dialyzer providing improved selectivity that extends the spectrum of toxins removed during treatment. The purpose of this study is to compare the MCO in-vitro plasma clearances of different middle molecules to those for different high-flux dialyzers.

Methods: Middle/large molecule clearances of Theranova 400 (MCO, Gambro), Revaclear 400 (HF-PAES, Gambro), Optiflux F180NR (HF-PSu, Fresenius) and Elisio 17H (HF-PES, Nipro) dialyzers were compared. HD treatments were simulated with Q_B=400 ml/min and Q_D=700 ml/min. In each experiment (n=3), 1 L of uniform human plasma (octaplasLG, protein concentration 60 g/L) was recirculated for 60 min and followed by a 60 min simulated treatment. Markers (human) were spiked into the plasma pool after 55 min of recirculation: β2-microglobulin (5 mg), myoglobin (500 µg), and κ-FLC (~300 mg), while interleukin 6 is comprised in plasma. Pool and dialysate samples were taken after defined time intervals. Each marker concentration was measured by nephelometry and the clearance was calculated from the first order kinetics for the pool concentration variation with time.

Results: In vitro clearances for the MCO dialyzer in HD were consistently higher than those shown by all other dialyzers investigated. For κ-FLC and IL-6, the largest markers, all regular high-flux dialyzers showed only one-digit clearance values.

Devices	Surface area [m²]	Clearances Q_B=400 ml/min [ml/min]			
		b2m	Myo	κ-FLC	IL-6
		12 kDa	17 kDa	22.5 kDa	20-26 kDa
MCO	1.7	93 ± 5	61 ± 1	20 ± 1	12 ± 2
HF-PAES	1.8	71 ± 2	19 ± 2	6 ± 1	5 ± 1
HF-PSu	1.8	44 ± 3	4.2 ± 0.3	0.1 ± 0.1	2 ± 3
HF-PES	1.7	71 ± 1	17.5 ± 0.1	5 ± 1	3 ± 1

Conclusions: MCO delivers slightly better in vitro plasma clearances for β2m to that of HF-PES and HF-PAES, and larger than that of HF-PSu. Additionally, MCO shows superior removal of molecules in the range between 15 and 30 kDa against all comparators. This expanded toxin removal is in good agreement with the results from pilot clinical studies recently conducted in Europe [Krieter et al, ERA-EDTA 2016].

Funding: Pharmaceutical Company Support - All authors are employees of the Gambro Dialysatoren GmbH, Hechingen (Germany). Gambro AB (including all direct and indirect subsidiaries) is now part of Baxter International Inc. Baxter is a manufacturer of dialysis devices. None of the authors has proprietary interest. All experimental information is given in great detail to exclude any bias on the results

TH-PO944

Bloodless Potassium Measurement Using Mathematically-Processed, Signal-Averaged Electrocardiography

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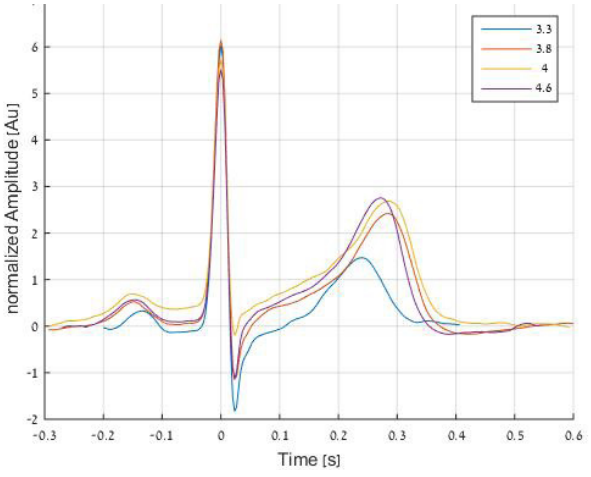
Background: Detecting hyperkalemia is limited by the need for blood testing. We have described non-invasive K measurement using the 12-lead, surface ECG. We now describe using these methods with a smartphone-based, single-lead device.

Methods: 14 adult hemodialysis patients had serum K and simultaneous, 2 minute ECG's recordings before dialysis, at 30 minutes, at 60 minutes at the end of dialysis, and optionally, on a non-dialysis day. ECG's (lead 1 only) were obtained by placing both hands on a 2-lead, Kardia device attached to the back of an Android smart phone. Using advanced signal processing, we used (t right slope)/(t amplitude)$^{1/2}$ from the first dialysis to create individual templates which were used to predict subsequent K values.

Results: 4 patients had inadequate data due to hand tremors or poor, lead-1 t wave morphology. Among the other 10 patients, mean K during the 1st dialysis was 5.2±0.7 maximum and 3.6±0.5 minimum. Subsequent K values were similar. For the predicted values, the mean absolute error (observed - predicted) was 0.4±0.2 mmol/L. Processed ECG changes between K 3.3 and 4.6 in one patient are shown in figure 1.



Conclusions: With signal processing, single-lead ECG can be used to bloodlessly measure potassium with clinically meaningful resolution. This enables remote and/or continuous K monitoring. Some patients require a device that is not affected by hand tremor or that can monitor a lead other than lead 1.

Funding: Other NIH Support - National Institute of Biomedical Imaging and Bioengineering

TH-PO945

Influence of Membranes and Hemodialysis Technique on Phenol and P-Cresol Clearance Jose A. Herrero, Mariana Garbiras, Amir Shabaka, Isabel Ortega, Mj Torrejon, Fernando Tornero, Virginia López de la Manzanara Pérez, Jesús Delgado-Domínguez. *Nephrology, Hospital Clinico San Carlos, Madrid, Spain.*

Background: Binding of Phenol and p-Cresol to proteins hinders their clearance in hemodialysis (HD). Our objective was to determine phenol and p-Cresol clearance with membranes of different adsorption and filtration capacity with different HD techniques.

Methods: In 16 patients, 13 males, mean age 62±17.5 years, Phenol and p-Cresol clearance was determined with; a)Toray polysulfone(PS) 2.1 m^2 Kuf 55 ml/h/mmHg on conventional HD(PS-HD), b)PS on online postdilutional hemodiafiltration(PS-HDF) c) Polymethyl methacrylate 2.1 m^2 Kuf 43 ml/h/mmHg (Great adsorption capacity) on HD(PMMA-HD), d)PMMA on HDF(PMMA-HDF). Each session lasted 4 hours and Phenol, p-Cresol, β_2-microglobulin(β_2-m), albumin and urea serum levels were determined before and after each session. Post-HD β_2-m, phenol and p-cresol levels were adjusted for variations in serum albumin. Their percentage reduction(PR), total processed blood volume(PBV) and infusion volume in HDF, and KT were measured.

Results: There were no differences in total PBV between the four procedures. Infusion volume in HDF was higher with PS than with PMMA (26.1±2.4 vs. 17.6±2.3 l/session,p=<0.001). There were no differences in Phenol and p-Cresol clearance between HDF and HD when using the same membrane. Phenol clearance was higher than that of p-Cresol in all combinations(p<0,001). Phenol and p-Cresol clearance was higher with PS than with PMMA in both HD and HDF. β_2-m clearance differed with different membranes and techniques.

	PMMA-HD	PMMA-HDF	PS-HD	PS-HDF
PR Phenol(%)	61.3±8.9	62.4±12.1	69.0±10.6[a]	68.7±8.9[b]
PR p-Cresol(%)	39.8±10.5	39.7±10.0	46.5±10.0	45.0±7.2
PR β_2-m(%)	53.1±5.2[c]	65.9±4.7[c]	70.9±3.8[c]	81.8±3.2[c]
KT(l)	54.0±4.4	56.1±4.9	56.7±3.7	59.9±3.3[d]

a)p=0.025 vs PMMA-HD;b)p=0.045 vs PMMA-HDF;c)p<0,05 in all values of β_2-m;d)p=0.02 vs the rest.

Conclusions: 1) In HD and HDF Phenol clearance is higher than that of p-Cresol. 2) PS membranes achieve a higher Phenol and β_2-m clearance than PMMA in both HD and HDF. 3) HDF does not increase Phenol or p-Cresol clearance compared to HD with neither PS nor PMMA.

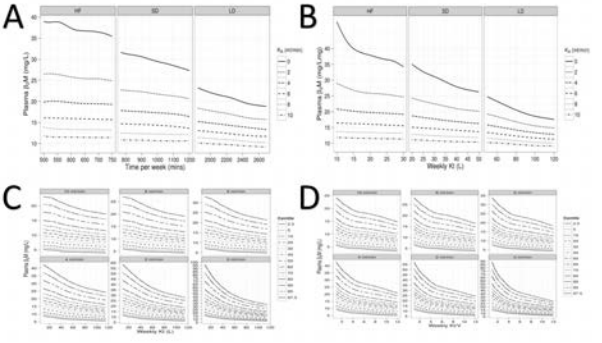
TH-PO946

Simplified Kinetic Indices and Population Exposures to Middle Molecules across the Range of Residual Renal Functions Hafiz Ali Sroya, Christos Argyropoulos, Maria-Eleni Roumelioti, Mark L. Unruh. *UNM School of Medicine.*

Background: Beta 2 Microglobulin (β2M) is a uremic toxin that accumulates in ESRD patients. Elevated plasma β2M concentrations is linked to higher mortality in patients undergoing hemodialysis. The population kinetics of β2M has been described in the literature but the application of available kinetic models to predict dialysis induced changes in β2M concentrations has been limited.

Methods: We did a quantitative patient-level review of available data of β_2M population kinetic models to predict plasma β2M concentrations in a population of simulated ESRD patients on hemodialysis with different levels of residual renal functions. We compared dialyzer clearance in patients receiving high flux dialysis under different regimes; conventional thrice weekly dialysis (HF), short daily (SD) and long daily (LD) sessions. We also examined the ability of simplified kinetic indices to quantify the effects of different dialysis schedules on plasma β_2M concentrations across the range of residual renal functions.

Results: Longer weekly dialysis time resulted in lower β_2M concentrations irrespective of dialysis regimes. There was a sharp reduction in mean predialysis β_2M concentration in patients with K_R < 4ml/min as Kt increased from 10 to 15 L, followed by a gradual decline. At population level, the effect of fixed Kt (or Kt/V) was different depending on residual renal functions. Only 2.5% of patients with K_R =10ml/min had β_2M >20mg/L versus 80% of patients with KR =0ml/min. The effect of Kt/V on population centiles of β_2M appeared to be biphasic, the steeper effect at Kt/V < 4 and less steeper at Kt/V >4.



Conclusions: While weekly Kt (or Kt/V) can be used to quantitate the effects of different dialysis regimes, understanding of its effect at population level can effectively be used prescribing dialysis dose across the population of patient at different residual renal functions.

TH-PO947

Hemodialysis Water Purification, Disinfection and Monitoring Practices in Bangladesh Sadiq Ahmed. *Nephrology, Univ of KY, Lexington, KY.*

Background: To provide ESRD patients with safe dialysis is a challenge due to technical & economic constraints in Bangladesh. In Bangladesh the numbers of ESRD patients are doubled in recent years. Most of these patients are on HD with very high mortality. Proper water purification is essential for providing safe HD treatment.This study looks at the dialysis water chemical composition and the disinfection protocols and monitoring practices in two major dialysis units in Dhaka, Bangladesh.

Methods: In 2015 two major chronic HD units, A & B, in Bangladesh were visited. The technicians and Nephrologists were interviewed. The samples of feed water and the final products before the dialysis was analyzed by Spectra lab USA. Some of the chemicals of the waters from units A & B in table: I and the water monitoring practices of the units are in table II. Table I shows that unit B has high levels of certain chemicals in the purified water. Table II shows that a routine disinfection and monitoring protocol is not followed.

Results: Table I

Analytes	A	B	Normal range mg/L
Aluminum	<.005	**0.184**	0.000-0.010
Arsenic	<.005	<0.005	0.000-0.006
Calcium	1.986	**6.699**	0.000-2.000
Copper	<.005	0.067	0.000-0.100
Fluoride	<0.10	<0.10	0.00-0.20
Lead	<0.002	**0.011**	0.000-0.005
Magnesium	0.737	1.190	0.000-4.000
Zinc	<.005	**0.644**	0.000-0.100

Table II

Water maintenance	Unit A	Unit B	USA
Check Chlorine and Chloramine	No	No	Yes. Before each shift
Routine check for endotoxin and bacterial culture	No	No	Yes
Chemical analysis	yearly	6 month	6 month
Routine disinfection of RO	No	No	Yes
Check Ph. and conductivity by a separate meter	No	No	Yes
Nephrologist involved in the process	None or minimum	None or minimum	Yes

Conclusions: Proper purification and disinfection protocols with routine monitoring of water quality is essential for safe hemodialysis. This is a challenge in the developing nations like Bangladesh due to cost but more due to lack of awareness. Routine monitoring of water quality & following disinfection protocols are not very expensive as the technology is locally available. Organizations like ISN or WHO can take initiatives to provide education & help in this area.

Funding: Private Foundation Support

TH-PO948

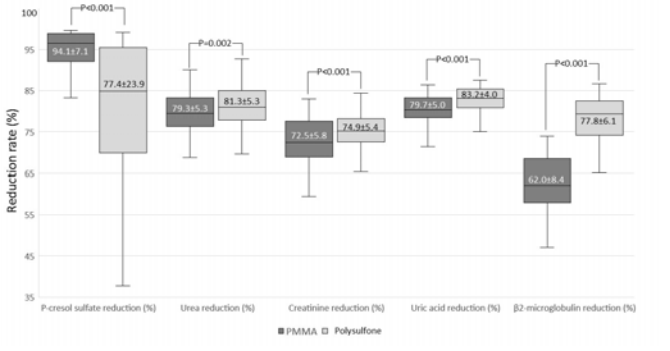
Combining Difussion, Convection and Absorption: A Pilot, Cross-Over Study of Polymethylmetacriylate versus Polysulfone High-Flux Dialysis Membranes in the Removal of P-Cresol Sulfate by On-Line Hemodiafiltration

Pablo Molina,[1] Julio Peiró-García,[2] Cristina Esteller Beltrán,[2] María Amparo Martínez Gómez,[3] Sandra Beltrán,[1] Belen Vizcaino,[1] Mercedes Gonzalez,[1] Irina Sanchis,[1] Luis M. Pallardo,[1] Francisco Maduell.[4] *[1]Nephrology, Dr Peset Univ Hospital, Spain; [2]Clinical Analysis, Dr Peset Univ Hospital, Spain; [3]Pharmacology, Dr Peset Univ Hospital, Sri Lanka; [4]Nephrology, Hospital Clinic Barcelona, Spain.*

Background: Only a few studies have examined how to improve the protein-bound toxins removal by extracorporeal strategies. This study tested the hypothesis that polymethylmetacriylate *(*PMMA) dialysis membranes with a high adsorptive capacity increase P-cresol sulfate removal compared to standard high-flux (HF) membranes, by on-line hemodiafiltration (OL-HDF).

Methods: 40 stable hemodialysis patients were enrolled in a prospective, cross-over study and treated with PMMA and polysulfone HF membranes by OL-HDF with postdilutional infusion. One session with each dialyzer was performed (PMMA BG2.1U, and polysulfone TS2.1). Primary end point was serum p-cresol sulfate reduction rate, determined by chromatography. Secondary end points included the convective volume achieved and the β_2-microglobulin (β2M) and small solute clearances. Dialysis procedures remained unchanged during both sessions.

Results: PMMA membrane achieved significantly greater p-cresol sulfate reduction ratio (94.1 vs. 77.4%; p<0.001). There was no difference in Kt/V (2.2±1.0 Vs. 2.2±0.4; p=0.325) although small molecules removal was better with polysulfone. The convection volume (20.4±3.3 Vs. 31.4±8.4 L/session; p<0.001) and β2M reduction ratio (62.0 Vs.77.8%; p<0.001) were significantly lower with PMMA membrane.



Conclusions: P-cresol sulfate removal by OL-HDF was superior with PMMA membranes, appearing to be a good dialysis strategy for improving dialytic clearance of p-cresol, enabling an adequate β2M and small solute clearances.

TH-PO949

Assessment of Inpatient Dialysis Adequacy Using On-Line Clearance: A Fellow Quality Improvement Project

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Background: A Hemodialysis (HD) single-pool Kt/V target of > 1.4 (Kt/V) is widely accepted as the minimum standard for outpatients dialyzing thrice weekly. Studies evaluating HD adequacy in hospitalized patients suggest worse outcomes when Kt/V is below standard outpatient goals. However, HD adequacy is rarely assessed in hospitalized settings. Online clearance monitoring (OCM) by sodium dialysance can accurately estimate urea clearance. In this project, we assessed OCM derived adequacy in hospitalized ESRD patients treated with HD.

Methods: Data were prospectively collected on all ESRD patients treated over a 2 week period. HD was performed on a Fresenius 2008T machine with Optiflux 180 dialyzer at Qb = 400 ml/min & Qd = 800 ml/min. Session durations were based on outpatient prescriptions or 4 hours when not available. Urea volume of distribution (Vd) was estimated by the Watson formula. OCM derived Kt/V values were recorded at the end of each HD session. Data are mean +/- (SEM).

Results: 21 patients were treated with 62 HD sessions. There were 10 AVF, 2 AVG, and 9 CVC responsible for 30, 8, and 24 treatments respectively. Treatment times were 227 +/- 31 min. OCM data indicated only 42% (26/62) of treatments achieved Kt/V ≥ 1.4 with 22% (14/62) having Kt/V < 1.2. Analysis of patients' initial HD treatment suggests high Vd and CVC access are associated with failure to meet Kt/V goal.

Kt/V Goal	Access	Vd (L)	Time (min)	UF vol (L)	spKt/V	eKt/V
Met n = 10	20% CVC	36.7 (1.1)	232 (6.3)	2.1 (0.4)	1.65 (0.07)	1.43 (0.06)
Fail n = 11	64% CVC	49.7 (2.7)	228 (8.0)	2.8 (0.5)	1.20 (0.06)	1.03 (0.05)
P-value	0.04	0.0003	0.34	0.16	0.06	0.05

Conclusions: These data suggest that inpatient HD frequently fails to achieve adequacy standards. OCM was easy to perform and only required calculation of Vd. We postulate that OCM directed therapy has the potential to improve HD delivery in the inpatient setting and possibly improve outcomes. Based on our results,we plan to utilize OCM in future determinations of dialysis session length.

TH-PO950

Early Patient Experience with the Tablo™ Hemodialysis System

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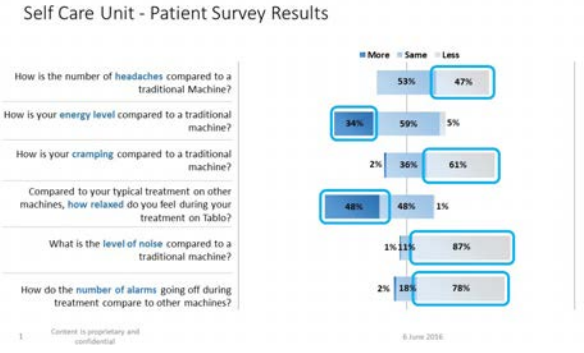
Background: Patients on in-center hemodialysis (ICHD) often experience a range of symptoms and disturbances during, immediately following, and between dialysis sessions. A goal for any innovation in hemodialysis is to minimize those symptoms. This study reports on the early patient experience using a new technology aimed at enabling in-center self-care hemodialysis (ICSCHD), the Tablo™ Hemodialysis System.

Methods: A subset of patients (n=33) from three dialysis centers, representing 152 treatments using the Tablo™ System were asked to complete surveys on their experience with Tablo™ compared to their previous dialysis machine.

Results: Patients reported experiencing 47% fewer headaches (n=54), 61% less cramping (n=92), 34% having more energy (n=53) and 48% being more relaxed (n=74). In addition, patients reported that the Tablo™ System was 87% quieter (n=129) and 78% had fewer alarms (n=119) compared to their previous dialysis machine.



Conclusions: Preliminary, uncontrolled results suggest that patients report a more favorable dialysis experience with the Tablo™ Hemodialysis System compared to their conventional ICHD device. These results may encourage patients to choose in-center self-care for which the device is designed.

Funding: Pharmaceutical Company Support - Outset Medical, Inc.

TH-PO951

Protein-Bound Uremic Toxin Adsorption by Hexadecyl-Immobilized Cellulose Beads in Hemodialysis

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Background: Protein-bound uremic toxin (PBUT) accumulation causes uremia-related complications. We examined the PBUT removal ability of a hexadecyl-immobilized cellulose bead-containing column for patients undergoing hemodialysis.

Methods: *In vitro,* adsorption of indoxyl sulfate (IS), a representative PBUT (0.25–2.0 mM), to hexadecyl-immobilized cellulose beads (1.0 g) for 0–4 hours was compared

with that to polysulfone (PS) and polymethyl methacrylate (PMMA). Clinically, patients undergoing hemodialysis (4–5 h for regular dialysis, thrice weekly) (n= 29) were randomly divided into 2 groups: one (n=15) used the hexadecyl column for direct hemoperfusion with a regular hemodialyzer for 2 weeks; the other (n=14), a PS or PMMA dialyzer. Patient sera before and after dialysis, and before and after passing the column, were assessed to measure clinical effects and adsorption performance, respectively. Serum IS, indoleacetic acid (IAA), phenyl sulfate (PhS), p-cresyl sulfate (PCS), β_2-microglobulin (β_2-m), urea nitrogen, and albumin levels were measured.

Results: Compared to PS and PMMA, hexadecyl-immobilized cellulose beads dose-dependently adsorbed more IS in vitro (7.5±0.6% vs. 55.4±1.4% adsorption of 1 mM IS for 1 hour, P<0.01). Only the hexadecyl column decreased protein-unbound IS, IAA, PhS, and PCS levels (by 34.4±30.0%, 34.8±25.4%, 28.4±18.0% and 34.9±22.1%, respectively), but did not significantly decrease their pre-dialysis serum levels after 2-week treatment. The hexadecyl column strongly adsorbed β_2-m (92.9±2.5%) but not urea nitrogen and albumin.

Conclusions: Hexadecyl-immobilized cellulose beads removed PBUTs by adsorption. Regular hemodialysis with adsorption treatment is an attractive blood purification treatment to increase PBUT and water-soluble intermediate removal.

TH-PO952

Intradialytic Kinetics of β-2-Microglobulin and κ Free Light Chains: Diffusion-Adjusted Regional Blood Flow Model J. Ken Leypoldt,[1] Markus Storr,[2] Baris U. Agar,[1] Adriana Boschetti-de-Fierro,[2] Manuel Voigt,[2] Michael Hulko,[2] Angelito A. Bernardo,[1] Alexander H. Kirsch,[3] Alexander R. Rosenkranz,[3] Detlef H. Krieter,[4] Bernd Krause.[2] *[1]Baxter Healthcare Corporation, Deerfield; [2]Gambro Dialysatoren GmbH, Hechingen, Germany; [3]Medical Univ of Graz, Graz, Austria; [4]Univ Hospital Wuerzburg, Wuerzburg, Germany.*

Background: The kinetics of β_2-microglobulin (b2m) during hemodialysis (HD) have been shown to be consistent with either a conventional two-compartment model (Ward et al, Kidney Int 2006) or a diffusion-adjusted regional blood flow model (DA-RBF, Maheshwari et al, Ann Biomed Eng 2011). Recent work has shown that a two-compartment model cannot be used to describe the kinetics of middle molecules with molecular weight (MW) larger than that for b2m unless the compartment volume from which dialyzer clearance occurs is less than plasma volume. We hypothesized that a DA-RBF model can adequately describe the kinetics of b2m (MW=11.8 kD) and kappa free light chains (κFLC, MW=22.5 kD).

Methods: Intradialytic serum and dialysate concentrations of b2m and κFLC were measured in 34 HD patients treated by Theranova (high flux with extended permeability) dialyzers during 2 prospective clinical trials (NCT02377570 & NCT023776222). Overall dialyzer clearance (K_{ovr}) was evaluated by total mass removed in the dialysate. In vitro experiments using human plasma spiked with κFLCs evaluated membrane adsorption of κFLC to the dialysis membrane (N=3). A DA-RBF model, including dialyzer clearance by membrane transport and adsorption, was used to estimate intercompartmental clearance (K_{ip}), total distribution volume (V_{tot}) and the blood flow percent to the high flow tissue region (f_h).

Results: Assuming the volume percent in the high flow region to be 5-20%, calculated model parameters expressed as medians for this range were:

Middle Molecule	K_{ip} (mL/min)	V_{tot} (L)	f_h (%)
β_2-microglobulin	61.3-62.0	15.3-17.9	90.7-94.0
κFLC	4.8-5.6	9.7-9.8	97.6-98.0

As expected, K_{ip} was higher for b2m than κFLC, but blood flow percent to the high flow tissue region was similar for both b2m and κFLC.

Conclusions: A DA-RBF model provides a physiological basis for intradialytic kinetics of both b2m and κFLC.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

TH-PO953

Middle Molecule Kinetics during Hemodialysis and Hemodiafiltration Based on a Two-Compartment Model J. Ken Leypoldt,[1] Markus Storr,[2] Baris U. Agar,[1] Adriana Boschetti-de-Fierro,[2] Angelito A. Bernardo,[1] Alexander H. Kirsch,[3] Alexander R. Rosenkranz,[3] Detlef H. Krieter,[4] Bernd Krause.[2] *[1]Baxter Healthcare Corporation, Deerfield; [2]Gambro Dialysatoren GmbH, Hechingen, Germany; [3]Medical Univ of Graz, Graz, Austria; [4]Univ Hospital Wuerzburg, Wuerzburg, Germany.*

Background: The kinetics of β_2-microglobulin (b2m) during hemodialysis (HD) are well described by a two-compartment (2C) model where clearance by the dialyzer is from a central compartment volume (V_1) that approximates plasma volume and a total distribution volume (V_{tot}) that approximates extracellular volume. The kinetics of middle molecules with molecular weight (MW) larger than b2m have not been extensively studied.

Methods: Intradialytic serum and dialysate concentrations of b2m (MW=11.8 kD), myoglobin (16.7 kD), and complement factor D (27.0 kD) were used to estimate 3 kinetic parameters from a 2C model (intercompartmental clearance or K_{12}, V_{tot} and V_1) in HD patients during 2 prospective clinical trials (NCT02377570 & NCT023776222) comparing the performance of high flux dialyzers/diafilters and medium cut-off (high flux with extended permeability) dialyzers. In this analysis, the results from all treatments were combined. Overall dialyzer clearance (K_{ovr}) was evaluated by total mass removed in the dialysate. In total, 345 sets of kinetic parameters from 35 patients were determined.

Results: K_{ovr} was dependent on MW and dialyzer; median (interquartile range) for the combined data was 49.5 (28.9-70.0) mL/min. Results are tabulated:

Middle Molecule	N	K_{12} (mL/min)	V_{tot} (L)	V_1 (L)
β_2-microglobulin	135	95.4 (78.2-115.8)	17.8 (13.8-21.6)	2.8 (2.1-3.6)
myoglobin	109	68.1 (56.5-88.2)	21.8 (15.4-31.7)	2.1 (1.1-2.6)
complement factor D	101	52.3 (38.0-75.6)	14.8 (11.6-19.1)	1.2 (0.6-1.6)

Although K_{12} and V_1 were smaller at larger MW, the strongest dependence of these parameters was on K_{ovr}. For the combined data: K_{12} vs. K_{ovr}, R=0.444, P<0.001 & V_1 vs. K_{ovr}, R=0.745, P<0.001. V_{tot} was independent of K_{ovr} (P=0.09).

Conclusions: A 2C model can only describe the kinetics of middle molecules with MW larger than b2m if the central compartment volume is small and dependent on dialyzer clearance.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

TH-PO954

Performance of Hemodialysis with Novel Medium Cut-Off Dialyzer Alexander H. Kirsch,[1] Lars-Goran Nilsson,[3] Werner Beck,[4] Michael Amdahl,[5] Christoph Wanner,[2] Alexander R. Rosenkranz,[1] Detlef H. Krieter.[2] *[1]Clinical Div of Nephrology, Medical Univ of Graz, Graz, Austria; [2]Div of Nephrology, Univ Hospital Würzburg, Würzburg, Germany; [3]Baxter Renal Therapeutic Area, Lund, Sweden; [4]Baxter Renal Therapeutic Area, Hechingen, Germany; [5]Baxter Healthcare Corporation, Round Lake, IL.*

Background: Compared to high-flux dialysis membranes (hfD), novel medium cut-off (MCO) membranes are more permeable for larger middle molecules.

Methods: In two prospective, open-label, controlled, randomized crossover pilot studies (NCT02377570, NCT02377622), 39 prevalent HD patients were studied in mid-week dialysis treatments using Theranova 400 AA dialyzer in HD (MCO HD) in comparison to, study 1, FX CorDiax 80 dialyzer in HD (hfHD) and, study 2, hfHD and high-volume hemodiafiltration (HDF; FX CorDiax 800; convective vol 24L). Instantaneous clearances (K_{inst}) at 30 and 120 minutes and reduction ratios (RR) of free light chains (FLC) and other larger middle molecules were analyzed with a mixed model.

Results: Study 1 (Q_B=300 ml/min): At 30min MCO HD provided higher FLC K_{inst} (κFLC, LS mean [SE]: 38.0 [3.63]; λFLC (15.2 [1.59] mL/min) compared to hfHD (20.1 [3.63] and 0.0 [1.59] mL/min, respectively); both P <0.001. At 120min κFLC K_{inst} was still significantly greater for MCO HD while λFLC K_{inst} was not. Also, FLC RR was higher with MCO HD (κFLC: 66.3% [1.85]; λFLC: 42.5% [2.06]) than hfHD (36.4% [1.88] and 12.9% [2.10] respectively); both P<0.001) Study 2 (Q_B=400 mL/min): MCO HD showed higher K_{inst} (30min) of λFLC compared to HDF (19.1 [2.65] vs. 6.6 [2.65] mL/min; P<0.001), while there was no difference in κFLC. Also, there was a significantly higher λFLC RR in MCO HD compared to HDF (48.1% [1.72] vs. 37.9% [1.76]; P<0.001). Additionally, MCO HD provided significantly better removal of β_2-microglobulin compared to hfHD and of myoglobin and complement factor D compared to both hfHD and HDF. Albumin loss to dialysate was moderate with MCO, but greater than in high-flux HD and HDF.

Conclusions: MCO HD effectively removes a wide range of middle molecules, substantially better than high-flux HD. It even exceeds the performance of HDF for several large solutes.

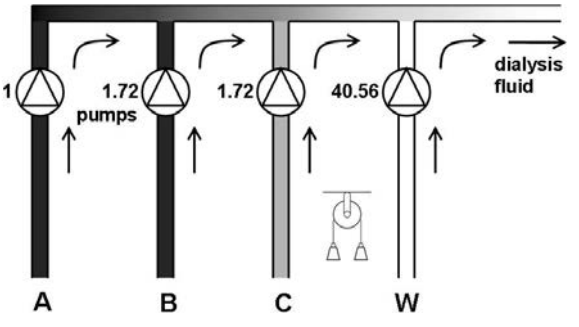
Funding: Pharmaceutical Company Support - Baxter

TH-PO955

A Novel Method of Widening the Range of Dialysis Fluid [Na] Using a 4-Stream Approach Susie Q. Lew,[1] Yuk Lun Cheng,[2] Todd S. Ing.[3] *[1]Medicine, George Washington Univ, Washington, DC; [2]Medicine and ICU, Alice Ho Miu Ling Nethersole Hospital, Hong Kong, China; [3]Medicine, Stritch School of Medicine, Loyola Univ Chicago, Maywood, IL.*

Background: The conventional, 45X, 3-stream, bicarbonate-based dialysis fluid (DF) delivery system consists of an acid concentrate stream (CS), **A**; a bicarbonate (BIC) CS, **B**; & H_2O stream, **W**. The flow rate ratios (FRR) for **A**:**B**:**W** are: 1:1.72:42.28 (totaling 45 or 45X). This system provides a DF [Na] range of 125-150 mM.

Methods: We devised a 4-stream DF delivery system to expand the [Na] range by adding a NaCl CS, **C**. An electronic pulley-like mechanism sits between **C** & **W.** Contributions to the final DF include: **A:** Chloride salts of Na(63 mM), K, Ca & Mg, & dextrose; **B**: 37 mM $NaHCO_3$; **C:** 37 mM NaCl; & **W**: H_2O. The FRR for **A**:**B**:**C**:**W** under normal conditions are: 1:1.72:1.72:40.56 (45 or 45X).



Results: To change the DF Na level, the FRR of **C** changes 1 way, & **W** changes by the same magnitude but in the opposite direction. For example, if **C**'s FRR decreases by

0.2 to 1.52 then **W**'s FRR will increase by 0.2 to 40.76. **C** will deliver less NaCl & **W** will deliver more H_2O to the final DF; lowering [Na] in the final DF. The opposite sequence of events will occur if **C**'s FRR increases. Patients with dysnatremia can be dialyzed with a wider range of DF Na levels without associated changes in BIC, K, Ca, Mg, & dextrose concentrations. Thus averting central pontine myelinolysis or cerebral edema, normally seen with rapid changes in serum [Na]. The ingredients in **A** & **B** remain unchanged because the sum of the FRR for **C** & **W**, a fluid volume that normally dilutes the ingredients of **A** & **B**, remains unchanged.

Conclusions: A pulley between **C** & **W** permits a wider DF [Na] range. The final concentrations of BIC, K, Ca,& Mg are not affected since the total volume of fluid that dilutes these elements remains intact.

TH-PO956

Acute Extracellular Calcium Regulation Is Independently Associated with Serum Undercarboxylated Osteocalcin in Chronic Hemodialysis Patients

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Background: In order to avoid excessive calcium (Ca) loading in hemodialysis (HD) patients, current guidelines suggest a dialysate calcium concentration (dCa) of 2,5 mEq/l based on relatively stable intradialytic serum Ca levels. However, the latter do not account for possible Ca storage in acutely accessible pools. A rapidly exchangeable Ca pool located at the bone level has been proposed to be involved in acute extracellular Ca regulation.

Methods: To obtain clinical evidence for a rapidly exchangeable Ca pool and its contribution in the maintenance of serum Ca levels we assessed dialysate-sided ionized Ca mass balance (iCa_{MB}) and change in extracellular fluid ionized Ca mass (ΔiCa_{ECF}) during two HD sessions in chronic HD patients using a dCa of 3,5 (n=28) and 2,5 (n=10) mEq/l. Acute calcium buffer capacity was calculated by setting ΔiCa_{ECF} in relation to iCa_{MB}. ELISA-based measurements of serum osteocalcin, the most abundant non-collagenous bone protein, were conducted prior to the first HD session.

Results: Considering pre- to postcapillary dialysate bicarbonate decline, iCa_{MB} was invariably positive for both 2,5 and 3,5 mEq/l dCa, with a mean of 434 (±125) and 725 (±162) mg/HD, respectively (p<0,001). The mean amount of intra-dialytic Ca load buffered (i.e. iCa_{MB} - ΔiCa_{ECF}) was 410 (± 116)mg/HD at 2,5 mEq/l dCa and 565 (±130)mg/HD at 3,5 mEq/l dCa (p<0,001). Acute Ca buffer capacity was 95 (±8)% and 78 (±7)% (mean at 2,5 and 3,5 mEq/l dCa) (p<0,001). Using 3,5 mEq/l dCa, acute Ca buffer capacityunivariately correlated with undercarboxylated osteocalcin (Glu-OC) (r=0,49, p<0,01), patient dry weigth (r=-0,47, p<0,05) and body mass index (r=-0,45, p<0,05). Multivariate regression analysis showed an independent association of acute Ca buffer capacity with Glu-OC (ß=0,512, p=0,002) only.

Conclusions: Our study revealed high Ca burden with standard dCa and provides strong evidence for the existence of a rapidly exchangeable calcium pool that counteracts acute serum Ca deviations. Our data provide - for the first time - experimental evidence for the involvement of bone in acute extracellular Ca regulation in vivo.

Funding: Government Support - Non-U.S.

TH-PO957

Validation of a Novel Mathematical Model of Protein-Bound Uremic Toxins Kinetics in Hemodialysis Patients

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Background: While accumulation of protein-bound uremic toxins (PBUTs) such as indoxyl sulfate (IS) and p-cresyl sulfate (pCS) is associated with mortality, their removal in conventional hemodialysis (HD) is limited. We developed a novel mathematical model to better understand PBUT kinetics. We validated the model with *in vivo* data on the dialytic removal of PBUTs (Deltombe *et al*. 2015), and *in vitro* data studying the effect of increased dialysate flow with concomitant increase in dialyzer size (K_oA) (Meyer *et al*. 2004).

Methods: The model comprises a multi-compartmental representation of the patient and a spatiotemporal representation of the dialyzer and accounts for albumin-toxin dynamic equilibrium. The model was calibrated using IS, PCS, and urea data from Eloot *et al*. (2016). A total of 6 model parameters, namely, (i-ii) mass transfer coefficients between plasma and interstitium ($K_{ip,T}$) and between interstitium and intracellular space ($K_{ic,T}$), (iii) the association constant (k_1), (iv-vi) and plasma, extracellular, and intracellular volumes (V_{pl0},V_{ex0},andV_{ic0}) were estimated.

Results:

Toxin	$K_{ip,T}$ (L/min)	$K_{ic,T}$ (L/min)	k_1 ($M^{-1}min^{-1}$)	V_{pl0} (L)	V_{ex0} (L)	V_{ic0} (L)
IS	1.55	0.3	3.72×10^5	2.5	12.4	24.7
pCS	1.44	0.26	4.36×10^5			
Urea	-	0.35	-			

Our model reproduces the published data accurately. During HD, the bound fraction of IS increases with time and across the dialyzer. The reduction ratio for the free fraction is much more pronounced compared to that of the total concentration (Figure 1A). Our model also describes the response to changing Q_d and K_oA (Figure 1B).

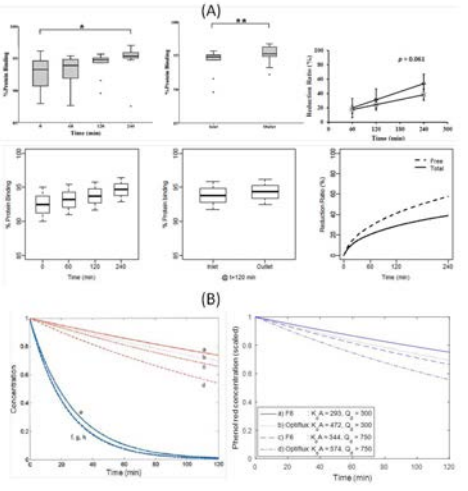

Figure 1: (A) Comparing indoxyl sulfate (IS) *in vivo* data (top row) (Deltombe *et al.* 2015) with model predictions depicted in bottom row. (B) Effect of and Q_d on removal of phenol red. Comparing Meyer *et al.* (2004) (left) and model simulations (right). In left panel: (a-d) in figure legend refers to same dialyzers, Q_d and combinations as in right panel. Plasma flow rate Q_b was 200 mL/min for all four scenarios.

Conclusions: The proposed model reproduces existing literature data closely. This model can be used for testing new approaches for removal of PBUTs such as pre-dilution hemodiafiltration and effect of enhanced removal by binding competitors.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-PO958

β-2 Microglobulin Removal by High-Flux Dialysis: A Meta-Analysis

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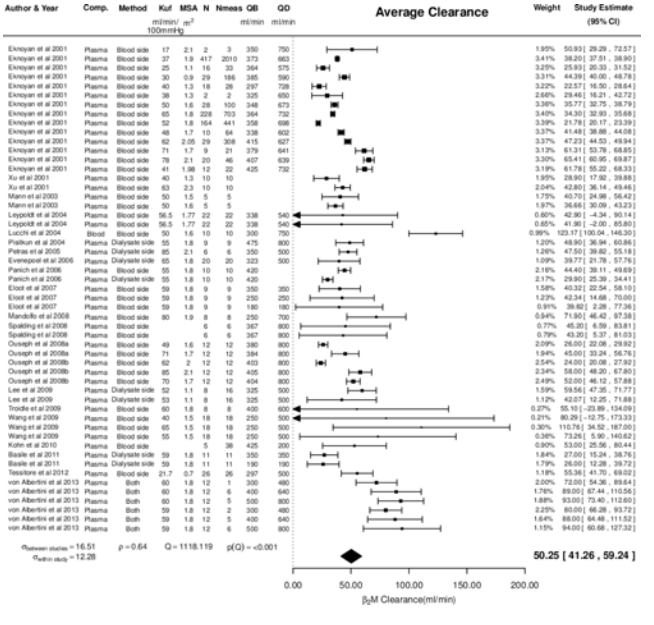
Background: Elevated beta-2 microglobulin (B2M) levels with adverse cardiovascular and infectious outcomes. There is limited quantitative data about the ability of high flux dialyzers (HF) to remove B2M.

Methods: We used ProQuest to search EMBASE and MEDLINE, for randomized controlled trials and observational studies in HF dialysis between 2001-2013. Clearance measurements at blood side and/or dialysate side were included and reported via random effects meta-analysis.

Results: Average clearance was 50.2 ml/min with substantial heterogeneity among the 37 studies identified.



In meta-regressions, we found a significantly lower B2M clearance for Polysulfone and Cellulose membranes.

	estimate	se	p-val
Intercept	22.2	14.2	0.1
Membrane Kuf (ml/min/100mmHg)	0.2	0.2	0.2
Membrane Surface Area (m2)	0.5	6.7	0.9
Blood (vs. plasma) clearance	58.7	13.3	**<0.001**
Dialysate (vs. blood side) clearance	-13.3	6.7	**0.05**
Blood flow (ml/min)	0.1	0.03	**0.04**
Membrane material (polyarylethersulfone is referent)			
Polysulfone	-17.6	3.6	**<0.001**
Cellulose	-19.17	8.01	**0.02**
Polyacrylnitrile	-13.36	6.88	**0.05**
Polymethylmethacrylate	-22.50	11.57	**0.05**
Secular trend	0.57	1.24	0.64

Adjusted dialysate-side and plasma clearances were lower than whole blood clearances. B2M reduction ratio was significantly higher for PS (-8.62 ± 4.28, p = 0.04 [-17.01, -0.22]) compared to other membrane materials.

Conclusions: Membrane material (e.g. PAES), but not surface area, plays a significant role in the efficient clearance of B2M. Due to methodological heterogeneity, this observation should be confirmed in prospective studies with highly standardized methods of analysis.

Funding: Clinical Revenue Support

TH-PO959

Combination of Sodium and Ultrafiltration Step-Down Is More Effective and Much Safer in Aged in Comparison to Younger Population Rather Than Any Alone

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Background: Intradialytic hypotension is the most common complication of haemodialysis (HD). This study on the effect of profiled hemodialysis on intradialytic hypotension(IDH) and related symptoms,nursing interventions during dialysis . Evaluated intradialytic hypotension related symptoms included muscle cramps, dizziness, headache,nausea and vomitting. Evaluated nursing interventions included saline infusion,decrease or stop ultrafiltration(UF) and session failure. In this study interdialytic weight and serum sodium concentration were evaluated also.

Methods: This study included 24 patients on maintenance haemodialysis who experienced frequent episodes of intradialytic hypotension were recruited. There were 17 female and 7 male patients.

Results: There was significant improvement of IDH (p<0.001) ,cramps(p<0.001) ,dizziness(p<0.001) , headache(p<0.001),saline infusion (p<0.001),decrease or stop UF (p<0.001), session failure (p<0.001). No significant difference in interdialytic weight gain, serum sodium concentration, nausea and vomiting.

	standard	profiled
Saline Bolus n (%)	69 (24%)	29 (10%)
Decrease of D/C UF n (%)	121 (42%)	45 (15.6%)
Session Failure n (%)	35 (12%)	10 (3.5%)
Hypotension n (%)	108 (37.5%)	41 (14.3%)
Cramps n (%)	38 (13.2%)	9 (3.2%)
Dizziness n (%)	62 (25.5%)	20 (7%)
Headach n (%)	44 (15%)	13 (4.5%)
Nausea & Vomiting n (%)	17 (5.9%)	14 (4.7%)

Conclusions: In conclusion, combination of step-down sodium and ultrafiltration profiles are simple and cost effective methods which improve the homodynamic stability with modulating the sodium dialysate and removal of fluids, so decreases the incidence of IDH and related symptoms (dizziness,cramps,headache) . Also decreasing all nursing interventions (saline infusion,decreasing or stopping ultrafiltration, session failure) with improvement of dialysis tolerance. Without significant interdialytic weight gain or sodium gain. Therefore combination of sodium and ultrafiltrationprofiles is recommended for IDH prevention.

TH-PO960

Vadadustat Maintains Hemoglobin (Hb) Levels in Dialysis-Dependent Chronic Kidney Disease (DD-CKD) Patients Independent of Systemic Inflammation or prior Dose of Erythropoiesis-Stimulating Agent (ESA)

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Background: DD-CKD is associated with systemic inflammation. Vadadustat is a novel, oral, hypoxia-inducible factor prolyl-hydroxylase inhibitor in development for the treatment of renal anemia.

Methods: A randomized, Phase 2, multicenter, open-label study assessed the Hb response to 3 starting doses of vadadustat over 16 weeks in 94 DD-CKD patients who were maintained on ESAs prior to study entry. Patients were converted from ESA to vadadustat, and assigned to 1 of 3 dose cohorts: 300mg once daily (QD); 450mg QD; and 450mg three times weekly (TIW). From week 8, vadadustat dose could be adjusted (150-600 mg) as needed to maintain Hb. A post-hoc analysis was performed to explore the relationship between final vadadustat dose, mean change in Hb, baseline markers of inflammation (hepcidin and C-reactive protein [CRP]), and weekly ESA dose prior to study entry.

Results: No correlation was observed between the final vadadustat dose and baseline markers of inflammation or ESA dose. (Tables 1, 2). Vadadustat maintained Hb independent of baseline CRP (p=0.07) and hepcidin (p= 0.11).

Table 1. QD vadadustat dose

	Mean baseline hepcidin (ng/mL)		Mean baseline CRP (mg/L)		Weekly ESA dose prior to study entry (Units/week)	
Final dose (mg/day)	n	Mean±SD	N	Mean±SD	n	Mean±SD
150	6	144.1±106.1	6	18±19	6	4816±4256
300	18	106.5±53.2	18	8±9	18	5005±3699
450	20	116.5±53.5	20	12±28	20	7025±4963
600	19	100.6±42.6	19	10±15	19	8152±4834
P-value based on ANOVA	p=0.4		p=0.6		p=0.3	

Table 2. TIW vadadustat dose

	Mean baseline hepcidin (ng/ml)		Mean baseline CRP (mg/L)		Weekly ESA dose prior to study entry (U/week)	
Final dose (mg/TIW)	n	Mean±SD	n	Mean±SD	n	Mean±SD
150	1	87.9	1	7.9	1	8000
300	4	88.4±33.0	4	6.1±3	4	6750±5909
450	12	125.1±62.0	12	26.3±47	12	8075±7561
600	14	94.4±30.7	14	11.5±19	14	6742±4754
P-value based on ANOVA	p=0.3		p=0.6		p=0.9	

Conclusions: The Hb response and vadadustat dose requirements for Hb maintenance are independent of underlying systemic inflammation and baseline ESA dose in patients with DD-CKD.

Funding: Pharmaceutical Company Support - Akebia Therapeutics, Inc.

TH-PO961

A Mirror in Time - Path to Dialysis from Education to Experience

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Background: All CKD patients starting dialysis should ideally have the opportunity to receive timely pre-dialysis education to make an informed choice about their preferred modality of long term renal replacement therapy (RRT), enabling dialysis start through a permanent access created ahead of its requirement for use. Our study aims were to review patients who started dialysis during a 12 month period and analyse trends and timelines in their decline in renal function, referral to our Pre-dialysis education service, access creation and transplant work up.

Methods: 39 patients commenced long term dialysis during the period between October 2014 and September 2015. Data was collected from electronic clinic letters for timelines of and blood results obtained from hospital IT system in January 2016. The data was analysed using EPI-INFO 7.

Results: 26(67%) patients were male. The mean age was 61. 34(87%) were white. 10 patients had diabetic nephropathy(25%) and 5 had IgAN(13%). 18 patients started haemodialysis through a line of whom 7 had chosen PD as their modality of choice for RRT. **No correlation was observed between the eGFR at referral for pre-dialysis education and start of RRT with haemodialysis catheter**.

Timeline & eGFR Trend	Mean ± SD	Median	Range
eGFR at referral for education – ml/min	13.5 ± 3.72	13	5 to 20
Time to access referral - months	11.2 ± 18.1	5	0 to 95
eGFR decline/change at access referral – ml/min	4.6 ± 3.56	3	0 to 9
Time to access creation after access referral - months	4.9 ± 11.1	1	0 to 47
Time to dialysis start after education - months	16.4 ± 22.9	13	-1 to 99
eGFR at dialysis start – ml/min	5.5 ± 1.83	5	3 to 11

Conclusions: Wide variability in the time interval from pre-dialysis education to the start of RRT could be explained by the variable rate of decline in eGFR, comorbid factors, patient concordance and other acute inter-current events. In spite of timely referral for primary definitive access based on individual assessment and clinical judgement, the risk of acute decompensation probably should prompt earlier definitive access although problems arising with definitive access could also be unpredictable.

TH-PO962

Anti-Aging Factors, Sirtuin 1 and αKlotho Concentration in Hemodialysis Patients

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Background: SIRT1 acts as an anti-aging protein due to anti-apoptotic, anti-oxidative and anti-inflammatory effect and is implicated in several diseases as diabetes or cardiovascular problems. SIRT1 renal overexpression indicates oxidative stress. Similarly,

Klotho was originally discovered as anti-aging factor. It is primary produced in kidney. It's deficiency is associated with renal disease progression and heart disease by affecting cardiac remodeling. The aim of the study was to asses the Sirtuin1 and αKlotho plasma concentration in hemodialysis (HD) patients comparing to healthy volunteers in regard to age, blood pressure control, residual renal function (RRF), diabetes, cardiovascular disease, time of dialysis and type of dialyzer.

Methods: The plasma level of SIRT1 and αKlotho was evaluated using ELISA tests in 103 HD patients, median age 62 years and in 21 volunteers. The blood pressure, residual diuresis, echocardiography and some dialysis parameters was assessed. HD group was divided according to the presence of residual diuresis.

Results: Plasma SIRT1 level was higher (Me=28.42 vs 2.71 ng/ml, p<0.0001) and αKlotho was lower (Me=433.9 vs 756.63 pg/ml, p<0.0001) in HD group comparing to control one. αKlotho was lower in those without RRF. There were no differences in SIRT1 concentration regarding residual diuresis. SIRT1 positively correlated with duration of hemodialysis. αKlotho negatively correlated with left ventricular posterior wall thickness. There were no significant relationship between SIRT1 and αKlotho level and age, blood pressure control, type of dialyzer, Kt/V and the diabetes.

Conclusions: The elevated SIRT1 concentration is associated with impaired kidney function as well as lowered αKlotho level. The decreased αKlotho level may also indicate the heart hyperthrophy and cardiac problem in maintained dialysis. Though, the role of SIRT1 and αKlotho as biomarkers/predictors of oxidative stress, inflammation and cardiovascular diseases needs further examination.

TH-PO963

Prediction of Intradialytic Arterial Oxygen Saturation in Chronic Hemodialysis Using Patient Characteristics Hanjie Zhang,[1] Israel Campos,[1] Stephan Thijssen,[1] Peter Kotanko.[1,2] *[1]Research, Renal Research Inst, New York, NY; [2]Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Recent evidence indicates that intradialytic arterial oxygen saturation (SaO2) is associated with inflammation, resistance to erythropoiesis stimulating agents, hospitalization, and all-cause mortality in hemodialysis (HD) patients (Meyring-Wosten, CJASN 2016). While SaO2 can be measured easily with the Critline monitor (CLM; Fresenius Medical Care, Waltham, MA), only a minority of HD facilities have deployed that technology. Therefore we explored if SaO2 can be predicted from demographic, clinical and laboratory data.

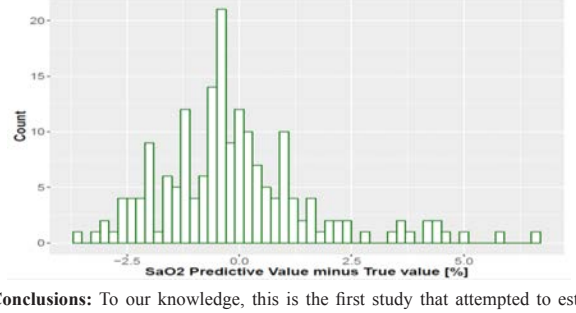
Methods: We studied HD patients with arterio-venous vascular access who had their SaO_2 measured by CLM during HD. Generalized linear model (GLM), generalized additive model (GAM), gradient boosting methods (GBM) and random forest (RF) were used to predict SaO_2 based on 16 predictors, including age, gender, race, body mass index, HD vintage, serum albumin, hemoglobin level, and comorbidities. We randomly sampled 80% of the data (derivation cohort) for model building; the remaining 20% were used as validation cohort.

Results: We studied 28,065 HD sessions in 910 chronic HD patients (mean age 61.5, 59% males, 51% white). Average SaO2 was 92.6% (SD 1.94%). There was no material difference in the predictive performance of the 4 models (Figure 1A; a histogram of GLM results is shown in Figure 1B).

Figure 1A: Predictive performance of the 4 models

	GAM	GBM	GLM	Random forest
Difference (prediction – measured) [% SaO2]	-0.07	-0.09	-0.09	-0.17
Standard deviation of the difference [% SaO2]	1.73	1.68	1.73	1.73
R^2	0.10	0.12	0.12	0.14

Figure 1B: Result of the GLM model



Conclusions: To our knowledge, this is the first study that attempted to estimate intradialytic SaO_2 using patient characteristics. While only 10-14% of the SaO2 variability could be explained by these models, the predicted SaO2 still provided a better SaO_2 estimate for an individual patient than the population average. Future studies need to explore additional biological predictors of SaO2, such as the degree of fluid overload.

Funding: Pharmaceutical Company Support - Fresenius Medical Care

TH-PO964

Characteristics of Markets and Patients Served by ESRD Seamless Care Organizations (ESCOs) R. Hirth,[1] J. M. Messana,[1] Brighita Mona Negrusa,[2] Court Q. Melin,[3] Yi Li,[1] G. Marrufo.[2] *[1]School of Public Health & Internal Medicine, Univ of Michigan, Ann Arbor, MI; [2]The Lewin Group, Falls Church, VA; [3]The Lewin Group, Eden Prairie, MN.*

Background: The Comprehensive ESRD Care Model (CEC) establishes ESCOs as an innovative care delivery structure, based on concepts of accountable care organizations with a focus on the complex needs of dialysis patients. Operations began 10/1/2015 with 13 ESCOs in 17 Core-based Statistical Areas (CBSAs). Because of CEC participation requirements (e.g., 350+ dialysis patients in each ESCO within 1-2 CBSAs and dialysis facilities and nephrologists willing to accept financial risk), the markets in which ESCOs choose to operate and consequently the patients they serve may differ from those not served by ESCOs. To project the model's scalability, we explored whether ESCOs' markets and patients are typical of the broader Medicare ESRD population.

Methods: We compared characteristics of CBSAs with and without ESCOs in 2015 in terms of size, Medicare spending, demographics and health system characteristics. ESCO-aligned and non-aligned patients were compared on demographics, comorbidities, Medicaid status and Medicare spending in 2014.

Results: ESCO CBSAs had substantially more Medicare ESRD beneficiaries than non-ESCO CBSAs (median 1851 vs. 122), had fewer white patients (60% vs. 81%), higher average household income ($51,345 vs. $43,815), higher Medicare Advantage penetration (24% vs. 18%), and more primary care physicians (7.1 vs. 6.3 per 10,000 Medicare beneficiaries) and specialists (8.3 vs. 4.8 per 10,000). Patients aligned to ESCOs were more likely to be treated in an urban area (98% vs. 84%), had higher monthly Medicare Parts A and B spending in 2014 ($6,118 vs. $5,703), and had comparable prevalence of most comorbidities (largest differences for Alzheimer's 16% vs. 10%, and rheumatoid arthritis 28% vs. 25%). All reported differences were significant with p<0.05.

Conclusions: By creating incentives for more effective care coordination, the CEC model has the potential to improve outcomes and reduce costs. To date, participation has been limited to larger markets, suggesting that the ability to extend the model to smaller markets should be monitored.

Funding: Other U.S. Government Support

TH-PO965

Starting Dialysis: From Refusals to Regrets, How Strong Is the Misperception? Mabel Habib Aoun,[1,2] Leony Antoun,[3] Dania Chelala.[2] *[1]Nephrology, Saint-Georges Hospital, Ajaltoun, Lebanon; [2]Nephrology, Saint-Joseph Univ, Beirut, Lebanon; [3]Internal Medicine, Kaslik Univ, Lebanon.*

Background: Dialysis is life-sustaining for end-stage renal disease (ESRD) patients and a way to better quality of life (QoL). Nephrologists try to convince patients of starting dialysis but may propose palliative care for elderly with reduced survival and QoL scores. The challenge is to discover what patients really want and whether their choices change. We studied 71 chronic haemodialysis (HD) patients, their initial refusal of dialysis, later regret, QoL and survival time in 3 age-groups.

Methods: Patients on HD in April 2015 were included and administered 2 questionnaires: (1) demographic data, dialysis refusal, later regret, major complaint; (2) Short Form 36 (SF-36) for QoL scores: physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health perceptions (GH), energy/vitality (VT), social functioning (SF), role limitations due to emotional problems (RE) and mental health (MH).

Results: Patients were divided in 3 groups according to age at dialysis start: < 70, 70-80 and > 80 [table 1]. 28% refused dialysis but changed their mind later. One regretted starting dialysis. 27% complained of the long sessions. Patients < 70 had longer survival on dialysis (p=0.001). QoL: No significant difference was found in SF-36 scores between the 3 groups.

Age	<70 (N=41)	70-80 (N=24)	>80 (N=6)	TOTAL (N=71)
M/F	27/14	14/10	4/2	45/26
Time on dialysis (months)	77.4	34	44.6	60
Refusal (N)	11	9	0	20
Regret (N)	1	0	0	1
No complaints	20	12	1	33
PF	45.5	38.9	14.1	40.6
RP	29.2	21.8	16.6	25.7
RE	35.3	29.1	0	30.2
VT	47.4	53.7	46.6	49.4
MH	50.2	54.9	60.8	52.7
SF	51.8	55.7	41.6	52.2
BP	53.2	51.3	42	51.6
GH	49.3	56.2	44.9	51.2

Conclusions: Higher prior refusals compared to negligible later regrets point out to the probable patients' misperception of dialysis. Age doesn't seem to affect patients' final choice as long as QoL scores are similar through different age-groups. Nephrologists should not be influenced by patient's old age and initial refusal of dialysis.

TH-PO966

Intradialytic Exercise May Not Break the Vicious Cycle of Frailty Hannah M.L. Young,[1] Daniel Scott March,[1] Darren R. Churchward,[1] Charlotte E. Grantham,[1] Patrick J. Highton,[1,2] Matthew P.M. Graham-Brown,[1,2] Alice C. Smith,[1] James Burton.[1] *[1]Dept of Infection, Immunity & Inflammation and John Walls Renal Unit, Leicester General Hospital; [2]School of Sport, Exercise and Health Sciences, Loughborough Univ; [3]Dept of Cardiac & Pulmonary Rehabilitation, Glenfield Hospital.*

Background: Frailty is associated with poor outcomes for hemodialysis (HD) patients. Intradialytic cycling is recommended, but effective interventions in the frail elderly include a wider range of exercises; the components of a program suited to frail HD patients are unknown. The purpose of this study is to examine the influence of frailty on exercise capacity, function, activity levels and exercise behaviors to inform a specific frailty intervention.

Methods: Frailty status was measured in 43 patients (30 male, 13 female, age 58, IQR 27.25). Exercise capacity was measured using walking tests (ISWT and ESWT), muscle endurance using the Sit to Stand 60 (STS60) and step count using accelerometry. Function and exercise behavior were assessed using the Duke Activity Status Index (DASI), exercise self-efficacy questionnaire and exercise benefits and barriers scale (DPPEBBS).

Results: 13 (30%) of the participants were 'robust', 23 (52%) 'pre-frail' and 7 (16%) were frail. Patients were well matched for age, vintage and co-morbidity. One-way ANOVA showed lower exercise and functional capacity (ISWT, $P<0.05$; ESWT, $P<0.05$; DASI, $P<0.05$) and muscle endurance (STS60, $P<0.05$). Post hoc analyses showed a significant decrease in ISWT distance in the frail group compared with robust (-294m,$p<0.05$) and pre-frail groups (-168m, $p<0.02$), in ESWT time between pre-frail and robust groups (-406s, $p<0.05$),in STS60 scores between frail, robust (-17.03, $p<0.02$) and pre-frail groups (-12.66, $p<0.02$) and between frail and robust groups (-21.95, $p<0.003$) for the DASI. Weekly steps were low in all groups (21436, IQR 29732), but self-efficacy was moderate and the DPPEBBS indicated that patients generally perceived more exercise benefits than barriers (66.11 ± 7.68).

Conclusions: This study reveals a high prevalence of frailty amongst HD patients and suggests that that a multi-component exercise program, rather than intradialytic cycling, may best address frailty in this population.

TH-PO967

The Spectrum of Symptoms Induced by Hemodialysis Kevin Quach,[1] Jennifer M. MacRae,[2] Braden J. Manns,[2] Michael Walsh.[1] *[1]McMaster Univ; [2]Univ of Calgary.*

Background: Hemodialysis induces symptoms in many patients that take time to recover from (recovery time). The symptoms induced and how they vary over time and between patients is unclear. We conducted a prospective cohort study to describe how recovery time symptoms vary over time and between patients.

Methods: We recruited prevalent in-center hemodialysis patients and measured their recovery time using multiple instruments. Instrument A presented a global question regarding how long it took to recover from the last dialysis treatment. Instrument B addressed the recovery time for each of 10 symptoms. Participants completed each instrument for each dialysis treatment for one week. We compared the distribution of recovery time found with each instrument.

Results: One hundred twenty participants from 2 centres completed 914 recovery time assessments. Fewer participants required no recovery time with Instrument A (14 to 17% of participants depending on day of week) as compared with identifying no symptoms with Instrument B (20 to 34% of participants depending on day of week) ($p=0.002$ for difference between groups). However, the maximum recovery time from any symptom in Instrument B (median 10 hours) was longer than the recovery time identified with Instrument A (median 3 hours) ($p=0.001$). Lack of energy was the most common symptom following dialysis (69% of all patients), with muscle cramps (41%), bone and joint pain (36%), shortness of breath (26%), and muscle soreness (33%)the next most frequent. Recovery time measured with instrument A correlated with the KDQoL Burden of Disease ($p=0.003$), Effects of Kidney Disease ($p=0.01$) and Mental Composite Score ($p=0.01$) but individual symptoms did not consistently correlate with domains of the KDQoL.

Conclusions: Recovery time is a complex of different symptoms that vary in duration. Further research is required to understand how dialysis induces each type of symptom in order to reduce recovery time.

TH-PO968

Prospective Study of the Gut Microbiome and Effects of P-Inulin in ESRD: Early Experience of the NIDDK Hemodialysis Novel Therapies (HDNT) Consortium Dominic S. Raj,[1] Ali Ramezani,[1] Hongzhe Li,[2] J. Richard Landis,[2] David M. Charytan,[3] Talat Alp Ikizler,[4] Jonathan Himmelfarb,[5] Alan S. Kliger,[6] Paul L. Kimmel,[7] John W. Kusek,[7] Laura M. Dember.[2] *[1]George Washington U; [2]Univ Pennsylvania; [3]Brigham & Women's Hospital; [4]Vanderbilt U; [5]U Washington; [6]Yale U; [7]NIDDK.*

Background: Preliminary evidence suggests that alterations in the gut microbiome contribute to ESRD-associated inflammation and cardiovascular disease. Prior to conducting clinical trials of interventions, such as pre- or pro-biotics, to restore microbial symbiosis, it is necessary to characterize the composition, function, and stability of the gut microbiome in ESRD patients.

Methods: The NIDDK HDNT Consortium is performing a non-randomized, open label, crossover study of at least 10 patients receiving maintenance hemodialysis at 4 centers. The study protocol requires intensive sampling of stool (1-2X/wk) and blood (1X/wk) during 3 phases: 1) pre-treatment-8 wks; 2) treatment with p-inulin pre-biotic, 8 g 2X/day-12 wks; and 3) post-treatment-8 wks. Microbiome composition will be assessed at the overall microbial diversity and individual taxon levels, and microbiome function will be assessed with metabolomic profiling and targeted metabolite measurements. 16S rRNA gene sequencing, metabolomic studies, and analytical approaches are being piloted in a sub-set of samples collected at wks 2 and 8 (phase 1) and wks 14 and 20 (phase 2).

Results: Of 12 patients enrolled, 2 withdrew (1 for transplantation; 1 for unwillingness to provide samples). The remaining 10 patients, followed for 143 pt-weeks thus far, have provided 152 of 154 (99%) blood samples and 157 of 161 (98%) stool samples, and have processed their stool samples generating 1564 of 1594 (98%) aliquots. Adherence to p-inulin as assessed by packet counts is 74% of the recommended dose. Analytical approaches to high-dimensional, repeated measures data have been developed to evaluate within-person variability of microbiome composition and function, and effects of p-inulin on both parameters.

Conclusions: The feasibility of intensive stool and blood sample acquisition and the tolerability of p-inulin both appear to be sufficient to generate data needed to design future clinical trials targeting the gut microbiome in ESRD.

Funding: NIDDK Support

TH-PO969

Disorders in Thyroid Morphology Observed in ESRD Patients on Maintenance Hemodialysis Syed Rizwan A. Bokhari,[1] Maria Rizwan Bokhari,[2] Syed A. Khalid,[1] Muhammad Zaman Khan Assir,[3] Abeera Mansur.[4] *[1]Nephrology, AIMC/JHL, Pakistan; [2]Radiology, AIMC/JHL, Pakistan; [3]Nephrology, DHMC, Pakistan.*

Background: Chronic kidney disease has been associated with changes in thyroid gland morphology and thyroid hormone metabolism. Goiter and thyroid nodules have been reported with increased frequency in end-stage renal disease (ESRD) patients, however its frequency is not known in developing countries. We aimed to study the thyroid gland morphology in our ESRD population and its correlation with patient demographics.

Methods: We enrolled 74 patients on maintenance (HD) at the dialysis center of Jinnah hospital Lahore. Two patients (3%) with preexisting thyroid disease were excluded. Thyroid ultrasound was done on all to assess thyroid volume, nodules and its echotexture.

Results: Total of 72 end stage renal disease (ESRD) patients on maintenance hemodialysis were included. Median age was 50 years (range 17-82 years). Fourty six (64%) were male. Twenty-two (31%) had DM ,43 (60%) had HTN, 4 (5%) patients had evidence of obstructive uropathy and 3 (4%) patients had ADPKD as the cause of ESRD. 32 (44%) had HCV infection. Median duration on hemodialysis was 3.5 years (range 1-12 years). 60 (83%) patients were on thrice weekly hemodialysis. Median thyroid volume was 8 ml (range 3-24ml). Thyroid nodules were seen in 31 (43%) patients. Significantly higher number of females (57%) had thyroid nodules as compared to males (32%) p-value 0.035, odds ratio 2.8 (95% CI 1.062-7.48). Twelve patients (17%) had single thyroid nodule, 14 patients (19 %) had 2-5 nodules, 5 patients (7%) had more than 5 nodules. Echotexture of thyroid gland was homogenous in 70 (95%) and heterogeneous in 4 (5%) patients.

Conclusions: There is high prevalence of thyroid nodules in our dialysis patient's population. Higher frequency was observed in female patients. No correlation was found with PTH levels, preexisting co morbidities, frequency and duration of hemodialysis, co-existing presence of renal cysts. Ultrasound evaluation of thyroid gland morphology should be considered in patients on maintenance hemodialysis.

TH-PO970

Routine Pre- and Post-Hemodialysis Blood Pressure as a Screening Tool for the Use of Ambulatory Blood Pressure Monitoring Yannick Begin, Simon Desmeules, Mohsen Agharazii, Sebastien Savard, Fabrice Mac-Way, Sacha A. De Serres. *Néphrologie, CHUQ- Hotel-Dieu de Quebec, Quebec, QC, Canada.*

Background: Routine pre- and post-hemodialysis (HD) blood pressure (BP) are poor indicators of BP control. Ambulatory blood pressure monitoring (ABPM) remains the gold standard for diagnosis and treatment of hypertension, but its availability is limited and it is especially uncomfortable in HD population. The aim of this study is to define pre- and post-HD blood pressure cut-offs where an ABPM would not be required for the assessment of blood pressure control.

Methods: In a single center cross-sectional retrospective study, we studied all complete routine ABPM that were performed in an HD population from April 2013 to February 2016. High BP was defined as a 44h ABPM systolic BP> 135 mmHg. ROC curve analysis, specificity, sensitivity, positive and negative predictive value (PPV and NPV) analysis were performed.

Results: There were 271 complete ABPM. The average of routine pre- and post-HD systolic BP (HD systolic BP) provided the best AUC (0.881) for an ABPM BP control of < 135 mm Hg. For a HD systolic BP threshold of 130 mmHg, sensitivity, specificity and NPV were respectively 97%, 42% and 94%. For a HD systolic BP threshold of 165 mmHg, sensitivity, specificity and PPV were respectively 45%, 97.4% and 94%. Overall, using these two thresholds, 45% of ABPM were in the zones of very high NPV or PPV.

Conclusions: To assess high BP, our study indicates that limiting ABPM use to patients with average of pre- and post-HD systolic BP of between 130-165 mm Hg reduces the use of ABPM by 45%. These findings could be useful for the management of health care resources and for the reduction of the level of intrusiveness.

TH-PO971

Impact of a Multi-Disciplinary Intensive Management Clinic on Incident Hemodialysis Patients in Singapore Priscilla P. How,[1,2] Catherine Ho,[1] Jia Jia Lee,[1] Hersharan Sran.[2] *[1]Dept of Pharmacy, National Univ of Singapore; [2]Dept of Medicine (Nephrology), National Univ Hospital.*

Background: Multidisciplinary models of care have been shown to be beneficial for patients with end-stage renal disease. The Hemodialysis Initiation and Transition (HIT) clinic provides consistent, intensive, multidisciplinary care to incident hemodialysis (HD) patients, and is the first of such clinic in Singapore. This study aimed to determine the clinical impact of this clinic.

Methods: Adult patients newly initiated on chronic HD from January 2013 to December 2014 were enrolled in this cohort study. Laboratory parameters, medication profiles, dialysis access, vaccination status, hospitalizations and mortality were assessed and compared between patients managed by the HIT clinic vs. conventional care.

Results: A total of 303 patients (216 HIT patients and 87 conventional care – control group) were included in the study. HIT patients achieved higher mean hemoglobin, corrected calcium and albumin levels (P<0.05). More HIT patients achieved albumin goals (HIT vs control 87.1% vs 65.8%, P<0.05), were using AV fistula (HIT vs control 54.2% vs 33.3%, P=0.008) and received Hepatitis B, influenza and pneumococcal vaccines (all P<0.05). More HIT patients were prescribed with renin-angiotensin-aldosterone blockers (HIT vs control 36.5% vs 20.9%), phosphate binders (HIT vs control 92.1% vs 77.6%) and IV iron (HIT vs control 81.5% vs 37.3%; all P<0.05). Fewer infection-related hospitalizations were observed among HIT patients (HIT vs control 0.3±0.6 vs 0.6±1.2, P=0.018) within the first 6 months of HD initiation although they had more access-related hospitalizations (HIT vs control, 0.3±0.8 vs 0.1±0.4, *P*=0.010), likely due to increased vigilance and follow-ups. No differences in mortality were observed between the groups (P>0.05).

Conclusions: Targeted multidisciplinary care can improve the morbidity, as well as management of ESRD-related complications, vaccination status and permanent access placement of our local incident HD patients.

TH-PO972

Clinical Significance of Serum Soluble α-Klotho Levels in Maintenance Hemodialysis Patients Shinya Nakatani,[1,2] Eiji Ishimura,[1] Mari Sakura,[2] Yu Tateishi,[2] Hideki Uedono,[1] Akihiro Tsuda,[1] Norihiko Usui,[2] Masaaki Inaba.[1] *[1]Nephrology, Osaka City Univ Graduate School of Medicine, Osaka, Japan; [2]Nephrology, Ishikiriseiki Hospital, Japan.*

Background: Humans with CKD exhibit markedly reduced serum soluble alpha-klotho (sαKl), progressively decreasing as renal function declines. However, in end-stage renal disease, the role of sαKl in pathogenesis of CVD, DM and CKD-MBD has not been fully studied.

Methods: Stable maintenance HD patients (n=188, 114 men and 74 women, 66.5 ±11.1 years, HD duration, 101±90 months) were enrolled. Serum sαKl levels were measured by recently developed ELISA methods (Yamazaki Y, et al. Biochem Biophys Res Commun. 2010).

Results: Serum sαKl levels in HD patients were 445±158 pg/ml, which was lower than those of healthy Japanese subjects (740 pg/ml; Yokoyama K, et al. Clin Nephrol. 2012). Although some previous studies have showed significantly correlations between sαKl and CKD-BMD parameters, serum sαKl levels in the present study showed no significant correlations between any of these markers. (FGF23: r=0.045, p=0.54; intact PTH: r=-0.06, p=0.44; phosphorus: r=0.01, p=0.89; calcium: r=0.06, p=0.46, respectively) When compared to DM *vs*. non-DM, and with CVD histories *vs*. without CVD histories, serum sαKl levels were not significantly different (DM; 447±170 *vs*. 444±148 pg/ml, p=0.75, CVD; 436±135 *vs*. 490±174 pg/ml, p=0.61, respectively). However, in HD patients with DM and CVD histories (n=38), these were significant correlations between serum sαKl and glycated albumin, a useful marker of glycemic control, (r=0.44, p=0.006), plasma glucose (r=0.32 p=0.005), calcium (r=0.34, p=0.004) and alkaline phosphatase (r=0.33, p=0.005). A multiple regression analysis showed that serum sαKl levels showed significant, independent associations with glycated albumin (β=0.40, p=0.006) and calcium (β=0.30 p=0.04) (R^2=0.43 p=0.0002).

Conclusions: In the presents study, clinical significance of measurement of serum sαKl is expected to be seen in HD patients with DM and CVD histories, which might reflect the parameters of anti-aging and/or anti-cachectic effects of alpha-Klotho. Clinical significance of serum sαKl levels on CKD-MBD may be smaller than that of anti-aging and/or anti-cachectic effects of alpha-Klotho.

TH-PO973

Residual Renal Function and Inflammation in Hemodialysis Patients Patricia De Sequera,[1] Elena Corchete,[1] Marta Albalate,[1] Rafael Perez-Garcia,[1] Lourdes Bohorquez,[3] Matilde Alique,[3] Jose M. Portoles,[2] María Marques Vidas,[2] Rafael Ramirez.[3] *[1]Nephrology, Univ Infanta Leonor Hospital; [2]Nephrology, Univ Puerta de Hierro Hospital; [3]Physiology, Univ Alcala de Henares, Madrid, Spain.*

Background: Residual renal function (RRF) contributes to overall clearance in dialysis patients. Previous studies have shown the relationship between inflammation and mortality in chronic kidney disease (CKD) patients. It has been described an increase in the percentage of proinflammatory monocytes CD14+/CD16++ in CKD stages 4-5, even without clinical evidence of inflammation and a reduction in the percentage of these monocytes by on-line hemodiafiltration (OL-HDF). Our objective was to investigate the relationship between RRF and inflammatory parameters in HD patients.

Methods: Prospective, observational, cross sectional study in 69 adult patients in chronic HD for at least 6 months. Epidemiological data and laboratory parameters were collected. RRF was measured by calculating average clearance of urea and creatinine in 24-h urine ((CCr+CU)/2). If>1 ml/min or urine>100 ml/day presence of RRF was considered. C-reactive protein (CRP) were quantified using nephelometry. Proinflammatory CD14+/CD16++ were measure with monoclonal antibodies followed by analysis in a flow cytometer.

Results: Average age:70.9 y, 38(55%) were male and 25(36.2%) diabetics. The average ((CrC+CU)/2):1.8 ml/min and urine V: 454(569) ml/day. RRF was associated with shorter renal replacement therapy vintage (39.7 vs 95.9 m;p=0.002); and lower OL-HDF prescription (56.6 vs 82%;p=0.021). There were no differences in vascular access, dialysis time, interdialitic weight gain or ultrafiltration (p Ns). Hemoglobin levels and predialysis systolic arterial blood pressure in patients with RRF were higher (11.8 vs 11.2 g/dl;p=0.024 and 144.2 vs 128.4;p=0.005) than in patients without it. Patients with RRF had lower β2microglobulin (19.9 vs 26.5 mg/l;p=0.0001), CRP levels (6.2 vs 21.4 mg/l;p=0.038) and proinflammatory CD14+/CD16++ percentage (17 vs 36.6%;p=0.006).

Conclusions: Patients with RRF in our study have lower inflammatory parameters. This is another reason to consider its preservation as a key objective in hemodialysis patients.

TH-PO974

Survival of People on Dialysis by Age Group between 1990 and 2010 in U.S.A., Australia and New Zealand Amy Kang,[1,2,3] Tadashi Toyama,[1,3] Yoichiro Hirakawa,[1] Vlado Perkovic,[1,2] Meg J. Jardine.[1,2] *[1]The George Inst for Global Health, Sydney, Australia; [2]ANZDATA Registry; [3]Equal Contribution.*

Background: The causes of death in End Stage Kidney Disease (ESKD) may reflect processes common to general population health and those specific to ESKD. We aimed to determine trends in absolute and relative mortality for people receiving dialysis compared with the general population in different age categories within the established dialysis healthcare systems of the USA, Australia (Aus) and New Zealand (NZ).

Methods: The included countries reported comparable publicly available age-specific annual mortality outcomes from 1990 to 2010. Annual mortality was derived from the dialysis registries and from national population statistics for young (0-44years), middle-aged (45-64years), senior (65-74years) and elderly (≥75years) people. Relative risks were calculated using a log-binomial model, with years included as piecewise-defined spline terms. Local regression using log relative risks was performed and slopes compared before and after each timepoint.

Results: Our study included 2,305,140 people receiving dialysis for a total of 7,334,427 person-years. Absolute mortality rates were higher for the dialysis and general populations in the US compared with Aus and NZ. For all groups in the USA, middle aged in Aus and NZ relative mortality worsened between 1990 and 2000 and then improved between 2000 to 2010. For seniors in Aus outcomes worsened between 1990 to 2000 and then did not change between 2000 to 2010. For young and elderly in Aus and young, senior and elderly in NZ there was no significant change in outcomes over the entire time period. Limitations include a relative lack of power for the young and elderly age groups in Aus and NZ.

Conclusions: Relative mortality rates for middle aged dialysis patients were stable overall between 1990 and 2010, after a transient worsening driven by a lag between improvements in the general and dialysis population mortality. Relative mortality rates for Australian senior dialysis patients appear to have worsened.

TH-PO975

Age-Stratified Incidence Rates of Cardiovascular Morbidity and Mortality in Both Diabetic and Non-Diabetic Dialysis Patients. Results from a 5-Year Prospective Study Masaki Ohsawa. *Dept of Internal Medicine, Iwate Medical Univ, Morioka, Japan.*

Background: It has not been sufficiently examined to what extent diabetic dialysis patients (DM) have the higher risk of cardiovascular events than the risk in non-diabetic dialysis patients (non DM).

Methods: A prospective study of 1,204 dialysis patients (DM (n=916) and non DM (n=298)) was conducted. Subjects were subdivided into four age categories (20-44, 45-64, 65-74, 75 years of age or older). Outcomes included all-cause death (ACD), cardiovascular death (CVD), incident heart failure (HF), incident stroke and incident acute myocardial infarction (AMI). Crude incidence rates and sex-and age-adjusted hazard ratios (95% confidence intervals) of outcomes using non-diabetic group as the reference were estimated in each group.

Results: There were 4793 observed patient-years (mean 3.9 years). Crude incidence rates (per 1000 patient-years) and hazard ratios (95% confidence intervals) are shown in the table.

age category	subjects (n)	ACD	CVD	HF	stroke	AMI
20-44 years	non DM (n=116)	19.0	9.5	24.4	7.7	0
	DM (n=21)	55.4	33.3	66.9	36.1	0
	HR (95% CI)	3.39 (1.12-10.2)	4.38 (1.00-19.3)	2.69 (0.94-7.67)	2.88 (0.52-15.9)	-
45-64	non DM (n=437)	52.1	29.0	50.9	37.9	10.7
	DM (n=142)	104.4	59.4	79.6	54.3	12.9
	HR (95% CI)	1.75 (1.26-2.44)	1.83 (1.18-2.85)	1.34 (0.91-1.98)	1.34 (0.75-2.40)	0.89 (0.37-2.13)
65-74	non DM (n=233)	108.8	36.3	99.3	71.5	8.9
	DM (n=96)	155.8	67.6	151.1	66.9	20.9
	HR (95% CI)	1.45 (1.03-2.05)	2.00 (1.15-3.47)	1.56 (1.06-2.30)	0.77 (0.32-1.83)	2.65 (0.92-7.62)
75+	nonDM (n=130)	269.8	133.5	169.4	114.9	28.4
	DM (n=39)	324.2	152.6	182.5	103.9	0
	HR (95% CI)	1.26 (0.85-1.86)	1.20 (0.85-1.86)	1.16 (0.68-2.11)	4.63 (1.10-19.5)	-

Conclusions: DM had significantly higher risks of ACD and CVD than the risks in non DM among patients aged less than 75 years. DM also had a higher risk of HF than the risk in non DM with marginal significance among patients aged less than 75 years. The risk ratio becomes lower with advance of age.

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TH-PO976

Cardiovascular Outcomes in Young Adults with ESRD: An Analysis of the USRDS Yee Lu,[1] Nan Ji,[2] Alissa Kapke,[2] Xue Dietrich,[2] Zubin J. Modi,[1] David T. Selewski,[1] Kevin C. Abbott,[3] Brett W. Plattner,[1] Brahmajee K. Nallamothu,[1] Douglas E. Schaubel,[1] Rajiv Saran,[1] Debbie S. Gipson.[1] *[1]Univ of Michigan, Ann Arbor, MI; [2]Arbor Research, Ann Arbor, MI; [3]NIH/NIDDK, Bethesda, MD.*

Background: Little is known about cardiovascular (CV) morbidity and mortality in young adults (YA) with end stage renal disease (ESRD).

Methods: Using national end stage renal disease (ESRD) data in the USRDS, all patients ages 1-29 yrs at ESRD initiation (2003-2013) were identified and grouped by age at ESRD initiation (1-11, 12-21, 22-29 yrs). CV mortality (CVM) events were identified from ESRD Death Notification Forms. Patients were censored if they died due to non-cardiovascular events, lost to follow-up, recovered or survived to the end of the study period (12/31/2014). Cox proportional hazards models were fit to determine the risk of CVM in YA (age 22-29), compared to patients age < 22 at initiation.

Results: Over 10 years, 1,787 (5.4%) of the 33,159 study patients experienced CVM. YA had the highest probability of CVM, as early as 3 months post initiation of ESRD. Characteristics associated with CVM are summarized in Table. Compared to YA with ESRD, the risk of CVM was lower among patients < 22 with cystic/hereditary/congenital (CHC) disease and children <12 with glomerulonephritis (GN) as the primary cause of ESRD.

Adjusted Hazard Ratios for CVM among Young Adults with ESRD

Variable	Hazard Ratio (95% CI)	p-value
Female	1.26 (1.14,1.38)	<0.001
Race (vs. White):		
Black	1.44 (1.3,1.59)	<.0001
Other	0.92(0.74, 1.14)	0.43
Incident Modality (vs. Transplant):		
HD	5.76 (3.71,8.94)	<.0001
PD	3.75 (2.37,5.93)	<.0001
Pre-ESRD Nephrology Care (vs. None)	0.88 (0.80,0.97)	0.01
Insurance (vs. Private):		
Public	1.73 (1.54,1.94)	<.0001
None	1.14 (0.98,1.32)	0.08
CHC ESRD Etiology (vs. age 22-29)		
Age 1-11	0.37 (0.18,0.76)	0.007
Age 12-21	0.58 (0.35,0.95)	0.03
GN ESRD Etiology (vs. age 22-29)		
Age 1-11	0.33 (0.16,0.70)	0.004
Age 12-21	1.02 (0.84,1.23)	0.88
Other ESRD Etiology (vs. age 22-29)*		
Age 1-11	0.58 (0.39,0.84)	0.004
Age 12-21	0.58 (0.48,0.70)	<.0001
Co-Morbidities at ESRD Initiation		
Congestive heart failure	1.78 (1.55,2.04)	<.0001
CV disease	1.37 (1.14,1.65)	0.001
Other cardiac disease	1.82 (1.53,2.16)	<.0001
Diabetes	2.16 (1.93,2.43)	<.0001

*Other: DM, Interstitial nephritis/pyelonephritis, Hypertension/large vessel disease, neoplasms/tumors, and miscellaneous. CVD: atherosclerotic heart disease, cerebrovascular disease/CVA/TIA, peripheral vascular disease; Other cardiac disease: as defined by Medical Evidence Form (CMS-2728)

Conclusions: In the setting of ESRD, YA have higher CVM than children. African Americans, dialysis at initiation, absent pre-ESRD nephrology care, public insurance, ESRD etiology, and pre-ESRD history of CV disease or diabetes mellitus are risk factors for CVM. These factors suggest areas for future research to improve CV survival.

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TH-PO977

Epidemiology and Mortality of Pulmonary Embolism: A Comparison between Chronic Dialysis Patients and the General Population Chih-Chiang Chien. *Dept of Nephrology, Chi-Mei Medical Center, Tainan City, Taiwan.*

Background: Pulmonary embolism (PE) is associated with increased mortality, but it is not clear whether end-stage renal disease (ESRD) dialysis patients have a higher incidence and mortality than dose the general population not on dialysis, especially in Asian.

Methods: Using the Taiwan National Health Insurance Research Database, we did a comparative cohort study on 45,040 incident ESRD patients undergoing dialysis and 90,080 gender- and age- matched (1:2) patients not on ESRD dialysis, between 2000 and 2005. The follow-up period was from the index date to PE, the date of death, the end of dialysis, or December 31, 2008. Multivariate Cox proportional hazards models were used to estimate the relative hazards, and the models were adjusted for demographic parameters and comorbidities.

Results: The incidence rate of PE was 18.96/100,000 person-years in general population not on dialysis and 40.44/100,000 person-years in ESRD dialysis cohort. After multivariate analysis, there were no significant differences between the two cohort (HR: 1.364; 95% CI: 0.942-1.974). Older age (HR: 1.028; 95% CI: 1.015-1.041), peripheral vascular disease (HR: 1.897; 95% CI: 1.104-3.261), and atrial fibrillation (HR: 2.084; 95% CI: 1.037-4.191) were independent risks for PE. The overall in-hospital mortality rate after PE was 13.3%. ESRD dialysis patients had almost twice (97%) the mortality risk after PE than did the non-ESRD cohort (HR: 1.972; 95% CI: 1.083-3.590).

Conclusions: In conclusion, no significant difference in the incidence rates of PE between patients on and not on ESRD dialysis in Taiwan. However, patients on ESRD dialysis had a higher mortality risk after PE.

TH-PO978

B-lines on Lung Ultrasound: A Biomarker for Cardiac Events and Mortality in Hemodialysis Patients Jeanne Kamal,[1] Wissam Mansour,[1] Marc M. Saad,[2] Boutros Karam,[1] Elias Moussaly,[1] Saqib Hussen Abbasi,[1] Elie El-Charabaty,[3] Suzanne E. El Sayegh.[3] *[1]Internal Medicine Dept, Staten Island Univ Hospital, Staten Island, NY; [2]Nephrology Dept, Emory Univ Hospital, Atlanta, GA; [3]Nephrology Dept, Staten Island Univ Hospital, Staten Island, NY.*

Background: Volume overload in End Stage Renal Disease (ESRD) patients on hemodialysis (HD) is an independent risk factor for death from cardiovascular events. B Lines detected on Lung ultrasound (BLUS) assess extravascular lung water and correlate with the physical performance of HD patients. This raises interest in its prognostic ability predicting cardiac events and mortality in this population.

Methods: 81 HD patients underwent lung Ultrasound (US) after achieving their dry weight and had their B Line scores categorized as mild (0-14), moderate (15-29), severe (30-59) and very severe (>60). 10 were lost to follow up (6 transferred to another unit; 4 had renal transplant). 71 were followed for cardiac events (myocardial infarction; electrocardiogram(ECG)-documented angina episodes; heart failure; ECG-documented arrhythmia; cerebrovascular accident or transient ischemic attack) and death.

Results: 71 subjects were followed for a mean duration of 1.19 years. 50 were males, mean age 60. 9 patients died, 20 had an incident cardiac event. A Kaplan-Meier survival analysis demonstrated an interval decrease in survival times in all-cause mortality and cardiac events with increased BLUS scores (p 0.0049). Multivariate cox regression analysis showed the independent predictive value of BLUS for mortality and cardiac events: patients in moderate and severe classes (grouped) and very severe classes had hazard ratios of 2.98 and 7.98 respectively compared to patients in mild class (p 0.025 and 0.013). The average hospitalization rate (1.88) was not significantly different between the categories (p 0.1).

Conclusions: BLUS is an independent risk factor for death and cardiovascular events in HD patients. Chest US helps detecting lung congestion among ESRD patients on HD even at its early stage when clinically asymptomatic. The application of chest US in this population may improve patients' clinical outcome and help refine prognosis.

TH-PO979

Extravascular Lung Water Monitoring in Low Cardiovascular Risk Hemodialysis Patients Dimitrie Cristian Siriopol,[1] Luminita Voroneanu,[1] Ionut Nistor,[1] Mihai Onofriescu,[1] Simona Hogas,[1] Mugurel Apetrii,[1] Mehmet Kanbay,[2] Adrian Covic.[1] *[1]Nephrology, "Grigore T. Popa" Univ of Medicine and Pharmacy, Iasi, Romania; [2]Medicine, Koc Univ School of Medicine, Istanbul, Turkey.*

Background: Fluid overload is one of the most common modifiable risk factor associated with the increased mortality risk observed in hemodialysis (HD) patients, but the precise assessment of hydration status in these patients remains a major challenge for nephrologists. Our study aimed to explore whether combining two bedside methods, lung ultrasonography (LUS) and bioimpedance, may provide complementary information to guide treatment in specific HD patients.

Methods: In total, 250 HD patients from two dialysis units were included in this randomized clinical trial. Patients were randomized 1:1 to have a dry-weight assessment based on clinical (control) or LUS and bioimpedance (active) guided protocol. The primary outcome was to assess the difference between the two groups on a composite of all-cause mortality and first cardiovascular event (CVE) - including death, stroke, and myocardial infarction.

Results: During a mean follow-up period of 21.3±5.6 months, there were 54 (21.6%) composite events in the entire population. There was a non-significant 9% increase in the risk for this outcome in the active arm (HR=1.09, 95%CI 0.64-1.86, p=0.75). Similarly, there were no differences between the two groups when analyzing separately the all-cause mortality and CVE outcomes.

Conclusions: This study shows that a LUS guided dry-weight adjustment protocol, as compared with clinical evaluation, doesn't reduce all-cause mortality and/or CVE in HD patients.

Funding: Government Support - Non-U.S.

TH-PO980

Volume Overload Hospitalization Identification among Hemodialysis Patients Using Administrative Claims Magdalene M. Assimon, Thuy Minh Nguyen, Suzanne L. Katsanos, Jennifer E. Flythe. *Univ of North Carolina, Chapel Hill, NC.*

Background: There is growing interest in fluid management practices and consequently a need to identify, quantify and monitor volume-related hospitalizations among hemodialysis (HD) patients. Administrative claims databases (e.g. the U.S. Renal Data System) are often used to study such outcomes, but these data are generated for billing purposes and may not capture clinical nuance. We conducted a validation study to assess the accuracy of claims-based definitions for volume overload (VO) hospitalizations.

Methods: We examined a random sample of 315 adult maintenance HD patients admitted to a large U.S. academic medical center from 2010-13. We performed standardized chart reviews to clinically adjudicate VO admissions. Using the medical center's administrative billing data, we built claims-based definitions for VO hospitalizations by combining various fluid-related ICD-9 discharge diagnosis codes. We computed the prevalence of claims-identified VO admissions and estimated validity metrics for each definition using adjudicated VO as the reference standard.

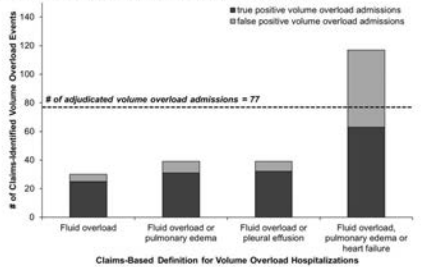
Results: Seventy-seven admissions (24.4%) were adjudicated as VO hospitalizations. The prevalence of claims-identified VO admissions varied across definitions (9.5-37.1%). Claims-based definitions tended to have low sensitivity and high specificity (**Panel A**). Definitions containing heart failure ICD-9 codes captured the most false positive events (**Panel B**). In sensitivity analyses, we added dialysis procedure codes to diagnosis code-based definitions and assessed validity. Small gains in definition specificity and decrements in sensitivity were observed (data not shown).

Panel A. Validity of Administrative Claims Definitions for Volume Overload Hospitalizations

Claims definition description	ICD-9 diagnosis codes*	Sensitivity (95% CI)[a]	Specificity (95% CI)[a]	PPV (95% CI)[a]	NPV (95% CI)[a]
Fluid overload	276.6, 276.69	32.5% (22.2%, 44.1%)	97.9% (95.2%, 99.3%)	83.3% (65.3%, 94.4%)	81.8% (76.8%, 86.1%)
Fluid overload or pulmonary edema	276.6, 276.69 or 514, 518.4	40.3% (29.2%, 52.1%)	96.6% (93.4%, 98.5%)	79.5% (63.5%, 90.7%)	83.3% (78.4%, 87.5%)
Fluid overload or pleural effusion	276.6, 276.69 or 511.9	41.6% (30.4%, 53.4%)	97.1% (94.0%, 98.8%)	82.1% (66.5%, 92.5%)	83.7% (78.8%, 87.9%)
Fluid overload, pulmonary edema or heart failure	276.6, 276.69 or 514, 518.4 or 402.x1, 404.x1, 404.x3, 428	81.8% (71.4%, 89.7%)	77.3% (71.5%, 82.5%)	53.8% (44.4%, 63.1%)	92.9% (88.4%, 96.1%)

*Definitions were constructed using ICD-9 discharge diagnosis codes billed in any position.
[a]Clinically adjudicated volume overload served as the reference standard.
Abbreviations: CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value.

Panel B. Number of Claims-Identified Volume Overload Hospital Admissions



Conclusions: Claims-based VO definitions are imperfect. Investigators and regulators must carefully consider the implications of missing and misclassifying events when evaluating and monitoring HD patient VO admissions with administrative data.

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TH-PO981

Management of Overhydration Using Bioelectrical Impedance Analysis in Chronic Hemodialysis Patients Chae Rim Kim, Jung-Ho Shin, Jin Ho Hwang, Su Hyun Kim. *Dept of Internal Medicine, Chung-Ang Univ Hospital, Seoul, Korea.*

Background: Fluid overload is common in end-stage renal disease (ESRD) patients receiving maintenance hemodialysis, and it may be an independent risk factor for cardiovascular events and all-cause death. Recently, bioelectrical impedance analysis (BIA) has been widely used as a non-invasive method to estimate volume status. We retrospectively investigated whether management of overhydration can reduce the rate of cardiovascular event and mortality in chronic hemodialysis patients.

Methods: ESRD patients who had been treated with outpatient hemodialysis were recruited. Using BIA, the ratio of extracellular fluid to total body fluid (ECF/TBF) was obtained every 6 months. Patients were divided into two groups according to ECF/TBW: the uncontrolled group included those with all measured ECF/TBW ≥0.40; and the controlled group included those with any measured ECF/TBW <0.40.

Results: A total of 142 patients (85 [59.9%] in the controlled group and 57 [40.1%] in the uncontrolled group) were included, and were followed for 29 (12, 42) months. The baseline ECF/TBW was 0.39 ± 0.01 in the controlled group and 0.42 ± 0.01 in the uncontrolled group, respectively (P < 0.001), this difference persisted during the study period (all P < 0.05 from baseline to 48 months). Patients in the uncontrolled group was older, and had higher Charlson comorbidity index and higher systolic blood pressure, compared to those in the controlled group (P = 0.006, P < 0.001 and P = 0.009, respectively). The risk of cardiovascular event was higher in the uncontrolled group (HR 2.4, 95% CI 1.2–5.1; P = 0.020), but it was disappeared after the adjustment with age, Charlson comorbidity index and systolic blood pressure (P = 0.344). On the other hand, patients in the uncontrolled group had higher risk of all-cause death, independent of age and Charlson comorbidity index (HR 3.6, 95% CI 1.1–11.5; P = 0.033).

Conclusions: Management of overhydration according to the ECF/TBF may be beneficial to prevent all-cause death in ESRD patients with maintenance hemodialysis.

TH-PO982

Does Fluid Balance or Rapid Fluid Removal Affect Outcome in Incident Hemodialysis Patients? Sandra Seidenfaden,[1] Runolfur Palsson,[1,2] Olafur S. Indridason.[2] *[1]Univ of Iceland; [2]Landspitali - the National Univ Hospital of Iceland, Reykjavik, Iceland.*

Background: Recent studies have shown that fluid balance affects survival in prevalent hemodialysis (HD) patients and that end-dialysis overweight (EDOW) of ≥0.3 kg and ultrafiltration rate (UFR) of more that 10-13 ml/kg/hr have been associated with decreased survival. In this study we examined if factors related to fluid balance are associated with survival in incident HD patients.

Methods: This was a retrospective study of all patients initiating HD at a University Hospital's Dialysis Unit and surviving for at least 3 months during 2003-2014. Data were obtained from medical records, including estimated dry weight, weight before and after dialysis, dialysis duration, blood pressure during dialysis and vascular access. The mean of values for each patient during the fourth month of HD (8-12 consecutive HD sessions) were used. Volume removed and fluid removal rate was calculated and EDOW was defined as the difference between attained post-dialysis body weight and dry weight. Kaplan-Meier method and Cox regression analysis were used to assess survival.

Results: A total of 197 patients began hemodialysis treatment during the study period. 153 patients survived for at least 3 months and had a full set of data available; 98 (64.0%) were men. EDOW ≥0.3 kg was observed in 36 (23.5%) of the HD patients , 63 (41.1%) spent ≤3.5 hours in each dialysis session. Sixty-five (42.3%) had UFR >10 ml/kg/hr and 20 (13.0%) >13 ml/kg/hr. The type of vascular access was a native fistula in 98 patients (64.0%), a HD catheter in 37 (24.2%) and a synthetic graft in 18 patients (11.8%). Cox regression analysis, adjusting for age, sex, access type, albumin and URR did not show association between survival and EDOW ≥0.3 kg (HR 0.7, 95% CI, 0.34-1.41), UFR >10 ml/kg/hr (HR 1.0, 95% CI, 0.60-1.69) or URF >13 ml/kg/hr (HR 1.18, 95% CI, 0.44-3.12).

Conclusions: The previously described association between UFR and EDOW does not appear to affect survival of incident HD patients. Residual kidney function could not be accounted for in our model but may be of importance in incident patients.

TH-PO983

A Higher Ultrafiltration Rate Is Associated with Worsening of the Echocardiographic Left Atrial Volume Index in Incident Hemodialysis Patients Jwa-Kyung Kim,[1] Sun Ryoung Choi,[2] Jae-Won Lee,[3] Sung Gyun Kim.[1] *[1]Internal Medicine, Kidney Research Inst, Hallym Univ Sacred Heart Hospital, Anyang, Korea; [2]Internal Medicine, Sahmyook Medical Center, Seoul, Korea; [3]Internal Medicine, G Sam Heart Hospital, Anyang, Korea.*

Background: Optimal fluid management is essential in caring hemodialysis patient. However, too rapid fluid removal and the resultant higher ultrafiltration rate (UFR) disadvantageously promote hemodynamic instability and cardiac injury. We evaluated the effects of the rapid UFR on the changes of echocardiographic left atrial volume index (LAVI) over period.

Methods: A prospective observational study was conducted with 124 patients who newly started hemodialysis. Echocardiography was performed at baseline and repeated 19.7 (11.3-23.1) months apart. Changes in LAVI per year (ΔLAVI/yr, mL/m$^{2.7}$/year) were arithmetically calculated, and the 75th percentile of the ΔLAVI/yr distribution was regarded as a "significant" increment. UFR was expressed in terms of mL/hr/kg , and we employed a mean UFR over 30 days (approximately 12-13 treatment).

Results: The meaninter-dialytic weight gain was 1.88±0.94 kg, and the UFR were 8.01±3.87 mL/h/kg. The significant pathological increment point in ΔLAVI/yr was 4.87 mL/1.73m^2/yr. Correlation analysis showed that ΔLAVI/yr was closely related to the baseline blood pressure (BP), hemoglobin level, residual renal function, and UFR. According to the ROC curve, the best cut-off of value of UFR for the predicting the pathological increment was 10 mL/h/kg, with the area under the curve of 0.712. In multivariate analysis, systolic BP, a history of coronary artery disease, hemoglobin <10 g/dL, and high UFR were significant predictors. An increase of 1 mL/h/kg in the UFR was associated with a 22% higher risk of a worsening of the LAVI (odds ratio, 1.22; 95% confidence interval, 1.05–1.41).

Conclusions: For patient starting hemodialysis, a rapid UFR over 10 mL/h/kg may be associated with maladaptive worsening of the LAVI, a strong predictor of long-term adverse outcomes.

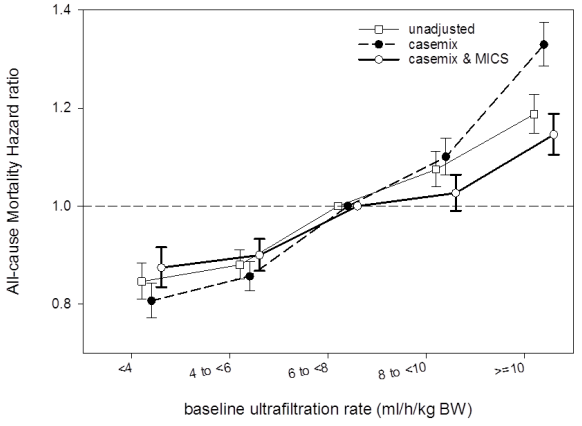
TH-PO984

Association of Ultrafiltration Rate with Mortality in Incident Hemodialysis Patients Tae Woo Kim,[1] Tae Ik Chang,[1] Tae Hee Kim,[1] Elani Streja,[1] Melissa Soohoo,[1] Connie Rhee,[1] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Univ of Tenn.*

Background: High ultrafiltration rate (UFR; ml/h/kg BW) may have a deleterious effect on survival in maintenance hemodialysis (MHD) patients. The main determinants of UFR are ultrafiltration and dialysis treatment time. Several studies have reported higher UFR was associated with increased all-cause and cardiovascular (CV) mortality in prevalent hemodialysis (HD) patients. However, the association of UFR with mortality in incident HD patients is not well known.

Methods: We examined a 5-year cohort of 110,880 patients who initiated MHD in the US from January 2007 to December 2011. UFR levels were divided into 5 ordinal categories (<4, 4 to <6, 6 to <8, 8 to <10, ≥10 ml/h/kg BW). We examined the association of UFR and all-cause mortality using Cox proportional hazard models with hierarchical adjustments for demographics, comorbidities and markers of malnutrition-inflammation-cachexia syndrome (MICS).

Results: The mean age of patients was 63±15 years, and included 43% females, 32% African Americans, 58% diabetics. In the case-mix and MICS adjusted model, higher baseline UFR was linearly associated with higher all-cause mortality risk. In addition, there were consistent and, incrementally higher associations of UFR with mortality irrespective of different urine volume, dialysis treatment time and post-dialysis systolic blood pressure categories.



Conclusions: High UFR is independently associated with increased all-cause mortality in incident HD patients. These results suggest that longer or more frequent dialysis therapy is needed to improve outcome for patients with high UFR.

Funding: NIDDK Support

TH-PO985

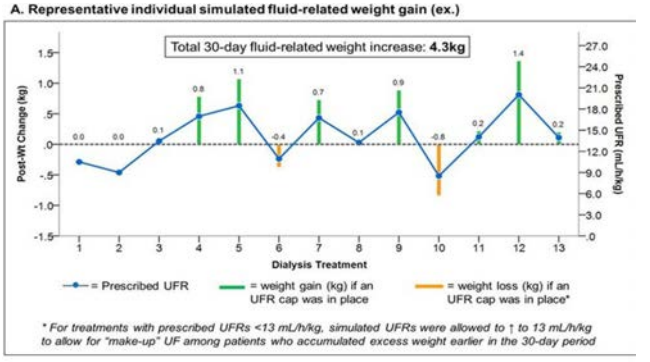
Weight Gain following Ultrafiltration (UF) Rate Threshold Implementation Jennifer E. Flythe, Magdalene M. Assimon. *Univ of North Carolina Kidney Center, Chapel Hill, NC.*

Background: Good fluid management is critical for optimal hemodialysis (HD) care. In 2015 the National Quality Forum endorsed an UF rate threshold quality measure but did not endorse a proposed companion target weight achievement measure. Lowering UF rates requires treatment time (TT) extension or interdialytic weight gain (IDWG) reduction. Often, patients are opposed to longer TTs and have difficulty with diet restrictions. In a national cohort we 1) examined target weight achievement, and 2) simulated weight gain over a 30-day period in the setting of UF rate threshold implementation without concurrent TT extension or IDWG reduction.

Methods: Using large dialysis organization data from 112,373 patients (1,754 facilities) in 2012, we analyzed facility-level target weight achievement according to the Kidney Care Quality Alliance-proposed target weight measure (post-HD weight ≥1 kg above or below target weight). Among 61,796 patients with complete pre- and post-HD weight and TT data, we simulated cumulative 30-day weight gains if UF rates were capped at 13 mL/h/kg without concurrent TT extension or IDWG reduction (Panel A).

Results: Facilities had, on average, 27.6 ± 10.1% of patients with post-HD weights ≥1 kg above or below target weights per KCQA measure specifications. Facilities in the highest target weight measure quartile (≥33.5% of patients with missed target weight) tended to be larger, located in the western U.S., and had more black patients and patients with shorter TTs (vs. lower quartile facilities). Overall, at the patient-level, implementation of an UF rate cap of 13 mL/h/kg with unchanged TTs and IDWGs resulted in a mean 30-day cumulative weight gain of 3 ± 4 kg. Panel B displays facility-level simulation results.

A. Representative individual simulated fluid-related weight gain (ex.)



** For treatments with prescribed UFRs <13 mL/h/kg, simulated UFRs were allowed to ↑ to 13 mL/h/kg to allow for "make-up" UF among patients who accumulated excess weight earlier in the 30-day period*

B. Facility-level % of patients with various 30-d weight changes after UF rate cap imposition.[a]

	% of Patients with 30-d Cumulative Difference in Post-HD Wt	% of Patients with 30-Day Cumulative Difference in Post-HD Wt	
	Overall	(-) Heart Failure	(+) Heart Failure
30-Day Cumulative Difference in Post-HD Wt	Mean ± SD Median (Q1, Q3)	Mean ± SD Median (Q1, Q3)	Mean ± SD Median (Q1, Q3)
≥ +2 kg	35 ± 15 35 (25, 45)	34 ± 17 33 (23, 44)	40 ± 26 39 (25, 54)
≥ +3 kg	28 ± 14 26 (17, 37)	26 ± 16 25 (15, 36)	32 ± 25 29 (15, 46)
≥ +4 kg	22 ± 13 21 (13, 30)	21 ± 14 19 (11, 29)	26 ± 23 23 (9, 39)

[a] Interpretation: Facilities had, on average, 35 ± 15% of patients with cumulative weight gains ≥2 kg 30 days after imposition of an UF rate cap of 13 mL/h/kg without TT extension or IDWG reduction.

Conclusions: Failure to balance UF rate thresholds with target weight achievement policies may lead to substantial weight gain if TTs are not extended and/or IDWG is not reduced.

TH-PO986

Association of Hemoglobin Levels Corrected by Interdialytic Weight Gain on Mortality in Japanese Hemodialysis Patients Tatsunori Toida,[1,2] Takashi Iwakiri,[2] Yuji Sato,[3] Hiroyuki Komatsu,[2] Kazuo Kitamura,[2] Shouichi Fujimoto.[1] *[1]Dept of Hemovascular Medicine and Artificial Organs, Faculty of Medicine, Univ of Miyazaki; [2]Fist Dept of Internal Medicine, Univ of Miyazaki Hospital; [3]Dialysis Div, Univ of Miyazaki Hospital.*

Background: Hemoglobin (Hb) levels are affected by a change in the body fluid status, the relationship between Hb levels and mortality while taking interdialytic weight gain (IDWG) at blood sampling into account has not yet been examined in hemodialysis (HD) patients.

Methods: Study design: Cohort study. Setting, Participants: Data from 1375 prevalent HD patients (median age (interquartile range), 69 (60-77) years; 42.3% female). Predictor: Patients were divided into 5 categories according to baseline Hb levels and two groups based on IDWG rates at blood sampling. Outcomes: All-cause and cardiovascular mortality during a 3-year follow-up. Measurements: Hazard ratios (HRs) were estimated using a Cox model for the relationship between Hb categories and mortality, and adjusted for potential confounders. Patients with Hb levels of 9-9.9g/dL were set as our reference category.

Results: 246 patients (18%) died of all-cause mortality, including 112 cardiovascular deaths. Lower Hb levels (<9.0g/dL) were associated with all-cause mortality, while Hb levels were not associated with cardiovascular mortality. When patients with IDWG 5.4% were divided into two groups using the median value of IDWG, the correlation between lower Hb levels and all-cause mortality disappeared in high IDWG patients (IDWG≥5.4%), but was maintained in low IDWG patients (<5.4%). Furthermore, about the cardiovascular mortality, a significant correlation was observed in both lower Hb levels in low IDWG patients and higher Hb levels in high IDWG patients (Table).

Conclusions: In HD patients, target Hb levels need to be selected in consideration of IDWG at blood sampling.

	Hb level (g/dL)				
	<9	9-9.9	10-10.9	11-11.9	≥12
IDWG<5.4%	3.10 (1.03-9.31)	1.00 (ref)	1.13 (0.44-2.91)	1.13 (0.39-3.21)	0.35 (0.07-1.87)
IDWG>5.4%	0.96 (0.28-3.26)	1.00 (ref)	1.68 (0.73-3.88)	1.70 (0.73-4.00)	3.01 (1.03-8.82)
Values shown are HRs (95%CI).					

TH-PO987

Association between Central Venous Oxygen Saturation and Ultrafiltration Volume in Chronic Hemodialysis Patients Lili Chan,[1] Hanjie Zhang,[2] Anna Meyring-Wosten,[2] Stephan Thijssen,[1,2] Peter Kotanko.[2] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Renal Research Inst, New York, NY.*

Background: Hemodialysis (HD) patients with congestive heart failure have higher mortality than those without. At rest with other factors being stable, central venous oxygen saturation ($ScvO_2$) can be used as a surrogate for cardiac output. Our goal was to examine if ultrafiltration volume corrected for post HD body weight (cUFV) is correlated with $ScvO_2$ at the end of HD and to assess the association between this correlation and mortality.

Methods: We conducted a retrospective study between 1/2012 and 8/2015 in 232 HD patients with central venous catheters as HD access. A 6-month baseline period with at least 10 HD treatments with $ScvO_2$ recordings preceded a 36-month follow-up. The $ScvO_2$ values during the last 10 minutes of treatments were averaged to obtain an end-HD $ScvO_2$. A slope was then obtained per patient between end-HD $ScvO_2$ and cUFV across all treatments. Survival was assessed with Kaplan Meier and spline analysis.

Results: 70% of the patients showed an inverse relationship between end-HD $ScvO_2$ and cUFV. During follow-up, there were 54 deaths. On spline analysis, there was no association between slope and mortality. Patients were then divided into groups of negative and positive slopes. Kaplan-Meier analysis indicated no survival difference between groups.

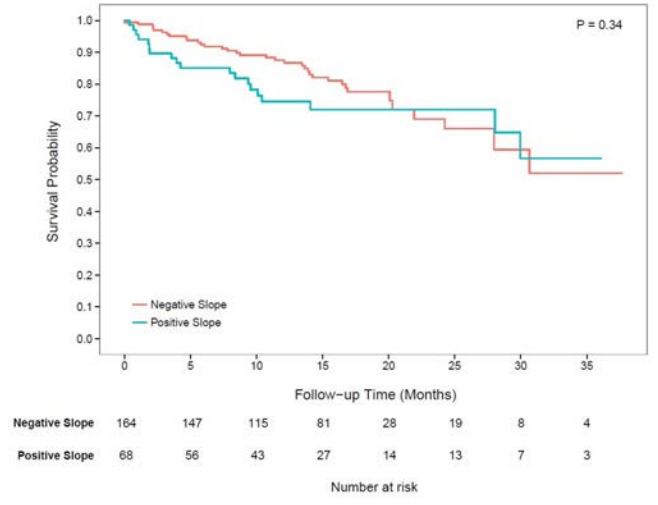


Figure 1: Kaplan-Meier estimates for survival probabilities between negative slope (red) and positive slope (green) patients, respectively. The number of patients at risk is indicated in the table below the graph.

Conclusions: As $ScvO_2$ is reflective of cardiac output at rest, the negative correlation of $ScvO_2$ with cUFV suggests that a majority of HD patients respond with a drop in cardiac output in the face of ultrafiltration. Patients with a negative slope did not have increased mortality. Further research is necessary to clarify the complex relationship between $ScvO_2$, UFV and cardiac output, in hopes of identifying a modifiable intradialytic target to improve outcomes in HD patients.

TH-PO988

Association between Peridialytic Systolic Blood Pressure Changes and Arterial Oxygen Saturation: Results from a Large U.S. Hemodialysis Cohort Anna Meyring-Wosten,[1] Ya Luo,[2] Hanjie Zhang,[1] Stephan Thijssen,[1] Yuedong Wang,[2] Peter Kotanko.[1,3] *[1]Renal Research Inst, New York; [2]Univ of California - Santa Barbara; [3]Icahn School of Medicine at Mount Sinai, New York.*

Background: While the physiological basis for peridialytic systolic blood pressure (SBP) decline has been studied extensively, the factors underlying a paradoxical SBP rise are not fully understood. Recent research indicated that 10% of chronic hemodialysis (HD) patients suffer from prolonged intradialytic hypoxemia [Meyring-Wösten, CJASN 2016]. Since hypoxemia induces a sympathetic response we entertained the hypothesis that SBP changes (ΔSBP) and intradialytic arterial oxygen saturation (SaO_2) may be associated.

Methods: We retrospectively analyzed intradialytic SaO_2 and ΔSBP (calculated as post-HD SBP minus pre-HD SBP) in chronic HD patients with arterio-venous vascular access. SaO_2 was recorded by Crit-Line® monitor (Fresenius Medical Care, Waltham, MA). Patients were followed over 6 months. Linear mixed effects models (LME) were used to explore associations between ΔSBP and (a) HD treatment time spent below 90% SaO_2 as well as (b) mean intradialytic SaO_2.

Results: We assessed 982 patients (29,869 HD treatments, 61% males; 52% whites). In patients with SaO2 > 90% during HD treatments mean ΔSBP was -10.24 mmHg (95% confidence interval -10.57 to -9.90). In contrast, in patients in whom SaO2 was < 90% throughout the entire treatment time mean ΔSBP was -6.04 mmHg (95% confidence interval -8.15 to -3.93). LME revealed that for every percent point increase of time spent below 90% SaO_2 ΔSBP increased by 0.03 mmHg (p=0.004) and that with every percent point increase in mean SaO_2 the ΔSBP decreased by 0.46 mmHg (p<0.001).

Conclusions: We observed an inverse relationship between intradialytic arterial oxygen saturation and the blood pressure response to HD. These findings support the notion that hypoxemia activates mechanisms that partially blunt the intradialytic blood pressure decline. We speculate that sympathetic surges resulting from intermittent hypoxemia may play a role. To further explore that hypothesis specifically designed prospective studies are required.

TH-PO989

Joint Effect of Pre-Dialysis Systolic Blood Pressure and Peridialytic Systolic Blood Pressure Change on Survival in Chronic Hemodialysis Patients Anna Meyring-Wosten,[1] Hanjie Zhang,[1] Ya Luo,[2] Alice Topping,[1] Jochen G. Raimann,[1] Yuedong Wang,[2] Franklin W. Maddux,[3] Peter Kotanko.[1,4] *[1]Renal Research Inst, New York; [2]Univ of California at Santa Barbara, CA; [3]Fresenius Medical Care North America, Boston, MA; [4]Icahn School of Medicine at Mount Sinai, New York.*

Background: Previous studies in chronic hemodialysis (HD) patients indicate an association between pre-HD systolic blood pressure (preSBP) and peridialytic SBP change (ΔSBP) on mortality. Yet, analyzing these two variables separately may not fully explore the nature of the interaction.

Methods: PreSBP and ΔSBP (post- minus pre SBP) were analyzed between 1/2001 and 2/2010. Baseline was defined as months 4-12 in the first year of HD, follow-up terminated at death, loss to follow-up, or the end of the study. Only patients who survived the baseline and had no missing covariates were included. We fitted Cox proportional hazard model with a bivariate spline for the main predictors, preSBP and ΔSBP, and adjusted for age, gender, diabetes, access type, relative interdialytic weight gain, body mass index and albumin.

Results: 5866 patients remained for final analysis (56% males; 50% whites). 1649 (28.1%) patients died during follow-up. Median follow-up time was 1.74 years. While with high preSBP, a SBP increase was associated with higher hazard ratio (HR), with low preSBP, a SBP increase was associated with lower HR (Fig.1). The results indicate a "trough" region of low HR.

Conclusions: Peridialytic SBP changes and pre-HD SBP are jointly associated with all-cause mortality in HD patients. While a peridialytic SBP increase may be particularly harmful in patients with high pre-HD SBP, it may be beneficial in those with low pre-HD SBP.

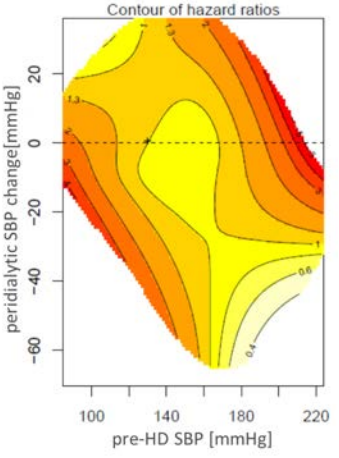


Figure 1: Contour plot showing the relationship between preSBP, ΔSBP and hazard ratios (HR) for all-cause mortality. Contour lines indicate discrete HR levels.

TH-PO990

Geographical and Seasonal Patterns of Blood Pressure in Hemodialysis Patients: A EURODOPPS Study Flore Duranton,[1] Anneke Kramer,[2] Brian Bieber,[3] Ziad Massy,[4,5] Christian Combe,[6] Francesca Tentori,[3] Kitty J. Jager,[2] Angel Argiles.[1,6] *[1]RD-Nephrologie, France; [2]ERA-EDTA Registry, AMC Amsterdam, Netherlands; [3]Arbor Research Collaborative for Health; [4]CHU Ambroise Paré and Inserm U1018, France; [5]CHU Bordeaux, France; [6]NDSG Sète, France.*

Background: In HD patients, we found that blood pressure (BP) before dialysis sessions was associated with seasons and outdoor temperature in a single facility. We wanted to extend our study to assess the geographical influences on BP.

Methods: Clinical data were obtained from the Dialysis Outcomes and Practice Patterns Study (DOPPS) phases 3-4 (2005-2011) for patients from 7 European countries (Sweden, United Kingdom, Belgium, Germany, France, Italy, Spain). Climate records corresponding to HD facilities were obtained. BP level was analyzed using mixed models with location (country or latitude), climate (season or outdoor temperature) and interactions as fixed effects, adjusting for study design and repeated measures.

Results: The study included 9655 HD patients from 151 locations and over 50 000 observations. Across Europe, pre- and post-dialysis BP were significantly lower in Southern places (fig-left, P≤0.02). Pre-dialysis BP was lower in summer and higher in winter (P<0.001) and was inversely associated with outdoor temperature (fig-right, P<0.01). Post-dialysis BP showed no clear association with seasons (P≥0.09) or temperature (P>0.1). The effect of temperature on preSBP was more pronounced in southern or warmer locations (P_{int}<0.01).

Conclusions: In Europe, patients from southern locations have lower pre- and post-dialysis BP. Pre-dialysis BP is lower in summer and with warmer temperature, and this effect is more pronounced in southern/warmer locations. There is a need to consider this variability when studying BP.

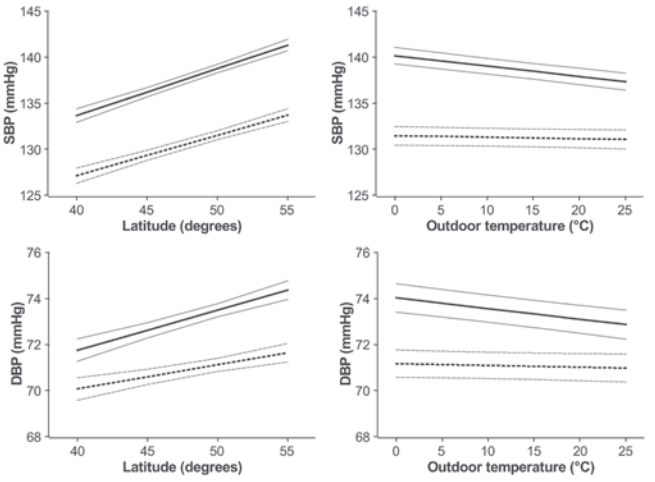


Fig: Pre-dialysis (solid line) and post-dialysis (dashed line) BP level by latitude and temperature. Estimates and 95% CI from mixed models.

Funding: Private Foundation Support

TH-PO991

Adequately Controlled Systolic Blood Pressure Is Significantly Associated with Better Survival Rate, Irrespective of Number of Antihypertensive Agents in Prevalent Dialysis Patients

Boyoung Nam,[1] Jong Hyun Jhee,[2] Ji Min Park,[1] Youn Kyung Kee,[2] Tae-Hyun Yoo.[1,2] *[1]Dept of Internal Medicine, College of Medicine, Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ, Seoul, Republic of Korea; [2]Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Republic of Korea.*

Background: The object of this study is to investigate optimal blood pressure (BP) target and adequate management of BP in prevalent dialysis patients group.

Methods: The data were retrieved from End-stage Renal Disease-Clinical Research Center (ESRD-CRC) which dialysis patients were prospectively enrolled from 2009 to 2014. Total 2,299 prevalent dialysis patients were analyzed. Eligible patients were assigned to five groups according to distribution of SBP (SBP<110, 110-129, 130-149, 150-169, and ≥170 mmHg). The primary outcome was all-cause mortality.

Results: The mean SBP in each group was 99.2, 119.7, 137.1, 155.9, and 179.2 mmHg, respectively (P<0.001). Baseline characteristics among the groups did not show significant differences except number of AHAs (1.3±1.4, 1.7±1.5, 1.9±1.4, 2.2±1.4, and 2.4±1.3 pills in each group, P<0.001). During a median follow up of 4.5 years, all-cause mortality was significantly higher in SBP <110 and ≥170 mmHg group [Hazard ratio (HR) 1.96, 95% confidential interval (CI) 1.40-2.74, P<0.001; HR 1.49, 95% CI 1.05-2.11, P=0.026], compared to reference group. Multivariate Cox analysis revealed that SBP <110 and ≥170 mmHg group had significantly higher risk of all-cause mortality after adjustment for age, sex, history of diabetes and cardiovascular events, duration of dialysis, serum albumin (HR 2.06, 95% CI 1.44-2.93, P<0.001; HR 1.53, CI 1.07-2.19, P=0.020). However, the number of AHAs being taken was not associated with survival rate in subgroup analysis with each BP group.

Conclusions: This study showed that lowest (<110) or highest (≥170 mmHg) SBP group had significantly higher risk of all-cause mortality, irrespective of number of AHAs. BP control with optimal target is significantly associated with better survival rate.

TH-PO992

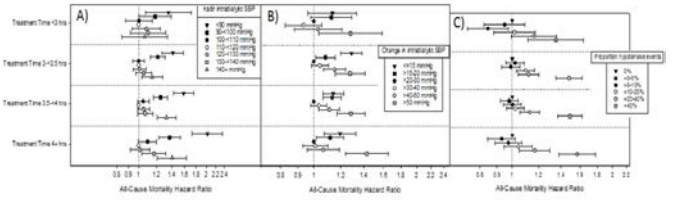
Impact of Hemodialysis Treatment Time on the Association of Intradialytic Hypotension and Mortality in Hemodialysis Patients

Jason Chou,[1] Elani Streja,[1] Connie Rhee,[1] Yoshitsugu Obi,[1] Melissa Soohoo,[1] Csaba P. Kovesdy,[2] John J. Sim,[3] Danh V. Nguyen,[1] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Univ of Tenn.; [3]Kaiser Permanente SC.*

Background: Intradialytic hypotension (IDH) occurs frequently and is associated with poor outcomes in hemodialysis (HD) patients. The HD treatment time (TT) may also be associated with survival. We hypothesize that longer TT attenuates the association of IDH with mortality.

Methods: We examined the association of nadir and change in intradialytic SBP (niSBP and ΔiSBP, respectively) and frequency of IDH with all-cause 5-year (2007–2011) mortality stratified by TT in a cohort of 112,015 incident (first 91 days of HD) adult HD patients using Cox regression models with adjustment for case-mix, comorbidities, and lab covariates. ΔiSBP was defined as pre-HD SBP minus niSBP. Frequency of IDH was defined as the proportion of HD treatments where patient's niSBP was < 90 mmHg.

Results: We found that lower and higher niSBP (< 100 and ≥ 140 mmHg, respectively) were incrementally associated with higher mortality. Frequency of IDH had an incremental quadratic association with death starting with > 20% frequency. Longer TT in these groups exhibited an increased IDH-mortality association. ΔiSBP of ≤15 and ≥ 50 mmHg were consistently associated with increased mortality while longer TT groups did not consistently show this trend. All associations were robust to adjustment for demographics, laboratory values and comorbidities.



Conclusions: Under longer hemodialysis TT, the IDH events and/or lower niSBP have a greater mortality risk. Further studies are needed to identify optimal niSBP goals and corresponding treatment times.

Funding: NIDDK Support

TH-PO993

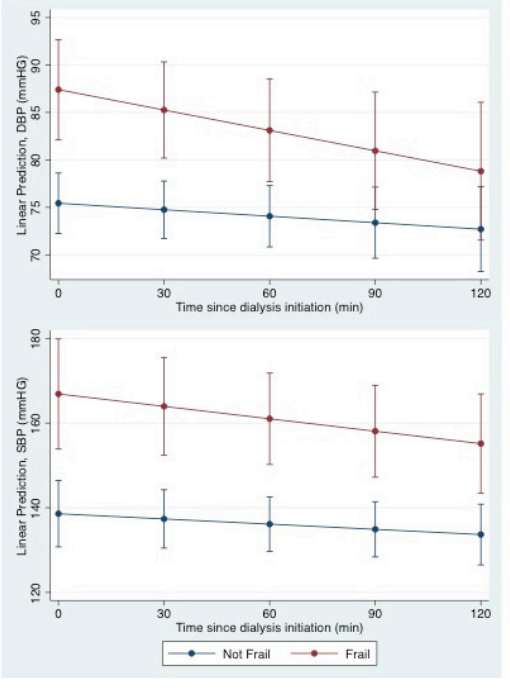
Frailty and the Blood Pressure Response to the Stressor of Hemodialysis among Older Patients

Mara McAdams-DeMarco, Qiong Huang, Hao Ying, Israel O. Olorundare, Morgan Grams, Dorry L. Segev. *Johns Hopkins.*

Background: Frailty is described as a multi-system dysregulation resulting in a vulnerability to stressors; yet evidence for this hypothesis is lacking. Hemodialysis represents a great stressor for older adults with ESRD. Sympathetic nervous system (SNS) activation is an essential compensatory mechanism for intradialytic blood pressure (iSBP/iDBP) maintenance. We hypothesized that frail dialysis patients have worse changes in BP while undergoing hemodialysis.

Methods: Frailty was measured on 163 older hemodialysis patients and pre- and post-dialysis BP measures were collected. We used adjusted linear regression to test for a difference in the pre- and post-dialysis change in SBP and DBP and adjusted logistic regression to test for a pre- and post-dialysis change of 15mmHg of SBP and 5mmHG of DBP by frailty. In a separate cohort, frailty was measured on 15 hemodialysis older patients who had 10 intradialytic BP measures and we used an adjusted linear growth curve model to test the association between frailty and iSBP/iDBP.

Results: Frail dialysis patients also had a greater change in their SBP (-4mmHg; p=0.24) and DBP (-7mmHg; p=0.001) while on dialysis. In adjusted analyses, those who were frail were had a 1.95-fold (95%CI:1.01-3.76; p=0.047) increased odds of a 15mmHg decline in SBP and 3.7-fold (95%CI:1.89-7.33; p<0.001) increased odds of a 5mmHG decline in DBP while on dialysis. For those who were frail, the rate of iSBP change was -2.93mmHG/30minutes (p=0.05) compared to -1.23mmHG/30minutes (p=0.22) for those who were nonfrail. Similar results were observed for iDBP (-2.15mmHG/30minutes [p=0.01] vs. -0.68mmHG/30minutes [p=0.21]).



Conclusions: Frailty represents a state of SNS dysregulation for patients in which adults undergoing the stressor of hemodialysis have a poor SBP and DBP response. This is the first evidence of SNS dysregulation among frail patients with ESRD.

Funding: Other NIH Support - NIA, Private Foundation Support

TH-PO994

Mannitol for the Prevention of Intra-Dialytic Hypotension - A Pilot Randomized Double-Blind Placebo-Controlled Trial

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Background: Intra-dialytic hypotension (IDH) is a common complication of hemodialysis (HD) and may be related to relatively rapid shifts in plasma osmolality. Interventions to minimize intra-dialytic changes in osmolality may prevent IDH.

Methods: In this double-blind single center RCT, patients requiring initiation of RRT for acute or chronic kidney disease were randomized to receive mannitol 0.25g/kg/hr or a similar volume of 0.9% saline during their first three HD sessions. Blood pressure was measured in a standardized fashion pre-, post- and every 30 minutes during HD. The primary endpoints were: 1) the average decline in systolic blood pressure (SBP); and 2) the proportion of total sessions complicated by IDH (SBP drop of ≥20 mmHg).

Results: A total of 52 patients were randomized, contributing to 156 study visits.

Baseline Characteristic	Placebo (n=27)	Mannitol (n=25)	P
Male, n (%)	14 (52)	12 (48)	0.78
Race, n (%)			0.90
Black	8 (29)	6 (24)	
White	18 (67)	18 (72)	
Other	1 (4)	1 (4)	
Age, yrs	58 ± 15	53 ± 17	0.34
Diabetes, n (%)	13 (48)	11 (44)	0.76
Heart Failure, n (%)	9 (33)	7 (28)	0.68
ESRD, n (%)	22 (82)	23 (92)	0.27
Catheter, n (%)	16 (59)	15 (60)	0.96
Pre-dialysis SBP, mmHg	144 ± 21	149 ± 26	0.48

There were no differences in the mean SBP decline between the mannitol and placebo groups (15.3±11.4 vs. 19.2±15.6 mmHg; P=0.31). This remained non-significant after adjusting for the pre-dialysis SBP (P=0.27). The proportion of total sessions complicated by IDH was lower in the mannitol group compared with placebo (25.3% vs. 43.2%), with a trend towards fewer repeated sessions complicated by IDH (OR 0.38; 95%CI 0.13-1.06; P=0.06).

Conclusions: In this pilot RCT for patients requiring the initiation of HD, we found no difference in the absolute SBP decline between those who received mannitol versus placebo. However, there were fewer overall IDH events and a trend towards lower risk of repeated sessions being complicated by IDH in the mannitol group. A larger multi-center RCT is warranted.

Funding: NIDDK Support

TH-PO995

Additional Volume Reduction Will Improve IDH Only in the Patients with Higher Pre-Dialytic BP

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Background: This study was conducted to investigate the main causes in intradialytic hypertension (IDH) patients, and whether additional volume reduction will result in improvement in either blood pressure (BP) or other benefits among IDH patients.

Methods: A prospective, open-label, single center study of 22 HD patients with IDH were involved in this study.IDH means an increase of blood pressure (ΔSBP>10mmHg) during dialysis session. 11 patients with normal pre-dialytic BP were entered in Group A, and other 11 patients with higher pre-dialytic BP were in Group B. Another 18 HD patients with normal BP were selected as CON. The whole study was lasted for 4 weeks. The blood samples of all patients were collected before dialysis at session 1st, 13th. Serum Ang-II, ALD, ACE, ET-1, NO and ADMA at same time were measured. Besides the control group, an additional weight loss of 0.1-0.2Kg body weights was prescribed per dialysis till additional ultrafiltration was not tolerated.

Results: The ultrafiltration of each dialysis session of IDH patients was higher than the CON, especially in Group B ($p < 0.05$). The serum levels of ACE, ALD , ET-1 and ADMA significantly increased in IDH patients than control group ($P < 0.05$). In Group A, the dry weight was reduced by 0.18Kg at 12 sessions and resulted in -3.18mmHg change in pre-SBP (p=0.973). In Group **B**, the dry weight was reduced by 0.67Kg at 12 sessions and resulted in 12.82 mmHg change in pre-SBP (p=0.021). The decrease of SBP was associated with decrease in the level of serum ACE, ALD, ET-1 and ADMA. However, the additional ultrafiltration treatment had no effects on diastolic blood pressure and blood pressure variability in these two groups.

Conclusions: (1) The reduction of dry weight is an efficacious maneuver to improve IDH patients with volume excess charactered with higher pre-dialytic BP. (2) The reduction of dry weight has no effect on IDH patients with normal pre-dialytic BP. (3) Activation of RAAS and endothelial dysfunction are the main causes that relate to intradialytic hypertension in MHD patients. (4) SBP may play a role in the effect on the decreasing of vascular contraction materials released.

Funding: Government Support - Non-U.S.

TH-PO996

Correlation of Weight Loss and Fluid Removal via Ultrafiltration in Patients with Acute Decompensated Heart Failure

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Background: Changes in weight and daily fluid balance are commonly used in clinical practice to monitor decongestive therapy in patients with acute decompensated heart failure (ADHF). It has recently been proposed that there exists a significant discrepancy between fluid balance and weight loss in ADHF patients who are managed with diuretics. The performance of these metrics has not been evaluated in patients undergoing ultrafiltration (UF) therapy.

Methods: Available data from clinical trials of UF in ADHF performed between January 2000 and March 2016 were included in the analysis. These studies evaluated decongestion both through weight change and fluid removal. Pertinent data were extracted and using Pearson product-moment correlation, the degree of linear dependence and correlation between these two variables was determined.

Results: A total of 14 studies (6 randomized controlled trials) with a total of 797 patients were evaluated. The mean age was 65.4 years. There existed substantial variation across studies in the reporting of surrogates of decongestion such as net and total fluid removal. Weight loss ranged from 2.6 to 10.7 Kg (mean 6.3 ± 2 Kg) and fluid removal ranged from 2.6 to 18.7 L (mean 8.6 ± 3.8 L). There was a strong positive correlation between weight loss and fluid removal (r = 0.87, 95% CI of Correlation 0.64-0.96, p = 0.00003).

Conclusions: Currently available evidence suggests that there is a strong correlation between weight loss and fluid removal in patients with ADHF who undergo UF therapy. Therefore, both markers may reliably be used to determine the degree of decongestion. These findings stand in contrast to patients who receive diuretics in ADHF. Future studies are needed to clarify whether this discrepancy is related to the inherent differences in sodium content of the ultrafiltrate versus urine sodium concentration or other less well explored factors such as local practice patterns and data collection.

TH-PO997

Renal Perfusion Falls during Hemodialysis: An Explanation for the Loss of Residual Renal Function in Dialysis Patients

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Background: Maintenance of residual renal function (RRF) has consistently been shown to confer survival benefit in hemodialysis (HD) patients, even in those with minimal urine output (UO). However, strategies for preservation are few, largely due to an inadequate understanding of the pathophysiology behind the characteristic rapid decline in RRF. The aim of this study was to directly examine the hypothesis that intradialytic circulatory stress results in significant ischemic challenge to the remnant kidney.

Methods: 12 patients with UO<500mL/24hrs underwent renal imaging before, during and after a session of dialysis. Detailed study of renal perfusion was performed using a novel dynamic-contrast imaging algorithm, in conjunction with a latest generation 256-slice CT scanner (GE Revolution). Images were analyzed offline to create functional maps for perfusion across the entire kidney. Echocardiography was done at baseline and prior to the end of dialysis to detect myocardial stunning, as a reference organ system for ischemic response to HD-induced circulatory stress (detected as regional changes in longitudinal strain using speckle tracking).

Results: Baseline renal perfusion was markedly reduced (48.2±26.4mL/min/100g), compared to normal control values, and was related to dialysis vintage (r=-0.67, p=0.01). HD resulted in significant reduction in renal perfusion to 25.9±16.1mL/min/100g (p=0.001) at peak stress (3 hrs). 10/11 patients in whom perfusion fell also exhibited myocardial stunning (>2 segments with >20% reduction in longitudinal strain), whereas stunning was not seen in the patient whose renal perfusion did not fall.

Conclusions: An acute drop in renal perfusion is observed during HD and is related to demonstrable organ injury in another vulnerable vascular bed. Cumulative exposure to circulatory stress may be a key pathophysiological factor in the loss of RRF observed in HD patients. Longitudinal studies are needed to examine whether amelioration of circulatory stress during HD helps to preserve RRF.

TH-PO998

Paradoxical Fluid Diversion into the Hepatic Circulation with Hemodialysis

Claire J. Grant,[1] Trevor Wade,[2] Charlie Mckenzie,[2] Christopher W. McIntyre,[1,2] Guido Filler,[1] Shih-Han S. Huang.[1,2] *[1]The Kidney Clinical Research Unit, Western Univ, London, Canada; [2]Dept of Medical Biophysics, Western Univ, London, Canada.*

Background: The hepatic circulation is involved in adaptive systemic responses to circulatory stress. However, it is vulnerable to both chronic hypervolemia and changes in cardiac function. The influence of hemodialysis (HD) and fluid removal upon the liver has never been specifically studied. We therefore conducted a detailed initial study to characterize the effects of HD upon liver water content and stiffness, referenced to peripheral fluid mobilization, total body water and cardiovascular stability.

Methods: We studied 55 established in-centre chronic HD patients without liver disease. To measure hepatic stiffness and body composition, all subjects underwent transient ultrasound-based elastography (Fibroscan®) in combination with bioimpedance

assessment (BIA) pre and post-HD. 16/55 patients also consented to additional magnetic resonance imaging (MRI) before and after HD, to determine changes in water content in both the liver and calf.

Results: Mean ultrafiltration (UF) volume was 26.3±14mL/kg. Fluid removal was accompanied with effective mobilization of peripheral water (measured with MRI within calf) from 0.84±0.3mL/g to 0.75±0.2mL/g, and reduction in total body water (36.8±7.7L to 35.5±9.1L, p<0.001), measured by BIA. However, MRI directly-measured liver water content increased (0.57±0.1mL/g to 0.79±0.3mL/g) accompanied by an increase in liver stiffness, measured by ultrasound elastography (5.65±2.5 vs. 6.31±2.9kPa, p=0.02). This increase was not proportional to UF volume, but was blunted in those with higher baseline stiffness (r=-0.37, p=0.006). The degree of liver water content increase was associated with significantly lower diastolic BP during HD (r=0.67, p=0.04).

Conclusions: Whilst fluid removal reduced peripheral and total body water content, liver water content (measured directly by MRI and indirectly by elastography) increased post-HD, consistent with movement of blood to the hepatic circulation. This novel observation suggests that there is a unique hepatic response to HD with UF and that the liver may play a more important role in HD response than currently appreciated.

TH-PO999

The Hepatic Response to Hemodialysis: Consequences for Uremic Toxin Exposure and Multi-Organ Injury Claire J. Grant,[1] Raanan Marants,[2] Nicholas Tonial,[3] Thomas Velenosi,[3] Brad Urquhart,[3] Ting Lee,[2,4] Christopher W. McIntyre.[1,2,4] *[1]The Kidney Clinical Research Unit, Western Univ, London, Canada; [2]Dept of Medical Biophysics, Western Univ, London, Canada; [3]Dept of Pharmacology, Western Univ, London, Canada; [4]Lawson Health Research Inst, London, Canada.*

Background: The liver provides the final functional barrier between gut-derived uremic toxins and the circulation. Hemodialysis (HD) has been demonstrated to result in widespread recurrent ischemic injury to vital organs (heart, brain). However, the liver's functional vulnerability has not been studied. To investigate potential metabolic and systemic hemodynamic consequences we performed a comprehensive evaluation of hepatic perfusion, excretory function and cardiac response during HD.

Methods: 15 patients underwent serial assessment of liver perfusion during HD using dynamic-contrast imaging with a latest generation 256-slice CT scanner [GE Revolution]. This allowed direct quantification of total liver (LBF), portal (PV) and hepatic arterial blood flow. Hepatic excretory function was measured with indocyanine green (ICG) clearance. HD-induced myocardial stunning was detected with serial echocardiography. Markers of tissue-specific endothelial stress and uremic toxin levels were measured.

Results: Total LBF was maintained over the course of dialysis. However, stability of LBF occurred at the expense of PV flow increasing, marked reduction in excretory function (ICG clearance falling from 916±423 to 789±350mL/min, p=0.002) and associated significant perfusion-dependent cardiac injury. Myocardial stunning was present in 80% of patients and severity was proportional to LBF (r=0.57, p=0.03) and degree of excretory function loss (ICG clearance, r=-0.64, p=0.02).

Conclusions: Failure of excretory function during HD, with concomitant increased delivery of uremic toxin-laden portal blood, results in increased systemic toxin exposure. Hepatic blood flow preservation occurs at the expense of concurrent critical organ injury. This maladaptive response to circulatory stress may be of central importance to understanding the limitations of current clearance measures to explain observed uremic symptoms as well as the pathophysiology of HD-induced organ injury.

TH-PO1000

The High Prevalence of Silent Myocardial Ischemia and Ventricular Arrhythmias Detected by Holter Monitoring during a Single Hemodialysis Session in a Brazilian Sample: An Exploratory Investigation of Associated Factors Marcia T.S. Martins,[1] Jean M. Monteiro,[1] Lucas Hollanda Oliveira,[3] Inaia A. Teixeira,[2] Pedro Guimarães Silva,[1] Marcelo Barreto Lopes,[1] Luis Claudio Correia,[2] Antonio Alberto Lopes.[1] *[1]Federal Univ of Bahia; [2]Escola Bahiana de Medicina; [3]Hospital São Rafael, Salvador, Brazil.*

Background: Maintenance hemodialysis (HD) patients seem to be highly susceptible to silent myocardial ischemia (SMI) and ventricular arrhythmia (VA). We used Holter monitoring during a single HD session to estimate prevalences of SMI and VA and to explore associations of echocardiographic findings and intradialitic hemodynamic changes with these outcomes.

Methods: Data (2013-2016) from 95 patients (mean age 51.1 yr, 73.7% males, 88.5% non-whites, 21.1% diabetics, median vintage=49 mo.) enrolled in the Prospective PROHEMO cohort in Salvador, Brazil. SMI was defined as ST depression at J-point ≥0.1mV. Cardiac function was assessed by echocardiography. Odds ratio (OR) and 95% confidence interval (95%CI) were estimated by logistic regression with adjustments for demographics, vintage and diabetes.

Results: Prevalences of both SMI and VA were 57% but VA prevalence did not vary by SMI diagnosis P=0.478). VA, but not SMI, increased steadily with age from 31.6% for 18-40 yr to 74.1% for ≥60 yr (P=0.005). VA prevalence was slightly higher in those with coronary artery disease (CAD) diagnosis (68.2 vs 53.4%), but SMI prevalence and ischemic load did not differ by CAD history. Adjusted odds of VA were positively associated with heart failure (OR=3.18, 95%CI=1.08-9.38) and echocardiographic findings: left ventricular volume index>28/mL/m^2 (OR=6.76, 95%CI=1.98-23.00), moderate-to-greater degree left atrial size (OR=3.85, 95% CI=1.47-10.12) and aortic insufficiency (OR=3.20, 95%CI=1.11-9.29). Fall in systolic BP during HD session was the hemodynamic variable strongest associated with VA (OR by 10% reduction=2.54, 95%CI=0.95-6.72). Associations of hemodynamic changes during HD session with SMI were not observed.

Conclusions: This study in MHD patients suggests that the high prevalences of SMI and VA in the HD session are driven by different mechanisms. It is likely that intradialytic SMI is largely caused by mechanisms other than CAD.

TH-PO1001

High Dialysate Calcium Concentration Is Associated with High Risk of Dialysis-Induced Myocardial Stunning Vitor B. Silva,[1] Thiago Andrade Macedo,[3] Luciano F. Drager,[1,3] Fabiana Graciolli,[1] Wagner Dominguez,[1] Rosa M.A. Moyses,[1,2] Rosilene M. Elias.[1] *[1]Nephrology, Univ de Sao Paulo, São Paulo, Brazil; [2]Univ Nove de Julho (UNINOVE), Brazil; [3]Cardiology, Inst do Coração, Brazil.*

Background: Myocardial stunning is associated with high ultrafiltration and consequent intradialytic hypotension. High dialysate calcium concentration (Ca 1.75 mmol/l) is associated with better hemodynamic tolerability, but whether this dialysate would reduce the risk of myocardial stunning during conventional hemodialysis (HD) is unknown.

Methods: In this randomized trial, patients under regular HD were assigned to two consecutive mid-week HD sessions, with high (Ca 1.75 mmol/l) and low (Ca 1.25 mmol/l) dialysate calcium concentration, and the same ultrafiltration. All patients performed transthoracic echocardiographybefore HD and at peak HD. Global longitudinal strain (GLS) and segmental strain were calculated by a single observed, blinded to the calcium concentration status.

Results: Nineteen patients were included (6 men, 44±13 years). The pre dialysis weight, systolic, diastolic and mean blood pressure (MBP) were similar between two HD sessions. Despite the same delta of weight (p=0.280), HD with low calcium had a greater drop of MBP (p=0.006), and was associated with more intradialytic hypotension and cramps (p=0.001). Segmental strain values were significantly worst in the peak HD with high calcium in almost all segments, except for basal inferolateral and mid-inferolateral. The GLS before HD was -19.8 ± 3.7 and went to -17.3 ± 2.9 and -16.1 ± 2.6% in HD with low and high calcium, respectively (p<0.0001). Post-test revealed that GLS during HD with high calcium was even worse than with low calcium (p=0.018). GLS was also worse among patients with parathyroid hormone >300pg/ml. GLS correlated with the delta of weight, ultrafiltration, serum transferrin, serum aldosteron and C-reative protein (all p values <0.005).

Conclusions: Although low dialysate calcium concentration may determine worse short-term hemodynamic tolerability, it may also lead to low risk of dialysis-induced myocardial stunning. Further studies are necessary to elucidate how the calcium delivered during HD may interfere with myocardial contractility.

TH-PO1002

Progressively Increased QTc Dispersion Was Associated with Sudden Cardiac Death in Patients with End Stage Renal Disease on Hemodialysis Dong-Ryeol Ryu, Seung-Jung Kim, Duk-Hee Kang, Kyu Bok Choi. *Dept of Internal Medicine, Ewha Womans Univ.*

Background: Patients with end stage renal disease (ESRD) on hemodialysis (HD) have a high risk of sudden cardiac death (SCD) due to serious ventricular arrhythmias. We performed an electrocardiogram wave pattern analysis of patients with ESRD on HD to find risk factors for predicting SCD.

Methods: We conducted a retrospective study involving 36 HD patients who died from SCD (SCD-HD) and 314 HD patients well controlled (Non-SCD) from January 2010 to June 2015 in 3 general hospitals (multi-centers). The QT interval, QT dispersion, and QT peak-end interval on all 12 leads, as well as some other 12-lead ECG parameters, were measured. We evaluated the first and last ECGs in 350 patients on HD.

Results: The SCD-HD patients were older (69.0±12.2 vs. 60.8±13.8 years, p=0.001) than the Non-SCD patients, while there was no significant difference in the gender, underlying disease, or body surface area between the two groups among the enrolled 350 patients (50.0% male, 61.7± 13.9 years) (p>0.05). However, a decreased QT peak-end interval (OR 0.961, p<0.001) in all pre-cordial leads (V1-V6) and a prolonged QTc dispersion (OR 1.023, p<0.001) were associated with an increase in SCD. The QTc dispersion increased progressively compared to those at the time of initial HD during mean follow-up duration of 2.5 years. (from 38.8±15.2 to 49.5±25.0ms, p=0.037). A multivariate analysis also revealed that prolonged QTc dispersion (OR 1.1, p=0.003) was an independent predictor of SCD in HD patients, and the area under the curve (AUC) for QTc dispersion was 0.653 in the receiver operator curve (ROC) analysis.

Conclusions: A decreased QT peak-end interval and prolonged QTc dispersion were independent predictors of SCD in patients with ESRD on HD. Therefore, serial ECG monitoring may have important clinical implications in patients with ESRD on HD.

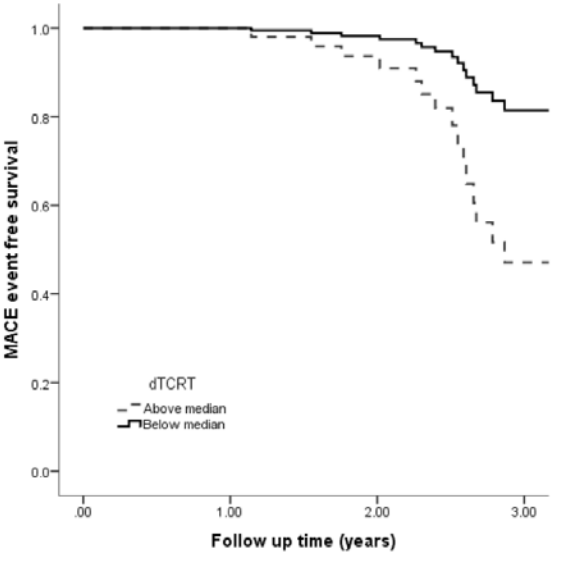
TH-PO1003

Longitudinal Change in QRS-T Angle Is More Significantly Associated with Cardiac Outcome in Hemodialysis Patients Than Standard ECG Parameters Darren Green,[1] Katerina Hnatkova,[2] Sofia Skampardoni,[1] Philip A. Kalra,[1] Marek Malik,[2] Dimitrios J. Poulikakos.[1] *[1]Salford Royal Foundation Trust, United Kingdom; [2]Imperial College, London, United Kingdom.*

Background: Wide QRS-T angle calculated from the surface digital ECG reflects global repolarisation heterogeneity and increase in QRS-T angle over time is linked with higher arrhythmic risk in the general population. We hypothesised that longitudinal changes in QRS-T angle would also be associated with adverse cardiac outcome in hemodialysis patients.

Methods: ECG was performed prospectively on adult haemodialysis patients on two occasions 1 year apart, both on midweek non-dialysis days. QRS-T angle was calculated from the ECG as total cosine R-to-T expressed in degrees (TCRT) using singular value decomposition with the aid of custom software. Follow up was until a major cardiac event (MACE: acute coronary syndrome, coronary revascularization, heart failure, arrhythmia, sudden cardiac death), or censored at transplant. Univariate associations of above vs below median annualised changes in TCRT and other ECG parameters with MACE was calculated using Cox regression, except for QRS which was adjusted for ultrafiltration volume due to potential confounding.

Results: There were 74 patients, age 62±14 years. Baseline TCRT was 86 ± 36° and median (range) annualised change was 5 (-84 to +127)°. The values for QRS were 107±16ms and +1 (-40 to +25)ms, for QT_c were 440±23ms & -1 (-194 to +108)ms, and for heart rate were 72±13 bpm and -1 (-19 to +40)bpm. Follow up was 2.3±0.7 years. There were 17 MACE end points. The hazard ratio for MACE in above versus below median change in TCRT (dTCRT) was 3.67 (1.27–10.60, p=0.036, see figure), for dQRS was 2.04 (0.77–5.41, p=0.148), for dQT_c was 1.15 (0.44–3.06, p=0.771), for dHR was 3.44 (0.98–12.03, p=0.053).



Conclusions: Longitudinal changes in QRS-T angle (dTCRT) may improve risk prediction in hemodialysis patients.

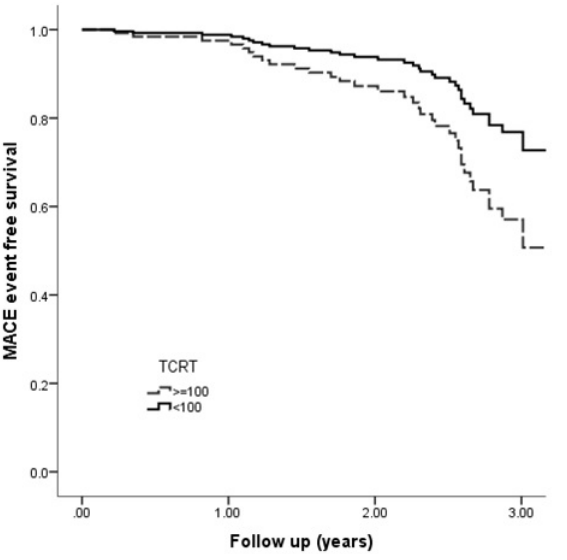
TH-PO1004

Global Electrical Heterogeneity as a Predictor of Mortality and Major Cardiac Events in Hemodialysis Patients Darren Green,[1] Katerina Hnatkova,[2] Sofia Skampardoni,[1] Philip A. Kalra,[1] Marek Malik,[2] Dimitrios J. Poulikakos.[1] *[1]Salford Royal Foundation Trust, United Kingdom; [2]Imperial College, London, United Kingdom.*

Background: Wide spatial QRS-T angle calculated from digital 12 lead ECG is a marker of global cardiac repolarization heterogeneity associated with worse prognosis in high cardiac risk populations. We assessed its prognostic value in hemodialysis patients.

Methods: Echocardiography and ECG were performed on adult hemodialysis patients on midweek non-dialysis days. QRS-T angle (TCRT) was calculated from the ECG as total cosine R-to-T using singular value decomposition aided by custom software, and expressed in degrees. Abnormal TCRT was defined as ≥100°. End points were death and major cardiac events (MACE: acute coronary syndrome, coronary revascularization, heart failure, arrhythmia, sudden cardiac death). The association of TCRT ≥100° with these was calculated by Cox proportional hazard models adjusted for age, gender, time on dialysis, left ventricular ejection fraction (LVEF), and left ventricular mass indexed to height (LVMI). Follow up was censored at transplant.

Results: There were 170 patients: age 61±15 years, time on dialysis 4±7 years, 66% male, LVEF 66±12%, LVMIht 50±19g/$m^{2.7}$, TCRT 88±39°. 70 patients (41%) had TCRT ≥100°. Follow up was 2.1±0.8 years with 40 deaths (24%) and 40 MACE. The adjusted hazard ratio (HR) for death if TCRT ≥100° was 0.80 (0.40–1.59), p=0.52). The HR for MACE was 2.1 (1.0–4.4), p=0.04.



For death, the significant variables were age (HR 1.02 [1.04-1.12], p,0.01), LVEF (HR 0.97 [0.94-0.99], p=0.04), and LVMI (HR 1.03 [1.01-1.05], p<0.01). For MACE, LVEF and LVMI were not significant but age was (HR 1.03 [1.00-1.03], p=0.04).

Conclusions: Wide QRS-T angle (TCRT) appears to be a better prognostic marker of risk for cardiac events than standard echocardiography. This likely reflects its association with arrhythmia and may become a useful prognostic indicator.

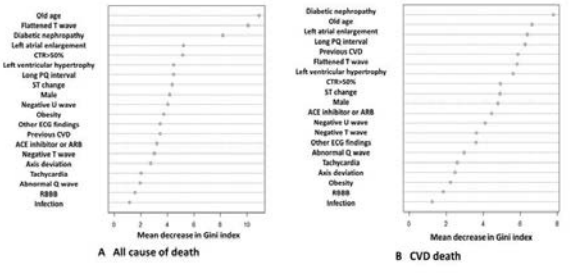
TH-PO1005

Evaluation of 15-Year Mortality Based on Electrocardiogram in Hemodialysis Patients Using Random Forest Machine Learning Algorithm Eiichiro Kanda,[1] Bogdan I. Epureanu,[2] Hiroshi Kawaguchi,[3] Yoichiro Tabata,[4] Noriyoshi Murotani,[5] Tomoko Maeda,[6] Hidetaka Itoh,[7] Haruki Itoh.[8] *[1]Tokyo Kyosai Hospital; [2]Michigan Univ; [3]Tokiwa-kai Medical Corporation; [4]Meysey-kai Medical Corporation; [5]Japan Community Health Care Organization Chiba Hospital; [6]Sakakibara Heart Inst Clinic; [7]Toranomon Mutual Aid General Hospital; [8]Sakakibara Heart Inst.*

Background: Cardiovascular disease (CVD) is a leading cause of death in hemodialysis (HD) patients. The aim of this 15-year prospective cohort study of HD patients in Japan was to determine which resting electrocardiography (ECG) findings are associated with long-term prognosis.

Methods: We developed a random forest which was an ensemble of 500 decision trees, to predict each patient's survival from a random subset of training data (N=304). Moreover, the ECG findings effective for identifying patients with a high risk of cause-specific death were identified from the mean decrease in the Gini index on a test dataset (N=305).

Results: Mean age and vintage were 52.5 and 5.6 years, respectively. 67.8% of the patients died. The random forest showed an estimation of sensitivity of 73.6% and specificity of 40.1%. Old age (>65 years) was the most discriminative variable for all-cause death, followed by flattened T waves, diabetic nephropathy, and left atrial enlargement.



Ranking of variables for prediction of death

Cox proportional hazard models adjusted for baseline characteristics showed that these ECG findings were associated with all-caused death; flattened T wave, adjusted hazard ratio (aHR) 1.32 (95% CI 1.03, 1.70); left atrial enlargement, aHR 1.25 (1.01, 1.54). Another random forest showed that the important ECG findings for the prediction of CVD-caused death were left atrial enlargement, long PQ interval, and flattened T wave.

Conclusions: In this study, we showed the importance of ECG findings for HD patients' prognoses. If changes in ECG findings are observed, detailed cardiac examination should be carried out.

TH-PO1006

Interplay between Arterial Functional and Structural Alteration and Their Contribution to Cardiac Abnormalities in Hemodialysis Patients

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Background: Hemodialysis (HD) patients often have altered arterial and cardiac features. The aim of this study is to examine the relationship between arterial structure and function and their contribution to left ventricular (LV) dysfunction and hypertrophy in HD patients.

Methods: 118 HD patients (55±12yr, BMI:32±8 kg/m², 59% males, 46% diabetes) were tested for blood pressure (BP), arterial wave reflection (AIx75), arterial stiffness (aortic pulse wave velocity (PWV), pulse pressure (PP) and β-stiffness), carotid artery lumen diameter (D), carotid intima-media thickness (IMT), subendocardial viability ratio (SEVR), LV ejection fraction (EF), LV early diastolic flow-tissue ratio (E/E') and LV mass (LVM) on a non-dialysis day.

Results: The presence of LV hypertrophy, systolic dysfunction (EF<40%) and diastolic dysfunction were 84.6% (concentric: 79.5% and eccentric: 10.7%), 17.7% and 45.6% respectively. There were positive associations between β-stiffness and IMT and between D and LVM and a negative association between AIx75 and LV EF (p <.05 for all). With adjustments for age and diabetes status, each of brachial and aortic systolic BP and aortic PP were independently associated with E/E', the severity of LV diastolic dysfunction and SEVR (p< .05 for all). The combination of aortic systolic BP and PP, but not individually, significantly predicted increased LVM (r=.319, p=.047).

Conclusions: This study confirms pathophysiological arterio-ventricular coupling in HD patients. Increased arterial wave reflection was accompanied with impaired LV systolic function. Augmented arterial stiffness was associated with arterial wall thickening, progression of LV diastolic dysfunction and LV enlargement. These findings may result in potential therapeutic interventions to prevent the progression of cardiovascular diseases in HD patients.

Funding: NIDDK Support

TH-PO1007

N-3 Polyunsaturated Fatty Acid (N-3 PUFA) Dietary Intake and All-Cause and Cardiovascular Mortality in Adults on Hemodialysis: The DIET-HD Multinational Cohort Study

Valeria M. Saglimbene,[1,2] Germaine Wong,[2] Marinella Ruospo,[1,3] Suetonia Palmer,[4] Katrina L. Campbell,[5] Vanessa Garcia Larsen,[6] Patrizia Natale,[1] Jorgen B.A. Hegbrant,[1] Jonathan C. Craig,[2] Giovanni F.M. Strippoli.[1,2,7] *[1]Diaverum Medical Scientific Office; [2]Univ of Sydney; [3]Amedeo Avogadro Univ of Eastern Piedmont; [4]Univ of Otago; [5]Princess Alexandra Hospital; [6]Imperial Collge London; [7]Univ of Bari on behalf of the DIET-HD Investigators.*

Background: N-3 PUFA intake is a protective factor for cardiovascular (CV) risk in the general population, but data in dialysis are scant. We investigated the association between n-3 PUFA dietary intake and CV and all-cause mortality in hemodialysis (HD).

Methods: The DIET-HD study is a cohort study (n=9235) conducted between January 2014-2016 in 11 countries in Europe and South America. It aims to examine the association between nutrition and dietary patterns with major health outcomes in HD patients. Participants received a food frequency questionnaire validated for N-3 PUFA. We used adjusted Cox regression analyses clustered by country to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for CV and all-cause mortality associated with N-3 PUFA dietary intake.

Results: 8142 patients (88%) provided complete responses. 3433 (42%) were women, mean age 63.1 years (SD: 15.0), median n-3 PUFA intake 1.2 g/wk (IQR: 0.3-2.4). During a mean follow up of 16.2 (5.3) months (8112 person-years), there were 1232 deaths, 520 from CV causes. N-3 PUFA was inversely associated with CV (adjusted HR 0.88; CI 0.79-0.99 per SD increase in log transformed g/wk intake) and all-cause mortality (HR 0.93; CI 0.86- 1.01). Adjusted HRs for CV and all-cause mortality for patients in the highest n-3 PUFA tertile (≥2.6 g/wk), compared with those in the lowest (<0.37 g/wk), were 0.71 (0.52- 0.97) and 0.84 (0.70-1.01), respectively. Higher (≥2.6 g/wk) compared to lower (<0.37 g/wk) n-3 PUFA intake was associated with an absolute risk reduction of 21 CV deaths per 1000 patients over 1 year.

Conclusions: Higher n-3 PUFA dietary intake is associated with lower CV mortality in HD patients. Strategies supporting dietary n-3 PUFA intake are potential candidate interventions for large-scale randomized trials in the dialysis setting.

TH-PO1008

The Effect of Polyunsaturated Fatty Acids Supplementation on Cardiovascular Risk Factors in Patients with End-Stage Renal Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background: Previous observational studies suggest that omega-3 fatty acids are associated with lower cardiovascular risk factors in adults; however, this association in patients with end-stage renal disease (ESRD) remains controversial. Therefore, the aim of the present study was to summarize the evidence from the investigations of randomized controlled trials (RCTs) related to omega-3 fatty acids supplementation on the major cardiovascular risk factors.

Methods: We performed electronic searches in PubMed, EmBase, and the Cochrane Library to identify RCTs on major cardiovascular risk factors through June 2015. Standard mean difference (SMD) and a random-effect model were used to measure the effect of omega-3 fatty acid supplementation on the risk of triglyceride, total cholesterol, LDL, HDL, homocysteine, SBP, DBP, and glucose. The analysis was further stratified by factors that could affect the treatment effects.

Results: We included 19 prospective studies reporting data on 1,415 patients with end stage renal diseases. Overall, omega-3 fatty acid supplementation produced a reduction of 0.68 mg/dl (SMD: -0.68; 95%CI: -1.10 to -0.26; P=0.001) for triglyceride, and a reduction of 0.36 mg/dl (SMD: -0.36; 95%CI: -0.69 to -0.03; P=0.033) in LDL. However, omega-3 fatty acid had no significant effect on total cholesterol (SMD: -0.31; 95%CI: -0.72 to 0.09; P=0.127), HDL (SMD: 0.49; 95%CI: -0.03 to 1.01; P=0.066), homocysteine (SMD: -1.41; 95%CI: -3.07 to 0.24; P=0.095), SBP (SMD: -1.07; 95%CI: -3.14 to 1.01; P=0.313), DBP (SMD: -1.52; 95%CI: -4.95 to 1.90; P=0.383), and glucose (SMD: 0.20; 95%CI: -0.46 to 0.85; P=0.560). Finally, a sensitivity analysis suggested that omega-3 fatty acid might be associated with lower total cholesterol (SMD:-0.42; 95%CI: -0.81 to -0.04; P=0.030).

Conclusions: Omega-3 fatty acid supplementation was associated with lower cardiovascular risk for patients with ESRD.

TH-PO1009

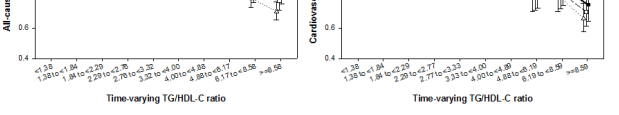
Elevated Nonfasting Serum Triglyceride to High-Density Lipoprotein Cholesterol Ratio Is Associated with Improved Outcomes in Incident Hemodialysis Patients

Tae Ik Chang,[1] Elani Streja,[1] Connie Rhee,[1] Moti L. Kashyap,[2] Nosratola D. Vaziri,[1] Kamyar Kalantar-Zadeh,[1] Hamid Moradi.[1,2] *[1]UC Irvine; [2]VA Long Beach.*

Background: Elevated serum triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio has been identified as a risk factor for cardiovascular (CV) disease and mortality in the general population. However, the association of this important CV marker with mortality has not been fully examined in patients with end stage renal disease (ESRD) on hemodialysis. Here we evaluated the association of nonfasting serum TG/HDL-C ratio with all-cause and CV mortality in incident patients with ESRD on maintenance hemodialysis.

Methods: We studied the association of nonfasting serum TG/HDL-C ratio with all-cause and CV mortality in a nationally representative cohort of 50,673 incident hemodialysis patients during 1/1/2007-12/31/2011. Association of baseline and time-varying TG/HDL-C ratios with mortality was assessed using Cox proportional hazard regression models.

Results: In fully adjusted models with case-mix and surrogates of malnutrition and inflammation complex, elevated TG/HDL-C ratios showed paradoxical association with better survival, in which the highest decile group (reference: 6th deciles) had a significantly lower risk of all-cause (HR, 0.88 [95% CI, 0.81-0.96] in baseline and 0.82 [0.75-0.90] in time-varying models) and CV mortality (0.81 [0.71-0.94] in baseline and 0.75 [0.64-0.87] in time-varying models). These associations remained consistent and significant across various subgroups.



Conclusions: Contrary to the general population, elevated TG/HDL-C ratio was associated with better CV and overall survival in hemodialysis patients. Our findings provide further support that the nature of CV disease and mortality in patients with ESRD is unique and distinct from other patient populations.

Funding: NIDDK Support

TH-PO1010

The Sit to Stand 60 Associates with Cardiovascular Fitness and Physical Activity in Hemodialysis Patients

Daniel Scott March,[1,2] Hannah M.L. Young,[1,2] Darren R. Churchward,[1,2] Charlotte E. Grantham,[1,2] Patrick J. Highton,[3] Matthew P.M. Graham-Brown,[2,3] James Burton.[1,2] *[1]Dept of Infection Immunity and Inflammation, Univ of Leicester, Leicester, Leicestershire, United Kingdom; [2]John Walls Renal Unit, Univ Hospitals Leicester NHS Trust, Leicester, Leicestershire, United Kingdom; [3]National College of Sport and Exercise Medicine, Univ of Loughborough, Loughborough, Leicestershire, United Kingdom.*

Background: The relationship between physical function, levels of physical activity and cardiovascular fitness in patients undergoing Hemodialysis (HD) is not well defined. The aim of this study is was to assess the association between physical function, physical activity and haemodynamic measurements in HD patients.

Methods: Sit to stand 60 (STS60), hemodynamic measurements and 7 day total steps (7DTS) data was collected for 36 prevalent HD patients. Demographic was collected

prospectively on all patients. Hemodynamic measurements (cardiac index {CI}, stroke volume index {SVI}, total peripheral resistance index {TPRI}, mean arterial pressure {MAP}, systolic blood pressure {SBP} and diastolic blood pressure {DBP}) were collected using the NICOM™, immediately prior to the second HD session of the week. StS60 was measured on a non-dialysis day. Pearson's correlation coefficient was performed to assess correlations between variables. Statistical significance was accepted at $P < 0.05$ level.

Results: STS60 significantly associated with CI (r=0.633, P<0.001), SVI (r=0.669, P<0.001), TPRI (r=-0.675, P<0.001) and SBP (r=-0.397, P<0.001). There were no significant associations between STS60 and DBP (r=-0.18, P<0.920) and MAP (r=-.250, P=0.168). STS60 was also significantly associated with 7DTS (r=0.702, P<0.001).

Conclusions: STS60 is a clinically relevant test significantly associated with cardiovascular fitness and levels of physical activity in HD patients. This highlights the relationship between physical function, physical inactivity and cardiovascular health in HD patients. Further research should investigate whether a concurrent improvement in cardiovascular fitness is observed when lower extremity strength is ameliorated in this patient population.

Funding: Government Support - Non-U.S.

TH-PO1011

Two Years of Regular Perdialytic Exercise Is a Protective Cardiovascular Factor in ESRD Patients Myriam Rouchon Isnard, Céline Coutard. *AURA Auvergne, Chamalières 63 400, France.*

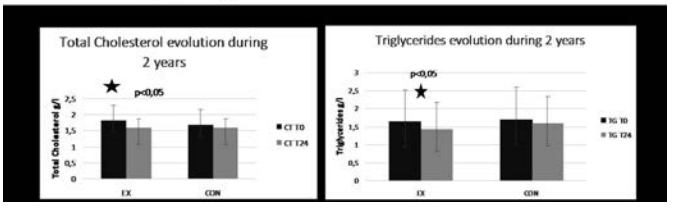
Background: The aim of the study was to show the effectiveness of Physical Activity (PA) during dialysis as a protective treatment against cardiovascular (CV) diseases.

Methods: Eighty volunteer patients were included in this multicentric prospective study and followed for two years: 40 patients in the Exercise group (EX), 40 patients in the Control group (CON). CV risk factors: Total Cholesterol, HDL Cholesterol (HDL-c), LDL cholesterol (LDL-c), Triglycerides (TG) and Hemoglobin (Hb), were checked at M0 (Month 0) and M24 (Month 24). The number of antihypertensive treatments and the Erythropoietin Stimulating Agent (ESA) required doses were collected too. We noted for each group during the follow-up the hospitalizations and their etiologies.

Results: At Year two, there are 35 patients left in the CON group: 4 deaths and 1 renal transplantation; 31 patients left in EX: 7 deaths and 2 transplantations [figure1]. We observed a significant decrease of Total Cholesterol in EX between M0 and M24: 1.82 ± 0.47 vs 1.6 ± 0.26 g/l (p<0,05) [figure1]. TG decreased significantly in EX after two years (1.63 ± 0.9 vs 1.44 ± 0.74 g/l) [figure1]. HDL, LDL Cholesterol and Hb remained stable in the 2 groups, but the required doses of Erythropoietin Stimulating Agent (ESA) decreased in EX between M0 and M24: 110,83 ± 70,8 vs 75,7 ± 69,7 µg/month. The number of antihypertensive drugs per patient decreased significantly ($p < 0.05$) in the EX group between M0 and M24 (1.85 ± 1.08 vs 0.75 ± 0.84 at M24).

	CON		EX	
	M0 (n=40)	M24 (n=35)	M0 (n=40)	M24 (n=31)
Age (years)	67,65 ± 13,4		66,8 ± 10,6	
Gender	23m, 17f		27m, 13f	
Charlson comorbidity index	5,22		5,23	
Ischemic cardiopathy	3 (7,5%)		7 (17,5%)	
Diabetes	12 (30%)		12 (30%)	
Hypertension	33 (82,5%)		34 (85%)	
Anti HTA treatments	1,35 ± 1,02	1± 1,03	1,85 ± 1,08	0,75 ± 1,06 *
Hemoglobin (g.dl^{-1})	11,79 ± 1.01	11,72 ± 0,9	11,70 ± 1,17	11,6 ± 0,88
ESA doses	89,63 ± 77,3	75,5 ± 70	110,83 ± 70,8	75,7 ± 69,7
Cardiovascular hospitalizations		**14**		**5**
Renal transplantation		**1**		**2**
Cardiovascular Death		**2**		**2**

Values are mean ± SD. CON : Control group ; EX : exercising-group
*: difference between EX and CON at M24, p< 0,05



The EX patients were 3 times less frequently hospitalized for cardiovascular reasons: 5 hospital stays in EX versus 14 for CON.

Conclusions: Our study demonstrates that an intradialytic aerobic cycling training program promotes beneficial effects on cardiovascular protection: Lipids and HTA control. PA also reduced CV events in our population during two years follow-up.

TH-PO1012

Intradialytic Exercise Does Not Alter the Frequency or Severity of Ventricular Arrhythmias Charlotte E. Grantham,[1,2] Darren R. Churchward,[1,2] Daniel Scott March,[1,2] Matthew P.M. Graham-Brown,[1,2,3] Hannah M.L. Young,[1,2] Patrick J. Highton,[1,2,3] Alice C. Smith,[1,2] Anna-Marie Marsh,[4] James Burton.[1,2,4] *[1]Dept of Infection, Immunity & Inflammation, Univ of Leicester; [2]John Walls Renal Unit, Leicester General Hospital; [3]National Centre for Sport and Exercise Medicine, Loughborough Univ; [4]Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital.*

Background: Haemodialysis (HD) patients are prone to ventricular arrhythmias, a leading cause of sudden cardiac death. Given that HD and exercise are known to be pro-arrhythmogenic, the safety of intradialytic exercise (IDE) warrants further attention. We aimed to assess whether IDE altered the characteristics of ventricular arrhythmias.

Methods: Twelve HD patients underwent two 48-hour Holter recordings starting immediately before a resting dialysis session and before a dialysis session including 45 minutes of moderate intensity intradialytic cycling. Recordings were analysed for frequency of premature ventricular complexes (PVC; % overall beats). Complex Ventricular Arrhythmias (CVA) were classified as Lown class 3 and above. Ultrafiltration volume (UF) was recorded for all studied sessions. Data were analysed using Wilcoxon sign rank, Fisher's exact test or Spearman correlation as appropriate.

Results: The average recording was 36±15 hours. PVCs were detected in 75% (9) patients with 56% (5) classed as having CVAs during the baseline recording. Similarly, 66% (8) patients had PVCs present with 75% (6) having CVAs during the exercise recording. During the baseline recordings, frequency of PVCs was higher during dialysis than the post-dialysis phase (0.04% vs. 0.008%, P=0.02). Exercise on dialysis did not significantly alter frequency of PVC (0.05% vs. 0.002%, P=0.21) or CVAs (P=0.67). UF was not associated with frequency or severity of ventricular arrhythmias ($P \geq 0.649$).

Conclusions: Our results confirm previous findings that HD is potentially arrhythmogenic however the addition of moderate intensity exercise during dialysis did not significantly alter frequency of PVCs or CVAs. Similarly, increasing UF was not associated with PVCs or CVAs. These data support the hypothesis that IDE is a safe strategy to improve cardiovascular health in HD patients.

Funding: Government Support - Non-U.S.

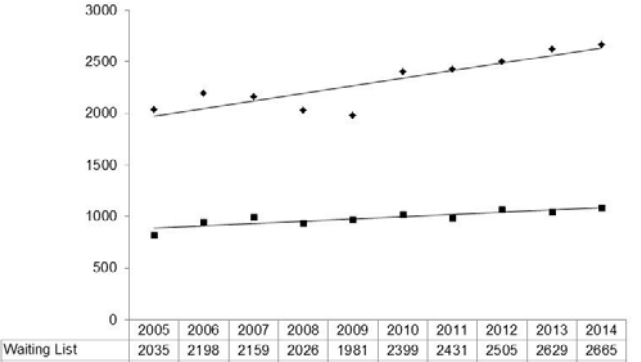
TH-PO1013

10-Year Trends in Kidney Dialysis and Transplantation Treatment for Patients with End-Stage Kidney Disease in Canada Juliana Wu,[1] Michael Terner,[1] Kevin Quach,[1] Kelvin Lam,[1] Joseph Kim,[2] Scott Klarenbach.[3] *[1]Canadian Inst for Health Information, Toronto, ON, Canada; [2]Univ of Toronto, Toronto, ON, Canada; [3]Univ of Alberta, Edmonton, AB, Canada.*

Background: The Canadian Organ Replacement Register (CORR) — a pan-Canadian information system for organ failure — is an important resource for examining trends in end-stage kidney disease (ESKD) and renal replacement therapies in Canada.

Methods: CORR data was used to calculate incidence and prevalence rates for ESKD patients who received dialysis or kidney transplants. Data from 2005 to 2014 for all provinces and territories in Canada, except Quebec, was included. Rates were calculated using the Statistics Canada population estimates.

Results: The number of patients starting dialysis in Canada has been increasing steadily over the past 10 years, rising from 4,244 (172 RPMP) in 2005 to 5,269 (193 RPMP) in 2014; prevalent number of patients has also similarly increased. Since 2005, patient survival for those on dialysis has increased marginally, with the most notable increase being 5-year survival for peritoneal dialysis patients (47.0% in 2005 and 52.5% in 2009). The number of deceased-donor kidney transplants has increased steadily over the past 10 years; whereas the increase in the number of living-donor kidney transplants has been much smaller. Both the number on the waiting list and the number of transplants performed steadily increased over the past 10 years, with a persistent 2.5 times differential gap between the two.



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Waiting List	2035	2198	2159	2026	1981	2399	2431	2505	2629	2665
Kidney Transplants	816	947	990	939	968	1019	987	1071	1043	1085

Conclusions: The need for renal replacement therapy is steadily rising in Canada, and increases in kidney transplantation have not kept pace with demand. This puts pressure on the health care systems to improve the efficiency of kidney transplantation and the organ donation process while ensuring all dialysis modalities are accessible for ESKD patients.

TH-PO1014

End Stage Renal Disease Patients in Asia-Pacific from 2005 to 2015: A Trend Towards Concern Xiaoqi Xu, Yun Shi. *Medical Affairs, Fresenius Medical Care Asia Pacific, Hong Kong, China.*

Background: The number of end-stage renal disease patients (ESRD) has continuously grown worldwide although multiple prevention strategies were implemented over the decades. There are many international registries have provided valuable demographic and epidemiologic information for ESRD. But there were very few information for entire Asia Pacific (AP) region.

Methods: ESRD patient information was collected and covers 25 AP countries in 2015 (AUS, BGD, BTN, BRN, KHM, CHN, HKG, IND, IDN, JPN, LAO, MAC, MYS, MDV, MMR, NPL, NZL, PAK, PHL, KOR, SGP, LKA, TWN, THA and VNM). The country surveys performed at the end of each calendar year focus on the total number of ESRD patients, treatment modality, products, patient care structure and funding. This report is the summary of 2005-2015.

Results: The total population in the survey comprised 3,916 million people which are more than 50% of world population in 2015. During the period numbers of ESRD and dialysis patients have been doubled to about 1.35 million and 1.25 million, respectively, with similar annual growth rate (AGR) around 10%. The ESRD prevalence increased from 153 per million population (pmp, 2005) to 345 (pmp) and dialysis prevalence reached 319 from 136 (pmp). While the transplantation (Tx) rate is rather low about 26 pmp in 2015 (17 pmp, 2005) and AGR is 6%. The individual dialysis prevalence ranged from 307 to 3,210 pmp (versus 40-1,807pmp in 2005). TWN has the highest rate followed by JPN, KOR, MYS and SGP (over 1100 pmp). 83% patients have received hemodialysis, 9% peritoneal dialysis and 8% Tx in 2015. PD has grown fast and steadily in this region with AGR about 12%. THA, CHN and MYS have higher AGR (38%, 25%, 13%) driven by favored policy or professional advocacy. CAPD is the dominant regimen but APD has been gradually adopted (more common in HKG, KOR and SGP) with proportion of 12% PD patients in 2015.

Conclusions: The dialysis prevalence has been rising with the economic development and inclusion of dialysis into healthcare plans in AP over the last decade. The impact on healthcare burden will be significant given the large number of population in this region.

TH-PO1015

Association of Community Health Indicators with Late Nephrology Referral, Health Status and Subsequent Outcomes in Patients Reaching End-Stage Renal Disease Jung-Im Shin, Mari Palta, Brad C. Astor. *Univ of Wisconsin School of Medicine and Public Health.*

Background: Previous studies have focused on individual-level factors to identify patients reaching end-stage renal disease (ESRD) at higher risk of late nephrology referral. The relationship of environmental and socioeconomic conditions of communities in which patients live with late nephrology referral and subsequent clinical outcomes remains unclear. Such data are necessary to develop effective interventions.

Methods: We assessed the association of community health indicators with late nephrology referral (n=590,710), health status at the start of renal replacement therapy (i.e. hypoalbuminemia (n=455,063), inadequate management of anemia (n=539,712), and arteriovenous fistula (AVF)/catheter use (n=535,307)), and mortality after dialysis (n=393,255) using data from the United States Renal Data System in 2005-2012 merged with County Health Rankings database. Multivariable multilevel logistic and Cox proportional hazards regression models were used to assess the independent association of community risk factors with outcomes of interest, accounting for the clustering of individual patients within communities.

Results: A significant dose-response relationship of community risk score with late nephrology referral was found, with an adjusted odds ratio (OR) of 1.28 (95% confidence interval [CI]: 1.08-1.53) for the highest ($\geq 90^{th}$ percentile) vs. lowest-risk ($<10^{th}$ percentile) communities. Higher community risk score also was associated with hypoalbuminemia (adjusted OR =1.38; 95% CI: 1.20-1.58), inadequate management of anemia (1.23; 1.13-1.33), AVF use (0.76; 0.67-0.88), and catheter use (1.24; 1.09-1.41). Higher community risk also was associated with mortality following initiation of dialysis (adjusted hazard ratio=1.23; 95% CI: 1.17-1.28).

Conclusions: Higher community risk is significantly associated with greater risk of late nephrology referral, poorer health status and vascular access preparation at initiation of dialysis, and subsequent mortality, independent of individual-level factors. Community risk may be an important consideration for developing interventions to improve access to pre-ESRD nephrology care and subsequent clinical outcomes.

TH-PO1016

Improved Access to Pre-End Stage Renal Disease Nephrology Care among Beneficiaries of the Military Health System Evan I. Fisher,[1] Christina M. Yuan,[1] Lawrence Agodoa,[2] Kevin C. Abbott,[2] Robert Nee.[1] *[1]Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; [2]NIDDK, National Insts of Health, Bethesda, MD.*

Background: Pre-end stage renal disease (ESRD) nephrology care is associated with lower rates of morbidity and mortality. We hypothesized that patients in the Department of Defense's Military Health System (MHS), a model of an integrated universal healthcare enterprise in the US, would have better access to pre-ESRD nephrology care.

Methods: In this retrospective cohort study using the United States Renal Data System database, we identified 2,073,543 patients initiated on maintenance dialysis from January 2, 1995 through December 31, 2014, of whom 2,096 (0.1%) were MHS incident dialysis patients. We assessed care by a nephrologist and dietitian, erythropoietin use and type of vascular access upon dialysis initiation, based on the Centers for Medicare and Medicaid Services Form 2728. We also conducted multivariable logistic regression, adjusted for demographics and comorbid factors, using the individual pre-ESRD care components as the outcome variable.

Results: The proportions of MHS and non-MHS patients who were under the care of a nephrologist were 82.2% and 64.4%, respectively (p<0.001). 62.3% of MHS patients were under the care of a kidney dietitian versus 11.6% of non-MHS patients (p<0.001). 52.3% of MHS patients received erythropoietin pre-ESRD versus 29.4% of non-MHS patients (p<0.001). 29.0% of MHS patients used an arteriovenous fistula (AVF) on dialysis initiation versus 14.8% of non-MHS patients (p<0.001). On logistic regression analysis, MHS patients were significantly more likely to have had pre-ESRD nephrology care (adjusted odds ratio [aOR] 2.5; 95% confidence interval [CI] 2.0-3.0); pre-ESRD dietary care (aOR 13.9; 95% CI 11.8-16.3); pre-ESRD erythropoietin use (aOR 2.5; 95% CI 2.3-2.8); and AVF on dialysis initiation (aOR 2.2; 95% CI 1.8-2.6).

Conclusions: Compared to the broader ESRD population, MHS patients have greater access to pre-ESRD nephrology care which may improve morbidity and mortality.

TH-PO1017

Decisions about and Use of Renal Replacement Therapy in the U.S. Department of Veterans Affairs, 2000-2011 Susan P.Y. Wong,[1] Paul L. Hebert,[2] Chuan-Fen Liu,[2] Nilka Rios Burrows,[3] Ann M. O'Hare.[2] *[1]Univ of Washington; [2]VA Puget Sound Health System; [3]Centers for Disease Control and Prevention.*

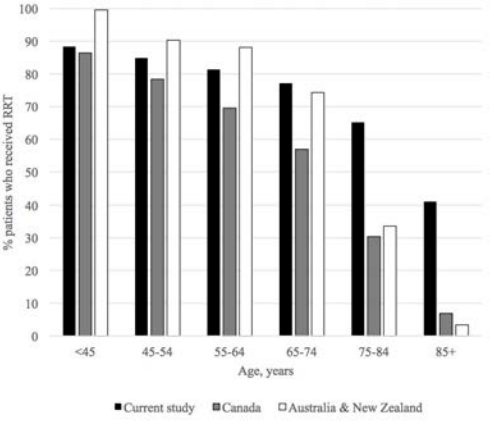
Background: It is not known what proportion of US patients with advanced chronic kidney disease (CKD) do not receive renal replacement therapy (RRT). In other developed countries, receipt of RRT is highly age-dependent and is the exception rather than the rule at older ages.

Methods: We conducted a retrospective study of a national cohort of 28,568 adults who had a sustained estimated glomerular filtration rate <15 ml/min/1.73m^2 between January 1, 2000 and December 31, 2009 and were receiving care within the Department of Veterans Affairs (VA). We used linked administrative data from the US Renal Data System, VA and Medicare to identify cohort members who received RRT (n=19,165). For a random 25% sample of the remaining 9,403 patients, we performed an in-depth review of clinical progress notes in the VA-wide electronic medical record to understand their clinical course.

Results: Two-thirds (67.1%) of cohort members received RRT based on administrative records. Based on the results of chart review, we estimate that an additional 7.5% (95% CI 7.2-7.8) of cohort members had in fact received dialysis, 10.9% (95% CI 10.6-11.3) were preparing for or discussing dialysis but had not started dialysis at most recent follow-up and, in 14.5% (95% CI 14.1-14.9), a decision had been made not to pursue dialysis. The percentage of cohort members who received or were preparing to receive RRT ranged from 96.2% (95% CI 94.4-97.4) for those <45 years to 53.3% (95% CI 50.7-55.9) for those aged ≥85 years. Results were similar after stratification by level of comorbid burden.

Conclusions: In this large US cohort of patients with advanced CKD, the majority received or were preparing to receive RRT. These findings suggest more liberal use of RRT among older members of this cohort as compared with other developed countries.

Figure. RRT uptake among patients with advanced CKD.



Funding: VA Support, Private Foundation Support

TH-PO1018

Developing a Set of Core Outcomes for Trials in Hemodialysis - An International Delphi Survey Nicole Evangelidis,[1] Allison Tong,[1] Braden J. Manns,[2] Brenda Hemmelgarn,[2] David C. Wheeler,[3] Tess Harris,[4] Wim Van Biesen,[5] Wolfgang C. Winkelmayer,[6] Jonathan C. Craig.[1] *[1]Univ of Sydney; [2]Univ of Calgary; [3]Univ College London; [4]PKD International; [5]Ghent Univ Hospital; [6]Baylor College of Medicine.*

Background: Survival and quality of life for patients on hemodialysis (HD) remain poor despite substantial research efforts. Existing trials often report surrogate outcomes that may not be relevant to patients and clinicians. The purpose of this study is to generate a consensus-based, prioritized list of core outcomes for trials in HD. A core outcome set that reflects stakeholder priorities would improve the relevance, efficiency, and comparability of HD trials.

Methods: In an online Delphi survey, participants rated the importance of outcomes using a 9-point Likert scale. In Round 2 and 3, participants reviewed the scores and comments of other respondents and re-rated the outcomes. For each outcome, we calculated the median, mean, and proportion rating 7-9 (critically important).

Results: 1,181 participants (202 [17%] patients/caregivers, 979 health professionals) from 73 countries completed Round 1 and 838 (150 [18%] patients/caregivers) completed Round 3 (71% response rate). Outcomes achieving consensus as high priorities across both groups were: vascular access complications, cardiovascular disease (CVD), mortality, dialysis adequacy and fatigue. Patients/caregivers rated four outcomes higher than health professionals: ability to travel (mean difference 0.9), dialysis-free time (0.5), dialysis adequacy (0.3), and washed out after dialysis (0.2). Health professionals rated 11 outcomes higher: mortality (1.0), hospitalisation (1.0), drop in blood pressure (1.0), vascular access complications (0.9), depression (0.9), CVD (0.8), target weight (0.7), infection (0.4), potassium (0.4), ability to work (0.3), and pain (0.3).

Conclusions: The top stakeholder prioritized outcomes were vascular access problems, CVD, mortality, dialysis adequacy and fatigue. Patients/caregivers gave higher priority to lifestyle-related outcomes than health professionals. This prioritized set of outcomes can inform the establishment of a core outcome set, to improve the value of trial evidence to support decision-making for people on HD.

Funding: Government Support - Non-U.S.

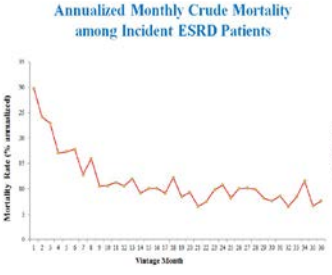
TH-PO1019

Pre-ESRD (Prelude) eGFR and the Relationship to Post-ESRD Mortality Outcomes among the Kaiser Permanente Southern California (KPSC) CKD Cohort John J. Sim,[1] Hui Zhou,[1] Jiaxiao Shi,[1] David K. Yi,[1] Shayna L. Henry,[1] Sally F. Shaw,[1] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh,[3] Steven J. Jacobsen.[1] *[1]Nephrology & HTN / Research and Evaluations, Kaiser Permanente Southern California; [2]Univ of Tennessee Health Science; [3]Univ of California Irvine Medical Center.*

Background: The eGFR values prior to transition to ESRD may provide insights on indications for starting renal replacement and also prognosticate early mortality after ESRD transition. We sought to evaluate the post ESRD mortality outcomes among a large diverse CKD population based on prelude eGFR values.

Methods: A retrospective cohort study over 13 years (1/1/2002-12/31/2014) within the KPSC health system of all incident CKD patients (eGFR<45 using serial measurments) who transitioned to ESRD [hemodialysis (HD), peritoneal dialysis (PD), or kidney transplant (TX)]. Post ESRD mortality outcomes were determined relative to the first outpatient ESRD treatment as the index date.

Results: A total of 5,476 CKD patients transitioned to ESRD (86% HD, 13% PD, 1% TX). Mean age 63yrs with 59% males. DM (53%) and HTN (19%) were most common ESRD causes. Prelude (pre-ESRD) eGFR was >15ml/min in 19% of the cohort at transition. This group had the highest rate of cardiac events, acute kidney injury (84%), and inpatient ESRD starts but the lowest fistula rates (16 vs 34%). This group also had the highest pre-emptive TX (1.9 vs 0.5%). Post transition mortality was highest immediately upon transition to ESRD and rates declined and stabilized around month 9 (Figure 1). The prelude eGFR groups >20 and 16-20 had the highest rate of mortality up to 1 yr compared to prelude eGFR <15 ml/min.



Conclusions: Among a CKD cohort who transitioned to ESRD, patients with a prelude eGFR >15 experienced the highest short term mortality. This subgroup is a potential area of focus in terms of CKD management strategies which may or may not include transition to ESRD.

Funding: NIDDK Support

TH-PO1020

Improved Early Survival Rates among Patients Initiated on Maintenance Dialysis in the Military Health System Robert Nee,[1] Evan I. Fisher,[1] Christina M. Yuan,[1] Lawrence Agodoa,[2] Kevin C. Abbott.[2] *[1]Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; [2]NIDDK, National Insts of Health, Bethesda, MD.*

Background: Previous reports have indicated increased mortality in the early period after initiation of maintenance dialysis in the general end stage renal disease (ESRD) population. We hypothesized that ESRD patients in the Department of Defense's Military Health System (MHS), a model of an integrated universal healthcare enterprise in the US, would have better survival rates during this early high-risk period.

Methods: In this retrospective cohort study using the United States Renal Data System database, we identified 2,073,543 patients initiated on maintenance dialysis from January 2, 1995 through December 31, 2014, of whom 2,096 (0.1%) were MHS incident dialysis patients. We conducted Cox regression analyses by sequential multivariable adjustment with all-cause mortality as the outcome variable. Covariates include demographic and clinical characteristics and other co-morbid conditions from the Medical Evidence Form 2728.

Results: MHS patients had significantly lower mortality rate compared to non-MHS patients during the first 12 months of dialysis initiation (17 vs. 26 per 100 patient-years [PY], respectively; p<0.001). Mortality rates peaked from the 4th to 8th week for both MHS and non-MHS patients (25 vs. 40 per 100 PY, respectively). The basic Cox model showed significantly lower death rates among MHS vs. non-MHS patients at 3 months (adjusted hazard ratio [AHR] 0.64; 95% confidence interval [CI] 0.52-0.79) and at 6 months (AHR 0.62; 95% CI 0.53-0.73). However, these differences in mortality rates were nonsignificant after further adjustment for pre-ESRD nephrology care and type of dialysis vascular access, becoming significant only at 12 months (AHR 0.79; 95% CI 0.64-0.98).

Conclusions: Compared to the broader ESRD population, MHS patients had better survival rates during the first 12 months after starting maintenance dialysis, likely due to improved access to predialysis care. Mortality was highest at week 4 to 8 for both cohorts but attenuated among MHS patients.

TH-PO1021

Co-Morbid Conditions of Incident Dialysis Patients Rita L. McGill, Eduardo K. Lacson, Robin Ruthazer, Klemens B. Meyer, D. Miskulin, Daniel E. Weiner. *Nephrology, Tufts Medical Center, Boston, MA.*

Background: US dialysis patient survival has improved. From 2004-2013, adjusted USRDS patient mortality fell by 22% for hemodialysis (HD) and 34% for peritoneal dialysis (PD). We examined trends in the comorbid diagnoses for incident patients, 2005-2011.

Methods: Cohorts of incident HD and PD patients with 2 years of prior Medicare were constructed for each 1-year period, so claims could be used to determine comorbid diagnoses present before dialysis initiation. Time trends in the proportions of each co-morbid condition were evaluated with logistic regression, with odds ratio (OR) >1 representing an increased frequency over the seven year period. Overall proportions of each diagnosis were compared between HD and PD patients using chi-square.

Results: 265,900 HD patients and 12,268 PD patients were assessed in 7 HD and 7 PD cohorts. Median age was 74 (IQR: 67,80) for HD and 72 (IQR: 67, 78) for PD. For each diagnosis, the percentage of affected patients was greater for HD than PD patients (P<0.001 for all).

Overall Prevalences and Odds Ratios for Trend over Seven Years for Each Comorbid Condition

	Hemodialysis			Overall Prevalence		Peritoneal Dialysis		
	Odds Ratio	95% CI	*P*	HD	PD	Odds Ratio	95% CI	*P*
Cardiac Disease	0.94	0.91, 0.97	0.007	62	53	0.98	0.84, 1.15	0.8
Diabetes	1.09	1.05, 1.13	<0.001	57	52	0.96	0.82, 1.13	0.6
Peripheral vascular disease	0.98	0.94, 1.02	0.3	26	20	0.94	0.77, 1.14	0.5
Chronic lung disease	1.03	0.99, 1.07	0.2	22	16	1.02	0.82, 1.26	0.9
Stroke	1.08	1.02, 1.14	0.004	13	9	1.34	1.02, 1.76	0.04
Cancer	1.06	1.00, 1.13	0.06	10	8	0.98	0.74, 1.30	0.9
Gastrointestinal (GI) bleeding	0.87	0.80, 0.94	<0.001	4	2	1.02	0.60, 1.74	0.9
Liver disease	1.35	1.22, 1.50	<0.001	4	2	1.21	0.69, 2.13	0.5
No comorbid diagnoses	1.03	0.98, 1.07	0.3	17	22	0.98	0.81, 1.18	0.8

Time trends in HD revealed small decreases in cardiac disease and GI bleeding, and increases in diabetes, liver disease and stroke; PD patients had increased stroke.

Conclusions: The large improvements in dialysis patient survival cannot be explained by the observed trends in the case-mix variables of incident patients. PD patients may have less pre-existing comorbid disease at dialysis initiation.

TH-PO1022

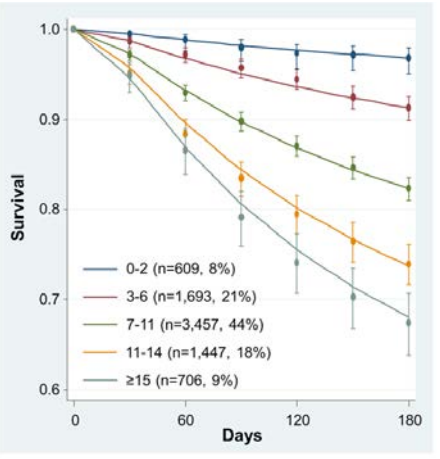
A Novel Comorbidity Score for Predicting Early Mortality upon Transition to ESRD among Incident Dialysis Patients Yoshitsugu Obi,[1] Elani Streja,[1] Connie Rhee,[1] Melissa Soohoo,[1] John J. Sim,[2] Csaba P. Kovesdy,[3] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Kaiser Permanente SC; [3]Univ of Tenn.*

Background: Mortality is exceptionally high during the first 6 months after transition to dialysis therapy. Development of a new comorbidity score for predicting early mortality by using pre-ESRD conditions may have important clinical and epidemiological implications.

Methods: In a nationwide cohort of 28,100 US veterans who transitioned to dialysis therapy between Oct 2007–Sep 2010, we derived a new comorbidity score comprised of primary ESRD causes and 16 comorbid conditions prior to ESRD by using a Cox model with adjustment for demographics(Full model). We evaluated the model fitness, discrimination, and calibration using 5 groups of the new comorbidity score (Score model), and then validated the model among those 7,912 who transitioned to dialysis Oct 2010–Sep 2011.

Results: The median comorbidity score was 9 (IQR, 6–12), ranging from 0 to 30. Compared to the middle risk group, adjusted HR(95%CI) for 6-month mortality in the lowest and highest risk groups were 0.37 (0.30–0.44) and 1.96 (1.81–2.12), respectively. C-index and adjusted R_D^2 were 0.69 and 0.20 in the Full model and 0.68 and 0.19 in the Score model, respectively. The difference in Akaike's information criterion was <0.01% between models. In the validation cohort, we observed consistent findings and also confirmed a good calibration by comparing predicted survival probability versus observed Kaplan-Meier estimates. Compared to Charlson comorbidity index, the new score appeared to have higher C-index (0.70 vs. 0.68) and adjusted R_D^2 (0.21 vs. 0.19).

Primary cause of ESRD	
Diabetic Nephropahty	2
Hypertension	3
GN/PKD	0 (Ref)
Others	6
Comorbidities	
Diabetes as non-primary cause of ESRD	0
Myocardial infarction	2
Congestive heart failure	5
PVD	0
CVA/TIA	1
Dementia	3
Paraplegia/Hemiplegia	3
COPD	2
Connective tissue dis.	0
Peptic ulcer	1
Liver disease	
Mild	1
Moderate/Severe	9
Cancer	
w/o metastasis	1
with metastasis	4
AIDS/HIV	5



Conclusions: The new pre-ESRD comorbidity score would provide important clinical information for patients transitioning to dialysis given a high predictive ability of early mortality among incident dialysis patients. It may also be useful for decision algorithms and comparisons in future early mortality analyses.

Funding: NIDDK Support

TH-PO1023

Long Term Survival in End Stage Renal Disease Patients Compared to General Population on a General Intensive Care Unit Ingi Elsayed. *Renal Dept, Sheffield Teaching Hospitals, United Kingdom.*

Background: Prevalence of chronic kidney disease (CKD) worldwide is increasing. UK Renal Registry reported an incidence rate of 109 per million population (pmp) of end stage renal disease (ESRD) in 2013. Mortality is higher in ESRD patients compared to general population. 1.3% of admissions to adult ICUs in UK between 1995 & 2004 were ESRD patients. Knowledge of long term mortality rates in this group of patients remains deficient. We sought to quantify long term outcomes of ESRD patients admitted to our ICU.

Methods: We retrospectively analysed prospectively collected data from all adult (>18 years) patients admitted to our 44-bed general ICU between Oct 2008-Oct 2013. ESRD patients were identified from renal database, as requiring long term renal replacement therapy prior to ICU admission. Patients were followed up for maximum of 6.25 years from admission to ICU. We used cox-regression analysis to examine survival and adjust for possible confounders.

Results: Study population comprised 132 ESRD & 3534 general patients admitted to ICU. 58% were male, median age 62 years (IQR 50-74), median APACHE II score 17 (IQR 12-22). 116 (82%) of ESRD patients survived to ICU discharge. Unadjusted Kaplan-Meier survival showed that long term mortality was significantly higher among patients with ESRD compared to general ICU patients (p=.00). There was no statistically significant difference in long term mortality between ESRD & general ICU patients (p=0.590, 95%CI: 0.753-1.175); when adjusting for age & APACHE II scores; using Cox-regression analysis. Age and APACHE II scores were independently associated with worse long term mortality (HR: 1.01, 95%CI 1.01-1.02, p=0.00 and HR: 1.07, 95% CI 1.06-1.08, p=0.00; respectively).

Conclusions: Our cohort suggests that significant proportion of ESRD patients admitted to ICU survive to unit discharge. In our cohort long term mortality was not different among ESRD compared to general ICU patients. This reflects improved mortality among ESRD patients over the years including those requiring higher intensity level of care. Our data can be useful in preoperative risk stratification.

TH-PO1024

Prognosis and Related Risk Factors of ANCA-Associated Vasculitis Patients on Maintaining Dialysis Fei Han, Xishao Xie, Ying Xu, Jianghua Chen. *Kidney Disease Center, First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China.*

Background: We retrospectively analyzed the prognosis and related risk factors for ANCA-associated vasculitis (AAV) patients on maintaining hemodialysis or peritoneal dialysis.

Methods: AAV patients on maintaining peritoneal dialysis (PD) or hemodialysis (HD) treated in our center from June 2007 to June 2015 were included, and their data were retrospectively compared and analyzed by Kaplan-Meier analysis and Cox regression model to know their survival rate and the risk factors.

Results: A total of 123 cases were included, with an average duration of dialysis for 1005 ± 739 days, and with 88 cases (71.5%) on HD and 35 cases (28.5%) on PD. Seventy-one patients (57.7%) were under the age of 65 years old and 52 patients (42.3%) were more than 65 years old. At the median follow-up time of 36 months, 39 patients (31.7%) were died. The main causes of death were cardiovascular events (30.8%) and infection (23.1%). COX regression analysis showed that patients older than 65 years old, with cardiovascular disease or interstitial pneumonia at the disease onset were independent risk factors affecting survival.

Conclusions: The factors including age older than 65 years, pre-dialysis cardiovascular disease and interstitial pneumonia were independent risk factors affecting survival of AAV patients on maintaining dialysis, and infections and cardiovascular events were the main causes of death.

Funding: Government Support - Non-U.S.

TH-PO1025

Epidemiology and Outcome of Acute Pancreatitis in End-Stage Renal Disease Dialysis Patients: A 10-Year National Cohort Study Chih-Chiang Chien. *Dept of Nephrology, Chi-Mei Medical Center, Tainan, Taiwan.*

Background: To determine the incidence and severity of acute pancreatitis (AP) in end-stage renal disease (ESRD) patient on dialysis and whether the dialysis modality [hemodialysis (HD) vs. peritoneal dialysis (PD)] confers a higher risk for AP as well as complications or mortality related to AP.

Methods: We analyzed data from the Taiwan National Health Insurance Research Database and included 67,078 ESRD patients who initiated dialysis between 1999 and 2007. The follow-up period was from the start of dialysis to death, end of dialysis, or December 31, 2008.Cox proportional hazards models were used to identify the related risk factors.

Results: The cumulative incidence rates of AP were 0.6%, 1.7%, 2.6%, 3.4%, and 4% at 1-, 3-, 5-, 7- and 9-year, respectively. The incidence of AP was 5.11 per 1,000-person years for those on HD and 5.86 per 1,000-person years for those on PD. Independent risk factors for AP on ESRD patient were elderly, being female, biliary stone, liver disease and on PD. Severe AP occurred in 44.9% of HD patients and in 36% of PD patients. Patients with AP on HD had a higher incidence of upper gastrointestinal (UGI) bleeding than did those on PD (p=0.002). In contrast, patients with AP on PD had a higher incidence of total parenteral nutrition (TPN) use than did those on HD (p=0.072).The overall in-hospital mortality was 8.1%. Furthermore, mortality after AP was associated with male gender, increasing age, severity of AP, and the presence of DM or liver disease.

Conclusions: Patient on PD had a higher risk than patient on HD for AP attack. UGI bleeding more commonly occurred in HD patients and TPN use was more common in PD patients.

TH-PO1026

Survival Outcomes of Children Starting Renal Replacement Therapy in the Second Year of Life Akira Ashida,[1] Mayumi Sako,[2] Eisuke Inoue,[2] Daishi Hirano,[3] Masataka Honda,[4] Shori Takahashi,[5] Motoshi Hattori.[6] *[1]Osaka Medical College, Osaka, Japan; [2]National Center for Child Health and Development, Tokyo, Japan; [3]The Jikei Univ School of Medicine, Tokyo, Japan; [4]Tokyo Metropolitan Children's Medical Center, Tokyo, Japan; [5]Nihon Univ School of Medicine, Tokyo, Japan; [6]Tokyo Women's Medical Univ, Tokyo, Japan.*

Background: Renal replacement therapy (RRT) for children with end-stage renal disease (ESRD) has been used for several decades; however, survival data for small children who start RRT are limited.

Methods: The Japanese Society for Pediatric Nephrology (JSPN) performed a cross-sectional, nationwide survey of Japanese patients aged less than 20 years who were newly diagnosed as having ESRD. This survey started in 2012 (Clin Exp Nephrol 19:933, 2015) and collected information every 3 years. The present study was performed using data from the JSPN survey database from January 1 2006 to December 31 2013, and examined survival outcomes of children starting RRT in the second years of life.

Results: A total of 152 patients who had been younger than 2 years of age at the start of RRT were identified. Among them, 112 patients had started RRT at 0 to 1 years of age; 52.0% were boys, and 88.8% had started with peritoneal dialysis. ESRD was mostly caused by congenital anomalies of the kidney and urinary tract (42.7%), followed by congenital nephrotic syndrome (12.5%) and cystic kidney disease (9.2%). A total of 21 deaths occurred during 520.7 patient-years (py), equivalent to a mortality rate of 40.3 deaths per 1000 py. The main known cause of death was infection (33.3%). The overall survival rate at 5 years was 81.0% (95% confidence interval (CI) 73.2-89.2%). The 5-year survival rates in the 0-1 year, and 1-2 year age groups were 76.8% (95%CI 67.7-87.0%) and 94.9% (95%CI 88.3-100%), respectively. Mortality was higher in children aged 0-1 year (49.1 deaths per 1000 py) than in children aged 1-2 years (14.9 deaths per 1000 py).

Conclusions: The present study indicates that the survival rate in children aged less than 1 year was poor. Specific therapeutic challenges continue to exist for children with ESRD aged less than 1 year who undergo RRT.

TH-PO1027

Racial/Ethnic Variations in Mortality Rates for End-Stage Renal Disease (ESRD) Patients Treated in U.S. Territories Compared to U.S. 50 States Keith C. Norris,[1] Guofen Yan,[2] Wei Yu,[2] Lawrence Agodoa.[3] *[1]UCLA; [2]Univ of Virginia; [3]NIH-NIDDK, Bethesda, MD.*

Background: Health outcomes for racial/ethnic minorities with ESRD treated in US territories may differ from patients treated in the US 50 states.

Methods: Using USRDS we examined 1,547,438 patients ≥18 years, with no prior transplantation and first dialysis between 4/1/1995 and 9/28/2012. Hazard ratios (HR) for death were calculated from the date of first ESRD treatment to 9/30/2012, censored at transplant. Adjustments included **Model 1**: demographics, yr of dialysis initiation, cause of ESRD, insurance and eGFR at ESRD onset; **Model 2**: Model 1 with addition of comorbidities and dialysis modality.

Results: Of 22,828 dialysis patients treated in territories (American Samoa, Guam, Puerto Rico, Virgin Islands), 321 were white, 666 black, 20,299 Hispanic, and 1,542 Asian. Of 1,524,610 US 50 states patients, 838,736 were white, 444,066 black, 182,994 Hispanic, and 58,814 Asian. After adjustments, the risk for death for white dialysis patients in the territories was 25% lower than US 50 states, but did not differ for black patients. Hispanic and Asian patients in the territories had 61% and 95% greater risk for death (Table). Using matched subcohorts significantly affected only whites, likely due to large differences in age; final HR 0.96 (p=0.72).

	Model 1		Model 2	
	HR for Territories vs. 50 States (95% CI)	P value	HR for Territories vs. 50 States (95% CI)	P value
White	0.69 (0.60-0.79)	<0.001	0.75 (0.65-0.86)	<0.001
Black	1.05 (0.96-1.16)	0.296	1.04 (0.94-1.15)	0.446
Hispanic	1.63 (1.60-1.66)	<0.001	1.61 (1.58-1.63)	<0.001
Asian	1.93 (1.81-2.06)	<0.001	1.95 (1.82-2.08)	<0.001

Conclusions: Mortality rates for ESRD patients in the US territories differ substantially by race/ethnicity compared to 50 US States. After matching, mortality risk did not differ for whites or blacks, but remained greater for Hispanics and Asians. A better understanding of these differences could lead to important health policy recommendations.

Funding: NIDDK Support

TH-PO1028

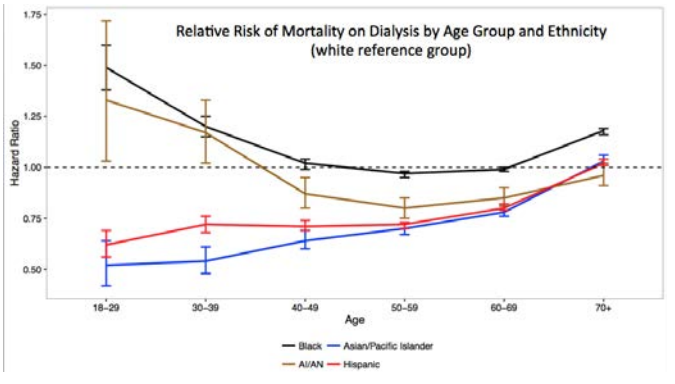
Ethnicity and Survival of Patients with End-Stage Renal Disease on Dialysis

Abdulkareem Agunbiade, Abhijit Dasgupta, Mohammed R. Chowdhury, Michael M. Ward. *NIAMS, NIH, Bethesda, MD.*

Background: End-stage renal disease disproportionately affects ethnic minorities, particularly blacks and Hispanics. Minorities have longer survival on dialysis than whites, but the reasons are unclear. Differences in rates of renal transplantation partially account for the survival difference, but differences in the rate of discontinuation of dialysis have not been explored as a contributor. We examined if ethnic differences in the rate of elective discontinuation from dialysis and in transplantation account for the survival advantage of ethnic minorities on dialysis.

Methods: We conducted a retrospective cohort study of the United States Renal Data System from 2003 and 2014, which included 1,131,409 adults with incident ESRD. We performed a multivariate survival analysis with two competing risks. Our primary independent variable was ethnicity (white, black, Hispanic, Asian, and American Indian/Alaska Native). The outcome was survival on dialysis.

Results: Both transplantation and discontinuation of dialysis were more common among whites than blacks and Hispanics. In multivariate survival models with two competing risks, mortality risks were higher for blacks compared to whites in those age 18-29 years (subdistribution hazard ratio 1.49, 95% CI [1.38, 1.60]), 30-39 years (1.20 [1.15, 1.25]), and 70 years and older (1.18 [1.16, 1.19]), while risks were similar in middle-age. American Indians/Alaska Natives also had higher mortality risks than whites among patients age 18-29 and 30-39 years. Hispanics and Asians had lower mortality risks than whites in all but those age 70 years and older.



Conclusions: Blacks with ESRD have no survival advantage on dialysis compared to whites after accounting for ethnic differences in renal transplantation and elective discontinuation of dialysis. Hispanics and Asians have lower risk of mortality on dialysis than whites among patients younger than 70 years.

Funding: Other NIH Support - NIH Medical Research Scholars Program

TH-PO1029

Impact of Race and HCV Co-Infection on HIV+ Dialysis Patient Survival

Deirdre L. Sawinski,[1] Jayme E. Locke,[2] Jordana B. Cohen,[1] Kimberly Autumn Forde,[3] Peter P. Reese.[1] *[1]Renal Medicine, Univ of Pennsylvania, Philadelphia, PA; [2]Surgery, Univ of Alabama at Birmingham, Birmingham, AL; [3]Gastroenterology, Univ of Pennsylvania, Philadelphia, PA.*

Background: Historically HIV+ dialysis patient survival has been inferior to HIV- patients. The effect of antiretroviral therapy on dialysis survival in the modern era is unknown. Since the removal of HIV as a comorbidity from the CMS 2728 form in 2005 it has been impossible to study outcomes for HIV+ dialysis patients using national registry data.

Methods: We obtained data from a national dialysis provider (Davita). Using home medications and laboratory data we identified 5356 HIV+ and 1864 HIV+/HCV+ patients who were compared to 411,363 HIV-/HCV- patients dialyzed from 2004-2014. Survival on dialysis was modeled using cox regression.

Results: HIV+ patients were younger (median age 46), more often male (67%) and black (74%). We found effect modification by race (p<0.001). In a model stratified by race accounting for age, sex, diabetes, dialysis exposure and modality, white HIV+ patient survival was similar to HIV-/HCV- (HR 1.05, 0.93-1.19) but non-white HIV patients had increased risk of death (HR 1.50, 1.42-1.58). HIV+/HCV+ patients had an increased risk of death regardless of race (white HR 1.59, 1.26-2.00; non-white HR 1.72, 1.62-1.87).

	White			Non-white		
	HR	p value	95% CI	HR	p value	95% CI
HIV-/HCV-	ref			ref		
HIV+	1.05	0.40	0.93-1.19	1.50	<0.001	1.42-1.58
HIV+/HCV+	1.59	<0.001	1.26-2.00	1.72	<0.001	1.62-1.87
Age (cont)	1.03	<0.001	1.03-1.03	1.04		
Male	1.04	<0.001	1.02-1.05	0.98	0.07	0.96-1.00
Diabetes	1.16	<0.001	1.14-1.17	1.14	<0.001	1.11-1.14
PreDavita dialysis exposure	1.30	<0.001	1.27-1.32	1.28	<0.001	1.25-1.31
PreDavita dialysis in years	0.99	0.004	0.99-0.99	1.01	<0.001	1.01-1.02
Hemodialysis	ref			ref		
Peritoneal dialysis	0.74	<0.001	0.72-0.77	0.81	<0.001	0.78-0.84

Conclusions: Race is an important modifier of survival on dialysis for HIV+ patients, but co-infection with HCV also contributes to increased mortality for that group.

TH-PO1030

The Impact of Gender on Prescription and Use of Vascular Access in Elderly Patients on Hemodialysis: A European Hemodialysis Multicenter Analysis

Andre L. Weigert,[1] Stefan H. Jacobson,[2,3] Werner Kleophas,[4] Mahesh Krishnan,[5] Abdulkareem Alsuwaida,[6] Fatima Ferreira Silva,[1] Maciej B. Drozdz.[7] *[1]DaVita, Portugal; [2]Karolinska Inst, Stockholm, Sweden; [3]DaVita, Europe; [4]DaVita, Germany; [5]DaVita Inc; [6]DaVita, Saudi Arabia; [7]DaVita, Poland.*

Background: The elderly constitute a substantial and growing fraction of the end stage renal disease population. Elderly patients on hemodialysis are a heterogeneous group with a high prevalence of comorbidities that reduce life expectancy. Although women have a survival advantage in the general population, women on hemodialysis do not survive longer than men.

Methods: In this analysis we included 1,247 patients on maintenance hemodialysis from Portugal (n=730) and Poland (n= 517) and focused on treatment prescription, use of vascular access and achievement of KDIGO targets in women and men ≥80 years of age respectively.

Results: Elderly patients (≥80 years) on hemodialysis were prescribed lower Qb and shorter treatments, but despite this they achieved significantly higher Kt/V and significantly better control of phosphorus and PTH. The proportion of CVC's was significantly higher and AVF's lower in the elderly. Women ≥80 years had lower prevalence of AVF than men, but there were no differences in the prescription of hemodialysis in relation to gender in the elderly. Elderly women had a higher Kt/V and lower body weight than corresponding men. Mean arterial BP pre HD, Charlson comorbidity index and ESA doses were similar in relation to both age and gender.

	Age yrs	Vint months	Bw post	Kt/V	TT min	Hb g/dl	Ferrit ug/l	Alb g/l	Ca mg/dl	P mg/dl	iPTH pg/ml	Qb ml/min	Tx blood volume	CVC %	AVF %
<80 yrs	63	61	72	1.8	732	11	586	42	8.8	4.5	588	377	1.32	14	80
>80 yrs	84	60	65	1.9	717	10.8	669	38	8.9	3.8	478	368	1.38	26	68
p	***	*NS*	***	***	***	*	*	*NS*	*NS*	***	***	**	**	***	***
Male >80 yrs	84	59	67	1.8	715	10.9	487	38	8.8	3.8	464	370	1.25	24	69
Female >80 yrs	84	61	63	2.0	719	10.7	698	38	8.9	3.8	495	366	1.28	22	57
p	NS	NS	**	***	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*

t-test *=0.05, **=0.01, ***=0.001

Conclusions: This indicates that there are no or small differences in clinical practice in relation to gender in elderly patients on hemodialysis in Portugal and Poland.

Funding: Pharmaceutical Company Support - DaVita

TH-PO1031

Racial-Ethnic Disparities in Indices of Bone and Mineral Metabolism in the Pediatric Dialysis Population

Marciana Laster,[1] Melissa Soohoo,[2] Elani Streja,[2] Keith C. Norris,[1] Isidro B. Salusky,[1] Kamyar Kalantar-Zadeh.[2] *[1]UCLA; [2]UC Irvine.*

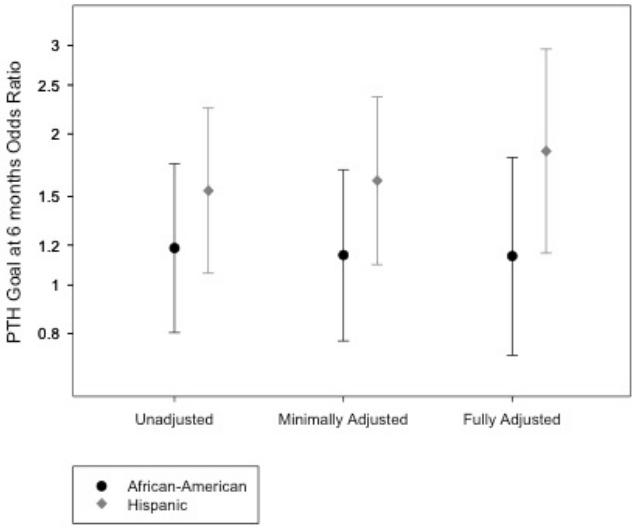
Background: Studies of healthy black adolescents show higher parathyroid hormone (PTH) and lower alkaline phosphatase (AP) levels when compared to white adolescents. Similarly, studies of adult dialysis patients have shown higher PTH in Black patients when compared to White patients. Little is known about racial-ethnic differences in markers of mineral bone metabolism (MBM) in the pediatric dialysis population.

Methods: In a pediatric dialysis population of 661 patients from a large dialysis organization, we explored racial-ethnic differences in MBM markers within the first 90 days after dialysis initiation. All lab values were provided from samples processed in a central laboratory. Using logistic regression, we explored the odds of reaching a PTH level between 200pg/ml to 600pg/ml by 6 months.

Results: Mean age of the cohort was 17±4 years of which 34% were White, 31% Black and 35% Hispanic. 68% of patients were treated with HD and 32% with PD. Black and Hispanic patients had significantly higher median PTH values than white patients. AP levels were lower in Black patients, while higher in Hispanic patients.

	White	Black	Hispanic	p
PTH (pg/ml)	368[203,584]	411[236,737]	471[277,779]	0.0048
S-Ca (mg/dl)	9.3±0.7	9.2±0.7	9.1±0.7	0.0008
S-P (mg/dl)	5.9±1.5	5.6±1.5	5.7±1.3	0.0937
AP (IU/L)	90.0[66.0,145.0]	82.0[64.7,115.3]	104.8[75.3,169.7]	<0.0001

In a model adjusted for baseline PTH, calcium, phosphorous, AP , binder type, 1,25$(OH)_2$D use, Cinacalcet use, modality, spKt/V and cause of ESRD, Hispanic ethnicity was associated with higher odds of meeting the PTH goal at 6 months (OR 1.85 [1.16, 2.95]).



Conclusions: Racial-ethnic differences in MBM exist in the pediatric dialysis population. Further studies are needed to evaluate how these differences affect the management of MBM in pediatric dialysis patients.

Funding: Other NIH Support - Ruth L. Kirschstein National Research Service Award

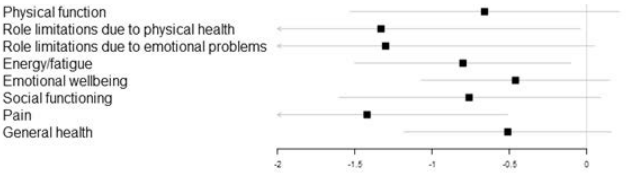
TH-PO1032

Thyroid Functional Disease, Quality of Life, and Mental Health in a Prospective Hemodialysis Cohort Connie Rhee,[1] Yanjun Chen,[1] Amy Seung You,[1] Csaba P. Kovesdy,[2] Steven M. Brunelli,[3] Gregory Brent,[4] Kamyar Kalantar-Zadeh,[1] Danh V. Nguyen.[1] *[1]UC Irvine; [2]Univ of Tennessee Health Science Center; [3]DaVita Inc; [4]UCLA.*

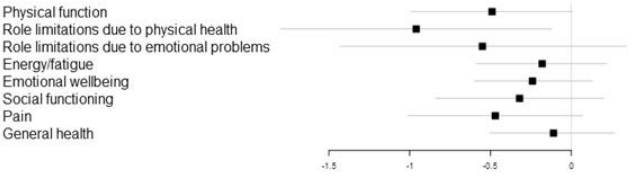
Background: In the general population there is increasing recognition of the impact of hypothyroidism on patient-centered outcomes such as health-related quality of life (HRQOL) and depression. While hypothyroidism is highly prevalent in hemodialysis (HD) patients, there has not been a prior study to determine if thyroid dysfunction is a risk factor for impaired HRQOL or mental health in this population.

Methods: Among 450 HD patients from the prospective *Malnutrition, Diet, and Racial Disparities in Kidney Disease* study, we examined the association of thyroid status defined by TSH with HRQOL and depressive symptoms over time. Patients were recruited from 17 HD facilities and underwent protocolized TSH testing and administration of Short-Form 36 (SF-36) surveys and Beck Depression Inventory-II (BDI-II) every 6 months over 2013-15. We examined the association of baseline and time-varying TSH with the 8 SF-36 domains as longitudinal outcomes using case-mix+laboratory adjusted linear mixed effects models. Analogous methods were used to examine baseline and time-varying TSH with BDI-II score.

Results: Higher baseline TSH levels (+Δ1mIU/L) were associated with lower (worse) scores across the SF-36 domains of role limitations due to physical health (β=-1.33, p=0.04), energy/fatigue (β =-0.80, p=0.03), and pain (β=-1.42 p=0.002). Higher time-varying TSH (+Δ1mIU/L) was associated with lower role limitations due to physical health scores (β=-0.96, p=0.03). Baseline and longitudinal TSH levels were not associated with BDI-II score.



Change in SF-36 domain score associated with +Δ1mIU/L higher baseline TSH



Change in SF-36 domain score associated with +Δ1mIU/L higher time-varying TSH

Conclusions: In HD patients higher TSH levels are associated with impaired HRQOL across domains of physical health, energy/fatigue, and pain. Future studies are needed to determine if thyroid-modulating therapy improves the HRQOL of hypothyroid HD patients.

Funding: NIDDK Support

TH-PO1033

Use of a Symptom-Reporting Survey in Renal Clinic Jeremy T. Moskovitch,[1,2] Peter F. Mount,[1,2] Matthew R.P. Davies.[1,2] *[1]Austin Health Nephrology Dept, Melbourne, Victoria, Australia; [2]Univ of Melbourne, Victoria, Australia.*

Background: Previous studies have reported a high prevalence of symptoms in dialysis patients. The POS-renal survey identifies the presence and severity of 17 symptoms in ESKD patients. Whether identification of symptoms with a survey leads to an improvement in symptoms has not been studied. Thus, the aims of this study are: To determine the prevalence and change in symptoms experienced by dialysis patients following introduction of a symptom-reporting survey in renal clinic, and to evaluate nephrologists' satisfaction with this survey.

Methods: This is a prospective observational study of 110 prevalent dialysis patients (HD and PD). POS renal surveys were collected at baseline and follow-up (median 3 months). Surveys were completed by patients and results were available to nephrologists at clinic appointments. An anonymous survey was distributed to nephrologists to determine satisfaction.

Results: Baseline prevalence of individual symptoms ranged from 17-66% (95%CI 11-26% and 57-75%). Most common symptoms were fatigue (66%) and trouble sleeping (55%).Median number of symptoms was 7/17 (IQR 4-10). 49% of patients rated at least one symptom as severe or overwhelming. On multivariate analysis PD was associated with an increased risk of vomiting and drowsiness. Restless leg syndrome was associated with diabetic nephropathy primary renal disease (OR 9, p<0.05). On average, an improvement in severity of individual symptoms identified at baseline was seen in 55% of patients (range 30-89%, 95%CI 18-46% and 67-98%). The symptoms which improved most commonly were GI symptoms (62-89%) and itch (60%). The percentage of patients rating at least one symptom as severe or overwhelming was reduced (p<0.05), but remained high at 39%. The median number of symptoms was unchanged at 7/17 (IQR 3-10). Overall, nephrologists found that the survey was useful for symptom identification, but were unsure if its use helped improve symptom management.

Conclusions: Use of the POS-renal survey in renal clinic identified a high symptom burden in dialysis patients, and may be associated with an improvement in symptom severity. However, overall symptom burden at follow-up remained high.

TH-PO1034

Subjective Symptoms and Feelings for Daily Lives Are Not so Deteriorated in Maintenance Dialysis Patients Compared with Non-Dialyzed General Population Ikuto Masakane, Minoru Ito. *Nephrology, Yabuki Hospital, Yamagata, Japan.*

Background: Quality of life of chronic dialysis patients are generally recognized to be severely deteriorated because of inevitable and endless dialysis sessions and uremia itself. However, there are fewer reports which directly compared QOL and subjective symptoms between dialysis patients (HD) and non-dialyzed general population (ND). We have evaluated the dialysis related subjective symptoms and QOL of chronic dialysis patients twice a year since 2005. We compared the subjective symptoms and feelings for daily lives between HD and ND.

Methods: 213 HD and 157 ND were enrolled into the study. The average age were 65 years old in HD and 66 years old in ND. The original assessment sheet for subjective symptoms and QOL for dialysis patients which is called "Patient-oriented Dialysis (POD sheet) were used for the current study. POD sheet contains 19 questions about dialysis related symptoms and feelings for daily lives. The 7 questions indicated only to HD such as "pain at cannulation", "intradialytic hypotension" and so on were not provided to ND.

Results: Skin itchiness and general fatigue were observed more often in HD than ND; 20.2% vs. 10.2% in itchiness, 17.8% vs. 8.3% in fatigue. A lack of satisfied feeling for daily life was also higher in HD than ND; 18.8% vs. 5.7%. However, irritation feeling was lower in HD than ND; 6.6% vs. 14.1%. Other subjective symptoms such as constipation, insomnia and depressive sense which were reported as to be closely related to dialysis were not different between 2 groups. The total POD score were not different between HD and ND; 13.0 vs, 11.1.

Conclusions: Overall subjective feelings evaluated by the total POD score were not so deteriorated in HD compared with ND in the current study. Skin itchiness and general fatigue were uniquely related to dialysis itself and they could be good markers to evaluate the dialysis quality. However, actual prevalence rate of skin itchiness and insomnia in HD were significantly lower in our facilities than that of the previous reports. We believe our dialysis prescription policy based on patient's symptoms could improve the QOL of chronic dialysis patients.

TH-PO1035

Analysis of Symptoms Suffered by Patients on Haemodialysis and Peritoneal Dialysis Hari Dukka, Madhavan S. Menon, Simon J. Davies, Dominic Detakats, Mark Lambie. *Renal, Univ Hospitals North Midlands, Stoke on Trent, United Kingdom.*

Background: Dialysis patients both on haemodialysis (HD) and peritoneal dialysis (PD) suffer from multitude of symptoms, irrespective of their clearances on dialysis. We analysed symptoms suffered by dialysis patients attending dialysis clinics prospectively.

Methods: A validated dialysis symptom index questionnaire published in the journal of pain and symptom management,modified to suit the local patient population has been used. The original questionnaire had 30 symptoms out of which 18 commonly complained symptoms were used. 123 patients answered the questionnaire before the doctor's consultation in the clinic. Parameters including age, co-morbidities and urea clearances were recorded.

Results: The mean age (Mean±SD) was 62±14 years.73% of the study group were patients on HD and remaining 27% were on PD. The top 5 symptoms among all patients were post dialysis tiredness (77.7%),joint and muscle pains (66.9%),feeling tired all the time (66.1%),itching (63.6%), breathlessness (61%).Among HD patients post dialysis tiredness (84.9%), joint and muscle pains (72.1%),feeling tired all the time (68.6%), muscle cramps (66.7%), itching (65.1%), were more common. In patients on PD, feeling tired all the time (59.4%), joint and muscle pains (59.4%), feeling low (59.4%) itching (59.4%), low appetite and breathlessness (54.5%) were more common. We did not find any correlation between the comorbid index, age or urea clearances and the number of symptoms complained. About 5 patients on PD and 12 on HD complained of uraemic symptoms defined as a combination of nausea, itching and loss of appetite, but had adequate urea clearances.

Conclusions: Dialysis patients complain of multitude of symptoms which may be unrelated to urea clearances, age or comorbid index. Thorough consultations and appropriate investigations should be conducted to identify different pathological processes which may be causing symptoms and possible solutions provided.

TH-PO1036

Patients on Dialysis following a Failed Renal Transplant Have Significantly Higher Levels of Depression as Identified by the Beck Depression Inventory and the Patient Health Questionnaire PHQ-9: The ASSERTID Study Michael K. Almond,[1] Karin Friedli,[2] Joseph Chilcot,[3] Andrew Davenport,[4] Ayman Guirguis,[2] Benjamin Spencer,[5] Ken Farrington.[2] *[1]Renal Unit, Southend Hospital, Essex, United Kingdom; [2]Centre for Life Sciences, Univ of Hertfordshire, Hatfield, Hertfordshire, United Kingdom; [3]Psychology Dept, Kings College, London, United Kingdom; [4]Centre for Nephrology, Royal Free Hospital, London, United Kingdom; [5]Psychiatry, Maudsley Hospital, London, United Kingdom.*

Background: The diagnosis of depression in the presence of End Stage Renal Failur, is difficult. There is evidence that depression affects the outcome (survival) of patients on haemodialysis. The impact of a previous failed renal transplant in this group is poorly documented.

Methods: 1110 haemodialysis patients from five UK centres were invited to take part in a screening programme for depression using the Beck Depression Inventory (BDI-II) and Patient Health Questionnaire – 9 (PHQ-9) and the results compared with social, demographic, physical and biological markers. The presence of a failed transplant was documented. 709 patients (64%) consented to screening.

Results: 114 of 709 patients (16.1%) had been transplanted. 699 patients completed the BDI and 702 the PHQ-9. A significant number of patients had a high BDI-II (≥ 16) and high PHQ-9 (≥ 10) (33% and 28% respectively). Patients with a failed transplant and now back on haemodialysis were more likely to score highly on both tools for depression than those never transplanted. Median BDI-II score in previously transplanted patients was 13.5 (IQR 20) and 10 (IQR 13) in the non-transplanted group (p = 0.022). Comparable scores for PHQ-9 were 8 (IQR 11) vs 5 (IQR 8) (p = 0.018). More patients with a failed transplant had a high BDI-II score (46% vs 31%: p = 0.002). The same was true for high PHQ-9 (40% vs 26%: p=0.001). A failed transplant was a significant predictor of high BDI-II (Odds Ratio 1.88: p= 0.035) and high PHQ-9 (Odds Ratio 1.97: p =0.026).

Conclusions: Depression is common in patients on dialysis. Having a failed transplant increases the likelihood of patients having high depression scores. Patients with a failing transplant likely to return to haemodialysis may benefit from intervention.

Funding: Government Support - Non-U.S.

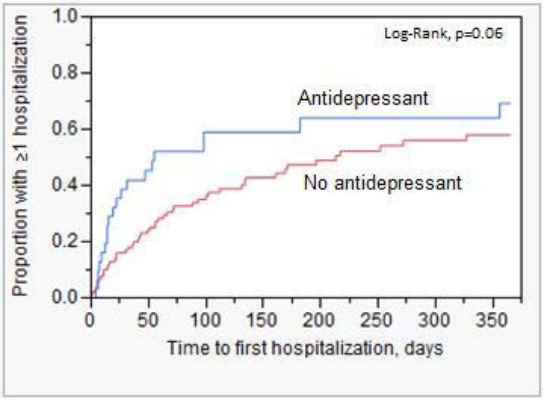
TH-PO1037

Young Adult Hemodialysis (HD) Patients: Antidepressant Use and Healthcare Utilization in the First Year Diana L. Vork,[1] Ziad El-Zoghby,[2] Robert C. Albright,[2] Sandra Herrmann,[2] Maria Lapid,[3] Terry D. Schneekloth,[3] LaTonya J. Hickson.[2] *[1]Mayo Medical School, Mayo Clinic; [2]Nephrology, Mayo Clinic; [3]Psychiatry, Mayo Clinic, Rochester, MN.*

Background: Despite having less comorbidity than older patients, young adult HD patients have high healthcare utilization. Depression and other psychosocial factors may contribute to this observation, and the relationship between antidepressant medication use and healthcare use in young adults has not been well described.

Methods: Retrospective cohort study of patients aged 18-44 years who initiated HD (01/2001-12/2013) and remained on dialysis ≥30 days at a single institution. Primary outcomes were hospitalization and ED visit rates within the 1st year of HD based on antidepressant use at baseline.

Results: Among 131 young adult HD patients, 31 (24%) were receiving ≥1 antidepressant for a mood indication at the time of HD initiation. The antidepressant group was more likely to have diabetes (61% vs. 32%), coronary artery disease (29% vs. 11%), heart failure (32% vs. 14%), and illegal drug use history (32% vs. 14%; all p<0.05). Time to 1st hospitalization was not different (Figure), but hospitalization rate was higher in the antidepressant group (0.0085 vs. 0.0035 per person days, p=0.003). This difference remained even when controlling for diabetes (p=0.01), coronary artery disease (p=0.01), heart failure (p=0.01), and illegal drug use history (p=0.03). Psychiatric hospitalizations were uncommon (1 event). ED visit rate was similar between groups (0.0022 vs. 0.0016 per person days, p=0.46).



Conclusions: Antidepressant use is common among young adult HD patients and is associated with a higher hospitalization rate during the 1st year compared to patients not on an antidepressant at initiation. Further studies may clarify the direct impact of depressed mood on healthcare use versus antidepressants as a marker of medical comorbidities.

TH-PO1038

Impact of Fluid Overload on Quality of Life in Haemodialysis Patients Carlos Adrián Chávez-Mendoza, Jose Luis Ortega Vargas, Olynka Vega, Ricardo Correa-Rotter. *Nephrology and Mineral Metabolism, National Medical Science and Nutrition Inst Salvador Zubiran, Mexico City, Mexico.*

Background: The overhydration (OH) in patients with end stage renal disease (ESRD) is associated with multiple outcomes. The aim of this study was to evaluate the effect of OH in quality of life (QoL) in Mexican prevalent chronic haemodialysis (HD) patients.

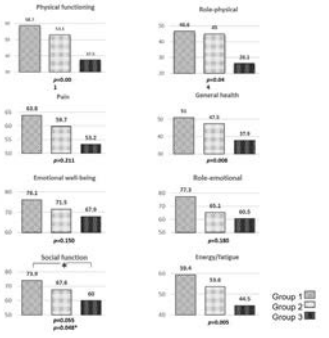
Methods: Observational comparative study that included 133 prevalent HD patients from 3 centers from Mexico City. Hydration status and body composition was assessed by bioimpedance spectroscopy employing BCM, Fresenius®. The degree of OH was defined by estimating the fluid overload/extracellular water (OH/ECW) index dividing the population into tertiles, being Group 1 with no OH and Group 3 with highest degree of OH. The cut off threshold for the definition of OH was set to 15% (OH/ECW index >0.15, Group 3). QoL was measured using KDQOL-36 instrument. Data analysis was carried out through descriptive and inferential statistics.

Results: General characteristics are shown in Table 1. No differences between groups were present in: age, Charlson index, time on dialysis, type of vascular access, and hospitalization days in the last year. Overhydrated HD patients had a higher prevalence of DM (p=0.02). The KDQOL-36 specific kidney disease composite summary was lower in Group 3 (p=0.01). The score of the group with the mayor overhydration was lower for all KDQOL-36 generic dimensions (Figure 1). The SF-12 physical and mental composite was lower in the subgroup with OH (Physical: 38.5, 38.1, and 33.7 (p=0.07), and, Mental: 52.4, 49.4, and 48.9 (p=0.3) in groups 1, 2 and 3 respectively).

Table 1. Differences between overhydrated and euvolemic patients in chronic HD

	Group 1	Group 2	Group 3	p
Age, years	51.7 ± 15.5	53.3 ± 17.8	53.7 ± 14.3	0.827
Sex (female), %	25 (40.9)	22 (36.1)	14 (22.9)	0.042
Diabetes Mellitus, %	18 (28.6)	16 (25.4)	28 (46)	0.018
Charlson index	4.5 ± 2.6	4.5 ± 2.6	5.1 ± 2.3	0.416
Body mass index, kg/ m²	26.5 ± 5.6	26.2 ± 4.7	24.4 ± 3.9	0.088
Interdialytic weight gain, mL/ kg	34.4 ± 15.3	33.3 ± 50.1	36.6 ± 15	0.890
Kt/V	1.4 ± 0.4	1.4 ± 0.3	1.4 ± 0.3	1.000
MAP predialysis, mmHg	100 ± 18.9	98.8 ± 21.1	101.6 ± 13.7	0.775
MAP postdialysis, mmHg	93.3 ± 14	96.5 ± 16.8	100.4 ± 13.1	0.077
OH/ECW	0.02 ± 0.04	0.11 ± 0.02	0.21 ± 0.05	<0.05
Lean tissue index [LTI], kg/ m²	14.7 ± 4.1	13.2 ± 3.4	13.5 ± 3.3	0.127
Fat tissue index [FTI], kg/ m²	12.1 ± 7.6	13 ± 6.7	10.3 ± 3.6	0.133
Body cell mas [BCM], kg	21.3 ± 8.9	18.9 ± 7.3	19.8 ± 7.1	0.351
Handgrip strength, kg	28.1 ± 9.9	27.9 ± 9.9	24.1 ± 8.8	0.237
Haemoglobin, mg/ dL	10.3 ± 1.3	10.1 ± 1.8	10 ± 1.7	0.737
Albumine, mg/ dL	3.6 ± 0.4	3.6 ± 0.3	3.5 ± 0.4	0.446
Cholesterol, mg/ dL	170.9 ± 35.7	159.5 ± 41.2	145.6 ± 39.7	0.025
Serum creatinine, mg/ dL	11.3 ± 3.8	10.6 ± 2.6	10.5 ± 2.6	0.394

Figure 1. Quality of life in chronic HD patients. KDQOL-36 generic dimensions (SF-36)



Conclusions: Quality of life is lower in patients with overhydration compared with euvolemic patients in HD. All dimensions that assess the components of SF-36 (generic) had lower scores in the subgroup patients with OH; not, in those specific dimensions of kidney disease.

TH-PO1039

The Association between Perceived Social and Family Support with Comorbidity and Clinical Outcome in Incident Hemodialysis Patients Seonghun Kim,[1] Su-Young Jung,[2] Ji Min Park,[1] Hyoungnae Kim,[2] Tae-Hyun Yoo.[1,2] *[1]Dept of Internal Medicine, College of Medicine, Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ, Seoul, Republic of Korea; [2]Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Republic of Korea.*

Background: The aim of this study was to investigate the association between the social and family support with charlson comorbidity index (MCCI) and mortality in dialysis patients.

Methods: A total 1,155 incident HD patients were prospectively enrolled in Clinical Research Center for End-Stage Renal Disease cohort from August 2008 to April 2013. The social support was assessed using by perceived support and family scale that are expressed by a range of scores from 1 to 4. The patients were categorized into three groups according to the summation of perceived social and family support; group 1, fully independent; group 2, partially dependent; group 3, fully dependent, respectively. The primary outcome was defined as all-cause mortality.

Results: The mean age was 58.5±14.4 years. Group 3 showed significantly higher MCCI (4.59±2.03 vs. 5.44±2.25 vs. 5.62±2.3, P=0.001) and lower mean arterial pressure (MAP, 103.82±16.6 vs. 99.66±14.7 vs. 97.59±14.80, P=0.007) compared to group 1 and 2. In multiple linear regression analysis, social and family support was closely related to MCCI (β=0.095, P=0.038) after adjustment for confounding factors. In multiple Cox analysis, group 3 revealed significantly higher all-cause mortality rate (HR, 3.28; 95% CI, 1.54-7.00; P=0.002) compared to group 1 even after adjustment for age, sex, education status, MCCI, serum albumin, Hb, and PTH levels.

Conclusions: The incident dialysis patients needed social and family support are significantly associated with high MCCI and low MAP, and associated with higher all-cause mortality.

TH-PO1040

Improvement of Quality of Life in Hemodialysis Patients with Uremic Pruritus as Measured by the Skindex-10 Questionnaire: Effect of a Novel κ Opioid Receptor Agonist, CR845 Vandana S. Mathur,[1] Robert H. Spencer,[2] Jiaan Illidge,[2] Joseph W. Stauffer,[2] Catherine Munera,[2] Frederique Menzaghi.[2] *[1]MathurConsulting, Woodside, CA; [2]Cara Therapeutics, Stamford, CT.*

Background: Uremic pruritus (UP) is a chronic systemic itching disorder frequently reported in hemodialysis (HD) patients, which causes suffering that negatively impacts quality of life (QOL). CR845 is a selective kappa opioid receptor agonist with combined anti-pruritic and anti-inflammatory effects. We aimed to examine the effects of itch reduction on QOL as measured by the Skindex-10 Questionnaire and its sensitivity to discriminate between CR845 and placebo in producing an improvement in QOL.

Methods: We evaluated intravenous CR845 (post-HD) in a double-blind, placebo-controlled trial in 65 HD patients with moderate-to-severe UP [i.e. ≥ 40 mm on a visual analog scale (VAS) of 0 mm (no itch) to 100 mm (worst imaginable itch)] for 2 weeks. Itch intensity (VAS) and QOL (Skindex-10, i.e., bothersomeness, emotional distress, and reduced social functioning due to itching) were recorded.

Results: 32 were randomized to placebo and 33 to CR845.Patients receiving CR845 (1 mcg/kg) had significant reductions in Skindex-10 score compared to those receiving placebo (p=0.031), demonstrating improvement in QOL. The mean change in the Skindex-10 score at week 2 correlated significantly with the itch intensity after CR845 treatment (r=0.83 p<0.001). Patients with both moderate (i.e. VAS ≥40 and <70 mm) and severe itch (i.e., VAS ≥70 mm) at baseline responded equally to CR845, suggesting that CR845 was similarly effective regardless of the itch severity. In a responder analysis, 63% of the CR845-treated patients had a change in Skindex-10 score greater than 30% from baseline compared to 39% in the placebo group.

Conclusions: Improvement in itching intensity with CR845 significantly improved QOL in HD patients with UP, regardless of baseline itch severity. The Skindex-10 correlated strongly with the measurement of itch intensity, and discriminated between treatments in QOL responses. CR845 shows promise as a treatment for UP and the Skindex-10 appears to be a useful instrument for quantifying QOL changes in this population.

Funding: Pharmaceutical Company Support - Cara Therapeutics

TH-PO1041

Antipruritic Effect of the Long-Acting Peripheral κ Opioid Receptor Agonist CR845: A Novel Approach for the Treatment of Uremic Pruritus in Hemodialysis Patients Robert H. Spencer,[1] Michael E. Lewis,[1] Joseph W. Stauffer,[1] Vandana S. Mathur,[2] Frederique Menzaghi.[1] *[1]Cara Therapeutics, Inc., Shelton, CT; [2]MathurConsulting, San Francisco, CA.*

Background: Despite the availability of off-label treatments, patients with uremic pruritus (UP) continue to be afflicted by this debilitating condition with no treatment approved in the US. Although the etiology of UP is unknown, it is likely multi-factorial, including systemic inflammation and deficiency in the kappa endogenous opioid system.

Methods: Non-clinical and clinical studies were conducted to demonstrate that the novel potent and selective kappa opioid receptor (KOR) agonist CR845 may be effective for the symptomatic treatment of UP in hemodialysis (HD) patients.

Results: CR845 is a small, synthetic peptide with full agonist activity at rodent and human KORs (EC_{50} = 0.16 nM) with no other detectable off-target activities. A sustained anti-itch activity (>24 hours) was demonstrated for CR845 using mouse models of itch. Additionally, CR845 demonstrated anti-inflammatory properties in rodents and human macrophages. CR845 was not detectable in the central nervous system, therefore CR845 is likely to activate KORs expressed in peripheral neurons and on immune cells. CR845 is primarily excreted unchanged in urine, resulting in prolonged exposure in patients with renal dysfunction compared to normal healthy subjects (up to >10-fold increase in half-life). In HD patients, CR845 was well tolerated at doses ranging from 0.5 to 2.5 mcg/kg with plasma levels remaining constant after a single injection post-HD until cleared at the following dialysis. HD patients with moderate to severe UP treated with intravenous CR845 (1 mcg/kg) post-HD for 2 weeks had a 50% decrease in itch intensity as measured by a visual analog scale of 0 to 100 (n=33) with a significant difference compared to placebo-treated patients (n=31, p=0.016).

Conclusions: These results suggest that peripheral kappa opioid receptors play an important role in the modulation of itch signals and represent a target for the development of novel antipruritic agents. The profile of CR845 makes this compound a suitable and promising candidate for the treatment of UP.

Funding: Pharmaceutical Company Support - Cara Therapeutics, Inc.

TH-PO1042

Efficacy and Safety of Pregabalin for the Treatment of Neuropathic Pain in Patients Undergoing Hemodialysis Tomoyasu Otsuki, Masanori Abe, Seishiro Baba, Noriaki Maruyama, Kazuyoshi Okada. *Divs of Nephrology, Hypertension and Endocrinology, Dept of Internal Medicine, Nihon Univ School of Medicine, Tokyo, Japan.*

Background: Pregabalin is a gamma aminobutyric acid derivative administered for neuropathic pain. It binds to α2Δ subunits of voltage-dependent calcium channels, and inhibits calcium inflow of synapses and the release of excitatory neurotransmitters. This study investigated the safety and efficacy of pregabalin in patients with peripheral neuropathic pain undergoing maintenance hemodialysis.

Methods: This prospective, open-label, single-arm, multi-center trial screened 257 patients. A total of 45 patients with peripheral neuropathic pain were included, of whom 35 patients (men, 23; women, 12; age, 71.5 ± 6.1 years; duration of dialysis, 64 ± 35 months) were analyzed. Patients were treated with an initial dose of pregabalin at 25 mg; this was then increased up to a maximum of 150 mg depending on the patient during a 12-week study period. Visual analogue scale (VAS), Short Form Health Survey (SF-8), and laboratory data were collected at baseline and the end of the study.

Results: The final mean dose of pregabalin was 50.7 mg daily. Mean VAS scores significantly decreased from 52.4 mm at baseline to 34.1 mm at the end of the study (P<0.01). Scores for all eight categories of the SF-8 significantly increased compared with baseline. Both physical and mental component summary scores of the SF-8 also significantly increased. There were no significant differences in serum urea nitrogen, albumin, electrolytes, lipid profiles, or C-reactive protein levels during the study period. Ten patients were withdrawn from the study due to drowsiness, dizziness, and invalidity; however, no serious adverse drug reactions were recorded.

Conclusions: If adverse effects are carefully monitored and administered dosage prudently determined, pregabalin can be an effective treatment for peripheral neuropathic pain, even in patients undergoing hemodialysis.

TH-PO1043

Association of Neuropathy and Physical Parameters in People on Maintenance Haemodialysis: A Prospective Study Ying Wang,[1] Cathie Sherrington,[1] Arun V. Krishnan,[2] Martin P. Gallagher,[1] Alan Cass,[3] Meg J. Jardine.[1] *[1]The George Inst for Global Health, Camperdown, NSW, Australia; [2]Prince of Wales Clinical School, Univ of New South Wales, Randwick, NSW, Australia; [3]Menzies School of Health Research, Darwin, NT, Australia.*

Background: Physical parameters are associated with physical quality of life (QOL) among people with end stage kidney disease (ESKD) on dialysis. While clinical or subclinical neuropathy affects 70-100% of dialysis patients, its effects upon physical parameters (muscle strength and mobility) remain poorly understood.

Methods: We recruited adult maintenance haemodialysis patients to this single centre prospective study. muscle strength (ankle dorsiflexion) and mobility performance (Short Physical Performance Battery, SPPB) were assessed at baseline, 12 and 36 months. Baseline neuropathy was assessed using total neuropathy score (TNS), a structured score for neurological symptoms, signs and nerve conduction study results. QOL was assessed using the SF-36 physical and mental component scores (PCS, MCS). Associations between variables at baseline were assessed with linear regression models.

Results: Thirty-one maintenance haemodialysis patients commenced this study and completed 12 months follow up. Among them, twenty patients (64.5%) completed 36 months follow up. At baseline, study participants had a mean age of 65.7 years (SD 11.4), with a median dialysis vintage of 43 (IQR 26-101) months. The majority of participants were male (17 participants, 55%). Diabetes was the most common cause for ESKD (38.7%). The mean baseline TNS was 7 (SD 6). Baseline QOL data were available for 29 (93.5%) participants, with mean PCS of 35.5 (SD 6.3) units and MCS of 35.4 (SD 10.1) units. In multivariate analysis, baseline TNS was not associated with QOL. Deterioration in patient mobility at 12 and 36 months was predicted by higher baseline TNS (i.e. more severe neuropathy). TNS was not a predictor of deterioration in muscle strength over time.

Conclusions: Severity of baseline neuropathy predicted subsequent deterioration in mobility but not muscle strength at 12 and 36 months. Further larger studies assessing the association of neuropathy, physical parameters and clinical events are needed.

TH-PO1044

Opioid Use, Morbidity and Mortality in U.S. Dialysis Patients

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Background: Pain is important for ESRD patients (PTs), linked to depression and diminished quality of life. Aggressive ESRD PT pain treatment has been advocated. Medicare prescription drug benefits allow tracking ESRD prescriptions and linkage to outcomes, but few data exist regarding outcomes associated with pain and opioid medication prescription (OMP) in ESRD. New Centers for Disease Control guidelines recommend caution in OMP. We assessed maintenance dialysis ESRD PT OMP prevalence, and determined associations between OMP and mortality, dialysis discontinuation and hospitalization, using 2006–2010 USRDS data.

Methods: We limited the study sample to continuously treated (≥365 d) dialysis PTs with full Medicare Part A, B, and D coverage in each study year to ensure complete PT claims. OMP was confirmed from Part D prescription claims. Cox proportional hazards regression models examined associations of OMP in 2010 with subsequent all-cause death, dialysis discontinuation, and hospitalization in the 2010 prevalent cohort (N=153,758), controlled for demographics, ethnicity, comorbidity and residence.

Results: Approximately 20% of PTs had a prescription for 90 d opioids yearly. The most common OMP in 2010 contained hydrocodone (11.7%), oxycodone (5.4%) and tramadol (2.5%). Compared with non-users, short-term (1-89 d supply) and chronic use (≥90 d) PTs had increased risk of death (adjusted HR: 1.04 [95%CI, 1.02-1.07], 1.27 [1.23-1.30], respectively), dialysis discontinuation (1.13 [1.04-1.22], 1.37 [1.26 -1.50]) and hospitalization (1.13 [1.11-1.14], 1.31 [1.29-1.33]). All opioid drugs were associated with increased death risk except for codeine, including class IV agent tramadol. Codeine was associated with increased hospitalization. Rural residents with OMP had higher mortality risk than urban PTs with OMP.

Conclusions: Opioid drug prescription is associated with increased dialysis PT risk of death, dialysis discontinuation and hospitalization. While causal relationships cannot be inferred, and opioid prescription may be an illness marker, efforts to treat pain effectively in dialysis PTs with less toxic interventions deserve consideration.

Funding: NIDDK Support

TH-PO1045

Executive Dysfunction among HD and PD Patients: A Comprehensive Long-Term Prospective Study

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Background: Cognitive impairment (CI) can range from a mild cognitive impairment to dementia. CI may be most prominent in pts with concurrent vascular disease, particularly among chronic kidney disease pts undergoing to dialysis. Mild CI may affect as many as 64% of dialysis pts and it is displayed by worse performances on tests of processing speed and executive function. Trials that examine long-term effects of chronic dialysis are needed. The aim of this study is to evaluate the 1-year progression of executive dysfunction in HD and PD pts.

Methods: We enrolled pts in chronic dialysis (HD or PD) from at least 3 months. Executive dysfunction was assessed by a Montreal Cognitive Assessment (MoCA) Equivalent Score (ES) <18,29. Statistical analysis was performed with SPSS20 software.

Results: We screened 207 dialysis pts: 73 were excluded and 133 were enrolled (mean age 64,09±13,65 yrs; 71% M) at T0. We performed MoCA test in 58 HD pts [mean age 64,90±14,27 yrs, 71% M, median dialysis time 5,66(2,70-10,97) yrs]and in 75 PD pts (63,46±13,22yrs, 71% M, 1,94(1,15-3,56)]. Median values of MoCA (ES) are shown in table 1.

MoCA (ES) median (25th-75th)	T0	T1	*p* value
ALL	23.33 (20.63-25.71)	23.37 (20.07-26.11)	0.056
HD	23.69 (20.28-25.70)	22.98 (19.40-25.60)	0.050
PD	23.33 (21.15-25.98)	23.72 (21.35-26.62)	NS
MoCA (ES) <18,29			
ALL	12%	14%	<0.001
HD	16%	19%	0.009
PD	9%	9%	NS

At T0 a MoCA(ES) <18,29 was present in 16% of HD pts and in 9% of PD pts. After a median follow-up of 1.02 (0.99-1.09) yrs, the rate of HD pts with a MoCA(ES) <18,29 significantly increased (19%), while no significant variations occurred in PD pts.

Conclusions: Median MoCA(ES) was not different between HD and PD pts, while the rate of pts characterized by MoCA(ES) < 18,29 was significantly different between T0 and T1 in HD pts. Our findings suggest that long-term HD pts develop a deterioration of the executive function.

TH-PO1046

Dementia as a Risk Factor for Mortality and Ischemic Stroke in Elderly Korean Patients on Hemodialysis

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Background: Cognitive dysfunction and dementia is common in ESRD patients on hemodialysis (HD). It is associated with worse quality of life and higher risk for mortality. This study aimed to investigate the incidence of major adverse cardiac and cerebrovascular event (MACCE) in elderly Korean patients initiating HD with dementia.

Methods: Using the database from the Health Insurance Review & Assessment Service, we analyzed 10,171 patients aged 65 years or older who had initiated dialysis from 2005 to 2008 and had followed up until 2009. MACCE was defined as a composite outcome including all-cause mortality, nonfatal acute myocardial infarction, target vessel revascularization, and nonfatal stroke. Kaplan-Meier method was used to compare the incidence of MACCE among elderly ESRD patients with and without dementia. The risk factors for all-cause mortality were identified by Cox proportional hazards model. In addition, we matched 1:2 patient pairs with similar propensity scores to reduce biases due to nonrandomization and then performed further comparisons.

Results: A total of 303 elderly patients (3.0%) starting HD had dementia. In all elderly incident HD patients, dementia was a significant predictor for MACCE (HR, 1.258; 95% CI, 1.088 – 1.454; P = 0.002) after adjustment of all eligible confounding variables. Dementia was also a risk factor for all-cause mortality (HR, 1.334; 95% CI, 1.140 – 1.562; P < 0.001), whereas it was not a risk factor for other endpoint of MACCE. However, when we perform analyses in propensity-score matched groups, dementia was an independent predictor for nonfatal ischemic stroke (HR, 1.492; 95% CI, 1.027 – 2.168; P = 0.036) as well as all-cause mortality (HR, 1.301; 95% CI, 1.053 – 1.607; P = 0.015).

Conclusions: Dementia is an independent risk factor for mortality and ischemic stroke in elderly ESRD patients initiating HD. Dialysis providers should pay more attention to patients with dementia to reduce the risk for mortality and ischemic stroke.

TH-PO1047

Frailty Is Correlated with Increased Length of Hospitalization and Death in Hemodialysis Patients

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Background: Research on prognostic indices in hemodialysis (HD) patients is of great importance. Frailty, a geriatric syndrome not adequately studied in HD patients is characterized by reduced physical and cognitive reserve under stress. It is correlated with increased health services utilization and death. We investigated the association of frailty with hospitalization and mortality in HD patients.

Methods: Forty nine (67.3% males) single unit HD patients were enrolled for this observational prospective (12 months) study. Patients were classified as nonfrail, prefrail, and frail according to the SHARE-FI instrument. Demographic, social, physical, and HD related data, medication, comorbidities and functional and nutritional status were recorded. The end points were death and days of hospitalization.

Results: At study beginning the mean (95% confidence interval: CI) age, Charlson Index, Barthel Index, Karnofsky scale, Kt/V, nPCR, serum albumin and CaXP were 76.7 (63.1–72.3)years, 3.2 (2.8–3.7), 18 (16.8–19.3), 73.6 (67.6–79.6), 1.24 (1.18–1.30), 0.98 (0.88–1.08), 3.8 (3.7–3.9) and 46.2 (42.8–49.6) respectively. Sixteen patients (30.6%) were nonfrail, 16 (32.7%), prefrail and 17 (34.7%) frail. Older age was associated with higher frailty rates (P<0.04). Subscapular skin fold thickness was larger in frails and prefrails (P≤0.04). Frailty was not associated with the gender, the lean body weight, the serum albumin, the Kt/V, the nPCR and the CaXP. One nonfrail, three prefrails (18.8%) and six frails (35.3%) died during the follow-up period. Lower serum albumin (P=0.02) and frailty (P=0.042) was associated with mortality. Mortality was not associated with the Kt/V, the nPCR and the CaXP. The mean (95% CI) length of hospitalization was significantly longer in the frails vs in the nonfrails 15.8 (7.5-24) vs 9.3 (0.2–18.3) days respectively.

Conclusions: Frailty was correlated with age among HD patients. Mortality and length of hospitalization within 12 months were significantly correlated with frailty.

TH-PO1048

Frail Elderly Patient Outcomes on Dialysis: An Update on the Longitudinal Study Osasuyi A. Iyasere,[1] Edwina A. Brown.[1] *[1]Imperial College Renal and Transplant Centre, Hammersmith Hospital, London, United Kingdom; [2]Imperial College Renal and Transplant Centre, Hammersmith Hospital, London, United Kingdom.*

Background: Assisted peritoneal dialysis (aPD) enables home dialysis for older patients. The Frail Elderly Patient Outcomes on Dialysis (FEPOD) study is a prospective 2 year longitudinal study comparing quality of life (QoL) between HD and aPD. Baseline analysis showed no differences between dialysis modality and that frailty was predominant predictor of poor outcomes.

Methods: 206 (106 aPD; 100 HD) patients > 60 years, on dialysis for > 3 months and hospitalisation free for 30 days were recruited from 20 UK centres. HD patients (requiring hospital transport) were matched to aPD recruits by age, sex, diabetes status, dialysis vintage, ethnicity and postcode Index of Deprivation. Frailty was assessed using the Clinical Frailty scale. QoL was assessed using Hospital Anxiety and Depression Scale (HADS), SF-12, Palliative Outcomes Symptom scale (renal) and Illness Intrusiveness Rating Scale (IIRS). Physical function was assessed using Barthel's score. Assessments were performed for 2 years, at 3 monthly intervals.

Results: There were 121 dropouts (death -59, study withdrawal-61, transplant -5). After linear mixed model analysis, dialysis modality was not associated with any QoL measures in patients completing 2 year follow-up except SF12 MCS. In the aPD cohort, SF12 MCS decreased with increasing frailty scores (PD* Frailty score ; effect estimate = -1.74, p = 0.032) . In the cox regression survival model, survival was poorer in female HD patients compared to female PD patients (Female Gender * PD vs HD, Exp B = 0.28, p =0.012) . The interaction between HD and male gender was not significant. The principal predictor for survival, though, was frailty (hazard increased by factor of 1.38 for unit increase in frailty score, p = 0.008).

Conclusions: There is no significant difference in QoL over time between matched older patients on aPD and HD. Survival is associated with frailty but may also be poorer in older female patients on aPD. These findings suggest that assisted PD should be considered as a valid alternative to HD in older patients, at least from a QoL viewpoint.This would allow for true patient choice.

Funding: Pharmaceutical Company Support - Baxter Healthcare, Private Foundation Support

TH-PO1049

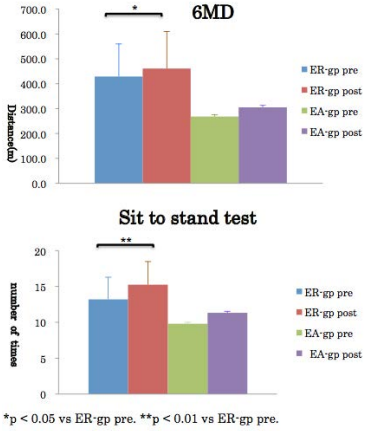
Comparing the Effect of Electric Bicycle Training and Conventional Exercise on Physical Function of End-Stage Renal Disease Patients Undergoing Hemodialysis Misa Miura,[1] Ryo Yoshizawa,[2] Aki Hirayama,[1] Osamu Ito,[3] Masahiro Kohzuki,[3] Shigeru Owada,[2] Teruhiko Maeba.[2] *[1]Health, Tsukuba Univ of Technology, Tsukuba, Ibaraki, Japan; [2]Asao Clinic, Kawasaki, Kanagawa, Japan; [3]Tohoku Univ Graduate School of Medicine, Sendai, Japan.*

Background: While chronic kidney disease (CKD) is common in older adults, approaches to treat geriatric patients with CKD remain undefined. However, exercise training for hemodialysis patients has been shown to improve fitness, physical function, quality of life, and cardiovascular disease markers such as arterial stiffness. This study aimed to determine whether aerobic training or electrical bike exercise for 12 weeks could improve physical function and/or relevant biochemical results in geriatric patients with end-stage renal disease (ESRD).

Methods: This controlled clinical trial consisted of 71 ESRD patients (38 males, 33 females;71.0 ± 7.3 years), randomized to receive 12 weeks of hemodialysis and concurrent aerobic training (ER-gp: n = 22), electrical bike training (EA-gp: n = 10), or no specific intervention (Con-gp: n = 39). The Borg scale was employed to control training intensity. At baseline and study completion, primary outcome measures included exercise tolerance, grip strength, quad muscle torque, balance, 10-m maximum walking and variousbiochemical outcomes.

Results: In the ER-gp, lower muscle endurance and exercise tolerance increased significantly

Figure 1. Result of 6-minute walk distance (6MD) test and sit-to-stand test



*p < 0.05 vs ER-gp pre. **p < 0.01 vs ER-gp pre.

Such effects were not observed in the Con-gp. Although quad muscle torque decreased in the EA-gp, other parameters were not significantly altered.

Conclusions: In this study, the safety and efficacy of aerobic training and electrical bike exercise during hemodialysis were confirmed without sudden drop of blood pressure or any other side effects. Therefore, training during hemodialysis sessions for 12 weeks may improve ESRD patient physical function by eliciting specific whole-body and local effects.

Funding: Government Support - Non-U.S.

TH-PO1050

The Effect of Intradialytic Exercise on Daily Physical Activity and Sleep Quality in Maintenance Hemodialysis Patients Ji-Hyung Cho, Jun Chul Kim. *Dept of Internal Medicine, CHA Gumi Medical Center, CHA Univ, Gumi-si, Gyeongsangbuk-do, Republic of Korea.*

Background: Physical inactivity and sleep disturbances are frequently observed and shown to relate with poor quality of life (QoL), higher rates of hospitalization and mortality in dialysis patients. We aimed to investigate the effect of intradialytic exercise (IDE) on daily physical activity (DPA) and sleep quality measured by accelerometer in maintenance hemodialysis (MHD) patients.

Methods: This study randomly assigned ambulatory MHD patients aged ≥20 years on dialysis ≥6 months, without hospitalization history for the previous 3 months to 4 groups: aerobic (AE), resistance (RE), combination exercise (CE), and control (CG). Stationary bike was used for AE and TheraBand®/theraball for RE. Twelve-week IDE program (3 times/week) was completed in AE (n=11), RE (n=10), and CE (n=12). CG (n=13) received warm-up stretching. At baseline and 12-week follow up, DPA and sleep quality were measured by a 3-axis accelerometer (wActiSleep-BT, ActiGraph LLC) during continuous 7-day wear period.

Results: Patients were 55±12 years of age (mean±SD) on MHD for 64±72 months, 50% female, 44% diabetic. We observed a significant increase of MET (Metabolic Equivalent; kcal/h/kg) in AE (1.02±0.03 vs 1.04±0.04, *P*=0.04) and CE (1.06±0.05 vs 1.09±0.08, *P*=0.003) at 12-week compared with baseline. When comparing between-group changes to MET there was a significant increase in CE (0.03±0.03 vs -0.01±0.04, *P*=0.014) compared with CG. The total number of sedentary bouts (per week) decreased significantly in AE (200±37 vs 174±36, *P*=0.016) and CE (180±45 vs 152±46, *P*=0.031) at 12-week compared with baseline. The average sleep fragmentation index indicating poor sleep quality decreased significantly at 12-week compared with baseline in AE (51.4±8.0 vs 44.5±9.6, *P*=0.041) and RE (52.3±7.3 vs 40.0±15.4, *P*=0.017).

Conclusions: These findings suggest that IDE may play a significant role in the improvement of DPA and sleep quality in MHD patients, although future studies with more study subjects and longer intervention duration are needed to confirm our findings and if this would also lead to improvement of clinical outcomes, such as QoL, hospitalization, and mortality.

TH-PO1051

Pattern of Dermatoses in Chronic Hemodialysis Patients Maria Soledad Ferrari,[1] Rodrigo Sarantes,[1] Paula Gauronas,[1] Andrea Nicola,[2] Silvana Mazzolini,[2] Lidice Dufrechou,[2] Patricia Larre Borges,[1] Alejandra Larre Borges,[2] Miguel Martinez,[2] Oscar A. Noboa.[1] *[1]Centro de Nefrologia; [2]Catedra de Dermatologia, Hospital de Clinicas, Univ de la Republica, Uruguay.*

Background: Skin diseases are highly prevalent in dialysis patients but are frequently overlooked. The aim of this study was to diagnose dermatoses in renal replacement therapy patients treated with hemodialysis (HD-RRT) and analyze the association with background, laboratory data and treatment.

Methods: A descriptive cross-sectional multicenter study was performed in a convenience cohort of patients over 18 years old in HD-RRT for more than 6 months. The Hospital ethic committee approved the study. Patients with previous renal transplant were excluded. Dermatologist performed systematic evaluation of skin.

Results: We evaluated 195 patients, 98 females (50.2%), mean age 64.4±0.9 years (31-94). The average time on HD-RRT was 3.9±0.3 years (0.75-25). At least one skin disease was diagnosed in 98.5 % (n=192) of patients. Xerosis 79% (n=154), pruritus (n=65, 33.7%), yellowish tint (n=60, 30.8%), onycholysis (n=55, 28.2%), purpura (n=53, 27.2%). Non melanoma skin cancer was diagnosed in 15 patients (7.6 %) and 2 patients were diagnosed with melanoma. The age of patients with non melanoma skin cancer was significantly higher (p=0.02). Time on HD-RRT was related with diffuse alopecia (p=0.034) and acquired perforating dermatitis (p=0.029), yellowish tint was related with hyperphosphatemia (p=0.038) and loss of hair shine with anemia (p=0.01).

Conclusions: Skin diseases were present in 98.5 % of the patients. Most prevalent dermatoses were xerosis and pruritus. Of note is the high prevalence of skin cancers with 7.6% with non melanoma skin cancer and 2 cases of melanoma. This data indicates the relevance of periodic skin assessment in patients treated with HD-RRT.

TH-PO1052

Higher Risk of Malignant Neoplasms in Young Adults with End-Stage Renal Disease under Hemodialysis: A Nationwide Population-Based Study Heng-Chih Pan. *Nephrology, Chang Gung Memorial Hospital, Keelung, Taiwan.*

Background: Malignant neoplasm is prevalent in elderly and negatively impacts patient outcomes. Previous investigations have shown that end-stage renal disease (ESRD) is associated with an increased risk of malignancies. Our study was designed to explore the contribution of ESRD for incidence of malignancy in patients with different ages.

Methods: We analyzed a nationwide cohort, retrieved from Taiwan's National Health Insurance Research Database(NHIRD), to study the incidence of malignancy in patients with and without receiving hemodialysis (HD). We obtained 1,000,000 random subjects and followed them from 2005 to 2013. 3086 of them developed ESRD and received regular HD during this period. For each HD patient, four age- and gender-matched control, a total of 12344 patients, were selected from the NHIRD. We further stratified the patients according to different ages. The study endpoint was the occurrence of malignancy.

Results: The incidence of malignancy was 6.71% and 4.42% for HD, and control patients, respectively. Among HD patients aged younger than 40 years, 40 to 49 years, 50 to 59 years, and 60 to 69 years, the incidence rate of malignancy was 4.15%, 4.72%, 6.22%, and 8.12%, which were significantly higher than that of control group. After adjustment for known risk factors, HD had the highest odds ratio of developing malignancy.

Conclusions: ESRD patients who received HD had a significantly higher risk of malignancy, especially in a relative young age. Based on the results of our study, we believe that the development of ESRD signifies higher risk of malignancy in young adults.

Incidence of Cancer	HD, n (%)	non HD or PD, n (%)	*P*	OR
	3,086 (100%)	12,344 (100%)		
H&N organs	16 (0.52%)	46 (0.37%)	0.2521	1.3933
GI organs	90 (2.92%)	251 (2.03%)	**0.0028**	1.4479
Respiratory organs	17 (0.55%)	100 (0.81%)	0.1376	0.6782
Bone, connective tissue, skin, and breast	12 (0.39%)	46 (0.37%)	0.8953	1.0436
GU organs	48 (1.56%)	88 (0.71%)	**<0.0001**	2.2005
Other sites	52 (1.69%)	133 (1.08%)	**0.0055**	1.5736
Lymphatic and hematopoietic tissues	14 (0.45%)	32 (0.26%)	0.0764	1.7534
Liver	43 (1.39%)	112 (0.91%)	**0.0154**	1.5433
Total	207 (6.71%)	545 (4.42%)	**<0.0001**	1.5566

TH-PO1053

Risk of Skin Cancer in Chronic Haemodialysis Patients: A Nationwide, Population-Based Study in Taiwan Yuh-Mou Sue,[1] Chia-Chen Wang.[2] *[1]Div of Nephropathy, Dept of Nephrology, Taipei Medical Univ-Wan Fang Hospital, Taipei, Taiwan; [2]Dept of Dermatology, Cardinal Tien Hospital, New Taipei City, Taiwan.*

Background: Chronic haemodialysis (HD) patients have a higher incidence of cancer. However, the risk of skin cancer in this population has rarely been investigated. The purpose of this study is to investigate the risk of non-melanoma skin cancer (NMSC) and cutaneous melanoma in chronic HD patients and explore the associated risk factors.

Methods: We performedretrospective cohort and nested case-control studies using records in the Taiwanese National Health Insurance Research Databasebetween 1999 and 2013. The HD cohort included 79,668 incident HD patients, of which the standardized incidence ratios (SIRs) for incident NMSC and cutaneous melanoma were determined. In the nested case-control study, HD patients with NMSC were matched to those without skin cancers. The impact of various factors on the development of NMSC was determined by conditional logistic regression analysis.

Results: Of the 79,668 HD patients, 248 cases of NMSC and 22 of cutaneous melanoma occurred after a mean 4.95 years of follow-up. The SIRs for NMSC and cutaneous melanoma in HD patients were 1.58 (95% confidence interval [CI], 1.39–1.79) and 1.44 (95% CI, 0.91–2.19), respectively. Of the patients with HD, a higher risk of NMSC was found in men (1.5-fold), South Taiwan residents (2-fold), and patients with uremic pruritus after long-term antihistamine treatment (1.53-fold). However, the incidence of NMSC was not increased in patients with uremic pruritus receiving ultraviolet-B (UVB) phototherapy.

Conclusions: Chronic HD patients are at higher risk of NMSC. Uremic pruritus further increases the risk of NMSC, which might be prevented by UVB phototherapy.

TH-PO1054

Cancer Diagnosis and Treatment for Patients under Hemodialysis; Multicenter Surveillance Takeshi Matsubara, Tatsuo Tsukamoto, Motoko Yanagita. *Dept of Nephrology, Kyoto Univ Graduate School of Mediciine, Kyoto, NA, Japan.*

Background: Cancer is the third leading cause of death among end-stage renal disease (ESRD) patients in Japan. However, little is known about the diagnosis and treatment of them. Therefore, the aim of this study is to clarify the clinical practice of cancer patients under hemodialysis (HD).

Methods: This retrospective case series study enrolled HD patients who subsequently developed cancer from 2010 to 2012 in 20 institutions. The clinical courses were reviewed in each patient with the cancer at the following primary sites: kidney, colorectum, stomach, lung, liver, bladder, pancreas, and breast. Data were collected about the cause of ESRD, time between initiation of HD and the diagnosis of cancer, disease status based on its surgical resectablity, and the primary therapy, anemia (Hb<10g/dL), hypoalbuminemia (ALB<3.0g/dL). The primary end point was death.

Results: From 686 patients enrolled at baseline, 509 patients registered. The main primary cancer sites were kidney (32%), followed by colorectum (17%), and stomach (14%). In all patients, the median time for cancer diagnosis after the beginning of HD was 74 months. Notably, median time was significantly longer in kidney cancer than others (142 vs 54 months, respectively). 391 (77%) cancers were assessed to be surgically resectable, and 366 (72%) cases underwent operation. On the other hands, 44 (8.6%) and 39 (7.7%) patients underwent chemotherapy and best supportive care, respectively. After a median follow-up of 25 months, there were 130 deaths, including 66 patients (51%) died of causes other than cancer. 2-year survival in all cancer was 75%. Kidney cancer showed better survival than other cancers (HR 0.43: 0.27-0.65, p<0.01). After multivariate adjustment for sex, cause of ESRD, cancer primary site, disease status and hypoalbuminemia, anemia was independently associated with mortality (HR: 1.64: 1.10 to 2.41, p=0.01) .

Conclusions: This is the first and largest study about cancer patients under HD in Japan. Kidney cancer had longer interval between HD initiation and diagnosis of cancer, but better prognosis than other cancers. Anemia could be a good predictor of the cancer mortality in HD patients.

Funding: Government Support - Non-U.S.

TH-PO1055

Pregnancies in Patients on Dialysis: A Multi- Center Retrospective Study on Outcomes and Prognosis Factors Gabrielle Laetitia Normand,[1] Xu Xiao Li,[3] Marine Panaye,[1] Anne Jolivot,[1] Sandrine Lemoine,[1] Fitsum Guebre-Egziabher,[4] Muriel Doret,[2] Laurent Juillard.[1] *[1]Service de Néphrologie, Hospices Civils de Lyon, Lyon, France; [2]Service de Gynécologie- Obstétrique, Hospices Civils de Lyon, Lyon, France; [3]Service de Néphrologie, CHU d'Amiens, Amiens, France; [4]Service de Néphrologie et Transplantation, CHU Grenoble, Grenoble, France.*

Background: Pregnancies in hemodialysis (HD) patients are rare and often associated with maternal and fetal complications. We aimed to determine pregnancies outcomes in HD patients and to identify maternal and fetal prognosis' risk factors.

Methods: This is a descriptive, retrospective, multi center study. Pregnant women on HD from 1985 to 2015 in France were included. A favorable fetal outcome was defined as a living infant discharged from hospital.

Results: We identified 100 pregnancies in 84 women on HD, from 41 centers, with a mean age of 30 years (± 5). Mean delay between initiation of dialysis and onset of pregnancy was 44.7 ± 59.7 months . Fourteen patients (14.9%) began chronic HD during their pregnancy explaining a high rate of catheter (19.8%) and a preserved residual diuresis for 43 patients (50%). Mean weekly dialysis time was 14.6 ± 4.6 hours, 19.1 ± 4.1 hours and 20.4 ± 3.9 hours for the first, second and third trimester respectively. Seventy- six (89.4%) women performed daily dialysis during the third trimester. Fetal survival was 78% with a mean gestational age of 33 ± 3.9 weeks and a mean birth weight of 1719 ±729 g. Fetal outcome worsened after 2010 with a fetal loss of 16% for pregnancies between 2010 et 2015, compared to 9% before 2010. No significant correlation was found between a lower urea concentration or a higher hemoglobin value and a favorable fetal outcome.

Conclusions: Our study is one of the largest series of pregnancies in HD patients. Its long observation period, multi center and retrospective design could explain the lack of correlation between classical prognosis factors and fetal outcome. The worsening of fetal outcome after 2010 could be explained by an increase in pregnancies number due to a better acceptance of these pregnancies by the medical community. Nevertheless, these pregnancies remain at high risk, reinforcing the need for an early nephrologist- obstetrician dialogue.

TH-PO1056

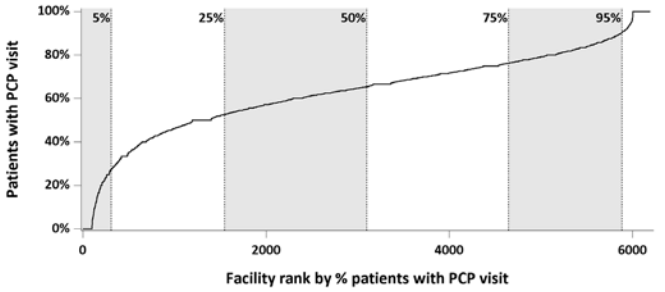
Dialysis Facility Variation in Primary Care Physician (PCP) Involvement in the Care of Chronic Dialysis Patients in the U.S. Vahakn B. Shahinian, Patrick Albertus, Sai Hurrish Dharmarajan, John Z. Ayanian, R. Hirth, William H. Herman, Rajiv Saran. *Univ of Michigan, Ann Arbor, MI.*

Background: We previously demonstrated increasing involvement of PCPs in the care of dialysis patients, and that PCP involvement is associated with greater delivery of preventive care compared to a nephrologist alone. In this study, we examined dialysis facility variation in PCP involvement.

Methods: Using the United States Renal Data System (USRDS), prevalent dialysis patients in 2013 with Medicare as primary insurer were identified. PCP involvement was based on ≥1 claim for an outpatient (non-dialysis) visit with a family practice, general medicine or geriatrics physician. The % of patients with ≥1 PCP visit for each facility was plotted in rank order. A multilevel logistic regression model was performed to examine facility level predictors (size, profit status, free-standing/hospital-based, % below poverty line in county of facility) of PCP involvement, adjusted for patient age, sex, race, and comorbidities. An intra-class correlation (ICC) was calculated to assess clustering by facility, unexplained by observed patient and facility level predictors.

Results: A total of 219,260 patients were assigned to 6,226 facilities. There was wide facility variation in PCP involvement (Figure). The median facility had 65% of its patients with PCP involvement, with interquartile range from 53 to 76%. The only significant facility level predictor was county poverty (Odds ratio 0.89 [95%CI 0.85,0.93] for ≥20% of residents below poverty line vs above). The ICC was 0.09, suggesting a moderate degree of clustering at the facility level.

Conclusions: Facilities in areas with greater poverty were less likely to have patients with PCP involvement. Substantial unexplained variation at the facility level may reflect differences in attitudes of nephrologists regarding who should be responsible for primary care of dialysis patients.



Funding: NIDDK Support

TH-PO1057

The Challenges of Achieving Universal Health Coverage for Chronic Conditions in Low Income Settings: A Case Study of Dialysis Outcomes in India Vivekanand Jha,[3] Oommen John,[3] Sradha S. Kotwal,[1] Martin P. Gallagher,[1] John Knight.[1] *[1]The George Inst for Global Health, Sydney, New South Wales, Australia; [2]The George Inst for Global Health, Delhi, India; [3]Medanta Hospital, New Delhi, India; [4]Post Graduate Inst of India, Chandigarh, India.*

Background: India has set itself the target of achieving universal health coverage by 2022. The provision of financial protection from the costs of treating high cost chronic conditions such as kidney disease is one of many challenges. Little is known about the economic impacts of maintenance dialysis in India. We conducted a prospective observational cohort study of incident dialysis patients to understand the household economic impact of dialysis, barriers to treatment continuation and the extent to which existing insurance programs provide financial protection.

Methods: Incident patients commencing hemodialysis at two North Indian centers are followed prospectively for 12 months. Baseline demographic and clinical outcome data were collected as well as data on direct, indirect costs and economic impact on the patient and family.

Results: Here we present the results of the 6 month interim analysis. A total of 119 patients (82 male, 37 female) have been enrolled thus far, 70 at a public hospital (Chandigarh) and 49 at a private hospital (Delhi). Median age at enrollment was lower at the public hospital compared to the private (37.5 yrs cf 60 yrs). Baseline Median monthly income was USD$90 at the public hospital and USD$377 in the private hospital. Of the 94 patients at the 6 month interim analysis, 18(19%) have died, 19(20%) have been transplanted , 47 (50%) remain on dialysis and 10 (11%) patients have discontinued dialysis. Median total monthly expenditure for dialysis was USD$231 in the public hospital and USD$1526 in the private hospital.

Conclusions: These relatively young Indian dialysis patients have high mortality and dialysis discontinuation rates but also a high rate of transplantation. Costs were high relative to income and are likely to impact upon ongoing treatment decisions and survival. The high and ongoing nature of such costs pose particular challenges to how risk protection programs are designed, particularly given the limited capacity to pay of its beneficiaries.

TH-PO1058

Undocumented with End Stage Renal Disease: Characteristics and Outcomes Associated with Delayed Initiation Nova Hou,[1] Chandan Vangala,[2] Rajeev Raghavan.[2] *[1]McGovern Medical School, Houston, TX; [2]Nephrology, Baylor College of Medicine, Houston, TX.*

Background: Most undocumented patients with ESRD in Houston, TX rely on emergent dialysis treatments. Each day, 50% of the patients who present to the hospital for dialysis are either admitted due to critical illness or are turned away without treatment. For this reason, physicians delay initiation of dialysis until absolutely necessary. This abstract characterizes the undocumented population at initiation and compares them to a representative cohort of patients in the United States Renal Data System (USRDS).

Methods: There were 155 undocumented patients who initiated dialysis at the county hospital system in Houston, TX between July 2009 and July 2014. Data was obtained from chart review. A standard mortality rate (SMR) was calculated for the 92 patients who received emergent dialysis for one year (2013) and this was compared to a representative USRDS cohort (Hispanics in Texas). Six of the 18 patients 'lost to follow-up' were presumed dead.

Results: The average Charlson Comorbidity Index (CCI) for the undocumented patients at initiation is 4.36 (±2.26). Data is presented in Table 1. The p-value was <0.05 for all comparisons except female gender and Hispanic race.

	Undocumented (n=155)	USRDS Cohort (n=18,411)
Demographics		
Age at Initiation (yrs)	44.7	60.2
BMI	26.7	29.8
Female*	40.6%	46.0%
Hispanic*	96.8%	100.0%
Etiology of ESRD		
Diabetes Mellitus	48.4%	68.0%
Unknown	20.0%	1.8%
Labs at Dialysis Initiation		
Albumin (g/dL)	2.86	3.08
Hemoglobin (g/dL)	7.81	9.26
Serum Creatinine (mg/dL)	13.94	6.93
Mortality		
Standard Mortality Ratio (SMR)	1.72	1.00

Conclusions: The undocumented patients who begin dialysis in Houston, TX have a high CCI score, which is correlated with increased mortality in the established ESRD population. These patients have significantly reduced hemoglobin and albumin levels at initiation; these biomarkers have an established correlation with increased mortality. Critical illness at initiation, along with inconsistent access to dialysis, places this population at a high risk of mortality despite younger age.

TH-PO1059

Effect of Citizenship Status on Hemodialysis Adherence Ishita Rajnish,[1] Tina Adjei-Bosompem,[1] Christopher Dijanic,[1] Gary Kwo,[2] Ellena A. Linden,[1] George N. Coritsidis,[1] Joani Pantiz,[2] Priya Pai.[2] *[1]Nephrology, Icahn School of Medicine- Elmhurst Hospital Center, Elmhurst, NY; [2]Broadway Dialysis Center.*

Background: Previous studies have shown that undocumented ESRD patients (UPs) tend to be younger and continue working once on hemodilaysis (HD). We explored whether UPs have difficulty with adhering to HD treatments by reviewing various clinical markers of adherence.

Methods: Records of all our adult HD patients were reviewed for one full year beginning 4/1/15. Yearly Kidney Disease Quality of Life (KDQOL) questionnaire was reviewed. Documentation status was determined by presence or absence of a social security number. Variables analyzed included sex, age, ethnicity, phosphorous (P), parathyroid hormone (PTH), potassium (K), interdialytic fluid gains, hospitalizations, missed and shortened treatments.

Results: 158 patients were analyzed: 44% of all patients were UPs (n=70). Hispanics made up majority of UPs (74%). PTH, P levels were higher in the UPS. UPs were more likely to shorten treatments. KDQOL was similar in both groups except for a higher score on physical health assessment in UPs.

Demographics	N=158(%)	Documented N=88(%)	UPs N=70(%)	p-values
Age		59±12.2	46±12.6	**<0.05**
Sex: %Male	108(68)	57(64)	51(73)	0.56
Race				
White	11(7)	8(9)	3(4)	
Black	17(11)	14(16)	3(4)	
Hispanic	82(51)	30(34)	52(74)	
Asian	42(27)	32(36)	10(14)	
Other	6(4)	4(5)	2(3)	
Shortened treatment, hours		5.1	7.3	**<0.05**
Missed treatment, sessions		2.6	1.9	0.8
Number of hospitalizations		1.0	0.9	0.5
Average P, mg/dL		5.2	5.7	**<0.05**
Average K, mg/dL		5.0	5.0	0.9
Average PTH, pg/mL		705	1004	**<0.05**
Average fluid gain, L		2.2	2.3	0.4
KDQOL	142			
Physical component summary score		37.9	40.9	**0.05**
Mental component summary score		44.9	47.1	0.2

Conclusions: UPs are less adherent with HD prescription as seen by higher P, PTH, greater likelihood of shortened treatments despite having higher physical health scores. Given similar KDQOL scores we postulate that the difficulty with adherence may be due to work burden and age.

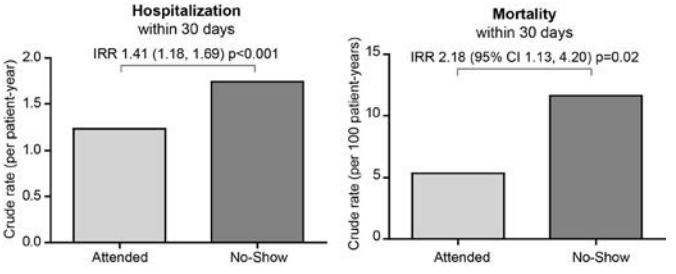
TH-PO1060

In-Center Hemodialysis Absenteeism: Prevalence and Association with Outcomes Steven M. Brunelli, Kathryn S. Gray, Dena E. Cohen. *DaVita Clinical Research, Minneapolis, MN.*

Background: Patients with end-stage renal disease often miss in-center hemodialysis (ICHD) treatments. Here, we estimated the percentage of missed treatments that were attributable to hospitalization, emergency department (ED) visit, or out-patient procedure, versus no identifiable cause ('no-show'), and estimated the impact of a single no-show on the short-term risk of hospitalization and mortality.

Methods: In one analysis, we retrospectively aligned treatment attendance records for calendar year 2012 with claims data for adult Medicare Parts A and B enrollees who received ICHD on a Monday/Wednesday/Friday (MWF) schedule at a large US dialysis organization (LDO). In a second analysis, we considered prevalent adult Medicare beneficiaries receiving MWF ICHD at the LDO who had not missed dialysis or been hospitalized between 21 Apr and 20 May 2012. We identified patients who had a no-show on 21 May 2012 and propensity matched them (1:5) to patients who attended treatment on that date. We compared hospitalization and death over the subsequent 30 days. The process was repeated for 23 and 25 May 2012, and data were pooled for all three dates.

Results: Of 462,028 missed treatments observed in 2012 (15.31 per patient-year at risk), 45.1% coincided with a hospitalization; 1.9% with an ED visit, and 0.1% with a procedure. The remaining 52.8% were no-shows. A single no-show (vs. attending the treatment) was associated with a significantly increased risk of hospitalization (adjusted odds ratio [aOR] 1.41, 95% confidence interval [CI] 1.18-1.69) and death (aOR 2.18, 95% CI 1.13-4.20).



Conclusions: In conclusion, over half of missed hemodialysis treatments are no-shows; ie, not resulting from hospitalization, ED visit, or procedure. Dialysis no-shows are potently and significantly associated with greater short-term risk of hospitalization and death. Reducing no-show rates may improve patient outcomes.

Funding: Pharmaceutical Company Support - DaVita, Inc

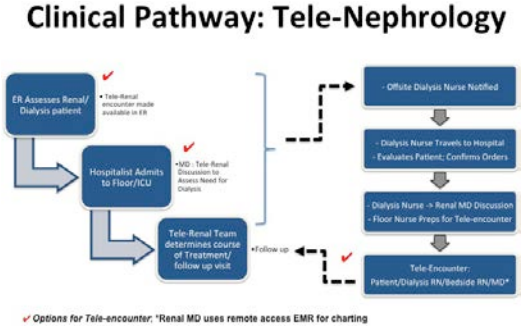
TH-PO1061

Tele-Nephrology: Delivering Acute Dialysis in Rural Hospitals via Telehealth Charuhas V. Thakar,[1,4] Mahmoud T. El-Khatib,[1] Amit Govil,[1] Doug Johnson,[2] Robert Parker,[3] Pam Kimmel,[1] Anya Sanchez.[1] *[1]Nephrology/Medicine, Univ of Cincinnati/UC Health, Cincinnati, OH; [2]Dialysis Clinics Incorporated, Nashville, TN; [3]Meadowview Regional Medical Center, Maysville, KY; [4]Cincinnati VA Medical Center, Cincinnati, OH.*

Background: 38% of the 4,926 community hospitals in the U.S.A. are designated as rural hospitals. Although dialysis use is similar across rural and urban areas (3.9 /1000 residents); 77% of remote rural counties lack an in-county dialysis facility. Only a third of rural hospitals offer acute dialysis due to lack of dialysis and/or renal providers.

Methods: We describe the development of a tele-nephrology program, partnering with a national dialysis provider (Dialysis Clinics Inc.), and Meadowview Regional (rural hospital) in Maysville, KY. Lack of dialysis providers had forced transferring of patients requiring acute dialysis to larger hospitals, resulting in transportation costs and real/intangible costs to patients.

Results: Key elements of implementation included: 1. Planning (needs assessment; technology; dialysis provider; contracting); 2. Stakeholders (business, nursing, informatics, hospitalist, pharmacy, renal). Metrics of success include: A. Clinical performance; B. Patient satisfaction; C. Provider satisfaction; D. Opportunity cost savings. After careful planning, the program went live in January 2016. Clinical pathway is shown in Fig 1. To date, we have treated 12 patients (32 bed-days; 20 dialysis treatments) via tele-health for conditions requiring medical/surgical/critical care. 67% of patients were successfully treated and discharged from the rural hospital.



Conclusions: By applying innovative technology, we demonstrate surmounting traditional barriers to deliver specialty renal care at rural/critical access hospitals. This patient-centered program plans to build a hub-and-spoke model for specialty care, and can be emulated nationally.

Funding: Clinical Revenue Support

TH-PO1062

Processes of Care and Outcomes of End Stage Renal Disease Hemodialysis Patients during a Man Made Disaster Majd Isreb,[1,7] Lina Murad,[3,7] Akram Almakki,[4,7] Mohamad Alhosaini,[5,7] Kamel Hatahet,[6,7] Mohamed A. Sekkarie.[2,7] *[1]PeaceHealth Medical Group, Vancouver, WA; [2]Nephrology & Hypertension Associates, Bluefield, WV; [3]Metropolitan Access Center, Washington, DC; [4]Indiana Univ Health System, West Lafayette, IN; [5]Loyola Univ, Springfield, IL; [6]Temple Univ Hospital, Philadelphia, PA; [7]Syrian National Kidney Foundation, Panama City, FL.*

Background: The health of dialysis patients is negatively impacted by natural disasters. The degree of this impact in the setting of war is not well known. Herein we compare processes of care and outcomes, including survival, in two ESRD hemodialysis facilities in Syria. Both units are charitable but one is located in a besieged area (B) where getting supplies and medications is very difficult, and the other has a fairly free access to these items (NB).

Methods: Baseline characteristic of all the patients dialyzing in the facilities on 1/1/2015, including demographics, etiology of ESRD, type of vascular access, smoking history, and history of major cardiovascular disorders were collected retrospectively. Follow up was for a maximum of one year and included data collection on availability of medications, dialysis duration and frequency, and survival.

Results: There were no statistically significant differences in patients' demographics, smoking history, and dialysis vascular access type. The average patient age was 47 years. Less than 5% of the patients dialyzed 3 times a week. Data on medications availability, dialysis duration and frequency, and outcomes are shown in the table.

Facility	WG > 4kg	Duration ≤ 3 hours	Once a week HD	ESA not available	HB < 8 gm/dl	V D not available	Died
B (N=31)	39%	97%	47%	65%	55%	71%	48%
NB (N=29)	0%	0%	7%	0%	48%	0%	21%
P value	.001	.001	.002	.001	NS	.001	.03

(B: besieged, NB not besieged, WG: Interdialytic weight gain, V D: active vitamin D, Statistics: two tailed Fisher exact test).

Conclusions: War has a strong negative impact on the health of ESRD hemodialysis patients especially when access to medications and supplies is restricted by beseigement. The renal community should be more involved in guaranteeing access of care to the vulnerable population of ESRD patients.

Funding: Private Foundation Support

TH-PO1063

Increased Hospitalizations and Costs Associated with Suboptimal Initiation of Chronic Dialysis Edwin J. Anand,[1] Kabir Jalal,[2] Brian M. Murray,[1] Pradeep Arora,[3] Rocco C. Venuto.[1] *[1]Nephrology, Univ at Buffalo, Buffalo, NY; [2]Biostatistics, Univ at Buffalo, Buffalo, NY; [3]Nephrology, VA Medical Center, Richmond, VA.*

Background: Initiation of maintenance dialysis with a catheter is associated with increased mortality. Nearly 80% of patients start dialysis with a catheter, despite concerted efforts to increase fistula use. Using data from a large 3rd party payer, we studied the comorbidities leading to increased hospitalizations and costs in the first 12 months after starting chronic dialysis.

Methods: We used data (costs, hospitalizations, labs, billing codes) from a large 3rd party payer in NY State from 2007-14. We identified patients with CKD based on eGFR <60 for at least 90 days. Patients with CKD who were started on dialysis formed our study cohort. Dialysis crash was defined as starting dialysis with a catheter. We performed logistic regression of factors associated with hospitalizations and costs over the 12 month period following dialysis initiation.

Results: Of the 1.3 million patients in the database, 38,857 had CKD. Of these, 1298 developed ESRD. There was a significantly higher rate of hospitalization (2.3 vs 1.9 P=0.008), as well as total medical costs in the first year ($104,674 vs $81,575) in patients who crashed vs those who did not . Presence of a fistula (mature or maturing) was associated with reduced hospitalizations (1.5 vs 2.1 P=0.001). Other variables that were associated with increased hospitalizations and costs on multivariate analysis were COPD, asthma, substance abuse and mental illnesses.

Variables	RR	Confidence internal
Crash	1.19	1.05-1.37
Fistula	0.70	0.56-0.87
COPD/Asthma	1.46	1.27-1.70
Depression	1.56	1.35-1.80
Substance abuse	2.25	1.8-2.78

Heart disease and diabetes were not associated with increased hospitalizations.

Conclusions: 1. Dialysis initiation with a catheter is associated with increased hospitalizations and costs 2. More effective interventions to increase fistula rates would reduce avoidable hospitalizations 3. Care coordination of ESRD patients with experts in respiratory diseases and mental illness should reduce hospitalizations and costs for this population.

TH-PO1064

Impact of Dialysis Access Modality on Emergency Department Utilization

Brendan P. Lovasik, Rebecca H. Zhang, Justin D. Schrager, Stephen O. Pastan, Rachel E. Patzer. *Emory Univ, Atlanta, GA.*

Background: Initiation of dialysis with an arteriovenous fistula (AVF) is associated with lower costs and improved patient survival. However, the impact of dialysis access modality on ED utilization among a national ESRD patient population has not been examined.

Methods: We examined a cohort of 103,155 incident adult ESRD patients in the United States Renal Data System data from 2005-2011. ED utilization, hospital admission, and diagnoses were obtained from the USRDS and Medicare Physician/Supplier and Inpatient databases for Medicare Part A/B claims. Multivariable Poisson regression was conducted to assess the association of relevant patient variables with ED utilization.

Results:

	ED Visits	ED Visits/Patient-Year	Multivariable Analysis		
			Rate Ratio	95% Confidence Interval	P-Value
All ESRD N=769,228	1,782,441	2.89			
AV Fistula N=94,801 (13%)	146,527	1.83	REF	REF	REF
Graft N=23,532 (3%)	53,078	2.63	1.220	1.213-1.228	<0.0001
Catheter N=550,737 (71%)	1,394,263	3.22	1.122	1.110-1.134	<0.0001
Peritoneal & Other N=100,158 (13%)	188,573	2.25	1.235	1.203-1.267	<0.0001

In the first year of ESRD, 55% of patients presented to the ED, with a total of 1,782,441 ED visits among 422,738 unique ESRD patients. The median Medicare claim for an ED visit by an ESRD patient was $466 (IQR:$274-$745). Extrapolating this cost yields an annual ED cost of $668 million for first-year ESRD patients. Only 13% of ESRD patients initiated dialysis with a mature AVF; AVF patients had the lowest rate of ED utilization (1.83 visits per patient year [PY]). Catheter-based dialysis patients had the highest rate of ED utilization (3.22 per PY). In multivariable analysis controlling for sociodemographic and clinical factors, patients with a graft (RR: 1.22; 95% CI:1.21-1.23) or catheter (RR:1.12; 95% CI:1.11-1.13) for dialysis access had higher rates of ED utilization compared to those with an AVF.

Conclusions: Despite Fistula-First guidelines, AVFs remain an underutilized dialysis access modality, with significant deleterious patient outcome and healthcare resource utilization implications. Initiatives to increase pre-ESRD nephrology referrals may improve AVF rates.

TH-PO1065

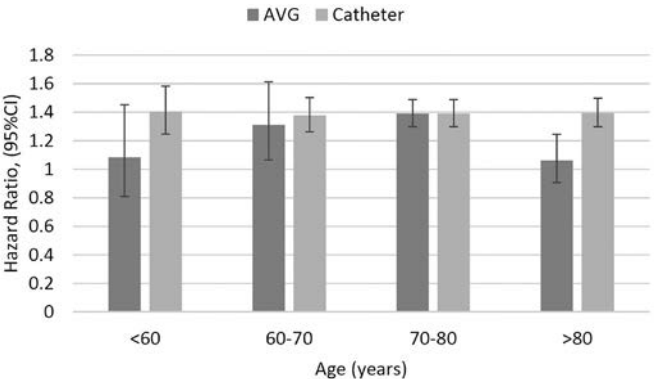
Vascular Access and Mortality in Elderly Incident ESRD Patients

Tarek H. Saleh,[1] Miklos Zsolt Molnar,[1] Keiichi Sumida,[1] Jun Ling Lu,[1] Praveen Kumar Potukuchi,[1] Elani Streja,[2] Kamyar Kalantar-Zadeh,[2] Csaba P. Kovesdy.[1,3] *[1]Univ of Tennessee Health Science Center, Memphis, TN; [2]Univ of California, Irvine, CA; [3]VA Medical Center, Memphis, TN.*

Background: Creating a mature AV fistula (AVF) can be challenging in elderly individuals. It is unclear if elderly incident HD patients derive a survival benefit from an AV fistula (AVF) over an AV graft (AVG) or a tunneled catheter (TC).

Methods: We examined 46,748 US veterans who transitioned to dialysis between 2007 and 2011 using an AVF, AVG or TC. We examined the association of AVG and TC (vs. AVF) with all-cause and cause-specific mortality in Cox and competing risk regression models adjusted for age, race, comorbidities and pre-dialysis Nephrology care in patients aged <60, 60–<70, 70–<80, and ≥80 years old. Effect modification by age was examined with interaction terms.

Results: Upon dialysis transition, patients were 70±12 years old, 94% male, 25% African-American, and 58% diabetic. 8,936 (19%) started HD with an AVF, 1,232 (3%) with an AVG, and 36,580 (78%) with a TC. 31,354 patients died (mortality rate 290/1000 patient-years, 95%CI: 287-293) over a median follow-up of 2.1 years. Use of a TC was associated with significantly higher all-cause mortality in all age groups (Figure), with no significant age interaction (p=0.6). TC use was also associated with both higher infectious mortality (HR 1.76, 95% CI 1.33 - 2.32) and CV mortality (HR 1.54, 95% CI 1.37 - 1.74) in patients ≥80 years old. Use of an AVG was not associated with higher risk of all-cause, infectious or CV mortality in patients >80 years old.



Conclusions: Staring HD with a TC is associated with higher mortality in all age groups, the risk being highest for infectious mortality. Use of an AVG appears to be associated with similar outcomes as an AVF in patients ≥80 years old. A catheter-last approach should be advocated in elderly incident HD patients.

Funding: NIDDK Support, VA Support

TH-PO1066

Predictors of Adverse Outcomes of Permanent Vascular Access (PVA) in Pediatric Hemodialysis (HD) Patients: A MWPNC Study

Ali Mirza Onder, Ellen G. Wood, Craig B. Langman, Chryso P. Katsoufis, Marissa J. Defreitas, Joseph T. Flynn. *Midwest Pediatric Nephrology Consortium.*

Background: Few data exist on what factors contribute to success or failure of PVA in pediatric HD. We investigated predictors of adverse outcomes of PVA in a large cohort of pediatric HD patients.

Methods: Retrospective chart reviews were performed in 20 participating centers. Variables collected included duration and number of non-permanent vascular access (NPVA), type of PVA, complications, interventions, and final outcome.

Results: PVA were created in 117 children during the study period: 103 (88%) were AV fistulas and 14 (12%) were AV grafts. AVF demonstrated better primary patency rates compared to AVG (p =0.0391, Wilcoxon signed rank test). Primary failure occurred in 16 PVA (13.6%). AVF's were about 2 times more likely to have primary failure compared to AVG (Odds ratio= 2.1). Secondary failure occurred in 14 PVA (12.2%). AVG's had about 3 times increased risk for secondary failure compared to AVF's (Odds ratio=3.334). As the number of NPVA increased, the probability of secondary failure decreased (p=0.0343, inverse correlation). Longer NPVA duration directly correlated with increased risk for secondary failure (p=0.0501). As Kt/V at the time of permanent vascular access creation increased, the probability of secondary failure increased (p=0.0263). There were 196 interventions in total. AVF's were more likely to be intervention-free (p=0.0456, Odds ratio=4.84). Twenty-seven interventions resulted in non-functional PVA. Both Intervention-free survival (p=0.0252, Odds ratio=0.093) and the total number of interventions were able to predict secondary failure (p=0.0006). For each additional intervention, the odds of having secondary failure increase by 1.535. Finally, intervention-free survival directly correlated with overall survival of PVA (p=0.0197, Spearman correlation coefficient = 0.28028).

Conclusions: We found that both the number and duration of NPVA, and baseline Kt/v may affect the outcomes of AVF and AVG. While most interventions were able to salvage the function of PVA, both the intervention-free survival and total number of interventions were predictive of secondary failure.

TH-PO1067

Predictors of Maturation Time for Permanent Vascular Access (PVA) in Pediatric Hemodialysis (HD) Patients: A MWPNC Study

Ali Mirza Onder, Ellen G. Wood, Matthew M. Grinsell, Larry T. Patterson, Jennifer G. Jetton, Joseph T. Flynn. *Midwest Pediatric Nephrology Consortium.*

Background: Maturation time is one of the limiting factors in using PVA for children on HD.Our objective was to investigate the predictors of maturation time of AVF's and AVG's in a large cohort of pediatric HD patients.

Methods: Retrospective chart reviews were performed in 20 participating centers. Variables collected included duration and number of non-permanent vascular access (NPVA), type of PVA, patient demographics, baseline laboratory findings at time of placement and final outcome.

Results: PVA were created in 117 children during the study period: 103 (88%) were AV fistulas and 14 (12%) were AV grafts. The average maturation time was 3.7± 3.9 months. AVG's had significantly shorter maturation times when compared to AVF's after exclusion of the 2 outlier centers (p=0.0028). In the logistic regression model for the predictors of maturation time, there were 4 predictors; Study site (p=0.0165), duration of NPVA (p<0.0001), number of previous NPVA (p=0.0061, inverse correlation),and age at placement (P<0.0001). When AVF and AVG were separately analyzed, these predictors were only significant for AVF's. The overall PVA survival was 23.9± 13.9 months, with AVF's being statistically indifferent from AVG's (p=0.8270). Maturation time could not predict secondary failure of either access type (p=0.8817). There was no difference in maturation times between PVA with secondary failure and those that were still functional at the end of the observation period (p= 0.3675).

Conclusions: We demonstrated that the study site, both the duration and number of NPVA and age at placement may affect the maturation times for AVF's. AVG's had significantly shorter maturation times and none of the variables could predict their maturation times. Time to maturation was not a predictor of secondary failure of PVA in this cohort.

TH-PO1068

The Role of Vascular Access on Medicare Reimbursement among Patients with Incident End-Stage Renal Disease Receiving Hemodialysis

Sarah H. Yi,[1] Sophia Kazakova,[1] Duc B. Nguyen,[1] Ibironke W. Apata,[1,2] John A. Jernigan,[1] Priti R. Patel.[1] *[1]Div of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, GA; [2]School of Medicine, Emory Univ, Atlanta, GA.*

Background: Previous studies suggest better outcomes among patients with end-stage renal disease (ESRD) initiating hemodialysis (HD) with arteriovenous fistulas (AVFs) versus central venous catheters (CVCs). We sought to compare Medicare reimbursements during the first year of HD by vascular access at initiation.

Methods: A retrospective cohort of patients with incident ESRD in 2011 or 2012 was selected from a 5% sample of all Medicare beneficiaries. We included patients aged ≥67 years, covered by traditional fee-for-service Medicare two years before and one year after HD initiation, and alive one year after HD initiation. Initial vascular access was identified using the first modifier code (V5-V7) on an outpatient hemodialysis claim in the initial 60 days of HD. Inpatient, outpatient, and other claims were utilized to obtain reimbursement data. Medicare reimbursement in the first year of HD was modeled as a function of vascular access, age, sex, race, healthcare setting of first HD, and reimbursement in the year prior to HD as a proxy for baseline health status and utilization using a generalized linear model.

Results: Of 1,635 included beneficiaries, 23% and 77% started hemodialysis with AVF and CVC, respectively. In the year prior to HD initiation, crude median reimbursements were $15,452 and $19,026 among those initiating via AVF and CVC. In the year after HD initiation, crude median reimbursements were $58,604 and $91,165 among those initiating via AVF and CVC. Adjusted reimbursement was 18% lower (0.82, 95% CI: 0.77-0.87, *P*<.0001) among beneficiaries initiating with fistula compared with CVC.

Conclusions: Among a fully covered Medicare ESRD cohort surviving the first year of HD, those with fistula had lower total Medicare reimbursements during the first year of care even after adjusting for baseline reimbursement and other characteristics. These findings suggest a missed opportunity to prevent excess healthcare costs to Medicare associated with HD initiation with CVC.

Funding: Other U.S. Government Support

TH-PO1069

Effect of Hemodialysis on Anterior Chamber Biometric Structure and Intraocular Pressure in Non-Diabetic Patients with End-Stage Renal Disease

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Background: To evaluate the short-term changes in the ophthalmologic findings after low-flux hemodialysis in non-diabetic end-stage chronic renal failure (CRF) patients.

Methods: Forty-three patients (86 eyes) selected so as not to have glaucoma or history of glaucoma were studied. We observed the patients on maintenance hemodialysis therapy more than 6 months. Their clinical characteristics and medical records before and after hemodialysis were reviewed through the way of self-control study. Detailed ophthalmologic examinations together with tomometre (intraocular pressure, IOP), A/B scan(lens thickness) and ultrasound biomicroscopy(central anterior chamber depth) were performed immediately before and after HD sessions. Demographic information including age, gender, underling systemic diseases, hemodialysis duration, and levels of body weight, blood urea nitrogen, and creatinine before and after hemodialysis were recorded.

Results: The mean age of the patients at the time of dialysis was 49.7±12.0 (range 33 to 65) years. 53.5%(23) were men.After hemodialysis treatment, the blood urea nitrogen, creatinine, patient weight decreased significantly *(P*<0.01); There was no significant difference in the change of serum calcium, serum phosphorus, serum albumin and hemoglobin after the treatment(*P*>0.05). Mean central anterior chamber depth also decreased significantly after HD, from 2.46±0.38 to 2.38±0.36 mum (paired t test, *P*<0.01). Mean lens' thickness significantly increased from 4.23±0.22 mm before HD to 4.30±0.12mm after HD (*P*<0.01) in group. However, Mean IOP increased from 12.32±4.31 mmHg to 14.31±2.98mmHg after HD (paired t test, P<0.01).

Conclusions: Conventional hemodialysis can affect the ophthalmologic findings. Patients with chronic renal failure should be checked of their anterior chamber structure and be given corresponding treatment before haemodialysis.

TH-PO1070

Persistent Disparities in Hemodialysis Vascular Access

Jonathan H. Segal, Sehee Kim, Shu Chen, Jeremy J. Phipps, Jennifer Sardone, J. Affholter, C. Dahlerus. *Univ of Michigan Kidney Epidemiology and Cost Center.*

Background: Despite gains over the past decade with AV fistula (AVF) creation, concerns remain about vascular access (VA) disparities. Prior studies are limited by sample size or ability to adjust for clinical risk factors that influence AVF creation. Using data on Medicare ESRD patients we analyze the impact of patient demographic factors on likelihood of different VA types after adjusting for incident and prevalent comorbidities.

Methods: We used 2014 CROWNWeb for monthly VA data for all Medicare hemodialysis patients in the US. Incident comorbidities were obtained from the CMS 2728, and prevalent comorbidities from the prior 12 months of Medicare claims. Multivariate generalized logistic regression modeled odds of AVF/AV graft (AVG)/catheter (CVC) use associated w/ demographic and clinical factors.

Results: Of 2,920,145 patient-months AVF and AVG were used in 65% and 21% of patient-months. After adjusting for ethnicity, BMI, nursing home status, pre-ESRD care, duration of ESRD and 12 categories of comorbidities those aged 75+ were 19% and 15% less likely to have an AVF versus (V) AVG and CVC. Black patients were 47% and 16% less likely to have AVF V AVG or CVC compared to whites/other race. Hispanic ethnicity was associated with higher AVF use V CVC. Females were 52% and 46% less likely than males to have AVF V AVG or CVC.

	AVF v CVC	AVF v AVG	AVG v CVC
	OR	*OR*	*OR*
25-≤59	0.97	***1.2***	***0.81***
Age Ref: 60-75	-	-	-
75+	***0.85***	***0.81***	1.02
Black race	***0.84***	***0.53***	***1.58***
Hispanic eth.	***1.28***	1.06	1.24
Female sex	***0.54***	***0.48***	1.12
Vintage Ref: 1-4y	-	-	-
5-≤8y	1.03	***0.77***	***1.32***
9+y	***0.76***	***0.48***	***1.50***

p<0.01

Conclusions: We observed differences in AVF use by demographic characteristics. After adjustment for patient comorbidities, patients >75y, of black race, and females were less likely to have an AVF compared to AVG or CVC. Absent strong biological bases for barriers to achieving optimal vascular access outcomes by race and sex, caution is required in considering these risk adjustment factors as part of public reporting to avoid masking potential care disparities.

Funding: Other U.S. Government Support

TH-PO1071

Timing of Arteriovenous Fistula Creation prior to Hemodialysis Start in the Veterans Affairs Healthcare System

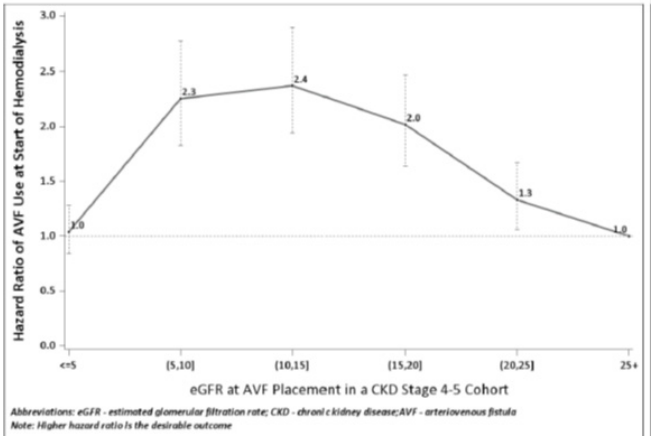
Rajiv Saran,[1] Anca Tilea,[1] Sai Hurrish Dharmarajan,[1] John Stephen,[1] Aaron Pearson,[1] Diane Steffick,[1] Brenda W. Gillespie,[1] Hal Morgenstern,[1] Eric W. Young,[1] Edward D. Siew,[2] Michael J. Fischer,[2] Karen Sovern,[2] Daniel F. Balkovetz,[2] Susan T. Crowley,[2] Vahakn B. Shahinian.[1] *[1]Univ of Michigan; [2]Veterans Affairs Healthcare System.*

Background: For quality assessment/improvement of VA clinical practice we analyzed existing data from the national Veterans Affairs Renal Information System (VA REINS) to determine incident HD vascular access rates and timing of AVF placement in VA that best predicts AVF at HD start.

Methods: VA 'user' is defined as ≥1 VA contact in 3 yrs. Users with eGFR <30 ml/min/1.73m^2 at any time (2008-13) were identified. Using procedure codes in VA, vascular access placements with corresponding eGFR (±3 mo) after the date of user entry into CKD stage4-5 were identified. Incident HD users and their access were identified from Medical Evidence Form 2728. Cox regression assessed predictors of AVF use at HD start. ESRD with access other than AVF (including those with catheters with maturing AVF) and pre-ESRD death were treated as competing risks. Adjustors were: age, sex, race, comorbidities, closest eGFR within 3 mo of AVF placement.

Results: Among the 349,020 users with CKD Stage4-5, 150,635 died; 40,313 patients started HD (16,968 with AVF; 1,723 AV Graft; 21,622 catheters). Wide variation in rates of AVF or Catheter with maturing AVF (34-64%) was observed across geographic areas. The estimated hazard ratios (HR), comparing eGFR values at the time of AVF placement are in Figure. The range of eGFR associated with highest HRs for Veterans starting HD with an AVF was 5-20ml/min/1.73m^2.

Figure: Adjusted HR (95% CI) for successful AVF use at HD start, by category of eGFR vs. eGFR ≥25 ml/min/1.73 m^2 (ref) at time of AVF placement in CKD Stage4-5.



Conclusions: In VA Healthcare System**,** placement of AVF early (eGFR>20) or late (eGFR <5) in users with CKD stage4-5 was associated with lower success in AVF use at HD start.The optimal window for AVF placement was eGFR in the 5-20 range. Geographic variation in VA AVF placement warrants further review.

Funding: VA Support

TH-PO1072

Use of a Vascular Access Coordinator to Increase Arteriovenous Fistula (AVF) Prevalence and Decrease Tunneled Catheter Duration and Use in an Inner City Hemodialysis Clinic Cesar Y. Cardona, Marquetta L. Faulkner. *Internal Medicine and Nephrology, Meharry Medical College, Nashville, TN.*

Background: The National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (NKF, KDOQI) push for dialysis practice standards envisioned a goal of <10% catheter use and >66% AVF use for each hemodialysis (HD) unit.[1] A major component of First Fistula Breakthrough Initiative is use of AVF within 90 days of first dialysis treatment to minimize time a tunneled catheter is present while awaiting AVF or arteriovenous graft (AVG) maturation in patients dialyzing via a tunneled catheter.[2] Goals of study are to establish, evaluate a protocol that can be replicated to minimize catheter use and maximize AVF prevalence and cannulation of AVFs or AVGs within 90 days of tunneled catheter placement.

Methods: In June, 2007 we designed a pilot program to increase prevalent AVF use from baseline of 19.9 % to greater than 60% by using a vascular access coordinator to coordinate care and monitor access creation and maturation.[3,4] We enrolled 60 patients based on inclusion criteria of GFR of less than or equal to 30 mL/min (assessed by MDRD equation) who were followed in the nephrology clinic or those who were referred to our clinic and met inclusion criteria or deemed appropriate by attending nephrologist for referral for vascular access placement. Patients were enrolled beginning June, 2007 to November, 2014.

Results: We were able to increase prevalent AVF use in our hemodialysis clinic from 19.9% to 56.9% (p<0.0001) and decrease catheter use for greater than 90 days from 32.5% to 12.6% (p<0.0001) and our total patients with catheters decreased to 18.9% from 42.5% (p<0.0001).

Prevalence June 2007	Prevalence February, 2015
AVF 19.9%	AVF 56.9%
Total Catheter (TC) 42.5%	TC 18.9%
Catheter > 90 days (C>90) 32.5%	C>90 12.6%

Conclusions: Use of a VAC helped increase AVF use and decrease both total tunneled catheter use and catheter use of greater than 90 days in an inner city hemodialysis clinic and results were statistically significant despite not reaching goals established by NKF and KDOQI.

Funding: Pharmaceutical Company Support - DCI helped support the funding for the position of the Vascular Access Coordinator

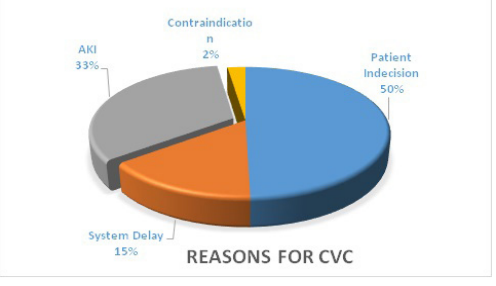
TH-PO1073

Why Not "Fistula First"? The Obstacles Sijie Zheng, Andrea Remeta, Joanna Mroz, Leonid Pravoverov. *The Permanente Medical Group, Oakland, CA.*

Background: In the US, 80% of patients initiate maintenance HD with a central venous catheter (CVC). One reason for low incidence of AVF/AVG was attributed to late referral. Kaiser Permanente Northern California (KPNC) is an integrated health care system providing health care to 3.9 million members. The East Bay service area provides health care to approximately 400,000 members with an estimate of 40,000 CKD patients.

Methods: A retrospective analysis was conducted of CKD patients who initiated dialysis in the KPNC East Bay Service Area from 2013 to 2015. For patients who initiated hemodialysis with a CVC, we analyzed the reasons for not having a matured AVF/AVG upon hemodialysis initiation.

Results: A total of 199 patients initiated HD from January 1, 2013 to December 31, 2015. Among them, 127 (63.8%) patients used CVC as their dialysis access upon initiation. 57 (28.6%) patients had a matured AVF at the start of dialysis and 15 (7.5%) patients had a matured AVG. We analyzed the reasons for failure to have a matured AVF/AVG and classified them into 4 categories: (1) delays due to patient indecision (63 patients, 49.6%), (2) system related delays (19 patients; 15%), (3) patients with Acute Kidney Injury (42 patients; 33.1%) and (4) medically contraindicated (3 patients; 2.4%).



Conclusions: In our integrated health care system, incident hemodialysis patients have lower CVC rates compared with the national average. Delays due to patient indecision and unexpected AKI requiring immediate dialysis initiation represent the majority of cases when permanent access is not established prior to initiation of dialysis. Patient education and close monitoring in the pre-dialysis period will likely have the highest effect in decreasing CVC rates in the future. In our integrated organization, system related delays represent a smaller overall opportunity to increasing the use of AVF/AVG as a primary access at initiation of dialysis.

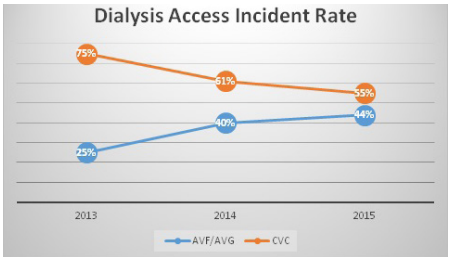
TH-PO1074

Strategies to Increase Incident AVF/AVG in Hemodialysis Patients Sijie Zheng, Andrea Remeta, Joanna Mroz, Leonid Pravoverov. *The Permanente Medical Group, Oakland, CA.*

Background: Despite higher mortality and complications associated with central venous catheter (CVC) use, 80% of incident HD patients in US are using CVC as their dialysis access. Kaiser Permanente Northern California (KPNC) is an integrated health care system providing health care to 3.9 million members. The East Bay service area provides health care to approximately 400,000 members with an estimate of 40,000 CKD patients.

Methods: We strengthened the collaboration between nephrologists and vascular surgeons by instituting a designated dialysis access nurse coordinator. Since June 2013, a dialysis access nurse coordinator to prospectively monitor patients approaching CKD 5. Patients with eGFR $\leq$ 25 ml/min/1.73 m^2 were referred for evaluation for AVF/AVG placement if they choose hemodialysis (HD). Protocols were developed to create consistent patient education about risks and benefits of various dialysis access types, uniform process of referral for vein mapping, pre-operative evaluation and operating room scheduling. In addition, the dialysis access nurse coordinator involved patient's caregivers, educating them on the importance of timely preparation for dialysis, thus improving adherence to appointments. Once the AVF/AVG was placed, a vascular surgeon examined the patient at 2 weeks and 8 weeks to ensure successful maturation of the AVF/AVG. The nurse coordinator ensured patient has follow up appointments with the vascular surgeons, nephrologists, duplex studies and AVF/AVG revision surgeries as needed.

Results: The incident AVF/AVG rate increased from 25% to 44% since 2013 to 2015, and the incident CVC rate decreased from 75% to 55% during the same period of time.



Conclusions: By increasing the overall integration of the pre-existing team of providers, an access nurse coordinator is able to significantly and consistently reduce rate of CVC in patients initiating hemodialysis in our integrated health care system.

TH-PO1075

Quality Improvement Project for Permanent Dialysis Access Rates in End-Stage Renal Disease Elliot M. Charen, Naitik Sheth, Chiarra Marie Ornillo, Nikolas B. Harbord. *Div of Nephrology and Hypertension, Mount Sinai Beth Israel, New York, NY.*

Background: Dialysis patients with central venous catheters (CVC) are expected to have more interventions for access dysfunction at higher cost, worse patency rates, and higher morbidity and mortality. Many incident dialysis patients initiate dialysis in the hospital and do not meet the expectation from NKF-KDOQI of CVC free by 90 days of dialysis initiation; many new-start dialysis patients have not consulted with a surgeon prior to initiation of dialysis.

Methods: New start chronic dialysis patients initiated while hospitalized and followed by the renal consult service were included. The retrospective first phase of data collection (January-March, 2014) involved a study of incident End-Stage Renal Disease (ESRD) patients who ultimately were discharged to an out-patient dialysis center. The hospital record (PRISM) was checked to see if the patient had a permanent dialysis access placed, a surgical consult for access was completed, or an out-patient office visit was scheduled. The prospective second phase (5 non-contiguous months from 2014-2015) involved teaching all new start ESRD patients about options for dialysis including the benefits of a permanent access and surgical evaluation with possible access placement.

Results: In the implementation phase as compared to the study phase, a greater percentage of patients had in-patient surgical consults (56% versus 29%, p=0.38) and out-patient surgical appointments (67% versus 43%, p=0.38). The amount of permanent dialysis accesses were no different between the two groups (28% versus 29%, p=1). The most common reason for not having an access placed during hospitalization was patient choice (n=7/18). The most common medical reason for not having an access placed was cardiac risk (n=3/18).

Conclusions: Patient education can be improved during an incident ESRD patient's hospitalization, but access planning education in the hospital may not allow patients sufficient time to make decisions about venous access placement.

TH-PO1076

AV Fistula Creation by Nephrologist: An Indian Experience Vinant Bhargava, Ritesh Kauntia, Devinder S. Rana, Anil Bhalla, Ashwani Gupta, Manish Malik, Anurag Gupta. *Nephrology, Sir Gangaram Hospital, New Delhi, India.*

Background: AV fistula is the preferred vascular access for long term hemodialysis as it has higher patency rates and lower infection rate, morbidity and mortality. The aim of the study was to assess the outcomes and primary patency rates of radiocephalic AV fistulae created by nephrologists.

Methods: A retrospective analysis of AV fistulas created by nephrology team in the year 2013 in Sir Gangaram Hospital, New Delhi, India was done. USG Doppler for forearm vein mapping was performed in cases where physical examination with tourniquet failed to reveal a cephalic vein of adequate diameter. Patients who did not have adequate caliber of cephalic vein were referred to vascular surgeon for brachial AV fistulae. Data was collected over telephonic conversation with the patients as well as physical examination in nephrology outpatient clinics.Primary failure was defined as an AV fistula which did not mature and could not be used for hemodialysis.

Results: 301 patients underwent AV- fistula surgery. 260 patients underwent 270 AV-fistula creation. 10 patients underwent AV fistula revision in view of primary failure. Data regarding maturation was not available for 41 patients. Analysis of 270 AV-Fistulae was done for primary maturation .The mean age of patients was 50.6±15.3years. 73.3%were males. 41.8% of patients had diabetes mellitus. Preexisting coronary artery disease was present in 20% and peripheral vascular disease was present in 1.85% of the patients. On follow up, 204 (75.56%) of AV fistula created had successful maturation. Primary failure was seen in 66 (24.44%) patients. Primary failure in patients with diabetes was seen in 38 out of 66 (57.57%) and 75 out of 204 (36.76%) had successful maturation (p=0.002). Coronary artery disease was present in 20 out of 66 (30.3%) patients with primary failure and 34 out of 204 (16.67%) patients with successful maturation (p=0.016).

Conclusions: This study shows that AV fistulae created by nephrologists have comparable success rates of maturation. Diabetes mellitus and coronary artery disease are significant risk factors for AV fistula primary failure.

TH-PO1077

Pre-Operative Venography and the Identification of Forearm Veins Compared to Ultrasound Vein Mapping Patrick McGlynn, Dirk M. Hentschel. *Nephrology, Brigham and Women's Hospital, Boston, MA.*

Background: The KDOQI guidelines advocate the creation of forearm over upper arm arteriovenous fistulas (AVFs), as these typically last longer and are associated with fewer access and systemic complications. In addition, forearm AVFs increase the success of secondary accesses created more proximally. Duplex ultrasound is the preferred method for pre-operative vessel mapping and has increased the successful creation of AVFs when compared to physical exam alone. However, in clinical practice many patients without a suitable forearm vein by US do in fact have forearm access options. Here, we describe the use of peripheral venography (PV) with serial released tourniquets to visualize the veins of the upper extremity and compare the peripheral vein findings from PV to that of ultrasound vein mapping (UVM).

Methods: The Brigham and Women's Interventional Nephrology Database was used for this study to identify a historical cohort of patients who received pre-operative PV and UVM between January 2008 and December 2015. The UVM and PV reports were reviewed for appropriate forearm veins to be used in AVF creation by Silva criteria. The presence of suitable veins was recorded as a dichotomous outcome. The extremities were treated as paired data-points and evaluated using McNemar's test.

Results: During the study period, 426 extremities were evaluated with peripheral venography in 246 patients. 202 extremities were evaluated using both PV and UVM, 44 forearm AVF created, and 49 extremities did not have an access created. PV identified 76 extremities with OR 4.38 (2.37-8.73). UVM recommended forearm AVF in 10 of the 44 created and venography recommended 18 of 44 created. The use of PV increased forearm AVF, however without clinical significance (p=0.06). The primary failure rate was similar in forearm accesses recommended by PV or UVM, 28% vs. 22% respectively.

Conclusions: This suggests the use of PV is associated with identifying more forearm veins to be used in the creation of AVFs, with similar primary failure rates.

Funding: NIDDK Support

TH-PO1078

The Use of Peripheral Venograms in Evaluating the Central Veins in Preparation for Permanent Dialysis Access Creation Patrick McGlynn, Dirk M. Hentschel. *Nephrology, Brigham and Women's Hospital, Boston, MA.*

Background: Ultrasound vein mapping (UVM) is the preferred method for pre-operative vessel mapping, and its use has increased the number of patients in whom an arterial venous fistula (AVF)is able to be placed. Despite pre-operative steps to optimize outcomes, 20-60% of AVFs are never usable for dialysis. The creation of an AVF requires a suitable outflow conduit, and central vein (CV) stenosis can impair maturation. Previous studies report that UVM can be used to assess the CVs for evidence of occlusion, with an 81% sensitivity and 97% specificity. Here, we describe the use of peripheral venography (PV) to visualize the CVs and compare CV findings from PV to that of UVM.

Methods: All patients with pre-operative PV between January 2008 and January 2016 at Brigham and Women's Hospitals were included. Images and reports were reviewed for the ability to visualize the CVs for patency, stenosis, or obstruction. PV used three serially released tourniquests (last in the axilla), and terminal, passive arm elevation to "dump" pooled contrast into the CVs (method established by Tom Vesely). The ability to visualize the CVs was recorded as 3= comparable to dedicated central venogram, 2= visible with confidence, 1=visible, but outline not distinct. CV were also evaluated via PV and UVM for evidence of CV stenosis or obstruction. The results were treated as paired data, and McNemar's test was used to evaluate a difference in detection in CV abnormalities.

Results: 426 extremities were evaluated via PV in 246 patients. 225 extremities were also evaluated with UVM. PV confirmed patency of the Superior Vena Cava 87% & 70%, Brachiocephalic 93% & 85%, and Subclavian veins 98% & 96% of the time on the right and left respectively. PV and UVM detected 52 and 5 extremities with CV stenosis or obstruction respectively. Only 2 of the 52 (4%) stenosis or occlusions detected with PV were identified with UVM (sensitivity=4%, specificity=98%). The use of PV was significantly associated with identifying CV stenosis with p= 0.00.

Conclusions: The use of PV can be used to evaluate the central veins. The utility of UVM in evaluating the CVs may be less useful than previously reported.

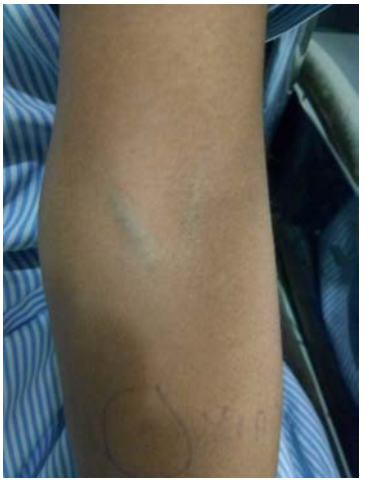
Funding: NIDDK Support

TH-PO1079

Prominent "V" at Elbow Is a Predictor of Successful Median Basilic to Brachial Artery Arteriovenous Fistula Sachin Soni.[1,2] [1]*Interventional Nephrology, United Ciigma Hospital, Aurangabad, Maharashtra, India;* [2]*Nephrology, MGM Medical College, Aurangabad, Maharashtra, India.*

Background: A functioning Arteriovenous fistula (AVF) is key to survival of patients on maintenance hemodialysis. In this study, we have looked at the outcome of side to side median basilic vein to brachial artery AVF. All surgeries are performed by the Nephrologist independently.This type of AVF is not discussed in literature frequently, but is technically very simple as the vein and the artery lie in close proximity just below the elbow crease.

Methods: In this prospective study, all patients undergoing median basilic vein to brachial artery AVF, were analysed for primary outcome of successful vascular access, defined as cannulable cephalic vein above elbow giving doppler flow more than 450 ml/min on surveillance monitoring and blood flow of more than 350 ml/min during dialysis after 3 weeks of surgery. We also looked at predictors of successful AVF and complications. Based on author's personal experience patients with prominent "V" at the elbow were taken for this type of fistula. (Prominent V at the elbow is formed by median basilic and median cephalic veins,).



Results: During the study period 122 patients underwent median basilic vein to brachial artery AVF. Of the study group 12 patients were lost to the follow up and 6 patients died before completing three weeks of post operative period. Of 104 patients, 96 patients (92.3%) patients had successful AVF. Male outnumbered females (66 males and 48 Females). Hypertension (78.8 %) was the most frequent co-morbidity, followed by Diabetes Mellitus (39.4%). Failure of maturation was seen in 8 patients and arm edema in 4 patients.

Conclusions: Side to side median basilic vein to brachial artery arteriovenous fistula is promising vascular access. Prominent "V" at the elbow is a strong predictor for success of such AVF.

TH-PO1080

Could Very Small Arteriovenous Fistulas Last Long Even in the Elderly on Hemodialysis? Hitoshi Iwabuchi, Manabu Asano, Kenichi Oguchi. *Bousei Hospital, Saitama, Japan.*

Background: The number of elderly patients who need hemodialysis treatment has been increasing here in Japan. Arteriovenous fistulas (AVFs) are the preferred choice for vascular access (VA); however, there is a debate over the utility of AVFs in older patients, particularly concerning fistula patency. We continued to make AVFs much smaller for preventing incidental load on the heart. The aim of this study was to verify that smaller size AVF might be appropriate for elderly patients.

Methods: A retrospective study was carried out on one hundred hemodialysis patients who underwent creation of a smaller size AVF. An average age of the subjects was 72.1±10.8 years, with 61 males and 39 females. Forty-seven of whom were lower than 75 years (GroupI) and the others were over 75 years (GroupII). The autologous radiocephalic fistulas at distal forearm were created by a single surgeon under the same method. The

anastomosis size by side to side was limited to just 3 mm. Primary VA patency was defined as the time to first VA intervention, and secondary patency as the time to creation of a new VA. Kaplan-Meier curves of primary and secondary AVF patency were generated. Also, comparisons between the two groups were performed using a log-rank test. Results were considered significant at P<0.05.

Results: The primary patency rates were 88.0% and 77.9% for GroupI and GroupII at 12 months, also 71.2% and 37.2% (p=0.03) at 36 months, respectively. The secondary patency rates for each were 92.2 % and 85.4 % at 12 months, also 78.6% and 59.8% at 36 months. Secondary AVF patency did not show any significant difference (p=0.34).

Conclusions: Our results disclosed lower patency rate of smaller AVFs in elderly patients. Although excessive blood flow must be unfavorable for any dialysis patient, our attempts to make AVF smaller were not able to show a new additional value for the elderly from the viewpoint of lives of VA.

TH-PO1081

Procedural Burden during Arteriovenous Fistula Maturation following Operative Placement: An Analysis of the United States Renal Data System Kenneth J. Woodside,[1] Kaitlyn Ratkowiak,[2] Purna Mukhopadhyay,[2] Sai Hurrish Dharmarajan,[1] Brett W. Plattner,[1] Douglas E. Schaubel,[1] Rajiv Saran,[1] Ronald L. Pisoni.[2] *[1]Univ of Michigan; [2]Arbor Research Collaborative for Health.*

Background: Over the last decade, the number of arteriovenous fistula (AVF) in the prevalent hemodialysis (HD) population has increased. We sought to determine the procedural burden required for successful AVF maturation in the incident United States HD population.

Methods: Using the United States Renal Data System (USRDS) Medicare claims and CROWNWeb data, we analyzed patients incident to HD from 7/1/12 to 6/30/13 with first-time AVF placements (after HD start) from 7/1/12 to 6/30/2014. Successful maturation was defined as documentation of first AVF use in CROWNWeb by 12/31/2014.

Results: Among the 102,703 incident HD patients, there were 24,416 first-time AVF placements of which 70.7% were successfully utilized, 25.5% failed to mature and 3.9% were lost to follow-up. Of those AVF that successfully matured, 44.2% required interventions during the maturation phase, with half of these interventions requiring angioplasty. Interventions were performed on 50.8% of AVFs that failed to mature. Not surprisingly, thrombectomies were carried out much more often in those with AVF maturation failure. Rates of interventions per patient (pp) are summarized in the Table.

Table. Interventions during AVF maturation.

	Successful Maturation	Failed Maturation
Patients	17,270	6,223
Patients with Interventions	7,629	3,271
Interventional Procedures	11,949 (0.69 pp)	9,685 (1.56 pp)
Diagnostic Fistulogram Only	2,659 (0.15 pp)	1,694 (0.27 pp)
Angioplasty	5,803 (0.34 pp)	3,154 (0.51 pp)
Thrombectomy	897 (0.05 pp)	3,601(0.58 pp)
Revision	2,144 (0.12 pp)	846 (0.14 pp)
Other	446 (0.03 pp)	390 (0.06 pp)

Conclusions: While there have been improvements in AVF utilization in the prevalent HD population, interventions on these AVF were exceedingly common during maturation. As such interventions are resource intensive, additional studies investigating patient and center level predictors of maturation success and interventional effectiveness are ongoing.

Funding: NIDDK Support

TH-PO1082

Risk Factors for Arteriovenous Fistula Nonmaturation in a European Cohort Bram M. Voorzaat, Koen E.A. van der Bogt, Jan Van Schaik, Friedo W. Dekker, Joris I. Rotmans. *Nephrology, Surgery and Clinical Epidemiology, Leiden Univ Medical Center.*

Background: Nonmaturation of permanent vascular access (VA) conduits is a significant burden for hemodialysis (HD) patients. European data about the current prevalence of nonmaturation are lacking. This study evaluated outcomes of VAs in a large Dutch retrospective cohort.

Methods: Clinical charts from 2004-2015 in 8 hospitals were retrospectively reviewed. Data were collected on VA configuration, procedures to improve maturation, medication and comorbidities. Maturation was assessed by clinical use of the VA. Risk factors for nonmaturation were identified through multivariable analysis. Next, the prediction model for nonmaturation by Lok, et al. was validated.

Results: 1383 arteriovenous fistulas (AVF) and 273 grafts (AVG) were included, for a total of 1656 vascular accesses in 1221 patients. Nonmaturation was defined as primary fistula failure. In patients requiring hemodialysis (HD), 24% (149/617) of radiocephalic AVFs (RCAVF) were never used for HD. For brachiocephalic AVFs (BCAVF) and AVGs these numbers were 11% (54/511) and 6% (13/229) respectively. Nonmaturation of RCAVFs was 23% (66/287) in prevalent HD patients and 25% (83/330) in pre-dialysis patients (p=0.533). Of RCAVFs used for HD, 21% (98/468) required additional procedures to assist maturation. A Lok-score over three did not predict nonmaturation of RCAVFs (score ≤ 3: 25%, score >3: 22%, p=0.505) or nonmaturation for all AVF configurations together. Female gender was a significant risk factor for nonmaturation, whereas age and diabetes were not.

Conclusions: This large cohort demonstrates a high incidence of nonmaturation in RCAVFs, with one out of every four RCAVFs never used, even in pre-dialysis patients. Female gender is associated with an increased incidence of nonmaturation. The Canadian Lok-score did not predict nonmaturation in this cohort.

Funding: Pharmaceutical Company Support - Proteon Therapeutics

TH-PO1083

A Prospective Cohort Study of Predictors of Upper Extremity Arteriovenous Fistula Maturation Aiza Waheed,[1] Agnes Masengu,[2] Tomas Skala,[3] Guiyun Li,[3] Jacek Jastrzebski,[4] Nadia Y. Zalunardo.[4] *[1]Dept of Medicine, Univ of British Columbia, Vancouver, BC, Canada; [2]Regional Nephrology Unit, Belfast City Hospital, Belfast, United Kingdom; [3]Vancouver General Hospital, Vancouver, BC, Canada; [4]Div of Nephrology, Univ of British Columbia, Vancouver, BC, Canada.*

Background: A substantial proportion of AVFs fail to achieve functional patency and cannot be used for hemodialysis (HD). We evaluated demographic and ultrasound data, and postoperative clinical assessment as predictors of AVF failure.

Methods: Prospective cohort study of patients with CKD at the Vancouver General Hospital (Canada) vascular access clinic who had an AVF created from April 2009 - April 2013. Vessel mapping was performed by an experienced vascular access nurse. The primary outcome was failure to achieve functional patency (HD with 2 needles, blood pump speed >=350 for 12 consecutive treatments). Stepwise logistic regression was used for multivariable analysis.

Results: Functional patency was assessed in 200 patients (of 247 total; 13 died, 21 remain CKD-ND) of which 123 (61.5%) were radiocephalic. At AVF creation: 54.5% were CKD-ND, mean age 63.1 yrs, 62.5% male, 47.5% white, 62.0% diabetes. 26.5% of AVFs failed (34.1% of lower arm vs. 14.3% of upper arm AVFs, P=0.002). Univariate predictors of AVF failure included: older age (P=0.03), female sex (P=0.05), smaller arterial diameter (P=<0.001), lower artery volume flow (P=0.04), smaller vein diameter (P=0.01), previous CVC or pacemaker (P=0.07). In multivariable analysis, age (OR 1.03, 95% CI 1.004-1.057), and artery diameter (OR 0.41, 95% CI 0.27-0.65) remained significant predictors of AVF failure; ischemic heart disease, peripheral vascular disease, race, and previous AVFs were not significantly associated. Vascular access nurse assessment 6 weeks postoperatively correctly predicted outcome in 83.8% of AVFs that achieved functional patency and 65.0% of AVFs that failed (kappa 0.45, p<0.0001).

Conclusions: Older age and smaller artery size predict a higher risk of AVF failure. Failure to achieve functional patency is common for radiocephalic AVFs despite use of preoperative ultrasound mapping. Further studies are needed to determine which patients should proceed directly to an upper arm AVF.

TH-PO1084

Maturation of Arteriovenous Fistula and Parameters That Predict Failed or Delayed Maturity - A Single Centre Study Pek Ghe Tan, Gail Theresa Read, Lisa S. Jeffs, Geoffrey S. Kirkland, Cheong Tatt Yew, Richard Yu, Matthew D. Jose. *Nephrology, Royal Hobart Hospital, Hobart, Tasmania, Australia.*

Background: Arteriovenous fistula (AVF) is the best vascular access for long-term haemodialysis. However, many fistulae (28-53%) never mature to support dialysis. The majority of these were salvageable with interventions. In our center, all fistulae have maturity assessment conducted by vascular access nurse between week 6 and 8. Those with maturation failure were investigated and/or discussed with primary vascular surgeon for appropriate early salvaging interventions.

Methods: We conducted a single center study to evaluate AVF maturation. Prospective data collected by vascular access nurse on all AVF created between January 2010 and December 2015 was reviewed. Patients who died before AVF maturity assessment were excluded. Clinically matured AVF was defined using the Kidney Disease Improving Global Outcomes (KDIGO) rule of 6's. Secondary outcomes evaluated include: causes of maturity failure; numbers of salvaging interventions performed and their success rate; and clinical predictors (e.g. age, gender, site of AVF, body mass index (BMI), venous and arterial diameter) for delayed maturity.

Results: 159 patients (71 females; mean age of 65) had primary AVF created and 42% (67/159) failed to mature. Significantly more female patients had failing to mature fistulae (p<0.05). There was no difference in mean age, diabetes, AVF site, arterial diameter and venous diameter. 78% of failed to mature fistulae (52/67) underwent salvaging interventions with 90% matured subsequently. Causes of maturity failure include: stenosis (44%), thrombosis (33%) steal syndrome (9%), accessory veins (4%) and deep AVF (13%). Factors associated with delayed maturation (>12 weeks, with or without salvaging interventions) were female gender (OR2.5; 95%CI1.2-5.2), obesity (BMI>30) (OR3.0; 95%CI1.4-6.4) and distal AVF (OR4.1; 95%CI1.3-12.5).

Conclusions: Failure to mature is a common issue with AVF but the majority is salvageable. Clinical assessment to detect early AVF failure is critical to improve rate of eventual maturation. Female gender, obesity and distal AVF were associated with delay maturation of AVF.

TH-PO1085

Correlation of AV Fistula Maturation with Scoring System - A Prospective Study from Developing Nation with Non White Population Hemant J. Mehta, Jhoomar R. Makhija, Soham Gohil, Wasi Shaikh. *Nephrology, Lilavati Hospital and Research Center, Mumbai, India.*

Background: Choosing the most appropriate vascular access site is guided by many factors. We investigated the clinical predictors of AV Fistula (AVF) Failure to mature (FTM) and applied an existing clinical risk prediction model for AVF FTM. The main objective of this study was to identify clinical risk factors that are related to Failure to Mature (FTM) AVF and whether such model can be applied to non white population.

Methods: A prospective study was designed that included all patients undergoing AVF creation between February 2014 and February 2016 in a single centre of a city from developing nation, whose functional AVF outcome was observed 6 weeks after creation of fistula. The preoperatively determined FTM predicted risk model (Lok et al) was applied to our cohort.

Results: Out of 113 AVF, 72 (63.7%) matured and 41 (36.3%) failed to mature at 6 weeks. The FTM scoring was applied to our cohort. The variables that were considered were age ≥65 years, Coronary Artery Disease and Peripheral Vascular Disease. In our study all patients were non white race, the scores ranged between 3-10.5 There were no patients in the low risk category because all patients start with a score of 3. In the moderate risk category (score 3); 44/59 fistulas matured and 15 did not. In the high risk category (score 3.1-6.9), 25/47 fistulas matured and 22 did not. In the very high risk category (score ≥7), 3/7 matured and 4 did not. Thus non maturation rates in the moderate, high and very high risk categories were 25.4%, 46.8% and 57.1% respectively, which was statistically significant (p=0.037).

Conclusions: Factors associated with AVF FTM are likely to vary from population to population. It is important to investigate local rates of AVF FTM and associated predictors of AVF patency in order to guide appropriate vascular access decision making. Clinical predictors of AVF FTM may not be sufficient on their own to improve vascular access functional patency rates. We suggest that the FTM score be revised as per population, and the categories be changed as follow for non white population: Low to moderate, moderate to high and very high risk categories.

TH-PO1086

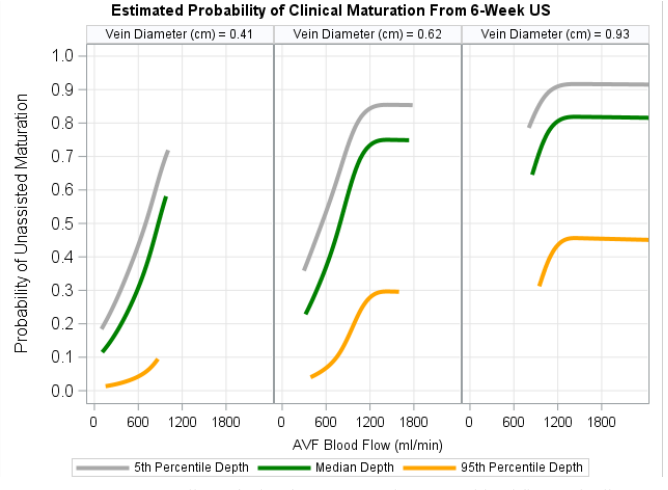
Prediction of AVF Clinical Maturation from Postoperative Ultrasound (US)

Michelle L. Robbin, Tom Greene, The HFM Study Group. *NIDDK, NIH.*

Background: The utility of early US measurements to predict AVF clinical maturation is uncertain. Primary unassisted and overall (assisted + unassisted) clinical AVF maturation were related to centrally measured US parameters.

Methods: We explored the prognostic accuracies of clinical maturation prediction from US parameters at 1 day, 2 and 6 weeks after AVF creation in 602 study participants of the 7-center Hemodialysis Fistula Maturation Study. A backward selection algorithm chose independent US predictors of unassisted and overall maturation among AVF blood flow, mean vein diameter, vein depth, arterial diameter, presence of stenosis, and presence of accessory veins, accounting for AVF location (upper arm vs. forearm), 5 case mix factors (age, sex, AVF location, diabetes, dialysis status) and clinical center. Missing US measures were multiply-imputed.

Results: At each time point, AVF flow, diameter, and depth were predictive of both unassisted and overall maturation (Figure). Accounting for AVF flow, diameter and depth, none of the remaining US parameters, AVF location, or case mix factors improved prediction, but maturation probabilities differed significantly among clinical sites after accounting for all these parameters. Cross-validated areas under ROC curves for prognostic models based on only the three US parameters increased from 0.69 at 1 day to 0.74 and 0.79 at 2 and 6 weeks for primary unassisted clinical maturation, and 0.69, 0.71, and 0.76 respectively for overall maturation. The US-prognostic models classified 6%, 11%, and 19% of subjects as having < 20% probability of unassisted clinical maturation at 1 day, 2 and 6 weeks.



Conclusions: Regardless of other factors, 6-week US AVF blood flow, vein diameter and depth are moderately predictive of clinical maturation.

Funding: NIDDK Support

TH-PO1087

Ultrasound-Guided Evaluation of Fistulas Safely Decreases Time to Cannulation and Catheter Removal

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Background: Use of bedside ultrasonography (USG) has dramatically increased in Medicine. Our dialysis center has used USG to evaluate arterio-venous fistula (AVF) maturation. Retrospective data from our center show significant improvement in time to cannulation without increased complications. We now present prospective data using USG as an aid to cannulation.

Methods: AVF cannulation based on physical exam alone from 2012-2014 was compared to AVF cannulation using USG 2014- 2016. AVF maturation criteria were: Diameter ≥6mm, Depth ≤6mm, Length ≥6cm. If by 4 weeks these criteria were not met the AVF was classified as failure of maturation (FOM). Examinations were done by fellows after completing the Emory renal-ultrasound course. Need for interventional radiology was considered a complication (early, 0-3 months; late, 4-12 months).

Results: 8/13 patients had USG for AVF cannulation compared to 12/29 as control. The remainder were FOM. Age and ethnic makeup were similar. USG examined AVFs had the shortest time to cannulation (17 days earlier, p< 0.05) and dialysis catheter (DC) removal (>100 days earlier, p<0.005). FOM results using USG were similar, except for fewer complications (0 vs. 10, p<0.05). Bloodstream infection rates were similar.

	UM with USG N=8	UM Control N=12	FOM with USG N=5	FOM control N=17
Female sex	25%	17%	20%	47%
Average Age	51±15	57±13	52±7	51±13
Race				
African American	12.5%	8.3%	20%	6%
Asian	12.5%	16.6%	40%	75%
Latino	75%	75%	40%	18%
White	0%	0%	0%	0%
PMH of DM	62.5%	50%	100%*	35%
Cannulation time, days	41±17*	58±18	81	150
DC removal time, days	70±34**	180±72	247±111	364±155
Early complications	1/8	8/12	0/5*	10/17
Late complications	3/8	8/12	1/5	7/17
Bacteremia, patients	2/8	2/12	2/5	10/17
Bacteremia, number	3	2	2	17
*p<0.05, **p<0.005				

Conclusions: USG resulted in early and safe AVF cannulation and earlier removal of DCs. USG also helped identify FOM allowing for earlier cannulation in this group (p 0.07).

TH-PO1088

Central Venous Oxygen Saturation as a Novel Means to Monitor Arterio-Venous Fistula Maturation

Israel Campos,[1] Hanjie Zhang,[1] Schantel Williams,[1] Stephan Thijssen,[1] Peter Kotanko.[1,2] *[1]Renal Research Inst, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Most patients start hemodialysis (HD) with a central-venous catheter (CVC) as vascular access. Whenever possible, an arterio-venous fistula (AVF) is created, which will serve as a permanent vascular access after an appropriate maturation time. Progress of fistula maturation is primarily evaluated clinically. Central venous oxygen saturation ($ScvO_2$) can be measured using Crit-Line® monitor in HD patients with a CVC. The main objective of this study was to assess the change in $ScvO_2$ after AVF creation.

Methods: We analyzed $ScvO_2$ measurements before and after AVF creation using Crit-Line® monitor (Fresenius Medical Care, Waltham, MA). We compared the four closest values of $ScvO_2$ before AVF creation, the first three $ScvO_2$ measurements after AVF creation and the last three $ScvO_2$ measurements before AVF cannulation; finally we compared these values with the first two $ScvO_2$ measurements after AVF cannulation day.

Results: We studied 6 patients. Mean $ScvO_2$ before AVF creation was 63.2 ± 0.3% and increased to 74.1 ± 0.8% after AVF creation. The average $ScvO_2$ of the final 3 HD sessions immediately preceding the first AVF cannulation was 76.1 ± 0.8%. After AFV cannulation arterial and no longer central venous blood circulated in the extracorporeal system with a mean oxygen saturation of 92.9 ± 0.2% (Figure 1).

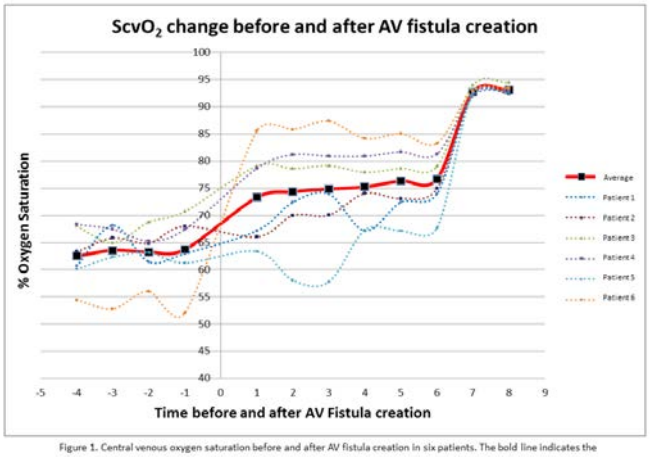


Figure 1. Central venous oxygen saturation before and after AV fistula creation in six patients. The bold line indicates the group average.

Conclusions: AVF creation results in increased contribution of arterial blood to the central venous backflow to the right heart. This increase in $ScvO_2$ is recorded by the Crit-Line® device. Prospective studies are warranted to further explore the feasibility of monitoring AVF maturation – or the failure thereof – using $ScvO_2$. We observed a $ScvO_2$ rise after AVF creation. If successful, $ScvO_2$ values could be used as a novel means to objectively track the AVF maturing process.

Funding: Pharmaceutical Company Support - Renal Research Institute

TH-PO1089

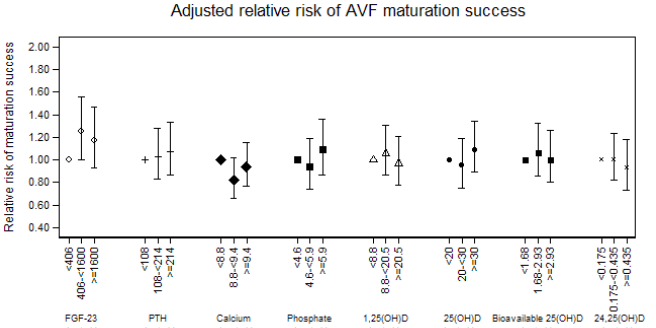
Mineral Metabolism Markers and Arteriovenous Fistula Maturation

Rachel W. Kubiak,[1] Bryan R. Kestenbaum,[1] Leila R. Zelnick,[1] Jonathan Himmelfarb,[1] Gerald J. Beck,[3] The HFM Study Group.[2] *[1]Univ of Washington; [2]NIDDK, NIH; [3]Cleveland Clinic Foundation.*

Background: The arteriovenous fistula (AVF) is central for providing life sustaining hemodialysis treatments. However, half of all AVFs fail to mature within the toxic environment of end stage renal disease (ESRD). Disturbances in mineral metabolism affect most ESRD patients and may impair AVF maturation by disrupting endothelial function and promoting vascular calcification. We hypothesized that lower serum concentrations of vitamin D metabolites and higher concentrations of FGF-23 and phosphate would be associated with AVF maturation failure.

Methods: We evaluated 562 participants from the Hemodialysis Fistula Maturation study, a multicenter study of ESRD patients undergoing planned AVF creation. At the pre-surgical study visit, we measured serum concentrations of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and 24,25-dihidroxyvitamin D using liquid chromatography-mass spectrometry, fibroblast growth factor-23 (FGF-23) and parathyroid hormone (PTH) using immunoassays, and phosphate and calcium. We used Poisson regression with robust errors to estimate associations of mineral metabolism markers with unassisted AVF maturation within nine months of surgical placement.

Results: A total of 263 participants (47%) achieved unassisted AVF maturation. In continuous analyses, serum concentrations of vitamin D metabolites, FGF-23, PTH, calcium, and phosphate were not associated with AVF maturation after basic adjustment. Further evaluation of associations with more complete adjustment and using restricted splines demonstrated no association of any markers with AVF maturation. Similarly, the calcium*phosphate product was not associated with AVF maturation.



Conclusions: Serum concentrations of mineral metabolism markers prior to surgery are not associated with AVF maturation in a large prospective cohort study of ESRD patients.

Funding: Other NIH Support - DK 094891, P30 DK035816

TH-PO1090

Postoperative Medial Fibrosis Predicts Maturation Failure in Two-Stage Arteriovenous Fistulas

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Background: The purpose of this study is to evaluate the impact of vascular fibrosis on arteriovenous fistula (AVF) outcomes.

Methods: Native vein and juxta-anastomotic AVF biopsies were obtained from patients undergoing two-stage AVF creation. Pre-existing, postoperative and change in intimal and medial fibrosis (% area of collagen) were quantified in Masson's trichrome stained cross-sections using color thresholding methods. Associations between vascular fibrosis and clinical outcomes (maturation failure and unassisted primary patency) were assessed using logistic regressions and Cox proportional hazards models adjusted for sex.

Results: Intimal and medial fibrosis in native veins (n=63) ranged from 10.1 to 71.7% and 16.2 to 64.4%, respectively. Nonetheless, neither measure of pre-existing fibrosis was associated with AVF outcomes. Postoperative intimal and medial fibrosis in AVF (n=78) ranged from 16.5 to 66.7% and 25.7 to 74.3%, respectively. Increased postoperative medial fibrosis, but not intimal fibrosis, predicted maturation failure (odds ratio [OR] 1.078, p=0.022), and this effect was more pronounced using the collagen/cell area ratio (OR 1.368, p=0.038). None of the measures of postoperative fibrosis were associated with primary patency. Change in fibrosis over time was assessed in 54 patients from whom both vein and AVF biopsies were available. Supporting the postoperative fibrosis association, a higher increment in medial fibrosis, but not intimal fibrosis, predicted maturation failure (OR 1.106, p=0.032) but not primary patency.

Conclusions: Our results suggest that elevated fibrosis and loss of medial smooth muscle cells are signatures of adverse AVF remodeling and predispose for early access failure. In contrast, increased fibrosis does not appear to determine the long-term patency of working fistulas.

Funding: NIDDK Support

TH-PO1091

Association between Preoperative Venous Medial Collagen Fiber Configuration and Arteriovenous Fistula Development

Yan-Ting E. Shiu,[1] Silvio H. Litovsky,[2] Alfred K. Cheung,[1,3] Daniel Pike,[1] C.S. Jason Tey,[1] Y. Zhang,[1] Carlton J. Young,[2] Michael Allon.[2] *[1]U of Utah; [2]U of Alabama; [3]VASLCHCS.*

Background: Arteriovenous fistula (AVF) maturation requires an increase in the diameter and blood flow of the fistula vein following its creation. The native vein wall's microstructure may affect the magnitude of these changes. We hypothesized that the orientation of collagen fibers in the venous media modulates the vein's capacity to dilate and mature.

Methods: Veins used for anastomosis were sampled during AVF creation surgery. The second harmonic generation (SHG) signals of collagen fiber bundles in vein samples were analyzed for anisotropy index (AI) and orientation angle (OA). AI ranged from 0 (random fiber network) to 1 (completely aligned fiber network). OA ranged from 0° (parallel to lumen) to 90° (perpendicular to lumen). The fiber configuration index (FCI) was defined as the product of AI and sin(OA). Unadjusted gamma regressions with natural cubic splines were used to model the association of the FCI in 84 patients and their 6-week AVF blood flow assessed using ultrasound.

Results: Venous medial collagen fiber patterns varied among patients with end-stage renal disease (Fig. 1A). The 6-week AVF blood flow was positively associated with the collagen FCI (per 0.1 unit difference in FCI: Δ blood flow = 131 ml/min; 95% CI, 8 to 254 ml/min; p=0.038) (Fig. 1B). The FCI of clinically matured AVFs (those successfully used for dialysis) was significantly higher than that of non-matured AVFs (0.13±0.07 vs. 0.08±0.05, p=0.02).

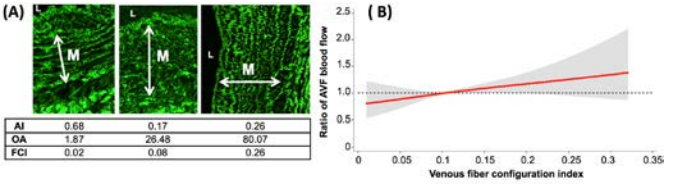

Fig. 1. (A) Representative SHG images of difference fiber patterns and FCI in the venous medial (M) layers. L: lumen. **(B)** The y coordinate is the ratio of the unadjusted geometric mean 6-week AVF blood flow at the indicated FCI to the unadjusted geometric mean 6-week AVF blood flow rate at the median FCI reference. N=84.

Conclusions: The venous medial collagen fiber orientation was associated with subsequent AVF development. Veins with collagen fibers more uniformly aligned perpendicular to the lumen were associated with higher AVF blood flow and clinical maturation by yet undefined mechanisms.

Funding: NIDDK Support

TH-PO1092

Uremic Regulation of Endothelial Krüppel-Like Factor 2 in Arteriovenous Fistula (AVF) Maturation Failure

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[1]Univ of Cincinnati; [2]Univ of Arizona.

Background: AVF maturation failure resulting in prolonged dialysis catheter exposure, is an important cause of clinical morbidity and mortality. The endothelial transcription factor Krüppel-like factor 2 (KLF2) is an important regulator of vascular homeostasis linking changes in hemodynamics to inflammation, vasodilation, and vascular remodeling. While KLF2 expression plays a critical role in atherogenesis, little is known about its role in AVF maturation failure. Our objective was to determine how endothelial KLF2 is regulated in-vitro by uremic metabolites and translate these findings into a uremic mouse model of AVF maturation failure.

Methods: Human umbilical vein endothelial cells (HUVECs) were cultured with uremic toxins, including carboxymethyl lysine (CML), an advanced glycation end product (AGE), and analyzed for KLF2 expression by qPCR and western blotting. In addition, C57BL/6J mice underwent 5/6 nephrectomy to produce renal insufficiency followed by AVF creation (after 14 days). The venous segment of the AVF was harvested 14 days post-AVF creation and KLF2 expression assessed by immunohistochemistry (IHC) and qPCR.

Results: CML treatment of HUVECs decreased KLF2 mRNA and protein expression, which was rescued by siRNA-RAGE ablation. Similarly, KLF2 was decreased in the endothelium of uremic versus non-uremic mice (IHC). Interestingly, KLF2 was upregulated (IHC) in the neointima of uremic mice, which corresponded to a three-fold increase in KLF2 venous segment mRNA expression in uremic versus non-uremic mice.

Conclusions: Our results suggest that uremia can suppress *endothelial* KLF2 in-vitro and in-vivo. However, uremia increases KLF2 expression within the neointima *(smooth muscle cells)* of the AVF. Ongoing studies utilizing endothelial and myeloid-specific KLF2 knockout mice will further delineate these mechanisms and also identify the specific roles of KLF2 in AVF stenosis. These data could then be used to develop novel therapies that target the KLF2 pathway in order to enhance AVF maturation rates.

TH-PO1093

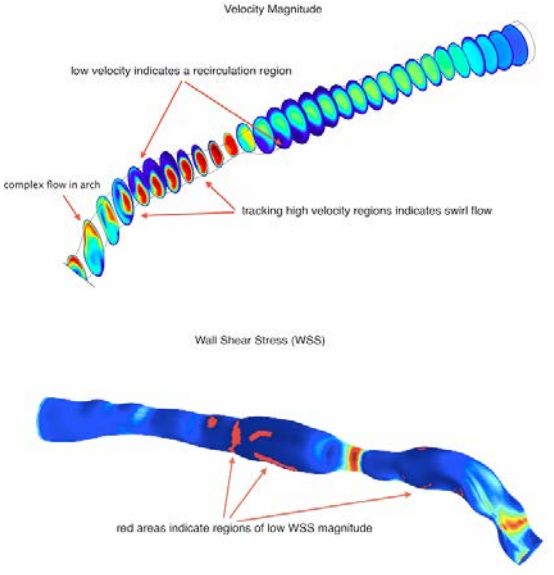
Computational Modeling from Intravascular Ultrasound in Arteriovenous Fistula Access

Mary S. Hammes,[1] Kevin Cassel,[2] Michael Boghosian,[2] S.M. Javid Mahmoudzadeh A.[2] *[1]Univ of Chicago; [2]Illinois Inst of Technology.*

Background: While angiography provides two-dimensional lumeography, the intraluminal surface of an arteriovenous fistula (AVF) is often a complex three-dimensional structure. Intravascular ultrasound (IVUS) is a technique using a high frequency ultrasound transducer on the tip of a catheter inserted directly into a blood vessel to obtain a series of high-resolution three-dimensional images. The aim of the current study was to reconstruct three-dimensional images of the cephalic arch in patients with brachiocephalic fistula access as the basis for computational modeling of the hemodynamics.

Methods: 13 IVUS procedures were performed in 8 subjects. A Doppler for blood flow velocity, venogram and blood sample were collected for whole blood viscosity. An IVUS catheter was then inserted into the cephalic arch to the axillary vein and pull back measurements were made. Image analysis and reconstruction with computational modeling were performed to determine the hemodynamics, including wall shear stress (WSS), velocity and pressure profiles.

Results: An example of a three-dimensional reconstruction is shown. The graphic on the top shows velocity magnitude contours highlighting regions of interest such as abnormally low and high velocities and locations of recirculation and swirl.



The graphic on the bottom shows WSS contours on the vein intimal surface. Areas of WSS below the normal range are indicated by a solid red color. WSS above the normal range are observed at the constriction.

Conclusions: The ability to assess vessel wall morphology and luminal characteristics of diseased veins in an AVF is a novel application of IVUS and may ultimately improve the understanding of hemodynamic determinates of AVF function.

Funding: NIDDK Support, Other NIH Support - National Institute of Diabetes and Digestive Diseases (NIDDK) and the National Institutes of Health (NIH) under award number RO1DK090769

TH-PO1094

Quantification of Venous Adaptation in Patients with Brachiocephalic Fistula Access

Mary S. Hammes,[1] Kevin Cassel,[2] Michael Boghosian,[2] S.M. Javid Mahmoudzadeh A.[2] *[1]Univ of Chicago; [2]Illinois Inst of Technology.*

Background: An autogenous arteriovenous fistula (AVF) is the optimal vascular access for hemodialysis. A brachiocephalic fistula (BCF) is often placed, but unfortunately cephalic arch stenosis (CAS) commonly develops leading to access failure. We have hypothesized that a contribution to fistula failure is low wall shear stress (WSS) (less than 0.076 *Pa*), resulting in neointimal hyperplasia (NIH) leading to venous stenosis. The aim of this investigation is to develop a novel graphical method to assist in characterization of vein adaptation response mechanisms which lead to CAS.

Methods: 12 patients that had BCF placed were included in this study. A venogram, Doppler to measure blood flow velocity, and whole blood viscosity measurement were performed at baseline, time of AVF maturation and when CAS was evident. Computational modeling was performed to determine areas of low WSS and geometric parameters. Zonal plots were created showing the relationship between local diameter change and WSS at various time points.

Results: WSS in a cephalic venous arch prior to AVF creation ranged from 0 *Pa* to 2.5 *Pa*. The majority of WSS measurements fell within the normal range (0.076 to 0.76 *Pa*) with an average WSS of 0.22 *Pa*. Post-fistula plots at time of maturation and beyond showed 4 scenarios: decrease in diameter change with WSS < 0.076 *Pa* (**NIH**); increase in diameter change with WSS < 0.076 *Pa* (**aneurism**); increase in diameter change with WSS > 0.076 *Pa* (**excess dilation**); decrease in diameter change with WSS > 0.076 *Pa* (**inward remodeling**). As an AVF matures, these zonal plots depict which of the mechanisms dominate locally, with particular emphasis on vein adaptation via NIH following maturation.

Conclusions: WSS outside the physiologic range 0.076 to 0.76 *Pa* predicts abnormal venous adaptation in an AVF. As an AVF matures, the optimal geometry of the cephalic arch is altered via NIH in an attempt to bring the WSS back within the physiologically acceptable range. The very mechanism that is intended by the body to mitigate the undesirable low WSS "over adapts" because of the excessively high blood flow velocity created when an AVF is placed, which is found to lead to CAS in a large proportion of patients.

Funding: NIDDK Support, Other NIH Support - National Institute of Diabetes and Digestive Diseases (NIDDK) and the National Institutes of Health (NIH) under award number RO1DK090769

TH-PO1095

In Vitro Analysis of Vascular Access Flow by Laser Doppler Vibrometry

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Background: A contact-free assessment of arterio-venous access (AVA) flow is currently elusive. Laser Doppler vibrometry provides a novel means to quantitate flow-induced AVA vibrations ("thrill") and may thus assist in diagnosing AVA malfunction.

Methods: We engineered an AVA bench model (Fig. 1) to systematically study the effects of lumen stenosis on radial velocities of an artificial AVA conduit. Flow (*Qa*) was provided by a pump delivering pulsatile patterns resembling arterial flow (Model 1423, Harvard Apparatus. Holliston, MA, USA). We kept *Qa* constant at 1500 mL/min (stroke volume 30 mL; stroke rate 50/min). AVA conduit inflow and outflow stenoses were applied by graduated lumen constrictions (Fig. 1). Stenoses were either partial (50% stenosis), or complete (100% stenosis). AVA conduit radial velocities were measured by laser Doppler vibrometry (PDV-100, Polytec, Waldbronn, Germany). Radial velocity data are presented in mm/s and as mean±SD.

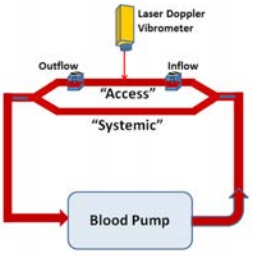


Fig. 1: AVA Bench Model

Table 1: Summary of velocity

Access Radial Velocity (mm/s)				
		Inflow Stenosis		
		None	Partial	Complete
Outflow Stenosis	None	0.21±0.014	0.19±0.03	0.08±0.021
	Partial	0.29±0.015	0.17±0.03	0.16±0.015
	Complete	0.47±0.02	0.44±0.02	0.05±0.015

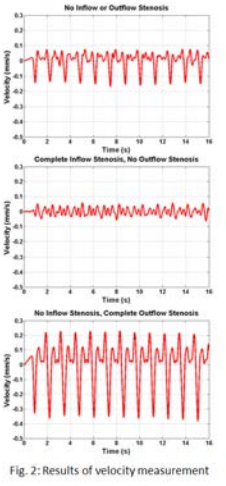


Fig. 2: Results of velocity measurement

Results: The highest radial velocities were observed with complete outflow stenosis and concurrent absent or partial inflow stenosis. Irrespective of the degree of outflow stenosis, any inflow stenosis drastically reduced radial conduit velocities (Table 1; Fig. 2).

Conclusions: This bench research shows that both inflow and outflow stenosis affects the radial velocities of AVA conduits to an extent that can be quantified by laser Doppler vibrometry. Moreover, this study indicates that laser Doppler vibrometry can potentially distinguish between inflow and outflow stenosis. While these results are encouraging, in vivo studies are warranted to determine if these experimental findings can be replicated in a clinical setting. To that end, analysis of access flow pressures and thrill frequency spectra may add to our understanding of the system dynamics.

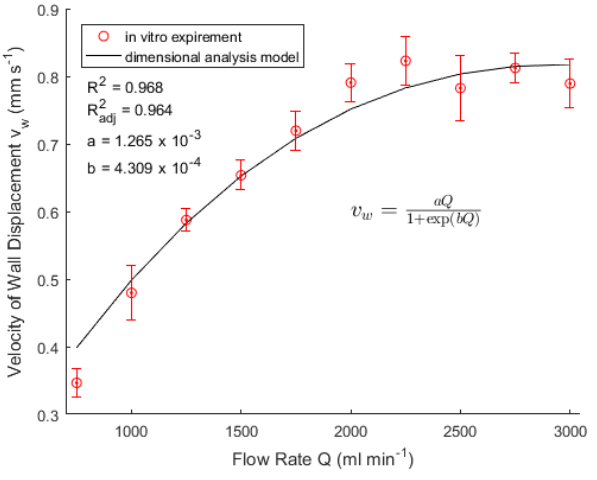
TH-PO1096

A Novel Mathematical Model to Non-Invasively and Contact-Free Assess Arterio-Venous Access Characteristics Alhaji Cherif,[1] Doris H. Fuertinger,[1] Vaibhav Maheshwari,[1] Israel Campos,[1] Camille Johnson,[1] Schantel Williams,[1] Jie Ma,[1] Laura Rosales,[1] Fansan Zhu,[1] Peter Kotanko.[1,2] *[1]Renal Research Inst, New York, NY; [2]Icahn School of Medicine, Mount Sinai Hospital, New York, NY.*

Background: While clinically desirable, a non-invasive and contact-free assessment of arterio-venous (AV) access characteristics is elusive. The aim of the current work is to assess the applicability of a novel theoretical model with laser Doppler vibrometer (LDV) data to analyze AV access characteristics.

Methods: We engineered a bench model where a pump (Model 1423, Harvard Apparatus. MA) produced pulsatile flow with arterial characteristics in a tube that resembled an AV access. The vibrations ("thrill") the AV access model were then quantitated with LDV (PDV-100, Polytec, DEU). Using dimensional analysis informed by a 1D Navier-Stokes equation describing the relationship between flow and cross-sectional area of a compliant vessel, we derive an expression (Fig. 1) relating the radial velocity of the vessel wall (V_w) and the flow rate (Q) with characteristic parameters $a=1/(2*pi*R_0*L)$ and $b=mu/(E*h)$, where R_0, L, E, h and μ are reference radius, vessel length, Young's modulus, wall thickness, and fluid viscosity, respectively.

Results: Using LDV signals, we fit the model to the data and estimated the characteristic parameters with goodness of fit coefficients R^2=0.968 and adjusted R_{adj}^2=0.964 (Fig. 1). The results show the relationship between the V_w and Q exhibits a functional shape where the velocity increases linearly until the vessel compliance (viscoelasticity) dominates.



Conclusions: The preliminary results illustrate the use of LDV and modeling to evaluate AV access characteristics with a good model-data fit. Further studies and modeling efforts are needed to explore the robustness of the modeling framework to identify the characteristics of AV access both in bench and clinical studies.

TH-PO1097

De Novo Induction of Mineralocorticoid Receptors in Vascular Tissue Mediates Hemodialysis Fistula Dysfunction Pei Wang,[1,2] Andrew S. Brem,[1] Xianhui Liang,[1] Minglei Lu,[1] Zhangsuo Liu,[2] Rujun Gong.[1] *[1]Nephrology, Brown Univ; [2]The First Affiliated Hospital of Zhengzhou Univ, China.*

Background: Fistula stenosis is a major cause of vascular access failure in patients undergoing maintenance hemodialysis (HD). Since mineralocorticoids can induce inflammation and fibrosis in vascular tissues, we hypothesized that these steroids may play a role in fistula failure.

Methods: Mineralocorticoid receptor (MR) expression was examined in normal human veins and in the dysfunctioning fistulae by immunohistochemistry. The effects of aldosterone were also measured in cultured vascular smooth muscle cells (VSMC) programmed to over express MR. Lastly, as a clinical correlation, HD patients on spironolactone because of cardiac disease were compared to age matched controls on HD and fistula patency was evaluated.

Results: Dysfunctioning stenotic fistulae exhibited a marked thickening of the intima and media, with affected VSMC demonstrating proliferation [staining for proliferating cell nuclear antigen (PCNA)] and hypertrophy [large cellular size plus staining for phosphorylated p70S6K, a transducer of the mTOR pathway associated with cellular hypertrophy]. While normal veins express minimal MR, a marked increase in MR expression was observed in affected VSMC with a pattern of distribution across all tunicae layers of the fistula, and this positively correlated with the intima-media thickness. Cultured VSMC over expressing MR (GFP-MR-147) showed excessive cellular proliferation [measured by the tetrazolium assay and PCNA expression] and hypertrophy [measured by protein to DNA ratios and expression of phosphorylated p70S6K] after exposure to aldosterone (10 nM). These effects were largely abolished by the MR antagonist spironolactone (1 μM). Lastly, patients on HD who received spironolactone exhibited an improved rate of fistula patency compared to control HD patients.

Conclusions: MR is induced in fistula VSMC probably from baro-trauma associated injury. Excess expression of MR in the presence of physiologic concentrations of aldosterone promotes cell proliferation and hypertrophy leading to fistula stenosis. MR antagonism may be a promising therapy for retarding the progression of fistula stenosis in patients on HD.

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

TH-PO1098

Association of Genetic Polymorphisms of Renin–Angiotensin–Aldosterone System-Related Genes with Arterio-Venous Fistula Malfunction in Hemodialysis Patients Chih-Ching Lin.[1,2] *[1]Div of Nephrology, Dept of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [2]School of Medicine, National Yang Ming Univ, Taipei, Taiwan.*

Background: Hemodialysis (HD) is the most commonly-used renal replacement therapy for patients with end-stage renal disease worldwide. Arterio-venous fistula (AVF) is the vascular access of choice for HD patients with lowest risk of infection and thrombosis. In addition to environmental factors, genetic factors may also contribute to malfunction of AVF. Previous studies have demonstrated the effect of genotype polymorphisms of angiotensin converting enzyme on vascular access malfunction.

Methods: We conducted a multicenter, cross-sectional study to evaluate the association between genetic polymorphisms of renin-angiotensin-aldosterone system and AVF malfunction.

Results: Totally, 577 patients were enrolled. Their mean age was 60 years old and 53% were male. HD patients with AVF malfunction had longer duration of HD (92.5 ± 68.1 *vs.* 61.2 ± 51.9 months, $p < 0.001$), lower prevalence of hypertension (44.8% *vs.* 55.3%, $p = 0.025$), right-sided (31.8% *vs.* 18.4%, $p = 0.002$) and upper arm AVF (26.6% *vs.* 9.7%, $p < 0.001$), and higher mean dynamic venous pressure (DVP) (147.8 ± 28.3 *vs.* 139.8 ± 30.0, $p = 0.021$). In subgroup analysis of different genders, location of AVF and DVP remained significant clinical risk factors of AVF malfunction in univariate and multivariate binary logistic regression in female HD patients. Among male HD patients, right-side AVF and upper arm location are two important clinical risk factors. In addition, two single nucleotide polymorphisms (SNPs), rs275653 (Odds ratio 1.90, $p = 0.038$) and rs1492099 (Odds ratio 2.29, $p = 0.017$) of angiotensin II receptor 1 (*AGTR1*), were associated with increased risk of AVF malfunction. After adjustment for age and other clinical factors, minor allele-containing genotype polymorphisms (AA and CA) of rs1492099 still remained to be a significant risk factor of AVF malfunction (Odds ratio 3.63, $p = 0.005$).

Conclusions: In conclusion, we demonstrated that rs1492099, a SNP of *AGTR1* gene,could be a potential genetic risk factor of AVF malfunction in male HD patients.

Funding: Government Support - Non-U.S.

TH-PO1099

Oxidative Stress-Induced High Mobility Group Box 1 (HMGB1) Stimulates Monocyte Chemoattractant Protein-1 (MCP-1) Expression in the Human Umbilical Vein Endothelial Cells (HUVECs) Jeong-Sun Han, Yaeni Kim, Yong-Soo Kim. *Div of Nephrology, Dept of Internal Medicine, The Catholic Univ of Korea College of Medicine, Seoul, Korea.*

Background: Oxidative stress and inflammation are the main causes of vascular intimal hyperplasia and subsequent stenosis of hemodialysis arteriovenous fistula. In our previous study, oxidative stress directly stimulated the MCP-1 expression. In this study, we studied whether HMGB1 was involved in the process of oxidative stress-induced MCP-1 expression.

Methods: HMGB1 mRNA and MCP-1 mRNA were measured by quantitative real-time PCR. MCP-1 protein was measured by ELISA. HMGB1 protein, MAPK, NF-κB and AP-1 activities were measured by western blot. Glycyrrhizin or a monoclonal antibody to TLR4 was used to inhibit HMGB1.

Results: After treating HUVECs with H_2O_2, MCP-1 mRNA and protein expression was significantly increased in a time- and dose-dependent manner. In addition, after treating HUVECs with H_2O_2, HMGB1 mRNA and protein expression was significantly increased in a time- and dose-dependent manner. When the cells were pre-treated with inhibitors of p38 (SB203580), JNK (SP60012), NF-κB (PDTC), or AP-1 (curcumin), H_2O_2–induced HMGB1 mRNA expression was significantly decreased. When the cells were treated with HMGB1, the MCP-1 mRNA and protein expression was significantly increased in a time- and dose-dependent manner. When the cells were pre-treated with glycyrrhizin or a monoclonal antibody to TLR4, the HMGB1-induced MCP-1 expression was blocked in a time- and dose-dependent manner. HMGB1 treated cells stimulated phosphorylation of p38, JNK, c-jun and p-65 together with a decrease in IkBa.

Conclusions: Oxidative stress-induced MCP-1 expression in HUVECs is partially mediated by HMGB1 via the TLR4/p38/JNK/NF-κB/AP-1 pathways. This study suggests that HMGB1 inhibition in vein endothelial cells might be a challenge to prevent venous neointimal hyperplasia in hemodialysis arteriovenous fistula.

Funding: Government Support - Non-U.S.

TH-PO1100

High-Mobility Group Box Protein 1 (HMGB1) Induces Endothelial-to-Mesenchymal Transition (EndMT) in Human Umbilical Vein Endothelial Cells (HUVECs) Jeong-Sun Han, Yaeni Kim, Yong-Soo Kim. *Div of Nephrology, Dept of Internal Medicine, The Catholic Univ of Korea College of Medicine.*

Background: Myofibroblasts are the major cells within the venous neointima in stenosed hemodialysis vascular access. However, the origin of the myofibroblasts has not been clealy determined. In our previous study, oxidative stress stimulated HMGB1 expression in HUVECs. In this study, we investigated whether HMGB1 induced EndMT in HUVECs.

Methods: After stimulating the HUVECs with HMGB1, the key biomarkers for endothelial and mesenchymal cells were evaluated by fluorescent immunocytochemistry and western blot. EndMT transcription factors (snail1, snail2, and twist1) were measured by western blot. Role of HMGB1 receptors (TLR4 and RAGE) and TGF-β1 in the mechanism of HMGB1-induced EndMT was studied.

Results: HUVECs were normal round shape with cobble stone appearance with strong labeling of CD31, VE-cad, and vWF, but a-SMA was not expressed in the cells. When the cells were exposed to HMGB1, cells changed into the spindle shape with decreased expression of CD31, VE-cad, vWF and high expression of a-SMA. Western blot revealed same changes in biomarkers before and after HMGB1 treatment. When the cells were pre-incubated with antibodies to HMGB1 receptors, TLR4 or RAGE, the changes in the HMGB1-induced endothelial and mesenchymal biomarkers were reversed in a dose dependent manner. HMGB1 stimulated the expression of EndMT transcription factors (snail1, snail2, and twist1)in a dose dependent and in a time dependent manner up to 48 hours. In addition, HMGB1 stimulated the expression of TGF-β1, and the phosphorylation of smad2/3 and NF-κB p65. When the cells were pre-treated with anti-RAGE antibody or Glycyrrhizin, the expression of TGF-β1 by HMGB1 were reduced. When the cells were pre-incubated with SB431542, the changes in the HMGB1-induced endothelial and mesenchymal biomarkers were reversed in a dose dependent manner.

Conclusions: To our knowledge, this is the first report showing that HMGB1 induces EndMT via the RAGE/TGF-β1signaling in the venous endothelial cells. These data might provide a mechanism of myofibroblasts accumulation within the venous neointima in stenosed hemodialysis vascular access.

Funding: Government Support - Non-U.S.

TH-PO1101

Selecting End Points for Pivotal Hemodialysis AV Fistula Clinical Trials - Anatomical Surrogates versus Functional Suitability Maria V. DeVita,[1] Eric S. Chemla,[2] Konstantine B. Kipiani,[3] Sriram Iyer.[4] *[1]Div of Nephrology, Lenox Hill Hospital, New York, NY; [2]Vascular Surgery, St. George's NHS Trust, London, United Kingdom; [3]Vascular Surgery, Georgian Center of Angiology and Surgery, Tbilisi, Georgia; [4]Vascular Therapies Inc, Cresskill, NJ.*

Background: Although an ultrasound (US) vein diameter (VD) of 4mm and AVF blood flows >500mL/min are often proposed/used as surrogates to support fistula functionality, these parameters have never been validated in large clinical trials. Anatomical AVF patency, a "success metric" in pre-dialysis patients, correlates poorly with functional use; in the DAC study 45% of AVF not suitable for dialysis (D) were anatomically patent.

Methods: 30 pts undergoing AVF surgery [22 Radiocephalic (RCF), 8 Brachiocephalic (BCF)] received a Sirolimus eluting collagen implant around the anastomosis. Serial US exams were performed. Cannulation decisions were based on clinical exam.

Results: Pre op mean±VD for RCF and BCF were 2.7±0.5 and 3.9±0.6mm. 4 RCF thrombosed within 2 weeks(w); 26 AVF (87%) were successfully cannulated for D (Mean 7w). Relative to cannulation, VD in 22/26 AVF (85%) was ≥6 mm (Range: 5.1-10.1mm), there were no infiltrations. At 12mos 74% of AVF maintained *functional patency*.

US Timing	6-8hrs Post-op	2w	4w	6w	8w		
VD ≥4mm (n=26) RCF n=18 BCF n=8	22/28*(79%) 14(70%) 8(100%)	24/26(92%) 16(89%) 8	25(96%) 17(94%) 8	26(100%) 18(100%) 8			
VD ≥6mm (n=26) RCF n=18 BCF n= 8	2/28*(7%) 0 2/8(25%)	8/26(31%) 2(11%) 6(75%)	16(62%) 8(44%) 8(100%)	21(81%) 13(72%) 8	26(100%) 18(100%) 8		
Cannulation success (n=26) RCF n=18 BCF n= 8			21 14 7			3 2 1	2 2
Time to cannulation			4 - 8w			8-10w	>12w
* 2 RCF thrombosed soon after surgery							

Conclusions: 1. 85% of cannulated AVF had VD ≥6.0mm; none were <5.1mm. 2. Absent surrogate validation, pivotal clinical trials evaluating the impact of a new treatment on AVF outcomes should use clinical end points that require demonstration of AVF cannulation and show continued functional durability during later time points. This would necessitate excluding patients not on dialysis at the time of AVF surgery.

Funding: Pharmaceutical Company Support - Vascular Therapies, Inc.

TH-PO1102

The Effect of Beraprost Sodium to Treat Primary Hemodialysis Vascular Access Failure Hyun Woo Kim,[1] Miyeon Kim,[1] Tae Hee Kim.[2] *[1]Dept of Internal Medicine, Jeju National Univ, School of Medicine, Jeju National Univ Hospital, Jeju-si, Jeju-do, Korea; [2]Dept of Internal Medicine, Inje Univ College of Medicine, Busan, Korea.*

Background: Hemodialysis vascular access dysfunction is a major cause of morbidity and hospitalization in the hemodialysis patients. The major cause of hemodialysis vascular access dysfunction is venous stenosis as a result of neointimal hyperplasia. Although several studies suggest a role for antiplatelet agents in the prevention of hemodialysis vascular access failure, it has not been complete. It has been reported that prostaglandin I_2 has pleiotropic effects including antiplatelet, vasodilating, anti-inflammatory and anti-atherogenic properties. In addition, several studies have shown that prostaglandin I_2 can inhibit the neointimal formation generated after vascular injury.

Methods: The purpose of this study was to research the effects of beraprost sodium, an oral synthetic analog of prostaglandin I_2 on vascular access patency in hemodialysis patients with primary hemodialysisvascular access failure. The primary outcome was secondary vascular access failure. Between April 2013 and February 2014, forty-nine patients with end stage renal disease on hemodialysis were prospectively chosen for this study. Twenty-three patients were assigned to be treated with 120 μg/day of beraprost sodium and the other patients (n=26) were assigned to a control group.

Results: After a median follow-up of 3.0 years (interquartile range 1.8-3.1 years), the secondary vascular access failure was detected in twelve patients (46%) in control group andfour patients (17%) inberaprost sodiumgroup, respectively (P = 0.032). Analysis of covariables indicated that this effect occurred principally as a result of beraprost sodium administration. No life-threatening adverse event or severe bleeding was recorded in both groups.

Conclusions: Our data indicated that oral prostaglandin I_2 analog is effective and safe for the prevention of secondary vascular access failure in hemodialysis patients with primary vascular access failure.

Funding: Private Foundation Support

TH-PO1103

Palliative and End of Life Care for End Stage Renal Failure Patients Managed without Dialysis in Denmark. A National Survey Jens Kristian Madsen,[1,2] Fliss E. Murtagh.[2] *[1]Dept of Renal Medicine, Aarhus Univ Hospital, Aarhus, Denmark; [2]King's College London, Cicely Saunders Inst, London, United Kingdom.*

Background: In Denmark, there is a growing focus on conservative kidney management (CKM) for older frail patients with end stage renal failure (ESRF). This survey aimed to assess the current provision of palliative and end of life (EOL) care to Danish patients with ESRF following a non-dialytic pathway or discontinuing dialysis.

Methods: An electronic questionnaire was sent to all Danish hospital-employed nephrologists and department nurses (15 centres). Data were handled anonymously. Descriptive statistics were used for analyses.

Results: 140 senior renal staff were invited. The response rate was 83%, including 93% (14/15) of medical directors/head physicians. All units had CKM patients, but numbers were mostly unknown. When asked whether nephrologists had same practice regarding choice of CKM for ESRF patients, 24% of respondents answered 'yes', 58% answered 'no', and 18% answered 'don't know'. Criteria of patients' suitability for CKM were similar. Criteria for timing discussion of CKM with patients differed (at a certain level of renal function, 33%; at low-clearance clinic referral, 17%; not known, 15%; when symptoms, 11%; other, 24%). One renal centre had a dedicated clinic, one centre had treatment guidelines, and 12% staff had training in CKM. Follow-up mostly occurred in general renal outpatient clinics (75%). Advance care planning (ACP) was formally practiced in two units. One third of respondents reported involvement of specialist palliative care (SPC) with CKM patients at EOL and when stopping dialysis. Only 7% did not see a future role for SPC for ESRF patients. Suggestions for improvement were more education (87%), better collaboration (67%), and implementation of ACP (64%).

Conclusions: Great variation exists in practice patterns of delivery of palliative and EOL care for Danish ESRF patients managed without dialysis or discontinuing dialysis. Formal CKM pathways are not yet developed. Nephrologists report that SPC is under-utilized among Danish ESRF patients at the end of life. Education and better collaboration between specialties are key elements in further development.

TH-PO1104

The Practice of Withholding of and Withdrawing from Dialysis Treatment to Patients with Persistent Vegetative State in Affluent Arabic Countries: Renal Physician Survey Omran Bakoush,[3] Ahmed Chaaban,[1] Mona Alrukhaimi,[2] Bassam Bernieh.[1] *[1]Nephrology Dept, Tawam Hopsital, Al Ain, AbuDhabi, United Arab Emirates; [2]Internal Medicine, Dubai Medical College, Dubai, United Arab Emirates; [3]College of Medicine and Health Sciences, United Arab Emirates Univ, Al Ain, AbuDhabi, United Arab Emirates.*

Background: Persistent vegetative state (PVS) is severe disability which requires full nursing care and is associated with poor outcome. The number of dialysis patients with persistent vegetative state (PVS) is increasing worldwide. In United Arab Emirates, 29 patients out of 650 patients on regular dialysis treatment were in PVS. This study aimed to explore the practice patterns of withhold and withdrawal of dialysis in patients with PVS in affluent Gulf Arabic countries.

Methods: Settings: Renal physicians taking care of dialysis patients in public and private sectors in Gulf Arabic counties. Interventions: A 24-item online self-administered questionnaire based on ASN Shared Decisions clinical practice guidelines. Primary and secondary outcome measures: The renal physicians' approach to manage PVS patients with severe kidney failure.

Results: The survey was completed by 29 nephrologists taking care of patients with ESKD. 83% of respondents will continue dialysis if a dialysis patient went into persistent vegetative state, furthermore dialysis will be initiated by 55% of respondents if a PVS patient developed severe renal failure. Institutional haemodialysis is most common dialysis modality (81%) offered to PVS. The respondents identify the cultural background (76%), the local policy (72%), and the religious background (65%) to be the major impacts on the decision making process for ongoing dialysis treatment for patients with PVS.

Conclusions: The contextual sociocultural factors and the preferences of the patient's proxy strongly influence the physician decisions for initiation and continuation of dialysis treatment for patients in PVS. Early integration of quality palliative care within the health care system for such severely ill patients is required to face the increasing burden of PVS in such developing affluent countries.

TH-PO1105

'La Familia es lo mas Importante': Palliative Care Perspectives of Latinos on Dialysis Lilia Cervantes,[1,2] Claudia Camacho,[2] Maria Francisca Zabalaga Palma,[2] Stacy M. Fischer.[1] *[1]Univ of Colorado; [2]Denver Health.*

Background: Patients with end-stage renal disease (ESRD) have a high symptom burden and mortality yet palliative care is often overlooked. Hispanics have a nearly 2-fold higher incidence of ESRD and suffer disproportionately at end-of-life (EOL) compared to non-Hispanic whites. The purpose of our study was to understand the palliative care experiences and preferences of Hispanics on dialysis.

Methods: We conducted qualitative, semi-structured interviews with Hispanic ESRD patients. We used an interview guide with open-ended questions to elicit the patient's palliative care preferences and experience with advance care planning. Interviews were audio-recorded, transcribed, and then analyzed by four members using a deductive approach.

Results: We interviewed 20 Hispanic ESRD patientsbetween October 2015 and January 2016. Our qualitative theme analysis yielded five main themes: Family, advance care planning (ACP), advance directives (AD), fatalism, and hospice. Patientsprioritizefamily needs over personal needs, and EOL preferences are thus centered around family. Patients express that ACP decisions should be made by the family as a whole. Patients also feel it is important to have ACP conversations early on before extreme illness, and as long as the provider initiating conversations maintained a positive outlook. Some patients feel that because their family is aware of their wishes, there is little value in signing an advance directive. For those with a documented signed AD, few were able to recall any details of their decisions. Fatalistic attitudes and a resignation to illness were expressed, such as illness being a punishment for past personal or parental behavior. Patients also feel that death and the process of death is predetermined and beyond their control, and thus take a passive disposition towards ACP. Regarding hospice, patients prefer to die at home with family.

Conclusions: With respect to palliative care, patients express the importance of integrating their family in ACP decision-making and describe barriers such as fatalism.

Funding: Private Foundation Support

TH-PO1106

Improving Comfort with Comfort Care Discussions Juliya Hemmett,[1,2] Elena Qirjazi,[1,2] Faisal Rehman,[1,2] Valerie Schulz,[2,3] Norman Muirhead.[1,2] *[1]Nephrology, London Health Sciences Centre, London, ON, Canada; [2]Schulich School of Medicine & Dentistry, London, ON, Canada; [3]Perioperative Medicine & Anesthesia, London Health Sciences Centre, London, ON, Canada.*

Background: Previous studies have demonstrated a gap in nephrology training on end of life discussions. We addressed this deficiency in the curriculum by creating a goals of care (GOC) discussions workshop using role plays and didactic teaching.

Methods: We designed and implemented a 3 hour workshop consisting of a didactic session on an evidence based approach to GOC discussions in chronic kidney disease patients, followed by small group simulations to practice this approach. Participants included nephrologists, a palliative care physician, nurses, social workers, Standardized Patients (SP) and nephrology fellows. Small group participants were divided into four teams led by a pre-selected staff nephrologist. Nephrology fellows led one, and observed one, of two simulated family meetings discussing: 1) withdrawing from dialysis in a frail patient and 2) conservative management in end-stage renal disease. At the end of each scenario the fellows received constructive feedback from the other participants. Participants evaluated their experience using anonymous surveys containing 7 questions evaluating the effectiveness of the workshop using a 5 point Likert scale and additional space for comments.

Results: 14 out of 16 participants completed the anonymous surveys. The workshop was ranked "very useful," "important," and "relevant" to their practice. In particular, the use of SPs was highlighted. Constructive feedback included providing the scenarios ahead of time and further clarifying the roles of the allied health. Importantly, nephrology staff leaders identified knowledge gaps such as what happens to patients when they stop dialysis, and were able to address them.

Conclusions: Our workshop is the first in Canada to teach GOC discussions using didactic teaching and dynamic simulations involving the main stakeholders in nephrology. This educational intervention proved to be effective in improving current knowledge and comfort levels of care providers.

TH-PO1107

Factors Influencing Supportive Care Discussions in Hemodialysis Patients Billie Axley, Michael R. O'Connell, Dugan Maddux, Marta Reviriego-Mendoza, John W. Larkin, Stephanie Johnstone, Michelle L. Gilliland, Rebecca L. Wingard, Tammy C. Green, Franklin W. Maddux. *Fresenius Medical Care North America.*

Background: Advanced care planning has been reported to be rarely discussed, despite that most hemodialysis (HD) patients desire better communication for supportive care needs (Goff SL, et al. 2015). We explored what factors are considered influential to initiating these discussions by surveying a group of HD nurses (RNs).

Methods: In March of 2016, a voluntary, electronic survey was offered to RNs at a Fresenius Medical Care nursing focused meeting. Survey questions and responses are as outlined in Figure 1. Questions 1 & 2 had 116 responses, and questions 3 & 4 had 68 responses.

Results: Based on this survey of dialysis clinic RNs, decreased quality of life (QOL) and multiple comorbidities were the most common reasons for care providers to have initiated conversations about supportive care (88% & 52%, respectively) (Figure 1A). Similarly, the patients/family members reported to have initiated conversations due to decreased QOL, followed by symptom burden from HD (89% & 49%, respectively) (Figure 1B). Responses from questions 3 & 4 found that 70% of RNs believe a private talking area could better enable clinic staff to initiate a supportive care discussions, followed by educational courses and materials for staff (Figure 1C). It was identified that the staff also believe patients would benefit from more educational materials (Figure 1D).

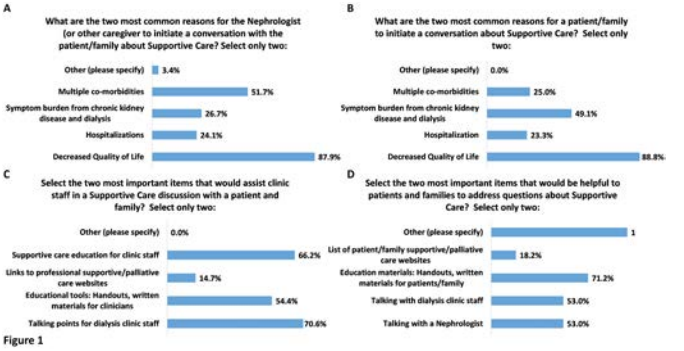


Figure 1

Conclusions: The survey results suggest that decreased QOL is the most common reason for patients and/or families to initiate supportive care discussions. The study also reveals tools that clinic staff and patients/families may find helpful to facilitate discussions on supportive care options. Overall, these survey findings reinforce the need for strategies that support patient's values and wishes in regards to supportive care.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

TH-PO1108

International Variation in Dialysis Discontinuation: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS) Sarbjit Vanita Jassal,[1] Maria Larkina,[2] Kitty J. Jager,[3] Fliss E. Murtagh,[4] Ann M. O'Hare,[5] Manjula Kurella Tamura,[6] Norio Hanafusa,[7] Richard D. Swartz,[8] Hal Morgenstern,[8] Friedrich K. Port,[2] Keith McCullough,[2] Francesca Tentori.[2] *[1]Univ Health Network, Toronto; [2]Arbor Research, MI; [3]Academic Medical Center, Amsterdam; [4]King's College London; [5]VA, Seattle; [6]Stanford Univ; [7]Univ of Tokyo Hospital; [8]Univ of MI, Ann Arbor.*

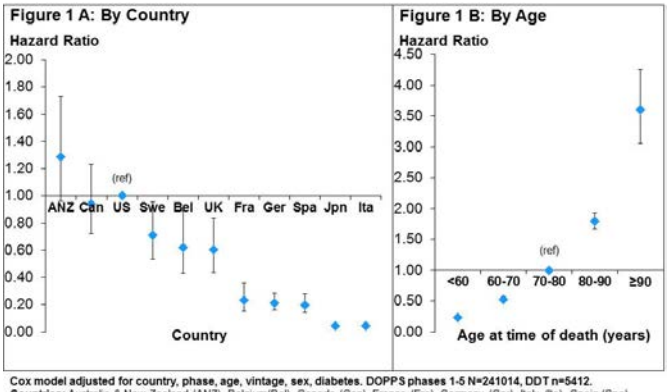
Background: Dialysis is a burdensome and difficult treatment. In some cases, patients, their families, or their healthcare team may consider discontinuation of dialysis therapy (DDT). DOPPS provides an opportunity to assess international variability in DDT across 12 countries and associated clinical characteristics.

Methods: Staff identified the reason each patient left a DOPPS facility, with DDT (n=5412) as an option (v. death, transfer, etc.) from 1996 to 2015. Adjusted Cox regression tested associations of DDT with country, age, sex, dialysis vintage, DOPPS phases, and diabetes status.

Results: Adjusted DDT HRs varied greatly, with 30-fold variation across countries (fig 1A) and 15-fold variation across age groups (fig 1B). DDT rates were highest within 4 months of dialysis initiation (HR[95% CI]=1.4[1.3, 1.5] v. >1 year), and those with diabetes (1.2[1.1,1.2]). No consistent era effect over DOPPS phases was seen.

Conclusions: The wide variation of DDT amongst 12 countries suggests sociocultural determinants are important contributor to DDT, and over how DDT is designated and accepted. The strong association of DDT with age and vintage may imply different considerations and practices with respect to DDT for different patient populations. Enhancing our understanding of DDT, particularly during the first few months of dialysis therapy, may help align practices when considering dialysis initiation and help us better understand the need for palliative renal care services.

Adjusted association of country and age with dialysis discontinuation



Cox model adjusted for country, phase, age, vintage, sex, diabetes. DOPPS phases 1-5 N=241014, DDT n=5412.
Countries: Australia & New Zealand (ANZ), Belgium(Bel), Canada (Can), France (Fra), Germany (Ger), Italy (Ita), Spain (Spa), Sweden (Swe), United Kingdom (UK), and United States (US)

Funding: Pharmaceutical Company Support - AbbVie, Amgen, Baxter Healthcare, F. Hoffmann-LaRoche, Hexal, Keryx, Kyowa Hakko Kirin, Merck, Proteon, Relypsa, Sanofi, Shire, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, WiNe Institute, Societies for Nephrology in Germany, Italy, & Spain

TH-PO1109

Dialysis Nurses' Perspectives on Advance Care Planning Katharine L. Cheung,[1] Bette J. Gilmartin,[2] Ann S. Laramee,[3] Prema R. Menon,[4] Robert Macauley,[5] Allison Tong.[6] *[1]Medicine-Nephrology, Univ of Vermont College of Medicine, Burlington, VT; [2]Dialysis & Apheresis, Univ of Vermont Medical Center, Burlington, VT; [3]Medicine- Cardiology and Palliative Care, Univ of Vermont Medical Center, Burlington, VT; [4]Medicine- Pulmonary/Critical Care, Univ of Vermont Medical Center, Burlington, VT; [5]Pediatrics, Univ of Vermont Medical Center, Burlington, VT; [6]School of Public Health, The Univ of Sydney, Sydney, New South Wales, Australia.*

Background: Advance care planning (ACP) is recommended for dialysis patients and yet there has been no systematic implementation. Dialysis nurses often spend more time with patients than other providers, and have the potential to contribute to ACP. We aimed to describe nurses' perspectives on their role and challenges of ACP in the dialysis setting.

Methods: Nurses with experience in dialysis from a university hospital network participated in face-to-face semi-structured interviews. Transcripts were coded using investigator triangulation. Results were based on grounded theory and thematic analysis.

Results: We interviewed 26 dialysis nurses, median age 55 (range 32-72), with 18 (1-45) years of dialysis experience. We identified five themes: advocating for patients (witnessing suffering, coaching healthy behaviors, facilitating communication); dispersed knowledge (operating in clinical silos, sense of helplessness, managing prognostic uncertainty); navigating family-like relationships (respecting patient's struggles, maintaining professionalism, expressing compassion); juxtaposition of frailty and resilience (working to survive, locus of control, balancing hope with anticipatory fear, chronicity of illness) and community of nurses (pooled wisdom and shared bereavement).

Conclusions: Nurses viewed themselves as advocates seeking to protect patients from worsening illness, and to prepare them for death by creating opportunities to explore their fears and wishes. At the same time, nurses sought to preserve hope and felt conflicted when patients survived acute illness. Although nurses had support from each other, they hoped for a greater sense of community and palliative care training.

Funding: Clinical Revenue Support

TH-PO1110

Abstract Withdrawn

TH-PO1111

A Novel Communication Skills Curriculum to Improve Shared Decision Making among Nephrology Fellows Jehan Z. Bahrainwala,[1] Niharika Ganta,[2] Nina R. O'Connor,[2] Karen M. Warburton,[1] Denise Lamarra,[3] Jeffrey S. Berns.[1] *[1]Renal, Electrolyte and Hypertension Div, Hospital of the Univ of Pennsylvania, PA; [2]Palliative Care Program, Div of General Internal Medicine, Hospital of the Univ of Pennsylvania, PA; [3]Standardized Patient Program, Perelman School of Medicine at the Univ of Pennsylvania.*

Background: Nephrologists are often faced with difficult conversations regarding goals of care. Most nephrology training programs lack formal communication training. Here we describe a novel communication skills curriculum aimed at improving shared decision making regarding dialysis and end of life care.

Methods: Curriculum: The curriculum included a one hour workshop conducted by palliative care faculty that was attended by 12 first and second year nephrology fellows. A new framework called "SUPER" (Setup, Understanding, Priorities, Explain, Review) was introduced to guide goals of care conversations. Fellows then participated in role play sessions with standardized patients (SP) to practice their skills. These sessions were observed by renal and palliative care faculty who provided real-time feedback. A debriefing session was conducted by renal and palliative care faculty 1 week later. **Measures:** Fellows completed self-assessment surveys measuring their comfort with goals of care communication prior to the workshop, immediately following the SP experience, and 6 weeks later.

Results: A comparison of the scores obtained across subjects during three time points (pre-workshop, post-workshop, 6 weeks post curriculum) demonstrated significant differences among their distributions (p=0.015). Post-hoc *t*-tests revealed a significant improvement in self-assessment scores in post-curriculum scores when compared to the pre- curriculum scores (p=0.02). This improvement was sustained as evidenced by the significant improvement in 6 weeks post-curriculum scores when compared to pre-curriculum scores (p=0.02).

Limitations: small sample size, self-reported rather than objective skills assessment, lack of control group.

Conclusions: A novel curriculum to enhance communication skills for nephrology fellows improved self-reported scores in communication.

TH-PO1112

Racial Disparities in the Utilization of Palliative Care in Dialysis Patients from the United States Renal Data System Haytham Alkhaimy,[1] Jennifer L. Waller,[1] Mufaddal F. Kheda,[1] Jake Everett Turrentine,[1] Rhonda E. Colombo,[1] N. Stanley Nahman,[1,2] Lu Y. Huber.[1] *[1]Augusta Univ, Augusta, GA; [2]Charlie Norwood VAMC, Augusta, GA.*

Background: CMS has approved payment for voluntary end-of-life counseling as part of its 2016 Medicare physician fee schedule. We queried the USRDS to investigate how palliative care (PC) has been utilized in the ESRD population.

Methods: All deaths of incident dialysis patients from 2004–2011, age 18-100, were queried. Those with an ICD-9 code V66.7, received hospice care or discontinued dialysis at least 4 days before death were defined as having received PC. Basic descriptive statistics were calculated. Kaplan-Meier analysis was used to estimate survival. Generalized linear models were used to estimate the relative risk (RR) of PC.

Results: Among the 874,777 incident dialysis patients, 459,679 (52%) died by the end of 2012. 30% (136,917) of deaths had PC, with increasing usage from 2004 to 2011 (2%, 6%, 9%, 11%, 13%, 15%, 17%, 20%, respectively). Compared to those who did not undergo PC (NPC), the PC group was significantly older at initiation of dialysis (72±12 vs. 67±14 years) and at time of death (74±12 vs 69±15), more likely to be female (47% vs. 44%), and be on HD when died (92% vs 78%). There were only 17% Blacks in PC comparing with 28% in NPC. The final multivariable model found that older age (RR=1.02), female (RR=1.09), death in more recent years (RR>1.06 for 2005-2012), and more hospitalizations (RR=1.04) were associated with use of PC, while being black (RR=0.65) or of "other" race (RR=0.73) were less likely to have PC. Cause of death for PC was less likely to be coded as cardiac (RR=0.39), GI (RR=0.42), infection (RR=0.52), metabolic (RR=0.83) or vascular causes (RR=0.62). There was no difference in time to death by PC status.

Conclusions: Age, gender, race and underlying chronic conditions all appear to influence the use of PC. Despite increasing utilization of PC since 2004, there has been a racial disparity in the employment of PC, with less frequent use in non-white patients. The reasons for this difference cannot be determined from this study; however, cultural and/or socioeconomic variables may play a role.

TH-PO1113

Patient Perspectives on Choosing Conservative Management of End-Stage Renal Disease Katherine Roza,[1] L. Ebony Boulware,[2] Ion D. Bucaloiu,[3] Frank Daniel Davis,[4] Patti Ephraim,[5] Christina Yule,[3] Jamie Alton Green.[3] *[1]Dept of Medicine, Geisinger Medical Center, Danville, PA; [2]Dept of Medicine, Duke Univ School of Medicine, Durham, NC; [3]Dept of Nephrology, Geisinger Medical Center, Danville, PA; [4]Bioethics, Geisinger Medical Center, Danville, PA; [5]Dept of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Welch Center for Prevention, Epidemiology and Clinical Research, Baltimore, MD.*

Background: Little is known about what factors are important in patients' decisions about conservative management of end-stage renal disease (ESRD).

Methods: We conducted semi-structured, telephonic interviews of patients with advanced chronic kidney disease (stages 4-5) who have opted not to pursue dialysis or have a renal transplant. We recruited patients from nine nephrology clinics in a large integrated health system in rural Pennsylvania. We asked patients to discuss 1) important factors in their decision about conservative management, 2) educational needs and resources, 3) support from family, friends, and providers, 4) decision-making ambivalence, and 5) advance care planning. We audio-recorded interviews for analysis.

Results: Of 13 eligible individuals, six (46%) patients completed interviews. Mean age was 81 years (range 74-88), and four (67%) were male. Factors reported as important in patients' decision to choose conservative management included: advanced age, impact of dialysis on health and quality of life, inconvenience of dialysis, desire to maintain independence, and desire to lessen caregiving burden. Religious faith and support of the healthcare team and loved ones aided decision-making. All interviewees felt they had enough information and support during the decision-making process to opt for conservative management and expressed satisfaction with their decision. Most (83%) had engaged in advanced care planning discussions.

Conclusions: Patients identified key factors in their decision to pursue conservative management. Our findings can inform interventions to improve shared decision-making and communication between patients and providers about conservative management of ESRD.

Funding: Private Foundation Support

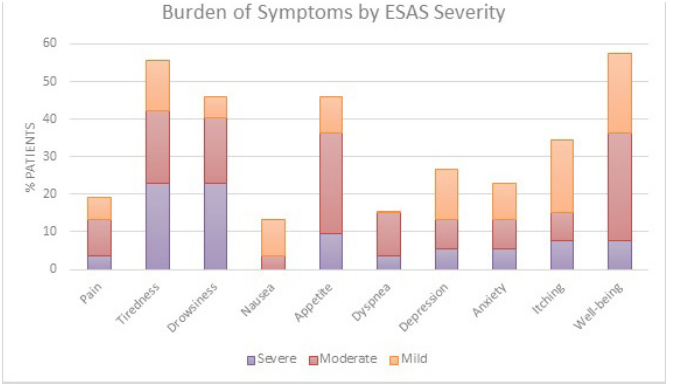
TH-PO1114

Symptom Burden in Veterans on Chronic Hemodialysis Matthew Tyler,[1] Joshua Hauser,[1] Shubhada N. Ahya.[2] *[1]Medicine - Palliative Care, Northwestern Memorial Hospital, Chicago, IL; [2]Medicine - Nephrology, Northwestern Memorial Hospital, Chicago, IL.*

Background: The Coalition for Supportive Care of Kidney Patients (CSCKP), a national organization of renal and palliative care health professionals, patients, and families, suggests "meticulous pain and symptom management" for ESRD patients. However, there is no consensus on what symptom assessment instrument to use or how to implement it at the point of care. This quality improvement project sought to assess the feasibility of administering the Edmonton Symptom Assessment Scale (ESAS) during a veteran's regularly scheduled outpatient hemodialysis (HD) session. We also sought to catalogue the physical symptom burden of our veterans receiving routine HD.

Methods: A palliative care physician administered the ESAS to each patient during their routine HD session at a VA hospital-affiliated dialysis center in a major metropolitan area. The physician also documented the time to complete each ESAS and the patient's self-perceived difficulty with completing the ESAS.

Results: Fifty-two patients completed an ESAS during their routine dialysis session. Of these, 36 (69%) patients reported at least 1 moderate to severe symptom, with 40% of patients endorsing at least 3 moderate to severe symptoms. Tiredness was the most commonly reported symptom, endorsed by 56% of patients. Thirty-eight (73%) patients were able to complete an ESAS in less than 5 minutes. Most patients (85%) did not find the ESAS challenging to complete, with the rest (15%) only finding it somewhat challenging.



Conclusions: Symptom burden in patients on chronic hemodialysis is high. The ESAS is an easy to use symptom inventory that most patients can complete in less than 5 minutes during their routine dialysis session. Implementation of routine symptom screening should be a high priority for dialysis centers but does not need to be resource-intensive.

TH-PO1115

Improving Palliative Care Communication Skills in Nephrology Training: Description and Outcomes of the NephroTalk Communication Program Jane O. Schell,[1] Jamie Alton Green,[2] Robert A. Cohen.[3] *[1]Nephrology, Univ of Pittsburgh Medical Center, Pittsburgh, PA; [2]Nephrology, Geisinger Health System, Danvillle, PA; [3]Nephrology, Beth Isreal Deaconess, Boston, PA.*

Background: Effective communication is essential to being a competent nephrologist. We describe NephroTalk communication curriculum for nephrology fellows and report educational outcomes utilizing two years of data. The three-day course includes didactics and small group practice with simulated patients addressing palliative care communication tasks in nephrology. The primary objective was to evaluate skill acquisition using a validated communication checklist analyzing pre- and post-training standardized patient encounters. Secondary objectives included fellow satisfaction with the course and changes in self-reported preparedness.

Methods: Nineteen first and second year fellows from six academic nephrology programs participated in Nephrotalk in 2014 and 2016. Audio-recorded pre- and post-training encounters with standardized patients giving bad news were evaluated using a modified communication checklist. Skill acquisition was measured using paired T-tests. Fellow experience and perceived improvement were measured using a 5-point Likert scale.

Results: Over half of participants were male and in the second year of fellowship. Sixty-five percent reported no formal education in either how to discuss conservative management or dialysis in a patient who may not do well. Training resulted in a significant increase in the total number of checklist communication skills used compared to pre-training encounter ($p = 0.002$). Fellows were more likely to respond to emotional cues with empathic statements in post-training compared to pre-training encounter ($p < 0.05$). Fellows were highly satisfied with the training and recommended it be part of routine fellowship education.

Conclusions: Our three-day communication course demonstrated increased communication skill acquisition, particularly in fellows responding to emotional cues using a modified validated communication checklist. These findings demonstrate the efficacy of palliative care education and communication skills training during nephrology fellowship.

TH-PO1116

Development of a Question Prompt Sheet for Patients with Advanced Kidney Disease to Promote Shared Decision Making Regarding Dialysis and Transplantation Arouna Senthilkumar,[2] Swati Lederer,[1,2] Hira T. Khan,[2] Michael J. Fischer,[1,2] Howard S. Gordon,[1,2] Anuradha Wadhwa,[2] Subhash Popli,[2] Elisa J. Gordon.[2,3] *[1]Jesse Brown VAMC and Univ of Illinois, Chicago, IL; [2]Hines VA Hospital, Hines, IL; [3]Northwestern Univ, Chicago, IL.*

Background: Patients with advanced chronic kidney disease (CKD) commonly receive suboptimal education about treatment options for end-stage kidney disease (ESKD). Thus, many information needs are unmet. Active participation in discussions can prepare patients for renal replacement therapy and improve health outcomes. Question prompt sheets (QPS) can increase patient involvement in discussions during crucial phases of their illness. No QPS is available for patients nearing ESKD.

Methods: We conducted a cross-sectional study with semi-structured interviews to develop a QPS for patients with advanced CKD. Initial interviews among patients with moderate to severe CKD assessed their general CKD information needs. Patients' feedback informed the development of a 53-item QPS. A new cohort of patients with ESKD from one VA facility were interviewed to assess the importance of asking each QPS question (on a 5-point Likert Scale) and to provide open-ended feedback about each of the 53 items. We used a mixed methods approach to analyze responses and refine QPS items.

Results: In all, 45 patients completed interviews for a 46% participation rate. Most were male (98%), white (51%), and the mean age was 64 years. Most patients were either on dialysis (62%) or had a kidney transplant (38%). The final QPS included 35 items divided into 2 key themes (dialysis, transplantation). Patients reported being 'completely' or 'very' willing to use an ESKD-QPS in their doctor visits (89%) and recommended that patients receive dialysis and transplant questions at the same time (68%).

Conclusions: Advanced CKD patients expressed interest in using an ESKD-QPS. Future research should evaluate the feasibility of using an ESKD-QPS in nephrology clinics and whether our 35-item QPS addresses patient information needs, fosters patient communication with care teams, and improves outcomes.

Funding: VA Support

TH-PO1117

Using Storify as a Learning Tool in Nephrology: The NephJC Experience Hector M. Madariaga,[1] Swapnil Hiremath,[2] Nikhil A. Shah,[3] Matthew A. Sparks,[4] Joel Topf.[5] *[1]Div of Nephrology, Univ of Maryland Medical Center, Baltimore, MD; [2]Div of Nephrology, Univ of Ottawa, Ottawa, ON, Canada; [3]Dept of Nephrology and Immunology, Univ of Alberta, Edmonton, AB, Canada; [4]Nephrology Div, Duke Univ, Durham, NC; [5]Nephrology Div, St. John's Providence Hospital, Detroit, MI.*

Background: Social media (SoMe) is increasingly being used in medical education and information is scattered across SoMe. It is difficult to bring information together, hence the importance of using hashtags (#). Storify is a tool that enables users to curate information from Social Networks, creating a digital narrative of events, media and tweets. We use it in our twice-a-month Twitter-based nephrology journal club, NephJC, to curate discussions and generate a narrative for others to review.

Methods: We performed an analysis to determine the utilization of Storify in the dissemination of tweetchats by examining the number of times people viewed each NephJC Storify and by performing a survey asking participants how they review NephJC information. We have hosted 50 chats since April 2014. Pageviews were quantified on www.storify.com through May 2016. Each tweetchat has two Storify versions: American and European chat.

Results: We have had a total of 2744 participants during the 50 discussions, with a total of 26521 tweets and average of 530 tweets per discussion. Storify narratives condense this down to a mean of 115 tweets per discussion. The total number of NephJC Storify page views was 6212, average of 124 page views per Storify and median 95(interquartile range 60,145). 13% of respondents said they interact with NephJC primarily through Storify.

Conclusions: Storify is an online tool to help users to gather information across SoMe by using hashtags and share. At NephJC we use it to preserve critical elements of chat discussions and make them easier to review. Without the curated Storify version, most of the individual conversational threads would be hard to retrieve and follow. Storify is a compelling tool for organizing and archiving real-time tweets for enriching the online continuing medical education experience.

TH-PO1118

Queen's Nephrology E-Learning: WhatsApp - Q-NEW Study Muhammad A. Bukhari, M. Khaled Shamseddin. *Nephrology, Queen's Univ, Kingston, ON, Canada.*

Background: Competency based medical education (CBME) is gaining more attention. E-learning is becoming a central modality of medical education. Social media applications are not yet a regular source of e-learning. WhatsApp Messenger allows exchange of messages and media, and holds promise as a CBME teaching tool.

Methods: We performed a pilot study of Nephrology Clinical Case problems sent to volunteers (Internal medicine trainees) via WhatsApp in an effort to assess and improve Nephrology competency. Responses were requested at 5 days. Answers and explanations were then sent out. Pre- and post-study surveys reported Trainees self-assessed competency in managing Nephrology topics.

Results: 29 (46%) out of 63 trainees enrolled (48% Females; 14, 10, & 5 PGY-1, 2, & 3, respectively). On a scale of 5; 1: very unconfident, 5: very confident, Trainees self-reported competency managing the problems. Scores improved significantly post-study, in specialized fields of Nephrology (e.g. Transplantation, Nephritis and Dialysis). There was no significant improvement in scores in more common areas like acute kidney injury.

Management	Post-Study Mean ± SD	Pre-Study Mean ± SD	95% CI Lower	95% CI upper	P Value
Acute Kidney Injury	4.00±0.54	3.93±0.46	-0.32	0.46	0.72
Acute Interstitial Nephritis	3.40±0.63	2.87±0.52	0.12	0.95	0.02
Nephritis	3.27±0.46	2.60±0.74	0.13	1.21	0.02
Nephrotic Syndrome	3.40±0.63	3.73±0.70	0.09	1.25	0.03
Electrolyte	3.53±0.64	3.27±0.70	-0.12	0.66	0.16
Hemodialysis	3.60±0.83	3.00±0.93	0.02	1.19	0.04
Peritoneal Dialysis	3.27±0.70	2.67±0.72	0.14	1.06	0.01
Chronic Kidney Disease	3.20±0.56	2.67±0.72	0.07	0.99	0.03
Transplantation	2.93±0.70	2.00±0.66	0.54	1.32	0.000
Hypertension	3.33±0.62	3.13±0.52	-0.23	0.63	0.33
Overdoses	3.20±0.0.68	2.80±0.86	-0.15	0.95	0.14

Conclusions: Trainees' competency improved using WhatsApp as a tool to enhance critical thinking. Most Trainees reported interest in e-learning and WhatsApp to learn Nephrology; however, the Trainee response rate diminished with time questioning the durability of using such a teaching method.

TH-PO1119

Enhancing Renal Physiology and Pathophysiology Education Using a Novel Mobile Learning Platform R. Lance Miller. *Medical Education, Inquizica LLC, Penn Valley, PA.*

Background: Optimal learning occurs when content is given in small, digestible chunks, which are followed up with regularly spaced out practice assessments to maximize retention. Our innovation leverages technology to make it easy for students to engage in the best educational practices, anywhere, anytime, and on any device and it makes it easy for medical educators to supplement in class lectures and track student progress in real-time to optimize content to maximize learning and promote a flipped classroom.

Methods: Using smartphone technology we automatically "feed" students content via text-messages containing links to 5 minute learning modules, i.e., videos or assessments. The student or educator can choose from the content library and enter associated exam dates, i.e., quizzes, mid-terms, and finals, our SMS-notification/scheduling system then automatically "feeds" the student content, in spaced out intervals. Results are reported by question and quiz and logged to the user's and/or educator's dashboard. If the student scores below a certain percentage, the system sends a text message with a link for remediation.

Results: We tested our platform on first year medical students (n=20) and undergraduates (n=15). After completing the mobile learning modules on first-year renal physiology (i.e., acid-base physiology, renal hemodynamics, and urine concentration mechanisms), medical students and undergraduate students scored 92 ± 3% and 83 ± 4% on the 25 question multiple choice quiz.

Conclusions: Greater than 90% of students found this approach highly favorable and thought it would be a helpful supplement to in class lectures. This novel mobile learning platform represents a viable approach to supplementing in class lectures and improving retention of difficult material, like renal physiology and pathophysiology.

TH-PO1120

The Acute Dialysis Orders Objective Structured Clinical Examination (OSCE): A Formative Assessment for Nephrology Fellows Lisa K. Prince,[1] Sam W. Gao,[2] Christopher J. LeBrun,[3] Dustin J. Little,[1] David L. Mahoney,[4] Robert Nee,[1] Mark C. Saddler,[5] Maura A. Watson,[1] Christina M. Yuan.[1] *[1]Walter Reed National Military Medical Center, Bethesda, MD; [2]Naval Medical Center, Portsmouth, VA; [3]Baptist Memorial Hospital Golden Triangle, Columbus, MS; [4]Private Practice, Fairfax, VA; [5]Mercy Regional Medical Center, Durango, CO.*

Background: Few quantitative, validated, Nephrology-specific simulations assess fellow competency. We developed and validated a formative OSCE to assess medical knowledge, patient care, and systems-based practice in acute dialysis.

Methods: There are 3 scenarios: acute CRRT in a septic, hypotensive oncology patient; chronic dialysis initiation in a volume-overloaded, moderately uremic patient; and acute dialysis in a ESRD patient with hyperkalemia and volume overload. Fellows use institutional protocols and order sets. The test was developed by 5 academic military nephrologists, and refined by 4 nephrologists (2 in rural practice and 2 in urban/suburban practice). Test committee members were board certified/participating in MOC. There were 49 test items, and 58 possible points. Passing score was determined by Ebel's method applied to each item. Passing threshold was 46/58 points. No item had median relevance less than "important", and 42/58 (72%) were of easy or medium difficulty.

Results: The test was validated by 10 external volunteers who were not on the test committee. All trained in the WRNMMC program; 7/10 were in the military. All were board certified in nephrology; a median 3.5 years (1-11) from graduation. Median time to take the test was 75 minutes. Mean score was 49 (95% CI 46-51). Interrater reliability: Kappa 0.68 (95% CI 0.59-0.77).

Conclusions: We will administer the test to first and second year fellows at the end of the 2016 training year. We hypothesize that performance will be significantly better in second vs. first year fellows, and associate with ITE score. We will also analyze performance on evidence-based questions. *The views expressed are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, the Department of the Army, the Department of Defense, nor the US Government.*

TH-PO1121

Best Practices to Increase Medical Student Interest in Nephrology: A Qualitative Study Stephen M. Sozio,[1] Kurtis Pivert,[2] Hitesh H. Shah,[3] Harini A. Chakkera,[4] Katlyn Leight,[2] Mark G. Parker.[5] *[1]Johns Hopkins U; [2]American Society of Nephrology; [3]Hofstra Northwell School of Medicine; [4]Mayo Clinic; [5]Maine Medical Center.*

Background: Interest in nephrology as a career has been declining. Understanding practices of medical schools that successfully generate nephrology interest is sorely needed.

Methods: This "Best Practices Project" was as an initiative designed by the ASN Workforce Committee to increase nephrology interest. Medical school graduates from 2002-2009 who became board certified in nephrology were identified through the AMA Masterfile. From the top 10 producing medical schools, renal educators were asked to participate in 1 of 4 directed focus groups inquiring about key factors in each school's success. Transcripts were analyzed using thematic content analysis with inductive reasoning.

Results: Of the 10 schools, 3 were in the Northeast, 3 Midwest, and 4 South. Median medical school class size was 185 students; 26% of graduates chose Internal Medicine. 18 educators from 9 institutions were recruited. Programs identified aspects in their renal course, rotations, research, and faculty that made them successful.

TOP THEMES	REPRESENTATIVE QUOTE
Early exposure	*Some of our medical students have the opportunity to work with us at the clinical and basic research level. I think it's a very early stage, but it makes an impact on them.*
Clinical relevance	*What seems to get students interested is getting the students early and making sure they already feel like they're mastering the pathophysiology. And then connecting that with the clinical case. That seems to be a good way to get students to realize the connection between what they're learning and clinically doing.*
Faculty interaction	*The faculty present a very good role model and good mentorship, so that when they do electives, we have good relationships with them and they get to see quite a bit of us.*
Variety	*Medical students rotate through nephrology, both inpatient as well as outpatient clinics, even early on in their third year rotation. So it does expose them to nephrology in various aspects.*

Conclusions: Early and consistent clinical experience and faculty contact with medical students are important to help generate interest in nephrology.

TH-PO1122

Outcomes of Tunneled Hemodialysis Catheters Insertion by Nephrology Fellows in Singapore Alicia Ong,[1] Ru Yu Tan,[2] Kian Guan Lee,[2] Suh Chien Pang,[2] Pei Loo Tok,[2] Chieh-Suai Tan.[2] *[1]Duke-NUS Medical School, Singapore; [2]Renal Medicine, Singapore General Hospital, Singapore.*

Background: Increasingly, nephrology fellows (NF) in Singapore are beginning to insert tunneled hemodialysis catheters (THC) under fluoroscopic guidance. This is done with the supervision of interventional nephrologists as part of fellowship training. Data on THC insertion outcomes are however lacking. This study aims to report their outcomes and complications rates.

Methods: In a single-center retrospective study of THC insertion performed from March 2015 to February 2016, outcomes of catheter insertion by NF and accredited proceduralists (AP) comprised of Interventional Radiologists, Vascular Surgeons, and Interventional Nephrologists were compared. Data were collected from electronic medical records and procedural reports. Patients were followed up from the time of insertion until hospital discharge. Primary outcomes evaluated included bleeding and infection. Secondary outcomes included procedural fluoroscopy time and patient radiation exposure.

Results: THCs were successfully inserted under fluoroscopic guidance in combination with real-time ultrasound cannulation in 140 patients (mean age of 61 ± 13 years old, 51.4% male, 69.3% Chinese). The majority of the insertions (n=91; 65%) were performed by AP although NF placed more catheters in newly diagnosed end stage renal failure patients compared to AP (65.3% vs. 46.2%, p=0.02). The right internal jugular was the preferred site of insertion in both groups (89.8% vs. 83.5%, p=0.37). There were no differences in post-procedural bleeding (6.1% vs 4.4%, p=0.47) and infection within 24 hours of placement (4.1% vs 2.2%, p= 0.44). In insertions done by NF, median fluoroscopy time [1.3mins (0.3, 17.9) vs. 1.1mins (0.1, 38.4), p=0.42] was higher whereas the median radiation exposure [57.6mGycm2 (5.6, 2207.9) vs. 102.5 mGycm2 (7.4, 8129.0), p=0.17] was lower although these differences did not reach statistical significance.

Conclusions: In carefully selected patients, tunneled hemodialysis catheter can be safely inserted by nephrology fellows with minimal complications rates and radiation exposure. Larger studies are necessary to validate our findings.

TH-PO1123

Development and Validation of a Clinical Competence Test for Dietitians Regarding Early Chronic Kidney Disease (CKD) Roxana Marquez-Herrera, Laura Cortes-Sanabria, Hector Martinez Ramirez, Alfonso M. Cueto-Manzano. *Unidad de Investigación Médica en Enfermedades Renales, Inst Mexicano del Seguro Social, Guadalajara, Mexico.*

Background: CKD is a serious public health issue. Appropriate nutritional care may help to prevent CKD onset in patients at risk, and slow progression in those at early stage. To improve care of patients with early CKD, it is mandatory to know the dietitian's clinical competence; however, no adequate tool to measure this issue has been published. Aim: to develop and validate a test to evaluate dietitian's clinical competence about nutritional care in patients with early CKD.

Methods: Development and evaluation of the test was performed as follows: 1) A group of experts in psychometrics and nutrition of early CKD was integrated; 2) Clinical competence and its dimensions were defined; 3) Four real clinical cases and questions (based on the latter) were elaborated; 4) content validity was established; 5) Test was applied to dietitians with or without previous CKD training; 6) Reliability assessment by question exclusion, based on internal consistency and discrimination index, was established. A Cronbach's alpha ≥0.70 and discrimination index ≥0.30 were considered adequate.

Results: Dietitians with previous training obtained higher scores than those with no training (123 *vs* 92, respectively, p<0.0001), confirming test validity criterion. As a first step to increase reliability, questions were dropped according a correlation coefficient cutoff value <0.15 (item/total correlation); from the latter, discrimination capacity of remaining questions was controlled by elimination of those with discrimination index <0.15. Final test contained 92 from the original 239 questions, increasing Cronbach's alpha value from 0.83 to 0.91, and discrimination index from 0.15 to 0.34.

Conclusions: The clinical competence test developed for dietitians is a consistent and suitable instrument to identify dietitians with or without adequate competence in nutritional care of early CKD patients. The availability of a reliable test to measure dietitian's clinical competence may help to improve care of early CKD patients.

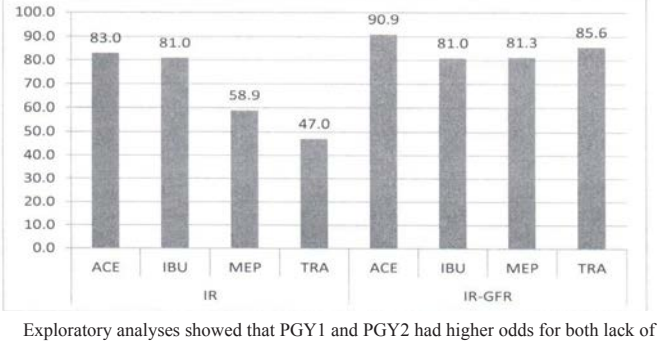
TH-PO1124

Awareness and Knowledge among House-Staff for Dose Adjustment of Analgesic Medications in Chronic Kidney Disease Chadi Y. Saad,[1] Joshua Fogel,[2] Sofia Rubinstein.[1] *[1]Nephrology and Hypertension, Nassau Univ Medical Center, East Meadow, NY; [2]Business Management, Brooklyn College, Brooklyn, NY.*

Background: Drug dosing errors result in adverse patient outcomes and are more common in patients with chronic kidney disease (CKD). As internists treat the majority of patients with CKD and pain is common in those with CKD, we study if Internal Medicine (IM) house-staff have awareness and knowledge about the correct dosage of commonly used analgesic medications for those with CKD.

Methods: We performed a cross-sectional survey of 353 IM house-staff. Our outcomes are the awareness of whether a medication needs dose adjustment in patients with CKD and whether there was knowledge at what level of glomerular filtration rate (GFR) a medication needs to be adjusted.

Results: There were high percentages for lack of awareness and knowledge. Lack of awareness and knowledge was highest for acetaminophen at 83.0% and 90.9%, respectively.



Exploratory analyses showed that PGY1 and PGY2 had higher odds for both lack of awareness and knowledge. Also, more Nephrology training and exposure was associated with lower odds for both lack of awareness and knowledge.

	Incorrect Response		Incorrect Response at GFR level			
Variables	Tramadol OR	95% CI	Acetamino-phen OR	95% CI	Mepered-ine OR	95% CI
PGY3	1.00		1.00		1.00	
PGY1	**2.37**	**1.22-4.62**	2.10	0.65-6.82	**4.01**	**1.81-8.89**
PGY2	**2.34**	**1.16-4.72**	2.29	0.64-8.12	**3.30**	**1.44- 7.59**
Nephrology rotation medical school	0.78	0.44-1.36	**0.37**	**0.14-0.99**	**0.41**	**0.2-0.83**

Conclusions: There is a poor awareness and knowledge among IM house-staff for dose adjustment of analgesic medications in CKD patients. Internal medicine house-staff should receive more Nephrology exposure and formal didactic training during residency to better manage complex treatment regimens and prevent medication dosing errors.

TH-PO1125

Health Literacy of Nephrology Patients and Their Family Caregivers Jamie Alton Green,[1] Deserae N. Clarke,[2] Amanda Young,[3] Jennifer L. Wolff,[4] Rebecca A. Stametz.[2] *[1]Nephrology, Geisinger Medical Center, Danville, PA; [2]Center for Clinical Innovation, Geisinger Medical Center, Danville, PA; [3]Biostatistics, Geisinger Medical Center, Danville, PA; [4]Health Policy and Management, Johns Hopkins Univ, Baltimore, MD.*

Background: Many patients with kidney disease rely on assistance from a family or informal caregiver to help manage their care. The presence of a caregiver may compensate for patient difficulties related to limited health literacy; however, little is known about what proportion of nephrology patients receive help from a caregiver, the health literacy of their caregivers, or how caregiver health literacy corresponds to that of the patient.

Methods: Patient-caregiver dyads were identified and surveyed utilizing a health information technology enabled process embedded into clinical nephrology care at a large integrated health system in Pennsylvania. Health literacy was assessed using a single item screening question, "How confident are you filling out medical forms by yourself" with response options of extremely, quite a bit, somewhat, a little bit, or not at all. A response of "somewhat" or less was used to define limited health literacy.

Results: Of 790 patients surveyed, 466 (59%) reported they receive help from a family caregiver with at least one health related activity. Caregivers were most often a spouse (61%) or an adult child (12%). Among 316 complete dyads, patients were overall more likely to have limited health literacy than caregivers (45% vs. 19%, p<0.01). Patient-caregiver dyad health literacy varied with 103 (33%) consisting of a patient with limited health literacy and a caregiver with adequate health literacy, 22 (7%) consisting of a patient with adequate health literacy and a caregiver with limited health literacy, 39 (12%) where both had limited health literacy, and 152 (48%) where both had adequate health literacy.

Conclusions: More than half of nephrology patients receive help from a family caregiver. Both patients and caregivers are at risk for limited health literacy which should be considered when providing patient instructions or education. Future studies should examine how patient and care giver health literacy affect patient outcomes.

Funding: Private Foundation Support

TH-PO1126

Primary Care Provider Education in Nephrology - Improving Chronic Kidney Disease Care on the Front Lines Rob Rope,[1] Nhat M. Pham.[2] *[1]Internal Medicine/Nephrology, Stanford Univ, Palo Alto, CA; [2]Internal Medicine/Nephrology, Santa Clara Valley Medical Center, San Jose, CA.*

Background: The majority of CKD care takes place in the primary care setting. Effective treatment can reduce disease progression and cardiovascular complications but is underutilized. This project demonstrates cost-effective educational outreach to PCPs designed to increase provider knowledge in CKD care.

Methods: The intervention consisted of five small-group lectures covering topics in CKD care: diagnosis/referral; preventing progression; cardiovascular disease; managing complications; and dialysis/post-transplant care. Lectures were given at 3 primary care sites within a county health system. Fifteen providers attended 4-5 talks. A control group of 9 providers received a review article only. 80% of participants were IM physicians with the remainder FM or NPs. The intervention was evaluated in 3 ways: a survey evaluating provider confidence in, and knowledge of, CKD management; chart reviews of all patients referred from the physicians in the intervention and control groups; and chart reviews of patients with CKD from the intervention and control clinics.

Results: 13 providers (intervention) and 7 (control) took the knowledge survey before and after the intervention. McNemar (paired Chi-square) testing indicated that knowledge improved in the intervention group (17% improvement, $p < 0.05$) but not in the control group (2% improvement, $p = 0.38$). Analysis of the confidence data is pending. Chart review of referrals for the year prior showed that 80% of referrals in both groups met KDIGO indications for referral. Chart review of care for patients with CKD revealed that < 75% of all patients were prescribed RAASi or statins and < 66% of patients were controlled to an SBP of < 140.

Conclusions: This project demonstrates that specialist led education can be effective in improving knowledge in CKD care. We also identified significant need for improvement in referrals to nephrology and CKD care. Follow-up data one year after the intervention will assess for improvements in the appropriateness of referrals as well as markers of CKD care (use of RAASi, use of statins, and BP control to < 140/90 mmHg).

Funding: Other NIH Support - Stanford University Division of Nephrology, T32 Training Grant provided funding for Rob Rope's salary

TH-PO1127

Replacement Modality Choice Knowledge in the Non-Renal Multidisciplinary Team - Experience from a Single UK Centre Fatima Abdelaal, Hatem Ali, Jyoti B. Baharani. *Renal Medicine, Birmingham Heartlands Hospital - Heart of England NHS Foundation Trust, Birmingham, United Kingdom.*

Background: Chronic Kidney Disease (CKD) is a common health problem which is on an upward trend. Dialysis treatment remains the mainstay for patients with End Stage Renal disease (ESRD). In the UK there has been a significant decline in home dialysis despite its benefits and cost effectiveness. There are many reasons for this including lack of awareness about availability and effectiveness of home dialysis by both patients and healthcare professionals. Patients with CKD often have multiple co-morbidities and are known to other medical specialties who they may continue to consult when approaching the need for dialysis. We wished to assess home dialysis awareness among the non renal Multi-Disciplinary Team (MDT).

Methods: Home dialysis awareness was assessed by an on-line survey sent to the choosing specialties likely to deal with CKD patients at our centre.The questionnaire aimed to assess knowledge of these individuals regarding home dialysis and establish whether further targeted education was warranted.

Results: 364 questionnaires were sent out with a 26.4% response rate. 69.32% of respondents were working in common specialties dealing with CKD patients (geriatrics 15.9%, cardiology 14.8%, haematology 10.2%, endocrinology 10.2%, urology 10.2% and vascular surgery 8%). 81.5% of non-renal MDT did not feel confident in discussing home dialysis options with patients despite seeing a large number of CKD patients. 70% felt that their knowledge about Home Haemodialysis (HHD) was poor and 74.5% felt that they needed further education about home dialysis.

Conclusions: Knowledge of home dialysis among the non-renal MDT is poor and they lack the confidence to discuss this with CKD patients. In our sample, respondents felt they would benefit from further education. This may increase the uptake of home dialysis by the multi-morbid CKD patient who has a consistent message delivered to them by all relevant healthcare teams about the benefits of home dialysis.

TH-PO1128

Early Validation of a Low-Literacy Smartphone and Web-Based Application on Chronic Kidney Disease Knowledge and Self-Management Maria E. Ferris,[1] Nina Jain,[1] Meaghan Nazareth,[1] Stephen James,[2] Melanie Livet,[2] Jordan Richards,[1] Alex Phillips,[1] Stephen R. Hooper,[1] Janey Sturtz McMillen.[2] *[1]UNC Chapel Hill, Chapel Hill, NC; [2]3C Inst, Durham, NC.*

Background: Effective disease self-management requires knowledge about chronic kidney disease (CKD). The effectiveness of patient education delivered via smartphone applications remains to be determined.

Methods: English-speaking adolescents and young adults (AYA) who attended the UNC Kidney Center utilized Planet K, a low-literacy smartphone and web-based application designed to teach about kidney function, chronic kidney disease (CKD) stages and self-management skills via interactive games. Pre-post performance on the Self-management and Transition to Adulthood with Rx=treatment ($STAR_x$) Questionnaire (Ferris 2015) was an outcome examined for patients using Planet K. In addition to completing the STARx Questionnaire before and after using the app, participants completed a pre-post 19-item CKD knowledge measure that was designed for this project.

Results: To date, 26 AYA aged 12-17 years (μ 15.2 ± 2.2) with CKD stages 1-5 had the following characteristics: 65% males, 61% White, 23% African American; mean age at diagnosis was 6.1 yrs (±5.7, range 0-17 yrs). The pre- and post-STARx Questionnaire scores on disease knowledge and resources utilization significantly increased after the use of Planet K. Knowledge (p=0.046) and resource utilization (p=0.028) were normally distributed and displayed significant increases when t-tests were used to compare pre- and post- scores after use of the application. The <a>mean knowledge score from the 19-item CKD knowledge measure increased from 0.77 to 0.88 (p<0.001).

Conclusions: The low-literacy smart phone and web-based Planet K application appears to have early findings of efficacy and utility for AYA with CKD. Further evaluation is underway.

Funding: Other U.S. Government Support

TH-PO1129

Assessment of Clinical Practices in the Management of Hyperkalemia Edward L. Jackson, Don Blatherwick, Karen Badal. *Medscape Education, LLC.*

Background: Concerns regarding hyperkalemia may contribute to the underuse of renin-angiotensin aldosterone system (RAAS) inhibitor therapies.The current study was developed to assess gaps in knowledge and competence of nephrologists regarding assessment and management of hyperkalemia.

Methods: A continuing medical education (CME)-accredited clinical practice assessment survey consisted of 25 multiple-choice questions, self-assessing knowledge, confidence and barriers with regard to hyperkalemia management. Hosted on the Medscape Education website, participant responses were collected between September 22, 2015 and November 22, 2015. Responses were de-identified and aggregated prior to analysis to maintain confidentiality. Questions were based on clinical trials, guidelines, and expert faculty recommendations.

Results: Data were collected from 394 nephrologists who participated during the study period. Key findings include: •While 88% correctly recognized that impaired potassium excretion was the primary cause of chronic hyperkalemia, only 55% correctly identified physiologic details of normal potassium regulation •Although 89% recognized that the presence and severity of CKD was the strongest associated risk factor for hyperkalemia, only 47% were able to correctly identify key predictors of risk •In a scenario of a patient with stage 3 CKD and type 2 diabetes, without effective treatments 40% opted for discontinuation of RAAS therapy in the event of an elevation in potassium, with a lower percentage (35%) instead opting for dose-reduction •Less than one-half (46%-49%) recognized the mechanisms of action for novel potassium binders •Only 57% of respondents were familiar with clinical trial data for a novel potassium binder •Among confidence and barrier questions, 93% of respondents indicated a likelihood to maximize RAAS therapy provided there were better treatment options for hyperkalemia, and 55% selected knowledge of new agents for hyperkalemia as the area of greatest educational need.

Conclusions: While general knowledge and confidence among nephrologists are high in several areas of hyperkalemia, gaps in the detailed understanding of clinical aspects remain. Educational efforts in management, tailored to nephrologists, are warranted to address these gaps.

Funding: Pharmaceutical Company Support - Relypsa

TH-PO1130

Iron Deficiency Anemia in Chronic Kidney Disease: Educational Effects from a Case-Based Online Intervention Edward L. Jackson, Don Blatherwick, Anne Le. *Medscape Education, LLC.*

Background: A study was conducted to determine whether an online educational intervention could address an underlying care gap in the area of evaluation and management of iron deficiency anemia in patients with chronic kidney disease (CKD).

Methods: The educational intervention consisted of a video panel discussion activity for nephrologists and primary care physicians (PCPs), with two case scenarios to guide discussion. Educational impact was assessed by comparing each participant's responses to the same 4 questions asked both pre- and post-education. A paired 2-tailed t-test was used to assess whether the mean post-assessment score was different from the mean pre-assessment score for each question. McNemar's χ^2 statistic was used to measure changes in responses to individual questions. Probability values (*P* values) were also calculated for both t-test and χ^2 statistics to determine significance, with a $P < .05$ as meeting statistical significance. Cramer's V was used to calculate the effect size of the intervention, with large effect sizes defined as $V > .30$.

Results: For nephrologists (n = 113) and PCPs (n = 214) who participated in the online activity and completed all pre- and post-education assessment questions, comparison of responses to pre- and post-education assessment questions demonstrated statistically significant improvements (P <.05) and a large effect (nephrologists, V = 0.321; PCPs, V = 0.319). Significant absolute increases in correct responses were observed in several specific areas of managing iron-deficiency anemia in CKD (all $P < .05$), including: •Contributors to iron-deficiency anemia in CKD (Nephrologists, 37%; PCPs, 41%) •Appropriateness of oral iron compounds for treatment (Nephrologists, 18%; PCPs, 27%) •Risks from intravenous iron replacement in CKD patients who are also being treated for comorbidities (Nephrologists, 27%; PCPs, 15%) •Options for iron replacement therapy (Nephrologists, 42%; PCPs, 44%).

Conclusions: As a result of participation in this case discussion-based educational activity in a video format, significant improvement in knowledge of nephrologists and PCPs was demonstrated in several important aspects of managing iron-deficiency anemia in patients with CKD.

Funding: Pharmaceutical Company Support - Keryx Biopharmaceuticals, Incorporated

TH-PO1131

Assessment of Current Clinical Practices in the Diagnosis and Management of Hepatorenal Syndrome Edward L. Jackson, Don Blatherwick, Susan Smith. *Medscape Education, LLC.*

Background: Hepatorenal syndrome (HRS) is a potentially devastating form of acute renal injury seen in clinical practice. The current study was conducted to assess gaps in knowledge and competence of nephrologists regarding diagnosis and management of patients with HRS.

Methods: A continuing medical education (CME)-certified clinical practice assessment survey was developed comprising 20 multiple-choice questions that assessed knowledge, attitudes, and confidence with regard to the diagnosis, clinical course, treatment, and management of patients with HRS. The survey questions were based on clinical trials, guidelines, and expert faculty recommendations. The survey was launched on August 14, 2015, and hosted on the Medscape Education website, and participant responses were collected through October 11, 2015. Confidentiality was maintained and responses were de-identified and aggregated prior to analyses.

Results: Data were collected from 198 nephrologists who participated in the survey during the study period. When asked about diagnosing HRS, 85% correctly recognized HRS as a diagnosis of exclusion, yet only 38% reported being fully confident in making the diagnosis. With respect to evaluation and staging, only 37% of nephrologists correctly recognized the most appropriate tests for evaluating kidney function in patients with cirrhosis and, when presented with a case scenario and laboratory test result, only 40% were able to properly stage the HRS presentation. In the area of HRS management, a majority of nephrologists (79%) correctly recognized that HRS is potentially reversible and 75% correctly stated that liver transplantation is the definitive treatment. However, only about one-half (54%) were able to identify the most appropriate pre-transplantation management strategy, and less than one-quarter (24%) were able to correctly answer a question related to effectiveness of therapeutic options.

Conclusions: Low self-reported confidence among nephrologists in establishing a diagnosis of HRS was substantiated by responses to specific questions on diagnosis and staging. Further gaps were identified in the area of pre-transplant management options. Educational efforts tailored to nephrologists are warranted to address these gaps.

Funding: Pharmaceutical Company Support - Mallinckrodt Pharmaceuticals

TH-PO1132

Identifying Utility and Challenges for an Established Online Journal Club: The NephJC Experience Swapnil Hiremath, Matthew A. Sparks, Thomas Oates, Francesco Iannuzzella, Paul J. Phelan, Hector M. Madariaga, Michelle N. Rheault, Matthew P.M. Graham-Brown, Nikhil A. Shah, Edgar V. Lerma, Graham E. Abra, Anna Marie Burgner, Ian Logan, Suzanne M. Norby, Joel Topf. *Medicine, Univ of Ottawa.*

Background: Online journal clubs have become widespread as a method for dissemination and discussion of new research. Since its inception in April 2014, the online twitter based journal club #NephJC, has conducted more than 50 tweet-chats. We developed a survey to characterize participants and better understand the perceived benefits and potential barriers to participation.

Methods: The online survey was conducted using the Google forms platform. We invited individuals to participate by a direct message to @NephJC Twitter followers, including a link in the weekly NephJC email digest for 2 weeks and displaying a link prominently on nephrology blogs. Institutional review board approval was obtained.

Results: 328 individuals responded to the survey: 221 men (68%), from North America (49%), Europe (25%), and rest of world (26%). 178 (54%) were practicing physicians, 81 trainees (25%) and the remainder being other healthcare professionals (44, 14%) or interested citizens (24, 7%). The responding physicians were mostly nephrologists (147, 82%). The overwhelming majority of the respondents (> 90%) compared it favorably to traditional journal clubs. There was considerable interest in discussing non-traditional articles, such as guidelines (220, 67%) and interesting case reports/series (131, 40%). Despite only 10 respondents working in basic science, there was enthusiasm for discussing basic science articles (120, 37%). The major barrier to active chat participation was lack of time in general (50%). Hence, 64 respondents (20%) actively participate in the live tweetchat, and most others follow the feed passively (34%) or review individual tweets (46%) or curated versions (13%). Others noted issues regarding the specific time of the chat (31%).

Conclusions: NephJC , the online journal club, has near-unanimous positive feedback. We identify lack of time as the most important barrier to participation. Online journal clubs are a promising tool which interest MDs and non-MDs alike from different specialties and training levels.

Funding: Clinical Revenue Support

TH-PO1133

The Renal Interactive Learning Module (ILM): A Novel Nephrology Curriculum for Interns Karen M. Warburton,[1] Dan Negoianu,[1] Jordana B. Cohen,[1] Serena Cardillo,[2] David J. Aizenberg.[2] *[1]Nephrology, Perelman SOM, Philadelphia, PA; [2]Medicine, Perelman SOM, Philadelphia, PA.*

Background: Interest in nephrology among US medical graduates is in decline, and this may be due to inadequate exposure to the more appealing aspects of this field during residency. It has been suggested that more exposure to ambulatory nephrology may stimulate interest in nephrology among residents. A dedicated nephrology ambulatory experience could highlight the longstanding relationships we often have with our patients and better demonstrate the variety in the clinical experience.

Methods: The Penn IM residency program recently adopted a 6+2 scheduling model, providing an opportunity for curricular innovation in the realm of ambulatory subspecialty experiences. Interns' schedules are templated such that they have 6 weeks of inpatient time, followed by two weeks of ambulatory time. The "+2" ambulatory time has been organized into six themed blocks called interactive learning modules (ILMs). As nephrology is relatively underrepresented in the clinical and didactic portions of our training experience, we included an immersive renal ILM into the curricular framework.

Results: All interns participated in the renal ILM course, repeated four times in succession to allow for standardized curriculum delivery to all four cohorts of interns. Components of the course included in-person themed content, subspecialty clinic experiences, core readings, and an interactive online forum. The in-person themed content consisted of a series of core lectures on topics relevant to ambulatory nephrology. Ambulatory experiences included the following clinics: transplant, complex hypertension, glomerular diseases, chronic kidney disease, home dialysis, in-center dialysis, and stones. The online forum provided an opportunity to review challenging cases and exchange questions and ideas regarding controversies in hypertension management.

Conclusions: Using the ILM framework, we supplemented traditional classroom-based experiences and provided our interns with exposure to a variety of career opportunities in nephrology. Future work will examine whether we were successful in quantifiably improving interest in nephrology as a career among residents.

TH-PO1134

Applying the Flipped Classroom Model in the Outpatient Renal Clinic: A Pilot Study Amir Kazory, Abhilash Koratala, Maryam Sattari. *Univ of Florida College of Medicine.*

Background: Suboptimal exposure to outpatient nephrology has been proposed as an important driving force for the fading interest in this subspecialty. We hypothesized that development of a focused educational activity for medical residents can increase their knowledge and interest. This pilot project was designed to evaluate the impact of a flipped classroom model and "Snapshot Exposure" in the outpatient nephrology setting on the knowledge of internal medicine residents about chronic kidney disease (CKD).

Methods: As part of the ambulatory rotation at the University of Florida, internal medicine residents attended a half-day CKD clinic between May 2013 and December 2015. A curriculum was developed focusing on evidence-based management of CKD. The flipped classroom model consisted of e-mailing the developed pre-clinic reading material to the residents prior to the clinic. The "Snapshot Exposure" consisted of a structured clinic session with the faculty nephrologist and a fellow. The baseline knowledge of residents was assessed at the beginning of the clinic through a multiple-choice pre-test. A post-test was administered at the end of the activity to assess the benefit of the clinic exposure. Student's t-test was used to compare the scores.

Results: Thirty seven medicine housestaff participated in this pilot study, attended the CKD clinic, and completed both the pre- and post-tests. The mean pre-clinic score was 3.87 + 0.38 out of 6 (range = 2-6) and the mean post-clinic score was 5.6 + 0.18 (range= 4-6). A statistically significant increase was seen in participants' knowledge as evaluated by the difference between the post-clinic versus pre-clinic scores (d=1.73; $P < 0.001$).

Conclusions: The main finding of this pilot study is that a snapshot exposure to CKD clinic can have a positive impact on the learners' knowledge. Moreover, the low pre-activity score implies that the conventional hand-out teaching might have limited impact on the knowledge of the learners. The next step would be to validate these findings in a larger population, and to evaluate the impact of this educational method on the interest and attitude of the learners regarding career choices.

TH-PO1135

Acute Kidney Injury (AKI) and Chronic Kidney Disease (CKD) Are amongst the Most Common Clinical Renal Questions Asked by Primary Care Providers (PCPs). Easily Identifiable Causes of AKI Are Frequently Missed Raimund H. Pichler,[1] Nancy M. Harris,[1] Maureen Germani,[1] Elizabeth A. Mattox,[1] Lauren Beste,[1] Michael F. Chang,[2] Bessie A. Young.[1] *[1]Dept of Veterans Affairs, Puget Sound Healthcare System, Seattle, WA; [2]Dept of Veterans Affairs, Portland Healthcare System, Portland, OR.*

Background: The Department of Veterans Affairs (VA) has used various forms of Telemedicine to improve care for Veterans. In 2010, the VA launched a form of electronic consultations (or non-visit consults (NVCs)) involving electronic medical record review of patients by specialists. To date there are little data on what renal clinical questions are most commonly asked by PCPs in referrals.

Methods: We conducted a qualitative chart assessment of NVCs (n=402) submitted to a Nephrology service; Using chart review, we determined clinical characteristics of the referred patients and qualitatively extracted the primary clinical question for referral.

Results: Of the 402 NVC referrals, 53% were for urban, 43% rural, 3% highly rural and 1% unknown patients. The most commonly asked clinical questions in descending order were regarding acute kidney injury (AKI) (25.7%), followed by AKI-on-chronic kidney disease (CKD) (18.7%), CKD (14.1%), request for medication review (13.4%), hypertension (10.5%), abnormal renal imaging (7%), and electrolyte imbalances (3.9%). Of all patients with AKI alone, 17% had a low blood pressure as defined by a systolic blood pressure of less than 120mm Hg, while 11% were taking non-steroidal anti-inflammatory drugs (NSAIDS). Consults for"renal imaging" referred to renal ultrasound reports that commented on "medical renal disease" and/or "renal cysts".

Conclusions: NVCs serve a relatively rural patient population. AKI and CKD are the most common clinical questions posed by PCPs in NVCs. Interestingly, low blood pressure and NSAID use appear to be overlooked causes of AKI amongst PCPs. Frequently reported and clinically insignificant abnormalities on renal imaging reports also prompt specialty consultation. The above results will help refine ongoing renal education outreach programs to address common knowledge gaps amongst PCPs.

Funding: VA Support

TH-PO1136

A Re-Evaluation of Pain Assessment in Hemodialysis Patients Tatiana Tanasiychuk, Muhammad Abd Elhalim, Daniel Kushnir, Victor Frajewicki. *Dept of Nephrology and Hypertension, Carmel Medical Center, Haifa, Israel.*

Background: Patients suffering from Chronic Kidney Disease treated by hemodialysis often complain about pain. The presence of chronic pain greatly impacts on patients quality of life (QOL) and may have effects on morbidity and mortality. The prevalence and severity of pain (acute or chronic) in this population and its influence on QOL is not well recognized. Although many sites use the Visual Analogue Scale (VAS) which includes just one question about the presence of current pain and its intensity, the best method for pain assessment has not be established.

Methods: VAS is routinely performed every treatment by our dialysis nurses. A modified Brief Pain Inventory (BPI) questionnaire includes 18 questions about localization, intensity and response to pain. BPI was given to our chronic hemodialysis patients. VAS results were obtained from the patients electronic files for the same session.

Results: 67 patients completed the questionnaire during the first week of 2016. Mean age was 73.5 years. 58% were diabetics, 68% were male. Average vintage on dialysis was 37.3 months. Only 1.5% of patients reported pain in VAS. In contrary, the BPI showed that 25% of patients had pain at that dialysis session and 61% suffered from pain for the previous 24 hours. Intensity of pain was significantly higher ($P<0.01$) with the BPI than with VAS. No significant differenced were detected between genders or diabetics/non-diabetics. In 52% of cases musculoskeletal pain was reported. Half of patients noted pain related reduced QOL defined by walk capability (54%), sleep disorders (57%), bad mood (64%), work disability (51%) or interference in familiar relationships (49%). Almost half of patients use any kind of analgesics and 10% use narcotics. Only 13% of patients reported to be pain free under analgesics treatment.

Conclusions: Pain is a frequent and debilitating condition in chronic hemodialysis patients, affecting all aspects of life, including not only the dialysis session. Standard short VAS may underdiagnose this problem leading to undertreatment and impairement of QOL. The use of a comprehensive pain tool may improve the outcomes.

TH-PO1137

Restless Legs Syndrome in Chronic Kidney Disease: Association with Objective Measures of Sleep/Wake Behaviors Maria-Eleni Roumelioti, Mark L. Unruh, Orrin Myers. *Internal Medicine, Div of Nephrology, UNM, Albuquerque, NM.*

Background: Restless legs syndrome (RLS) is a common sleep disturbance among patients with kidney failure and leads to severe initiation insomnia, daytime sleepiness and increased mortality risk. In this cross-sectional study we examined the prevalence of RLS and its effect on objective measures of sleep/wake behavior among patients with CKD (stages 4b-5) and chronic dialysis patients.

Methods: Objective measures of sleep/wake behavior included one in-home polysomnography and wrist actigraphy for two weeks. Presence of RLS was estimated with the Hopkins RLS Questionnaire.

Results: We studied 96 patients with stages 4b-5 CKD, 159 hemodialysis (HD) and 29 peritoneal dialysis (PD) patients. Average age was 54.7y, 60.2% were men, 64.4% were white. RLS was found in 36.8% of CKD, 28.7% of HD, and 44.4% of PD patients. Increased risk of RLS was associated with higher BMI, presence of DM and hyperglycemia .

	All	No RLS	RLS	p-val
Age	54.7(15.1)	56(16)	54(13)	0.2
Males(%)	60.2	62	57	0.4
Whites(%)	64.4	61	69	0.1
BMI	27.8(5.5)	27(5)	29(6)	**0.03**
Smoking	50.3	49	52	0.6
Caffeine(%)	70.4	69.5	72	0.7
Ferritin	464(422)	455(358)	476(506)	0.7
Glc	122(55)	117(52)	131(59)	**0.05**
Ph	5.4(5.2)	5.6(6.7)	5.2(1.4)	0.1
DM(%)	34.2	31	38	**0.009**
PSG data				
TSA(min)	336(111)	344(106)	325(117)	0.3
AHI	21.2(25.3)	20.2(24.6)	23.4(26.8)	0.4
PLMI	4.4(4.9)	3.9(4.5)	5.1(5.4)	0.1
Actiwatch data				
AvgOf ACSLPTOT	337(93)	344(102)	327(76)	0.2
AVGOFACWASO	81(34)	76(29)	89(39.5)	0.06
AvgOfACSE	69(11)	70(14)	67(14)	**0.04**
AvgOfACSL	43(46)	41(50)	46(42)	0.06

RLS was associated with decreased average of actigraphy scored sleep efficiency (SE), and with a trend towards increased actigraphy-scored wake after sleep onset and sleep latency.

Conclusions: RLS is common across the whole spectrum of CKD and is associated with decreased actigraphy-measured SE. Assessing appropriately and treating RLS in obese patients with CKD, especially due to DM, may improve their sleep and long-term outcomes.

Funding: Other NIH Support - NIH and foundation, Clinical Revenue Support

TH-PO1138

Predicting 1-Year Mortality in Peritoneal Dialysis Patients by the Surprise Question, Palliative Care Screening Tool, and Clinical Risk Score Cheng Ching I,[1] Chun-Fu Lai.[2] *[1]Dept of Nursing, National Taiwan Univ Hospital and National Taiwan Univ College of Medicine, National Taiwan Univ Hospital, Taipei, Taiwan; [2]Renal Div, Dept of Internal Medicine, National Taiwan Univ Hospital and National Taiwan Univ College of Medicine, National Taiwan Univ Hospital, Taipei, Taiwan.*

Background: Identifying potential candidates is an important issue to facilitate palliative care into the dialysis population. This study aimed to develop risk models to predict the 1-year mortality risks of patient under peritoneal dialysis (PD).

Methods: A total of 422 adult patients under PD for ≥ 3 months were recruited in March 2015. In addition to obtaining clinical characteristics and parameters, each patient was evaluated by the "surprise question" and the "palliative care screen tool" by the primary care nurse in the PD unit. Subjects were followed up from April 1, 2015 until March 31, 2016 for the outcome of all-cause mortality. The developed using Cox proportional hazards regression.

Results: During the 1-year follow-up, 34 (8.06 %) patients died. Kaplan-Meier analysis showed significantly worse survival in patients of the "no, not surprised" group or those with a score ≥ 4 of the palliative care screening tool (both log-rank $P<0.0001$).The area under the receiver operating characteristic curve (AUROC) to predict 1-year mortality by the two methods were comparable (0.743 v.s. 0.763, P=0.59). We also defined a clinical risk model that included gender, malignancy, Karnofsky Performance Status score, hemoglobin, white blood cell count, fasting serum glucose, serum creatinine, and intact parathyroid hormone level with good discrimination to predict 1-year mortality. Combining the above clinical model with the surprise question and the palliative care screen tool increased the AUROC to 0.938.

Conclusions: These results underscored the values of the surprise question and the palliative care screen tool to identify vulnerable patients undergoing PD.

Funding: Government Support - Non-U.S.

TH-PO1139

Medication Related Hospitalizations in Hemodialysis Patients Harold J. Manley, Jessica L. Baugh, Margaret Mcnamara, Doug Johnson. *Dialysis Clinic Inc, Albany, NY.*

Background: Hemodialysis (HD) patients' medication regimens are complex with 10-12 medications daily and medication related problems (MRPs) are common. The frequency and preventability of medication-related hospital (MED-HOSP) admissions in HD patients is unknown.

Methods: An observational study was conducted Sept. 2014-Sept 2015. MED-HOSP frequency, preventability (definite, possible, not-preventable), associated MRPs, length of stay (LOS) and potential risk factors were determined via ≥ 75% consensus within a group (3 pharmacists and 1-2 pharmacy students, 1-2 nurses). Reviews included information from discharge summaries and corresponding electronic medical record information (e.g., lab results, medical diagnoses, medications, progress notes). Patient age, number of medications prescribed, hospitalization type (index or readmit) and LOS for each event was recorded.

Results: A total of 343 (194 index; 149 readmit) hospitalizations in 218 unique patients (55.4% female; 59.2±15.1 yr) were included. Overall 35.3% (n=121) hospitalizations were MED-HOSP. Index admissions were less likely to be MED-HOSP events compared to readmits; 29.4% versus 42.9% respectively (p=0.012). MED-HOSP were considered definitely (35.4%), possibly (61.2%), or not-preventable (3.3%) of time. MRPs contributing to a MED-HOSP were dosing errors [27.3%; high (19%) or low (8.3%)], adverse drug event (24.8%), failure to receive drug (24.8%), indicated drug not prescribed (16.5%), different drug needed (3.3%), drug interaction (1.7%), and drug without indication (1.7%). MED-HOSP events were not predicted by gender (p=0.50) or number of medications (p=0.21). However, MED-HOSP events was associated with younger age (57.3±18 v. 61.4±13 yr; p=0.037) and had shorter LOS (5.8±4.7 v 7.3±7.8 days, p=0.026) compared to non-MED-HOSP events.

Conclusions: MED-HOSP events occur frequently and are preventable in HD patients. Dosing errors, adverse drug events, and failure to receive prescribed therapy (e.g., adherence) are the most common causes of MED-HOSP events. The impact of structured medication reviews to reduce MED-HOSP warrants investigation.

TH-PO1140

Fixing the Gap in Vancomycin Use among Patients on Hemodialysis at a Dialysis Center Nishkarsh Saxena, Laura J. Maursetter. *Nephrology, Univ of Wisconsin School of Medicine and Public Health, Madison, WI.*

Background: Vancomycin is the first line antibiotic for resistant gram positive infections, particularly MRSA. Its dosing should be guided by serum trough level with therapeutic goal of 15 to 20 mcg/mL. 30 to 40% of the drug is removed during 3 to 4 hour session of hemodialysis (HD). Pre-HD drug level can be used to guide vancomycin dose after accounting for extracorporeal elimination of the drug.

Methods: We first determined if there is a gap in dosing and monitor of vancomycin in patients on HD at a dialysis center [Wisconsin Dialysis, Inc. (WDI): WDI East (WDI-E) and WDI,Fitchburg (WDI-F)]. Among patients on HD at WDI who received vancomycin within a three month period (10/1/15 - 12/31/15), we calculated: a) Percentage of serum vancomycin level drawn to the total number of dose given. b) Percentage of serum vancomycin level within therapeutic range (15 to 20 mcg/mL).

Results: Among patients on HD at WDI who received vancomycin within a three month period (10/1/15 - 12/31/15), serum vancomycin level was drawn only 23% of the time and only 36% of the serum drug levels were within therapeutic range (15 - 20 mcg/mL).

	Serum vancomycin level drawn % (n;N)	Therapeutic range (15 - 20 mcg/mL) % (n;N)
WDI-F	23.59% (n=21; N=89)	38.09% (n=8;N=21)
WDI-E	25% (n=4;N=16)	25% (n=1;N=4)
WDI-E + WDI-F	23.8 (n=25;N=105)	36% (n=9;N=25)

Conclusions: Of the small percentage of serum vancomycin levels drawn, only 36% fell in the therapeutic range with a potentially much larger group that were not monitored falling outside the target range as well. The gap in care can lead to sub-optimal treatments and complications including multidrug resistant organisms, recurrent infections and increased mortality. To overcome this gap, we plan to implement a protocol and train the dialysis staff to use the protocol for vancomycin dosing for patients on HD at WDI.

Loading dose (LD) algorithm

Dry body weight (kg)	Vancomycin LD (20-25 mg/kg)✢
< 60	1250 mg IV
60.1 to 80	1500 mg IV
80.1 to 100	1750 to 2000 mg IV
> 100	2000 mg IV

✢ Maximum dose 2000 mg IV

Initial maintenance dose (MD):
< 70 kg and anuric: 500 mg IV
70 to 100 kg or if residual renal function present: 750 mg IV
> 100 kg: 1000 mg IV

Maintenance dose (MD) algorithm

Serum vancomycin level (mcg/mL)	Vancomycin MD✢
< 10	Increase dose by 50 % and inform MD/NP/RPh □✢
10 to 14.9	Increase dose by 25% □✢
15 to 19.9	Continue same dose of vancomycin □
20 to 24.9	Decrease dose by 25% □✢★
≥ 25	Hold dose and inform MD/NP/RPh

✢ Maximum dose 2000 mg IV
□ Round off to the nearest increments (or decrements) of 250
★If patient was on 500 mg dose, then continue the same.

TH-PO1141

Targeted Deprescribing in an Outpatient Hemodialysis Unit: A Study to Decrease Polypharmacy Marisa Battistella,[1,2] Caitlin McIntyre,[1,2] Chaim Bell,[3] Rory F. McQuillan.[3] *[1]Nephrology, Univ Health Newwork, Toronto, ON, Canada; [2]Pharmacy, Univ of Toronto, Toronto, ON, Canada; [3]Medicine, Univ of Toronto, Toronto, ON, Canada.*

Background: Polypharmacy in hemodialysis patients can result in a higher risk of non-adherence, adverse drug events, hospitalizations, and mortality. Deprescribing tools can reduce polypharmacy yet no method exists for an outpatient hemodialysis population. We aimed to (1) develop a deprescribing tool for target medications with poor evidence for efficacy and safety; (2) determine its effectiveness in decreasing polypharmacy; and (3) monitor patient safety and satisfaction.

Methods: In a single-center prospective observational study, a deprescribing tool for specific medications was developed, validated, implemented and evaluated in a tertiary care center - outpatient hemodialysis unit. All 240 patients in the unit were screened using the deprescribing tool. The primary outcome was the proportion of target medications completely deprescribed at 6 months. Patient safety and satisfaction were monitored during the trial using drug-specific monitoring parameters outlined in the tool.

Results: Five medication classes were selected: quinine, diuretics, alpha-1 blockers, proton pump inhibitors, and HMG Co-reductase inhibitors (statins). There were 171/240 (71%) patients prescribed at least one of the five target medications and 71 patients (80 medications) underwent a deprescribing trial. After applying the tool, 35/40 (88%) eligible patients initiated a deprescribing trial. There were 31 of 40 (78%) target medications successfully deprescribed. Six months after the trial, only 5/31 (16%) medications discontinued were re-prescribed. This decreased the average number of medications per patient [from 13.4 ± 4.3 (SD) to 12.7 ± 4.4 medications in 35 patients]. No adverse events were observed.

Conclusions: Deprescribing tools can be applied successfully in an outpatient hemodialysis unit to reduce polypharmacy while maintaining patient safety and satisfaction.

Funding: Government Support - Non-U.S.

TH-PO1142

Prolonged Intravenous Antibiotic Use in Hemodialysis Patients Evamaria Anvari, Laura Ferreira Provenzano. *Nephrology and Hypertension, Cleveland Clinic.*

Background: Infection is common in hemodialysis patients. The presence of a hemodialysis catheter and a weak immune system are recognized risk factors. Infections could be bacterial or non-bacterial, and bacterial infections include blood stream infections, pneumonia, urinary tract infections and others. Recognizing which patients to treat with antibiotics is essential, as bacterial infections are the second most common cause of death in hemodialysis patients, but treating patients with antibiotics when not needed, might lead to many adverse events. Despite this, many hemodialysis providers prescribe empiric antibiotics when patients are found to be febrile on hemodialysis, assuming a bacterial blood stream infection, sometimes without a clinical evaluation. In addition, many times blood cultures are not checked and prolonged antibiotic courses are given.

Methods: We analyzed blood culture and antibiotic use data from 10 hemodialysis units from a single dialysis provider in the Cleveland area, from January to November 2015. Patients were under the care of both private and academic practice physicians.

Results: During this period, 279 patients had blood cultures sent. Of these patients, only 49 had positive cultures. (17.6 %) and 230 were negative (84.4%). A total of 124 patients received antibiotics during hemodialysis, 75 of which ended having negative blood cultures. 33/75 of culture negative patients received more than 3 doses of antibiotics (range: 1-24 doses). Of the 49 patients with positive blood cultures, 33 had catheters.

Conclusions: Our data shows that there is significant variability in antibiotic use and duration in patients in hemodialysis. We found significant number of patients that received antibiotics without a clear indication. Protocols to help providers could help identify patients that require antibiotics in hemodialysis are needed, to avoid improper or prolonged use of antibiotics in the dialysis units.

TH-PO1143

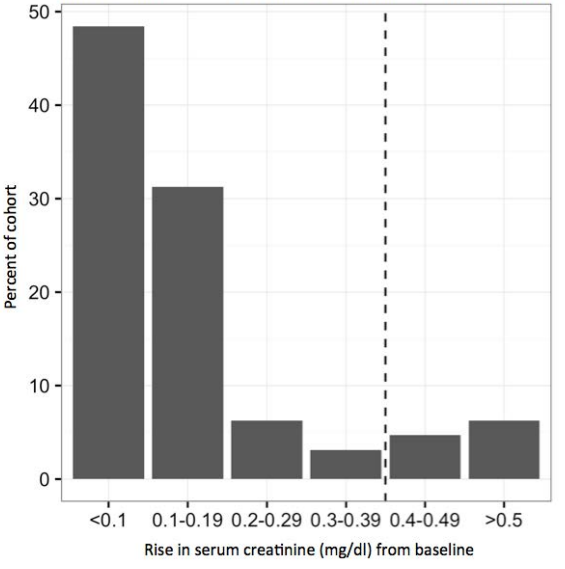
Safety and Efficacy of Novel Direct-Acting Antiviral Therapies in Patients with Chronic Kidney Disease Meghan E. Sise,[1] Gregory L. Hundemer,[1] Guillermo Ortiz,[1] Elke Backman,[2] Donald Chute,[3] Joseph Brancale,[3] Ravi I. Thadhani,[1] Raymond T. Chung.[3] *[1]Medicine/Nephrology, Massachusetts General Hospital, Boston, MA; [2]Pharmacy, Massachusetts General Hospital, Boston, MA; [3]Medicine/Gastroenterology, Massachusetts General Hospital, Boston, MA.*

Background: Sofosbuvir-based therapy has revolutionized the management of Hepatitis C Virus infection; however, little is known about the safety of this medication in patients with chronic kidney disease (CKD). The active metabolite of sofosbuvir, GS-331007, is renally eliminated. Recent studies suggest that patients with baseline CKD may experience adverse events including nephrotoxicity when treated with sofosbuvir.

Methods: Retrospective study of patients with CKD who began DAA treatment (tx) between 11/01/2013 - 12/31/15. CKD defined by mean eGFR < 60mL/min or albuminuria > 30mg/g in the 6months prior to tx. Safety, tolerability and laboratory results were assessed by chart review. Mean and standard deviation (SD) are presented.

Results: 107 subjects were included. Mean age 62 years (SD 8), 77% male, 46% White, 19% Black. 45% had diabetes, 86% hypertensive, 12% HIV co-infected, 37% were cirrhotic, 33% prior liver or kidney transplant recipients. 50% were HCV tx naïve. Regimens used were SOF/simeprevir 42%, SOF/ledipasvir 24%, and SOF/ribavirin 34%. 6% had a transient creatinine rise of >= 0.5mg/dL during tx.

Figure 1. Peak Rise in serum creatinine during direct acting antiviral therapy



Despite transient rises on therapy, average creatinine 12 weeks after therapy was 1.24mg/dL (SD 0.8) compared to baseline 1.26mg/dl (SD 0.37). SVR was 81%. Causes of renal and other serious adverse effects are presented, with discussion of relationship to DAA tx.

Conclusions: SOF-containing DAA regimens are effective and appear relatively safe in patients with CKD, although side effects were common; significant nephrotoxicity was noted in 6% percentage of cases.

Funding: NIDDK Support

TH-PO1144

The Drugs That Mostly Frequently Induce Acute Kidney Injury: A Case-Non-Case Study of a Pharmacovigilance Database Sophie Liabeuf,[1,2] Marion Pierson Marchandise,[1] Julien Moragny,[1] Kamel Masmoudi,[1] Valérie Gras.[1] *[1]Regional Pharmacovigilance Centre, Div of Clinical Pharmacology, Amiens Univ Hospital, Amiens, France; [2]Inserm U1088, UPJV, Amiens, France.*

Background: Acute kidney injury (AKI) is associated with a high hospitalization rate, accelerated long-term decline in kidney function and a high mortality rate. Adverse drug reactions (ADRs) constitute one of the most important modifiable factors in the context of AKI. Most studies of drug-induced AKI have focused on a sole drug class. The objective of the present survey was to establish a comprehensive overview of drug-induced AKI on the basis of ADRs spontaneously reported in the French national pharmacovigilance database (FPVD).

Methods: We performed a case/non-case study of drug-induced AKI. Cases of AKI were reported in the FPVD between January 1st, 2015, and December 31st, 2015. The non-cases corresponded to all other reports during the same period. Data were expressed as a reporting odds ratio (ROR) with its 95% confidence interval.

Results: Of the 38782 ADRs recorded in the FPVD during the study period, 3.2% were classified as cases of AKI. A total of 1254 patients experienced AKI (males: 55%; mean ± standard deviation age: 68.7 ± 15.0; median age: 70). Two or more concomitantly administered drugs were involved in 66% of the cases of AKI. The most frequently implicated drug classes were antibacterials for systemic use (29.5%), diuretics (18.5%), agents acting on the renin-angiotensin system (16.3%), antineoplastic agents (10.2%) and anti-inflammatory agents (5.4%). Gentamicin, eplerenone, spironolactone, candesartan, cisplatin and aciclovir had the highest RORs (>10).

Conclusions: Drug-induced AKI is a preventable event. A comprehensive study of a national pharmacovigilance database enabled us to identify the drug classes that most frequently induced AKI. Even though most of the identified drugs were already known to induce AKI, the present work should raise physicians' awareness of the compounds responsible for triggering this potentially life-threatening condition.

TH-PO1145

Incidence of Hyperphosphatemia and Hypocalcemia Secondary to Phosphate Enema Administration Javier Villacorta, Ana M. Tato, Gema Fernandez Juarez. *Nephrology, Hospital Fundacion Alcorcon, Alcorcon, Spain.*

Background: The use of sodium phosphate solutions as a purgative implies an exogenous phosphorus administration 8 times the normal daily intake. This overload of phosphorus can lead to a significant increase in phosphatemia within the first 24 hours, which is usually accompanied by a decrease in serum calcium levels. This has been demonstrated in patients undergoing bowel preparation with oral phosphate solutions, but few studies have analyzed electrolyte abnormalities after the use of phosphate enemas.

Methods: This study aim to analyze changes in serum phosphorus and calcium levels following the administration of sodium phosphate enemas in a cohort of hospitalized patients. During a follow-up period of three months, all patients admitted in the Foundation Hospital Alcorcon who recieved sodium phosphate enemas were studied prospectively. Serum phosphorus and calcium determinations were performed 48 hours before and 24 hours after sodium phosphate enema exposure.

Results: Changes in serum calcium and phosphorus levels were studied after 22 exposures to phosphate enemas in fourteen patients. In most cases a single enema (dosage of 8 gr of sodium phosphate; Casen Fleet Enema 250 cc) was administered. The average serum concentration of phosphorus and calcium before enema administration was 2.94 +/- 0.46 and 8.3+/-0.65 mg/dl, respectively. The average concentration of phosphorus and calcium after sodium phospate exposure was 3.2 +/- 0.67 and 8 mg/dL+/-0.61, respectively. In fourteen patients (63.5%) the sodium phosphate enema led to positive phosphorus balance and negative calcium balance. The mean increase in serum phosphorus was 0.34 mg/dl after administration of the enema, and the mean decrease in plasma calcium was - 0.2 mg/dl. Two patients (9%) developed mild hyperphosphatemia and 5 patients (22.7%) with previous normal calcium levels developed relevant hypocalcemia.

Conclusions: The use of sodium phosphate enemas led to an increase in serum phosphorus levels and decrease in serum calcium levels in a high percentage of patients. These electrolytes changes are mild and transient in most cases, but may determine the onset of significant hyperphosphatemia or hypocalcemia in a significant number of patients.

TH-PO1146

Monitoring Urinary Protein Excretion in Patients with Heart Transplant Receiving mTor Inhibitors-Need for Raising Awareness Negiin Pourafshar,[1] Ashkan Karimi,[2] Jon A. Gregg,[1] Amir Kazory.[1] *[1]Div of Nephrology, Univ of Florida, Gainesville, FL; [2]Div of Cardiovascular Medicine, Univ of Florida, Gainesville, FL.*

Background: The inhibitors of the mammalian target of rapamycin (mTORi) are used in the setting of orthotopic heart transplantation (OHT) mainly to avoid the nephrotoxicity of calcineurin inhibitors (CNI) or to slow the progression of allograft vasculopathy. Proteinuria is a well-recognized complication of mTORi use in the renal transplant recipients but there is limited data in the OHT population. We studied the monitoring of patients with OHT who received mTORi-based regimens with respect to development of proteinuria.

Methods: This is a retrospective study of patients who underwent OHT between January 2000 and December 2015 at our institution. Patients on mTORi, whether de novo or following conversion from a CNI-based regimen, were included. The clinical and laboratory records were reviewed and monitoring of urinary protein excretion through qualitative (urine analysis) or quantitative measurements were explored before and after the initiation of mTORi.

Results: A total of 411 OHT patients were studied, of which 91(22%) received mTORi (72 Sirolimus and 19 Everolimus). mTORi was started de novo in 32/91 (35 %) of patients. Prior to the initiation of mTORi, urine protein excretion had been assessed in 56/91 (62%) of the patients with either urinalysis (26/91 [29%]) or quantitatively (30/91 [33%]). After the initiation of mTORi therapy only 60/91 (66%) had at least one-time evaluation for proteinuria during follow-up by urine analysis 26/91 (29 %) or quantitatively 34/91 (37%). Among patients who received mTORi, 31/91 (34%) patients had no assessment of proteinuria throughout follow-up.

Conclusions: This single-center study reveals that a significant subset of OHT recipients who are treated with an mTORi-based regimen may not undergo assessment of proteinuria prior to or following initiation of mTORi, possibly resulting in underdiagnosis. Raising awareness regarding regular screening and timely diagnosis of this complication may conceivably lead to long-term preservation of renal function and overall improvement in the outcomes of these patients.

TH-PO1147

Management of Hyperkalemia in Emergency Department: Computerized Physician Order Entry Reduces Hypoglycemia Associated with Insulin-Dextrose Treatment Bairbre A. McNicholas, Mai Huong Pham, Chang Huei Chen, Hien Pham. *Div of Nephrology, Univ of Washington, Seattle.*

Background: Hyperkalemia is commonly treated in the ED (emergency department) with insulin-dextrose being a cornerstone of treatment. The use of insulin can result in clinically significant hypoglycemia. Computerized physician order entry (CPOE) has been shown to reduce preventable adverse events. We assessed use of CPOE for hyperkalemia management on hypoglycemia incidence in the ED.

Methods: Two retrospective studies of hyperkalemia management at Harborview Medical Center ED were carried out, an initial study from June-December 2013 and a follow up study from July 2015 to January 2016. Following the initial study, Education sessions were provided to ED staff on CPOE for hyperkalemia management. For both studies, data related to presentation, laboratory values and pharmacological management of hyperkalemia (K^+>6mEq/L) was collected using chart review for each patient.

Results: In the initial study, 125 patients had 155 presentations of K^+>6mEq/L compared to 98 patients with 116 presentations in the follow up study. In the initial study, pharmacological treatment was used in 99(63%) of cases with management in 62(62%) ordered using CPOE for hyperkalemia. 75(75%) patients were treated with insulin-dextrose. In the follow-up study, pharmacological treatment was used in 68(58%) of cases and 51(75%) were ordered using CPOE for hyperkalemia. 66(97%) patients were treated with insulin-dextrose. When subjects with hyperkalemia associated with hyperosmolar hyperglycemia (blood glucose>600mg/dl) were excluded from treated groups (n=3 for initial study, n=3 for follow up study), the number of cases managed using CPOE for hyperkalemia trended higher on follow-up (62/96 (64%) vs 51/65(78%), p=0.07). The number of cases of hypoglycemia associated with insulin treatment was reduced at follow up (21/76 (27.6%) vs. 7/66 (10.6%), p=0.02) and there were no cases with blood glucose <40mg/dl compared to 3 cases in the initial study.

Conclusions: Increased use of CPOE for management of hyperkalemia was associated with a reduction in number of patients with hypoglycemia associated with insulin-dextrose treatment.

TH-PO1148

Atypical Hemolytic Uremic Syndrome: Quality Measures for Detection Jibran Ahmed,[1] Hussein Hamad,[2] Olha Huzo,[3] Carolyn S. Brecklin.[4] *[1]Internal Medicine, John Stroger Hospital of Cook County, Chicago; [2]Internal Medicine, John Stroger Hospital of Cook County, Chicago; [3]Saint James School of Medicine; [4]Nephrology, John Stroger Hospital of Cook County, Chicago.*

Background: Atypical hemolytic uremic syndrome (aHUS) is a major thrombotic microangiopathy (TMA). TMA include aHUS, Shiga-toxin producing E.Coli (STEC) associated HUS and thrombotic thrombocytopenic purpura (TTP). It is essential to differentiate aHUS from TTP as these two entities require different treatment. We conducted a retrospective study to determine whether patients receiving plasma exchange for TMA had appropriate initial testing done.

Methods: We identified 30 patients who received plasma exchange for presumed TTP between January 2010 and June 2015 at an inner city hospital and recorded socio-demographic, clinical and laboratory data. Mean values were calculated, univariate analysis was conducted.

Results: Male patients accounted for 73% of the group and 73% were African-American. Diarrhea at presentation was recorded in 16% (5 pts) of which only 2 (6.6%) had testing for STEC sent. Cancer (26.7%) and infection (23.7%) were the two most common risk factors. The mean platelet count (plts) at diagnosis was 31,600 and the mean creatinine (Cr) was 3.46 mg/dl. Haptoglobin was checked in 23 pts (76.6%) and was not low in 4 pts (13.3%). ADAMTS 13 was checked in only 20 pts (66.6%) and levels below 5% were observed in only 5 pts (16%). Normalization of plts after 10 sessions of plasma exchange occurred in about 50% of patients and 16% had relapse by 1 month. Dialysis was required in 16%. Cr level at diagnosis did not correlate with plts normalization after 10 sessions of plasma exchange (p=0.088) or with relapse at one month (p=0.76) but did correlate with the need for dialysis (p=0.003).

Conclusions: Our review showed that appropriate pre-plasma exchange labs were not always performed when TTP was presumed, including STEC test, haptoglobin and most importantly ADAMTS13 level. The relapse at one month, although not unexpected, should raise the question of the accuracy of initial TTP diagnosis and the provision of ADAMTS13 level testing is crucial. Further studies should help define the recommended testing algorithms for TMA.

TH-PO1149

Effectiveness of UV Light in the Disinfection of Peritoneal Dialysis Catheter Connections

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Background: The purpose of the current study was to evaluate the microbiological performance (log reduction) of a modified ultraviolet (UV) light-based peritoneal dialysis catheter connection system. The system included an enhanced UV light generating device which provides greater coverage for the UV transparent connector incorporated into the transfer set and a modified UV transmissive connector which improves patient ease of use.

Methods: Prior to being coupled to the non-UV transmissive Y-set connector with a membrane sealing the distal lumen which is attached to a PD solution bag, each UV transparent transfer set was inoculated with 10µl of cultured inoculum consisting of either *S. aureus, E. coli,* or *C. albicans*. After being inoculated, the Y-set connector was attached to the transfer catheter connector creating a sealed chamber, then placed in a UV generating device, and the chamber was exposed to a UV light dose of approximately 350-400 mJoules/cm^2. After being exposed to the UV light, the membrane seal was broken, the plunger valve on the UV transmissive transfer catheter was pushed to the open position, and 10 mL of dialysate was flushed through the connection over 7 seconds. The flushed solution was collected, diluted, and plated on agar medium matched to the organism. All plates were incubated for a 24 hour period (48 for C. albicans). Sample results were compared to positive controls which were collected in an identical manner but without exposure to the UV light.

Results: Twenty-nine (29) separate test samples, 3 positive controls, and 1 negative control were collected for each organism. All positive control samples had significant bacterial growth and negative controls had no growth following the 24 hour incubation period. All test samples exposed to UV light had complete kill of bacteria. Log reduction ranged from 4.93 in the *C. albicans* group, to 5.56 in the *S. aureus* group, to 6.24 in the *E. coli*.

Conclusions: The application of 400 mJ/cm^2 of UV light (254nm) combined with an easier to use UV transmissive transfer catheter connector produces a germicidal effect upon microorganisms which have been found to be associated with peritonitis in patients receiving peritoneal dialysis.

Funding: Other U.S. Government Support

TH-PO1150

Application of Comfeel Hydrocolloid Transparent Dressing Combined Specific Electromagnetic Wave in the Patients with Arteriovenous Fistula Complicated with Subcutaneous Hematoma

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Background: Comfeel transparent dressing is a hydrocolloid dressing which can promote local blood circulation, relieve pain and Reduce inflammatory reaction. And Teding Dianci Pu (TDP) special electromagnetic wave irradiation instrument can diminish inflammation and promote the growth of the local epithelial tissue. The purpose of this study is to explore the effect of Comfeel transparent dressing combined TDP irradiation treatment in the chronic kidney disease patients with arteriovenous fistula (AVF) complicated with subcutaneous hematoma.

Methods: 30 patients (14 male, 16 female) were involved in this study. All the patients were randomly divided into observation group (n=15) and control group (n=15). There was no significant difference in gender, age, primary disease, use time of AVF and the size subcutaneous hematoma between the two groups. The methods of control group included clean the local skin and use the Hirudoid ointment to massage, 3 times a day, but not to use within 6 hours after hemodialysis. The methods of observation group included clean the skin, paste the Comfeel transparent dressing (No.3533), and use TDP irradiation for 15 minutes, twice a day, but not to use TDP within 24 hours after hemodialysis. The transparent paste was replaced every 3 days. The effect of treatment was recorded daily, and the skin ecchymosis, swelling, local pain (NRS Pain Assessment Scale), AVF tremor and patient satisfaction were assessed after 1 week.

Results: The subsidence of the skin ecchymosis and swelling was faster ($P < 0.05$) in the observation group. And the pain assessment showed pain scores of observation group were lower than the control ones ($P < 0.05$). There were no differences in the AVF tremors and patient satisfaction ($P > 0.05$).

Conclusions: The research results show that use of Comfeel transparent paste combined TDP irradiation can effectively relieve the local pain, and promote the subsidence of the skin ecchymosis and swelling. It is worthy to be popularized in clinic practice.

TH-PO1151

Beyond the Bundles: Reducing Central Line Related Infections - Permanent Catheter (PC) in Haemodialysis (HD) Patients at Five Community-Based Dialysis Centres (CB-DCs)

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Background: Catheter Bundles were implemented for PC care over five year period to reduce infections at NKF. Changes included hand hygiene compliance, barrier precautions, use of alcohol based 2% chlorhexidine antisepsis, patient education and ensuring PC dressing is intact/dry The Catheter Bundles decreased infection rates, however it did not approach zero after interventions. Reducing catheter infection rate is essential for safe care and patient safety. This study adopts CDC Approach to Bloodstream Infections (BSI) Prevention in Dialysis Facilities. Aim of the study is to determine the contributing factors for catheter-related infections, develop creative solutions and reduce the PC infections at NKF.

Methods: From Jan 2014 to Dec 2014, 115 HD patients had catheter - related infections. Five CB-DCs had surpassed PC infection rate equal and above 4.32 per 100 patient months. Catheter Bundles Audit (4th Quarter 2014) showed 90% compliance rate. AS-IS Diagram, three starbursts were identified; hand hygiene non-compliance, lack of patient education and poor "Scrub The Hubs" technique. Interventions includes training on "Dialysis Catheter Workshop" was conducted in Feb 2015 with participations from 42 clinicians, development of patient educational brochure, video on "Catheter Care", PC "E" kit to promote self management and Catheter Bundle Audit to monitor the compliance with procedures.

Results: Results revealed catheter-related infection rate declines from 7.14 per 100 patient months in Nov 2014 to 1.23 per 100 patient months in Apr 2015, reduction in hospitalisation episodes from 16 to 9 cases, cost savings and increase compliance with Catheter Bundles from 90% to 94%.

Conclusions: This study promotes compliances through catheter management with standardisation of PC training (video), patient educational brochure and PC "E" kit. While the national average is 4.32 per 100 patient months, ours is down to around overall average 2.10 per 100 patient months in Apr 2015. Active surveillance, sharing of catheter-related infection rates and catheter bundle audit results with clinicians helps to raise awareness on the importance of PC care.

TH-PO1152

Efficacy and Cost-Effectiveness of DDAVP Administration prior to Renal Biopsy when eGFR Is Below 30: A Retrospective Chart Review

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Background: Renal biopsy is an essential diagnostic tool in management of renal disease. Life-threatening bleeding, while uncommon, is a serious and feared complication. Higher serum creatinine has been shown to predict postbiopsy bleeding (Whittier et al.). In 2011, Manno et al. found a 0.45 relative risk reduction in postbiopsy bleeding with DDAVP compared to placebo. In 2014, our Radiology Department implemented a protocol giving 0.3mcg/kg of IV DDAVP to all patients with eGFR below 30 prior to ultrasound-guided renal biopsy.

Methods: A retrospective chart review was done for all patients who underwent a renal biopsy one year prior to and after protocol implementation. We collected data on patient age, baseline blood pressure, hemoglobin, renal function, coagulation and evidence of minor or major bleeding. Minor bleeding is defined as: perinephric hematoma and gross hematuria. Major bleeding is defined as the need for angiography or embolization.

Results: Of 156 patients who did not receive DDAVP, 24 were noted on imaging to have a perinephric hematoma and 5 required renal artery embolization. Of 144 patients who did receive DDAVP, 13 had a hematoma and none required angiography or embolization.

Conclusions: Despite what appear to be promising outcome trends with the administration of DDAVP, our findings were not statistically significant. We believe our analysis is limited primarily by sample size. However, at an institution cost of $2/mcg, the total cost of DDAVP given to our treatment group was $7,041. This is far less than Medicare reimbursements (HCPCS36253) for one renal angiogram. Therefore, given the favorable trend toward bleeding prevention, if administration of DDAVP prevents at least 1 embolization, it proves to be a cost-effective adjunct therapy in a higher risk population.

TH-PO1153

Arterial Stiffness Is an Independent Risk Factor for Anemia after Percutaneous Native Kidney Biopsy

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Background: Bleeding is the most common complication after renal biopsy. There are many previous reports on the predictors of bleeding. While physicians can perform procedures carefully, anemia is frequently unavoidable. Whether arterial stiffness affects bleeding complications remains unclear.

Methods: We performed an observational study of the renal biopsies that were performed over an approximately 6-year period (March 2010 to March 2016) at our Division. They were all percutaneous ultrasound-guided biopsies. The clinical and laboratory factors were analyzed to reveal the risk factors associated with bleeding, with a focus on anemia (defined as a ≥10% decrease in hemoglobin (Hb) after biopsy). The brachial-ankle pulse wave velocity (baPWV) was measured to evaluate the arterial stiffness.

Results: This study included 462 patients (244 males, 218 females). Of these, 2 patient (0.43 %) required a blood transfusion after the biopsy; no patients required nephrectomy

due to continuous bleeding. Macrohematuria occurred in 5 patients (1.0 %), and perirenal hematoma was observed on ultrasonography in 386 patients (85.0 %). The median decrease in Hb was 0.33 g/dl. Anemia (defined above) was observed in 54 patients (11.7 %). The risk of anemia was higher in women, older patients, and patients with lower serum albumin, lower eGFR and lower diastolic blood pressure after biopsy. A multivariate analysis revealed that anemia was strongly associated with female gender, lower serum albumin, and lower diastolic blood pressure after biopsy. Next, we performed a further analysis in 187 patients for whom baPWV data was available. A higher baPWV value was found to be a risk factor of anemia. The ROC analysis for predicting anemia revealed baPWV 1839 m/s to be the best performance (AUC 0.689, $p < 0.005$).

Conclusions: An increase in the baPWV, which is non-invasive parameter of arterial stiffness, was the factor significantly associated with anemia after biopsy, and thus may be a more valuable predictor of bleeding complications than any of the other reported risk factors.

TH-PO1154

Outpatient Percutaneous Native Renal Biopsy: Safety Profile in a Large Monocentric Single Operator Cohort Dario Roccatello, Savino Sciascia. *Nephrology Dept, San Giovanni Bosco Hospital, Torino, Italy.*

Background: Debate exists on the appropriate observation period after percutaneous native renal biopsy. We evaluated the safety of performing renal biopsy as an outpatient procedure compared to the traditional inpatient policy.

Methods: We retrospectively studied native kidney biopsies performed in our Institution (Jan 2000-Nov 2015).Since Jan 2012, we began performing renal biopsies as outpatient procedures. Two groups of patients were considered; Group I: biopsy was performed and followed by at least 1-day hospital admission;Group II: biopsy was performed as outpatient and followed by 6 hours' observation period and then by outpatient visits. All biopsies were performed by a single nephrologist with the use of real-time ultrasound and automated biopsy needle (18 gauge),following a structured protocol.

Results: 462 biopsies were reviewed, 210 (45.5%) of patients were female and the mean age was 54.7±17.9 years. 129 (27.9%) of these biopsies were performed in outpatients. A total of 36 (7.8%) of patients developed a complication, and of those 9 (1.9%) suffered for a major complication [arteriovenous fistula (6 cases,1.2%), ischaemic stroke (2, 0.4%), thromboembolic pulmonary embolism (1, 0,2%)] and 27 (5.8%) for minor [macroscopic haematuria (12 cases, 2,6%), haematomas on sonography not requiring intervention (15 cases, 3,2%)]. When comparing the complication rate between group I and II, no statically difference were observed [overall 24/333 (7,2%) complications in group 1 and 12/129 (9,3%) in group II; 5/333 (1,5%) and 4/129 (3,1%) major, 19/333 (5,5%) and 8/129 (6.2%) minor complications, respectively in group I and II]. When analysing together both groups, after multivariate analysis, serum creatinine >3 mg/dl (OR 2.03 95%CI 1.18-6.81) and known severe hypertension (OR 2.01 95%CI 1.2-4.7) were found to be independent risk factors for minor and major complications, respectively. We found no association of risk with the biopsy passes, gender, age, diagnosis, presence of haematuria before the kidney biopsy nor the degree of proteinuria.

Conclusions: Outpatient biopsy could be a valuable, safe, and perhaps cost-effective method of obtaining diagnostic renal tissue in the majority of patients.

TH-PO1155

Complications of Percutaneous Renal Biopsy Performed by Nephrology Fellows: Analysis of 1071 Procedures Manuel Alejandro Marquez,[1] Monica Chapa,[2] Ricardo Correa-Rotter,[1] Juan M. Mejia-Vilet.[1] *[1]Nephrology, Inst Nacional de Ciencias Médicas y Nutrición, Mexico; [2]Radiology, INCMNSZ, Mexico.*

Background: The performance of percutaneous renal biopsies(PRB) is a key element for renal diagnosis and nephrology training. The aim of this study was to evaluate safety and efficacy of PRB performed by nephrology fellows(NF) in an academic training program and to determine risk factors for major complications(MC).

Methods: All PRB performed by NF between 2008-2015 were analyzed.PRB procedures were ultrasound-guided and supervised by staff.In all patients, a doppler ultrasound(US) was performed 10min after the procedure. MC were defined as those requiring medical intervention(blood transfusion, renal angiography, surgery or death). Chi-square, t-student or Mann-Whitney tests were used for comparison of those with or without MC. A predictive model for MC was constructed by logistic regression.

Results: A total of 1071 PRB were analyzed,≥10 glomeruli were obtained in 989(92%) and were appropriate for diagnosis in 1067(99.6%). MC presented in 33(3.1%). All corresponded to hematomas requiring blood transusion, 3(0.3%) renal angiography and 1(0.09%) patient died after a laparotomy due to severe hemorrhage. Predictors of MC in the logistic regression model are shown

Risk factor	Prebiopsy Risk factors			+ Post-biopsy ultrasound		
	OR	95% CI	p Value	OR	95% CI	p Value
Female	3.68	1.21-11.2	0.022	3.27	1.04-10.2	0.042
Blood urea nitrogen>50mg/dl	4.82	2.15-10.8	<0.001	5.09	2.18-11.9	<0.001
Hemoglobin <11g/dl	4.23	1.73-10.4	0.002	3.39	1.34-8.58	0.010
Platelets <150 per mm3	6.00	2.76-13.0	<0.001	5.04	2.20-11.5	<0.001
Hematoma in ultrasound	--	--	--	8.23	3.35-20.2	<0.001

The predicting AUC was 0.89. There were no differences in MC in 28 patients who had total anticoagulation(suspended prior to PRB). The absence of a renal hematoma in the immediate post-procedure US had a NPV of 99%. The addition of postprocedure US to the model improved the AUC to 0.92.

Conclusions: The study allowed the identification of specific high-risk factors for selection and decision of performance of a PRB. The absence of a renal hematoma in the immediate postprocedure US had a high NPV for MC. RPB is a safe procedure when performed by NF, as MC presented in a similar pattern and percentage as compared to large published series.

TH-PO1156

Safety of Outpatient Kidney Biopsies Bojana Gardijan, Mihaela Gunjaca, Branislav Cingel, Mladen Knotek. *Renal Div, Dept of Medicine, Univ Hospital Merkur, Zagreb, Croatia.*

Background: Kidney biopsy (bx) is an essential part of nephrological diagnostic work-up. In our center it is frequently performed as an outpatient procedure. Aim of this study was to evaluate the safety of bx in the outpatient setting.

Methods: We analysed native and transplant kidney bx performed from July 2013 to June 2015. 255 bx performed in the outpatient setting were identified. There were 216 bx in transplant pts, and 39 native kidney bx, including 3 solitary kidney bx. All were performed under US guidance using a 16G or 18G needle. In all patients with eGFR<30ml/min desmopressin (0.4 µg/kg BW i.v.) was administered prior to the procedure. Patients were observed for 6 h before discharge, with a CBC and a urine test performed after 4 hours. Ultrasonography was performed upon attending clinician discretion. Study outcomes were minor complications, defined as macrohematuria, significant reduction in Hb levels (>10% without need for RBC transfusion), local hemorrhage or major complications, defined as hemorrhage requiring therapeutic intervention including RBC transfusion.

Results: There were 71 female and 184 male patients. Average age was 42.6 ±16.1yrs. Indications for native kidney bx included nephrotic syndrome (51%), subnephrotic proteinuria with hematuria (29%), follow-up bx (15%), and other (5%). From 216 transplant bx 31% were indication and 69% were protocol bx. The glomerular yield in 96.9% of bx was sufficient for analysis. There were no major complications. In 18% of patients there was a Hb rise after biopsy. Average postbx Hb decline in the other 82% was 5% (1-16%). In 13.3% pts there was >10% reduction in Hb level, with no evident bleeding, including by US. In 2% of the patients postbx macrohematuria was present, without requirement for intervention or blood transfusion. In univariate analysis age, gender, serum creatinine, prebx Hb and indication for bx were not predictive for postbx Hb decline. There were no therapeutic interventions required for bx complications.

Conclusions: We found that kidney biopsy performed in an outpatient setting in select patients is only rarely associated with adverse events and is a safe procedure.

TH-PO1157

Self-Monitoring Creatinine after Kidney Transplantation: Reliability of Patient Reported Data Céline Lianne van Lint,[1] Wenxin Wang,[2] Sandra Van Dijk,[1,4] Ton Rovekamp,[3] Ton J. Rabelink,[1] Willem-Paul Brinkman,[2] Paul J. Van der Boog.[1] *[1]Nephrology, Leiden Univ Medical Center, Leiden, Netherlands; [2]Computer Science, Delft Univ of Technology, Delft, Netherlands; [3]Technology in Healthcare, Prevention and Health (TNO), Leiden, Netherlands; [4]Health, Medical and Neuropsychology & Behavioural Sciences, Leiden Univ, Leiden, Netherlands.*

Background: Our previous study shows that self-monitoring creatinine can significantly decrease the high number of outpatient visits in the first year post-transplantation without compromising on quality of care. In the current study we analyzed data from this same self-management RCT to investigate the reliability of patient reported measurements.

Methods: During the first year post-transplantation 54 patients registered their self-measured creatinine values in an online Self-Management Support System (SMSS) which provided automatic feedback (e.g. contact hospital). Values registered in the SMSS were compared to those logged in the creatinine device to study reliability of registered data. Adherence to measurement frequency was determined by comparing number of requested with number of performed measurements. To study adherence to provided feedback, SMSS logged feedback and information from the electronic hospital files were analysed.

Results: Level of adherence was highest during month 2-4 post-transplantation with over 90% of patients performing at least 75% of the requested measurements. Ninety percent of all registered creatinine values was entered correctly, although values were often registered several days later. In case more measurements were performed than registered on a single day (10%), registered values were significantly lower than unregistered values ($p < .05$) suggesting selection of lower creatinine values. Adherence to SMSS feedback ranged from 53-85% depending on the specific feedback.

Conclusions: Self-monitoring creatinine enables the high number of outpatient visits to be reduced. However, patients' tendency to postpone registration and to select lower creatinine values for registration and the suboptimal adherence to the SMSS provided feedback might challenge safety. These issues can mostly be overcome by transferring measured data automatically.

TH-PO1158

Eradication of Chronic *Helicobacter pylori* Infections in Immigrant Patients with Chronic Renal Insufficiency Alexander M. Swan, Kay Thwe Kyaw. *NHRTRT, LLC, Avenel, NJ.*

Background: Based on some epidemiological studies, there are more frequent infection rate of Helicobacter pylori (H. pylori) in children of developing nations. Surprisingly, more than 50 % of second-generation immigrants are infected with H. pylori. Some studies showed that those differences are somewhat related to socioeconomic status. Most route of transmission of H pylori is either oral-to-oral or fecal-to-oral contacts. Some patients with

H pylori do not present symptoms. When comes to treatment, triple therapy regimen is the first line treatment of H. Pylori. It is critical to aware of known complications of H. pylori such as gastric adenocarcinoma, gastric MALToma, and squamous cell esophageal cancer.

Methods: This study is a non-randomized parallel clinical trials study design. The study population was selected from renal failure patients who were H. Pylori Ig G Ab positive after treated with standard triple regime, consisting of 88 participants of renal failure ranging from CKD Stage one to five, with age between 20 to 65, 80 participants finished and 8 drops out from the study. There are 16 participants contributed in each chronic kidney disease stage from one to five. The participants were given the new treatment, which includes Nitazoxanide 500 mg PO twice daily; Omeprazole 40 mg capsule delayed release daily; Levaquin 500 mg tab daily; and Doxycycline 100 mg twice daily, and the renal dose adjustments were done according to creatinine clearance. The duration of new treatment was 4 weeks. H. pylori Ig G Ab levels were measured before and after new treatment.

Results: At the end of the study, H. Pylori Ig G Ab of all patients in the study population was reduced to "0". The outcome measure is a complete resolution of symptoms of H. Pylori and the disappearance of H. pylori Ig G antibody.

Conclusions: There is evidence that the new treatment regimen reduced H. pylori Ig G level to 0, and clearly showed that more effective in eradication of H pylori infection in patients who have chronic renal failure. The drawback of the new treatment is expensive. However, more researches with larger populations are needed for developing a new guideline for eradication of H pylori in all patients to prevent complications H. pylori infections.

TH-PO1159

Improving Post-Kidney Transplant Immunisation: A Clinical Practice Improvement Project

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Background: Kidney transplant recipients (KTR) are at increased risk of influenza and invasive pneumococcal disease. Audit after 2 cases of pneumococcal infection in KTR at our institution identified low prevalence of pneumococcus (35%) and influenza (30%) vaccination. We devised a quality improvement program in partnership with primary care, who manage vaccination in Australia, to improve up-to-date vaccination to>90% in this population.

Methods: We conducted a single centre prospective clinical practice improvement study on a KTR cohort over 3 years (2013-15). The diagnostic phase indicated low awareness of vaccination importance, non-adherence to local immunisation guidelines and suboptimal communication with primary care doctors. Two interventions of annual reminders to primary care doctors with local immunisation guidelines were devised. The primary outcome was up-to-date vaccination reported in annual surveys. A logistic regression model using Generalized Estimating Equations was used in analysis. The study was approved by our ethics board.

Results: Surveys were sent to the primary care doctors of 59 KTR. Responses were received to 48/59(81%) and 37/59(63%) surveys to interventions 1(2014) and 2(2015) respectively. For pneumococcus 34% of eligible patients were reported to have received vaccination in the period prior to baseline survey, increased to 69% by the second survey; while up-to-date influenza vaccination increased from 45% to 59% in the same period. KTR were significantly more likely to have up to date vaccination by the second survey for pneumococcus, OR 3.4 (95% CI:1.8–6.4; p<0.001) but not influenza, OR 1.8 (95% CI:0.9–3.5; p=0.09). No reported cases of IPD during the study.

Conclusions: The clinical practice improvement method resulted in significant improvements in reported vaccination documentation and up-to-date status but overall rates remain sub-optimal.

TH-PO1160

Emergency Preparedness in the Kidney Transplant Community

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Background: In the ten years since Hurricane Katrina, the Centers for Medicare and Medicaid Services and KCER (Kidney Community Emergency Response) Coalition have taken several steps to regulate and mandate emergency preparedness planning in dialysis units. Similar steps have not been taken to ensure the safety of kidney transplant patients who rely on specialized pharmaceuticals to maintain the function of their allografts. The objective of this study was to develop and pretest a self-administered questionnaire to assess the disaster preparedness of a cohort of kidney transplant recipients in an earthquake-prone region of the United States.

Methods: Based on information obtained from the National Kidney Foundation Planning for Emergencies handbook, we designed a preliminary questionnaire. We recruited 10 Bay Area patients and 5 kidney transplant providers from the transplant clinic at the University of California San Francisco and the general nephrology clinic at San Francisco General Hospital. Our two-step protocol included a self-administered questionnaire followed by an interview regarding attitudes and barriers around preparedness and feedback on the survey. Three researchers coded and analyzed the data and categorized the responses into themes.

Results: The questionnaire was easily readable but subjects had difficulty in understanding the context of the questions. Most defined disasters as man-made terrorism instead of the intended meaning of natural disasters. Patients reported lack of salience and relevance of the issue and lack of access to information as major barriers to disaster preparation. Providers cited their patients' education and motivation as key determinants of their level of preparedness. We modified the questionnaire to include a hypothetical scenario to frame the questions, and organized the questions into sections. Providers' deficiencies in understanding and recognizing transplant patients as a vulnerable population contributed to their complacence in providing them with preparedness information.

Conclusions: We noted serious deficiencies in disaster awareness and planning in the kidney transplant community. Ongoing research and collaboration between medical and city services are necessary to ensure safety in disaster-prone regions.

Funding: NIDDK Support

TH-PO1161

Digital Urine Sediments: Keeping the Attending in the Loop

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Background: Busy nephrology fellowships may necessitate that fellows assess the urine sediment (U-Sed) without faculty presence. This may dilute the educational and clinical value of findings. To address this, we theorized that smart phone digital pictures of the U-Sed, taken by fellows and texted to faculty, may enhance educational and clinical value. To address this, we assessed a random group of U-Sed images for quality, discrimination of elements, and diagnostic utility.

Methods: Three fellows submitted U-Sed images from the inpatient consult service for assessment. U-Sed were photographed through the microscope eye piece. In a group PowerPoint session, fellows and faculty (all blinded to the diagnosis) scored each image for 17 variables, including image quality (acceptable or not), diagnostic utility (yes/no), casts (presence + 5 types), cells (presence + 3 types), and other (yeast, crystals, or debris).

Results: 45 U-Sed images were assessed by a group of 5 faculty and 5 fellows. Control images were carefully scrutinized and classified by 2 faculty prior to the session. Results are in the table.

	Parameter recognized or scored		
Parameter	All	Faculty	Fellows
Image quality (acceptable)	73%	80%	66%
Diagnostic use (useful)	44%	44%	44%
Elements seen			
Casts	42%	39%	45%
Cells	24%	21%	28%
Crystals	16%	16%	15%
Debris	37%	66%	30%
Candida	4%	6%	2%
Control images			
Muddy brown casts	NA	100%	96%
Crystals	NA	100%	88%
Debris	NA	100%	60%
Red cells	NA	100%	100%
Candida	NA	88%	20%

Conclusions: Most smart phone digital images of U-Sed are of acceptable quality. Muddy brown casts, crystals, and red cells can be recognized, but candida is less obvious. Sampling error may occur based on the experience of photographer. Keeping faculty in the loop by sharing U-Sed images may be of educational and clinical utility.

FR-PO001

Infectious Endocarditis Mimicking ANCA Associated Pulmonary-Renal Syndrome with Crescentic Necrotizing Glomerulonephritis
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Introduction: Pulmonary renal syndrome (PRS) is a life threatening disease requiring early diagnosis and prompt treatment. Its most common cause is ANCA- associated pauci immune crescentic Glomerunephritis (Granulomatosis with polyangiitis, GPA). Treatment usually involves high dose steroids, an immunosuppressant, and plasmapheresis. However, ANCA- associated pauci immune crescentic GN can also be the result of infection. This case illustrates the dilemma of medical management until these forms of PRS can be clearly differentiated.

Case Description: A 57- year old white man with bioprosthetic aortic valve placement 5 years earlier transferred to our medical center with altered mental status and PRS. Diagnostic work up was significant for oliguria with Scr 3.5mg/dl, anemia, thrombocytopenia, positive PR3-ANCA, low complements and diffuse alveolar hemorrhage by bronchoscopy. He received hemodialysis, plasmapheresis and intravenous methylprednisolone. Kidney biopsy showed severe crescentic and necrotizing glomerulonephritis with C3 and IgM mesangial staining on immunofluorescence and rare paramesangial electron dense deposits. While on steroids, he develops fever. Blood cultures from the referring hospital showed MRSE. A transesophageal echocardiogram showed vegetations on the aortic and mitral valve along with a perivalvular aortic abscess. Appropriate antibiotic coverage was begun. Plasmapheresis and immunosuppression were stopped. He was too unstable for surgical intervention. The family decided to withdraw care. He died seven days later.

Discussion: PRS due to infection can be difficult to distinguish from GPA. In this case clues to the presence of infection included low complement (C3 32, C4 <8) and fever after starting immunosuppression.

FR-PO002

Proteinuria, Edema, and Hypertension: A Case of Lupus Podocytopathy
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Introduction: Lupus podocytopathy is an emerging subgroup classification of lupus nephritis with proteinuria but there is no immune deposition or endocapillary proliferation on biopsy. The biopsies are often diagnosed as minimal change disease (MCD) or FSGS. We report a case of lupus podocytopathy as per American College of Rheumatology proposed diagnostic criteria, with co-existing focal glomerular tip lesion on biopsy.

Case Description: 39 year old male with hypertension for 12 years presented with abdominal pain, facial and leg edema. He was found to have blood pressure readings consistently over 160/80 despite two blood pressure medications. Blood work showed a creatinine of 1.08mg/dL, cholesterol of 392, triglyceride of 530, serum albumin of 2.2g/dL with normal HgA1C. Two days after our office visit he was hospitalized with flank pain and found in acute kidney injury with a creatinine of 2.9mg/dL. Hospital work up showed normal anti-DNA, complement level, HIV, hepatitis profile, immunofixation and ANCA. Laboratory result showed proteinuria of 2.9 gram/gram of creatinine, positive anti-Smith antibody and ANA>1280. He admitted to NSAID use in the last month. With his worsening kidney function, a kidney biopsy was performed. Biopsy showed podocytopathy, focal glomerular tip lesion approximating minimal change disease. There was accompanying speckled nuclear positivity for IgG, suggesting characterization as a lupus podocytopathy. A formal diagnosis of lupus based on systemic and serologic findings is being strongly considered by rheumatology. High dose steroid was initiated and thus far creatinine has improved to 1.2mg/dL.Rrepeat proteinuria quantification is pending.

Discussion: Lupus podocytopathy is an emerging subgroup classification of lupus nephritis, where there is no immune deposition or endocapillary proliferation on biopsy, but significant proteinuria and MCD or FSGS is noted. Ongoing literary work and case reports have aimed at defining lupus podocytopathy as its own entity in order to better categorize the disease and provide directed treatment plan.

FR-PO003

A 61 Year Old Male with Dense Deposit Disease and Monoclonal Gammopathy of Undetermined Significance
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Introduction: Dense deposit disease (DDD) is a rare cause of glomerulonephritis (GN), predominantly seen in children and young adults. Dysregulation of the alternative complement pathway (AP) is implicated in the development of DDD. Monoclonal gammopathy of undetermined significance (MGUS) has been linked to AP activation. Here we report a case of biopsy proven DDD in an adult male with MGUS.

Case Description: A 61 year old Caucasian male presented with newly diagnosed hypertensive urgency and acute kidney injury with an increase in serum creatinine to 2.7 mg/dL from baseline of 0.8 mg/dL after a recent URI. Exam was significant for a BP of 160/80 and lower extremity edema. Urinalysis was significant for 2+ protein, 3+ blood, 3-10 RBC/hpf, no red cell casts. Spot quantification revealed approximately 3.2 grams of proteinuria per gram of creatinine. Serum immunofixation was remarkable for IgG kappa with a normal serum kappa:lambda ratio. Further work up done at the time, showed normal/negative ANA, anti-dsDNA, C3, C4, CH50, HBsAg, HCV, ANCA and anti-GBM. Renal biopsy findings included membranoproliferative and exudative pattern of glomerulonephritis, with isloated C3 deposits, and highly electron dense deposits, consistent with DDD. Subsequent bone marrow biopsy demonstrated a 3% clonal population Patient was treated with high-dose prednisone and rituximab induction. Seven months post treatment, patient appears to be in remission with a negative urinalysis, no significant proteinuria on spot sample, and a serum creatinine of 1.96 mg/dL. Patient is due for maintenance rituximab therapy. Complement testing for alternate pathway dysregulation is underway.

Discussion: DDD is a rare cause of GN, attributable to dysregulation in the alternative pathway of the complement system. MGUS has been linked to AP dysregulation. This case report demonstrates a patient with DDD & MGUS successfully treated with prednisone and B-cell depleting therapy (rituximab) leading to short term remission of GN.

FR-PO004

Concomitant Diagnosis of Fibrillary Glomerulonephritis Secondary to Multiple Myeloma and Mycosis Fungoides: Simultaneous Diagnosis of B and T Cell Malignancies
Farah Piracha, Neeraj Sharma, Michael Yudd, Jennine Michaud. *Nephrology, East Orange Veterans Affairs, East Orange, NJ.*

Introduction: Fibrillary glomerulonephritis (FGN) is a rare proliferative glomerulonephritis associated with malignancies including Multiple Myeloma (MM). B cell disorders including MM and T cell lymphomas including Mycosis fungoides (MF) occur concomitantly at a higher rate than expected by chance.

Case Description: 71 year old African American male underwent a kidney biopsy for nephrotic syndrome and hematuria. His creatinine was 1.2 mg/dL, serum M spike of 0.5g/dL, 24 hour urine protein 4 grams, urine M spike of 4.5%, C3 was low at 53 mg/dL. Renal biopsy revealed C3 and monoclonal IgG κ deposits on immunofluorescence with randomly arranged, Congo Red negative, fibrils 15-23nm in diameter in a mesangioproliferative pattern. Bone marrow biopsy revealed 4% plasma cells; flow cytometry showed 0.4% IgG κ restricted plasma cells. Serum κ free light chains were 7730 mg/L with a serum free light chain (SFLC) ratio of 228, establishing the diagnosis of MM. Several large hyperpigmented lesions were noted on his trunk; biopsy proven to be MF. MM was treated with cyclophosphamide, bortezomib and dexamethasone; topical steroids for MF. After 4 cycles, serum free κ decreased to 3110 mg/dL, SFLC ratio to 142; proteinuria decreased to 1.2 grams.

Discussion: FGN is seen in 0.5-1% of kidney biopsies with 10% having monoclonal deposits; an M spike can be seen in up to 17% of patients. A contemporaneous cutaneous T cell lymphoma was found in the this patient. A 2009 review from the Mayo Clinic found a higher than expected incidence of concomitant B and T cell disorders which can present simultaneously or sequentially. Proposed theories for this include immunosuppressive medication for one malignancy stimulating another, direct immune suppression of one malignancy leading to a second malignancy, genetic predisposition or release of stimulatory cytokines. In this review, 23 were patients identified with B and T cell disorders, 11 having MM and Amyloidosis; however there were no cases of FGN identified. To our knowledge, this is the first case of MM with FGN and simultaneous MF.

FR-PO005

Collapsing Glomerulopathy Secondary to Schitosoma Mansoni: A Case Report
Precil Diego Miranda de Menezes Neves,[1] Ramaiane Aparecida Bridi,[1] Bernardo V. Reichert,[1] Janaina de Almeida Mota Ramalho,[1] Lectícia Jorge,[1] Luis Yu,[1] Viktoria Woronik,[1] Leonardo Abreu Testagrossa,[2] Denise M. Malheiros,[2] Cristiane B. Dias.[1] *[1]Nephrology Div, Univ of Sao Paulo, Sao Paulo, Brazil; [2]Pathology Div, Univ of Sao Paulo, Sao Paulo, Brazil.*

Introduction: Schistosomiasis is a disease caused by Schistosomiasis mansoni (SM). In the kidney, the glomerulus is the main site of lesion and the most frequent patterns of histologic lesion are Membranoproliferative Glomerulonephritis and Focal Segmental Glomerulosclerosis. At our knowledge, no cases of Collapsing Glomerulopathy (CG) were described. We report a case of CG secondary to SM.

Case Description: Male, 35-years old, previously healthy, complaining for eight months of lower limbs edema, foamy urine and increased abdominal girth. He had had a recent diagnosis of schistosomiasis, with hepatosplenic involvement and had been treated with Praziquantel (50mg/kg). Laboratory tests: urea: 51mg/dL, serum creatinine: 1.8mg/dL (CKD-EPI:54ml/min/1.73m^2), no electrolyte/acid-base disorders, no hematuria/leukocyturia, 24h-proteinuria: 6.56g, serum albumin: 1.9g/dL, total cholesterol: 531mg/dL, LDL: 426mg/dL, hemoglobin: 13.8g/dL, leukocytes: 6440/mm^3, platelets: 115000/mm^3, normal serum complement proteins. Autoantibody and serologic tests (hepatitis B, hepatitis C and HIV) were negative. The aspect of kidney were normal at ultrasonography. Light microscopy at renal biopsy revealed 16 glomeruli (2 completely sclerotic), mesangial hipercellularity, hipertrophy and hyperplasia of podocytes, 25% of glomeruli presenting synechiae, tubules with mycrocistic dilatation, diffuse interstitial fibrosis and arteriolar hyalinosis. Immunofluorescence stain was positive to IgM:+2/+3 e C3:+3/+3, with granular, focal and segmental pattern. Ultrastructural findings at electron microscopy supported the diagnosis of CG. As the treatment of parasitic disease had been taken, we started Prednisone 1mg/kg/d. In spite of treatment, patient undergone progressive end-stage renal disease and need of renal replacement therapy.

Discussion: Despite a rare disease, CG must be kept in mind as a differential diagnosis of nephrotic syndrome in patients with SM.

FR-PO006

Fibrillary Glomerulonephritis in a Patient with Systemic Lupus Erythrematosus Mohit Gupta, Rupesh Raina, Karla Detoya. *Internal Medicine, Akron General Medical Center, Akron, OH.*

Introduction: Fibrillary Glomerulonephritis (FGN) is a rare disorder that is characterized by nephrotic range proteinuria, hematuria and reduced renal function. It has a reported incidence of 0.6 – 1.5% in adults and carries a poor prognosis. It is rarely associated with systemic disorders but has been recently linked to Systemic Lupus Erythrematosus (SLE). Herein, we report a case of a patient who presented with worsening kidney function and was found to have fibrillary glomerulonephritis associated with SLE.

Case Description: A 70 year old Female with a known history of CKD III initially presented to us with a complaint of progressive diarrhea. Upon presentation she was found to have a Creatinine of 5.3 mg/dL significantly above her baseline of 1.5 mg/dL. She was started on IV Fluids for a suspected pre-renal injury. Creatinine improved initially but not to baseline. During the next 2 days, she worsened clinically and developed bilateral pleural effusions. She was consequently diuresed for worsening oxygen requirements. Urinalysis showed proteinuria in excess of 3.8g/day. ANA pattern was positive with nucleolar pattern and a titre of 1:80. She remained oliguric despite diuretics and was transitioned to renal replacement therapy. Renal biopsy was planned for suspected Lupus nephritis and she was placed on pulse dose steroid therapy. Biopsy revealed the presence of extensive Congo Red Negative electron dense deposits arranged in fibrils measuring 20 to 25 nm along the mesangium and glomerular walls. This was consistent with a diagnosis of fibrillary glomerulonephritis associated with SLE. She was discharged with renal replacement therapy, but later opted for comfort care only.

Discussion: SLE associated fibrillary glomerulonephritis is a rare disorder and only a handful of cases have been reported till date. It differs from other forms of fibrillary glomerulonephritis in that fibrils are generally arranged in a fingerprint pattern of concentrically curved lines. Immunosuppressive therapy with cyclophosphamide, steroids and recently Rituximab have been used in the treatment of this disorder. However, given its rare incidence and lack of studies, the treatment of the same still remains a therapeutic challenge.

FR-PO007

Thin Basement Membrane Disease or Alports Syndrome Albara Said, Cybele Ghossein. *Nephrology, Northwestern Univ Feinberg School of Medicine, Chicago, IL.*

Introduction: Thin basement membrane disease (TBMD) is characterized by diffuse thinning of the glomerular basement membrane (GBM). It is a common disorder that is frequently familial in nature and is caused by genetic defects in COL4A3 or COL4A4, genes that encode type IV collagen. These same alleles are affected in patients with Alports. In fact biopsies done early in patients with Alports frequently reveal diffusely thin GBMs as seen in TBMD. Clinically, however, TBMD has a much more benign course. TBMD patients typically present with hematuria and mild proteinuria while Alports frequently progresses to end stage renal disease (ESRD). We present a patient with presumed familial TBMD and no family history or ESRD whose biopsy revealed Alports.

Case Description: A 29 year-old male with a history of TBMD presented to our clinic for evaluation. The patient had been followed yearly from early childhood for hematuria and proteinuria. He states his mother, brother, and sister have the same disease and they all were given the presumptive diagnosis of TBMD. There was no family history of kidney dysfunction or hearing loss. None of his family members had ever undergone a kidney biopsy. Labs revealed a creatinine of 0.84 mg/dL and a 24 hour urine protein of 2400mg. A renal biopsy was performed and this revealed variably thickened basement membranes from 130nm to 780nm consistent with Alports. Genetic testing was performed and an in-frame deletion of three amino acids in the triple helix repeat domain of the COL4A5 protein was found. This variant has been reported to cause Alports.

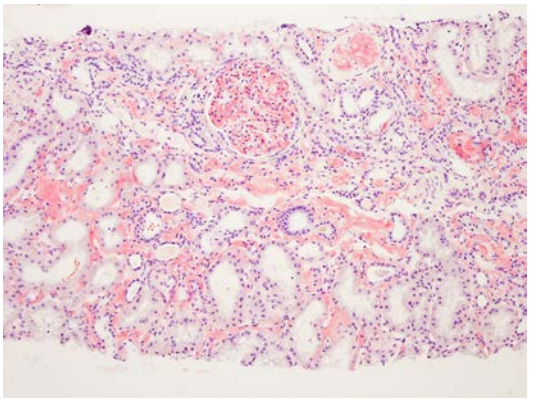
Discussion: TBMD is an often familial GBM disease that causes hematuria. Patients with this disease tend to follow a benign course, have minimal proteinuria, and almost never have kidney disease progression. For this reason biopsies are rarely performed and the diagnosis is frequently a clinical one. However it is important to consider alternative diagnoses if the clinical picture isn't clear. Our patient exhibited a higher than expected level of proteinuria and thus a biopsy was performed revealing Alports. This diagnoses will help with genetic counseling in our patient and may affect future management.

FR-PO008

Leukocyte Cell-Derived Chemotaxin 2(ALect2) Associated Renal Amyloidosis: A Case Report Benjamin Kwesi Sarsah,[1] Amy Nicole Sussman,[1] Erika R. Bracamonte,[2] Bijin Thajudeen.[1] *[1]Nephrology, Banner Univ of Arizona Medical Center, Tucson, AZ; [2]Pathology, Banner Univ of Arizona Medical Center, Tucson, AZ.*

Introduction: ALect2-associated renal amyloidosis(RA) is a recently recognized and distinctive clinicopathologic type of amyloid manifested in adults by varying degrees of impaired kidney function and proteinuria. There are limited number of cases reported in the literature.

Case Description: We present a 64-year-old Hispanic female with a history of hypertension who was referred for CKD management. Review of her laboratory tests revealed a serum Cr of 1.5-1.8 mg/dl and microalbuminuria (in the presence of a bland urine sediment) in the past one year. She denied any history of diabetes, rheumatologic disorders or exposure to intravenous contrast, NSAIDs, herbals and heavy metals. Serological work up was negative. A renal biopsy was performed. Light microscopy showed diffuse infiltration of glomerulus with pale eosinophilic material strongly positive for Congo red stain. A similar eosinophilic material was present throughout the interstitium



Immunofluorescence study was negative. Electron microscopy showed marked infiltration of mesangium, capillary loops and interstitium with haphazardly arranged fibrillary deposits. Liquid chromatography tandem mass spectrometry was performed on peptides extracted from Congo red positive, microdissected areas of the paraffin- embedded kidney specimen and showed ALect2-type amyloid deposition.

Discussion: ALect-2 amyloidosis should be suspected in renal biopsy specimens exhibiting extensive and strong mesangial as well as interstitial congophilia. Individuals with ALect2 RA have varying prognosis depending on the extent and rate of deposition. Therapeutic options include supportive measures (including dialysis when necessary) and consideration of kidney transplant from a histocompatible donor for those with ESRD.

FR-PO009

A Case of Waldenstrom's Macroglobulinemia Presenting as Acute Renal Failure and Nephrotic Syndrome Sumeet Munjal, Edwin J. Anand. *Div of Nephrology, Univ at Buffalo, NY.*

Introduction: Waldenstrom's macroglobulinemia (WM) is a rare B-cell disorder characterized by bone marrow (BM) infiltration of B lymphocytes and plasma cells along with a serum monoclonal immunoglobulin M (IgM) component. Renal involvement is uncommon compared to other dysproteinemias. We report a case of WM presenting with severe acute kidney injury (AKI) and Minimal change disease (MCD).

Case Description: A 56 year old WF with no history of renal disease developed shortness of breath and anasarca of 4 weeks duration. Clinical exam showed signs of volume overload and labs showed severe AKI (below). She was admitted and diuresed. CXR showed a large left pleural effusion and ECHO showed a normal EF. Admission creatinine was 7.5 mg/dl, Hemoglobin 9 gm/dl and 24hr urine protein was 18.4 grams. ANCA and ANA were negative. SPEP and UPEP showed monoclonal spike and IFE labeled it as IgM kappa. Serum IgM levels was elevated at 1940 mg/dl and free kappa level was 667.Kappa to lambda ratio was 56. Bone marrow biopsy confirmed a lymphoplasmacytic lymphoma consistent with WM. Renal biopsy showed minimal glomerular changes (MCD), immunofluorescence showed dominant IgM deposition with kappa light chain restriction in the subendothelial space and no amyloid. Our patient did not have neurological symptoms and serum cryoglobulins were negative ruling out hyperviscosity. She was started on plasmapheresis with a rapid reduction in serum IgM to 204. She received bortezomib, rituximab and steroids without improvement in renal function and needed dialysis. Chemotherapy for B-cell lymphoma (cyclophosphamide, rituximab, steroid) was given for 6 cycles. She achieved full remission of lymphoma, and was weaned off dialysis.

Discussion: Renal involvement in WM is rare and is usually due to amyloidosis. We report this case of WM with AKI requiring dialysis and MCD caused by IgM kappa in the glomeruli and no amyloidosis. There are only a few cases in the literature with a similar presentation. We also show that the renal injury could be permanent despite full remission of the WM with aggressive chemotherapy and plasmapheresis.

FR-PO010

ANCA-Negative Pauci-Immune Necrotizing Glomerulonephritis in a Patient with Multicentric Castleman's Disease Dilini M. Daswatta, John J. Doran. *Nephrology, Emory Univ.*

Introduction: Castleman's Disease is a rare lymphoproliferative disorder first described by Dr. Benjamin Castleman in 1956 in patients with lymphadenopathy having hyalinized follicles and interfollicular vascular proliferation. It is classified as unicentric (UCD) or multicentric disease (MCD) where MCD presents with lymphadenopathy, hepatosplenmegaly and fevers and is associated with Human Herpes 8 (HH8) in HIV infection. Kidney involvement in MCD is unusual and case reports have noted various lesions, mostly amyloidosis, membranoproliferative glomerulonephritis (GN) and thrombotic microangiopathy. Other lesions were rarely seen less including 3 cases of crescentic GN. We describe a case of MCD disease with HHV 8 presenting with hematuria, proteinuria, and near normal renal function whose kidney biopsy showed Pauci-immune necrotizing GN with cellular crescents.

Case Description: A 55-year-old African American male patient with HIV and wasting came to Grady Memorial Hospital with fevers, and weight loss. CT chest and abdomen

showed diffuse lymphadenopathy (LAD). An infectious workup ruled out JCV, HSV, CMV, cryptococcos and tuberculosis. Five months later, he developed lower extremity edema, was diagnosed with a deep venous thrombus and was discharged on lovenox. He was readmitted for gross hematuria, thought secondary to lovenox, but it persisted despite discontinuation. CT of chest/abdomen/pelvis showed a ureterolith thought recently passed and worsening LAD. Lymph node biopsy revealed MCD, with positive HHV-8 staining. Cystoscopy and bladder cytology were negative. Cr ranged 0.6 to 1.0 mg/dL and urine showed dysmorphic RBCs and 1.5 g/g proteinuria. ANA, ANCA and anti-GBM AB were negative. Kidney biopsy showed pauci-immune, focal, necrotizing GN with cellular crescent formation. Global or focal sclerosis was mild (14%) with little interstitial fibrosis or tubular atrophy. Treatment was begun with prednisone and Rituximab. Urinalysis demonstrates resolution of proteinuria and hematuria. 5 months later Cr remained stable at 0.9mg/dL.

Discussion: Kidney involvement in MCD is unusual, and we report a case of ANCA-negative crescentic pauci immune GN in a HHV-8 positive HIV patient.

FR-PO011

A BPI-ANCA Associated Rapidly Progressive Glomerulonephritis with Immune Complexes: A Case Report Bojana Gardijan,[1] Danica Galesic Ljubanovic,[2] Zeljka Jurekovic,[1] Branislav Cingel,[1] Mladen Knotek.[1] *[1]Renal Div, Dept of Medicine, Univ Hospital Merkur, Zagreb, Croatia; [2]Dept of Pathology, Univ Hospital Dubrava, Zagreb, Croatia.*

Introduction: Antineutrophil cytoplasmic antibodies are a major cause of rapidly progressive glomerulonephritis (RPGN). Routinely tested ANCA are MPO and PR3. A number of atypical ANCA is also known, such as anti-bactericidal/permeability-increasing protein(BPI) ANCA, which is a well-described cause of vasculitis. Overlap syndromes of pauci-immune ANCA GN and immune complexes (IC)-mediated GN have been reported. After a review of literature, this is the first reported case of BPI-ANCA associated RPGN with IC.

Case Description: A 35-year-old Caucasian male with cryptogenic liver cirrhosis was referred to our hospital with the diagnosis of hepatorenal syndrome. At admission, the pt was dialysis-dependent and oliguric. An active urine sediment (E >50, L 15, casts) was noted with P/C 2.6 (g/g). Kidney biopsy was performed. The finding was diffuse endocapillary proliferative glomerulonephritis, active, without signs of chronicity. Immunoflorescence (IF) was positive for IgG, IgM, C3, κ and λ chains. ANA, ENA, dsDNA, RF, anti-CCP, LAC, cardiolipin IgG and IgM, beta-2 glycoprotein were negative. Serum C3 was 0.53 g/L (0.90-1.80) and C4 0.15g/l (0.10-0.40). Testing for HCV, HBV and HIV was negative, as well as bacterial respiratory and urine cultures. ANCA was positive by IF (1:640), with negative ELISA for PR3- and MPO-ANCA. ANCA was specified as BPI-ANCA. The pt was treated with combination of PEX, steroid pulses and iv cyclophosphamide (CYC). After 4 PEX, ANCA declined to 1:160. After 10 days the pt was no longer dialysis-dependent. He received in total 6 CYC pulses. After a follow-up of 6 months, his eGFR is 115ml/min/1.73m^2, without pathological proteinuria.

Discussion: This is to our knowledge the first described case of BPI-ANCA-associated RPGN with IC. Pathohistology corresponded to lupus grade IVa nephritis (lupus-like nephritis, as serology was negative). Due to ANCA, PEX was added to steroids and CYC. This is an educational case demonstrating the presence of BPI-ANCA in a pt with IC GN. ANCA testing by IF is important for detection of atypical ANCA.

FR-PO012

Two Cases of Cryoglobulinemic Glomerulonephritis after Successful Hepatitis C Treatment Nupur Gupta,[1] Allon N. Friedman,[1] Melissa D. Anderson.[1] *[1]Nephrology, Indiana Univ School of Medicine, Indianapolis, IN; [2]Pathology, Indiana Univ School of Medicine, Indianapolis, IN; [3]Nephrology, Indiana Univ School of Medicine, Indianapolis, IN; [4]Nephrology, Indiana Univ School of Medicine, Indianapolis, IN.*

Introduction: Chronic hepatitis C viral (HCV) infection are associated with cryoglobulinemic glomerulonephritis. With recent HCV- anti-viral therapy, sustained virologic response rates have diminished risk of kidney disease. We report two cases which both developed Cryoglobulinic Glomerulonephritis after being treated by antivirals.

Case Description: Case I 63 y/o man with successfully treated HCV infection using Harvoni, presented with recurrent hematuria, proteinuria, low serum complements, worsening creatinine and palpable purpura. Given his clinical presentation kidney biopsy was done which demonstrated cryoglobulinemic glomerulonephritis with immune complex deposition. Repeat testing for serum cryoglobulins was positive. Case II 58 y/o male presented clinic for evaluation of chronic kidney disease. He had past medical history of hepatitis C treated with ribavirin, interferon alpha and telaprevir. He initially presented with Raynaud's phenomenon and biopsy proven leucocytoclastic vasculitis. His Complement 4 level was low. It was felt he had a positive serum cryoglobulins and was diagnosed with mixed cryoglobulinemia related to hepatitis C. His hepatitis C viral load was negative. He had proteinuria and worsening kidney function. In order to assess etiology of his kidney disease, kidney biopsy was done. The Immune complex glomerulonephritis with organized deposits , compatible with cryoglobulinemic glomerulonephritis.

Discussion: Patients with Cryoglobulinemic Glomerulonephritis who have sustained virologic and vasculitic response continue to be negative for cryoglobulins. We had ruled out other causes of cryoglobulinemia such as parvo virus and rickettsial infection. These cases illustrate the possibility of emerging renal pathology in anti- viral therapy treated patients. The postulated mechanism is molecular mimicry for HCV Antigen which triggers immune response despite HCV RNA negative.

FR-PO013

Can We Chalk It All up to Myeloma? Hans Jensen,[1] Mitchell P. Sternlieb,[2] Lia Desposito,[2] Vishnu S. Potluri.[2] *[1]PCOM; [2]Lankenau Medical Center.*

Introduction: Multiple Myeloma (MM) is a disease diagnosed utilizing the CRAB score (hypercalcemia, renal failure, anemia, bone lesions) in addition to serologic and pathologic testing. We present a case of hypercalcemia where the diagnosis was complicated due to a history of parathyroidectomy with supplemental calcium use and volume depletion, thereby upending the basis of calcium and creatinine levels for diagnosis.

Case Description: A 65-year-old Caucasian woman with a distant history of a total parathyroidectomy presented with dizziness, constipation and abdominal pain for 2 weeks. She reported a 3-day history of anorexia and clumsiness. Her family added that she had confusion and slurred speech. Home medications notable for hydrochlorothiazide and furosemide for hypertension, calcitriol, 4000 mg daily Ca^{2+} and metformin. Vitals were BP 137/76 mmHg, HR 104 bpm, RR 20/min and SpO_2 of 95%. On exam, she was obese and lethargic but non-toxic, mildly confused with dry mucous membranes. She had mild epigastric tenderness without peritoneal signs; neurological exam was notable for slurred speech. BMP revealed corrected Ca^{2+} of 15.6 mg/dL, markedly elevated lipase, total protein of 9.6 g/dL and albumin of 3.9 g/dL. CT showed peri-pancreatic fat stranding. BMP 4 days prior was completely normal. The admission working diagnosis was acute pancreatitis and mental status change due to acute hypercalcemia from milk-alkali syndrome and thiazides. She received aggressive IV fluids and her Ca^{2+} completely normalized. Subsequent workup consisted of serum protein electrophoresis with immunofixation and serum free light chain ratio, which showed IgG monoclonal protein and K:λ of 39.3. Bone marrow biopsy had 20% clonal plasma cells, but skeletal survey did not reveal any lytic lesions.

Discussion: Presented is a case with acute pancreatitis, likely secondary to acute hypercalcemia that was, in and of itself, multifactorial in etiology—undiagnosed MM, high dose calcium ingestion, and hypovolemia while on a thiazide diuretic. This case illustrates how medical and surgical history impact interpretation of CRAB criteria in the recognition of new malignancy. It further evidences the importance of thorough medication reconciliation when creating a differential diagnosis and treatment strategy.

FR-PO014

Bacteremia Caused by Campylobacter Upsaliensis in a Patient with Minimal Change Disease following Rituximab Treatment Sachiko Fukushima,[1] Naoki Takahashi,[1] Seiji Yokoi,[1] Kyoko Hisada,[2] Yukio Hida,[2] Yukie Morikawa,[1] Mamiko Kobayashi,[1] Daisuke Mikami,[1] Hideki Kimura,[2] Kenji Kasuno,[1] Masayuki Iwano.[1] *[1]Div of Nephrology, Fukui Univ, Fukui, Japan; [2]Dept of Clinical Laboratories, Univ of Fukui Hospital, Fukui, Japan.*

Introduction: *Campylobacter upsaliensis* (*C. upsaliensis*) infection is a cause of sporadic gastrointestinal disease. The colonization of *C. upsaliensis* was found in more than 50% of house hold pets, the pet ownership is a risk factor for *C. upsaliensis* infections. Recently, successful treatment of rituximab (RTx) injection at an interval of 6 months for minimal change disease (MCD) in adults was reported. Although the efficacy of RTx for various renal diseases was reported, the immunocompromised status may be the risk of disease transmissible from animals to humans. Here, we report a patient diagnosed with bacteremia caused by *C. upsaliensis* with MCD following RTx treatment.

Case Description: A 30-year-old man was admitted to our hospital with fever. He had been diagnosed with steroid resistant and frequently relapsed MCD at the age of 28. He has been treated with cyclic RTx and low dose predonine for these 2 years and complete remission was maintained. Four months before admission, he had paroxysmal fever higher than 38 degree without gastrointestinal symptoms and C reactive protein was elevated and naturally decreased. Physical examination findings were normal expect moderate atopic dermatitis. Hematological tests revealed moderate leukocytosis and no B-lymphocyte. Urinalysis revealed normal findings. Systemic enhanced computed tomography and FDG-PET showed no particular lesion. *C. upsaliensis* was detected by his blood culture. After minocycline treatment and lactic acid bacterium administration was started, he became afebrile.

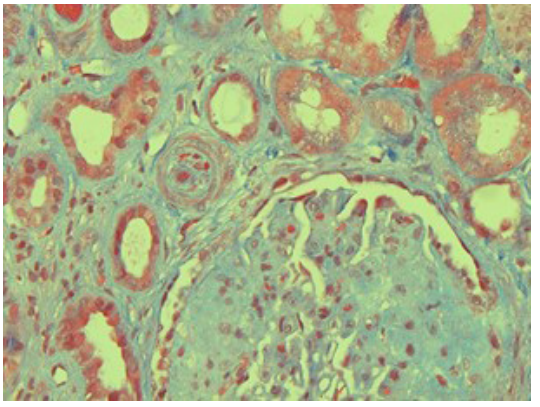
Discussion: To our knowledge, this is the first report of a patient with bacteremia caused by *C. upsaliensis* with MCD following RTx treatment. We suppose that *C. upsaliensis* may be transmitted from his house hold dog and bacterial translocation by his immunocompromised status may lead to bacteremia. We should take *C. upsaliensis* infection into consideration in fever of unknown origin following RTx treatment.

FR-PO015

Recurrent aHUS Post Kidney Transplantation Leading to Kidney Allograft Loss Despite Treatment with Terminal Complement Blockade Elwaleed Elnagar, Wael S. Hassan. *UAMS.*

Introduction: Complement disorders and aHUS are now increasingly recognized as causes of morbidity and mortality, leading to ESRD and, in kidney transplant recipients, to kidney allograft loss. Eculizumab, a terminal complement inhibitor, was found to improve renal parameters, leading to discontinuation of dialysis, and transplant protection[1].

Case Description: A 56 years old woman, with ESRD due to TTP, received a DDKT 3 years later and was treated with Prednisone, Mycophenolate Mofetil, and Prograf. A year later, a kidney allograft biopsy showed TMA. Prograf was switched to monthly Belatacept. Her kidney function returned to baseline. She did well until two years later when she was admitted with a second episode of AKI. She was anemic, with few schistocytes, low haptoglobin, increased LDH, and mild thrombocytopenia. ADAMTS13 activity was 87% (Normal >70%). C4 was normal and C3 was very low. CFH and CFB were low, CFI was normal, and anti CFH antibodies were not detected. A transplant kidney biopsy again showed a TMA



Genetic testing for complement factors revealed a mutation in CFH gene. She was started on Ecluzimab. Unfortunately, 12 months later she is still requiring intermittent hemodialysis.

Discussion: In Eculizumab trials in aHUS, younger age, higher baseline LDH and lower baseline hemoglobin were associated with greater eGFR improvements. Early Eculizumab initiation led to improved renal recovery. Mean eGFR change from baseline at 1 year was significantly higher in patients treated in ≤7 days than >7 days (57 vs. 23 ml/min/1.73 m^2, p = 0.0098). After 1 year, 17/21 and 36/76 patients in the ≤7 and >7 day groups, respectively, achieved a sustained increase in $eGFR^2$. Retrospectively, in this patient, he delay in initiation of Eculizumab may have impacted our patient, leading to non-recovery. Also, Eculizumab is a terminal (C5) complement blocker that may not work better in higher complement disorders.

FR-PO016

Membranous Nephropathy and Autoimmune Hemolytic Anemia in a Patient with a History of Hodgkin Lymphoma and Immune Thrombocytopenic Purpura

Molly Fisher, Yelena Rekhtman Drexler. *Nephrology, Montefiore Medical Center, Bronx, NY.*

Introduction: We report the first known case of a patient with a history of Hodgkin lymphoma and immune thrombocytopenic purpura (ITP), both in remission, who developed membranous nephropathy (MN) and autoimmune hemolytic anemia (AIHA) in the absence of any overt clinical signs of a lymphoma recurrence.

Case Description: 41 year-old female with a history of Hodgkin lymphoma and ITP who presented with nephrotic syndrome. In 2010, she was diagnosed with Stage II Hodgkin lymphoma and was treated with rituximab and radiation therapy, resulting in a complete remission. In 2014, she was diagnosed with ITP, which remitted with IVIG and steroids. In June 2015, she presented with two months of gradual onset lower extremity edema, 40-lb weight gain, and foamy urine. Labs showed serum albumin 1.8 g/dL, total cholesterol 586 mg/dL, 16g of protein on a 24hr urine collection, and serum creatinine 0.5 mg/dl. Serologic evaluation, including SPEP, ANA, and testing for HIV and hepatitis B and C, was negative. Renal biopsy showed MN with extensive subepithelial and a few mesangial deposits and negative glomerular staining for PLA2R. She had no evidence of lymphoma recurrence, and age-appropriate cancer screening was negative. She was treated with an ACE inhibitor without improvement in proteinuria. Therefore, tacrolimus was started, but proteinuria remained at 14 g/day. A CBC performed in anticipation of starting cyclophosphamide revealed a macrocytic anemia with hemoglobin 5.6 g/dL compared to 11.1 g/dL five months prior. A direct Coombs test was positive, consistent with a diagnosis of AIHA. Prednisone was initiated, followed by rituximab to treat both MN and AIHA. She received rituximab 375 mg/m^2 weekly for four weeks, resulting in an improvement in her hemoglobin to 11.4 g/dL, albumin to 3.8 g/dL, and proteinuria to 2.7 g/day.

Discussion: Rare cases of MN associated with Hodgkin lymphoma, ITP, or AIHA have been described but this is the first reported co-existence of all four diseases. We suspect these diseases may share a common autoimmune basis. Treatment with rituximab resulted in a complete remission of AIHA and a partial remission of membranous nephropathy.

FR-PO017

De Novo Collapsing Glomerulopathy in Renal Allograft: A New Potential Culprit?

Yorg Al Azzi, Oluremi Williams, David J. Cohen. *Medicine, Columbia Univ, New York, NY.*

Introduction: Collapsing glomerulopathy(CG) is a disease than can recur post-transplantation however its occurrence de novo is very rare. Case reports described de novo CG in renal allografts and in most of them no etiology was identified. We report a case of de novo CG in a renal allograft recipient with CMV being the potential culprit.

Case Description: 34yo AAF with ESRD 2/2 HTN on HD for 7 years s/p DDRT 07/14 from 20yo AAM (COD:GSW,KDPI 33%,multiple HLA-I and II DSA,EBV and CMV IgG D+/R+). She was induced with alemtuzumab, Rituximab and IVIG and maintained on tacrolimus and mycophenolic acid with rapid steroid withdrawal. Post-reperfusion bx showed ATN and diffuse glomerular fibrin thrombi. On 7/23/14, 1-wk protocol bx showed AMR and features of acute TMA(SCr 10.4). Started plasmapheresis 3 times/week with IVIG repletion and tacrolimus was switched to belatacept. She was re-biopsied after 6 sessions of PP(no rejection,no TMA,no more DSAs). She was maintained on belatacept,mycophenolic acid,prednisone 5mg daily. SCr reached 0.92. On 7/14/15, 1-yr protocol bx revealed CG (CMV stain neg). Urine P/C ratio 5.3 and SCr 0.9. No events of renal ischemia, no new medications including no OTC medications. Viral serologies including HIV, parvoB19,adenovirus.BK,CMV and EBV PCRs were sent. CMV PCR resulted 5033 IU/mL, she was started on valganciclovir 900mg BID and followed with weekly labs. By the following week, CMV PCR levels were decreased to 353 IU/mL, and on the 3rd week CMV PCR was negative and remains negative to date.

	Urine protein/creatinine ratio	Serum creatinine (mg/dL)
August 2014	0.4	1.4
October 2014	0.3	0.89
November 2014	0.2	0.88
January 2015	0.3	0.83
July 2015	5.3	0.9
September 2015	0.7	0.88
December 2015	0.6	0.94
January 2016	0.5	0.89

Discussion: To our knowledge, this is the first case report of de novo CG occurring in a renal allograft in the setting of CMV viremia. The timing of CMV viremia and development of proteinuria as well as resolution of the viremia with improvement of the proteinuria, in the absence of history of FSGS, addition of new medications and episodes of hypotension and renal ischemia, suggest that CMV might be the potential etiology of this de novo CG.

FR-PO018

Idiopathic Collapsing FSGS Presenting as "Forme Fruste" Lupus

Thalia Salinas, Karim El Hachem, Steven D. Smith. *Nephrology, Icahn School of Medicine at Mt. Sinai St. Luke's, New York/NY, NY.*

Introduction: Patients with SLE commonly develop lupus nephritis during their disease course. Only a subset of patients have been described to have lupus podocytopathy, a form characterized by a full nephrotic syndrome in the setting of overt SLE with diffuse and severe foot process effacement on Electron Microscopy, in the absence of subendothelial or subepithelial immune deposits.

Case Description: A 45-year-old African American man on hemodialysis presented for shortness of breath and was found to have a large pericardial effusion with a tamponade physiology. He underwent pericardiocentesis with drainage of 700 cc of exudative fluid. His laboratory studies and his clinical presentation allowed a diagnosis of active SLE. Six years prior he presented with nephrotic syndrome and kidney failure requiring hemodialysis. His biopsy revealed collapsing FSGS presumed to be ideopathic at which time he did not meet clinical or serologic criteria for lupus.

Test	Admission year 0 (Renal Failure)	Admission year 6 (Lupus Flair)
ANA	1:640	1:160
anti-dsDNA (0-29 IU/mL)	26.0	>300
C3 (90-180 mg/dL)	101	55
C4 (10-40 mg/dL)	34.7	20
Platelets (150-450 K/uL)	238	87
HIV	negative	negative
Hepatitis C antibody	negative	negative
Hepatitis B surface Antigen	negative	negative
Serum Albumin (3.4-5.4 g/dL)	2.0	3.1
Urine protein to creatinine ratio	3.34 gm	--
TB quantiferon gold	Negative	Negative

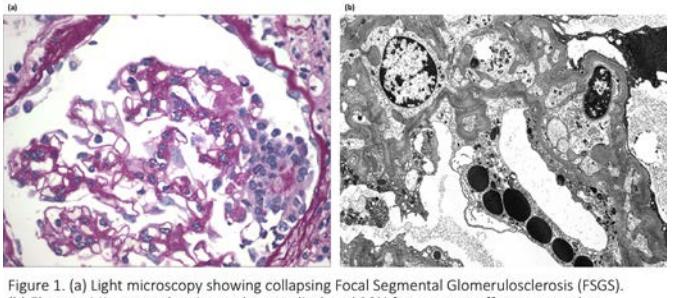


Figure 1. (a) Light microscopy showing collapsing Focal Segmental Glomerulosclerosis (FSGS). (b) Electron Micrscopy showing podocytes displayed 90% foot process effacement and, no immune type electron dense deposits or endothelial tubuloreticular inclusions. The patient's immunofluorescence was negative.

Discussion: This case illustrates that idiopathic collapsing FSGS could represent a lupus podocytopathy in the absence of overt lupus on initial presentation. We suggest following patients with idiopathic collapsing FSGS closely for possible subsequent development of SLE and perhaps treating them similarly to LN classes 3 and 4.

FR-PO019

Recurrent Atypical Anti-Glomerular Basement Membrane Disease after Successful Kidney Transplantation: A Rare Case Masaaki Yamada,[1] Andres G. Chiesa-Vottero,[2] Leal C. Herlitz,[2] Richard A. Fatica.[1] *[1]Nephrology, Cleveland Clinic, Cleveland, OH; [2]Pathology, Cleveland Clinic, Cleveland, OH.*

Introduction: Renal anti-glomerular basement membrane (GBM) disease typically presents with rapid renal dysfunction and crescentic glomerulonephritis. Several published reports describe an indolent variant of anti-GBM disease with atypical clinical and pathological features compared to classic anti-GBM disease. Patients with atypical anti-GBM disease manifest a smoldering disease course with hematuria, proteinuria, and more gradual decline in GFR.

Case Description: The patient was a 53 year-old never-smoker Caucasian female with a long history of microscopic hematuria whose serum creatinine rose from 0.7 to 1.3 mg/dL over 5 years. She developed proteinuria (1.4 g/day) and hypertension around the onset of renal dysfunction. All serological evaluations were negative including RF, ANA, ANCA, complements, hepatitis B and C, HIV, anti-GBM antibody. Kidney biopsy revealed a sclerosing glomerulonephritis without crescent formation. Immunofluorescence showed strong linear GBM staining for IgG and lambda with negative kappa. Electron microscopy showed no electron-dense deposits but was notable for lucent subendothelial expansion and mesangial interpositioning suggestive of glomerular microangiopathy. Further tests; Scl-70, SS-A, SS-B, antiphospholipid, repeat anti-GBM antibodies, and M protein, were negative and no clinical evidence of a systemic thrombomicroangiopathy. Her renal function was steady for the first 5 years, but started to decline over the next 3 years despite a trial of oral prednisone. Repeat kidney biopsy showed findings similar to the initial biopsy and no crescents were seen. She was preemptively transplanted from a three antigen HLA mismatched living-related donor. She had an excellent graft function but microscopic hematuria persisted. A 2-year post-transplant biopsy revealed focal segmental mesangial and endocapillary proliferation and linear IgG and lambda staining again in the GBMs. Atypical anti-GBM disease was diagnosed and retrospectively considered her original disease.

Discussion: This is the second reported case of recurrent atypical anti-GBM antibody disease after renal transplant.

FR-PO020

Collapsing Glomerulopathy due to Lupus Podocytopathy: Successfully Treated - A Case Report Arani D. Nanavati,[1] Leal C. Herlitz,[2] Juan C. Calle.[1] *[1]Nephrology, Cleveland Clinic Foundation; [2]Pathology, Cleveland Clinic Foundation.*

Introduction: Collapsing glomerulopathy (CG) is described in SLE patients and represents a severe form of lupus podocytopathy (LP). The diagnosis of LP requires podocyte effacement without peripheral capillary wall immune deposits. We report a case of CG superimposed on membranous (class V) lupus nephritis (LN V) who was successfully treated and became dialysis free.

Case Description: A 49 year old African American male, recently diagnosed with SLE, presented initially with proteinuria of 2 gm/day and serum creatinine (SCr) of 0.9 mg/dL. Renal biopsy at that time revealed LN V. Therapy with mycophenolate mofetil and prednisone was recommended; however he was lost to follow up and did not comply with treatment. He presented again one month later with confusion, weakness. Lab studies revealed SCr of 9.75 mg/dl, urine protein-cr ratio of 4.1. He was started on dialysis for anuric renal failure with uremia and was empirically treated with intravenous (IV) pulse methylprednisolone. Repeat renal biopsy revealed CG superimposed on the previously documented LN V. There was no evidence of endocapillary proliferation, necrosis or glomerular basement membrane rupture. Work up for HIV, EBV, parvovirus and CMV was negative. In the absence of known infectious causes of CG the diagnosis of LP was favored. The patient was treated with pulse IV cyclophosphamide. After 4 weeks of hemodialysis and within 12 days of IV cyclophosphamide dose, renal function began to recover. His SCr continued to trend down to 1.1 mg/dL. He continues to have proteinuria with recent urine protein/cr ratio of 2.7.

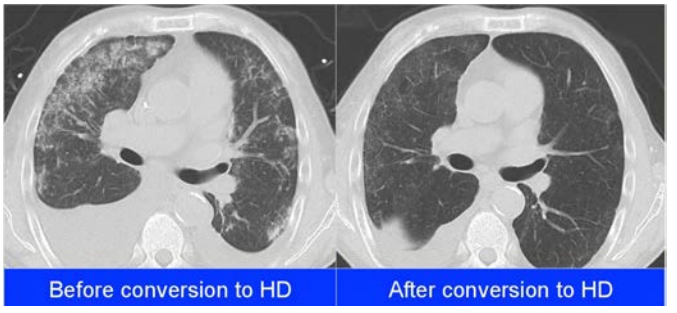
Discussion: The diagnosis of LP in this case is somewhat controversial given the underlying membranous changes. However, the presence of collapsing features, which are not seen in membranous lupus alone and the dramatic clinical deterioration supported the diagnosis of collapsing LP superimposed on class V lupus nephritis. While collapsing glomerulopathy is typically aggressive with poor outcomes, our case demonstrates that an excellent clinical response to the immunosuppressive regimen of cyclophosphamide and steroids is possible.

FR-PO021

Metastatic Pulmonary Calcification with Progressive Respiratory Failure in the Course of Peritoneal Dialysis Yuna Onozawa, Yosuke Nakagawa, Naoto Hamano, Masahiro Koizumi, Takehiko Wada, Masafumi Fukagawa. *Dept of Nephrology and Metabolism, Tokai Univ School of Medicine, Isehara, Japan.*

Introduction: Metastatic pulmonary calcification is characterized by deposition of calcium salts in the normal alveoli and is commonly caused by end-stage renal disease (ESRD). It is often asymptomatic, but can develop respiratory failure.

Case Description: A 56 year-old male peritoneal dialysis (PD) patient was referred to our hospital due to progressive shortness of breath with pulmonary abnormal shadow on chest X-ray. He had been on PD for 10 years and had uncontrolled secondary hyperparathyroidism (SHPT). His intact PTH level stayed around 500 pg/mL despite of a year-long treatment with cinacalcet. The abnormal shadow on chest X-ray had been observed for a year. Initially he was asymptomatic, however, he presented with progressive dyspnea just before the referral. Chest computed tomography (CT) showed consolidation in bilateral lungs with diffuse calcification as well as cardiac enlargement and pleural effusion. Bone scintigraphy revealed intense uptakes in bilateral lungs. Taken together, he was diagnosed as metastatic pulmonary calcification and chronic heart failure. In echocardiogram anterior wall motion was decreased and coronary artery calcification score (CACS) was calculated to over 3,000 in multi-detector CT, indicating severe coronary artery stenosis due to metastatic calcification. In order to control his SHPT, he was switched to hemodialysis (HD) to improve his dialysis efficiency. In addition, percutaneous coronary intervention was performed to improve his cardiac function. Respiratory failure gradually improved although he remained on oxygen therapy. On a follow-up CT at 3 months after the conversion to HD, the calcification was obviously diminished.



Discussion: This case suggested that improved dialysis efficiency might reverse metastatic pulmonary calcification.

FR-PO022

Lupus Podocytopathy and Collapsing Glomerulopathy in a Patient without Nephrotic Syndrome Delin Wang, Lance D. Dworkin. *Nephrology, Brown Univ, Providence, RI.*

Introduction: Lupus podocytopathy is an unusual type of lupus nephritis characterized by nephrotic syndrome with podocyte foot process effacement and mesangial electron-dense deposits. We encountered a patient with lupus-like disease whose kidney biopsy showed pathological features of lupus podocytopathy and collapsing glomerulopathy but only exhibited microalbuminuria.

Case Description: A 39-year-old African-American female with history of hypertension, hypothyroidism, and obesity status post gastric bypass surgery presented with an elevated serum creatinine (sCr) at 1.83 mg/dL, eGFR 31 mL/min/1.73m^2, which had increased from 1.62 mg/dL 4 months prior. She was transiently on Chlorthalidone which was discontinued due to normalization of blood pressure (BP). Physical exam was remarkable for BP of 154/82 and frontal alopecia. Urine microalbumin-to-creatinine ratio (UMCR) was 265mg/gm. Serologic tests revealed high-titer antinuclear antibody (1:2560) with normal complements C3/C4 and anti-dsDNA (<1:10). Antiphospholipid antibodies were negative. Patient underwent a kidney biopsy which showed collapsing focal segmental glomerulosclerosis with podocyte foot process effacement and mesangial electron-dense deposits. Viral studies including HIV, Hepatitis B/C, Epstein-Barr virus, Parvovirus B19, and Cytomegalovirus were negative. Because of progressive renal failure, she was treated with Mycophenolate Mofetil (MMF) 3 grams/day, Prednisone 60mg/day, and an angiotensin-converting-enzyme inhibitor (ACEI). Bactrim was used for prophylaxis. After four months of therapy, her sCr has increased to 2.27 mg/dL, although Bactrim may be contributing. In contrast, microalbuminuria has declined to 43 mg/gm per UMCR.

Discussion: To our knowledge, this is the first published case of a patient with collapsing lupus podocytopathy who lacks nephrotic range proteinuria. Although lupus podocytopathy often responds to immunosuppressive therapy, the limited number of reported patients with collapsing glomerulopathy have had a much poorer response. Additional patients and longer term follow-up are needed to determine whether the combination of MMF, steroid and ACEI helps induce remission and prevent progressive renal failure in patients with the collapsing variant.

FR-PO023

Renal Limited Polyarteritis Nodosa with Positive Anti Myeloperoxidase Darwish Naji, Rupal Mehta. *Nephrology Dept, Northwestern Medicine, Chicago, IL.*

Introduction: Polyarteritis Nodosa (PAN) is a systemic necrotizing vasculitis that typically affects medium-sized muscular arteries.

Case Description: M.W. is a 71-year-old Caucasian female with no past medical history who complained of fatigue, decrease urine output, lower extremity swelling, weight gain of 53 pounds over 2 months, and new elevated blood pressure. Laboratory investigation demonstrated an elevated creatinine of 4.6 mg/dL (baseline of 0.51 mg/dL one month prior). Urinalysis demonstrated non-dysmorphic red blood cells with no casts. Antinuclear antibody, complement levels, Hepatitis panel, serum and urine protein electrophoresis were unremarkable. Renal ultrasound revealed one incident microanuerysm and normal size kidneys. Renal biopsy demonstrated fibrinoid necrosis with little glomerular involvement (Figure 1A). Renal angiogram to investigate the microanuerysm demonstrated numerous microanuerysms (Figure 1B). Serology later returned with a positive anti-neutrophil cytoplasmic antibody (ANCA) titer of 1:640 and positive anti-myeloperoxidase (MPO) at 91 units. M.W. was started on pulse dose steroids and Cyclophosphamide for treatment of PAN.

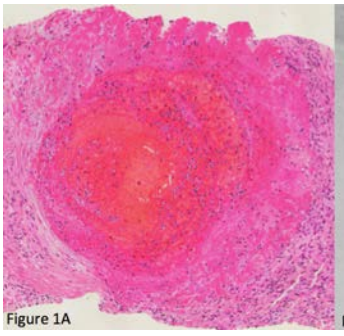


Figure 1A

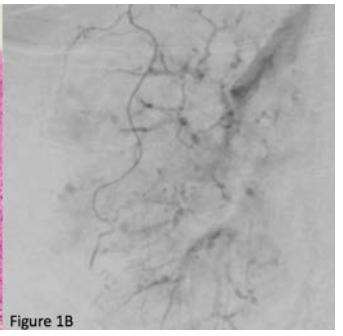


Figure 1B

Discussion: We describe an atypical presentation of PAN, which manifested with acute renal failure and positive serologies, without any other systemic organ involvement.All prior reported cases of MPO-ANCA positive PAN manifested with systemic involvement. Our patient presented with renal-limited disease with a moderate to strong positive MPO-ANCA. She was diagnosed with renal limited PAN based on renal angiogram findings of diffuse bilateral small aneurysms. Biopsy findings of arterial fibrinoid necrosis and no glomerulonephritis confirmed our diagnoses and helped guide treatment.

FR-PO024

A Case of C4 Dense-Deposit Disease Keisuke Kawashima,[1] Saori Nishio,[1] Mitsuru Yanai,[2] Yozo Ishikawa,[1] Fumihiko Hattanda,[1] Minoru Makita,[1] Yoshihiro Kusunoki,[1] Junya Yamamoto,[1] Yasunobu Ishikawa,[1] Yuichiro Fukazawa,[2] Tatsuya Atsumi.[1] *[1]Medicine 2, Hokkaido Univ Hospital, Sapporo, Japan; [2]Pathology, Sapporo City Hospital, Sapporo, Japan.*

Introduction: Traditionally, Membranoproliferative Glomerulonephritis (MPGN) was categorized into three subtypes according to the location of electron dense deposits. Recently, MPGN has been classified into immune complex-mediated GN and complement-mediated GN (dense deposit disease; DDD and C3 nephropathy). This classification is grounded upon etiology and immunofluorescence(IF) findings of each case. We experienced a case of MPGN presented in none of the classification.

Case Description: 63-year-old man with hypertension presented with hematuria and nephrotic-range proteinuria (urinary protein-to-creatinine ratio of 4.4). His renal function was normal. He had mild hypocomplementemia. Urinalysis showed dysmorphic erythrocytes. Evaluation for autoimmune disease, hepatitis and monoclonal gammopathy gave negative results. He was asymptomatic. Renal biopsy was performed. Microscopic evaluation showed MPGN, with diffuse mesangial and endocapillary hypercellularity. Periodic acid-Schiff stain showed diffuse thickening of capillary wall, proliferation of mesangial cells and endocapillary cells. Jones silver-methenamin stain showed reduplication of glomerular basement membrane(GBM). IF showed bright staining for C4d along the capillary walls, and no glomerular staining for IgG, IgM, IgA, C1q, C3, kappa or lambda light chain. Electron microscopy showed ribbon-like subendothelial dense deposits lining the GBM. No deposits along Bowman capsule or tubular basement membranes were visible. We performed ELISA to access the acitivity of each complement pathway.ELISA showed abnormal activation of lectin pathway. The diagnosis was C4 glomerulopathy(C4 DDD). He was treated with valsartan and immunosuppressive drugs. Nephrotic range proteinuria was prolonged, but his renal function remained unchanged.

Discussion: Recently, it has been reported that C4d deposition serves as a marker for complement (especially lectin pathway)-mediated GN, and clinical entity 'C4 glomerulopathy', C3-negative proliferative GN characterized by C4d deposition is proposed. This is the first case report of C4 DDD in Asian population.

FR-PO025

MGUS-Acquired Von Willebrand Disease Transitioning to Myeloma and Presenting as Type 1 Croglobulinemic Vasculitis and RPGN Mohamed Elsayed,[1,2] Ahmed Alghali,[1,2] Alaa M. Ali,[1,2] Arunkumar Aruna Udayakumar,[1,2] Muhammad Umair Sharif,[1,2] Austin G. Stack.[1,2,3] *[1]Graduate Entry Medical School, Univ of Limerick; [2]Nephrology Dept, Univ Hospital Limerick; [3]Health Research Inst, Univ of Limerick, Ireland.*

Introduction: Cryoglobulinemia type 1 vasculitis (CryoVas1) is a rare manifestation of Multiple Myeloma.Reports of renal involvement as RPGN in this setting are very scarce. Moreover,the emergence of such presentation from a longstanding MGUS causing acquired Von Willebrand disease(vWD)has to our knowledge never been reported.

Case Description: A70-year old woman with a15 year history of acquired vWD associated with life-threatening bleeding episodes and a long term history of IgG λ MGUS, presented with a painful purpuric rash on both legs confirmed to be leukcytoclastc vasculitis on skin biopsy.Initial studies showed normal kidney function(Creat 0.85 mg/dl),and benign urine sediment.Vasculitis work up revealed type 1 cryoglobulinemia. Hepatitis B and C serology was -ve.She was started on oral steroids but presented 2 weeks later with worsening rash,microscopic hematuria,nephrotic-range proteinuria and RPGN with low C3&C4 levels.She became anuric and her creatinine peaked over 6.2 mg/dl necessitating urgent dialysis.The vWD bleeding disorder posed a challenge to invasive procedures due to low FVIIIc&vWF levels,which were poorly responsive to IVIG and vWF replacement.A kidney biopsy was deemed unsafe.She received pulse IV steroid therapy and 7 plasmapharesis sessions.A bone marrow biopsy confirmed 30%plasma cells and she was started on (CyBorD)regimen.After 2 cycles of chemotherapy & 4 weeks on dialysis, the rash resolved,renal function recovered (Creat 0.66 mg/dl)& cryoglobulins were no longer detected in serum.vWF levels normalized with no further bleeding or need for replacement therapy.

Discussion: MGUS-acquired vWD presenting as CryoVas1 and RPGN is extremely rare and is associated with poor outcome.Rapid identification of croglobulins and confirmation of MM allowed a multi-pronged approach of steroids,plasmapharesis and bortezomib chemotherapy with an excellent outcome.An early aggressive approach to management of MGRS is warranted especially when associated with vWD or features of cryovasculitis.

FR-PO026

Strongyloid-Associated Membranous Nephropathy Josef Bautista, Katherine Mikovna Scovner. *Section of Kidney Diseases and Hypertension, Brown Univ - Rhode Island Hospital, Providence, RI.*

Introduction: Secondary membranous nephropathy may be caused by drugs, malignancy or infection. While it is known that infections can cause renal diseases little is known about the associations between parasitic infections and specific nephrotic syndromes. Here we present the first reported association between strongyloid infection and membranous nephropathy.

Case Description: This is a 65-year-old Nigerian man with history of hypertension on lisinopril and hydrochlorothiazide who was referred for proteinuria and elevated creatinine. The patient reported chronic diarrhea. Physical examination showed gross leg edema. Serum creatinine was 2.2 mg/dl, and his urine protein/creatinine ratio was 7 g/g. Renal biopsy showed mesangial proliferation and thickened glomerular basement membrane. Anti-PLA2R immunofixation was negative, and electron microscopy showed intramembranous deposits. Final biopsy read was membranous nephropathy. The patient denied NSAID use or use of other medications associated with membranous nephropathy. His age-appropriate cancer screening was up-to-date. Interestingly, his blood differential showed persistent eosinophilia of 20%. This prompted an investigation for a parasitic cause of his membranous nephropathy. Strongyloid antibody was positive, and the patient received ivermectin. His antihypertensive medications were continued. One-month follow-up showed improvement in his proteinuria to 4 g/g and creatinine to 1.4 mg/dl.

Discussion: This case demonstrates the first reported association between strongyloid infection and membranous nephropathy. While strongyloid infection is known to cause nephrotic syndrome, most of the biopsies show minimal change disease. Strongyloid parasitemia may induce type 2 T helper cells to produce eosinophils, interleukin 5 and IgE which results in a nephritogenic immune response and subsequent membranous nephropathy.

FR-PO027

IVIG as First Line Therapy for Thrombotic Microangiopathy Triggered by Ischemia-Reperfusion Injury Post-Kidney Transplant Kamel Hatahet,[1] Swati Rao,[1] Mythili Ghanta,[1] Duncan B. Johnstone,[1] Ashish Gummadi,[1] Serban Constantinescu,[1] Avrum Gillespie,[1] Crystal A. Gadegbeku,[1] Xu Zeng,[2] Iris J. Lee.[1] *[1]Section of Nephrology and Transplantation; [2]Pathology, Lewis Katz School of Medicine at Temple Univ, Philadelphia, PA.*

Introduction: Thrombotic microangiopathy (TMA) is a severe complication post kidney transplant (KT). Allograft biopsy findings include arteriolar and intraglomerular capillary thrombosis/occlusion with fibrin deposition. Calcineurin inhibitors (CNI) and antibody-mediated rejection (AMR) are the most common etiologies of *de novo* TMA. Prolonged allograft ischemia causes ischemia-reperfusion injury (IRI), which increases the risk for post-transplant TMA. Therapeutic plasma exchange (TPE) is the mainstay of treatment for severe cases of TMA. Intravenous immunoglobulin (IVIG) is used in conjugation with TPE only in cases of AMR related TMA, with Eculizumab reserved for resistant cases. We present a case of post-transplant TMA due to extensive IRI managed by IVIG monotherapy.

Case Description: A 60 yr old male with ESRD on hemodialysis underwent cadaveric KT. During the surgery, recipient's external iliac artery dissected requiring re-implantation of the allograft after arterial repair. In the first week post-KT, patient had delayed graft function and developed severe anemia and thrombocytopenia. TMA was diagnosed with elevated lactate dehydrogenase (900 units/L), low haptoglobulin (<6 mg/dl), and schistocytes. Allograft biopsy revealed TMA without features of rejection. CNI had not been initiated. There were no donor specific antibodies and normal level of ADAMTS13. Due to patient's critical condition, TPE/Ecluzimab were withheld and IVIG therapy was initiated. Platelets and hemoglobin rapidly improved to normal.

Discussion: Our case represents TMA triggered by extensive IRI of the allograft. The proinflammatory cytokine milieu likely caused endothelial cell activation and injury resulting in activation of the complement cascade. IVIG inhibits C3 activation and mitigates C5b-9 mediated tissue injury. Interestingly, IVIG is not recommended as first line therapy for TMA. We propose that for TMA that appears to be complement mediated, IVIG should be further investigated as a primary or additional therapy.

FR-PO028

A Necrotizing Glomerulonephritis Associated with Mantle Cell Lymphoma Mamta Shah, Valerie Jorge Cabrera, Anushree C. Shirali. *Dept of Nephrology, Yale School of Medicine, New Haven, CT.*

Introduction: Mantle cell lymphoma (MCL) is a rare and aggressive B-cell non-Hodgkin's lymphoma. The association of MCL with glomerulonephritis (GN) is uncommon. We report here a case of necrotizing GN in a patient with MCL.

Case Description: A 72-year-old man with recently diagnosed MCL presented with a serum creatinine (Cr) of 4.1 mg/dL, from a prior baseline of 1.1mg/dL. On exam, blood pressure was 144/77 mmHg and cervical and axillary lymphadenopathy was noted. Urine microscopy showed dysmorphic red blood cells. Spot urine protein/creatinine ratio was 0.3 g/g and serologies were unrevealing. Kidney biopsy showed a focal and segmental necrotizing GN with an active interstitial nephritis. Immunofluorescence (IF) was positive for IgM, IgG, C3, C1q, kappa, lambda and fibrinogen. No electron dense deposits were identified on electron microscopy. His Cr rose to 7.2 mg/dL despite receiving high dose steroids, and plasmapheresis was initiated. He received a total of 7 plasmapheresis sessions along with R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). He didn't require dialysis and his Cr subsequently improved to and has stayed stable at 2 mg/dL. He is currently on maintenance rituximab every 3 months and his lymphoma is in remission.

Discussion: Renal involvement in lymphoma occurs through direct or indirect mechanisms. Direct mechanisms include lymphomatous infiltration or obstruction. Indirect effects include GN, paraproteinemia and cryoglobulinemia. Kidney injury secondary to tumor lysis, drugs or infections may also occur. The first case of MCL associated GN was reported in 1999 and since then, only 14 cases have been reported in the literature. The most common presentation is proliferative GN, with or without crescent formation. IF typically includes IgG, IgM and C3 staining. In most cases, chemotherapy leads to resolution or improvement of MCL associated GN. In conclusion, MCL associated GN can precede, coexist or occur following the diagnosis of lymphoma. Decline of renal function and microscopic hematuria should increase the suspicion for a glomerular process in patients with MCL and prompt a renal biopsy.

FR-PO029

Focal Segmental Glomerulosclerosis in a Patient with Multiple Myeloma and Autologous Hematopoietic Cell Transplantation Bogdan Obrisca, Roxana Adriana Jurubita, Marina Felicia Paraschiv, Andreea Gamala, Andreea Andronesi, Gener Ismail. *Nephrology and Internal Medicine, "Carol Davila" Univ, Bucharest, Romania.*

Introduction: Glomerulopathies occur less often in recipients of autologous as compared to allogeneic hematopoietic cell transplantation (HCT) and, therefore, renal pathology in this setting is less well characterized.

Case Description: A 54 year-old man is admitted for the evaluation of a nephrotic-range proteinuria. His past medical history included a λ light chain secreting multiple myeloma (MM) diagnosed 4 years ago, treated with bortezomib and dexamethasone. Two years ago, the patient underwent autologous HCT. During the past two months, proteinuria at subsequent check-ups was 3,9 g/day and 4,8 g/day, respectively. A relapse of MM was ruled out by bone marrow biopsy. At the time of admission, the clinical examination was unremarkable. Initial testing showed a proteinuria of 5,6 g/day, but without other signs of NS (normal serum albumin and lipid panel). Urinalysis was unremarkable, the renal function was normal, the serologic and virological studies were negative and there were no signs of active MM. The patient underwent a kidney biopsy that revealed perihilar focal and segmental glomerulosclerosis (FSGS) and was started on cyclosporine 5 mg/kg/day. After 4 months of immunosuppressive therapy, the patient experienced a partial remission (proteinuria of 2 g/day).

Discussion: Glomerulopathies occurring after allogeneic HCT reveal a close temporal relationship between the onset of NS and the diagnosis of chronic graft-versus-host disease (GVHD), indicating a possible pathogenic link. Similarly, in autologous HCT, GVHD-like manifestations have been described as a result of a possible immune dysregulation. Review of the literature reveals several cases of membranous nephropathy and minimal-change disease occurring after autologous HCT, but, to our knowledge, FSGS in this setting wasn't described before. As in previous reported cases of glomerulopathies diagnosed after autologous HCT, our patient didn't show any sign suggestive of a GVHD-like manifestation. Whether there is a pathogenic link or it is just a coincidental finding remains debatable.

FR-PO030

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin G Deposits in Pediatric Patients: A Possible Differential Diagnosis of Membranoproliferative Glomerulonephritis Eiji Nakano,[1,2] Ken-Ichiro Miura,[1] Shoichiro Kanda,[2] Yuji Tomii,[1] Keiichi Takizawa,[1] Naoto Kaneko,[1] Tomoo Yabuuchi,[1] Kiyonobu Ishizuka,[1] Hiroko Chikamoto,[1] Yuko Akioka,[1] Yutaka Harita,[2] Yutaka Yamaguchi,[3] Motoshi Hattori.[1] *[1]Dept of Pediatric Nephrology, Tokyo Women's Medical Univ, Shinjuku-ku, Tokyo, Japan; [2]Dept of Pediatrics, the Univ of Tokyo, Bunkyo-ku, Tokyo, Japan; [3]Yamaguchi's Pathology Laboratory, Matsudo-shi, Chiba, Japan.*

Introduction: Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a newly described entity of glomerulonephritis, which is characterized by glomerular staining for a single light-chain isotype and a single heavy-chain subtype. In adults, the biopsy incidence of PGNMID is 0.17%, and the most frequent histologic pattern is membranoproliferative glomerulonephritis (MPGN) (56.8%). To date, reports of PGNMID in pediatric patients are very limited.

Case Description: The patient was a 15-year-old boy. At the age of 9, mild hematuria and proteinuria were notedby chance during a school urine screening test. The amount of urinary protein gradually increased and a renal biopsy was performed at 15 years old. Light microscopy showed MPGN pattern, and immunofluorescence (IF) revealed granular staining for monoclonal immunoglobulin of IgG3-kappa along the glomerular capillary loops. On electron microscopy, glomerular immune deposits were predominantly subepithelial. There was no clinical and serological evidence of cryoglobulinemia. Based on these results he was diagnosed as PGNMID. Next, 14 pediatric cases diagnosed as MPGN in our hospital between 1994 and 2013 were examined for monoclonal IgG deposits using IF staining. Two patients (14.3%) showed glomerular deposits staining for a single light chain isotype and a single heavy chain subtype (IgG3-kappa in one patient and IgG3-lambda in the other), which was suggestive of a diagnosis of PGNMID.

Discussion: We experienced a pediatric case of PGNMID. Furthermore, our preliminary study found two cases with PGNMID pattern in pediatric MPGN patients. Further studies are clearly needed; our data indicate that pediatric patients showing MPGN may require immunostaining for monoclonal IgG deposits for a definite diagnosis.

FR-PO031

An Exceptional Case of Lyme Disease Associated MPGN Shraddha Rana, Apurv Khanna, Tiffany Nicole Caza, Sylvia L. Betcher. *Nephrology Dept, Syracuse VA Medical Center, Syracuse, NY; SUNY Upstate Medical Univ, Syracuse, NY.*

Introduction: Lyme disease, an endemic multisystem disorder caused by the tick-transmitted spirochete *Borrelia burgdorferi*, is known to cause glomerulonephritis in canine species. It has been postulated that the chronicity of this infection leads to an initial IgM response with polyclonal B cell activation with possible formation of cryoglobulins with eventual IgG response against spirochete polypeptide. Injury is mediated by the classical complement pathway. In the few cases of Lyme disease related glomerulonephritis reported in humans, patients had systemic manifestations of classical Lyme disease.

Case Description: A 70 year old man presented with increasing creatinine and proteinuria over 4 months. PMH included DM type II, HTN, Hyperlipidemia, chronic hematuria with negative urological work up and recent history of tooth extraction for dental infection. He denied usual symptoms of Lyme disease. Exam was significant for a obese male with BP of 169/75 mmHg and mild lower extremity edema. Laboratory data showed creatinine 3.2 mg/dl, urine protein:creatinine ratio = 8, albumin 2.5 mg/dl, microscopic hematuria. Serology work up revealed ESR 120 mm/hr, CRP 3.59 mg/dl, RF 1:1 titer, C4 <1.5, C3 96.1, C-ANCA <1:20, P-ANCA 1:320, anti PR3 8.6 U/ml, MPO 11.8 U/ml, cryoglobulins positive. Kidney biopsy showed immune complex crescentic MPGN with mostly fibrocellular but a few active cellular crescents, tubular atrophy, interstitial fibrosis and IF staining positive for IgG, IgM, C3, C1q. Extensive work up to rule out infectious process or malignancy was negative except for a positive Lyme screen with confirmation Immunoblot positive. Hemodialysis had to be initiated due to declining renal function.

Discussion: This case is unusual as our patient has positive Lyme serology and MPGN with circulating cryoglobulins and positive ANCA antibodies, but absence of the usual symptoms of Lyme disease. This case highlights that Lyme disease may manifest as renal limited and should be considered when unexplained MPGN occurs where Lyme disease is endemic.

Kirmizis D, *et al*. AJKD 43:544-551, 2004; Finnian R, *et al*. Nephrol Dial Trans. 26:3054–3056, 2011.

FR-PO032

A Novel Case of Renal Pathergy Reaction in a Behçet's Disease Patient Complicated by IgA Vasculitis Takaaki Higashihara,[1] Akira Okada,[2] Akira Shimizu,[3] Hideki Takano.[1] *[1]Nephrology, Tokyo Teishin Hospital, 2-14-23, Fujimi, Chiyoda-ku, Tokyo, Japan; [2]Nephrology and Endocrinology, The Univ of Tokyo Graduate School of Medicine, 7-3-1, Hongo, Bunkyo-ku, Tokyo, Japan; [3]Analytic Human Pathology, Graduate School of Medicine, Nippon Medical School, 1-1-5, Sendagi, Bunkyo-ku, Tokyo, Japan.*

Introduction: A pathergy reaction is defined as a hyperreactivity of the skin in response to minimal trauma, which is important in the diagnosis of Behçet'sdisease (BD). However, a pathergy reaction may not be restricted to the skin, and little is known about whether an invasive medical procedure can induce the reaction. Here we present a pathergy reaction induced by renal biopsy, an invasive procedure.

Case Description: A 46-year-old man who was diagnosed with IgA vasculitis (IgAV) at the age of 38 was treated with prednisolone and mizoribine. However, complications such as common carotid arteritis or recurrent oral ulcer suggested the possibility of another pathophysiology. Later, increasing urine protein developed, suggesting disease aggravation. However, renal biopsy showed arteriosclerotic changes caused by hypertension and diabetes mellitus, negating exacerbation. After renal biopsy, his renal dysfunction and body temperature fluctuated, and detailed examinations revealed recurrent oral and genital ulcers and a folliculitis-like rash on his scrotum. Later, he complained of myodesopsia caused by hemorrhage in the ocular fundus due toocclusive vasculitis. Complete BD was diagnosed after development of the symptoms, and he was treated with prednisolone and colchicine.

Discussion: Co-occurrence of BD with IgAV is very rare and may be associated with immune disorders. Interestingly, a renal biopsy revealed BD, which was masked by the presence of IgAV, and elucidated the etiology of the unexplainable symptoms. To the best of our knowledge, this is the first report of renal pathergy. This case enlightens clinicians to the fact that not only a needle stimulation but also an invasive procedure can cause a pathergy reaction, and we should perform focused history-taking and physical examinations when some signs and symptoms in a patient cannot be explained fully by one form of vasculitis, for example, IgAV.

FR-PO033

Lupus Flare Presenting as Acute Pericarditis in a Patient with Stage V CKD on Hemodialysis Secondary to Lupus Nephritis Sai Prasad Gadapa,[1] Siwadon Pitukweerakul,[2] Sree V. Pilla.[3] *[1]Internal Medicine, St. Francis Hospital, Evanston, IL; [2]Internal Medicine, St. Francis Hospital, Evanston, IL; [3]Internal Medicine, St. Francis Hospital, Evanston, IL.*

Introduction: Development of end-stage renal disease (ESRD) does not always result in resolution of the extra-renal manifestations of Systemic Lupus Erythematosus (SLE). Lupus flare is the cause of pericarditis in a patient with stage V CKD on hemodialysis secondary to lupus nephritis until proven otherwise.

Case Description: A 41-year-old AA woman with a medical history of SLE, HTN, Gout, HLD and CKD stage V on hemodialysis presenting with one day duration severe chest pain, pleuritic in nature. Her last lupus flare was more than three years. She is on hemodialysis for more than one year. Her medications include amlodipine, metoprolol tartrate, sevelamer, prednisone 5 mg, and atorvastatin. On examination, the patient had temp. of 99.9 F. Her HR was 102/minute, BP 93/50 mm Hg, RR 28/minute, and oxygen saturation 98% on room air. The BUN level 36 mg/dL. Chest XR revealed marked cardiomegaly. The EKG revealed sinus tachycardia. 2D echo revealed moderate posterior pericardial effusion with borderline tamponade. She received naproxen. Pt also received intensive hemodialysis. Despite above treatment her symptoms did not improve, pericardial rub was heard, her 2D echo also showed no improvement of pericardial effusion. On hospital day 4, SLE studies and inflammatory studies revealed dsDNA Ab 79 IU/mL, C3 complement 67 mg/dL, C4 complement <8 mg/dL and C - reactive protein level 22.5 mg/dL. Naproxen was switched to oral prednisone 20 mg twice daily. On hospital day 7 2D echo revealed small pericardial effusion with no tamponade.

Discussion: Uremic pericarditis occurs in 6-10% of patients with advanced uremia just before initiation of dialysis or immediately after; it is associated with high blood urea levels (>60 mg/dL). SLE activity tends to decrease overtime in patients on dialysis. However, a number of papers report a high rate of flare in dialysis patients. This case report underscores the importance of close follow up of SLE patients on hemodialysis for lupus activity. It also helps making decision regarding renal transplantation.

FR-PO034

Nephrotic Syndrome with Cancer Immunotherapies Abhijat Kitchlu,[1] Warren Fingrut,[1] C. Avila-Casado,[2] Heather N. Reich.[1] *[1]Div of Nephrology, U. of Toronto, Canada; [2]Lab. Med. & Pathobiology, U. of Toronto, Canada.*

Introduction: Oncologic immunotherapy utilizes a patient's immune response to eliminate tumour cells by disruption of immune checkpoints, including programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) pathways. Autoimmune sequelae, including cases of acute kidney injury from interstitial nephritis have been reported; however glomerular disease appears rare. Here we describe two cases of nephrotic syndrome in patients treated with these agents.

Case Description: Patient 1, a 43 year old male, received the anti PD-1 antibody pembrolizumab, after a 9 year history of Hodgkin's lymphoma. Following his second dose he developed edema and nephrotic syndrome (proteinuria 5.6 g/d) and acute kidney injury (creatinine 4.9 mg/dL). Renal biopsy showed diffuse foot process effacement and mild acute tubular injury. Following cessation of pembrolizumab and corticosteroid treatment he had resolution of his proteinuria and renal insufficiency. Patient 2, a 45 year old male with melanoma, received the CTLA-4 antibody ipilimumab. Following four cycles he developed anasarca and nephrotic syndrome (proteinuria of 9.5 g/d) with normal kidney function. Biopsy was compatible with minimal change disease. Ipilimumab was stopped and proteinuria resolved following corticosteroid treatment. Two years later ipilimumab was restarted as salvage therapy, and he developed recurrent proteinuria. Both patients ultimately died from their underlying cancer.

Discussion: These cases provide insights into the pathogenesis of nephrotic syndrome. While affecting T cell regulation at different stages of T cell activation, both the PD-1 and CTLA-4 pathways modulate T cell activation through signals involving antigen presenting cell CD80 (B7.1). These cases may support the hypothesis of a 'permeability factor' causing podocyte injury. Release of T cell regulation by these drugs may have promoted production of such a factor and subsequent foot process effacement. However a more direct effect on podocyte CD80 engagement cannot be excluded and merits investigation. Given the increasing prevalence of these therapies, monitoring patients for renal sequelae as well as potential early biopsy and intervention may be warranted.

FR-PO035

Nephrotic Syndrome after Autologous Hematopoietic Stem Cell Transplant: A Manifestation of Graft-versus-Host Disease? Madhuri Ramakrishnan,[1] Siva Sagar Taduru,[1] Omkar U. Vaidya,[3] Rakesh Gaur.[2] *[1]Internal Medicine, Univ of Missouri, Kansas City; [2]Hematology/Oncology, Saint Luke's Hospital, Kansas City; [3]Nephrology, Univ of Missouri Kansas City, Kansas City.*

Introduction: Renal involvement in Graft-vs-Host Disease (GVHD) is rare, but has been described following allogenic hematopoietic stem cell transplant (HSCT). Recently, GVHD is being identified as a complication of autologous-HSCT, especially in association with Multiple Myeloma. The manifestations of this type of GVHD are similar to those after allogenic-HSCT, though no cases involving the kidney are described. We describe a case of Nephrotic Syndrome in a patient after autologous-HSCT for Multiple Myeloma.

Case Description: The patient is a 58 year old African American female diagnosed with Multiple Myeloma, who underwent chemotherapy with Bortezumib, Lenalidomide, and Dexamethasone, and subsequent autologous-HSCT. A 100 day bone marrow biopsy revealed no disease process, and the patient was in complete remission. She presented 5 months after transplant with increased weight, lower extremity and facial edema. Initial labs showed AKI- Cr of 3, a 24-hour urine protein of 22 gram (previous urine Protein/Creatinine ratio was normal 4 years prior), and a serum albumin of 2.0. Work up for her Nephrotic Syndrome, including ANA, dsDNA, and ANCA were negative. A renal biopsy was performed, that showed Focal Segmental Glomerulo-Sclerosis, with no evidence of myeloma deposits. Following biopsy results, she was started on high dose Prednisone-120 mg every other day. Her kidney function improved, with Cr of 1.2, and serum albumin improved to 3.8.

Discussion: Given that no other secondary causes were identified, and the temporal relation with transplant, we consider that our patient's Nephrotic Syndrome could be a manifestation of GVHD after autologous-HSCT. Renal manifestations of GVHD are rare, but have been described, though only in patients undergoing allogenic-HSCT. Since GVHD is now also being described in patients undergoing autologous-HSCT, especially for multiple myeloma, kidney disease in relation to this, if presents, is worth investigating. Recognition of more cases is required to elucidate the renal pathophysiology involved.

FR-PO036

A Case of Secondary Membranous Glomerulonephritis Rami Mouayad Azem,[1,2] Minesh Rajpal,[1] Georges Nakhoul,[1] Leal C. Herlitz,[1] James F. Simon.[1] *[1]Nephrology, Cleveland Clinic Foundation, Cleveland, OH; [2]Internal Medicine, Summa Health System, Akron, OH.*

Introduction: Membranous Glomerulonephritis (MGN) is the second leading cause of nephrotic syndrome in adults. MGN can be a primary disease or secondary to underlying etiologies such as autoimmune diseases, including Sjogrens disease. Secondary MGN has also been attributed to IgG4 related disease (IgG4-RD), an immune-mediated disease that involves lymphoplasmacytic infiltration with IgG4 enriched plasma cells.

Case Description: A 61 year old female with past medical history of Sjogrens disease, IgG4-RD, CKD Stage III (baseline creatinine [Cr] 1.0-1.2), retroperitoneal fibrosis with history of bilateral hydronephrosis requiring stent placement and ureterolysis, presented with sore throat, shortness of breath, and productive cough. Cr was 2.4 mg/dL on admission and increased to 4.5 mg/dL within 2 days, accompanied by urine protein/Cr (P:Cr) ratio of 2.5, and an active urinary sediment. There was no evidence of recurrent ureteral obstruction. She was treated for pneumonia with antibiotics and started on pulse dose solumedrol 1 gram daily for 3 days with prednisone subsequently. CRP was 1.5, with negative HIV, ANA, C3, C4, c-ANCA, p-ANCA, DS-DNA, syphilis IgG, phospholipase A2-receptor antibody (PLA2R), and abnormal elevations in IgG subclasses I-IV. IgG subclass IV levels were normal at 113.6, however were elevated 3 weeks prior at 195.5. Renal biopsy showed MGN with focal mesangial and subendothelial deposits, but no IgG4 tubulointerstitial nephritis. She responded to solumedrol with a decrease in Cr from 4.5 mg/dL on 4/21 to 2.76 mg/dL on 5/3, and 1.46 mg/dL on 6/1. Her urine P:Cr ratio however increased from 2.4 on 4/23 to 9.6 on 6/1.

Discussion: This patient had biopsy proven MGN with mesangial and subendothelial deposits and negative anti PLA2R serologies, strongly favoring a secondary form of MGN. While PLA2R testing along with histology can help exclude primary MGN, there is no reliable way to differentiate between secondary MGN due to Sjogrens disease versus IgG4-RD. This case underscores the need for a more thorough understanding of how the many secondary causes of MGN cause this pathology so that therapy can be targeted appropriately.

FR-PO037

Acute Parvovirus B19-Associated Nephrotic Syndrome in a Patient with Sickle Cell Disease Nupur N. Uppal, Jeny Varghese, Hitesh H. Shah. *Nephrology, Hofstra Northwell School of Medicine, Great Neck, NY.*

Introduction: Human parvovirus B19 (HPV B19) infection is a common cause of transient aplastic crisis (TAC) in patients with sickle cell disease (SCD). However, nephrotic syndrome (NS) has been rarely associated with acute HPV B19 infection in patients with SCD. We present an interesting case of abrupt onset severe NS and AKI secondary to acute HPV B19 infection.

Case Description: 37-year-old AA female with history of SCD was hospitalized with fever and severe anemia. Both serum creatinine (Scr) and albumin were normal on admission. Pt. was found to have TAC secondary to acute HPV B19 infection. HPV B19 DNA by PCR was elevated (1.8×10^8 IU/ml). HPV B19 IgM was positive. Scr increased to 1.9 mg/dL during hospitalization. Pt. was thought to have prerenal AKI secondary to hemodynamic changes. There was no obstructive uropathy on renal ultrasound. Pt. received IV fluids and Scr decreased to 1.8 mg/dL on the day of discharge. Five days later, pt. presented to the clinic with worsening lower extremity (LE) swelling, abdominal distention and 35 lbs weight gain. Pt. was noted to have significant LE edema on exam. Urinalysis showed proteinuria. Spot urine total protein to creatinine ratio (TP/CR) was elevated at 56. Serum albumin was low (1.8 g/dL). Scr remained elevated at 1.8 mg/dL. Serological work up for NS including HIV infection was negative. Pt. was subsequently rehospitalized for management of generalized body swelling that was resistant to oral diuretic therapy. Pt. received IV albumin and diuretic therapy during hospitalization. Kidney biopsy performed subsequently revealed collapsing FSGS that was thought to be secondary to acute HPV B19 infection. Scr peaked to 3.4 mg/dL during that hospital stay. Three months after initial presentation, Scr however remains elevated at 2.7 mg/dL. Pt. also continues to have significantly elevated spot urine TP/CR (21.5) and NS despite decreasing HPV B19 DNA levels.

Discussion: Collapsing FSGS as a result of acute HPV B19 infection has been rarely described in patients with SCD. Optimal therapy and renal outcomes in such cases are unknown. Our patient continues to have significant renal failure and severe NS, 3 months after initial presentation.

FR-PO038

Resolution of Hepatitis C Related Membranoproliferative Glomerulonephritis after Treatment with Combination Ledipasvir/ Sofosbuvir Hayden Novak, Kosunarty Fa. *Methodist Dallas Medical Center, Dallas, TX.*

Introduction: Advent of new medications indicated for the treatment of Hepatitis C has drastically changed the landscape of end- stage liver disease. With the increased use of these new modalities their effect on other virus- related pathologies has yet to be fully established.

Case Description: KB is a 56 year old female with end- stage liver disease secondary to chronic hepatitis C cirrhosis listed for orthotopic liver transplant. December 15, 2014 patient is noted to have apparently normal kidney function with creatinine 0.94. However by mid- January her creatinine is noted to be increased and on January 23 2015 she is admitted with shortness of breath, anasarca, and acute kidney injury, leading to a preliminary diagnosis of nephrotic syndrome (16.7 grams proteinuria). Creatinine peak was 4.1 on 30 January 2015. Renal biopsy did show membranoproliferative glomerulonephritis (MPGN) and acute tubular injury without vasculitis. She did later develop a vasculitic rash of both legs. In addition to treatment with solumedrol, plasmapheresis, and rituximab, ledipasvir/ sofosbuvir (Harvoni) therapy was initiated on 30 January 2015. In April 2015, creatinine had improved to 1.2 and vasculitic rash resolved. 24 hour collection in June 2015 showed 245 mg proteinuria. In November 2015 patient completed 24 weeks' duration of ledipasvir/ sofosbuvir treatment, and creatinine was 0.89.

Discussion: This report of biopsy- proven MPGN in the setting of cryoglobulinemia related to HCV, with recovery to baseline of renal function after ledipasvir/ sofosbuvir treatment is unique in the current literature. The resolution of MPGN in this patient enabled evaluation for single organ transplant in lieu of double organ transplant. With this association, new avenues for investigation are opened into the treatment and management of end- stage renal disease secondary to HCV- associated conditions.

FR-PO039

PLA2R-Antibody Positive Membranous Nephropathy Associated with Inflammatory Demyelinating Radiculopathy after Hepatitis B Vaccination Reejis Stephen, Evamaria Anvari, Laura Ferreira Provenzano. *Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH.*

Introduction: PLA2R is a biomarker of idiopathic membranous nephropathy (MN). However, it can be positive in some secondary cases, including hepatitis B (HBV) associated MN. MN has also been associated with inflammatory demyelinating diseases, but the nature of the association remains unclear. This case describes a case of PLA2R positive MN associated with an inflammatory demyelinating polyradiculopathy in the background of a recent HBV vaccination.

Case Description: A 56-year-old Caucasian male was referred for a second opinion regarding MN. He initially presented with joint pain and bilateral extremity paresthesias. He soon developed marked edema and hypertension, with over 20 lbs weight gain, associated with weakness and unsteady gait. No preceding illness was reported, but he had received hepatitis B vaccination one month prior. He had taken NSAIDs for pain but no other medications. He was found to have 17 grams of proteinuria/24 hs and was diagnosed with nephrotic syndrome. His renal function was normal. Serological workup including C3/ C4, ANA, RF, ANCA, anti-GBM antibodies, hepatitis panel, SPEP, UPEP was negative. A screening colonoscopy 6 years prior and a PSA level were normal. Renal biopsy showed membranous nephropathy. PLA2R was positive (1:40). Concomitantly, he was diagnosed with inflammatory demyelinating polyradiculopathy and was started on prednisone 60 mg daily. Over the next several months he showed neurological improvement, and the steroid dose was titrated down. Proteinuria also improved (<1g /24 hrs) and the nephrotic syndrome resolved. Repeat PLA2R levels have been negative.

Discussion: To our knowledge, this is the first case of MN associated with a inflammatory demyelinating radiculopathy with PLA2R positivity. The time correlation with the hepatitis B vaccination series raises the possibility that the HBV antigen triggered the autoimmune response.

FR-PO040

Crescentic and Necroziting Glomerulonephritis with IgA Depositions and Circulating IgG and IgA ANCA Sonia Brigitte Boyer,[1,2] Elizabeth Alderman McInnis,[1] Volker Nickeleit,[1] Patrick H. Nachman.[1] *[1]UNC Kidney Center, Univ of North Carolina; [2]Dept of Medicine, CHU Nice, Nice, France.*

Introduction: Several observations of crescentic and necroziting glomerulonephritis (CNGN) with IgA depositions and IgG ANCA have been reported in literature, suggesting an overlap between IgA nephropathy (IgAN) and ANCA-associated vasculitis (AAV). In this situation, we evaluate the presence of ANCA of IgA isotype.

A 22 year-old male with no previous medical history presented with acute kidney injury (serum creatinine 3mg/L). His symptoms were nausea and one episode of vomiting. Workup was significant for active urine sediment (red blood cell casts, dysmorphic hematuria and oval fat bodies), urine protein/creatinine ratio was 2.78g/g. PR3-ANCA was positive at 185.7U/mL(normal < 20U/mL), ANA was negative and complement was in normal range.

Kidney biopsy revealed diffuse CNGN involving 80-90% of glomeruli and diffuse acute tubular injury with scattered tubular red blood cell casts. Immunofluorescence showed 2+ for IgA and C3 staining in mesangial regions. Initial treatment included methylprednisolone 500mg IV x 3, cyclophosphamide 15mg/kg and 7 plasmapheresis sessions. The patient responded to treatment, with improved serum creatinine to 1.3mg/L.

We investigated the presence of IgA-ANCA by indirect immunofluorescent (IFI) on ethanol fixed neutrophils and western blot electrophoresis on purified MPO, PR3 and Neutrophil extract. The IFI was positive for cytoplasmic staining. The western blot substantiated the presence of an circulating IgA anti-PR3.

Discussion: Only 19 cases of AAV and associated IgAN have been reported in the literature. These patients presented with systemic symptoms in 60% of cases, had a proteinuria > 2g/24h and ANCA were mostly anti-MPO subtype. Morever, studies found that proteinuria is higher in CNGN-ANCA than in crescentic IgAN. A recent study comparing CNGN-ANCA to ANCA-vasculitis showed greater proteinuria in CGCN-ANCA. IgA-ANCA have the capacity to modify neutrophils degranulation and so, could play a role in CGCN-ANCA pathogenesis. Our observation suggests an overlap between IgAN and AAV, and IgA-ANCA could be involved in the physiopathology of this entity.

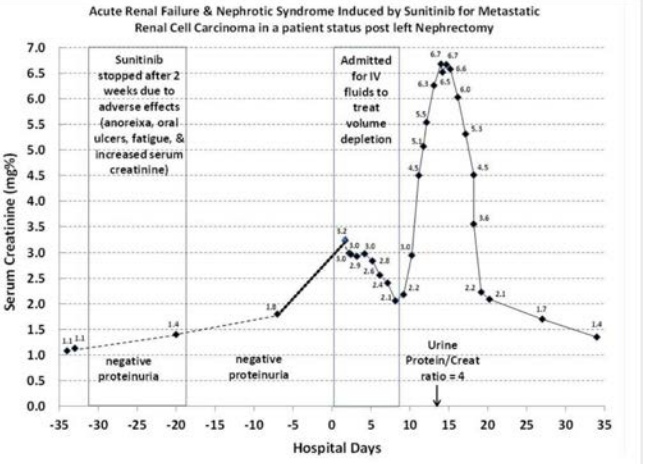
FR-PO041

Severe but Reversible Acute Renal Failure (ARF) and Nephrotic Syndrome (NS) Induced by Sunitimib (Sutent), an Inhibitor of Receptor Tyrosine Kinase (RTK) Used to Treat Metastatic Renal Cell Carcinoma (m-RCC) Sushanta K. Goswami,[1,2] Kai Lau.[1,2] *[1]Dept of Nephrology, Univ of Oklahoma, Oklahoma City, OK; [2]Medical Service, VA Medical Center, Oklahoma City, OK.*

Introduction: Sunitinib is a multi-target RTK inhibitor including VEGFR. Used in many advanced cancers (breast, lung, colon and RCC), it has many extra-renal & renal side-effects. We here report a 51 year old man with m-RCC, prior left nephrectomy, admitted for severe ARF & NS evolved over 4-5 weeks.

Case Description: We reviewed all clinical & lab data in this man consulted for ARF & NS. His hypertension & hyperuricemia were controlled. We excluded all potential causes like NSAID, contrast dye, sepsis, obstruction, rhabdomyolysis & tumor lysis. 2 weeks into 50 mg/d of sunitinib, he developed diarrhea & steadily climbing serum creatinine (Scre) from a stable baseline of 1.1 mg%.

Afebrile, his vital signs & exam were normal. Hydronephrosis was absent. Chest X rays, urine & blood cultures were negative. Hgb was 9 g%, WC 8 k, platelet 21 k (normal bone marrow). Liver function, LDH, CPK, haptoglobin, troponin were normal. IV fluid yielded only mild transient drop in Scre. Initial urinalysis was normal but NS soon emerged. Anasarca was resolved by diuresis, thrombocytopenia by N-plat. 3 weeks after peak Scre of 6.7, his ARF spontaneously & largely resolved.



Discussion: 1. RTK inhibitors, like sunitinib, could cause nephrotoxicities, including thrombotic microangiopathy, interstitial nephritis, proteinuria & mild-to-moderate ARF. Among the dozen reported cases, ours seemed to have the worst renal failure compounded by NS that spontaneously resolved by supportive care & stopping sunitibnib. 2. Given the growing use of these agents in many cancers, we would call attention to these hitherto little described renal toxicities & urge regular monitoring of renal functions.

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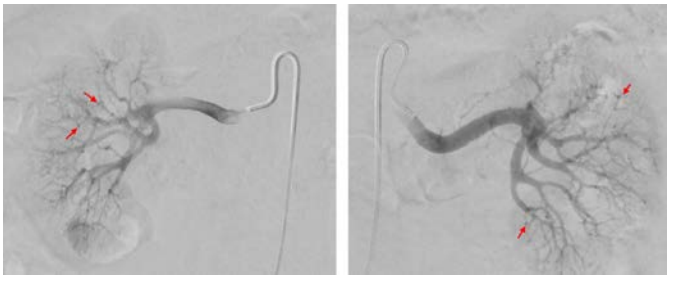
FR-PO042

A Case of Isolated Renal Involvement of Polyarteritis Nodosa Successfully Treated with Steroid Monotherapy Negiin Pourafshar, Eric S. Sobel, Mark S. Segal. *Univ of Florida, Gaineville, FL.*

Introduction: Polyarteritis nodosa(PAN) is a systemic necrotizing vasculitis that typically affects medium-sized arteries, with occasional involvement of small arteries. Renal involvement would frequently result in variable degrees of renal insufficiency, proteinuria and hypertension.

Case Description: A 75-year-old man was referred for management of uncontrolled hypertension and worsening renal function. Patient recently developed uncontrolled HTN as well as renal function impairment. Further work-up of hypertension was unremarkable. A renal angiogram was then obtained due to suspicion for renal artery stenosis which revealed patent renal arteries, marked irregularity of the interlobar branches of the renal arteries with multiple areas of strictures as well as numerous microaneurysms involving interlobar branches of renal arteries (figure 1), suspicious for PAN.



He was initially started on prednisone 40 mg/day which was subsequently increased to 60 mg/day. While on the increased dose of steroids, his hypertension and renal impairment improved. He did not require anti-hypertensive therapy.

Discussion: Renal failure and uncontrolled hypertension could represent renal involvement in PAN. Diagnosis of PAN is based on the recognition of a vasculitic syndrome with supportive evidence deriving from radiologic or pathologic studies or both. Biopsy of an organ is ideal for verifying the diagnosis of vasculitis. However, angiography is similarly valuable or even preferable to tissue sampling for diagnosis. We believe that our patient's worsening renal function and uncontrolled hypertension resulted from diffuse renal necrotizing vasculitis with occlusive lesions of small-sized arteries. Our case report demonstrates successful treatment of renal failure and hypertension with steroid monotherapy.

FR-PO043

The Importance of Adrenal Venous Sampling in Young Patients with Primary Aldosteronism Mamta Shah,[1] David Geller.[2] [1]*Dept of Nephrology, Yale Univ School of Medicine, New Haven, CT;* [2]*Dept of Nephrology, Yale Univ School of Medicine/Veteran Affairs, West Haven, CT.*

Introduction: Primary aldosteronism (PA) is a leading cause of resistant hypertension, which can be treated with surgical removal of a unilateral adenoma. Previous recommendations held that adrenal venous sampling (AVS) was not necessary in patients ≤ 40 years of age with evidence of PA and unilateral adenoma on adrenal imaging, on the premise that nonfunctioning adrenocortical adenomas are rare in young people.

Case Description: A 39 year-old man with a 7-year history of difficult to control hypertension and mild hypokalemia presented for initial evaluation. He had serum and urinary laboratory parameters suggestive of hyperaldosteronism and CT adrenal imaging showed adrenal nodularity on the left consistent with microadenoma vs. hyperplasia with no abnormality on the right. However, AVS demonstrated clear lateralization to the right side. He eventually underwent right adrenalectomy based on AVS, with resultant better blood pressure control on one anti-hypertensive agent and normalization of the serum potassium.

Discussion: Current guidelines advocate the use of AVS in addition to adrenal imaging before considering unilateral adrenalectomy. Based on previous recommendations, this patient might not have had AVS given his age, clinical evidence of PA, and the CT findings, but that would have resulted in the removal of functionally normal gland. A recent study showed AVS changed management in 30% of patients ≤40 years of age. Newer recommendations state AVS should be done in PA patients over 35 years of age. We believe that AVS should ideally be performed in all patients with PA in whom surgical treatment is a consideration.

FR-PO044

The Crystal Clear Answer to Methotrexate Toxicity? Mamta Shah, Juan Calderon, Anushree C. Shirali. *Dept of Nephrology, Yale School of Medicine, New Haven, CT.*

Introduction: Methotrexate (MTX) is a potent anti-cancer drug that antagonizes active division of tumor cells. This often comes at the expense of nephrotoxicity with an incidence of 2-10% with use of high-dose MTX (>500mg/m2). Treatment approaches for toxic MTX levels include high-flux hemodialysis (HF-HD) and Carboxypeptidase-G2 (CPDG2) administration. While HF-HD is more often employed for clearance of MTX, rebound of MTX levels post dialysis has been a concern. We report here a case of MTX toxicity treated with CPDG2 alone, with no rebound of MTX levels after treatment.

Case Description: A 72 year-old man with newly diagnosed Diffuse Large B-cell Lymphoma and baseline serum creatinine (Cr) of 1.0 mg/dL was initiated on MTX at a dose of 2gm/m^2 with leukovorin rescue and intravenous sodium bicarbonate. Within 6 hours of the infusion, he was oliguric with a Cr of 1.6mg/dL, which continued to rise to 3.4mg/dL in 24 hours and 5.5mg/dL in 72 hours. His vital signs and physical exam were unremarkable. No mucositis was noted. MTX levels at 24 and 48 hours were 51μmoles/L and 17μmoles/L respectively. The patient received one dose of CPDG2 at 72 hours with a drop in MTX levels to <1μmole/L which did not rebound. He did not require renal replacement therapy. Cr peaked at 6.5mg/dL the following day and then improved to 1.8mg/dL over the next ten days.

Discussion: In our patient, treatment with CPDG2 resulted in prompt clearance of MTX. Importantly, no rebound was observed and the patient did not require any dialysis. MTX is a small molecule which is 50% protein-bound with a large volume of distribution. This makes it an acceptable drug for dialytic clearance. However, it is an invasive procedure which can put cancer patients at higher infection and bleeding risk. Additionally, post-HD drug levels frequently rebound, requiring repeated dialysis sessions. CPDG2 is fairly well tolerated, is noninvasive and is not associated with rebound. When access to either approach is readily available, use of CPDG2 to treat toxic MTX levels may be more favorable than HF-HD.

FR-PO045

Successful Revascularization of Critical Proximal Renal Artery Stenosis with Early Bifurcation with Two Kissing Coronary Stents Sonali Biligiri, Navneet Kaur, Sandeep Aggarwal, Ellie Kelepouris. *Internal Medicine, Div of Nephrology, Drexel Univ College of Medicine, Philadelphia, PA.*

Introduction: RA stenting is treatment of choice for RAS with uncontrolled hypertension, pulmonary edema, rapid deterioration of renal function and preservation of renal mass. According to living donor studies, renal artery anomalies including accessory renal arteries are present in 30%-47% cases. Usually the accessory RA is non-dominant and is "sacrificed" during intervention without significant loss of renal mass. We present a case of severe RAS of a solitary kidney and very short early bifurcating main RA with 2 co-dominant segmental arteries after successful endovascular revascularization using 2 side by side "kissing" coronary stents.

Case Description: 66 year old black female presented for management of uncontrolled hypertension and worsening renal function with serum creatinine increasing from 2.6 to 3.3 mg/dL in 1 month; her BP had been >180 mmHg systolic despite multiple anti-hypertensives including a diuretic. NM MAG3 scan showed a non-perfused small left kidney with right kidney contributing 100% of renal function suggestive of solitary functional right kidney. Renal doppler showed parvus tardus waveform and normal RI (<0.7) in the right RA suggestive of critical stenosis with preserved parenchyma. An angiogram confirmed severe right renal artery ostial stenosis with near immediate bifurcation into 2 co-dominant segmental arteries. A single stent could not be placed since length of stent would be longer than main renal artery leading to stenting of one segmental artery with potential sacrifice of co-dominant renal artery. Two balloon expandable "kissing" coronary stents were successfully deployed in upper and lower pole renal arterial branches in main renal artery. Patient had marked improvement in BP and renal function with patent stents on post-procedure doppler.

Discussion: Our patient's presentation with progressive kidney dysfunction and uncontrolled hypertension warranted immediate intervention. Her atypical anatomy with immediate renal artery bifurcation proved a challenge for stent placement, but clinical improvement successfully achieved with a unique solution of two "kissing" stents.

FR-PO046

Therapeutic Plasma Exchange for Amlodipine Overdose Latoya L. Brathwaite,[1] Mahwash Kamal,[1] N. Ganesh Yadlapalli.[1] [1]*Nephrology, Univ of Cincinnati Medical Center, Cincinnati, OH;* [2]*Nephrology, Univ of Cincinnati Medical Center, Cincinnati, OH.*

Introduction: Amlodipine is the most prescribed long-acting dihydropyridine calcium channel blocker (CCB). Amlodipine toxicity is associated with poor outcomes and largely treated with supportive therapies. There are no recommended treatments for enhanced removal of CCBs from blood. We report a case of Amlodipine toxicity treated with total plasma exchange (TPE).

Case Description: A 62 year old Caucasian female was admitted with Amlodipine overdose. She was unconscious, hypotensive with bradycardia on admission. She ingested about 500mg of amlodipine. She developed oliguric acute kidney injury, anion gap metabolic acidosis and concomitant respiratory acidosis which required continuous renal replacement therapy. The patient required large amounts of pressor support to maintain hemodynamics. She received high dose IV calcium, IV glucagon, high dose insulin and fat emulsion infusions. After five days of continued high pressor requirements despite aggressive management, she received 1 session of TPE with 1 volume exchange and 100% replacement with 5 % albumin. Amlodipine level prior to TPE was 140ng/ml and after 1 session of TPE, the level had decreased to 70ng/ml. The patient's pressor requirements decreased. At this point, the patient's family decided to withdraw care. We were unable to conduct the second session of TPE as planned. We were also not able to get repeat levels to evaluate a post TPE rebound effect.

Discussion: Amlodipine is 93% protein bound with a large volume of distribution and unable to be removed by hemodialysis. Its long half-life of 30-50hours increases in setting of overdose and places the patient at risk of a prolonged hospitalization requiring a high pressor support requirement and the associated adverse outcomes. In our case, we noticed reduction in pressor requirement after a decrease in amlodipine level with TPE. There is not much data that exist about drug removal with TPE except a few case reports. This case report supports TPE as a modality for removal of highly protein bound substances like amlodipine. The use of TPE earlier in the treatment course may improve outcomes.

FR-PO047

Non-Steroidal Anti-Inflammatory Drugs for Treatment of Severe Refractory Orthostatic Hypotension: Thinking Outside the Box! Julia Brown, Rie Hirai, Anil K. Bidani, Kavitha Vellanki. *Nephrology, Loyola Univ Medical Center, Maywood, IL.*

Introduction: Orthostatic hypotension is recognized as a paraneoplastic effect of bronchial carcinoma, reported in 10-20% of patients with the disease. While the exact pathophysiology is unknown, the role of vasodilatory peptides secreted by the tumors has been explored. Here we present a unique case of refractory orthostatic hypotension in a patient with lung carcinoma in which symptomatic relief was achieved with non-steroidal anti-inflammatory drugs (NSAIDs).

Case Description: A 66 year old male with a recent diagnosis stage IIIb squamous cell lung carcinoma presented with complaints of generalized weakness. He was found to be orthostatic and remained orthostatic despite aggressive fluid resuscitation. His blood urea nitrogen and creatinine were stable. Cisplatin-induced salt wasting nephropathy

was ruled out (fractional excretion of sodium <1% repeatedly). He continued to be symptomatic despite receiving salt tablets 4 grams 3 times daily, midodrine 5 mg 3 times daily, fludrocortisone 0.1 mg twice daily, an abdominal binder, and thigh-high compression stockings. We hypothesized that systemic and renal vasodilatation, possibly paraneoplastic in origin, were playing a role in the patient's severe orthostatic hypotension. Low systemic vascular resistance calculated from the patient's echocardiogram further reinforced our hypothesis. We therefore started ibuprofen, after which there was a dramatic improvement in the patient's clinical symptoms and he was able to walk after being bed bound for more than a week (Table 1).

Discussion: In appropriate clinical conditions, NSAIDs can be considered for treatment of severe refractory orthostatic hypotension.

	Supine BP	Standing BP	Supine HR	Standing HR
Prior to NSAID	123/88	96/76	77	111
	133/89	117/76	86	121
	128/82	83/56	84	140
	113/64	91/63	95	145
	139/84	92/74	80	126
	85/57	70/49	96	142
	117/64	121/78	85	121
	106/67	74/53	95	142
	125/86	96/64	87	140
After ibuprofen 400mg twice daily	138/86	115/79	82	109
	131/81	103/75	84	123
	133/90	111/82	80	126
After ibuprofen 400mg three times daily	138/90	125/91	82	129

FR-PO048

Reversible Heart Failure and Nephrotic Syndrome Associated with Massive Protein Intake in a Bodybuilder

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Introduction: High protein diet in addition to anabolic steroid ingestion is common among bodybuilders to promote muscle development/hypertrophy. Acute tubular necrosis and focal segmental glomerulosclerosis have been described in the setting of high protein intake and anabolic steroid use.

Case Description: We present a case of a previously healthy 42 year-old African American male bodybuilder, on anabolic steroid supplements, who was consuming a 150g of protein/kg/day diet -for a total intake of >1500 g of protein a day- who was hospitalized for decompensated heart failure.

On evaluation, he was found to have a decreased ejection fraction (EF) of 15% and proteinuria of 6g/day. Serum protein electrophoresis did not show any gammapathies, and Urine protein electrophoresis revealed that his urinary protein consisted mainly of albumin. His GFR based on creatinine clearance was 113ml/min. A renal biopsy to evaluate proteinuria showed mild chronic tubule-interstitial disease without acute tubular necrosis. His myocardial biopsy showed hypertrophied myocytes, but no specific etiology for his heart failure. Five days later, while still an inpatient, his proteinuria decreased to 2g/day while on a hospital low protein diet. He was started on an ACE inhibitor and asked to modify his lifestyle. Six months later his proteinuria was reduced to 115mg/day and his EF has improved to 45%.

Discussion: This unique case highlights a rarely recognized cause of heavy proteinuria and acute heart failure attributable to massive protein intake and possibly anabolic steroids use. In addition to the reversible heart failure associated with myocyte hypertrophy our case illustrates that chronic tubular interstitial nephropathy can develop as well. The proteinuria and tubular damage observed in this case resembles the overload proteinuria caused experimentally by albumin infusion to rodents.

FR-PO049

Secretory Paraganglioma of the Head and Neck

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Introduction: Paragangliomas are rare neuroendocrine extra-adrenal tumors of sympathetic or vagal ganglion cells. Catecholamine secreting Paragangliomas are present mostly in the abdominal para-aortic region (75 percent). Nonsecreting vagal Paragangliomas (95 percent) are located mainly in the head and neck.

Case Description: We report a 58 year old gentleman with the diagnosis of panic disorder for 7years was referred to Hypertension clinic with labile hypertension. He was on appropriate therapy(Lisinopril 40mg daily, Indapamide 1.25mg daily, Verapamil 240mg daily, Carvidolol 25mg twice daily, Olmesartan 40mg daily) but was experiencing episodic fluctuations in blood pressures with panic attacks. Work up for pheochromocytoma was initiated and his plasma free Normetanephrines was 16nmol/L (Normal <0.90). The 24 hour urine Normetanephrine was 32,340 nmol/L. CT scan of Abdomen and pelvis was negative. I-123MIBG was also negative. With high clinical suspicion F-18-FDG PET scan was performed and showed localized left cervical Paraganglioma. CT Angiography of the Head/Neck confirmed a heterogeneous mass 4x2x5.6 cms at the base of the skull. He underwent selective Left neck dissection with excision of Para-pharyngeal mass and lymph nodes. Pathology was consistent with malignant paraganglioma with negative lymph nodes. Repeat Plasma Normetanephrines were 1.2 nmol/L.

Discussion: Catecholamine secreting Paragangliomas of head and neck are rare (3 percent). F-18-FDG PET scan is more sensitive then I-123MIBG scan (85 versus 52 percent) in diagnosing Paraganglioma of the neck.

FR-PO050

The Mysterious Polish Supplement: A Case Report of Cardiac Glycoside Poisoning with Lily of the Valley Extract

Payam Pourhassani, Christopher Richard Kern, Hasan Arif. *Internal Medicine, Drexel Univ College of Medicine, Philadelphia, PA.*

Introduction: The plant *convallaria majalis* (Lily of the Valley) contains multiple cardiac glycosides similar to those found in the pharmaceutical drug Digoxin, derived from the *digitalis lanata* (foxglove) plant. These plants are responsible for a number of cases of acute poisonings yearly. We report a case of cardiotoxicity, AKI, and hyperkalemia in an elderly female caused by the health supplement Cardiol-C, which contains Lily of the Valley extract.

Case Description: An 86-year-old Polish female with history of CAD and HTN presented to the ED with nausea, vomiting, and weakness for 5 days. While her cardiac medications were at first unknown, she admitted to a 3-month use of Cardiol-C. Her BP was as low as 64/32 and heart rate 42bpm. Initial EKG showed junctional bradycardia with old LBBB. Labs revealed potassium level of 7.2 mMol, creatinine 3.8 mg/dL (baseline unknown), bicarbonate of 17 mMol. She was given atropine and DigiFab with improvement of hemodynamics, symptoms, and EKG, and transferred to the ICU for monitoring of possible symptom recurrence secondary to xenobiotic redistribution. Her potassium normalized with temporizing measures, including intravenous fluids and diuretics; her discharge creatinine was 1.59 mg/dL.

Discussion: Although the degree of hyperkalemia correlates with cardiotoxicity in acute ingestion, special care was made not to lower the potassium drastically as hypokalemia can enhance the effect of cardiac glycosides. Our patient's glycoside-induced hyperkalemia was likely exacerbated by a prerenal AKI and her use of medications known to induce hyperkalemia. This case illustrates the importance of asking patients about over-the-counter (OTC) supplement use as there can be lethal consequences, most of which patients are unaware of. Cardiol-C also contains Hawthorn extract, which has been shown to interfere with digoxin immunoassay measurements and compete with Na+/K+ ATPase. Given the narrow therapeutic index of cardiac glycosides, extreme caution—if not complete avoidance—should be used with their non-standardized use as toxicity often occurs even with close monitoring.

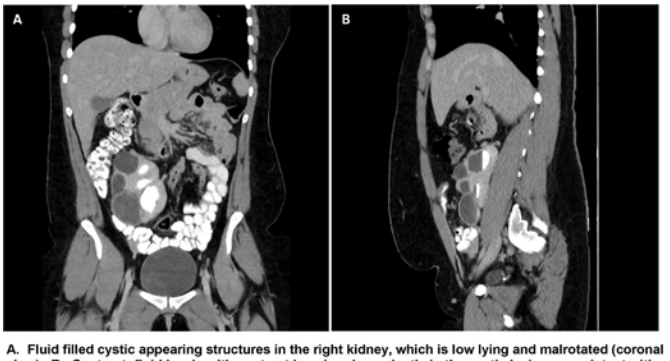
FR-PO051

An Unusual Case of Hypertension and Acute Kidney Injury during Pregnancy and Postpartum Course

Mahrukh Rizvi, Sai Subhodhini Reddy, Andrea Zynda-Weiss, Guan Wu, Wei Chen. *Univ of Rochester School of Medicine.*

Introduction: New onset hypertension (HTN) complicates 6-8% of pregnancies. Approximately 20% of women remain hypertensive beyond 3 months postpartum. We present an interesting case of new onset HTN and acute kidney injury (AKI) during pregnancy that persisted beyond 3 months postpartum.

Case Description: A 28 year old Hispanic woman with no significant past medical history was referred to Nephrology for persistent HTN and elevated creatinine (Cr 1.1mg/dL, baseline 0.7) 3 months postpartum. During the third trimester, she developed HTN with blood pressure (BP) in 140/90's (baseline BP 120/70's), proteinuria (~400 mg/day) and AKI with a peak Cr of 1.4 mg/dL. She was diagnosed with pre-eclampsia and induced at 38 weeks. Despite delivery, she continued to have HTN with a mean BP of 150/90's. This prompted work up for secondary HTN. Renal ultrasound showed bilateral renal cysts. Follow up CT scan and MRI revealed malrotated right pelvic kidney, bilateral ureteropelvic junction configurations with moderate to severe hydronephrosis and areas of cortical thinning.



A. Fluid filled cystic appearing structures in the right kidney, which is low lying and malrotated (coronal view). B. Contrast- fluid levels with contrast layering dependently in the cystic lesions consistent with contrast filling the dilated collecting system. Right kidney demonstrated slightly delayed enhancement compared to the left kidney (sagittal view). Both images were obtained 6 minutes after contrast administration.

She subsequently underwent right ureteral stent placement and pyeloplasty. Cr and BP remained stable after the surgical intervention.

Discussion: New onset HTN during pregnancy that persists >3-6 months postpartum warrants further evaluation. Our work up led to the unexpected diagnosis of significant congenital anomalies (bilateral ureteropelvic junction configurations and right pelvic kidney) requiring surgical intervention. The congenital anomalies, pre-existing hydronephrosis and

increasing fetal size (which could exacerbate the hydronephrosis) likely all contributed to the development of preeclampsia and AKI. Interestingly, the hydronephrosis was first thought to be renal cysts on ultrasound. This highlights the importance of pursuing further workup for multiple renal cysts in young individuals.

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FR-PO052

Canagliflozin (Invokana) Induced Ketoacidosis and Proximal Renal Tubular Acidosis in the Setting of Euglycemia following Sugery

Robert Fleyshman, Christopher Richard Kern, Hasan Arif. *Hahnemann Univ Hospital, Philadelphia, PA.*

Introduction: Canagliflozin, a selective sodium glucose cotransporter-2 (SGLT-2) inhibitor, works by blocking glucose reabsorption at the proximal tubule. Its most significant side effect is hypoglycemia. A rarer side effect in type 1 diabetics improperly labeled as type 2 diabetics is normoglycemic diabetic ketoacidosis. We present a case of canagliflozin-induced ketoacidosis and proximal renal tubular acidosis (RTA2) following surgery in the setting of euglycemia in a patient with type 2 diabetes mellitus (DM2).

Case Description: 55 year old female with past history of DM2 (diagnosed 4 years prior) and left breast cancer status post mastectomy was admitted for left breast reconstruction surgery. Her home medications included anastrozole, insulin glulisine and insulin detemir. Metformin and canagliflozin were added several weeks prior and last taken one day prior to surgery. On post-operative day 2, she was noted to have pH of 7.08, serum chloride 114 mmol/L, serum bicarbonate of 6 mmol/L, anion gap of 16, serum potassium of 3.2 mmol/L, serum calcium of 7.1 mg/dL, blood sugar of 155 mg/dL and normal lactic acid. After surgery, she reported nausea along with decreased appetite and oral intake. Elevated beta-hydroxybutyric acid on day 3 confirmed likely euglycemic DKA, accounting for her significant gap acidosis. Her abnormal delta ratio, revealing a concurrent non-gap acidosis, was thought to be secondary to a canagliflozin-induced RTA2, in the setting of glucosuria and abnormal urinary electrolytes. She was treated with IV bicarbonate and sliding scale insulin until her anion gap closed on post-operative day 5. Her hypokalemia, hypophosphatemia, and hypomagnesemia were treated with aggressive electrolyte repletion; each derangement normalized by post-operative day 7.

Discussion: Canagliflozin is approved for DM2. Most common side effects include genital mycotic infections and urinary tract infections. A rare, but significant side effect, is hypoglycemia when used with other diabetic medications. Our case illustrates a rare but serious side effect of ketoacidosis and RTA2 in the setting of euglycemia following surgery and decreased oral intake.

FR-PO053

Severe Metabolic Acidosis as a Complication of an Oral SGLT-2 Inhibitor

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Introduction: Sodium-Glucose Cotransporter 2 (SGLT-2) inhibitors, a novel class of anti-glycemics, work by inhibiting the SGLT-2 cotransporter in the proximal tubule, leading to significant glucosuria. There is also evidence that they increase insulin sensitivity and decrease gluconeogenesis. Canagliflavin was approved by the FDA in 2013 for Type II Diabetes Mellitus (DM), but is occasionally used as an off-label treatment for Type I DM as well.

Case Description: KR is a 40 year old lady with a past medical history of Diabetes Type I and hypertension who presented to the hospital with two days of nausea, vomiting, abdominal pain, and confusion. Blood glucose levels at home had not been elevated. Physical exam was remarkable for tachycardia, dry mucous membranes, and abdominal tenderness, but was otherwise unremarkable. Laboratory investigations revealed an arterial pH of 6.845, pCO2 of 25, bicarbonate of 3, anion gap of 28, glucose of 222, creatinine of 1.24 (from a baseline of 0.8), small ketones in the serum, and 3+ ketones on urinalysis. She was treated for Diabetic Ketoacidosis (DKA) with an insulin drip and fluid repletion. Creatinine peaked at 1.7, and then recovered to baseline over the course of one week. Upon further questioning, she was on an insulin pump for diabetic control, and also on Canagliflavin orally. Because her blood glucose levels were normal, she had not been receiving an adequate dose of subcutaneous insulin, which was thought to be the trigger of her DKA episode.

Discussion: This case illustrates the recently described phenomenon of euglycemic DKA in the setting of Canagliflavin use. This medication is currently only approved for use in type II DM, and caution must be exercised if used off-label in type I DM. In this case, the patient was not receiving an adequate amount of insulin because serum glucose levels were within normal limits, and developed DKA. Recognition of this disorder in the euglycemic patient is important in order to avoid delays in diagnosis and treatment.

FR-PO054

Lactic Acidosis: A Potential Complication of SGLT2 Inhibitors

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Introduction: SGLT2 inhibitors have been shown to improve glycemic control in patients with diabetes mellitus type 2 (DM2). These agents have been show to increase the risk of ketoacidosis, however lactic acidosis is not currently a known complication.

Case Description: JG is a 48 year old female referred to nephrology in April 2015 for further evaluation of CKD and metabolic acidosis. At that time she was taking Metformin and Invokana for DM2. She was advised to stop Metformin and sodium bicarbonate was started. Seven months later, she was noted to have worsening metabolic acidosis. She was taking the sodium bicarbonate; however she also continued the Metformin and Invokana. At this point she agreed to stop taking both medications. Repeat labs showed improved serum bicarbonate and normal lactic acid. Four months later, her endocrinologist restarted her Invokana due to poor glycemic control. Two months after Invokana was restarted, she developed worsening metabolic acidosis and lactic acid was elevated (see table). Although she was asymptomatic she was referred to the ED for further evaluation. Repeat labs showed persistent lactic acidosis. Workup for DKA, sepsis, and hypoperfusion was negative. Furthermore there was no clear cause of the lactic acidosis. Invokana was stopped and repeat labs showed that her lactic acid and serum bicarbonate had normalized.

Date:	Serum Bicarbonate (mmol/L)	Serum Cr (mg/dl)	Anion Gap	eGFR (ml/min/1.73m2)	Lactic Acid (mmol/L)	Medications	Changes
4/10/15	21	1.28	12	50	-	Metformin Invokana	NaHCO3 started
11/12/15	16	1.38	19	45	-	Metformin Invokana NaHCO3	Metformin/ Invokana stopped
11/25/15	22	1.27	15	50	1.3	NaHCO3	Invokana restarted
5/2/16	18	1.28	17	49	-	NaHCO3 Invokana	Labs repeated
5/12/16	16	1.62	20	37	4.2	NaHCO3 Invokana	Hospitalized, Invokana held
5/14/16	21	1.16	11	55	1.6	NaHCO3	Discharged, Invokana not restarted

Discussion: Although ketoacidosis has been reported as a potential complication of SGLT2 inhibitors, to our knowledge this is the first reported case of lactic acidosis secondary to Invokana. Clinicians should be aware of this potential complication among patients taking SGLT2 inhibitors.

FR-PO055

Oxymorphone Hydrochloride (Opana) Related Acute Kidney Injury with Lamellated Bodies in Podocytes

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Introduction: Opana (Oxymorphone hydrochloride) is a semi-synthetic oral opioid analgesic used for management of severe pain. While side effects of CNS, respiratory and GI depression are well known, acute kidney injury (AKI) is generally not expected.

Case Description: A 61yo white male presented with a two-month history of progressive peripheral edema and dyspnea. He had underling CKD stage III A, related to prolonged use of NSAID's. He had baseline creatinine of 1.6 mg/dl in the absence of proteinuria. He was abstinent from NSAID's for the last 2 years. On physical examination he had weight gain of 20 lb and +2 edema of LE extending to the abdominal wall. There was an acute rise in creatinine of 2.4 mg/dl. UA showed proteinuria 0.4 mg/gm without hematuria. Serological work up, evaluation of thyroid, liver and heart function was unremarkable. Review of the medications revealed recent modification of his pain regimen with substitution of extended release morphine (MS Contin) by Oxymorphone hydrochloride (Opana), occurring 4 months prior to presentation. Renal biopsy was performed. Electron microscopy showed presence of lamellated lipid containing curvilinear bodies in the cytoplasm of podocytes referred to as "myeloid or zebra bodies". Alpha galactosidase activity in serum was normal. Therefore, drug induced podocyte injury was suspected. Opana was discontinued, with resolution of edema and creatinine improvement to prior baseline.

Discussion: Opana has been described to cause thrombotic microangiopathy in the kidney. This case illustrates an unusual link between the use of Opana and development of AKI. Lamellated bodies in the podocytes were first described in Fabry's disease. Similar structures with curvilinear appearance have been later described in association with drug toxicity from Chloroquine, Hydroxychloroquine and Amiodarone but never associated with Opana. Importantly, discontinuation of Opana has led to resolution of edema and AKI. While renal complications from use of opioid analgesics are uncommon, awareness of this rare nephrotoxicity is important.

FR-PO056

Cola-Colored Urine and Acute kidney Injury after Type A Aortic Dissection Repair

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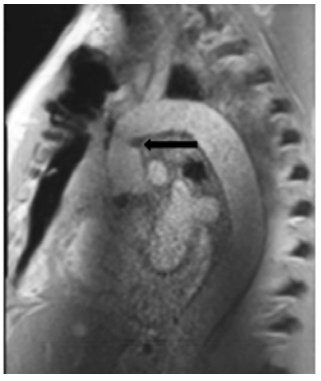
Introduction: Hemolysis after mechanical heart valve replacement is caused by trauma from shearing force on red blood cells (RBCs) resulting in release of RBC products and acute kidney injury (AKI). We report a case of hemolysis presenting with cola-colored and AKI nine days after surgical repair of type A aortic dissection.

Case Description: A 57 y/o man presented with fatigue, dyspnea, and cola-colored urine, nine days after repair of an aortic dissection with hemi-arch placement and re-suspenison of native aortic valve. UA color was black, with large prot, large bld, 70 RBCs. Urine p/c ratio 1.48 g/g, Hgb 5 g/dL and serum creatinine (SCr) 2.4 from 1.1 mg/dL post-operatively. LDH 3,116 U/L, myoglobin 207 ng/mL, CPK 960 U/L, reticulocytes 7.26%, unconjugated bili 2.1 mg/dL, haptoglobin < 4, normal G6PD, ADAMTS13, ANA, ANCA, C3, C4. He received RBC transfusions without improvement in his Hgb. MRI showed focal kinking of the ascending aortic graft with resultant turbulent jet (see Figure).



His SCr increased to 4.1 mg/dL despite therapy with IV fluids and metoprolol. He was taken back to surgery and found to have a portion of the aortic hemashield graft wrapped around the distal aorta. The mean gradient pressures decreased by 50% after surgical release of the wrap graft. Intraoperatively, within minutes of the revision, urine color turned from black to amber and six hours later, was yellow. In the ensuing days, hemolysis resolved and his SCr improved to 1.9 mg/dL.

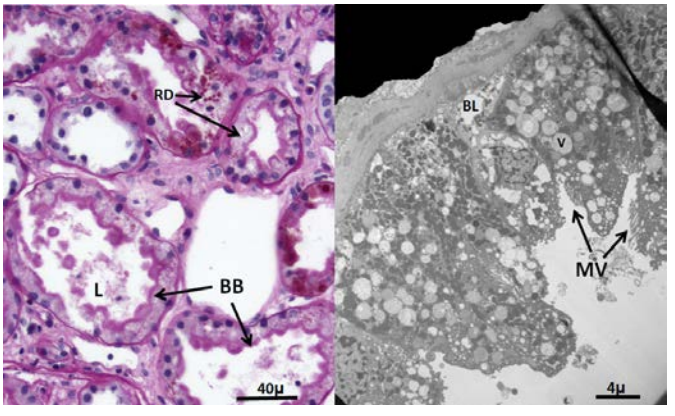
Discussion: We present a patient with hemolysis and AKI after repair of an aortic dissection due to focal kinking of the ascending aortic graft causing a turbulent blood flow. Hemolysis improved and dialysis was avoided after surgical repair.

FR-PO057

Alirocumab (Praluent) Induced Renal Injury: A Novel Side Effect of a Novel Drug Valerie Suzanne Barta,[1] Kenar D. Jhaveri,[1] James M. Pullman.[2] *[1]Nephrology and Hypertension, NorthShore-LIJ Health System, Great Neck, NY; [2]Pathology, Montefiore Medical Center, Bronx, NY.*

Introduction: We report the first case of biopsy-proven acute tubular injury (ATN) associated with alirocumab, a monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9), shown to be a valuable treatment of hypercholesterolemia.

Case Description: A 62 year old AA woman recently started on alirocumab 75 MG/ML SQ every 2 weeks. Medications included aspirin, metoprolol succinate, rosuvastatin, doxazosin, clopidogrel and ramipril. 2 weeks later her creatinine rose to 5 mg/dl from baseline 2.3mg/dl and continued to rise despite holding ramipril. Kidney biopsy on light microscopy (LM) showed ATN in a background of chronic hypertensive nephropathy with secondary FSGS. Electron microscopy (EM) confirmed tubular injury, with features of toxicity.



Proximal tubule injury. Left, LM: sloughing of necrotic proximal tubule epithelial cells into the lumen (L), absorption droplets (RD), degeneration of brush border (BB). PAS stain 20X. Right, EM: proximal tubule with only residual brush border microvilli (MV) and basolateral processes (BL), numerous cytoplasmic vacuoles (V). 2700X.

Discussion: The clinical picture, pathology and time course of ATN coincided with alirocumab as the cause, and renal function returned to baseline 1 month following cessation of this agent. A mechanism of alirocumab-induced ATN may be suppression of the PCSK9 overexpression in the kidney that occurs during inflammation, likely a cellular protective response to injury. CKD may be an additional risk factor. Of note, ATN was also documented as an effect of SPC5001, an antisense oligonucleotide which interferes with PCSK9 expression. Internists, cardiologists and nephrologists need to be aware of ATN as a potential side effect of alirocumab, and possibly other drugs that downregulate PCSK9 expression.

FR-PO058

Combined Anti-CTLA-4 and Anti-PD1 Immunotherapy Induced AIN Valerie Suzanne Barta,[1] Nupur N. Uppal,[1] Rimda Wanchoo,[1] James M. Pullman,[2] Kenar D. Jhaveri.[1] *[1]Nephrology, Hofstra Northwell School of Medicine; [2]Pathology, Montefiore Medical Center.*

Introduction: Both anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-program death 1 (PD-1) have been used more frequently to combat an increasing variety of cancers. Their nephrotoxic side effects are only recently being discovered. We present a case of acute interstitial nephritis (AIN) caused by combined treatment of nivolumab and ipilimumab.

Case Description: A 62 year old male with metastatic melanoma was started on nivolumab 5 months prior to consultation for acute kidney injury (AKI). He experienced arthritis and dermatitis as side effect treated and resolved with course of prednisone. His baseline creatinine (SCr) was 1.2 mg/dL throughout treatment. Within 2 weeks of starting combination therapy with addition of ipilimumab, Cr rose to 1.6mg/dL and absolute eosinophils (AEC) went from 0 to 0.9 K/uL. There were no other new medications started in this time and no exposure to contrast or other nephrotoxins aside from occasional use of NSAIDS in the past. Urine eosinophils were positive and serological work up for AKI was negative. SCr and eosinophil increases coincided temporally post infusions of combined immunotherapy. SCr peaked at 1.8 mg/dL. A kidney biopsy confirmed moderate interstitial fibrosis and tubular atrophy with focal chronic inflammation and eosinophils suggestive of chronic interstitial nephritis. Both agents were held after third cycle secondary to AIN and prednisone 1mg/kg was initiated. SCr decreased to 1.38 mg/dL and AEC back down to 0 K/uL. Currently, the patient's cancer is not progressing.

Discussion: Immune checkpoint inhibitors such as nivolumab and ipilimumab are known to cause AIN. Their combined use seems to confer an increased risk. Only one prior case exists of combined therapy leading to AIN in a native kidney. AIN appears to be related to an immune response to the kidney. It is essential for nephrologists and oncologists to understand this risk. Frequent monitoring of Scr during treatment and swift referral to nephrology for AKI can aid in early diagnosis of this newly recognized side effect and early initiation of treatment to prevent continued renal damage in these patients.

FR-PO059

Cytokine Storm and T-Cell Dysregulation Drives Acute Tubular Necrosis and Glomerular Disease in an SLE Patient with Hemophagocytic Lymphohistiocytosis (HLH) Ashish Gummadi, Iris J. Lee, Swati Rao, Kamel Hatahet, Xu Zeng, Duncan B. Johnstone. *Nephrology, Temple Univ Hospital, Philadelphia, PA.*

Introduction: HLH is a rare condition of dysregulated activation of the innate immune system and abnormal T-cell function that can result in multi-organ failure and death. Renal involvement in HLH is not well characterized, but few cases report findings of acute tubular necrosis (ATN) and variable podocyte injury. Diffuse podocyte effacement and collapsing glomerulopathy have been described. We report a case of HLH in a woman with systemic lupus erythematous (SLE) who presented with nephrotic range proteinuria and acute kidney injury (AKI).

Case Description: A 57 year old Caucasian female with history of hepatitis C cirrhosis was admitted to hospital for fever and placed on broad spectrum antibiotics. An extensive work up for infection was negative. The patient had a non-blanching erythematous macular rash, pancytopenia, splenomegaly, mental status changes and continued fevers. Peripheral smear and bone marrow biopsy were non-diagnostic. Ferritin levels >7500ng/ml, prompted consideration of HLH. Clinical findings and levels of soluble IL-2 Receptor (5295U/ml), later confirmed HLH. Treatment was started with steroids, IVIG and Etoposide. Inflammatory markers, CRP and Ferritin improved, but patient then developed AKI and nephrotic range proteinuria (5 grams) with microscopic hematuria. Serologies were positive for ANA (1:160), P-ANCA (1:80), and low complements. Renal biopsy confirmed a diagnosis of SLE, but only demonstrated class II lupus nephritis. A severe nephrotoxic ATN was seen on biopsy.

Discussion: We found both features of ATN and nephrotic range proteinuria in our patient with SLE and HLH. Our patient unexpectedly showed minimal glomerular damage related to SLE, as we only found class II lupus nephritis, which uncommonly presents with severe nephrotic range proteinuria. It has been proposed that in HLH, a soluble factor, and/or yet to be identified cytokine or lymphokine may contribute to podocyte damage and modifications resulting in nephrotic range proteinuria which was present in our patient.

FR-PO060

Severe Cisplatin Induced Renal Salt Wasting Pavani Reddy,[1] Ashvin Kamath,[1] Golriz Jafari,[1] Phuong-Thu T. Pham,[2] Phuong-Chi T. Pham.[1] *[1]OVMC; [2]UCLA.*

Introduction: Cisplatin is known to induce Fanconi syndrome and renal salt wasting (RSW). RSW typically only requires transient normal saline (NS) support. We report a severe RSW case that required >12L of 3% saline.

Case Description: A 57-year old woman with limited stage small cell cancer was admitted for cisplatin (80 mg/m^2) on day 1, and etoposide (100 mg/m^2) daily, day 1, 2, and 3 . On day 3, patient's serum sodium (SNa) decreased from 133 to 125 within 24 hours. A diagnosis of syndrome of inappropriate antidiuretic hormone secretion was made. Urine studies revealed osmolality (Uosm) 693 mosm/kg, UNa 205 mEq/L, and potassium (UK) 40 mEq/L. While plan for strict free H_2O restriction was being placed, patient's SNa fell to 119 within 5 hours in association with acute onset of headaches, nausea, and dizziness. Given the rapid fall in SNa and rapid onset of neurological symptoms, 3% saline (3%S) was initiated to raise SNa by 5%. Despite the initial 3%S infusion, her SNa continued to

decrease in association with increasingly high volume of hypertonic urine (average 100-150 mL/h, up to 600 mL/h of urine with UNa+UK up to 265+73 mEq/L respectively). Higher 3%S infusion rates up to 1400 mL/day were required to maintain SNa at 135. Empirical fludrocortisone 0.1 mg bid did not ameliorate the natriuresis. Thyroid stimulating hormone was 1.5 mIU/L. Studies to evaluate for Fanconi syndrome revealed glucosuria up to 70 mg/dL in the absence of serum hyperglycemia and hypophosphatemia at 2.7 mg/dL (baseline phosphorus level was 4 mg/dL). The natriuresis slowed down by 2.5 weeks, but 3%S support was continued for a total volume of 12L over 3.5 weeks. Patient was eventually discharged on NaCl 2g bid. During the natriuretic phase, other attempts to slow down her glomerular filtration included ibuprofen 200 mg tid and benazepril 10 mg bid.

Discussion: Fanconi syndrome and RSW have been reported with cisplatin. Our data were consistent with both conditions following a one time use of cisplatin. To our knowledge, this is the most severe case of RSW ever reported with cisplatin. With the exception of 1 case where 3%S was required for 3 days, all other reported cases only required NS infusion. Our patient required over 12L of 3%S over a prolonged course of 3.5 weeks.

FR-PO061

A Rare Case of Harvoni (Ledipasvir with Sofosbuvir) Induced Acute Interstitial Nephritis Dilek Yarar,[1] Jean Luc Franck,[1] John J. Doran,[1] Carla L. Ellis.[2] *[1]Nephrology Dept, Grady Memorial Hospital, Atlanta, GA; [2]Renal Pathology Dept, Emory Univ, Atlanta, GA.*

Introduction: Harvoni is a novel agent approved by the FDA for the treatment of hepatitis C infection. Scant data concerning Harvoni and its nephrotoxicity profile are available; we report a case of biopsy proven acute interstitial nephritis (AIN) associated with Harvoni.

Case Description: A 62-year-old female with hypertension, insulin dependent diabetes mellitus, chronic liver disease secondary to hepatitis C infection and chronic kidney disease stage 3 was admitted to Grady Memorial Hospital due to a recent rise in her serum creatinine level. Beside starting on Harvoni four weeks prior to presentation, the patient denied other changes in her medications which included insulin, amlodipine, hydralazine and losartan. She denied use of non-steroidal anti-inflammatory agents or herbal products. Her physical examination was only remarkable for a bilateral lower extremity pitting edema. Admission labs were notable for a creatinine level of 2.5 from a baseline of 1.7. Urine sediment analysis showed presence of white blood cells casts. Those findings prompted a renal biopsy which was performed. Histopathological findings showed mild to focally moderate acute interstitial nephritis with focally increased interstitial eosinophils and neutrophils and evidence of diabetic nephropathy. The decision to hold Harvoni was made, and on follow up the patient had near complete resolution of her acute kidney injury with her creatinine almost back to baseline.

Discussion: Harvoni is a novel medication for the treatment of chronic hepatitis C infection. To our knowledge this is the second case of biopsy-proven AIN induced by Harvoni reported. This case emphasizes the need for nephrologists and hepatologists to be aware of this potential side effect of Harvoni.

FR-PO062

Bile Acid Nephropathy Successfully Treated with Plasmapheresis Sam Kant,[1] Orla M. Crosbie,[2] Syed Akbar Zulquernain,[2] Liam Plant.[1] *[1]Dept of Renal Medicine, Cork Univ Hospital, Cork, Ireland; [2]Dept of Gastroenterology, Cork Univ Hospital, Cork, Ireland.*

Introduction: Anabolic steroids are well documented to cause cholestatic jaundice. With the institution of supportive care, predominantly withdrawal of offending agent, recovery usually ensues. Concomitant acute kidney injury secondary to bile acid nephropathy, is increasingly being recognised in this cohort of patients.

Case Description: A 44 year old man presented with severe jaundice and pruritis. He had been consuming testosterone enthanate and oxymetholone for the past 12 weeks. Of note, his sister has a history of end stage liver disease, on the waiting list for a liver transplant, and 8 first degree relatives (including a 15 year old daughter) have a history of cholecystectomy. On admission, bilirubin was 513 umol/L and creatinine 113 umol/L. Subsequent Magnetic Resonance Cholangipancreatography did not reveal any biliary duct pathology, along with negative viral, autoimmune and hereditary liver disease screens. Liver biopsy demonstrated severe cholestasis with neutrophilic infiltrate around bile ducts and central veins. Concomitantly, creatinine worsened and in the absence of clear etiology, a renal biopsy was performed, which demonstrated evidence of tubular injury with bile acid casts in the distal tubules. In light of progressive worsening of bilirubin, pruritis and renal function(creatinine peaking at 650 umol/L)- plasmapheresis was initiatated. He underwent 7 cycles , which led to a progressive improvement in the bilirubin and creatinine levels and offsetting the need for dialysis.

Discussion: Anecdotal evidence exists that plasmapheresis help reduce bile acid-associated pruritis, and a recent case report, demonstrated success in a very similar setting of bile acid nephropathy. With respect to our patient, sustained improvement in overall clinical status was noted post plasmapheresis. A hypothesis for a genetic bile transporter defect, considering family history, is being entertained. This case highlights that plasmapheresis can be an effective treatment to arrest acute kidney injury secondary to bile acid nephropathy, which in turn emanates from cholestatic jaundice, especially in a population that consumes predisposing agents.

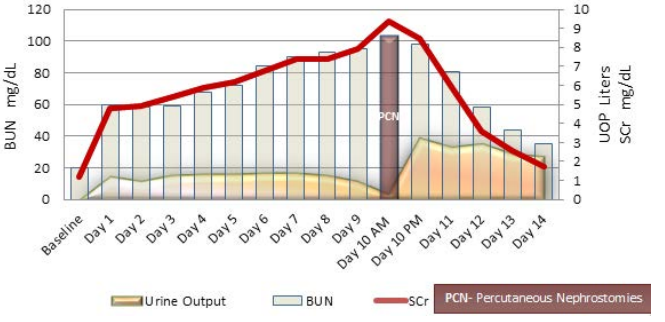
FR-PO063

Progressive AKI after Relief of Urinary Tract Obstruction Volodymyr Chornyy, Muna T. Canales. *Nephrology, Hypertension and Renal Transplantation, Univ of Florida, Gainesville, FL.*

Introduction: Urine output (UOP) is not a good indicator of urinary tract obstruction (UTO) as damage to the kidney may occur in the presence of only partial obstruction. Herein we present a case of partially relieved UTO with adequate UOP which progressed over days to complete renal failure.

Case Description: An 82 year old man with history of CKD stage 3 and chronic urinary retention due to enlarged prostate requiring clean intermittent self-catheterizations (CISC) presented with generalized weakness & 20 lbs unintentional weight loss over 6 months. He was able to void naturally 3-4 x/day & while being busy on his farm, decreased the number of CISC. He presented with elevated serum creatinine (SCr) of 4.8 mg/dL from baseline of 1.2 mg/dL 6 months prior. Ultrasound demonstrated severe bilateral (b/l) hydroureteronephrosis. Upon decompression with Foley catheter, 1500 cc of urine was evacuated. Given history of non-adherence with CISC, post-obstructive uropathy was diagnosed & recovery was anticipated. However, despite urinary output (UOP) of ~1500 cc/day, his renal function continued to deteriorate

Figure 1. SCr and Urine Output Trend



All work-up for intrinsic causes of AKI was negative. Within 10 days, he developed uremic symptoms, his urine output decreased. Urology (GU) attempted retrograde ureterograms which revealed obstruction at the level of b/l ureteral orifices. After placement of b/l percutaneous nephrostomy tubes, immediate post obstructive diuresis ensued with steady recovery of renal function. Follow-up GU evaluation revealed high grade prostate cancer infiltrating both ureteral orifices.

Discussion: We report the evolution from partial UTO with satisfactory UOP to complete UTO over 2 weeks. To avoid irreversible renal damage, physicians should have a high index of suspicion for ongoing partial UTO in the setting of progressive renal failure despite apparent decompression of UTO.

FR-PO064

Candida Glabrata Pyelonephritis Leading to Bilateral Renal Papillary Necrosis and End Stage Renal Disease Katherine Akers, Beatrice P. Concepcion, Julia Lewis. *Vanderbilt Univ Medical Center.*

Introduction: Candiduria often represents contamination or colonization in otherwise healthy individuals. However, *Candida spp.* can cause severe, invasive infections of the urinary tract. We present a case of invasive *C. glabrata* pyelonephritis that led to bilateral renal papillary necrosis and ESRD in a diabetic.

Case Description: 57/F with DM I, HTN, CAD, nephrolithiasis presented in 5/2010 with irritative voiding symptoms and sterile pyuria despite several courses of empiric antibiotics. Urine culture ultimately grew *C. glabrata*. She developed ARF and hydronephrosis which did not resolve despite ureteral stenting and Voriconazole. She had multiple hospitalizations for *C. glabrata* pyelonephritis with repeated episodes of acute on CKD and initiated dialysis 1/2012. Patient was admitted in 5/2012 with another episode of *C. glabrata* pyelonephritis. CT showed bilateral hydronephrosis, pyelonephritis, papillary necrosis, and a fungus ball in the renal collecting system. Patient was treated with Amphotericin and Flucytosine, and maintained on high dose Fluconazole for suppressive treatment. Cystoureteroscopy from 10/2012 showed necrotic debris containing degenerating fungal forms. Due to persistent flank pain and low grade fever, she underwent staged bilateral nephrectomies. Pathology showed caseating granulomas with associated degenerating fungal forms and necroinflammatory debris within the right collecting system. PCR of fungal forms was consistent with *C. glabrata* but cultures remained negative.

Discussion: Patients with genitourinary abnormalities, instrumentation of the urinary tract, diabetes, and immunosuppression are at increased risk for invasive fungal urinary tract infections. Fungal infections should be on the differential for recurrent or persistent UTI symptoms despite antibiotic treatment or in the setting of "sterile pyuria." While fungal species can grow from bacterial urine cultures, the sensitivity for detecting fungal UTIs is higher with urine fungal cultures. Particularly in high risk patients, fungal UTIs should be taken seriously; if not treated in a timely manner they can become invasive, difficult to treat, and can lead to serious complications including papillary necrosis and ESRD.

FR-PO065

Estimation of Renal Function in Patients with Acute Kidney Injury or Chronic Kidney Disease Who Are Receiving Dolutegravir Hafiz Ali Sroya, Faisal Anwar, Christos Argyropoulos. *UNM School of Medicine.*

Introduction: Dolutegravir (DTG) is integrase inhibitor used for the treatment of HIV infection. Data suggests that DTG increases serum creatininine by inhibiting organic cation transporter 2, which is responsible for tubular secretion of creatinine. It has been shown that DTG can decrease creatinine clearance (CrCl) by 14% in healthy individuals. However in patients with impaired renal function (either AKI or CKD), the effect of DTG on CrCl is likely to be quantitatively more important, as tubular secretion contributes significantly in CrCl under these conditions. Measuring CrCl and using eGFR equations in this situation may significantly underestimate the GFR that can adversely affect the patient's management. We present a case that illustrates these points.

Case Description: A 57 YO female with HIV/AIDS and CKD3bA3 was admitted with non-oliguric AKI on CKD. Her HIV/AIDS was controlled since diagnosis on a regimen of Tribild (cobicistat/elvitegravir/emtricitabine/tenofov) with most recent CD4 count 393 and viral load <20. A native kidney biopsy was consistent with ATN and mild tubular atrophy. She was started on hemodialysis due to worsening metabolic acidosis, uremia and hyperkalemia. Stribild was discontinued and a regimen of Abacavir, Lamivudine & Dolutegravir was started. She remained dialysis dependent with no signs of renal recovery based on pre & post dialysis creatinine levels. Her eGFR calculated by MDRD equation was consistently <2ml/min and 24h urine CrCl that was 1ml/min. We measured serum Cystatin C level (3.4 mg/l) and did eGFR calculations using CKD Epi, CKD Epi Cystatin C, CKD Epi Cys-Cr equations with eGFR 7, 14 and 10ml/min respectively. Finally, we did NM GFR measurement using Tc-99m DTPA that was 22 ml/min/1.73sq-m. We stopped dialysis and patient remained stable for 2 weeks but her recovery was complicated by another episode of AKI necessitating initiation of dialysis.

Discussion: Dolutegravir's effect on CrCl is probably more pronounced in patient with low eGFR. GFR should be calculated using compounds that are freely filtered, not secreted or reabsorbed instead of eGFR or CrCl for correct estimation of renal function in patients with AKI or CKD receiving dolutegravir.

FR-PO066

Gemcitabine Associated Interstitial Nephritis Maryam Gondal,[1] Namrata Krishnan.[2] *[1]Nephrology, Yale New Haven Hospital, New Haven, CT; [2]Nephrology, VA, West Haven, CT.*

Introduction: Gemcitabine is widely used as a first line chemotherapeutic agent for various solid organ malignancies. Nephrotoxicity with this agent is rare and typically presents as hemolytic uremic syndrome (HUS). Acute interstitial nephritis (AIN) has not been previously reported with its use. We describe a case of gemcitabine induced AIN.

Case Description: A 69 year old male diagnosed with pleomorphic rhabdomyosarcoma of the neck and left supraclavicular fossa with osseous metastases was started on Adriamycin/ifosfamide and Mesna for treatment. He developed severe biopsy proven acute tubular injury(ATI) and acquired fanconi syndrome related to ifosfamide use within 3 months of starting treatment. Ifosfamide was stopped and patient was switched to gemcitabine for further therapy of his sarcoma. After receiving 3 cycles of gemcitabine, he was found to have evidence of further acute kidney injury (creatinine rose from 2.9mg/dl to 5.9mg/dl) associated with the development of a morbilliform, diffuse, skin rash. Urine sediment was noted to be bland. Renal US showed mild stable bilateral hydronephrosis secondary to mild benign prostatic hyperplasia. No evidence of HUS was found. Renal biopsy revealed areas of robust acute and chronic interstitial nephritis with a mixed infiltrate (neutrophils/ lymphocytes/ eosinophils) along with persistent severe ATI from previous ifosfamide exposure. Patient was diagnosed with a gemcitabine induced AIN. He was pulsed with IV solumedrol and transitioned to a 3 month oral prednisone taper. His creatinine improved down to 2.9mg/dl-3.1 mg/dl after completion of therapy.

Gemcitabine was approved in early 1990's and is included among first-line treatments in some adjuvant and palliative settings for non–small cell lung, ovarian, breast, and pancreatic cancers. It is generally well tolerated with minimal complications. It causes rare nephrotoxicity typically manifested as a hemolytic uremic syndrome (incidence 0.015–1.4%). To our knowledge, our case is the first reported in the literature of gemcitabine induced AIN.

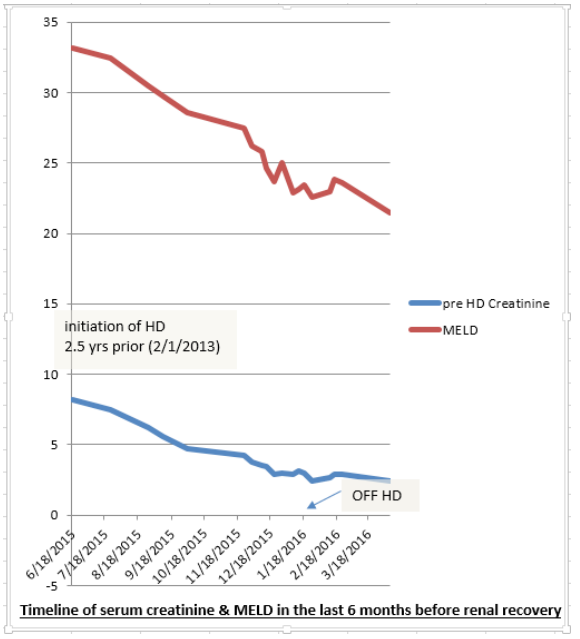
Discussion: Interstitial Nephritis should be considered in the differential diagnosis of patients with acute kidney injury on Gemcitabine therapy.

FR-PO067

Kidney Recovery after Three Years of Dialysis for Hepatorenal Syndrome Type I Louisette Soussan, Sandeep Aggarwal, Gregory Malat, Ellie Kelepouris, Alden Michael Doyle. *Transplant Nephrology, Drexel Univ College of Medicine.*

Introduction: Kidney recovery from Hepatorenal Syndrome (HRS) type 1 that requires dialysis is unusual but is sometimes possible with the combination of albumin, octreotide and midodrine; terlipreressin, or norepinephrine. HRS is generally felt to be irreversible after 8 weeks of dialysis therapy is required but has occasionally been described after months of dialysis in the setting of successful liver transplantation. Here, we describe a case of kidney recovery after 3 years of dialysis without transplantation.

Case Description: Patient is a 51 y/o M with a history of alcoholic cirrhosis, hepatic encephalopathy, esophageal varices, portal hypertension, and ascites requiring paracentesis, who presented with decompensated liver failure. Patient had a MELD score of 42, woresening jaundice, ascites, thrombocytopenia, coagulopathy, hyponatremia and AKI. He was oligoanuric with a serum creatinine of 9 mg/dL, low urine sodium, bland UA and a normal kidney USG. Patient was diagnosed and treated for HRS type I with albumin, octreotide, and midodrine. Despite therapy, patient remained oliguric and required dialysis. Patient was listed for simultaneous liver and kidney transplant and was discharged to our outpatient dialysis unit where he remained stable but virtually anuric. Over the next 3 years, patient was abstinent from alcohol and had slow but steady improvement in liver function and decreased MELD score.



Timeline of serum creatinine & MELD in the last 6 months before renal recovery

Patient started to make more urine and was given a trial off dialysis. Patient now has stage IIIB CKD with a 24-hour creatinine clearance of 34 mL/min with appropriate metabolic changes.

Discussion: Late recovery of severe kidney injury is possible after HRS type I. In this era of rapidly expanding options for direct acting anti-viral therapies, nephrologists should be aware of this possibility in patients whose MELD scores are improving while on dialysis.

FR-PO068

Rare Cause of Granulomatous Acute Interstitial Nephritis Ankita Tandon,[1] Jaya Kala,[1] Amit Lahoti,[2] Ala Abudayyeh.[2] *[1]Div of Renal Disease and Hypertension, UT Health Science Center at Houston-McGovern Medical School, Houston, TX; [2]Section of Nephrology, UT-MD Anderson Cancer Center, Houston, TX.*

Introduction: With the emergence of new novel myeloma drugs, there has been increasing interest on their effects of the kidneys. We present a case of bortezomib induced granulomatous acute interstitial nephritis as a rare cause of acute kidney injury.

Case Description: A 73-year-old man with myeloma diagnosed three years ago presented with a creatinine of 1.8 mg/dl along with an increase in the light chain. Patient was started on bortezomib. A week later, he presented with nausea,vomiting and hematuria. His creatinine was 6.4 mg/dL, urine showed large blood, 300 protein, >100 WBC, >100 RBC and positive urine culture that he was treated for with ceftriaxone. Free kappa light chains were 10,964 mg/L. The kidney dysfunction was presumed to be due to myeloma kidney. He was started on hemodialysis due to persistent hyperkalemia. He was continued on bortezomib due to persistence of the untreated myeloma. Unclear etiology for AKI prompted kidney biopsy, which showed acute granulomatous tubulointerstitial nephritis with diffuse kappa light chain-dominant glomerular and tubular basement membrane highlighting. The patient was started on prednisone which did not help improve renal function. Patient remained on bortezomib while on dialysis and when completed his cycle, started urinating and came off dialysis within a week. Creatinine a month later is at 1.4 mg/dl.

Discussion: Bortezomib treatment is used extensively in patients with Multiple Myeloma, and in trials on patients with immunological diseases. However, there has been only one case report of Bortezomib induced acute interstitial nephritis with granulomas reported thus far. The patient was being treated for his C3 Glomerulonephritis. To the best of our knowledge, this is the second case of biopsy proven granulomatous acute interstitial nephritis secondary to bortezomib. A high index of suspicion is necessary to recognize this as there are multiple etiologies of acute kidney injury in multiple myeloma. Discontinuation of the offending agent will be of utmost importance in the patient to keep them off potential need for renal replacement therapy.

FR-PO069

A Very Rare Case of HARVONI Causing Acute Tubular Necrosis
Rameen Hashemiyoon, Savneek S. Chugh, Rahul N. Pawar. *Nephrology, New York Medical College, Valhalla, NY.*

Introduction: With the approval of the newer agents, patient with hepatitis C virus (HCV) are now having an effective cure. One of these agents is HARVONI, a combination pill containing Ledipasvir and Sofosbuvir, an effective and more importantly an interferon free regimen. It was approved in 2014 for the treatment of hepatitis C genotype 1 virus infection with sustained virological response of more than 95%. Although there were no cases of Acute Kidney Injury (AKI) seen in the trial phase, lately some case reports of HARVONI induced AKI have surfaced. Recently, one case of Acute Interstitial Nephritis was published but we are reporting another unique case of Acute Tubular Necrosis mediated by HARVONI.

Case Description: 58 year old female with history of HCV on HARVONI, Hypertension and DM, presented to the ER with 5 days of dysphagia and odynophagia. She was subsequently found to be in AKI with serum creatinine (SCr.) of 11.06 and potassium of 7.2. She had no known history of kidney disease with baseline SCr. 0.9mg/dl. She was eventually started on hemodialysis. Urinalysis showed 1+ protein but no blood which on quantification was 625mg in 24 hours and negative for monoclonal pattern on immunofixation. Serum HCV quantitative was less than 15, cryoglobulins were negative, and C3, C4 were normal respectively. ANA was elevated at 63.3 yet double stranded DNA antibodies were negative. Her renal ultrasound showed normal size kidneys with no evidence ofhydronephrosis. She underwent percutaneous renal biopsy which revealed acute tubular injury associated with widespread oxalate deposits and very scant eosinophils. Eventually the patient was weaned off dialysis and discharged with SCr. of 2.5mg/dl.

Discussion: Our patient had a normal creatinine just a few months ago and the only new drug introduced to her was HARVONI, thus it is most likely caused the ATN and responsible for the AKI. It is a very effective medication and with its growing use, more and more of these cases are being discovered. We are reporting, to our knowledge, the first ever case of ATN caused by this agent. The exact mechanism is unclear and more studies should be done in pursuit of clearly identifying the renal adverse effects of this highly marketable drug.

FR-PO070

Worcestershire Sauce Induced Nephropathy: Case Report
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Introduction: Histopathology damage by Worcestershire sauce was unknown; however, the excessive use causes oxalate deposit. Acute oxalate nephropaty (AON) due Worcestershire sauce is a rare cause of kidney failure. It's secondary to calcium oxalate crystals deposits that induce chronic tubular damage, tubulointerstitial fibrosis and progressive kidney failure. A high load of oxalate, causes hyperoxaluria that increases the risk of nephrolitiasis and nephrocalcinosis; also, triggers like dehydration and/or metabolic acidosis, could cause acute kidney injury.

Case Description: 51-year-old latin american male, without past medical history, presented to the emergency room with a 2 week history of diarrhea, approximately 10 stools per day, with abdominal cramping during defecation. Blood Chemistry: Creatinine: 23.06 mg/dL, BUN: 117.5 mg/dL, Na: 134.8 mmol/L, K: 4.22 mmol/L, Cl: 96.8 mmol/L, Albumin: 3.47 g/dL, BUN/Cre: 5.09. Chest X-Ray: Bilateral pleural effusion of approximately 30%. 24-hour urine protein: 9820 mg. Urine protein/creatinine ratio: 12.27 g/g. Renal ultrasound: Normal size and anatomy. Acute hemodialysis treatment and later a kidney biopsy were performed: acute oxalate nephropaty and fibrosis grade 0. Directed inquiry approach, the patient reported consuming 400 ml of Worcestershire sauce per week. The patient received 8 hemodialysis sessions with partial renal recovery. Hospital's discharge with hemodialysis requirements during 1 month and high dose of piridoxine. In the follow up, the patient had renal recovery with creatinine leves of 1.49 mg/dL, without proteinuria. He was discharged from hemodialysis clinic with subsecuent follow up.

Discussion: Only 5 cases reported since 1971, 3 of them had bilateral nephrolithiasis and aminoaciduria; 1 had malignant hypertension and end-stage kidney disease; the remaining patient had mild to moderate kidney damage that reverted upon suspending the consumption of Worcestershire sauce. Although it is a rare cause of kidney failure, Worchestershire sauce induced nephropathy should be intentionally inquired if there isn't any other apparent cause.

FR-PO071

Acute Renal Failure, Aneurysm and Deep Vein Thrombosis - Connecting the Dots
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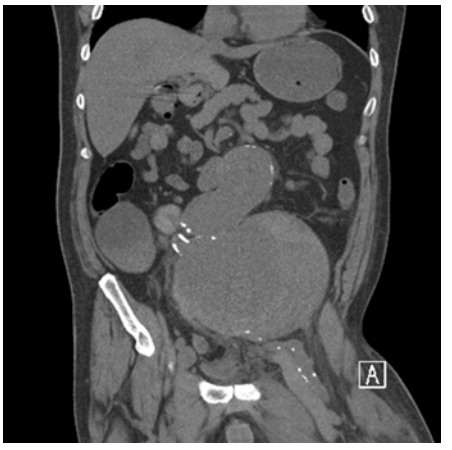
Introduction: Anuric Acute kidney injury (AKI) is uncommon but it can be seen with acute tubular necrosis, renal cortical necrosis and bladder outlet obstruction. Herein we report an unusual case of anuric AKI.

Case Description: A 62-yr-old man with a solitary left kidney, presented to the ER, with complaint of left thigh pain and anuria for 4 days . His past history included, R nephrectomy, HTN & CKD stage 3 with eGFR 53ml/min. On exam, BP was 165/110mmHg; with swelling and pain of left hip and thigh. Lab values were: K 6.5 meq/l, BUN 119mg/dl, Cr 13.1mg/dl. A Foley catheter insertion did not yield urine. The Patient was given insulin- D50, kayexalate & IV $NaHCO_3$. Renal US showed left kidney length of 16 cm, with moderate hydronephrosis. US duplex of left thigh veins showed DVT extending from left common femoral vein to the trifurcate veins. Nephrology consult recommended a non-contrast CT scan of the abdomen and pelvis, repeat doses of kayexalate, insulin-D50 & and $NaHCO_3$ IV drip The CT scan showed a ruptured left common iliac artery aneurysm(IAA), a large retroperitoneal hematoma (17.7 cm x 14.7 cm) and a bilobular infrarenal AAA of 5.8 cm", causing obstruction of the left ureter and DVT of the left femoral vein.



Emergent laparotomy confirmed a massive left IAA and thrombosis of the thigh veins. The patient underwent open repair of AAA and the left IAA with a bifurcated prosthesis along with placement of a ureteral stent. At 3-month follow-up, eGFR was 50ml/min suggesting a favorable outcome.

Discussion: Obstructive anuria from IAA (in a solitary kidney) is rare, with only 4 cases reported in the literature. Our case illustrates IAA should be considered in the differential diagnosis of anuric AKI. This case emphasizes the utility of CT scan of abdomen and pelvis as a diagnostic tool in the evaluation of anuric AKI.

FR-PO072

A Rare Cause of AKI in a Renal Allograft: A Case Report
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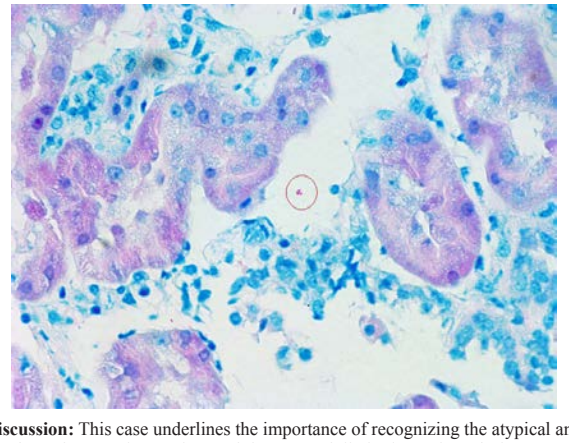
Introduction: AKI is common complication in renal transplant recipients. Differential diagnosis is broad and includes multiple infectious etiologies. However, it is rare for mycobacteria to infect the allograft and cause AKI. We present here the case of a renal transplant recipient who presented with an FUO and was diagnosed with disseminated MAC with renal allograft involvement.

Case Description: 50yo M ESRD 2/2 PCKD is s/p LURT (alemtuzumab induction,rapid steroid withdrawal,maintained on tacrolimus and mycophenolate). No history of acute rejection and his creatinine stabilized at 1.5. Twenty months post-transplant, he presented with 2wk of worsening fevers (99-103F in past 3 months) and dry cough. No weight loss, dyspnea, or GU symptoms. Routine blood work was notable for AKI (Cr 2.2),Chest CT with left paraortic mass and an enlarged retroperitoneal lymph node. Lymph node biopsy was positive for acid fast bacilli, NAAT testing neg for TB). Blood and urine cx were negative, IGRA indeterminate and Fungitell positive. He was started on azithromycin, ethambutol and rifampin. His Cr rose to 3. Renal allograft biopsy showed severe interstitial inflammation,lymphocytic tubulitis and rare acid fast bacilli identified on special stain. At this time MAC speciated from the lymph node biopsy. By hospital day 11, Cr decreased to 2.2. IVIg was given for treatment of possible concurrent allograft rejection. High grade fevers persisted throughout the 2wk admission. He was discharged on a 12mo course of Rifampin, Ethambutol, and Azithromycin. Cr was 1.8 upon discharge. Blood cultures sent on admission ultimately were positive for MAC. Three months after his initial presentation, he was clinically improved, with resolution of fevers. His Cr had decreased to 1.7.



Discussion: This case underlines the importance of recognizing the atypical and rare causes of AKI in a renal transplant recipient, especially in the setting of a known ongoing infection.

FR-PO073

Prolonged AKI Caused by Severe Rhabdomyolysis due to Genetic Disorder of Muscle ATP Metabolism Kilian Steden, Sahana R. Kamalanabhaiah, Joachim Hoyer. *Internal Medicine and Nephrology, Univ Marburg, Marburg, Hessen, Germany.*

Introduction: Carnitine Palmitoyltransferase (CPT) II deficiency is an autosomal recessive disorder characterized by a disruption of mitochondrial oxidation of long-chain fatty-acids, thus leading to an impaired ATP catabolism. First clinical symptoms of the myopathic form are observed in childhood and are characterized by weakness, exercise-induced muscular pain and myoglobunuria often triggered by fasting, lengthy muscular activity, viral infection or cold temperature.

Case Description: A 54 year old female physiotherapist returns from a skiing trip, complaining of pain in the proximal lower limbs as well as brown coloured urine. Laboratory reports showed an fulminant rhabdomyolysis (CK 235.000 U/l) accompanied by an acute kidney failure (serum creatinine 10,3 mg/dl). Treatment included alkalization of urine and volume management. As kidney function only slowly recovered, a more thorough evaluation of the underlying cause of rhabdomyolysis was performed. The patient did not report any trauma, chronic alcohol abuse, steroid medication or neoplasia. Serological testing ruled out autoimmune disorders. MR imaging showed disseminated muscular edema and signs of myositis. The muscle biopsy showed single fibre necrosis and type-II-fibre-hypotrophy with no signs indicating myositis or mitochondrial disease. We considered a genetic disorder. The patient reported of occasionally suffering from muscular pain since childhood. Testing for genetic myopathies revealed CPT II deficiency due to two heterozygous mutations in exon 1 and 3 of the CPT II gene. Over a prolonged time period of 5 weeks kidney function improved significantly with an almost normalized kidney function to this date (GFR 75 ml/min).

Discussion: Besides common causes for rhabdomyolysis such as trauma, arterial thrombosis, infections and autoimmune diseases, genetic disorders need to be considered in inconclusive or complex cases. CPT II deficiency is a rare disorder (currently 300 reported cases), but should be considered as differential diagnosis. Therapy includes strict low-fat diet high on carbohydrates in addition to oral intake of L-carnitine to prevent rhabdomyolysis and muscle pain.

FR-PO074

Hand2 Inhibits Kidney Specification while Promoting Vein Formation within the Posterior Mesoderm Elliot Perens. *Div of Biological Sciences and Dept of Pediatrics, Univ of California, San Diego, La Jolla, CA.*

Background: The kidneys and urinary tract are derived from the intermediate mesoderm (IM), yet the regulatory pathways that determine precise IM dimensions and that separate the IM from neighboring portions of the posterior mesoderm are poorly understood.

Methods: To study the genetics of early kidney development, we are using zebrafish. Like mammalian kidneys, zebrafish kidneys are derived from the IM, which expresses the same conserved transcription factors (such as *lim1* and *pax2*) as the mammalian IM. Using a combination of loss-of-function and gain-of-function analysis, we have sought to determine the role of *hand2* in IM development.

Results: We have found that the bHLH transcription factor Hand2 limits the size of the embryonic kidney by refining IM dimensions. In zebrafish *hand2* mutants, the IM is expanded, and it is diminished when *hand2* is overexpressed. *hand2* is expressed within the posterior mesoderm, laterally adjacent to the IM. A set of venous precursors arise at the interface between these two territories, and *hand2* promotes their development while suppressing IM formation in this region. Furthermore, Hand2 and the similarly localized zinc-finger transcription factor Osr1 have functionally antagonistic influences on pronephron formation.

Conclusions: Together, our data illuminate a previously unrecognized regulation of IM development and suggest a model in which *hand2* functions in opposition to *osr1* to balance the formation of IM and venous progenitors by regulating cell fate decisions in the posterior mesoderm. Our findings have implications for understanding the genetic basis of congenital anomalies of the kidney and urinary tract (CAKUT) and for developing new approaches in regenerative medicine.

Funding: Other U.S. Government Support, Private Foundation Support

FR-PO075

Heterozygosity for Six2 Increases Ureteric Branching and Final Nephron Number Alexander N. Combes,[1,2] Sean Wilson,[2] Belinda Phipson,[2] Brandon Binnie,[3] Ali Ju,[4] Cristina Cebrian Ligero,[5] Sarah L. Walton,[6] Karen M. Moritz,[6] Alicia Oshlack,[2] Melissa H. Little.[2,7] *[1]Anatomy and Neuroscience, Univ of Melbourne, Melbourne, Vic, Australia; [2]Murdoch Childrens Research Inst, Melbourne, Vic, Australia; [3]Inst for Molecular Bioscience, Univ of Queensland, Brisbane, Qld, Australia; [4]Translational Research Inst, Univ of Queensland, Brisbane, Qld, Australia; [5]Dept of Internal Medicine, Univ of Michigan, Michigan, MI; [6]School of Biomedical Sciences, The Univ of Queensland, Brisbane, Qld, Australia; [7]Dept of Paediatrics, Univ of Melbourne, Melbourne, Vic, Australia.*

Background: SIX2 is a transcription factor that regulates the maintenance of progenitor state within the cap mesenchyme (CM) during kidney development. Complete loss of *Six2* in mouse results in premature differentiation of the CM.

Methods: In this study, we examined kidney development in mice heterozygous for *Six2 (Six2*$^{GCE/+}$*)* using quantitative multiscale imaging and transcriptional profiling.

Results: *Six2* mRNA and SIX2 protein levels were reduced by 50% in the *Six2* Het. Surprisingly, these mice had an average of 18% more niches than wild-type mice from 15.5 dpc to postnatal day (P)2. Total glomerular number was also 18% higher. RNA-Seq of *Six2* Het kidneys revealed a decrease in genes associated with the uninduced CM state, including *Cited1*, *Crym*, and *Meox1*. Several renal vesicle-enriched genes, such as *Tcf23* and *Pcdh8,* were upregulated but there was no evidence of ectopic nephogenesis. *Six2* Het mice had increased CM and ureteric tip proliferation and upregulation of CM-expressed genes associated with proliferation and metabolism. Direct and dose-sensitive SIX2 targets were identified by further analysing transcriptional changes in CM from 11.5 dpc *Six2* KO and Het kidneys, with these genes showing high overlap with published SIX2 ChIP data.

Conclusions: In summary, this represents a rare example of a genetic change resulting in increased nephron number by subtly shifting the molecular regulation of proliferation and differentiation in the CM. It also suggests a dose-sensitive separation between the role of SIX2 in regulating CM proliferation and the maintenance of CM identity.

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FR-PO076

Increased Hedgehog Signaling in Renal Progenitors Disrupts Stromal Cell Development and Nephrogenesis Norman D. Rosenblum, Sepideh Sheybani-Deloui. *Div Neph, Dev and Stem Cell Biol, Depts Ped and Physiology, Hosp Sick Children, U Toronto, Toronto, Canada.*

Background: *Foxd1+* stromal cells are essential for renal development. Abnormal stroma is a signature feature of CAKUT. While *Foxd1+* stromal as well as *Six2+* nephrogenic cells both arise from *Osr1+* and their daughter *Sall1+* progenitor cells, the molecular mechanisms that control the specification and the relative proportion of *Foxd1+* and *Six2+* cells are undefined. Since renal injury causes Hedgehog (HH)-dependent proliferation of stoma-derived cells, we hypothesize that HH signaling controls specification of *Foxd1+* cells during embryogenesis.

Methods: HH signaling was activated in a temporal manner in vivo with Tamoxifen (TM) in mice expressing *Ptc1*^{loxP}and *Sall1-Cre*^{ERT2} or *Osr1-GFP-Cre*^{ERT2} alleles. Lineage tracing was performed using a *ROSA*^{tdTomato} allele. Cell proliferation was analyzed using Ki-67 and phospho-histone H3. *Osr1+GFP+* cells were purified from metanephric mesenchyme by FACS.

Results: TM injection at E9.5 in *Sall1-Cre*^{ERT2}*;ROSA*^{tdTomato} mice induced TOMATO expression in both SIX2+ nephrogenic and PBX1+ stromal cells. TM injection at E9.5 in *Sall1-Cre*^{ERT2}*;Ptc1*$^{loxP/-}$ mice decreased *Ptc1* mRNA by 50% and increased expression of the HH signaling reporter, *Ptc1-lacZ*, in situ. E14.5 mutant kidneys demonstrated a 78% increase in PBX1+ cells and ectopic expression of *Raldh2* in the medulla and presumptive ureteropelvic junction. Also at E14.5, PBX1+ cells associated with ureteric bud tips were mis-patterned and were increased in number by 20% (n=4, $p<0.05$). Proliferation of PBX1+ cells was not significantly changed. The number of NCAM+ nephron progenitor structures and WT1+ glomeruli was decreased by 28% and 20%, respectively (n=4, $p<0.01$). Yet, the number of SIX2+ cells was not significantly different than controls. In *Osr1+* cells isolated from metanephric mesenchyme of E11.5 *Osr1-Cre*^{ERT2}*;Ptc1*$^{loxP/-}$ mice injected with TM at E9.5, *Foxd1* mRNA was increased by 60% but *Six2* mRNA was unchanged compared to that in control *Osr1+* cells (n=5, $p<0.05$).

Conclusions: Increased HH signaling in renal progenitor cells increases generation of stromal cells, disrupts stromal patterning, and decreases nephron formation.

Funding: Government Support - Non-U.S.

FR-PO077

Bim Gene Dosage Is Critical in Modulating Nephron Progenitor Survival in the Absence of Dicer Activity Debora Malta C.S. Santos, Andrew J. Bodnar, Yu Leng Phua, Neil A. Hukriede, Jacqueline Ho. *Dept of Pediatrics, Children's Hospital of UPMC, Pittsburgh, PA.*

Background: Low nephron endowment has been implicated in an increased risk of hypertension and chronic kidney disease. We have previously reported that in *Six2-TGC*$^{Tg/+}$; *Dicer*$^{flx/flx}$ mutant kidneys, nephron progenitors lacking mature miRNAs undergo increased apoptosis, and express increased levels of the pro-apoptotic protein, Bim.

Methods: In this study, we investigated the functional significance of increased Bim expression in *Six2-TGC*$^{Tg/+}$; *Dicer*$^{flx/flx}$ mutant kidneys. To address this question, we generated a mouse model with conditional deletion of both *Dicer* and *Bim* from nephron progenitors in the developing kidney.

Results: While mutant kidneys exhibited a reduced number of nephron progenitors and developing nephron structures, the deletion of a single allele of *Bim* was sufficient to reduce the apoptotic rate of nephron progenitors and improve nephron formation. Next we used bioinformatics tools to identify potential binding sites for the nephron progenitor-enriched miRNAs, *miR-10a*, *miR-17*, *miR-24-1* and *miR-106b*, in the 3'-untranslated region (3'-UTR) of *Bim*. All four miRNAs negatively modulated the endogenous expression of Bim and the activity of a luciferase reporter containing the intact *Bim* 3'-UTR *in vitro*. Furthermore, *pri-mmu-miR-10a*, *pri-mmu-miR-17*, *pri-mmu-miR-24-1* and *pri-mmu-miR-106b* repressed EGFP expression in *Xenopus laevis* embryos injected with a synthetic mRNA containing the *EGFP* sequence fused to mouse *Bim 3'-UTR*.

Conclusions: Together these data suggest that the coordinated action of *miR-10a*, *miR-17*, *miR-24-1* and *miR-106b* sets a threshold of Bim expression, regulating the balance between apoptosis and survival in nephron progenitors.

Funding: NIDDK Support

FR-PO078

Temporal Down-Regulation of Spontaneous Calcium Activity in Metanephric Mesenchymal Cells Inhibits Branching Morphogenesis
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Background: Calcium signaling is of fundamental importance for the development of early vertebrates, but little is known about the role of calcium in mammalian embryogenesis.
Methods: We have used explanted kidneys from 14-day-old rat embryos cultured for 1 or 2 days to study calcium activity in metanephric mesenchymal (MM) cells, branching morphogenesis and synaptotagmin expression.
Results: We have recorded spontaneous calcium activity, characterized by stochastic calcium spikes of different amplitude and shape, in MM cells. This pattern of irregular calcium spikes is compatible with the calcium activity observed in cultured mesenchymal cells exposed to mechanical forces. Spontaneous activity was abolished following inhibition of the SERCA pump in the endoplasmic reticulum (ER) membrane, but remained intact during acute exposure of the kidney to calcium free medium. Partial depletion of ER calcium stores for 24 hours caused a temporal down-regulation of the spontaneous calcium activity. This resulted in deformation of ureter buds, significant reduction of ureter branching points and order and fewer newly formed renal vesicles. Proliferation of MM cells remained intact. We have hypothesized that metanephric spontaneous calcium activity is required for secretion of the morphogenic factors that mediate the reciprocal interaction between the MM cells and the ureter bud, a prerequisite for ureter branching morphogenesis and nephron formation. In support of this hypothesis we demonstrate expression of the calcium dependent excretory protein synaptotagmin 1 in MM cells.
Conclusions: This study has identified calcium as a novel indispensible link in the events involved in development of the mammalian kidney.
Funding: Government Support - Non-U.S.

FR-PO079

The Transcription Factor tfap2a Directs Progenitor Fate Decisions during Nephron Development
Brooke E. Chambers, Gary Gerlach, Rebecca A. Wingert. *Biological Sciences, Univ of Notre Dame, Notre Dame, IN.*

Background: Vertebrate kidney development consists of the differentiation and intricate patterning of specialized epithelial cells into discrete segments that form the nephron. However, the molecular and genetic pathways involved in cell fate decisions during nephrogenesis are poorly understood. The zebrafish provides a powerful, conserved system to discover developmental mechanisms driving nephron formation.
Methods: By performing a forward genetic screen and utilizing whole mount *in situ* hybridization to assess nephron segmentation, we isolated a mutant line with abrogated distal segment development. Whole genome sequencing revealed that the genetic lesion disrupted splicing of *transcription factor AP-2 alpha* (*tfap2a*), which has been described as essential for neural crest and epidermis differentiation, but was not known to be active during renal ontogeny.
Results: We found that *tfap2a* exhibits a dynamic expression pattern in renal progenitors, eventually restricting to the distal segments of developing nephrons. Deficiency of *tfap2a* recapitulated the mutant phenotype, and *tfap2a* mutants also failed to complement a previously characterized *tfap2a*^{m819} strain, which encodes a missense mutation that also disrupts transcript splicing. In addition to distal tubule defects, *tfap2a* abrogation was associated with a significant increase in multiciliated cells, which supports the hypothesis that *tfap2a* may mediate cell fate choice within the nephron. Taken together, these studies support a novel role for *tfap2a* in epithelial cell fate decisions during nephrogenesis. Interestingly, during mouse embryogenesis, *tfap2a* expression is abundant within the developing urogenital tract encompassing structures such as the ureteric tip, early tubule, and late tubule.
Conclusions: Thus, our continuing efforts to characterize the molecular activities of *tfap2a* in renal progenitors may uncover aspects of nephron formation that are relevant to human kidney development and disease states.
Funding: NIDDK Support

FR-PO080

Hopx-Expression Marks a Multipotent Progenitor Cell Pool during Kidney Development in Mice
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Background: The homeodomain-containing transcription factor Hopx has been recently identified as a marker of progenitor cells in a variety of embryonic and adult tissues, including the lung, skin, heart, brain, taste bud and gut. We sought to determine whether Hopx-expression marks a progenitor cell population during kidney development.
Methods: We used quantitative PCR and a Hop3xF-GFP reporter mouse to analyze the expression of Hopx during murine nephrogenesis. We used a Hop-Cre and a tamoxifen-inducible Hopx-ER-Cre line to fate map Hopx-derivatives during embryonic development.
Results: We found that Hopx is expressed in the metanephros as early as E13.5, with expression increasing through gestation and peaking postnatally at P7. At E13.5, Hopx-positive cells localize to the condensing metanephric mesenchyme and by E14.5, these cells expand in number and are surrounded by Wt1-positive podocyte precursor cells. Hopx-positive cells at E13.5 stain for mesenchymal markers, and these cells fate map to mesangial cells and the Renin-expressing cells of the juxtaglomerular apparatus - suggesting a common progenitor for these two cell populations. In the postnatal mouse, Hopx-expression is maintained in mesangial and Renin-positive cells, as well as in scattered proximal tubular cells and cells in the renal papilla; the latter two areas having previously been cited as potential stem cell niches in the adult.
Conclusions: Hopx-expression marks a progenitor cell pool during embryogenesis that gives rise to Renin-expressing cells in the JGA as well as intraglomerular mesangial cells. Hopx is also expressed in several putative stem cell niches in the postnatal murine kidney, an area which requires further investigation.
Funding: Other NIH Support - Analysis of a Novel Homeobox Gene in Cv Development

FR-PO081

mTORC1 Activity in Renal Progenitor Cells Is Correlated with Nephrogenesis and Kidney Size
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Background: Low nephron number is correlated with adverse health outcomes, including hypertension and chronic kidney disease in adulthood. mTORC1 complex is a member of the serine/threonine kinase family and is a central regulator of cell metabolism, growth, proliferation and survival. TSC1 is an inhibitor of the mTORC1 complex together with TSC2. Although mTORC1 has been shown to regulate stem cells of the hematopoietic system, its role in regulating stem cells in the kidney and nephrogeneis has not been defined.
Methods: Knockout of mTORC1 or TSC1 in progenitor cells in embryonic mice was achieved using Cre-LoxP technology. Six2-CREGFP:mTORC1$^{+/F}$ or Six2-CREGFP:TSC1$^{+/F}$ males were mated with mTORC1lox/lox or TSC1lox/lox respectively females to generate embryos carrying a homozygous deletion or CD1 females to generate heterozygous deletion. Kidney weight was measured relative to the body mass. Kidney morphology was evaluated and nephron counts were determined using acid digestion. In addition, kidney function was measured using serum urea at 5 to 6 months.
Results: Tissue specific deletion of mTOC1 in renal cell progenitors led to renal agenesis and severe dysplasia of the kidney, resulting in death a few days after birth. Analysis of mTOR+/F animals reduction in nephron endowment compared to control mice. Furthermore, kidney function in mTOR+/F animals was reduced as well. On the other hand, complete deletion of TSC1 led to significant increase in kidney size and their death few days of birth but apparently secondary to tubular injury. Heterozygous deletion of TSC1 led to significant nephromegaly compared to control type in addition to 50% increase in nephron numbers compared to controls. Kidney function in adult mice with heterozygous deletion of mTORC1 or TSC1 has decreased kidney function as measured by urea level.
Conclusions: Our results indicate that mTORC1 pathway plays an important role in kidney development, and mTORC1 is a significant regulator of nephrogenesis.
Funding: NIDDK Support

FR-PO082

PPAR Signaling Regulates Nephron Development
Joseph M. Chambers, Shahram Jevin Poureetezadi, Eric Donahue, Rebecca A. Wingert. *Biological Sciences, Univ of Notre Dame, Notre Dame, IN.*

Background: At present, the genetic and molecular mechanisms directing nephron segmentation during kidney development are not well understood. Embryonic zebrafish have a simplified kidney, the pronephros, comprised of proximal and distal segments that display conservation with mammalian nephrons, including humans.
Methods: Through a novel chemical genetic screen, we discovered that peroxisome proliferator-activated receptor (PPAR) signaling is essential for normal nephron segment development. PPARs are a group of nuclear receptor proteins that are activated by agonists such as fatty acids and act as transcription factors by heterodimerization with retinoid X receptor (RXR) to regulate cell differentiation and, in addition, have diverse roles in metabolism.
Results: We found that treatment with the PPAR agonist bezafibrate during nephrogensis resulted in a decreased length of the distal tubule while increasing the proximal straight tubule domain. Interestingly, the co-activator, *ppargc1a*, which binds to activated PPARs to regulate transcription of target genes, is expressed specifically in renal progenitors. To test the functional role of this co-activator during nephron segmentation, we knocked down *ppargc1a* and found deficiency reduced distal tubule formation. Next, we examined nephron development in ppargc1a^{sa13186} mutant zebrafish and found that the distal tubule was likewise abrogated.
Conclusions: Taken together, our studies reveal for the first time that PPAR activity is required for nephrogenesis. These findings may lead to a better understanding of the therapeutic value of PPARs in relation to the human kidney, as they have been shown to have renoprotective properties.
Funding: NIDDK Support

FR-PO083

Genetic Mechanisms of Multiciliated Cell Genesis during Renal Ontogeny
Amanda N. Marra, Shahram Jevin Poureetezadi, Rebecca A. Wingert. *Biological Sciences, Univ of Notre Dame, Notre Dame, IN.*

Background: The differentiation of multiciliated cells (MCCs) has become an increasingly attractive area of research because of their association with fluid flow and disease across tissues, including the kidney. There is evidence for a core, conserved pathway of MCC development that includes the Notch signaling pathway as an inhibitor to MCC fate.

Methods: The embryonic zebrafish kidney, or pronephros, has emerged as a useful tool to study MCC genesis, where the transcription factor *mecom* acts upstream of Notch to restrict MCC development while Retinoic Acid (RA) signaling promotes MCC fate by inhibiting *mecom* and promoting expression of the ETS transcription factor *etv5a*. Here, we report phenotype analysis of the *etv5a*^{sa16031} allele, which encodes a nonsense mutation in the ETS binding domain of *etv5a*.

Results: Embryos with one copy of this allele displayed a reduced number of MCCs, suggesting that *etv5a* is a haploinsufficient gene. Next, we found that *mecom* inhibits *etv5a* expression in the kidney, as knockdown of *mecom* caused an expansion of the *etv5a* domain. Further, we uncovered a novel role for prostaglandin (Pg) signaling in MCC development. Treatment with the Pg agonist PgE2 increased average MCC number in the pronephros, where inhibition of the Pg pathway via Indomethacin or concomitant knockdown of the Pg biosynthesis enzymes Cox1 and 2 reduced MCC number. Importantly, PgE2 treatment also increased the *etv5a* domain in the pronephros. Conversely, *mecom* expression was reduced after PgE2 treatment.

Conclusions: In conclusion, we have discovered a novel relationship between the Pg pathway, *etv5a*, and *mecom* during MCC genesis in the pronephros. Ongoing studies will further examine the epistatic relationship between these factors to illuminate the mechanism by which *etv5a*, *mecom*, and Pgs direct MCC development.

Funding: NIDDK Support, Other U.S. Government Support

FR-PO084

Multiciliated and Transporter Cell Fate Decisions Are Regulated by the Iroquois Transcription Factors irx2a/3b during Nephrogenesis Christina N. Cheng, Rebecca A. Wingert. *Biological Sciences, Univ of Notre Dame, Notre Dame, IN.*

Background: The genetic mechanisms that control cell fate decisions during kidney development remain poorly understood. The zebrafish pronephros provides a simplified yet genetically conserved model for renal ontogeny, being composed of segments with two major epithelial populations, transporter and multiciliated cells (MCCs). The expression of solute carriers within the transporter cells is used to demarcate distinct segments, and the MCCs are distributed in a "salt-and-pepper" fashion throughout the pronephros. Previous research in *Xenopus* revealed that *Iroquois (irx) homeobox 3* regulates tubule segment formation, whereas *irx1/2* were implicated to have redundant downstream functions during nephrogenesis. Furthermore, *irx3b*, the zebrafish paralog of *irx3,* was found to have conserved roles in proximodistal segmentation.

Methods: Here, we have used a combination of expression and functional studies to study the roles of *irx* genes during nephrogenesis.

Results: We report that *irx2a* and *irx3b* influence MCC fate as the loss of *irx2a* or *irx3b* resulted in decreased MCC density. Interestingly, the proximal straight tubule became expanded in *irx2a* or *irx3b* deficient embryos suggesting that these genes may help modulate the balance between MCC versus transporter cell lineages during kidney development. Our current work also implicates interplay between *irx3b* and *single-minded family bHLH transcription factor 1a (sim1a)* in the patterning of the proximal tubule cells and the corpuscles of Stannius, endocrine glands that control calcium homeostasis and are closely associated with the kidney lineage. Ongoing epistasis experiments aim to further delineate *irx2a/3b* redundancy and their relationship to *sim1a,* Notch signaling and *etv4/5a*, which are important regulators of nephrogenesis.

Conclusions: This study reveals exciting novel roles for *irx2a/3b* during renal epithelial cell specification. Further investigation of the genetic regulators involved in these events will enhance our overall understanding of the molecular pathways that govern kidney development, and may have significant implications for CAKUT therapies and renal reprogramming in the near future.

Funding: NIDDK Support

FR-PO085

New Strategy for Kidney Regeneration Using DiSCAS: The Drug-Induced Specificity Cell Ablation System Shuichiro Yamanaka, Toshinari Fujimoto, Susumu Tajiri, Kei Matsumoto, Makoto Ogura, Takashi Yokoo. *Internal Medicine (Nephrology and Hypertension), Jikei Univ School of Medicine, Japan.*

Background: The kidneys develop through reciprocal and sequential interactions between the ureteric bud (UB) and surrounding cap mesenchyme (CM). To date, the cell transplant to a nephrogenic niche has achieved very low engraftment efficiency, and the competition with the existing native host cell occupying a niche is considered to be its underlying cause. We demonstrated the development of living scaffold for kidney regeneration using the drug-induced specificity cell ablation system (DiSCAS). We found that DiSCAS is an efficient kidney regeneration method to eliminate the existing native nephron progenitor cells (NPCs) that behave competitively in the nephrogenic niche.

Methods: We generated a mouse model with ablation only NPCs using an induction drug. Subsequently, metanephros (MN) was isolated from the embryos and an induction drug was added to the organ culture dish for the elimination of native NPCs only. MN through DiSCAS provided a scaffold mainly comprising living UBs. Donor mouse NPCs that were not affected by the drug were then transplanted into MN through DiSCAS. We examined donor NPC engraftment to CM and their differentiation to a neo nephron. We analyzed the organ culture of MN using immunostaining.

Results: Donor NPCs were noted in the broad engraftment in CM, which ablated native NPCs using the drug. In addition, regenerative nephrons comprising only transplant cells were provided. The neo nephron expressed glomerular and tubular markers. We observed the connection with host collecting ducts and neo nephrons. The engraftment range of the transplant cells accounted for 48.7% of MN with DiSCAS and obtained a wide range of neo nephrons.

Conclusions: Using DiSCAS, it was shown that competing native NPCs were completely replaced by transplant cells in CM. Furthermore, the replaced transplant cells displayed reciprocal interactions with the host UB, and a complete differentiation to nephrons. Living scaffolds in DiSCAS were considered to have the ability to organize neo nephrons from transplant cells and to have good biological compatibility. The new method may facilitate the regeneration of kidneys in future.

Funding: Government Support - Non-U.S.

FR-PO086

Human Nephrogenesis from Single Cell Suspension - A New Model for Renal Toxicity Studies? Amnah Alharbi,[1] Mona Elhendawi,[2] Jamie Davies,[2] Paul Winyard.[1] *[1]Inst of Child Health, London, United Kingdom; [2]Univ of Edinburgh, Edinburgh, United Kingdom.*

Background: Recent research used predominantly mouse renal tissues aimed at engineering new kidneys from early dissociated renal cells has resulted in a method for generating multiple nephron segments, in a 3-dimensional structure.In theory, it should also be possible to form kidneys using directly isolated human renal progenitor cells. If this can be achieved, with demonstrable renal function, then these neo-organs may provide a better model to assess nephrotoxicity and identify nephroprotective strategies.

Methods: Early renal progenitor samples were dissociated into single cells then re-aggregated into cell clumps by centrifugation.These potential mini-kidneys were cultured for 5-6 days and morphologically analysed by dual immunofluorescence microscopy labelled with nephrogenic markers delineating early and later stages of nephrogenesis. Function was assessed by measuring anion (6 carboxyfluorescein) and cation (DAPI) uptake.

Results: Dissociated human kidney progenitor cells were able to self-organise into nephron-like structures.These structures contained diverse normal nephron tubule segments including proximal tubules and distal tubules, as assessed using Lotus tetragonolobus lectin binding and e-cadherin immunohistochemistry respectively, and putative glomeruli with rounded clusters of WT-1 positive cells suggestive of glomerular podocytes. Specific organic anion and cation transport was demonstrated in histologically-identified proximal tubule segments during the fifth day of culture. This was subsequently lost despite persistent morphological and immunohistochemical evidence of numerous proximal tubules.

Conclusions: We have shown that early human renal progenitor cells can self-organise from single cell suspension to develop nephron structures with demonstrable proximal tubule transport activity. Future studies will aim to maintain transport activity over the full length of culture and test other functions in different nephron segments. These mini-kidneys represent a novel potential model to study both human nephrogenesis and nephrotoxicity.

Funding: Private Foundation Support

FR-PO087

Prostaglandin Signaling Regulates Nephron Proximo-Distal Cell Fate Decisions Shahram Jevin Poureetezadi, Christina N. Cheng, Joseph M. Chambers, Rebecca A. Wingert. *Biological Sciences, Univ of Notre Dame, Notre Dame, IN.*

Background: Despite several discoveries furthering our understanding of nephrogenesis, the factors that influence segmentation decisions remain largely unknown. The zebrafish forms a simple embryonic kidney organized in a proximal-distal pattern of contiguous segments that are conserved with the human nephron.

Methods: Here, we performed a multiplex chemical genetic screen to determine factors that regulate proximal and distal nephron fate choices.

Results: Employing this method we identified prostaglandins as a major player in nephrogenesis, which have been previously shown to dictate liver versus pancreas cell fate. Prostaglandin agonists restricted distal segment formation and expanded the proximal segment lineage during nephrogenesis. Genetic abrogation or inhibition of the prostaglandin producing Prostaglandin-endoperoxide synthase 1 or 2a (also known as Cox-1, Cox-2), or the Prostaglandin E receptor 2a or 4a (Ptger2a, Ptger4a), which we found to be expressed in renal progenitors, triggered an alteration in the balance of distal segment fates. Notably, distal segment fate in Ptgs1 or Ptgs2a deficient embryos was rescued by exogenous prostaglandin treatment. Further, we saw that modifying levels of prostaglandin pathway components significantly altered renal progenitor expression domains, including *sim1a*, *irx3b*, and *mecom* - which are required for proximal and distal tubule patterning. Epistasis studies revealed that prostaglandin signaling is working upstream of these transcription factors.

Conclusions: Taken together, these findings show for the first time that prostaglandin signaling is an essential component of nephron cell fate choice, suggesting that prostaglandins may have considerable implications for therapeutic treatment of congenital kidney diseases as well as end stage renal disease.

Funding: NIDDK Support

FR-PO088

The Transcription Factor emx1 Is Required for Distal Segment Formation during Nephrogenesis Elvin E. Morales, Rebecca A. Wingert. *Biological Sciences, Univ of Notre Dame, Notre Dame, IN.*

Background: The developmental pathways that establish nephron segment identities from renal progenitors are poorly understood. The zebrafish embryo forms a simple two-nephron pronephros that possesses a conserved segment anatomy with higher vertebrates. *emx1* is a homeobox gene that has an essential role in brain development, and although it is also expressed in the pronephros, its role in nephrogenesis has not been established.

Methods: Here we characterized the spatiotemporal expression of *emx1* in renal progenitors and performed functional analyses.

Results: Using whole mount *in situ* hybridization, we found that *emx1* is dynamically expressed in renal progenitors, becoming localized to the distal segments. *emx1* deficient embryos had a normal distal nephron territory, but had alterations of the individual segments within it, with an expanded distal early (DE) segment and a reduced distal late (DL) segment. These data suggest that *emx1* is essential to promote the DL, and that it may restrict the DE and/or negotiate the site of the DE/DL boundary. *emx1* deficient embryos had reduced expression domains of several components that direct distal nephron segmentation, such as *irx3b* and *sim1a*, suggesting *emx1* acts upstream of these factors. However, expression of *mecom* was unchanged in *emx1* deficient embryos, suggesting *mecom* acts upstream or independently of *emx1*. Furthermore, *emx1* expression in renal progenitors was responsive to changes in retinoic acid (RA), a morphogen which is essential to induce proximal segments and repress distal segments during nephrogenesis. RA treated embryos had a restricted *emx1* domain, while exposure to the RA biosynthesis inhibitor DEAB conversely expanded *emx1* expression, indicating that RA signaling acts to negatively regulate *emx1* expression within renal progenitors.

Conclusions: Taken together, this work reveals for the first time that *emx1* has essential roles in distal nephron patterning. As expression of *Emx1* has also been annotated in the mouse metanephros, and because of the similarity between the zebrafish and mammalian genomes, this research can provide insights into regulatory networks that direct renal progenitor patterning during nephron formation.

Funding: NIDDK Support, Private Foundation Support

FR-PO089

Differential Usage of Enhancers for Bmp7 in Different Lineages of Kidney Development In Vitro Taro Tsujimura,[1,2] Osamu Takase,[1,2] Masaomi Nangaku,[2] Keiichi Hishikawa.[1,2] *[1]Advanced Nephrology and Regenerative Medicine, The Univ of Tokyo Hospital, Tokyo, Japan; [2]Nephrology and Endocrinology, The Univ of Tokyo Hospital, Tokyo, Japan.*

Background: BMP7 plays pivotal roles in kidney development and diseases. The function of the gene is critically determined by its expression pattern. Therefore, unveiling the regulation is essential to better understand the process. We previously reported that the downstream region of the gene is dispensable for development of the kidney. In addition, an element within the intron 1 of *Bmp7* was identified as an enhancer active in the ureteric bud (UB), but not in the metanephric mesenchymes (MM), during development. However, enhancers essential for the *Bmp7* expression in these different cell-types remain elusive. To deepen our understanding, we explored the *cis*-regulatory regions of the locus.

Methods: We first investigated the publically available ChIP-seq data from ENCODE of H3K27ac marks around the locus in the kidney at different stages. We next generated deletion lines of mouse ES cells each for the upstream and downstream regions of the *Bmp7* gene body, and for the UB enhancer. Then we applied two differentiation protocols towards kidney lineages to test the functionality of the deleted regions.

Results: We found that the pattern of H3K27ac mark changes considerably, suggesting that different enhancers are utilized for the *Bmp7* expression at different times and spaces. Upon differentiation towards interemediate mesoderm via activation of Osr1 (Mae et al. 2013), the deletion of the intron1 enhancer showed significant reduction of the *Bmp7* expression, while those of the others did not. Interestingly, however, none of the deletions changed the expression level of *Bmp7* upon differentiation specifically towards UB lineage (Takasato et al. 2015).

Conclusions: Taken together, these results show that different enhancers, particularly within the introns that were not tested yet, appear to regulate the expression of *Bmp7* in different cell types of the kidney. Deletion of these elements individually *in vivo* should further clarify their roles in regulation as well as the precise functions of BMP7 secreted from different domains of the kidney.

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

FR-PO090

The Basic Helix-Loop-Helix Transcription Factor, Tcf21/ Pod1 in Renal Stroma Is Essential for Crosstalk between Nephrons and Interstitia Shintaro Ide,[1] Yoshiro Maezawa,[1] Rizaldy P. Scott,[3] Tuncer Onay,[3] Yoshihiro Akimoto,[2] Kana Ide,[1] Minoru Takemoto,[1] Susan E. Quaggin,[3] Koutaro Yokote.[1] *[1]Clinical Cell Biology and Medicine, Chiba Univ Graduate School of Medicine, Chiba, Chiba-ken, Japan; [2]Dept of Anatomy, Kyorin Univ School of Medicine, Mitaka, Tokyo-to, Japan; [3]Feinberg Cardiovascular Research Inst and Div of Nephrology and Hypertension, Northwestern Univ, Chicago, IL.*

Background: Renal stromal cells provide a supportive scaffolds for nephrons and the collecting duct system, produce erythropoietin, undergo myofibroblast-like transformation to induce renal fibrosis.Tcf21/Pod1 is a bHLH transcription factor highly expressed in both renal stromal and nephron progenitor population. A standard Tcf21 KO mouse dies in the perinatal period with disrupted nephron development and disorganized interstitial patterning. However, given the complexity of the Tcf21 KO phenotype and early lethality, the precise role of Tcf21 in stromal cells remains unclear.

Methods: In order to clarify the role of Tcf21 in renal stromal development and function, Tcf21 floxed mice were bred with FoxD1Cre mice that provide specific gene deletion in renal stromal cells and its derivatives.

Results: Mice that lack Tcf21 in renal stroma ($Tcf21^{str/str}$) develop massive polyuria with significantly reduced urinary creatinine and osmolarity, increase of urinary sodium and chlorine excretion. Mutant kidneys are significantly smaller, show disorganized stromal structure, and prominent decrease in collecting ducts and loops of Henle. Ultrastructural analysis show thinning of endothelial cells, morphological changes of interstitial fibroblasts, and accumulation of extracellular matrices. Expression profiling using RNA-seq reveals possible downstream targets of this transcription factor including type 6 and type 7 collagens.

Conclusions: Together, these data demonstrate a crucial role of stromal Tcf21 in the development of tubular/collecting duct system. Identification of direct targets of this transcription factor could provide a novel insight into the interaction between stromal compartment and nephrons.

FR-PO091

Stromally Expressed B-Catenin Controls Proper Differentiation of the Medullary Stroma Felix Julien Boivin, Darren Bridgewater. *Pathology and Molecular Medicine, McMaster Univ, Hamilton, ON, Canada.*

Background: The renal stroma is a population of fibroblast cells essential for proper kidney development. Yet, stromal lineage formation, maintenance, and differentiation are poorly understood. In stromal progenitors, β-catenin is essential for establishing cortico-medullary patterning and formation of the medulla. While deletion of β-catenin specifically in stromal progenitors results in the absence of medulla, its underlying mechanism is not clear. **We hypothesize stromal β-catenin is essential to regulate differentiation of the medullary stroma.**

Methods: We generated mice with a β-catenin deficiency in stromal progenitors ($\beta\text{-cat}^{S-/-}$).

Results: The overall stromal population in $\beta\text{-cat}^{S-/-}$ kidneys revealed a 16.67% reduction using the stromal nuclear marker Pbx1 at E15.5. Analysis of the cortical stroma using FoxD1 and Tn-C did not reveal significant changes in their expression in $\beta\text{-cat}^{S-/-}$ by IF and qPCR, suggesting β-catenin is not essential for cortical stroma progenitor formation. In contrast, the analysis of medullary stroma markers Pod1, Wnt4, Bmp4, and p57Kip2 revealed marked reductions of medullary stroma in $\beta\text{-cat}^{S-/-}$. To further investigate the contribution of β-catenin to the regulation of genes essential for medullary stroma formation, we developed a mouse model where β-catenin is overexpressed in stromal cells ($\beta\text{-cat}^{GOF-S}$). The levels of Wnt4 and Bmp4, genes necessary for medullary stroma formation,were significantly increased in $\beta\text{-cat}^{GOF-S}$ in an expanded cell population overexpressing β-catenin. This demonstrates β-catenin regulates the expression of genes essential for medullary stroma differentiation and medulla formation. Considering the reduced medullary stroma in $\beta\text{-cat}^{S-/-}$, we suspected stromal cells that did not differentiate properly to form the medullary stroma were eliminated by apoptosis. Analysis of apoptosis revealed a significant increase in TUNEL and Casp3+ stromal cells. These apoptotic cells were found in clusters below the nephrogenic zone just prior to medullary stromal formation.

Conclusions: Taken together, our results suggest β-catenin specifically regulates medullary stroma differentiation and survival by regulating *Bmp4* and *Wnt4* for proper medulla formation.

Funding: Government Support - Non-U.S.

FR-PO092

Loss of Zeb2 in Stromal Progenitors in Developing Mouse Kidney Leads to Renal Fibrosis Sudhir Kumar, Hila Milo Rasouly, Richa Sharma, Xueping Fan, Weining Lu. *Renal Section, Boston Univ Medical Center, Boston, MA.*

Background: Renal fibrosis is a leading cause of chronic kidney disease and renal failure worldwide and is characterized by fibroblasts to myofibroblasts transition and deposition of fibrillary matrix such as collagen. ZEB2 is a SMAD-interacting transcription factor expressing in stromal cells and fibroblasts in developing kidney. However, the link between ZEB2 and renal fibrosis is not known.

Methods: We generated *Zeb2* stroma-specific conditional knockout mice (cKO) by crossing *Zeb2* flox mice with *Foxd1Cre* mice and analyzed the phenotype of homozygous $Zeb2^{flox/flox}$;$Foxd1Cre^{+}$ mice (*Zeb2* cKO) and their wild-type littermate controls. Kidney histology, renal function, and lifespan were studied in *Zeb2* cKO. Protein expression analyses were performed by immunostaining of ZEB2, Phospho-SMAD3 and several markers for stromal progenitors, fibroblasts, and myofibroblasts in *Zeb2* cKO and wild-type controls.

Results: We found that ZEB2 is highly expressed in FOXD1+ renal stromal progenitors and PDGFR-β+ fibroblasts during mouse kidney development. Deletion of *Zeb2* flox allele using *Foxd1Cre* mice leads to growth retardation, renal failure, and early mortality in homozygous cKO. Immunohistochemical analysis showed that newborn *Zeb2* homozygous cKO kidneys have reduced expression of PDGFR-β and Tenascin-C, two stromal cell and fibroblast markers. At 3 weeks of age, interstitial fibroblasts showed markedly increased expression of α-smooth muscle actin indicating fibroblast to myofibroblast transition. Increased myofibroblasts lead to renal fibrosis with expanded collagen deposition as measured by Masson trichrome, picrosirius red and collagen-1 staining. Further analysis showed that *Zeb2* homozygous cKO mice have increased number of p-SMAD3+ interstitial cells suggesting enhanced TGF-β/SMAD3 signaling activation.

Conclusions: ZEB2 is important for renal interstitial fibroblast development and loss of *Zeb2* in stromal progenitor cells during mouse kidney development leads to fibroblast to myofibroblast transition and renal fibrosis via enhanced TGF-β/SMAD3 signaling.

Funding: NIDDK Support, Private Foundation Support

FR-PO093

Prorenin Receptor Controls Renal Branching Morphogenesis via Wnt/β-Catenin Signaling Renfang Song, Adam T. Janssen, Yuwen Li, Samir S. El-Dahr, Ihor V. Yosypiv. *Pediatrics, Tulane Univ, New Orleans, LA.*

Background: The prorenin receptor (PRR) is a receptor for renin and prorenin, and an accessory subunit of the vacuolar proton pump H^+-ATPase. Renal branching morphogenesis, defined as growth and branching of the ureteric bud (UB), is essential for mammalian kidney development. Previously, we demonstrated that conditional ablation of the *PRR* in the UB in $PRR^{UB-/-}$ mice causes severe defects in UB branching, resulting in marked kidney hypoplasia at birth (PLoS ONE, 2013).

Methods: Here, we investigated UB transcriptome using whole-genome-based analysis of gene expression in UB cells FACS-isolated from $PRR^{UB-/-}$and control kidneys at birth (P0) to determine the primary role of the PRR in terminal differentiation and growth of UB-derived collecting ducts.

Results: Three genes with expression in UB cells previously shown to regulate UB branching morphogenesis, including *Wnt9b*, *β*-catenin and *Fgfr2*, were upregulated, whereas the expression of *Wnt11*, *Bmp7*, *Etv4* and *Gfrα1* was downregulated. We next demonstrated that infection of immortalized UB cells with shPRR *in vitro* or deletion of the UB *PRR* in double-transgenic $PRR^{UB-/-}/BatGal^{+}$ mice, a reporter strain for *β*-catenin transcriptional activity, *in vivo* increases *β*-catenin activity in the UB epithelia. In addition to UB morphogenetic genes, the functional groups of differentially expressed genes within the downregulated gene set in UB cells FACS-isolated from $PRR^{UB-/-}$ mice included genes involved in molecular transport, metabolic disease, aminoacid metabolism and energy production.

Conclusions: Together, these data demonstrate that UB PRR performs essential functions during UB branching and collecting duct morphogenesis *via* inhibition of *β*-catenin signaling and control of hierarchy of genes that control UB branching and terminal differentiation of UB-derived collecting duct cells.

FR-PO094

Grainyhead-Like 2 Regulates Urinary Concentrating Ability by Facilitating Collecting Duct Barrier Function Christian Hinze,[1,2] Janett Ruffert,[2,3] Katharina Walentin,[2] Jonathan M. Barasch,[4] Kerim Mutig,[1] Sebastian Bachmann,[1] Nina Himmerkus,[6] Markus Bleich,[6] Kai M. Schmidt-Ott.[1,2] *[1]Charité, Berlin, Germany; [2]Max Delbrueck Center for Molecular Medicine, Berlin, Germany; [3]Urological Research Laboratory, Berlin, Germany; [4]Columbia Univ, New York; [5]Univ of Kiel, Kiel, Germany.*

Background: The transcription factor grainyhead-like 2 (Grhl2) is highly expressed in renal collecting ducts. Mice with collecting duct-specific Grhl2 deficiency show a decreased ability to concentrate urine and are more susceptible to water restriction and prerenal acute kidney injury. The leading causes for this phenomenon, however, remain unknown. Potential explanations include alterations of the epithelial barrier or of cellular water transport. Here, we investigated the differential impact of Grhl2 on transepithelial resistance and on cellular water transport in freshly isolated collecting ducts.

Methods: We generated Hoxb7/Cre; $Grhl2^{flox/-}$ mice, which exhibit a deletion of functional Grhl2 protein in most cells of the collecting duct. Collecting ducts (CD) from the inner stripe of the outer medulla were freshly isolated and perfused using a double-barreled perfusion system with electrodes inside and outside the CD to analyze transepithelial resistance. To evaluate the relevance of Grhl2 to water transport, we imaged CD after lowering the basolateral solution osmolality inducing water influx and consecutive swelling of the cells. Afterwards, we exposed the CD to forskolin inducing deswelling of cells due to apical insertion of aqpaporin 2.

Results: Our data show that the transepithelial resistance of ISOM collecting ducts of Hoxb7/Cre; $Grhl2^{flox/-}$ conditional knockout mice is reduced by 52% when compared to littermate controls (control vs. knockout: 107.6 vs. 51.2 Ωcm², no. animals, no. ISOM CD: 5 vs. 5, 9 vs. 14, $p<0.001$). However, dynamics of swelling and deswelling showed no difference between Grhl2 knockout animals and controls.

Conclusions: In the renal collecting duct, Grhl2 is primarily required to maintain the transeptithelial barrier, but is dispensable for cellular water transport dynamics. This might be of relevance to diseases involving defective renal responses to water deprivation and conditions of prerenal acute kidney injury.

Funding: Government Support - Non-U.S.

FR-PO095

The Role of Planar Cell Polarity Signaling in Nephric Ciliogenesis and Tubulogenesis Rachel Katherine Miller,[1,2,3] Bridget D. Delay,[1] Vanja Stankic,[1,2] Mark E. Corkins,[1] Tanya A. Baldwin,[2] Malgorzata Kloc,[3,4] Pierre D. Mccrea,[2,3] Andrew B. Gladden.[2,3] *[1]Pediatrics-Research Center, Univ of Texas McGovern Medical School, Houston, TX; [2]Univ of Texas Graduate School of Biomedical Sciences, Houston, TX; [3]Genetics, Univ of Texas MD Anderson Cancer Center, Houston, TX; [4]Immuno-Biology Laboratory, Houston Methodist Research Inst, Houston, TX.*

Background: Kidney tubules consist of a ciliated epithelium, and disruption of cilia polarity leads to aberrant nephrogenesis and cyst development. Recent work suggests that planar cell polarity (PCP) genes influence the development of cilia, but the mechanism behind this involvement is unknown. Daam1, a component of the PCP pathway is expressed during nephrogenesis, and knockdown of Daam1 leads to decreased kidney tubulogenesis in *Xenopus laevis* (frog) embryos. Dishevelled, a component upstream of Daam1 in the PCP pathway, is known to influence ciliogenesis. We hypothesize that Daam1 modulates kidney tubule formation through formation of cilia.

Methods: Using *Xenopus laevis* (frog) embryos, supplemented polarized mammalian kidney cell (MDCK), we assess the roles of PCP components in kidney tubule ciliogenesis and morphogenesis utilizing knockdown, CRISPR/Cas9-mediated knockout, overexpression, immunostaining, yeast 2-hybrid and biochemical techniques.

Results: Our preliminary data suggest that knockdown of Daam1 leads to reduction of cilia in *X. laevis* kidneys and MDCK cells, supporting a working hypothesis that a reduction in kidney cilia may contribute to nephrogenesis defects. Our initial assessments using CRISPR/Cas9-mediated knockout of Daam1 support its role in ciliogenesis and nephric morphogenesis. Yeast 2-hybrid screening and co-immunoprecipitation assays indicate that Daam1 interacts with Tuba, a component of the exocyst complex that is required for primary ciliogenesis. Our recent data also suggest that knockdown of Tuba in the kidney results in reduced tubulogenesis and that CRISPR-Cas9-mediated Tuba knockouts also have defects in nephrogenesis.

Conclusions: Together, these results indicate that PCP signaling is necessary for tubulogenesis within the developing kidney, in part due to effects upon ciliogenesis.

Funding: NIDDK Support

FR-PO096

Genetic Analysis of Mutations Affecting Kidney Development Audra White, Gary Gerlach, Rebecca A. Wingert. *Biological Sciences, Univ of Notre Dame, Notre Dame, IN.*

Background: How the segment cell types of the nephron arise remains a major unresolved question in the field of nephrology. The zebrafish embryonic kidney, or pronephros, has become a progressively prevalent model to analyze renal development and disease. The zebrafish pronephros is composed of two nephrons that contain a series of functional proximal and distal segments, comparable to mammals.

Methods: To discover the repertoire of genes that direct nephron segmentation, a novel haploid forward genetic screen was conducted after random mutagenesis with ethylnitrosurea.

Results: The screen was performed on approximately 700 genomes and resulted in the collection of 15 mutant lines to date. Ongoing complementation studies have suggested that these mutations represent at least 12 different nephrogenesis genes. The kidney phenotypic classes include models of podocyte deficiency, as well as expansions or reductions in the domains of individual proximal and distal tubule segments. Here, we report the characterization of several recessive, embryonic lethal mutations affecting kidney development. For example, line 363 lacks the proximal straight tubule, such that the proximal convoluted tubule and distal tubule form adjacent to one another. Current efforts are directed at identifying the genetic lesion underlying mutation 363. In comparison, line 154 had reduced proximal and expanded distal segments, hallmarks of a defect in retinoic acid (RA) biosynthesis. To test this, we performed complementation analysis with *aldehyde dehydrogenase1a2* ^{nz15} (*aldh1a2*), as well as rescue studies, which revealed that 154 is a novel allele of *aldh1a2*.

Conclusions: This collection of kidney mutations will provide a useful resource to uncover the genes that direct nephrogenesis pathways and may provide new models to study human congenital kidney defects.

Funding: NIDDK Support

FR-PO097

Genetic Networks of Distal Tubule Patterning during Nephrogenesis Bridgette Drummond, Yue Li, Nicole Handa, Amanda N. Marra, Christina N. Cheng, Rebecca A. Wingert. *Biological Sciences, Univ of Notre Dame, Notre Dame, IN.*

Background: The nephron is composed of a variety of cell types that are arranged into distinguishable proximal and distal segments. Previous studies have utilized the simplified nephron system of the zebrafish embryo to identify novel components of nephrogenesis, such as the key roles for retinoic acid (RA) signaling in inducing proximal nephron fates, and the transcription factor encoded by *mecom*, which is required for distal segment formation.

Methods: In this study, the T-box transcription factors *tbx2a* and *tbx2b* were found to be expressed by renal progenitors that give rise to the distal tubule. Loss of function studies revealed that deficiency of *tbx2a*, *tbx2b* or both *tbx2a/b* led to similar reductions in distal tubule formation.

Results: Interestingly, knockdown of *tbx2a* reduced the domain of *tbx2b* expression in renal progenitors, and distal tubule development in *tbx2a* deficient embryos was partially rescued by *tbx2b* overexpression, indicating that *tbx2a* acts upstream to induce or maintain *tbx2b* during distal tubule development. To test the relationship of *tbx2a/b* with the RA pathway, wild-type embryos were treated with exogenous RA or a RA biosynthesis inhibitor, which revealed that *tbx2a/b* are negatively regulated by RA signaling. Next, using *in situ* hybridization, we found that *mecom* transcripts maintained a consistent expression domain in the distal segments of *tbx2a*, *tbx2b*, and *tbx2a/b* deficient embryos. In contrast, *mecom* deficient embryos had significantly decreased *tbx2a* and *tbx2b* domains. Further, the diminished distal tubule typically seen with loss of *mecom* was partially rescued by coninjecting *tbx2a/b* capped RNA. This indicates that *mecom* acts to promote *tbx2a/b* expression, which in turn promotes the formation of the distal tubule.

Conclusions: Taken together, these findings demonstrate that *mecom, tbx2a,* and *tbx2b* are necessary and sufficient factors for distal tubule development, which is pertinent for other developmental and regenerative medicine studies.

Funding: NIDDK Support, Other U.S. Government Support

FR-PO098

Elf5 Is a Principal Cell Lineage Specific Transcription Factor That Contributes to Normal Expression of Aqp2 and Avpr2 Kameswaran Surendran, Malini Mukherjee, Jennifer DeRiso. *Children's Health Research Center, Sanford Research, Sioux Falls, SD.*

Background: The collecting ducts of mammalian kidneys are populated by intermingled intercalated and principal cells that are critical for water, electrolyte and acid-base homeostasis. Comparison of the gene expression profiles of normal developing mouse kidneys versus kidneys with Notch-signaling-deficient collecting ducts, in which most duct cells are aberrantly fated to become intercalated instead of principal cells, led us to identify Elf5 as a potential principal cell specific transcription factor. We have determined whether Elf5 is an early principal cell lineage specific factor and whether it is required for principal cell differentiation.

Methods: We determined the renal *Elf5* expression pattern using transgenic mice in which GFP or reverse tetracycline transactivator (rtTA) are expressed under the control of the Elf5 regulatory region and mice in which LacZ is knocked into the Elf5 locus. Lineage tracing experiments were performed to determine the fate of Elf5 expressing cells using Elf5->rtTA;Tet-o-Cre; Rosa $^{+/tdtomato}$ mice. We performed dual luciferase assays to test the ability of Elf5 to promote the transcriptional activity of proximal promoters of principal cell specific genes. We also analyzed mice with conditional inactivation of *Elf5* in the collecting ducts.

Results: *Elf5* is expressed prior to Aquaporin-2 within the developing collecting ducts as early as E14.5. Lineage tracing of *Elf5*-expressing cells between E16.5 and E17.5 revealed that *Elf5*-expressing cells develop into mature principal cells expressing Aquaporin-4, and Aquaporin-2. Elf5 mildly activates the proximal promoters of *Aqp2* and *Avpr2* in cultured principal cells, consistent with a 20% reduction in *Aqp2* and *Avpr2* gene expression levels in the kidneys with Elf5-deficient collecting ducts.

Conclusions: Although Elf5 is expressed early in the developing collecting ducts and becomes restricted to the principal cell lineage by E16.5, the contribution of Elf5 to regulation the of principal cell specific genes is minimal. The Elf5->rtTA mice will be useful for genetically labeling principal cells and inactivating genes specifically in the principal cell lineage.

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FR-PO099

Prenatal Renal Tract Abnormalities in Murine Models of Spina Bifida Overexpressing Grainyhead-Like 2 and Grainyhead-Like 3 Daniyal Jalil Jafree,[1,2] Oleksandr Nychyk,[1] Nicholas Greene,[1] Andrew Copp,[1] Paul Winyard.[1] *[1]UCL Inst of Child Health, Univ College London, London, United Kingdom; [2]Div of Surgery and Interventional Sciences, Univ College London, London, United Kingdom.*

Background: Given the prenatal manifestation of spina bifida, associated renal tract abnormalities may originate prenatally. Mouse fetuses with spina bifida overexpressing the *grainyhead-like* genes, *grainyhead-like 2* (*Grhl2*) and *grainyhead-like 3* (*Grhl3),* could serve as a model of the human condition. The present study aimed to use this murine model to assess the potential for prenatal renal tract abnormalities in spina bifida.

Methods: Matings were performed of heterozygous *Axd* mice, which overexpress *Grhl2* (*Grhl2^{Axd}*) and transgenic *curly tail* mice, which overexpress *Grhl3* (*Grhl3*;Tg). Renal tracts were dissected from fetuses at embryonic day (E)18.5, embedded, sectioned at 3 μm and analyzed using histology and immunohistochemistry.

Results: Of *Grhl2^{Axd}* fetuses with spina bifida at E18.5, 2 / 4 (50.0%) had abnormal kidney morphology, with no histological abnormalities. 7 / 9 (77.8%) *Grhl3;*Tg fetuses with spina bifida exhibited ureteral tortuosity (n = 4, 44.4%) or dilation (n = 3, 33.3%) at E18.5. Ureteral dilation was also observed in 2 / 5 (40.0%) *Grhl3*;Tg fetuses without spina bifida. Immunohistochemistry suggested indistinguishable innervation and smooth muscle differentiation in bladders and ureters of *Grhl3;*Tg fetuses with spina bifida (n = 2) compared to controls (n = 2). No renal tract abnormalities were observed in heterozygotes at E18.5, but 2 / 4 (50.0%) fetuses carrying both the *Axd* allele and the *Grhl3* transgene had spina bifida and renal pelvic dilation.

Conclusions: In conclusion, spina bifida is a feature of mouse fetuses overexpressing either *Grhl2* or *Grhl3* at E18.5, but associated renal tract abnormalities result from *Grhl2* and *Grhl3* overexpression, not from spina bifida itself. This is suggested by the observation of renal tract abnormalities in fetuses without spina bifida, the variation in defects between strains and evidence of innervation in renal tracts of fetuses with ureteral abnormalities. This study provides insight into the importance and interaction of *Grhl2* and *Grhl3* during renal tract development.

Funding: Private Foundation Support

FR-PO100

The Establishment of Horseshoe Kidney Animal Model Induced by Retinoic Acid and Its Possible Molecular Mechanism Yuansheng Xie,[1] Yan Qi,[1] Panpan Hu,[1,2] Qinggang Li,[1] Xiang-Mei Chen.[1] *[1]Dept of Nephrology, Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing, China; [2]Dept of Nephrology, Civil Aviation General Hospital.*

Background: Horseshoe kidney(HSK) is a common renal fusion malformation, and disorders in cell adhesion and migration during kidney development may involve in its formation. In this study, we established HSK models of fetal mice with retinoic acid (RA) and tried to reveal the underlying mechanism.

Methods: Eight-week-old mature female ICR mice were mated with male ones, and the identification of a vaginal semen plug was defined as embryonic day 1 (E1d). At E8d, pregnant mice were injected with RA at a dose of 25mg/kg intraperitoneally. Fetal mice were taken out by cesarean delivery at E13d, E15d and E17d, respectively. The morphology of fetal mice and their kidneys were observed and recorded. Five factors including RA receptor β(Rarβ),Wnt5a,Tcf3,Snai2 and Rhob which related with RA signaling pathway,non-canonical Wnt signaling pathway,cell adhesion and migration were selected as candidates through literature review. Real-time PCR was used to detect their expression in normal and horseshoe kidneys as well as normal and RA stimulated embryonic renal cells.

Results: Among all the 11 fetal littermate mice acquired at E13d, 3 of them had HSK, 2 of them were unclear and 6 of them had normal renal morphology. As for the 4 fetal littermate mice acquired at E15d, all of them had HSK. Two pregnant mice were killed at E17d, one had 13 fetal mice, 3 of them had HSK, 1 was unclear and 9 had normal morphology. And the other had 12 fetal mice, 8 of them had HSK and 4 had normal morphology. Up-regulation of Rarβ, Wnt5a, Tcf3 and Snai2 and down-regulation of Rhob were found in HSK and RA stimulated embryonic renal cells compared with fetal kidneys in normal morphology and unstimulated cells.

Conclusions: RA can induce HSK models of fetal mice which can be used to investigate its molecular mechanism. RA induced HSK maybe related to the promotion of cell adhesion and inhibition of cell migration throughnon-canonical Wnt signaling pathway.

Funding: Government Support - Non-U.S.

FR-PO101

Cubilin/AMN-Mediated Protein Reabsorption in Nephrocytes Affects Drosophila Lifespan through Regulating the Senescence of Brain and Muscle Tissues Fujian Zhang, Xiaoming Feng, Qiuxia Fan, Fan Fan Hou. *Div of Nephrology, Nanfang Hospital, Southern Medical Univ, Guang Zhou, Guang Dong, China.*

Background: Living-kidney donors have an increased risk of cardiovascular, ESRD and all-cause mortality compared with matched healthy nondonors. However, the underlying mechanism is unknown . The *Drosophila* nephrocyte shares remarkable anatomical, molecular and functional similarity to the glomerular podocyte for protein ultrafiltration, and the renal proximal tubule for protein reabsorption. In this study, we aimed to elucidate the effect of Cubilin/AMN-mediated protein reabsorption on lifespan in Drosophila and its underlying molecular mechanism.

Methods: First, we established Cubilin/AMN knock-down flies and examined the effect of protein reabsorption defect on lifespan. Then, we investigated the effect of enhanced protein reabsorption on lifespan with over-expressing AMN receptor in nephrocytes. We also examined the effect of protein reabsorption on the neuronal and muscular function using negative geotaxis assay. We monitored the proteostasis in hemolymph and tissues using proteomic approach. Furthermore, we performed the immuno-staining and H&E staining to evaluate the effect of protein reabsorption on the senescence of other organs.

Results: We found that defect in nephrocyte protein reabsorption leads to shortened lifespan, whereas, enhanced protein reabsorption in nephrocytes extends *Drosophila* lifespan. We also found that nephrocyte protein reabsorption affects the proteostasis in hemolymph using proteomic approach. Furthermore, we also observed declined neuronal and muscular activities in flies with protein reabsorption defect. Finally, we found that protein reabsorption defect in nephrocytes impairs proteostasis and organ ageing in muscle and brain tissues, suggesting that Cubilin/AMN-mediated protein reabsorption in nephrocytes may affect the senescence of other organs via the tele-proteostasis mechanism.

Conclusions: This study not only discovered the effect of protein reabsorption in nephrocytes on lifespan and its underlying molecular mechanism, but also laid the foundation for the investigation of the effect of tele-proteostasis on aging and its molecular mechanism.

Funding: Government Support - Non-U.S.

FR-PO102

Cakutome, a High-Throughput Tool for Molecular Diagnosis and Identification of Novel Genes for Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) Laurence Heidet,[1] Vincent Moriniere,[2] Lara De Tomasi,[3] Charline Henry,[3] Raphaelle Campait,[2] Olivier Alibeu,[4] Cecile Fourrage,[5] Remi Salomon,[1,3] Sophie Saunier,[3] Cecile Jeanpierre.[3] *[1]Pediatric Nephrology Dept, Reference Center MARHEA, Necker Hospital, Paris, France; [2]Genetic Dept, Necker Hospital, Paris, France; [3]Inserm UMR1163, Imagine Inst, Paris Descartes Univ, Paris, France; [4]Genomic Platform, Imagine Inst, Paris, France; [5]Bioinformatic Platform, Paris Descartes Univ, Paris, France.*

Background: CAKUT are major causes of chronic kidney disease in children. They are phenotypically and genetically heterogeneous diseases, with more than 50 genes reported as mutated in patients, mostly in syndromic forms. Most of the mutations are heterozygous, with autosomal dominant inheritance and variable expressivity. The most frequently mutated genes are *HNF1B, PAX2, EYA1* and *SIX1,* all encoding transcription factors. Many of the other genes are mutated in only few patients and their implication is sometimes elusive.

Methods: To improve molecular diagnosis and identify new causative genes, we developed a targeted exome sequencing strategy (" cakutome ") focusing on 388 genes including known causative or likely causative genes, genes whose knock-out in mouse lead to CAKUT, genes involved in cellular processes/signaling pathways relevant for kidney development, as well as candidates that we had previously identified by whole exome sequencing of CAKUT familial cases. 214 unrelated patients were analysed, 63 previously tested for *HNF1B*, *PAX2*, *EYA1* and/or *SIX1* mutations by Sanger sequencing, and 151 new cases.

Results: Mutations/deletions of *HNF1B, PAX2, EYA1* or *SIX1* were identified in 23 of the 151 cases. This rate is nearly similar to that obtained by Sanger sequencing. We identified mutations in *ANOS1* (Kallmann syndrome), *GATA3* (hypoparathyroidism, deafness and kidney disease) and *SALL1* (Townes-Brocks syndrome) in 6 isolated cases. Moreover, we identified variants in several genes never reported as mutated in CAKUT patients, whose pathogenicity is currently being tested.

Conclusions: This approach is suitable for diagnosis and should allow us to validated new CAKUT causative genes.

Funding: Government Support - Non-U.S.

FR-PO103

Low Nephron Number in Japanese Subjects without Overt Renal Disease: The Effect of Race and Hypertension Go Kanzaki,[1,2] Victor G. Puelles,[1] Luise A. Cullen-McEwen,[1] Wendy E. Hoy,[3] Yusuke Okabayashi,[2] Nobuo Tsuboi,[2] Akira Shimizu,[4] Takashi Yokoo,[2] John F. Bertram.[1] *[1]Dept of Anatomy and Developmental Biology, Monash Univ, Australia; [2]Dept of Internal Medicine, The Jikei Univ School of Medicine, Japan; [3]Centre for Chronic Disease, The Univ of Queensland, Australia; [4]Dept of Analytic Human Pathology, Nippon Medical School, Japan.*

Background: Nephron number in normal human kidneys varies widely and some racial groups with low nephron number have a higher incidence of hypertension and chronic kidney disease (CKD). In Japan, CKD has reached epidemic proportions, but the reasons for this remain unclear.

Methods: Autopsy kidneys from 18 male Japanese subjects without overt kidney disease were collected at Nippon Medical School, Tokyo, Japan and were carefully age-matched to archival data from 18 Caucasian Americans from Mississippi, USA. Demographic data were obtained from autopsy reports and medical records. Total nephron number and mean glomerular volume were estimated by design-based stereology. Glomerulosclerosis was determined using a standardized glomerulosclerotic index.

Results: Significant differences were found between Japanese and Caucasian Americans for height, weight, and thereby BSA ($P<0.001$ for all). Japanese kidneys weighed 21.8% less than those from Caucasian Americans ($P<0.01$). Caucasian American kidneys (955,843±52,781) contained 42.4% more nephrons than Japanese kidneys ($P<0.01$, 550,392±41,787). This difference was still present after adjustment for BSA. Glomerular hypertrophy was observed in association with hypertension ($P=0.04$), but not race. Interestingly, kidneys of hypertensive subjects contained fewer nephrons than normotensives in both races ($P= 0.002$, Japanese; $P= 0.046$, Caucasian Americans) even after glomerulosclerosis adjustment.

Conclusions: This study shows for the first time that Japanese subjects have fewer nephrons than Caucasian Americans, and also indicates that hypertension is associated with lower nephron number. Although it remains unclear whether Japanese subjects were born with fewer nephrons and/or show accelerated nephron loss, the lower nephron number in Japanese people would be compatible with their susceptibility to CKD.

Funding: Government Support - Non-U.S.

FR-PO104

Loss of the Planar Cell Polarity Gene Fuzzy Causes Severe Renal Hypoplasia Elena Torban, Yanran Wang. *Medicine, Div of Experimental Medicine, McGill Univ and McGill Univ Health Center Research Inst, Montreal, QC, Canada.*

Background: Fuzzy is a PCP effectors gene, originally identified in Drosophila, where it regulates actin organization in wing cells. Disruption of Fuzzy in mice causes severe malformations including neural tube defects, polydactyly and facial defects among others. In vertebrates, Fuzzy also affects ciliogenesis by interacting with other PCP effectors to regulates recruitment of some intraflagellar group A transport proteins. Thus, Fuzzy may affect organogenesis by acting both on planar cell polarity signaling and on ciligenesis, two processes important for kidney development.

Methods: Fuzzy gene-trap embryos were harvested at E14.5 and genotyped. Fuzzy homozygous mutants and matching controls were paraffin-embedded, sectioned and processed for immunofluorescent microscopy with various markers: calbindin (ureteric bud), Six2 (nephron progenitors), N-CAM (early mesenchyme-derived nephron structures), WT1 (glomerular podocytes). Hematoxilin and eosin were used to conduct morphometric studies. PNCA and Tunnel assay were used to visualize proliferating and apoptotic cells. In situ hybridization was used to ascertain Fuzzy localization in kidney structures.

Results: We found that E14.5 Fuzzy-/- mutants display severe kidney hypoplasia (~ 50% of the size of control animals) accompanied by ~ 50% reduction in the ureteric bud structures and corresponding 50% reduction of early glomeruli. However, the size of the Six2-positive progenitor pool, the proportion of early nephron structures and the number of podocytes per glomeruls were unaffected. Proliferation and apoptosis within mesenchymally-derived structures were similar to control, yet proliferation and apoptosis within the ureteric bud structures were affected. ISH study revealed that Fuzzy is highly expressed in the collecting duct and at a lower level in other structures.

Conclusions: Our studies indicate that defective UB branching is the major cause of renal hypoplasia in Fuzzy-/- mutants. We will investigate whether loss of Fuzzy affects c-Ret/GDNF, Wnt and/or Shh signaling, Hippo kinase pathway and causes aberrant tubular elongation in the collecting duct lineage.

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

FR-PO105

Vitamin D Effect on the Disturbances of Renal Function and Structure Induced by Losartan Exposure during Lactation in Rats Lucas Ferreira Almeida, Heloisa Francescato, Cleonice Silva, Terezila Machado Coimbra. *Physiology, Univ of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil.*

Background: Renal development in rats is completed between 10 and 15 days after birth. Rat exposure to angiotensin II antagonists during lactation presents disturbances in renal development. Vitamin D (Vit D) has been envolved with cellular differentiation and inflammation and in the regulation of renin gene. Besides this the lack of tubular differentiation in losartan treated rats can affect the Vit D activation. This study evaluates the effect of Vit D in the renal changes provoked by losartan exposure during lactation.

Methods: Male Wistar rats were divided in 4 groups: 1-Control and 2-Control+Vit D, pups treated or not Vit D, 3-Losartan and 4-Losartan+Vit D, pups treated or not Vit D from dams that received losartan. Treatment with losartan (100 mg/kg/day) was conducted during lactation. Vit. D (6 ng/day,calcitriol-*Abbott*), administered by a mini-osmotic pump (*Alzet*), was introduced on day 30 after birth and continued until day 60. Blood pressure (BP) was determined 60 after birth, and blood and urine samples collected to measure creatinine levels. The kidneys were removed for morphometric and immunohistochemical studies.

Results: The animals exposed to losartan presented higher blood pressure (140±0.77 mmHg), decreased glomerular filtration rate (0.56±0.12 ml/min/100g) and albuminuria (80.78±3.80 mg/24h), compared to control. These alterations were attenuatted by Vit D treatment (129.5±0.74 mmHg, 0.77±0.16, 49.93±3.00, respectively, $p<0.05\%$). Rats treated with losartan also showed decreased glomerular area media (5,800 μm^2), higher interstitial area (21.1±1.66%), macrophage number (13.5±0.47/0.100 mm^2), and incresead score for fibronectin and alfa-SM-actin expression in renal cortex (1.4±0.08, 1.9±0.18 respectively). These alterations less intense in Losartan+Vit D group (6,300 μm^2, 15.8±1.75%, 8.9±0.49, 1.0±0.08, 1.3±0.10, respectively).

Conclusions: Vit D treatment reduced the BP and the renal disturbances provoked by losartan exposure during lactation. These effects were associated with renal cellular differentiation and decrease of inflammation in the rats treated with Vit D.

Funding: Government Support - Non-U.S.

FR-PO106

Iron Deficiency Induces Cystic Chronic Kidney Disease Rongjia Deng,[1] Jacob Stauber,[1] Christian Hinze,[2] Christian Rosenberger,[2] Andong Qiu,[1] Jonathan M. Barasch.[1] *[1]Medicine/Nephrology, Columbia Univ, New York, NY; [2]Nephrology, Max Delbrueck Center for Molecular Medicine, Berlin, Germany.*

Background: Iron deficiency is a threat to embryonic and early postnatal development.

Methods: We investigated dietary and transferrin iron deficiency during embryogenesis and in the immediate postnatal period.

Results: Iron malnutrition produced a severe phenotype with nearly complete loss of the proximal tubule (E15) while TfR1-/- produced only a mild glomerular and tubular insufficiency (E15). However, after birth both iron deficiency and TfR1 -/- produced fulminant phenotypes reflected by severe disruption of the proximal tubule and severe deficits in TALH development. TfR1 -/- (Six2Cre) demonstrated striking hypoplasia, tubular dilation, interstitial fibrosis and widespread cortical cystic transformation with Bardet-Biedel (BBS) or Nephronothesis (NPHP) deficiency. These defects were due to iron deficiency because introduction of NTBI (venofer) normalized the growth abnormalities. In addition, relocating the TfR1 knockout to the TALH (KspCre), relocated cystogenesis to the cortical-medullary junction, confirming a direct effect of defective iron traffic in cystogenesis. RNAseq revealed that both dietary and genetic models induced the HIF-1 pathway. TfR1 -/- resulted in a decrease in kidney Epo and the duodenal iron transporters Dcytb and Dmt1, as well as an increase in Liver Hamp1. In contrast, after small molecule activation of HIF (FG-4592) the hypoplastic cystic phenotype was dramatically rescued, EPO increased in the kidney, HAMP expression decreased in liver, and iron transporters were normalized in the duodenum. Indeed, HIF activation rescued body weight, kidney weight, and serum creatinine.

Conclusions: In sum, while TfR1 was not absolutely essential for embryonic development, kidney TfR1 was critical after birth; TfR1-/- disrupted systemic iron balance and induced kidney cystic hypoplasia. These changes resulted from dysregulation of HIF and altered iron-dependent gene expression. The phenotype was rescued with iron and HIF modulators which increased systemic iron. These results demonstrate an unexpected connection between iron deficiency and cystic CKD and point to two therapeutic interventions for the treatment of cystic CKD.

Funding: NIDDK Support

FR-PO107

A Clinical Perspective of Glomerular Hyperfiltration in Health and Disease Go Kanzaki,[1,2] Victor G. Puelles,[1] Luise A. Cullen-McEwen,[1] Yusuke Okabayashi,[2] Nobuo Tsuboi,[2] Akira Shimizu,[3] Takashi Yokoo,[2] John F. Bertram.[1] *[1]Dept of Anatomy and Developmental Biology, Monash Univ, Australia; [2]Dept of Internal Medicine, The Jikei Univ School of Medicine, Japan; [3]Dept of Analytic Human Pathology, Nippon Medical School, Japan.*

Background: It has been proposed that a nephron deficit marks the risk for renal disease. This hypothesis is supported by the development of glomerular hyperfiltration in settings of nephron deficiency. However, the clinical study of human glomerular hyperfiltration is problematic, mostly due to limited access to adequate tissue samples and functional data. This study combines for the first time clinical and morphological data for a comprehensive analysis of glomerular hyperfiltration in human health and disease.

Methods: Autopsy kidneys from 25 Japanese subjects were collected and were divided into three age-matched groups: normotensives (n=9;eGFR>70), hypertensives (n=9;eGFR>60), CKDs (n=7;eGFR<52). Total nephron number (Nglom) and mean glomerular volume (Vglom) were estimated by design-based stereology. Hyperfiltration was assessed by glomerular hypertrophy, single nephron GFR (snGFR;eGFR/Nglom) and the ratio of eGFR per glomerular volume (eGFR/Vglom).

Results: Nglom was significantly lower in hypertensives (423,498±89,716) than in normotensives (666,140±159,755), even though eGFR was similar in the two groups. CKDs (312,277±91,160) had significantly fewer nephrons than hypertensives and normotensives. Nglom was the best morphological predictor of eGFR (R^2;0.46,P<0.001). Glomerular hypertrophy was associated with hypertension and CKD. SnGFR was elevated in hypertensives (P<0.05 vs normotensives), but was similar in normotensives and CKDs. eGFR/Vglom was reduced in hypertensives (P<0.05 vs normotensives) and in the CKDs (P<0.0001 vs hypertensives, P<0.001 vs normotensives).

Conclusions: This study shows for the first time in humans that nephron number predicts eGFR. Physiological markers of glomerular hyperfiltration elevated snGFR were observed in hypertensive subjects. While CKD patients showed glomerular hypertrophy and reduced eGFR/Vglom, snGFR was unaltered. This suggests these glomeruli have already exhausted their physiological capacity to compensate for glomerular loss.

Funding: Government Support - Non-U.S.

FR-PO108

Impact of Enzyme Replacement Therapy on Cardiac and Renal Tissues: A Post-Mortem Case Series Andrew S. Talbot,[1] Kathleen M. Nicholls,[1,3] Moira J. Finlay.[2,3] *[1]Nephrology, Royal Melbourne Hospital, Melbourne, Victoria, Australia; [2]Anatomical Pathology, Royal Melbourne Hospital, Melbourne, Victoria, Australia; [3]Medicine, Univ of Melbourne, Melbourne, Victoria, Australia.*

Background: Fabry Disease an X-linked lysosomal storage disease, caused by deficiency in alpha-galactosidase (aGAL), leads to accumulation of globotriaosylceramide (Gb3) within vascular endothelial cells. Limited long-term pathology on enzyme replacement therapy (ERT) is available. We describe post-mortem findings of 3 patients after ≥ 12 yrs ERT.

Methods: Post-mortem cardiac and renal samples were compared with tissue collected prior to initiation of ERT. Renal function was determined by annual ^{51}Cr-EDTA clearance while cardiac function by echocardiography.

Results: Demographics

	Case 1	Case 2	Case 3
Age Mutation aGAL Level	65yo Male Mis-sense 0.01%	45yo Male Mis-sense Undetectable	68yo Female Nonsense 0.24nmol/ml/mg
ERT (Years)	13	13	12
Renal Stage Proteinuria (g/24hr) GFR Decline (ml/min/1.73m^2/yr)	CKD 4 0.5 1.91	Renal Transplant x 2	CKD 3 2.5 1.77
Diastolic Dysfunction Systolic Function Cardiac Wall Thickness (mm) pre & Post ERT	Moderate Grade 1 14/12 & 10/10	Severe Grade 1 10/12 & 21/17	Moderate Grade 3 14/12 & 14/12
Brain MRI	Basal Ganglia Infarcts White Matter Lesions	Severe Dolichoectasia Cerebellar Infarcts	Basal Ganglia Infarcts White Matter Lesions
Cause of Death	Cardiovascular	Cerebrovascular	Cardiovascular

Renal Histology: Male 1: Biopsies pre-ERT and post-mortem showed similar glomerular sclerosis, podocyte vacuolation and interstitial fibrosis. Male 2: Transplant parenchyma - no vacuolation with moderate renovascular disease. Female: Minimal vacuolation, moderate interstitial fibrosis and hyaline thickening due to renovascular disease. Cardiac Histology: All patients showed hypertrophied cardiomyocytes, intracellular vacuolation and patchy interstitial fibrosis. No glycosphingolipid inclusions in cardiomyocytes on electron microscopy.

Conclusions: Initiation of ERT prior to CKD5 leads to stabilisation of function with renal parenchyma remaining viable. Long-term ERT resulted in clearance of Gb3 from cardiomyocytes but did not prevent cardiac events or diastolic dysfunction.

FR-PO109

Comprehensive Analysis of IgA1 Hinge-Region *O*-Glycoforms in Patients with IgA Nephropathy Kazuo Takahashi,[1] Hisateru Yamaguchi,[1] Yukako Ohyama,[1] Akihiro Kato,[1] Tomohiro Mizuno,[1] Yoshiyuki Hiki,[1] Matthew B. Renfrow,[2] Jan Novak,[2] Yukio Yuzawa.[1] *[1]Fujita Health Univ School of Medicine, Toyoake, Aichi, Japan; [2]Univ of Alabama at Birmingham, Birmingham, AL.*

Background: The serum level of IgA1 with galactose (Gal)-deficient hinge-region (HR) *O*-glycans (Gd-IgA1) is elevated in the majority of IgA nephropathy (IgAN) patients. To characterize the involvement of IgA1 in the pathogenesis of IgAN, *O*-glycan microheterogeneity and attachment sites should be analyzed, as each HR has nine potential sites for *O*-glycosylation. Recently, a relative quantitative workflow was developed for the analysis of IgA1 HR *O*-glycoforms, including for identification of attachment sites of *O*-glycans, using high-resolution liquid chromatography-mass spectrometry (LC-MS) and electron-transfer dissociation (ETD) tandem MS. A limitation of this protocol is throughput, as the sites of attachment of Gal-deficient *O*-glycans in all the *O*-glycoforms should be assigned.

Methods: To increase the throughput of the analysis, we developed a sequential enzymatic deglycosylation protocol, which leaves only Gal-deficient *O*-glycans on HR; this workflow was tested to analyze the *O*-glycoforms of serum IgA1 from a patient with IgAN.

Results: After neuraminidase treatment, 13 glycopeptides corresponding to HR variants with 3-6 *O*-glycans attached to the His^{208}-Arg^{245} backbone amino acids were detected. Nine of the 13 glycopeptides possessed up to 3 Gal-deficient *O*-glycans. After sequential enzymatic treatment, only Gal-deficient *O*-glycans remained on HR, and the sites with Gal-deficient *O*-glycan, including structural isomers, were successfully identified based on the amino-acid position of the attached glycans by on-line LC ETD tandem MS. The results show that Gal-deficient *O*-glycan is attached at specific sites. Once the attachment sites of Gal-deficient *O*-glycans are localized by ETD tandem MS, comparison of the isomeric distributions can be easily accomplished in a large number of samples.

Conclusions: Our new workflow using high-resolution LC-MS with ETD tandem MS after removal of galactosylated *O*-glycans is a promising powerful method to identify specific glycoforms and specific sites for Gal-deficient *O*-glycans in IgA1 from patients with IgAN.

Funding: Government Support - Non-U.S.

FR-PO110

The Levels of Urinary J Chain-Containing IgA-IgG Complexes Are Elevated in Patients with IgA Nephropathy Guanhong Li, Ruitong Gao, Xuemei Li. *Dept of Nephrology, Peking Union Medical College Hospital, Beijing, China.*

Background: IgA nephropathy (IgAN) is characterized by polymeric IgA (pIgA) containing immune complexes deposition in the renal mesangium, inducing kidney injury. Only one previous study has demonstrated that the elevation of urinary IgG anti-IgA autoanbibodies (IgA-IgG) of some patients with IgAN. It is known that J chain is critical in the structure of pIgA, but there has no report about the urinary J chain-containing IgA-IgG complexes (J-IgA-IgG) in patients with IgAN.

Methods: Spot morning urine samples were collected from 10 patients with biopsy-proven IgAN (IgAN group), 11 patients with non-IgA nephropathies (diseases control group) and 33 healthy volunteers (healthy control group). The levels of urinary IgA-IgG and J-IgA-IgG complexes were measured by sandwich enzyme-linked immunosorbent assay (ELISA), and the latter was measured with J chain specific monoclonal antibody generated by our laboratory.

Results: The levels of urinary IgA-IgG and J-IgA-IgG complexes were higher in IgAN group than that in diseases control group (1.55±0.35 vs. 0.76±0.12, *P*=0.0377; 2.54±0.29 vs. 1.82±0.17, *P*=0.0380, respectively) and healthy control group (1.55±0.35 vs.0.35±0.03, *P*< 0.0001; 2.54±0.29 vs. 0.90±0.07, *P*< 0.0001, respectively). We observed that higher levels of urinary IgA-IgG complexes were significantly associated with higher levels of J-IgA-IgG complexes (r=0.92, *P*=0.0001) in patients with IgAN. Both the levels of urinary IgA-IgG and J-IgA-IgG complexes in patients with IgAN were associated positively with serum creatinine (r=0.92, *P*=0.0002; r=0.84, *P*=0.0025, respectively) and negatively with eGFR (r= -0.70, *P*= 0.0251; r= -0.65, *P*=0.0438, respectively), but not significantly associated with 24-hour urine protein (r= 0.62, *P*= 0.0558; r=0.50, *P*=0.1462, respectively).

Conclusions: Our results suggested urinary IgA–IgG and J-IgA–IgG complexes were higher and negatively associated with renal function in patients with IgAN. However, further research with larger sample sizes is needed to identify the role of urinary IgA–IgG and J-IgA–IgG complexes in IgAN.

FR-PO111

Serum BCMA Levels Are Elevated in IgA Nephropathy Karen Molyneux,[2] David Harry John Wimbury,[1] Jonathan Barratt.[1] *[1]Dept of Infection, Inflammation and Immunity, Univ of Leicester, Leicester, Leicestershire, United Kingdom; [2]The John Walls Renal Unit, Leicester General Hospital, Leicester, Leicestershire, United Kingdom.*

Background: IgA nephropathy (IgAN) is a glomerulonephritis characterised by the mesangial deposition of IgA1-containing immune complexes. Two of the key events in the pathogenesis of IgAN are the appearance in the serum of poorly galactosylated IgA1 molecules and IgA and IgG anti-IgA1 autoantibodies directed against the aberrant O-galactosylation. In this study we determined whether levels of serum biomarkers, with particular focus on factors known to be important in B-cell activation, are associated with the development of IgAN and the risk of progressing to ESRD.

Methods: Serum samples from patients with progressive IgAN (a doubling of serum creatinine or ESRD during follow-up), non-progressive (NP) IgAN, (<10% change in serum creatinine over 10 years), membranous nephropathy (MN) and healthy controls were selected from the UK Glomerulonephritis DNA Bank and the concentrations of 49 candidate biomarkers were measured using a bead-based multiplexing immunoassay (Luminex). We analysed the relationship of biomarker concentration with:renal function (eGFR), a diagnosis of IgAN, risk of progression in IgAN, specificity of biomarker changes in IgAN by comparison with matched MN.

Results: There was a clear correlation between the majority of the selected biomarker serum concentrations and eGFR, suggesting that as renal function falls the levels of these biomarkers rise independent of the underlying primary renal disease. With regard to B-cell specific factors; levels of soluble BCMA (sBCMA, TNFRSF17, a receptor for B-cell survival factors BAFF & APRIL) were significantly higher in IgAN and MN compared to healthy subjects, independent of eGFR.

Conclusions: Our results suggest levels of sBCMA are significantly elevated in patients early in the natural history of IgAN (patients with normal renal function) and elevated levels mark out a group of patients at high risk of developing progressive renal disease. Our results highlight the importance of B-cell activation in IgAN and suggest shedding of BCMA by plasma cells may provide a valuable biomarker for B-cell involvement in IgAN.

FR-PO112

VIS649-A Highly Potent Anti-APRIL Antibody for the Treatment of IgA Nephropathy James Myette, Hedy Adari, Gregory Babcock, Ketan Deotale, Karthik Viswanathan, Andrew M. Wollacott. *Visterra, Inc., Cambridge, MA.*

Background: IgA Nephropathy (IgAN) is the most prevalent cause of primary glomerular disease worldwide. There are currently no effective, disease specific therapies for treatment. The cytokine APRIL (A Proliferation Inducing Ligand, TNFSF13) is emerging as a potentially key player in IgAN pathogenesis and disease progression based on a compilation of genetic, biochemical, and clinically relevant data. We report here the discovery and optimization of VIS649, a highly potent, fully humanized anti-APRIL antibody for therapeutic consideration.

Methods: The VIS649 antibody scaffold was identified through epitope-targeted screening of a mouse hybridoma library designed for achieving maximal antagonism of APRIL-receptor interactions. Full humanization of antibody variable regions was successfully achieved using both standard and proprietary computational methods.

Results: The attributes of VIS649 include picomolar APRIL binding affinity and sub-nanomolar receptor blocking activity to both TACI and BCMA *in vitro*. VIS649 likewise demonstrates functional interference of APRIL mediated downstream cellular signaling through the canonical NFkB activation pathway. Further biological characterization of VIS649 *in vitro* demonstrates effective reduction of B cell proliferation and directly relevant inhibition of APRIL-mediated IgA production. Early *in vivo* data indicate effective neutralization of biological activity based on targeted reduction in serum IgA levels with minimal perturbation of overall B and T cell homeostasis indicating a selective immunomodulatory mechanism of action. VIS649 has been successfully engineered as an IgG2 subtype for purposes of clinically mitigating against antibody-dependent exacerbation of complement recruitment in the kidneys of IGAN patients.

Conclusions: APRIL (TNFSF13) represents a logical biological target for the treatment of IgA nephropathy. Toward this end, VIS649, a fully humanized IgG2 based anti-APRIL antibody with high biological potency and low complement activation is currently under pre-clinical development.

Funding: Pharmaceutical Company Support - Visterra, Inc.

FR-PO113

MicroRNA-155 Induced T Lymphocyte Subgroup Drifting in IgA Nephropathy Wei Qin, Yi Tang. *Dept of Nephrology, West China Hospital of Sichuan Univ, Chengdu, Sichuan, China.*

Background: This study was performed to explore the relationship between miR-155 in peripheral blood mononuclear cells (PBMCs), T lymphocyte subgroups, T lymphocyte regulators and clinical manifestations of IgAN patients.

Methods: Sixty IgAN patients and 25 healthy controls were included. Expression of miRNAs in PBMCs was determined using microRNA microarray and real-time RT-PCR. T lymphocyte subgroups (Th1, Th2, Treg and Th17), differentiation regulators (c-Maf, STATA-6, GATA-3, SOCS-1 and Fxop3), cytokines (IFN-γ, IL-5, IL-10 and IL-17), serum IgA1 glycosylation level and Cosmc expression level were measured using flow cytometry, qPCR and ELISA. PBMCs from IgAN patients were cultured with miR-155 mimic or inhibitor with LPS in vitro.

Results: Microarray analysis and qPCR suggested that miR-155 level of PBMCs in IgAN patients was significantly lower than healthy controls ($p<0.01$). Expression level of Gata3, SATA-6 and SOCS-1 in IgAN patients were significantly higher, while Foxp3 and Cosmc expression were remarkably lower. Flow cytometry found that peripheral blood Th1 and Treg cells percentages in IgAN patients were significantly lower. However, Th2 and Th17 cells percentages were remarkably higher. ELSIA results indicated that serum Th1 cytokine INF-γ and Treg cytokine IL-10 levels were apparently lower, while Th2 cytokines IL-5 and Th17 cytokine IL-17 were significantly higher in IgAN patients than normal controls. Significant correlations were found between miR-155 levels and Foxp3, Cosmc level, 24hr urine protein amount, urine RBC count, serum IgA concentration and IgA1 dys-glycosylation level. In vitro study, we also found that miR-155 mimic treatment will reverse T lymphocyte drifting and decrease the IgA dys-glycosylation level; while miR-155 inhibitor treatment will aggrevated the T lymphocyte drifting and increase the IgA dys-glycosylation level.

Conclusions: Remarkable lower expression of peripheral lymphocytes miR-155 was observed in IgAN patients, which leads to T lymphocyte subgroup drifting (increase of Th2 and Th17 along with decrease of Th1 and Treg), which inhibits Cosmc gene expression and worsen the aberrant glycosylation of IgA1 molecular in IgAN patients.

Funding: Government Support - Non-U.S.

FR-PO114

T-follicular Like Helper Cells Drive the Proliferation and Expansion of IgA Antibody Secreting Cells in IgA Nephropathy Nicholas J. Steers, Jason Mccutchan, Stacy E. Piva, Drew A. Bradbury, Michael Divecchia, Maddalena Marasa, Ali G. Gharavi. *Columbia Univ, New York, NY.*

Background: Dysregulated IgA1 response is a central defect in the development of IgA nephropathy (IgAN), but it is not clear if the altered IgA1 response is solely attributable to dysregulation of IgA-antibody secreting B-cells (ABS) or whether additional immune cells contribute.

Methods: We studied peripheral B-cells in 8 IgAN patients, 8 healthy controls (HC), 5 lupus nephritis (LN), and 5 CKD controls.

Results: In the steady state, IgAN individuals had an increased number of IgA-ABS (88 per 1000 activated B-cells) in the peripheral blood compared to the HC, LN and CKD controls (20, 58 and 27, per 1000 activated B-cells, respectively), correlating with increased levels of IgA and IgA1 detected in the serum. *In vitro* stimulation with IL-4, IL-6, IL-21 and CD40L demonstrated increased IgA-B cell proliferation of IgAN patients was heavily influenced by IL-21, facilitated through the increased surface expression of IL-21R on non-class switched B-cells compared to the controls. We next asked the question whether this enhanced proliferative capacity was attributable to T-follicular (T_{FH}) like helper cells, a subset of T-cells that secrete IL-21 upon contact with naive B-cells, and have been shown to drive naïve cells into immunoglobulin secreting cells *in vitro*. Co-culturing T_{FH} likecells and naïve B-cells, an enhanced capacity to drive the naïve B-cells to activated B-cells *in vitro* was observed using cells isolated from IgAN patients, resulting in 13.5% of the B-cell population having an activated B-cell phenotype (vs 6.9% of the B-cell population in HC). IgA was detected in the supernatants of the cell co-cultures of IgAN patients (658ng/ml vs 518ng/ml of HC cell co-cultures ($p < 0.05$).

Conclusions: Collectively our data suggest that an altered balance of T_{FH} likecell and B-cell interactions may contribute to increased expansion and proliferation of IgA-ABS in IgAN, leading to greater numbers of IgA-ABS in the peripheral blood in the steady state.

Funding: NIDDK Support

FR-PO115

Cationic Lipids Enhance Autoantigen Production in IgA1-Producing Cells from IgA Nephropathy Patients and Healthy Controls Colin Reily,[1] Koshi Yamada,[3] Dana Rizk,[1] Bruce A. Julian,[1,2] Jan Novak.[1,2] *[1]Medicine, UAB; [2]Microbiology, UAB; [3]UAB; Juntendo Univ Faculty of Medicine, Tokyo, Japan.*

Background: IgA nephropathy (IgAN) is an autoimmune disease characterized by elevated production of autoantigen, IgA1 with some *O*-glycans deficient in galactose (Gd-IgA1). Increased pro-inflammatory cytokines, such as IL-6, have been shown to increase synthesis of Gd-IgA1, but only in cells from patients with IgAN. Here we show, for the first time, that a cationic lipid can enhance Gd-IgA1 production in IgA1-producing cells of patients with IgAN as well as healthy controls.

Methods: Peripheral blood mononuclear cells were isolated from IgAN patients and healthy controls, EBV immortalized, and IgA1producing cells were subcloned using limiting dilution. IgA1-secreting cells from IgAN patients and healthy controls were stimulated with cationic lipids, and IgA1 production and *O*-glycosylation were assessed.

Results: Cationic lipids were supplemented to the cell-culture medium of a panel of IgA1-producing cells from IgAN patients and healthy controls. This supplementation enhanced production of Gd-IgA1 (HC 3.81 *vs.* HC+Lipid 7.84 U Gd-IgA1, and IgAN 4.32 *vs.* IgAN+Lipid 6.48 U Gd-IgA1) without affecting total IgA1 production. Together, these data for the fist time identified a general mechanism controlling galactosylation of IgA1 *O*-glycans.

Conclusions: This is the first studythat revealed an effect of cationic lipids on glycosylation. Specifically, these lipids reduced galactosylation of IgA1 *O*-glycans without affecting total IgA1 production. Ongoing experiments will identify mechanisms involved. Understanding of the pathways controlling glycosylation in IgA1-producing cells may identify targets for manipulation of IgA1 *O*-glycosylation in patients with IgAN.

Funding: NIDDK Support, Private Foundation Support

FR-PO116

Circulating CD89-IgA Complex Does Not Predict Progression of IgA Nephropathy Ji Min Park, Hyoungnae Kim, Youn Kyung Kee, Jong Hyun Jhee, Min-Uk Cha, Seung Hyeok Han. *Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.*

Background: Pathogenesis of IgA nephropathy (IgAN) is a multi-step process. CD89 is a soluble receptor and CD89-IgA complex facilitates the formation of immune-complex. However, there is lack of evidence supporting circulating levels of CD89-IgA complex is associated with disease progression. Thus, this study aimed to delineate whether circulating CD89-IgA levels can predict the renal outcome in patients with IgAN.

Methods: A total of 344 patients with biopsy-proven IgAN between 2005 and 2014 were included in this study. Patients with estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2 were excluded from the analysis. Demographic and laboratory data were recruited from the Glomerulonephritis Registry of Yonsei University Health System. Circulating CD89-IgA complex levels were determined by sandwich ELISA method. The study outcome was a 30% decrease of eGFR during the follow-up.

Results: The median value of CD89-IgA complex was 7.20ng/ml (inter-quartile range 4.25 to 12.98). Patients were categorized into 3 groups by tertiles of circulating CD89-IgA complex levels. Circulating CD89-IgA complex levels were not correlated with eGFR at the time of biopsy and did not differ among chronic kidney disease stages. During follow-

up, 23 (34.3%), 25 (37.3%), and 19 (28.4%) patients in the lowest, middle, and highest tertiles reached the study endpoint, respectively (P=0.59). In a multiple Cox model adjusted for confounding factors, circulating CD89-IgA complex levels were not associated with developing a 30% decrease in eGFR [lowest versus middle, HR 0.95, 95% CI 0.44-2.07, P=0.89 and lowest versus highest, HR 1.14, 95% CI 0.49-2.61, P=0.76).

Conclusions: Although CD89-IgA complex mediates formation of immune complex, our findings suggest that its circulating level is not a predictor of adverse renal outcome in IgAN.

FR-PO117

Deficiency of C3a/C5a Receptors Reduce Renal Injury in IgA Nephropathy In Vivo and C3a/C5a Receptors Antagonism Inhibit Mesangial Cells Proliferation In Vitro Guolan Xing, Ying Zhang. *Dept of Nephrology, First Affiliated Hospital of Zhengzhou Univ, Zhengzhou, Henan, China.*

Background: Complement activation has a deep pathogenic influence in IgA nephropathy (IgAN). C3a and C5a,as key pro-inflammatory effectors of complement system, contribute to the development of IgAN. Therefore, C3a, C5a and their receptors are potential therapeutic targets for the disease. This study aimed toinvestigate whether deficiency of C3a/C5a receptors could attenuate renal injury in IgAN mice model, and define the effect of C3a/C5a receptors inhibition on cultured human mesangial cells (HMCs).

Methods: An IgAN mice model induced by Sendai virus (SV) infection was employed on wild type and several knockout mouse strains ($C3aR^{-/-}$ or $C5aR^{-/-}$). Mice were immunized with inactivated SV at gradually increasing dose intranasally for 14 weeks, combined with 6.25×10^8 dose challenge intravenously twice. Urine protein, renal function and renal histologic lesion are assessed. Expression of pro-inflammatory cytokines and chemokines in kidney tissue were detected by immunofluorescence and RT-qPCR. Cultured HMCs were stimulated with 100ug/L IgA. Cell proliferation was measured by MTT assay. Production of cytokines and chemokines in response to C3aR/C5aR antagonists were analyzed by Western blot and RT-qPCR.

Results: In the SV-induced IgAN model, C3aR/C5aR deficient mice had significantly reduced proteinuria than WT mice, but not lower levels of BUN and SCr. C3aR/C5aR deficient mice also showed remarkable lower renal IgA and C3 deposition, less histologic damage and reduced mesangial proliferation compared to the WT mice. Furthermore, both C3aR and C5aR deficiency significantly inhibited the gene expression and protein synthesis of TNF-α, TGF-β, IL-1β, IL-6 and MCP-1, especially C3aR deficiency. *In vitro*, C3aR/C5aR antagonism prevented IgA-induced HMCs proliferation and TNF-α, TGF-β, IL-1β, IL-6, MCP-1 production.

Conclusions: These results demonstrate that deficiency of C3a/C5a receptors reduce renal injury in IgAN mice model, and verify the inhibition of HMCs proliferation by C3a/C5a receptors antagonism *in vitro*. Our findings suggest that pharmaceutical targeting of C3aR/C5aR may have potential in the treatment of IgAN.

Funding: Government Support - Non-U.S.

FR-PO118

Anti-Symmetric Dimethylarginine Autoantibodies (anti-sDMA) in Systemic Lupus Erythematosus Andrew Z. Wei, Pan Liu, Cybele Ghossein, Jing Jin. *Nephrology/Hypertension, Northwestern Univ Feinberg School of Medicine, Chicago, IL.*

Background: Systemic lupus erythematosus (SLE) is a complex multi-system autoimmune disease characterized by the loss of tolerance to self-antigens and subsequent production of self-reactive antibodies. The most well-known and clinically-tested class of antibodies are the anti-nuclear antibodies (ANA), which include antibodies against ribonucleoproteins (anti-RNPs) such as the smith proteins (anti-Sm). Glycine-arginine (GR) dipeptide repeats of the Sm protein contain symmetrical dimethylarginines (sDMA), a post-translational modification, which form an antigenic epitope for autoantibodies. The presence of anti-Sm has been associated with an increased risk of kidney involvement due to production of immune complex deposits. The purpose of this ongoing study is to elucidate the potential involvement of arginine methylation of GR repeats in neoantigenic responses of lupus.

Methods: Serum from 31 SLE patients with renal involvement and 6 healthy controls was collected (28 females and 3 males, age = 23-66yrs, median= 42yrs). Through the use of peptide-array technology, we generated an array containing 270 distinct antigen peptides (all 15 amino acids in length) derived from 76 human proteins, and screened SLE patient sera for antibody reactivity towards sDMA and non-modified epitopes. Serum from healthy subjects, antibody standards such as Y12 and SYM10 were used as negative controls.

Results: 17/31 SLE patients demonstrated strong selectivity of sDMA-containing vs. non-methylated epitopes. Anti-sDMA positive serum reacted to a wide range of proteins with low sequence specificity. Selectivity for sDMA epitopes were not seen in heterogeneous healthy controls.

Conclusions: Anti-sDMA that preferentially target sDMA epitopes are seen in a large subset of patients with SLE. These antibodies bind to a wide variety of sDMA-containing epitopes found in human cells and may contribute to the pathogenesis of SLE and development of immune complexes in lupus nephritis. The EBNA-1 protein of the Epstein Barr virus contains a region rich in GR and provides an interesting hypothesis through the generation of anti-sDMA through molecular mimicry.

FR-PO119

Annexin II-Binding Immunoglobulin Level Correlates with Renal Histological Features in Lupus Nephritis Kwok Fan Cheung, Susan Yung, Mel Chau, Desmond Y.H. Yap, Daniel Tak Mao Chan. *Dept of Medicine, The Univ of Hong Kong, Hong Kong.*

Background: Annexin II on the surface of mesangial cells mediates anti-dsDNA antibody binding and downstream inflammatory and fibrotic processes in lupus nephritis. We investigated the relationship between annexin II-binding immunoglobulins and renal histology in lupus nephritis.

Methods: Archived serial serum samples from 28 patients with Class III/IV lupus nephritis were retrieved, and annexin II-binding immunoglobulin level was measured with an in-house ELISA. Glomeruli were isolated from NZBWF1 mice, and annexin II gene and protein expression was investigated by real-time PCR and cytochemical staining respectively. Ultrastructural localization of annexin II was determined by immunogold staining and electron microscopy.

Results: Associations between serum annexin II-binding IgG level, anti-dsDNA level, and disease activity were observed in 42% of lupus nephritis patients. Annexin II-binding IgG level correlated with activity index (r=0.44, p=0.04), leukocyte infiltration score (r=0.52, p=0.01), and karyorrhexis/fibrinoid necrosis score (r=0.66, p=0.002) as stated in the patients' renal biopsy reports, and also the semi-quantitative mesangial electron-dense deposit score (r=0.63, p=0.009). Glomerular annexin II expression increased with active nephritis and decreased with glomerulosclerosis in NZBWF1 mice. Annexin II expression co-localized with electron-dense deposits in the mesangium, along the glomerular basement membrane and around podocytes.

Conclusions: The association between annexin II-binding IgG level and histological features of severe nephritis and the co-localization of annexin II with electron-dense deposits both implicate annexin II in the pathogenesis of lupus nephritis.

Funding: Government Support - Non-U.S.

FR-PO120

Interferon Regulatory Factor 5 Signaling in Myeloid Cells Is Not Required for the Development of Lupus and Lupus Nephritis Abraham Cohen-Bucay, Kei Yasuda, Barry K. Horne, Prachi Shukla, Ian R. Rifkin, Ramon G. Bonegio. *Renal Section, Boston Univ Medical Center, Boston, MA.*

Background: Recent genetic studies have associated systemic lupus erythematosus (SLE) and gain-of-function polymorphisms in the interferon regulatory factor 5 (IRF5) gene. In lupus prone mice, IRF5 knockouts develop less active lupus and less severe lupus nephritis (LN). A growing body of literature indicates a critical role for myeloid cells including macrophages, monocytes, and neutrophils in the pathogenesis of autoimmunity. This led us to hypothesize that IRF5 signaling in myeloid cells may play a critical role in the development of autoimmunity and end-organ damage in SLE.

Methods: We generated an IRF5 conditional knockout (cKO) targeting myeloid cells using the Cre-loxP system in lupus-prone FcγRIIb-/- knockout (R2) mice. Littermate R2 (R2-/-.IRF5fl/fl.LysMCre-/-) and R2.IRF5cKO (R2-/-.IRF5fl/fl.LysMCre+/-) mice were evaluated for evidence of SLE by measuring splenomegaly, lymphadenopathy, and antinuclear antibodies (ANA) titers. Albuminuria, renal histopathology and analysis of immune cell infiltrate of the kidney by flow cytometry were used to compare the severity of lupus nephritis.

Results: SLE developed in both the R2 (n=22) and R2.IRF5cKO (n=19) littermates as evidenced by similar degrees of spleen and lymph node enlargement and similar titers of ANA. Analysis of the lupus nephritis revealed that all mice had severe immune complex glomerulonephritis (glomerular score 2.03 vs 2.17, on a scale of 0 to 4), with severe proteinuria (urine protein/creatinine ratio 133.59 ± 63.07 mg/mg vs 32.24 ± 25.04 mg/mg, p=0.18). Analysis of the renal immune cell infiltrate by flow cytometry demonstrated that myeloid and lymphoid cell infiltrated the kidney during the course of SLE however; the infiltrate was similar in the R2.IRF5cKO and R2 control mice.

Conclusions: IRF5 signaling in neutrophils, monocytes and macrophages is not required for the development of SLE or damage to end organs like the kidneys in lupus-prone R2 mice.

Funding: NIDDK Support

FR-PO121

Growth Factor Midkine Exacerbates Lupus Nephritis by NFAT-Regulated Activation of T Cells Tomohiro Masuda,[1] Kayaho Maeda,[1] Tomoharu Watanabe,[1] Tomoki Yoshioka,[1] Hiroshi Kojima,[1] Yuka Sato,[1] Tomoki Kosugi,[1] Yukio Yuzawa,[2] Shoichi Maruyama.[1] *[1]Nephrology, Nagoya Univ, Nagoya, Aichi, Japan; [2]Nephrology, Fujita Health Univ School of Medicine, Toyoake, Aichi, Japan.*

Background: Midkine (MK), a heparin-binding growth factor, regulates cell growth, cell survival and migration in nephrogenesis and development. Its pathophysiological roles are diverse, ranging from the occurrence of acute kidney injury to progression of chronic kidney disease, often accompanied by hypertension and diabetes. In autoimmune diseases, however, molecular mechanism involving MK is unknown. In current study, we elucidated the role of MK in the activation and differentiation of T cellsubset in lupus nephritis (LN).

Methods: *In vivo* study, LN was induced in MK-deficient ($Mdk^{-/-}$) or wild-type mice ($Mdk^{+/+}$) with an intraperitoneal injection of pristane.Mice were sacrificed at 6 months later. Serum, urine, kidney and spleen were analyzed. *In vitro* study, we examined the activation of $CD4^+$ splenocytes and differentiation of T cell subset.

Results: *In vivo* study: Glomerular injuries in $Mdk^{+/+}$ mice were severer than those of $Mdk^{-/-}$ mice. $CD68^+$ macrophages and $CD4^+$ T cells infiltration were prominent in glomeruli of $Mdk^{+/+}$ mice, consistent with the profiles of albuminuria and renal function. In proportion to LN disease activity, the frequency of splenic $CD69^+$ T cells and T helper (T_H) 1 cells, but not regulatory T cell (Treg), was augmented in $Mdk^{+/+}$ mice with skewed cytokine production. MK expression was also enhanced in activated $CD4^+$ T cells. *In vitro* study: MK induction in splenocytes was found during the activation of T cells, and supplemental administration of MK protein to $Mdk^{-/-}$ activated T cells induced the activation of the nuclear factor of activated T cells (NFAT) signaling and CD69 expression with a profile similar to that in $Mdk^{+/+}$ activated T cells. In addition, MK selectively regulates population and differentiation into T_H1 cells, which is independent of Treg population.

Conclusions: MK serves an indispensable role in the NFAT-regulated activation of $CD4^+$ T cells and T_H1 cell differentiation, eventually leading to the exacerbation of LN.

FR-PO122

Gene-Environment Interactions Promote Nephritis-Associated Autoimmunity Amy G. Clark,[1,2] Emma Zhao,[1] Anastasiya Birukova,[1] Elizabeth Sarah Buckley,[1,2] Jeffrey Ord,[1,2] Yohannes G. Asfaw,[1] Robert Matthew Tighe,[1,2] Mary H. Foster.[1,2] *[1]Medicine, Duke Univ Med Ctr, Durham, NC; [2]Durham VAMC, Durham, NC.*

Background: Occupational exposure to inhaled crystalline silica dust is clearly associated with autoimmune diseases such as lupus and ANCA-associated vasculitis with glomerulonephritis where autoantibody (autoAb) production is a prominent disease component. A key question is how lung exposure to silica breaks tolerance and unleashes autoreactive B cells and autoAb that destroy kidneys and other organs. We hypothesize that pathogenic B cell dysregulation occurs in ectopic/tertiary lymphoid structures (ELS) that form during relevant environmental exposures in genetically susceptible individuals.

Methods: Wildtype (WT) and autoAb transgenic (Tg) mice of C57BL/6 (B6) and genetically distinct lupus-prone NZB, MRL, and BXSB backgrounds were exposed to inhaled silica or vehicle. After 1-3 months, lung pathology and lymphocyte infiltration were scored using H&E, PAS and immunofluorescent stained sections. AutoAb levels in bronchoalveolar lavage fluid (BALF), supernatants from cultured lung and spleen cells, and serum were assayed by ELISA.

Results: All WT and autoAb Tg+ silica-exposed strains showed extensive lung pathology with B and T cell infiltrates and ELS compared to vehicle controls. The percentage lung area containing ELS following silica exposure varied by strain (WT BXSB>MRL>B6>NZB, p=0.03). Significant increases in autoAb production (anti-DNA and anti-MPO) with silica exposure were observed in WT BALF, lung cell supernatants, and serum, in a strain-dependent manner. In autoAb Tg+ mice, Tg+ B cell counts in lung were significantly higher from silica- vs vehicle-exposed B6 (6.6±1.4 vs 3.0±0.7) and BXSB (35.8±20.0 vs 6.8±2.3) backgrounds (cell #, $x10^3$, mean±SD, $p<0.05$). Tg+ Ig levels in BALF were significantly higher in silica-exposed mice in these strains ($p<0.05$).

Conclusions: In genetically susceptible subjects, pulmonary exposure to silica leads to B and T cell accumulation with ELS formation in lung, enhancing local as well as systemic autoAb production. This data suggests that a gene-environment interaction leading to autoAb production is a potential mechanism promoting nephritogenic autoimmunity.

Funding: NIDDK Support, Other NIH Support - NIEHS, VA Support

FR-PO123

Major Glomerular Infiltrating Alternatively Activated Macrophage in Lupus Nephritis and Emigration Dependence on CD11b Sun-Sang J. Sung,[1] Yan Ge,[1] Chao Dai,[1] Hongyang Wang,[1] Jing Yu,[2] Rahul Sharma,[1] Young Hahn,[3] Thu H. Le,[1] Mark D. Okusa,[1] Kline Bolton,[1] Jessica R. Lawler.[1] *[1]Medicine, CIIR, U of Virginia, Charlottesville, VA; [2]Cell Biology, U of Virginia; [3]Microbiology, U of Virginia.*

Background: Despite the general acceptance that glomerulus-infiltrating leukocytes play critical roles in glomerulonephritis (GN), studies on the dynamics of leukocyte emigration into the glomerulus during disease progression and functional attributes of the leukocyte populations are lacking.

Methods: The lupus-prone NZM2328 (NZM) mice developing spontaneous LN with chronic GN (cGN) or anti-GBM-induced LN with acute GN (aGN) were studied. Confocal microscopy were used to identify marker expression. Highly purified glomeruli obtained from magnetic bead trapping were used to prepare single cell suspensions for flow cytometry analysis.

Results: $MHCII^{dim}$ and $F4/80^{dim}$ macrophages expressing high levels of the M2 markers Mac2, PD-L1, MMR, and Mgl1/2, and other macrophage markers CD11b, CD14, and SLAMf9 constituted the largest population of infiltrating leukocytes in NZM mice with cGN, comprising 60% - 80% of total $CD45^+$ cells and their numbers correlated with proteinuria severity. $I\text{-}A^+CD11b^+$ DC-like cells constituted the next largest leukocyte population (10%-20%). PMN and T cells were only about 2% of total leukocytes. Leukocytes in young NZM mice lacking GN have 10 - 30 times fewer infiltrating leukocytes and lower percentages of PMN. In anti-GBM-treated NZM mice, $CD11b^+I\text{-}A^-$ macrophages remained the largest glomerular leukocyte population (50%) whereas PMN increased to 30% of $CD45^+$ cells at the expense of reduced $CD11b^+$ DC numbers (4%). Blocking of CD11b, the predominant marker on both macrophages and PMN with anti-CD11b or anti-ICAM-1 mAb reduced macrophage and PMN infiltration by 80% and 70% respectively, and reduced proteinuria by 95%.

Conclusions: The results showed that in cGN, M2 macrophages are the predominant glomerular infiltrating leukocytes whereas higher contribution of infiltrating PMN and reduced numbers of DC occur in aGN. Infiltration of both macrophages and PMN are heavily dependent on CD11b-ICAM-1 interaction. Controlling macrophage infiltration and function is potentially beneficial in GN treatment.

Funding: Clinical Revenue Support

FR-PO124

Macrophage Mediators of Tissue Fibrosis Are Found in Murine Kidneys after Experimental Glomerulonephritis Gaia Muallem.[1,2] *[1]Renal, Hypertension, and Electrolyte Div, Univ of Pennsylvania, Philadelphia, PA; [2]Dept of Pathobiology, Univ of Pennsylvania, Philadelphia, PA.*

Background: Crescentic glomerulonephritis (GN) is an important cause of kidney injury, and immune-mediated damage is thought to be a significant contributor to chronic kidney fibrosis. A transition in macrophage phenotype from classical (M1) to alternative (M2) activation has been associated with tissue fibrosis in other organ systems, and limiting this transition has attenuated fibrotic lung and liver injury in preclinical studies. Understanding whether this pathway contributes to renal fibrosis in GN could have significant implications for monitoring and abrogating disease progression.

Methods: Wild type (WT) C57BL/6 mice were treated with sheep IgG on day 0. Nephrotoxic serum (NTS) or control IgG was then injected intravenously on day 5 to induce immune complex deposition at the glomerular basement membrane. Kidneys were harvested at day 9. Half of the kidney was fixed in formalin for histology and half was preserved in Trizol for qPCR. Paraffin-embedded slides were stained with fluorescent antibodies against the macrophage marker CD68 and the M2 macrophage marker Ym1. qPCR was performed to evaluate for macrophage markers and regulatory cytokines.

Results: Preliminary experiments confirm an influx of M2 macrophages in the glomerulus, as identified by the markers CD68 and Ym1 that occurs as early as 3 days after NTS injection. Furthermore, qPCR analysis of whole kidney tissue reveals an increase in transcripts of the cytokine IL-13, which is produced by M2 macrophages, and of Fizz1 and Ym1, two markers of alternative activation in macrophages.

Conclusions: This work identifies a clear population of M2 macrophages in inflamed kidneys during GN. These macrophages are important mediators of fibrosis in other organs, and their presence suggests that they may drive chronic renal injury after acute immune-mediated disease. Further work will focus on manipulating endogenous regulatory pathways to limit M2 polarization in the kidney after GN. A better understanding of the immune pathways that contribute to renal fibrosis will facilitate the development of therapies to slow or reverse disease progression.

Funding: NIDDK Support

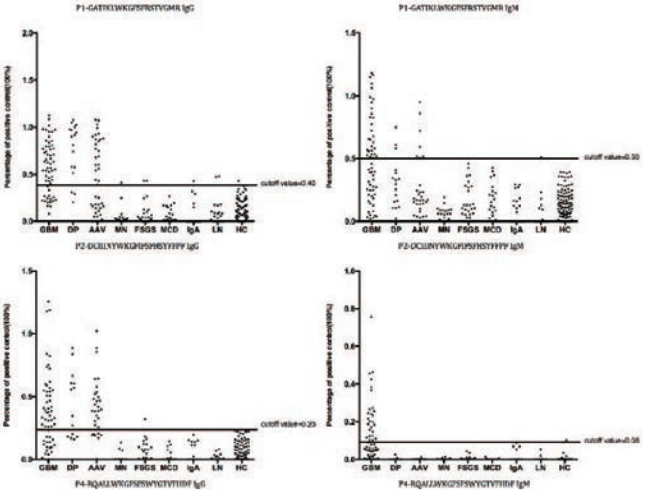
FR-PO125

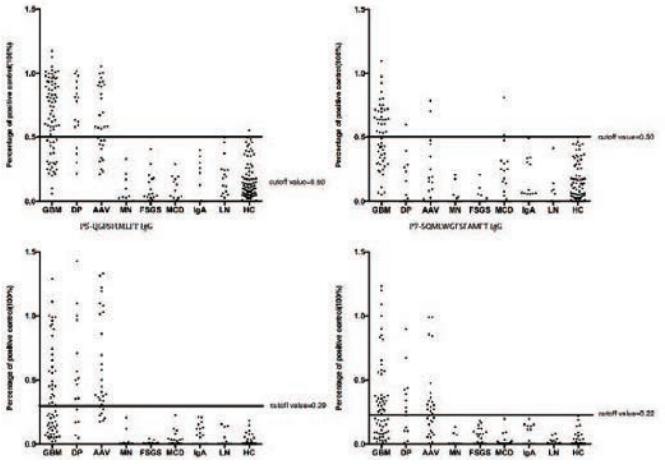
Plasma from Patients with Anti-Glomerular Basement Membrane Disease Could Recognize Microbial Peptides Jian-Nan Li, Xiao-Yu Jia, Zhao Cui, Ming-Hui Zhao. *Renal Devision, Dept of Medicine, Peking Univ First Hospital, Beijing, China.*

Background: Infection has long been suspected as one etiology of anti-glomerular basement membrane (GBM) disease, however, the evidence is insufficient and the mechanism is unclear. Molecular mimicry to the T cell and B cell epitopes on α3(IV)NC1 was hypothesized in this study.

Methods: Microbe originated peptides were searched from Uniprot database based on a previously defined critical amino acid motif within α3(IV)NC1, which is $\alpha3_{136-146}$, with five critical amino acid residues, isoleucine137, tryptophan140, glycine142, phenylalanine143 and phenylalanine144. Seven human-infected microbial peptides were identified and were further synthesized. Circulating IgG and IgM antibodies against these peptides were detected using ELISA from plasma of 76 patients with anti-GBM disease.

Results: Four peptides were recognized by both IgG and IgM antibodies, and one peptide was recognized by IgG antibodies only. Peptides from Bacteroides, Saccharomyces cerevisiae, and Bifidobacterium thermophilum possessed the highest recognition frequency with the prevalence of 73.7%, 61.8% and 67.1% for IgG, and 56.6%, 44.7% and 67.1% for IgM, respectively.





Patients with antibodies against these microbial peptides showed more severe kidney injury, including higher serum creatinine and higher percentage of crescents formation. Circulating antibodies against the microbial peptides were also detected from patients with ANCA associated vasculitis with similar clinical associations, but not from patients with idiopathic membranous nephropathy, primary focal segmental glomerular sclerosis, minimal change disease, IgA nephropathy, lupus nephritis, or healthy blood donors.

Conclusions: In summary, antibodies against microbial peptides were identified in plasma of human anti-GBM disease, implying its etiological mechanism through molecular mimicry to the epitopes on α3(IV)NC1.

Funding: Government Support - Non-U.S.

FR-PO126

Pathogenesis of Antimicrobial Peptides LL-37 and CpG-ODN in ANCA Associated Vasculitis Guangqun Xing. *Nephrology Dept, Affiliated Hospital of Qingdao Univ, Qingdao, Shandong, China.*

Background: We hypothesized that AAV patients have ANCA-producing B lymphocytes in the circulation, and that these cells can be triggered and prone to produce ANCA in response to LL-37 and (or) CpG-ODN both of which related to infection.

Methods: 15patients with AAV were enrolled. 16 patients with chronic bronchitis (CB) were selected as disease control groups. 15 cases of healthy people were as healthy control group. PBMC collected from those groups were cultured and stimulated by LL-37and (or) CpG-ODN for 7 days.The IFN-α and ANCA in vitro were measured by ELISA.The serum IFN-α and LL-37 was measured also.

Results: The serum level of IFN-α in AAV group much higher than that in CB group, and that in healthy control group .The serum level of LL-37 in AAV group was much higher than that in CB group, and that in healthy control group .Also the level of IFN-α showed a significant positive relationship with ANCA in AAV group whether in serum or in supernatants of PBMC culture stimulated by LL-37 and (or) CpG-ODN.In AAV patients, the level of IFN-α by supernatant in PBMC culture stimulated by LL-37 and (or) CpG-ODN was higher than that without stimulating factor ($p<0.05$).The supernatant level of IFN-α in cultured PBMC stimulated by LL-37only was lower than that stimulated by CpGA only. But The supernatant level of IFN-α in cultured PBMC stimulated by LL-37only was higher than in that stimulated by CpGB only .The supernatants level of IFN-α in cultured PBMC stimulated by both LL-37 and CpG-ODN was higher than that stimulated by LL-37 or CpG-ODN only. Whether it is stimulated by LL-37 or CpG-ODN or both the level of IFN-α by supernatant in PBMC culture in AAV patients was highest , that in healthy controls was the lowest.Whether stimulated by LL-37 or CPG-ODN ,or both, the levels of ANCA production in vitro in AAV groups were statistically significantly higher than that in CB group and that in healthy control group.

Conclusions: There was higher level of LL-37and IFN-α in the peripheral blood of AAV patients. IFN-α could reach a higher level stimulated by LL-37 and CpG-ODN. AAV patients have ANCA-producing B lymphocytes in the circulation and that these cells can be triggered by infection.

Funding: Government Support - Non-U.S.

FR-PO127

Atypical Glycosylation of the Constant and Variable Domains of Immunoglobulin G from Patients with ANCA-Associated Systemic Vasculitides: Relation to Disease Activity Olivier Lardinois,[1] Leesa Deterding,[2] Caroline J. Poulton,[1] Candace Henderson,[1] Patrick H. Nachman,[1] J. Charles Jennette,[1] Ronald J. Falk.[1] *[1]UNC Kidney Center, Univ of North Carolina, Chapel Hill, NC; [2]Collaborative Mass Spectrometry Group, National Inst of Environmental Health Sciences, Research Triangle Park, NC.*

Background: Anti-neutrophil cytoplasmic autoantibodies (ANCA) directed against myeloperoxidase (MPO) and proteinase 3 (PR3) are considered pathogenic in ANCA-associated vaculitides (AAV). The aim of the present study is to investigate the changes in Fc and Fab glycosylation with disease activity in detail, and examine the association of glycosylation aberrancies with disease parameters in a cohort of AAV patients.

Methods: IgGs were isolated from serum samples from 30 patients with AAV and 23 control subjects. Isolated IgGs were digested with trypsin and the released glycopeptides were analyzed for subclass-specific Fc glycosylation by LC-MS. Fab glycosylation was determined by fluorescence labeling and chromatography of glycans released by PNGase treatment. The hydrazide glycoprotein capture approach and MS were used to determine the exact localization of *N*-glycans on Fc and Fab fragments.

Results: IgG1 Fc galactosylation and sialylation of total IgG purified from plasma was significantly reduced in AAV patients compared to controls. The levels of galactosylated and sialylated glycoforms on Fc portion of total IgG from PR3-ANCA patient significantly increased during disease remission. In contrast, Fc *N*-glycans levels of total IgG from MPO-ANCA patient did not correlate with disease activity. Hydrazide capture and LC-MS/MS analysis identified six *N*-glycosylation sites on Fab fragments of anti-MPO specific IgGs.

Conclusions: Significant differences exist between MPO and PR3-ANCA diseases regarding the changes in amounts and types of glycans on Fc portion of total IgGs with disease activity. A major fraction of anti-MPO specific IgGs isolated from serum samples of MPO ANCA patients harbor extensive glycosylation within the variable domain on the Fab portion. These differences may contribute to significant clinical differences in the disease course, severity, or relapse rate observed between the two diseases.

Funding: NIDDK Support

FR-PO128

Assessment of HLA-DPB1*04:01 and Time to Relapse in an Evenly Divided Cohort of PR3-ANCA and MPO-ANCA Vasculitis Patients Katherine G. Stember,[1] Yichun Hu,[2] Susan L. Hogan,[2] Caroline J. Poulton,[2] Candace Henderson,[2] J. Charles Jennette,[1,2] Ronald J. Falk,[2] Meghan E. Free,[2] Dominic J. Ciavatta.[2,3] *[1]Pathology and Laboratory Medicine, Univ of North Carolina at Chapel Hill, Chapel Hill, NC; [2]UNC Kidney Center, Univ of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Genetics, Univ of North Carolina at Chapel Hill, Chapel Hill, NC.*

Background: GWAS identified HLA-DPB1 as a risk factor for ANCA-associated vasculitis (AAV), specifically for patients with PR3-ANCA. Whether specific HLA-DPB1 alleles predict patient outcome is unclear. One recent study (Arthritis & Rheum. 2016 DOI 10.1002/art.39620) found that carriers of HLA-DPB1*04:01 (DPB4) had a significantly increased risk of relapse compared to non-carriers, regardless of ANCA subtype.

Methods: We sequenced the HLA-DPB1 gene in 203 patients with AAV. Differences in DPB4 genotype (null, heterozygous, or homozygous) between ANCA subtype were analyzed by Fisher's exact test. Kaplan-Meier estimates and log rank test were used to analyze the relapse probability of DPB4 genotypes in all AAV patients and ANCA subtypes alone.

Results: In our cohort the DPB4 allele frequency was 81% and 68% among patients with PR3-ANCA and MPO-ANCA, respectively, compared to 43% among US Caucasians (Allele Frequency Net Database). Patients with PR3-ANCA were more likely to be homozygous for DPB4 compared to patients with MPO-ANCA ($p=0.0012$). In our cohort of 96 PR3-ANCA and 107 MPO-ANCA patients, the risk of relapse was not different based on DPB4 genotype ($p=0.5$). When stratified by ANCA subtype, PR3-ANCA patients showed a trend toward increased risk of relapse in DPB4 heterozygotes and homozygotes compared to non-carriers ($p=0.06$). In contrast, MPO-ANCA showed no difference in risk of relapse, regardless of DPB4 genotype ($p=0.6$).

Conclusions: Contrary to previous work, in our cohort of AAV patients, DPB4 carriers did not have a significantly greater probability of relapse. The difference may be a consequence of 65% MPO-ANCA patients in our cohort compared to 25% in the previous cohort. We conclude that DPB4 carrier status may be informative for PR3-ANCA patients, but is not predictive of relapse in a combined or MPO-ANCA only cohort.

Funding: NIDDK Support

FR-PO129

Circulating Complement Activation Products in MPO and PR3 ANCA Vasculitis Eve Wu, Sonia Brigitte Boyer, Elizabeth Alderman McInnis, Yichun Hu, Susan L. Hogan, Caroline J. Poulton, Peiqi Hu, Hong Xiao, Ronald J. Falk, J. Charles Jennette, Patrick H. Nachman, Donna O. Bunch. *Univ of North Carolina.*

Background: An anti-MPO murine model suggests complement activation is important in ANCA-associated vasculitis (AAV). Correlation between complement activation products and disease activity has also been shown in an MPO-AAV cohort. These observations have not been confirmed in others, and complement activation has not been studied in PR3-AAV. We investigate complement activation in MPO- and PR3-AAV.

Methods: Subjects included 31 active AAV (BVAS>3, 14 MPO, 17 PR3), 36 remission AAV (BVAS=0, 15 MPO, 21 PR3), and 27 age- and gender-matched healthy controls (HC). Plasma samples were obtained on ice in EDTA tubes including no or 100mcg/mL of futhan. Properdin (Hycult) and Bb, C3a, C5a, and sC5b-9 (Quidel) were measured by ELISA. No futhan samples were used for analyses except Bb and sC5b-9, where futhan significantly affected values. Group comparisons were made using Wilcoxon two-sample test. After Bonferroni correction, $p<0.0083$ was considered statistically significant.

Results: In PR3-AAV, Bb, C3a, and sC5b-9 were higher in active disease compared to HC (Table, median values). Bb and C3a were higher in remission compared to HC. C3a in remission was lower than in active disease, but Bb did not differ by disease state. C5a was not different. In MPO-AAV, C3a, C5a, and sC5b-9 were higher in active disease compared to HC. Bb and C3a were higher in remission compared to HC, but did not differ from active disease. There was no difference in properdin among groups.

	HC	Active PR3	Remission PR3	Active MPO	Remission MPO
Bb(mcg/mL)	0.58	0.74[A]	0.73[A]	0.63	0.69[A]
C3a(ng/mL)	32.84	84.99[A,B]	41.05[A]	68.18[A]	80.89[A]
C5a(ng/mL)	6.47	8.24	7.74	12.36[A,B]	8.21
sC5b-9(ng/mL)	114.46	194.60[A,B]	115.98	154.21[A]	141.41
[A]Significant difference from HC					
[B]Significant difference from remission					

Conclusions: Complement activation occurs in MPO- and PR3-AAV. The complement activation profile differs by ANCA serotype and disease activity. We are confirming results with larger sample size. Complement's role in AAV pathogenesis and disease monitoring warrants more study.

Funding: NIDDK Support

FR-PO130

The Role of Myeloperoxidase as a Critical Mediator of Damage in Diverse Forms of Crescentic Glomerulonephritis Marilina Antonelou, Alan D. Salama. *Centre for Nephrology, Univ College London.*

Background: Myeloperoxidase(MPO) is a heme-containing peroxidase stored in neutrophils and monocytes. It is a key component of innate immune defense, a major autoantigen in ANCA associated vasculitis but also a potential mediator of tissue damage in renal diseases that can lead to crescentic glomerulonephritis(CGN).

Methods: We examined the MPO deposition in renal biopsies of patients with various forms of glomerulonephritis(GN). Clinical and laboratory data were obtained from hospital records and pathology archives. Sections were stained for MPO and a neutrophil marker, CD15. Extra- and intracellular MPO deposition was quantified using Image J analysis software and expressed as a percentage of the total biopsy area. Intracellular MPO was defined as MPO co-expressed with CD15, while extracellular MPO was independent of CD15 staining.

Results: Immunohistochemistry was performed on 14 biopsies from patients with first presentation of glomerulonephritis: 10 with pauci-immune GN, (5 MPO-ANCA, 3 PR3-ANCA, 2 ANCA-negative), 2 anti-GBM disease and 1 post-infectious GN. The median(IQR) age was 57(30-78) years. Nine (64.3%) patients were male. The median number of glomeruli on each biopsy was 16(9-34). We demonstrated intra- and extracellular MPO staining, irrespective of MPO-ANCA positivity.[figure1] The median urine protein creatinine ratio(uPCR) was 257(10-1747) mg/mmol and serum creatinine (sCr) 169(87-694) µmol/L. There was a positive correlation between total MPO deposition and disease severity as defined by uPCR (Spearman's r=0.55,p=0.44) and sCr (Spearman's r 0.55, p=0.04).

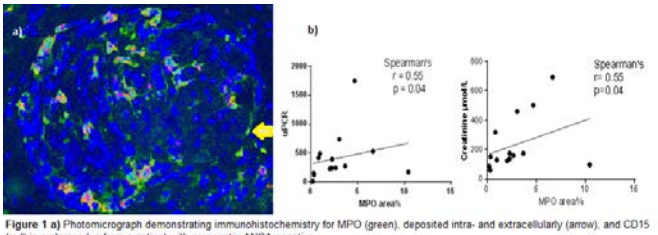


Figure 1 a) Photomicrograph demonstrating immunohistochemistry for MPO (green), deposited intra- and extracellularly (arrow), and CD15 (red) in a glomerulus from a patient with crescentic ANCA negative glomerulonephritis (x630) (DAPI nuclear stain blue), **b)** correlation between MPO deposition and disease severity expressed as proteinuria (uPCR) and serum creatinine (µmol/L).

Conclusions: We have shown that MPO can be detected both intra- and extracellularly in inflamed glomeruli from patients with various forms of CGN. This suggests the role of MPO as a critical mediator of tissue injury, not only as a key autoantigen in MPO-ANCA disease but as a generalised phenomenon in all forms of CGN.

FR-PO131

Granzyme B Producing B-Cells Have Immunoregulatory Function and Are Diminished in Patients with ANCA-Vasculitis Benjamin Wilde,[1] Zhu Jiqiao,[1] Sebastian Dolff,[1,2] Oliver Witzke.[1,2] *[1]Dept of Nephrology, Univ Duisburg-Essen, Univ Hospital Essen, Essen, Germany; [2]Dept of Infectious Diseases, Univ Duisburg-Essen, Univ Hospital Essen, Essen, Germany; [3]Immunology, Maastricht Univ, Maastricht, Netherlands.*

Background: Regulatory B-cells **(**Breg) have recently been identified as a cell population with immunoregulatory capacity and play a role in autoimmunity. Breg suppress pro-inflammatory T-cell responses. The exact mechanisms of suppression are unknown.The aim of this study was to investigate mechanisms of Breg-mediated immunoregulation.Thus, the immunoregulatory properties of Granzyme-B-secreting B-cells were further studied and also characterized in patients with ANCA-vasculitis (AAV).

Methods: 19 patients with inactive AAV were recruited and PBMC were isolated from peripheral blood. B-cells and peripheral blood mononuclear cells (PBMC) from 20 healthy blood donors (HC) were isolated. Purified B-cells/PBMC were stimulated with CpG or IgG+IgM or CD40L in presence of varying cytokines. After 24-72 hours of culture,B-cells/PBMC were analyzed for IL-10 and granzyme B (GrB) expression.

Results: In HC, CpG or IgG+IgM or CD40L stimulation without additional cytokines induced IL-10 in B-cells. Under these conditions, IL-10^{pos}Breg and IL-10^{neg}B-cells did not produce GrB. In contrast, CpG or IgG+IgM or CD40L stimulation in presence of IL-2/IL-21 induced an additional, separate GrB^{pos}IL-10^{neg}B-cell subset. GrB^{pos}B-cells were able to suppress anti-CD3-induced T-cell proliferation. In patients with inactive AAV, B-cells showed a diminished production of GrB upon IgG+IgM/CD40L stimulation in presence of IL-21 (AAV vs. HC; IgG+IgM: 21.1±17.8% vs. 29.4±15.2%,p=0.0427; CD40L: 3.4±2.6% vs. 6.5±3.8%,p=0.0111).

Conclusions: Depending on the cytokine environment, a separate GrB producing B-cell population can be induced. GrB confers cytotoxic capacity to B-cells and allows suppression of T-cells. Thus, GrB^{pos} B-cells can be regarded as an additional Breg subpopulation. This GrB^{pos} B-cell-population is diminished in patients with ANCA-vasculitis.

Funding: Private Foundation Support

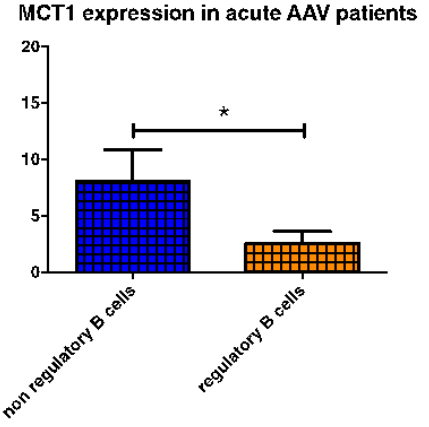
FR-PO132

Investigating the Role of MCT Pathway in ANCA Associated Vasculitis Fernanda Florez-Barros,[1] Graham Paul Belfield,[2] Alan D. Salama.[1] *[1]Centre for Nephrology, UCL Medical School, Royal Free Hospital, Univ College London, London, United Kingdom; [2]Respiratory, Inflamation, Autoimmunity, iMed, AstraZeneca, Sweden.*

Background: Monocarboxylate transporters (MCT) are critical for exporting lactate from actively proliferating cells and if inhibited lead to an intracellular accumulation of lactate and cell death. MCT1 inhibitors are currently in clinical oncology trials, but there is only limited knowledge of their role in the context of kidney inflammation and autoimmune disease. The aim of this study was to investigate MCT1 inhibition in vasculitis and glomerulonephritis.

Methods: a)*In vitro* experiments with samples from acute and remission ANCA vasculitis patients and healthy controls. We studied MCT1&4 expression in B and T cells, and also the effect of MCT1 inhibition on cytokine production and changes in B and T subsets. b)*In vivo* experiments using the MCT1 inhibitor in the nephrotoxic nephritis model, evaluating the potential benefit on different parameters of renal function.

Results: a)There was a significantly lower expression of MCT1 in regulatory B cells compared with non-regulatory B cell subsets in patients with acute disease ($p<0.05$).



b)We found a decrease in IL17 production, both in patients and healthy controls. c)MCT1 inhibitor was not toxic to the mice over a week of treatment. We found an improvement in renal function associated with a benefit on tubulointerstitial damage and a decrease in the humoral response.

Conclusions: The differential expression of MCT1 in B cell subsets, suggests that its inhibition may produce a favorable immune regulatory profile. A non-significant reduction in IL-17 production needs further investigation. On-going research will determine the effect of MCT1 inhibition on antigen-specific and non-specific T and B cell activation. Together, these preliminary data suggest MCT1 may be a useful adjunctive immunotherapy in inflammatory renal disease.

FR-PO133

Annexin A1 Plays a Protective Role in Myeloperoxidase Anti-Neutrophil Cytoplasmic Antibody Associated Glomerulonephritis Takeshi Fujita,[1] Poh-Yi Gan,[2] A. Richard Kitching,[3] Stephen R. Holdsworth.[3] *[1]Nephrology, Hirosaki Univ, Hirosaki, Aomori, Japan; [2]Dept of Medicine, Monash Univ, Melbourne, Victoria, Australia; [3]Dept of Nephrology, Monash Univ, Melbourne, Victoria, Australia.*

Background: Myeloperoxidase-ANCA associated glomerulonephritis (MPO-ANCA GN) results from autoimmunity to MPO. To date, corticosteroids are still first line therapy despite their adverse effects. Annexin A1 (AnxA1) is an endogenous anti-inflammatory protein ubiquitously expressed by glomerular cells and significantly overexpressed in inflammatory diseases. This study aimed to assess the role of AnxA1 and its importance in immunomodulating this disease model.

Methods: We compared the development of anti-MPO autoimmunity and the extent of induced GN in C57BL/6 (WT, n=8) and AnxA1$^{-/-}$ (n=7) mice developing experimental MPO-ANCA GN.MPO autoimmunity was induced by immunizing mice with MPO in Freund's adjuvant and GN triggered using subnephritogenic dose of anti-glomerular basement membrane globulin.

Results: AnxA1 deficiency significantly augments MPO-ANCA GN. AnxA1$^{-/-}$ mice developed more severe functional renal injury as measured by urinary albumin/creatinine ratio (2±0.5 vs 5±1, P<0.01) and structural glomerular damage (glomerular segmental necrosis; 21±2 vs 60±3%, P<0.0001), compared to WT mice. Additionally, AnxA1$^{-/-}$ mice had significantly increased infiltration of glomerular macrophages (0.2±0.05 vs 0.5±0.07 cells/glomerular cross section [c/gcs], P<0.01) and neutrophils (0.4±0.2 vs 0.8±0.2 c/gcs, P<0.05) compared to WT mice. To determine the role of AnxA1 in the development of systemic MPO-ANCA GN, spleens from WT and AnxA1$^{-/-}$ mice with induced MPO-ANCA GN were assessed. AnxA1$^{-/-}$ mice had increased numbers of activated splenic CD4+ T cells (CD4+CD44+; 26±2 vs 34±2%, P<0.05 and CD4+CD69+; 27±4 vs 33±1%, P<0.05) and CD8+ T cells (CD8+CD44+; 20±0.5 vs 30±1, P<0.0001 and CD8+CD69+; 13±2 vs 20±1, P<0.05) compared to WT mice.

Conclusions: This study highlights the importance of Annexin A1 in modulating the extent of MPO-ANCA GN and deficiency in Annexin A1 increases the severity of GN.

Funding: Government Support - Non-U.S.

FR-PO134

Deoxyribonuclease 1 Treatment Attenuates Neutrophil Extracellular Trap Formation, Leukocyte Infiltration and Inflammation in Experimental Anti-Myeloperoxidase Glomerulonephritis Kim M. O'Sullivan,[1] Poh-Yi Gan,[1] A. Richard Kitching,[1,2] Stephen R. Holdsworth.[1,2] *[1]Centre for Inflammatory Diseases, Dept of Medicine, Monash Univ, Clayton, Australia; [2]Dept of Nephrology, Monash Health, Clayton, Australia.*

Background: Accumulating evidence suggests that a dysregulation of neutrophil extracellular trap (NETs) could be associated with the pathogenesis of anti-neutrophil cytoplasmic antibody (ANCA) vasculitis. This study investigates the contribution of NETs in the pathogenesis of experimental anti-myeloperoxidase ANCA associated glomerulonephritis (MPO-ANCA GN), and investigates the therapeutic possibility of deoxyribonuclease 1 (DNase1) to disrupt NET formation *in vivo*.

Methods: Experimental MPO-ANCA GN was induced using a standard protocol, by MPO immunisation and glomerulonephritis triggered using a subnephritogenic dose of anti-glomerular basement membrane globulin. Twice daily intravenous DNase 1 (10mg/kg, n=10 or saline control, n=9) was administered to disrupt NET formation after establishment of MPO autoimmunity until termination of the experiment.

Results: NET accumulation identified by co-localisation of extracellular DNA, citrullinated histone 3 (H3Cit), protein arginine deiminase 4 (PAD4), and MPO, was prominent in glomeruli of mice receiving the saline control (38±5.6%) compared to DNase 1 treated mice (2.5%±1.5%, P<0.0001). Functional kidney injury assessed by proteinuria was significantly reduced (24 hour albuminuria 1650±515.7µg in controls vs 368.7±166µg, P<0.05). Histological assessment of kidneys demonstrated prominent segmental necrosis in the saline treated group (38.5±1.5%) versus a reduction in the treated group (13.2 ±1.9%, P<0.05). Leukocyte infiltration was attenuated in the DNase 1 treated group with CD4 and CD8 T Cells, macrophages and neutrophils significantly reduced (all, P<0.05). MPO induced Delayed Type Hypersensitivity assessed by footpad swelling was significantly reduced in the DNase 1 treated group (P<0.003) as was glomerular fibrin deposition (P<0.05).

Conclusions: DNase 1 successfully attenuates *in vivo* formation of NET formation in experimental MPO-ANCA GN, and reduces functional kidney injury, glomerular pathology and inflammation.

FR-PO135

Enhancing Immunoregulation in Anti-Myeloperoxidase Glomerulonephritis by Human Amniotic Epithelial Stem Cells Andrea Savina Godfrey, Poh-Yi Gan, A. Richard Kitching, Stephen R. Holdsworth. *Centre for Inflammatory Diseases, Monash Univ, Clayton, VIC, Australia.*

Background: Human amniotic epithelial stem cells (hAECs) isolated from the placenta retain their stem cell like anti-inflammatory and low antigenicity properties, making them an attractive stem cell based therapeutic. As their use in anti- myeloperoxidase glomerulonephritis (anti-MPO GN) has not been explored, we sought to determine whether hAECs can attenuate MPO-ANCA GN by enhancing immunoregulation.

Methods: We compared disease between C57BL/6 (WT) mice receiving either hAECs or saline. Anti-MPO autoimmunity was induced by MPOimmunisations and GN triggered using a low subnephritogenic dose of anti-glomerular basement membrane globulin Ig.

Results: *In vitro* co-cultures of MPO-specific effector splenocytes and hAECs showed significant suppression of MPO-specific T cell recall responses (2.7±0.6 vs 7.5±0.8% bromodeoxyuridine^{+}CD4^{+} cells, P<0.01). *In vivo*, when used as a preventative, hAECs attenuated MPO-specific dermal delayed-type hypersensitivity (DTH; 0.1±0.03 vs 0.5±0.Δmm, P<0.05), while enhancing proliferation of foxp3^{+}CD25^{+} regulatory T cells (1.20±0.09 vs 0.84±0.13%, p<0.05). Increased IL-10 production of CD4+ cells (0.05±0.01 vs 0.26±0.09% p<0.05) and intracellular expression of indoleamine 2,3 dioxygenase^{+} (0.027±0.004 vs 0.28±0.08%, P<0.05) indicate an immunomodulatory phenotype. Therapeutic administration of hAECs attenuated the development of glomerulonephritis (segmental necrosis: 15.6±2.2 vs 40.6±2.2%, p<0.05) while enhancing CD4+ TGFβ^{+} producing cells (1.35±0.3 vs 0.46±0.07% p<0.05) and reducing anti-MPO specific CD4^{+} IL-17A^{+} cells (1.1±0.3 vs 1.9±0.21% p<0.05). hAECs reduced infiltrating glomerular leukocytes (macrophages;0.2±0.04 vs 0.4±0.06 cells/glomerular cross section [c/gcs], p<0.05, CD4+ cells (0.3±0.03 vs 0.4±0.05 c/gcs, p<0.05 and neutrophils;0.2±0.03 vs 0.4±0.03 c/gcs, p<0.01) and systemic anti-MPO autoimmunity (DTH: 0.01±0.01 vs 0.4±0.06Δmm, p<0.05).

Conclusions: hAECs successfully inhibit MPO-specific autoimmunity and glomerulonephritis by enhancing immunoregulation. These findings may be relevant in developing better and more targeted therapies for patients with MPO-ANCA glomerulonephritis.

Funding: Government Support - Non-U.S.

FR-PO136

IL-10 Receptor Signaling Empowers Tregs to Control Th17 Responses and Protects from GN Paul Diefenhardt,[1] Anna Nosko,[1] Malte A. Kluger,[1] Claudia Wegscheid,[2] Yasushi Kobayashi,[3] Gisa Tiegs,[2] Richard A. Flavell,[3] Rolf A. Stahl,[1] Oliver M. Steinmetz.[1] *[1]III. Medical Clinic, Univ Hospital Hamburg Eppendorf, Germany; [2]Experimental Immunology and Hepatology, Univ Hospital Hamburg Eppendorf, Germany; [3]Dept of Immunobiology, Yale Univ School of Medicine.*

Background: Th17 cells are central pathogenic mediators of glomerulonephritis (GN). It was recently proposed that IL-10 Receptor (IL-10R) signaling enables Tregs to suppress Th17 responses. Since, little is known about this pathway in inflammatory diseases, we studied the IL-10R function on Tregs in crescentic GN.

Methods: Specific IL-10R deletion was achieved using Foxp3Cre and CD4CrexIL-10Rfl/fl mice and nephrotoxic nephritis (NTN) was analyzed. Treg in vivo and in vitro functions were assessed. IL-10 effects on Th17 immunity were analyzed by competitive cell transfer into Rag1-/- mice.

Results: Naïve Foxp3Cre x IL-10Rfl/fl mice showed spontaneously overshooting Th17 immunity and enhanced Th17 inflammation after induction of NTN. In line, NTN was aggravated in terms of renal function, histology and inflammatory cell infiltration. Analyses of Tregs revealed unchanged numbers and percentages. In particular, expression of Th17 type chemokine receptor CCR6 was maintained on IL-10R-/- Tregs, indicating mechanisms for control of Th17 immunity, different from those of Stat3+ Treg17 cells. Instead, we found reduced suppressive capacity and selective impairment of IL-10 secretion by IL-10R-/- Tregs. In order to assess, whether reduced IL-10 production might be causative for the hyper Th17 phenotype, we co-transferred splenocytes from CD45.2 CD4Cre x IL-10Rfl/fl mice together with IL-10R intact CD45.1 splenocytes into Rag1-/- recipients and induced NTN. Confirming a crucial role for IL-10 in controlling Th17 responses, Th17 cells among IL-10R deficient T cells massively outcompeted those among IL-10R intact wild type T cells.

Conclusions: Our data indicate that IL-10R signaling enables Tregs to control Type17 immunity. As one mechanism, we hypothesize a feed forward loop, whereby IL-10R signalling enhances IL-10 secretion by Tregs. IL-10 in turn suppresses Th17 responses, protects from crescentic GN and thus represents a promising therapeutic target.

Funding: Government Support - Non-U.S.

FR-PO137

IL-17C/IL-17RE Axis Drives Renal TH17 Responses in Glomerulonephritis Sonja Krohn, Jasper Nies, Jan-Hendrik Riedel, Anna Kaffke, Anett Peters, Alina Borchers, Hans-Joachim Paust, Rolf A. Stahl, Ulf Panzer. *III. Medizinische Klinik, Univ Hamburg-Eppendorf, Germany.*

Background: The T_H17 effector cytokines, IL-17A and IL-17F have been shown to play a central role in the pathogenesis of crescentic glomerulonephritis. However the importance and function of other IL-17 family cytokines in immune responses and inflammatory diseases have not been studied so far. IL-17C acts via the activation of the IL-17RA/RE receptor complex. The role of the IL-17C/IL-17RE axis in autoimmune diseases is largely unknown. Thus the goal of this study is to elucidate the role of the IL-17C/IL-17RE axis in the inflamed kidney.

Methods: Using a mouse model of experimental crescentic GN (nephrotoxic nephritis) we studied the IL-17C mRNA expression level in the inflamed kidney. Studies using IL-17C- and IL-17RE-gene-deficient mice as well as adoptive transfer experiments into Rag1$^{-/-}$ mice were performed to study the role of the IL-17C/IL-17RE axis in renal tissue injury.

Results: Here we demonstrate an increased renal IL-17C mRNA expression level in the early course of experimental GN. In studies using IL-17C- and IL-17RE-gene-deficient mice we demonstrated that these mice developed significantly less severe disease with respect to proteinuria, renal function and histological injury, which was associated with a reduced T_H17 response. Moreover adoptive transfer experiments in Rag1$^{-/-}$ mice were performed to study the intrinsic effect of IL-17RE on CD4^{+} T cells. These studies demonstrated that CD4^{+} T cells expressing IL-17RE might play a role in driving nephrologic T_H17-cell responses in renal autoimmunity.

Conclusions: These findings indicate a specific function of the IL-17C/IL-17RE axis in the development of renal tissue injury in experimental GN and might provide the basis for a better targeting of the T_H17 pathway in crescentic GN.

FR-PO138

Inhibition of Protein Kinase C-α Restores Mitochondrial Disfunction in Kidney Endothelial Cells Nino Kvirkvelia,[1] Maggie McMenamin,[1] Marie Warren,[2] Raghavan Raju,[2] Michael P. Madaio.[1] *[1]Medicine, Augusta Univ, Augusta, GA; [2]Biological and Radiological Technology, Augusta Univ, Augusta, GA.*

Background: We have shown that glomerular targeted PKC-α inhibition in nephrotoxic nephritis (NTN) limits inflammation and enhances recovery. We aimed to understand the underlying mechanism and identify candidate proteins that were differentially affected.

Methods: Using quantitative mass spectrometry, we analyzed proteomes from mice cortexes from the following groups: 1) controls, 2) NTN, 3) NTN + PKC-α inhibitor Ro-32-0432 given i.p. after induction of nephritis on day 2, and 4) NTN + PKC-α inhibitor conjugated to the human mAb F1.1, directed against α3(IV) collagen. Mitochondrial function was investigated by measuring mitochondrial respiration (assessed as OCR), and glycolytic lactic acid production, (assessed as ECAR) in cultured kidney endothelial cells.

Results: Combined analysis of microdissected cortexes identified total of 4187 proteins in all four samples. Functional protein groups most affected by NTN were mitochondrial proteins associated with respiratory processes, such as ATP synthase, Cytochrome b-c1 complex, NADH dehydrogenase, Superoxide dismutase, which were down regulated in NTN mice (fold changes compared to the same protein levels found in healthy mice were 0.52±0.15), while their expression was restored with PKC-α inhibition (both systemic and glomerular specific, with fold changes 0.90±0.14, p≤1.054E-14), suggesting a role for proteins that regulate oxidative phosphorylation. In cultured kidney endothelial cells, NTS reduced basal oxygen consumption rates (OCR) from 225 pmol/min to 185 pmol/min and increased ECAR from 42 to 62 mpH/min. The PKC-α inhibitor (at 10nM and 50nM) normalized NTS mediated changes in OCR and ECAR levels.

Conclusions: The results suggest that PKC-α is an important regulator of antibody mediated glomerulonephritis and that targeted inhibition of this enzyme protects the kidneys from the damage associated with severe inflammation by restoring oxidative phosphorylation at the glomerular cell level. This has therapeutic implications for treatment of human disease.

Funding: NIDDK Support

FR-PO139

Loss of DNA Methylation Triggers Transcription of Silenced Laminin Genes in Aging Kidneys Oleg N. Denisenko, Karol Bomsztyk. *Medicine, Univ of Washington, Seattle, WA.*

Background: Aging kidney is associated with aberrant gene expression of extracellular matrix components that leads to gradual structural changes and progressive decrease in glomerular filtration rates. We examined contribution of epigenetic changes to dysregulation of laminin genes in aging rat kidneys.

Methods: RT qPCR was used to examine renal expression of all 11 laminin genes in kidneys from 4, 24 and 28 months old (mo) F344 rats; and from 4, and 30 mo FBN-F1 hybrid rats. Chromatin immuno-precipitation (ChIP) and DNA methylation (MeDIP) assays were used to assess renal histone and DNA modifications, respectively.

Results: While no changes were detected in the abundant laminin transcripts Lama2, Lamb1, Lamb2, Lamc1, silenced genes Lama3, Lamb3, and Lamc2 were transcriptionally upregulated in old animals ($p<0.05$). ChIP and MeDIP analyses revealed reduction in the density of silencing marks H3K27m3 and DNA methylation (5mC) at Lamc2 gene in old kidneys. Loss of these epigenetic marks at Lamc2 gene was associated with no detectable global changes in the levels of these marks in old kidneys by Western blot analysis of histones and dot blot analysis of DNA. Mechanistic studies in renal cell culture revealed no effect of H3K27m3 loss (by Ezh2 inhibitor) on Lama3, Lamb3, Lamc2 expression, whereas treatment with DNA methylation inhibitor 2'-deoxy-5-azacytidine was sufficient to upregulate these genes *in vitro*.

Conclusions: We found that three laminin genes normally silenced in young kidney, Lama3/Lamb3/Lamc2 (components of Laminin 5), are de-repressed in old kidney. Our results suggest that loss of DNA methylation at these genes re-activates their expression during aging *in vivo*, and define DNA methylation system as a potential target for therapeutic interventions. These studies were supported by grants from Nathan Shock Center of Excellence in the Basic Biology of Aging, University of Washington, and NIH RO1 DK094934 (OD), and R01 DK083310, R37 DK45978 (KB).

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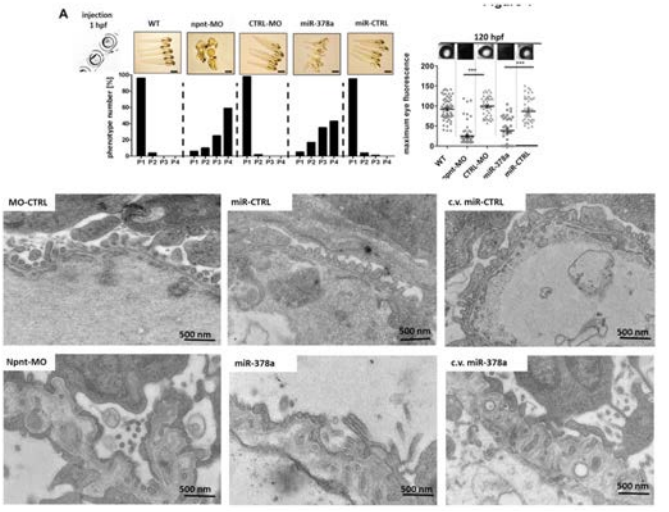
FR-PO140

Podocytes Regulate Expression of Glomerular Basement Membrane Protein Nephronectin via miR-378a in Glomerular Diseases Janina Müller-Deile,[1] Meei-Hua Lin,[3] Jenny C. Nystrom,[2] Jeffrey H. Miner,[3] Johan Lorenzen,[1] Thomas Thum,[4] Mario Schiffer.[1] *[1]Dept of Medicine/Nephrology, Hannover Medical School, Hannover, Germany; [2]Dept of Physiology and Dept of Nephrology Sahlgrenska Academy, Washington Univ School of Medicine, Univ of Gothenburg, Gothenburg, Sweden; [3]Div of Nephrology, Washington Univ School of Medicine, St. Louis.*

Background: MicroRNAs (miRs) play an important role in gene regulation and therefore seem to be promising candidates involved in glomerular diseases.

Methods: We used the zebrafish and mice model to investigate the role of miR-378a in glomerular diseases.

Results: We identified miR-378a, as specifically increased in urine samples of patients with nephrotic primary membranous glomerulonephropathy, focal segmental glomerulosclerosis and minimal change disease. Nephronectin is a predicted target of miR-378a, which is predominantly located in the glomerular basement membrane (GBM). In patients, glomerular miR-378a expression was increased and glomerular nephronectin levels were reduced in focal segmental glomerulosclerosis and membranous glomerulonephropathy. In our zebrafish model, nephronectin knockdown by morpholino or miR-378a overexpression caused edema, proteinuria and structural impairments of the glomerular filtration barrier with podocyte effacement and widening of the lamina rara interna of the GBM.



In mice pharmacological overexpression of miR-378a confirmed the phenotype with increased levels of albuminuria, podocyte effacement and altered expression of GBM proteins.

Conclusions: In summary, we demonstrate that miR-378a is an important regulator of proteinuria development in humans, mice and zebrafish. It exerts its function through regulation of its target nephronectin. MiR-378a controlled nephronectin expression is a novel mechanism for proteinuria development in active glomerular diseases in patients.

Funding: Private Foundation Support

FR-PO141

Podocyte Specific ZHX2 Overexpression Worsens Focal Segmental Glomerulosclerosis and Improves Minimal Change Disease Maria Del Nogal Avila, Hector Donoro Blazquez, Camille E. Mace, Caroline B. Marshall, Lionel C. Clement, Sumant S. Chugh. *Div of Nephrology, Dept of Medicine, Univ of Alabama at Birmingham, Birmingham, AL.*

Background: Zinc fingers and homeoboxes (ZHX) transcriptional factor family are major regulators of podocyte gene expression and are mostly expressed as heterodimers bound to transmembrane proteins. ZHX2-ZHX1 heterodimers are present mostly in the podocyte body and ZHX2-ZHX3 in the slit diaphragm. Loss of heterodimerization, is common in podocyte diseases and promotes nuclear entry of ZHX proteins.

Methods: To induce loss of heterodimerization of ZHX2 related complexes, podocyte-specific ZHX2 transgenic rats were generated. Following baseline characterization, we induced Adriamycin nephrosis, a model of FSGS, and puromycin aminonucleoside, a model of MCD.

Results: Three founder lines of ZHX2 podocyte-specific transgenic rats were characterized (TG 14, TG 142, TG 144). Glomerular RNA expression of ZHX2 in heterozygous rats showed a fold-increase of 1.13 ± 0.10 in TG 14, 1.50 ± 0.09 in TG 142 and 4.09 ± 0.69 in TG 144. Confocal characterization of heterozygous TG 144 rats revealed increase expression of ZHX2 in podocyte cell membrane distribution. Expression of ZHX3 and ZHX1 was unchanged. None of the ZHX2 transgenic rat lines had proteinuria at baseline. When compared with Sprague Dawley rat, NPHS2-promoter-ZHX2 TG rats had more proteinuria and more severe glomerular disease than controls (TG 144 and TG 142 > WT; proteinuria/18h: 310.4 ± 41.5 mg, 204.8 ± 29.9 mg and 102.6 ± 20.3 mg, respectively) ($p<0.01$). Also, backcross of the ZHX2 transgene into the Buff/Mna rat background, a model of FSGS, for 8 generations was associated with more proteinuria (301.9 ± 27.4 mg in 18 h) than the Buff/Mna at age 8 month (193.8 ±23.7 mg in 18 h) ($p<0.05$). By contrast, proteinuria in PAN was less severe 10 days after treatment (TG 144 and TG 142 < WT; proteinuria/18h 178.9 ± 13.4 mg, 169.1 ± 37.8 mg and 351.7 ± 38.9 mg, respectively) ($p<0.05$).

Conclusions: Loss of heterodimerization caused by overexpression of ZHX2 in podocytes had a protective effect in MCD but worsens the development of FSGS. These findings suggest a major role of ZHX2 in nephrotic syndrome.

Funding: NIDDK Support, Private Foundation Support

FR-PO142

Nanoproteomics and 2-Photon Glomerular Micropuncture (2PGM) Reveal LRP2 Ligands in Glomerular Filtrate Michael Hutchens,[1] Rumie Wakasaki,[1] Kirsti A. Golgotiu,[1] Paul D. Piehowski,[3] Sharon Anderson.[2] *[1]Anesthesiology & Perioperative Medicine, Oregon Health & Science Univ, Portland, OR; [2]Internal Medicine, Div of Nephrology & Hypertension, Oregon Health & Science Univ, Portland, OR; [3]Biological Separations and Mass Spectrometry, Pacific Northwest National Laboratory, Richland, WA.*

Background: The proximal tubular (PT) transporter LRP2 (megalin) mediates endocytosis of >50 ligands. LRP2 ligands such as albumin and myoglobin alter tubular function and survival in kidney disease. In order to access subsurface cortical glomeruli,

we developed 2PGM and coupled this with simplified nanoproteomics (SN), developed at the Pacific Northwest National Laboratory, to test the hypothesis that LRP2 ligands may be quantified in glomerular filtrate.

Methods: Cortical glomeruli were accessed in anesthetized C57BL/6 mice with 2 photon guidance using the novel technique. Imaging excluded vascular injury. GF was aspirated, frozen, and underwent in-column trypsin digestion and inline LC/MS analysis with MS identification against the Uniprot mouse proteome. Urine from mice with mosaic PT deletion of LRP2 (LRP2 fl/fl;ApoE cre) was assessed by conventional proteomics to confirm the findings obtained with novel techniques.

Results: Cortical glomeruli (depth 63±7μm) were accessed with 100% survival. In GF, 18 proteins were identified (MW 57.5±12kD), albumin the most abundant, consistent with GF. Urine of LRP2 fl/fl;ApoE cre mice was selectively enriched in 320 proteins relative to cre- control, including all known LRP2 ligands. 38% of the GF identifications were among the 320 LRP2 deletion-selective proteins.

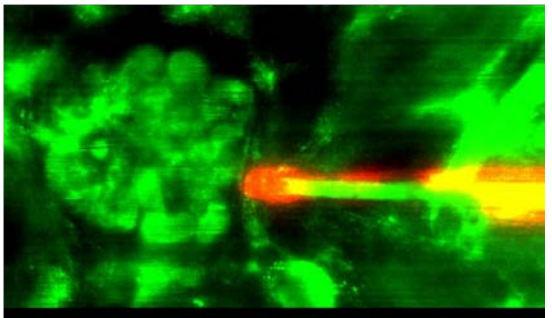


Figure: 2-photon image of red fluorophore-coated micropipette during placement in Bowman's space, 36 um below the renal capsule. The vasculature is partially opacified with fluorescein-isothiocyanate 2000kD dextran

Conclusions: We identified known and possible LRP2 ligands in glomerular filtrate using novel methodology. 2PGM allows access to subsurface glomeruli, enhancing micropuncture. 2PGM coupled with SN may provide important data regarding glomerular protein filtration.

FR-PO143

Podocyte-to-Podocyte Propagation of Damage Takes Place in an Accelerated Manner in Males Masahiro Okabe,[1,2] Masaru Motojima,[1] Yoichi Miyazaki,[2] Takashi Yokoo,[2] Taiji Matsusaka.[1] *[1]Tokai Univ School of Medicine, Isehara, Japan; [2]Jikei Univ School of Medicine, Tokyo, Japan.*

Background: Our recent studies demonstrated that injury incurred in a fraction of podocyte population causes secondary damage in other initially intact podocytes. This podocyte-to-podocyte propagation of damage may drive the progressive nature of glomerulosclerosis. Since male patients commonly develop renal failure faster than females following various kidney diseases, we hypothesized that male podocytes are more susceptible to this secondary injury.

Methods: We established a new mosaic mouse model in which approximately 50% of podocytes express hCD25 and the other podocytes express EGFP. Injection with hCD25-targeted immunotoxin, LMB2, injured not only hCD25-positive but also -negative podocytes, and the mice developed FSGS without increase in blood pressure. To study impact of sex on secondary podocyte injury, five male and five female mosaic mice (28 weeks) were injected with LMB2.

Results: FACS analysis in mosaic mice without LMB2 revealed that the proportion of hCD25-positve podocytes was not different between the male and female mice. Seven days after the induction of podocyte injury, urinary Alb/Creatinine ratios (ACR) were similarly increased in both groups (male 84.8±14 vs. female 85.1±14 mg/mg). Thereafter, the male mice continuously showed high ACR (89.2±50 at day 21) and two died at day 18 and 24. In contrast, ACR in the female mice decreased (19.2±16 at day 21, $p<0.01$ vs. male). Renal histological analysis at day 25 revealed that male glomeruli showed severer sclerosis, higher desmin expression, and fewer EGFP-positive cells than female glomeruli. Glomerular nephrin was diminished globally in the male mice while only segmentally in the female mice. To verify that LMB2 causes similar primary podocyte injury in males vs. females, NEP25 mice (5 males and 5 females), in which all podocytes express hCD25, were injected with LMB2. No sex difference was observed in proteinuria, glomerulosclerosis, nephrin or desmin expressions.

Conclusions: Propagation of podocyte-to-podocyte injury takes place more aggressively in males, which may underlie more rapid progression of renal failure in male than female patients with kidney diseases.

Funding: Government Support - Non-U.S.

FR-PO144

The Effect of Maternal Low Protein Diet on Podocyte Endowment Victor G. Puelles, Luise A. Cullen-McEwen, James William Van der Wolde, John F. Bertram. *Dept of Anatomy and Developmental Biology, Monash Univ, Melbourne, Australia.*

Background: It is well established that an adverse feto-maternal environment such as a maternal low protein diet (LPD) can result in low nephron endowment – a permanent deficit in nephron number. Given that podocytes are post-mitotic cells with limited capacity for regeneration, we investigated whether a maternal LPD also resulted in reduced podocyte endowment.

Methods: Kidneys were collected at postnatal day 21 in rat offspring exposed to a maternal LPD (8%) or normal protein diet (NPD; 20%) starting at 3 weeks prior to pregnancy until weaning. Total nephron number was estimated by design-based stereology. Podocyte number was determined using a combination of immunofluorescence, confocal microscopy and optical clearing; and glomerular volume by model-based stereology. Podocyte density was also calculated. A total of 300 whole glomeruli were analysed: 10 glomeruli from the outer and 10 from the inner cortex per rat (NPD, n=8, and LPD, n=7).

Results: Body weight and nephron number were 43% ($P<0.0001$) and 32% ($P<0.0001$) lower in LPD compared to NPD offspring. Glomerular volume was 42% lower in LPD offspring ($P<0.01$; 50% for outer and 37% for inner glomeruli). Interestingly, glomeruli from the LPD group contained 13% fewer podocytes than those from the NPD cohort ($P<0.0001$; 18% for outer and 8% for inner). Consequently, podocyte density was increased by 60% in LPD offspring ($P<0.001$; 66% for outer and 50% for inner). Inner glomeruli were larger and had lower podocyte densities than glomeruli from the outer cortex in both NPD and LPD rats ($P<0.001$ for all). While there was no zonal difference in podocyte number in NPD rats, there were 14% more podocytes in glomeruli from the inner cortex in LPD rats ($P<0.0001$).

Conclusions: This is the first report that podocyte endowment is directly affected by an adverse feto-maternal environment. The observation that outer glomeruli in LPD rats had particularly low podocyte number suggests glomeruli formed in the latter stages of nephrogenesis were particularly affected. Studies focused on the adult consequences of low podocyte endowment are underway in our laboratory.

FR-PO145

Podocyte Number Increases after Birth in Mice and Humans Victor G. Puelles,[1] James William Van der Wolde,[1] Luise A. Cullen-McEwen,[1] Peter G. Kerr,[2] David J. Nikolic-Paterson,[2] John F. Bertram.[1] *[1]Dept of Anatomy and Developmental Biology, Monash Univ, Melbourne, Australia; [2]Nephrology, Monash Medical Centre, Melbourne, Australia.*

Background: Podocyte depletion is a direct cause of glomerulosclerosis and is observed in a wide range of glomerular diseases. However, the presence of postnatal podocyte gain remains a controversial topic.

Methods: Kidneys were collected from *Pod^{iCre}iDTR* mice injected with 50ng/kg of diphtheria toxin (DT) and age-matched controls (6-14 weeks of age). Total podocyte number per glomerulus was obtained using a combination of immunofluorescence, optical clearing and confocal microscopy. A total of 740 whole glomeruli were analysed (20 per mouse). Podocyte number was also estimated in human nephrectomy (n=3 adults) and autopsy tissue (n=18 children) using model-based stereology in 10-20 glomeruli per subject for a total of 350 glomeruli.

Results: Podocyte number increased approx. 20% in control mice from 6 to 14 weeks of age ($P<0.0001$). Podocyte number decreased by 13% ($P<0001$) 1 week after DT injection (7 weeks of age). However, by week 14 of age, podocyte number increased by 12% ($P<0.001$) in DT-injected mice. While there was no statistical difference in podocyte number between 6-week control mice and 14-week DT-injected mice ($P=0.59$), the difference between DT-injected and age-matched control mice at 14 weeks remained at 15% ($P<0.0001$). Body weight increased in both control (37%; $P<0.001$) and DT-injected mice (47%, $P<0.001$). Glomeruli from children 3-36 months of age and adults contained approx. 30% more podocytes than children 0-2 months of age ($P<0.0001$). Podocyte number was similar in children 3-36 months of age and adults. Body surface area increased dramatically in children 3-6 months of age (50%; $P<0.001$), 12-36 months of age (154%; $P<0.01$), and adults (680%; $P<0.0001$) compared to children 0-2 months of age.

Conclusions: These findings suggest that podocyte number increases by 20-30% after birth in both mice and humans. This increase in podocyte number may align with normal physiological growth in the early period of postnatal life. Future studies using cell fate tracking are urgently needed to confirm these findings.

FR-PO146

Podocyte Injury Is Involved in Albuminuria in the Rat Model of Hyperuricemia Shin-Ichiro Asakawa, Shigeru Shibata, Daigo Toyoki, Yosuke Kawamorita, Yoshifuru Tamura, Yoshihide Fujigaki, Shunya Uchida. *Dept of Intern Med, Teikyo Univ School of Medicine, Tokyo, Japan.*

Background: We have recently shown that high level of serum uric acid (UA) may deteriorate kidney function in CKD patients using propensity score analysis (Uchida S et al. PLoS One 2015). In the present study, we have evaluated the kidney injury and its mechanism in a rat model of hyperuricemia.

Methods: Male Sprague-Dawley rats received 2% oxonic acid (OA group) as a uricase inhibitor to increase serum UA level. Blood pressure and urinary albumin excretion were monitored during the experiment. At 8 weeks, kidney histology and urine albumin excretion were evaluated by immunostaining.

Results: Rats received OA had significantly higher levels of uric acid than control group (1.3 ± 0.1 mg/dL vs. 0.7 ± 0.1 mg/dL, n =10; p = 0.002). OA group showed time-dependent increase in systolic blood pressure and thickening of arcuate arteries and afferent arterioles as assessed by a-smooth muscle actin staining. Of note, OA caused significant increase in urinary albumin excretion, and the immunostaining of desmin, a podocyte injury marker, showed marked increase in its positivity. The presence of podocyte injury in this model was further confirmed by electron microscopy. To address the mechanism of UA-induced kidney injury, we analyzed the levels of 8OHdG, the oxidative stress marker, and found that urinary 8OHdG levels, as well as 8OHdG staining in the glomeruli, were significantly increased in the OA group as compared with the control. Moreover, urinary 8OHdG was highly correlated with UAE ($R^2 = 0.49$; $p < 0.001$), suggesting the importance of oxidative stress as a cause of podocyte injury. However, oral administration of tempol, a potent antioxidant, decreased blood pressure but not UAE, suggesting that the cause of UAE is distinct from that of hypertension and is relevant to podocyte injury.

Conclusions: High levels of serum UA can cause arteriopathy/arteriolopathy and albuminuria, the latter of which is attributable to podocyte injury. Oxidative stress induced by higher serum UA may underlie the mechanism of the kidney injury.

FR-PO147

miR-21 Mediates Podocyte Injury and Mitochondrial Dysfunction via Targeting Mitochondrial Gene Dnm1l Aihua Zhang,[1] Mi Bai,[1] Guixia Ding,[1] Yue Zhang,[1] Songming Huang,[1] Zhanjun Jia.[2] *[1]Dept of Nephrology, Nanjing Children's Hospital affiliated to Nanjing Medical Univ, Nanjing, China; [2]Nanjing Key Lab of Pediatrics, Nanjing, China.*

Background: Emerging evidence indicated that the maintenance of mitochondrial structure and function is critical for preventing podocyte injury. Recently, some miRNAs have been proven to play roles in modulating mitochondrial function. Our preliminary data from a miRNA array analysis showed a remarkable elevation of renal miR-21 in a podocytopathy mouse model. By bioinformatics analysis, mitochondrial Dnm1l was predicted to be a direct target of miR-21. Thus we conducted experiments to determine the role of miR-21 in podocyte injury and mitochondrial dysfunction.

Methods: Puromycin aminonucleoside (PAN) or Adriamycin (ADR) was used to induce podocyte injury in cultured podocytes or animals. Genetic approaches were applied to define the roles of miR-21 in mediating podocyte injury and mitochondrial function in vitro and in vivo.

Results: Following PAN treatment in SD rats and podocytes, miR-21 was dramatically induced by 4.8-fold in kidney and 4.2-fold in cells, respectively. Strikingly, overexpression of miR-21 alone in podocytes induced mitochondrial dysfunction evidenced by the increase of ROS (+3.1 folds) and decrease of Mitochondrial membrane potential (MMP) (-27%) and mitochondrial DNA (mtDNA) copy number (-24%), and cell injury shown by increased cell apoptosis (+81%) and decreased nephrin (-70%) and podocin (-45%) expression. By luciferase reporter assay and miR-21 overexpression, we identified that Dnm1l is a direct target of miR-21. And overexpression of Dnm1l could largely abolish miR-21 effects on inducing mitochondrial dysfunction and podocyte injury. More importantly, the miR-21 inhibitor attenuated PAN/ADR-induced podocyte injury in both in vitro cells and in vivo animals shown by 70% blockade of albuminuria and remarkable amelioration of podocyte injury markers in line with markedly attenuated mitochondrial dysfunction.

Conclusions: miR-21 mediated podocyte injury and mitochodnral dysfunction via targeting mitochondrial gene Dnm1l.

FR-PO148

Succinate Receptor GPR91 Regulates Mitochondrial Metabolism and Contributes to Diabetic Nephropathy Progression Ju Young Moon,[1,2] Dorinne Desposito,[1] Anne Riquier-Brison,[1] Bahram Nadim,[1] Janos Peti-Peterdi.[1] *[1]Dept of Physiology and Biophysics, Univ of Southern California, Los Angeles, CA; [2]Dept of Internal Medicine, College of Medicine, Kyung Hee Univ, Seoul, Korea.*

Background: Succinate is traditionally known as an intermediate of the mitochondrial citric acid (TCA) cycle, but its novel signaling role as a ligand of the cell membrane GPR91 receptor (also called SUCNR1) is emerging. Succinate and GPR91 have been implicated in metabolic diseases including hypoxia (ischemia), lipolysis (obesity), and diabetic nephropathy (DN), however the pathophysiological role of GPR91 signaling in DN has been elusive. The purpose of the studies was to validate the importance of GPR91 in DN, and to investigate the pathomechanism of succinate/GPR91 signaling. We hypothesized genetic GPR91 inhibition attenuates the progression of DN by regulating mitochondrial metabolism and hypoxia response in the kidney.

Methods: Our study included four mouse groups: 1) C57/BL6 (Wild type, WT CON); 2) C57/BL6+Streptozotocin+Nω-Nitro-L-arginine methyl ester hydrochloride (Wild STZ+L-NAME, 1g/L administered in the drinking water); 3) GPR91$^{-/-}$ (KO CON); and 4) GPR91$^{-/-}$+STZ+L-NAME (KO STZ+L-NAME). Intravital multiphoton microscopy was used to measure mitochondrial metabolism in the intact kidney *in vivo*, by quantitatively visualizing mitochondrial ROS generation (using Mitosox) and depolarization of the mitochondrial membrane potential (using MitoTracker-Red).

Results: We found significant reductions in hyperglycemia-induced mitochondrial ROS generation and depolarization of the mitochondrial membrane potential in distal tubule-collecting duct epithelial cells in KO vs. WT STZ+L-NAME mice. Also,the hypoxia-inducible factor HIF1α was highly expressed in KO kidney compared to WT. These findings were also linked with attenuated systolic blood pressure, albuminuria,mesangial expansion, and Type IV collagen deposition in KO vs. WT STZ+L-NAME groups.

Conclusions: Taken together, these data support the direct role of GPR91 in activating mitochondrial ROS generation and depolarization of mitochondrial membrane potential, contributing to the progression of DN. GPR91 is a promising new therapeutic target for DN.

Funding: Pharmaceutical Company Support - Amgen

FR-PO149

Over-Expression of Dynamin-Related Protein 1 Contribute to Podocyte Injury by Facilitating Mitochondria Fragmentation Na Guan, Qijiao Wei, Xiaoya Liu, Han Xu. *Pediatrics, Peking Univ First Hospital, Beijing, China.*

Background: Mitochondria fragmentation during podocyte apoptosis has been found. Dynamin- related protein 1 (Drp1) can facilitate mitochondria fragmentation. This study aimed to test the hypothesis that Drp1 might lead to podocyte injury by facilitating mitochondria fragmentation.

Methods: Thirty SD rats were divided into adriamycin nephropathy and control group. Proteinuria, podocyte mitochondria morphology and density, glomerular staining and cortical expression of Drp1 were analyzed at 2, 4 and 6 week. Glomerular expression of Drp1 in children with nephrotic syndrome was also analyzed. The effects of over-expression of Drp1 on mitochondria morphology and apoptosis were analyzed using mouse podocyte MPC5. Data was expressed as mean±SD.

Results: In adriamycin group, compared with controls, proteinuria appeared at 4 week (150.5±87.7 vs. 16.0±9.2mg, P=0.01) and 6 week (226.9±106.9mg vs. 12.0±4.4mg, P<0.01); podocyte mitochondria density increased at 2 week (0.17±0.00 vs. 0.14±0.01, P<0.01), mitochondria area density decreased (0.71±0.11 vs. 0.87±0.12, P=0.02) at 6 week; glomerular staining intensity of Drp1 increased at 4 week (0.025±0.013 vs. 0.003±0.001, P=0.02) and 6 week (0.008±0.003 vs. 0.0004±0.003, P=0.01); renal cortical Drp1 expression increased at 4 week (0.38±0.09 vs. 0.03±0.02, P=0.05) and 6 week (0.39±0.14 vs. 0.07±0.10, P=0.02).

Glomerular staining intensity (r=0.48, p=0.01) and renal cortical expression of Drp1(r=0.47, p<0.01) correlated positively with urinary protein. Glomerular staining area ratio (r=-0.44, P=0.02) and cortical expression of Drp1 (r=-0.46, p=0.01) correlated negatively with mitochondria density in podocyte. The cortical expression of Drp1 correlated negatively with podocyte mitochondria aspect ratio (r=-0.49 , P=0.01).

Glomerular staining of Drp1 increased dramatically in some children with nephrotic syndrome, and co-localized with synaptopodin.

Over-expression of Drp1 lead to increase of apoptosis in mouse podocyte MPC5 compared with control (31.2±10.4% vs. 5.7±4.0%, P=0.02) and fragmentation of mitochondria.

Conclusions: Over-expression of Drp1 lead to podocyte injury possibly by facilitating mitochondria fragmentation.

Funding: Government Support - Non-U.S.

FR-PO150

CHOP Deficiency Inhibits Proteinuria by Promoting Nephrin Expression in a Mouse Model of Chronic Kidney Disease Zahraa Mohammed-Ali,[1] Mandeep K. Marway,[1] Chao Lu,[2] Kjetil Ask,[1,3] Jeffrey G. Dickhout.[1,2] *[1]Health Sciences, McMaster Univ, Hamilton, ON, Canada; [2]Nephrology, St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada; [3]Firestone Inst for Respiratory Health, St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada.*

Background: CHOP (GADD153/DDIT3) is a transcription factor that is upregulated during endoplasmic reticulum (ER) stress in chronic kidney disease (CKD). CHOP impacts protein translation during ER stress. It induces GADD34 that relieves the block in translation caused by eIF2a phosphorylation. Nephrin is the key component of the podocyte slit diaphragm maintaining the glomerular filtration barrier to albumin. Under conditions of ER stress-induced translation attenuation, predominant in CHOP knockout, nephrin has been shown to be preferentially translated. Therefore, we hypothesized that CHOP deficiency would result in higher nephrin expression, a more intact glomerular structure, and lower proteinuria in response to CKD.

Methods: Our model of CKD was based on reduced renal mass and Angiotensin II/DOCA infusion in C57BL/6 male mice. CHOP deficient mice on the C57BL/6 genetic background were used to test the effect of CHOP knockout in the CKD model. CKD was assessed using blood pressure and 24h total urinary protein and albumin excretion. On day 21 of the model, mice were sacrificed. PAS staining was used to evaluate renal pathology and glomerular damage. Nephrin mRNA levels were measured using Nanostring analysis and nephrin protein levels from renal tissue lysates.

Results: In response to the CKD model, both CHOP$^{-/-}$ and wild type (WT) mice showed similar significant increases in systolic and diastolic blood pressure. However, CHOP$^{-/-}$ mice showed significantly lower proteinuria and albuminuria. In addition, CHOP deficiency significantly decreased intertubular cast formation and glomerular sclerosis index. CHOP$^{-/-}$ mice, however, had significantly higher levels of nephrin mRNA and protein in the kidney in response to CKD.

Conclusions: CHOP deficiency resulted in a decrease in proteinuria and improved glomerular structure as well as increased nephrin expression. These findings indicate CHOP inhibition as a mechanism to maintain glomerular integrity. Funding: Government Support-MOP-133484.

Funding: Government Support - Non-U.S.

FR-PO151

Caspase-1 Activation Contributes to Hypertension-Induced Glomerular Injury and Focal Segmental Glomerulosclerosis Jinghui Luo,[1] Yingbao Yang,[1] Stephanie Wylie,[1] Tamra J. Reed,[2] J. Michelle Kahlenberg,[2] Jeffrey B. Hodgin.[1] *[1]Pathology, Univ of Michigan; [2]Rheumatology, Univ of Michigan, Ann Arbor, MI.*

Background: Hypertension is a leading cause of end-stage kidney disease and a significant determinant of focal segmental glomerulosclerosis (FSGS). However, the cellular and molecular responses to glomerular hyperfiltration are not well understood. Recent studies highlight the inflammasome in the pathogenesis of diabetic nephropathy and related podocyte injury. We find a robust upregulation (priming) of inflammasome-related gene expression in glomeruli of diabetic and non-diabetic patients with FSGS and/or hypertension. We hypothesize that caspase-1 activation contributes to hypertension-mediated albuminuria and FSGS.

Methods: Caspase-1 knockout (KO) and wildtype (WT) BALB/c mice (n=8-10 per group) were uninephrectomized, implanted with osmotic minipumps releasing Ang2 (1.2 ug/kg/min), and given 1% salt water for 4 weeks (wks). Control groups received sham, saline infusion, and normal water. Blood pressure (BP) and albumin/creatinine ratio (ACR) were measured at 2-wk intervals and kidneys harvested for histology. Immortalized human podocytes were treated with Ang2, LPS, +ATP to investigate caspase-1 activation.

Results: Ang2 similarly elevated BP in both WT and KO mice at 2 and 4 wks versus control. At 2 weeks, ACR was increased in both groups (10mg/mg), however ACR in WT >doubled by 4 wks, whereas KO mice remained stable ($p<0.01$). Histologic analysis revealed 3-fold more FSGS in Ang2 treated WT vs KO mice ($p<0.05$). In cultured podocytes, Ang2 alone (500nM & 1mM) activated caspase-1 6-8-fold vs controls, and 8-10-fold combined with LPS (Ang2 as inflammasome activator) or ATP (Ang2 as inflammasome primer). LPS+ATP increased caspase-1 activity 14-fold. Westerns showed increased caspase-1, ASC, and IL1beta with Ang2 and LPS.

Conclusions: Caspase-1 loss significantly abrogates Ang2/hypertension-mediated albuminuria and FSGS in our model, and Ang2 primes and activates the inflammasome in human podocytes. Our mouse and human data demonstrate an important role for caspase-1 activation in the pathogenesis of hypertension-mediated podocyte injury and FSGS that may prove therapeutically targetable.

Funding: NIDDK Support

FR-PO152

RNA-seq Based Differential Expression Analysis in Rats with Slit Diaphragm Specific Dysfunction: The Glomerular Gene Expression Profiles of Nephropathy Induced by Anti-Nephrin Antibody Ying Zhang, Yoshiyasu Fukusumi, Hiroshi Kawachi. *Dept of Cell Biology, Kidney Research Center, Niigata Univ, Niigata, Japan.*

Background: Slit diaphragm (SD) dysfunction is understood to be involved in the development of proteinuria in several types of glomerular diseases. However, the pathogenic mechanism of the SD dysfunction is not well elucidated. The aim of this study is to identify novel molecules involved in the SD dysfunction.

Methods: The glomerular gene expression profiles of rat nephropathy induced by the injection of anti-nephrin antibody were examined by RNA sequencing (RNA-seq) with the Next-Generation Sequencer. Differentially expressed molecules were further analyzed by Gene Ontology (GO) and KEGG pathway analysis using DAVID.

Results: mRNA expressions of 870 genes were reduced to less than 50% at 1h when abnormal proteinuria was not detected yet, and those of 601 genes were reduced on day 5 when proteinuria peaked.mRNA expressions of 880 and 794 genes were increased to more than 2 folds at 1h and on day 5, respectively.We focused on 870 molecules which are down-regulated at 1h, since they are supposed to be potential molecules involved in the onset of proteinuria. GO analysis indicated 163 of the 870 genes were clustered in plasma membrane, and enrichment analysis revealed transmembrane receptor tyrosine kinase activity was the most significant over-represented molecular function for these 163 plasma membrane molecules. KEGG pathway analysis showed RAP1 signaling pathway is most significantly enriched. In the 870 molecules the most evidently down-regulated molecule is Hmgcs2 (3.8% to normal) and the second is Slc5a8 (4.3%). The reduction in gene expression levels of these two molecules were validated by real-time PCR. Glomerular expressions of these molecules were detected by Western blot analysis and the distribution of Slc5a8 in podocyte was observed by immunohistochemical analysis.

Conclusions: RNA-seq analysis with nephrotic glomeruli showed Hmgcs2 and Slc5a8 are involved in the early event of the SD dysfunction. GO and KEGG analyses showed the altered RAP1 pathway modulated by receptor tyrosine kinases participates in the development of proteinuria in the SD dysfunction.

Funding: Government Support - Non-U.S.

FR-PO153

Preservation of Glomerular Architecture in Aged Mice via Systemic Late-Age Intervention with SS-31 Mariya T. Sweetwyne,[1] Jeffrey W. Pippin,[1] Diana G. Eng,[1] Kelly L. Hudkins,[2] Charles E. Alpers,[2] Ying Ann Chiao,[2] Hazel H. Szeto,[3] Peter S. Rabinovitch,[2] Stuart J. Shankland.[1] *[1]Nephrology, Univ of Washington, Seattle, WA; [2]Pathology, Univ of Washington, Seattle, WA; [3]Pharmacology, Weill Cornell Medical College, New York, NY.*

Background: The mitochondrial targeted peptide, SS-31, prevents mitochondrial damage and reduces cellular injury. Mitochondrial damage and oxidative stress accumulate with age. Thus, we hypothesized that SS-31 peptide would prevent/limit the progression of glomerular disease with aging.

Methods: 24-month old mice (~70 yr-old human) received either 8w of SS-31, or saline, by osmotic pump. Animals were sacrificed at 26m (~79 yr-old human) and tissues analyzed by quantitative histology. Untreated 24m-old animals were used to perform baseline measurements.

Results: SS-31 partially but significantly, inhibited the development of glomerulosclerosis (PAS). The age-associated decrease in podocyte density was not altered, but SS-31 treatment limited podocyte injury (desmin), and improved podocyte integrity (synaptopodin). 26m-old 8w SS-31 treated mice also had higher glomerular endothelial cell density (CD31). Parietal epithelial cells (PEC) were the most protected glomerular cell as SS-31 treatment significantly increased PEC density above 24m baseline and yet decreased PEC activation markers (staining for active phospho-ERK1/2, α-smooth muscle actin, COLIV). Thus suggesting that PEC responses are still malleable at late age. Glomerular mitochondrial damage was evident in 26m-old saline treated mice by electron microscopy but was attenuated in PECs and podocytes in SS-31 treated aged mice. Consistent with decreased oxidative activity, SS-31 reduced Nox4 staining in podocytes, mesangium and PECs. Cellular senescence (p16) was also reduced in tuft cells and PECs of aged SS-31 treated mice as compared to saline controls.

Conclusions: In mice of advanced age, mitochondrial protection via SS-31 intervention lowers glomerulosclerosis, increases PEC density but lowers their activation, improves podocyte and endothelial cell integrity, and reduces senescence. This demonstrates that age-induced renal injury can be attenuated even in individuals of advanced age.

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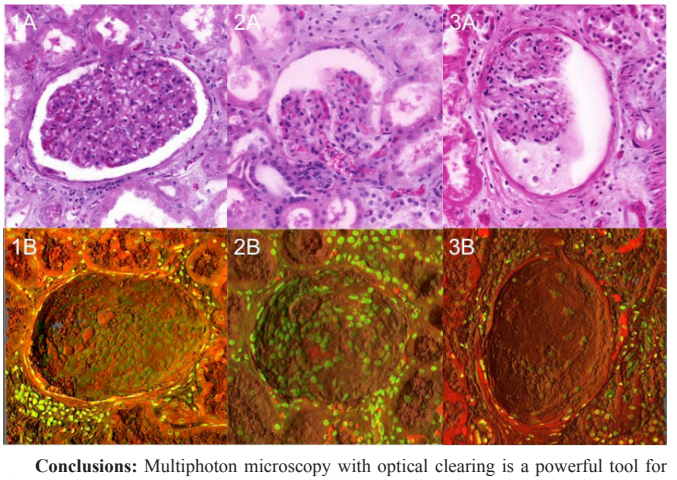
FR-PO154

Morphologic Changes in Human Parietal Epithelial Cells Using 3D Capsular Reconstructions Parker C. Wilson,[1] Gilbert W. Moeckel,[1] Robert L. Safirstein,[2] Richard Torres.[1] *[1]Pathology and Laboratory Medicine, Yale Univ School of Medicine; [2]Nephrology, Yale Univ School of Medicine.*

Background: There has been recent interest in the role of parietal epithelial cells (PEC) in the evolution of kidney disease. However, PEC morphology cannot be adequately visualized using traditional microscopy due to the limitations of 2D histologic sections. We employed a new imaging method based on multiphoton microscopy and chemical clearing to improve glomerular capsule visualization.

Methods: High-resolution 3D microscopic images of entire glomeruli were obtained from autopsies with well-preserved kidneys and varying degrees of chronic kidney disease (CKD). Tissue clearing was performed to enable high resolution deep tissue imaging on a home-built multiphoton microscope. Glomeruli were digitally removed to reveal capsular surface morphology on 3D reconstruction.

Results: Individual kidneys showed a range of capsular morphologies. In the absence of CKD, parietal epithelial cells (PEC) had rounded nuclei and were evenly-spaced in a single layer covering the capsule (1A,1B). In patients with CKD, disorganized architecture and nuclear elongation was a feature of capsules from otherwise normal-appearing glomeruli with patent proximal tubules (2A,2B). Severely affected capsules from patients with CKD showed marked reduction in epithelial cell number and was associated with capsular thickening, fibrotic capsules with coarse contours, and damaged proximal tubules (3A,3B).



Conclusions: Multiphoton microscopy with optical clearing is a powerful tool for visualization of glomerular capsules, atubular glomeruli, and associated proximal tubule changes in human specimens. Glomerular capsule changes may be linked to proximal tubule damage in chronic kidney disease.

FR-PO155

Progressive Pathological Profile of the Passive Nephrotoxic Nephritis Model in CD1 and C57BL/6 Mice Maria Katarina Ougaard,[1,2] Peter Helding Kvist,[1] Henrik Elvang Jensen,[2] Constanze Hess,[1] Claus Haase,[1] Henrik Søndergaard.[1] *[1]Diabetes Complications Pharmacology, Novo Nordisk A/S, Denmark; [2]Dept of Veterinary Disease Biology, Uni. of CPH, Denmark.*

Background: When modelling human diseases in mice, different susceptibility to specific diseases needs to be considered. CD1 mice are a commonly used outbred stock of mice for studies of chronic kidney disease, supposedly due to their proneness to develop kidney fibrosis. In this study C57BL/6 (B6) and CD1 mice were compared for their susceptibility to develop nephropathy in the passive nephrotoxic nephritis (NTN) model.

Methods: Initially, 100 and 250 µl of sheep anti-rat GBM antibody containing nephrotoxic serum (NTS) was identified as the preferred doses to induce NTN in CD1 and B6 mice, respectively. In a longitudinal study, the urinary albumin excretion rate (UAER) was measured on day 2-3, 6-7, 16-17, and 36-37 post NTS injection. On day 7, 21, and 42 post NTS injection, kidneys were harvested and stained with Perl, PAS and collagen III by immunohistochemistry. Mesangial expansion (ME) was graded from 0 to 3, in a blinded fashion.

Results: NTN induction resulted in significantly increased UAER already on day 2-3 in CD1 and B6 mice (mean±SD 233.7mg/24h±134.4; 68.2mg/24h±75.5) compared to their healthy controls (mean±SD 97.1mg/24h±31.2; 40.1±17.7), and this continued until day 36-37. On day 2-3, 6-7, and 16-17 UAER was significantly increased in CD1 NTN mice compared to the B6 NTN mice. Both CD1 and B6 NTN mice revealed significant, but similar progressive ME on day 7, 21, and 42, suggesting that disease might exacerbate beyond day 42. Perl staining showed increased renal iron accumulation on day 21 and 42 in both CD1 and B6 NTN mice, suggesting that iron accumulation is a pathological feature in this model. An increased deposition of collagen III was observed in the renal cortex in CD1 and B6 NTN mice on day 21 and 42, suggesting a similar renal fibrosis development in CD1 and B6 mice.

Conclusions: Taken together, CD1 and B6 mice show significant, progressive, but similar renal pathology up to day 42 when subjected to passive NTN. Moreover, both murine strains are useful for studies related to UAER, ME progression, and renal fibrosis, when subjected to NTN.

FR-PO156

Gene Expression Profiling of Proximal Tubular Cells - A Novel Experimental Technique James Alexander Tomlinson,[1,2] Claire Bruce-Cobbold,[1] James M. Leiper.[1] *[1]MRC CSC, Imperial College, London, United Kingdom; [2]Renal Section, Dept of Medicine, Imperial College, London, United Kingdom.*

Background: Gene association and experimental studies implicate the proximal tubule (PT) as a major effector cell in progressive renal fibrosis but PT-specific maladaptive responses to injury *in vivo* are not well-defined. Previous techniques to isolate tubular cell genetic material remain limited by residual contamination from other kidney cell-types and gene expression changes elicited by the isolation technique itself. We have developed a novel ribosomal protein tag-and-capture technique to isolate proximal tubular cell messenger RNA (mRNA) transcripts from whole kidneys.

Methods: The *RiboTag* mouse strain has a mutated ribosomal protein L22 (Rpl22) locus with three copies of the haemagglutinin (HA) epitope after a STOP codon. When bred with a proximal tubule-specific kidney androgen-sensitive protein Cre recombinase (*KAPiCre*) strain, female mice expressed HA-tagged Rpl22 protein confined to kidney proximal tubular cells induced by testosterone treatment.

Results: Western blot analysis of whole kidney tissue showed strong HA protein expression in *Ribotag* homozygous mice, >50% less in heterozygous mice and not in the absence of either *KAPiCre* or *Ribotag* genes. Immunohistochemical staining revealed strong HA protein expression within proximal tubules and not in other kidney structures. Ribosomal immunoprecipitation yielded 100-300ng/uL of RNA from a single kidney, with negligible yield from control *KAPiCre* negative animals (<5ng/uL). Proximal tubular-specific gene markers including megalin, *NHE3* and *AQP1* were enriched (2 – 3-fold), whilst gene markers associated with other cell types, *αSMA* (mesenchymal cells/fibroblasts) and *UMOD* (thick-ascending limb cells) were reduced (upto 10-fold) compared to whole kidney extract.

Conclusions: This novel technique permits proximal tubular gene expression analysis at any given time-point during the evolution of renal fibrosis using targeted RT-qPCR or non-biased RNA sequencing. Future studies using this experimental tool will provide new insights into how the proximal tubule responds to renal injury and repair, thus making a valuable contribution to our understanding of CKD pathogenesis.

FR-PO157

Proximal Tubule-Specific Intracellular-Type Nampt Conditional Knockout Mice Exhibited Renal Fibrosis and Basement Membrane Thinking via Suppression of Sirt1 and/or 6 Hirokazu Muraoka, Kazuhiro Hasegawa, Shu Wakino, Hiroshi Itoh. *Dept of Endocrinology, Metabolism and Nephrology, Keio Univ, Shinanomachi, Tokyo, Japan.*

Background: Intracellular-type Nicotinamide phosphoribosyltransferase (iNampt) cooperates with NAD-dependent deacetylase Sirtuins, to exert the potentiation of stress resistance and longevity. We previously reported that proximal tubule (PT)-specific Sirt1 transgenic mice are protected against diabetic nephropathy (DN), and that PT-conditional knockout (CKO) mice exhibited aggravation of DN (Nature Medicine,2013). We also showed that the high expression level of iNampt in PTs contributes to the sufficient supply of nicotinamide mononucleotide (NMN), a precursor of NAD, to glomeruli. In this study, we established PT-specific conditional Nampt-deficient mice to investigate the role of iNampt in DN.

Methods: We generated PT-specific, iNampt-deficient mice by crossing $Nampt^{flox/flox}$ mice with γ-GT-Cre mice. Wild-type (WT) and CKO mice were injected with saline (SAL; control) or streptozotocin (STZ) to induce DN. The phenotypes of mice, WT+Sal, CKO+Sal, WT+Sal, and CKO+STZ, were analyzed at 8 and 24 weeks after treatment.

Results: Periodic acid methenamine silver, Masson-trichrome, and Elastica van Gieson staining revealed notable thickening of the tubular basement membrane and basement membrane of Bowman's capsule. Peritubular and periglomerular fibrosis in the cortex and perivascular fibrosis surrounding interlobular arteries and veins in the medulla were clearly detected in CKO mice. DNA microarray showed that expression of tubular tissue inhibitor of metalloproteinase 1 (TIMP-1) and latent transforming growth factor beta binding protein 2 (LTBP-2) was elevated in CKO mice, which might cause the histological changes. Among all isoforms of sirtuin proteins, the activity of only SIRT1 and SIRT6 were significantly decreased in the CKO mice.

Conclusions: We revealed that iNampt deficiency in PTs has unfavorable effects on the phenotype of broad bridging fibrosis through the overproduction of TIMP-1 and LTBP-2. The decreased activities of SIRT1 and 6 would be responsible for this change. Nampt in PTs is a safeguard against the initiation and progression of DN-induced fibrotic progression.

FR-PO158

Modulation of Proximal Tubule Endocytic Capacity by Shear-Stress Stimulated Cell Differentiation Kimberly R. Long,[1] Katherine Shipman,[1] Youssef Rbaibi,[1] Megan Eshbach,[1] Ora A. Weisz.[1,2] *[1]Medicine - Renal/ Electrolyte, Univ of Pittsburgh School of Medicine, Pittsburgh, PA; [2]Cell Biology, Univ of Pittsburgh School of Medicine, Pittsburgh, PA.*

Background: Epithelial cells that line the proximal tubule (PT) of the kidney are responsible for the reabsorption of low molecular weight proteins and other small molecules from the glomerular ultrafiltrate. Efficient uptake of these filtered proteins is essential to prevent tubular proteinuria.

Methods: Because cells in the kidney are continuously exposed to flow and the accompanying fluid shear stress (FSS), we asked whether continuous growth under FSS affects cell morphology and constitutive endocytic capacity. To this end, opossum kidney cells were plated on permeable filter supports, and the following day were exposed to orbital FSS or maintained under static conditions for an additional four days.

Results: Filters exposed to FSS had roughly 25% more cells than those maintained under static conditions as quantified using DAPI staining. Additionally, cells exposed to FSS were taller, had a more extensive brush border, and contained more apical endocytic compartments than cells grown under static conditions. Endocytic capacity per cell, quantified based on uptake of fluorescently-labeled albumin, was also dramatically increased (>2-fold) in cells cultured under FSS. This effect could be reset by overnight incubation under static conditions prior to albumin uptake. Interestingly, cells exposed to twice our normal orbital speed had a 5-fold increase in endocytic capacity per cell, and albumin uptake could be rapidly modulated by changes in FSS in these cells. Ultrastructural analysis revealed striking differentiation of the apical brush border and endocytic pathway in these cells, similar to that observed in PT cells *in vivo*.

Conclusions: Growing cells under continuous FSS better replicates the characteristics of PT cells *in vivo* and may represent a more physiologic *in vitro* model system in which to study protein uptake and the endocytic pathway in PT cells.

Funding: NIDDK Support

FR-PO159

Deleting the TGF-β Receptor in the Proximal Tubule Worsens the Response to Chronic Injury due to Altered β-Catenin Activation Stellor Nlandu Khodo,[1] Surekha Neelisetty,[1] Melanie Phillips,[1] Raymond C. Harris,[1,2] Leslie S. Gewin.[1,2] *[1]Medicine, Vanderbilt Medical Center, Nashville, TN; [2]Medicine, Veterans Affairs Hospital, Nashville, TN.*

Background: TGF-β is arguably the strongest profibrotic factor in chronic kidney disease (CKD), but its effects vary depending upon the target cell type. We previously demonstrated that blocking TGF-β signaling in the proximal tubule (PT), the main target of renal injury, protected renal function after acute kidney injury (AKI) in mice; how TGF-β signaling in the PT affects CKD progression is still unclear.

Methods: To address this, we selectively deleted the TGF-β type II receptor (TβRII) in the PT using the γGT-Cre. These conditional knockout (KO) mice and littermate controls were injured by either aristolochic acid (AA) or uninephrectomy/angiotensin II. To define the mechanism underlying the observed response, we used PT cells with and without TβRII as well as mice with conditional stabilization of β-catenin in the PT.

Results: Surprisingly, conditional KO mice had a worse response to chronic injury as assessed by increased tubular injury (histology, KIM-1 levels), fibrosis (collagen I expression), and renal function. In addition, deleting the TβRII increased epithelial apoptosis both in vivo and in PT cells treated with AA in vitro. As TGF-β signaling interacts with the β-catenin pathway, and β-catenin activation has been shown to reduce apoptosis in murine AKI, we investigated how abrogating TGF-β signaling alters β-catenin activity. Both renal cortices from injured conditional KO mice and $T\beta RII^{-/-}$ PT cells had reduced nuclear β-catenin and axin2 mRNA compared to tissue and cells with the receptor intact. The increased apoptosis in AA-treated $T\beta RII^{-/-}$ PT cells was reduced by pharmacologically augmenting β-catenin activity. We crossed our conditional KO mice with those containing conditional activation of β-catenin and injured them using AA. The activating β-catenin mutation reduced the renal injury in mice lacking TβRII in the PT.

Conclusions: In conclusion, genetically inhibiting TGF-β signaling in the PT worsened the response to chronic injury by increasing epithelial apoptosis, in part, due to compromised β-catenin signaling.

Funding: VA Support

FR-PO160

Thioredoxin Interacting Protein: A Novel Regulator of Tubular Autophagy and Mitophagy in Diabetic Nephropathy Chunling Huang, Xinming Chen, Carol A. Pollock. *Renal Lab, Kolling Inst, Univ of Sydney, Sydney, NSW, Australia.*

Background: Dysregulation of autophagy contributes to the development of diabetic nephropathy. Hyperglycemia upregulates TXNIP expression, which in turn induces the generation of reactive oxygen species (ROS), inflammatory and fibrotic responses in diabetic nephropathy. The aim of the study is to define the interaction of thioredoxin interacting protein (TXNIP) with autophagy/mitophagy in diabetic nephropathy.

Methods: Transgenic (mRen-2) rats with streptozotocin-induced diabetes were given TXNIP DNAzyme or scrambled DNAzyme for 12 weeks respectively. Total collagen deposition, type I collagen expression, mitochondrial function and mitochondrial ROS (mtROS) production were assessed. The formation of autophagosomes and autophagic clearance were determined in kidneys from both human and rats with diabetes. The colocalization of LC3 and P62 within mitochondria was used to monitor mitophagy. Autophagic signaling molecules including BNIP3, mTOR and p70S6 were examined.

Results: TXNIP DNAzyme dramatically attenuated total collagen deposition and type I collagen expression in the kidneys of diabetic rats compared to the control DNAzyme. LC3 and P62 expression were increased in the renal tubular cells of human diabetic kidneys compared to non-diabetic controls, which indicates accumulated autophagosomes and reduced autophagic clearance. The increased LC3 and P62 in the renal tubular cells of diabetic rats were reversed by TXNIP DNAzyme. High glucose induced mitochondrial dysfunction, mtROS production, and inhibited mitophagy in the renal tubular cells, which were reversed by TXNIP siRNA. Inhibition of TXNIP suppressed diabetes-induced BNIP3 expression and activation of the mTOR signaling pathway.

Conclusions: Hyperglycemia-induced TXNIP contributes to the dysregulation of tubular autophagy and mitophagy in diabetic nephropathy through activating mTOR signaling pathway.

FR-PO161

Hypoxia-Inducible Factor Agonist Ameliorates Impact of Tubulointerstitial Injury on Subsequent Glomerular Injury Jun Zou,[1] Jianyong Zhong,[2,3] Taiji Matsusaka,[4] Volker H. Haase,[5] Haichun Yang,[2,3] Agnes B. Fogo.[2,3] *[1]Nephrology, Xin Hua Hospital, Shanghai, China; [2]Pathology, Microbiology and Immunology, Vanderbilt Univ; [3]Pediatric Nephrology, Vanderbilt Univ; [4]Inst of Medical Science, Tokai Univ, Isehara, Japan; [5]Nephrology, Vanderbilt Univ, Nashville, TN.*

Background: We previously found that tubulointerstitial injury sensitizes to subsequent glomerular injury, with increased peritubular capillary permeability and tissue hypoxia in folic acid-induced tubulointerstitial injury. Hypoxia-inducible factors (HIFs) regulate hypoxia and angiogenesis. In this study, we evaluated whether dimethyloxalylglycine (DMOG), an inhibitor of HIF-α degradation, can ameliorate tubulointerstitial injury and its impact on subsequent glomerular injury.

Methods: Col I-luciferase mice, with luciferase in the collagen I promoter, were mated with Nep25 mice, which express human CD25 receptor on podocytes, and develop glomerulosclerosis when LMB2 toxin is administered. Mice, 12 wk old males, received folic acid (FA, 240mg/kg BW, i.p.) or vehicle (VE), and subgroups were treated with DMOG (8 mg qod, i.p.) from wk 3 till 6. Uninephrectomy was performed at wk 6 to assess extent of tubulointerstitial fibrosis, and LMB2 was injected at wk 7. Ten days later, mice were sacrificed.

Results: Kidneys from UniNx, before added glomerular injury, showed that DMOG elevated HIF-1α and HIF-2α mRNA in FA+DMOG vs FA. Pimonidazole, a tissue marker of hypoxia, was attenuated in FA+DMOG vs FA. VEGFA mRNA was significantly increased and collagen I reduced in FA+DMOG vs FA. CD31 staining, a marker of peritubular capillaries, was not different among groups. At sacrifice, body weight increase (marker of edema) was less in FA+DMOG vs FA, despite similar proteinuria. Collagen I bioluminescence signal was also decreased in FA+DMOG vs FA. Mice with FA+podocyte injury showed increased mortality, which was also reduced by DMOG (FA+DMOG 14.3 vs. FA 55.6% death rate), linked to improved renal function.

Conclusions: Our findings indicate that hypoxia contributes to tubular injury sensitizing to subsequent glomerular injury, and restoring HIFs may blunt this adverse crosstalk of tubules to glomeruli.

Funding: NIDDK Support

FR-PO162

Darunavir Protects Renal Tubular Epithelial Cells against HIV-Induced Injury via Mechanisms Independent of Suppression of HIV Replication Xiaobo Gao, Alan Rosales, Heidi Karttunen, Michael J. Ross. *Medicine, Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: HIV-associated nephrology (HIVAN) is an important cause of end-stage renal disease (ESRD) in HIV-positive patients. HIVAN is caused by infection of renal epithelial cells, but viral replication in these cells is not necessary to induce disease. Expression of HIV Vpr and Nef proteins causes dysregulation of cellular signaling pathways, including Stat3, ERK, and Src, and activation of innate immune responses. Antiretroviral therapy (ART) markedly reduces the risk of progression to ESRD without eradicating HIV in the kidney and the mechanism(s) by which ART protects kidneys from HIVAN is poorly understood.

Methods: Described in results section.

Results: Since previous suggest that HIV protease inhibitors have pleiotropic effects on cell signaling, we tested our hypothesis that HIV protease inhibitors protect the kidneys from HIVAN via HIV-independent mechanisms. Conditionally immortalized human tubular epithelial cells (RTEC) were infected with *gag/pol*-deleted HIV (does not express HIV protease and cannot replicate), Vpr lentivirus, or control lentivirus and subsequently treated with the HIV protease inhibitor darunavir (DRV) or vehicle control. Western blotting studies demonstrated that DRV significant attenuated HIV and Vpr-induced activation of Stat3, ERK, and Src. DRV also decreased HIV and Vpr induced expression of IL-6 and IL-8, which we had previously demonstrated to be important mediators of inflammation in HIVAN. Moreover, DRV also decreased cleavage of PARP1 in HIV and Vpr-transduced RTEC, suggesting that DRV prevented caspase-induced apoptosis.

Conclusions: Since the HIV and Vpr vectors used in these studies were replication-defective and did not encode HIV protease, the protective effects of DRV were likely mediated by direct effects upon RTEC signaling pathways. Together, these data support our hypothesis that ART protects the kidney against HIV-induced injury and inflammatory response in part, via mechanisms that are independent of suppression of HIV replication.

Funding: NIDDK Support

FR-PO163

Renin Accelerates Progression of HIVAN via Enhanced HIV Gene Expression Partab Rai, Manoj K. Tembhre, Vinita Vishnoi, Nairuti H. Shah, Judith Eng, Ashwani Malhotra, Pravin C. Singhal. *Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY.*

Background: The activation of renin angiotensin system (RAS) has been demonstrated to play an important role for the the progression of HIVAN. Recently, cells of renin lineage have been shown to convert into podocytes in deactivated RAS. We have previously demonstrated that HIV enhances kidney cell renin expression. We now hypothesize that HIV-induced renin production might be causing kidney cell injury through enhancement of HIV gene expression.

Methods: Human podocytes (HPs) were tranducded with either vector (V/HP) or HIV (NL4-3, HIV/HP). To increase endogenous renin production, V/HPs and HIV/HPs were transfected with siRNA vitamin D receptor (siRNA-VDR/HIV/HPs) or scrambled (Scr-siRNA/HIV/HP) siRNA; protein blots were probed for renin and actin. To evaluate the effect of renin *in vivo*, mRNA expressions of HIV genes from renal tissues of HIVAN (Tg26) mice with high endogenous renin (Tg26 mice either with 2, 3 and 4 copies of angiotensinogen [Agt] or lacking VDR) were quantified by qPCR. To down regulate renal tissue renin expression, Tg26 mice were treated with either vehicle or a VDR agonist (VDA) for 2 weeks and then renal tissues were evaluated for HIV gene expression. in addition, gene expression and progression of renal lesions were compared in Tg26 mice and Tg26 mice lacking renin.

Results: HIV enhanced renin expression in HPs. Silencing of VDR in HIV/HPs further enhanced expression of Nef, Tat, and Vif. However, VDA down regulated HIV gene expression in HIV/HPs. Renal tissues of Tg26-Agt-4 displayed 2-4 fold increase in mRNA expression of gp120, Vpr, Tat, Nef and Vpu vs. Tg26-Agt-2. Similarly, Tg26 mice lacking VDR displayed greater HIV gene expression when compared with Tg26 mice with intact VDR. VDA treatment of Tg26 mice not only down regulated renal tissue expressions of renin but also attenuated expression of HIV genes. Tg26 mice lacking renin, displayed attenuated renal tissue HIV gene expression and slowed progression of renal lesions.

Conclusions: Renin enhances renal tissue and podocyte HIV gene expression and induces accelerated progression of renal lesions.

Funding: NIDDK Support

FR-PO164

Reciprocal Interaction between (Pro)renin Receptor and Wnt/β-Catenin Drive Kidney Injury and Fibrosis Zhen Li,[1] Lili Zhou,[1] Xue Hong,[1] Jinhua Miao,[1] Youhua Liu.[1,2] *[1]Div of Nephrology, Nanfang Hospital, Southern Medical Univ, Guangzhou, Guangdong, China; [2]Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA.*

Background: The (pro)renin receptor (PRR) is a newly discovered, multi-functional protein that plays a critical role in the activation of the renin-angiotensin system (RAS). However, its regulation and potential role in the pathogenesis of chronic kidney disease (CKD) are poorly understood. In this study, we show that PRR not only is a downstream target but also an upstream regulator of Wnt/β-catenin signaling.

Methods: The expression of PRR in three models of kidney disease induced by ischemia/reperfusion injury (IRI), adriamycin or chronic angiotensin II infusion was assessed by Western blot and immunostaining. Human kidney tubular cells (HKC-8) were transfected with Wnt1 and/or PRR expression vectors. In vivo expression of Wnt1 and/or PRR was also carried out in mouse model of IRI.

Results: In various models of CKD, PRR was upregulated predominantly in renal tubular epithelium, and over-expression of either Wnt1 ligand or β-catenin induced PRR mRNA and protein expression *in vitro*. Interestingly, over-expression of PRR potentiated Wnt1-mediated β-catenin activation and promoted the expression of its downstream target genes such as fibronectin, plasminogen activator inhibitor 1 and α-smooth muscle actin. Conversely, knockdown of PRR by siRNA abolished β-catenin activation and its target

genes expression induced by Wnt1, suggesting that PRR is an obligatory component of the Wnt/β-catenin signaling. We found that the effect of PRR on Wnt/β-catenin signaling was independent of renin. In mouse model of IRI, expression of either exogenous PRR or Wnt1 promoted β-catenin activation and aggravated kidney dysfunction and fibrotic lesions. Furthermore, co-expression of both PRR and Wnt1 accelerated kidney function decline, and deteriorated interstitial fibrosis and inflammation after ischemic injury.

Conclusions: These results establish that PRR is both a target and an essential component of Wnt/β-catenin signaling. Our studies suggest that PRR induction and Wnt/β-catenin activation constitutes a vicious cycle, which drives kidney dysfunction and fibrosis after injury.

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

FR-PO165

Renal Tissues of HIV Transgenic Mice (Tg26 and Vpr) and Parietal Epithelial Cells Display Attenuated miR-193a Expression

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Background: MicroRNAs (miR) regulates gene transcription both in physiological and pathological conditions. Both parietal epithelial cells (PECs) and podocytes (PD) are derived from mesenchymal lineage during embryogenesis. miR-193a is highly expressed in matured PECs but least expressed in matured PDs. miR193a acts as a switch to determine the phenotype of both PDs and PECs via modulation of WT1, a master transcriptor of podocalyxin and nephrin. Recently, enhanced expression of miR-193a has been considered to play critical role in the development and progression of focal segmental sclerosis. However, the role of miR193a in the development of HIV associated nephropathy (HIVAN) has not been elucidated to date.

Methods: Renal tissues from 4 week old control (FVBN) and HIV transgenic mice (Tg26 mice on FVB/N background), 4 week old control and Vpr mice (treated with doxycycline for 6 weeks) were harvested. Human immortalized PECs and PDs were transduced with either HIV (NL4-3) or vector. A microarray-based approach in combination with real-time PCR to profile the miR expression patterns in HIV-1 transgenic mice. Both renal tissues and transduced cells were evaluated for expression of miR193a using the miRNeasy kits from Qiagen. Renal cortical sections of control and HIV mice were also evaluated for kidney cell expression of miR-193a utilizing *in situ* hybridization technique.

Results: 13 miRNAs, which belong to 11 miR families, were down regulated in HIVAN when compared with control mice. Expression of miR-193a was down regulated by 5 and 10 fold in renal tissues of Tg26 and Vpr transgenic mice, respectively. In situ hybridization studies revealed down regulation of miR193a in PECs in HIV transgenic mice. In vitro studies, HIV- transduced PDs as well as PECs displayed attenuated expression of miR193a when compared to respective vector-transduced cells.

Conclusions: HIV down regulates miR193 both in podocytes and PECs *in vitro* as well as *in vivo*.

FR-PO166

PGC-1α Protects against Notch1-Induced Kidney Injury

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Background: PGC1α is known as a key regulator of energy metabolism and mitochondrial biogenesis. However, there is lacking of evidence on whether PGC1α provides a protective effect against kidney damage. This study evaluated the effect of PGC1α on kidney fibrosis using mice with tubule-specific double overexpression of Notch1 and PGC1α.

Methods: For animal study, we crossed mice expressing *Pax8-rtTA/tetO-ICN1* (N) with mice harboring *Pax8-rtTA/tetO-Ppargc1a* (P) to create *Pax8-rtTA/tetO-ICN1/tetO-Ppargc1a* (NP) mice. Using kidney tissues from these mice, we examined fibrotic changes, fatty acid oxidation pathway, and cell death. To delineate relationship between Notch1 and PGC1α,chromatin immunoprecipitation (ChIP) assay and luciferase assay were performed using primarily cultured tubular epithelial cells.

Results: Compared to control mice, normal renal architecture was lost and severe tubular dilatation and fibrosis developed in Nmice. In contrast, these findings were almost null in NP mice. Fatty acid oxidation was impaired in N mice and this alteration was significantly restored by PGC-1α overexpression. In addition, PGC-1α overexpression attenuated the increased apoptosis rate in N mice. ChIP assay revealed that the transcriptional repressor Hes1, a downstream target of Notch1 signaling, directly regulated PGC-1α in kidney tubular epithelial cells. Furthermore, Hes1 overexpression significantly inhibited *Ppargc1a* promoter–driven luciferase reporter activity.

Conclusions: Tubule-specific Notch1 overexpression decreased PGC-1α expression and impaired fatty acid oxidation, resulting in severe kidney fibrosis. Notch1-induced kidney injury was almost nullified by PGC-1α. In addition, PGC-1α was directly regulated by Notch signaling. Our findings suggest that restoring PGC-1α activity can be a promising therapeutic strategy in the management of chronic kidney disease.

FR-PO167

Early Intervention through Induced Genetic Deletion of Cell Division Autoantigen 1 Attenuates Diabetes-Associated Renal Fibrosis

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Background: CDA1 plays a key role in the development of diabetic nephropathy, where it enhances the profibrotic actions of the TGF-β signalling pathway. This was demonstrated *in vivo* where global CDA1 knockout mice exhibited an attenuation in renal fibrosis in a model of diabetic nephropathy. Whether inhibiting CDA1 activity after the development of disease can attenuate renal fibrosis has yet to be experimentally investigated. This study focuses on the effect of an early intervention by induced genetic deletion of CDA1 on the progression of renal fibrosis in a *streptozotocin* (STZ)-induced mouse model of diabetic nephropathy.

Methods: Male CDA1flox/ERCre mice were rendered diabetic and killed 10 weeks later for analysis of various metabolic and renal parameters. After 5 weeks of diabetes, these mice were administered either tamoxifen to delete the CDA1 gene or vehicle to leave CDA1 intact.

Results: Analysis showed that diabetic mice exhibited expected changes in metabolic parameters such as hyperglycemia, polyuria and renal hypertrophy. Tamoxifen administration, while having no effect on any metabolic parameters in both non-diabetic and diabetic CDA1flox/ERCre mice, led to a reduction of renal CDA1 mRNA expression of ~70-80% ($p<0.001$). Expression levels of profibrotic genes, such as fibronectin, collagen I and MMP2, were elevated by ~2.6-3.5 fold ($p<0.01$) in vehicle-treated/CDA1 "wildtype" diabetic mice. This increase was attenuated by ~40-70% ($p<0.05$) in CDA1 deficient diabetic mice. Additionally, renal extracellular matrix deposition as determined by Masson's Trichrome staining was increased ~40% in diabetic mice ($p=0.062$), and this increase was attenuated in CDA1 deficient mice.

Conclusions: In conclusion, reduction in CDA1 expression at an early stage of diabetic nephropathy is able to attenuate diabetes-associated renal fibrosis, emphasising the potent antifibrotic potential of utilizing this approach in diabetic nephropathy.

FR-PO168

Metformin-Induced Inhibition of Mammalian Target of Rapamycin (mTOR) Pathway Slows Down the Progression of HIVAN

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Background: Since patients with HIV infection are now living almost a normal life style including the development of metabolic syndrome. we hypothesized that use of metformin in this population would not only control insulin resistance but would also slow down the progression of kidney lesions in HIV-associated nephropathy. To test our hypothesis, we studied the effect of meformin on the progression of renal lesions in a mouse model of HIVAN (doxycycline-inducible Vpr [podocyte specific] transgenic mice).

Methods: Vpr mice in groups of eight were fed either doxycycline with or without metformin for six weeks followed by evaluation for renal biomarkers (Blood urea nitrogen, urine protein:creatinine ratio, grading of severity of renal lesions and immunoblotting for phospho-mTOR and down stream molecular markers). In *in vitro* studies, mouse proximal tubular epithelial cells (MPTECs) were transduced with either empty vector (EV) or NL4-3 without *gag* and *pol* (HIV). EV/MPTECs or HIV/MPTECs were incubated in media containing either buffer or metfromin (0.5μM) for 48h. Protein blots of EV/MPTECs and HIV/MPTECs were probed for phospho-mTOR, phospho-p70S6 kinase, phospho-eEF2, p-eIF4B, and p-4EBP-1. The same blots were stripped and reprobed for actin.

Results: Vpr mice displayed sclerotic glomerular lesions, microcyst formation, proteinuria and activation of mTOR pathway; metformin not only attenuated proteinuria but also decreased severity of renal lesions. Moreover, metformin downregulated activation of the mTOR pathway. In vitro studies, protein blots of HIV/MPTEC displayed 2-fold increase in phospho-mTOR, 2.5-fold increase in phospho-p70S6K, and 2-fold increase both in p-eIF4B and p-4EBP-1when compared to EV/MPTECs. On the other hand, metformin inhibited HIV-induced mTOR phosphorylation and associated down stream signaling.

Conclusions: Metformin slows down the progression of HIVAN through down regulation of mTOR pathway.

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FR-PO169

The Effects of Aminophylline and Adenosine on the Tubular Damage Induced by Methotrexate in the Rats

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Background: Methotrexate (MTX causes kidney damage in high doses. Adenosine is recently suggested in the prevention of tubular damage associated with diabetic nephropathy. Aminophylline is a potent peripheral vasodilator possibly due to adenosine receptor antagonism. We aimed to investigate the potential of adenosine and aminophylline for preventing MTX-induced renal tubular damage.

Methods: Twenty-eight Sprague-Dawley adult male rats were included in the study. No drug was administered to 7 rats (n=7), which served as controls. Twenty one rats were administered a single dose of 20mg/kg intraperitoneal injection of MTX to induce MTX toxicity. 21 rats with MTX toxicity were divided into 3 groups; one group was treated with 1 ml/kg saline/day (MTX + saline) intramuscularly for 5 days, second group was treated with 4 mg/kg/day adenosine (MTX + adenosine) intramuscularly for 5 days, third group was treated with 50mg/kg/day aminophylline (MTX + aminophylline) intramuscularly for 5 days. At the end of the fifth day, all animals were euthanized and blood and urine samples were collected. BUN and creatinine were measured in plasma samples. Kidneys were harvested for histopathological tubular damage scoring, determination of renal malondialdehyde (MDA) , and glutathione (GSH). Urine was examined by dipstick for proteinuria.

Results: n MTX + saline group, proteinuria, plasma BUN, creatinine, renal malondialdehyde (MDA) levels and proximal tubular damage score were found significantly increased compared to controls ($p<0.05$). In MTX + adenosine group, plasma creatinine and proximal tubular damage score were found significantly increased compared to MTX + saline group. In MTX + aminophylline group, proteinuria, plasma BUN, creatinine levels and proximal tubular damage score were found significantly decreased compared to MTX + saline and MTX + adenosine groups ($p<0.05$).

Conclusions: Aminophylline reduced proximal tubular damage score induced by MTX and aminophylline may be an useful therapeutic agent for preventing MTX toxicity.

FR-PO170

Sirt1 Prevents Age-Associated Kidney and Cardiac Dysfunction Ashley R. Bellin,[1,2] Yanling Zhang,[1] Kim Connelly,[1,2] Richard E. Gilbert.[1,2] *[1]Li Ka Shing Knowledge Inst, St. Michael's Hospital, Toronto, ON, Canada; [2]Univ of Toronto, Toronto, ON, Canada.*

Background: Aging is a major contributing factor to both chronic kidney disease (CKD) and heart failure (HF). Sirtuin 1 (Sirt1), an NAD^+-dependent lysine deacetylase, mediates health span extension in a wide range of organisms, and has been shown to be downregulated in both CKD and HF. Accordingly, we hypothesized that a genetically engineered diminution in Sirt1 activity may accelerate cardio-renal aging.

Methods: To test this hypothesis, we compared wild type CD1 mice with $Sirt1^{Y/Y}$ mice that have undetectable Sirt1 catalytic activity, examining both young (4 week) and old (14 month) animals. Glomerular filtration rate (GFR) was assessed by FITC-inulin clearance, and cardiac function was assessed using conductance catheterization. At termination, kidneys were perfusion-fixed with formalin, paraffin embedded, and stained with hematoxylin and eosin for glomerular counting.

Results: When compared with their wild type counterparts and indexed to body weight, catalytically inactive $Sirt1^{Y/Y}$ mice had lower GFR ($p=0.0004$) with fewer glomeruli ($p=0.0005$) at both time points.

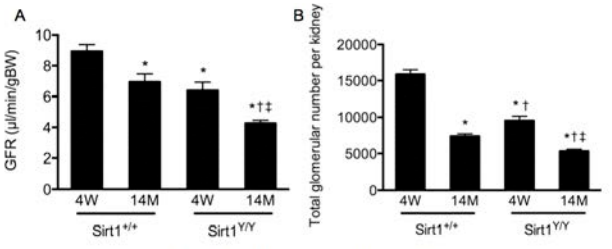

Figure 1: Comparison of the $Sirt1^{+/+}$ wild type mice and the catalytically inactive $Sirt1^{Y/Y}$ mice at 4 week and 14 month time points in regards to (A) GFR and (B) total glomerular number per kidney. * $p<0.05$ vs 4W $Sirt1^{+/+}$, † $p<0.05$ vs. 14M $Sirt1^{+/+}$, ‡ $p<0.05$ vs. 4W $Sirt1^{Y/Y}$.

Kidney weight was also lower in the $Sirt1^{Y/Y}$ mice ($p<0.0001$). Blood pressure, urinary albumin excretion, and heart weight were, however, similar in wild type and $Sirt1^{Y/Y}$ mice. Measures of cardiac function, including stroke volume (10.2±1.1 vs. 6.5±0.4µl, $Sirt1^{+/+}$ vs. $Sirt1^{Y/Y}$, $p=0.01$), ejection fraction (40.1±4.2 vs. 25.9±3.9%, $p=0.03$), and cardiac output (44±5 vs. 30±2ml/min, $p=0.02$), were lower in the 14 month $Sirt1^{Y/Y}$ mice.

Conclusions: These findings indicate that Sirt1 is both a determinant of glomerular endowment and age-associated cardio-renal disease. Strategies that increase the abundance or activity of Sirt1 may offer a new therapeutic approach to CKD and concomitant cardiac complications.

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FR-PO171

Functional Characterization of the Role of the Transcription Factor Grhl2 in Cystic and Neoplastic Kidney Diseases Zeliha Yesim Yurtdas,[1,2,3] Peter Boor,[4] Klaus Jung,[3,5] Kai M. Schmidt-Ott.[1,2] *[1]Max-Delbrück Center for Molecular Medicine, Berlin, Germany; [2]Dept of Nephrology, Charité Universitätsmedizin, Berlin, Germany; [3]Berlin Inst for Urologic Research, Berlin, Germany; [4]Inst of Pathology & Dept of Nephrology, Univ of Aachen, Aachen, Germany; [5]Dept of Urology, Charité Universitätsmedizin, Berlin, Germany.*

Background: Cystic and neoplastic kidney diseases are characterized by a dysregulation of epithelial morphogenesis and epithelial hyperproliferation. Grainyhead-like 2 (GRHL2) is a transcription factor specifically expressed in distal and collecting duct epithelia of the kidney. We have previously shown that Grhl2 regulates epithelial morphogenesis and barrier formation and controls lumen expansion of kidney tubules. However, the functional role of GRHL2 in kidney disease remains unknown.

Methods: We conducted a comprehensive immunohistochemical analysis of GRHL2 expression in patient samples with renal carcinomas and cystic kidney disease and in parallel, studied GRHL2 functionally in genetic mouse models.

Results: GRHL2 expression was upregulated in chromophobe carcinomas and oncocytomas when compared with other renal carcinomas and its expression was partially lost in cyst-lining epithelia in ADPKD. To assess the role of GRHL2 in cystic and neoplastic kidney diseases *in vivo*, the proto-oncogene MYC was conditionally overexpressed in the collecting duct (HoxB7Cre;R26StopFLMYC). These mice developed cysts with epithelial hyperplasia which tended to transform to adenomas. Both cysts and adenomas displayed strong Grhl2 expression and were primarily derived from intercalated cells of the collecting duct as shown by their positivity for VATPaseB1/B2. Furthermore, conditional deletion of Grhl2 in the kidneys of these mice (HoxB7Cre; R26StopFLMYC; Grhl2 flox/flox) resulted in a marked aggravation of cyst development. While HoxB7Cre; R26StopFLMYC mice survived to advanced ages, HoxB7Cre; R26StopFLMYC; Grhl2 flox/flox mice died of renal failure 5 weeks of age, displaying massively expanded cysts.

Conclusions: Our data indicate that Grhl2 is strongly expressed in collecting duct epithelia-derived cysts and neoplasms and acts as a gatekeeper of epithelial hyperproliferation and uncontrolled cyst expansion.

Funding: Private Foundation Support

FR-PO172

Anti-Angiogenic Factors Regulate the Cytoprotective Thrombomodulin Pathway in the Kidney In Vitro and In Vivo Manon Bos,[1] Rosanne Jane Turner,[1] Maria Elisabeth Penning,[1] Pascal Bus,[1] Aiko P.J. De Vries,[2] Marion Scharpfenecker,[1] Lukas J. Hawinkels,[4] Kitty Bloemenkamp,[3] Jan A. Bruijn,[1] Hans J. Baelde.[1] *[1]Pathology, LUMC, Netherlands; [2]Nephrology, LUMC, Netherlands; [3]Gastroenterology-Hepatology, LUMC, Netherlands; [4]Obstetrics, UMCU, Netherlands.*

Background: An excess of angiogenic factors is associated with a variety of renal syndromes, e.g. preeclampsia and diabetic nephropathy. Levels of soluble thrombomodulin increase in these syndromes, but if endothelial thrombomodulin changes and if this affects anti-coagulative and cytoprotective signalling in the kidney is unknown. Hence, we investigated thrombomodulin signalling in patients and experimental models of preeclampsia and diabetic nephropathy.

Methods: HUVECs were treated with VEGF or soluble Flt-1. Kidneys from 12 mice treated with endoglin or VEGF receptor neutralizing antibodies and from 5 pigs with metabolic syndrome after a high-fat diet, 5 pigs diabetic after streptozotocin injection and 5 control pigs were collected. Kidney tissue from 22 pregnant women and 11 preeclampsia patients was collected. Gene expression of thrombomodulin, endothelial protein C receptor (EPCR) and tissue factor was measured with qPCR. Thrombomodulin protein expression was investigated with immunohistochemistry.

Results: sFlt-1 decreased endothelial thrombomodulin *in vitro*. Glomerular thrombomodulin protein was increased in diabetic pigs and in mice treated with anti-angiogenic compounds. In diabetic pigs, thrombomodulin, EPCR, and VEGF mRNA increased (all $P<0,05$), which correlated inversely with tissue factor mRNA. In preeclampsia, glomerular thrombomodulin was increased compared to pregnant controls and this correlated with podocyte nephrin expression (both $P<0.01$).

Conclusions: Angiogenic factors regulate renal thrombomodulin expression, *in vitro* and *in vivo*. Increased thrombomodulin expression is accompanied by less tissue factor expression and increased podocyte nephrin expression, indicative of a protective effect on the glomerulus. These results indicate an attempt of glomerular endothelial cells to maintain cytoprotection; investigating pathways through which thrombomodulin expression is increased in endothelial cells could reveal clues to restore or prevent endothelial kidney damage.

FR-PO173

VEGFR1 Neutralization Reverses Murine Diabetic Nephropathy Zhonghua Qi, Dianna L. Jaqua, Yuan Su, Martin S. Cramer, Bhaskarjyoti Sarmah, Shannon Marie Harlan, Tamer Coskun, Kathleen Heinz-Taheny, Josef G. Heuer, Ying Tang, Matthew D. Breyer. *Eli Lilly and Company, Indianapolis, IN.*

Background: The role of VEGFA in the pathogenesis of renal disease remains controversial. The proangiogenic effects of VEGFA are primarily mediated by its receptor VEGFR2 whereas these effects are antagonized by ligand binding to its inhibitory receptor VEGFR1 (flt1).

Methods: A specific VEGFR1 monoclonal antibody (MF1) was studied in CKD mice.

Results: The present study demonstrated that MF1 dramatically improved albuminuria and renal histology in three distinct mouse models of CKD including uninephrectomized db/db mice, $eNOS^{-/-}$ db/db mice, and 129S6 remnant kidney mice. MF1 treatment increased circulating VEGFA levels consistent with ligand displacement from VEGFR1, and this was accompanied by increased renal VEGFR2 phosphorylation, suggesting VEGFR2 activation. Interestingly MF1 treatment was accompanied by a sustained decrease in blood pressure of approximately 10mmHg in both db/db and $eNOS^{-/-}$ db/db mice receiving MF1, showing that the decreased blood pressure was not exclusively dependent on the downstream activation of eNOS by VEGFR2. In contrast to previous reports, we found blocking either VEGFA or VEGFR2 via administration of neutralizing antibodies to VEGFA or VEGFR2 (DC101) worsened albuminuria and renal histological injury scores in db/db mice, an effect consistent with clinical observations of proteinuria and hypertension following treatment with Bevacizumab (Avastin). VEGFR1 blockade with MF1 also protected $eNOS^{-/-}$ db/db mice from serum creatinine (Scr) increases and significantly reduced mortality in these

mice. The effects of MF1 were not dependent on the VEGFR1 tyrosine kinase (tk) domain since treatment of VEGFR1 tk-/tk- remnant kidney mice with MF1 didn't significantly impair its beneficial effects on albuminuria and renal histology.

Conclusions: These data demonstrate monoclonal antibody VEGFR1 blockade prevents renal failure progression by increasing VEGFA and VEGFR2 activity in diverse mouse models of kidney disease. These findings are consistent with recent observations of reduced VEGFA levels in human DN and suggest they may contribute to the pathogenesis of DN.

Funding: Pharmaceutical Company Support - Eli Lilly and Compnay

FR-PO174

Bone Marrow Myeloid Progenitor Cells Are Contributing to a Wide Variety of suPAR Associated Kidney Diseases

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Background: Systemic soluble urokinase plasminogen activator receptor (suPAR) is implicated in the onset and progression of chronic kidney disease (CKD). To investigate the potential relevance of suPAR in other renal diseases, we examined the levels of suPAR and Gr-1^{lo} bone marrow (BM) myeloid cells in multiple animal models of proteinuria.

Methods: Bone marrow transplantation (BMT), adoptive transfer, ELISA, and flow cytometric analysis were performed.

Results: BM chimera and adoptive transfer studies revealed that hematopoietic cells, specifically BM myeloid cells, are responsible for suPAR production and proteinuria development in lipopolysaccharide (LPS)-induced proteinuric mouse model. In this model, BM myeloid cells increased uPAR expression , and LPS stimulation led to a significant increase in the percentage of Gr-1^{lo} cells in the BM. Next, we examined the levels of suPAR and Gr-1^{lo} BM myeloid cells in 5 additional animal models of proteinuria. i) A genetic model of podocyte injury (Pod-Rac1), in which podocyte-specific Rac1 activation causes podocyte dysfunction, ii) Adriamycin (ADR)-induced nephropathy, iii) Albumin TGF β_1 transgenic (TGF β_1 Tg) mice, iv) Nephrotoxic serum (NTS) nephritis, and v) BTBR *ob/ob* diabetic mice with nephropathy. All tested animals exhibited proteinuria. Unlike LPS model, Pod-Rac1 and ADR models, in which podocytes are the direct target of injury, were not characterized by elevated systemic suPAR levels. There was also no change in the BM Gr-1^{lo} cell population. In contrast, TGF β_1 Tg, NTS, and BTBR *ob/ob* mice, showed elevated suPAR levels, which was accompanied by an expansion in Gr-1^{lo} BM myeloid cells. Transplantation of BM from healthy into NTS mice ameliorated the degree of kidney disease.

Conclusions: Expansion of Gr-1^{lo} BM myeloid cells and their overproduction of suPAR may represent a common upstream event in immunologically associated kidney disease with high systemic suPAR. BM transplantation may be one new therapeutic strategy to combat a disturbed BM-kidney disorder.

Funding: NIDDK Support

FR-PO175

Synergism of CD40 Autoantibodies and suPAR in FSGS Recurrence

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Background: FSGS is a histopathological lesion leading to end stage kidney disease requiring dialysis and transplantation. Primary FSGS however has a 40-80% risk of recurrence of disease in the transplanted kidney, with resultant accelerated graft loss. The disease pathophysiology has been difficult to unravel despite a large body of evidence suggesting a role of circulating factors. Recent studies in recurrent FSGS (rFSGS) suggested a potential role suPAR and CD40 auto-antibody (autoAb) isolated from the sera of FSGS patients.

Methods: We evaluated affinity in between CD40 autoAb isolated from rFSGS patients with suPAR and synergistic role of suPAR and CD40 Ab from rFSGS in rodent model in causing kidney damage in terms of proteinuria. Anti-CD40 autoAb isolated from rFSGS and non-recurrent FSGS (nrFSGS) were injected (i.v.) to C57BL/6 mice with predetermined amount of CD40 autoAb isolated from rFSGS and nrFSGS. Injection of CD40 autoantibody was given 6 times, every other day. Six hours after the last dose of CD40 autoantibody, recombinant human suPAR protein was given i.v. at 5 µg/ml to all mice in order to analyze the additive effect of suPAR on proteinuria. Urine was collected before and every day after the first injection of CD40 autoantibody to analyze urinary albumin and creatinine. Surface plasmon resonance (SPR) was used to find affinity in among autoAbs, suPAR and integrin αvβ3.

Results: There was an increase in proteinuria (p=0.04) with the injection of CD40 auto Ab from rFSGS. The injection of suPAR along with CD40 autoAbs from rFSGS increased proteinuria significantly compared to CD40 autoAb alone (p=0.004). CD40 autoAbs isolated from rFSGS, nrFSGS patients directly demonstrated affinity towards integrin αvβ3 as a similar binding affinity (KD = ~26 to 84 nM). Only human CD40 autoAb from rFSGS have specific interaction as the RUmax values of those from nrFSGS and no-FSGS patients are small. Only human CD40 autoAbs from rFSGS patient, not from nrFSGS patients had specific affinity to suPAR.

Conclusions: Through this study we demonstrated that suPAR and CD40 autoAbs from rFSGS can aggravate proteinuria in mouse model and suPAR exhibits specific affinity to CD40 autoAbs isolated from rFSGS.

FR-PO176

PPARα and PPARγ Attenuate the Anti-Glomerular Basement Membrane Glomerulonephritis through the Actions on the Different Inflammatory Cells, T Cells and Macrophages

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Background: Peroxisome proliferator activated receptor-alpha (PPARα) and -gamma (PPARγ) agonists modulate inflammatory responses and attenuate the renal injury in glomerular diseases, but the mechanisms are not well understood. In this study, we examined the protective effects of PPARα and PPARγ agonists, fenofibrate and pioglitazone, in anti-glomerular basement membrane glomerulonephritis (anti-GBM GN) characterized by the invasion of Inflammatory cells such as macrophages and CD8+ T cells.

Methods: Male Wister-Kyoto rats at 5 weeks of age were divided into 7 groups and received fenofibrate (30, 100, 300mg/kg/day), pioglitazone (12.5, 50, 100mg/kg/day) or vehicle (control) the day before induction of anti-GBM GN. At 7 days after the induction, 24-hr urine samples were collected and the kidneys were harvested. The expression of cytokines, chemokines and cell surface markers in isolated glomeruli were evaluated by real time PCR analysis.

Results: Both the treatments reduced the level of proteinuria, glomerular infiltration of CD8+ T cells and ED1+ macrophages and prevented the development of necrotizing and crescentic lesions dose dependently. Notably, pioglitazone showed greater reduction in infiltration of ED1+ macrophages with down-regulation of the M1 macrophage marker including TNF-α, IL-1β and iNOS, and increase in infiltration of ED2+ M2 macrophages with up-regulation of the M2 macrophage marker, TGF-β and mannose receptor. In contrast, fenofibrate showed greater reduction in infiltration of CD8+ T cells and up-regulation of Th2 cell-associated cytokines, IL-4 and IL-10.

Conclusions: PPARα and PPARγ dose-dependently attenuated glomerular inflammation in anti-GBM GN through the regulation of the different inflammatory cells. Our results suggested that PPARα suppresses CD8+ T cell infiltration with increase in the production of Th2 anti-inflammatory cytokines, and PPARγ suppresses inflammatory macrophage infiltration with promotion of the anti-inflammatory macrophage infiltration.

FR-PO177

Whole Genome Transcriptome, Methylome, and Transcription Factor Binding in Nephrotoxic Nephritis

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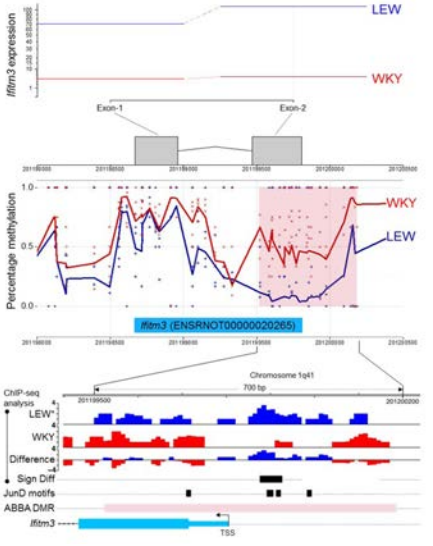
Background: Nephrotoxic nephritis (NTN) is a macrophage dependent model of crescentic glomerulonephritis in which the Wistar-Kyoto (WKY) rat is susceptible to disease and the Lewis (Lew) rat is resistant. Previous work has suggested a role for the AP-1 transcription factor (TF), JunD, in the pathogenesis of NTN. TFs are fundamental regulators of gene expression but additional regulation may result from local methylation of DNA cytosine bases. Given the interaction between TF activity, DNA methylation and gene expression, we integrated distinct whole-genome datasets to try and identify novel determinants of NTN pathogenesis.

Methods: DNA methylation data were produced in WKY and Lew bone marrow-derived macrophages (BMDMs) by whole genome shotgun bisulphite sequencing and integrated with previously generated RNA-seq, and JunD ChIP-seq data.

Results: We identified 1,004 genomic regions that showed differential methylation between WKY and Lew BMDMs. 427 of these regions overlapped with known genes and integration with RNA-seq data elucidated three genes that showed differential expression and differential methylation within their promoter region. Using the ChIP-seq dataset, we also found that, interferon-induced transmembrane protein 3 (*Ifitm3*), had differential binding of JunD within its promoter.



Conclusions: Integration of distinct whole genome datasets in NTN allows consideration of multiple determinants of gene expression and has revealed a potential new candidate gene (*Ifitm3*) for glomerulonephritis susceptibility.

Funding: Government Support - Non-U.S.

FR-PO178

The Association and Its Mechanism between Microbiota Alteration and Intestinal-Barrier Function in Mice with Chronic Renal Failure Seiji Itano, Minoru Satoh, Yuji Sogawa, Atsushi Uchida, Kengo Kidokoro, Hajime Nagasu, Tamaki Sasaki, Naoki Kashihara. *Dept of Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Okayama, Japan.*

Background: The intestinal microbial flora consists of diverse bacterial species. These bacteria are necessary for the ontogeny, regulation of the immune system, and for intestinal homeostasis. Alterations of the intestinal barrier and intestinal bacterial flora in chronic kidney disease have been reported to affect uremic toxin influx. Antimicrobial peptides contribute to maintenance of microbiota. We examined the mechanisms of the mutual relation between intestinal bacterial flora and intestinal-barrier function by using a mouse model of chronic renal failure.

Methods: We used 13-week-old male ICR-derived glomerulonephritis (ICGN) mice as the renal-failure group and ICR mice as the control group. Gene expression patterns of the whole bacterial flora in the intestine were analyzed by means of terminal restriction fragment length polymorphism. Fecal and serum bacterial products (phenol, para-cresol, indole/indole sulfate, and skatole) were examined by quantitative chemical analysis. Intestinal tight junction protein (occludin or claudin-1) and glycocalyx were evaluated by immunostaining of the ascending colon. Expression levels of antimicrobial-peptide genes (defensin beta-1, 2, and 3) in the colon were measured by quantitative polymerase chain reaction (PCR).

Results: The proportion of pathogenic bacteria *Clostridium* increased while that of the opportunistic pathogen *Bacteroides* decreased in the intestinal bacterial flora of ICGN mice. Fecal bacterial products phenol and para-cresol were upregulated in the feces of ICGN mice, but indole concentration remained unaffected. On the other hand, serum indoxyl sulfate was upregulated in ICGN mice. Intestinal tight junction and glycocalyx were impaired in ICGN mice. The mRNA expression levels of defensins beta-1 and beta-3 in the ascending colon decreased in ICGN mice compared to those in the control mice.

Conclusions: The intestinal bacterial flora was altered and tight junctions were impaired in mice with chronic renal failure. Defensins beta-1 and beta-3 may contribute to these changes in bacterial flora.

FR-PO179

Acetate from Microbiota Contributes to Tubulo-Interstitial Inflammation and Fibrosis in Lupus Nephritis Daniel Tak Mao Chan, Qing Zhang, Mel Chau, Ping Lung Chan, Susan Yung. *Dept of Medicine, The Univ of Hong Kong, Hong Kong.*

Background: The gut microbiota is implicated in the pathogenesis of autoimmune diseases. Bacterial products could gain access into the bloodstream and exert effects on distant organs. Acetate is a short chain fatty acid (SCFA) produced by gut microbiota. We previously reported that lupus nephritis patients had higher serum acetate levels compared with healthy controls, and acetate level correlated with activity of nephritis. We further investigated the role of acetate and its receptors in inflammatory and fibrotic processes in murine lupus and cultured proximal renal tubular epithelial cells.

Methods: Renal expression of SCFA receptors GPR-41 and GPR-43 was investigated in NZBWF1 mice with progressive lupus nephritis. HK-2 cells were incubated with acetate (1-50mM) or serum-free medium for 24h, and the secretion of IL-6, IL-8 and MCP-1, and expression of fibronectin and laminin determined.

Results: GPR-41 and GPR-43 expression was markedly increased in NZBWF1 mice with active nephritis, and was predominantly localized in the tubulo-interstitium. Acetate induced ERK, p38 MAPK and JNK phosphorylation in HK-2 cells, accompanied by increased IL-6, IL-8 and MCP-1 secretion. The expression of GPR-41, GPR-43, fibronectin and laminin expression was also induced by acetate in a time- and dose-dependent manner. GPR-41 and GPR-43 upregulation was mediated in part through IL-6, IL-8 and MCP-1, which in turn increased fibronectin synthesis through activation of MAPK and PI3K signaling pathways.

Conclusions: The results show that acetate from microbiota may contribute to tubulo-interstitial inflammation and fibrosis in lupus nephritis.

Funding: Government Support - Non-U.S.

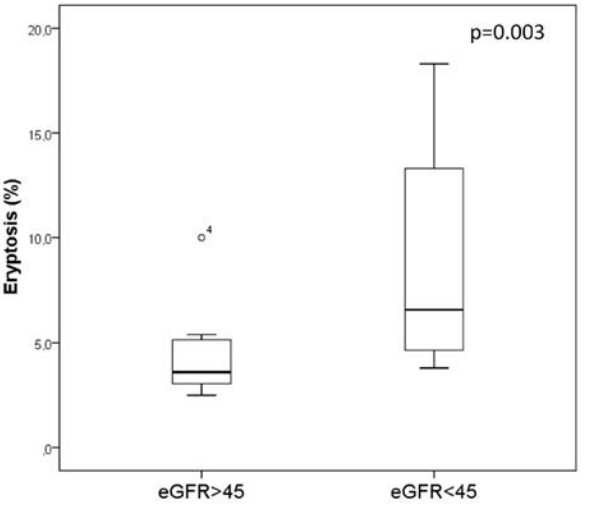
FR-PO180

Mechanisms and Pathophysiological Significance of Eryptosis in Chronic Kidney Disease and Anemia Grazia Maria Virzì, Alessandra Brocca, Anna Clementi, Massimo de Cal, Claudio Ronco. *IRRIV.*

Background: Anemia is a common complication of CKD resulted from compromised erythropoiesis or decreased lifespan of erythrocytes(RBCs). Eryptosis, suicidal death of RBCs, is characterized by cell shrinkage and membrane scrambling with phosphatidylserine (PS)-exposure at the RBC surface. Exposed PS is recognized by macrophages that engulf and degrade the affected cells. Enhanced eryptosis is observed in CKD, which invariably leads to anemia. The purpose of this study was to assess and study eryptotic changes in RBC exposed in vitro to uremic toxins and CKD patients'plasma.

Methods: RBC from healthy subject were incubated at a hematocrit of 0.4% in RPMI solution with different concentrations of uremic toxins and with plasma from CKD patients for 24hours. CKD patients were divided in 2groups(eGFR>or<45ml/min/1.73m^2). RBC volume and morphology was estimated, PS exposure was estimatetestedd by AnnexinV-binding by flow cytometric. Each experiment was tested 5times.

Results: Increasing concentrations of uremic toxins significantly modify RBCs volume, dramatically derange their morphology and progressively enhance the percentage of PS in vitro. Moreover, the median values of eryptosis showed significant differences between the 2CKD groups.The RBCs exposed to CKD plasma from patients with eGFR<45ml/min/1.73m^2 show strong eryptotic changes and high eryptosis(p=0.003).Eryptosis increases with CKD progression.



P-cresol (mg/l)	0	5	15	20	30	40	60
Median Eryptosis %	2.7	6.4	22.1	38.9	54.8	83.5	99
Urea (mg/l)	0	50	100	150	200	250	300
Median Eryptosis %	2.3	5.4	7.9	8.7	12	19.3	24

Conclusions: In conclusion, uremic toxins induce morphological changes in RBCs and stimulate eryptosis in vitro. Increasing concentrations of these uremic toxins and their additive combination in vivo may be responsible for higher eryptosis that leads to anemia in CKD. CKD plasma contains components which trigger an increasing eryptosis;different stages of CKD may induce different levels of RBC death. Our data suggests that progression of CKD may progressively increase eryptosis and anemia in vivo.

Funding: Private Foundation Support

FR-PO181

Enzymatic Active and Inactive Ubiquitin C-Terminal Hydrolase L1 (UCH-L1) Exert Differential Effects in Podocytes Julia Reichelt, Anna Reinicke, Jan Hendrik Knop, Catherine Meyer-Schwesinger. *Nephrology, Internal Medicine, Univ Medical Center Hamburg-Eppendorf.*

Background: UCH-L1 is a major deubiquitinating enzyme of the central and peripheral nervous system. Biochemically, UCH-L1 is thought to regulate the intracellular pool of monoubiquitin, required for ubiquitination procedures. In the central nervous system oxidative-modifications and mutations (such the I93M point mutation) of UCH-L1 result in enzymatic inactivity of UCH-L1. These conditions are associated with the development of neurodegenerative disease. We could demonstrate a de novo expression of UCH-L1 in podocytes in patients with membranous nephropathy. Chemical inhibition of the enzymatic activity of UCH-L1 in a rat model of membranous nephropathy attenuated podocyte injury by increasing proteasomal activity and reducing the accumulation of polyubiquitinated proteins.

Methods: In an attempt to dissect the function of UCH-L1 in the development of podocyte injury in membranous nephropathy, we specifically overexpressed enzymatic-active (wildtype) and -inactive (I93M) UCH-L1 in podocytes in mice. We first investigated the basic phenotype of these mice by morphological and biochemical analyses. Furthermore, we investigated the effects of inducible overexpression of wildtype and I93M point mutated UCH-L1 in cultured podocytes.

Results: Inducible overexpression of I93M UCH-L1 in cultured podocytes resulted in increased levels of monoubiquitin and polyubiquitin partly through increased transcription of ubiquitin precursor proteins. No changes in ubiquitin levels were observed in podocytes overexpressing wildtype UCH-L1. Specific analyses of proteins that were polyubiquitinated in I93M-overexpressing cultured podocytes demonstrated that I93M overexpression resulted in an enhanced K48-polyubiquitination and degradation of alpha-actinin-4. In mice, overexpression of wildtype enzymatic active UCH-L1 resulted in podocyte loss and the development of proteinuria with increased proteasomal activity. Astonishingly, overexpression of enzymatic inactive I93M UCH-L1 on the other hand reduced podocyte-loss and proteinuria and decreased proteasomal activity.

Conclusions: UCH-L1 influences podocyte integrity and function through its enzymatic activity.

Funding: Government Support - Non-U.S.

FR-PO182

Long-Term Selective ETA Receptor Antagonism Prevents Renal Injury in Humanized Sickle Cell Mice Malgorzata Kasztan, Carmen De Miguel, Jennifer S. Pollock, David M. Pollock. *Dept of Medicine, Div of Nephrology, Univ of Alabama at Birmingham, Birmingham, AL.*

Background: Elevated plasma endothelin-1 (ET-1) levels reported in sickle cell disease (SCD) patients correlate with microalbuminuria, suggesting a pathophysiological link between ET-1 and sickle nephropathy (SN). The current study was designed to determine if early intervention with an endothelin antagonist would prevent renal injury in a mouse model of SN.

Methods: Humanized sickle cell mice (HbSS) and genetic controls (HbAA) were treated with ambrisentan (ET_A antagonist), A-182086 ($ET_{A/B}$ antagonist) (10mg/kg/day) or vehicle for 10 weeks (beginning at the time of HbF to HbS switch into adulthood).

Results: Chronic administration of ambrisentan prevented histo-pathological lesions including hyperthrophy, sclerosis, vascular congestion and tubulointerstitial fibrosis, as well as preserved brush border thickness in HbSS mice. Also, ambrisentan reduced tubular iron deposition in HbSS mice (3.5±0.5 vs. 7.1±0.6 Mpixel/μm), and was associated with similar levels of urinary NGAL, tubular iron binding protein, compared to non-disease HbAA mice (33.3±3.3 and 29.2±9.9 in HbAA vs. 107.5±28.4 ng/24 in untreated HbSS). Correspondingly, functional analysis of renal injury revealed that ambrisentan prevented nephrinuria (15.4±3.9 vs. 53.9±5.5 μg/24h), albuminuria (16.7±3.3 vs. 67.0±18.9 μg/24h), proteinuria (1.1±0.3 vs. 3.57±0.8 mg/24h), as well as preserved glomerular permeability to albumin (0.14±0.03 vs. 0.52±0.04), GFR (231±13 and 233±8 μm/min in HbAA) and excretion of markers of tubular injury (NAG: 5.8±2.1 and 5.4±2.5 in HbAA vs.14.5±1.2 mU/24h in HbSS; KIM-1: 90.5±23.9 and 24.2±10.7 in HbAA vs. 285.3±90.3 pg/24h in HbSS) to the levels of non-disease controls. The dual $ET_{A/B}$ antagonist had some effect to reduce glomerular injury markers (nephrin, P_{alb}), but no effect on the changes in renal structure and function in HbSS mice.

Conclusions: ET-1 contributes to SN via ET_A receptor activation and long-term ET_A receptor antagonism may provide a strategy for the prevention of renal complications of SCD.

Funding: Other NIH Support - NIH/NHLBI: U01 HL117684-01

FR-PO183

Topiroxostat, a Novel Xanthine Oxidase Inhibitor, Exerts Renoprotective Role via Antioxidant Effects in Puromycin Aminonucleoside Nephrotic Rats Yosuke Kawamorita, Yoshifuru Tamura, Shigeru Shibata, Shunya Uchida. *Teikyo Univ School of Medicine, Tokyo, Japan.*

Background: Topiroxostat (Topi) is a newly developed drug for gout and hyperuricemia belonging to xanthine oxidase inhibitor (XOI) like allopurinol. It has been proposed that allopurinol not only reduces serum uric acid (UA) level but also urine protein excretion in puromycin-aminonucleoside (PAN) nephrotic rats. Topi may decrease urine protein excretion (UPE) in addition to hypouricemic action. In the present study we aimed to examine change in UPE in response to Topi and its molecular mechanism using PAN rats.

Methods: PAN nephrosis was induced by a single intraperitoneal injection of PAN (10 mg/100 g body weight). Rats were divided into four groups: Control rats (Cont); PAN rats (PAN); Control rats with Topi 0.5 mg/kg/day (Topi); PAN rats treated with Topi (PAN + Topi).

Results: Topi significantly decreased tissue UA in the kidney cortex and UPE by 30% at day 10 after PAN injection. To elucidate the protective effect of Topi we focused on the oxidative stress in the kidney. Firstly, PAN significantly decreased the number of WT-1-positive podocytes and reduced podocin immunoreactivity, both of which were partially improved by Topi. Next, nitrotyrosine and 8-OHdG in the kidney induced by PAN were significantly decreased by Topi treatment. Moreover, increased amounts of XO and NOX4 in the cortex induced by PAN were completely reverted in response to Topi. Of note was that serum UA did not vary significantly.

Rats	Tissue uric acid	Urinary protein at 10 days	Oxidative stress markers		
(n = 6)	mg/day	mg/day	Nitrotyrosine	NOX4	Xanthine oxidase
Cont	0.76 ± 0.34	7.3 ± 5.5***	1.00 ± 0.15**	1.00 ± 0.25	1.00 ± 0.06**
PAN	1.42 ± 0.35	308.2 ± 130.8	2.86 ± 1.29	2.57 ± 0.50	2.80 ± 1.58
Tx	0.78 ± 0.19	9.6 ± 7.5***	0.94 ± 0.32**	0.72 ± 0.27**	1.25 ± 0.49*
PAN + Tx	0.87 ± 0.21	201.7 ± 83.0*	1.58 ± 0.72*	1.56 ± 0.52**	1.35 ± 0.33*
*P<0.05, **P<0.01, ***P<0.001 vs. PAN.					

Conclusions: Topi ameliorates proteinuria and renal injury apart from serum UA in PAN rats, thus Topi may play a renoprotective role through antioxidant effects beyond uric acid lowering action.

FR-PO184

Pathological and Molecular Characteristics of Adenine-Induced Chronic Kidney Disease (CKD) Model in Rats Erika Abe,[1] Li Xiao,[1] Yuumi Iida,[1] Naoko Oyama,[1] Rika Fujino,[2] Hirofumi Jono,[1,2] Hideyuki Saito.[1,2] *[1]Dept of Clinical Pharmaceutical Sciences, Kumamoto Univ School of Pharmacy, Kumamoto, Japan; [2]Dept of Pharmacy, Kumamoto Univ Hospital, Kumamoto, Japan.*

Background: The process leading to CKD from acute kidney injury (AKI) is known to be caused by strength and frequency of proximal tubule injury. Although attempts were made to develop experimental CKD model, a suitable animal model is not yet established. In this study, we generated the adenine-induced CKD model using rats, and characterized pathological and moelcular aspects for investigating factors involved in the CKD progression.

Methods: Wistar rats (8-weeks-old) were fed diet powdery without or with adenine (0.3, 0.5 and 0.75%, respectively) for 4 weeks, followed by control diet for 4 weeks. Rats were sacrificed after 8 weeks, and kidney tissues were collected. In adenine-induced CKD model rats, body weight, water intake, urine volume, kidney weight, index of renal function, renal tubular damage markers (Kim-1, Ngal), oxidative stress-related factors (Nrf2, 4-HNE), fibrosis marker (αSMA), uremic toxin indoxyl sulfate (IS), organic anion transporters OAT1 and OAT3 mediating basolateral uptake of serum IS, and autophagy-related factors LC3-2 were examined.

Results: Body weight was significantly decreased and urine volume/water intake were increased in adenine group. Adenine treatment caused the decreases in urine urea nitrogen, Cr and marked increases in BUN and SCr. The marked increases in renal Kim-1 and Ngal, and histochemical injury of renal tubules were evident in adenine group. In adenine rats, the elevated 4-HNE and Nrf2 levels in the kidney indicated induction of oxidative stress. Moreover, LC3-2, a maker of autophagy, which often increases with oxidative stress, was also induced. The expressions of OAT1&3 were downregulated in adenine rat kidney, resulting in serum accumulation of IS. The appearance of interstitial αSMA indicated fibrotic response in adenine rat kidney associated with Masson's trichrome positive staining.

Conclusions: Adenine-induced CKD model rats exibited a significant deterioration of renal function, severe tubule injury, elevation of oxidative stress, accumulation of serum IS and autophagic and fibrotic responses.

Funding: Government Support - Non-U.S.

FR-PO185

Omics Characterization of Ethanol and Lipopolysaccharide Impact on the Renal Cortex Christine E. Dolin,[1] Lauren G. Poole,[1] Daniel Wade Wilkey,[2] Gavin E. Arteel,[1] Eric C. Rouchka,[3] Michelle T. Barati,[2] Michael Merchant.[1,2] *[1]Pharmacology & Toxicology, Univ of Louisville; [2]Medicine, Univ of Louisville; [3]Computer Engineering & Computer Science, Univ of Louisville.*

Background: Chronic, heavy ethanol (EtOH) consumption impacts the kidney through the hepato-renal syndrome. The direct renal effects of moderate chronic EtOH consumption and sensitization to secondary hits are unclear. We hypothesized that moderate EtOH consumption can alter renal transcriptomic/proteomic responses to acute exposure to lipopolysaccharide (LPS).

Methods: Mice were pair fed EtOH-containing Lieber-DeCarli diet for 6 weeks and/or injected i.p. with LPS 4h prior to sacrifice. Kidney cortex sections were isolated and snap frozen. Comparative Omics studies used (a) two-dimensional liquid chromatography-mass spectrometric analysis with an Orbitrap Elite and TMT labeling reagents and (b) mirVana™ isolation of total RNA, library preparation using the TruSeq Stranded Total RNA LT Sample Prep Kit-Set A with Ribo-Zero Gold and data collected using Illumina NextSeq 500/550 with the RNASeq protocol. Proteomic and transcriptomic data were filtered by Benjamini-Hochberg (BH) corrected ANOVA p-value <0.05 and fold change (FC). Ingenuity Pathways Analysis (IPA) was used to identify pathways changed by EtOH, LPS, and/or the combination. Individual protein changes were validated with immunoblot.

Results: 170 of1863 proteins were significantly different abundance at FC ≥1.2 across groups.853 of 47,719 transcripts were significantly differentially abundant at FC ≥2 across groups. The majority of these effects LPS derived. Expected increases in Fibrinogen A protein and transcript were observed in LPS-exposed samples. IPA results show EtOH attenuated LPS effects on LXR/RXR and Nrf2-mediated pathways. Immunoblots of Nrf2 target proteins validated proteomic findings.

Conclusions: This study on the effects of EtOH and/or LPS on the renal transcriptome and proteome supported expected observations andrevealed new changes in proteins, transcripts and pathways. We hypothesize these changes will provide insight into mechanisms by which EtOH affects the kidney and alters response to a second pathologic stimulus.

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FR-PO186

Near-Infrared Autofluorescence Is Useful for Non-Invasive Imaging of Injured Kidneys in Mice Isao Matsui,[1] Hiroshi Fushiki,[2] Nobuhiro Hashimoto,[1] Keiichi Kubota,[1] Tatsufumi Oka,[1] Daisuke Mori,[1] Yusuke Sakaguchi,[3] Takayuki Hamano,[3] Yoshitsugu Takabatake,[1] Yoshitaka Isaka.[1] *[1]Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; [2]Translational Science Research Labs, Drug Discovery Research, Astellas Pharm Inc., Tsukuba, Ibaragi, Japan; [3]Comprehensive Kidney Disease Research, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan.*

Background: Tubulointerstitial injury (TI) is a final common pathway leading to end-stage renal disease. One of the major problems in the field of TI is the lack of strategies that enable us to evaluate the progression of TI non-invasively.

Methods: Near-infrared autofluorescence (AF) of injured kidney was non-invasively evaluated by IVIS imaging system. A combination of excitation filter 710 nm and emission filter 810-875 nm was employed. Two models, unilateral ureteral obstruction and folic acid induced nephropathy, in BALB/c mice were analyzed. The origin of the renal AF was also analyzed.

Results: The AF levels were positively correlated with the degree of TI in both animal models. Microscopic analysis of the kidney sections revealed that the AF was originated from the injured tubular cells. Because porphyrins are intrinsic fluorescent substrates that have near-infrared emission peak, we analyzed renal expression levels of enzymes that participate in the metabolism of porphyrin. Among 10 enzymes, only coproporphyrinogen oxidase (CPOX) was suppressed in the injured kidneys in both animal models, suggesting that coproporphrinogen III and its spontaneously oxidized product, coproporphyrin III, were accumulated in the injured kidneys. Authentic sample of coproporphyrin III had identical fluorescent properties observed in the injured kidneys. Intraperitoneal injection of Δ-aminolevulinic acid, a substrate of porphyrin synthesis, enhanced the AF of the injured kidneys. BALB/c-nct/nct mice, a mouse strain that retains only 15% of the wild type CPOX activity, showed the identical AF observed in the injured kidneys.

Conclusions: Near-infrared AF derived from coproporphyrin III is useful for non-invasive imaging of the TI.

Funding: Pharmaceutical Company Support - Astellas

FR-PO187

CTGF Is Critically Involved in Lymphangiogenesis of Obstructive Nephropathy Hiroshi Kinashi,[1,2] Lucas Falke,[1] Tri Q. Nguyen,[1] Yasuhiko Ito,[2] Andrew Leask,[3] Roel Goldschmeding.[1] *[1]Pathology, Univ Medical Center Utrecht, Utrecht, Netherlands; [2]Nephrology and Renal Replacement Therapy, Nagoya Univ Graduate School of Medicine, Nagoya, Japan; [3]Schulich School of Medicine and Dentistry, Western Univ, London, ON, Canada.*

Background: Lymphangiogenesis is correlated with the degree of renal interstitial fibrosis. TGF-β induces VEGF-C production, which is the main driver of lymphangiogenesis. CTGF (aka CCN2) is an important determinant of fibrotic tissue remodeling, but its possible involvement in lymphangiogenesis has not been explored.

Methods: Wild-type mice (WT, n=5) and CTGF knockout mice (CTGF-KO, n=9) underwent unilateral ureteral obstruction (UUO), and both the obstructed kidney (OBK) and contralateral kidney (CLK) were collected on day 14 after UUO. We analyzed the number of lymphatic vessels and VEGF-C expression by IHC and qPCR. Human proximal tubular epithelial cells (HK-2) were treated with CTGF or CTGF siRNA under the treatment with TGF-β1, and VEGF-C expression in HK-2 cells was assessed by qPCR and ELISA. Interaction of CTGF with VEGF-C was examined in a solid phase binding assay. We finally assessed the CTGF effect on VEGF-C stimulated growth and tube formation of human lymphatic endothelial cells (HMVEC).

Results: In vivo, CTGF knock-out inhibited lymphangiogenesis in OBK, as evidenced by reduction of the increase of LYVE-1-positive lymphatic vessels ($p<0.05$) and VEGF-C positive area ($p<0.001$). LYVE-1 and VEGF-C mRNA was reduced in CTGF-KO OBK as compared to WT OBK ($p<0.05$). In HK-2 cells, CTGF enhanced VEGF-C expression, while, CTGF siRNA suppressed TGF-β1-induced VEGF-C mRNA ($p<0.05$) and protein ($p<0.01$). Solid-phase binding assay revealed direct physical interaction between CTGF and VEGF-C. VEGF-C treated HMVEC efficiently formed capillary-like structures. Remarkably, this was significantly suppressed by the addition of full length CTGF ($p<0.05$). We are currently testing whether proteolysis of CTGF reverses this inhibition, as reported previously for VEGF-A inhibition.

Conclusions: CTGF is critically involved in renal lymphangiogenesis through interactions with VEGF-C.

FR-PO188

Swimming Exercise Training(EXE) Does Not Change Inflammatory Parameters but Increase Creatinine Clearance(CrCl) and Low Glomerulosclerosis and Mortality in Rats with 10 Weeks of Chronic Kidney Disease(CKD) by 5/6 Nephrectomy(5/6Nx) Rafael DaSilva Luiz, Rodolfo Rosseto Rampaso, Kleiton Augusto Santos Silva, Luciana Jorge, Edson Andrade Pessoa, Maria A. Gloria, Mario Luis Ribeiro Cesaretti, Nestor Schor. *Nephrology Div, Escola Paulista de Medicina/UNIFESP, Sao Paulo, SP, Brazil.*

Background: We evaluated the EXE effects on serum inflammatory markers, renal function and glomerulosclerosis in rats with 5/6Nx.

Methods: Adult Wistar rats were divided in groups(n=8): Control(C), Control+Exercise(E), Sedentary 5/6Nx(NS) and 5/6Nx+Exercise(NE). The protocol was employed in 5/6Nx rats after 7 days from the surgical procedures. EXE periods were 60min/day, 5 days a week/8 weeks. It was evaluated inflammatory parameters as IL1 alpha and beta, IL2, IL6 and TNF-alpha (Luminex), mean arterial pressure(MAP), maximal exercise test(MEte/st), CrCl, BUN, proteinuria(uProt), glomerulosclerosis(%) as well mortality rate.

Results: EXE did not modify the profile of inflammatory markers.

	C	E	NS	NE
IL1 alpha(pg/ml)	2.0±0.1	2.2±0.1	2.0±0.1	2.3±0.1
IL1 beta(pg/ml)	1.6±0.4	2.7±1.0	0.7±0.1	1.1±0.4
IL2(pg/ml)	0.6±0.1	0.9±0.4	0.9±0.2	0.9±0.1
IL6(pg/ml)	11.7±0.6	12.5±1.5	11.8±0.7	12.9±0.8
TNF-alpha(pg/ml)	0.1±0.0	0.1±0.0	0.1±0.0	0.1±0.0

There is an increment in MAP but prevent, at least in part, a lower decline in the MEtest caused by 5/6Nx(29±1vs16±2m/min $p<0.05$). Higher CrCl in NEvsNS, 2.3±0.3vs1.0±0.2ml/min, respectively($p<0.05$). BUN was normalized in NEvsNS(43.6±7.3vs180.6±49.2mg/dL $p<0.05$). Proteinuria was not significantly different in NEvsNS group (36.9±3.5vs40.1±2.4mg/24h). Glomerulosclerosis was 48% higher in NSvsNE($p<0.05$). A higher mortality rate was observed in NS(70%) vs NE(39%$p<0.05$).

Conclusions: Results suggested that 8 weeks of EXE did not change the inflammatory markers but minimize the impact of 5/6Nx by decreasing glomerulosclerosis and reduce the impact on CrCl. Finally, the decreasing mortality rate in NE vs NS and by minimizing the impact of 5/6Nx on CrCl indicate that exercise, at least swimming in this protocol, induced partial protection on renal function. Thus, it is reasonable to suggest that EXE could be an additional strategy to be employed in CKD.

Funding: Government Support - Non-U.S.

FR-PO189

SRGAPs Is Essential for Podocyte Cytoskeletons and Its Downregulation Facilitates Podocyte Injury and Diabetic Nephropathy Yu Pan, Song Jiang, Qing Hou, Dandan Qiu, Jingsong Shi, Zhao-Hong Chen, Ming-Chao Zhang, Zhihong Liu. *National Clinical Research Center of Kidney Diseases, Research Inst of Nephrology, Jinling Hospital, Nanjing, Jiangsu, China.*

Background: Podocytes injury is involved in the development of diabetic nephropathy (DN). Disruption of cytoskeletons in podocytes underlies podocyte foot process effacement and detachment from the glomerular basement membrane, leading to podocyte loss, proteinuria and glomerulosclerosis in DN. At present, the mechanism underlying podocyte cytoskeletal damage is incompletely understood.

Methods: We performed high-throughput microarray transcriptomics analyses of the micro-dissected glomeruli samples from the patients with early or late stage type 2 diabetic nephropathy. We performed bioinformatics analyses of the data to identify the genes associated with the progression of DN. We performed a variety of molecular and cell biology studies with cultured podocytes, db/db mice and zebrafish to investigate the role of the candidate gene in podocyte injury.

Results: Systems and network analyses of the microarray data identified that actin cytoskeleton is one of the top dysregulated pathways in the glomeruli of diabetic patients and that SRGAP2 downregulation is associated with the progression of DN. We further found that SRGAP2 is mainly expressed in podocytes in glomeruli and confirmed its downregulation in the podocytes of patients with DN at protein level. Consistently, SRGAP2 was also downregulated in the cultured podocytes treated with high glucose or TGF-β1. Furthermore, SRGAP2 knockdown was found to enhance podocyte mobility through altering RhoA/Cdc42 interaction, which was reversed by exogenous SRGAP2 overexpression. *In vivo*, SRGAP2 delivery ameliorated podocyte injury in db/db mice. Lastly, SRGAP2 knockdown in zebrafish by morpholino oligonucleotide (MO) resulted in developmental defects of podocytes and proteinuria.

Conclusions: SRGAP2 is a critical regulator of RhoA/Cdc42 activity, through which it maintains cytoskeleton stability. In DN, its expression is downregulated in podocytes, leading cytoskeleton disruption and podocyte injury. It is a potential therapeutic target for the treatment of DN.

FR-PO190

Sphingomyelinase Induces Podocyte Ferroptosis in HIV Milieu Kamesh R. Ayasolla, Waqaar Khawar, Nairuti H. Shah, Judith Eng, Seyedeh Shadafarin Marashi Shoshtari, Vinita Vishnoi, Ashwani Malhotra, Pravin C. Singhal. *Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY.*

Background: Loss of podocytes in HIV-associated nephropathy has been attributed to both apoptosis and pyroptosis; however, the role of ferroptosis in HIV-induced podocyte injury has not been investigated to date. Ferroptosis is a programmed caspase independent cell death initiated by cellular non-chelated iron and driven by altered lipid environment (reduced glutathione and lipid alterations) and condensed mitochondrial structures. We asked whether lipid alteration mediated ferroptosis contributes to the loss of podocytes in HIV-associated nephropathy (HIVAN). To elucidate this aspect, we examined the role of sphingomyelinase (SMase) in the induction of podocyte ferroptosis in HIV milieu, *in vivo* as well as *in vitro*.

Methods: SMase activities of renal tissues of control (FVB/N, n=5) and HIVAN (Tg26, n=6) mice and vector (V/HP) - and HIV-transduced human podocytes (HIV/HPs) were determined. To evaluate the effect of sphingomyelinase inhibitor (GW48), V/HPs and HIV/HPs were incubated in media containing either buffer or GW48 for 48 hours. Subsequently,

cells were evaluated for SMase activity and lipid peroxidation. V/HPs and HIV/HPs were evaluated for cell death with or without blockers of ferroptosis, caspase-1, and caspase-3 at different time periods. Additionally, role of PKC-ζ and NF-κB on SMase-induced HIV/HPs' downstreamBoyBoy signaling was evaluated.

Results: ζRenal tissues of Tg26 mice and HIV/HPs displayed several fold increase in SMase activity. HIV/HP-induced SMase activity could be effectively blocked by GW48. Additionally, HIV/HPs displayed increase in lipid peroxidation that could be inhibited by GW48. A vast numbers of HIV/HPs succumbed to death during 96 hours. The relative cell survival using blockers of ferroptosis, Caspase-1, and Caspase 3 were 35%, 45%, and 20% respectively. HIV activated PKC-ζ and NF-κB and inhibitors of PKC-ζ and NF-κB prevented HIV induced ferroptotic cell death.

Conclusions: HIV induces ferroptosis in podocytes through the activation SMase activity and associated downstream signaling.

Funding: NIDDK Support

FR-PO191

APOL1 Risk Variants Down Regulate Podocytes Nephrin Protein Expression: Role of Endoplasmic Reticulum Stress Xiqian Lan, Seyedeh Shadafarin Marashi Shoshtari, Judith Eng, Ashwani Malhotra, Pravin C. Singhal. *Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY.*

Background: Two coding sequence variants (G1 and G2) in *APOL1* gene have been implicated for higher rates of chronic kidney diseases in African Americans when compared to European Americans. Previous studies from our group as well as from other investigators have elucidated that the APOL1 G1 and G2 variant proteins are more toxic to kidney cells when compared with wild type APOL1 G0; nonetheless, the involved mechanisms are not clear. Nephrin is an important constituent of the slit diaphragm and animals lacking this gene have been reported to develop massive proteinuria. We hypothesize that APPOL1 risk variants down regulate translation of podocyte nephrin as a consequence of endoplasmic reticulum (ER) stress.

Methods: In these studies, we used human podocytes (HPs) stably expressing APOL1G0, G1, or G2 (Vec/HPs, G0/HPs, G1/HPs, and G2/HPs). After differentiation for 7 days, the cell lysates were collected, and were subjected to Western blot to examine the protein expression of nephrin. We also isolated RNA samples from these cells, and detected the changes of nephrin mRNA levels by using real time-PCR. To study the role of endoplasmic reticulum stress, we evaluated the effect of APOL1 variants on podocyte phosphorylation of eIF-2α. To establish a causal relationship, podocytes expressing APOL1G0/G1/G2 were incubated in media containing either buffer or ER stress inhibitors (either salubrinal or 4-PBA-1) during differentiation followed by immunoblot analysis for nephrin.

Results: Expression of nephrin protein in G1 and G2 podocytes was dramatically decreased when compared with that in G0. Since the neprhin mRNA levels didn't change, it appears that APOL1 risk variants affect nephrin expression at translation step. APOL1G1 and G2 dramatically increased its phosphorylation of eIF-1α, indicating that they these cell undergoing the ER stress. ER stress inhibitors rescued nephrin expression in APOL1G1 and G2 podocytes.

Conclusions: APOL1 risk variants suppress neprhin translation through enhanced ER stress.

FR-PO192

Triptolide Attenuates Proteinuria and Podocytes Apoptosis in Zebrafish via GADD45 Ling Wang, Zhao-Hong Chen, Qing Hou, Xiao-Dong Zhu, Wei-Song Qin, Cai-Hong Zeng, Zhihong Liu. *National Clinical Research Center of Kidney Diseases, Research Inst of Nephrology, Jinling Hospital, Nanjing, Jiangsu, China.*

Background: Dysfunction or loss of podocytes causes proteinuria, which has been associated with both acute and chronic glomerular diseases. However, podocyte target treatments are still limited. Triptolide, a major active component of Tripterygium wilfordii Hook F, has dramatic antiproteinuric effect, but the mechanism is unclear. A transgenic zebrafish model of inducible podocyte injury has been established previously. In this transgenic zebrafish, the bacterial nitroreductase (NTR) is expressed specifically in podocytes under the control of zebrafish podocin promoter, the prodrug metronidazole (MTZ) can be converted into a cytotoxin only in podocytes, which leading to podocyte injury.

Methods: We examined the effect of tripolide on transgenic zebrafish model of inducible podocyte injury. We treated zebrafish embryos with triptolide, then observed edema, measured proteinuria level as well as analyzed changes of podocin expression and foot process by immunostaining and Transmission Electron Microscope respectively. Furthermore, we performed an activated caspase-3 staining and applied microarray in tripolide-treated human podocyte. Finally, we validated the result of microarray by qRT-PCR in vitro and in vivo.

Results: Triptolide effectively alleviated edema and proteinuria in zebrafish model. The antiproteinuric effect was associated with improvement of foot process effacement, restoration of podocin expression and distribution as well as inhibition of podocytes apoptosis. Comparison of the mRNA profile by microarray analysis showed GADD45 family expression was downregulated in triptolide treated human podocytes *in vitro*. GADD45B has been implicated in podocytes apoptosis. Triptolide could suppress the expression of GADD45 in both MTZ-treated zebrafish glomeruli and PAN-treated human podocytes.

Conclusions: These results demonstrate that triptolide has direct effect on podocyte. Triptolide attenuates proteinuria and podocyte injury via reversing podocyte apoptosis and downregulation of gadd45 expression.

FR-PO193

MicroRNA193a-Induced Oxidative Stress Contributes to Puromycin Aminonucleoside (PAN) Mediated Podocyte Injury Vinod Sharma, Waqaar Khawar, Seyedeh Shadafarin Marashi Shoshtari, Judith Eng, Nairuti H. Shah, Ashwani Malhotra, Pravin C. Singhal. *Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY.*

Background: MicroRNA193a negative regulates Wilms tumor (WT1) gene and plays an important role in the development of focal segmental glomerulosclerosis (FSGS). PAN induces FSGS through a loss of critical number of podocytes. PAN has been shown to be an inducer of apoptosis in podocytes, both *in vitro* and *in vivo* studies. We asked whether pro-apoptotic effect of PAN was mediated via miR193a-induced reactive oxygen species (ROS) generation by podocytes.

Methods: Immortalized human podocytes (HPs) were incubated in media containing either buffer or PAN (30 μg/ml) for 24 hour and 48 hours (n=3). To determine the dose response effect, HPs were treated with variable concentration of PAN (0, 10, 20, 30 μg/ml) for 24 hours. Subsequently, RNAs were extracted and cDNAs were probed for miR193a. To establish a causal relationship, HPs were incubated in media containing either buffer, PAN (30 μg/ml), miR193 inhibitor (miR, 50 nM), and PAN + miR inhibitor for 24 hours followed by apoptosis assay. In parallel sets of experiments, effect of miR193a inhibitor on PAN-induced podocyte ROS generation was measured after DCFDA loading of control and experimental cells followed by measurement of ROS by a fluorometer. In another set of experiment, mice (n=4) were administered either normal saline or PAN. After 8 days, renal cortical sections were prepared for *in situ* hybridization for miR193a expression and immuno-histochemical analysis for glomerular cell WT1 expression.

Results: PAN enhanced podocyte expression of miR193a in a dose dependent manner. PAN promoted ROS generation and apoptosis in podocytes, however, these effects of PAN were partially inhibited by an inhibitor of miR193a. *In situ* hybridization studies displayed enhanced miR193a expression by scattered podocytes in PAN mice. PAN mice also displayed decreased number of WT1 stained glomerular cells (control, 27.2 ± 7.6 vs. PAN, 13.2±3.7 +ve cells/glomerulus, $P<0.05$).

Conclusions: PAN contributes to podocyte injury through enhancing podocyte miR193a expression.

Funding: NIDDK Support

FR-PO194

DNA Hypermethylation of sFRP5 Contributes to Indoxyl Sulphate-Induced Renal Fibrosis Yanlin Yu, Jinghong Zhao. *Dept of Nephrology, Inst of Nephrology of Chongqing and Kidney Center of PLA, Xinqiao Hospital, Third Military Medical Univ, Chongqing, China.*

Background: Renal fibrosis is the most common outcome of chronic kidney disease (CKD), whereas the molecular mechanisms underlying CKD-associated renal fibrosis are not fully understood.

Methods: In this study, we used high-performance liquid chromatography (HPLC), Masson's trichrome staining, Immunohistochemistry, Methylation-specific PCR (MSP), bisulfite-sequencing PCR (BSP), Semi-Quantitative RT-PCR, Western blotting, Immunoprecipitation.

Results: In this study, we found that in CKD patients the progress of renal fibrosis was positively related to the increase in the serum indoxyl sulphate (IS), a typical protein-bound toxin, and there was a close correlation between serum IS level and β-catenin expression in the kidneys ($r=0.908$, $p<0.001$).It was then demonstrated that intraperitoneal injection with IS for 4 weeks was able to induce renal fibrosis, accompanied by significant activation of Wnt/β-catenin signaling in uninephrectomized mice. Further investigations revealed that in cultured human renal tubular HK-2 cells,IS exhibited a strong ability to silence *sFRP5*, an extracellular Wnt antagonistic gene, by increasing DNA methylation level of the promoter CpG island. A significant increase in ROS production and ERK1/2 phosphorylation, accompanied by increased expression of DNA methyltransferases (DNMTs), were detected before *sFRP5* decline in IS-treated HK-2 cells. Similar to the inhibition of ROS production and ERK1/2 activation, treatment with 5-aza-2'-deoxycytidine, the inhibitor of DNMTs, significantly constrained IS-induced sFRP5 down-regulation and Wnt/β-catenin activation. In vivo, intraperitoneal injection with recombined sFRP5 protein or 5-aza-2'-deoxycytidine could remarkably alleviate IS-induced Wnt/β-catenin activation and interstitial fibrosis in the kidney.

Conclusions: Our results demonstrate that DNA hypermethylation of *sFRP5* is involved in IS-induced Wnt/β-catenin activation that contributes to the development of renal fibrosis, which provides new insights into the pathogenesis of CKD-associated renal fibrosis.

Funding: Government Support - Non-U.S.

FR-PO195

A Novel Mouse Model Demonstrates the Role of Bone Marrow-Derived Fibrocytes in Gadolinium-Associated Systemic Fibrosis Catherine Do,[1,2] Chunyan Tan,[2] Viktor Drel,[2] Brent Wagner.[1,2] *[1]Medical Service, South Texas Veterans Health Care System, San Antonio, TX; [2]Medicine, Univ of Texas Health Science Center at San Antonio, San Antonio, TX.*

Background: Intravenous gadolinium (Gd)-based contrast is now associated with a number of conditions, including 'nephrogenic' systemic fibrosis/gadolinium-associated systemic fibrosis. The pathophysiology has been largely unexplored, particularly with mouse models.

Methods: Mice with partial nephrectomies underwent lethal irradiation then salvaged with bone marrow from green fluorescent protein (GFP)-expressing donors. After an engraftment period, these recipients were randomized to control (n=5) or Gd-based contrast treatment (n=6, 2.5 mmol/kg, 20 doses intraperitoneally over 4 weeks). Gd was assessed with inductively-coupled plasma mass spectroscopy.

Results: Gd was elevated in the skin, kidney, and liver; it was barely detected in brain. Dermal cellularity was increased in contrast-treated mice. Compared to control, skin GFP, fibronectin, and type I collagen were all increased in the contrast-treated animals as assessed by Western blot and immunofluorescence. Importantly, CD45RO, a marker for myeloid fibrocytes, was abundant in the dermis of contrast-treated animals, frequently expressed by the myeloid cells. Many of these cells expressed cytoplasmic α-smooth muscle cell actin, a marker of myofibroblast activation. We also show that C-C chemokine receptor (CCR)-2 and -7 as well as CCR2 ligand monocyte chemoattractant protein-1, are all increased in skin from contrast-treated mice.

Conclusions: Systemic fibrosis can be induced by Gd contrast in mice. That GFP levels and expression increase in an involved organ, the skin, in tandem with a fibrocyte marker—CD45RO—supports the blood-borne circulating fibrocyte hypothesis of the disease. Importantly, similar to what is observed in a rat model, our data strongly suggest that inflammatory chemokines play a critical role in the pathogenesis of Gd-induced systemic fibrosis. Our study demonstrates that mice are an appropriate model to investigate the deleterious effects of gadolinium and will allow proceeding with mechanistic studies using relevant genetically-modified mice.

Funding: NIDDK Support, VA Support

FR-PO196

The Novel sGC Stimulator IW-1973 Inhibits Renal Inflammation and Fibrosis in Preclinical Animal Models Guang Liu, Courtney Shea, Renee T. Sarno, George Todd Milne, Mark G. Currie, Jaime L. Masferrer. *Ironwood Pharmaceuticals, Cambridge, MA.*

Background: Defects in NO-soluble guanylate cyclase (sGC)-cGMP signaling are implicated in several cardiovascular diseases. IW-1973, a novel sGC stimulator has been shown to reduce blood pressure and preserve kidney function in the Dahl-ss rat model (Dss) of hypertension. Mechanistically IW-1973 demonstrates direct anti-fibrotic effects through blocking TGFβ-mediated signaling in human renal proximal tubular cells. This study evaluated the effect of IW-1973 on renal inflammation and fibrosis in Dss and unilateral ureteral obstruction (UUO) rat models.

Methods: In Dss rats, IW-1973 treatment (1, 3 and 10 mg/kg/d) started 2 weeks after rats began a high salt diet and continued for 6 weeks (total 8 weeks). For the UUO model, rats underwent surgery then received IW-1973 in chow for 2 weeks.

Results: Analysis of kidneys from IW-1973-treated Dss rats demonstrated a dose-dependent reduction in the expression of inflammatory genes TNFα, NFkB-1, ICAM and VCAM. Acute administration of IW-1973 (1 and 10 mg/kg) significantly reduced LPS-induced increases in IL-6 and TNFα ($p<0.01$), and increased IL-10 levels ($p<0.01$) in C57BL/6 mice, supporting the anti-inflammatory activity observed in the Dss rat model. In the UUO model, rats had statistically significant increases in renal inflammation ($p<0.01$), tubular degeneration ($p<0.001$) and interstitial fibrosis ($p<0.001$) 14 days after surgery compared with healthy controls. Treatment of UUO rats with 10 mg/kg/d IW-1973 resulted in a reduction of interstitial fibrosis from marked (histology score=4) to mild (histology score=3) in 6 out of 8 rats, compared to a median histological score of 3.8 for the UUO vehicle control group. The reduction in histological score was consistent with decreases in Col1a1 mRNA level and hydroxyproline content in the kidneys of IW-1973-treated rats.

Conclusions: These preclinical data suggest that sGC stimulation represents a mechanism that warrants investigation for the treatment of renal inflammatory and fibrotic diseases.

Funding: Pharmaceutical Company Support - Ironwood Pharmaceuticals, Inc.

FR-PO197

PGC-1α Protects TGF-β Induced Fibrosis by Suppressing TGFβRI Expression Affected to Smad2/3 Activation Hoon In Choi, Jung Sun Park, Eun Hui Bae, Seong Kwon Ma, Jong Un Lee, Soo Wan Kim. *Dept of Internal Medicine & Physiology, Chonnam National Univ Medical School, Gwangju, Republic of Korea.*

Background: Renal fibrosis results from aberrant accumulation of extracellular matrix mainly driven by transforming growth factor-β (TGF-β). This process is initiated by binding of active TGF-β1 to TGF β type I and type II receptor (TGFβRI and II) complex, which is transduced to intracellular signals for pro-fibrotic gene expression through Smad2/3 activation. Peroxisome proliferator-activated receptor gamma co-activator 1 alpha (PGC-1α) is a key metabolic regulator that stimulates mitochondrial biogenesis, and may play a role in oxidative stress and inflammation. However, the physiological effects of PGC-1α in renal fibrosis have not been fully characterized. We investigated whether PGC-1α may regulate TGF-β/Smad signal pathways in the pathogenesis of renal fibrosis.

Methods: As *in vivo* and *in vitro* model of renal fibrosis, Left kidneys of C57BL/6J mice were subjected to unilateral ureteral obstruction (UUO) for 7 or 14 days. Human proximal tubule (HK-2) cells were stable transduced with human PGC-1α expression vector ($PGC\text{-}1\alpha^{O/E}$) or empty vector ($PGC\text{-}1\alpha^{Mock}$) containing selective marker and were treated with TGF-β for the indicated time. The changes of pro-fibrotic marker proteins in TGF-β treated $PGC\text{-}1\alpha^{Mock}$ and $PGC\text{-}1\alpha^{O/E}$ HK-2 cells were assessed by western blotting and immunofluorescence.

Results: The level of PGC-1α was diminished throughout the course of ureter obstruction and conversely associated with increased levels of fibrotic cytokine and fibrotic markers, such as TGF-β, fibronectin, vimentin, and alpha-smooth muscle actin (α-SMA). Consistent with *in vivo* data, the level of PGC-1α were reduced in TGF-β treated HK-2 cells. Stable expression of PGC-1α ($PGC\text{-}1\alpha^{O/E}$) in HK-2 cells attenuated the TGF-β induced upregulation of fibrotic markers (fibronectin, vimentin, and α-SMA) and downregulation of epithelial marker (E-cadherin), compared to $PGC\text{-}1\alpha^{Mock}$. Overexpression of PGC-1α significantly suppressed TGFβRI expression, and subsequently phosphorylation of Smad2/3 was reduced.

Conclusions: PGC-1α regulates canonical TGF-β/Smad signal pathway by targeting TGFβRI expression, resulting in anti-fibrotic effect.

Funding: Government Support - Non-U.S.

FR-PO198

Indoxyl Sulfate Triggers Increased Oxidative Stress and Eryptosis Gabriela Ferreira Dias,[1] Natalia Borges Bonan,[1] Viktoriya Kuntsevich,[4] Silvia Daniele Rodrigues,[3] Lia S. Nakao,[3] Stephan Thijssen,[2] Peter Kotanko,[2] Roberto Pecoits-Filho,[1] Andrea Novais Moreno-Amaral.[1] *[1]PUCPR, Brazil; [2]RRI; [3]UFPR, Brazil; [4]MSBI.*

Background: Uremic toxins increase oxidative stress and red blood cell (RBC) death (eryptosis). We explore the effect of indoxyl sulfate (IS) on reactive oxygen species (ROS) production and eryptosis, and its effect on the RBC antioxidant system.

Methods: RBC from 6 healthy subjects were incubated for 6, 12 and 24h with buffer (negative control – NC) or IS (4.49; 23.1; and 44.5mg/L) in the presence or absence of diphenyleneiodonium chloride (DPI; 10μM). Flow cytometry was used to determine eryptosis (by AnnexinV-PE staining) and ROS production (by DCFH-DA probe). Levels of reduced glutathione (GSH) were measured by spectrophotometry using tert-Butyl hydroperoxide (TBHP) as positive control. Data are presented as mean±SD.

Results: IS increased ROS in a time- and dose-dependent manner (Table 1) between 6 and 12h, and stabilized after 24h. Eryptosis increased in a dose- and time-dependent fashion (Table 1), without significant eryptosis after 6h. In the presence of DPI, ROS production and eryptosis were inhibited to levels compared to NC. IS did not change GSH concentration (Table 1).

Table 1. ROS production, Eryptosis and GSH levels

ROS (MFI)	NC	TBHP	IS 4.49	IS 23.1	IS 44.5
6h	2.9±1.2	-	8.5±5	13±2.9*	23±6.7*
12h	2.7±1.6	-	13±6.3*	21±7.4**	26±6.1**
24h	3.9±0.9	-	11±3.2*	14±4.8**	20±5.7**
Eryptosis					
12h	4.3±1	-	8.6±2.3	14±3.2*	16±4**
24h	4.5±2.6	-	9.53±2*	20±2.8**	30±7.3**
GSH					
6h	3.9±1	0.1±0.05**	3.8±1	4±0.9	4±1.1
12h	2±0.2	0.1±0.05**	2.8±0.2	2.1±0.2	2.2±0.2
24h	2.1±0.2	0.1±0.01**	1.9±0.1	2.1±0.2	1.9±0.1

Mean Fluorescence Intensity (MFI); μmol GSH/μg protein; *$p<0.05$; **$p<0.01$ *vs*. NC.

Conclusions: IS promoted ROS production and eryptosis in a dose- and time-dependent fashion, both NADPH oxidase-dependent processes. At the same time, IS did not affect RBC GSH, which indicates limited ability of RBC antioxidant enzymes to respond to high levels of oxidative stress.

Funding: Government Support - Non-U.S.

FR-PO199

Role of APE1/Ref-1 in Hydrogen Peroxide-Induced Apoptosis in Human Renal HK-2 Cells Ha Yeon Kim,[1] Jung Sun Park,[2] Eun Hui Bae,[1] Seong Kwon Ma,[1] Jong Un Lee,[2] Soo Wan Kim.[1] *[1]Dept of Internal Medicine, Chonnam National Univ Medical School, Gwangju, Korea; [2]Dept of Physiology, Chonnam National Univ Medical School, Gwangju, Korea.*

Background: Apurinic/apyrimidinic endonuclease 1/redox factor-1 (APE1/Ref-1) is multipotent protein that plays an essential role in the cellular response to oxdiative stress. In the present study, we investigated the role of APE1/Ref-1 in ischemia-refusion (IR) injury in rat kidney and hydrogen peroxide (H_2O_2) induced renal tubular apotosis.

Methods: Kidney IR injury in rats was established by clamping the both renal arterys for 50 minutes followed by 2 or 5 days of reperfusion.

Results: APE1/Ref-1 is predominantly localized in the nucleus in the kidney tubule cell, while there was lack of APE1/Ref-1 in the glomerulus. The fluorescence of APE1/Ref-1was most prominent in the proximal tubule. Consistenct with the expression of APE1/Ref-1, the level of APE1/Ref-1 protein also was highest in the cortex, modest in the outer meulla, and lowest in the inner medulla. In rat model of renal IR injury, the level of APE1/Ref-1 protein was increased compared with that in kidneys subjected to sham operation. We found that over-expression of APE1/Ref-1 in HK-2 cell enhanced the ratio of Bax/Bcl-2. The suppression of APE1/Ref-1 by the pharmacologic inhibitors E3330 in HK-2 cell with H_2O_2 exposure, resulted in decreased ratio of Bax/Bcl-2 and altered phosphorylation of ERK1/2, p38, JNK1/2, and NF-κB.

Conclusions: These findings suggest that APE1/Ref-1 inhibitor attenuates H_2O_2-induced apoptosis in HK-2 cells by modulating the ERK/p38 signaling pathways.

FR-PO200

Novel Non-Coding RNA Regulated by HIF-1 Suppresses Apoptosis in Renal Tubular Epithelial Cells Imari Mimura,[1] Yosuke Hirakawa,[1] Natsuki Kushida,[1] Yasuharu Kanki,[2] Yutaka Suzuki,[3] Hiroyuki Aburatani,[4] Masaomi Nangaku.[1] *[1]Div of Nephrology and Endocrinology, The Univ of Tokyo, Tokyo, Japan; [2]Isotope Science Center, The Univ of Tokyo, Japan; [3]Graduate School of Frontier Sciences, The Univ of Tokyo, Japan; [4]Div of GenomeScience, Div of GenomeScience, Research Center for Advanced Science and Technology, Japan.*

Background: We have reported that chronic tubulointerstitial hypoxia plays an important role as the final common pathway to end-stage renal disease. HIF-1 (hypoxia inducible factor-1) is a master transcriptional factor under hypoxia, regulating downstream target genes. Genome-wide analysis of HIF-1 binding sites using high throughput sequencers has clarified various kinds of downstream targets and made it possible to demonstrate the novel roles of HIF-1, which interacts with epigenetic histone modifiers. Our aim of this study is to identify novel HIF-1 downstream epigenetic factors which may play important roles in the kidney.

Methods: HK2 (human kidney-2) and primary cultured tubular cells (RPTEC: renal proximal tubular epithelial cells) are exposed to 1% hypoxia. We performed genome-wide analysis of RNA-seq to clarify the expressions of mRNA and large intergenic non-coding RNA (lincRNA). We also examined ChIP-seq using HIF-1 antibody to identify HIF-1 binding sites under hypoxia.

Results: RNA-seq identified 580 lincRNAs which are up-regulated under hypoxic condition in both cells. ChIP-seq analysis demonstrated that HIF-1 also binds to the lincRNAs under hypoxia. The expression of novel lincRNA, DARS-AS1 (aspartyl-tRNA synthetase anti-sense 1), is up-regulated only under hypoxia and HIF-1 binds to its promoter region, which includes two HREs (hypoxia responsive elements). Its expression is also up-regulated with cobalt chloride exposure, while it is not under hypoxia when HIF-1 is knocked down by siRNA. To clarify the biological roles of DARS-AS1, we measured the activity of caspase 3/7 using anti-sense oligo of DARS-AS1. As a result, apoptotic cell death deteriorated by knockdown of DARS-AS1.

Conclusions: We firstly identified the novel lincRNA regulated by HIF-1 under hypoxia and clarified that DARS-AS1 plays important roles in inhibiting apoptotic cell death in renal tubular cells.

Funding: Government Support - Non-U.S.

FR-PO201

Dimethyl Fumarate Treatment Regulates Macrophage Polarization upon Oxidative Stress in Renal Inflammation Yi Li, Li Wang. *Renal Div and Inst of Nephrology, Sichuan Provincial People's Hospital, Chengdu, Sichuan, China.*

Background: Characterized by macrophage polarization, renal inflammation represents a ubiquitous human health problem, effective therapies with limited side effects are still lacking. In this study, we examine the role of Dimethyl fumarate (DMF) in macrophage polarization induced by oxidative stress of renal inflammation.

Methods: Balb/c mice (n=10) were administrated by 50 mg/kg DMF then injected with 10 μg/kg LPS. After tested renal dysfunction and histological features upon LPS nephritis, RT-PCR detected the level of IL-6, MCP-1, TNF-α, IFN-γ, IL-10 and CD206 in murine kidney. Before stimulated with LPS, the Raw264.7 macrophage cells were respectively pre-treated with DMF, Nrf-2 agonist SFN or ROS inhibitor NAC. The results of mito-tracker staining were observed by confocal. Flow cytometry measured the production of ROS by DCF-HDA and the expression of M1 macrophage marker iNOS. Western blot detected the expression of Nrf-2 and Sirt-1 *in vivo* and *in vitro*.

Results: DMF ameliorated murine LPS nephritis on renal dysfunction by reduction of blood urea nitrogen and serum creatinine, then decreased the histological features following renal injury. DMF also reduced mRNA level of IL-6, MCP-1, TNF-α and IFN-γ after LPS injection, whereas it did not decrease the level of IL-10 and CD206. Compared with LPS induced Raw264.7 cells, DMF significantly inhibited the expression of iNOS and reduced the production of Nitrite. Current study also revealed the role of DMF in protecting against intracellular ROS accumulation and mitochondria dysfunction upon LPS induced nephritis. DMF increased the level of Nrf-2 and Sirt-1 following *in viv*o and *in vitro* LPS treatment.

Conclusions: This study showed that DMF augmented LPS-induced acute nephritis and related cellular malfunction, indicating protective effects of DMF on regulating macrophage polarization upon oxidative stress in LPS induced acute renal inflammation via Nrf-2-mediated pathway.

FR-PO202

Following Site-Selective Endothelial Injury, Endothelial Cells Die from Necrosis and Apoptosis, but Not from Necroptosis Jan Sradnick,[1] Anika Luedemann,[1] Kathleen Fischer,[1] Andreas Linkermann,[2] Bernd Hohenstein,[1] Christian Hugo.[1] *[1]Div of Nephrology, Dept of Internal Medicine III, Univ Hospital CGC, Dresden; [2]Clinic for Nephrology and Hypertension, Univ Hospital, Kiel, Germany.*

Background: Since the introduction of our site-selective endothelial injury model in murine kidneys, we have shown that particular cell types do (platelets) or do not (extrarenal progenitor cells) play a role for the occurrence or repair of endothelial cell (EC) lesions. With respect to the initiation of disease and cellular response, the mechanism of EC death might be relevant. We here aimed to investigate EC death following EC injury (ECI) in mice.

Methods: Using renal-arterial perfusion of Concanavalin(ConA)/anti-ConA, selective ECI was induced in C57Bl/6 mice. Kidneys were harvested after 24h (n=5) and 72h (n=6), 5 mice served as controls. Flow cytometry was used to analyze inflammatory cells and different death markers in EC, defining them either as necrotic (7AAD+), apoptotic (annexinV+) or necroptotic (pMLKL+). Additionally ECI or ischemia reperfusion (I/R) was induced transgenic mice carrying a constitutive EC-specific Tie2 GFP signal. Kidneys were harvested 24h following model induction.

Results: Kidneys demonstrated EC lesions reflected by a EC reduction of 25% measured after 24h and 72h (sham 10%±2 vs d1: 7%±1; d3: 7%±1 FACS). As described previously neutrophils were increased 24h, T-cells and macrophages 72h after ECI. The amount of 7AAD+ EC was raised after 24h (14%±5; $p<0.01$) and 72h (16%±2; $p<0.01$) compared to controls (8%±1). More apoptotic EC were found after 24h (1.1% ±0.4 vs. sham 0.3%±0.1; $p<0.01$). In contrast, less necroptotic EC were found and stayed unchanged over time (contr.: 0.16%±0.1; 24h: 0.15%±0.2; 72h: 0.3%±0.2). Similar data were found in Tie2 transgenic mice injured with ECI and I/R.

Conclusions: Necrosis and apoptosis represent the dominant EC death mechanism during the initial time course of our disease model, while necroptosis is no major cell death mechanism in EC in this disease model. These findings will now have to undergo further validation using interventional strategies blocking the individual mechanisms.

FR-PO203

Tumor Necrosis Factor (TNF) α-Converting Enzyme Inhibitors Attenuate Lipopolysaccharide-Induced Reactive Oxygen Species and Mitogen-Activated Protein Kinase in HK 2 Cells Eun Hui Bae,[1] Seong Kwon Ma,[1] Jong Un Lee,[2] Soo Wan Kim.[1] *[1]Internal Medicine, Chonnam National Univ Medical School, Gwangju, Korea; [2]Physiology, Chonnam National Univ Medical School, Gwangju, Korea.*

Background: Lipopolysarralide (LPS) induce acute kidney injury (AKI), which key mediator is tumor necrosis factor-1 (TNFα). TNFα-converting enzyme (TACE) is responsible for the shedding of cell surface TNF. It is also associated with ACE2 shedding. We hypothesize that LPS suppresses ACE2 by increasing TACE and TACE inhibitors attenuate LPS injury in HK 2 cells.

Methods: Intravenous LPS (10mg/kg) in male mice induced increased serum creatinine, TNFα, and urinary neutrophil gala (NGAL).

Results: LPS increased Angotension II, angiotensin II type 1 receptor, mitogen activated protein kinase (MAPK), TACE expression and TACE activity, while decreased ACE2 expression in LPS induced AKI mice model and LPS-treated HK2 cell. LPS induced reactive oxygen species (ROS) and down-regulation of ACE2 expression were prevented by TACE inhibitors in HK 2 cells. Cell vioability also increased by TACE inhibitor treatement in LPS treated in HK2 cells. TACE inhibition also attenuated mitogen activated protein kinase (MAPK), cyclooxygenase 2 (COX2), and hemoxygenase-1 (HO-1) which is oxidative stress markers.

Conclusions: Our findings indicate that LPS-induced TACE activation partially contribute to ACE2 shedding and TACE inhibitors attenuate LPS-induced ROS and MAPK pathway in HK 2 cells.

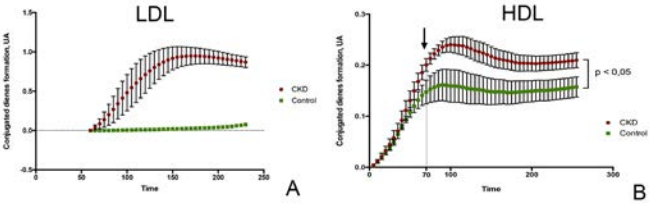
FR-PO204

Enhanced Oxidation of HDL in a Rabbit Model of Chronic Kidney Disease Nans Florens,[1,2] Caroline C. Pelletier,[1,2] Sandrine Lemoine,[1,2] Laurent Juillard,[1,2] Christophe O. Soulage.[2,3] *[1]Nephrology, Hospices Civils de Lyon, Lyon, France; [2]INSERM U1060 - CarMeN, Villeurbanne, France; [3]INSA, Villeurbanne, France.*

Background: Recent studies have shown modified proprieties for HDL in chronic kidney disease (CKD). As the cardiovascular mortality remains the major cause of death in CKD and as oxidative stress is raised in CKD, we aimed to explore the specific role of renal dysfunction, on lipoproteins modifications in a rabbit model of CKD.

Methods: Rabbits were nephrectomized with a surgical 5/6-fold reduction technique. Lipoproteins were isolated from plasma by potassium bromide stepwise density gradient ultracentrifugation.Malondialdehyde (MDA) was measured by high performance liquid chromatography (HPLC). 4-hydroxy-nonenal (HNE) and 4-hydroxy-2-hexenal (HHE) adducts were assayed by dot-blot. Copper-induced oxidation of lipoprotein was performed with the addition of CuSO4 and formation of conjugated dienes were monitored.

Results: 8 CKD rabbits were compared with 9 Sham operated. Creatinine levels were significantly higher in CKD group (93 vs 214 μM, $p<0.001$) as well as plasmatic level of MDA (0,14 vs 1.45 μM, $p<0.001$). Anti-oxidant activity of the plasma was lower in the CKD group (0.98 vs 0.83 mM, $p<0.05$). MDA levels in LDL were not altered in the CKD group while increased in the HDL from CKD rabbits (0.89 vs 2.64 nmol/mg of proteins, $p<0.05$). HNE-adducts were also raised in the HDL of CKD group ($p<0,05$) while HHE-adducts were only raised in LDL of CKD group ($p<0,05$). Copper-induced oxidation showed higher production of conjugated dienes in LDL and HDL from CKD animals.



Conclusions: CKD rabbits exhibited extensive oxidative modifications in HDL even if LDL seemed to be more sensitive to oxidation. This observation is consistent with the modified functions of HDL in CKD reported in the literature.

Funding: Government Support - Non-U.S.

FR-PO205

Antioxidant Modulates Diabetes Induced Cardiorenal Injury in an Experimental Model of Cardiorenal Syndrome Firoozeh Farahmand. *Internal Medicine, Div of Nephrology, Saint Louis Univ, Saint Louis, MO.*

Background: There is growing evidence that oxidative stress is one of the key mediators of cardiorenal syndrome (CRS), and has a key role in pathological processes in diabetic nephropathy, as well as diabetic cardiomyopathy. Therefore, an understanding of cellular pathways involved in both renal and cardiac oxidative stress is essential in the development of novel and effective therapeutic strategies to improve the survival and prognosis in CRS patients.

Methods: Diabetes was induced in rats with single injection of streptozocin (STZ). Animals were randomly divided into 4 groups: CONT, CONT+Losartan, Diabetics Control, and Diabetics+Losartan. At 4 weeks left ventricle (LV) systolic pressure (LVSP), aortic systolic (AS)pressure, LV diastolic pressure, LV hypertrophy (LVH), and LV function were measured, and the slope of the LV end-diastolic P-V relationship (EDPVR) as index of LV stiffness were calculated. After sacrificing the animals, the renal cortex and the heart were removed for histology, antioxidant enzymes, and lipid peroxidation measurement.

Results: In STZ-induced diabetics group at 4 weeks there was a significant drop in LVSP and ASP associated with increased renal and myocardial lipid peroxidation, and decreased in antioxidants enzymes. These effects were inhibited by losartan. In Diabetics+Losartan group losartan also significantly reduced renal and myocardial histopathological alterations.

Conclusions: Our results indicate diabetic nephropathy and diabetic cardiomyopathy are associated with antioxidant deficit that can be reversed with losartan. Improved cardiac function with losartan may be due to the recovery of the antioxidants in the heart. Oxidative stress, as an important trigger in diabetes complication, may offer a unique therapeutic option for the treatment of cardiorenal injury in diabetes, and benefit reducing diabetes-induced renal damage.

FR-PO206

Assessing the Impact of Primary Cilia Loss on Epithelial Phenotype and Function in a Human Renal Proximal Tubular Epithelial Cell Line Michael Higgins, Tara McMorrow. *School of Biomolecular and Biomedical Science, Conway Inst, Univ College Dublin, Dublin, Ireland.*

Background: The primary cilium is a hair-like microtubule based structure, protruding from nearly all mammalian cells. The primary cilium is well established as a crucial signalling hub with receptors for Wnt and hedgehog localized to the cilium. Primary cilia have been found to be implicated in a range of diseases collectively called ciliopathies. In recent years there has been increased interest in the link between the primary cilium and the development and progression of cancer, with several cilia associated genes dysregulated in numerous cancers. The primary cilium has been found to be absent in renal cell carcinomas, breast and pancreatic cancers. The aim of this study was to assess the impact of cilia loss on epithelial and mesenchymal marker expression and to investigate the effects on epithelial function by assessing epithelial barrier function.

Methods: A number of known deciliating chemicals were used to induce primary cilia loss. The immunofluorescent labelling of ciliary markers ARL13b and acetylated alpha tubulin were employed to confirm the absence or presence of a primary cilium in human renal cells. Western blotting and Real Time PCR were used to assess epithelial, mesenchymal and tight junction protein and gene expression following deciliation. Epithelial barrier function was also assessed by measuring trans-epithelial electrical resistance (TEER).

Results: Deciliation of human renal cells by the deciliating compounds was confirmed by acetylated alpha tubulin/ARL13B staining. Deciliation was found to cause an altering of tight junction protein expression, specifically effecting members of the claudin family. Cilia loss also caused an increasing trend in TEER, suggesting a decrease in tight junction permeability and a change in epithelial barrier function following deciliation.

Conclusions: Preliminary results suggest cilia loss in renal epithelial cause an altering of epithelial tight junctions and effect epithelial barrier function. Further analysis is currently being carried out to establish the link between primary cilia and the maintenance of epithelial phenotype and function.

Funding: Government Support - Non-U.S.

FR-PO207

Reactive Oxygen Species Control Primary Cilia Length in Kidney Tubule Cells Sang Jun Han,[1] Jee In Kim,[2] Kwon Moo Park.[1] *[1]Dept of Anatomy and BK 21 Project, Kyungpook National Univ School of Medicine, Daegu, Republic of Korea; [2]Dept of Molecular Medicine and MRC, Keimyung Univ School of Medicine, Daegu, Republic of Korea.*

Background: Primary cilium is involved in kidney function. Recent studies have demonstrated that primary cilium length changes are associated with acute kidney injury, suggesting that primary cilia may play an important role the progression of various kidney diseases. Here, we investigated whether renal mass reductions induced by unilateral nephrectomy (UNx) and transient unilateral ischemia (UI) affect primary cilia length and its molecular mechanisms.

Methods: Mice were subjected to either unilateral nephrectomy (UNx) or unilateral ischemia for 30 min (UI). Some mice were administered Mn(III) Tetrakis (1-methyl-4-pyridyl) porphyrin (MnTMPyP, a ROS scavenger) for 8 days daily beginning on 1 day after those operations. Primary cilium was visualized by immunofluorescence staining using anti-acetylated-α-tubulin antibody and its length was determined under microscope.

Results: UNx increased primary cilium length in all tubular segments including proximal, distal, Henle's loop and collecting duct, and parietal cells of the remaining kidney 9 days later. UI also increased primary cilium length in tubule cells and parietal cells of the UI-exposed kidneys. UNx and UI increased reactive oxygen species (ROS) levels in the remaining kidneys and UI-induced kidneys, respectively. Treatments of MnTMPyP prevented those elongations of primary cilia and increases of ROS production. UNx resulted in the hypertrophy of the remaining kidneys 9 days later. UI induced tubular cell damage and fibrosis in the UI-induced kidneys 9 days after the operation. Treatments of MnTMPyP prevented the hypertrophy of the remaining kidney after UNx and post-UI kidney tubule cell damage and fibrosis. In the MDCK cells, a cultured tubular epithelial cell line cells, H_2O_2 induced the elongation of primary cilium length. This elongation was prevented by MnTMPyP treatment.

Conclusions: UNx and UI elongated the length of primary cilia via increased production of ROS in the remaining kidney after UNx and UI-exposed kidney. These results suggest that ROS-induced changes of primary cilia length may play an important role for compensatory response to UNx- or UI-induced renal mass reductions.

Funding: Government Support - Non-U.S.

FR-PO208

High Glucose Stimulation of Mitochondrial Metabolism and Superoxide Generation Is Mediated by Thioredoxin Interacting Protein (TXNIP) Anu Shah,[1,2] Ling Xia,[2] Lemieux Luu,[1] Michael B. Wheeler,[1] James W. Dennis,[1,2] Ivan George Fantus.[1,2] *[1]Dept of Physiology, Univ of Toronto, Toronto, ON, Canada; [2]Lunenfeld Tanenbaum Research Inst, Mount Sinai Hospital, Toronto, ON, Canada.*

Background: Thioredoxin-interacting protein (TXNIP) is an endogenous inhibitor of thioredoxin (Trx), a thiol oxidoreductase that regulates cellular redox status. TXNIP is upregulated by high glucose (HG) and augments reactive oxygen species (ROS). We recently showed that a reduction of TXNIP inhibits HG-induced mitochondrial membrane potential and superoxide production in cultured renal mesangial cells (MCs) (JBC, 2013) and that $TXNIP^{-/-}$ mice are protected from diabetic nephropathy (DN) (JASN 2015).

Methods: To investigate mechanisms, metabolic profiling and bioenergetics of HG-treated C3H (wild type) and Hcb-19 (TXNIP deficient) MCs were assessed.

Results: Metabolomic analysis revealed higher glycolytic, but significantly reduced citrate and isocitrate, TCA cycle intermediates, in HG-treated Hcb-19 compared to C3H. As well, a 2-fold increase in malonyl CoA was observed in Hcb-19 cells suggesting that acetylCoA was driven towards lipogenesis. These data were supported by a lower PDHE1α and citrate synthase protein and activity in these cells. Assessment with the SeahorseXF analyzer revealed that Hcb-19 cells displayed lower mitochondrial oxygen consumption and a reduced respiratory capacity. Furthermore, Hcb-19 cells displayed a markedly lower protein expression of electron transport chain complexes (ETC) I, II, and III, the key generators of mitochondrial superoxide.

Conclusions: The results indicate that TXNIP promotes mitochondrial glucose oxidation via the TCA cycle and ROS generation via the ETC, thereby stimulating a HG-oxidative stress pathway mediating DN.

Funding: Government Support - Non-U.S.

FR-PO209

High Glucose-Induced Fibronectin Upregulation in Cultured Mesangial Cells Involves Caveolin-1-Dependent RhoA-GTP Activation via Src Kinase Yiqiao Li, Juan Jin. *Zhejiang Province People's Hospital, Dept of Nephrology, Hangzhou, China.*

Background: Increasing evidence indicates that diabetic-mediated renal interstitial fibrosis through extracellular matrix protein (ECM) accumulation is a key event in the development of diabetic kidney disease (DKD). High glucose (HG) promotes excessive accumulation of ECM proteins and expression of fibrotic factors in mesangial cells (MCs), which leads to subsequent diabetic renal dysfunction. The activation of RhoA and its downstream mediator Rho-kinase act as crucial mediators of strain-induced the matrix protein fibronectin (FN) secretion in MCs, which depend on intact caveolae. However, the involvement of caveolae/caveolin-1 in HG-induced dysfunction of MCs has not been assessed.

Methods: Primary MCs were obtained from Sprague-Dawley rat glomeruli by differential sieving and cultured in DMEM supplemented with supplemented with 20% fetal calf serum, streptomycin, and penicillin. Experiments were carried out using cells between passages 6 and 15. We then examined the influence of HG on caveolin-1/RhoA signaling and FN secretion in mouse MCs.

Results: We show that high levels of glucose time and dose dependently increased matrix protein FN production in primary rat MC. Rho pathway inhibition blocked HG-induced FN upregulation. HG-induced RhoA activation was prevented by disrupting caveolae with filipin III or caveolin-1 siRNA and rescued by exogenous caveolin-1. HG also increased caveolin-1/Src association and activated Src kinase, and Src inhibitor blocked RhoA activation and FN upregulation. Src mediated phosphorylation of caveolin-1 on Y14 has also been implicated in signaling responses. Overexpression of nonphosphorylatable caveolin-1 Y14A mutant prevented HG-induced RhoA activation and FN upregulation.

Conclusions: HG-induced FN upregulation require caveolae and caveolin-1 interaction with RhoA and Src kinases. Interference with Src/caveolin-1/RhoA signaling may provide new avenues for the treatment of DKD.

FR-PO210

Activation of PDGF Receptor beta (PDGFRb) by High Glucose (HG) Forces mTORC1 Signaling to Induce Proximal Tubular Epithelial Cell (PTEC) Hypertrophy and Matrix Expansion Falguni Das,[1] Nandini Ghosh-Choudhury,[2] Meenalakshmi M. Mariappan,[1] Balakuntalam S. Kasinath,[1] Goutam Ghosh-Choudhury.[1] *[1]Medicine, UTHSCSA, San Antonio, TX; [2]Pathology, UTHSCSA, San Antonio, TX.*

Background: Increased expression of PDGF BB and PDGFRb has been reported in both glomerular and proximal tubular compartments in human and rodent diabetic nephropathy. Whether hyperglycemia activates PDGFR-mediated signaling in renal cells has not been investigated.

Methods: Human PTEC, immunoblotting, siRNA transfection, protein synthesis and cell hypertrophy assays, and mouse model of Type 1 diabetes were used.

Results: High glucose (HG) significantly increased phosphorylation of PDGFRb at the autophosphorylation site Tyr-857 and PI 3 kinase binding site Tyr-751 in a time-dependent manner. A PDGFRb-specific inhibitor JNJ-10198409 (JNJ) blocked these phosphorylations, resulting in inhibition of association of PI 3 kinase with the PDGFRb leading to suppression of Akt activation in response to HG. Similarly, siRNAs against PDGFRb abolished HG-induced Akt activation. Both JNJ and siPDGFRb inhibited HG-induced phosphorylation of two mTORC1 endogenous inhibitors PRAS40 and tuberin and, consequently suppressed mTORC1 activation, as judged by phosphorylation of S6 kinase, rps6 and 4EBP-1. Interestingly, JNJ and siPDGFRb did not have any effect on HG-stimulated MEK/Erk1/2 activation and phosphorylation of their downstream target eIF4E. Furthermore, inhibition of PDGFRb attenuated protein synthesis and PTEC hypertrophy and, expression of fibronectin and collagen I (alpha2) in response to HG. Finally, we observed increased phosphorylation of PDGFRb and its complex formation with PI 3 kinase in the renal cortex of OVE26 mice with type 1 diabetes. The renal cortical PDGFRb activation was associated with phosphorylation of Akt and mTORC1 activation, and expression of fibronectin and collagen I (a2) in the diabetic mice.

Conclusions: These results provide the first direct evidence for the requirement of PDGFRb activation in HG-induced PTEC injury found in diabetic nephropathy. Furthermore, we uncover a specific role of mTORC1 signaling downstream of PDGFRb in hyperglycemia-induced stimulation of PTEC hypertrophy and matrix protein synthesis.

Funding: NIDDK Support, VA Support

FR-PO211

mTORC2/PKCβ II Node Contributes to TGFβ (TGFβ)-Induced Twist1 Expression and Proximal Tubular Epithelial Cell (PTEC) Injury Falguni Das,[1] Nandini Ghosh-Choudhury,[2] Balakuntalam S. Kasinath,[1] Goutam Ghosh-Choudhury.[1] *[1]Medicine, UTHSCSA, San Antonio, TX; [2]Pathology, UTHSCSA, San Antonio, TX.*

Background: TGFb contributes to renal fibrosis via the master regulator Twist1, which regulates epithelial-mesenchymal transition (EMT) in the proximal tubular epithelial cells. But the mechanistic basis by which TGFb increases Twist1 and fibrotic marker expression remains elusive.

Methods: Human PTEC, immunoblotting, siRNA transfection, plasmid-derived overexpression, protein synthesis and cell hypertrophy assays were used.

Results: TGFb time-dependently increased the expression of Twist1 in PTEC. Both PI 3 kinase inhibitor Ly294002 and mTOR inhibitor rapamycin blocked TGFb-induced Twist1 expression. Similarly, shRNAs against raptor and rictor, exclusive and required components of mTORC1 and mTORC2, respectively, individually inhibited the expression of Twist1 in response to TGFb, suggesting roles of both mTOR complexes. Importantly, overexpression of Twist1 and siRNAs against Twist1, respectively, increased and decreased the TGFb-induced protein synthesis, PTEC hypertrophy and the expression of fibronectin, collagen I (alpha2) and, the EMT marker alpha-smooth muscle actin (aSMA). Interestingly, TGFb increased the hydrophobic motif site Ser-660 phosphorylation of PKCbeta II (PKCb II) in a time-dependent manner. Use of rictor shRNA to inhibit mTORC2 blocked PKCb II phosphorylation. Importantly, siRNA against PKCbII inhibited Twist1 expression by TGFb. Similarly, the non-phosphorylatable mutant PKCbII Ser660Ala abolished TGFb-stimulated Twist1. Finally, siPKCb II or PKCb II Ser660Ala inhibited the expression of fibronectin, collagen I (alpha2) and aSMA in response to TGFb.

Conclusions: These results for the first time outline the principal mechanisms utilized by TGFb for the expression of Twist1 and its downstream effects on PTEC hypertrophy, matrix protein expression and EMT. We define a regulatory module involving mTORC2 and PKCb II for Twist1 expression and PTEC pathology induced by TGFb.

Funding: NIDDK Support, VA Support

FR-PO212

Investigating the Role of the PAR-1 Receptor and Th17 Cells in Idiopathic Nephrotic Syndrome Carl J. May,[1] Gavin Iain Welsh,[1] Moin Saleem.[1,2] *[1]Bristol Renal, Univ of Bristol, Bristol, Avon, United Kingdom; [2]Bristol Royal Children's Hospital, Bristol, Avon, United Kingdom.*

Background: There is increasing evidence that a subset of T helper (Th17) cells can survive steroid treatment and may be driving steroid resistant inflammatory conditions such as uveitis, ulcerative colitis and asthma. Additionally there is evidence to suggest a role for a circulating factor(s) released by T cells in idiopathic nephrotic syndrome. Work published previously by our group demonstrated that nephrotic plasma is capable of increasing podocyte motility. This factor signals via the PAR-1 receptor. We hypothesised that the Th17 cells are capable of signalling to the podocyte and that this signalling occurs via the PAR-1 receptor.

Methods: Th17 cells were cultured and their culture supernatants were retrieved and applied to conditionally immortalised wild-type human podocytes. Protein was extracted and used in western blotting experiments to investigate intracellular signalling. Scratch assays were performed to look at podocyte motility. A Par-1 agonist containing the sequence of the tethered ligand was used to look at the effect of PAR-1 stimulation on the podocyte.

Results: Th17 cell culture supernatant treatment of the podocytes stimulated p38 MAPK and JNK signalling pathways. Only the JNK target site (S178) of paxillin was also phosphorylated. Th17 cell culture treatment also significantly increased podocyte motility. This effect was blocked by both JNK inhibition and Protease inhibition. Suggesting that the effector molecule in the Th17 cell culture supernatant is a protease that acts via JNK. PAR-1 agonist treatment of podocytes stimulated the same signalling events. The PAR-1 agonist treatment had such a large effect on adhesion that motility could not be measured.

Conclusions: This work suggests that there is a hitherto unknown protease present in Th17 cell culture supernatant that signals via the PAR-1 receptor on the podocyte and via JNK and Paxillin phosphorylation affects podocyte motility and/or adhesion. Further inhibitor studies are required to confirm this pathway. However, if shown to be correct, this work provide multiple therapeutic targets that could be used to protect the podocyte against the circulating factor.

Funding: Government Support - Non-U.S.

FR-PO213

p70S6K Cross Talk with p66ShcA Modulates Progression of HIV-Associated Nephropathy (HIVAN) Manoj K. Tembhre,[1] Partab Rai,[1] Vinod Sharma,[1] Hanan K. Tawadrous,[2] Anil K. Mongia,[2] Seyedeh Shadafarin Marashi Shoshtari,[1] Judith Eng,[1] Ashwani Malhotra,[1] Pravin C. Singhal.[1] *[1]Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY; [2]Pediatrics, Down State Medical Center, Brooklyn, NY.*

Background: Down regulation of p66ShcA has been demonstrated to provide protection against HIV mediated kidney cell injury. At present there is no effective tool to inhibit p66ShcA pathway. We observed a cross talk between p66ShcA and p70S6K. On that account we hypothesize that inhibition of p70S6k would also down regulate p66ShcA pathway and would prevent progression of HIVAN.

Methods: Renal tissue lysates of sex and age matched control, Tg26/p66$^{+/+}$, Tg26/p66$^{+/-}$ mice were evaluated for phospho-p70S6K and downstream signaling. Control and Tg26 mice were administered either normal saline or PF47 (an inhibitor of p70S6K, 5mg/Kg/every other day, intraperitoneally) for 4 weeks. Urinary protein analysis was carried out and renal tissues were evaluated for severity of renal lesions. Renal tissue lysates were probed for phospho-p66ShcA and total p66ShcA. For *in vitro* studies, mouse proximal tubular cells (MTC) were transduced with either empty vector (EV/MTC) or NL4-3 (HIV/MTC) and transfected with siRNAp66, siRNAp70S6K, and scrambled siRNA. Subsequently, protein blots were probed for p66ShcA, p70S6K and actin. To study molecular binding, EV/MTC and HIV/MTC lysates were immunoprecipitated with anti- p66ShcA antibody and probed for p70S6K.

Results: TG26/p66$^{+/-}$ mice displayed attenuated renal tissue expression of phospho-p70S6K, whereas, Tg26/PF47 mice displayed attenuated expression of p66ShcA. PF47-receiving Tg26 mice displayed decreased proteinuria as well as less advanced renal lesions. HIV/MTC displayed enhanced expression of phospho-p66ShcA and phospho-p70S6K. MTC silenced for p66ShcA displayed attenuated expression of phospho-p70S6K, whereas, MTC silenced for p70S6K exhibited attenuated expression of p66ShcA both under control and HIV milieus. EV/MTC and HIV/MTC lysates immunoprecipitated with anti-p66 antibody demonstrated expression of p70S6k.

Conclusions: Cross talk between p66ShcA and p70S6K plays a role in the progression of renal lesions in HIVAN mice.

Funding: NIDDK Support

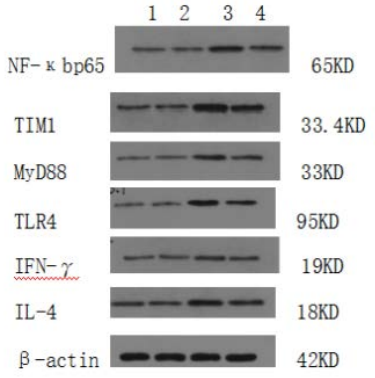
FR-PO214

The Role of TIM-1 Signaling Pathway in the Pathogenesis of IgA Nephropathy Mouse Ying Wang. *The First Affiliated Hospital of Nanchang Univ, Nanchang, Jiangxi, China.*

Background: Studies have shown that the pathogenesis of IgAN may be related to Th1 / Th2 balance to Th2 bias related and TIM-l play an important role in regulating Th2 responses and it may influence TLR4 each other to adjust the kidney inflammation.Based on above basis,we investigate the expression of TIM ,TLR4 and IFN-γ, IL-4 in renal tissue of IgAN mouse, and explore the role and the possible mechanism of TIM-1 signaling pathway in renal injury of IgAN mouse.

Methods: 36 mice were randomly divided into normal control group,normal control + anti - TIM1 group,IgAN model group,IgAN + anti - TIM1 group,each group of 9 mice. The protein expression of TIM-1, TLR4, MyD88, NF-κB, IFN-γ, IL-4 in mice kidney was detected by Westernblot. Semi-quantitative RT-PCR was used to examine the mRNA expression of TIM1, TLR4, MyD88, NF-κB , IFN-γ,IL-4 in renal cortex.

Results:



The protein expression of TIM1、TLR4、MyD88、NF-κbp65、IL-4、IFN-γ in mice kidney tissues of four groups (Westernblot).

Note: 1 represents normal control group, 2 represents normal control + anti - TIM1 group , 3 represents IgAN model group, 4 represents IgAN + anti - TIM1 group.

Group					
Index	n	Normal Control group	Normal+anti-TIM1group	IgAN group	IgAN+anti-TIM1 group
TIM1	9	0.98±0.17	0.88±0.15	2.09±0.17[a]	1.54±0.19[a,b]
TLR4	9	1.14±0.16	0.93±0.02	1.98±0.15[a]	1.50±0.14[a,b]
MyD88	9	1.13±0.16	0.93±0.02	2.01±0.22[a]	1.50±0.18[a,b]
NF-κbp65	9	0.93±0.15	1.00±0.02	2.17±0.17[a]	1.51±0.14[a,b]
IL-4	9	0.93±0.07	1.03±0.06	1.94±0.29[a]	1.38±0.11[a,b]
IFN-γ	9	0.89±0.10	0.99±0.06	1.29±0.15[a]	1.07±0.19
Note: compared with normal control group, [a]P<0.05; compared with IgAN model group, [b]P<0.05.					

Compared with IgAN model group, the expression quantity of TIM1,TLR4, MyD88, NF-κbp65 in IgAN + anti-TIM-1 group was significantly lower(P <0.01); the protein expression of TIM1,TLR4,MyD88,NF-κbp65,IL-4,IFN-γ was lower (P<0.05); the expression quantity of TIM1,TLR4,MyD88,NF-κbp65,IL-4mRNA was lower (P<0.01).

Conclusions: In the pathogenesis of IgAN, TIM-1 signaling pathway may be involved in the pathogenesis and progression of the disease. Blocking the TIM1 signaling pathways may delay the development of IgAN through reducing the expression of TLR4, etc.

Funding: Government Support - Non-U.S.

FR-PO215

Kidney Risk Variants Apolipoprotein L1 Increase Efflux of Rubidium in Human Embryonic Kidney Cells Opeyemi A. Olabisi,[1] Jiayue Zhang,[2] David J. Friedman,[2] Martin R. Pollak.[2] *[1]Internal Medicine, Massachusetts General Hospital, Boston, MA; [2]Internal Medicine, Beth Israel Deaconess Medical Center, Boston, MA.*

Background: The proposed mechanism of trypanosome lysis by human Apolipoprotein L1 (APOL1) includes APOL1-mediated ion transport across trypanosome membranes. It is unknown if pathomechanism of APOL1 mediated kidney disease also involves aberrant ion transport by kidney risk variants APOL1 (G1 or G2). We recently reported that expression of G1 or G2 APOL1 in human embryonic kidney (HEK) cells increased efflux of cellular potassium which ultimately led to cell death via induction of stress activated protein kinase signaling. To further characterize this initial finding that G1 or G2 APOL1 or their surrogate act as potassium channels in mammalian cells, we investigate if the expression of G1 or G2 APOL1 would increase the efflux of rubidium (RB^+)—a well-established tracer of potassium movement across cell membrane.

Methods: Stably transfected HEK cells were induced to express APOL1 (G0, G1, or G2) for 5 or 9Hr. The cells were loaded with Rb^+ for 3Hr, then washed, and incubated in efflux buffer. Rb^+ content in the efflux buffer and in the cell monolayer was measured.

Results: We found that relative to G0, expression of G1 or G2 APOL1 in HEK cells for 9 Hr. results in significant increase of extracellular, but decrease of intracellular Rb^+. Expression of G1 or G2 APOL1 for 5Hr did not significantly alter transmembrane Rb^+ transport.

Conclusions: These results corroborate our prior findings and raise the possibility that aberrant depletion of cellular potassium by G1 or G2 APOL1 may be integral to APOL1 nephropathy in individuals of recent African Ancestry.

Funding: NIDDK Support, Other NIH Support - T32-DK007199, T32-DK07540, NIH MD007898, and MD007092, Private Foundation Support

FR-PO216

Effect of a Novel Pan-NOX Inhibitor on Phenotype Transition of Mesothelial Cells and Peritoneal Fibrosis Jiyeon Ko,[1] Eun Sun Ryu,[1] Dal-Ah Kim,[1] Sun-Hee Park,[2] Yong-Lim Kim,[2] Duk-Hee Kang.[1] *[1]Div of Nephrology, Ewha Womans Univ School of Medicine, Seoul, Republic of Korea; [2]Div of Nephrology, Kyung-Pook National Univ School of Medicine, Dae-gu, Republic of Korea.*

Background: Oxidative stress plays a key role in the development of peritoneal fibrosis, and NADPH oxidases (NOX) substantially contribute to generation of ROS in peritoneum. However, it is not known whether each isoforms of NOX (NOX-1, -2, -4) play a differential role in peritoneal damage. Recent data suggested epithelial-to-mesenchymal transition (EMT) of peritoneal mesothelial cells is an early process of peritoneal fibrosis. Anti-oxidant effect of a novel pyrazole derivative pan-NOX inhibitor Ewha-18278 was recently reported in animal model of osteoporosis.

Methods: EMT was evaluated by an alteration of morphology and the expressions of E-cadherin and α-SMA. ROS generation & the expression of NOX isoforms were measured in TGFβ1-exposed human peritoneal mesothelial cells (HPMCs). We investigated the effect of Ewha-18278 on EMT, the expression of antioxidant [reduced/oxidized glutathione ratio (GSH/GSSG), superoxide dismutase (SOD)] and peritoneal fibrosis in animal model of peritoneal dialysis (PD) by 8-week infusion of dialysate via intraperitoneal catheter.

Results: TGFβ1 enhanced NOX activity and ROS generation. NOX-1 was the major NOX detected in HPMCs, however TGFβ1 upregulated only NOX-4 mRNA expression. Despite an absence of NOX-1 up-regulation by TGFβ1, both siNOX-1 and siNOX-4 ameliorated TGFβ1-induced EMT. Ewha-18278 decreased TGFβ1-induced ROS generation and EMT of HPMC. In animal model of PD, intraperitoneal administration of Ewha-18278 decreased the peritoneal fibrosis with an increase in GSH/GSSG and SOD activity in peritoneal dialysate whereas it decreased the expression of nitrotyrosine in peritoneum and 8-hydroxy-2'-deoxyguanosine in dialysate.

Conclusions: Increased NOX-1/2 activity with an enhanced NOX-4 expression plays a major role in ROS generation & EMT of peritoneum. Our result indicates a novel pan-NOX inhibitor as a new therapeutic agent for treatment of peritoneal fibrosis.

FR-PO217

Glycocalyx Shedding as a Novel Mechanism of Uric Acid-Induced Endothelial Dysfunction Jiyeon Ko,[1] Eun Sun Ryu,[1] Dal-Ah Kim,[1] Richard J. Johnson,[2] Duk-Hee Kang.[1] *[1]Div of Nephrology, Ewha Womans Univ School of Medicine, Seoul, Republic of Korea; [2]Div of Nephrology, Univ of Colorado.*

Background: Recent data suggested a causative role of uric acid (UA) in the development renal disease. Endothelial dysfunction is regarded as one of the key mechanisms of UA-induced renal disease. Endothelial-to-mesenchymal transition (EndoMT) is an early process of endothelial dysfunction, and is known to play a role in the progression of renal fibrosis. Glycocalyx is a structure covering endothelium composed of membrane-bound proteoglycans and glycoproteins with adsorbed plasma components, which can cause endothelial dysfunction via intraluminal shedding.

Methods: EndoMT was evaluated by cell morphology and a comparison of the expression of VE-cadherin or CD31 and α-SMA in HUVECs and animal model of hyperuricemia (Sprague-Dawley rats fed with 2% oxonic acid for 6 weeks). NAPDH oxidase (NOX) activity, ROS generation, endothelial permeability and markers of glycocalyx shedding (syndecan-1, heparin sulfate & lectin staining) were assessed. To investigate the role of glycocalyx shedding in endoMT, the effect of GM6001 (matrix metalloproteinase inhibitor) on UA-induced endo-MT was examined.

Results: UA induced endoMT (48 hours) and ROS generation via NOX (15 min) and mitochondrial activation (6 hours) with an increase in glycocalyx shedding (6 hours). UA-induced endoMT, glycocalyx shedding and increase in vascular permeability were blocked by probenecid (500 μM). Anti-oxidant treatment ameliorated endoMT, however did not change glycocalyx shedding in HUVEC. GM6001 (10 μM) also alleviated UA-induced endoMT. In the kidney of hyperuricemic rats, endothelial staining in peritubular capillaries (PTC) was decreased with de-novo expression of α-SMA in PTC. Plasma levels of syndecan-1 & heparin sulfate were increased in hyperuricemic rats, which were ameliorated by allopurinol.

Conclusions: UA per se induced a phenotypic transition of endothelial cells via both oxidative stress and glycocalyx shedding, which could be one of the mechanisms of uric acid-induced endothelial dysfunction and nephropathy.

FR-PO218

Non-Canonical Regulation of Heterotrimeric G-Protein Subunits by Accessory Proteins in the Collecting Duct Taketsugu Hama,[1,2] Jeffrey D. Pressly,[1] Frank Park.[1] *[1]Pharmaceutical Sciences, The Univ of Tennessee Health Science Center, Memphis, TN; [2]Pediatrics, Wakayama Univ, Wakayama, Japan.*

Background: Heterotrimeric G-proteins are known to play a fundamentally central role in the biological homeostasis of renal tubular epithelial cells. Recent studies have shown that renal tubular epithelial cells can exhibit atypical modes of regulation on G-protein subunits through the actions of intracellular accessory proteins. Accessory proteins can bind to distinct G-protein α or βγ subunits to control a multitude of biological functions, including the repertoire of intracellular signaling, modulation of signaling amplitude, and alteration in protein mobilization within the cell.

Results: In this study, our group describes the ability of a novel accessory protein, thyroid receptor interacting protein 13 (TRIP13), to control MAPK signaling networks by interacting with various combinations of Gβγ dimers, most notably $G\beta_1\gamma_7$. Of the 5 known β and 12 γ isoforms, we demonstrated that only 4 β (β1, β2, β4, and β5) and 5 γ (γ5, γ7, γ10, γ11 and γ12) isoforms were expressed in collecting duct mRNA from two different mouse lines by RT-PCR analysis. Transient over-expression of $G\beta_1$ with either $G\gamma_2$, $G\gamma_5$ or $G\gamma_7$ subunits promoted MAPK activity for ERK1/2, p38 MAPK, and SAPK/JNK, but not ERK5. In the presence of TRIP13, however, $G\beta_1\gamma_7$ signaling was found to selectively regulate the phosphorylation of ERK1/2 and p38 MAPK, with no observable change in the activation status for ERK5 or SAPK/JNK. The other Gβγ dimer combinations, $G\beta_1\gamma_2$ and $G\beta_1\gamma_5$, were observed to either partially or complete lose their ability to activate ERK1/2 and p38 MAPK in the presence of TRIP13. Genetic knockdown of $G\gamma_7$ using 2 distinct short hairpin RNA constructs or over-expression of TRIP13 in collecting duct cells demonstrated accelerated wound closure by 21-47% compared to control cells, which could be partially blocked by the selective p38 MAPK inhibitor, SB203580.

Conclusions: In conclusion, TRIP13 is a newly identified accessory protein, which can selectively sequester $G\beta\gamma_7$ and accelerate cell migration following tissue damage, and may be a future therapeutic target to control wound healing of tubular epithelial cells in the kidney.

Funding: NIDDK Support

FR-PO219

Ergothioneine Plays a Key Role in Kidney-Intestinal Interaction of CKD through Organic Cation Transporter 1 Dysfunction Yasuyuki Shinozaki, Kengo Furuichi, Shinji Kitajima, Tadashi Toyama, Akinori Hara, Yasunori Iwata, Norihiko Sakai, Miho Shimizu, Takashi Wada. *Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Japan.*

Background: Chronic kidney disease (CKD) affects other organ damages. We hypothesized that ergothioneine (ERGO), which is the antioxidant derived from diet, was related to the progression of CKD and kidney-intestinal interaction. We focused on organic cation transporter 1 (OCTN1) and PDZ domain containing 1 (PDZK1). OCTN1 is a specific transporter for ERGO, and PDZK1 is a regulator of transporter stabilization on apical cellular membrane and modulates transporter function.

Methods: To evaluate the effects of intestinal OCTN1 function in CKD, everted sac method was used in CKD model or control mice. Furthermore, the pathological changes and oxidative stress in the kidney of OCTN1-/- or OCTN1+/+ were evaluated in the CKD model mice. Moreover, the expression of OCTN1 and PDZK1 in small intestine were confirmed by RT-PCR, Western blot and immunohistochemistry.

Results: The uptake of ERGO in everted sac significantly decreased in CKD mice than control mice. Kidney interstitial fibrosis, evaluated by azan stain, sirius red stain, and the content of hydroxyproline of injured kidney, was significantly advanced in OCTN1-/- CKD mice. Moreover, oxidative stress, assessed by 4-HNE stain and carbonyl protein ELISA, was exaggerated in OCTN1-/- CKD mice kidney. The mRNA and protein level of intestinal OCTN1 were not different in CKD mice, however, the localization on apical cellular membrane decreased in CKD mice intestine. The expression level of PDZK1 decreased in CKD mice.

Conclusions: The reduction of OCTN1 function and ERGO uptake may participate in oxidative stress and progression of kidney injury. The decreased PDZK1 expression may disturb OCTN1 function and stabilization on cellular membrane, which may relate the mechanism of kidney-intestinal network in CKD.

Funding: Government Support - Non-U.S.

FR-PO220

Indoxyl Sulfate Up-Regulates P-Glycoprotein Transporter through the Aryl Hydrocarbon Receptor Pathway Tacy Santana Machado,[1,2] Nathalie Mc Kay,[1] Pascale Paul,[1,4] Bertrand Dussol,[1,3] Francoise Dignat-George,[1,4] Philippe Brunet,[1,3] Stephane Burtey,[1,3] Claire Cerini.[1] *[1]VRCM, INSERM UMR-S 1076, Aix-Marseille Univ, Marseille, France; [2]CAPES Foundation, Ministry of Education of Brazil, 70040-020, Brasília, DF, Brazil; [3]APHM, Hôpital de la Conception, Centre de Néphrologie et Transplantation Rénale, Marseille, France; [4]APHM, Hôpital de la Conception, Service d'Hématologie et de Biologie Vasculaire, Marseille, France.*

Background: Chronic kidney disease (CKD) is associated with profound changes in drug metabolism. Reduction of drug renal clearances is a major reason, but some drugs with only hepatic metabolism have modified half life during CKD. CKD induces an accumulation of many solutes called uremic toxins. Aryl hydrocarbon receptor (AhR) is a transcription factor which is activated by indolic uremic toxins and mediates their toxic effects. It has been shown that uremia can inhibit the function and expression of hepatic drug metabolizing enzymes and drug transporters. The objective of this work is to study the effects of the indolic uremic solute indoxyl sulfate (IS), on the expression and activity of the efflux cellular transporter, P-glycoprotein (P-gp) which is encoded by ABCB1.

Methods: Levels of ABCB1 mRNA were studied by RT-PCR, the P-gp levels by flow cytometry and by western blotting. The activity of P-gp was measured with rhodamine 123 in the presence or absence of an inhibitor, verapamil. The role of AhR was studied using small interfering RNA. Transplant patients were recruited from APHM.

Results: In a human hepatocellular liver carcinoma cell line, IS increased both the mRNA and protein levels of P-gp. IS increased the efflux activity of P-gp, an effect that was partially inhibited after incubation with verapamil. The effects of IS on P-gp are AhR-dependent. Dioxin, a well known agonist of AhR, also increased the expression and activity of P-gp. In heart and kidney transplant recipients receiving cyclosporine A (n=109), a substrate for P-gp, patients with higher serum levels of IS need higher doses of cyclosporine to achieve the target blood level.

Conclusions: In conclusion, IS acting through AhR activates the xenobiotic efflux transporter P-gp and could modify the hepatic clearance of drugs such as cyclosporine.

Funding: Government Support - Non-U.S.

FR-PO221

Urinary Exosomes Contain MicroRNAs Capable of Paracrine Modulation of Tubular Transporters Fiona E. Karet,[1] Tannia Gracia,[1] Xiaonan Wang,[2] Ya Su,[1] Elizabeth Norgett,[1] Pablo Moreno,[1] Gos Micklem.[3] *[1]Medical Genetics, Univ of Cambridge, Cambridge, United Kingdom; [2]Pathology, Univ of Cambridge, Cambridge, United Kingdom; [3]Genetics, Univ of Cambridge, Cambridge, United Kingdom.*

Background: Exosomes derived from all nephron segments are present in human urine, where their full functionality is poorly understood, but is known to include direct antimicrobial activity. Although one report has suggested *in vitro* uptake of exosomes by renal cortical collecting duct cells, most studies of human urinary exosomes have focused on biomarker discovery rather than exosome function. Exosomes from other sources have been demonstrated to contain microRNA (miRNA) species.

Methods: Urinary exosomes were isolated from healthy volunteers.The miRNA repertoire of these exosomes was identified using deep sequencing of miRNA-enriched fractions. Targets for the identified miRNAs were predicted using 5 different algorithms and a selection was validated by exposing renal tubular epithelial cells to fresh urinary exosomes and measuring their protein levels. Live cell microscopy examined cellular uptake of exosomes.

Results: 276 mature miRNAs were identified in urinary exosomes, together with some miRNA precursors, mRNA and other non-coding RNAs. For the top 10 miRNAs we found an enrichment of target genes encoding a variety of channels and transporters (eg of organic molecules and mono- and divalent ions). DAVID enrichment analysis highlighted the possibility of these identified miRNAs exerting effects on regulators of key functions such as sodium reabsorption and potassium secretion in the kidney in a paracrine manner. Selected targets were validated by qRT-PCR, and to provide proof of concept, cultured renal epithelial cells were exposed to pools of urinary exosomes, cellular exosomal uptake was confirmed and downregulation of SNAT2 and ROMK protein expression levels was observed.

Conclusions: The significant presence of miRNAs in urinary exosomes demonstrated the potential regulatory roles that these noncoding RNAs could play in the kidney. These data suggest that exosomes could be suitable for biomarker development and therapeutic options for kidney diseases, which will require future *in vivo* studies.

FR-PO222

PDLIM5 Is Required for Membrane Targeting of AE1 in Kidney Fiona E. Karet,[1] Ya Su,[1] Thomas F. Hiemstra,[1] Yahui Yan,[1] Hannah Karet,[2] Pablo Moreno.[1] *[1]Univ of Cambridge, United Kingdom; [2]Univ College London, United Kingdom.*

Background: Anion exchanger 1 mediates Cl^-/HCO_3^- exchange across the plasma membranes of erythrocytes and kidney epithelial cells (kAE1). In kidney, AE1's main activity is basolaterally in type A intercalated cells of the collecting duct where it is functionally coupled with apical proton pump to maintain normal bodily acid-base homeostasis. Mutations in *SLC4A1* are associated with distal renal tubular acidosis. The major pathogenic mechanisms have been attributed to intracellular retention and aberrant membrane targeting of kAE1, but molecular basis of the mis-targeting is unclear. AE1's C-terminus (AE1C) is rich in membrane targeting motifs which are known to play an important role in its normal membrane residency. To inform disease-causing mechanisms, we sought binding partners for AE1C.

Methods: Co-immunoprecipitation-coupled mass spectrometry (co-IP-MS) screen was performed using anti-AE1 antibody to precipitate AE1 associated proteins from MDCK-kAE1 cell lysates. A potential AE1-PDZ interaction was confirmed by ELISA. Significance of the interaction was investigated by GST pulldown and overexpression/ knockdown studies in HEK293 cells.

Results: The co-IP-MS screen yielded PDLIM5, a PDZ protein, as a potential binding partner for kAE1. The interaction was confirmed *in vitro* and demonstrated to be direct, with actual binding between the PDZ domain in PDLIM5 and the PDZ binding motif in AE1C. SiRNA-mediated depletion of PDLIM5 in cell culture resulted in significant reduction in kAE1 at the cell surface, whereas overexpression of kAE1 increased PDLIM5 level, underscoring the functional importance of PDLIM5 for proper membrane residency of kAE1. GST pull-down from both human kidney tissue and HEK-kAE1 cell lysates revealed not just PDLIM5, but also integrin linked kinase, an actin associated protein, indicating formation of a multiprotein complex by these proteins.

Conclusions: These data establish both physical and functional links between kAE1 and PDLIM5 in kidney and suggest PDLIM5 as a crucial linker between kAE1 and actin cytoskeleton associated proteins; this is critical for proper movement of kAE1 to its normal functional location.

FR-PO223

Calcineurin Inhibitor-Induced Endothelial Cell Injury and Dysfunction – A Role for Complement? Chia Wei Teoh,[1] Magdalena Riedl,[1] Lisa Robinson,[1,2] Christoph Licht.[1,2] *[1]Div of Nephrology, The Hospital for Sick Children, Toronto, Toronto, ON, Canada; [2]Dept of Paediatrics, Univ of Toronto, Toronto, ON, Canada.*

Background: Calcineurin inhibitors (CNI) are widely used immunosuppressive agents which are in up to 14% of renal graft biopsies associated with thrombotic microangiopathy (TMA) (in up to 90% subclinical). Evolving evidence suggests a central role for complement dysregulation in the pathogenesis of CNI-induced TMA. It has recently been shown that CNI can induce endothelial cell (EC) release of complement-activating microparticles that lead to bystander EC injury. However, the exact mechanism of CNI-induced complement-mediated injury and possibly resulting EC dysfunction remains unknown.

Methods: EC cytotoxicity was assessed via LDH assay. Complement activation/regulation were assessed by flow cytometry for C3c and surface bound complement regulators CD46, CD55 and CD59. EC repair was assessed by scratch wound assay. Blood outgrowth endothelial cells (BOECs) were incubated with various concentrations/durations of cyclosporine (CsA) 10 microgram/ml for 24 hours and subsequently exposed to 50% normal human serum (complement active) or heat inactivated serum (complement inactive).

Results: CsA cytotoxicity was dose and duration-dependent. An optimal balance of EC survival and CNI effect was obtained with CsA 10 microgram/ml for 24 hours. The sequence of CsA incubation (above) and 50% NHS resulted in enhanced EC complement (C3c) deposition and cell death. In addition, scratch wound healing was also significantly impaired. Of note, CsAled to upregulation of CD46, CD55 and CD59.

Conclusions: CsA induced EC cytotoxicity is dose and duration dependent. CsA causes complement activation on EC with increased cell death and impaired endothelial repair. Unexpectedly, we found that CsA led to upregulation of surface-bound complement regulators CD46, CD55 and CD59. Further experiments are ongoing to unravel the mechanism of CsA induced complement activation and its effects on EC injury and dysfunction.

FR-PO224

TLR4 Links Uric Acid with the Innate Immune System to Mediate Injury in Proximal Tubule Cells Giacomo Garibotto,[1] Daniela Verzola,[1] Samantha Milanesi,[1] Barbara Bonino,[1] Francesca Cappadona,[1] Emanuele L. Parodi,[1] Abitha Murugavel,[1] Francesca Viazzi,[1] Roberto Pontremoli.[1] *[1]IRCCS AOU San Martino-IST; [2]IRCCS AOU San Martino-IST; [3]IRCCS AOU San Martino-IST; [4]IRCCS AOU San Martino-IST; [5]IRCCS AOU San Martino-IST; [6]IRCCS AOU San Martino-IST; [7]IRCCS AOU San Martino-IST; [8]IRCCS AOU San Martino-IST; [9]IRCCS AOU San Martino-IST; [10]IRCCS AOU San Martino-IST.*

Background: Hyperuricemia has been linked to the development of inflammation and progression of renal damage. However the mechanisms by which uric acid (UA) may cause these effects are poorly explored. Tubular cells (pTCs) posses both the afferent and efferent limbs of the innate immune system, including Toll like receptors (TLRs) and both early and late-phase cytokines. TLRs mediate signal transduction pathways through the activation of transcription factors that regulate cytokines.Toll-like receptor4 (TLR4)recognize pathogen-associated danger signals but is also activated *via* endogenous ligands. The aim of the present study was to examine the immune activation induced by UA in (pTCs).

Methods: Human pTCs line (HK-2) was exposed for 0-5 hours to UA (12 mg/dl). Cells were pretreated with 1 um TLR4 antagonist (Tak 242) or valsartan (5 um) or losartan (10 um). TLR4 gene and protein expression were evaluated by rtPCR and western blot; P65 activation by western blot and MCP1 and NOX4 by rtPCR.

Results: Exposure of HK-2 to UA resulted in increased gene and protein expression of TLR4 ($p<0.05$) and in upregulation of proinflammatory cytokine MCP-1 ($p<0.05$) and prooxidant NOX4 ($p<0.01$). UA induced NF-κB signaling (phosphorylated-p65) and p65 inhibition blunted the upregulation of TLR4 mRNA ($p<0.001$). Pretreatment with Tak242 attenuated the UA induced expression of both MCP-1 and NOX4 mRNA ($p<0.001$). While preincubation with valsartan did not affected the effects investigated, URAT-1 transport inhibition by losartan blunted both MCP-1 and NOX4 mRNAs.

Conclusions: Our results show that TLR4 links UA with the innate immune system to mediate injury in pTCs. These effects are prevented by inhibition of UA intracellular transport. These results might explain the chronic tubulointerstitial damage observed in hyperuricaemic states and suggest that UA transport in pTCs is necessary for urate-induced effects.

FR-PO225

Pro224/Ala Mutation of Rat Na/K-ATPase α1 Subunit Attenuates Na/K-ATPase Signaling Functions without Affecting Na/K-ATPase Activity in Renal Proximal Tubular Cells Yanling Yan,[1] Anna P. Shapiro,[2] Zi-Jian Xie,[1] Joseph I. Shapiro,[1] Jiang Liu.[1] *[1]Marshall Univ JCE School of Medicine; [2]Univ of Toledo College of Medicine.*

Background: Cardiotonic steroids (CTS, such as ouabain) signaling through Na/K-ATPase, regulate sodium reabsorption in the renal proximal tubule (RPT). Carbonylation modification of the Na/K-ATPase α1 subunit regulates Na/K-ATPase signaling and subsequent transepithelial sodium transport in RPTs.

Methods: Expression of the Pro224/Ala of rat α1 subunit mutant in α1 knockdown pig LLC-PK1 cells. Determinations of the followings: activation of c-Src and ERK1/2, protein carbonylation, [^{3}H]ouabain binding, Na/K-ATPase activity, active $^{22}Na^+$ transport, cellular redistribution of Na/K-ATPase, etc.

Results: Comparing to control wild type cell (AAC-19, expressing rat α1 subunit in α1 knockdown pig LLC-PK1 cells) and mutation control cell (A416P, expressing Ala416/Pro mutation of rat α1 subunit in α1 knockdown pig LLC-PK1 cells), mutation of Pro224 to Ala of rat α1 subunit attenuates ouabain-stimulated activation of c-Src and ERK1/2, tyrosine phosphorylation of multiple proteins, protein carbonylation, redistribution of Na/K-ATPase, and inhibition of active transepithelial $^{22}Na^+$ transport. However, as seen in AAC-19 and A416P cells, this Pro224/Ala mutation has no effect on ouabain-induced inhibition of Na/K-ATPase enzymatic and ion-exchange activities assessed by ouabain-sensitive enzymatic activity of the Na/K-ATPase in crude membrane preparations as well as the ion-exchange activity assayed by ouabain-sensitive $^{86}Rb^+$ uptake.The data indicate that P224A mutation did not change the characteristics of ouabain-induced Na/K-ATPase inhibition but attenuated ouabain-induced signaling function.

Conclusions: Pro224 of rat α1 subunit plays an important role in ouabain-mediated Na/K-ATPase signaling and related sodium handling in RPTs.

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FR-PO226

Cardiotrophin-Like Cytokine Factor 1 (CLCF1): An Intrinsically Disordered Promiscuous Cytokine in Focal Segmental Glomerulosclerosis (FSGS) Plasma Mukut Sharma,[1,2,3] Andrew Keightley,[4] Fei Philip Gao,[5] David Genochio,[1] Jianping Zhou,[1] Alok De,[2] Tarak Srivastava,[6,2] Ellen T. McCarthy,[3] Ram Sharma,[1] Jean-Francois Gauchat,[7] Virginia J. Savin.[1,3] *[1]Research, Kansas City VA Medical Center, Kansas City, MO; [2]Research, MBRF, KC VA Medical Center, Kansas City, MO; [3]Kidney Inst, KU Medical Center, Kansas City, KS; [4]Mass Spectrometry and Proteomics Center, UMKC, Kansas City, MO; [5]Structural Biology Center, Univ of Kansas, Lawrence, KS; [6]Nephrology, CMH, UMKC, Kansas City, MO; [7]Pharmacology, Univ of Montreal, Montreal, QC, Canada.*

Background: CLCF1, an IL-6 family cytokine, detected in FSGS plasma is believed to secrete and circulate with cytokine-receptor like factor1 (CRLF1) and soluble ciliary neurotrophic factor receptor (sCNTFR). CLCF1 carries a weak net charge and aggregates at physiological pH suggesting intrinsic disorder (ID) and potential binding with multiple proteins.

Methods: ID in CLCF1 was determined using CSpritz bioinformatics tools. Surface plasmon resonance (SPR) was used to study interaction of immobilized rhCLCF1 with anti-CLCF1 antibody (Ab), apo-lipoprotein E (ApoE) and the multi-ligand receptor protein sortilin. LC-MS and Western blotting (WB) were used to compare distribution of CLCF1 in normal and FSGS sera. Glomerular albumin permeability (P_{alb}) assay and WB were used to compare the effect of monomeric CLCF1 and heterodimer CRLF1-CLCF1 on P_{alb} and JAK-STAT activation, respectively.

Results: In silico analysis showed 33.33% ID in the CLCF1 molecule due to 5 disordered segments 10-23 amino acids long. Low pH buffers favored monomeric stability of CLCF1. SPR analysis showed that CLCF1-ApoE binding was stronger (200%) but CLCF1-sortilin interaction was weaker (12%) compared to CLCF1-Ab interaction (100%). SDS-PAGE, LC-MS and WB showed that CLCF1 associated with several fractions. CRLF1-CLCF1 blocked the CLCF1-induced increase in mouse podocyte STAT3 phosphorylation and rat glomerular P_{alb} ($P<0.001$).

Conclusions: Significant ID determines the molecular characteristics of CLCF1. CLCF1 may function as a "hub" interacting with several proteins including CRLF1 and CNTFRα with varying affinity to modulate cell-type specific functions.

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FR-PO227

MicroRNA-148b Suppresses Megalin Expression and Is Associated with Downregulation of This Receptor in Mice Subjected to Unilateral Ureteral Obstruction Lu Wen,[1,2] Pia K. Andersen,[1] Dina Michelle Baarts Pedersen,[3] Rikke Norregaard,[3] Henrik Birn.[1] *[1]Dept of Biomedicine, Aarhus Univ, Aarhus, Denmark; [2]Dept of Nephrology, First Affiliated Hospital of Zhengzhou Univ, Zhengzhou, China; [3]Dept of Clinical Medicine, Aarhus Univ, Aarhus, Denmark.*

Background: Tubular proteinuria has been observed in unilateral ureteral obstruction (UUO)–induced kidney injury. Proximal tubule uptake of filtered protein is mediated through the multiligand endocytic receptors megalin and cubilin. However, the expression of megalin and the mechanisms of its regulation in UUO-induced kidney injury are unresolved.

Methods: UUO kidney injury was induced in 10-week old male C57BL/6 mice by ligation of the left ureter for 7 days. The expression of megalin was evaluated by quantitative PCR (qPCR), Western blotting and immunofluorescence. The levels of microRNA-148b (miR-148b) were detected by qPCR. *In silico* miRNA target prediction analysis combined with dual-luciferase reporter assay in HEK293 cells was used to confirm the potential interaction between miR-148b and megalin expression. LLC-PK1 cells were transfected with miR-148b mimic or inhibitor to examine the effect of miR-148b on megalin expression *in vitro*.

Results: Megalin expression was dramatically decreased in mice kidney of UUO associated with an upregulation of miR-148b in kidneys from UUO mice. The relative luciferase activity in HEK293 cells was reduced when co-transfected with miR-148b mimic and wild type megalin-3'-UTR, whereas luciferase activity of mutant megalin-

3'-UTR was not affected. Transfection of LLC-PK1 cells with miR-148b mimic reduced both endogenous megalin mRNA and protein levels, while transfection with miR-148b inhibitor resulted in an increase.

Conclusions: MiR-148b directly suppresses megalin expression in LLC-PK1 cells. This indicates that miR-148b may negatively regulate megalin expression in UUO-induced kidney injury leading to tubular proteinuria. Thus, miR-148b may be a potential therapeutic target for modulation of tubular protein reabsorption in obstructive kidney injury. Further studies should examine if miR-148b is important for megalin expression in other conditions.

FR-PO228

Loss of Mitochondrial Heat Shock Protein, Mortalin during Renal Cold Storage and Transplantation Nirmala Parajuli, Lee Ann MacMillan-Crow. *Pharmacology/Toxicology, Univ of Arkansas for Medical Sciences, Little Rock, AR.*

Background: Long-term graft viability continues to be problematic after transplantation, especially in kidneys that require cold storage (CS). Our prior study reported that renal CS leads to increased mitochondrial injury and renal damage following transplantation (J. Kidney, 2: 114, 2016). However, the molecular mechanisms responsible for worsening mitochondrial and renal damage following transplantation of kidneys preserved with CS are poorly understood. Mortalin is a *heat-uninducible* mitochondrial chaperone within the heat shock protein 70 (mtHsp70) family that maintains proper folding of mitochondrial proteins. A reduction in mortalin expression in normal cells leads to mitochondrial fragmentation and dysfunction. The goal of this study is to evaluate if mortalin is altered during renal CS and transplantation.

Methods: Male Lewis rat kidneys exposed to CS (18 hr) followed by transplantation (*in vivo*) and a rat kidney proximal tubular cells (NRK) exposed to CS (0-18 hr) followed by rewarming (*in vitro*) models were used. MKT-077 (a rhodacyanine dye) was used to inhibit mortalin function in NRK cells. Mitochondrial function was assessed via high resolution respirometry.

Results: Mortalin expression was decreased after CS plus transplantation (*in vivo*) or rewarming (*in vitro*). NRK cells treated with the mortalin inhibitor, MKT-077 (without CS) showed a dose dependent increase in mitochondrial reactive oxygen species, cell death, and impaired mitochondrial respiration. These studies suggest that inhibition of mortalin function contributes to renal mitochondrial dysfunction.

Conclusions: These data suggest, for the first time, that renal CS leads to altered mortalin expression/activity leading to mitochondrial dysfunction, oxidative stress, and renal cell death. New studies designed to preserve the mortalin function may have promising therapeutic implications for better outcomes after renal transplantation.

Funding: NIDDK Support

FR-PO229

Mass Spectrometry and Cellular Bioenergetics Analysis Reveals Altered Mitochondrial Function in the Kidneys of Na-H Exchanger Regulatory Factor Isoform 1 (NHERF1) Deficient Mice Amanda R. Sherwood,[1] Syed J. Khundmiri,[2] Caryl Conklin,[1] Kenneth Gagnon,[1] Michelle T. Barati,[1] Adrienne M. Bushau,[1] Michael Merchant,[1] Eleanor D. Lederer.[1,5] *[1]Dept of Medicine, Univ of Louisville School of Medicine, Louisville, KY; [2]Dept of Physiology, Howard Univ, Washington, DC; [3]Nephrology, Robley Rex VA Medical Center, Louisville, KY.*

Background: NHERF1 is a protein that plays a critical role in both defining the renal proximal tubule brush border membrane (BBM) composition and regulating ion transport through modulation of its trafficking and anchoring functions. In a NHERF1-deficient opossum kidney cell line, we have observed disrupted trafficking of transporters to the BBM.

Methods: As the role of NHERF1 in total BBM protein composition has not previously been explored in the kidney cortex, we used ID-RP (C18) nanoflow ultra high performance liquid chromatography and nanoelectrospray-mass spectrometry (MS) to examine the composition of the BBM of proximal tubule cells from 4 month old NHERF1 KO mice. To investigate the biological impact of these findings, we isolated and cultured primary proximal tubule cells from the kidney cortex of 2-month old wild-type and NHERF1 KO mice and measured both mitochondrial respiration and glycolysis rates.

Results: The BBM of NHERF1 KO mice exhibited decreased abundance of ion channels, cytoskeleton-associated proteins, and cell survival proteins, and increased abundance in proteins involved in vesicular transport. Our proteomics analysis also identified a large amount of proteins typically associated with the mitochondria with significantly decreased abundance in the NHERF1 KO BBM. NHERF1 KO proximal tubule cells also exhibited decreases of 35% in glycolytic reserve capacity, 40% in baseline mitochondrial respiration rate, 40% in mitochondrial reserve capacity.

Conclusions: NHERF1 may play a role in membrane protein composition in not only the BBM but membranes of cellular organelles such as the mitochondria, leading to a lower oxidative capacity and the potential for increased susceptibility to cell injury.

Funding: VA Support

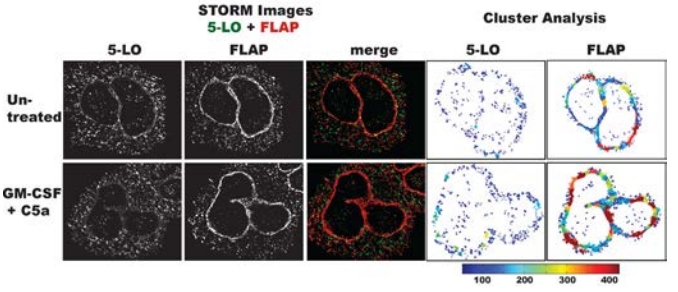
FR-PO230

Organization of the Leukotriene Synthetic Complex in Neutrophils as an Indicator of Disease State Angela Bair Schmider,[1] Matthew Godin,[1] Hunter Elliott,[2] Roy J. Soberman.[1] *[1]Medicine, Massachusetts General Hospital, Charlestown, MA; [2]Cell Biology, Harvard Medical School, Boston, MA.*

Background: The recruitment and activation of neutrophils is a prominent component of tissue injury in anti-neutrophil cytoplasmic autoantibody-vasculitis (AAV). The chemotactic lipid, leukotriene (LT)B_4 plays a role in the initial recruitment of neutrophils from the vasculature. We previously identified the LT synthetic complex to involve multiple steps in its organization on the nuclear envelope resulting in LTB_4 synthesis. We hypothesized that organization of the core members of this structure, 5-lipoxygenase (5-LO) and 5-lipoxygenase-activating protein (FLAP), form supramolecular structures as an additional regulatory step in LTB_4 synthesis resulting in enhanced neutrophil recruitment and activation.

Methods: We paired *S*tochastic *O*ptical *R*econstruction *M*icroscopy (STORM) with cluster analysis and *F*luorescence *L*ifetime *I*maging *M*icroscopy (FLIM) to show the reorganization of 5-LO/FLAP into supramolecular clusters on the nuclear envelope in response to priming and activation from neutrophils of patients with AAV and healthy controls. Primary antibodies against 5-LO/FLAP were used for all microscopy experiments. STORM required secondary antibodies Cy3b and AlexaFluor647. To test the hypothesis that LT synthetic complexes were organized into larger groups, we developed unbiased automated cluster analysis algorithms to analyze primary STORM data. FLIM required AlexaFluor488 and 594 secondary antibodies.

Results: The priming and activation of neutrophils results in reorganization of 5-LO and FLAP into supramolecular clusters.



Conclusions: Using a novel approach we have identified novel supramolecular complexes of LT synthetic enzymes that play a major regulatory role in neutrophil activation and are potentially an indicator of disease state.

Funding: NIDDK Support

FR-PO231

Attenuation of Na/K-ATPase Mediated Oxidant Amplification with pNaKtide Partially Reverses PNx-Induced Experimental Uremic Cardiomyopathy Jiang Liu,[1] Muhammad A. Chaudhry,[1] Kyle D. Maxwell,[1] Yanling Yan,[1] Xiaoliang Wang,[1] Preeya Tushar Shah,[1] Asad A. Khawaja,[1] Rebecca Martin,[1] Christopher A. Drummond,[2] Steven T. Haller,[2] David J. Kennedy,[2] Jiang Tian,[2] Zi-Jian Xie,[1] Joseph I. Shapiro.[1] *[1]Marshall Univ JCE School of Medicine; [2]Univ of Toledo College of Medicine.*

Background: In C57BL/6 mice, Na/K-ATPase mediated oxidant amplification is involved in 5/6 renal partial nephrectomy (PNx) induced cardiac fibrosiswith at week 4 of post-surgery. Here we report that attenuation of Na/K-ATPase mediated oxidant amplification with pNaKtide ameliorates experimental uremic cardiomyopathy.

Methods: PNx was performed and C57BL/6 mice were allowed to develop uremic cardiomyopathy for 4 weeks. At week 4 of post-surgery, the mice were randomly divided. During the fifth week post-surgery, pNaKtide was administered i.p. at a dose of either 0, 1, 5, 10 or 25 mg/kg body weight on day 0, day 2, and day 4, and the mice were sacrificed on day 7 of that week. Transthoracic echocardiography, western blot of proteins, hematocrit, heart/body weight ratio, and renal function were determined.

Results: Comparing with PNx group 5 weeks post-surgery, pNaKtide appeared to reverse PNx-induced anemia and cardiac hypertrophy based on heart weight/body weight ratio. Many (but not all) of the echocardiographic features of uremic cardiomyopathy were reversed by pNaKtide in a dose dependent fashion after one week administration. Specifically, left ventricular wall thickness (anterior, posterior and relative wall thickness) as well as left ventricular mass index (LVMI) were ameliorated by pNaKtide at the higher doses. The myocardial performance index (MPI) changes were not reversed by pNaKtide. At higher doses, pNaKtide also reversed the fibrosis as assessed by histology and collagen-1 expression. Administration of pNaKtide also attenuated left ventricular c-Src activation and ERK1/2 activation as well as oxidant stress as assessed by protein carbonylation. pNaKtide at higher doses reversed PNx-mediated increases in plasma creatinine and BUN, but not plasma cystatin C.

Conclusions: Attenuation of Na/K-ATPase mediated oxidant amplification with pNaKtide is able to partially reverse PNx-induced experimental uremic cardiomyopathy.

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FR-PO232

Activation of Gβγ-Akt Signaling Mediates the Differential Effects of β2 Adrenoceptor Agonists on Mitochondrial Biogenesis Robert Bruce Cameron, Craig Cano Beeson, Rick G. Schnellmann. *Drug Discovery and Biomedical Sciences, Medical Univ of South Carolina, Charleston, SC.*

Background: AKI is associated with suppression of mitochondrial function, and drugs that induce mitochondrial biogenesis (MB) are effective in preclinical models of AKI. Formoterol, a β_2 adrenoceptor (β_2AR) agonist, induces MB and stimulates recovery of renal function following AKI in mice, but the β_2AR agonist clenbuterol does not induce MB. We sought to determine the differences in signaling between formoterol and clenbuterol in renal MB.

Methods: For *in vitro* studies, renal proximal tubule cells (RPTC) were treated with 30nM formoterol or 30nM clenbuterol. RPTC were also pretreated with 100nM gallein, 100nM MK2206, 10μM L-NAME, or 5μM ODQ. For *in vivo* studies, C57BL/6 mice received 0.3 mg/kg formoterol or 0.3 mg/kg clenbuterol (i.p.). MB was assessed by FCCP-uncoupled oxygen consumption rate using a Seahorse instrument and by mRNA expression of PGC-1α and NDUFS1 using RT-qPCR.

Results: In both RPTC and mice, formoterol, but not clenbuterol, increased Akt phosphorylation after 30 min. Pretreatment with the Gβγ inhibitor gallein blocked formoterol-induced increases in Akt phosphorylation in RPTC. At 1 h, formoterol, but not clenbuterol, increased eNOS phosphorylation, which was prevented by pretreatment with gallein or the Akt inhibitor MK2206 in RPTC. Both formoterol and clenbuterol increased cGMP in RPTC. Formoterol-induced MB was attenuated by pretreatment with gallein, MK2206, the NOS inhibitor L-NAME, and the sGC inhibitor ODQ in RPTC.

Conclusions: Formoterol induced MB by activating the Gβγ-Akt-eNOS-cGMP pathway, leading to increased MB gene transcription and oxidative metabolism. In contrast, clenbuterol did not activate Akt or induce MB. Because formoterol and clenbuterol increased cGMP production, cGMP is necessary but not sufficient for β_2AR-dependent MB. We propose that structural differences between formoterol and clenbuterol result in distinct receptor interactions that cause differential activation of the Gβγ-Akt pathway. Compounds that selectively activate the Gβγ-Akt pathway are efficacious inducers of MB and potential therapeutics for renal MB and injury.

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FR-PO233

HIF1A Activates the TGF-β/SMAD3 Pathway in Kidney Tubular Epithelial Cells Natsuki Kushida,[1,2] Seitaro Nomura,[2] Imari Mimura,[1] Hiroyuki Aburatani,[2] Masaomi Nangaku.[1] *[1]Div of Nephrology and Endocrinology, The Univ of Tokyo, Bunkyou, Tokyo; [2]Div of Genome Science, Research Center for Advanced Science and Technology, The Univ of Tokyo, Meguro, Tokyo.*

Background: Kidney injury, including chronic kidney disease and acute kidney injury, is a worldwide health problem. Hypoxia and TGF-β are well-known factors that promote kidney injury. Hypoxia-inducible factor (HIF) and SMAD3 are their main downstream transcriptional factors. Hypoxia-HIF pathway and TGF-β/SMAD3 pathway play crucial roles in the progression of kidney injury. However, reports of their interactions are limited, and the global transcriptional regulation under their control is almost unknown.

Methods: Kidney tubular epithelial cells (HK2: human kidney-2) were cultured and stimulated by 1% hypoxia and TGF-β. We detected global binding sites of HIF1A and SMAD3 in the cells using chromatin immunoprecipitation (ChIP)-Seq, and examined genome-wide gene expression profiling by using RNA-Seq. ChIP-qPCR of SMAD3 was performed after knocking down of HIF1A to quantitatively evaluate the effect of HIF1A on the bindings of SMAD3.

Results: ChIP-Seq revealed that 2,065 and 5,003 sites were bound by HIF1A and SMAD3, respectively, with 614 sites co-occupied by the both factors.RNA-Seq showed that hypoxia and TGF-β stimulation causes synergistic upregulation of 249 genes, containing collagen type I alpha 1 (COL1A1) and serpin peptidase inhibitor, clade E, member 1 (SERPINE1), which are well-known genes related to fibrosis. Ontology of the 249 genes implied that the interaction of HIF1Aand SMAD3 is related to biological processes such as fibrosis. ChIP-qPCR of SMAD3 at HIF1Abinding sites near COL1A1 and SERPINE1 indicated that HIF1A promotes the bindings of SMAD3 induced by TGF-β.

Conclusions: These findings suggest that HIF1A induced by hypoxia activates the TGF-β/SMAD3 pathway. This mechanism may promote kidney injury, especially by upregulating genes related to fibrosis.

FR-PO234

Minichromosome Maintenance Protein 3 Regulates Renal Tubule Cell Signaling Associated with Nrf2 Activation Andrew Birton Smith, Susan M. Isaacs, Madhavi J. Rane, Jon B. Klein, Michael Merchant, Michelle T. Barati. *Kidney Disease Program, Univ of Louisville.*

Background: Altered tubule cell function contributes to progression of diabetic nephropathy (DN). Previous studies in our lab showed upregulation of minichromosome maintenance protein 3 (MCM3), a member of MCM2-7 DNA helicase, in renal tubules of diabetic mice. In addition, MCM3 protein associated with and stabilized Nrf2 in cultured tubule cells and MCM3 knockdown augmented high glucose concentration-induced caspase-3 cleavage. This study addressed the hypothesis that MCM3 regulates cell signaling pathways involved in Nrf2 stabilization and DN.

Methods: HK-11 human proximal tubule cells (PTCs) were transfected with MCM3 DNA or MCM3 siRNA to overexpress or knockdown MCM3, respectively. Total and phosphorylated-ERK and p38 MAP Kinases and glycogen synthase kinase 3β (GSK3β), MCM7 and p21 were analyzed by immunoblotting. Kidney sections of OVE26 diabetic and FVB control mice were immunostained for MCM7.

Results: Activation of ERK induces Nrf2 while p38 MAPK deactivates Nrf2 and overexpression of MCM3 in PTCs transiently increased phosphorylation of ERK1/2 followed by decreased p38 phosphorylation. Overexpression or knockdown of MCM3 in PTCs did not alter phospho-S9GSK3β, a kinase known to deactivate Nrf2. Overexpression of MCM3 increased expression of p21, a cyclin kinase inhibitor that stabilizes Nrf2 and is upregulated in DN. Alternatively, knockdown of MCM3 in tubule cells decreased p21 expression. Unlike MCM3, another member of the MCM2-7 helicase, MCM7, was not increased in renal tubules of diabetic mice, but was down-regulated in PTC following knockdown of MCM3.

Conclusions: In conclusion, regulation of ERK and p38 MAPK are likely mechanisms by which MCM3 stabilizes Nrf2 and may also serve to regulate PTC responses associated with DN. Regulation of p21 in PTC by MCM3 may also serve to stabilize Nrf2, as well as, regulating tubule cell cycle arrest and/or cell death associated with DN or other renal pathologies. Lack of MCM7 regulation in tubules of diabetic mice suggests that MCM3 induction during diabetes may have roles independent of the MCM2-7 helicase.

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FR-PO235

Suppression of SIRPa Signaling Affecting Adipose Tissue and Muscle Metabolism: Evidence for Organ Cross-Talk in Chronic Kidney Disease Jiangling Dong,[1] Jiao Wu,[1] Zhaoyong Hu,[1] William E. Mitch,[1] Sandhya S. Thomas.[2,1] *[1]Medicine, Baylor College of Medicine, Houston, TX; [2]Medicine, Michael E. Debakey Veteran Affairs Medical Center, Houston, TX.*

Background: A major complication of chronic kidney disease (CKD) is insulin resistance, causing metabolic dysregulation of carbohydrate, protein, and lipid metabolism. The large scope of metabolic interrelationships between fat and muscle tissues in CKD suggest there is organ crosstalk between fat and skeletal muscle tissues that worsens insulin resistance. Signal Regulatory Protein alpha (SIRPα), regulates muscle metabolism, we hypothesized that SIRPα mediates organ crosstalk in CKD.

Methods: SIRPα whole body mutant (Mt) mice and wildtype mice (WT) were compared after inducing subtotal nephrectomy. DEXA was used to assess body composition. Skeletal muscles and adipose tissues were evaluated by western blot and qPCR.

Results: Compared to WT CKD mice, SIRPα Mt mice with CKD had improved insulin sensitivity signified as increased tyrosine phosphorylation of IRS1 and pAkt in skeletal muscles and adipose tissues; there also were increased markers of white adipose tissue (WAT) browning (i.e., UCP-1, >2-fold) plus significant increases in mitochondrial activity (acetyl-CoA carboxylase, PGC-1α >5-fold). SIRPα Mt mice also had increased lean mass vs. responses of wild type mice (WT) with CKD.

Conclusions: SIRPα mediates impaired insulin signaling by interfering with intracellular insulin signaling. Suppression of SIRPα improves insulin signaling, promotes lean mass and increases browning of WAT. We conclude that in CKD, SIRPα mediates cross talk between muscle and adipose tissue promoting dysregulation of protein and lipid metabolism likely exacerbating mortality.

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FR-PO236

Urinary Vesicles and Differential Centrifugation: Failure of Full Vesicle Content Recover Luca Musante,[1] Dorota Ewa Tataruch,[1] Harry B. Holthofer.[2] *[1]Centre for BioAnalytical Sciences, Dublin City Univ, Dublin, County, Ireland; [2]Freiburg Inst for Advanced Studies, Albert-Ludwigs Univ, Freiburg, Germany.*

Background: Urinary extracellular vesicles (UEVs), especially the exosome fraction, are an ideal, uninvasive source of biomarkers. The bulk of protocols designed for their isolation are based on differential centrifugations at relative centrifugation force (RCF) of 2000g (P2), 40.000g (P40) and 200,000g (P200) respectively. However, a fraction of EVs sediments already at P40 and yet another fraction is in the final supernatant (SN200) to be normally discarded. This means loss of diagnostic EVs throughout the process.

Methods: We used here hydrostatic filtration-dialysis (HFD) to enrich UEVs followed by differential centrifugation. Western blot (WB), ELISA and Tunable Resistive Pulse Sensing (TRSP) were used to characterize and quantify UEVs. Additionally, transmission electron microscopy (TEM) and mass spectrometry (MS) were employed to characterize leftover vesicles in the final ultracentrifugation supernatant. All fractions were also subjected to RNA extraction, quantification and electrophoretic profiling.

Results: Screening and relative quantification for specific UEV marker CD9 in WB and ELISA showed that ~25% of exosomes are recovered in P40, ~50% in P200 and ~25% in SN200 (normally discarded) in respect to the amount of starting material recovered with HFD. Additionally, TEM analysis showed a variety of small size vesicles remaining in SN200. MS identifications matched accurately with the protein listed in the Vesiclepedia. Finally, extraction of the small RNA (snRNA) species from vesicles confirmed that the bulk of RNA is found in P40 with no snRNA was detected in SN200 vesicles.

Conclusions: Notably, exosomes sedimenting already in P40 are grossly lost in the subsequent centrifugation at 200,000g. These results unequivocally call for serious re-evaluation of the isolation workflows used and suggest that alternative methods, like HFD, need to be used. Notably, with HFD all the losses in the conventional serial centrifugations can be avoided to guarantee the catch of the whole vesicle repertoire.

Funding: Government Support - Non-U.S.

FR-PO237

Identification of Differentially Regulated Pathways in Cellular Models of Mutant Uromodulin Expression Celine Schaeffer, Matteo Trudu, Elena Pasqualetto, Stefania Merella, Dejan Lazarevic, Davide Cittaro, Luca Rampoldi. *San Raffaele Scientific Inst, Milan, Italy.*

Background: Uromodulin is the most abundant urinary protein. It is exclusively produced and released in the urine by renal epithelial cells lining the thick ascending limb of Henle's loop (TAL). Mutations in *UMOD*, the gene encoding uromodulin, cause autosomal dominant tubulointerstitial kidney disease uromodulin-related (ADTKD-*UMOD)*. While the primary effect of all mutations, retention in the endoplasmic reticulum (ER), is well established, its downstream effects are still unknown.

Methods: To gain insight into ADTKD-*UMOD* pathogenesis, we performed transcriptional profiling and biochemical characterisation of cellular models (immortalised mouse TAL cells) of robust wild-type or mutant (C150S) GFP-tagged uromodulin expression.

Results: Similar to previous studies, mutant uromodulin is ER retained, but its expression does not impact on cell viability and proliferation. Transcriptional profiling identified 45 up- and 20 down-regulated (fold change >1.5, adjusted p-value< 0.05) genes in mutant cells relative to wild type ones. Up-regulated genes include several ER resident chaperones and protein disulphide isomerases. Consistently, pathway enrichment analysis indicates that mutant uromodulin expression affects ER function, protein homeostasis and calcium signalling. Interestingly, among the three branches of the Unfolded Protein Response (UPR), i.e ATF6, PERK and IRE1, only the one driven by IRE1 is induced, as shown by an increased splicing of XBP1. Treatment with specific IRE1 inhibitor suggests that such induction is not necessary for cell survival and could be maladaptive. Consistent with UPR induction, results obtained by co-immunoprecipitation experiments show association of mutant uromodulin with ER chaperones, as Bip and calnexin. Using metabolic labelling, we also demonstrate that while autophagy plays no role, mutant protein is partially degraded by the proteasome through ER-associated degradation.

Conclusions: Our work shows that ER stress is the main effect induced by mutant uromodulin expression. This cell model will be an interesting tool where to further dissect the molecular pathways of ADTKD-*UMOD* pathogenesis.

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FR-PO238

A Personalized Drosophila Model of COQ2 Nephropathy Rescued by the Wild-Type Human COQ2 Allele and Dietary Q10 Supplementation Zhe Han, Patricio E. Ray, Yulong Fu, Jun-Yi Zhu, Adam Richman. *Children's National Health Systems.*

Background: Clinical studies have identified patients with nephrotic syndrome (NS) caused by mutations in genes involved in the biosynthesis of Coenzyme Q10 (CoQ_{10}), a lipid component of the mitochondrial electron transport chain and an important antioxidant. However, the cellular mechanisms through which these mutations induce podocyte injury remain obscure.

Methods: We developed *Drosophila* models of COQ-related renal diseases by exploiting the striking similarities between *Drosophila* nephrocytes and human podocytes. We performed the first systematic *in vivo* analysis for each of the 10 COQ genes using nephrocyte-specific gene silencing, with various of function assays, as well as electron microscopy.

Results: We found that silencing each of these COQ genes specifically in nephrocytes shortened the life span of flies. Moreover, nephrocyte-specific silencing of Coq2, Coq6, and Coq8, which are genes involved in the CoQ_{10} pathway that have been associated with genetic NS in humans, induced dramatic adverse changes in these cells. In particular, Coq2-silencing led to an abnormal localization of slit diaphragms, collapse of lacunar channels, and increased number of dysmorphic mitochondria. In addition, Coq2 deficient nephrocytes showed elevated levels of reactive oxygen species, and increased sensitivity to oxidative stress. These phenotypes were rescued by expressing the wild-type human COQ2 gene specifically in nephrocytes, but not the mutant allele derived from a patient with COQ2 nephropathy. Furthermore, dietary supplementation with Coenzyme Q10 reversed this phenotype.

Conclusions: We conclude that transgenic *Drosophila* lines carrying mutations in the CoQ_{10} pathway genes are a clinically relevant model to explore the pathogenesis of podocyte injury, and could serve as a new drug-testing platform for novel therapeutic approaches.

Funding: NIDDK Support

FR-PO239

Mesenchymal Stromal Cells Accelerate Epithelial Tight Junction Assembly via the AMP-Activated Protein Kinase Pathway, Independently of Liver Kinase b1 Pascal Rowart,[1] Pauline Erpicum,[1] Jean-Marie H. Krzesinski,[1] Michael Sebbagh,[2] Francois Jouret.[1] *[1]Univ of Liège, Belgium; [2]Centre de Recherche en Cancérologie de Marseille, France.*

Background: Disruption of epithelial tight junctions (TJ) is one of the earliest hallmarks of acute kidney injury (AKI). Mesenchymal stromal cells (MSC) represent a heterogeneous population of adult fibroblast-like multipotent cells capable of tissue repair properties following AKI. Hence, we hypothesized that MSC may modulate TJ. We focused on the AMP-activated protein kinase (AMPK) pathway since it participates both in energy salvation and TJ maintenance.

Methods: Madin-Darby canine kidney (MDCK) cells were cultured alone or in direct contact with rat bone marrow derived MSC (upon a 3:1 ratio) for 5 days. Next, a Ca^{2+} switch, i.e. switching cells from [5μM] Ca^{2+} (for 48h) to [1.8mM] Ca^{2+} (up to 2h), was performed. TJ formation was assessed upon ZO-1 relocation by immunofluorescence, and AMPK phosphorylation was quantified by immunoblotting. Experiments were repeated using MDCK stably expressing ShRNA against the AMPK kinase, Liver kinase b1 (Lkb1), or against Luciferase (LUC, used as control).

Results: Following Ca^{2+} switch, ZO-1 relocation occurred significantly faster in MDCK/MSC *versus* MDCK. Correspondingly, phospho-AMPK/total AMPK ratio was 1.7-fold increased in MDCK/MSC *versus* MDCK alone (n=4, p<0.001). Of note, AMPK was not detectable in MSC alone. As previously reported, Ca^{2+}-induced ZO-1 relocation to TJ was significantly delayed in Lkb1-ShRNA *versus* LUC-ShRNA MDCK. However, after 48-hour Ca^{2+} deprivation, TJ-associated ZO-1 was significantly more abundant in MSC co-culture systems of either ShRNA in comparison to corresponding ShRNA MDCK alone. Following Ca^{2+} switch, ZO-1 relocation occurred twice faster in ShRNA MDCK/MSC *versus* ShRNA MDCK alone (n=4, p<0.001). Phospho-AMPK/total AMPK ratio was 1.5-fold increased following Ca^{2+} switch in ShRNA MDCK/MSC *versus* ShRNA MDCK alone (n=4, p<0.001). No difference in phospho-AMPK/total AMPK ratio was observed between Lkb1-ShRNA *versus* LUC-ShRNA MDCK following Ca^{2+} switch.

Conclusions: Our results suggest that MSC may modulate AMPK activation in epithelial cells at the time of Ca^{2+}-induced TJ assembly, independently of Lkb1.

FR-PO240

nrip2 Is Required for Megalin-Dependent Endocytosis via Retinoic Acid Pathyway in Zebrafish Pronephric Tubule Qing Hou, Wei-Bo Le, Xiao-Dong Zhu, Ling Wang, Wei-Song Qin, Zhao-Hong Chen, Zhihong Liu. *National Clinical Research Center of Kidney Diseases, Research Inst of Nephrology, Jinling Hospital, Nanjing, Jiangsu, China.*

Background: Nuclear receptors are transcription factors which require multiple protein-protein interactions to stimulate or repress target gene expression. Nuclear Receptor Interacting Protein 2 (Nrip2) can down-regulate transcriptional activation by binding to retinoic acid receptor in the mouse brain. Retinoic acid (RA) is essential for directing the patterning of the proximodistal nephron segmentation in zebrafish. However, the role of *nrip2* and its association with RA are still unknown in zebrafish kidney.

Methods: We investigated the expression pattern of *nrip2* in zebrafish by *in situ* hybridization. To examine the role of *nrip2*, we generated *nrip2* knock-out (KO) zebrafish using CRIPSR/Cas9 system. Transmission Electron Microscope (TEM) and zebrafish pronephric tubule uptake were carried out. We also detected the expression of *megalin* by immunostaining and analyzed the promoter region of *megalin*.

Results: *nrip2* is expressed predominately and dynamically in zebrafish pronephric tubule during embryogenesis. We introduced a double-strand DNA break in exon2 of *nrip2* and established *nrip2* KO zebrafish. TEM images show *nrip2* deficiency results in reduced amount of endocytic apparatus and cilia in the pronephric tubule. Endocytosis is impaired in the *nrip2* deficiency embryos, the tracer 10KD FITC-Dextran were injected into the cardinal vein of embryos, which are efficiently taken up by the renal tubular cells of control embryos, in contrast, uptake is severely impaired in the *nrip2* deficiency embryos. The expression of *megalin* is reduced in *nrip2* deficiency embryos compared with wild-type embryos. There are two RA response elements are contained in the promoter region of *megalin*, indicating the expression of *megalin* could be altered by RA.

Conclusions: These results suggest that loss of *nrip2* results in impaired *megalin*-dependent endocytosis in zebrafish pronephric tubule and indicate that *nrip2* acts upstream regulator of *megalin* via RA pathway, which will be investigated furthermore.

FR-PO241

Glomerular Endothelial Cells Exposed to Salt-Stress and Aldosterone Loose Key Components from their Glycocalyx Resulting in Functional Impairment Matthew J. Butler, Simon C. Satchell. *Bristol Renal, Univ of Bristol, United Kingdom.*

Background: Aldosterone and salt excess exacerbate proteinuria and may contribute to the progression of kidney disease. We investigated the effects of aldosterone and salt on conditionally immortalised glomerular endothelial cell (CiGEnC) glycocalyx; a protective glycoprotein layer on cells' luminal surface which forms part of the glomerular protein barrier and contributes to laminar shear stress (LSS) detection, as a potential mechanism of damage.

Methods: CiGEnC were exposed to standard media (125mmol NaCl, no aldosterone) or supplemented media (145mmol NaCl, 0.1nM aldosterone). Glycocalyx damage was assessed using immunofluorescence. Functional damage was assessed using cells reaction to LSS; studying up-regulation of Krupple like factor 2 (KLF2) mRNA as an index of LSS response.

Results: 145 mmol NaCl and 0.1nM aldosterone for 5 days resulted in significant up-regulation of matrix metalloproteinases (MMP) 2 and 9 mRNA, but not heparanase mRNA, and significantly reduced surface expression of heparan sulphate (HS) and syndecan 4 (Synd 4). Reduced expression was associated with a functional impairment in cells ability to up-regulate KLF2 in response to LSS.

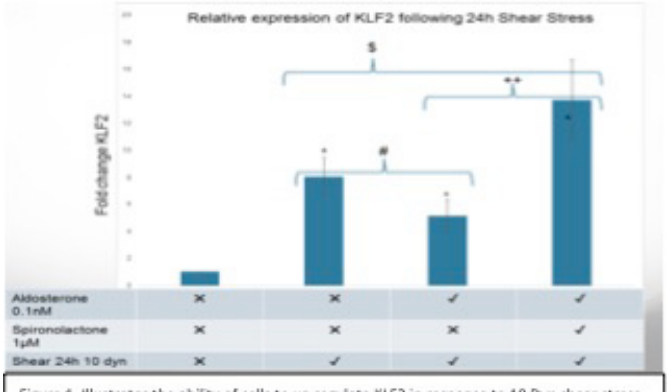

Figure 1. Illustrates the ability of cells to up regulate KLF2 in response to 10 Dyn shear stress for 24h. Aldosterone significantly reduced the response to shear stress ($p<0.05$ #). Spironolactone restored the response suggesting Aldosterone is acting via the mineralocorticoid receptor to elicit damage.

Inhibition of MMPs using the broad spectrum inhibitor Batimistat (5μm) partially restored cells surface expression of HS and Synd 4 and maintained cells ability to up-regulate KLF2 in response to LSS.

Conclusions: Physiologically relevant levels of aldosterone, when combined with elevated salt concentrations, damage CiGEnC glycocalyx. Synd 4 is a LSS sensitive molecule within the glycocalyx. MMP 2 and 9 are known to cleave Synd 4 from the glycocalyx. Inhibition of MMP 2 and 9 prevents HS and Synd 4 loss from the glycocalyx and restores the physiological response to LSS. This work suggests MMP inhibitors may protect the glycocalyx from the damaging effects of aldosterone and salt exposure.

Funding: Government Support - Non-U.S.

FR-PO242

Drug Repositioning Screening for the Discovery of Inhibitors of Keap1–Nrf2 Interaction Using Fluorescent Correlation Spectroscopy Yuki Yoshizaki, Eisei Sohara, Takayasu Mori, Eriko Kikuchi, Daiei Takahashi, Moko Zeniya, Yuya Araki, Yutaro Mori, Fumiaki Ando, Naohiro Nomura, Tatemitsu Rai, Shinichi Uchida. *Nephrology, Tokyo Medical and Dental Univ, Bunkyo-ku, Tokyo, Japan.*

Background: The Keap1-Nrf2-ARE pathway signal is the major regulator of cyto-protective responses to oxidative and electrophilic stress. Recently, activation of the Nrf2 defense response has been shown to protect against several kinds of diseases, such as diabetes, cardiovascular disease, inflammation and cancer. Moreover, the Nrf2 activator Bardoxolone methyl is now clinically evaluated for the treatment of chronic kidney disease. In this study, we focused on the disruption Keap1–Nrf2 interaction, in order to up-regulate the expression of ARE-controlled cyto-protective oxidative stress response enzyme, such as HO-1. We screened the inhibitors of Keap1-Nrf2 protein-protein interaction, in terms of drug repositioning, using Fluorescent Correlation Spectroscopy (FCS).

Methods: FCS is a method capable of measuring the fluctuation rate of a fluorescently labelled single peptide as output of the diffusion times. For this screening, we used FCS to detect the inhibition of Keap1-Nrf2 binding by drugs.

Results: We succeeded to detect the protein interaction between fluorescent TAMRA-labeled small peptides of Nrf2 and GST-Keap1, and performed drug screening using chemical screening library for drug repositioning, arranged by Tokyo Medical and Dental University chemical library center. We judged that the compound had an inhibitory effect on the binding when the measured diffusion time was not increased, compared to the sample without Keap1 protein. As a result of screening 1633 drugs, we extracted 13 drugs that reproducibly disrupted the binding of Nrf2 to Keap1 in FCS. In HepG2 cells, protein level of Nrf2 was actually increased by administration of 11 of the 13 screened drugs. Furthermore, we detected the up-regulation of ARE gene promoter activity and increasing HO-1 mRNA by 2 drugs.

Conclusions: We screened the inhibitors of Keap1-Nrf2 interaction using FCS. These two compounds could be the promising drug candidates for activation of Nrf2-ARE pathway.

Funding: Government Support - Non-U.S.

FR-PO243

The Adaptor Protein CD2AP and L-type Lectin LMAN2 Regulate GPRC5B Trafficking for Its Exosome Release Kenneth Kwon,[1] Sekyung Oh,[4] Marisa Nacke,[3] Keith Mostov,[2] Joshua H. Lipschutz.[1] *[1]Medicine, Medical Univ of South Carolina - MUSC, Charleston, SC; [2]Anatomy and Biochemistry/ Biophysics, Univ of California School of Medicine — UCSF, San Francisco, CA; [3]Cancer Research UK Beatson Inst, Glasgow, United Kingdom; [4]Stanford Univ, Palo Alto, CA.*

Background: Exosomes, 40-100 nm extracellular vesicles, transport biological macromolecules that mediate intercellular communications. While exosomes are known to originate from maturation of endosomes into multivesicular bodies (MVBs) with subsequent fusion of the MVBs with the plasma membrane, it remains unclear how cargos are selected for exosomal release. Previously we have shown that GPRC5B, an orphan G protein coupled receptor is induced during *in vitro* renal tubulogenesis and loaded on exosomes released from renal tubule cells in culture and in human kidneys. Interestingly, intercellular transfer of GPRC5B via exosomes can drive *in vitro* renal tubule growth.

Methods: Using an inducible expression system for the exosome cargo protein GPRC5B and following its trafficking trajectory, combined with CRISPR/Cas9 technology.

Results: we show here that CD2AP is required for internalization of GPRC5B for exosomal release, while LMAN2 (also known as VIP36) inhibits exosome release of GPRC5B. LMAN2 appears to be specifically required for the accumulation in the trans Golgi network (TGN), thereby restricting GPRC5B movement along the exosomal pathway by interfering with TGN-to-endosome transport of GPRC5B.

Conclusions: We propose that GPRC5B is released into exosomes through a TGN-traversing pathway in which LMAN2 critically impedes the flux of exosomes.

FR-PO244

Combinateion of Omega-3 Fatty Acids and Vitamin D Has Synergic Effect on Up-Regulation of NRF-2 Expression and Down-Regulation of SREBP-1 in 5/6 Nephrectomy Rats Young Ki Son,[1] Kitae Kim,[1] Su Mi Lee,[1] Sung Hyun Son,[2] Won Suk An,[1] Seong Eun Kim.[1] *[1]Internal Medicine, Dong-A Univ Hospital, Busan, Korea; [2]Nephrology, BHS Han Seo Hospital, Busan, Korea.*

Background: The Nrf-2 regulates antioxidant and anti-inflammatory process in kidney injury model. Recent study showed that SREBP-1 mediates angiotensin II-induced pro-fibrogenic responses. The present study aimed to investigate whether omega-3 FA and vitamin D which were related with anti- inflammatory process affects the Nrf-2 and SREBP-1expression and has anti-inflammatory, anti-apoptotic, and anti-fibrotic processes in 5/6 nephrectomy rats.

Methods: Male Sprague Dawley rats were divided into five groups: sham control (0.9% saline), 5/6 subtotal nephrectomy (Nx) (0.9% saline), 5/6 Nx treated with vitamin D (cholecalciferol 3000 IU/kg/week) group, 5/6 Nx treated with omega-3 FA (300 mg/kg/day by gastric gavage) group, 5/6 Nx treated with vitamin D and omega-3 FA groups. The expression of IK-b, transforming growth factor (TGF-β1), α-smooth muscle actin (α-SMA), E-cadherin, Smads for inflammation and fibrosis, caspase-3, caspase-7, BAX, and Bcl-2 for apoptosis, and Nrf2 and SREBP-1 were examined. The expression levels of apoptosis-associated factors were examined by western blot analysis.

Results: Serum BUN and creatinine was the lowest in 5/6 Nx treated with omega-3 FA and vitamin D group among 5/6 Nx rat models. Compared with control, 5/6 Nx group significantly up-regulated caspase 3, caspase7, IkB, a-SMA, E-cadherin, SREBP-1, TGF β and Smad2/3 expression and down-regulated Smad6 and Nrf2 expression. We found that omega-3 FA prevented these up and down regulations related with apoptosis, inflammation, and renal fibrosis. There were no significant differences on expression of these factors between 5/6 Nx with untreated group and 5/6 Nx with vitamin D group. However, increased expression of Nrf2 and decreased SREBP-1 expression was distinguished by omega-3 FA and vitamin D combination in 5/6 Nx rats.

Conclusions: Nrf-2 activation and SREBP-1 reduction are potential mechanism induced by omega-3 FA supplementation attenuating pro-inflammatory pathway, fibrotic processes and apoptosis. These mechanisms may be reinforced by additional vitamin D supplementation.

FR-PO245

Molecular Insights into the Program of Proximal Tubules Surviving a Resolving Acute Kidney Injury Aurélien Bataille,[1] Pierre Galichon,[1,2,3] David Legouis,[1] Eric Rondeau,[1,2,3] Alexandre Hertig.[1,2,3] *[1]Inserm UMR_S 1155, Paris, France; [2]Sorbonne Univs, UPMC Université Paris 06, Paris, France; [3]Urgences Néphrologiques et Transplantation Rénale, Hôpital Tenon, Assistance Publique - Hôpitaux de Paris, Paris, France.*

Background: In human beings, even a reversible episode of acute kidney injury (AKI) increases the risk of chronic kidney disease. "Maladaptive repair" was coined to name the pro-fibrotic epithelial changes observed in the aftermath of an AKI. Our aim was to interrogate the effect of a history of a reversible AKI on the transcriptomic pattern of tubular epithelial cells facing a second aggression.

Methods: Adult C57BL6/J wild-type mice were subjected to a left nephrectomy, with (AKI group) or without (Sham group) 20 minutes clamping of the right renal vascular pedicle. Histological recovery was assessed at day 28. At this time point, all mice were subjected to a second hit: angiotensin 2 was continuously administered via subcutaneous pumps (1 $\mu g.kg^{-1}.min^{-1}$). Renal fibrosis was assessed by sirius red coloration. Ex vivo isolation of proximal tubular cells at day 0, 28 and 56 was performed to access total mRNA for high-throughput sequencing.

Results: At day 2, AKI mice displayed acute tubular necrosis at the cortico-medullary junction, and impaired renal function. At day 28, histological recovery was complete, and indistinguishable from sham-operated mice. Arterial pressure and heart rate response to angiotensin 2 was similar in both groups. At day 56, mice with a previous history of AKI displayed significantly more renal fibrosis ($p<0.01$). Investigating the transcriptome of proximal tubular cells, a principal component analysis and clustering individualizes specialized transcriptomes within experimental groups. Up-regulation of metabolic pathways (oxydative phosphorylation, fatty acid metabolism, glycolysis, PPAR signalling pathway) was found in the AKI group compared to the Sham group at day 56.

Conclusions: A resolving episode of AKI poised for activation genes involved in metabolic pathways and durably sensitizes differentiated epithelial cells in a way that promotes energetic hyperactivity concurrently to organ fibrogenesis.

Funding: Pharmaceutical Company Support - Astellas Pharma; Behring, Private Foundation Support

FR-PO246

GDF11 Improves Tubule Regeneration after AKI in Elderly Mice Xiang-Mei Chen, Lingling Wu. *Dept of Nephrology, Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing.*

Background: The effects of GDF11 on organ regeneration and repair after injury in elderly mice are highly controversial questions. However, this does not imply the autocrine and paracrine GDF11 is without effect. GDF11 is necessary in metanephric development, and its expression level is highest in the adult kidneys. The function of GDF11 on kidney regeneration and its molecular mechanism were explored in this study.

Methods: Firstly, GDF11 was restoredin the kidney of old mice aged 23-24 months by four dose of intraperitoneal (i.p.) injection of recombinant GDF11 (0.3 mg/kg/d) 48h before bilateral kidney ischemia-reperfusion injury (IRI), and the control group was given an equal volume of vehicle. Renal function, tubular injury scores, tubule cells dedifferentiation and proliferation were assessed at IRI 72h. Next, TGF-β Pathway Phosphorylation Antibody Array was used to analyze phosphorylation events at specific sites in human primary proximal renal epithelial cells (hPTC) treated by rGDF11 or equal volume of 0.1% BSA. Finally, tubule cells dedifferentiation, proliferation and migration were assessed in HPTCs treated by rGDF11 in the presence or absence of the ERK1/2 inhibitor U0126 (10 uM).

Results: Firstly, GDF11 supplementation in the kidneys of aged mice increased dedifferentiation marker vimentin and Pax2 expression and the percentage of 5-ethynyl-2′-deoxyuridine (EdU) positive proximal tubular epithelial cells. GDF11 improved the renal repair, kidney functional recovery and survival of elderly mice at IRI 72 h. Next, GDF11 upregulated Abl1, c-Myc, ERK1/2, Smad1 and Akt phosphorylation by above 1.5 fold in hPTCs. Finally, the ERK1/2 signaling pathway was activated *in vitro* and *in vivo* after GDF11 treatment, and GDF11 regulated dedifferentiation and proliferation in proximal tubule cell via an ERK1/2-dependent pathway in vitro.

Conclusions: Our study indicated that GDF11 could increase tubule cell dedifferentiation and proliferation and improve tubule regeneration after AKI in old mice though ERK1/2 signaling pathway.

FR-PO247

Mesenchymal Stromal Cell-Elaborated Stromal Cell Derived Factor-1 (CXCL12) Is a Potency Marker, Essential for Their Migration and Renoprotective Efficacy in AKI Anna Gooch,[1] Ping Zhang,[1] Zhuma Hu,[1] Christof Westenfelder.[1,2] *[1]Medicine, U of Utah and VA Medical Centers, SLC, UT; [2]Physiology, U of Utah, SLC, UT.*

Background: We and others showed in preclinical and clinical studies that Mesenchymal Stem Cells (MSCs) are renoprotective when administered within hours of an acute kidney injury (AKI), due largely to (1) MSCs homing to kidneys in response to increased renal expression of SDF-1 and (2) MSC release of protective and reparative cytokines. While renal SDF-1 is upregulated in response to AKI MSCs also express SDF-1. As SDF-1 expression decreases with passaging of MSCs, and as off-the-shelf MSC therapeutic applications rely on cell passaging and banking for dose production, we investigated the role of MSC-expressed SDF-1 in MSC (1) homing and (2) renoprotection.

Methods: 1) The ability of P2 wild type (wt) MSCs vs. MSCs in which SDF-1 was knocked down by siRNA (siMSCs) to migrate toward normal or injured (ATP depleted) Normal Rat Kidney (NRK) cells was assessed in a transwell system. 2) IRI AKI was induced (renal pedicle clamp) in 3 groups of 6 Fischer344 rats. Post reflow, rats were infused i.a. with 2x10e6/kg (a) wt MSCs, (b) siMSCs or (c) vehicle. Renal function, renal and urinary SDF-1 levels and mortality were assessed.

Results: 1) siMSC migration toward ATP depleted NRK cells was significantly decreased vs. wt MSCs. 2) Renal function was protected and improved by wt MSCs, and all animals survived. Vehicle or siMSC administration was ineffective and associated with significant mortality. Parallel to worsened kidney function, renal and urinary SDF-1 levels were significantly higher post AKI in vehicle and siMSC treated rats than in wt MSC-treated rats.

Conclusions: SDF-1 is a known renal cell survival factor and distress signal. Increased renal expression post AKI promotes MSC homing through CXCR4, SDF-1's cognate receptor that is expressed on MSCs. We show here that MSCs' SDF-1 expression is also essential to homing toward injured cells by yet to be elucidated mechanisms, and to their renoprotective, therapeutic efficacy. As SDF-1 expression decreases with MSC passaging, as a potency marker, SDF-1 expression levels must be monitored in MSCs destined for renotherapeutic applications.

Funding: Other U.S. Government Support, VA Support

FR-PO248

Tenascin-C Protects Kidney against Acute Ischemic or Toxic Injury through Augmenting Wnt/β-Catenin Signaling Shuangqin Chen,[1] Lili Zhou,[1] Haiyan Fu,[1] Youhua Liu.[1,2] *[1]Div of Nephrology, Nanfang Hospital, Southern Medical Univ, Guangzhou, Guangdong, China; [2]Dept of Pathology, Univ of Pittsburgh, Pittsburgh, PA.*

Background: Tenascin-C (TNC) is an extracellular matrix glycoprotein and plays an important role in regulating cell survival, proliferation and differentiation. TNC is abundantly expressed during embryonic development and induced in a variety of organ after injury. However, the potential role of TNC and its underlying mechanism in acute kidney injury (AKI) have not been elucidated. In this study, we investigated the potential role and mechanism of TNC in AKI.

Methods: In mouse models of ischemia-reperfusion injury (IRI) and cisplatin nephropathy, renal TNC was knocked down by shRNA-mediated inhibition. Renal function and tubular injury and apoptosis were examined. In cultured tubular epithelial cells (HK-2), cisplatin and staurosporine were used to induce apoptosis, as determined by both FACS and TUNEL. The interaction between TNC and Wnt was also examined by co-transfection of TNC and Wnt1 plasmids.

Results: TNC was upregulated in the interstitial area in AKI following IRI or cisplatin treatment. Knockdown of TNC further deteriorated serum creatinine and blood urea nitrogen, aggravated tubular apoptosis, compared to AKI alone. This effect of TNC inhibition was associated with a reduced β-catenin upregulation, suggesting the relevance TNC to an altered Wnt signaling. In cultured HK-2 cells, recombinant TNC significantly inhibited cisplatin or staurosporine-induced apoptosis, as assessed by FACS and TUNEL, and inhibited caspase-3 activation and Bax and FasL expression. We found that TNC physically interacted with Wnt ligand, as shown by co-immunoprecipitation. Such an interaction augmented Wnt-induced β-catenin activation.

Conclusions: These studies indicate that TNC expression is rapidly upregulated after AKI and this induction of TNC is renal protective. Our data also suggest that the protective effect of TNC is mediated by its regulation of Wnt/β-catenin signaling via physical interaction.

Funding: Government Support - Non-U.S.

FR-PO249

Age-Dependent Tertiary Lymphoid Tissue Formation in the Kidney as a Novel Therapeutic Target Yuki Sato,[1,2] Akiko Mii,[1] Hirosuke Nakata,[1] Shingo Nishiyama,[1] Motoko Yanagita.[1] *[1]Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; [2]Medical Innovation Center TMK Project, Kyoto Univ Graduate School of Medicine, Kyoto, Japan.*

Background: There has been a worldwide increase in the number of patients with end-stage renal disease, predominantly in the elderly population in developed countries. Clinical studies demonstrated that the elderly show a reduced capacity for renal regeneration after acute kidney injury (AKI), yet the precise mechanism remains unclear.

Methods: To evaluate the impact of aging on the prognosis of AKI, we induced 3 different kidney injury models to young and aged mice.

Results: Aged mice developed multiple tertiary lymphoid tissues (TLTs) after AKI, whereas young mice did not. As kidney injury progressed, TLTs expanded and destroyed adjacent nephrons. The size of TLTs correlated well with impaired renal function, increased expression of pro-inflammatory cytokines and homeostatic chemokines, suggesting that TLTs in aged injured kidney are detrimental and contribute to sustained inflammation and maladaptive repair after AKI. Notably, lineage tracing analysis demonstrated that resident fibroblasts diversified into fibroblasts with distinct phenotypes, including p75 neurotrophin receptor expressing fibroblasts, retinoic acid producing fibroblasts and homeostatic chemokine producing fibroblasts. Interventions with anti-CD4 monoclonal antibody as well as dexamethasone abolished TLTs and improved renal outcomes. TLTs were also observed in aged human kidneys, whose cellular and molecular components were similar to those of mouse TLTs.

Conclusions: TLTs represent a novel therapeutic target of AKI in the elderly.

Funding: Pharmaceutical Company Support - Mitsubishi Tanabe Pharma Corporation, Government Support - Non-U.S.

FR-PO250

Kidney Damage Triggers a PGC1α-to-c-MYC Warburg Shift Perpetuating the Activation of Fibrogenic Progenitor Cells Dario R. Lemos,[1] Gamze Karaca,[1] Ivan G. Gomez,[1] Graham Marsh,[1] Bryce Gordon Johnson,[1] Benjamin D. Humphreys,[2] Jeremy Stuart Duffield.[1] *[1]Biogen, Cambridge, MA; [2]Div of Nephrology, Washington Univ, St. Louis, MO.*

Background: CKD is characterized by fibrosis & inflammation, two major factors impairing tissue regeneration. This inflammatory milieu is deleterious to epithelial cells. In the same environment, however, mesenchymal progenitor cells proliferate and differentiate into myofibroblasts, suggesting inflammatory signals have a positive impact on fibroblast metabolism.

Results: Whole genome analysis of kidney from patients with CKD & fibrosis revealed a unique metabolic signature characterized by reduced expression of genes involved in oxidative phosphorylation (Ox Phos), mitochondrial (mito) activity, and elevated glycolysis and autophagy. Using the kidney ischemia reperfusion model, we found a similar metabolic shift within 72hs after damage. The injured kidney displays increased autophagy, reduced levels of the autophagy cargo protein P62/SQSTM1, loss of the mito biogenesis regulator PGC1a, and the concomitant upregulation of the glycolysis master regulator c-MYC and downstream targets. Nuclear localization of c-MYC in interstitial fibrogenic cells, indicated c-MYC is active 72hs after damage. *S*timulation of PDGFRb+ fibrogenic progenitors from human and mouse kidneys *in vitro* with IL1b, TNFa and LPS, induced autophagy, loss of P62, reduced mTOR signaling, and triggered the PGC1a-to-c-MYC switch. This transcriptional shift resulted in a metabolic phenotype characterized by lower Ox. Phos. capacity and increased aerobic glycolysis. The latter driven by c-MYC as indicated by the inhibitory effect of JQ1 or 10058-F4, two previously characterized c-MYC inhibitors. Similar to observations in cancer cells, the inflammatory signals induce proliferation of PDGFRb+ progenitor cells in a c-MYC-dependent manner. Direct interaction with P62 regulates c-MYC levels in human PDGFRb+ progenitors.

Conclusions: We have identified a novel molecular mechanism driving the activation of mesenchymal fibrogenic progenitors in response to damage. The mechanism relies on a metabolic switch that resembles the Reverse Warburg effect observed in cancer associated fibroblasts.

Funding: Pharmaceutical Company Support - Biogen

FR-PO251

Myeloid Cell Heme Oxygenase-1 Expression Regulates the AKI to CKD Transition Jeremie M. Lever,[1] Ravindra Boddu,[1] Oreoluwa O. Adedoyin,[1] James George,[2] Anupam Agarwal.[1,3] [1]*Div of Nephrology, Dept of Medicine, Univ of Alabama at Birmingham, Birmingham, AL;* [2]*Div of Cardiothoracic Surgery, Dept of Surgery, Univ of Alabama at Birmingham, Birmingham, AL;* [3]*Birmingham VA Medical Center, Birmingham, AL.*

Background: Acute kidney injury (AKI) is a major public health concern, accounting for up to 3% of hospitalized patients. Those who experience AKI requiring dialysis are at a 28-fold increased risk of chronic kidney disease (CKD). Heme oxygenase-1 (HO-1) is an inducible, ubiquitous, cytoprotective enzyme that catabolizes heme. Its induction is protective in animal models of AKI. We have demonstrated that myeloid cell HO-1 mitigates damage following renal ischemia-reperfusion injury (IRI) in the acute setting.

Methods: For this study, we modeled the AKI to CKD transition in mice using unilateral IRI, leaving the contralateral kidney intact, and followed the animals for 3 weeks. Given the importance of macrophages (MΦs) in regulating kidney damage after AKI, we *hypothesized* that HO-1 deficiency in myeloid cells would lead to worse outcomes in this model. We used cre-lox mice in which HO-1 is deleted in myeloid cell populations (LysM-HO-$1^{-/-}$).

Results: Surprisingly, we found LysM-HO-$1^{-/-}$ mice exhibited less proteinuria and renal fibrosis, when compared with floxed control mice (LysM-HO-$1^{+/+}$) (urinary ACR: 0.131 ± 0.02 and 0.188 ± 0.02 in LysM-HO-$1^{-/-}$ and LysM-HO-$1^{+/+}$, respectively, $p = 0.04$). In addition, greater absolute numbers of bone marrow-derived MΦs ($F4/80^{low}CD11b^{hi}$, $7.22x10^6 \pm 6x10^5$ vs $4.90x10^6 \pm 6x10^5$, $p = 0.03$) and NK cells ($NK1.1^+$, $4.51x10^6 \pm 6x10^5$ vs $2.44x10^6 \pm 5x10^5$, $p = 0.02$) were observed in injured kidneys from LysM-HO-$1^{-/-}$ mice, indicating these cell types may play a protective role in this model. Further, myeloid cell HO-1 deficiency resulted in a trend toward lower proportions of pro-fibrotic tissue-resident MΦs ($F4/80^{hi}CD11b^{low}$, 12.14 ± 1.3% versus 16.56 ± 1.6%, $p = 0.07$).

Conclusions: These studies demonstrate that HO-1 expression in myeloid cells regulates progression in the AKI to CKD model, having potential implications for developing cell-based therapy or strategies involving modulation of HO-1 expression in the AKI to CKD transition.

Funding: NIDDK Support, Other NIH Support - NIGMS Medical Scientist Training Program

FR-PO252

Proximal Tubule-Specific Heme Oxygenase-1 Modulates the Progression of AKI to CKD Laurence Marie Black,[1] James George,[2] Anupam Agarwal,[1,3] Subhashini Bolisetty.[1] [1]*Nephrology Research and Training Center, Div of Nephrology, Dept of Medicine, Univ of Alabama at Birmingham, Birmingham, AL;* [2]*Dept of Surgery, Univ of Alabama at Birmingham, Birmingham, AL;* [3]*Birmingham VA Medical Center, Birmingham, AL.*

Background: Acute Kidney Injury (AKI) is associated with high morbidity and mortality, and can to lead to chronic kidney disease (CKD), though the mechanism(s) are unclear. AKI is ameliorated by the induction of heme oxygenase-1 (HO-1), a cytoprotective enzyme that catalyzes the breakdown of pro-oxidant heme, into pro-survival by-products. Such induction of HO-1 occurs predominately in renal proximal tubules (PT), which are important for fluid, nutrient, and electrolyte homeostasis and thus consume significant energy.

Methods: To evaluate the role of PT-specific HO-1 in the transition from AKI to CKD, we used transgenic mice, generated using the cre-lox system, to manipulate HO-1 expression specifically in the PT. We examined the progression to CKD using unilateral kidney ischemic injury (30 minutes) followed by reperfusion and leaving the contralateral kidney intact.

Results: We demonstrate that selective PT-specific HO-1 deletion lessens the severity of fibrotic remodeling in the injured kidney, as evident by decreased expression of fibronectin, α-smooth muscle actin, and reduced collagen deposition. PT deletion of HO-1 also led to significantly reduced expression of inflammatory markers, such as TNF-α, in the injured kidneys compared to wild-type littermates. Interestingly, HO-1 led to decreased levels of urinary neutrophil gelatinase-associated lipocalin (NGAL), a biomarker of AKI, at 24h post-injury and reduced NGAL gene expression in the injured kidneys at day 21.

Conclusions: These results suggest a role of PT-specific HO-1 in modulating fibrotic remodeling post-ischemic injury and may provide insight into the generation of therapies for preventing progression from AKI to CKD.

Funding: NIDDK Support, VA Support

FR-PO253

Inhibition of TGF-β Activation by an RGD Small Molecule Alpha V Integrin Inhibitor Reduces Fibrosis in a Mouse Model of Nephrotoxic Injury Jeannine M. Basta,[1] Lynn R. Robbins,[1] David W. Griggs,[1] Michael I. Rauchman.[1,2] [1]*St. Louis Univ, St. Louis, MO;* [2]*St. Louis VA Medical Center, St. Louis, MO.*

Background: Targeting TGF-β activity is an attractive strategy for anti-fibrotic therapy. However, clinical trials have shown that global targeting of TGF-β signaling has serious adverse effects. A more promising approach is to disrupt TGF-β activation specifically in the injured tissue. TGF-β is held in an inactive state by binding of the Latency Associated Peptide (LAP) in the extracellular matrix (ECM). Binding of alpha v integrins to the arginine-glycine-aspartic acid (RGD) LAP motif is a major mechanism that releases biologically active TGF-β. Inhibition of integrin binding to the RGD motif prevents TGF-β activation.

Methods: CWHM-12 is novel highly potent peptidomimetic that inhibits all RGD integrins. CWHM-12 potently blocked TGF-β activation by LTC-14 myofibroblasts with a mean IC_{50} value of 1.5 nM (SD = 0.78; n=4). To determine if inhibition of RGD integrins could prevent kidney fibrosis, we tested CWHM-12 in mice exposed to the nephrotoxin Aristolochic Acid-I (AA). Active drug was infused by osmotic mini-pumps at a rate of 100 mg/kg body weight per day. Kidney injury was induced by a single intra-peritoneal injection of AA (5 mg/kg body weight) 1 day after drug infusion.

Results: 28 days after injury, serum creatinine was significantly less (0.15 vs. 0.32 mg/dl, P=0.011) in animals treated with CWHM-12 compared with vehicle, indicating partial recovery of renal function. CWHM-12 significantly attenuated the up-regulation of *Col1a1* mRNA (32 vs 7-fold), a major component of ECM deposition in injured kidneys; this was confirmed by Sirius red staining. Smooth muscle actin staining revealed a significant decrease (26% area) in drug treated kidneys versus vehicle (n=3, P <0.001). RNA-seq analysis revealed a significant decrease in many profibrotic (*Col3a1*, *Mmp2*, *Fn1*, *Ctgf*) and activated myofibroblast genes (*Rgs16*, *Crlf1*, *Gli1*, *Pdgrfb*) in injured kidneys treated with CWHM-12.

Conclusions: Inhibition of RGD integrins is a promising novel therapeutic approach to slow progressive CKD by limiting fibrosis.

FR-PO254

Umbilical Cord-Derived Cells Protect against Maladaptive Repair in Renal Ischemia/Reperfusion Injury Camila Eleuterio Rodrigues, Jose Manuel Condor Capcha, Ana C. de Bragança, Talita R. Sanches, Priscila Queiroz Gouveia, Denise M. Malheiros, Patricia Ferreira Oliveira, Mirela Santinho, Rildo A. Volpini, Irene L. Noronha, Lucia Andrade. *Univ of Sao Paulo, Brazil.*

Background: Human umbilical cord-derived mesenchymal stromal cells (huMSCs) are a treatment option in ischemia/reperfusion injury (IRI)-induced AKI, but their role in slowing progression to CKD is unclear.

Methods: Male rats were induced to renal IRI, i.p. injected 6h later with saline or 1×10^6 huMSCs and euthanatized on day 2 (D2), D7 or D49. We evaluated plasma and urinary parameters. In kidney tissue, we performed western blotting (AQP2, βgal, p21, p16, TGFβ, klotho and heme oxygenase-1), immunohistochemistry (for macrophage) and qPCR (for miRNA expression). Data are mean±SEM.

Results: On D2, renal filtration and tubular function were better in treated rats. Recovery was similar on D7, but treated rats showed less dysfunction on D49.

Parameter	Control	IRI2	IRI+ huMSC2	IRI7	IRI+ huMSC7	IRI49	IRI+ huMSC49
Urea, mg/dl	52 ±2.5	234 ±36.3[a,b]	108 ±19.6	59.8 ±14.8	43.7 ±4.5	65 ±26.7[a,d]	52 ±5.0
Creat, mg/dl	0.3 ±0.02	2.4 ±0.4[a,b]	0.9 ±0.17	0.7 ±0.20	0.5 ±0.2	0.9 ±0.26[a,d]	0.6 ±0.03[a]
Cl Creat, ml/min/100g BW	0.59 ±0.04	0.10 ±0.02[a,b]	0.23 ±0.05[a]	0.25 ±0.06[a]	0.22 ±0.03[a]	0.29 ±0.08[a]	0.42 ±0.1
FENa, %	0.10 ±0.01	3.27 ±1.10[a,b]	0.48 ±0.09	0.38 ±0.13[a,c]	0.14 ±0.02	0.07 ±0.03[a,d]	0.03 ±0.01
Urinary flow, ml/min/100g BW	0.002 ±0.0004	0.005 ±0.0006[a]	0.006 ±0.0007[a]	0.004 ±0.0009[a,c]	0.002 ±0.0003	0.002 ±0.0009	0.005 ±0.0013

[a]p<0.05 vs. control; [b]p<0.05 vs. IRI+huMSC2; [c]p<0.05 vs. IRI+huMSC7; [d]p<0.05 vs. IRI+huMSC49

Urinary osmolality was higher in treated rats (D2: 450±23 vs. 354±24 mOsm/kg; D49: 513±39 vs. 480±61 mOsm/kg, p<0.05), as was AQP2 expression (D2: 112.0±5.6 vs. 61.9±7.2%; D49: 122.8±3.3 vs. 100.0±7.7%, p<0.05). On D2, treated kidneys showed less macrophage infiltration; lower levels of βgal, p21, p16, TGFβ, miR-29a and miR-34a; and higher heme oxygenase-1 and Klotho protein expression. On D49, treated rats showed higher renal Klotho expression, less βgal expression, and less histological damage.

Conclusions: Treatment with huMSCs might slow progression from AKI to CKD. (Supported by FAPESP).

Funding: Government Support - Non-U.S.

FR-PO255

Tenascin-C Expressing Stromal Cell Is a Potential Niche for the Injury Repairing of the Kidney following Ischemia-Reperfusion Injury Qionghong Xie, Min Zhang, Xiaoyi Mao, Da Shang, Chuanming Hao. *Div of Nephrology, Huashan Hospital, Shanghai, China.*

Background: Tenascin-C (TNC), a non-structural extracellular matrix glycoprotein, is involved in creating a specific microenvironment for cell survival, proliferation and migration. The study examined the role of tenascin-C in ischemic reperfusion (IR) induced acute kidney injury (AKI).

Methods: A TNC promoter driven inducible CreER2 knock-in mouse line with an EGFP was generated and IR was used as an AKI model. Homozygous $TNCCreER^{+/+}$ ($TNC^{-/-}$) was used to examine the role of TNC in AKI. The cellular distribution of TNC in the kidney was determined using immunofluorensce and TNC reporter transgenic mice. The double-transgenic TNC-$CreER2^{+/-}$Rosa-$tdTomato^{+/-}$ mice were used for cell lineage chasing.

Results: TNC is normally expressed in renal medullar interstitial cells (RMIC) and markedly induced in the whole kidney, especially in the outer medulla and the cortex

adjacent to medulla after IR. Increased TNC was also observed in biopsy tissues from AKI patients. Deletion of TNC significantly aggravated IR induced AKI (BUN 113 vs 11.2mmol/L at day 2) and reduced survival (5/10 vs 10/10 by 7 days following IRI). To determine the nature of TNC expressing cells, we co-stained TNC reporter eGFP with kidney cell markers and found that the TNC expressing cells were restricted in the interstitium. They did not express CD68 and F4/80, nor CD44(+), CD34(+) and FSP1(+). Some of the TNC expressing cells (40%) expressed αSMA. Cell linage-chasing experiment suggested that the TNC expressing cells in the injured area were not originated from medullary cells that normally express TNC, and TNC was induced in certain stromal cells following IR. Hypoxic response element is identified in the promoter region of TNC and a HIF stabilizer markedly induced renal TNC expression in mice and in cultured primary interstitial cells. Cell cultured studies showed that exogenous TNC induced activation of STAT3. The activation of STAT3 was also found lower in $TNC^{-/-}$ than WT mice following IR, consistence with a STAT3 signaling mechanism involved in the protective effect of TNC.

Conclusions: Matrix protein TNC alleviates IR-induced AKI by interacting with epithelial cells through STAT3 pathway.

FR-PO256

NecroX-7, Necroptosis Inhibitor, Attenuates Cisplatin Nephropathy

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Background: Reactive oxygen species (ROS) generation and necrosis play a important role in cisplatin nephrotoxicity. There have been developed NecroX series that can attenuate necroptosis pathway. Especially, NecroX-7 showed anti-necroptotic and anti-oxidative feature. We investigated the effect of NecroX-7 on cisplatin nephrotoxicity in mice.

Methods: C57BL/6 mice were divided into 4 groups; normal control group (n=7), NecroX-7 treated control group (n=7), vehicle with cisplatin (20mg/kg, intraperitoneal injection) treated group (n=9), and NecroX-7 (2mg/kg, intraperitoneal injection) with cisplatin treated group (n=9). We measured BUN and serum creatinine. Also we examined histologic findings (H&E and PAS stain). We examined molecular study for oxidative stress and necroptosis.

Results: The levels of BUN and serum creatinine in NecroX-7 with cisplatin treated mice were significantly lower than that of vehicle with cisplatin treated mice(p <0.05). In microscopy, NecroX-7 significantly reduced renal tubular epithelial cell necrosis and detachment in cisplatin treated mice kidney. NecroX-7 significantly reduced RIP1, RIP3, MLKL, and PARP in cisplatin treated mice kidney. Also it reduced p22phox expression and 8-OH deoxyguanosine positive cells in cisplatin treated mice kidney. It elevated UCP2 expression in cisplatin treated mice kidney.

Conclusions: NecroX-7 attenuates oxidative and necroptotic renal injury in cisplatin induced nephrotoxicity.

FR-PO257

Par1b Deficiency Leads to Polarity Defects in Acute Kidney Injury

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Background: Partitioning defective (Par)1 is a serine threonine kinase member of Par polarity protein family, first found to be important in establishing embryonic polarity in C.elegans. Par1a and Par1b are functionally redundant mammalian homologues that are highly expressed basolaterally in the developing kidney and regulate cell adhesion and polarity. Mice with 1 of 4 copies of *Par1a* or *1b* die after birth and have hypoplastic kidneys with abnormal proximal tubular cell-cell adhesion. Increased expression of Par1a and Par1b is noted in acute kidney injury in mice and humans. Apico-basal polarity and adhesion defects are hallmarks of acute kidney injury which lead to transport defects and back-leak of toxins. We hypothesize that Par1 proteins play an important role in acute kidney injury recovery by regulating polarity and adhesion.

Methods: To test the effect of Par1a and 1b deletion on development of renal tubular injury, cisplatin was injected in *Par1a* and *1b* knockout mice. Controls were cisplatin injected wild-type (WT) and un-injected WT and knockout mice.

Results: Using immunofluorescence and western-blot, we identified increased baso-lateral Par1a/1b expression following cisplatin injury. Periodic Acid Schiff staining demonstrated increased number of dilated tubules and protein casts in cisplatin treated *Par1a* and *1b*-/- vs WT, with most severe injury in *Par1b*-/- mice. Quantification of TUNEL positive nuclei indicated a three-fold greater increase in apoptotic nuclei in *Par1b*-/- vs. WT mice following cisplatin injury (p<0.05). Severe mis-localization of basolateral adhesion molecules, E-cadherin, N-cadherin and β-Catenin, and luminal transporters Aquaporin-1 and Megalin was observed in cisplatin injected *Par1b* knockout mice that was not present in controls.

Conclusions: Mice with loss of *Par1a* or *1b* exhibited more severe tubular injury following cisplatin injection in mice. This was associated with severe mis-localization of cell-cell adhesion proteins and increased apoptosis. This experimental model suggests that Par1b in contributes to cellular polarity and renal regeneration in the setting of acute kidney injury.

Funding: NIDDK Support, Other NIH Support - NIH RO3 DK105242, Clinical Revenue Support

FR-PO258

Persistent Kidney Injury Molecule-1 (Kim-1) Expression Promotes AKI to CKD Transition after Severe Renal Ischemia-Reperfusion Injury (IRI)

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Background: Maladaptive repair after acute kidney injury (AKI) driven by renal tubular epithelial cell (TEC) secretion of profibrotic factors results in tubulointerstitial fibrosis and chronic kidney disease (CKD). Kim-1 is a phosphatidylserine receptor upregulated on proximal TECs during AKI. We showed Kim-1 mediates phagocytic clearance of apoptotic and necrotic cells and protects against renal damage acutely after bilateral renal IRI. However, transgenic overexpression of Kim-1 in TECs promotes spontaneous kidney fibrosis. We thus investigated whether Kim-1 can promote AKI to CKD transition.

Methods: We subjected Kim-1 deficient (KO) and wild-type (WT) mice to unilateralrenal pedicle clamping for 35 min (moderate) or 45 min (severe) (n=3-5/group/experiment). Mice were euthanized at 3 and 28 days. Renal damage and fibrosis were assessed by a pathologist blinded to mouse genotype using standard scales. Quantitative RT-PCR was used to detects expression of profibrotic factors (Collagen-1&4) and inflammatory cytokines (MCP-1, IL-1β, IL-6, TNF-α) and Kim-1.

Results: As expected, KO mice exhibited worse renal injury (median injury score 4/5 vs. 3/5, p<0.05) and greater MCP-1, IL-1β and IL-6 mRNA expression (p<0.05 for each) than WT mice 3 days after moderate UIRI. Surprisingly, these differences were not present 3 days after severe UIRI. At 28 days, renal fibrosis, profibrotic factors, and inflammatory cytokines were not different between KO and WT mice after moderate UIRI, but after severe UIRI KO mice had less renal fibrosis (3.5/5 vs. 5/5, p=0.016), less collagen-1&4, IL-1β and TNF-α expression (p<0.05 for each). Significantly higher renal Kim-1 expression was observed at 28 days after severe compared to moderate UIRI (p<0.05).

Conclusions: Our data suggest that KIM-1's protective role during the acute phase of AKI can be overwhelmed if the injury is severe, and that persistent KIM-1 expression after severe injury can promote long-term renal fibrosis. These results have implications when considering potential therapeutic options that target Kim-1 during AKI.

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FR-PO259

Sustained Increased microRNA-21 Drives Aristolochic Acid Induced AKI to CKD Progression

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Background: To investigate the role of microRNA-21(miR-21) in the development of renal tubulointerstitial fibrosis secondary to aristolochic acid induced acute kidney injury.

Methods: C57BL/6J male mice were intraperitoneally injected witharistolochic acid at a dose of 10 mg/kg. Blood samples and kidneys were harvested at day1, 3, 7, 14, 28 after aritolochic acid treatment. Locked nucleic acid-modified anti-miR-21 oligonucleotides (10mg/kg) were administered intravenously to mice via the tail vein less than 30mins prior to aristolochic acid exposure, and the dose was repeated at day5 and day10.

Results: Renal tubulointerstitial fibrosis developed at 14 days after aristolochic acid treatment. The abundance of miR-21 increased at day 7 after aristolochic acid dosing, peaked at day14 and thereafter maintained at a high level. Protein expression of α-SMA, vimentin and collagen I were significantly up-regulated at day 7 and peaked at day 28 (P < 0.01), while protein abundance of E-Cadherin decreased at day 14 and thereafter (P<0.01). Anti-miR-21 treatment relieved renal injury with reduced serum creatinine (P<0.05) and attenuation of renal tubulointerstitial fibrosis. Besides, the protein expression of PTEN, a target of miR-21, was up-regualted and the ratio of its downstream genes p-AKT/AKT was decreased after anit-miR21 treatment (P <0.05).

Conclusions: Sustained increased abundance of miR-21 was imperative for the development of chronic kidney disease secondary to aristolochic acid induced acute kidney injury. Renal tubulointerstitial fibrosis could be partially reversed by inhibiting miR-21 via PTEN/ p-AKT pathway.

FR-PO260

Animal Models for Progression from Acute to Chronic Kidney Injury in Mice

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Background: Recently, epidemiologic studies have suggested that acute kidney injury (AKI) is one of the important precipitating factors in the progression of chronic kidney disease (CKD). However, mechanism of CKD progression after AKI has not been investigated sufficiently. Animal model that mimics clinical features of AKI-to-CKD is necessary.

Methods: We developed two mouse AKI-to-CKD models by combining renal ischemia reperfusion and nephrectomy; unilateral ischemia-reperfusion injury with contralateral nephrectomy (UIR+UNx) and without contralateral nephrectomy (UIR), and evaluated their differences of post-ischemia injury and drug responses.

Results: Serum creatinine and BUN was elevated in the UIR+UNx group, but the UIR group showed no increase. Quantitative analysis revealed that interstitial fibrosis in the kidney of the UIR+UNx group was significantly milder than that of the UIR group.

Glomerular abonormalities including sclerosis were not found in the both groups. Orally administration of telmisartan, an angiotensin II receptor blocker, improved interstitial fibrosis not in the UIR+UNx group, but in the UIR group. In addition, telmisartan administration inhibited mRNA expression of profibrotic factors (αSMA, TGF-β1, and Galectin-3) only in the UIR group. After induction of anemia by hemolysis with phenylhydrazine administration, serum erythropoietin concentration was significantly higher in the UIR group than in the UIR+UNx group, but renal EPO-mRNA expression in the ischemic kidney is higher in UIR+UNx group than in UIR group.

Conclusions: We found the differences in post-ischemic fibrosis, an anti-fibrotic effect of telmisartan, and erythropoietin producing ability in response to anemia between the two AKI-to-CKD models. These differences will suggest that careful interpretation is necessary for animal experiments that evaluate AKI to CKD progression.

FR-PO261

Human Mesenchymal Stromal Cells Derived Extracellular Vesicles Alleviate Renal Ischemic Reperfusion Injury and Enhance Angiogenesis in Rats Xiangyu Zou, Di Gu, Yingjian Zhu. *Dept of Urology, Shanghai XinHua Hospital Affiliated to Shanghai Jiaotong Univ, School of Medicine, Shanghai, China.*

Background: Mesenchymal stromal cells (MSCs) derived extracellular vesicles (EVs) were regarded as a potent medium for kidney injury repair and angiogenesis plays an important role in tissue repair. However, MSC-EVs' pro-angiogenesis effect in ischemia-reperfusion induced kidney injury and its potential mechanisms has yet to be determined.

Methods: EVs were isolated from the conditioned medium of human Wharton-Jelly mesenchymal stromal cells (hWJMSCs) (treated with RNase or not) were injected in rats intravenously after unilateral kidney ischemia. Animals were sacrificed at 24h and 2 weeks after injury respectively. Next, we examined the renal functions and histology to assess the therapeutic effect of the EVs. Moreover, we investigated the pro-angiogenesis effects and the probable mechanisms.

Results: It was observed that human MSC-EVs could reduce cell apoptosis and enhances cell proliferation 24h after kidney injury, meanwhile renal function was improved and histological lesion was mitigated. Moreover, at this time point we found VEGF was up-regulated in EVs group and HIF-1α was down-regulated. Further, the capillary vessel density was increased in EVs group after 2 weeks and the renal fibrosis was reduced as well. In vitro, EVs could both deliver human VEGF directly to renal tubular epithelial cells (TECs) and induced rats VEGF synthesis in TECs under hypoxic conditions. Most important, all the beneficial effects of MSC-EVs were abrogated by RNase treated except for the delivery of human VEGF.

Conclusions: MSC-EVs could protect against IRI kidney injury through pro-angiogenesis effects, and both the delivery of pro-angiogenesis related proteins and RNAs involve in this process.This provides the direction for future clinical applications.

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FR-PO262

FTY720 Reduced Acute Kidney Injury in a Sepsis Rat Model via Sphk1 Pathway Jun Yan Fang,[1] Lei Zhang,[2] Xin Li,[1] Feng Ding.[1] *[1]Dept of Nephrology, The 9th People's Hospital of Shanghai The Medicine College of Shanghai JiaoTong Univ, Shangha, China; [2]Dept of Nephrology, Shanghai Jiaotong Univ Affiliated First People's Hospital Baoshan Branch, Shangha, China.*

Background: Sphingosine kinase-1(Sphk-1), an enzyme which is active in neutrophils and macrophages, regulates proinflammatory responses that are important in endotoxemia and sepsis. Recent study shows that Sphk-1 and its product sphingosine-1-phosphate(S1P) promote inflammation via TNF-αsignalling and the canonical NF-κB activation pathway. FTY 720, a S1P analog, is a FDA approved sphingosine-1 phosphate (S1P) receptor agonist. Recent evidences demonstrate that FTY720 offers therapeutic potential against lung injuries in murine sepsis models. We therefore hypothesized that treatment with FTY720, could ameliorate the acute renal injury induced by sepsis through Sphk-1 pathway.

Methods: Male rats (250-300g, 2 months, n=5 for each group) underwent standardized procedures of cecal ligation and puncture (CLP) to induce sepsis. The rats were treated with 4mg/kg/day FTY720 or vehicle right after surgery by gavage for 5 days.

Results: CLP rats exhibited increased Sphk-1, S1P and TNF-a level accompanied by acute tubular cell injury. Five days FTY720 treatment improved the survival rate by 50% (80% vs 40%) and the acute tubular injury score by 53.2%(1.800±0.1144 vs 3.85±0.1163), and reduced BUN and serum creatinine levels by 23.0%(9.520 ±1.443mmol/L vs 12.37±4.139mmol/L)and 20.2%(137.5±12.50umol/L vs 172.3±17.48 umol/L)respectively in CLP rats compared with CLP rats treated with vehicle. Moreover, FTY720 inhibited Sphk-1 expression in CLP rats kidney and decreased S1P concentration of kidney by 40.6% (939.6±52.03 vs 1583.0±161.7 nmol/L) compared with CLP rats treated with vehicle. Furthermore, TNF-α levels in CLP rats kidneys was reduced by 24.8%(325.4±25.86 ng/L vs 432.7±19.03ng/L) by FTY720 treatment.

Conclusions: FTY720 reduced the mortality and prevented renal functional decline in CLP rats via down-regulation of the Sphk-1 pathway and amelioration of inflammation.

FR-PO263

Endothelial Colony Forming Cells (ECFCs) in Murine AKI: Implications for Future Cell-Based Therapies Daniel Patschan, Susann Patschan, Gerhard A. Mueller. *Clinic of Nephrology and Rheumatology, Univ Hospital of Göttingen, Göttingen, Niedersachsen, Germany.*

Background: Early Endothelial Progenitor Cells (eEPCs) have been proven as effective tool in murine ischemic AKI and in diabetic nephropathy. Only few data in contrast have been published about the role of so-called Endothelial Colony Forming Cells (ECFCs - late EPCs) in ischemic AKI. We thus aimed to investigate ECFC effects on postischemic kidney function and structure over several weeks. Our special interest focused on endothelial-to-mesenchymal transition (EndoMT), peritubular capillary density (PTCD), endothelial alpha-Tubulin (aT - cytoskeletal integrity), and endothelial p62 (marker of autophagocytic flux).

Methods: 8-12 weeks old male C57/Bl6N mice were subjected to bilateral renal pedicle clamping for 35 and 45 minutes, respectively. Donor-derived syngeneic ECFCs (0.5×1.000.000) were i.v. injected at the end of ischemia. Animals were analyzed 1, 4, and 6 weeks later.

Results: Cell therapy improved kidney function exclusively at week 1 (35 and 45 min). Ischemia-induced fibrosis was diminished in all experimental groups by ECFCs, while PTCD loss remained unaffected. Significant EndoMT was detected in only two of 6 groups (35 min, week 4 and 45 min, week 6), ECFCs reduced EndoMT only in the latter. Endothelial aT declined under almost all experimental conditions and these effects were further aggravated by ECFCs. p62 was elevated in endothelial cells, more so after 45 than after 35 minutes of ischemia. Cell therapy did not modulate p62 abundances at any timepoint.

Conclusions: ECFCs act AKI-protective in the mid- to long-term. There are certain differences in renal outcome parameters between eEPCs and ECFC. The latter do not prevent animals from peri-tubular capillary loss and they also do not further elevate endothelial p62. We conclude that differences between eEPCs and ECFCs result from certain mechanisms by which the cells act around and within vessels. Overall, ECFC treatment was not as efficient in preventing mice from ischemic mid- to long-term damage as eEPC therapy.

FR-PO264

The Role of C1q in Apoptotic Cells Phagocytosis In Vitro and Obstructive/ Ischemic Renal Injury In Vivo Eoin D. O Sullivan, Jeremy Hughes, David A. Ferenbach. *MRC Centre for Inflammation Research, Univ of Edinburgh, Edinburgh, United Kingdom.*

Background: C1q initiates classical complement activation and is implicated in glomerular disease pathology. C1q binds to antibodies/surface proteins, activates C3 binding, mediates apoptotic cell (AC) clearance and modulates macrophage phenotype. Recent studies demonstrate that C1q levels increase in aging rodents and man, and via intracellular Wnt signaling inhibits skeletal muscle regeneration in aged mice. We tested the hypothesis that increased C1q may augment fibrosis and worsen AKI/inflammation via complement-mediated injury.

Methods: Serum was obtained and used for *in vitro* studies of primary murine bone marrow derived macrophage (BMDM) phagocytosis. C57Bl6 and C1q KO animals underwent unilateral ureteric obstruction and ischaemia-reperfusion injury.

Results: *In vitro*, serum from aged mice had higher C1q levels (170.5±7.5 vs 92.7±14.8ug/mL; p<0.05 O vs Y), and augmented AC phagocytosis by BMDM (%phago 45.1±0.9 vs 27.8±1.8; p<0.05 O vs Y). AC treated with C1q depleted serum showed absent C3 labelling, which was fully restored by addition of recombinant C1q. BMDM phagocytosis of ACs was assessed with C1q replete and C1q depleted human serum. Compared to serum free the addition of C1q alone had little effect on phagocytosis (%phago 31.8±1.3 vs 34.0±1.1), the addition of human serum augmented phagocytosis (%phago 56.6±2.1 p<0.01 vs serum free), with C1q depleted serum ineffective (%phago 29.3±0.8 p<0.01 vs normal serum). The addition of C1q to C1q deplete serum augmented phagocytosis (%phago 51.6±2.1) demonstrating that serum is essential for propagation of the C1q phagocytosis signal. *In vivo*, baseline renal collagen expression in C1qKO and wild-type mice was comparable. C1qKO animals showed no protected phenotype (equal creatinine and ATN) after acute IRI and worse fibrosis after d7 unilateral ureteric obstruction (%collagen deposition 14.2±2.1 vs 8.5±1.3; C1qKO vs WT, p=0.04).

Conclusions: We found no improvement in injury levels in C1qKO mice with worsened scarring after UUO *in vivo.* I*n vitro* experiments showed major defects in AC clearance in the absence of C1q. Inadequate labeling and uptake of ACs may lead to increased tissue injury and fibrosis.

Funding: Private Foundation Support

FR-PO265

Ischemic Rat Kidneys: Alive, Dead or in Suspended Animation? Jesus H. Dominguez,[1,2] James M. Dominguez,[2] Katherine J. Kelly.[2] *[1]Medicine, VAMC, Indianapolis, IN; [2]Medicine, IUMC, Indianapolis, IN.*

Background: Severe acute kidney injury (AKI) from ischemia/reperfusion (IR) destroys nephrons. There is no cure, and recovery is uncertain.

Methods: Rats with 50 min of bilateral renal IR were treated with intravenous renal exosomes (exo) from normoxic (Norexo) or ischemic preconditioned (IPCexo) renal cells, 24 and 48 hrs post IR.

Results: ICAM1 protein ratio (n = 5) on IPCexo/Norexo was 1.85 fold (p = 0.002). IPCexo fused with renal cells. There were 312 mRNAs in exos, and 25 differentially expressed, with mRNA in IPCexo higher for Drd4 (78 fold), TMEM80 (10 fold) Ptdss2 (8 fold) among others. There were 4 rat groups, Sham, untreated IR (IRUn), IR given Norexo, and IR given IPCexo (n = 5). Renal function was negligible 24 hrs post-IR, and it

recovered in IRIPCexo by 24 hrs, but not in IRUn. Rats were terminated 6 days post IR and renal phenotypes and RNAseq genotypes obtained. Kidneys from IRUn group had severe lipid peroxidation, inflammation, fibrosis, proliferation, and loss of microvasculature, but IRIPCexo group did not, $p < 0.05$ for all. Genotypes included 12,159 genes in each group, and were compared with each other. MDS plots of log-fold changes for each transcriptome pair showed the largest separation between Sham and IRUn (3141 altered genes), a midrange between Sham and IRNorexo (1599 altered genes), and near overlap between Sham and IRIPCexo (71 altered genes), $p < 0.05$ for all. Gene pathways activated in IRUn, but not in IRIPCexo, included metabolic, proliferation, DNA replication, cell cycle, phagosome, protein digestion apoptosis, and ECM receptor interaction, $p < 10^{-7}$ for all.

Conclusions: Severe renal IRUn is followed by cell death, with deranged phenotypes and genotypes. However, IR non-functional kidneys do not change immediately from life to death, but transition to SA, with full potential to recover within a 24 hrs window. IPCexo promote near full recovery of SA kidneys, assuring integrity and function. IPCexo genetic cargo contains recovery mRNAs in the form of enzymes, receptors, or structural proteins.

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FR-PO266

Early Inhibition of p53 Leads to Renoprotection and Attenuation of Senescence Arpita Baisantry,[1,2] Birgit Berkenkamp,[1] Raj Bhayadia,[1] Inga Soerensen-Zender,[2] Hermann G. Haller,[2] Anette Melk,[1] Roland Schmitt.[2] *[1]Kidney, Liver and Metabolic Diseases, Children's Hospital, Hannover Medical School (MHH), Hannover, Germany; [2]Nephrology, MHH, Hannover, Germany.*

Background: Early inhibition of p53 has been reported to be renoprotective during acute kidney injury (AKI). These positive effects were mainly attributed to a reduction in apoptosis. Since p53 through its main transactivational target p21 is also involved in the development of senescence, we aimed to investigate the short- and long-term effects of p53 targeting siRNA in a mouse model of renal ischemia reperfusion (IR) injury.

Methods: Mice undergoing IR injury received 6 injections of p53 specific or scrambled siRNA until D10 and were harvested at Day 14 or Day 30 (early treatment groups). In an additional continuous treatment group mice received 11 doses of p53 specific or scrambled siRNA until Day 26 and were harvested at Day30.

Results: At D14, we found that p53 siRNA treatment protected against IR injury and significantly ameliorated the development of senescence (fewer senescence-associated-ß-galactosidase and γ-H2AX positive cells, less $p16^{INK4a}$ expression). The beneficial effects (less acute injury and chronic tubular atrophy, reduced inflammation, less fibrosis and better preservation of peritubular capillaries) persisted even with a prolonged observation period of D30. However, most of these positive effects were lost when p53 siRNA treatment was continued until D30.

Conclusions: Our results showing attenuated senescence through early p53 inhibition are in line with the known dual function of p53. The reversal of the renoprotective effects in the group of continuously treated animals suggests that the function of p53 differs between the early and later phase after IR and that latent expression of p53 is essential for long-term recovery. These data are important in the light of therapeutic approaches using p53 targeting siRNA to prevent AKI and delayed graft function.

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FR-PO267

ERK1/2 Rapidly Downregulates PGC-1α Expression in Renal Physiological and Pathological Conditions Justin B. Collier, Ryan Whitaker, Rick G. Schnellmann. *Drug Discovery and Biomedical Sciences, Medical Univ of South Carolina, Charleston, SC.*

Background: Previous studies demonstrated that suppression of mitochondrial biogenesis (MB) through decreased peroxisome proliferator-activated receptor gamma coactivator-1a (PGC-1a) is an important contributor to renal ischemia reperfusion (IR) injury and repair. While ERK1/2 regulates numerous cell signaling pathways, the role of ERK1/2 in renal PGC-1a regulation physiologically and after renal IR remains limited.

Methods: Renal proximal tubule cells (RTPC) were treated with the MEK1/2 inhibitor trametinib (10nM) and the epidermal growth factor receptor (EGFR) inhibitor, erlotinib (100nM). Trametinib (1mg/kg) and erlotinib (50mg/kg) were administered to naïve mice, as well as 1 hour before 18 min of IR injury. Signaling was explored using RT-qPCR, subcellular fractionation, and immunoblot analysis.

Results: Trametinib and erlotinib exposure blocked ERK1/2 phosphorylation and increased PGC-1a mRNA in RPTC after 1 and 4 hr. The mRNA levels of PGC-1a targets NDUFS1, NRF1, and TFAM increased at 1, 4, and/or 24 h after ERK1/2 inhibition. Trametinib and erlotinib administered to naive mice increased PGC-1a mRNA at 4 h in the cortex and trametinib increased PGC-1a and TFAM proteins. Trametinib decreased nuclear pFOXO3a by 60% at 30 min in RPTC and *in vivo* nuclear pFOXO1 decreased 60% in the cortex, leading to increased expression of downstream FOXO3a/1 genes, including PGC-1a. In the IR AKI model, pERK1/2 increased 4-fold at 1 and 3 h post IR and was linked to decreased mRNA levels of PGC-1a, NRF1, and TFAM. Pretreatment with trametinib attenuated the suppression of PGC-1a and NRF1 mRNA at 3 h, increased TFAM protein 2.5-fold, and attenuated renal dysfunction as measured by BUN.

Conclusions: We have linked physiological ERK1/2 phosphorylation to the regulation of PGC-1a and MB through the EGFR and subsequent FOXO3a/1 inactivation. In IR kidney injury, PGC-1a and related genes decreased and ERK1/2 inhibition restored PGC-1a. These results demonstrate that ERK1/2 regulates MB in the kidney rapidly through the pathway, EGFR/ERK1/2/FOXO3a/1/PGC-1a under physiological and pathological conditions.

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FR-PO268

IL233 Hybrid Cytokine bearing Interleukin (IL)-2 and IL-33 Activities Protects from Nephrotoxic Injury Rahul Sharma,[1] Marta Stremska,[1] Saleh Mohammad,[1] Amandeep Bajwa,[1] Gilbert R. Kinsey,[1,2] Diane L. Rosin,[2] Mark D. Okusa.[1] *[1]Div of Nephrology, Dept of Medicine, Univ of Virginia, Charlottesville, VA; [2]Dept of Pharmacology, Univ of Virginia, Charlottesville, VA.*

Background: Acute kidney injury induced by chemotherapy drugs limits their use. Earlier we showed that IL-2 and IL-33 cooperate to promote regulatory T-cells (Treg), and a hybrid cytokine (IL233) bearing these activities in a single molecule protected mice from ischemia-reperfusion Injury. Here we investigated whether immuno-modulation by IL233 also protects from nephrotoxic drugs.

Methods: Male Balb/C mice (12-wk) were injected (ip) with saline or 66pmoles/day IL233 for 5 days and 10mg/kg Doxorubicin (Dox) (iv) on day 8. In another model, 12-wk old C57Bl/6 males were injected with IL233 (66pmoles/day) or saline as above and 20mg/kg Cisplatin (Cis) on day 8. Plasma creatinine (PCr) and blood urea nitrogen (BUN) were measured (mg/dL; mean±SEM). Blood, spleen and lymph nodes (LN) were analyzed for immuno-phenotype. Kidneys were analyzed for inflammation and injury.

Results: In mice administered Dox, saline or IL233 treatment did not prevent loss of renal function initially. However, IL233-treated mice recovered rapidly and normalized PCr by day 28 (0.23±0.01), whereas all saline-treated mice were moribund and had elevated PCr (0.56±0.11). By H&E, all saline treated mice had leukocytic infiltration, tubular necrosis, proteinaceous casts, mesangial expansion and fibrosis, whereas the IL233-treated mice showed normal histology. IL233 treatment not only increased $Foxp3^{+}$ Treg in blood and renal LN and production of IL-2 and IL-10, but also lowered IFNγ and TNFα production compare to the saline-treated mice. Cis treatment in saline control mice caused an increase in BUN (95±12) and death by day 4, whereas all the IL233-treated mice survived and had comparatively preserved BUN (44±7). IL233 treatment in the Cis models also increased Treg and IL-10 production while inhibiting IFNγ and IL-17 production.

Conclusions: The novel cytokine IL233 harboring the activities of IL-2 and IL-33 promotes Treg and suppresses inflammation to protect from nephrotoxic injury and bears therapeutic potential.

Funding: NIDDK Support

FR-PO269

Finerenone Protects against the Acute and Chronic Consequences of Renal Ischemia/Reperfusion Injury Jonatan Barrera-Chimal,[1] Alan Le Mercier,[1] Soumaya El Moghrabi,[1] Peter Kolkhof,[2] Frederic Jaisser.[1] *[1]INSERM, U1138, Centre de Recherche des Cordeliers, Paris, France; [2]BAYER Pharma AG, Cardiology Research, Wuppertal, Germany.*

Background: One of the most common causes of acute kidney injury (AKI) is renal ischemia/reperfusion (IR). Mineralocorticoid receptor (MR) antagonism has shown beneficial effects against renal IR consequences. The potential benefit of novel non-steroidal MR antagonists such as finerenone has not been explored. Therefore, we evaluate the efficacy of finerenone to prevent the acute and chronic consequences of ischemic AKI.

Methods: For the acute study (24 hours), 18 rats were divided in: sham, rats subjected to bilateral renal ischemia of 25 min and rats that received three doses of finerenone at -48 h, -24 h and -1 h before the ischemia. For the chronic study (4 months), 21 rats were divided in: sham, rats with 45 min of bilateral ischemia and rats treated with Finerenone at day -2, -1 and 1h before IR. The left kidney was used for histology and the right kidney for molecular analysis.

Results: After 24 h of reperfusion, the untreated IR rats presented a 3-fold increase in plasma creatinine, accompanied by 40% of tubules presenting cell detachment and casts. Kim-1 and NGAL mRNA levels were induced by 30-fold. In contrast, the rats that received finerenone presented normal creatinine and significantly fewer injured tubules (11%) and a less pronounced induction of kim-1 and NGAL (8-fold). After 4 months, the untreated IR rats developed chronic kidney disease (CKD), evidenced by kidney dysfunction, increased proteinuria (121.6 vs. 14.3 mg/24h in sham) and renal vascular resistance (16.8 vs. 11.4 mmHg/mL in sham). Tubular dilation, extensive tubule-interstitial fibrosis and an increase in kidney TGF-ß and Collagen-I mRNA levels also characterized CKD. The transition from AKI to CKD was fully prevented by finerenone administration at the time of IR.

Conclusions: Altogether, our data shows that finerenone is able to prevent AKI induced by IR as well as the chronic and progressive deterioration of kidney function and structure.

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FR-PO270

Kidney Injury Molecule-1 Overexpression Promotes Healing of Injured Kidney Epithelial Cells and Induces Alternative Activated Macrophage Polarization Joseph C.K. Leung,[1] Loretta Y.Y. Chan,[1] Kar Neng Lai,[2] Sydney C.W. Tang.[1] *[1]Dept of Medicine, The Univ of Hong Kong, Hong Kong; [2]Hong Kong Sanatorium & Hospital, Hong Kong.*

Background: Kidney injury molecule-1 (KIM-1) acts as a double-edged sword in injured kidney. We aim to study the effects and mechanism of KIM-1 overexpression on healing of injured kidney proximal tubular epithelial cells (PTEC) and macrophage polarization.

Methods: Oxidative injury model by H_2O_2 was established in murine PTEC with KIM-1 overexpression ($KIM\text{-}1^{hi}$ PTEC). Cell viability, proliferation and apoptosis were

determined from 24 to 120 hours after injury. The expression of vimentin, N-cadherin, TNF-α, MCP-1, TGF-β1 and CSF-1; were determined by real-time PCR or ELISA. To delineate the role of humoral factors released by injured KIM-1^{hi} PTEC on macrophages (Mø) polarization, bone marrow–derived Mø were cultured with injured PTEC in transwell setup. The temporal expression of markers for classical M1 or alternative activated M2 including iNOS, TNF-α, IL-23, CD206, IL-10 and arginase-1 were evaluated.

Results: Apoptosis induced by H_2O_2 was ameliorated in KIM-1^{hi} PTEC. During recovery, injured KIM-1^{hi} PTEC exhibit enhanced cell proliferation and dedifferentiation, with up-regulated expression of TNF-α, MCP-1, TGF-β1 and CSF-1. The expression of TGF-β1 or CSF-1 by the injured KIM-1^{hi} PTEC was diminished by blockade of phagocytosis with annexin V. Injured KIM-1^{hi} PTEC promote M1 to M2 conversion as reflected by the temporally decrease of iNOS, TNF-α and IL-23, and concomitant increase of CD206, IL-10 and arginase-1 expression. Notably, this M2 polarization was diminished by blockade of soluble CSF-1, TGF-β1 or phagocytosis.

Conclusions: In acute tubular cell injury, KIM-1 overexpression accelerates the phagocytosis-dependent healing. The enhanced M2 polarization by TGF-β1 and CSF-1 released from the injured KIM-1^{hi} PTEC, further contributes to the recovery process. Persistent KIM-1 overexpression leads to sustained release of inflammatory cytokines including TNF-α and MCP-1, plus M1 polarization and infiltration. Our results implicate that enhanced KIM-1 expression is beneficial in acute but undesirable in chronic tubular cell injury.

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FR-PO271

Disruption of Hypoxia-Inducible Factor-1 Alpha Deteriorates Renal Ischemia-Reperfusion Injury through Dysregulation of Kv2.2-Induced Apoptosis in Tubules Kazuma Ota,[1] Yoshitaka Kihira,[1,2] Reina Kishibuchi,[1] Yuki Izawa-Ishizawa,[1] Yuya Horinouchi,[1] Yasumasa Ikeda,[1] Toshiaki Tamaki.[1] *[1]Pharmacology, Tokushima Univ Graduate School, Tokushima, Japan; [2]Clinical Pharmacy, Fukuyama Univ, Fukuyama, Hiroshima, Japan.*

Background: Hypoxia-inducible factor (Hif)-1α is upregulated during renal ischemia-reperfusion (I/R) and is involved in induction of apoptosis and the following proliferation in renal proximal tubular cells (PTCs). The intracellular ion homeostasis is disrupted before the I/R-induced apoptosis; increase in intracellular Ca^{2+} concentration, $[Ca^{2+}]i$, and decrease in $[K^+]i$. It is known that the voltage-gated potassium channel Kv2 activated by Ca^{2+} influx is involved in induction of neuronal apoptosis. In this study, we explored the role of Kv2 in renal I/R injury (IRI) and its relationship to Hif-1α.

Methods: Hif-1α heterozygous knockout mice (hKO) and their wild type littermates (WT) were used. For induction of IRI, the right kidney was removed and the left renal vessels were clamped for 45 min followed by reperfusion.

Results: hKO showed severer renal dysfunction and reduced expression of Kv2.2 compared with WT. The preadministration of 4-aminopyridine (4AP), an inhibitor of Kv2 channels, exacerbated renal dysfunction in C57BL/6 mice after I/R. In addition, the treatment of dimethyloxaloylglycine, a Hif-1α activator, with human PTC line HK2 increased Kv2.2 expression levels. These results indicate that Kv2.2 is involved in reduction of IRI and is regulated by Hif-1α. Moreover, the delayed induction of apoptosis in PTCs was observed in hKO mice. 4AP inhibited Ca^{2+} ionophore ionomycin-induced apoptosis in HK2 cells. Therefore, Kv2.2 is probably responsible for apoptosis induction in PTCs. Localization and molecular weight of Kv2.2 were changed by I/R in the kidney of C57BL/6 mice and the changes were mimicked by the treatment of ionomycin with HK2, indicating that Ca^{2+} influx activates Kv2.2 in renal PTCs.

Conclusions: The present study shows that Hif-1α plays an important role in recovery from IRI trough induction of Kv2.2 which leads to PTC apoptosis. PTC apoptosis mediated by Hif-1α-Kv2.2 pathway is considered a key to recovery from IRI.

Funding: Private Foundation Support

FR-PO272

Coenzyme Q10: A Potential Candidate for Contrast-Induced Acute Kidney Injury in Diabetic Rats Cassiane Dezoti da Fonseca, Maria De Fatima Vattimo, Mirian Watanabe. *School of Nursing, Univ of Sao Paulo, Sao Paulo, Brazil.*

Background: Diabetic nephropathy and contrast-induced acute kidney injury (CI-AKI) involve tubular and glomerular defects, oxidative damage, mitochondrial cytopathies and the induction of protective enzymes, as coenzyme Q10 (COQ10). This study evaluated DM as a risk factor for CI-AKI and the role of COQ10 on this model.

Methods: Male Wistar rats, 250-280g, were randomized into groups: **Citrate -** citrate buffer (streptozotocin vehicle); **DM** - streptozotocin (65 mg/kg, iv).; **DM+IC -** DM animals that after 4 weeks received iodinated contrast (IC, 6 ml/kg, ip); **DM+IC+CO-Q10 -** DM preconditioned animals (COQ-10, (10 mg/kg, ip). Physiological parameters, renal function (inulin clearance).urinary neutrophil gelatinase- NGAL, oxidative profile (urinary peroxides, thiobarbituric acid reactive substances-TBARS, nitric oxide-NO in urine and thiols in renal tissue) and renal hemodynamics (renal vascular resistance- RVR) were analyzed.

Results:

Groups (n)	Inulin Clearance (mL/min/kg)	NGAL (mg/dL)	RVR (mmHg/mL/min)	Urinary Peroxides (nmol/g creatinine)	TBARS (nmol/g creatinine)	Thiols (nmol/mg protein)	NO (μM/g creatinine)
Citrate (5)	0.96 ±0.18	37.9 ±0.8	11.2 ±2.1	2.0 ±0.8	0.2 ±0.1	24.6 ±4.3	15.1 ±8.0
DM (5)	0.55 ±0.08*	53.8 ±17.8	23.9 ±8.3*	7.3 ±3.9*	14.0 ±2.6*	15.5 ±2.0*	48.7 ±24.7*
DM+IC (5)	0.17 ±0.02*#	99.8 ±18.7*#	38.4 ±9.3*#	18.5 ±3.6*	30.3 ±2.9*#	7.6 ±2.1*#	102.1 ±16.9*#
DM+IC +COQ10 (5)	0.53 ±0.08*°	61.4 ±18.5*°	18.5 ±2.9*°	3.4 ±1.2#°	12.5 ±2.8*°	17.8 ±1.9*°	43.7 ±15.6*°

*P<0.05 vs citrate; #p<0.05 vs DM; °p<0.05 vs DM+IC. Diabetic groups showed polyphagia, polydipsia, polyuria, high levels of blood glucose and reduction in body weight. IC reduced inulin clearance, increased urinary NGAL and elevated RVR. Oxidative damage was confirmed by increased urinary peroxides, nitric oxide and TBARS with the consumption of antioxidant reserve. These parameters were significantly changed by COQ-10.

Conclusions: Our results indicated that DM improves renal vulnerability to the toxicity of CI. COQ-10 showed to be a potential drug for modifying risk factor for CI-AKI in chronic disease, DM.

Funding: Government Support - Non-U.S.

FR-PO273

HO-1 Gene Modification Promotes Proliferation and Differentiation of Bone Marrow-Derived Mesenchymal Stem Cells in the Acute Injured Kidney via Stimulation of AKT and ERK Signaling Nanmei Liu. *Dept of Nephrology, Jiming Hospital of Shanghai, Shanghai, China.*

Background: Bone marrow-derived mesenchymal stem cells (BMSCs) transplantation offers therapeutic potential for acute kidney injury (AKI), but with limited efficacy. Heme oxygenase-1(HO-1) possesses the cytoprotective activity. Here we tested the effect of HO-1 overexpression on the survival and differentiation ability of BMSCs under the AKI microenvironment, and its impact on the repair of AKI was also observed.

Methods: SD HO-1-BMSCs and eGFP-BMSCs were prepared by the gene transfection method. Ischemia/reperfusion (I/R)-AKI kidney homogenate supernatant (KHS) was prepared to treat BMSCs, eGFP-BMSCs and HO-1-BMSCs in vitro. The cell cycle, proliferating cell nuclear antigen (PCNA) expression, cytokeratin 18 (CK18) expression and cytokine secretions for the cultured BMSCs were all measured. Signaling pathways involved were also analyzed. In the in vivo experiment, survival and differentiation of the implanting BMSCs in the AKI rat model as well as the renal function were also assayed.

Results: HO-1-BMSCs showed a remarkable expression of HO-1. HO-1-BMSCs became better with the less proportion of cells at the G0/G1 phase, the higher proportion of cells expressing PCNA and CK 18. Levels of monocyte chemotactic protein 1 (MCP-1), tumor necrosis factor-α (TNF-α) and interleukin 1β (IL-1β) decreased significantly in supernatant of HO-1-BMSCs. Expressions of the phosphorylated Akt and phosphorylated ERK were increased in HO-1-BMSCs. Either LY294002 or PD98059 inhibited the above effects. The in vivo study showed increased proportion of $PCNA^+$ HO-1-BMSCs and $CK18^+$ HO-1-BMSCs in the injured kidneys with improved renal function and reduced ATN score.

Conclusions: HO-1 overexpression in BMSCs can enhance the survival and the renal-epithelial differentiation of BMSCs in the AKI microenvironment. Stimulations of PI3K/Akt and MEK/ERK signal pathways can be taken as the possible mechanisms. Thus, HO-1 gene-modified suggests a better kidney repair effect.

Funding: Government Support - Non-U.S.

FR-PO274

Laser-Irradiation in a Closed Microcirculation System to Study Endothelial Regeneration Mechthild Roesler,[1] Florian Schmieder,[2] Jan Sradnick,[1] Udo Klotzbach,[2] Vladimir T. Todorov,[1] Frank Sonntag,[2] Christian Hugo,[1] Bernd Hohenstein.[1] *[1]Div of Nephrology, Dept of Internal Medicine III, Univ Hospital CGC, Dresden, Germany; [2]Fraunhofer Inst for Material and Beam Technology IWS, Dresden, Germany.*

Background: Microfluidic systems are small, chip-sized platforms, which can be used as cellularized organoid systems to study cell processes and cell-cell interactions. To investigate regeneration, the generation of specific cell damage in the channels is necessary but difficult due to limited accessibility. The present project aimed to establish a well-defined lesion in a human endothelial cell (EC) layer without removing dead cells and signaling molecules.

Methods: Microfluidic platforms were produced by Fraunhofer IWS by layer laminate manufacturing according to the experimental needs, containing reservoirs, channels, valves and an integrated micropump. Human umbilical vein EC (HUVEC) and outgrowth EC (OEC) were used. Laser ablation was performed using an Olympus Spinning Disc Microscope with a laser diode at a wave length of 405nm for 5 to 15 minutes with a power of 2 - 2.4mW. EC injury was observed by phase contrast microscopy and LIVE/DEAD® Viability/Cytotoxicity Kit whereas Time-lapse recording was used to visualize the regeneration of the injured EC layer.

Results: Following an initial attachment phase (4 hours), the fibronectin-coated channels were covered with a cellular monolayer at a density of approximately $7{,}5x10^4$ cells/cm² within 3 to 6 days under pulsatile flow. Laser irradiation of 10 minutes minimum

created a selective destruction of the EC-monolayer in areas of approximately 200x200µm or 120x120µm (x40 or x60 objective, respectively). EC density showed an influence on the time needed to induce cell injury. Time-lapse recordings indicate that surrounding EC start movement and proliferation towards the damaged site and are able to fill the gap within two to three days.

Conclusions: Pre-defined EC lesions in channels of microfluidic systems can be created by laser-irradiation reproducibly. This method in combination with kidney-specific EC will allow to further understand central mechanisms of EC regeneration and signaling upon injury.

FR-PO275

The Role of IL-6 Signaling on the Transition of Acute Kidney Injury to Chronic Kidney Disease Myung-Gyu Kim, Hiroshi Kojima, Jonathan Street, Xuzhen Hu, Peter S.T. Yuen, Robert A. Star. *NIDDK, National Insts of Health, Rockville, MD.*

Background: IL-6 is a multifaceted cytokine and a novel molecular target in several inflammatory diseases (rheumatoid arthritis, asthma, colitis). Recent studies showed that trans-signaling by a IL-6/sIL-6 receptor complex (which then binds cell-attached gp130) can protect against acute kidney injury (AKI); however, the role of IL-6 signaling in renal disease remains largely unexamined. Here, we studied the role of IL-6 signaling during the AKI to chronic kidney disease (CKD) transition.

Methods: C57BL/6 mice were subjected to ischemia reperfusion injury (IRI, 28'). CD-1 mice were treated with folic acid (250mg/kg). 14 days later, glomerular filtration rate (GFR) was measured using FITC-labeled sinistrin, and renal fibrosis was evaluated by Masson's Trichrome.

Results: Serum IL-6 and sIL-6R levels significantly increased on day 1 following IRI and remained higher than sham group through day 5, whereas serum soluble gp130 level did not change. These data suggest persistent IL-6 trans-signal activation during the post-AKI recovery phase. To investigate the effect of exogenous IL-6 during recovery from IRI, rmIL-6 or PBS was administered by osmotic mini pump (0.1µg/hr) from day 2 to day 9. On day 14 after IRI, blood urea nitrogen and GFR showed no significant differences between IL-6- and PBS-treated groups. However rmIL-6 treatment significantly decreased renal fibrosis (3.2±0.1 vs. 2.3±0.3). Interestingly, renal function at day 14 post-IRI did not correlate with the degree of renal fibrosis on day 14 post-IRI. The effect of rmIL-6 treatment was also examined following folic acid-induced AKI. Folic acid was injected with 0.3M $NaHCO_3$ i.p. and then mice were treated with rmIL-6 from day 2 to 9. Treatment with rmIL-6 did not alter either renal fibrosis or GFR following folic acid exposure.

Conclusions: Increased IL-6 trans-signaling during the recovery phase may be associated with AKI to CKD transition. However treatment of IL-6 alone a) slightly altered fibrosis without detectable effects on renal function following I/R and b) had no effect in a folate nephropathy model. The dissociation of renal fibrosis and GFR was unexpected, and warrants further study.

Funding: NIDDK Support

FR-PO276

Rat and Human Renal Exosomes Protect Ischemic Rat Kidneys and Cells James M. Dominguez,[1] Jesus H. Dominguez,[1,2] Katherine J. Kelly.[1] *[1]Medicine, IUMC, Indianapolis, IN; [2]Medicine, VAMC, Indianapolis, IN.*

Background: Acute kidney injury (AKI) from ischemia/reperfusion (IR) can result in early or late loss of kidney structure and function. There is no available therapy that prevents renal cell death following severe IR.

We hypothesized that rat renal exosomes (rexo) from normal tubule cells (rNKC) limit cell death in IR rats. In order to evaluate clinical use, human renal exosomes (hexo) from hypoxia-resistant immortalized proximal tubule cells (hNKC, gift of Dr. R Bacallao) were also tested.

Methods: rNKC (4 hrs) and hNKC (24-48 hrs) were cultured in normoxia or 1 % O_2 hypoxia, and normoxic or ischemia pre-conditioned (IPC), rexo or hexo, were harvested for 72 more hours while back in normoxia. IPC rexo had higher levels of ICAM-1 protein than normoxic rexo (1.85 fold = 0.002). IPC rexos fused with target cells.

Results: IPC rexos had higher mRNAs encoding Catalase, SOD1, HSP27, and HIF (fold increase over normoxic rexos: 1.3, 1.5, 1.7, 1.6; $p < 0.05$). IPC rexos prevented rat renal cell injury given intravenously 24 hours after 50 minutes of IR. These effects included renal phenotypes and genotypes comparable to sham controls, while untreated IR rats had very advanced renal damage: damaged microvasculature, severe inflammation, scarring, and proliferation. Lipid peroxidation and cell proliferation were also elevated, $p < 0.05$. We then tested hexo from hNKC, which were resistant to 48 hrs of 1 % hypoxia. Hexos were added to rat NRK52 cells, and HLA mRNA transfer from hexos to rat cells confirmed fusion. NRK52E cells were subjected to 24 hrs of hypoxia and 24 hrs of re-oxygenation. Cell viability was unaffected by hypoxia, and increased 5.3 fold after re-oxygenation ($p < 0.05$). Hexos lowered mortality of hypoxic/re-oxygenated NRK52E cells by 55 %, $p < 0.05$.

Conclusions: IPC rexos communicate the ischemia preconditioned state and limit most renal changes from IR in rats. IR kidneys of rats treated with IPC rexos do not spend energy in regenerating de novo, and transition to a near normal state from suspended animation. Hexos from hypoxic-resistant hNKCs transfer the resistant state to rat kidney cells subjected to severe hypoxia and re-oxygenation. Hence, renal hexos are a new biological tool to treat AKI from IR.

Funding: NIDDK Support, VA Support, Private Foundation Support

FR-PO277

Hypoxia Inducible Factor-1α Activation Attenuates Renal Ischemia/Reperfusion Injury by the miR-21, Thrombospondin 1, and Angiogenesis Pathway Xialian Xu,[1] Nana Song,[1] Xiaoyan Jiao,[1] Jiachang Hu,[1] Mingyu Liang,[2] Xiaoqiang Ding.[1] *[1]Nephrology, Zhongshan Hospital, Shanghai, China; [2]Physiology and Center of Systems Molecular Medicine, Medical College of Wisconsin, Milwaukee, WI.*

Background: Angiogenesis contributes tothe repair process after renal ischemia/reperfusion injury. In the present study, we tested the hypothesis that miR-21 induced angiogenesis by inhibiting a novel target gene thrombospondin 1.

Methods: Cobalt chloride was administered intraperitoneally 24h prior to renal ischemia/reperfusion. Human umbilical vein endothelial cells were treated by 1% O_2 for 24h. Locked nucleic acid modified anti-miR-21 or scrambled anti-miR was transfected into hypoxic cells or delivered into the mice via tail vein injection less than 1h prior to cobalt chloride treatment. Morphologic and functional parameters, vascular density, miR-21 and thrombospondin 1 expression in vivo and in vitro were assessed 24h after reperfusion or hypoxia.

Results: Hypoxia up-regulated hypoxia inducible factor-1α, vascular endothelial growth factor and miR-21, down-regulated predicted miR-21 target gene thrombospondin 1, and increased tube formation in endothelial cells. Inhibition of miR-21 led to increased thrombospondin 1 abundance and decreased tube formation in hypoxic endothelial cells. Cobalt chloride activated hypoxia inducible factor-1α and attenuated renal ischemia/reperfusion injury in mice, accompanied by up-regulation of miR-21 and increased angiogenesis. Thrombospondin 1 expression was down-regulated. These effects of cobalt pretreatment were attenuated by inhibition of miR-21.

Conclusions: hypoxia inducible factor-1α induced angiogenesis by increasing not only vascular endothelial growth factor but also miR-21 via inhibiting a novel target gene thrombospondin 1. Both of them may contribute to the protective effect of hypoxia inducible factor-1α on renal ischemia/reperfusion injury.

Funding: Government Support - Non-U.S.

FR-PO278

Rosuvastatin Treatment Ameliorated Renal Tubulointerstitial Fibrosis in Murine Model of Chronic Kidney Disease Hyeong Cheon Park,[1] Hyunwook Kim,[1] Mirae Lee,[1] Taeyeon Kim,[1] Hoon Young Choi,[1] Jung Eun Lee,[2] Hyung Jong Kim.[3] *[1]Internal Medicine, Yonsei Univ College of Medicine Gangnam Severance Hospital, Seoul, Korea; [2]Internal Medicine, Yonsei Univ College of Medicine Yongin Severance Hospital, Yongin, Gyeonggi-do, Korea; [3]Internal Medicine, Bundang Cha Medical Center, Cha Univ, Seongnam-si, Gyeonggi-do, Korea.*

Background: Tubulointerstitial fibrosis plays an important role in progressive chronic kidney disease (CKD). Lysyl oxidase like-2 (LOXL2), a member of the lysyl oxidase (LOX) family, promotes crosslinking of collagen and elastin that has been implicated in liver and lung fibrosis. Rosuvastatin (ROS)'s pleiotropic actions include anti-fibrotic effects. Aim of the study was to investigate the effect of ROS on renal LOXL2 activity and tubulointerstitial fibrosis in a murine CKD model.

Methods: Male FVB mice were subjected to 42 minutes of unilateral ischemic acute kidney injury and after 2 weeks the mice underwent contralateral nephrectomy to induce a murine model of CKD. Animals were divided into 2 groups: vehicle (methylcelluose) or rosuvastatin (10mg/kg/day) by gavage. After 4 weeks, mice were sacrificed and kidneys were harvested for analysis.

Results: Our murine CKD model showed increased BUN (47.8 ± 4.7 vs. normal 24.3 ± 3.6 mg/dL, $p<0.01$) and renal anemia (hemoglobin level: 11.0 ± 1.0 g/dL vs. normal 13.2 ± 0.4 g/dL, $p<0.01$) and overt proteinuria compared to age-matched control mice. F4/80 positive inflammatory cell infiltration in the interstitium was significantly reduced by ROS treatment (2.8 ± 1.2 vs. 39.8 ± 8.3 /HPF, $p<0.01$). The mRNA expression of TGF ß1, LOXL2 and collagen 1 was increased in CKD kidney; ROS treatment significantly decreased TGF ß1 (1.54 ± 0.42 vs. 2.91 ± 1.33, $p<0.03$, ROS vs. vehicle).and LOXL2 expression (1.29 ± 0.24 vs. 2.85 ± 0.70, $p<0.02$, ROS vs. vehicle) as well as collagen I mRNA expression (3.61 ± 1.21 vs. 7.72 ± 3.46, $p<0.03$, ROS vs. vehicle). Furthermore, tubulointerstitial fibrosis assessed, by Sirius Red staining, was significantly attenuated with ROS treatment (2.08 ± 0.49 vs. 7.75 ± 3.16, $p<0.03$, ROS vs.vehicle).

Conclusions: Rosuvastatin treatment showed significant anti-fibrotic effects via down regulation of renal LOXL2 expression.

FR-PO279

Endothelial Colony Forming Cells and Secreted Factors Attenuate Acute Kidney Injury Jason Andrieu Collett,[1] William C. Shelley,[2] Mervin C. Yoder,[2] David P. Basile.[1] *[1]Cellular and Integrative Physiology, Indiana Univ School of Medicine; [2]Pediatrics, Indiana Univ School of Medicine, Indianapolis, IN.*

Background: Damage to endothelial cells contributes to AKI by leading to impaired perfusion, while the loss of the capillary network has been suggested to promote CKD. Targeting endothelial impairment with endothelial progenitor cells has shown promise in preserving endothelial integrity and alleviating the severity of AKI. Endothelial colony-forming cells are endothelial precursor cells with high proliferative capacity, pro-angiogenic activity and in vivo vessel forming potential. We hypothesized that ECFCs may ameliorate the degree of AKI and/or promote repair of the renal vasculature.

Methods: ECFCs with high proliferative potential (HPP;form colonies>10,000 cells) or low proliferative potential (LPP:form colonies between 500-2000 cells) were isolated from rat pulmonary microvasculature or pulmonary artery, respectively. Human HPP ECFCs were isolated and expanded from cord blood. SD rats were subjected to 40 minutes IRI and supplemented with HPP-ECFC, LPP ECFC, ECFC conditioned media (CM) or vehicle and were allowed to recover for between 2hrs to 7 days.

Results: Serum creatinine (sCre) peaked at 5.2 ± 0.4 mg/dl at 48hrs following renal IRI in vehicle-treated rats and returned to pre-surgery values at 7 days. In rat HPP ECFC-treated rats, sCre values were significantly lower at 1, 2, 3 and and 5 days compared with vehicle, while rats treated with LPP-ECFCs were not different. Protection by HPP ECFCs was associated with significantly improved tubular morphology at 2 and 7 days. Administration of ECFCs also significantly prevented reductions in medullary blood flow 2hrs following reperfusion in vehicle treated rats (Vehicle -22.5±7% vs. ECFC +10±6%; $p<0.05$). We isolated and administered concentrated (10X) human cord blood-derived ECFC-CM. A single injection of ECFC-CM significantly reduced the severity of injury (sCre 4.5mg/dl vs. 2.8mg/dl; $p<0.05$) and promoted repair following ischemic AKI.

Conclusions: Taken together, these data suggest that HPP ECFC ameliorate AKI secondary to the production of soluble factors, in part by promoting improvement in renal vascular function.

Funding: NIDDK Support

FR-PO280

Heme Oxygenase-1 Modulates Renal Inflammation Associated Lymphangiogenesis Sarah Ann Bowhay, Anupam Agarwal, Abolfazl Zarjou. *Medicine, Univ of Alabama at Birmingham, Birmingham, AL.*

Background: Inflammation associated lymphangiogenesis (IAL) is characteristic of many pathological conditions such as tumorigenesis, wound healing and transplant rejection. Despite its prominent role in many conditions, little is known about IAL in the kidney. Previous studies have focused on developmental lymphangiogenesis in the kidney leaving large gaps in understanding IAL in the kidney. The purpose of this study was to explore the role of heme oxygenase-1 (HO-1), a well characterized stress inducible enzyme with potent anti-inflammatory and pro-angiogenic properties, in regulating IAL in the kidney.

Methods: To study IAL in acute kidney injury and determine the role of HO-1 in this process, we induced renal injury in HO-$1^{+/+}$ and HO-$1^{-/-}$ mice via unilateral ureteral obstruction (UUO), a model of renal inflammation and fibrosis. Protein and mRNA levels of the lymphangiogenic growth factors [vascular endothelial growth factors (VEGFs), namely VEGF-C, VEGF-D, and their receptor VEGF-R3] were analyzed at baseline and on days 1 and 7 after surgery. Additionally, to determine the roles of individual cell types in this process, primary proximal tubule cells, and bone marrow derived monocytes were cultured and exposed to hypoxia to mimic ischemic conditions and the levels of lymphangiogenic markers were analyzed.

Results: Higher levels of VEGF-R3 expression were observed in the kidneys of HO-$1^{-/-}$ mice at baseline and 7 days after UUO compared to their wild-type littermates. Also, higher levels of VEGF-D were seen in the kidneys of HO-$1^{-/-}$ mice 7 days after UUO compared to HO-$1^{+/+}$ kidneys. A similar pattern of expression was found in the macrophages: in the HO-$1^{-/-}$ cells, VEGF-R3 expression was higher at baseline and this increased further after hypoxia. The expression of markers associated with lymphangiogenesis was reversed in the proximal tubule cells with a significant decrease in VEGF-R3 expression after hypoxia in the HO-$1^{-/-}$ cells.

Conclusions: These results suggest that HO-1 plays a major role in the cross-talk between tubular and inflammatory cells following kidney injury to modulate IAL and hence may serve as a major regulator of the inflammatory process and resolution following kidney injury.

Funding: NIDDK Support, VA Support

FR-PO281

Hepcidin-Dependent Dynamic Regulation of Renal and Splenic Iron Balance Dictates Outcomes of Renal Injury Ewa U. Mandziak, Yogesh M. Scindia, Saleh Mohammad, Sundararaman Swaminathan. *Medicine, Univ of Virginia, Charlottesville, VA.*

Background: Renal fibrosis is one of the major outcomes following acute kidney injury. It is a maladaptive response that leads to excess deposition of extracellular matrix components such as collagen and fibronectin. Systemic iron depletion strategies using iron chelators or diet-induced iron deficiency have been shown to reduce renal interstitial fibrosis. However, the exact mechanisms of this effect are unknown. Hepcidin is a master regulator of iron homeostasis in the body. We hypothesized that hepcidin levels and associated dynamic changes in renal and splenic iron content may modulate renal fibrogenesis.

Methods: Mice, C57BL/6J (WT), hepcidin knockout (*Hamp*$^{-/-}$) and *Hamp*$^{+/-}$ (both on C57BL/6J background) were treated with Folic Acid (FA) 250 mg/kg (i.p.). BUN was measured on day 2 to confirm the onset of kidney injury. Renal function, collagen deposition, immune cell infiltration and mRNA expression levels for fibrosis markers were examined 19 days after FA injection.

Results: Kidney function (measured by BUN) in WT mice was reduced on day 19 after folic acid treatment. This was significantly ameliorated in both *Hamp*$^{+/-}$ and *Hamp*$^{-/-}$ mice. However, renal collagen deposition (Masson's Trichrome staining) was reduced in *Hamp*$^{+/-}$ (partial hepcidin deficiency) mice but not *Hamp*$^{-/-}$ (complete hepcidin deficiency). Kidney αSMA and TGF-β paralleled the changes in collagen deposition. This reduction in renal fibrosis was associated with change in the balance of spleen and kidney iron content. *Hamp*$^{+/-}$ mice with low iron content in both splenic and renal compartments had the least fibrosis. In contrast, *Hamp*$^{-/-}$ mice with low splenic iron but high kidney iron demonstrated fibrosis comparable to WT mice.

Conclusions:

	Splenic iron	Kidney iron	Outcome
WT	High	Low	Fibrosis
***Hamp*$^{+/-}$**	**Low**	**Low**	**Protection**
***Hamp*$^{-/-}$**	Low	High	Fibrosis

Our studies reveal a novel protective role of partial hepcidin deficiency in renal fibrosis through dynamic modulation of splenic and renal parenchymal iron content thereby offering a novel therapeutic approach to prevent progression of kidney disease.

Funding: NIDDK Support

FR-PO282

Exercise Preconditioning Reduces Acute Ischemic Renal Injury in Rats Weslei Vicente Lima, Nestor Schor, Waldemar S. Almeida. *Nefrologia, UNIFESP, São Paulo, São Paulo, Brazil.*

Background: Acute kidney injury (AKI) can be defined as the sudden loss of renal function associated with structural changes in the kidneys. Currently 13.3 million people die of AKI around the world. Normally aerobic exercise is used both as/for the treatment and prevention of high blood pressure, metabolic disease and DM. Nevertheless, exercise preconditioning must be an important resource in the prevention and mitigation of the LRA. Evaluate the effects of the exercise precontioning on renal function in Wistar rats subjected to I/R.

Methods: We used male Wistar rats with 10 weeks of life and they were separated into three groups Sham (S), control (C) and trained (T). After 4 weeks all groups were subjected to injure I/R. Moreover, the rats were recuperating for 24 hours and after that, they were placed in metabolic cages for 24 hours.We evaluate renal function from serum creatinine, urea and proteinuria. Then, renal morphological study by optical microscopy.

Results: At the end of the protocol, the T group had a lower weight than the groups S and C (S 383 vs 384 vs C T 356g $p<0.05$). After 48h of renal I/R, increased proteinuria levels (S 9 ± 1.6 vs C 20 ± 6.3 vs T 15 ± 4.2 mg/24h; $P<0.05$), creatinine (C 2,1 ± 1.6 vs S 0.53 ± 0.02 vs T 0.73 ± 0.09; $P<0.05$) and urea (S 164 ± 123.3 vs C 35 ± 2.9 vs T 59 ± 20 7; $P<0.05$) in the C and T groups. Renal histological analysis showed that 90% of the animals the group C had degrees of acute tubular necrosis (ATN) significantly greater than 90% of the animals of group T (C grade 3 and 4 vs. T 1 and 2, respectively).

Conclusions: The group that held aerobic exercise preconditioning had lesser impairment of renal function and morphology compared to the control group, suggesting that aerobic exercise preconditioning was renoprotective in this IR model.

FR-PO283

KIM-1 Regulates the Proximal Tubular Cell Immune Response to Kidney Injury Craig R. Brooks, Melissa Y. Yeung, Takaharu Ichimura, Joseph V. Bonventre. *Renal Div, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.*

Background: We have reported that Kidney injury molecule-1 (KIM-1), the most upregulated proximal tubular cell (PTC) protein following a variety of kidney injuries, functions as a phosphatidylserine phagocytosis and scavenger receptor. Mutation of KIM-1 mucin domain (KIM-$1^{\Delta mucin}$) results in reduced binding to and clearance of apoptotic cells, increased inflammation and decreased kidney function following acute kidney injury in mice, suggesting a link between KIM-1-mediated phagocytosis and inflammation.

Methods: Primary PTCs were isolated from wild-type and KIM-$1^{\Delta mucin}$ mice. KIM-1 interaction with p85 was determined by immunoprecipitation. NFkB activity was analyzed by immunoblot and Luciferase assay. Gene expression microarray data from KIM-1 or empty vector expressing cells were analyzed via Ingenuity Pathway Analysis. MHC presentation was measured in primary PTCs directly using specific antibodies by flow cytometry. Functional implications were determined by activation of CD4+ and CD8+ T cells.

Results: KIM-1 expression limited cytokine production in primary PTCs stimulated with LPS or TNFα, which was further suppressed by KIM-1-mediated phagocytosis. Microarray analysis revealed KIM-1 expression suppressed components of the NFκB pathway. KIM-1 expression and phagocytosis was confirmed to down-modulate NFκB phosphorylation and activity. Material phagocytosed by KIM-1 was processed and presented as antigens on MHC I and MHC II in an autophagy dependent manner. While KIM-1-mediated phagocytosis lead to greater antigen presentation, the increased presentation resulted in reduced CD4+ T cell activation and increased Tregs. Mechanistically, phosphorylated KIM-1 directly interacted to the PI3 kinase p85 and knockout or inhibition of p85 reversed the anti-inflammatory phenotype associated with KIM-1-mediated phagocytosis.

Conclusions: Thus, in acutely injured kidneys, KIM-1 facilitates repair by removal of luminal debris, leading to anti-inflammatory antigen presentation, decreased CD4+ T cell activation, increased Tregs and down-regulation of the PTC immune response via NFκB suppression.

Funding: NIDDK Support

FR-PO284

Exosome Production and Its Regulation of EGFR during Wound Healing in Renal Tubular Cells Xiangjun Zhou,[1,2] Qisheng Yao,[1] Zheng Dong.[2] *[1]Dept of Urology, Taihe Hospital, Hubei Univ of Medicine, Shiyan, Hubei, China; [2]2 Dept of Cellular Biology and Anatomy, Medical College of Georgia at Augusta Univ and Charlie Norwood VA Medical Center, Augusta, GA.*

Background: Kidney repair following injury involves the reconstitution of a structurally and functionally intact tubular epithelium. Growth factors and their receptors, such as epidermal growth factor receptor(EGFR), are important to the repair of renal tubules. Exosomes are cell-produced small (~100nm in diameter) vesicles that contain and transfer proteins, RNAs and DNAs between cells. In this study, we examined exosomes production in a scratch wound healing model of renal tubular cells. We further examined the relationship between exosomes production and EGFR activation.

Methods: A scratch wound healing model was established by using renal proximal tubular cells (RPTC) cells. Rate of wound healing and EGFR activation after scratch wounding were analyzed with and without application of an EGFR inhibitor, gefitinib. Exosomes were isolated from the culture media of RPTC cells after wound with and without treatment of gefitinib. The expression of EGFR in exosomes was investigated by testing the effect of the gefitinib and the exosomes production inhibitor, GW4869.

Results: EGFR activation occurred shortly after scratch wounding. Wound repair after injury was significantly inhibited by Gefitinib . Interestingly, scratch wounding induced a significant increase of exosomes production, which was not affected by gefitinib. EGFR was observed in exosomes and EGFR expression in exosomes increased after injury. Nonetheless, inhibition of exosome release by GW4869 do not decreased the expression of EGFR in exosomes.

Conclusions: Scratch wounding in renal tubular cells leads to EGFR activation, which is critical to wound healing. Wound healing is associated with exosome production. Exosome production does not depend on EGFR, but the release of exosome may be favor to increases the rate of wound healing in renal tubular cells.

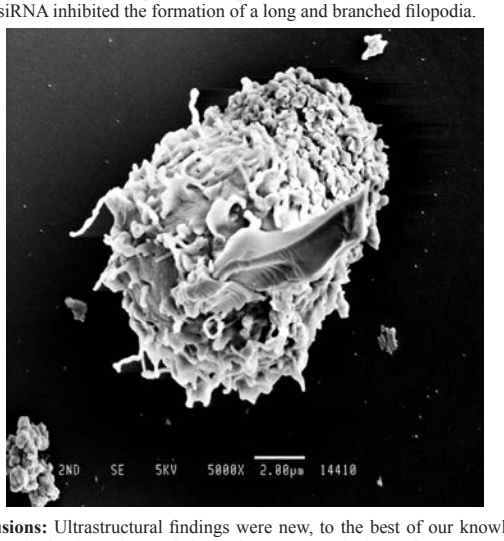
FR-PO285

Establishment of Scanning Electron Microscopic (SEM) Analysis at Various Stages of Renal Tubular Epithelium Subculture Kiyoko Inui,[1] Hiroyuki Morita,[2] Yoshihiko Inoue,[1] Tadahide Maezumi,[1] Tomohito Mizuno,[1] Fumihiko Koiwa,[1] Ashio Yoshimura.[1,3] *[1]Div of Nephrology, Showa Univ Fujigaoka Hospital, Yokohama, Kanagawa, Japan; [2]Div of Endocrinology and Metabolism, Aichi Medical Univ School of Medicine, Nagakute, Aichi, Japan; [3]Yokohama Dai-ichi Hospital, Yokohama, Kanagawa, Japan.*

Background: Renal tubular epithelium (RTE) are capable of regenerating themselves after a severe injury seen, for example, in acute kidney injury (AKI) where cell migration plays a pivotal role. RTE subculture serves as a tool to study cell migration *in vitro*. However, little is known about ultrastructure of cell migration in vitro. In the present study, we established an experimental protocol for scanning electron microscopy (SEM) in RTE subculture to study fine ultrastructural changes.

Methods: *Rattus norvegicus* kidney tubular epithelial cells, NRK-52E (ATCC® CRL-1571) were subcultured. Early floating cells and subsequent adherent ones were fixed, and subjected to SEM examinations. Minor modifications were made to the original SEM protocol. In separate experiments, small interfering RNA (siRNA) for actin related protein 3 (Arp3) was added to culture medium.

Results: We optimized SEM protocol (figure), and found that there were 2 types of floating cells: one with small sphere structures and the other with microvilli on a cell surface, that lamellipodia developed through a full 360-degree in early stages of subculture, and that very long and branched filopodia developed at later stages. Arp3 gene knockdown with exogenous siRNA inhibited the formation of a long and branched filopodia.



Conclusions: Ultrastructural findings were new, to the best of our knowledge. We claim that we obtained a tool to study how a known gene playing an important role in actin assembly influences ultrastructure in cell migration, and that further study may contribute to find a clue for constructing a new therapeutic strategy for AKI.

FR-PO286

Endothelial Nitric Oxide Synthase Gene Polymorphism in Diabetic Patients with and without Nephropathy Nishu Bhardwaj,[1] Satendra Sharma,[1] Om Prakash Kalra,[2] Anil Kumar Yadav,[2] Meera Sikka,[1] Sonal Sharma.[1] *[1]Dept of Pathology, UCMS and GTB Hospital, Delhi, India; [2]Dept of Medicine, UCMS and GTB Hospital, Delhi, India.*

Background: Nitrous oxide (NO) is a major regulator of renal hemodynamics, its production being catalysed by endothelial nitric oxide synthase (eNOS). Reduction in the generation of NO acts as a deteriorating factor for progressive renal disease. Polymorphisms in the eNOS gene may alter its expression, thus affecting the production of NO. Familial clustering in diabetic nephropathy (DN) points to a role of genetic factors in the pathogenesis of renal disease.The present study was conducted to evaluate the association of eNOS G894T gene polymorphism with the risk of developing DN.

Methods: The study comprised of 3 groups with 50 subjects in each (group 1: DN cases; group 2: diabetics without nephropathy; group 3: controls). Venous blood was collected from all subjects for measurement of serum NO level by spectrophotometry and for DNA extraction by phenol-chloroform method followed by PCR-RFLP to determine the eNOS G/T polymorphism.

Results: The frequencies of GT and TT genotypes were significantly higher in DN patients (34% and 26%, respectively) than in diabetics without nephropathy (22% and 4%, respectively) and controls (24% and 4%, respectively) ($p < 0.001$).The frequency of G allele in groups 1, 2 and 3 was 0.57, 0.85 and 0.86, respectively, whereas, that of T allele was 0.43, 0.15 and 0.14, respectively ($p < 0.001$). Thus, a positive association was observed between the eNOS G894T gene polymorphism and development of DN. Serum NO level in subjects with GG genotype ($45.1 \pm 27.8\mu M$) was significantly higher than in those with TT genotype ($26.9 \pm 18.1\mu M$) ($p = 0.029$). The carriers of T allele were seen to have significantly lower serum NO level ($35.4 \pm 24.8\mu M$) as compared to subjects with only G allele ($45.1 \pm 27.8\mu M$) ($p = 0.034$), indicating that the eNOS G894T gene polymorphism may alter the expression of eNOS.

Conclusions: This study indicates a possible role of eNOS gene polymorphism in the pathogenesis of DN. The eNOS G894T polymorphism may be a potential genetic marker for the risk of developing nephropathy in diabetic patients, and hence, may help in early identification of high-risk patients.

FR-PO287

Diabetic Nephropathy Candidate Genes Revealed by Whole-Genome Sequencing in Finnish Type 1 Diabetic Sib Pairs Discordant for Complications Miina K. Öhman,[1] Eudora Eng,[1] Yang Sun,[1] Anne-May Österholm,[2] Bing He,[2] Jing Guo,[2] Erkka A. Valo,[3] Valma Harjutsalo,[3] Niina Sandholm,[3] Carol Forsblom,[3] Per-Henrik Groop,[3] Karl Tryggvason.[1] *[1]Cardiovascular and Metabolic Disorders, Duke-NUS Medical School, Singapore; [2]Medical Biochemistry and Biophysics, Karolinska Inst, Stockholm, Sweden; [3]Folkhälsan Inst of Genetics, Folkhälsan Research Inst, Helsinki, Finland.*

Background: Diabetic nephropathy (DN) is the most devastating complication of diabetes and the most common cause of end-stage renal disease. The pathogenesis of DN is poorly understood, but epidemiologic studies support a role for genetic predisposition. To identify mutations predisposing to, or protecting from DN, we performed whole-genome sequencing (WGS) using a discordant sib pair (DSP) cohort from the homogeneous Finnish population, consisting of T1D sib pairs (n=85) who have remained discordant for complications for >30 years ("Discovery cohort"). The replication cohort consisted of 4,177 unrelated T1D patients (cases n=1,986, controls n=2,191) from the FinnDiane ("Replication") cohort and was used to screen for the variants found in the WGS.

Methods: Only sib pairs with extreme phenotypes were used for WGS: the case individuals had either persistent proteinuria, were on dialysis, had kidney transplant or died from kidney disease, and they also had retinopathy, whereas the controls had never developed a nephropathy despite 30 years of diabetes. WGS was carried out using Illumina and Complete Genomics platforms. The genetic variants found in the Discovery cohort were screened in the Replication cohort.

Results: From WGS, a total of 12,784,778 single-nucleotide variants (SNV) and 6,021,219 indels were found. Of all the SNVs, 101,734 were located in exons. We focused on the exon mutations that were either nonsense or frameshift, and narrowed them down to the mutations, which were found in homozygous form only in cases (n=15) or in controls (n=19), representing potential susceptibility or protective mutations for DN.

Conclusions: Candidate gene mutations found in the WGS are inserted into mouse genomes using the CRISPR/Cas9 technology and the mice are made diabetic by breeding with Akita mice or using streptozotocin. The mice are then monitored for potential development of DN.

Funding: Government Support - Non-U.S.

FR-PO288

Epigenetic Regulation of Myo-Inositol Oxygenase (MIOX) by Hyperglycemia - A New Mechanism Relevant to the Tubulo-Interstitial Pathobiology in Diabetic Nephropathy Isha Sharma, Neel Kamal Singh, Yashpal S. Kanwar. *Dept of Pathology, Northwestern Univ, Chicago, IL.*

Background: Kidney is one of the target organs affected by biochemical and hemodynamic derangements induced by hyperglycemia. Most of the studies have focused on mechanisms relevant to glomerular pathology, while tubulo-interstitium remains under

emphasized. MIOX, an enzyme expressed in proximal tubules, is up-regulated under high glucose (HG) ambience. It channels distal intermediaries of glycolytic pathway into glucuronate-xylulose pathway with the generation of reactive oxygen species (ROS).

Methods: We investigated epigenetic regulation of MIOX to delineate various mechanism(s) that lead up to its upregulation, generation of ROS and relevant downstream events under high glucose ambience.

Results: Kidneys of mice with STZ-induced diabetes had increased expression of MIOX with hypomethylation of its promoter spanning up to -750 bp, as assessed by bisulfite sequencing. Likewise hypomethylation was observed in HK-2 cells under HG ambience. *In silico* program analysis of the promoter region revealed putative binding site for Sp-1 transcription factor, the region enriched with GC dinucleotides. EMSA studies indicated markedly increased binding of Sp-1 to MIOX promoter under HG ambience, which was significantly reduced by the selective Sp-1 inhibitor, mithramycin. A smaller 261 bp promoter DNA fragment encompassing binding region of Sp-1 was isolated to asses Luciferase activity. Activity was increased under HG ambience, while it was reduced following a single base pair substitution (C to T) in the Sp-1 binding region. Sp-1 siRNA treatment led to decreased expression of Sp-1, MIOX, HIF-1alpha, and of an ECM protein, fibronectin. Importantly, Sp-1 siRNA treatment reduced the generation of ROS, both from the mitochondrial and NADPH oxidase sources, as assessed by immunofluorescence studies and FACS analyses.

Conclusions: This study highlights the epigenetic regulation of MIOX that influences downstream events, such as, generation of ROS and accumulation of ECM proteins, both being the hallmark of tubulo-interstitial pathology relevant to the progression of diabetic nephropathy.

Funding: NIDDK Support

FR-PO289

Cytosine Methylation and Associated Gene Expression Changes in Kidney Tubules of Patients with Diabetic Kidney Disease

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Background: The epigenome is a key determinant of gene expression. The epigenome is dynamic and is influenced by environment alterations, as occur in diabetes. Epigenetic modifications are maintained during cell division, thus solidifying "the memory" of environmental effects. The aim of the current project was to determine whether cytosine methylation changes can be observed in kidney tubule cells of patients with diabetic kidney disease (DKD).

Methods: Our primary data set included 91 microdissected human kidney tubule samples (22 DKD cases, 69 controls) associated with clinical and histological data. Illumina Infinium 450K Chips were used to determine genome wide cytosine methylation. Affymetrix RNA microarray was used to define transcript level changes. We used linear regression models to correlate identified changes with clinical and histological outcomes.

Results: Our analysis identified 519 probes that showed significant linear correlation with degree of interstitial fibrosis on histology after Bonferroni correction for alpha=0.05 (p-value<$1.19x10^{-7}$). To identify functionally important methylation changes we correlated differential methylation with transcript level changes. A large subset of differentially methylated probes correlated with gene expression changes (p-value=8e-5). Gene ontology analysis for methylation-expression pairs included significant enrichment for immune response, tissue remodeling and transport.

Conclusions: Human kidney tubule samples obtained from patients with diabetic kidney disease show differences in cytosine methylation patterns. The differential methylation of several probes correlated with gene expression changes, which may indicate that methylation changes are functionally important in diabetic kidney disease development.

Funding: NIDDK Support

FR-PO290

Reversal of Epigenetic Alterations in Diabetic Nephropathy (DN) Was Associated with a Decrease in Proteinuria

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Background: Recently, Ang II has been demonstrated to down regulate expression of podocyte neprhin via alterations in epigenetic profile. We hypothesize that blockade of Ang II would partially reverse epigenetic alterations in DN and low dose hydralazine (HYDZ, non-hypertensive dose) would further augment the effect of Ang II blockade contributing to a decrease in proteinuria in diabetic mice.

Methods: Protein blots of renal tissues/cortical sections of 2, 4, and 6 month old control and Akita mice (diabetic, n=3) were probed for methylation at histone (H)3 lysine (K)4 residues, acetylation at H3 lysine (K)9 residues, SNAIL, vitamin D receptor (VDR), and nephrin. *In vitro* studies, protein blots of control and high glucose (30 mM, HG) treated human podocytes (HPs) were probed for SNAIL, VDR, nephrin, H3K4me3, H3K9ac and actin. Podocyte VDR and nephrin gene methylation status (pyrosequencing) and SNAIL binding at VDR and nephrin promoters (ChIP assay) were determined. Control and Akita mice (n=4) were treated with losartan (an Ang II receptor blocker, 10 mg/Kg/day) with/without HYDZ (10 mg/kg/day, 4 weeks) followed by evaluation of proteinuria and renal epigenetic alterations.

Results: Protein blots of renal tissues/cortical sections of Akita mice and HG/HPs displayed enhanced expression of SNAIL and H3K4me3 but down regulation of VDR, nephrin and H3K9ac. Losartan not only decreased proteinuria but also partially reversed epigenetic alterations and associated SNAIL, VDR and nephrin expressions; HYDZ alone has similar effects on proteinuria and epigenetic markers and further augmented these effects when combined with losartan. Both nephrin and VDR displayed more than 70% cytosine methylation (CpG islands). HG/HP displayed deacetylation of nephrin and degradation via ubiquitation. ChIP assays revealed binding of SNAIL at VDR and nephrin promoters.

Conclusions: Reversal of epigenetic alterations in renal tissues contributed to decrease in proteinuria in diabetic mice.

Funding: NIDDK Support

FR-PO291

Hyperglycemia-Dependent Epigenetic and Gene Expression Profiles in Human Kidney Mesangial Cells

Akinobu Ochi,[1] Helena Kristiansson,[1] Dong Chen,[1] R. Paul Fracasso,[2] Noelynn Oliver,[2] Gilbert W. Moeckel.[1] *[1]Dept of Pathology, Yale Univ School of Medicine; [2]Boehringer Ingelheim Pharmaceuticals, Inc.*

Background: Hyperglycemia induces gene expression changes in glomeruli. Epigenetic modifications have been implicated as a mechanism contributing to dysregulated gene expression by hyperglycemia. We investigated the effects of hyperglycemia on histone and DNA methylation status in human mesangial cells (HMCs). We performed comprehensive RNA-seq analysis to assess changes in gene expression and identify candidate genes that may be affected by epigenetic modifications.

Methods: We isolated RNA, DNA and histones from cultured HMCs in osmolality-adjusted high glucose (HG, 25mM) or normal glucose (NG, 5.6mM) medium for 10 or 20 days. We compared histone3 lysine residue methylation changes by using EpiGentek ELISA plates. DNA methylation status was evaluated by Yale Center for Genome Analysis using Infinium HumanMethylation450 DNA analysis BeadChip kit. We determined gene expression by RNA-seq analysis.

Results: Most lysine residues showed increased histone methylation at the mono, di and tri methylation modification level in HG condition. Especially, H3K4me3, H3K9me1, H3K3me3, H3K36me2, H3K79me1 and H3K79me3 were strongly hypermethylated; only H3K36me1 was hypomethylated. DNA methylation analysis showed that 2279 CpG islands were hypermethylated and 995 CpG islands were hypomethylated in HG condition at day10. RNA-seq analysis showed that a total 941 mRNAs were changed in HG condition at day20. Combining results of our epigenetic and gene expression analyses identified candidate genes for epigenetic changes due to hyperglycemia. Included among them are: *CCL2,* a known marker of renal disease; *CDKN1a,* which has a role in mesangial cell hypertrophy; and *TXNIP,* known to be upregulated by hyperglycemia, thought to play a critical role in diabetic nephropathy (DN). For all of these genes, mRNA expression was strongly upregulated.

Conclusions: Hyperglycemia affects the histone and DNA methylation status, and changes expression levels of many genes in HMCs. Further analysis will clarify the precise mechanisms of these epigenetic changes and relationships among the affected genes in DN progression.

FR-PO292

ERK/MAPK Signaling-Depended Cytosolic Translocation of Dnmt3a Plays a Role in High Glucose-Induced CTGF Hypo-Methylation in Mesangial Cells

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Background: Diabetic nephropathy (DN) has become a major cause of end stage renal disease. Connective tissue growth factor (CTGF), a fibrogenic factor, played an important role in the pathogenesis of DN. We have previously identified that high glucose induces the expression of CTGF by decreasing DNA methylation . Researches in tumor cells have confirmed that ERK/MAPK signaling pathway were involved in regulation of DNA methyltransferases (Dnmts), while no relevant research were reported in human mesangial cells (HMCs). The aim of this study was to investigate the mechanisms of the CTGF hypo-methylation in a ERK/MAPK signaling involved way in HMCs .

Methods: Human mesangial cells are treated with normal glucose (5mM) or high glucose (30mM) respectively. Immnofluorescence staining, real-time PCR or western blotting was performed to determine the cellular distribution and expression of CTGF and Dnmt3a. ChIP-PCR assay was applied to investigate the capability of Dnmt3a binding the CpG island of CTGF, Methylation specific PCR was used to detect the methylation state of CTGF promoter. ERK/MAPK signaling inhibitor was used to verify ERK/MAPK signaling in high glucose-induced Dnmt3a cytosolic translocation.

Results: High glucose induced both mRNA and protein expressions of CTGF ($p< 0.05$). Although the protein expression of total Dnmt3a were not altered, nuclear Dnmt3a was significantly reduced and cytosolic Dnmt3a were elevated after high glucose treatment, No significant change was observed in Dnmt1 and Dnmt3b.The binding between Dnmt3a and the CpG island of CTGF was significantly lowered ($p< 0.01$) and the methylation of CpG island of CTGF promoter was time-dependently reduced in the presence of high glucose ($p< 0.05$). Co-treated with ERK/MAPK pathway inhibitors significantly decreased cytosolic translocation of Dnmt3a and expression of CTGF induced by high glucose ($p< 0.05$).

Conclusions: High glucose induces cytoplasmic translocation of Dnmt3a, possibly through activating ERK/MAPK signaling pathway, which contributes to the decreased binding of Dnmt3a on CTGF promoter and the subsequent CTGF hypo-methylation in mesangial cells.

FR-PO293

Activated Protein C Reverses Sustained Tubular p21-Expression and Senescence via a Methylation Dependent Mechanism Moh'd Mohanad Ahmad Al-Dabet, Khurrum Shahzad, Fabian Bock, Berend Heinrich Isermann. *Clinical Chemsistry and Pathobiochemistry, Otto-von-Guericke Univ, Magdeburg, Sachsen-Anhalt, Germany.*

Background: The importance of tubular damage in diabetic nephropathy (dNP) is increasingly recognized. Tubular damage in dNP is characterized by tubular hypertrophy and senescence, but the pathophysiological mechanistic relevance, the underlying mechanisms, and therapeutic structures allowing targeting such mechanisms are lacking. Furthermore, it is not known whether these changes are related to the hyperglycemic memory in diabetes. Interestingly, (aPC) ameliorates glomerular damage epigenetically. We hypothesized that tubular damage is epigenetically controlled and that aPC may target the underlying mechanism.

Methods: Type-1 (streptozotocin) diabetic mice were analyzed. dNP was validated based on albuminuria. A subset of mice was treated with SGLT-2 inhibitor, aPC, or 5aza-deoxycitidiene alone or in combination for 6 weeks.

Results: Gene-expression analyses identified p21 as the prominently induced gene in dNP (STZ model). Expression of p21 was further increased in mice with low aPC levels. *In-vitro* study showed that glucose induced p21 expression remains high after normalization of glucose concentration, suggesting that p21 is epigenetically controlled. Intriguingly, exposure of aPC at time of glucose normalization (25 to 5.5 mM) reversed p21 expression. In parallel, glucose reduced DNMTs activity and DNMT1/3b expression, which remained low despite glucose normalization. These glucose-induced persistent changes were reversed by aPC. Likewise, in diabetic mice (16 weeks of DM) p21 expression in renal tubular compartment remained high despite blood glucose normalization for the last 6 weeks using SGLT-2 inhibitor. aPC treatment during the last 6 weeks abolished hyperglycemia induced sustained p21 expression and protected from tubular damage (histological damage, KIM-1) and senescence (SA-βgal). Concomitant treatment with 5aza-dC abolished aPC's protective effect.

Conclusions: This suggests that p21 induces tubular senescence in dNP, which is sustained despite normalization of glucose level. Importantly, persistent p21-expression and tubular senescence can be reversed by aPC.

Funding: Private Foundation Support

FR-PO294

Transcriptome Analysis of Kidneys Identifies Novel Pathogenic Canonical Pathways in Experimental Diabetic Nephropathy Sharma S. Prabhakar, Aumyot Prongdong, E Chepchumba K. Yego. *Internal Medicine, Texas Tech Univ Health Sciences Center, Lubbock, TX.*

Background: Diabetic nephropathy (DN) is the most common cause of end stage renal disease worldwide and its current therapy remains ineffective as the pathogenesis remains unclear. In this study we examined genomic profile of kidneys from an experimental DN to obtain better insights into pathogenesis.

Methods: We used obese ZSF_1 rats, an established model of DN, and maintained from 8-26 weeks to harvest kidneys at sacrifice. Lean ZSF_1 littermates, which do not develop DN served as controls. RNA was isolated from the kidneys and processed for transcriptome analysis using Illumina HiSeq 2500. RNA from obese and lean ZSF_1 rats was compared. The differential gene list from this analysis was imported into Ingenuity Pathway Analysis (IPA) for global transcriptome analysis and pathway mapping.

Results: The top canonical pathways with a significant *Z* score include Wnt-β catenin and anti-oxidant pathway, Endothelin-1, AMP kinase, complement system, calcium signaling, eNOS signaling, cAMP, IL-1, IL-8, leptin signaling, RAS and aldosterone pathways. Significantly expressed but not hitherto reported pathways include G-protein coupled receptor, hepatic fibrosis, Ca+ transport signaling and heparin sulfate biosynthesis. The molecules significantly upregulated (fold change in parenthesis) include D4, zinc and double PHO finger family (x79), PG E receptor 2 (x28)cholinergic receptor CHRNA5 (x12), Phospholipase A PLA2G2A (x16), PLA 2G2F (x15), adrenoreceptor α1D (x10) LPS binding proteins and HMG co A. Significantly negatively regulated molecules include Cyt P450 2c8 (x2351), Heparin sulfate glucosamine HS3ST3A1 (x556) HS3ST3B1 (x334), MAP kinase 10 (x95), sulfotransferase 1E1 (x401), aldehyde dehydrogenase 3 family (x71), FABP (Fatty acid binding protein)-1 (x1359) Acyl coA synthase Acsl 6 (x39) and chondroitin 6 (x51).

Conclusions: Next Gen sequencing of kidneys with DN revealed pathways which regulate inflammation, oxidative stress, cell cycle and fibrosis. The pathogenic significance of these proteins particularly cyt P450, FABP-1, zinc finger proteins, HS3ST3 proteins adrenergic and cholinergic receptors in DN warrant more systematic investigation.

Funding: Private Foundation Support

FR-PO295

Heterogeneous Nuclear Ribonucleoprotein F Overexpression Stimulates Sirtuin 1 and Ameliorates Kidney Injury in Mice with Type 2 Diabetes Induced by High Fat-Diet/Streptozotocin Chao-Sheng Lo,[1] Anindya Ghosh,[1] Chin-Han Wu,[1] Shuiling Zhao,[1] Isabelle Chenier,[1] Janos G. Filep,[2] Julie R. Ingelfinger,[3] Shao-Ling Zhang,[1] John S.D. Chan.[1] *[1]CRCHUM, Univ of Montreal, Montreal, QC, Canada; [2]Res Ctr, Maisonneuve-Rosemont Hosp., Montreal, QC, Canada; [3]Pediatr Nephrol Unit, Mass Gen Hosp, Boston, MA.*

Background: We investigated the impact of overexpression of heterogeneous nuclear ribonucleoprotein F (hnRNP F, a transcription factor) on the expression and signaling of the NAD+-dependent deacetylase sirtuin 1 (SIRT1) and the development of renal proximal tubular cell (RPTC) inflammation and tubulointerstitial fibrosis in mice with type 2 diabetes induced by high fat-diet (HFD) and streptozotocin (STZ).

Methods: 4-week old hnRNP F-transgenic (hnRNP F-Tg) mice overexpressing hnRNP F in their RPTCs and non-transgenic littermates (C57BL/6 strain) were fed a normal diet (ND) or a HFD for 16 weeks and received a single STZ injection (45 mg/kg, i.p.) at week 8. Body weight and blood glucose were monitored weekly. Glucose tolerance and insulin sensitivity were assessed at week 19. At week 20, kidneys were processed for histology. Renal proximal tubular (RPT) gene and protein expression were evaluated by real time-qPCR and Western blotting, respectively. In vitro studies were performed on immortalized rat PTCs (IRPTCs) stably transfected with hnRNP F cDNA or Sirt1 gene promoter.

Results: HFD/STZ-treated mice developed obesity, hyperglycemia, hyperinsulinemia, insulin resistance and tubulointerstitial fibrosis parallel with markedly increased expression of pro-inflammatory (TNF-α, MCP-1 and PAI-1) and pro-fibrotic (TGF-β1, Col IV and FN1) markers and decreased expression of SIRT1 in RPTCs. These changes were attenuated in HFD/STZ-hnRNP F-Tg mice. In vitro, hnRNP F overexpression in IRPTCs stimulated Sirt1 gene promoter activity via a DNA responsive element (nucleotides N-973 to N-962 upstream of the transcriptional start site).

Conclusions: Our findings indicate that hnRNP F overexpression can attenuate RPTC inflammation and fibrosis in type 2 diabetes induced by HFD/STZ via up-regulation of Sirt1 gene expression and signaling.

Funding: Government Support - Non-U.S.

FR-PO296

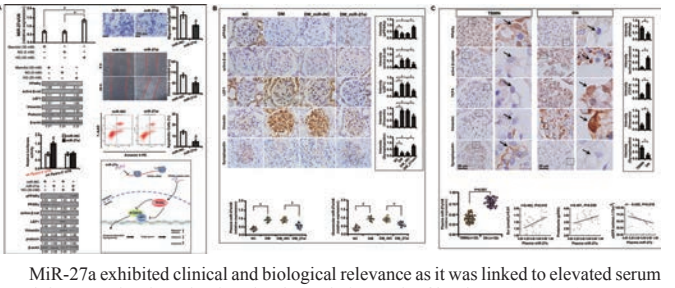
MicroRNA-27a Promotes Podocyte Injury via Suppression of PPAR gamma/β-Catenin Signaling in Diabetic Nephropathy Xiaoyan Bai. *Nephrology, Nanfang Hospital, Southern Medical Univ, Guangzhou, Guangdong, China; National Clinical Research Center for Kidney Disease, State Key Laboratory of Organ Failure Research, Guangdong Provincial Inst of Nephrology.*

Background: Podocyte injury plays a pivotal role in diabetic nephropathy (DN). MicroRNA-27a (miR-27a) upregulation has been identified in diabetes. We asked whether miR-27a mediates podocyte injury through PPAR gamma/Wnt/beta-Catenin signaling in DN.

Methods: The expression and functional relevance of miR-27a, PPAR gamma, and beta-Catenin were investigated in cultured podocytes and glomeruli of diabetic rats and patients using in vitro and in vivo approaches. Biological parameters were analyzed using enzyme linked immunosorbent assay (ELISA).

Results: High glucose stimulated miR-27a expression and promoted podocyte injury via repression of PPAR gamma/beta-Catenin signaling. Plasma miR-27a downregulation improved renal function and attenuated podocyte injury in diabetic rats (table 1) and DN patients.

Variables	DM_miR-iNC (n=7)	DM_miR-27ai (n=7)
Scr (umol/L)	114.37±7.56	67.25±2.28*
Serum BUN (mmol/L)	15.63±4.24	11.05±1.52*
Blood glucose (mmol/L)	26.31±1.36	25.70±2.15
UAER (ug/min)	1.45±0.21	0.67±0.06#
UACR (ug/mmol)	27.32±2.32	15.35±1.16#
Ccr ($mL \cdot min^{-1} \cdot Kg^{-1}$)	3.48±0.45	7.37±0.82#



MiR-27a exhibited clinical and biological relevance as it was linked to elevated serum creatinine, proteinuria and reduced estimated glomerular filtration rate (eGFR).

Conclusions: We propose a novel role of the miR-27a/PPARγ/β-catenin axis in fostering podocyte injury in DN. Targeting miR-27a could be evaluated as a potential therapeutic approach for DN.

FR-PO297

The miR-21/PDCD4/JNK Circuit Plays a Key Role in the Pathogenesis of Diabetic Nephropathy Hao Wu,[3,4] Yonggang Wang,[1] Yunfeng Qiao,[2] Tie Li,[4] Fuchun Wang.[4] *[1]China-Japan Union Hospital of Jilin Univ, China; [2]Jilin Province People's Hospital, China; [3]The Second Hospital of Jilin Univ, China; [4]Changchun Univ of Chinese Medicine, China.*

Background: c-Jun N-terminal kinase (JNK) and microRNA-21 (miR-21) play key roles in the pathogenesis of diabetic nephropathy (DN). However, it is unknown whether the two factors have reciprocal interactions which may form a positive feedback circuit that contributes to the pathogenesis of DN.

Methods: 8-week-old male C57BL/6J mice were induced to diabetes by injection of streptozotocin. A specific JNK inhibitor, SP600125, was administrated to diabetic mice in the presence or absence of a specific miR-21 mimic (miR-21-M). In addition, a specific miR-21 inhibitor (miR-21-I) was administrated to diabetic mice to determine its effect on JNK. To determine whether programmed cell death protein 4 (PDCD4), a known target of miR-21, was the key factor through which miR-21-I inhibited JNK function, the PDCD4 siRNA was delivered to miR-21-I treated mouse mesangial cells under high glucose condition.

Results: Both SP600125 and miR-21-I markedly inhibited JNK function. Furthermore, the inhibitors decreased renal miR-21 along with increased mRNA and protein levels of *pdcd*4. As a result, they both produced similar defences against diabetes-induced renal inflammation, fibrosis and albuminuria. Interestingly, co-administration of miR-21-M abolished the inhibitory effect of SP600125 on JNK function; indicating miR-21 as the upstream of JNK. Finally, PDCD4 siRNA abolished the inhibitory effect of miR-21-I on JNK function in high glucose cultured mouse mesangial cells.

Conclusions: The present study indicates a positive feedback loop between JNK and miR-21, which may play a key role in the pathogenesis of DN.

Funding: Government Support - Non-U.S.

FR-PO298

Screening miRNAs in Urine Exosomes as New Biomakers for Diabetic Kidney Disease Jing Zhang, Junwei Yang. *Center for Kidney Disease, Second Affiliatted Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Diabetic kidney disease (DKD) is the main cause of chronic renal failure, while the diagnosis of DKD is still based on proteinuria, serum creatinine, et al, which has some limitations. In this study, we would like to detect the miRNAs in urine exosomes of patients with type 2 diabetes mellitus (T2DM), to explore its correlation with proteinuria and renal function, and screening new biomarkers for early diagnosis of DKD.

Methods: Thirty inpatients with T2DM were enrolled in this study. According to the presence of microalbuminuria or clinical proteinuria, patients were randomly divided into three groups: group one is the patients without microalbuminuria or clinical proteinuria, group two is with microalbuminuria but without clinical proteinuria, and group three is with clinical proteinuria. Another ten healthy people were enrolled as control. Morning urine samples were collected from those patients, and urine exosomes were isolated by the kit and observed by transmission electron microscopy. Quantifications of urinary miRNAs were performed using stem-loop qRT-PCR followed by TaqMan PCR, and the correlations between miRNAs and proteinuria and renal function were analyzed.

Results: The exosomes isolated by the kit from 2ml of urine samples appeared as clusters of vesicles of 30-100nm in diameter under electron microscope. Compared with healthy controls, the levels of miR-21, miR-192 and miR-377 in urine exosomes of patients with T2DM were significantly increased, while the levels of miR-29a were significantly decreased ($P < 0.05$). And between each two of the three groups of T2DM, the levels of miR-21, miR-192, miR-377 and miR-29a changed significantly ($P < 0.05$). Moreover, the levels of miR-21 have a negative correlation with the estimated glomerular filtration rate (eGFR), while have positive correlations with blood urea nitrogen, serum creatinine and proteinuria ($P < 0.05$).

Conclusions: Compared with healthy control, the levels of miRNAs in urine exosomes of patients with T2DM change significantly, and have some correlations with proteinuria and renal function, which may be use as the new biomarkers of DKD.

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FR-PO299

microRNAs and Epigenetic Regulation of Genes in Diabetic Nephropathy Beina Teng, Janina Müller-Deile, Hermann G. Haller, Mario Schiffer. *Nephrology, Medical School Hannover, Hannover, Germany.*

Background: DNA methylation and microRNAs has been identified as two key mechanisms that underlie the evolutionarily conserved phenomenon associated with developmental and pathological gene regulation, thus may cause different pathological conditions in humans. Increasing evidence suggested that dysregulation of the epigenome and miRNA is involved in diabetic nephropathy, which is a serious complication of diabetes mellitus and is associated with high mortality.

Methods: We examined the expression profiling of miRNAS by performing a screening with urin from patient with diabetic nephropathy and healthy human, or human podocytes under diabetic conditons. A genome-wide methylation was screened in human podocytes stressed for 7 days with 30 mM glucose and mannitol as osmotic control. Samples for RNA expression microarrays were isolated from glomeruli of type I diabetic mice or human podocytes treated with high glucose for no less than seven days.

Results: We found that expression of 25 miRNAs were stastically significantly different not only in the patient with diabetic nephropathy but also human podocytes under diabetic conditions. Using prediction tool, we identified top 20 targets for all the 25 miRNAs and compared the candidates with RNA expression profiling. Furthermore we analyzed miRNA expression profiles and DNA methylation in a cross-sectional study of diabetic nephropathy and was able to identify the changes in miRNA expression under diabetic conditions that are regulated by aberrant DNA methylation.

Conclusions: Diabetic nephropathy is always accociated with dyregulation of several genes, which are epigenetically regulated or by miRNAs, which could be useful as biomarkers for diagnosis of diabetic nephropathy. Using an antagonist or mimic of miRNAs could be potential therapeutic strategy for diabetic nephropathy.

FR-PO300

miRNA Expression Correlates with Fibrosis in Diabetic Nephropathy Francesca Conserva,[1,2] Mariagrazia Barozzino,[2] Paola Pontrelli,[2] Annarita Oranger,[2] Francesco Pesce,[2] Federica Giannattasio,[2] Matteo Accetturo,[2] Massimo Papale,[2] Maria Teresa Rocchetti,[2] Giuseppe Castellano,[2] Simona Simone,[2] Salvatore Di Paolo,[3] Giovanni B. Pertosa,[2] Loreto Gesualdo.[2] *[1]IRCSS, Maugeri Fundation, Cassano Murge (BA), Italy; [2]Nephrology Unit, Dept of Emergency and Organ Transplant, Univ of Bari, Italy; [3]Nephrology Unit, Dimiccoli Hospital, Barletta (BA), Italy.*

Background: Diabetic Nephropathy (DN) is the primary cause of End Stage Renal Disease. We discovered that urines of DN patients (pts) are enriched in free ubiquitin and accumulation of lysine63-ubiquitinated (K63Ub) proteins at tubular level is involved in epithelial-to-mesenchymal transition (EMT). By microarray, we identified a set of miRNAs deregulated in DN kidneys. Aim of our study was to identify miRNAs regulating the increased expression of K63Ub proteins and involved in the progression of fibrosis in DN.

Methods: Total RNA was extracted from cell free urine of 10 biopsy-proven DN pts with type 2 diabetes (T2D), 10 pts with T2D and membranous nephropathy (MN) and 10 pts with T2D and normal renal function. miRNA expression was assessed by qPCR.

Results: Among deregulated miRNAs in DN kidney, we selected 9 miRNAs deregulated in DN pts (FC >1.5) compared to controls and T2D-MN. *In silico* we found 3 miRNAs with a predicted interaction with UBE2V1, an ubiquitin-conjugating E2 enzyme variant that mediates the formation of K63Ub chains. These miRNAs downregulation was further validated on both kidney biopsies ($p<.01$, DN vs CTRL, $p<.03$ T2D-MN vs CTRL, $p<.05$ DN vs T2D-MN) and *in vitro* on tubular cells in a model of hyperglycemia (FC=-2.3). Since those miRNAs were described as correlated to EMT, we tested their prognostic strength in the progression of kidney damage by matching urinary expression with the degree of fibrosis at the tissue level. Interestingly 1 miRNA was significantly downregulated in urines of DN pts compared to other groups. Moreover, this miRNA urinary levels were independent predictors of the degree of renal fibrosis in DN ($p=.03$).

Conclusions: In conclusion we confirm the role of ubiquitination as a pathogenic mechanism in the progression of kidney damage and suggest the validation of this miRNA as diagnostic biomarker of tubular-interstitial fibrosis progression in DN.

FR-PO301

Altered Distribution of HDL, Extracellular Vesicle and Argonaute-2 Associated Circulating microRNAs in Diabetic Nephropathy and Systemic Microvascular Damage Barend W. Florijn,[1,2] Jacques Duijs,[1,2] Geesje M. Dallinga-Thie,[3] Anita N. Böing,[4] Wendy Stam,[1,2] Ton J. Rabelink,[1,2] Marlies Reinders,[1] Roel Bijkerk,[1,2] Anton Jan Van Zonneveld.[1,2] *[1]Dept of Internal Medicine, Leiden Univ Medical Center, Leiden, Netherlands; [2]Einthoven Laboratory for Experimental Vascular Research, Leiden Univ Medical Center, Leiden, Netherlands; [3]Dept of Vascular Biology, Amsterdam Medical Center, Leiden, Netherlands; [4]Dept of Clinical Chemistry, Amsterdam Medical Center, Leiden, Netherlands.*

Background: We previously demonstrated an association between total plasma levels of specific microRNAs (miRNAs) and microvascular injury in patients with diabetic nephropathy (DN). Circulating miRNAs are carried by extracellular vesicles (EVs), RNA-binding protein Argonaute2 (Ago2) or high-density lipoprotein (HDL). Identification of the carrier specificity of these miRNAs can enhance the biomarker potential of miRNAs. In addition, carrier-specific transfer of miRNAs to vascular cells may play a causal role in vascular injury.

Methods: Here we assessed the plasma carrier distribution of miRNAs in DN (n=21), diabetes mellitus (DM; n=15; eGFR ≥ 30 mL/min) patients and healthy controls (n=15). EVs, HDL and Ago2 were isolated using size exclusion chromatography, KBr density gradient ultracentrifugation and immunoprecipitation respectively. MiRNA expression was determined using TaqMan® miRNA Arrays and correlated to markers of vascular injury, including angiopoietin-1 (Ang1), angiopoietin-2 (Ang2),soluble thrombomodulin (sTM) and capillary density.

Results: Specific miRNA-carrier complexes were identified to be associated with DN and vascular injury. EV-miR-21 and Ago2-miR-660 levels displayed a significant increase in both DM and DN groups compared to healthy controls and correlated with capillary tortuosity and sTM respectively. Furthermore, HDL-miR-132 levels decreased in DN and correlated with levels of Ang2, while both HDL-miR-152 and Ago-miR-152 levels displayed a significant increase in DN. Interestingly, only Ago-miR-152 levels correlated with levels of Ang2 and sTM.

Conclusions: Our data suggest that miRNAs in specific carriers may contribute to vascular injury and could improve selectivity and sensitivity of biomarkers for microvascular injury in DN.

FR-PO302

Characterizing the Urinary Peptidome of Early Type 1 Diabetes to Infer Protease Activity in the Kidneys Julie Anh Dung Van, Ashley Di Meo, Eleftherios P. Diamandis, James W. Scholey, Ana Konvalinka. *Medicine, Univ of Toronto, Toronto, ON, Canada.*

Background: Proteolytic activity in the kidney may induce early functional and structural changes in type 1 diabetes. Evidence suggests that this activity may be specific to some proteases and their protein substrates, and that resulting peptides generated within kidney may be excreted into the urine and provide a footprint of intrarenal proteolysis. We aim to compare urinary peptidomes of adolescents with uncomplicated type 1 diabetes and healthy peers and to infer protease activity in the kidney by using differentially excreted peptides.

Methods: We collected second-morning, midstream urines from 15 cases with type 1 diabetes and 15 age- and sex-matched controls from the observational arm of the Adolescent Diabetes Cardio-Renal Intervention Trial at The Hospital for Sick Children in Toronto. Urine volumes normalized to 90 umol of creatinine were subjected to 10kDa filter centrifugation to isolate naturally occurring peptides. Filtered peptides were then fractionated by strong cation exchange liquid chromatography and analyzed on Q-Exactive mass spectrometer. MaxQuant software was used for peptide/protein identification and label-free quantification. Peptide Extractor and Proteasix were used to infer protease activity based on the amino acid sequence of peptides.

Results: While our study is currently ongoing, our preliminary data revealed promising results. A total of 1098 peptides from 307 unique proteins were identified in a healthy volunteer urine sample. The coefficients of variation were 35% for samples processed on the same day and and 40% for samples processed on different days. Uromodulin, collagen and clusterin fragments were among the most abundant kidney-derived peptides. Bioinformatic analyses showed that proteolysis occurred near the C-terminus of the proteins and that it was perhaps carried out by plasmin and trypsin.

Conclusions: Our preliminary findings suggest that we can identify urine peptides with good reproducibility. Furthermore, we computationally predicted endogenous protease activity by examining the urinary peptidome. Future work will be conducted in a cross-sectional study of patients with diabetes and healthy controls.

FR-PO303

Global Proteomic Analysis of Insulin Action in Glomerular Podocytes Salman Hosawi,[1] Richard Coward,[2] Martin J. Humphries,[1] Rachel Lennon.[1,3] *[1]Wellcome Trust Centre for Cell-Matrix Research, Univ of Manchester, United Kingdom; [2]Academic Renal Unit, Univ of Bristol, United Kingdom; [3]Inst of Human Development, Univ of Manchester, United Kingdom.*

Background: Diabetic nephropathy (DN) is a leading cause of kidney failure world wide. In DN, there is progressive glomerular dysfunction and recent studies have demonstrated that the podocyte is a direct target for insulin action. Furthermore, deletion of the insulin receptor (IR) from podocytes leads to progressive kidney damage and eventually kidney failure. This study utilised a global unbiased proteomic approach to examine insulin signaling in podocytes under normal and resistant conditions, with the aim of identifying key molecules that could be targeted for diagnostic or therapeutic purposes.

Methods: Mouse and human immortalised podocyte cell lines were used under normal or resistant conditions (induced by the free fatty acid palmitate). The IR was isolated following whole cell immunoprecipitation (IP) or plasma membrane immunoprecipitation (PM-IP) and label-free mass spectrometry (MS) was used to detect alterations in insulin signaling. Western blotting was used for candidate validation and glucose uptake assays were employed to assess functional responses to insulin stimulation.

Results: Both human and mouse podocytes responded to insulin stimulation, and this response was abolished in the presence of 500uM palmitate. The conditions for isolating the IR using (IP) from whole cell lysates and (PM-IP) were optimised. 23 of the previously described IR interactors were detected by MS in addition to a number of potentially novel or podocyte-specific interactors. Furthermore, palmitate-induced insulin resistance altered the IR interactome in podocytes.

Conclusions: This study provides insight into the complexity and specificity of insulin signaling in podocytes, and may explain how insulin resistance can affect the integrity of the glomerular filtration barrier in diseases such as DN. The different methods of isolating the IR provided a better view on the level of disruption of the insulin signaling pathway. Selected candidates from the MS data could be targeted for therapeutic purposes, or could be used as diagnostic markers for podocyte injury.

Funding: Government Support - Non-U.S.

FR-PO304

Silac-Based Proteomics of Primary Human Kidney Cells Reveals a Novel Link between Male Sex Hormones and Impaired Energy Metabolism in Diabetic Kidney Disease Sergi Clotet-Freixas,[1,2] Maria Jose Soler,[2] Marta Riera,[2] Julio Pascual,[2] Fei Fang,[1] Clara Barrios,[2] Eleftherios P. Diamandis,[3] James W. Scholey,[1] Ana Konvalinka.[1,3] *[1]Univ Health Network, Toronto, ON, Canada; [2]Nephrology, Hospital del Mar-Inst Hospital del Mar d'Investigacions Mèdiques, Barcelona, Spain; [3]Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, ON, Canada.*

Background: Male sex predisposes to many kidney diseases.We hypothesized that dihydrotestosterone(DHT) would alter the biology of the renal tubular cell by inducing changes in the proteome.

Methods: We employed spike-in SILAC to accurately quantify the proteome in DHT- and 17β-estradiol(EST)-treated human proximal tubular epithelial cells(PTEC). Top candidate proteins were verified in vitro and in vivo by Western Blot.Renal oxidative stress(OS) was assessed by nitrotyrosine immunostaining.

Results: Of the 5043 quantified proteins, 104 were differentially regulated. Biological processes related to energy metabolism were significantly enriched among DHT-regulated proteins.SILAC ratios of 3 candidates representing glycolysis,N-acetylglucosamine metabolism and fatty acid β-oxidation, namely glucose-6-phosphate isomerase(GPI),glucosamine-6-phosphate-N-acetyltransferase 1(GNPNAT1) and mitochondrial trifunctional protein subunit alpha(HADHA),were validated in vitro and in vivo.Males showed significantly higher renal GPI,GNPNAT1 and HADHA in 2 models of diabetes.Enrichment analysis revealed a link between our DHT-regulated proteins and OS in the diabetic kidney,which was validated in vivo.

Candidate proteins for validation	Median SILAC ratio (n=3-4)		In vitro validation studies (n=3-4)		
	DHT/CONT	EST/CONT	CONT	DHT	EST
GPI	12.1±9.1*	1.2±3.2	0.32±0.2	1.30±0.2*	0.78±0.4
GNPNAT1	5.6±1.6*	2.2*±0.0	0.22±0.1	1.58±0.2*	0.40±0.4
HADHA	8.0±1.1*	0.9±0.7	0.96±0.3	2.02±0.5	1.33±0.1
	*p<0.05 according to significance A (Perseus software)		*p<0.05 vs CONT (U test)		
	In vivo validation studies (n=5-7)				
	Female-CONT	Male-CONT	Female-STZ	Male-STZ	Female-Akita	Male-Akita
Renal GPI	0.59±0.0	0.90±0.1*	0.85±0.1	1.16±0.2	0.67±0.1	1.22±0.3
Renal GNPNAT1	0.98±0.1	0.66±0.1	0.76±0.1	0.88±0.1	0.55±0.1	1.01±0.1*
Renal HADHA	0.48±0.0	0.87±0.1*	0.65±0.1	0.97±0.1*	0.65±0.1	1.25±0.2*
Renal nitrotyrosine (% positive area)	8239±2.0	22262±4.2*	13917±1.6	22038±2.3*	N.A	N.A
	*p<0.05 vs Female (U test)					

Conclusions: This is the most in depth quantitative proteomic study of human primary PTEC response to sex hormones.We suggest for the first time that male sex hormones perturbed energy metabolism in kidney cells,resulting in increased oxidative stress in the cortex.We propose a novel link that may help to understand the more rapid kidney disease progression ascribed to male sex.

FR-PO305

Id1 Expression in Kidney Endothelial Cells Protects against Diabetes Induced Microvascular Injury Matthew D. Plotkin,[1] Shree G. Sharma.[2] *[1]Nephrology, UAMS and John L McClellan VA Hospital, Little Rock, AR; [2]Nephropath, Little Rock, AR.*

Background: The inhibitor of differentiation (Id) family of transcription regulators are induced in response to growth factors and oxidative stress and have an important role in promoting cell proliferation and inhibiting senescence. Id1 expression in endothelial cells (EC) is required for a normal response to injury. Id1 expression is limited to EC in the normal kidney. Because endothelial dysfunction is an important mechanism in the development of diabetic nephropathy, we determined if endothelial Id1 expression prevents microvascular injury and nephropathy in response to hyperglycemia.

Methods: Streptozotocin treated Id1 knockout and WT B6;129 littermates were examined at 3 and 6 months. EC were isolated from these mice by FACS and used for whole genome microarray analysis.

Results: Id1 expression was increased up to 15-fold in WT diabetic kidney EC. Id1 diabetic KO mice developed mesangial and peritubular and glomerular myofibroblast proliferation and matrix deposition. Electron microscopy demonstrated peritubular capillary endothelial cell injury and lumen narrowing. EC damage in KO mice was associated with increased albuminuria compared with WT mice. Fluorescence microangiography showed a 45% reduction in capillary perfusion area despite no significant reduction in CD31 stained areas. Gene expression microarray analysis of EC isolated from WT and KO control and diabetic mice demonstrated upregulation of type I bHLH transcription factors and activation of cell senescence pathways in KO cells. Kidneys from KO diabetic mice showed increased EC macroH2A.1.1 expression, a senescence associated heterochromatin marker. Examination of cultured EC showed that Id1 expression was induced by low level oxidative stress and KO resulted in decreased cell proliferation, increased p53 expression and expression of DNA damage and senescence markers compared with WT cells.

Conclusions: These results suggest that endothelial Id1 upregulation in response to hyperglycemia is an adaptive response that protects against microvascular injury and senescence and the development of nephropathy.

Funding: VA Support

FR-PO306

Heparanase-2 Antagonizes Heparanase-1-Induced Shedding of Endothelial Glycocalyx and Prevents Endothelial Dysfunction and Albuminuria in Zebrafish Hermann G. Haller, Yulia Kiyan, Sergey Tkachuk, Klaus Stahl, Anna Bertram, Sarah Berger, Mario Schiffer. *Clinic of Hypertension and Nephrology, Hannover Medical School, Hannover, Germany.*

Background: Heparanase-1 is induced by hyperglycemia and mediates the deleterious effects of hyperglycemia on the endothelium. Heparanase-2, a homologue of heparanase-1, associates physically with heparanase-1 and inhibits heparanase enzymatic activity. Using (1) cultured endothelial cells in a microfluidity chamber and (2) a zebrafish model of glomerular albuminuria we have tested the hypothesis that heparanase-2 prevents heparanase-1-induced downregulation of endothelial glycocalyx and exerts ant-inflammatory effects.

Methods: Endothelial glycocalyx was assessed by confocal microscopy and dot-blot analysis in cultured microvascular endothelial cells (MEC). Gene expression was analysed by RT-PCR and microarray. Heparanase-2 was down-regulated by morpholino in transgenic zebrafish Tg(l-fabp:DBP:EGFP) and proteinuria assessed by the Fabp-eye-assay. Glomerular endothelial cells were assessed by EM. Gene and protein expression was analyzed by real-time qPCR and western blot analysis.

Results: High glucose induced expression of heparanase-1 and shedding of glycocalyx. Overexpression of heparanase-2 prevented the loss of glycocalyx, while silencing of heparanase-2 exacerbated glycocalyx loss. In addition, heparanase-2 overexpression reduced monocyte adhesion, reduced NFkB signalling and led to an anti-inflammatory cytokine pattern. In zebrafish silencing of heparanase-2 induced edema, endothelial cell swelling and massive proteinuria in the zebrafish. Rescue experiments with different heparanase-2 constructs demonstrated that the C-terminus is responsible for the protective effects on the glomerular endothelial cells.

Conclusions: Heparanase-2 stabilizes the endothelial glycocalyx and prevents heparanase-1 induced endothelial damage and dysfunction. It is the first endogenous heparinase-1 inhibitor and induction of heparanase-2 may be a therapeutic strategy in diabetic nephropathy and other glomerulopathies.

FR-PO307

Soluble Nogo-B Improves Altered Angiogenesis: Implication for Diabetic Kidney Disease Luigi Gnudi,[1] Jiaqi Pan,[1] Xiaoyan Bai,[2] Anthea Elaine Hayward,[1] Kathryn E. White,[3] Fan Fan Hou,[2] David A. Long.[4] *[1]Cardiovascular Div, King's College London, London, United Kingdom; [2]Nanfang Hospital, Southern Medical Univ, Guangzhou, China; [3]Electron Microscopy Unit, Univ of Newcastle upon Tyne, Newcastle upon Tyne, United Kingdom; [4]Inst of Child Health, Univ College London, London, United Kingdom.*

Background: Abnormal angiogenesis is involved in the pathogenesis of diabetic nephropathy (DN). Neurite outgrowth inhibitor (Nogo)-B is expressed in endothelial cells (EC) and vascular smooth muscle cells. A soluble form of Nogo-B (sNogo-B) has been identified in the circulation and promotes angiogenesis by binding to the Nogo-B receptor NgBR on EC. We asked whether Nogo-B is expressed in glomeruli and whether its expression is modulated by diabetes, further we explored whether sNogo-B could ameliorate abnormal angiogenesis in an experimental model of DN with human cells incubated with patients' serum.

Methods: Nogo-B expression in glomeruli of control and diabetic mice was assessed with immunogold and western immunoblotting. Kidney biopsies of patients with DN and thin basement membrane nephropathy (as control) were utilised for Nogo-B expression analysis with immunoistochemistry. Angiogenesis assay was conducted with human umbilical vein endothelial cells (HUVEC) on matrigel; HUVEC were incubated with serum (4%vol/vol) of patients with type 1 diabetes with (T1DM/DN+) or without a history of albuminuria (T1DM/DN-); T1DM/DN+ and T1DM/DN- patients had similar clinical characteristics. sNogo-B was overexpressed with viral vector.

Results: Full length Nogo-B was expressed in glomerular EC and podocytes; Nogo-B was downregulated in glomeruli of diabetic mice and of patients with DN ($p<0.04$). Overexpression of sNogo-B rescued the altered angiogenesis (reduced tube length/number) observed in HUVEC incubated with T1DM/DN+ serum ($p<0.02$), while no effect was observed in the angiogenesis of HUVEC incubated with serum from T1DMDN-patients. Overexpression of sNogo-B in HUVEC was paralleled by a decrease in AKT^{Ser473} phosphorylation ($p=0.02$), no change was observed in AKT^{Thr308} phosphorylation.

Conclusions: Nogo-B is downregulated in diabetic glomerulopathy. sNogo-B could represent a potential treatment of abnormal angiogenesis in DN.

FR-PO308

Expression of Complement Components in Primary Human Glomerular Endothelial Cells after a Diabetic-Like Insult Julie Williams,[1] Troels Krarup Hansen,[2] Kamilla Pajecka.[1] *[1]Diabetes Complications Research, Novo Nordisk A/S, Måløv, Denmark; [2]Dept of Endocrinology and Diabetes, Aarhus Univ, Aarhus, Denmark.*

Background: Low-grade inflammation (e.g. elevated serum TNFα and IL1β), hypoxia and dysregulated innate immunity are well-recognized contributors to diabetes mellitus (DM) and therefore diabetic nephropathy (DN). The glomerular endothelium becomes pro-inflammatory in DN patients, yet it is unclear if and to what extent the endothelium contributes to the production of complement components and regulators. In this study we analyzed complement gene expression in primary human glomerular endothelial cells (hGEnCs) with and without a DM-like insult.

Methods: Primary hGEnCs were grown in RPMI medium supplemented with either 6.5 mM (normal) or 25 mM (high) glucose. The cells were cultured for 8 days with a media change every 48 h to allow exposure to a diabetic-like environment. During the final 48 h in culture, the cells were exposed to a second insult, i.e. TNFα, IL1β or hypoxia, to mimic DN pathopysiology. The gene expression level was quantified by qPCR.

Results: Untreated hGEnCs expressed moderate amounts of C2, C3, C4, C5, C7, C8g, CFB, CFD, CFP and VTN and very low levels of C9. They also expressed high levels of CFH, CFI, CD46, CD55, CD59 and CLU. Neither unstimulated nor stimulated hGEnCs expressed C6, C8a, C8b, C4BPB, or CD35. The expression of only a very few components was regulated. C2 was increased 4x with TNFα, while C3 was greatly up-regulated by IL1β and TNFα (both approx. 500x). Neither hypoxia nor pre-treatment with high glucose had any effects. CFB was also highly regulated. Its expression increased 40x after TNFα and 20x after IL1β treatment, but remained unchanged after 48 hours of hypoxia. CFP, CLU and VTN were decreased (3-8x) after TNFα or IL1β treatment and hypoxia had a moderate effect on their expression.

Conclusions: Human GEnCs expressed the majority of the main and auxiliary complement components, but at different levels. Their expression was modulated by pro-inflammatory cytokines involved in DN pathology (TNFα and IL1β) as well as hypoxia. The cytokines caused a considerable up-regulation of C3 and CFB molecules, which are known to be up-regulated in glomeruli from DN patients.

Funding: Pharmaceutical Company Support - Novo Nordisk A/S

FR-PO309

Increased Serum Platelet Microparticle Contributes to Glomerular Endothelial Injury in Diabetic Nephropathy Yang Zhang, Kun Ling Ma, Zebo Hu, Gui Hua Wang, Liang Liu. *Inst of Nephrology, Southeast Univ, Nan Jing City, JIang Su Province, China.*

Background: The release of Platelet microparticles(PMPs) is considered to be proinflammatory and eliciting cytokine reponses. This study was undertaken to investigate the role of PMPs in glomerular endothelial injury in diabetic nephropathy (DN).

Methods: Eight-week old male *Sprague-Dawley* rats were divided into three groups: nondiabetic rats (control), streptozotocin-induced diabetic rats (DM), and diabetic rats treated with Aspirin (DM+ Aspirin). The determination of PMPs was used by flow cytometry and confocal microscopy. The inflammatory cytokines released from PMPs was checked by protein microarray contain a variety of inflammatory cytokines, immunohistochemical staining, or Western blot. The glomerular endothelial injury was evaluated through measuring the change of endothelial surface layer (ESL), endothelial fenestration, cellular junction, and glomerular permeability by electron microscope, immunofluorescence staining and Western blot. The ratio of urinary microalbumin to creatinine (ACR) was detected by enzyme-linked immunosorbent assay.

Results: Compared to the control, the serum level of PMPs was significantly increased in DM rats, while it was reduced by Aspirin. Aspirin treatment decreased the production of inflammatory cytokines in PMPs suspension, blood serum and glomerulus. Using confocal microscopy, the enhanced interaction between PMPs and glomerular endothelium was observed in DM rat, which was inhibited by Aspirin. Interestingly, the elevated PMPs and production of inflammatory cytokines from PMPs were correlated with the glomerular endothelial injury by decreasing the ESL thickness and endothelial fenestration, destroying cellular junction, increasing glomerulus permeability and the level of ACR in DM rats. Decrease of serum PMPs and production of inflammatory cytokines by Aspirin ameliorated the glomerular endothelial injury compared to the DM group.

Conclusions: Elevated serum PMPs contributes to glomerular endothelial injury in diabetic nephropathy through the release of inflammatory cytokines from PMPs.

FR-PO310

The Progression of Diabetic Nephropathy in CSE-/-, eNOS-/-, db/db, CSE-/- db/db, and eNOS-/- db/db Murine Models: A Comparative Study Eric Linville, Deborah J. McCarthy, Christopher G. Kevil, Kevin J. McCarthy. *Dept of Pathology and Translational Pathobiology, LSU Health Sciences Center, Shreveport, LA.*

Background: Targeted deletion of eNOS ($eNOS^{-/-}$ *db/db* mouse) is associated enhanced development of glomerulosclerosis. However, the role of another gasotransmitter, hydrogen sulfide, (H2S) in the onset and progression of diabetic nephropathy is still not entirely clear. The purpose of this study was to compare the development of diabetic nephropathy between $CSE^{-/-}$, $eNOS^{-/-}$,$CSE^{-/-}$*db/db,*and $eNOS^{-/-}$*db/db* models.

Methods: Age matched (16 wks) $CSE^{-/-}$, $eNOS^{-/-}$ and $eNOS^{-/-}$*db/db*, $CSE^{-/-}$*db/db* mice were used. Prior to sacrifice, blood was drawn for H2S measurement. After sacrifice, the kidneys were removed, and processed for light and electron microscopy, a segment of the kidney used for sulfide measurement. Morphology readouts included measurement of glomerular areas (AT), mesangial areas (AM), and calculation of the AM/ AT ratio. Pedicel effacement was determined by TEM. H2S levels and the presence of H2S metabolites in plasma and tissues was measured by HPLC.

Results: There were no differences in AT between $CSE^{-/-}$, $eNOS^{-/-}$ glomeruli; however an increase ($p<0.0001$) in AT was seen in $CSE^{-/-}$*db/db* and $eNOS^{-/-}$*db/db* glomeruli when compared to the former groups. There was no difference in AT between the *db/db*, and $eNOS^{-/-}$*db/db* glomeruli, but AT was less ($p<0.0001$) in the $CSE^{-/-}$*db/db* glomeruli. Mesangial areas (AM) followed a similar trend, except that AM increased ($p<0.0001$) in the $eNOS^{-/-}$*db/*

db glomeruli over all groups. The AM/ AT ratio, an indicator of mesangial expansion, was not different among the diabetic animal models. There were no differences in the ultrastructural morphology among the diabetic models. H2S metabolites were significantly reduced in plasma and kidneys of *db/db* mice. Measurement of discrete biochemical sulfide forms revealed that bound sulfane sulfur was blunted in $CSE^{-/-}$ and *db/db* mice, with $CSE^{-/-}$*db/db* mice showing the greatest reduction in bound sulfane sulfur in the kidney.

Conclusions: These reductions suggest a potential difference in sulfide dependent signaling responses, the mesangial cells appear to be most affected by changes in H2S.

Funding: NIDDK Support, Other NIH Support - NHBLI

FR-PO311

Altered Hemodynamic Responses to Infused Insulin in TALLYHO/Jng Obese Mice Carolyn M. Ecelbarger,[1] Swasti Tiwari,[2] Hwal Lee,[1] Lijun Li.[1] *[1]Dept of Medicine, Georgetown Univ, Washington, DC; [2]Sanjay Gandhi Post-Graduate Inst of Medical Sciences, Lucknow, India.*

Background: Insulin resistance blunts glucose uptake in the major metabolic tissues; however, the impact of "insulin-resistance" within the cardiovascular-renal system remains unclear. Previously we showed reduced protein expression for the insulin receptor (IR) in different regions of the kidney in obese, relative to lean rats; however, the main metabolic factors driving IR expression in kidney were unclear, as well as, whether these changes were associated with altered hemodynamics.

Methods: We infused young, adult lean (C57Bl6) and obese (TALLYHO/Jng) male mice (n = 6/group) with insulin (40 U/kg bw/d) for 2 weeks while monitoring blood pressure (BP) and heart rate (HR) by radiotelemetry. In additional mice (F2 cross, 75% TALLYHO/25% C57Bl6) we correlated metabolic factors with IR protein in different regions of the kidney to determine which factors were best correlated with IR.

Results: Obese mice had significantly higher basal BP (10-12 mm Hg) with a slight fall in BP (mean 4 mm Hg) in the first 3 days of insulin infusion, which returned to basal levels by day 14. In contrast, lean mice demonstrated a mean 7 mm Hg fall in the first 3 days, followed by a fairly substantial rise (15 mm Hg). Basal HR was significantly higher in the obese mice (mean 650 versus 540 beats per minute); however, HR rose in the lean mice sharply in the first 2 days then stabilized at a higher level. This rise was not seen in obese mice. At two weeks, no significant differences existed between lean and obese mice for HR or BP. Body weight was significantly negatively correlated with IR protein in kidney cortex and outer medulla. Glucose peak during a glucose tolerance test was also negatively correlated with IR protein in the outer medulla.

Conclusions: Hemodynamic responses to insulin infusion are attenuated in obese mice indicating "insulin resistance" of these cardiovascular responses. Chronic insulin infusion abrogated differences between lean and obese mice suggesting insulin, per se was the direct cause of these differences. Reduced renal IR expression may partially explain attenuated responses to insulin infusion in obese mice.

Funding: NIDDK Support, Clinical Revenue Support

FR-PO312

Deficient Endothelial Heparan Sulfate Prevents Renal Inflammation and Fibrosis in Murine Diabetic Nephropathy Ditmer Talsma,[1] Kirankumar Katta,[2] Marieke A.B. Ettema,[1] Berna Kel,[1] Marion Kusche-Gullberg,[2] Coen A. Stegeman,[1] Jacob van den Born,[1] Lianchun Wang.[3] *[1]Dept of Neph., UMCG, Netherlands; [2]Dept of Biomed., Univ of Bergen, Norway; [3]Dept of Glycoconjugates in Animal Dev., Disease & Cancer, Univ of Georgia.*

Background: Recent findings suggest a role for inflammation in the development of diabetic nephropathy (DN). Endothelial heparan sulfate (HS) is known for its cytokine/chemokine binding capacities and subsequent presentation to high affinity receptors on leukocytes. For the sulfation and function of HS the enzyme N-deacetylase N-sulfotransferase-1 (NDST-1) is essential. In this study we aim to assess the role of endothelial HS in renal inflammation and fibrosis in a mouse DN model.

Methods: To induce diabetes, age matched C57Bl/6J^{-} WT and Tie2 Cre^{+} NDST-$1^{f/f}$ mice were intraperitoneally injected with streptozotocin (50 mg/kg). Control mice received citrate buffer (n=8-10/group). At baseline, two and eight weeks follow up urine and plasma was collected and plasma glucose, urinary creatinine and albuminuria were measured. Two months after diabetes induction the animals were sacrificed and kidneys were immunohistochemically stained for macrophages, collagen III and αSMA. Expression of VCAM-1, collagen I, III, IV, TGF-β1 and fibronectin was measured using qRT-PCR.

Results: Diabetes induction was evidenced by significant increased values of blood glucose and albuminuria, without differences between WT and KO animals. Compared to WT, NDST-1 KO animals showed decreased interstitial macrophages ($p<0.05$). The reduction in inflammation was confirmed by a reduced mRNA expression of VCAM-1 ($p<0.001$). KO animals also showed a reduced interstitial collagen III deposition ($p<0.001$) and myofibroblast shown by a reduction interstitial αSMA staining ($p<0.01$). The reduction in fibrosis was confirmed a reduced mRNA expression of collagen I ($p<0.001$), III ($p<0.05$), IV ($p<0.01$), TGF-β1 ($p<0.01$) and fibronectin ($p<0.001$). Furthermore, glomerulosclerosis was reduced in the NDST-1 KO animals ($p<0.001$).

Conclusions: Our results show the role of endothelial HS in the development of renal inflammation and subsequent fibrosis in DN in mice. These results suggest that HS can be a possible target for therapy in DN.

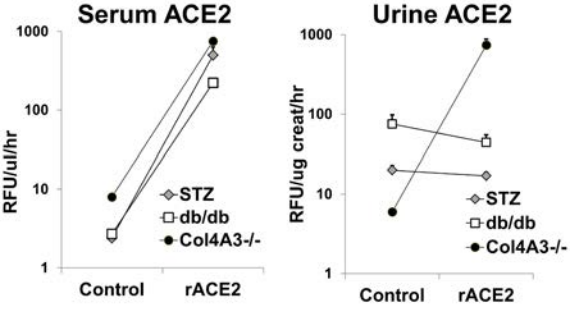
FR-PO313

Delivery of Murine Recombinant ACE2 in Different Mouse Models of Albuminuria Jan A. Wysocki, Minghao Ye, Daniel Batlle. *Northwestern Univ, Chicago, IL.*

Background: Targeting RAS is the mainstay of therapy for CKD. New approaches, based on fostering the degradation of Ang II, rather than blocking the formation or action of AngII could be complementary or even better. ACE2, the main enzyme that degrades Ang II, is a large 100kD protein that normally is not filterable by glomeruli. This study examined whether murine recombinant (r)ACE2 can increase urinary and kidney ACE2 in three models of kidney disease with different degrees of albuminuria.

Methods: *db/db* mice, mice with STZ-induced diabetes and Alport model of CKD due to *col4A3* gene deficiency that results in advanced alterations in the glomerular basement membrane and robust proteinuria were used. Serum ACE2 was overexpressed chronically using ACE2 minicircle (MC) in STZ mice or acutely via i.p. injection of rACE2 to *db/db* and *Col4A3-/-* mice. ACR was 534±70, 87±23 and 3902±495 ug/mg in *db/db*, STZ and Alport mice, respectively.

Results: In McACE2-treated STZ mice, serum ACE2 activity was markedly augmented, but urine ACE2 activity did not increase (Figure). In *db/db*, infusion of rACE2 increased serum ACE2 activity markedly without any increase in urine ACE2 activity (Figure). By contrast, in mrACE2-treated *Col4A3-/-* mice, the increase in serum ACE2 activity was associated with a marked increase in kidney (5.5 vs. 13.5±3.6 RFU/ug prot/hr) and urinary ACE2 activity (Figure).



Conclusions: A large enzyme such as ACE2 cannot be filtered in mouse models of diabetes-induced moderate glomerular injury such as in STZ and db/db with modest albuminuria. When glomerular permeability is sufficiently altered, as in the *Col4A3 -/-* model of CKD with robust proteinuria, an increase in serum ACE2 results in an increase in both kidney and urinary ACE2 activity. The potential renoprotective action of this enzyme will likely depend on local kidney delivery rather than systemic levels in the circulation.

Funding: NIDDK Support, Private Foundation Support

FR-PO314

Effect of ACE2 Deletion on Circulating and Renal ACE in Non-Obese Diabetic (NOD) Mice Vanesa Palau, Heleia Roca Ho, Marta Riera, Marta Rebull, Javier Gimeno, Julio Pascual, Maria Jose Soler. *Nephrology, Hospital del Mar Medical Research Inst (IMIM), Barcelona, Spain.*

Background: ACE2 is altered in diabetic nephropathy(DN). Downregulation of ACE2 either by gene deletion or by pharmacological inhibition worsens DN in STZ and Akita model of type 1 diabetes. We demonstrated that loss of ACE2 contributes to an increase in DN progression in the non-obese diabetic(NOD) mice. We hypothesized that ACE is altered in ACE2KO mice under NOD and NOR background.

Methods: NOD and non-obese resistant(NOR) mice with a deletion on ACE2 gene compared to NOD and NOR WT mice after 30 days of diabetes were studied. Systolic blood pressure(SBP), glucose and urinary albumin excretion(UAE) were measured. ACE enzymatic activity in serum and renal cortex were assessed by a fluorometric method. Renal cortex protein expression was studied by western-blot.

Results: NOD diabetic mice present significant increase in blood glucose, SBP and UAE as compared to NOR mice. However, no differences were observed between WT and KO mice. NODACE2 KO mice showed higher serum ACE activity compared with NORACE2 KO. NODACE2 KO mice showed a decreased circulating ACE activity as compared to NODACE2 WT. Renal ACE activity was increased in NORACE2 KO as compared to NORACE2 WT.

Conclusions: Diabetes increases blood glucose, SBP, UAE and serum ACE activity. Interestingly, ACE2 deletion decreases serum ACE activity in NOD mice and increases renal cortex ACE activity in NOR mice. These results suggested that ACE2 deletion exerts a different effect on circulating and renal ACE activity in diabetic and non-diabetic mice.

	Glucose (mg/dL)	SBP (mmHg)	UAE (µg Alb/mg Crea)	Serum ACE activity (RFU/µL)	Renal cortex ACE activity (RFU/µL)	Renal protein expression (ECA/β-actin)
NOR-ECA2$^{+/+}$ n=13	150,5±5,8	109,4±2,7	17,6±4,0	17982,5±985,2	1434,4±100,2	0,8±0,1
NOR-ECA2$^{-/-}$ n=10	153,8±3,1	104,2±2,4	19,9±3,7	19007,7±718,8	1823,6±159,7$^{\$}$	1,0±0,1
NOD-ECA2$^{+/+}$ n=13	596,5±3,5*	117,4±2,5*	770,1±270,2*	30519,5±1809,3*	1231,0±162,2	0,7±0,1
NOD-ECA2$^{-/-}$ n=10	600,0±0,0*	117,1±3,3*	512,0±288,3*	23794,4±2577,1*$^{\$}$	1361,1±184,1	0,9±0,1
* p≤0,05 NOD vs NOR; $ p≤0,05 KO vs WT						

FR-PO315

Effects of Angiotensin 1-7 on Klotho, mTOR and Podocyte Proteins Expression in Zucker Diabetic Fatty Rats

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Background: Current information indicates a link between Klotho deficiency and increased mTOR signaling which is associated with oxidative stress and inflammation/renal fibrosis in diabetic nephropathy. The RAAS blockade modulates Klotho, however, the role of angiotensin 1-7(ANG1-7) on Klotho and mTOR is still unclear. This study evaluates the effect of (ANG1-7)on Klotho, mTOR and podocyte proteins expression in kidney of Zucker Diabetic Fatty (ZDF) Rats.

Methods: ZDF and controls lean Zucker rats (LZR) were used: 1) ZDF+saline,2) ZDF+ANG1-7, 3) LZR+saline. For 4 wks, animals received either saline or ANG1–7 (100 ng·kg1·min1) by subcutaneous osmotic pumps. Kidneys were removed at the end of the experiment.Renal variables were evaluated at baseline/end of the experiment. Quantification and localization of Klotho, mTOR,WT1,Synaptopodin,Thioredoxin (Trx), Heat shock protein (HSP27)was evaluated by IHCh. Electron Microscopy was performed in order to evaluate potential GBM changes.

Results: Table1. IHCh data after four-week infusion

Mean±SD	ZDF+saline	ZDF+ANG1-7	LZR+saline
Trx¶	23.4±2.8	10.1±1.6†	2.2±0.5§
Klotho¶	5.8±1.5	12.5±2.4†	18.6±2.6§
mTOR♣	8.7±1.6	4.9±1.4†	3.2±1.7§
WT1♣	3.2±1.3	9.1±2.3†	10.8±2.6§
Synaptopodin♣	2.8±0.8	7.5±1.0†	8.0±1.3†
HSP27¶	23.3±2.7	8.0±2.1†	1.6±0.4§

¶% positive staining/area ♣ Number positive cells/glomerlus § p<0.01 vs. all groups † p<0.05 vs. ZDF+saline.

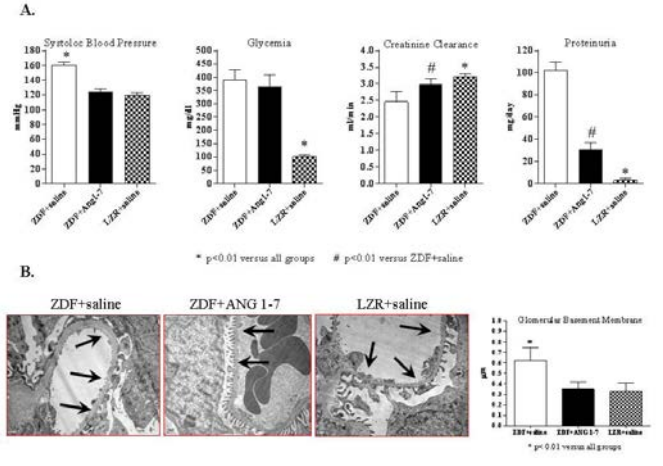

Figure 1. A.Relevant variables at the end of the experiment **B**.EM images of GBM (arrows).

Conclusions: Ang 1-7 infusion increased Klotho expression and modified favorably mTOR in kidney of ZDF rat. Furthermore, podocyte protein expression was also improved. These changes were associated with reduction in Trx, HSP27 and GBM thickness.

FR-PO316

Angiotensin Converting Enzime 2 Silencing Alters Podocyte Rearrangement

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Background: Renin angiotensin system(RAS) blockade has been shown to be effective in delaying diabetic nephropathy(DN) progression. Podocytes are key cells in glomerular filtration barrier with their own RAS. In the puromycin model of podocyte damage, an imbalance toward a more dynamic actin cytoskeleton and increased migration could underlie podocyte dysfunction. Our objective is to study the effect of ACE2 or InsRecp gene silencings in the growing and migration capability of podocytes. Furthermore the expression of genes related to fibrosis was also tested.

Methods: A conditionally immortalized mouse podocyte cell line proliferating was used. Differentiation was induced by non-permissive conditions removing γ-interferon at 37ºC for 10 days. Cells were then transfected with Silencer®Select siRNAs against ACE2 or InsR. After 24 hours, live time series were continuously recorded using Zeiss Cell Observer HS microscope with an incubation chamber (37°C, 5%CO2) for 17h. Comparisons were done between 0h and 17h of recording. Cells were stained for F-actin. Image processing was done by ImageJ.

Results: ACE2 gene silenced-podocytes showed a differentially cytoskeletal rearrangement as compared to the non-silenced cells. No differences were observed when InsR were silenced. This effect was correlated with a different pattern of growing after 17h. Podocytes not expressing ACE2 were significantly smaller than the control cells. On the contrary, the total perimeter of cells was similar indicating that ACE2-silenced podocytes presented more gaps between cells with fewer contact points(table). No differences were detected on TGF-β, Col4 or Fn1 gene expressions.

Conclusions: ACE2 may help to keep the shape and integrity of podocytes cytoskeleton. On DN RAS imbalance is changed and ACE2 loss may contribute to podocyte rearrangement, aggravating the disease.

Experimental condition	Number of cells per field	Area with cells per field (um²)	Area per cell in field (um²)	Total of cellular perimeter in field (um)	Increase of area with cells (%)
Cont_0h	36.4 ± 3.6	334999.1 ± 29271.6	9357.3 ± 804.7	7839.8 ± 588.1	-
Cont_17h	38.9 ± 3.5	473133.4 ± 37515.1	12303.6 ± 965.0*	7844.8 ± 1205.7	145.92 ± 2.49
siACE2_0h	39.5 ± 1.7	298807.1 ± 9789.8	7598.3 ± 247.8*	7634.5 ± 766.4	-
siACE2_17h	40.6 ± 2.4	438639.0 ± 14494.8	10987.5 ± 556.8§	9511.0 ± 1167.0	147.04 ± 3.39
siInsR_0h	36.38 ± 1.6	304381.5 ± 16444.0	8370.1 ± 452.1	7571.8 ± 573.6	-
siInsR_17h	36.0 ± 1.4	412168.3 ± 21071.5	11458.3 ± 585.3	7334.2 ± 627.8	136.91 ± 3.46

*p<0.05 vs. Cont_0h; §p<0.05 vs. Cont_17h

Funding: Government Support - Non-U.S.

FR-PO317

Vascular Actions of AT1 Angiotensin Receptors Do Not Contribute to Albuminuria or Hyperfiltration in Diabetic Kidney Disease

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Background: Blockade of the renin angiotensin system (RAS) reduces albuminuria, attenuates hyperfiltration, and slows the progression of diabetic nephropathy (DN) by preventing vasoconstriction and subsequent increases in glomerular hydrostatic pressure. Since RAS blockade disrupts Ang II signaling in all tissues, the specific contribution of vascular AT1R in DN has been difficult to delineate.

Methods: We generated 129SvEv mice with cell-specific loss of AT1A from VSMCs (SMKOs) using *Cre-loxp*. To remove AT1R from VSMCs, we crossed the SMKOs with AT1BR -/- mice, lacking the minor AT1B isoform. To study the impact of vascular AT1R in DN, we crossed AT1B-*null*SMKOs with mice having the *Ins2*^{C96Y} AKITA mutation, which develop DM1 early. To enhance kidney injury, mice underwent uninephrectomy (UNX) at 11wks.

Results: Glucose levels were elevated (~500mg/dL) and similar at 10, 16 and 24wks between the groups. Prior to UNX, albuminuria was similar between Control AKITA and (62±10 versus 107±27 µg/24hrs, P=NS). Albuminuria increased with age but with no significant differences between the groups at 16wks (307±106 Control AKITA vs 313±117 AT1B-*null*SMKO AKITA µg/24hrs; P=NS) or 24wks (494±236 versus 730±217 µg/24hrs; P=NS), despite a trend toward higher albuminuria in AT1B-*null*SMKO AKITAs. There was no significant difference in GFR (via FITC-inulin) between non-diabetic Control and AT1B-*null*SMKO (15.6±1.2 vs 14.8±0.8 µl/min/g BW), and hyperfiltration was observed in both Control AKITA (23.7±2.4 µl/min/g BW; P=0.003) and AT1B-*null*SMKO AKITA (20.7±1.7 µl/min/g BW; P=0.01) relative to their non-DM comparators. There was no difference in GFR between ControlAKITA and AT1B-*null*SMKO AKITA (P=NS). We measured mRNA levels by qPCR of putative kidney injury markers and found no differences in *Col1A1*, *NGAL*, or *TGFB1* between Control AKITA and AT1B*null*SMKO AKITA.

Conclusions: Our studies indicate that the absence of vascular AT1R responses is not sufficient to reduce albuminuria and prevent hyperfiltration in a mouse model of DN. This suggests that blockade of AT1R in other cell lineages may contribute to beneficial actions of ARBs in DN.

Funding: NIDDK Support, VA Support

FR-PO318

Altered Expression of Urate Transporters URAT1 and ABCG2 in Diabetic Rats and Their Response to Hypoglycemic Agents

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Background: Co-incidence of hyperuricemia is a common finding in diabetic patients, and previous studies suggest that insulin resistance is associated with the decreased renal clearance of uric acid (UA). Recent data also demonstrated that a Na^+-glucose co-transporter 2 (SGLT2) inhibitor can reduce serum UA in type 2 diabetes (Zinman et al. NEJM 2015). However, the detailed regulation of urate transporters in diabetes has remained unclear. Using rat models, we evaluated the changes in renal UA handling and urate transporters in diabetes, as well as their response to hypoglycemic agents.

Methods: SD rats received i.p. injection of streptozotocin (STZ; 70 mg/kg). Some rats received ipragliflozin (Ipra) (an SGLT2 inhibitor; 15 mg/kg chow) or insulin (s.c. *via* osmotic pump). After urine collection, kidneys were removed at day 7.

Results: Daily UA excretion was markedly increased in STZ rats as compared with controls (5.59 ± 0.32 mg/day in STZ vs. 0.46 ± 0.17 mg/day in control). Fractional excretion of UA (FEUA) was also increased, suggesting an altered tubular handling of UA. In the membrane fraction of the kidney, Slc22a12 (URAT1; urate transporter 1) was significantly decreased, whereas ABCG2 (ATP-binding cassette sub-family G member 2) was increased, consistent with the increased renal UA clearance. Moreover, treatment with insulin but not Ipra decreased UA excretion in this model together with the reversal of the changes in URAT1 and ABCG2 levels. To clarify the contribution of insulin and glycosuria to the altered UA handling, we administered insulin or Ipra to non-diabetic rats. Results showed that insulin significantly increased URAT1 and decreased ABCG2, resulting in the reduced renal UA clearance. In contrast, there were no significant changes in urinary UA in Ipra-treated rats.

Conclusions: These data show that insulin decreases renal UA clearance *via* modulation of URAT1 and ABCG2, providing a mechanism for the inverse association between hyperinsulinemia and hypouricosuria. The data also indicate that renal urate handling in diabetic patients is influenced by the types of hypoglycemic agents.

FR-PO319

Basolateral High Glucose Induces Sodium Glucose Transporter Expression via GLUT2/Importin 1 alpha/HNF 1 alpha: Pathway in Renal Tubular Cell
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Background: We recently reported the nephroprotective effects of sodium/glucose cotransporter 2 (SGLT2) inhibitors through the maintenance of renal sirtuin 1 expression, although, the mechanism underlying increased SGLT2 expression in diabetic nephropathy remains unknown.

Methods: We constructed a 2-chamber culture system, with the upper layer representing the renal tubular cells of the lumen and the lower layer representing the vascular lumen. Normal glucose (NG) and high glucose (HG) culture media were used for the upper or lower layer. By using cultured primary proximal renal tubular cells, we investigated the presence of polarity, i.e., whether SGLT2 expression was dependent on glycemic stimulus from an upper or lower layer.

Results: SGLT2 expression increased in HG medium in the lower chamber, indicating that hyperglycemic stimulus from vascular lumen is responsible. Using small interfering RNA to inhibit the expression of membrane proteins localized to the basolateral side of the cells, we found that decreased glucose transporter 2 (GLUT2) expression led to decreased SGLT2 expression. GLUT2 was bound to importin α1, an intranuclear transport protein, in cells maintained in NG. Reportedly, when GLUT2 sensed retrograde glucose flow which is in the opposite direction of normal glucose flow in HG, GLUT2 dissociated from importin α1, which translocated from the cytoplasm to the nucleus. We used MEGA® alignment software to predict protein binding and identified a DNA motif for HNF1α transcription factor binding to importin α1. HNF1α was present in the cytoplasm of 50% of the renal tubular cells in NG. With HG stimuli to renal tubular cells, we observed that HNF1α translocated to the nucleus via importin α1, which contributed to the increased expression of SGLT2.

Conclusions: These findings suggested that detection of hyperglycemia on the basolateral side by GLUT2 during early stage diabetes mellitus leads to retrograde signal transduction which is in a direction opposite to that of the normal glucose flow via the GLUT2-importin α1-HNF1α pathway, with subsequent upregulation of SGLT2 expression. We propose this pathway interception as a new therapeutic target.

FR-PO320

The Role of TLR4/NF-κB Signaling Pathway on Mitochondria-Related Apoptosis in Tubular Cells in Diabetic Kidney Disease
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Background: The role and precise mechanism of TLR4 in mitochondria-related oxidative damage and apoptosis of renal tubular in diabetic kidney disease (DKD) remains unclear.

Methods: We examined the expression of TLR4 in renal biopsy tissues and analyzed its correlation with tubulointerstitial damage of DKD patients. In HK-2 cells, we detected the expression of TLR4, NF-κB and cleaved Caspase-3 by quantitative real-time PCR and western blotting, and analyzed mitochondrial function and apoptosis by flow cytometry and immunofluorescence. PGC-1a plasmids were used for the overexpression of PGC-1a in HK-2 cells.

Results: Results showed that TLR4 was extensively expressed in the renal tubular of DKD patients, coexistent with mitochondria swelling and deformation. The level of TLR4 was positively related to the tubulointerstitial damage reflecting by tubular interstitial damage score and urinary b-NAG levels. In vitro, the expression of TLR4 increased in HK-2 cells treated with high glucose (HG), leading to activation of NF-κB, decreased expression of PGC-1α, mitochondrial deformation, cytochrome C redistribution, increased expression of cleaved caspase-3 and even apoptosis, while TLR4/NF-κB blockers and PGC-1α over-expression reversed these trends.

Conclusions: Data indicated that TLR4/NF-κB signaling pathway might be the upstream of PGC-1α and promote the tubular damage of DKD by modulating the mitochondria-related oxidative damage and apoptosis.

Funding: Government Support - Non-U.S.

FR-PO321

RhoA Activation Contributes to Hyperplastic Phenotype of Proximal Tubular Cells in the Initiation of Obesity-Related Kidney Damages
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Background: Hyperplastic phenotype is supposed to trigger the initiation of obesity-induced renal damages. A small GTP-binding protein, RhoA, and its effector, Rho-kinase, have several pathological functions including cell motility, proliferation and inflammatory response. We have previously demonstrated that excess fat intake causes obesity-induced renal injuries, which are mediated by an activated Rho/Rho-kinase pathway in proximal tubules and inflammatory process. In the present study we examined whether Rho/Rho-kinase contributes to the hyperplastic phenotypes in obesity-induced renal injury.

Methods: We created mice that overexpressed dominant negative RhoA genes specifically in proximal tubules (PT) under the control of promoter of sodium-phosphate co-transporter (PT-DN-RhoA) in C57BL/6J backgrounds. PT-DN-RhoA mice and their wild-type littermates (WT) were fed a high fat (HFD) or low fat diet (LFD) for 12 weeks.

Results: WT on HFD (WT-HFD) not only developed obesity but also manifested renal histological changes, including the enlargement in proximal tubules, tubular hyperplasia, and a marked increase in the number of PCNA and Ki-67 positive tubular epithelial cells compared with WT on LFD as early as 2 weeks after the HFD feeding, which paralleled the increase in urinary excretion of NGAL (neutrophil gelatinase-associated lipocalin). These hyperplastic phenotypes were ameliorated in HFD-fed PT-DN-RhoA mice.Among cell cycle regulators, cyclin-dependent kinase inhibitors p27 was remarkably reduced in WT-HFD, which were restored in DN-RhoA TG mice with HFD.

Conclusions: Excess fat intake causes the hyperplastic phenotype of obesity-induced renal injury, which is mediated by an RhoA activation and subsequent downregulation of p27 pathway in proximal tubules. The intervention of Rho/p27 pathway may constitute a novel strategy blocking the initiation process of obesity-induced renal damages. Urinary NGAL can be useful markers for the detection of this hyperplastic phenotype.

FR-PO322

Subclinical Lithium Dose Attenuates Glomerulosclerosis but Causes Tubular Injury in Diabetic BTBR ob/ob Mice
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Background: Type 2 diabetes mellitus (T2DM) is the most important risk factor to develop chronic kidney disease (CKD). Glycogen synthase kinase 3 (GSK3) plays an important role in the development of both DM and renal injury, as moderate GSK3 inhibition increases glucose uptake in insulin-insensitive muscle and adipose tissue, while in acute kidney injury it reduces albuminuria and glomerulosclerosis. The only clinically available GSK3 inhibitor is lithium, however in bipolar patients chronic lithium administration (0.6-1 mM in blood) increases the chance to develop tubulointerstitial nephropathy. Therefore, our aim was to investigate the effect of subclinical lithium doses on the development of DM and kidney injury in a mouse model of diabetic nephropathy.

Methods: Twelve-week old female BTBR ob/ob mice were treated for 12 weeks with 0, 10 and 40 mmol LiCl/kg after which DM parameters, urine albumin-creatinine ratio (ACR), FITC-inulin clearance, and renal histology were analyzed and compared to wild type (wt) BTRB mice on regular chow.

Results: In comparison to wt BTBR mice, ob/ob mice demonstrated elevated bodyweight, increased blood glucose/insulin levels, albuminuria, glomerulosclerosis and hyperfiltration. The lithium-10 and -40 diets did not affect body weight and resulted in blood lithium levels of respectively <0.25 mM and 0.48 mM. Lithium-40 significantly reduced non-fasting blood glucose levels, but did not affect non-fasting insulin levels or fasting blood glucose levels. Importantly, lithium-40 reduced the development of glomerulosclerosis. In contrast, lithium-40 augmented the ACR, which coincided with an increased number of atrophic tubuli. The glomerular filtration rate was not significantly altered by lithium.

Conclusions: Altogether, administration of subclinical lithium dose to BTBR ob/ob mice reduced glomerulosclerosis, but simultaneously increased tubular damage and albuminuria. These results are in agreement with recent findings that albuminuria does not always represent glomerular damage, but can also be a sign of tubular injury. Better tools to diagnose early glomerular injury are required.

FR-PO323

Metformin Ameliorates Peripheral Insulin Resistance by Inhibiting the Activity of SHIP2
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Background: The expression of lipid phosphatase SHIP2 is elevated in kidney, adipose and muscle tissue in diabetes. Thus, SHIP2 is a potential therapeutic target to treat insulin resistance. To date only a few chemical compounds possessing an inhibitory effect on SHIP2 are known. All of them have poor bioavailability and none have reached clinical use.

Methods: To identify novel small molecules that inhibit SHIP2 we performed virtual screening of chemical libraries followed by validation using cultured cells, diabetic db/db mice and kidney tissue from patients with T2DM.

Results: Virtual screening of chemical libraries containing 88680 molecules revealed metformin as a potential SHIP2 inhibitor. Although metformin has been used to treat T2DM for long, the exact molecular mechanism by which it enhances peripheral insulin sensitivity has remained elusive. We found that metformin inhibits the catalytic activity of the *in vitro* produced and purified SHIP2 phosphatase domain. Metformin also inhibited the activity of SHIP2 in cultured rat skeletal muscle cells and human podocytes, and protected podocytes against SHIP2 overexpression-induced apoptosis. Metformin also enhanced glucose uptake, which was reduced by SHIP2 overexpression in these cells. *In vivo*, metformin reduced the activity of SHIP2 in skeletal muscle and kidney tissue of metformin-treated diabetic db/db mice. Furthermore, we observed that T2DM patients on insulin medication showed increased SHIP2 activity in the kidney compared to patients without T2DM. In patients receiving metformin the activity of SHIP2 in the kidney was similar to that observed in patients without T2DM.

Conclusions: Metformin inhibits the activity of SHIP2, providing a mechanism by which metformin ameliorates peripheral insulin resistance. This highlights the potential of

SHIP2 as a drug target and provides an avenue to identify and design novel molecules, such as the ones identified in our virtual screening, which can be used to develop new insulin sensitizers for future clinical trials.

Funding: Private Foundation Support

FR-PO324

Changes of DPP-4 and DPP-4 Substrates According to Aging in Kidney

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Background: The incretin-based agents such as dipeptidyl peptidase IV (DPP-IV) inhibitor and glucagon-like peptide-1 (GLP-1) agonist was associated with diverse protective effect including renoprotective effect except lowering glucose. Aging kidney was characterized by decreased glomerular filtration rate, impaired electrolyte balance, decreased plasma renin activity and histological changes such as glomerulosclerosis and tubular atrophy. We investigated the renal function, albuminuria, the concentration and activity of DPP-4 and DPP-4 substrates in serum and urine, and expression of incretin hormone in renal tissue with aging in mice model.

Methods: C57BL/6 mice were divided into three groups according to age differences; 2 months-old (N=8), 12 months-old (N=8), and 24 months-old (N=8). We measured renal function, histological change in aging mice. Also, the concentrations and expressions of DPP-4 and DPP-4 substrates were measured in serum and renal tissue in aging mice.

Results: According toaging, albuminuria (16.5 ± 1.1 ng/24hr vs. 41.5 ± 8.4 ng/24hr, 65.5 ± 10.4 ng/24hr; $p < 0.05$ vs. 2M) was increased and Creatinine clearance ($p > 0.05$ vs. 12M) was decreased. There were increases in mesangial volume and tubulointerstitial fibrosis in 24-month-old mice ($p < 0.01$). There were also increases in F4/80 expression (0.11 ± 0.06% vs. 0.4 ± 0.11%, 2.5 ± 0.52%; $p < 0.01$) and in apoptosis detected by TUNEL (positive mesangial cells, 0.27 ± 0.09% vs. 0.53 ± 0.12%, 2.6 ± 0.63%; glomerulus and cortical tubular areas, 0.27 ± 0.09% vs. 0.53 ± 0.12%, 2.8 ± 0.67%.01). Urine isoprostane (7.4 ± 0.3% vs. 19.4 ± 0.78%, 21.9 ± 1.9%) excretion increased with aging. DPP-IV concentrations in serum and DPP-IV activities in renal tissue were gradually increased ($p<0.001$ and $p<0.05$, respectively). GLP-1 receptor and DPP-IV protein levels in renal tissue were significantly increased with aging in western blot ($p<0.001$ and $0<0.05$, respectively).

Conclusions: It is suggested that incretin based treatment is a possible strategy for preventing an aging process in the kidney.

FR-PO325

Sodium-Glucose Cotransporter 2 Inhibition Partly Phenocopies Calorie Restriction in Kidneys of a Type 2 Diabetes Mouse Model

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Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors lower blood glucose levels by increasing glucose/calorie loss in urine. However, the long-term effect of SGLT2 inhibition on the kidney, independent of glycemic control, is unknown. Thus, we compared renal changes induced by ipragliflozin treatment and those induced by calorie restriction (at similar blood glucose levels) in a mouse model of type 2 diabetes.

Methods: Male BTBR ob/ob mice, aged 4 weeks, were divided into three groups: vehicle, ipragliflozin (0.002%; in feed), and 70% calorie restriction. Male BTBR wild type littermates were used as controls. All mice were euthanized at 22 weeks of age.

Results: At euthanasia, HbA1c levels in the ipragliflozin (5.8±0.2%) and calorie restriction (6.2±0.3%) groups were comparable and significantly lower than those in the vehicle group (8.7±0.2%). Urinary albumin levels at 10 weeks of age in the ipragliflozin (947±228 μg/mgCr) and calorie restriction (809±142 μg/mgCr) groups were significantly lower than those in the vehicle group (3447±481 μg/mgCr), and this difference persisted until 22 weeks. Ipragliflozin treatment and calorie restriction prevented glomerular hyperfiltration at 13 and 22 weeks of age (GFR at 22 weeks: 461±13, 853±20, 753±7, and 735±44 μL/min in the control, vehicle, ipragliflozin, and calorie restriction groups, respectively) and mesangial expansion, and improved serum lipid profile at euthanasia, in equal measure. In contrast, kidney weight, glomerular tuft area, interstitial fibrosis, macrophage infiltration, and MCP-1 mRNA expression in the cortex were significantly reduced by calorie restriction but remained unaffected by ipragliflozin.

Conclusions: Our data showed that ipragliflozin treatment partly phenocopied calorie restriction toward protection in BTBR ob/ob mouse kidneys. Amelioration of glomerular hyperfiltration and reduction of albuminuria, mesangial expansion, and serum lipid profile were achieved by both interventions, while kidney/glomerular hypertrophy, inflammation, and fibrosis were improved only by calorie restriction.

Funding: Government Support - Non-U.S.

FR-PO326

Dapagliflozin Improves Glycemic Control, Hypertension and Is Neutral on Severe Renal Impairment in Uni-Nephrectomized SDT Fatty Rat, a 10-Week Model of Advanced Renal Complications and Glomerular Filtration Rate Decline

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Background: Sodium glucose cotransporter 2 inhibition (SGLT2i) represents a promising new class of glucose lowering drugs but may not be recommended in type 2 diabetic patients with severe renal impairment. To investigate the effects of SGLT2i, later in the course of diabetic nephropathy, dapagliflozin (DAPA) was evaluated in uni-nephrectomized Spontaneously Diabetic Torii (SDT) fatty rat. This novel hypertensive, obese, type 2 diabetic model, develops advanced renal complications and >50% glomerular filtration rate (GFR) decline within 10 weeks.

Methods: Male, 6-week old SDT fatty rats underwent unilateral nephrectomy (Unx; n=16) or sham operation (Sham; n=8). After a 1-week recovery, rats had free access to Purina 5008 chow diet and drinking water supplemented with 0.3% salt for 10 weeks. After 3 weeks of diet to enhance kidney complications, 8 Unx rats were treated with DAPA 1mg/kg/day for 7 weeks.

Results: After 10 weeks of diet and compared to Sham rats, albuminuria was 206% higher in Unx control rats, while plasma creatinine clearance and GFR (FITC-inulin injection) were substantially reduced by 46 and 60% ($p<0.01$ vs. Sham). Histology analysis (Periodic acid-schiff, ED1 immunostaining and Sirius Red) confirmed advanced glomerulosclerosis, inflammation and fibrosis in Unx control rats (all scores $p<0.05$ vs. Sham). The major finding was that compared to Unx control rats, DAPA treatment of Unx rats for 7 weeks did not change GFR decline, glomerulosclerosis, inflammation and fibrosis scores. We also observed reduction in HbA1c and blood pressure by 3.1% and 19%, respectively, with DAPA (both $p<0.01$ vs. control).

Conclusions: Our data suggest that SGLT2i with DAPA has no detrimental effect in uni-nephrectomized SDT fatty rat with advanced renal complications and >50% GFR decline. Whether treatment with DAPA at an earlier time point would prevent renal impairment in this model should be investigated.

FR-PO327

The Comparative Effects of a Pan-Nox Inhibitor APX-115 and Angiotensin Receptor Blocker on Diabetic Nephropathy in Type 2 Diabetic Mice

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Background: Targeting all Nox components may be a promising therapeutic strategy to ameliorate renal damage from reactive oxygen species in diabetic nephropathy. Therefore, we investigated the comparative effect of a first in class pan-Nox inhibitor, APX-115 and L158809 (angiotensin II receptor blocker, ARB) and their combination on diabetic nephropathy in type 2 diabetic mice.

Methods: 8 to 10 week old db/m and db/db mice were treated with APX-115 for 12weeks. APX-115 was administered by oral gavage at a dose of 60mg/kg/day. To compare the effects of APX-115 with ARB, other groups were treated with LC158809 (1.5mg/kg/d) or treated with both APX-115 and LC158809 for 12 weeks.

Results: Interestingly, both APX-115 group and ARB group showed significantly improved systemic oxidative stress (plasma 8-isoprostane and tissue lipid peroxidase levels), and lipid profiles compared to diabetic control group. Importantly, both APX-115 and ARB groups showed a significant decrease in urinary albumin excretion with a similar potency. Consistent with urinary albumin excretion, urinary loss of nephrin was also significantly reduced. Renal histology showed reduced mesangial expansion, fibrosis and inflammation in all treatment groups. Renal Nox1,2 and 4 protein expressions were decreased in APX-115 and combination group, whereas only Nox2 was decreased in ARB group. Although there were no additive beneficial effects in oxidative stress and lipid abnormality, combined treatment of APX-115 and ARB showed additive renoprotective effects in urinary albumin excretion and renal structural changes.

Conclusions: Our results provide evidence that pan-Nox inhibition by APX-115 may have similar renoprotective potential with ARB, and combination therapy with APX-115 and ARB may have better renoprotective potential in diabetic nephropathy. These findings suggest that an agent that simultaneously inhibits various Noxs therefore holds a considerable promise as a new antidiabetic drug.

FR-PO328

Renal Effects of LJ-2698, a Highly Selective Adenosine3 Receptor Antagonist and Combination Treatment with Angiotensin Receptor Blocker in Streptozotocin Induced Type 1 Diabetic Mice

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Background: Concentration of adenosine in normal kidney increases markedly in response to cellular damage. Extracellular adenosine binds to four adenosine receptors (AR), all of which exist in the kidney. Among four subtypes, A3AR is known to be up-regulated during renal injury. In this study, we investigated the comparative effects of a novel A3AR antagonist LJ-2698 and L158809 (angiotensin II receptor blocker, ARB) and their combination on diabetic nephropathy in streptozotocin(STZ)-induced type 1 diabetic mice.

Methods: To define the mechanism of LJ-2698, we performed in vitro experiments using podocytes. For animal experiment, type I diabetes was developed using STZ injection (50mg/kg IP for 5days) in C57BL6 mice. Diabetic mice were treated with 1) LJ-2698 (10mg/kg/day by gavage), 2) LC158809 (1.5mg/kg/d mixed in drinking water) and 3) both LJ-2698 and LC158809 for 12 weeks.

Results: In cultured podocytes, high glucose(HG), palmitates(PA) and angiotensin-II(Ang-II) significantly up-regulated A3AR expression. Prior treatment with LJ-2698 markedly suppressed HG, PA and Ang-II-induced activation of TGFb1, MCP-1 and type IV collagen synthesis. In type 1 diabetic mice, treatment with LJ-2698 showed improvement in insulin resistance. Interestingly, urinary albumin excretion was significantly decreased in both LJ-2698 and ARB groups with a similar potency, and there was an additive decrease in combination treatment group. In addition, urinary nephrin excretion was significantly decreased in both LJ-2698 and ARB groups. Renal glomerular mesangial expansion, fibrosis and inflammation were decreased in all treatment groups. Renal protein expressions of TGF-β1, PAI-1, NF-kb were attenuated in LJ-2698 and combination groups compared to diabetic control.

Conclusions: Our results showed that A3AR antagonist may have a similar renoprotective effects with ARB through protection of podocyte injury. These findings suggest that targeting A3AR may have a promising potential in diabetic nephropathy.

FR-PO329

Factor Xa Inhibition with Rivaroxaban Reduces Hyperglycemia-Induced Inflammation in the Kidney by Inhibition of PAR-1 Signaling in Endothelial Cells in an Animal Model of Diabetic Nephropathy Anna Bertram, Nelli Shushakova, Joon-Keun Park, Torsten Kirsch, Jan Menne, Florence Njau, Hermann G. Haller. *Clinic of Hypertension and Nephrology, Hannover Medical School, Hannover, Germany.*

Background: Activated factor Xa (FXa) plays an important role in the coagulation cascade. In addition, FXa binds to protease-activated receptors PAR-1 and PAR-2 and may exert cellular function in the endothelium. We tested the hypothesis that (1) treatment with a FXa inhibitor prevents or ameliorates proteinuria and inflammatory changes in diabetic mice and (2) that this effect is mediated via endothelial PAR-1 and/or PAR-2.

Methods: Streptozotocin (125 mg/kg)-treated mice (STZ) (*n*=8), and control animals were used in these experiments. They received either sham or rivaroxaban RIVA (15 mg/kg). After 2 and 8 weeks of hyperglycemia, the animals were analyzed. Albumin concentration samples was measured by ELISA. Immunohistochemistry was performed on cryostat or on paraffin sections. Gene and protein expression was analyzed by real-time qPCR and western blot. Intracellular effects of FXa were assessed in cultured microvascular endothelial cells (MEC) by measuring ERK phosphorylation (pERK) and cytokine release.

Results: Treatment with RIVA reduced the hyperglycemia–induced macrophage infiltration in the diabetic kidneys. Concomitantly, the increase in inflammatory cytokines (Il-6, TNF-alpha) and adhesion molecules (ICAM-1) in diabetic animals was also reduced by RIVA treatment. The increase in pERK in diabetic glomeruli was diminished by RIVA treatment. These changes were associated with a reduced increase in proteinuria in STZ mice. In MEC the FXa-induced pERK was reduced by RIVA treatment. Downregulation of PAR-1 abolished the effects of RIVA while loss of PAR-2 did not change the effects of RIVA.

Conclusions: Treatment with the factor Xa inhibitor rivaroxaban prevents renal inflammation in animal models of diabetes by inhibition of adhesion molecule expression and cytokine release. This effect seems to be mediated by inhibition of PAR-1 signaling by rivaroxaban in endothelial cells.

Funding: Pharmaceutical Company Support - Bayer Pharma AG

FR-PO330

Late Intervention with PBI-4050 Offers Renoprotection in a Mouse Model of Renin-Dependent/Streptozotocin-Induced Nephropathy Jean-François Thibodeau,[1,2] Eldjonai Kamto,[2] Lyne Gagnon,[1] Pierre Laurin,[1] Richard L. Hebert,[2] Chris R. Kennedy.[2] *[1]ProMetic BioSciences Inc., Laval, QC, Canada; [2]Kidney Research Center, Ottawa Hospital, Ottawa, ON, Canada.*

Background: PBI-4050, a novel first-in-class orally active compound which is currently in clinical phase Ib/II in CKD patients, displays antifibrotic activities via a novel mechanism of action. PBI-4050 reduces functional and structural renal dysfunction in models of diabetic kidney disease. The aim of this study was to investigate the impact of PBI-4050 treatment on renal injury progression in a mouse model of diabetic kidney disease.

Methods: We used a recently developed mouse model of diabetic kidney disease in which low-dose streptozotocin (STZ)-dependant type-1 diabetes is induced in human prorenin-overexpressing mice (C57BL/6-TTRhRen) yielding a hypertensive/diabetic phenotype (HD). After 12 weeks of hypertension/diabetes, mice were treated with oral administration of vehicle or PBI-4050 (200 mg/kg) for 4 weeks, and sacrificed at 16 weeks post-STZ.

Results: At endpoint, PBI-4050 had no effect on bodyweight or blood glucose levels, but slightly increased renal hypertrophy (HD, 8.01±0.4 vs HD+PBI4050, 9.60±0.6, mg/mm, P=0.047). While PBI-4050 slightly decreased systolic blood pressure, glomerular filtration was significantly reduced to normal levels (HD, 503±42 vs HD+PBI4050, 380±27, μL/min, P=0.040). Reductions in urine albumin-to-creatinine ratios were also observed in the PBI-4050 treatment group compared to vehicle (HD, 199.3±33; HD+PBI4050, 109.7±18, μg of albumin per mg of creatinine, P=0.035), which corresponded to decreased glomerular mesangial matrix expansion, and tubulointerstitial injury. In addition, PBI-4050 treatment reduced α-smooth muscle actin (HD, 1.53±0.2 vs HD+PBI4050, 0.81±0.1, relative expression, P=0.0038) and connective tissue growth factor mRNA expression in the cortex (HD, 1.41±0.2 vs HD+PBI4050, 0.91±0.1, relative expression, P=0.055).

Conclusions: Taken together, PBI-4050 administration beginning at 12 weeks of hypertension/type-1 diabetes reduced the extent of renal injury, independently of its effects on blood glucose, which further supports its use as a potential renoprotective therapy in the context of diabetic kidney disease.

FR-PO331

Effect of an Oral Adsorbent AST-120 on Type 2 Diabetes Rats with Unilateral Nephrectomy Rieko Aoki, Yusuke Yamashita, Hiroko Iijima, Kaori Kikuchi, Mariko Kato, Yoshiharu Itoh. *Pharmaceuticals & Agrochemicals Div, Kureha Corporation, Tokyo, Japan.*

Background: Diabetic nephropathy is a major complication of diabetes and the leading cause of end-stage renal disease. An oral adsorbent AST-120 has been used clinically in Japan as a medicine for patients with chronic kidney disease (CKD) to slow down the progression of CKD. However, there is little evidence to support therapeutic efficacy of AST-120 for early stage overt diabetic nephropathy. In the ASN Kidney Week 2015 we showed that the administration of AST-120 reduced the urinary protein and albumin excretion on SHR/NDmcr-cp (SHR/ND) rats, rodent model of metabolic syndrome/ type 2 diabetes, and suppressed the podocyte injury and tubular injury. However, the renal function in SHR/ND rats didn't decrease and the effect of AST-120 on the renal function was unclear. In this study, we investigated whether the administration of AST-120 from the early stage of diabetic nephropathy is effective strategy for the suppression of the reduction of renal function using the unilateral nephrectomized (UNX) SHR/ND rats.

Methods: Male SHR/ND rats, aged 8 weeks, underwent either UNX (n=20) or sham (n=6) surgery under anesthesia. UNX rats were divided into two groups; one group was administered 8% AST-120 in their diets. WKY rats were also used as normal rats. At every 3 weeks, serum and 24-hour urine samples were collected for biomedical studies. The level of uremic toxins in serum were also measured at every 6 weeks.

Results: The levels of serum creatinine, blood urea nitrogen, serum uremic toxins, urinary protein and albumin excretion increased, and creatinine clearance decreased in UNX-SHR/ND rats compared to Sham-SHR/ND rats. Therefore, it indicated that there was the reduction of renal function in UNX-SHR/ND rats. AST-120-administered UNX-SHR/ND rats showed significantly lower levels of urinary protein and albumin excretion, serum creatinine, blood urea nitrogen and uremic toxins compared to the UNX-SHR/ND rats, and also maintained higher levels of creatinine clearance than UNX-SHR/ND rats.

Conclusions: These results indicate that the administration of AST-120 from the early stage of diabetic nephropathy has a protective effect on the reduction of renal function.

FR-PO332

CS-3150, a Novel Mineralocorticoid Receptor Antagonist, Reduces Albuminuria in Type 2 Diabetes Mice in Combination Treatment with Angiotensin II Receptor Blocker Kiyoshi Arai,[1] Yuka Morikawa,[2] Naoko Ubukata.[1] *[1]End-Organ Disease Laboratories, Daiichi Sankyo Co., Ltd., Tokyo, Japan; [2]Rare Disease & LCM Laboratories, Daiichi Sankyo Co., Ltd., Tokyo, Japan.*

Background: An angiotensin II receptor blocker (ARB) is currently recommended as first-line therapy for diabetic nephropathy (DN). Recently, it has been demonstrated that add-on treatment of a mineralocorticoid receptor (MR) antagonist with ARB shows further beneficial effects on DN patients. Our previous studies have shown that CS-3150 is a novel, highly potent and selective MR antagonist with non-steroidal structure and shows strong antihypertensive and cardiorenal protective effects in hypertension models. In this study, we evaluated the renal protective effect of CS-3150 in KK-Ay mice, a type II diabetic model, in combination with olmesartan (OLM, an ARB).

Methods: CS-3150 (3 mg/kg), OLM (1 mg/kg) or both of them was orally administered to male KK-Ay mice from 10 weeks of age for 8 weeks. At every 4 weeks, urine samples for 24 h were collected and urinary parameters (albumin, creatinine, podocalyxin and MCP-1) were measured. Systolic blood pressure (SBP) and blood glucose (BG) level were measured at 3 and 7 weeks after administration, and serum K^+ level was measured at necropsy.

Results: In KK-Ay mice at 10 weeks of age, urinary albumin-to-creatinine ratio (UACR) and BG levels were significantly higher than C57BL/6J mice, non-diabetic controls, meaning that KK-Ay mice developed DN. The combination treatment with CS-3150 and OLM significantly reduced UACR, while each monotherapy tended to reduce UACR but not significant. Urinary podocalyxin and MCP-1 excretion were also reduced. In contrast, this combination therapy did not show any significant effect on SBP, BG and serum K^+ level.

Conclusions: These results indicate that in KK-Ay mice, CS-3150 significantly reduced albuminuria without any effect on SBP, BG and serum K^+ in combination with OLM. This direct renal protective effect could be, in part, due to podocyte protective and anti-inflammatory actions. CS-3150 is currently under development as a drug candidate in the clinical phase II trials for hypertension and DN in Japan.

FR-PO333

Cyanate Improves Glucose Homeostasis and Hepatic Steatosis in Normal and High Fat-Fed Mice Seong Sik Kang,[1,2] Yaerim Kim,[1,2] Sang Mok Yeo,[1,2] Woo Yeong Park,[1,2] Kyubok Jin,[1,2] Sung Bae Park,[1,2] Seungyeup Han.[1,2] *[1]Dept of Internal Medicine, Keimyung Univ School of Medicine, Daegu, Republic of Korea; [2]Keimyung Univ Kidney Inst, Daegu, Republic of Korea.*

Background: Obesity is an important contributing factor to progression of chronic kidney disease. Cyanate, being generally known as uremic toxin, is an electrophile produced spontaneously from urea or by myeloperoxidase-catalyzed oxidation of thiocyanate.

Methods: In the current study, we explored the *in vivo* and *in vitro* metabolic effects of cyanate in normal chow diet (NCD)- and high fat diet (HFD)-fed mice.

Results: Contrary to our expectations, we found that cyanate treatment improved glucose tolerance, increased insulin sensitivity and alleviated hepatic steatosis in both NCD- and HFD-fed mice compared with corresponding control groups. Histological analyses of kidney and serum levels of blood urea nitrogen and creatinine revealed no significant differences between cyanate-treated and control mice groups. Interestingly, we found that cyanate treatment reduced appetite and body weight in both diet groups. And we also found that cyanate treatment decreased lipid peroxidation levels in the sera and kidney, attenuated reactive oxygen species (ROS) levels in the kidney. Thus we examined *in vitro* carbamylated albumin (cAlb) in Caki-2 kidney cell lines for antioxidant effects of cyanate. We found that cAlb significantly reduced ROS generation compared with Alb.

Conclusions: Taken together, the results in this study may indicate that cyanate improves glucose tolerance and hepatic steatosis possibly via exerting anorexic and antioxidative effects.

FR-PO334

Iron Chelation Ameliorates Fibrotic Pathways in ZSF1 Obese Rat

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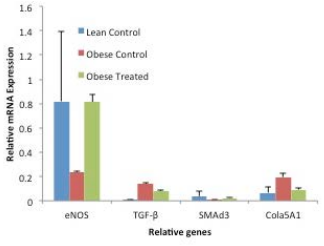
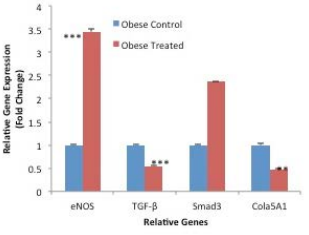
Background: Labile iron, by virtue of its ability to participate in free-radical reactions, plays an important role in diabetic nephropathy. Chelating catalytic iron would provide beneficial effects including amelioration of oxidative and consequently fibrotic pathways involved in progression.

Methods: The oral iron chelator deferiprone was administered to ZSF1 obese rats beginning age 8 weeks over a 24 week treatment period at a dose of 125mg/kg of body weight, dissolved in drinking water. A lean and obese ZSF1 rat group was also followed simultaneously without intervention and served as control groups. Real time quantitative PCR in rat kidneys was done to determine the activity of the oxidative and fibrotic pathways. cDNA was synthesized from RNA, isolated post treatment from control and treated kidneys. Taqman PCR Gene Expression reagents were used to detect eNOS, TGF-β, Smad-3 and Collagen 5A1 chain (Cola5A1) and reference genes. cDNA and relative gene expression were calculated from Cq values using a ΔΔCq. Statistical significance relative to control is shown, **p<0.01, ***p<0.0001.

Results:





Relative mRNA Expression	eNOS	TGF-β	Smad3	Cola5A1
Lean Control [5]	0.818	0.008	0.038	0.066
Obese Control [10]	0.235	0.138	0.009	0.194
Obese Treated [10]	0.811	0.076	0.022	0.092

Conclusions: Treatment with oral iron chelator deferiprone down regulated the oxidative and fibrotic pathways in the ZSF1 obese rat, an F1 hybrid model of type 2 diabetic nephropathy. The relative gene and messenger RNA expression levels of eNOS, TGF-β, and Cola5A1 in treated obese rats returned to the levels expressed in non- diabetic lean rats with significant improvement compared with the obese non- treated group. Iron chelation may provide a new therapeutic modality for halting progression of diabetic nephropathy.

Funding: Private Foundation Support

FR-PO335

An Immunomodulatory Device Improves Insulin Resistance in an Obese Porcine Model of Metabolic Syndrome

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Background: Obesity is associated with tissue inflammation which is a crucial etiology of insulin resistance (IR). This inflammation centers around circulating monocytes (MO) which form pro-inflammatory adipose tissue macrophages (ATM). Specific approaches targeting MO/ATM may improve IR without the adverse side effects of generalized immunosuppression.

Methods: An extracorporeal based biomimetic membrane leukocyte processing device, called the Selective Cytopheretic Device (SCD), was evaluated to assess the therapeutic impact in an Ossabaw miniature swine model of IR with metabolic syndrome (MetS). Pigs received three 6 hour SCD therapy (Rx) sessions over a 1 week period, with measurements for assessing changes in IR via IV glucose tolerance test (GTT) and homeostatic model assessment (HOMA)-IR scores followed up to 2 weeks post Rx. Leukocyte parameters were assessed to determine impact of SCD Rx on the inflammatory state associated with MetS. Circulating neutrophil (NE) activation was measured by CD11R3 and Ne apoptotic rates were assessed via Annexin V assay. Systemic MO numbers were determined by manual white blood cell counts.

Results: SCD Rx in this porcine model demonstrated a significant (p=0.033) effect on decreasing circulating NE activation levels as measured by CD11R3 and on returning Ne apoptotic rates toward naïve, non-inflammatory rates (p=0.023). For MO, a reduction in the absolute circulating MO counts was observed pre to post SCD Rx (p=0.007). These changes were associated with improvements in IR as determined by GTT. These improvements were also reflected in lowering of HOMA-IR scores for up to 2 weeks post SCD Rx. A decrease in TNFα was also consistently observed post SCD Rx, achieving significance at p=0.0022.

Conclusions: The above study provides strong evidence that SCD Rx reduced the chronic systemic inflammation associated with MetS as presented in this model. These results allow for the planning of first in man studies in obese type 2 diabetic patients.

Funding: Other NIH Support - NIH RR013223 and HL062552 to M. Sturek and the Comparative Medicine Center of the Indiana School of Medicine and Purdue University in developing the Ossabaw Swine Resource, Other U.S. Government Support

FR-PO336

Low Admission Serum Creatinine Concentration Predicts Mortality in Hospitalized Patients Independent of Body Mass Index

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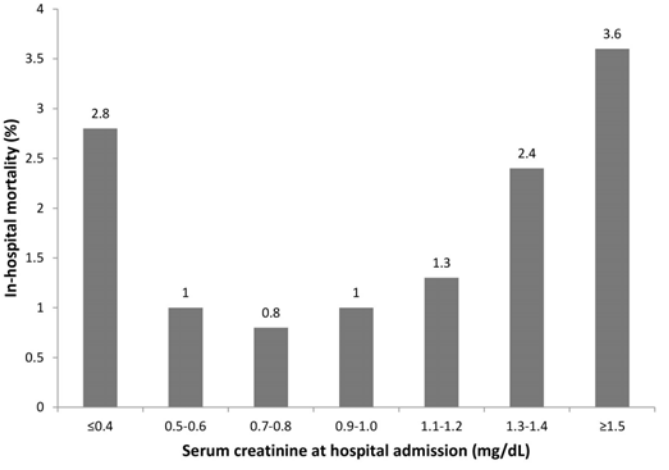
Background: Low serum creatinine was associated with poor outcomes in critically ill and dialysis patients. The association between low admission serum creatinine and risk of in-hospital mortality is limited. The aim of this study is to assess the independent association between low admission creatinine and in-hospital mortality in hospitalized patients.

Methods: This is a single-center cohort study conducted at a tertiary referral hospital. All hospitalized adult patients who had admission creatinine available from January 2011 to December 2013 were included. Admission creatinine was categorized into 7 groups (≤0.4, 0.5-0.6, 0.7-0.8, 0.9-1.0, 1.1-1.2, 1.3-1.4 and ≥1.5 mg/dL). The primary outcome was in-hospital mortality. Logistic regression analysis was performed to obtain the odds ratio of in-hospital mortality of various admission creatinine levels using creatinine 0.7-0.8 mg/dL as the reference group.

Results: Of 73,994 patients included, 973 (1.3%) died in the hospital. The association between different categories of admission creatinine and in-hospital mortality assumed a U-shaped curve, with both low and high creatinine associated with higher in-hospital mortality.



When adjusting for age, sex, ethnicity, principal diagnosis and comorbidities, very low creatinine (≤0.4 mg/dL) was significantly associated with increased mortality (OR 3.29; 95% CI 2.08-5.00), exceeding the risk related with markedly elevated creatinine (OR 2.65; 95% CI 2.11-3.35 for creatinine ≥1.5 mg/dL). The association remained statistically significant following adjustment for body mass index.

Conclusions: Low admission creatinine was independently associated with increased in-hospital mortality in hospitalized patients. Low serum creatinine might be a better surrogate marker of low muscle mass than a low body mass index.

FR-PO337

Free and Bound Serum Sialic Acid Profiling of End Stage Renal Disease Patients

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Background: Sialic acids (Sias) are a diverse family of molecules found at the outer tips of the glycan forest that covers all vertebrate cells. Previous studies reported increased serum total Sia associated with atherosclerosis in the general population and in patients with end stage renal disease (ESRD) undergoing hemodialysis (HD) therapy. However, there has been no profiling of the types of sialic acids in ESRD patients.The aim of this study was to analyze which types of free Sias and Sia-containing glycans accumulate in the sera of ESRD patients. Analysis focused on *N*-Acetylneuraminic acid (Neu5Ac), N-glycolylneuraminic

acid (Neu5Gc, which is not naturally made by humans), and the common lower vertebrate Sia 3-deoxy-D-glycero-D-galacto-nonulosonic acid (Kdn). Kdn is almost undetectable in normal human tissues except in some cancer.

Methods: Serum samples from HD patients (N=60) and normal controls (N=20) were analyzed for free and protein bound Sias by DMB derivatization, high performance liquid chromatography (HPLC) and matrix-assisted laser desorption/Ionization time-of-flight mass spectrometry (MALDI-TOF MS). Bound Sias were released by mild acid. Sialylated N-glycans were released by PNGase F followed by 2-aminobenzamide (2-AB) labeling. The fluorescently tagged sialoglycans were analyzed with or without sialidase pretreatment.

Results: Several unknown fluorescent DMB adduct peaks were detected only in ESRD patients, as well as much higher levels of free Neu5Ac and Kdn. No free form of Neu5Gc was detected. However, small amounts of peak corresponding to bound Neu5Gc were detected in both HD and normal control samples. N-glycan profiling using 2-AB labeling showed that sialidase resistant anionic peaks were detected only in HD serum.

Conclusions: We show accumulation of free Neu5Ac and Kdn in HD patients, and possible bound Neu5Gc (presumably of dietary origin from red meat) in HD patients and in normal controls. These findings suggest that human and non-human Sias can accumulate in HD patients and be potentially used by human cells. We are currently studying the sialidase-resistant peaks.

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Bioimpedance Vectorial Analysis as a Tool for Early Diagnosis of Acute Kidney Injury Luis Ignacio Bonilla,[1,3] Sara Samoni,[2,3] Allina Primavera Flores Mendoza,[1] Jesus Cruz Valdez,[1] Claudio Ronco.[3] *[1]Nephrology Dept, Hospital Univ, Monterrey, Mexico; [2]Inst of Life Sciences, S. Anna School of Advanced Studies, Pisa, Italy; [3]International Renal Research Inst, San Bortolo Hospital, Vicenza, Italy.*

Background: Fluid overload(FO) is a frequent condition in critically ill patients.FO increases the volume of distribution of creatinine, thus decreasing serum creatinine (sCr) concentration, which may contribute to delay the diagnosis of Acute Kidney Injury (AKI) and underestimation of its severity.Our aim was to assess the incidence of AKI based on corrected creatinine according to a formula usingtotal body water(TBW) estimated by bioimpedance.

Methods: This is a prospective, dual-center study.Body fluid status was assessed in 40 adult patients during the first 24 hours after admission to ICU.Total body Bioelectric Impedance Analysis (BIA) was performed to evaluate TBW(kg) and the hydration scale with vectorial analysis (BIVA).Patients were eligible if: i)baseline sCr levels were available and ii)BIVA hydration level was more than 81% of lean body mass, indicating moderate to severe hyper-hydration.We applied the following correction formula:(measured sCr*TBW)/(0.6*Body Weight).Acute Kidney Injury was diagnosed from sCr increase, according to KDIGO criteria, before and after creatinine correction.

Results: 26 pts. (61.5% male; median age 76.5 years)were considered eligible for the study. The average baseline value of sCr was 0.93±0.36. 24 hours after admission, sCrwas 1.18±0.85. The average increase of uncorrected sCr value was 0.24±0.63.After correcting sCr for fluid overload, the average value of was 1.33±0.89 with an increase of 0.40±0.66. The incidence of AKI was 38.4% and 42.3%, respectively before and after correction. Taking into account measured sCr, 34.6%, 0% and 3.8% of patients developed AKI stage I, II and III. After correction for TBW overload, the percentages of pts. with stage I, II and III of AKI were 26.9%, 11.5% and 3.85%.

Conclusions: We suggest the utilization of TBW estimated by BIA to early diagnose AKI in hyper-hydrated patients. Further studies, including more patients, are needed to assess the correlation of AKI diagnosed with our formula with major outcomes.

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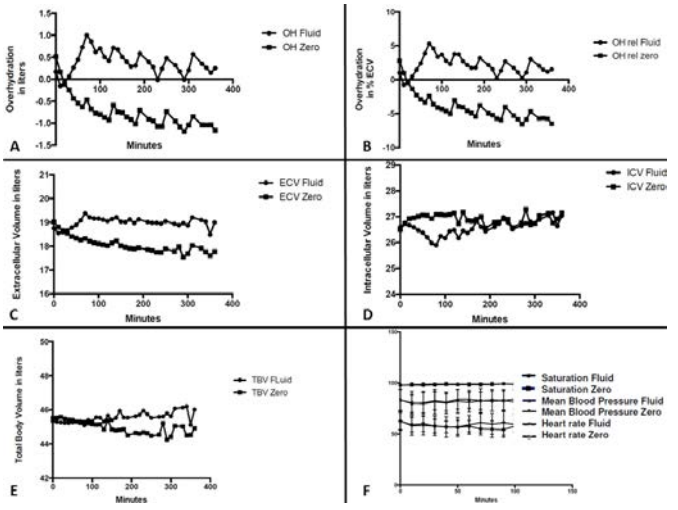
Bioimpedance Spectroscopy for Assessment of Volume Changes during Intravenous Fluid Therapy: A Crossover Study in Healthy Volunteers Manfred Hecking,[1] Matthäus Ernstbrunner,[2] Peter Wabel.[3] *[1]Nephrology, Medical Univ of Vienna, Austria; [2]Anesthesiology, Medical Univ of Vienna, Austria; [3]Fresenius Medical Care Germany.*

Background: Intravenous (iv) fluid therapy is among the most common medical tasks, but its immediate and intermediate effects on the fluid compartments and hemodynamics of the human body remain enigmatic to the majority of clinicians. We therefore tested bioimpedance spectroscopy (BIS) for assessment of volume changes in healthy volunteers.

Methods: After an overnight fast, 15 males received isotonic fluid therapy (Elo-mel®, Fresenius) at a rate of 0,5ml/kg/min during 60 minutes on study day "Fluid", and no fluid therapy on study day "Zero". BIS was performed every 10 minutes using the Body Composition Monitor (Fresenius). All volunteers remained in a supine position for 350 minutes, unless urinating (every 60 minutes). Hemodynamic parameters included peripheral capillary oxygen saturation, electrocardiogram and blood pressure (NCT02296294).

Results: Mean age, height and weight of the volunteers was 29.3±5.5y, 182.7±8.8cm and 77.4±13.2kg, respectively. In minute 60, subjects on the "Fluid" day had received 2.2±0.2L iv fluid and produced 0.6±0.3L urine, while they had remained thirsting and produced 0.1±0.2L urine on the "Zero" day. Overhydration (OH) in liters and % of extracellular volume (ECV) increased to 1.0±0.9L (5.5±4.8% ECV) in minute 70 on the "Fluid" day before gradually decreasing, whereas OH decreased to -1.3±1.2L (-7.2±5.9% ECV) overall in minute 350 on the "Zero" day ($p<0.01$, panels A,B). Hemodynamics did not differ between both days (panel F). For ECV, intracellular and total body volume, see panels C-E.



Conclusions: BIS-based assessment revealed a clinically meaningful and sustained increase in ECV after iv fluid therapy, up to 50% of the infused volume. Similar studies in subjects with illness are needed to quantify the OH cut-off for worse outcomes.

FR-PO340

Residual Water Permeability: A Novel Concept Challenging Current Diagnosis of Syndrome of Inappropriate ADH Hormaz Dara Dastoor,[1] Chandra Mauli Jha,[2] Ken J. Donaldson,[3] Thalakunte Muniraju,[3] Hatem Mohyeldin Ebeid,[4] Samra Abouchacra.[5] *[1]Div of Nephrology, Rahba Hospital- Johns Hopkins International, United Arab Emirates; [2]Div of Nephrology, Burjeel Hospital, United Arab Emirates; [3]Div of Nephrology, Dumfries and Galloway Royal Infirmary, United Arab Emirates; [4]Div of Nephrology, Al Noor Hospital, United Arab Emirates; [5]Div of Medicine, Tawam Hospital, United Arab Emirates.*

Background: Residual Water Permeability (RWP) is a mechanism by which up to 5 liters of water can absorbed down the osmolar gradient between Tubular and Medullary Interstitium, and is active only in the complete absence of ADH activity. We describe a case of a patient labeled as Syndrome of Inappropriate ADH (SIADH), however by showing an active RWP system, we challenged the diagnosis of SIADH and relabelled this as a case of Reset Osmostat with concomitant Primary Polydipsia.

Methods: A 71-year-old lady presented with nausea, vomiting, Plasma Sodium (Pna)-113 mol/l and Uosm – 137mOsm/kg. She was treated with 2.4 liters of 0.9% Normal Saline over 48 hours, with improvement of Pna to 117mol/l. However over the next 24 (Day 3) hours she developed Polyuria of 5.4 liters, which was approximately 3 liters in excess of the total infused fluids with a concomitant rise in Pna to 124 mmol/l. The patient's polyuria was attributed to loss of RWP mechanism, caused by increased solute delivery in the absence of ADH secretion.

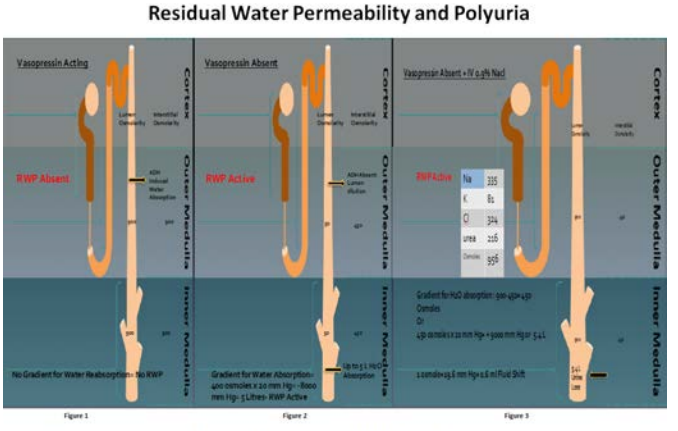


Figure 1: In the presence of vasopressin there is no absorption of water across the collecting ducts due to lack of osmotic gradient
Figure 2: In the absence of vasopressin up to 5 liters of water are absorbed across the Tubulo- Interstitial gradient
Figure 3: In the presence of vasopressin and a solute load (0.9% Nacl) , the osmotic gradient is reversed to induce a water diuresis of 5.4 liters

Results: The case highlights that an RWP system implies complete absence of ADH activity and rules out SIADH as a diagnosis despite Uosm> 100mOsm/kg.

Conclusions: This case report challenges the current diagnostic paradigm for SIADH and shifts focus to often overlooked diagnosis of Reset Osmostat, Hyper responsiveness to ADH, Age related Inability to reduce Free Water excretion as causes of Euvolemic Hyponatremia.

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The Effect of Vasopressin Antagonism on Renal Handling of Water and Sodium and Central and Brachial Blood Pressure during Inhibition of the Nitric Oxide System in Healthy Subjects: A Dose-Response Study

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Background: Nitric Oxide (NO) has an effect on renal water and sodium excretion, but the effect is unknown in the principal cells of the nephron. In a dose-response study, we measured the effect of tolvaptan on renal handling of water and sodium and systemic hemodynamics during baseline and NO-inhibition with L-NMMA.

Methods: In a randomized, placebo-controlled double blind, cross over study, 15 healthy subjects received tolvaptan 15, 30 and 45mg or placebo. L-NMMA was given as a bolus followed by continuous infusion during 60 minutes. We measured GFR, urine output (UO), free water clearance (C_{H2O}), fractional excretion of sodium (FE_{Na}), urinary aquaporin-2 excretion (u-AQP2), urinary excretion of the γ-fragment of the epithelial sodium channel (u-ENaCγ), plasma vasopressin (p-AVP), and central blood pressure (cBP).

Results: During baseline, tolvaptan increased UO and C_{H2O}, whereas GFR and FE_{Na} were unchanged. P-AVP increased three fold. After NO inhibition, UO and C_{H2O} decreased, but to a lesser extent during tolvaptan. FE_{Na} decreased only after placebo. U-AQP2 decreased to the same extent during all tolvaptan doses. U-ENaCγ decreased only after placebo. Central BP increased after NO-inhibition.

Conclusions: During baseline conditions, tolvaptan increased renal water excretion in a dose dependent way. NO-inhibition antagonized the increases in renal water and sodium excretion by tolvaptan. The lack of decrease in u-AQP2 by tolvaptan could be due to a counteracting effect of elevated p-AVP.

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Evidence of Early Enhanced Effects of Vasopressin Type 2-Receptor Antagonist on Urinary Sodium and Potassium Excretion

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Background: Vasopressin type 2-receptor antagonist (V2-R antagonist) is well known to promote water diuresis by blocking the permeability to water of the collecting ducts. However, the possible effects of V2-R antagonist on sodium and potassium handling remain to be determined. Recent experimental models suggest that V2-R antagonist induce natriuresis by inhibiting V2-R mediated stimulation of epithelial sodium channel in the collecting duct, and also increase potassium excretion by a flow-dependent mechanism. This study evaluated whether the V2-R antagonist influence the sodium and potassium excretion in humans.

Methods: 5 patients with autosomal dominant polycystic kidney disease (ADPKD) were administered 45mg oral nonpeptide V2-R antagonist, tolvaptan (Tlv). Urine flow, sodium and potassium excretion in the next 3 hours were compared with basal values obtained 2 hours prior administration of Tlv.

Results: Urinary flow rate (93±33®433±112ml/hr; p<0.01), sodium and potassium excretion rate (sodium 8.2±1.8®12.3±2.8 mEq/hr; p<0.01, potassium 2.2±1.2®2.7±1.1 mEq/hr; p<0.01) significantly increased in the first 3 hours after Tlv administration. Subjects significantly lost weight (-0.49±0.30kg, p=0.02) without altering their serum sodium concentration (143.0±2.4®143.6±0.9mEq/L, p=0.61) and plasma osmolality (289.8±4.7®291.6±2.2mOsm/kg•H_2O, p=0.45).

Conclusions: Tlv rapidly increases urinary sodium and potassium excretion in patients with ADPKD.

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Role of Vasopressin in Dehydration-Associated Kidney Disease

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Background: The role of vasopressin in rats undergoing mild thermal dehydration followed by 2 h rehydration with fructose or water, by administering conivaptan, a V1a and V2 antagonist was studied.

Methods: Four groups of male Wistar rats were exposed to hyperthermia (37°C/ 1 h/ day) and rehydrated with water (W) or 10%fructose (F) during 2 h for 30 days. Two groups received vehicle (W+Veh and F+Veh), and two received Conivaptan (C, 3 mg/kg BW, W+C, and F+C). After rehydration rats received tap water and food ad libitum. A group of normal control (NC) rats was also included. At the end of the study, plasma and urine osmolality and plasma copeptin were evaluated. In renal cortex homogenates sorbitol, fructose, uric acid, oxidative stress as well as the expression of aldose reductase, fructokinase, xanthine oxidase, Nox4, p22phox, gp91phox and vasopressin receptors V1a and V2 were assessed.

Results: Chronic recurrent heat stress was associated with mild renal functional changes (decreased CrCl, and tubular injury with systemic inflammation and renal oxidative stress as well as mitochondrial dysfunction) that were markedly exacerbated by rehydration with fructose. Fructose rehydration also markedly enhanced copeptin levels and activation of the aldose reductase-fructokinase pathway in the kidney. Treatment with C effectively blocked the amplification of injury induced by fructose, decreased oxidative stress and reduced the upregulation of the aldose reductase-fructokinase pathway as well as the V1a and V2 receptor induction that occurred in this condition.

Conclusions: Heat stress and recurrent dehydration induce renal injury by stimulating vasopressin. Importantly, this pathway is greatly amplified by fructose provided in rehydration solutions, even at small doses. Thus, these studies may provide insights into the pathogenesis of heat stress nephropathy, and also suggest that the type of rehydration solution may be critical for overall systemic and renal health.

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FR-PO344

A Serine Protease Inhibitor Increases Osmotic Free Water Excretion Together with Inhibition of Urinary AQP2 Excretion

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Background: Serine proteases (SPs) have pivotal physiological roles in our body. In the kidney, it is reported that the epithelial sodium channel (ENaC) is activated via the proteolytic cleavage of α and γ subunits by SPs . We reported that a synthetic SP inhibitor (SPI) camostat mesilate (CM) inhibited the cleavage of γENaC and increased urinary sodium excretion in aldosterone-infused rats. These results suggest the important roles of SPs within the kidney in the regulation of sodium homeostasis and blood pressure. However, physiological roles of SPs in the kidney still remain unclear. In this study, we administered CM to normal rats in order to explore novel physiological roles of SPs in renal tubule and water homeostasis.

Methods: Six-week-old male Sprague-Dawley rats were divided into control and CM groups. CM group rats were subcutaneously implanted with sustained-release pellets of CM (14 mg/day). After 24h urine collection was performed, rats were sacrificed at day 7 to obtain blood and kidney samples. In another experiment, desmopressin (20ng/h) was infused subcutaneously to rats which were treated with CM.

Results: CM significantly increased urine volume in about two-fold throughout the experimental period independently of sodium and osmolyte excretion, indicating that CM increased osmotic free water excretion. The levels of vasopressin, potassium and calcium in blood as well as osmolality in the inner medulla, that is important for urine concentration, were not changed by CM. Urinary exosomal aquaporin-2 (AQP2) excretion was downregulated by CM, indicating that CM suppressed vasopressin signal in collecting duct. The infusion of desmopressin recovered urinary AQP2 excretion and diminished polyuria caused by CM.

Conclusions: Our results suggest that SPs are associated with water homeostasis in the kidney and that SPI could be the new class of diuretics.

FR-PO345

Role of Adenylyl Cyclase 6 in Li+-Induced Nephrogenic Diabetes Insipidus

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Background: Li^+ is a drug widely used for treating bipolar disorders. Around 50% of patients treated with Li^+ develop nephrogenic diabetes insipidus (NDI). How Li^+ treatment causes NDI is poorly understood. One mechanism that has previously been postulated is that Li^+ competes with Mg^+ as a co-factor for adenylyl cyclases (AC), leading to reduced synthesis of cAMP and dysregulation of aquaporin-2 (AQP2) in renal connecting tubule cells and principal cells. Here, we tested the contribution of AC6, the isoform mediating the majority of vasopressin-induced inner medullary cAMP formation, to Li^+-induced NDI.

Methods: We examined the effects of dietary Li^+ intake in whole body AC6 knockout ($AC6^{-/-}$) mice and in newly developed principal cell-specific AC6 knockout mice ($AC6^{loxloxCre}$; Cre expression driven by the AQP2 promotor).

Results: AC6 protein was absent from $AC6^{-/-}$ mice, and significantly reduced in the inner medulla of $AC6^{loxloxCre}$ mice. Similar to $AC6^{-/-}$ mice, $AC6^{loxloxCre}$ mice had ~50% lower urine osmolality and almost double the water intake vs. control mice. Dietary Li^+ administration for 2 weeks exacerbated these effects in $AC6^{-/-}$ and $AC6^{loxloxCre}$ mice vs. controls. Consistent with $AC6^{-/-}$ mice, medullary AQP2 and pS256-AQP2 abundances were significantly lower in $AC6^{loxloxCre}$ vs. control mice during baseline conditions, and levels were further reduced after Li^+ administration. Phosphorylation of glycogen synthase kinase-3 beta (S9-GSK3β), believed to partially mediate Li^+-induced NDI, was significantly increased in $AC6^{loxloxCre}$ vs control mice after Li^+ treatment. $AC6^{loxloxCre}$ mice had a higher number of proliferating cell nuclear antigen-positive cells compared to control mice, indicating increased cellular proliferation as commonly seen during Li^+ administration.

Conclusions: Our results suggest that AC6 plays a minor role in the development of Li^+ induced NDI. Furthermore, the results suggest that the onset of Li^+ NDI is independent of cAMP production in the inner medulla.

Funding: NIDDK Support, Pharmaceutical Company Support - Novo Nordisk Foundation, Government Support - Non-U.S.

FR-PO346

Inhibition of Mitochondrial Oxidative Stress Attenuates the Downregulation of AQP2 in Obstructive Kidney Disease: Role of COX-2/PGE2/V2 Receptor Pathway

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Background: Downregulation of aquaporins (AQPs) in obstructive kidney disease has been well demonstrated with elusive mechanisms. Our previous study indicated that mitochondrial dysfunction played crucial role in this process (ASN abstract, 103A, 2014). However, it is still uncertain that how mitochondrial dysfunction affected the AQPs in obstructive kidney disease.This study was undertaken to investigate the role of mitochondria-derived oxidative stress in mediating obstruction-induced downregulation of AQPs.

Methods: Mice with unilateral ureteral obstruction (UUO) or sham surgery were subjected to MnTBAP (a SOD2 mimic) or vehicle treatment by osmotic minipumps.

Results: After UUO for 7 days, renal SOD2 (mitochondria-specific SOD) was reduced by 50% accompanied by a 2.2-fold increase of oxidative stress marker TBARs. Meantime, AQP1, AQP2, and AQP4 were remarkably downregulated by 70-90% as determined by Western blotting and qRT-PCR. Administration of MnTBAP significantly attenuated AQP2 downregulation by 40% ($p<0.05$) in line with complete blockade of TBARs elevation, while AQP1 and AQP4 reduction was not affected. COX-2/PGE2 pathway has been reported to be a contributor of AQPs' reduction in obstructed kidney, thus we detected renal COX-1/2, mPGES-1/2, and PGE2 secretion in the fluid in obstructed ureter by qRT-PCR, Western blotting, or ELISA. Significantly, MnTBAP selectively reduced expressions of COX-2, mPGES-1, and renal secretion of PGE2 by 20 to 30% ($p<0.05$). Moreover, Western blotting and qRT-PCR revealed a marked decrease of V2 receptor by 80%, which was ameliorated by 35% ($p<0.05$) after MnTBAP treatment.

Conclusions: The findings suggested an important role of mitochondrial oxidative stress in mediating AQP2 downregulation in obstructed kidney possibly via modulating COX-2/mPGES-1/PGE2/V2 receptor pathway.

FR-PO347

Abstract Withdrawn

FR-PO348

Extracellular Vesicular Release of Aquaporins in Rats after Kidney Transplantation

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Background: Kidney transplantation is known to cause diuresis. Renal AQP2 expression has been reported to be down-regulated in an experimental kidney transplantation model, and this reduction is considered to be a cause of the diuresis. Aquaporin-1 (AQP1) and AQP2, water channel proteins, are released into urine via a subset of extracellular vesicles, exosomes. However, the level of urinary exosomal release of those AQPs after renal transplatntion is largely unknown. In this study, we investigated the urinary exosomal release of AQP1 and AQP2 in a rat syngenic kidney transplantation model.

Methods: All animal studies were approved by the committee on the Care and Use of Laboratory Animals at the University of Miyazaki. Male SD rats were used as graft recipients and donors. The donor right kidney was transplanted into the recipient rat in which the right kidney had been removed, and thereafter the remaining left kidney was removed (Tpx group). For the control animal, a simple left kidney nephrectomy was performed. Urine samples were collected at 3 (day 3) and 7 days, and kidney samples were obtained at 7 days after the surgery. Urinary exosomes were isolated by differential centrifugation.

Results: The urinary exosomal release of AQP1 on days 3 and 7, and AQP2 on day 7 were significantly lower in the Tpx group in comparison with the control group. The level of urinary exosomal AQP1 or AQP2 was positively correlated with its renal abundance in the renal cortex. The urinary exosomal release of Alix and TSG101, exosomal marker proteins, were not different in between the Tpx and the control groups.

Conclusions: Urinary exosomal release of AQP1 and AQP2 after kidney transplantation was decreased, and this reduction might be mediated by their renal expression levels but not by a lesser number of exosomes released into urine. Urinary exosomal AQPs might be useful for the estimation of their renal expression levels in renal transplantation.

FR-PO349

Genome-Wide Identification of CREB1 and CEBPB Binding Sites in Vasopressin-Responsive mpkCCD Cells

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Background: In collecting duct principal cells, vasopressin signaling regulates expression of several genes, including those that code for aquaporin-2 (AQP2) and ENaC (β and γ subunits), in part through differential transcription factor (TF) binding. One such TF may be cAMP-responsive element binding protein 1 (CREB1). CREB1 can heterodimerize with another basic-leucine zipper TF, CCAAT/enhancer-binding protein β (CEBPB), which translocates to the nucleus in response to vasopressin. To identify genomic binding sites for CREB1 and CEBPB in vasopressin-responsive mouse mpkCCDc11 cells, we used chromatin immunoprecipitation (ChIP) followed by deep sequencing (ChIP-Seq).

Methods: Cultured mpkCCDc11 cells were treated with the vasopressin analog dDAVP (100pM) or vehicle for 30 min (n=4 pairs for CREB1 and n=2 pairs for CEBPB). Cells were crosslinked and ChIP was performed with ChIP-grade antibodies. DNA libraries were generated and sequenced using an Illumina HiSeq 2000 sequencer. Mapping (mouse UCSC version mm10), peak calling and motif analysis were performed using standard software.

Results: For CREB1, we identified 1634 peaks in vehicle-treated cells and there was no change in response to dDAVP. 70% of these were in the promoter regions of genes. CREB1 did not bind anywhere within 390 kB of the *Aqp2* gene. For CEBPB, we identified 209 binding sites in vehicle-treated cells and the number of sites increased to 2401 with dDAVP. At the 209 sites common between vehicle and dDAVP, CEBPB binding was markedly increased by dDAVP (RPM ratio [dDAVP/vehicle]=2.25). Only about 30% of CEBPB sites were at gene promoters, but there were many intronic sites (40% of total). A strong CEBPB binding site was seen 400 bp downstream from the *Aqp2* gene body. CREB1 and CEBPB sites coincided at 20 positions in the presence of dDAVP.

Conclusions: CREB1 and CEBPB both have potential roles in vasopressin-mediated transcriptional regulation. If CREB1 is involved in regulation of *Aqp2* gene expression, its effect must be indirect since there is no binding site in the vicinity of the *Aqp2* gene. In contrast, the increase in CEBPB binding at many sites in response to dDAVP indicates a likely role for CEBPB in the broad transcriptional effects of vasopressin.

Funding: Other NIH Support - NHLBI Intramural

FR-PO350

Urine AQP2 Comes from Exosome Pathway and Represents a Long-Term Regulation of Vasopressin

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Background: Urine AQP2 is measured in water-balance disorders as a biomarker of vasopressin (VP) action on kidney collecting ducts. VP action consists of two time phases; a short-term regulation starts within minutes and represents increased accumulation of AQP2 at the apical membrane, whereas a long term regulation occurs in hours/days and represents increased abundance of whole AQP2 in the cell. It is unclear which time-phase effects are responsible for the effect of VP on urine AQP2 excretion.

Methods: Stably AQP2-transfected MDCK cells were grown on permeable support and excretion of AQP2 to the apical medium was measured. Human urine EVs were obtained by centrifugation and stored at -25°C to disrupt EVs membranes. Then, AQP2-bearing EVs were obtained by immunoprecipitation with AQP2 antibody and analyzed by LC-MS/MS.In 20 healthy subjects, urine AQP2 was measured by ELISA before and after 500ml water drinking. Urine samples were pretreated with alkali to disrupt EVs membranes.

Results: 1) AQP2 excretion was relatively constant and forskolin 10^{-5}M did not evoke further increases up to 3 hr. **2)** The MS analysis identified 137 proteins in the order of endocytosis pathway proteins (including TSG101, CHMP4, ALIX, VPS4)>MAPK signaling proteins=actin cytoskeleton proteins, suggesting that AQP2-EVs are endocytosis-exosome origin, and may not be ectosome origin. Western blot analysis confirmed the presence of TSG101. **3)** After water drinking, urine osmolalities, creatinine concentrations and AQP2 concentrations decreased from 750 to 371 mOsm/l, from 136.4 to 48.5 mg/dl, and from 5.07 to 1.93 ng/ml, respectively. However, after urine AQP2 values were corrected for creatinine, uAQP2/Cr were not significantly different, 3.37+0.32 and 3.43+041 ng/mg (mean+SE).

Conclusions: Urine AQP2 excretion is mediated by exosome pathway and represents a long term regulation of VP.

Funding: Government Support - Non-U.S.

FR-PO351

Depletion of Vacuolar Protein Sorting-Associated Protein 35(Vps35) Is Associated with Increased Lysosomal Degradation of Aquaporin-2

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Background: Carboxyl-terminus of AQP2 (AQP2c) undergoes post-translational modifications, including phosphorylation and ubiquitination, for the regulation of aquaporin-2 (AQP2) translocation and protein expression. We aimed to identify novel proteins interacting with AQP2c.

Methods: Recombinant AQP2c protein was made in *E. coli* BL21 (DE3) by exploiting the pET32 TrxA fusion system. Lysates of rat kidney inner medullary collecting duct (IMCD) tubule suspensions were interacted with rat AQP2c bound to Ni^{2+}-resin. LC-MS/MS proteomic analysis demonstrated 18 proteins, including vacuolar protein sorting-associated protein 35 (Vps35).

Results: Co-immunoprecipitation assay demonstrated that Vps35 interacted with AQP2c. Immunohistochemistry of rat kidney revealed that AQP2 and Vps35 were co-localized at the intracellular vesicles in the collecting duct cells. The role of Vps35 in the dDAVP-induced AQP2 regulation was examined in mpkCCDc14 cells. Cell surface biotinylation assay demonstrated that dDAVP-induced apical translocation of AQP2 was significantly decreased under the siRNA-mediated Vps35 knockdown. dDAVP-induced AQP2 up-regulation was less prominent in the cells with Vps35 knockdown than control. Moreover, AQP2 protein abundance was decreased to a greater extent during the withdrawal period after dDAVP stimulation under the Vps35 knockdown, which was significantly

inhibited by chloroquine (a blocker of the lysosomal pathway) treatment, but not by MG132 (a proteasome inhibitor) treatment. Immunocytochemistry demonstrated that internalized AQP2 was more associated with lysosomal marker (LAMP-1) in the primary cultured IMCD cells under the Vps35 knockdown.

Conclusions: Vps35 is an interacting protein with AQP2c and depletion of Vps35 is likely to be associated with increased lysosomal degradation of AQP2 protein.

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FR-PO352

AQP2 Abundance Is Regulated by the E3-Ligase CHIP via HSP70 as Possible Anchoring Protein for the E3-Ligase MDM2 Mariangela Centrone,[1] Marianna Ranieri,[1] Sante Princiero Berlingerio,[1] Annamaria Russo,[1] Annarita Di Mise,[1] Peter M.T. Deen,[2] Olivier Staub,[3] Giovanna Valenti,[1] Grazia Tamma.[1] *[1]Univ of Bari Aldo Moro, Italy; [2]Radboud Univ Medical Center, Netherlands; [3]Univ of Lausanne, Switzerland.*

Background: AQP2 is mainly controlled by vasopressin-dependent changes in protein abundance which is in turn regulated by AQP2 ubiquitylation and degradation, but the proteins involved in these processes are largely unknown. Here, we investigated the potential role of the CHIP E3 ligase in AQP2 regulation.

Methods: Coimmunoprecipitation and Western Blotting experiments were performed to evaluate CHIP involvement on AQP2 half-life and phosphorylations.

Results: AQP2 complexes with CHIP in kidneys and renal MCD4 cells. Expression of CHIP increased proteasomal degradation of AQP2 and HSP70 abundance, a molecular signature of HSP90 inhibition. Chemical inhibition of HSP90 with 17-AAG led to increased level of HSP70 and AQP2 degradation. Increased HSP70 level, secondary to CHIP expression, promotes ERK signaling which increases of phosphorylation of AQP2 at S261. Phosphorylation of AQP2 at S256 and T269 were instead downregulated. Next, we investigated HSP70 interaction with AQP2 which is important for endocytosis. Compared with AQP2-wt, HSP70 binding decreased in AQP2-S256D and AQP2-S256D-S261D while increased in AQP2-S256D-S261A. Surprisingly, expression of CHIP-delUbox, displaying a loss of E3 ligase activity, still induced AQP2 degradation, indicating that CHIP does not ubiquitylate and degrade AQP2 itself. Interestingly, the AQP2 half-life was increased with CHIP-delTPR. Its TPR domain binds Hsc70/Hsp70 and Hsp90. So, which E3 ligase then mediates AQP2 degradation with CHIP? Importantly, HSP70 has been reported to bind other E3 ligases such as MDM2. Interestingly, we found that co-expression of CHIP and MDM2 increased AQP2 degradation, whereas co-expression of CHIP with MDM2-delRING, an inactive form of MDM2, impaired AQP2 degradation.

Conclusions: Our findings indicate CHIP as master regulator of AQP2 degradation via HSP70 that has dual functions: (1) as chaperones for AQP2 (2) as possible anchoring protein for MDM2 E3 ligase, which appears to be committed to AQP2 degradation.

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FR-PO353

Use of CRISPR and Phosphoproteomics to Investigate the Role of Myosin Light Chain Kinase in Vasopressin Signaling Kiyoshi Isobe, Viswanathan Raghuram, Chin-Rang Yang, Pablo Sandoval, Chung-Lin Chou, Mark A. Knepper. *Systems Biology Center, NHLBI, NIH.*

Background: Vasopressin regulates trafficking of aquaporin-2 (AQP2) to and from the plasma membrane. We have previously reported that Ca^{2+}-calmodulin and myosin light chain kinase (MLCK) are involved in AQP2 trafficking, although the mechanisms are unclear. To address this issue, we generated MLCK knock-out (MLCK-KO) collecting duct cell lines using genome editing (CRISPR-Cas9) in mouse mpkCCD cells.

Methods: Four independent KO lines were generated using different guide RNAs. Control cells with intact MLCK were generated in the same experiments. Successful deletion was confirmed by western blotting and genomic sequencing.

Results: The MLCK-KO cells were viable and grew at approximately the same rate as control cells. However, the MLCK-KO cells were broader and flatter. Phalloidin staining revealed that vasopressin-mediated dissolution of basolateral stress fibers was slower in the MLCK-KO cells. Vasopressin-stimulated AQP2 phosphorylation at Ser256 and Ser269 did not differ versus control cells (western blotting and immunofluorescence). Upon vasopressin washout, AQP2 rapidly appeared in early endosome antigen 1 (EEA1)-positive intracellular vesicles in control cells. However, in MLCK-KO cells, AQP2-EEA1 co-localization was markedly delayed (STED microscopy), suggesting that MLCK plays a role in trafficking at the level of early endosomes. Also, EEA1-positive vesicles were much smaller in the MLCK-KO cells. To assess the signaling pathways affected, we carried out quantitative phospho-proteomics of vasopressin-treated MLCK-KO cells versus control cells (SILAC). There was a substantial decrease in phosphorylation of 18 proteins at TpS motif sites in addition to myosin regulatory light chain, identifying putative MLCK substrates. Interestingly, activation loop phosphorylation increased in several protein kinases including ERK1, ERK2, p38α, p38Δ, GSK3α and protein kinase D3, implying that MLCK may be involved in negative feedback of other kinase pathways.

Conclusions: These results indicate a role for MLCK in AQP2 trafficking at the level of early endosomes, and in signaling pathways beyond phosphorylation of myosin regulatory light chain.

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FR-PO354

Gain-Of-Function Mutations in the Vasopressin Type 2 Receptor Causing Nephrogenic Syndrome of Inappropriate Antidiuresis (NSIAD): Evidence for Vasopressin-Independent Increase in AQP2 Trafficking and Osmotic Water Permeability Marianna Ranieri, Grazia Tamma, Tommaso Pellegrino, Giovanna Valenti, Susanna Cotecchia. *Univ of Bari Aldo Moro.*

Background: Nephrogenic syndrome of inappropriate antidiuresis (NSIAD) results from gain-of-function mutations in the *AVPR2* gene coding for vasopressin receptor 2 (V2R) and is characterized by spontaneous antidiuresis and undetectable vasopressin circulating levels. Here, we investigate the effects of two mutations, R137C and F229V, on receptor-mediated intracellular signaling controlling AQP2 trafficking and function.

Methods: M1 cells were stably co-transfected with human AQP2 and wild type (WT) V2R or its mutants V2-R137C and V2R-F229V. AQP2 trafficking was evaluated by confocal studies and western blotting experiments. Osmotic water transport was evaluated by a calcein-based method. Intracellular cAMP was measured by cAMP ELISA kit.

Results: Confocal studies revealed that in cells expressing V2R-R137C, AQP2 was in part localized to the plasma membrane while a clear plasma membrane localization was found for cell expressing V2R-F229V. Functional experiments revealed a slight though significant increase in temporal osmotic response in cells expressing V2R-R137C whereas expression of V2R-F229V strongly increased the osmotic water permeability compared to cells expressing the WT receptors. Since AQP2 trafficking can be regulated by phosphorylation, we next evaluated AQP2 phosphorylation state in cells expressing the receptors. A significant increase in AQP2-S256 and AQP2-T269 phosphorylation, associated with significantly higher cAMP levels, was found in cells expressing V2R-F229V. Interestingly, in cells expressing V2R-R137C significantly lower levels of AQP2-S261 phosphorylation paralleled by decreased phosphorylation of p38-MAPK, the kinase committed to phosphorylate S261, were observed likely resulting in lower extent of AQP2 degradation.

Conclusions: These findings suggest that the constitutive activity of the V2R-R137C and V2R-F229V mutants upregulates AQP2 trafficking through two different signaling pathways. Whereas, V2R-F229V induces a cAMP-dependent increase of AQP2 phosphorylation, V2R-R137C seems to increase AQP2 abundance in cells.

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FR-PO355

Acute Activation of AMPK Inhibits Aquaporin-2 Nuria M. Pastor-Soler,[1] Mohammad M. Al-Bataineh,[2] Hui Li,[1] Kazuhiro Omi,[1] Fan Gong,[2] Allison L. Marciszyn,[2] Sajid Naveed,[2] Xiaoqing Zhu,[3] Dietbert Neumann,[3] Qi Wu,[4] Lei Cheng,[4] Robert A. Fenton,[4] Kenneth R. Hallows.[1] *[1]Div of Nephrology and Hypertension, Kidney Research Center, Keck School of Medicine of USC, Los Angeles, CA; [2]Renal-Electrolyte Div, Univ of Pittsburgh, Pittsburgh, PA; [3]Molecular Genetics, Maastricht Univ, Maastricht, Netherlands; [4]Biomedicine, Aarhus Univ, Aarhus, Denmark.*

Background: Aquaporin-2 (AQP2) maintains water homeostasis and traffics from intracellular vesicles to the apical membrane of principal cells in response to vasopressin (AVP), which is released with low intravascular volume. Decreased kidney perfusion activates AMP-activated kinase (AMPK), a metabolic sensor that inhibits several transport proteins. We hypothesized that AMPK inhibits AQP2 possibly to protect the interstitial gradient required for urine concentration during metabolic stress when low intravascular volume induces AVP release and there is decreased distal nephron perfusion.

Methods: We used ex vivo kidney slices, hypotonic lysis of AQP2-expressing *Xenopus* oocytes, surface biotinylation of $mpkCCD_{cl4}$ cells, phosphorylation assays, and mass spectrometry.

Results: Acute AMPK activation with 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR; 75 min) in kidney slices prevented baseline AQP2 apical accumulation in principal cells but did not prevent AQP2 apical accumulation in response to the AVP analog desmopressin (dDAVP). Prolonged AMPK activation prevented AQP2 cell membrane accumulation in response to forskolin in mouse collecting duct cells. Moreover, AMPK inhibition accelerated hypotonic lysis of *Xenopus* oocytes expressing AQP2. AMPK promoted Ser-261 phosphorylation and antagonized dDAVP-dependent phosphorylation of other AQP2 COOH-terminal sites. Although AMPK weakly phosphorylated immunoprecipitated AQP2 *in vitro*, no direct AMPK phosphorylation of the AQP2 C-terminus was detected by mass spectrometry.

Conclusions: Our findings suggest an increasing, time-dependent antagonism of AMPK on AQP2, as AICAR inhibits cAMP-dependent apical accumulation and AVP-dependent phosphorylation of AQP2. AMPK inhibition of AQP2 likely does not involve direct AQP2 phosphorylation by AMPK.

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FR-PO356

Effects of Nephrotoxins on Claudin 2 Expression and Paracellular Water Transport Anja Wilmes, Paul Jennings. *Physiology and Medical Physics, Physiology, Innsbruck, Tirol, Austria.*

Background: Tight junction proteins are important for the selective permeability of the paracellular route and thus tissue specific function. In the proximal tubulus the pore forming claudins, claudin 2 and 10 are highly expressed, contributing to the high permeability within this part of the nephron. Recently it has been shown that claudin 2 is not only permeable to

cations, but also to water and thus has a critical role in proximal tubule paracellular water transport. We have previously shown that claudin 2 is decreased and water transport is inhibited in response the nephrotoxin cyclosporine A. Here we investigate a potential link between oxidative stress, claudin-2 regulation and paracellular water transport.

Methods: The human proximal tubular cell line RPTEC/TERT1 was cultured on micropourous growth supports (PET filters) and exposed to sub-toxic concentrations of oxidative stress inducing nephrotoxins, including diquat dibromide and potassium bromide and pharmacological Nrf2 activators, including bardoxolone methyl (CDDO methyl ester) and AI-1. Trans-epithelial electrical resistance (TEER) and apical to basolateral water transport were monitored. Claudin 2 and 10 expressions were measured by western blotting or immunofluorescence.

Results: All compounds induced downstream targets of the Nrf2 oxidative stress response pathway, including heme oxygenase 1 (HMOX1) and NQO1. Both, nephrotoxins and Nrf2 activators, affected claudin 2 expression and inhibited water transport. For most compounds neither claudin-10 nor TEER were affected.

Conclusions: The results suggest that claudin 2 expression is linked to Nrf2 activation and that oxidative stress is likely to decrease proximal tubule water reabsorption.

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FR-PO357

Regulated Ser-261 Dephosphorylation Combined with Ser-256 and Ser-269 Phosphorylation in the C-Terminus of Aquaporin-2 Water Channel

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Background: AQP2 has multiple vasopressin-sensitive phospho-serine sites in its C-terminus. It is known that pS261 decreases and pS269 increases stimulated by vasopressin with a constant Ser-256 phosphorylation, however; how these phosphorylation and dephosphorylation is regulated in combination remains to be clarified.

Methods: In this study, we performed combinatorial analysis of AQP2 phospho-regulation in the acute phase of forskolin (FK) stimulation. AQP2-MDCK cells were either treated or not treated with FK (20 μM) and then subjected to phospho-specific immunoprecipitation assays.

Results: First, we performed time-series analysis of phosphorylation in the initial phase of FK stimulation. A significant increase of pS269 was detectable within 1 min. A significant decrease of pS261 was detectable at 10 min, however; it was not occurred at 1 min. During the stimulation, pS256 status was constant. This demonstrated that Ser-269 phosphorylation preceded Ser-261 dephosphorylation. Next, pS256-positive AQP2 was isolated by the phospho-specific immunoprecipitation. In the steady state, pS256-positive AQP2 was strongly phosphorylated at Ser-261. After 10 min of FK treatment, pS269 signal significantly increased (1.00±0.12 to 5.62±0.25,P<0.01, n=4) and pS261 signal strongly decreased (1.00±0.05 to 0.30±0.13,P<0.01, n=4) in the pS256-positive AQP2 population. Further, pS269-positive AQP2 was isolated after 1 min or 10 min of FK treatment. At 1 min, pS261 signal was strongly detectable in the pS269-positive AQP2. After 10 min of the treatment, pS261 signal in the pS269-positive AQP2 population strikingly decreased (1.00±0.07 to 0.30±0.12,P<0.01, n=4).

Conclusions: In conclusion, pS256-positive AQP2 is strongly phosphorylated at Ser-261 to form pS256-pS261-AQP2 in the steady state. Upon FK stimulation, it quickly transformed into pS256-pS261-pS269-AQP2 and then converted to pS256-pS269-AQP2 dephosphorylated at Ser-261 a little later. These results first directly defined the basic principle of combinatorial AQP2 phospho-regulation in the cell, showing that Ser-261 dephosphorylation is involved in the pS256- and pS269-intervened acute AQP2 regulation.

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FR-PO358

Protein Phosphatase 2c Is Responsible for S261 De-Phosphorylation, but Did Not Affect Aquaporin-2 Trafficking

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Background: Aquaporin-2 (AQP2) trafficking and degradation are regulated by phosphorylation and de-phosphorylation of 4 essential serine sites on the AQP2 c-terminus. Upon vasopressin (VP) stimulation, it is thought that S256 needs to be phosphorylated first for other serine residues (S264 and S269) to be phosphorylated or dephosphorylated (S261). We were interested in identifying the phosphatase that de-phosphorylates S261, and determining whether this process is dependent on S256, the major regulator of AQP2 trafficking.

Methods: We pretreated LLC-PK1 cells stably expressing AQP2 (LLC-AQP2) with protein phosphatase (PP) inhibitors including, okadaic acid, an inhibitor of PP1, PP2a, PP3 and PP5; cyclosporine, an inhibitor of PP2b, and sanguinarine, which inhibits PP2c. After 10 min VP treatment, we used immunocytochemistry to determine AQP2 localization, and western blot and specific phospho-antibodies against S256 and S261 to measure phosphorylation. We also treated *rat* kidney tissue slices to confirm AQP2 localization in situ by pre-treating tissues with PP inhibitors before VP.

Results: Inhibition of protein phosphatases (PP) with okadaic acid, cyclosporine or sanguinarine did not lead to a noticeable alteration of AQP2 trafficking in LLC-AQP2 cells or in our *in situ* rat kidney slice model. They also did not induce a significant change in S256 phosphorylation or S261 dephosphorylation on their own. Interestingly, we found that VP-induced de-phosphorylation of S261 occurred not only in LLC-AQP2 cells, but also S256A mutant cells. Importantly, VP induced S261 de-phosphorylation was almost completely prevented by inhibiting PP2c with sanguinarine but not the other PP inhibitors. Blocking S261 dephosphorylation with sanguinarine did not, however, affect VP-induced AQP2 membrane accumulation in either cultured cells or kidney tissue.

Conclusions: Our results show that S261 de-phosphorylation is dependent on protein phosphatase 2C activity, and is independent of S256 phosphorylation. These findings suggest an independent pattern of phosphorylation of some AQP2 C-terminal serine residues that will allow more detailed study of their physiological functions.

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FR-PO359

Proteomic Analysis of a Proximal Tubular Specific Polycystic Kidney Disease Model of AQP11 Deficient Mice

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Background: AQP11 is expressed at the ER of proximal tubular cells and its disruption leads to polycystic kidney disease (PKD) by a failure of polycystin-1 trafficking to the plasma membrane due to its defective glycosylation at the ER. As the cyst comes solely from the proximal tubule, it will be a good model to clarify whether the cystogenesis of the proximal tubule is similar to that of the collecting duct in ADPKD. Here we conducted proteomic analysis of the kidney from AQP11-null mice.

Methods: Mouse Kidneys from 3 week old AQP11-null mice and their wild-type littermates were compared at the beginning of cyst formation. Tissue samples were sonicated and digested in a sodium deoxycholate buffer. Each sample was labeled with 6-plex TMT labeling reagent, a mixture of the samples were separated by nano-flow HPLC and introduced to mass spectrometer, Q-Exactive (Thermo Fisher Scientific).

Results: A total of 755 differently expressed proteins were identified, in which 205 proteins were more abundant and 534 proteins were less abundant in AQP11-null mice. The increased proteins included transgelin (transformation sensitive actin crosslinking protein), galectin-3 (lectin family) and uromodulin (UMOD: Tamm-Horsfall protein). The enhanced UMOD may indicate a tubular injury of the distal nephron by ectatic proximal tubules or its stimulated compensatory function. AQP11-null kidney also displayed an increase of extracellular matrix-related proteins including vimentin, collagen and fibulin, and of cytoskeleton-related proteins including paladin, alpha-actinin, and keratin. On the other hand, mitochondrial proteins were decreased including succinyl-CoA ligase, lysophospholipid acyltransferase, and a Pi transporter (slc25a3), which may reflect a mitochondrial dysfunction leading to apoptosis.

Conclusions: Proteomics approach of the kidney from AQP11-null mice presented itself to be a promising tool to clarify a unique pathology of early stage of proximal tubular specific polycystic kidneys, which will lead to the discovery of key molecules for the formation and progression of the proximal tubular cysts in ADPKD.

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FR-PO360

Gender Comparison of Volume Regulating Hormones and Aquaporin-2 Excretion following Graded Central Hypovolemia

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Background: Central hypovolemia induced by orthostatic loading induces reno-vascular changes that can lead to syncope. In this study we investigated volume regulating hormonal responses and reno-vascular changes in male and female subjects as they underwent central hypovolemia, induced by graded lower body negative pressure (LBNP).

Methods: 37 subjects (n = 19 males; n = 18 females. ages: 18 - 30 yrs) were subjected to graded LBNP until LBNP of 40 mmHg. Blood and urine samples were collected at rest and after 10 min recovery. The volume regulating hormones Vasopressin (measured as copetin); Brain natriuretic peptide (BNP), ACTH and adrenomedullin (ADM) were measured in the plasma using standard methods. Urinary-AQP2 excretion was measured by ELISA as biomarker for the renal system response to vasopressin.

Results: Under basal conditions, males had significantly higher vasopressin levels compared with females. However both sexes responded to the central hypovolemia with a significant reduction of vasopressin levels, as measured at 10 min of recovery. BNP, secreted by the ventricles of the heart in response to excessive stretching of heart, was higher in males than in female under basal conditions and increased significantly after the orthostatic stress only in female. Conversely, ADM, a vasodilator peptide hormone, increased significantly after orthostatic loading only in males. u-AQP2 excretion was significantly higher in females than in males at rest and did not change significantly after 10 min recovery.

Conclusions: Analysis of volume regulating hormones indicate that soon after returning to the supine position at the end of the central hypovolemia, the expected sudden volume loading should stimulate afferent inputs to the brain, leading to inhibition of vasopressin release in males and females and stimulating a preferential adaptive vascular response in males as shown by the increases in ADM, whereas females showed a preferential renal response as shown by the increases in BNP.

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FR-PO361

Sex-Dependent Differences in Water Homeostasis in Wild-Type and V-ATPase B1 Knockout Mice Anil V. Nair, Teodor G. Paunescu, Richard Bouley, Dennis Brown. *Prog. in Memb. Biol. and Div of Nephrology, Mass. Gen. Hospital, Boston, MA.*

Background: Since the extent of dehydration in humans during prolonged exercise is sex-dependent, we investigated water homeostasis in male and female wild-type (WT) C57BL/6 mice. Since renal β-intercalated cells (ICs) were reported to play a role in fluid balance, we also assessed the water concentrating ability of mice deficient in the V-ATPase B1 subunit ($B1^{-/-}$ mice).

Methods: We assessed the water concentrating ability of male and female mice using urine analysis in metabolic cage experiments, immunofluorescence and immunoblotting.

Results: Baseline urine osmolality trended towards higher values in females (2756±278 mOsm/kg) than in males (2420±185 mOsm/kg). 12 h water deprivation decreased urine output by 57% in females (3664±244 mOsm/kg) and by 52% in males (3468±318 mOsm/kg). Urine output increased significantly in B1-/- mice compared to WT, by 10% in males and 29% in females. Whereas in water-deprived B1-/- mice it decreased by 46% in females, but by only 17% in males, compared to WT. AQP2 protein levels were lower in B1-/- than in WT males, but higher in B1-/- than in WT females. The baseline subcellular localization of AQP2 in principal cells (PCs) was more polarized towards the apical membrane in WT females than in males. In both genotypes, AQP2 relocates towards the apical pole of PCs to a larger extent in water-deprived females than in males. Urine output of water-deprived WT decreased, from 1.35 to 0.66 (p=0.004) in males and from 1.55 to 0.68 ml/12 h/animal (p<0.001) in females. In water-deprived B1-/- mice, urine output decreased significantly only in females, from 2.17±0.22 to 1.16±0.15 (p<0.001), whereas the decrease in B1-/- males was not significant (1.5±0.19 vs 1.24±0.14 ml/12 h/animal). Intriguingly, water deprivation caused a decrease in urine pH only in B1-/- females (7.01 to 6.71, p=0.016). We also found females to have a higher IC/PC ratio than males, and B1-/- mice of both sexes to have a higher ratio than WT.

Conclusions: Our data support the idea that ICs are involved not only in maintaining acid-base balance but also in water homeostasis, that the mechanism is at least partially mediated by the V-ATPase, and that these processes are sex-dependent.

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FR-PO362

Sex-Specific Relationship of Serum Uric Acid with All-Cause Mortality in Adults with Normal Kidney Function—An Observational Study Eunjeong Kang, Dong Ki Kim, Kook-Hwan Oh, Kwon Wook Joo, Yon Su Kim, Hajeong Lee. *Dept of Internal Medicine, Seoul National Univ Hospital, Seoul, Korea.*

Background: Serum uric acid (SUA) levels are associated with cardiovascular mortality and other diseases such as hypertension, diabetes, and chronic kidney disease. Although SUA possibly influences on all-cause mortality in individuals with normal kidney function, studies are lacking in normal kidney function.

Methods: Participants aged over 40 years who underwent routine health check-ups at Seoul National University Hospital between 1995 and 2006 were recruited. Individuals with estimated glomerular filtrations rates <60 mL/min/1.73 m^2 and who received lab study and colonoscopy on the same day were excluded. The association between SUA and all-cause mortality was evaluated using the COX proportional hazard regression models with adjustment for covariates including diabetes, hypertension, age, body mass index, blood pressure, creatinine, albumin, hemoglobin, C-reactive protein, smoking, and exercise.

Results: SUA levels were higher in men than in women (5.7±1.2 mg/dL for men and 4.2±0.9 mg/dL for women, $P < 0.001$). SUA levels declined as age increased in men but increased with age in women. During 12.3±3.6 years of follow-up, 1,402 deaths occurred. 6.9% of men and 3.1% of women died. The overall mortality rate had a U-shaped association with SUA levels, a J-shaped association in men, and no association in women. There was a significant interaction of sex for the SUA-mortality association (P for interaction = 0.049); therefore, survival analysis was conducted by sex. In men, the lower SUA group had a higher mortality rate after adjustment (SUA, <4.0 mg/dL, adjusted hazard ratio [HR] 1.550, 95% confidence interval [CI] 1.235–1.946, $P < 0.001$) compared with the reference group (SUA, 6.1–8.0 mg/dL). A higher SUA contributed to an insignificant increased mortality in men (>8.0 mg/dL, adjusted HR 1.305, 95% CI 0.904–1.884, $P = 0.16$). Women failed to show any significant association between SUA and mortality.

Conclusions: This study provided novel evidence that SUA-mortality association differed by sex. We demonstrated that a lower SUA was an independent risk factor for all-cause mortality in men with normal kidney function.

FR-PO363

Uric Acid Predicts Mortality and Ischemic Stroke in Subjects with Diastolic Dysfunction - The Tromso Study 1994-2013 Jon V. Norvik,[1,2] Henrik Schirmer,[1,2] Trond G. Jenssen,[2] Bjorn Odvar Eriksen,[1,2] Maja-Lisa Løchen,[2] Marit D. Solbu.[1,2] *[1]Univ Hospital of North Norway, Tromsø, Norway; [2]UiT The Arctic Univ of Norway, Tromsø, Norway.*

Background: Elevated serum uric acid is associated with cardiovascular disease and increased mortality in patients with heart failure. We investigated whether serum uric acid predicts adverse outcomes in persons with indices of diastolic dysfunction in a general population.

Methods: We performed a prospective cohort study among 1460 women and 1480 men from 1994 to 2013. Endpoints were all-cause mortality, incident myocardial infarction and incident ischemic stroke. We analyzed hazard ratios (HR) for these endpoints per 59 μmol/L increase in baseline uric acid. We stratified the analyses by echocardiographic markers of diastolic dysfunction.

Results: Multivariable adjusted Cox regression analyses showed that uric acid predicted all-cause mortality in subjects with E/A ratio < 0.75 (HR 1.12, 95% confidence interval [CI] 1.00-1.25, p = 0.04) or E/A ratio > 1.5 (HR 1.51, 95% CI 1.09-2.09, p = 0.01, p for interaction between E/A ratio category and uric acid = 0.02). Uric acid also increased mortality risk in persons with E-wave deceleration time < 140 ms or > 220 ms (HR 1.46, 95% CI 1.01-2.12, p = 0.04 and HR 1.13, 95% CI 1.02-1.26, p = 0.02, respectively; p for interaction = 0.04). Furthermore, in participants with isovolumic relaxation time ≤ 60 ms, mortality risk was far higher with increasing uric acid (HR 4.98, 95% CI 2.02-12.26, p < 0.001, p for interaction = 0.004). Finally, uric acid predicted ischemic stroke in subjects with severely enlarged left atria (HR 1.62, 95% CI 1.03-2.53, p = 0.04, p for interaction = 0.047).

Conclusions: Uric acid was a predictor of all-cause mortality in subjects with echocardiographic indices of diastolic dysfunction, and was associated with increased ischemic stroke risk in persons with severely enlarged left atria.

Funding: Government Support - Non-U.S.

FR-PO364

ITM2B Inhibits the Urate Transporter GLUT9: A Link between Uric Acid Homeostasis and Neurodegeneration? Asim Mandal,[1] David B. Mount.[1,2] *[1]Renal Div, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Renal Div, VA Boston Healthcare System, Boston, MA.*

Background: The level of serum uric acid (SUA) has both causative and protective roles in human disease, with protective effects of hyperuricemia in neurodegenerative diseases. Of the multiple genes associated in genome-wide association studies with SUA, variation in the SLC2A9 gene encoding the urate transporter GLUT9 is a primary determinant; basolateral GLUT9 functions as the exit pathway for urate in the proximal tubule, with widespread expression including brain.

Methods: Here we report the identification of a GLUT9-interacting protein, ITM2B, isolated from a human kidney cDNA library using the ubiquitin ligase, membrane associated yeast two-hybrid system. ITM2B is implicated in the processing of beta-amyloid in Alzheimer's disease, genetic mutations in ITM2B are furthermore associated with Danish Dementia, British Dementia and a form of retinal dystrophy.

Results: ITM2B and GLUT9 mRNAs are readily detectable in a human renal proximal tubule cell line; ITM2B protein is also detectable by immunohistochemistry in human proximal tubule. Strong physical interaction between ITM2B and N- GLUT9 isoforms was confirmed by co-immunoprecipitation followed by Western blot analysis, in both transiently co-transfected HEK-293T cells and in *Xenopus laevis* oocytes. Coexpression with ITM2B resulted in a reduction in complex N-glycosylation of GLUT9. However, N-glycosylation mutants of GLUT9 revealed that N-glycosylation of GLUT9 is redundant for interaction with ITM2B, expression at the plasma membrane, and urate transport function. However, ITM2B mutants associated with Danish and British dementia,retinal dystrophy, or defective N-glycosylation (N170Q) physically interacted with GLUT9 isoforms but were significantly less potent than wild-type ITM2B in inhibiting GLUT9-mediated urate transport.

Conclusions: ITM2B associates with GLUT9 and inhibits urate transport, with an attenuated effect for ITM2B mutants associated with neurodegenerative disorders. The interaction between ITM2B and GLUT9 provides a provocative mechanistic link between urate homeostasis and neurodegenerative disorders.

Funding: Other NIH Support - NIAMS

FR-PO365

Fractional Uric Acid Excretion Is Increased in Mice Lacking SGLT2 Aleksandra Novikov,[1] Yiling Fu,[1] Akira Onishi,[1] Panai Song,[1] Winnie Huang,[2] Volker Vallon.[1] *[1]Nephrology, Univ of California San Diego, San Diego, CA; [2]Nephrology, VA San Diego, San Diego, CA.*

Background: Glycosuric diabetic patients have higher urinary uric acid (UA) excretion and lower serum UA levels. This is also seen with glycosuric SGLT2 inhibitors in diabetics indicating that increased tubular glucose may facilitate urinary UA excretion. To test this further we studied A) non-diabetic mice lacking SGLT2 (Sglt2-/-) or SGLT1 (Sglt1-/-) and B) the SGLT1/SGLT2 inhibitor, phlorizin.

Methods: A) Retrobulbar blood samples and urine were collected from Sglt1-/-, Sglt2-/- and corresponding littermate wild type mice (WT). Serum and urine was analyzed for creatinine (HPLC) and UA (Amplex red uric acid assay) to calculate fractional renal excretion (FE), together with urinary glucose; n=6-10/group. B) C57 mice were saline loaded by oral gavage (30 μl/g bw) to facilitate subsequent quantitative urine collection in metabolic cages for 3 hours plus given either an i.p. injection of phlorizin (400 mg/kg) or vehicle (50% mix of propylene glycol/saline); n=5-7/group.

Results: A) Sglt1-/- presented the expected modest increase in urine glucose to creatinine ratio (Gl:Cr; μmole/mg) compared with WT (92±6 vs 4±1; P<0.005), but the FE of UA (FeUA) was not different (12±1 vs 14±3%; NS). Urine Gl:Cr was strongly increased in Sglt2-/- vs WT (4194±550 vs 3±1) and this was associated with a significant increase in FeUA (21±5 vs 2±1%)(both P< 0.001). B) In saline loaded mice, phlorizin induced glucosuria (841±109 vs 3±1 nmol/min; P<0.001), but unexpectedly reduced UA excretion (0.16±0.04 vs 1.39±0.29 nmol/min; P<0.001) while phosphate excretion remained unchanged (1.2±0.3 vs 1.8±0.7 ng/min).

Conclusions: Mice lacking SGLT2 are glucosuric and show an increase in FeUA consistent with observations using SGLT2 inhibitors in patients. Absence of SGLT1 induced

a lesser glucosuria without affecting FeUA. Unexpectedly, i.p. phlorizin application in saline-loaded mice acutely reduced urinary UA excretion despite inducing glucosuria. Further studies will test a) whether increasing plasma UA levels in mice to human levels (by blocking uricase) affects the quality of the latter response and b) the response to selective SGLT2 inhibitors.

Funding: NIDDK Support, VA Support

FR-PO366

Evidence of Phospho-Degron Regulating Expression of Urate Secretory Transporter ABCG2

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Background: ABCG2 is a high capacity urate secretory transporter of the renal proximal tubule. The common Q141K ABCG2 mutation causes gout in humans through an increased instability of the nucleotide-binding domain leading to enhanced degradation and reduced function.

Results: Here, we found ABCG2 protein rescued from degradation with the proteasome inhibitor MG-132 is phosphorylated; raising the possibility that a phospho-degron regulates ABCG2 trafficking and expression. An *in silico* analysis of ABCG2 revealed a limited number of predicted phosphorylation sites, including S195, a serine conserved in the mammalian lineage. The upstream RXRXS represents a target motif for AKT1 and PKA, which both co-immunoprecipitated with ABCG2. Specifically, endogenous AKT1 pulled down both over expressed ABCG2 in HEK293 cells as well as endogenous ABCG2 in mouse kidney lysate. AKT1 and ABCG2 transcript co-localize in the proximal S2 segment of the mammalian nephron and inhibiting the AKT1 kinase cascade with PI3K inhibitor LY294002, or with growth factor receptor (RTK) inhibitor Vandetanib, dramatically up-regulated ABCG2 expression. Conversely, activating the AKT1 cascade with FBS down-regulated ABCG2 expression. Replacement of the S195 residue with a phosphomimetic aspartic acid resulted in significant reduction in ABCG2 expression, localization of ABCG2 to peri-nuclear compartments, and significant sensitivity to MG-132; confirming the S195 residue as a phospho-degron. Finally, a non-phosphorylatable S195A substitution led to the complete rescue of the Q141K gout mutant protein expression and trafficking.

Conclusions: Modeled ABCG2 structure indicates phosphorylation of the S195 residue may only be possible when the nucleotide-binding domains are separated, suggesting the S195 phospho-degron may be part of a novel regulatory mechanism for function and trafficking in ABC transporters. **American Heart Association: 14SDG18060004 & Ardea BioSciences**.

Funding: Pharmaceutical Company Support - Ardea BioSciences, Private Foundation Support

FR-PO367

Aldosterone and Vasopressin Are Erythropoietic Hormones

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Background: Erythropoietin (Epo) is produced by the renal tubules in response to hypoxia and/or anemia (Nagai T, et al. BBRC 2014). We investigated the effects of aldosterone and vasopressin on mRNA expression of Epo in distal nephron segments.

Methods: Tubule suspensions (TS) of cortex (CX), outer medulla (OM) and inner medulla (IM) were prepared from 5-7 week-old rats. Nephron segments were microdissected after the incubation of kidney slices in solution containing collagenase and VRC. TS or nephron segments were incubated with 10^{-9} M and 10^{-6} M aldosterone, vasopressin or vehicle for 2 hrs at 37°C. After the RNA extraction, the expressions of GAPDH, Epo, EpoR, HIF2α, HIF1α, PHD2, mineralocorticoid receptor (MR), glucocorticoid receptor, EGFR, vasopressin V2 and V1a receptors (V2R and V1aR, respectively), GATA2 and GATA3 mRNAs were examined using real time PCR.

Results: Epo mRNA expression was detected in TS of CX, OM and IM (CX=OM>IM) and was time-dependently decreased. Aldosterone and vasopressin increased Epo mRNA expression in TS of CX and OM and vasopressin increased Epo mRNA in TS of IM. In microdissected nephron segments, Epo mRNA was decresed with time. After 2-hr incubation with vehicle, Epo mRNA expression was not observed in CAL and MAL, while its expression was remained at detectable level in the collecting ducts. Aldosterone and vasopressin stimulated the expression of Epo mRNA in CAL, MAL, CCD, OMCD and IMCD. Aldosterone and vasopressin stimulated mRNA expression of MR and V2R/V1aR, respectively. Aldosterone and vasopressin stimulated the expression of Epo mRNA along with the increase of HIF2α, GATA 2 and GATA 3 mRNAs but not with HIF1α. Aldosterone and vasopressin also stimulated EpoR mRNA expression in IMCD.

Conclusions: Epo is produced by the distal nephrons in normal condition. Aldosterone and vasopressin are erythropoietic hormones that are possibly under the control of HIF2α and GATA2/3 pathways in the distal nephrons.

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

FR-PO368

Aldosterone-Regulated miRNAs and Their Target Genes in Mouse Cortical Collecting Duct Cells

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Background: Mature microRNA (miRNA) is a modulator in the post-transcriptional regulation. The present study aimed to identify the aldosterone-regulated miRNAs and their target genes in mpkCCDc14 cells. Target genes of the selected miRNAs and their biological functions and processes were predicted.

Methods: Microarray chip assay (Affymatrix GeneChip miRNA 4.0 array) was done in the mpkCCDc14 cells in the absence or the presence of aldosterone treatment (10^{-6} M) for 3 d. The candidate miRNAs were selected by 1) more or less than 30% of significant fold-changes (protocol 1), or 2) differential expression analysis carried out using the R package 'bridge' (Gottardo R. bridge: Bayesian Robust Inference for Differential Gene Expression. R package version 1.34.0., protocol 2). To predict putative target genes of identified miRNAs and miRNAs-enriched pathways, DIANA-mirPath program was exploited.

Results: In protocol 1, 29 miRNAs were significantly up-regulated more than 1.3 fold-change and 27 miRNAs were markedly down-regulated less than 0.7 fold-change in mpkCCDc14 cells after aldosterone treatment. In protocol 2, 5 up-regulated and 7 down-regulated miRNAs (more than 1.2 fold-change and less than 0.8 fold-change) were selected with high posterior probabilities (> 0.95). According to DIANA-mirPath program, 55 KEGG pathways (protocol 1) and 29 KEGG pathways (protocol 2) were profiled. In particular, Wnt signaling pathway, which was the most highly ranked, was selected. The quantitative changes of 7 up- and 8 down-regulated mature miRNAs enriched in the Wnt signaling pathways were further examined by qPCR and particularly miR-130b-3p was significantly increased. Six target genes (*Rock1, skp1a, Tbl1xr1, Ppp2re, Wnt2b, Plcb1*) of miR-130b-3p were identified, which need to be further evaluated for the aldosterone-induced pathophysiology.

Conclusions: Aldosterone induces significant changes in miRNA expression in mpkCCDc14 cells, which could be involved in a number of pathways including Wnt signaling.

Funding: Government Support - Non-U.S.

FR-PO369

Elevated Polymorphonuclear Myeloid Deprived Suppressor Cell in Patients with End-Stage Renal Disease associated with Infectious Events

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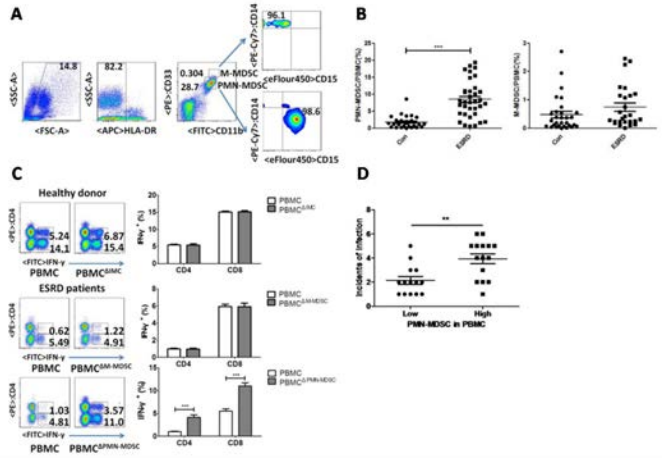
Background: Infectious disease is one of the common complications in patients with end-stage renal disease (ESRD) due to systematic immuno-suppression and inflammation without clear mechanism. The present study was aimed to determine the Myeloid Deprived Suppressor Cells (MDSCs) level in ESRD patients and its association with infectious events.

Methods: A total of 29 ESRD patients and 30 matched health control were tested the MDSC in peripheral blood monouclear cells (PBMC) by Flow cytometry. PMN-MDSC was defined as HLA-$DR^{-/low}CD11b^{+}CD33^{+}CD14^{-}CD15^{+}$) with M-MDSC defined as HLA-$DR^{-/low}CD11b^{+}CD33^{+}CD14^{+}CD15^{-}$ [figure1A]. MDSC depleted (Δ MDSC), or undepleted PBMCs were stimulated with anti-CD3/anti-CD28 for 3 days to test T cell responses by intracellular IFN-γ production. The association of MDSC with infectious events including respiratory tract infection, catheter related bloodstream infection and infection of digestive canal within 1 year before testing was analyzed retrospectively.

Results: The frequency of PMN-MDSCs was higher in ESRD patients as compared to healthy controls ($p<0.001$) with M-MDSC unchanged [figure1B]. Removal of PMN-MDSCs increased the expansion of antigen non-specific IFN-γ+ T cells, which indicated that PMN-MDSC suppressed immune responses. M-MDSC and immature myeloid cells (IMC) in health control were not suppressive [figure1C]. The ESRD patients were classified into two subsidiary sets according to PMN-MDSC levels. ESRD patients with higher level of PMN-MDSC >6.41845% displayed increased infectious events within 1 year before this study ($p<0.01$) [figure1D].



Conclusions: In summary, the present study firstly indentified increased PMN-MDSC in ESRD patients and its association with infectious events.

FR-PO370

Effect of Omega-3 Fatty Acids on STAMP2 Expression in 5/6 Nephrectomized Rat Model Su Mi Lee,[1] Yun Jung Oh,[2] Sung Hyun Son,[3] Young Ki Son,[1] Seong Eun Kim,[1] Won Suk An.[1] *[1]Dong-A Univ, Busan, Republic of Korea; [2]Cheju Halla General Hospital, Jeju, Republic of Korea; [3]BHS Han Seo Hospital, Busan, Republic of Korea.*

Background: Six transmembrane protein of prostate 2 (STAMP2) is known as critical modulator of inflammation and metabolism in adipose tissue. In recent study, STAMP2 had an important role in hepatic steatosis, but there is no data about the expression of STAMP2 in chronic kidney disease which is inflammatory status and related with metabolic disorder. This study aimed to investigate the STAMP2 expression of heart and kidney in 5/6 nephrectomy (Nx) rats. In addition, we evaluated the effect of omega-3 fatty acid (FA) and vitamin D which are related with inflammation and metabolic disorder on STAMP2 expression.

Methods: Sprague Dawley rats were divided into four groups: sham control (0.9% saline), 5/6 Nx (0.9% saline), 5/6 Nx treated with omega-3 FA (300 mg/kg/day by gastric gavage) group, 5/6 Nx treated with vitamin D (cholecalciferol 3000 IU/kg/week) and omega-3 FA groups. The expression of IκB, NF-κB, AMPK, SREBP1, Nox4, LXRab and STAMP2 were examined by western blot analysis.

Results: BUN and creatinine were the lowest in 5/6 Nx treated with omega-3 FA and vitamin D group among 5/6 Nx rat model. Compared with control, there was significant up-regulation of NF-κB, IκB, SREBP1, Nox4, and LXRab expression and a down-regulation of STAMP2 and phosphorylated AMPK expression in kidney and heart on 5/6 Nx model. We found that omega-3 FA prevented these up and down regulations related with inflammation and metabolic disorder of lipid. The STAMP2 expression was significantly up-regulated by omega-3 FA supplementation in both kidney and heart. In particular, STAMP2 expression was much more up-regulated in 5/6 Nx rats treated with omega-3 FA and vitamin D.

Conclusions: The STAMP2 suppression of heart and kidney was found in 5/6 Nx rats. STAMP-2 activation induced by omega-3 FA supplementation may be one of potential mechanisms attenuating inflammation and metabolic disorder.

FR-PO371

Targeted Metabolomic Analysis of Kidney from the Subtotal Nephrectomy Mouse Model of Chronic Kidney Disease Hiroaki Kikuchi,[1] Naohiro Nomura,[1] Yoji Andrew Minamishima,[2] Tatemitsu Rai,[1] Shinichi Uchida,[1] Eisei Sohara.[1] *[1]Nephrology, Tokyo Medical and Dental Univ; [2]Molecular and Cellular Biology, Medical Inst of Bioregulation, Kyushu Univ.*

Background: Metabolome analysis is a powerful tool for the identification and the quantification of the critical metabolites closely related to diseases. Little is known about the changes of metabolomic profile in chronic kidney disease (CKD).We applied a global targeted metabolome profiling approach to kidney samples obtained from C57BL/6J mice performed with subtotal nephrectomy (STN) which is the most common model of nondiabetic CKD.

Methods: Using capillary electrophoresis-time-of-flight mass spectrometry (CE-TOF-MS), we analyzed low molecular weight metabolites of kidney in the CKD mice (n=4) and sham control mice (n=4). The acquired data were analyzed using principal component analysis (PCA) followed by Kruskal-Wallis test and Dunn's post-test to assess the statistical significance.

Results: CE-TOF-MS analysis showed metabolomic profiles of kidney comprised of 278 metabolites. We found that 78 metabolites were significantly increased, and 13 metabolites were significantly decreased in kidney samples from CKD model mice. In the STN kidney, well-known uremic toxin such as 3-indoxylsulfuric acid, creatinine, and hippuric acid were significantly increased, indicating that our disease mouse model properly developed CKD. Interestingly, energy-related metabolites such as ATP, UTP, CTP were significantly decreased, compared with sham control.

Conclusions: Metabolomic analysis of kidney from CKD mice provided the useful information for identifying novel markers and elucidating the pathophysiology of CKD. The results suggested that some renal ATP-generating pathways were apparently impaired in CKD.

Funding: Government Support - Non-U.S.

FR-PO372

Calciprotein Particle Ripening Induces Mitochondrial Damage and Activates the NLRP3 Inflammasome Edward R. Smith,[1] Timothy D. Hewitson,[1] Parisa Aghagolzadeh,[2] Matthias Bachtler,[2] Andreas Pasch,[2] Stephen G. Holt.[1] *[1]Royal Melbourne Hospital, Australia; [2]Univ of Bern, Switzerland.*

Background: Calciprotein particles (CPP) accumulate and ripen from an amorphous (CPPI) to crystalline (CPPII) state in uremia and are associated with inflammation, vascular dysfunction and mortality. *In vitro* studies implicate NLRP3 inflammasome activation, but the mechanism and evidence of *in vivo* effects remains unproven.

Methods: NLRP3 priming/activation was evaluated in human monocyte-derived macrophage and in differentiated THP-1 cells. Uptake and effects on lysosomal/mitochondrial function/cell fate were assessed by flow cytometry. Live-cell imaging and particle localisation were assessed by laser-scanning confocal and super-resolution microscopy. For in vivo studies, CPPI/II or vehicle were administered to 12 week-old uremic or non-uremic Wistar rats via tail vein injection (twice daily for 5 days). Some animals received additional treatment with an NLRP3 inhibitor (MCC950) via subcutaneous minipump, or a mitochondria-targeted antioxidant (MitoQ10) via intraperitoneal injection or vehicle controls (n=6 for each treatment). Serum was collected after 6 days to assess inflammation/oxidative stress.

Results: *In vitro,* CPPI failed to prime or activate the NLRP3 inflammasome. In contrast, CPP-II primed inflammatory cytokine synthesis via Toll-like receptor 4/6/NF-κB-signalling. Binding and endocytosis of CPPII resulted in marked changes in intracellular calcium that were not apparent with CPPI. CPPII induced lysosomal destabilisation, loss of mitochondrial (mt) membrane potential, increased mtROS production and a release of mtDNA. NLRP3 activation, as well as sustained excursions in intracellular calcium, amplified mitochondrial damage via mitochondrial transition pore opening and induced interleukin (IL)-1β secretion. In uremic rats, intravenous administration of CPPII, but not CPPI, resulted in elevations in IL-1β, IL-6 and oxidative stress over 6 days, which were attenuated by concurrent treatment with MCC950 or MitoQ10 compared to vehicle controls.

Conclusions: CPP ripening drives inflammation via NLRP3 activation and effects on mitochondrial function. Targeting these pathways may have therapeutic potential in patients with CKD.

Funding: Pharmaceutical Company Support - Amgen Australia, Private Foundation Support

FR-PO373

Exercise Improves Skeletal Muscle, but Does Not Alter Disease Progression in a Rat Model of Chronic Kidney Disease Keith Avin,[1,2] Neal X. Chen,[2] Sharon M. Moe,[2,3] Matthew R. Allen,[2,3,4] Jason M. Organ.[2,3] *[1]Physical Therapy, Indiana Univ, Indianapolis, IN; [2]Nephrology, Indiana Univ, Indianapolis, IN; [3]Anatomy and Cell Biology, Indiana Univ, Indianapolis, IN; [4]Veterans Affairs Medical Center, Indianapolis, IN.*

Background: Chronic kidney disease (CKD) is associated with musculoskeletal deterioration characterized by decreased skeletal muscle size (i.e. atrophy) and impaired muscle function. Currently, exercise interventions have experienced tempered success which may be the result of a lack of understanding of the pathogenesis of muscle dysfunction.

Methods: We used a slowly, progressive, naturally occurring, CKD rat model (Cy/$^{+}$ rat) and its normal littermate (NL). A graded 10- week treadmill exercise protocol began at 25 weeks of age (~CKD stage 2/3) and concluded at 35 weeks. At 35 weeks, we tested muscle strength in vivo, sacrificed and collected tissues and prepared for histology or RNA analysis using real time qPCR.

Results: Sarcopenia was first demonstrated in CKD rats (compared to NL) by reduced muscle fiber cross sectional area ($p<0.05$) and impaired strength ($p<0.05$); defined as the force produced during maximal, electrically stimulated dorsiflexion. CKD rats demonstrated altered gene expression responses in muscle regeneration (Pax-7, MyoD and myogenin ($p<0.05$)) and proteolysis (Atrogin-1 and MuRF-1 ($p<0.05$)). CKD rats who performed 10 weeks of treadmill training restored gene expression markers of skeletal muscle regeneration and muscle proteolysis similar to NL levels ($p<0.001$; CKD vs CKD exercise). At 30 weeks of age maximal torque production (20%, $p=0.05$) and power (27%, $p<0.01$) were higher, when comparing CKD to CKD-exercise although there were no differences at 35 weeks of age. Aerobic exercise did not alter disease progression as there was no difference in PTH, BUN, calcium and phosphorous between CKD and CKD exercised rats ($p>0.05$).

Conclusions: In a progressive rat model of CKD, exercise restored the regenerative and proteolytic profile to that normal littermates with improved strength at 30 weeks of age (stage 4/5 CKD). However, exercise did not alter the disease progression or end-stage disease muscle strength.

Funding: Private Foundation Support

FR-PO374

The Role of microRNA-26 on Muscle-Heart Crosstalk in Mice with Chronic Kidney Disease Bin Wang,[1,2] Aiqing Zhang,[1] Faten Hasounah,[1] Xiaonan H. Wang.[1] *[1]Renal Div, Emory Univ, Atlanta, GA; [2]Dept of Nephrology, Huashan Hospital of Fudan Univ, Changzhou, Jiangsu, China.*

Background: Uremic cardiomyopathy and muscle atrophy contribute to CKD-induced morbidity and mortality. Exosomes, natural carriers of many signal molecules including microRNA (miR), mediate organ to organ communication. We hypothesized that miR-26 would benefit both CKD-induced muscle wasting and cardiomyopathy through exosome-mediated muscle-heart crosstalk.

Methods: CKD model in mice: 5/6 subtotal nephrectomy for 10 weeks. NanoSight instrument was used to quantify exosomes. A miR deep sequencing assay and qPCR were used to identify microRNA. Cardiac ultrasound was used to detect heart size and function.

Results: We found that serum-derived exosomes from CKD mice are larger than shams using NanoSight. MiRdeep sequencing revealed increased miR-26a-5p in serum from both CKD mice and humans. However, miR-26a-5p was decreased in CKD mouse skeletal and cardiac muscle. Uremic serum enhanced secretion of miR-26a exosomes in cultured C2C12 skeletal and H9C2 cardiac muscle cells. We injected miR-26a-5p into tibialis anterior (TA) muscle and observed increased muscle cross-section area and decreased CKD-induced upregulation of atrogin-1 and MuRF1. We saw increased miR-26a expression in the heart following TA muscle injection. Interestingly, cardiac fibrosis was partially depressed in miR-26a overexpressing CKD mice. We further confirmed that FoxO1, α-SMA, GSK-3β, CTGF, fibronectin and Collagen1α were decreased by exogenous miR-26a in CKD mice. Cardiac sonography also showed that the percentage of ejection fraction was increased in CKD mice treated with miR-26a. In a cell culture model, we showed that exosomes containing miR-26a from skeletal muscle cells can transfer miR-26a to H9C2 cardiac cells and attenuate uremic serum-induced upregulation of FoxO1 in H9C2 cell, providing indirect evidence of skeletal and cardiac muscle crosstalk.

Conclusions: Exogenous miR26a not only attenuated skeletal muscle atrophy but also ameliorated uremic cardiomyopathy by targeting multiple mRNAs, possibly through exosome-mediated muscle-heart crosstalk.

Funding: Other NIH Support - NIH R01 AR060268

FR-PO375

Mitochondrial Dysfunction in Uremic Muscle Maria P. Martinez Cantarin,[1] Zhao Lin,[2] Bonita E. Falkner.[1] *[1]Medicine, Thomas Jefferson Univ Hospital, Philadelphia, PA; [2]Kimmel Cancer Center, Thomas Jefferson Univ, Philadelphia, PA.*

Background: Muscle wasting is associated with uremia leading to increased mortality. Different factors have been associated with increased muscle wasting in chronic kidney disease models. Mitochondrial biogenesis is a key component of skeletal muscle function and structure. We set up to determine if inflammation and or reactive oxygen species (ROS) play a role in the uremic muscle's metabolic dysfunction.

Methods: We studied mitochondrial function in muscle of ESRD patients using the protein expression of TOMM20 by western blot. We exposed a myoblast cell line (C2C12) to uremic and normal human serum (2%, 5% and 10% serum for 24h) with and without N-acetyl cysteine (NAC) 10nM and then studied mitochondrial function by mitotracker orange. We also exposed C2C12 cells to ascending concentrations of TNFα (0.1, 1, 10 ng/ml) and IL6 (0.01, 0.1, 1 ng/ml) with and without adiponectin (1 ug/ml) and determined mitochondrial activity by mitotracker orange. We also assessed TOMM20 protein expression of C2C12 exposed to TNFα.

Results: We demonstrate lower TOMM20 protein expression in ESRD patients compared with controls by western blot analysis consistent with reduced mitochondrial function. C2C12 cells exposed to uremia show a decrease in mitotracker activity with increasing uremic serum concentrations compared to cells exposed to normal serum ($p<0.01$ for 2% and 5% serum and $p<0.05$ for 10% serum). When NAC was added to uremic serum, cells exposed to uremia and NAC were able to rescue mitotracker activity to similar levels of cells exposed to normal serum ($p<0.05$). Mitochondrial activity in C2C12 cells decreases with increasing concentrations of TNFα and IL6 ($p<0.01$ for both cytokines). Exposure to TNFα and the anti-inflammatory adiponectin results in an increase in mitochondrial function compared to cells exposed to TNFα alone although only at low TNFα doses (1 ng/ml, $p<0.05$). Similar to human muscle exposed to uremia, we demonstrated that TOMM20 protein expression decreases in C2C12 exposed to high concentrations of TNFα.

Conclusions: In summary, our data suggest that inflammation and oxidative stress promote mitochondrial dysfunction in ESRD.

Funding: Private Foundation Support

FR-PO376

Adipose Tissue Inflammation in ESRD Maria P. Martinez Cantarin,[1] Diana Whitaker Menezes,[2] Bonita E. Falkner.[1] *[1]Medicine, Div of Nephrology, Thomas Jefferson Univ Hospital, Philadelphia, PA; [2]Medical Oncology, Kimmel Cancer Center, Thomas Jefferson Univ, Philadelphia, PA.*

Background: ESRD patients have increased inflammation with high levels of circulating inflammatory markers. Systemic inflammation is associated with poor outcomes in patients with ESRD. Multiple mechanisms have been proposed to explain why ESRD is a chronic inflammatory state but each one's contribution is unknown. Adipose tissue is a major source of immune cell-derived inflammatory factors so we set up to study if the adipose tissue of ESRD could contribute to systemic inflammation in ESRD.

Methods: Participants were recruited from the Thomas Jefferson University Hospital (TJUH) transplant program. Criteria for inclusion in the study included having ESRD and undergoing kidney transplantation at our institution. The control group consisted of kidney donors with normal kidney function. While the participants were under general anesthesia for kidney donation or kidney transplantation, 250 mg of omental visceral fat and 250 mg of subcutaneous fat were obtained. Fixed adipose tissue samples were paraffin embedded. Paraffin-embedded sections of visceral and subcutaneous adipose tissue were immunostained for the macrophage marker CD163. Adipose tissue macrophage infiltration was measured as the number of CD163+ cells in 10 randomly chosen 40X areas (high power field) by 2 independent pathologists. Number of CD163+ cells was normalized by 100 adipocytes.

Results: Compared to controls, ESRD patients have increased macrophage infiltration in visceral and subcutaneous adipose tissue, as determined by the quantification of CD163+ cells per 100 adipocytes ($p<0.001$ for both adipose tissues). After participants were stratified by BMI as obese (BMI>30) versus non-obese (BMI<30), non-obese ESRD patients continue to present higher macrophage infiltration in subcutaneous and visceral adipose tissue compared to controls ($p<0.01$ for both tissues).

Conclusions: Our study demonstrates that the adipose tissue of uremic patients has increased macrophage infiltration, including in non-obese individuals. We propose that adipose tissue is a potential source of inflammation in ESRD that is not related to increased adiposity.

Funding: Private Foundation Support

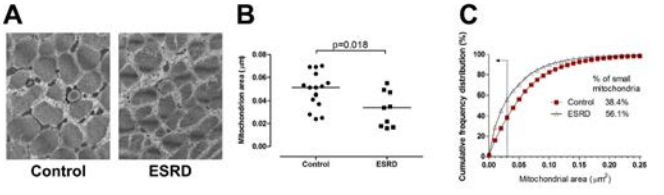
FR-PO377

Mitochondrial Fragmentation in Patients on Maintenance Hemodialysis Jorge Gamboa,[1] Theodore F. Towse,[2] Emily C. Bush,[2] Baback Roshanravan,[3] Serpil Muge Deger,[1] Talat Alp Ikizler.[1] *[1]Medicine, Vanderbilt Univ Medical Center, Nashville, TN; [2]Physical Medicine and Rehabilitation, Vanderbilt Univ Medical Center, Nashville, TN; [3]Medicine, Univ of Washington, Seattle, WA.*

Background: Frailty and sarcopenia, defined as a reduction in muscle mass and/or muscle strength, are common in patients on maintenance hemodialysis (MHD). Mitochondria are important for proper muscle function. Mitochondria are organelles that are constantly undergoing either fusion, to become larger structures, or fission, a process of mitochondrial division. A balance between mitochondrial fusion and fission is essential for proper mitochondrial function. Increased mitochondrial fission will result in mitochondrial fragmentation and smaller mitochondria. Thus, we evaluated the hypothesis that mitochondrial fragmentation is increased in patients on MHD.

Methods: We measure mitochondrial size using electron microscopy. We evaluated 10 patients on MHD and 15 controls with no CKD that were matched by age, gender, and BMI. We also measured OPA-1 and Fis-1, markers of mitochondrial fusion and fission respectively, by western blot.

Results: Controls and patients on MHD were similar in terms of age (52.8±8.7 *vs.* 50.3±15.1), BMI (30.6±7.3 vs. 29.0±5.1), and gender. We found that mitochondria are smaller in patients on MHD compared to individuals with no CKD (Figure 1A and B). Frequency distribution of individual areas showed a shift to the left in patients on MHD (Figure 1C). We did not find any difference in the abundance of either OPA-1 or Fis-1 between the groups.



Conclusions: Smaller mitochondria in skeletal muscle of patients on MHD may be the consequence of increased mitochondrial fission for segregation and elimination of damaged mitochondrial. Future studies are required to study how changes in mitochondrial dynamic and function may impact frailty and sarcopenia in patients on MHD.

Funding: NIDDK Support

FR-PO378

Renoprotective Effect of Shen-Yan-Fang-Shuai Formula in Type 2 Diabetic Kidney Disease Rats Model by Inhibiting the TNF-α/NF-κB Signaling Pathway Jie Lv, Zhen Wang, Jingwei Zhou, Yaoxian Wang. *Nephrology, Dongzhimen Hospital Affiliated to Beijing Univ of Chinese Medicine, Beijing, China.*

Background: Diabetic Kidney Disease(DKD)is the leading cause of end stage kidney disease and satisfactory therapeutic strategies have not yet been established. Shen-Yan-Fang-Shuai-Formula (SYFSF), a traditional Chinese Formula composed of Astragalus, Angelica, Rhubarb and four other herbs, has been widely used as an effective treatment for DKD patients in China.Studies have shown that SYFSF components including emodin or flavonoids inhibit renal inflammation. However little is known about the underlying molecular mechanisms of SYFSF protection. In this study, we compared the renoprotective effect of SYFSF to ARB in a type 2 DKD rat model.

Methods: The male Wistar rats were divided into four groups: control group (n=10), DKD model group (vehicle treated, n=9), DKD model with SYFSF (DKD+S) group (n=10) and DKD model with Irbesartan (DKD+I) group (n=10). The type 2 DKD rat model was induced by high-fat diet, low-dose intraperitoneal injection of streptozotocin(STZ) and

uninephrectomy. Blood glucose level >16.7 mmol/l was defined as Highglucose. Rats were treated for 8 weeks with SYFSF once daily by oral gavage. The kidneys were harvested for histology, immunohistochemistry, western-blot, and real-time quantitative PCR analysis.

Results: SYFSF significantly decreases 24 hour albuminuria (10.12± 3.7 VS 40.41± 16.72 mg, P<0.01) and serum Creatinine levels, with no changes in glucose levels compared to DKD group and Irbesartan group. In addition, SYFSF ameliorates the glomerulosclerosis and interstitial fibrosis induced by DKD (P<0.01). These renoprotective affects were associated with reduced kidney cortex expression of TNF-α,NF-κB P65,TGF-β1 and Col-IV (P<0.05).

Conclusions: SYFSF provides significant renoprotective effects in type-2 DKD rats independently of glucose levels compared to Irbesartan treatment. This is associated with the inhibition of TNF-α/NF-κB inflammatory pathway. Therefore, SYFSF may be a beneficial treatment for DKD patients.

Funding: Government Support - Non-U.S.

FR-PO379

Hyperphosphate Increases the Expression of Inflammatory Factors in Monocytes via Sodium-Dependent Phosphate Cotransporter Pit-1

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Background: Hyperphosphatemia and systemic inflammation are known risk factors for cardiovascular calcification in maintenance hemodialysis (MHD) patients, however, the mechanisms of which are still under investigation. The aims of this study were to explore whether hyperphosphate could increase the secretion of inflammatory factors in peripheral blood monocytes via sodium-dependent phosphate cotransporter Pit-1 and its possible mechanisms.

Methods: Human primary peripheral blood monocytes(isolated from healthy donors' PBMCs) were cultured and divided into four groups: normal phosphate (NP), high phosphate (HP), HP+PFA and HP+PD98059 groups. Antagonists of sodium-dependent phosphate cotransporters (phosphonoformic acid (PFA)) and the ERK inhibitor (PD98059) were used to determine the possible signaling pathways caused by HP. The protein level of TNF-α and IL-6 were examined by ELISA. The mRNA expression level of TNF-α, IL-6 and Pit-1 were measured by Real-time PCR. The protein level of Pit-1, ERK1/2 and p-ERK1/2 were detected by Western Blot.

Results: 1. After 48h exposure of peripheral blood monocytes to Pi (4M), the concentration of TNF-α (pg/ml) and IL-6 (pg/ml) was increased comparedwith the NP group by ELISA (P<0.05 *vs.* NP). PFA and PD98059 could inhibit this effect significantly (P<0.05 *vs.*HP). 2. TNF-α, IL-6 and Pit-1 mRNA expression were increased compared with the NP group (P<0.01 *vs.* NP), while PFA could inhibit this effect (P<0.05 *vs.*HP). PD98059 showed similar effects in decreasing the mRNA expression of TNF-α, IL-6 and Pit-1 (P<0.05 *vs.*). 3. Pit-1 and p-ERK1/2 protein abundance were increased (P<0.05 *vs.* NP) after the treatment of Pi (4M) for 48h, and PFA could inhibit this effect (P<0.05 *vs.*). PD98059 showed similar effects in decreasing the protein abundance of Pit-1 and PERK1/2 (P<0.05 *vs.*).

Conclusions: We conclude that hyperphosphate could increase the expression of Pit-1 in peripheral blood monocytes and promoted the synthesis and secretion of TNF-α and IL-6 via ERK1/2 pathway.

FR-PO380

Chronic Alcohol Mediated Hyper-Acetylation of Kidney Mitochondrial Proteins Causes Renal Dysfunction

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Background: Studies have shown that sirtuins (SIRTs) are beneficial in kidney injury. In particular SIRT3, a NAD-dependent deacetylase, protects renal tubular cells through antioxidative and anti-inflammatory effects, especially in proximal tubular cells. Chronic alcohol exposure is known to cause protein hyperacetylation in the mitochondria that may play a critical role in the pathogenesis of alcoholic liver disease, but the mechanism through which chronic ethanol consumption damages the kidney has not been studied. We hypothesize that hyperacetylation of kidney mitochondrial proteins may be responsible for renal dysfunction during chronic alcohol consumption.

Methods: SIRT3$^{+/+}$ and SIRT3 $^{-/-}$ mice were pair-fed 6% ethanol or Control liquid diet (Lieber-De Carli, Dytes Inc, PA) for 6 weeks. 24 hour urine, collected at the start and at the end of the 6 weeks, was used to measure the albumin/creatinine ratio (ACR). The animals were then sacrificed, the kidneys aliquoted for isolation of mitochondria, immunohistochemistry and western blot analyses. Fresh renal mitochondria were used for respiration studies by Seahorse Analyzer and measurement of reactive oxygen species (ROS).

Results: The ACR was increased in both SIRT3$^{+/+}$ and SIRT3 $^{-/-}$ mice that were fed ethanol liquid diet. More importantly, the ACR was significantly higher in SIRT3 $^{-/-}$ compared to SIRT3 $^{+/+}$ (ACR 1200µg/mg vs 1008µg/mg, respectively; p<0.05). Mitochondrial state 3 and uncoupling respiration were significantly lower in both SIRT3 $^{-/-}$ and ethanol fed mice, suggesting that acetylation modification impairs mitochondrial oxidative phosphorylation. Indeed, the western blot analyses showed a significant increase of the acetylation status of renal mitochondrial proteins involved in energy metabolism and ROS production, SIRT3$^{-/-}$ mice fed with ethanol. Moreover, ROS production was significantly higher in chronic ethanol-fed SIRT3 $^{-/-}$ group compared to the ethanol-fed SIRT3 $^{+/+}$ group.

Conclusions: Chronic alcoholic-mediated hyper-acetylation of kidney mitochondrial proteins causes renal dysfunction.This study can unveil therapeutic strategies to reverse and/or delay renal damage during chronic alcohol consumption.

Funding: Other NIH Support - NIH K22 Award

FR-PO381

Evaluation of the Impact of Gut Microbiota on Uremic Solute Accumulation by CE-TOFMS-Based Metabolomics Approach

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Background: Gut microbiota is involved in the metabolism of several uremic solutes. However, the precise contribution of microbiota to retention of uremic solutes in chronic kidney disease (CKD) is obscure.

Methods: To clarify this issue, we compared adenine-induced chronic kidney disease (KD) mice and control mice under germ-free (GF) or specific pathogen-free (SPF) conditions, and examined their metabolic profiles of plasma, feces and urine using CE-TOFMS-based approach.

Results: We found that GF condition demonstrated profound changes in the plasma metabolites of the KD mice. Among 57 uremic solutes that accumulated in plasma of SPF-KD, plasma levels of 11 solutes were significantly lower in GF-KD than that in SPF-KD, suggesting that these solutes were considered to be "gut microbiota-derived uremic solutes" (GM-US), including indoxyl sulfate, cholate, hippurate, *p*-cresyl sulfate, phenyl sulfate, trimethylamine *N*-oxide, phenaceturate, dimethylglycine, γ-guanidinobutyrate, glutarate, and 2-hydroxypentanoate. Metabolic pathway profiling also suggested that microbiota are involved in the metabolism of GM-US. Thus, GF condition attenuated the accumulation of the harmful uremic solutes in CKD condition: however, we revealed that renal damage was unexpectedly more severe in GF-KD than in SPF-KD, suggesting that gut microbial action such as production of colonic short-chain fatty acids played renoprotective roles and that loss of the beneficial microbial effects exacerbated renal damage in GF-KD.

Conclusions: Collectively, our findings indicated that gut microbiota largely contributes to the production of harmful uremic solutes and,meanwhile, microbiota has potential beneficial effects against CKD progression. Gut microbiota therefore would represent dual roles in the pathophysiology of CKD.

Funding: Government Support - Non-U.S.

FR-PO382

25 (OH)D Treatment Improve Inflammatory Pathway on Monocytes Lineage (U937) in Uremic Environment

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Background: The 25(OH)D has been associated as a modulator of inflammatory response. It has been recognized that the uremic environment induce inflammation, mainly for presence of uremic toxins in plasma from uremic patients. This inflammation state in these patients is associated with a high risk for cardiovascular disease and infectionsThe aim of this study was evaluated the effect of 25(OH)D on inflammatory pathway as: toll-like receptor 4 (TLR4), oxidative stress (ROS) and expression of vitamin D receptor (VDR), 24 hydroxylase (CYP24) and hidroxilase 1-α (CYP27) on monocytes cells in uremic environment.

Methods: The human monocytes (U937 lineage) were pre-treatment with and without of 25(OH)D (30 ng/mL) (D) for 24 hours and after that these were incubated with 50% of healthy serum (HS) or uremic serum (US)for 24 hours at 37ºC and 5% CO_2.The monocytes were characterized by CD14+ expression. The TLR-4, VDR, CYP24, CYP27 were evaluated by human monoclonal antibody conjugated with different fluorophores and ROS were evaluated by DCFH-DA. The flow cytometer was used to detect the expression of these markers.

Results: We observed a high expression of TLR-4 in monocytes incubated with uremic serum (US) and low expression after 25(OH)D treatment (US = 4010±518 vs HS = 1786±403 and US+D = 3113±316 vs HS+D = 1121±221; p < 0.004) and lower expression of VDR in monocytes+US compared with HS (US = 7812±618 vs HS = 9659±908; p = 0.01). The CYP24 were higher in monocytes+ US than monocytes+HS (p < 0.008). CYP27 and ROS not showed differences.

Conclusions: These preliminary results shown that uremic environment induce inflammation by increase TLR-4 and diminish intracellular VDR and increase CYP24. The treatment with 25(OH)D indicate an improve in these parameters and may result in less inflammation in uremic environment.

FR-PO383

The Effect of Different BCG Measurement Procedures on Serum Albumin Levels in Patients with ESRD on Hemodialysis

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Background: Low serum albumin is associated with mortality in hemodialysis patients. The K/DOQI-recommended value for albumin is 4.0 g/dL as measured by any bromcresol green (BCG) method, but approximately 60% of dialysis patients have an albumin that is lower. To our knowledge, no study has assessed the effect of different manufacturers' BCG measurement procedures on the proportions of dialysis patients with serum albumin ≥4.0 and/or ≥3.5 g/dL.

Methods: In a previous study, we defined the relationships of albumin results of 9 commercially available BCG methods; the relationships were assessed by measurements of fresh, nonfrozen serum samples from patients in the hemodialysis centers at the University

of Virginia (UVA) (Yu M et al., Abstract A154, Annual Meeting, Am Assn Clin Chem, 2015). Linear regression equations of data from that study relate results of the 9 BCG methods to each other. In the present study, serum albumin was measured by one of the BCG methods (Abbott Architect) in blood samples from hemodialysis patients at UVA in February (n = 831 patients) and March (n = 852) of 2016. We used the regression equations developed earlier to define for each of the Architect albumin results the corresponding values by each of the other 8 measurement procedures.

Results: Depending on the assay used, the mean (±SD) albumin varied from 3.7 (±0.4) to 4.1(±0.4) mg/dL. The proportion of BCG albumin results ≥4.0 g/dL varied more than 2-fold, from 30% to 64%, depending on the assay used. Similarly, the proportion of albumin results ≥3.5 g/dL ranged from a low of 79% to a high of 93%. The differences of mean albumin results among 11 dialysis centers in the UVA system were smaller than the differences among the 9 BCG methods.

Conclusions: Serum albumin results of the most widely used BCG methods in the U.S. differ widely. Fixed decision limits for clinical decisions or for quality indicators are not appropriate.

FR-PO384

The Influence of Acute Aerobic Exercise on Immune Cell Subsets in Renal Transplant Recipients Patrick J. Highton,[1,2] Jill Neale,[1] Darren R. Churchward,[1] Charlotte E. Grantham,[1] Nicolette C. Bishop,[1,2] Alice C. Smith.[1,2] *[1]Leicester Kidney Exercise Team, Univ of Leicester, Leicester, Leicestershire, United Kingdom; [2]School of Sport, Exercise and Health Sciences, Loughborough Univ, Leicester, Leicestershire, United Kingdom.*

Background: Renal Transplant Recipients (RTRs) are immunologically vulnerable due to immunosuppression and systemic inflammation. In health, moderate exercise reduces systemic inflammation and is beneficial for immune function, but intense exercise can elicit inflammatory cytokine release and transiently suppress immunity leaving an "open window" for infection. Physical activity has many potential benefits for RTRs, but guidelines for safe and effective exercise for this unique population are lacking. In this study, we investigated the impact of exercise on immune and inflammatory cells in RTRs.

Methods: 15 RTRs (13 male; age 53±15 years) completed 20 minutes of continuous walking at 85% of individual maximum speed defined at a previous visit. Blood samples were obtained before, immediately after and 1 hour after this standardised walk. T cell and monocyte cell subsets were analysed by flow cytometry.

Results: Intermediate monocytes ($CD14^{++}16^{+}$) decreased immediately following exercise (3.80±0.31% vs 3.07±0.21%, p=.012), whilst non-classical monocytes ($CD14^{+}16^{++}$) increased (5.99±0.82% vs 7.25±1.03%, p=.022). There was no change in $CD14^{++}16^{-}$ classical monocytes. Number and % of $CD8^{+}$ T cells decreased during the hour of recovery ($0.60±0.12x10^{9}$/L vs $0.51±0.11x10^{9}$/L, p=.049; 31.62±4.07% vs 28.84±4.17%, p=.025). Regulatory T cells (T Regs) were increased by exercise (5.59±0.54% vs 6.55±0.73%, p=.005).

Conclusions: A bout of exercise exerts significant effects on monocyte and T cell populations in RTRs. Anti-inflammatory classical monocytes were unaffected, but intermediate monocytes decreased and non-classical monocytes increased. Both of these subsets are considered pro-inflammatory and elucidation of the overall inflammatory significance requires further investigation. The reduction in circulating $CD8^{+}$ T cells may represent an "open window" for infection after exercise. T Regs are anti-inflammatory and critical for graft tolerance: their increase after exercise is reassuring and may be beneficial.

FR-PO385

Loss of CD127 Expression on Circulating CD8+ T Cells in Patients with End-Stage Renal Disease and Its Association with Resistance to Erythropoiesis-Stimulating Agents Kenichiro Iio, Yutaka Ando. *Nephrology, National Hospital Organization, Osaka Minami Medical Center, Kawachinagano, Osaka, Japan.*

Background: IL-7 is important for T cell homeostasis. In response to an infection, IL-7 enhances $CD8^{+}$ T-cell proliferation and cytolytic activity. Decreased CD127 (IL-7alphaR) expression on $CD8^{+}$ T cells may contribute to the loss of $CD8^{+}$ cytotoxic T lymphocyte activity, thereby increasing susceptibility to infection. Resistance to erythropoiesis-stimulating agents (ESAs) is associated with cardiovascular disease and increased mortality in end-stage renal disease (ESRD) patients. Immune disorders such as chronic inflammation are also involved.

Methods: The present study compared the T cell phenotypes between 53 patients with stage 5 or 5D chronic kidney disease (CKD) and 16 control patients with stage 1 to 3a CKD. Furthermore, multivariate regression analysis was performed to detect the association between T cell phenotypes and the erythropoietin resistance index (ERI; μg/kg/Hb/week). Flow cytometric analysis was performed to detect $CD127^{hi}$ $CD8^{+}$ T cells, $CD3^{+}$ T cells, $CD4^{+}$ T cells, and $CD8^{+}$ T cells among the peripheral blood mononuclear cells.

Results: The proportion of CD127-expressing $CD8^{+}$ cells and the numbers of $CD3^{+}$ T cells and $CD4^{+}$ T cells were significantly lower in ESRD patients than in the controls. Based on multivariate linear regression analysis, the proportion of $CD127^{hi}$ $CD8^{+}$ cells, but not the numbers of $CD3^{+}$ cells or $CD4^{+}$ cells, was associated with the ERI ($\beta = -0.0006$; $p = 0.02$).

Conclusions: A decreased proportion of $CD127^{hi}$ $CD8^{+}$ T cells and decreased numbers of $CD3^{+}$ T cells and $CD4^{+}$ T cells may be indicators of an ESRD-related immunological abnormality. Additionally, CD127 expression on $CD8^{+}$ T cells was associated with resistance to ESAs. Immunological changes that increase susceptibility to infection may indicate resistance to ESAs.

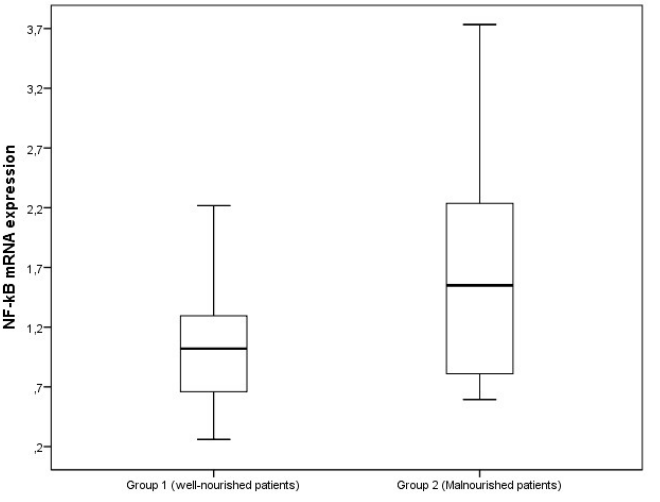
FR-PO386

Subjective Global Assessment Is Linked to Nuclear Factor-κB Expression in Hemodialysis Patients Denise Mafra,[1] Viviane Oliveira Leal,[2] Najla Elias Farage,[1] Ludmila F.M.F. Cardozo,[1] Milena Barcza Stockler-Pinto,[1] José Carlos Carraro-Eduardo,[1] Denis Fouque.[3] *[1]Federal Univ Fluminense; [2]State Univ of Rio de Janeiro; [3]Univ Claude Bernard, Lyon 1.*

Background: Wasting and inflammation are common symptoms in chronic kidney disease (CKD) patients on hemodialysis (HD). Muscle loss and malnutrition are stimulated by inflammation. Nuclear factor-kappa B (NF-κB) is a central integration site for pro-inflammatory signals that are overexpressed in HD patients and could be associated with nutritional status assessed by Subjective Global Assessment (SGA). The aim of this study was to evaluate a possible association between NF-κB expression and SGA in hemodialysis.

Methods: Eighty-three HD patients (57% men, 52.3±14.4 yr, 60 (36-108) months on dialysis, 15.7% diabetes, BMI 24.8±3.9 Kg/m^2) were enrolled. Fasting blood samples were collected and peripheral mononuclear cells were isolated. Real time PCR was performed to evaluate NF-κB mRNA expression.

Results: The 7-point SGA was performed and patients were allocated into two groups (gr1 well-nourished and gr2-malnourished). According to SGA, 32.5% presented malnutrition and a higher NF-κB expression (1.75 [0.77-2.34] when compared to well-nourished patients (1.0 [0.64 – 1.33], p=0.03).



Conclusions: In conclusion, SGA may indicate an altered NF-κB expression and an inflammatory upregulation in chronic HD patients.

FR-PO387

Lack of Polyfunctional Cytomegalovirus-Specific T Cells in Hemodialysis Patients Fang-Yun Lay,[1] Tzu-Ying Chou,[1] Kai-Hsiang Shu,[1,2] Yi-Fang Chuang,[3] Jean-San Chia,[4] Yen-Ling Chiu.[1,2] *[1]Nephrology, Far Eastern Memorial Hospital; [2]Medicine, National Taiwan Univ Hospital; [3]Epidemiology, National Yang Ming Univ; [4]Graduate School of Immunology, National Taiwan Univ.*

Background: Polyfunctional T cells are critical for maintaining protection against pathogens. Patients with end-stage renal disease (ESRD) are at increased risks for infectious complications and chronic inflammation. The current study intends to investigate T cell immunity and systemic inflammation by analyzing T cell differentiation and polyfunctionality response against cytomegalovirus (CMV) in patients with and without renal disease.

Methods: 17 healthy individuals, 13 patients with stage V chronic kidney disease (CKD) and 37 hemodialysis (HD) patients were enrolled in this study. All the donors were seropositive. Peripheral blood mononuclear cells were isolated by density gradient centrifugation. A panel of T cell differentation markers were used to identify the following T cell subsets: naive (TN), central memory (TCM), effector memory (TEM) and effector memory with RA expression (TEMRA). CMV peptide pools (IE1 and pp65) were used to stimulate PBMCs and four effector functions were measured by multicolor flow cytometry (IL-2, TNFα, IFNγ and CD107a) to identify polyfunctional T cells. Statistical comparisons were performed using Kruskal-Wallis rank test.

Results: The age of the three groups were similar (mean, 60 years old). Patients with renal disease, especially the HD patients, showed decrease in CD4+ and CD8+ TN cells and increase in CD4+ and CD8+ TEM and TEMRA cells. In addition, polyfunctional cells were dramatically reduced in HD patients. HD patient also showed higher level of systemic inflammation and CMV viral load. Among healthy individuals, CKD and HD patients, CD4+ CMV-IE1-reactive polyfunctional cell frequencies were 2.0%, 2.2%, and 0%, respectively (p=0.002) and the CD8+ CMV-pp65-reactive polyfunctional cell frequencies were 12.4%, 8.8% and 0.8%, respectively (p<0.001).

Conclusions: The lack of polyfunctional T cells in hemodialysis patients might explain the increased infectious complications in this population. Such phenomenon might contribute to subclinical cytomegalovirus activation and chronic inflammation in HD patients.

Funding: Government Support - Non-U.S.

FR-PO388

Branched-Chain Amino Acids Promote Oxidative Stress, Inflammation and Migration of Human Peripheral Blood Mononuclear Cells via mTORC1 Activation

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Background: Leucine, isoleucine and valine are essential aminoacids termed branched-chain amino acids (BCAA) due to its aliphatic side-chain. In several pathological and physiological conditions increased BCAA plasma concentrations have been described. Elevated BCAA levels predict insulin resistance development. Moreover, BCAA levels higher than 2 mmol/L are neurotoxic by inducing microglial activation in maple syrup urine disease. However, there are no studies about the direct effects of BCAA in circulating cells and the mechanisms involved.

Methods: We have explored whether BCAA (range 0.1 to 12 mmol/l) could promote oxidative stress and pro-inflammatory status in peripheral blood mononuclear cells (PBMCs), obtained from healthy donors.

Results: In cultured PBMCs, 10 mmol/L BCAA increased the production of reactive oxygen species (ROS), via by both NADPH oxidase and the mitochondria. BCAA activated mTOR and Akt signaling, as demonstrated by increased phosphorylation of mTORC1 and Akt, respectively. The redox-sensitive transcription factor NF-KB regulates many immune and inflammatory responses. BCAA caused p-p65 NF-KB phosphorylation, its nuclear translocation and increased p65-dependent DNA binding activity. BCAA also up-regulated several pro-inflammatory molecules under NF-KB control, such as interleukin-6, TNF-α, ICAM-1 and CD40L. Finally, we have found that BCAA induced PBMCs cell migration. By using several inhibitors and activators of these molecular pathways we have described that mTOR activation by BCAA is linked to ROS production and mitochondrial dysfunction. Moreover, BCAA, by a redox mechanism, activated the NF-KB/inflammatory pathway and regulated cell migration.

Conclusions: Elevated BCAA blood levels can promote the activation of circulating PBMCs, by a mechanism that involve ROS production and NF-KB pathway activation. These data suggest that high concentrations of BCAA could exert deleterious effects on immune cells and therefore could contribute to the pro-inflammatory and oxidative status observed in several pathophysiological conditions.

Funding: Government Support - Non-U.S.

FR-PO389

The Application of Magnetic Resonance Apparent Diffusion Coefficient in the Diagnosis of Acute Pyelonephritis

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Background: Acute pyelonephritis (APN) is a non-specific suppurative inflammatory process secondary to ascending or haematogenous bacterial diffusion. It is widely accepted that functional Magnetic resonance imaging (MRI) provides additional information: diffusion-weighted imaging (DWI) with the apparent diffusion coefficient (ADC) represents an additional parameter which can indicate focal lesions or changes in renal function. DWI has recently been proposed as an alternative to CT for both the diagnosis and follow-up of APN. The aim of the study was to assess reliability of ADC value for differentiating normal renal parenchyma, APN and abscesses.

Methods: 56 patients (mean age 39 years) with clinical suspicion of APN were retrospectively reviewed. The contrast-enhanced MRI and DWI were applied in these patients. MRI found that 34 patients had renal abscess, and 22 had no abscess. Then ADC values which were calculated at the area of healthy parenchyma, APN and abscessed were compared in these cases.

Results: On DWI sequences inflammatory foci appeared as areas of reduced diffusivity of water molecules with high signal on DWI and low ADC values compared to healthy parenchyma (mean ADC: healthy parenchyma $(2.32\pm0.18)\times10^{-3}$ mm^2/s; APN foci $(1.52\pm0.24)\times10^{-3}$ mm^2/s; abscess $(1.16\pm0.34)\times10^{-3}$ mm^2/s, b factor=600s/mm^2).The results showed the difference between ADC values of the APN and healthy parenchyma groups ($P<0.05$), similarlythe difference between ADC values of the abscess and APN groups was significant ($P<0.05$).

Conclusions: MR ADC values showed reliable in the diagnosis and follow-up of acute pyelonephritis, and it could provide a reasonable alternative to contrast-enhanced MRI. This is especially useful when administration of contrast agent is contraindicated.

FR-PO390

Differential Effects of Angiotensin II Receptor Blocker (ARB) versus ACE Inhibitor (ACEI) on HDL Functionality in Patients on Maintenance Hemodialysis (MHD)

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Background: ACEI/ARB reduce cardiovascular disease (CVD) in the general population. Although MHD are at greatly increased CVD risk, few studies have directly addressed their efficacy and recent evidence suggests differences in this population. Previously we showed HDL of MHD loses their protective function, therefore, we compared the effects of ARB or ACEI treatment on HDL functionality in MHD.

Methods: Following 3 weeks washout period, we randomly assigned 40 MHD to placebo, ramipril or valsartan. HDL was isolated at the starting point (B) and 3-6 months later (A). Cholesterol efflux was measured by cholesterol content in THP-1 cells after HDL exposure; anti-oxidative response and methylarginine were measured by HPLC; inflammatory markers were evaluated by RT-PCR and serum amyloid A (SAA) by ELISA.

Results: Compared to placebo, ARB and ACEI maintained cholesterol efflux (%)(B: 23.96 vs Placebo-A: 15.23 $P<0.01$; vs ARB-A:23.92 ns; vs ACEI-A: 22.10 ns). Cellular ROS production was reduced in response to HDL isolated from MDP on either ARB or ACEI compared to HDL of placebo-treated MHD (U/ml)(B: 21.03 vs Placebo-A 20.64 ns; ARB-A: 16.52 $P<0.01$; ACEI-A: 17.95 $P<0.01$). Neither ARB nor ACEI improved HDL anti-inflammatory effects, and ACEI rather potentiated TNF-α, IL-1β response compared to placebo or ARB. Both ARB and ACEI decreased plasma asymmetric dimethylarginine (ADMA) (μM)(B: 0.68 vs Placebo-A 0.58, ns; ARB-A 0.46 $P<0.01$; ACEI-A 0.48 $P<0.01$), but did not affect HDL content of ADMA. There was no difference in SAA levels in plasma or HDL among the groups.

Conclusions: ARB/ACEI treatment in MHD stabilized cholesterol acceptor capacity of HDL and promote its anti-oxidative effects. By contrast, neither ARB nor ACEI improve HDL's anti-inflammatory effects and ACEI may even amplify this response. ARB/ACEI did not affect postulated modulators of HDL functionality, including ADMA and SAA but reduced circulating ADMA. These results suggest a mechanism for potential superiority of ARB vs ACEI in MHD.

Funding: Other NIH Support - NIHP01HL116263

FR-PO391

The Adiponectin/Leptin Ratio as a Predictor of Mortality in a Prospective Hemodialysis Cohort

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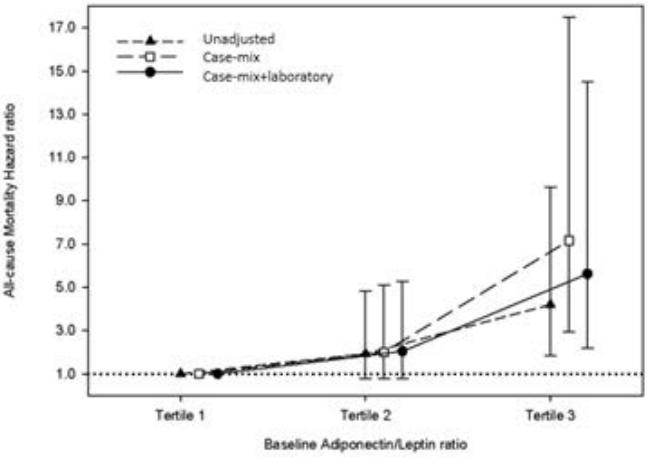
Background: Adiponectin and leptin are major adipocytokines believed to play key roles in the regulation of cardiovascular and metabolic status. While animal studies show that adiponectin and leptin have inverse effects on the cardiovascular system (adiponectin reduces atherosclerosis, while leptin accelerates vascular injury), it has been suggested that the adiponectin-to-leptin (A/L) ratio may be an important predictor of cardiovascular disease and death. Despite their exceedingly high cardiovascular risk, no studies have examined the association of A/L ratio with mortality in hemodialysis (HD) patients.

Methods: Among 448 HD patients from the prospective *Malnutrition, Diet, and Racial Disparities in Kidney Disease* study who underwent adiponectin and leptin measurement over 2014-15, we examined the association of A/L ratio with all-cause mortality using Cox regression with 3 adjustment levels: unadjusted, case-mix (age, sex, race, ethnicity, diabetes, vintage, vascular access), and case-mix+laboratory (albumin, creatinine, nPCR, IL-6) adjusted models.

Results: The median (IQR) of adiponectin and leptin were 15.2 (9.1, 24.2) and 16.5 (5.7, 54.6) mcg/ml, respectively. When examined as tertiles, the highest A/L ratio tertile was associated with higher death risk vs. the lowest tertile across all models: HR (95%CI) 5.63 (2.18-14.50) in case-mix+laboratory analyses. When examined as a continuous variable, higher levels were associated with higher mortality risk across all models: HR (95%CI) 1.20 (1.05-1.37) for +Δ1-standard deviation increments of the A/L ratio.



Conclusions: In a prospective cohort of HD patients, a higher A/L ratio was associated with higher mortality risk. Further studies are needed to confirm findings and to determine underlying mechanistic pathways.

Funding: NIDDK Support

FR-PO392

Pro-Inflammatory RAGE Ligand (EN-RAGE, S100A12), Circulating Soluble Receptor for AGE (sRAGE) and Mortality in Patients with Chronic Kidney Disease Stages 3-5 Marcelo M. Nascimento,[1] Shirley Yumi Hayashi,[2,3] Miguel C. Riella,[4] Bengt Lindholm.[2] *[1]Univ Federal do Parana, Curitiba, Parana, Brazil; [2]Renal Medicine & Baxter Novum, Karolinska Inst, Stockholm, Sweden; [3]KTH School of Technology and Health Research, Stockholm, Sweden; [4]Pro-Renal Foundation, Curitiba, Parana, Brazil.*

Background: Activation of the receptor for AGE (RAGE) is implicated in development and progression of vascular complications. Here we investigated associations of circulating concentrations of RAGE ligand S100A12, also known as EN-RAGE (extracellular newly identified receptor for advanced glycation end products binding protein) and soluble receptor for AGE (sRAGE) with all-cause and cardiovascular disease mortality in patients with chronic kidney disease (CKD) stages 3-5.

Methods: In 145 CKD patients (median age 61 years, 61% males) comprising 36 hemodialysis (HD), 55 peritoneal dialysis (PD) and 54 CKD stages 3-5 patients clinical characteristics were documented, and markers of mineral metabolism (including fibroblast growth factor-23; FGF-23), inflammation (s-albumin, high-sensitivity C-reactive protein; hsCRP, and interleukin-6; IL-6) as well as plasma concentrations of S100A12 and sRAGE were measured at baseline. All survivors completed 66 months of follow-up.

Results: S100A12 and sRAGE were positively associated with C-reactive protein ($\rho = 0.24$; $p < 0.05$; and $\rho=0.24$; $p<001$) and interleukin-6 ($\rho = 0.25$; $p < 0.01$, and $\rho=0.25$; $p<0.001$), respectively. After up to 66-months follow-up, the survival rate by Kaplan–Meier analysis was significantly different according to S100A12 plasma levels ($\chi2=8.09$; $P<0.01$) but not to sRAGE ($\chi2=2.19$; $P=0.13$). Finally, in Cox analysis, only S100A12 (HR=2.08 ((95% CI) 1.21-3.66) and age (HR= 1.81(95% CI 1.06-3.06) were independently associated with increased risk of death.

Conclusions: Increased concentrations S100A12 associated with inflammation - possibly reflecting activation of RAGE in the context of accelerated vascular disease - and increased all-cause mortality in CKD patients.

Funding: Pharmaceutical Company Support - Baxter Healthcare, Government Support - Non-U.S.

FR-PO393

A Malnutrition-Inflammation Score Predicts Patients Survival and Gives Strategies to Improve the Mortality of Maintenance Dialysis Patients Minoru Ito, Ikuto Masakane. *Nephrology and Dialysis Center, Yabuki Hospital, Yamagata, Japan.*

Background: Malnutrition-Inflammation Score (MIS) was reported as an assessment tool of malnutrition inflammation complex syndrome of dialysis patients. It consists of 10 components (weight change, dietary intake, gastrointestinal symptom, functional capacity, vintage and morbidity, subcutaneous fat, muscle wasting, BMI, albumin, TIBC). In this study, we validated the utility of the MIS and analyzed which component had the most effect on their mortality.

Methods: 319 hemodialysis patients (209 men, 110 women; age, 65.5 ± 12.9 years) were enrolled in this study. The MIS was assessed on all 319 patients by trained nutritionists at December 2009. They were followed up for 3 years. All patients were classified into three subgroups corresponding to each MIS points, normal nutritional group (MIS 0-3), mildly impaired group (MIS 4-7), severely impaired group (MIS over 8) respectively. The survival rates were compared among the three groups using the Kaplan-Meier analysis. The Cox's proportional hazard model was used in multivariate analyses of survival data adjusted for age and diabetes.

Results: 3-year survival rates of the 3 groups were 97.9% (normal), 94.9% (mildly impaired) and 80.3% (severely impaired) respectively. We found a significant difference in the mortality between the severely impaired group and the other two groups with a Log-Rank test. Among 10 MIS components, any component didn't affect their mortality independently. However, the total score of 10 MIS components was significant prognostic factor (HR 1.26; 95% C.I. 1.14-1.38; $p<0.0001$).

Conclusions: MIS is a comprehensive nutritional assessment tool and consists of 10 components. According to the scores of each component, we can determine treatments for each patient with malnutrition individually. Interestingly, each component was not independent prognostic factor by itself. However, the total point of MIS was a significant predictive index for their prognosis. It shows that the nutritional status can't be assessed by one parameter. In conclusion, a comprehensive andmultidisciplinary assessment procedure is required to manage the malnutrition of dialysis patents.

FR-PO394

Plasma Protein Thiolation Predicts Mortality in Maintenance Hemodialysis Patients Shweta Bansal,[1,2] Khaled Khazim,[3] Daniela Giustarini,[4] Sue Cunningham,[5] Ranieri Rossi,[4] Paolo Fanti.[1] *[1]Medicine/Renal, Univ of Texas HSC at San Antonio, SA, TX; [2]Renal Section, South Texas Veterans Healthcare System, SA, TX; [3]Faculty of Medicine in Galilee Medical Center, Bar-Ilan Univ, Safed, Israel; [4]Life Sciences, Univ of Siena, Siena, Italy; [5]UTHSC at Houston.*

Background: Oxidative stress present in CKD is implicated in the progression and complications of this disease state; however, direct measurement of oxidants such as reactive oxygen species (ROS) is difficult. Byproducts of oxidative degradation such as oxidized lipids and nucleotide etc. predict outcomes in CKD but represent the late steps in the oxidative process and therefore, may not be modifiable. We have previously shown that plasma protein thiolation index (PTI), an expression of thiol redox balance- a critical first line of defense against ROS, is altered in dialysis patients. Now, we aim to evaluate whether PTI can predict CKD outcomes.

Methods: We selected 72 clinically stable hemodialysis patients, analyzed their baseline PTI and followed them for mortality over 2.9±0.3 years. PTI is the molar ratio of protein mixed disulfides and free protein thiols in plasma and is measured by spectrophotometry. Since it is a ratio the value is not influenced by content of plasma proteins.

Results: In univariate Cox regression, death was predicted by PTI (HR 6.44;95%CI 1.07-36.7;p=0.042), serum creatinine (HR 0.75;CI 0.62-0.91;p=0.003), and Charlson comorbidity index (CCI) (HR 1.24;CI 1.01-1.53;p=0.042). In multivariate Cox proportional hazard regression (model 1: Chi-square 14.3; p=0.002), PTI predicted mortality (HR 24.6; CI 3.03-199.9; p=0.003) when adjusted for creatinine and CCI. Moreover, the model 2 including adjustments for 10 additional co-variates showed high overall predictive power (chi-square 24; p=0.008) and independent contribution of PTI (p=0.009). Furthermore, ROC curve analysis established 0.80 as cutoff value for binary PTI. High and low PTI subgroups included 33 and 38 subjects and experienced 42.5% vs. 16.2% mortality (HR 3.06; CI 1.17–7.97;p=0.02).

Conclusions: Our data supports presence of a link between oxidative stress and clinical outcome in ESRD and identifies PTI as a suitable candidate biomarker to identify dialysis patients at higher risk of mortality.

Funding: Other NIH Support - NCCAM-AT004490, VA Support

FR-PO395

Is the Association between the Malnutrition-Inflammation Score and Mortality Modified by Age, Gender and Diabetic Status? Marcelo Barreto Lopes,[1] Raissa B. Peixoto,[1] Gildete Barreto Lopes,[1] Priscila S. Carvalho,[1] Jéssica S. Fernandes,[1] Marcia T.S. Martins,[1] Luciana Ferreira Silva,[2] Antonio Alberto Lopes.[1] *[1]Univ Federal da Bahia; [2]Univ do Estado da Bahia, Salvador, Brazil.*

Background: The malnutrition-inflammation score (MIS) has been positively associated with mortality in maintenance hemodialysis (MHD) patients but it is important to show if the association is similar for patients of different subgroups. The objective was to investigate if associations of MIS with mortality vary by age, gender and diabetic status subgroups.

Methods: Prospective study of 627 patients (mean age = 48.5±14 yr) enrolled in the PROHEMO cohort, Salvador, Brazil. MIS (range 0-30) was categorized as <6 (n=364) and ≥6 (n=263). Cox regression was used to estimate adjusted hazard ratios and test for interaction.

Results: The adjusted hazard of death (Table) was 52% higher for MIS ≥6. The associations followed the same direction across subgroups, without significant interaction (P values >0.2) by age, gender, and diabetic status.

Death Rates and Hazard Ratios of Associations between MIS and Mortality in the Total Sample and by Gender, Age and Diabetic Status

		Death Rates per 100 person-years		Hazard Ratio (95% Confidence Intervals)		
	N	MIS≥6	MIS<6	Unadjusted	Adjusted*	P value for Interaction
Total Cohort	627	13.2	7.4	1.82 (1.38, 2.39)	1.52 (1.13, 2.05)	
Gender						0.918
Men	256	15.7	7.9	2.03 (1.43, 2.88)	1.36 (0.83, 2.23)	
Women	371	10.7	6.5	1.69 (1.07, 2.69)	1.68 (1.15, 2.48)	
Age (yr)						0.251
<60	485	9.4	5.6	1.71 (1.19, 2.45)	1.59 (1.08, 2.34)	
≥60	142	24.3	17.5	1.40 (0.90, 2.17)	1.28 (0.77, 2.12)	
Diabetes						0.207
Yes	122	10.5	5.9	1.81 (1.29, 2.53)	1.66 (1.15, 2.38)	
Not	505	24.7	17.7	1.53 (0.94, 2.49)	1.37 (0.74, 2.54)	

** Adjusted for age, gender, education, living with family, race, Kt/V, vintage, vascular access, hemoglobin, creatinine, erythropoietin use, diabetes, heart failure, cerebrovascular disease and peripheral vascular disease.*

Conclusions: The results of this Brazilian cohort provide support to the utility of MIS as a tool for predicting outcomes in MHD patients of different subgroups of age, gender and diabetic status.

FR-PO396

Circulating Tamm-Horsfall Protein (Uromodulin) Correlates with Sepsis Severity Varun Gaur,[1] Chadi A. Hage,[2] Ranjani N. Moorthi,[1] Simit Doshi,[1] Radmila Micanovic,[1] Sharon M. Moe,[1] Tarek M. El-Achkar.[1] *[1]Medicine-Nephrology, Indiana Univ and Indianapolis VA Medical Center; [2]Medicine-Pulm Critical Care, Indiana Univ, Indianapolis, IN.*

Background: Tamm-Horsfall protein (THP, also known as Uromodulin), is a glycoprotein uniquely expressed by the kidney and secreted in the urine. A small amount of THP also circulates in the plasma (pTHP), the significance of which remains unclear. In sepsis, invading pathogens overwhelm the host immune system, frequently leading to a maladaptive response of injurious inflammation. Mortality in THP-/- mice is significantly increased compared to THP+/+ after cecal ligation and puncture, suggesting that THP is protective in the setting of sepsis. Since THP may have immuno-modulatory functions, we hypothesized that the level of pTHP will correlate with the severity of sepsis and be a useful biomarker.

Methods: This is a prospective pilot study to measure pTHP in 26 patients with severe sepsis, at the time admission (T0), and after 48 hours (T48). Sepsis severity was assessed using the sequential organ failure assessment (SOFA) score. SOFA score incorporates 6 distinct organ associated variables, including serum creatinine.

Results: The average age was 57 ±15 years. Diabetes and hypertension were present in 42.3% and 73.1% of the study population, respectively. 30.7% of patients had CKD. Between T0 and T48, 15 patients (57.6%) had improvement in their SOFA score. The median pTHP trended lower between T0 and T48: 46.5 (32.7; 59.4) vs. 33.6 (25.5; 60.9) ng/ml, respectively (p=0.2). Although pTHP 0 and 48 did not correlate individually with SOFA 0 and 48, changes in pTHP between T0 and T48 positively correlated with SOFA 48 (p=0.03) and marginally with changes in SOFA (p=0.1). These findings suggest that an increasing pTHP level correlates with more severe sepsis.

Conclusions: We showed that increases in pTHP correlate with the severity of sepsis in this pilot study. The increase in pTHP may be reactive and part of an acute response to limit the disease. Larger studies are needed to validate the role and use of pTHP as a biomarker of clinical utility in sepsis.

Funding: VA Support

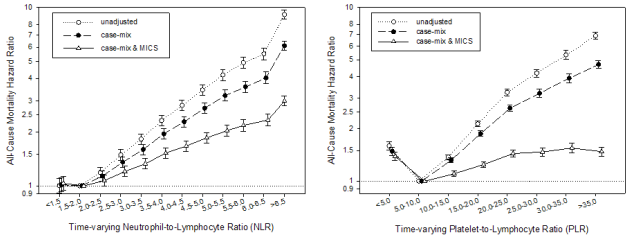
FR-PO397

Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios and Mortality in Incident Hemodialysis Patients Christina J. Catabay, Yoshitsugu Obi, Elani Streja, Melissa Soohoo, Kamyar Kalantar-Zadeh. *UC Irvine.*

Background: Both neutrophil-to-lymphocyte ratio(NLR) and platelet-to-lymphocyte ratio(PLR), calculated from complete blood count, were suggested as oncologic prognostic markers. Recent preliminary studies indicate that NLR and PLR may be associated with inflammatory status and mortality in hemodialysis(HD) patients.

Methods: We examined the association of NLR and PLR with all-cause mortality in a cohort of 107,737 HD patients from a large dialysis organization from 2007-2011 using baseline Cox proportional hazards regression with hierarchical adjustments for case-mix (demographics, comorbidities) and markers of malnutrition and inflammation (MICS) covariates. NLR was divided into 12 categories(<1.5, ≥6.5 and ten 0.5 increments in-between) and PLR was divided into 8 categories(<5, ≥35 and six 5 categories in-between). We also conducted time-varying models to examine their short-term associations.

Results: The mean age (±SD) of the patients was 63±15 years old, and they included 44% females, 59% diabetics, and 32% African Americans. The median(IQR) NLR and PLR at baseline were 3.6 (2.7, 5.0) and 13.1 (9.5, 18.5), respectively. Both indices were positively associated with ferritin levels and negatively associated with levels of albumin, hemoglobin, and iron saturation. Unadjusted baseline Cox models showed that lowest risk at the second lower groups for both NLR and PLR and higher levels were linearly associated with all-cause mortality risk. However, these associations were attenuated in the fully-adjusted models. Time-varying models exhibited consistent trends but a more pronounced association of both NLR and PLR with mortality.



Conclusions: Higher NLR and PLR are strongly associated with higher short-term mortality risk in HD patients especially in unadjusted time-varying models, suggesting the effectiveness of these ratios as simple predictors of approaching death.

Funding: NIDDK Support

FR-PO398

Claudia-12 Is Expressed in the Proximal Tubule and Forms a Calcium Permeable Pore R. Todd Alexander, Megan R. Beggs, Wanling Pan, Emmanuelle Cordat. *Paediatrics & Physiology, The Univ of Alberta, Edmonton, AB, Canada.*

Background: The majority of filtered calcium, approximately 2/3rds, is reabsorbed from the proximal tubule by a passive paracellular mechanism. This process depends on active sodium and water reabsorption, and a calcium permeable pore between proximal tubule cells. Claudin-12 is expressed along the intestine and forms a calcium permeable pore in Caco-2 cells. Renal localization and function is not known.

Methods: We expressed Claudin-12 in OK cells and in MDCK cells using a tet-off system. A claudin-12 knockout mouse was generated by replacing the coding exon with Beta-galactosidase from *E.Coli* and the calcium phenotype interrogated using altered diets and clearance methods.

Results: Claudin-12 mRNA was detected in microdissected proximal tubules. Expression of claudin-12 in OK cells decreased TEER and increased calcium flux, but did not alter the pNa/pCl. Over-expression of claudin-12 also decreased claudin-1 and -6 mRNA expression relative to cells expressing empty vector. Expression of claudin-12 under a tet-off promoter in MDCK cells did not alter endogenous claudin expression but decreased TEER and increased pNa/pCl. X-gal staining of claudin-12$^{+/-}$ kidney sections demonstrated exclusively cortical staining that colocalized with aquaporin-1. Claudin-12$^{-/-}$ animals weighed the same as the wild-type, had the same serum calcium, PTH and creatinine levels. Renal TRPV5, clabindin-D_{28K} and claudins -3, -10a, -14, -16 and -19 mRNA expression was not different between genotypes. Claudin-8 expression was significantly reduced in claudin$^{-/-}$ mice. Knockout mice had the same urine calcium excretion on a low, normal and high calcium diet as wild-type controls. Further, claudin-12$^{-/-}$ mice were able to reduce their urinary calcium excretion to the same extent as wild-type littermates. However, feeding claudin-12$^{-/-}$ mice a high calcium diet after fasting attenuated urinary calcium excretion relative to wild-type animals.

Conclusions: Claudin-12 is expressed in the proximal tubule where it forms a cation and calcium permeable pore, however, its genetic deletion does not alter urinary calcium excretion at steady state.

Funding: Government Support - Non-U.S.

FR-PO399

Acute Effects of Exercise on Serum A-Klotho, Phosphate and Glucose in Healthy Volunteers: A Pilot Study Sven-Jean Tan,[1,2] Melissa Minhui Chu,[1] Michael Ming Xin Cai,[1,2] Timothy D. Hewitson,[1,2] Stephen G. Holt,[1,2] Nigel David Toussaint.[1,2] *[1]Nephrology, The Royal Melbourne Hospital, Parkville, Victoria, Australia; [2]Medicine (RMH), The Univ of Melbourne, Parkville, Victoria, Australia; [3]The Royal Melbourne Hospital.*

Background: Aim: To investigate the effect of exercise on soluble α-klotho (sKl) in healthy adults. **Background:** Membrane-bound α-klotho, predominantly expressed in the kidney, functions as a co-receptor for fibroblast growth factor-23 (FGF23) to regulate phosphate excretion. Circulating sKl, derived from membrane α-klotho cleavage, has extra-renal actions. sKl can affect ion channels and insulin signaling pathways and is inversely associated with mortality. Effects of physical exercise on sKl are unknown.

Methods: Ten fasting healthy volunteers underwent a standard Bruce protocol exercise test on a treadmill. sKl, serum phosphate (sPi) and blood glucose levels were measured in samples collected 1-week prior, immediately pre (Tpre), 0 (Tpost), 30 (T30), 240 (T240) minutes and 1-week post exercise. Changes were assessed using repeat measures ANOVA or Friedman's test with Dunn's multiple comparison.

Results: Median (IQR) age of participants was 47.5 (44-51) years; five (50%) were male. All study participants achieved at least 90% predicted maximum heart rate. Compared with Tpre, an acute increase in sKl was seen at Tpost (median 483pg/mL vs 602pg/mL, p<0.01) followed by non-significant decline in sPi at T30 (mean 0.94mmol/L vs 0.83mmol/L). Exercise led to a reduction in blood glucose by T240, following an initial non-significant rise, with median glucose levels at Tpre, Tpost, T30 and T240 of 6.0, 6.5, 6.3 and 5.7mmol/L respectively.

Conclusions: High intensity exercise is associated with a transient increase in sKl, decrease in sPi levels and delayed blood glucose reduction in healthy adults. Evaluation of long-term effects of cardiovascular fitness programs on sKl and sPi in healthy individuals and disease cohorts are required to identify potential lifestyle modifications to improve chronic disease management and long-term outcomes.

Funding: Government Support - Non-U.S.

FR-PO400

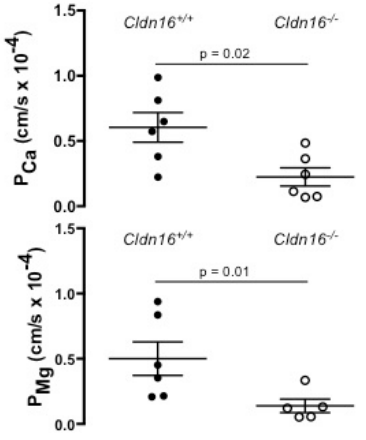
Role of Claudin-16 in Basal and PTH-Stimulated Ion Transport in the Thick Ascending Limb of Henle's Loop Marie-Lucile Figueres,[1,2] Claire Bardet,[2,3] Dominik Müller,[4] Catherine Chaussain,[2,3] Pascal Houillier.[1,2] *[1]Centre de Recherche des Cordeliers, Renal Physiology, INSERM U1138, ERL8228, Paris, France; [2]Paris Descartes Univ, France; [3]EA2496, Montrouge, France; [4]Charité Univ, Berlin, Germany.*

Background: Claudin-16 is specifically expressed at the tight junction of thick ascending limb of Henle's loop (TALH) cells. Inactivating mutations of the gene encoding claudin-16 causes Familial Hypomagnesemia with Hypercalciuria and NephroCalcinosis

(FHHNC), a rare genetic disorder responsible for a renal loss in magnesium and calcium, nephrocalcinosis and early renal insufficiency. However, the role of claudin-16 in basal and parathyroid hormone (PTH)-stimulated ion transport in the TALH remains unclear.

Methods: We used in vitro microperfusion of TALH dissected from *Cldn16*$^{-/-}$ and *Cldn16*$^{+/+}$ mice to measure paracellular ion permeabilities and to assess the effect of basolateral PTH (10^{-10} M) on transepithelial calcium absorption.

Results: Paracellular permeabilities to calcium (PCa) and magnesium (PMg) were significantly decreased in *Cldn16*$^{-/-}$ mice (PCa = 0.22x10^{-4} versus 0.60x10^{-4} cm/s in *Cldn16*$^{+/+}$ mice (p = 0.02) ; PMg = 0.14x10^{-4} versus 0.50x10^{-4} cm/s in *Cldn16*$^{+/+}$ mice (p = 0.01)). Calcium and magnesium absorption was decreased by ~50 % in TALH from *Cldn16*$^{-/-}$ mice, relative to *Cldn16*$^{+/+}$ mice.



Permeabilities to sodium, chloride and potassium were unaffected in *Cldn16*$^{-/-}$ mice. PTH significantly increased calcium reabsorption in TALH from both *Cldn16*$^{+/+}$ and *Cldn16*$^{-/-}$ mice.

Conclusions: Claudin-16 is required for normal paracellular permeability to calcium and magnesium in the TALH, under basal condition. However, the lack of claudin-16 does not prevent the PTH-elicited increase in calcium absorption.

FR-PO401

Serum Calcification Propensity Is Improved by Increased Dialysate Bicarbonate and Dialysate Magnesium: The BicMag Pilot Study

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Background: Serum Calcification Propensity can be measured by a novel blood test, which determines the transformation time (T_{50}) from amorphous primary to crystalline secondary Calciprotein Particles. Epidemiological and in vitro data suggest that Bicarbonate and Magnesium may be of beneficial influence on T_{50}.

Methods: We conducted a 7-week prospective open label pilot study in n=12 prevalent ambulatory dialysis patients with a baseline T_{50} ≥200 min. (10 male, vintage 31 [14-92] months). T50 was determined twice at baseline, twice after increase of dialysate bicarbonate from 32 to 37 mmol/L (n=6) or dialysate magnesium from 0.75 to 1.0 mmol/L (n=6), and twice during the combined increase of bicarbonate and magnesium (n=12). Furthermore, T_{50} was determined after a washout phase of 1 week.

Results: One patient, hospitalized during this study due to an unrelated problem, was excluded from the analysis. Increasing dialysate magnesium led to an increase of serum magnesium from 1.04±0.17 to 1.15±0.17 mmol/L (p<0.01) and increasing dialysate bicarbonate led to an increase of serum bicarbonate from 20.2±1.7 to 23.4±1.8 (p<0.01). T_{50} was 242±40 min. at baseline, 265±61 min. while on increased bicarbonate, and 267±57 min. while on increased magnesium. Combining increased bicarbonate and magnesium resulted in a T_{50} of 282±67 min. (p<0.014 when compared to baseline). After 1 week washout, serum magnesium was 1.04±0.19 mmol/L, serum bicarbonate 19.6±1.7 mmol/L, and T_{50} 255±52 min.

Conclusions: Serum calcification propensity is improved by increasing dialysate bicarbonate and magnesium. Further studies with longer observation periods and individualized treatments are needed.

Funding: Pharmaceutical Company Support - Calciscon AG, Bern, Switzerland, Government Support - Non-U.S.

FR-PO402

Does Reducing Serum Phosphate in Dialysis Patients Result in Improved Clinical Outcomes - Is a Large Scale Trial Feasible?

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Background: High phosphate is associated with increased mortality in dialysis patients. However no RCTs have demonstrated that reducing serum phosphate improves quality or length of life. The required size and scope of such a trial is unknown; therefore we conducted a prospective, randomised, feasibility study to inform the design of a definitive trial.

Methods: Dual centre, prospective, parallel group, RCT feasibility study. 104 HD patients were randomized to lower range (LRG phosphate target 2.5 to 4.3mg/dL) or higher range group (HRG 5.6 to 7.4mg/dL). Non-calcium containing binders, questionnaires & an adherence self-help programme were used to achieve target phosphate. End points included - number titrated to required range & maintained in range over the maintenance period, consent rates, pill burden, drop-out rates & cardiovascular events.

Results:

	HRG	LRG	P-value
N	51	53	
Age(y)	59.59 (SD 13.83)	62.70 (SD 11.19)	NS
F:M	16:35	20:33	
Serum Phosphate(mg/dL)	6.6+/-0.19	6.9+/-0.25	NS
PTH(pg/ml)	436.7+/-62.17	424.2+/-54.36	NS
Albumin(g/L)	32.97+/-0.78	32.66+/-0.75	NS
Cholesterol(mmol/L)	3.21+/-0.16	4.05+/-0.22	NS
Diabetes(Yes:No)	15:36	11:42	<0.05
CAD(Yes:No)	15:36	10:43	<0.05
RRT duration(y)	2.5 (1.5,5.0)	2.0 (1.0,5.7)	NS

Table1:Pre-randomization values. 65% patients completed the 12 month study. For phosphate the mean difference between the groups throughout maintenance period was >1.00 mg/dL, p <0.05 at weeks 10,13 and 21. 9 patients died in HRG vs only 2 in LRG. Consent withdrawal 8 LRG vs 4 HRG. Pill burden was higher in LRG. Dialysis access problems 9 in HRG vs 3 in LRG.

Conclusions: 65% retention rate is similar to other interventional RCTs in dialysis patients. 10% mortality is as expected for this cohort, but was higher in HRG. With a 13% randomization rate and 65% annual retention rate, 3 - 4,000 patients would need to be recruited for 1000 to complete 2 years follow-up. This suggests a target dialysis population of about 25,000, necessitating a multi-national approach.

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FR-PO403

Examining Risk Factors for Calciphylaxis

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Background: Calciphylaxis or calcific uremic arteriolopathy (CUA) is a rare but serious disorder, occurring in dialysis patients and characterized by systemic medial calcification of the arterioles that leads to ischemia and subcutaneous necrosis. Despite its first description over 50 years ago, clinical predictors remain to be clearly identified given that much of the work done to date has consisted of smaller and single-center studies. We therefore utilized national data on dialysis patients from the United States Renal Data System (USRDS) to examine risk factors for CUA.

Methods: Patients on chronic dialysis with Medicare as primary insurance were identified from 2007 through 2014 using USRDS data. Potential risk factors were identified from the Medical Evidence Form 2728 (age, sex, race, diabetes, vintage), dialysis claims (hematocrit, BMI, IV iron) and Medicare Part D claims (warfarin, calcimimetics, calcium-based phosphate binders) in the 6 months after cohort entry. The primary outcome was the new development of CUA based on a validated claims-based algorithm. Cox regression was used to model the rate (cause-specific hazard) of CUA, treating death and transplantation as competing risks.

Results: A total of 1413 cases of CUA were identified with results comparing characteristics of cases and non-cases presented in Table 1. In the multivariable model, younger age, female sex, longer dialysis vintage, higher BMI, diabetes mellitus, calcimimetic use and warfarin use were significant predictors of CUA.

Table 1. Baseline characteristics (Risk factors) and their Hazard Ratios.

Characteristics			
	CUA cases (n=1413)	Non-Cases (n=375,658)	Adjusted HR (95%CI)
	% or mean	% or mean	
Age at cohort entry (y):			
<22	0	1	1.27 (0.38, 3.14)
22-45	23	14	2.66 (1.96, 3.67)
46-65	51	39	2.15 (1.61, 2.95)
66-80	22	36	1.30 (0.96, 1.79)
>=81	3	11	1 (ref)
Mean Age	56.5	63.0	
Female:	66	48	1.92 (1.7, 2.1)
Race:			
White	53	59	1
Black	44	35	0.90 (0.91,1.01)
Dialysis Vintage (y):			
<2 year	14	12	1
2-4	22	16	1.21 (1.01, 1.4)
>=5	19	11	1.38 (1.13, 1.7)
Mean Vintage	4.5	4.1	
Diabetes:	55	49	1.29 (1.15, 1.4)
BMI:			
19-25	17	34	1
26-30	20	25	1.42 (1.2, 1.7)

Conclusions: This represents the first truly national and the largest study to date evaluating risk factors for CUA. A better understanding of the risk factors for CUA may help identify prevention strategies for this devastating complication.

FR-PO404

Determination of Changes in Trans- and Paracellular Divalent Cation Transport Pathways in Renal and Intestinal Epithelia during Lactation
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Background: Significant alterations in maternal divalent cation balance occur postpartum during lactation. As such, Ca^{2+} is mobilized to breast milk by demineralization of the skeleton as well as by changes in intestinal and renal Ca^{2+} transport. However, the specific molecular alterations in divalent cation transport pathways across renal and intestinal epithelia during lactation have not been clearly delineated.

Methods: To ascertain which changes occur during lactation, female mice were divided into 3 groups, non-pregnant controls, lactating mice with litters maintained for 12 days after birth, or mice undergoing involution with litters removed after birth and maintained for 12 days.

Results: Urinary excretion and fractional excretion of Ca^{2+} and Mg^{2+} increased during lactation. Renal 1-alpha hydroxylase and 24-OHase mRNA levels increased by 900%. This was accompanied by significant increases in intestinal expression of *Trpv6* and *Calbindin-D_{9K}* in lactating mice. No significant alterations in the cation permeable claudins (-2, -12 or -15) were observed in any intestinal segments. In kidney, increased expression of *Trpv5 and Calbindin-D_{28K}* were observed during lactation. Increased Calbindin-D_{28K} and TRPV5 protein expression was found by immunohistochemical analysis, while no changes in claudin-2 were noted, consistent with the mRNA expression. Colonic *Trpm6* expression increased during lactation, while renal *Trpm6* was not significantly altered.

Conclusions: Transcellular Ca^{2+} transport pathways increase during lactation, likely due to increased Vitamin D dependent-stimulation. Increased urinary mineralexcretion can be explained on the basis of intestinal hyperabsorption and bone demineralization, despite enhanced selective transcellular renal Ca^{2+} uptake. Only transcellular Mg^{2+} absorption in intestine appeared significantly regulated during lactation, while expression of paracellular transport proteins were unchanged.

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FR-PO405

Phosphate Reabsorption Is a Parabolic Function of Parathyroid Hormone and Fibroblast Growth Factor-23 Concentrations
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Background: The serum phosphorus concentration ($[P]_s$) is the sum of excretion and reabsorption rates of P per volume of filtrate ($E_p/C_{cr} + TR_p/C_{cr}$, C_{cr} = creatinine clearance; *Clin Nephrol* 2015;83:167). If subjects with normal and reduced GFR are considered together, TR_p/C_{cr} is a parabolic function of E_p/C_{cr}, and the horizontal limb of the parabola commences at values of E_p/C_{cr} that are typical of early CKD (unpublished data). Since [PTH] and [FGF23] are direct linear functions of E_p/C_{cr} (*Clin Nephrol* 2016;85:251), we hypothesized that TR_p/C_{cr} is a parabolic function of [PTH] and [FGF23].

Methods: We obtained morning fasting specimens of plasma, serum (s), and urine (u) from 30 subjects with CKD (eGFR 14-49 mL/min/1.73m^2) and 28 controls with eGFR > 60. [PTH]1-84 and intact [FGF23] were measured with ELISAs (Scantibodies and Immuotopics, respectively). E_p/C_{cr} was calculated as $[P]_u[cr]_s/[cr]_u$, and TR_p/C_{cr} as $[P]_s - E_p/C_{cr}$ (*Clin Nephrol* 2015; 83:167). Linear regressions of TR_p/C_{cr} on 100/[PTH] and 100/[FGF23] were sought; after significance was demonstrated, we used the regression equations to compute idealized TR_p/C_{cr} for each value of 100/[PTH] and 100/[FGF23]. We then plotted idealized TR_p/C_{cr} against [PTH] and [FGF23].

Results: TR_p/C_{cr} was a linear function of 100/[PTH] and 100/[FGF23] and thus a parabolic function of [PTH] and [FGF23]. Linear and parabolic equations, R^2, and *P*-values are summarized in the Table. TR_p/C_{cr} fell abruptly to a nadir along vertical limbs of parabolas as [PTH] and [FGF23] rose in controls. Horizontal limbs commenced at the nadir, and TR_p/C_{cr} fell minimally as [PTH] and [FGF23] rose further in CKD.

Hormone	PTH		FGF23	
Type of equation	Linear	Parabolic	Linear	Parabolic
x	100/[PTH]	[PTH]	100/[FGF23]	[FGF23]
y	TR_p/C_{cr}	TR_p/C_{cr}	TR_p/C_{cr}	TR_p/C_{cr}
Equation	$y = 0.23x + 1.97$	$y = (23/x) + 1.97$	$y = 0.063x + 2.21$	$y = (6.3/x) + 2.21$
R^2	0.26	--	0.11	--
P	< 0.001	--	0.01	--

Conclusions: TR_p/C_{cr} is a parabolic function of [PTH] and [FGF23]. Although both concentrations rise as GFR falls, the hormones inhibit P reabsorption maximally in early CKD.

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FR-PO406

Low Serum Magnesium Is Associated with an Increased Risk of Prediabetes
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Background: Previous studies identified an association between serum magnesium and incident diabetes mellitus. However, this association may be explained by reverse causality, as hyperglycemia can lower serum magnesium through urinary magnesium loss. Prediabetes is less likely to cause urinary magnesium loss, because hyperglycemia is less severe. Therefore, we studied, for the first time, the association between serum magnesium and prediabetes.

Methods: The association was analyzed in the population-based Rotterdam Study using Cox proportional hazard models adjusted for age, sex, lifestyle factors, comorbidities, kidney function, other electrolytes and diuretic use. In addition, a mediation analysis was performed to study if the risk is mediated through insulin resistance (HOMA-IR levels) or influenced by common genetic variation in eight magnesium transporter genes.

Results: 8555 participants (mean age 64.7 years) with normal glucose levels at baseline were included; the median follow-up was 7.0 years. A 0.1 mmol/L decrease in serum magnesium level was associated with an increase in diabetes risk (HR:1.15, 95%CI 1.02-1.31), confirming previous studies. Of interest, a similar association was found between serum magnesium and prediabetes (HR:1.12, 95%CI 1.01-1.26). The effect of serum magnesium on prediabetes was mediated for 34.6% through HOMA-IR levels. Genetic variation in *CNNM2* decreased prediabetes risk, which was completely mediated by increasing serum magnesium levels (indirect effect: OR:0.96, 95%CI 0.94-0.98), whereas genetic variation in *FXYD2* increased prediabetes risk, which was completely mediated by decreasing serum magnesium levels (indirect effect: OR:1.03, 95%CI 1.01-1.05).

Conclusions: The observation that lower serum magnesium levels are not only associated with diabetes but also with prediabetes makes reverse causation less likely. The effect of serum magnesium on prediabetes is partially mediated through insulin resistance. Common variants in magnesium transporter genes modify prediabetes risk by influencing serum magnesium. Hence, serum magnesium may be a modifiable risk factor for diabetes.

FR-PO407

Ghrelin Stimulates the Epithelial Magnesium Channel TRPM6 via Gαs Signaling
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Background: Osteoporosis after bariatric surgery is an increasing health concern as the rate of bariatric surgery has risen significantly. In animal studies mimicking bariatric procedures, bone disease, together with decreased serum levels of Ca^{2+}, Mg^{2+} and the gastric hormone Ghrelin were described. Ghrelin is a 28 amino acid peptide and regulates metabolism by binding to the growth hormone secretagogue-receptor 1a (GHSR1a). GHSR1a is also expressed in the kidney. We tested the hypothesis that Ghrelin deficiency after bariatric surgery contributes to osteoporosis via reduced upregulation of the renal calcium channel TRPV5 or the magnesium channel TRPM6.

Methods: We expressed GHSR1a with TRPV5 or TRPM6 channel in HEK293 cells and treated them with purified Ghrelin. Whole-cell current density was analyzed by patch-clamp recording.

Results: After Ghrelin exposure whole-cell current density did not change for TRPV5 but increased for TRPM6 (82 ± 9 vs 255 ± 27 *p*A/*p*F for control vs Ghrelin; $p<0.001$). This effect was dose-dependent. We confirmed the stimulatory role of Ghrelin towards TRPM6 by applying the Ghrelin-mimetic (D-Trp^7, Ala^8,D-Phe^{10})-α-MSH (6-11) amide, which increased TRPM6 current density, and Ghrelin-mimetic with GHSR1a blocker (D-Lys^3)-GHRP6, which inhibited the effect (84 ± 15 vs 219 ± 13 *p*A/*p*F vs 96 ± 22 *p*A/*p*F for control vs mimetic vs mimetic+blocker; $p<0.0001$). As GHSR1a initiates downstream signaling via protein kinase A (PKA), we tested the effect of the PKA inhibitor H89 which abrogated TRPM6 stimulation by Ghrelin (204 ± 29 vs 32 ± 5 *p*A/*p*F for Ghrelin vs Ghrelin+H89; $p<0.005$). The role of PKA signaling in TRPM6 regulation was verified by the fact that only transfected $G\alpha_s$, but not the $G\alpha_s$ mutant Q227L, nor $G\alpha_i$, $G\alpha_q$, or $G\alpha_{12/13}$ upregulated TRPM6 current density.

Conclusions: Ghrelin stimulates TRPM6 channel via $G\alpha_s$-PKA signaling. Rising Ghrelin levels with hunger may contribute to increased renal Mg^{2+} reabsorption to compensate for less enteral Mg^{2+} reabsorption. Ghrelin deficiency after bariatric surgery may contribute to renal Mg^{2+} wasting and osteoporosis as 50% of total body Mg^{2+} is stored in bones.

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FR-PO408

Novel VDR Gene Mutation R343H Responsible for Vitamin D-Resistant Rickets with Alopecia Min-Hua Tseng,[1] Shih-Hua P. Lin.[2] *[1]Nephrology, Pediatrics, Chang Gung Memorial Hospital, Taoyuan, Taiwan; [2]Nephrology, Medicine, Tri-Service General Hospital, Taipei, Taiwan.*

Background: Hereditary vitamin D-resistant rickets (HVDRR) is an autosomal recessive disorder caused by *vitamin D receptor* (*VDR*) gene mutation featuring hypocalcemic and hypophospatemic rickets with or without alopecia. Despite more than 50 VDR mutations reported, the study of the VRD mutant on RXR-binding domains remains very rare. This study was to identify the *VDR* gene mutation in a family with HVDRR and alopecia, and determine the mechanisms of this VDR mutant causing the phenotype.

Methods: The genotype and phenotype with follow-up in a Chinese family with HVDRR were performed. In vitro studies included situ-directed mutagenesis for expression of mutant VDR constructs, fluorescence microscopy for the nuclear localization of different enhanced green fluorescent protein-tagged VDR proteins, and luciferase reporter driven by the human *CYP24A1* gene promoter for measuring transcriptional activity of VDR.

Results: A novel homozygous R343H mutation in the exon 11 of VDR were identified in the proband and his affected sister and not found in 200 healthy subjects. Supraphysiological dose of active vitamin D_3 and calcium supplement therapy improved their biochemical and radiographic abnormalities but not alopecia. This R343H mutant did not eliminate the expression of VDR and change the conformation of VDR by using antibody against HA-tag and VDR C-terminal region, respectively. This mutant also did not affect normal nuclear localization of VDR, but actually impair the *CYP24A1* promoter activity in the presence of 1,25 $(OH)_2$ vitamin D_3.

Conclusions: Although novel VDR R343H mutation in HVDRR does not affect the expression, conformation, and nuclear location of VDR, it impairs the transactivation activity of VDR on downstream transcriptional events and may account for typical clinical features with alopecia.

FR-PO409

Salivary Pi Handling May Be under the Control of Gastrointestinal Pi Sensing Kayo Ikuta, Hiroko Segawa, Shihoko Yuki, Ichiro Kaneko, Ai Hanazaki, Toru Fujii, Aoi Kushi, Sawako Tatsumi, Ken-Ichi Miyamoto. *Dept of Molecular Nutrition, Tokushima Univ, Tokushima, Japan.*

Background: A hyperphosphoric salivary content, which correlates linearly with serum inorganic phosphate (Pi), has been reported in hemodialysis (HD) patients and therefore the addition salivary Pi binding to traditional phosphate binders has been suggested to be a useful approach for improving the treatment of hyperphosphatemia in HD patients. In addition, gastrointestinal and salivary grand Pi sensing may be involved in improving hyperphosphatemia. In the present study, we investigated factors, which affect salivary Pi level.

Methods: Mice were used for hyperphosphatemic adenine-induced nephritis (adenine), acute kidney injury (AKI) models, and administration of Pi solution via oral or intravenous route. To measure salivary flow rates, osmolality, and Pi levels, mice were given an intravenous injection of pinocalpine.

Results: Hyperphosphatemic adenine mice showed high levels of salivary Pi. In contrast, AKI mice showed hyperphosphatemia, but not hyperphosphoric saliva. Adenine mice showed abnormal salivary parameter, e.g. low flow rates and high osmolality. In adenine mice, dietary P restriction significantly decreased the plasma and salivary Pi levels with the abnormal salivary parameter. It suggests that salivary Pi level is regulated by dietary Pi contents. Low Pi diet decreased plasma Pi, urinary Pi excretion and salivary Pi levels. In contrast, high Pi diet showed completely opposite results. Dietary Pi contents did not change salivary parameters. Next, we examined the effect of differential administration route on salivary Pi levels. An intravenous injection of Pi solution significantly increased plasma Pi and urinary Pi excretion, but not salivary Pi levels. In contrast, oral administration of Pi solution significantly increased plasma Pi, urinary Pi excretion, in addition to salivary Pi levels. Furthermore, only oral administration of Pi solution, but not intravenous injection, acutely changed membrane localization of salivary slc34a2.

Conclusions: Gastrointestinal Pi level may be a determinant for salivary Pi level. This study indicates that gastrointestinal Pi sensing improves salivary Pi and renal Pi excretion levels.

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FR-PO410

Calcification Propensity (Serum T50) Predicts Longitudinal Progression of Coronary Artery Calcification in CKD: The CASCADE Study Angela Yee Moon Wang,[1] Sharon Yui Ling Cheung,[1] Matthias Bachtler,[2] Ck Wong,[3] Miu Ting Chu,[3] Yat Y. Yau,[4] Andreas Pasch.[2] *[1]Medicine, Univ of Hong Kong, Queen Mary Hospital, Hong Kong, Hong Kong; [2]Clinical Chemistry, Univ Hospital Bern, Bern, Switzerland; [3]Chemical Pathology, Chinese Univ of Hong Kong, Hong Kong, Hong Kong; [4]Diagnostic Radiology, Central Biomedical Imaging Center, Hong Kong, Hong Kong.*

Background: Calcification propensity (T50) is a measure of extra-skeletal mineral stress and predicts mortality in CKD. This study aims to determine if serum T50 predicts longitudinal progression of vascular calcification over a prospective follow-up of 24 months in CKD and may thus explain its association with mortality.

Methods: 300 non-dialysis CKD 3–5 subjects (age: 60±10yrs, 56%men) underwent plain multi-slice computed tomography (MSCT) to estimate coronary artery calcium scores (CACS) and blood collection. MSCT was repeated after 24 months to determine changes in CACS over 24 months. Those with changes in CACS in the upper tertile (n=88) were defined as progressors while those in the middle and lower tertiles were defined as non-progressors.

Results: The mean T50 of all CKD subjects was 281 ± 59 mins. The progressors were older [P<0.001], had higher systolic blood pressure [P<0.001], serum phosphate [P<0.001] and intact parathyroid hormone [P=0.001], but lower serum albumin [p=0.014], T50 [268 ± 63 vs 289 ± 56mins; P=0.006], magnesium [P=0.047] and eGFR $_{CKD\text{-}EPI}$ [P<0.001]. In the stepwise multiple logistic regression adjusting for age, gender, background diabetes, atherosclerotic vascular disease, Framingham risk factors, baseline CACS, eGFR, high sensitivity C-reactive protein and intact parathyroid hormone, T50 significantly predicted CACS progression over 24 months [adjusted odds ratio [OR], 0.993, 95% confidence intervals (CI), 0.987 – 1.000, P=0.044]. Adjusting for the same covariates, phosphate, an important determinant of T_{50}, marginally lost significance in predicting CACS progression [P=0.069].

Conclusions: These data for the first time show that calcification propensity is related to progression of CACS in CKD 3-5, adding evidence to support its usefulness in reflecting mineral stress in CKD.

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FR-PO411

Hepatocyte Nuclear Factor 1 Homeobox B as Novel Transcriptional Regulator of the KIR4.1/KIR5.1 Potassium Channel Joost Hoenderop,[1] Andreas Kompatscher,[1] Jeroen H.F. De Baaij,[1] Karam S. Aboudehen,[2] Peter Igarashi,[2] René J. Bindels.[1] *[1]Physiology, Radboud Inst for Molecular Life Sciences, Nijmegen, Gelderland, Netherlands; [2]Medicine, Univ of Minnesota Medical School, Minneapolis, MN.*

Background: Patients with mutations in transcription factor hepatocyte nuclear factor 1 beta (HNF1B) present with autosomal dominant tubulointerstital kidney disease (ADTKD-HNF1B), which is characterized by renal cysts and electrolyte loss. Strikingly, it was found that ~50% of mutation carriers were affected with hypomagnesemia. The origin of hypomagnesemia in patients with HNF1B mutations can be traced to the distal convoluted tubule (DCT) of the kidney, where the final urinary Mg^{2+} excretion is determined. The aim of this research is to explain hypomagnesemia in HNF1B patients by identifying target genes of HNF1B in the DCT.

Methods: To find targets of *Hnf1b* that are relevant to Mg^{2+} reabsorption in the kidney, a chromatin immunoprecipitation and subsequent sequencing (chIP-seq) was performed in an immortalized mouse DCT cell line. Luciferase assays, siRNA-mediated knockdown of *Hnf1b* in DCT cells and RT-qPCR on HNF1B mutant mouse kidneys were performed to assess the transcriptional regulation of *Hnf1b* on candidate genes *in vitro* and *in vivo*.

Results: By performing a chIP-seq on *Hnf1b*, >7000 Hnf1b binding sites were detected genome-wide, which could be mapped to >3000 unique genes. A conserved Hnf1*b* binding site was found in the promoter of the *Kcnj16* gene, encoding Kir5.1. Luciferase assays demonstrated that *Hnf1b* increases the activity of the *Kcnj16* promoter. siRNA knockdown of *Hnf1b* resulted in decreased *Kcnj16* transcript levels. Furthermore a decrease in expression of the *Kcnj10* gene, encoding Kir4.1, was observed. Decreased expression of *Kcnj10* and *Kcnj16* was also found in the kidneys of HNF1B mutant mice.

Conclusions: These results implicate HNF1B as an enhancing transcriptional regulator ofKir5.1. Active transport of Mg^{2+} in the DCT requires the constant extrusion of K^+ by the heteromeric inwardly rectifying K^+ channel Kir4.1/Kir5.1. Therefore, impaired regulation of Kir4.1/Kir5.1 by HNF1B may explain the hypomagnesemia found in HNF1B patients.

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FR-PO412

Regional Expression of NaPi-IIb, PiT1 and NHE3 mRNA in the Proximal Small Intestine of Rats and Humans Evans Ohenhen Asowata,[1] Lars Fandriks,[2] Anna Casselbrant,[2] Robert J. Unwin,[1] Joanne Marks.[1] *[1]Dept of Neuroscience Physiology and Pharmacology, Univ College London, Rowland Hill Street, London, United Kingdom; [2]Dept of Gastrosurgical Research and Education, Inst of Clinical Sciences, Univ of Gothenburg, Sahlgrenska Academy, Sweden.*

Background: Previous findings have shown that the proximal small intestine is responsible for the absorption of dietary phosphate in rats and humans. Several studies investigating NaPi-IIb inhibitors, which target the transporter considered responsible for intestinal phosphate absorption, have been carried out in rats, but the effectiveness of these agents in the treatment of hyperphosphatemia in humans is still uncertain. We aimed to understand the difference in the efficacy of these therapeutic agents by comparing the mRNA levels of phosphate transporters in the different regions of rat and human proximal small intestine.

Methods: Total RNA was isolated from gut mucosa scrapes obtained from paired rat duodenum (2cm distal to pylorus) and jejunum (5cm distal to ligament of Treitz). Paired duodenal (20cm distal to pylorus) and jejunal (50cm distal to ligament of Treitz) biopsies were collected from healthy volunteers. NaPi-IIb, PiT1 and NHE3 transcript levels were established using qPCR.

Results: Our result shows that the regional profile for NaPi-IIb in humans is different from that in rats. The mRNA expression levels of NaPi-IIb were significantly higher in the human duodenum compared with the jejunum (D=0.096±0.028 *vs*. J=0.017±0.0006; p<0.05, n=5), which is in contrast to the finding of higher NaPi-IIb expression levels in the rat jejunum (D=0.0028±0.001 *vs*. J=0.028±0.004, p<0.0001, n=6). A trend for increased PiT1 expression in the human duodenum was observed, in contrast to higher PiT1 expression in the rat jejunum. The expression of NHE3, which is also a proposed regulator of phosphate transport, has a similar regional profile in both species.

Conclusions: Our results suggest that the seeming lack of therapeutic efficacy of NaPi-IIb inhibition in treating hyperphosphatemia in humans may result from differences in the regional profile of the phosphate transporters compared with rats in which NaPi-IIb inhibitors have been shown to be effective.

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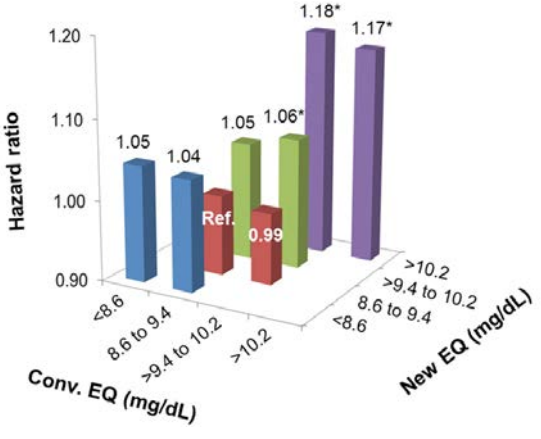
FR-PO413

Improved Mortality Predictability of Total Serum Calcium by Novel Correction Equation in Hemodialysis Patients Yoshitsugu Obi,[1] Elani Streja,[1] Matthew B. Rivara,[2] Wei Ling Lau,[1] Connie Rhee,[1] Csaba P. Kovesdy,[3] Rajnish Mehrotra,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Univ of Wash.; [3]Univ of Tenn.*

Background: Hidden hypercalcemia, characterized as high ionized calcium with normal albumin-corrected total calcium, has been reported to be associated with high mortality in hemodialysis (HD) patients. We hypothesized that the development of a new correction equation offers better mortality predictability.

Methods: In a national cohort of HD patients in the US, a novel equation comprising total calcium, albumin, and phosphorus was derived and validated among 808 hemodialysis patients with measured ionized calcium data. We then categorized 87,779 HD patients according to calcium status (i.e., low [<8.6 mg/dL], low-normal [8.6–9.4 mg/dL], high-normal [>9.4–10.2 mg/dL], and high [>10.2 mg/dL]) based on the novel vs. conventional correction equation. The association with all-cause death was evaluated using multivariable Cox regression analysis with adjustment for relevant demographics, comorbidities, and laboratory variables including albumin and phosphorus.

Results: The novel equation was expressed as 1.35×total calcium (mg/dL) – 0.65×albumin (g/dL) – 0.15×phosphorus (mg/dL) + 0.3. Adjusted R^2 was 0.79 (vs. 0.68 for the conventional equation), and net reclassification index among patients with ionized hypercalcemia was 23%. Among patients who were categorized as high-normal calcium status by the conventional equation, there appeared incremental mortality risk across higher calcium status according to the new equation. The mortality risk was consistent across calcium status according to the conventional equation within the categories by the new equation.



Conclusions: A novel equation derived for correction of total calcium performs significantly better in identifying patients with hidden hypercalcemia in HD patients than the conventional equation and helps better identify patients at high risk for mortality.

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FR-PO414

Replacement of Acetate with Citrate in Hemodialysis Fluid: Effect on Calcium Balance Fabio Malberti, Laura Cosmai, Marina Foramitti. *Nephrology, Istituti Ospitalieri di Cremona, Cremona, Italy.*

Background: Bicarbonate based hemodialysis (HD) fluids require an acid component in order to balance pH and, commonly, acetic acid is used. Citric acid (Ci) has been proposed instead of acetate (A) to improve the dialysis fluid biocompatibility for its antioxidant and anti-inflammatory properties. However, Ci could reduce the diffusible Ca in dialysis fluid by binding Ca ions, resulting in more negative Ca balance compared to A at similar total Ca concentrations.

Methods: Dialysis Ca balance (CaB) was evaluated by collecting dialysis fluid during HD sessions using 4 different dialysis solutions (D) as regards Ca, A and Ci concentrations: DCi-1.0 (Ca 1.50, Ci 1.0, A 0 mmol/L); DCi-0.8 (Ca 1.50, Ci 0.8, A 0.3 mmol/L); DA1.50 (Ca 1.50, A 3 mmol/L), DA1.25 (Ca 1.25, A 3 mmol/L).

Results: Pre-HD serum ionized Ca (SiCa) was comparable with the 4 HD solutions. D ionized Ca (DiCa) was lower (P<0.001) in DCi-1.0 vs DCi-0.8 vs DA1.25 vs DA1.50 so resulting in more negative diffusion gradients between D and blood in DCi-1.0 (-0.26±0.6 mmol/L) and DCi-0.8 (-0.15±0.05 mmol/L) compared to DA1.25 (-0.02±0.07) and DA1.50 (+0.17±0.07).

	DCi-1.0	DCi-0.8	DA-1.50	DA-1.25
DiCa mmol/L	0.89±0.03	0.98±0.01	1.33±0.06	1.12±0.03
SiCa start HD mmol/L	1.15±0.05	1.14±0.05	1.16±0.07	1.14±0.05
SiCa end HD mmol/L	1.07±0.03	1.11±0.04	1.25±0.05	1.13±0.04
Diffusive CaB mg	-306±112	-155±62	404±130	65±119
Convective CaB mg	-89±42	-114±35	-138±60	-101±42
Total CaB mg	-395±134	-269±81	266±116	-36±130

Therefore, diffusive and total CaB was much more negative in DCi-1.0 compared to DCi-0.8 and DA1.25, respectively. CaB was positive in DA-1.50 (table). SiCa unchanged during HD with DA1.25, significantly increased with DA1.50 and decreased with DCi-1.0 and DC-0.8.

Conclusions: 1) Citrate-containing HD fluids have lower iCa concentrations compared to A-containing fluids at equal total Ca concentrations. This induces more negative iCa diffusion gradients between D and blood resulting in a more negative CaB. 2) Citrate fluids with 1.50 mmol/L of Ca induce more negative CaB also compared with A fluids containing 1.25 mmol/L of Ca.

FR-PO415

Effect of Dialysate Calcium Conversion on Mineral Metabolism in Maintenance Hemodialysis Pateints Han Ro, Ae Jin Kim, Ji Yong Jung, Jae Hyun Chang, Hyun Hee Lee, Wookyung Chung. *Dept of Internal Medicine, Gachon Univ Gil Medical Center, Incheon, Republic of Korea.*

Background: The recommended dialysate calcium (DCa) concentration has been changed several times and the appropriate DCa concentration remains controversial. Our hemodialysis center reduced the default DCa concentration from 1.75 to 1.5 mmol/L in February 2013. This study compared the effect of DCa on serum markers of mineral bone disorders and drug requirements between conversion and no conversion (1.75 mmol/L) groups.

Methods: We retrospectively reviewed the patients undergoing maintenance hemodialysis using a consistent DCa concentration for the period between February 2012 and January 2014. We compared the serum markers of mineral metabolism and drug utilization before and after 1 year of DCa conversion between the two groups. Data were collected at 3-month intervals for 2 years. Our hemodialysis center reduced the default DCa concentration from 1.75 to 1.5 mmol/L in February 2013. This study compared the effect of DCa on serum markers of mineral bone disorders and drug requirements between conversion and no conversion groups.

Results: Thirty-two patients were maintained at a DCa of 1.75 mmol/L and 26 patients underwent conversion of DCa from 1.75 to 1.5 mmol/L. DCa conversion to low calcium increased serum phosphorus level (4.4±0.8 mg/dL vs. 4.7±0.9mg/dL, p=0.027) and parathyroid hormone level (112.6±107.2pg/mL vs. 254.0±224.5 pg/mL, p<0.001). Total amount of phosphate binder was not different in patients without conversion (p=0.993). However, DCa conversion to low calcium increased total equivalent dose of phosphate binder (p=0.012), especially calcium based phosphate binder (p=0.040).

Conclusions: In conclusion, our results demonstrate that compared with maintaining 1.75 mmol/L DCa, lowering DCa from 1.75 to 1.5 mmol/L lead to a significant change in mineral metabolism and drug requirements ofphosphate binder in maintenance hemodialysis patients. pan>224.5 pg/mL, p<0.001). Total amount of phosphate binder was not different in patients without conversion (p=0.993). However, DCa conversion to low calcium increased total equivalent dose of phosphate binder (p=0.012), especially calcium based phosphate binder (p=0.040).

FR-PO416

Tamoxifen Causes Hypophosphatemia and Phosphaturia through the Downregulation of NaPi-IIa Expression in the Rat Kidney Proximal Tubule
Hassane Amlal, Sihame Amlal, Sulaiman Sheriff. *Internal Medicine, Univ of Cincinnati, Cincinnati, OH.*

Background: Estrogen regulates renal inorganic phosphate (Pi) handling in women as well as in experimental animals. We recently showed that estrogen directly targets proximal tubule cells and downregulates NaPi-IIa in rats and both NaPi-IIa and NaPi-IIc in mice. The objective of this study was to test whether Specific Estrogen Receptor Modulators (SERMs) can also target Pi transport in the kidney proximal tubule.

Methods: Ovariectomized rats were placed in metabolic cages with free access to rodent chow and water. After acclimation period, rats were divided into 3 groups and treated with 500µg/100g BW tamoxifen (TAM) or Raloxifene (RAL) or vehicle (Control). Daily food intake, water intake and urine volume were monitored. After 3 days, rats were sacrificed for blood and kidney collection. Cortex tissues were isolated and used for molecular studies.

Results: Only rats treated with TAM exhibited a significant hypophosphatemia vs. Control animals. Blood electrolytes, acid-base and BUN are normal in all groups. Food intake decreased sharply in TAM- and only slightly in RAL-treated animals vs. Control group. Despite the reduction in food/Pi intake, Pi/creatinine excretion slightly increased in TAM over control group. The mRNA expression and protein abundance of NaPi-IIa were sharply downregulated in TAM vs. Control animal. In RAL group, Pi/creatinine excretion was decreased and correlated with food intake and NaPi-IIa protein was not significantly altered vs. Control group.

Conclusions: Tamoxifen causes phosphaturia and hypophosphatemia in female rats. This effect results from the downregulation of NaPi-IIa at both mRNA and protein levels. For the same dose, phosphaturia and hypophosphatemia are more pronounced in TAM than in RAL-treated rats. Hence, TAM is the most potent estrogen agonist with respect to its effect on Pi transport in the kidney, and could be used to correct hyperphosphatemia in chronic kidney disease with significant residual renal function or other conditions associated with impaired Pi balance.

Funding: NIDDK Support, Clinical Revenue Support

FR-PO417

Contributors to Mortality in Calcific Uremic Arteriolopathy: Role of Site and Severity of Skin Lesions
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Background: Calcific Uremic Arteriolopathy [CUA] is often fatal with mortality that ranges from 50 -80%. Adverse prognostic factors include: advanced age, female gender, large body mass index [BMI], and severity of skin lesions. Survival outcome has been improved with the use of intravenous sodium thiosulfate [STS]. The relationship between mortality at 2-yrs and site/severity of skin lesions is re-examined in this study.

Methods: We retrospectively reviewed our end stage renal disease [ESRD] patient's records over a 10-year period and identified 45 biopsy confirmed cases of CUA. Skin lesions located above the elbows and knees were considered proximal while those below elbows/knees were distal. Lesions were classified as mild , moderate , or severe according to previously described criteria. Associations between mortality and various demographic, and clinical variables were assessed using t-tests, Mann-Whitney-U tests, and chi-squared as appropriate. Multivariate logistic regression models were fitted to adjust for confounders. Survival analysis utilized Kaplan-Meier plots.

Results: The mean age of the patients was 63±10 yrs, 60% were female. Mean BMI was 34±5 and mean dialysis vintage was 4±2 yrs. Patients with proximal lesions had a higher mortality (48% vs 20 %, p=0.05) and larger BMI than those with distal lesions (35±5 vs 34±6, p=0.6) respectively. Of the deceased patients, 11 0f 19 (58%) had severe skin lesions while 13 of 26 survivors (50%) had mild lesions, p=0.003. Multiple regression analysis showed a significant association between mortality and : serum phosphate level, (OR 3.4, (CI 1.1-10.5); p=0.03); proximal lesion, (OR 8.4, (CI 0.98-71.5);p=0.05); and severe lesions (OR 17.0, CI (1.3-221.9); p=0.03). Age, gender, dialysis vintage, diabetes, BMI, use of Cinacalcet, serum albumin, calcium, and PTH levels had no statistically significant associations with mortality.

Conclusions: Serum phosphorus level, proximal and severe skin lesions appear to be major determinants of survival in CUA. Phosphate levels should be monitored closely and adequately controlled in patients with CUA.

Funding: Other NIH Support - RCMI /ACTSI, Clinical Revenue Support

FR-PO418

Development of Phosphatemic Index for Evaluation of Phosphate-Containing Foods in Healthy Japanese
Yoko Narasaki, Michiyo Yamasaki, Misaki Katsumoto, Yutaka Taketani. *Clinical Nutrition and Food Management, Tokushima Univ, Tokushima, Japan.*

Background: High dietary phosphorus (P) intake increases phosphorus retention or load, serum FGF23 and PTH levels, and finally causes hyperphosphatemia and poor prognosis of CKD. Therefore, decrease in dietary P intake should be required for CKD patients. Here, we propose "Phosphatemic Index: PI" to evaluate the effect of P-containing foods on serum P homeostasis.

Methods: Twenty healthy young subjects (10 men and 10 women, 20-30 y.o.) were recruited. In this study, 10 different foods (pork, ham, soy bean, tofu, milk, processed cheese, egg, buckwheat noodle, red sea bream, broccoli) containing 200 mg of P were randomly ingested with an interval of 7 days or more as lunch. Blood were collected at 0, 0.25, 0.5, 1, 2, 4, and 6 h after the food ingestion, and measured serum P and PTH level. Then, each area under the curve (AUC) of time-P concentration curve was calculated. PI of the tested food was calculated by following equation: PI = (AUC of tested food)•100/(AUC of 200 mg of sodium phosphate). This study was performed by open-label crossover study and approved by ethical committee of Tokushima University Hospital.

Results: As PI of sodium phosphate was 100, PI of milk was 108, processed cheese was 99, ham was 75, pork 54, soy bean was 33, tofu was 20. We found that PIs of vegetable foods including soy and tofu was lower than those of animal foods. In addition, PI of pork showed lower than that of ham. This result might be due to food additives containing P. Furthermore, in milk and cheese, because they showed significant low secretion of PTH and low urinary excretion of P, we discussed that high calcium in milk would suppress the secretion of PTH and urinary P excretion and resulted to show high PI.

Conclusions: PI can appropriately reflect the effect of P-containing foods on serum P level, and be useful tool to evaluate and select foods by CKD patients who need P restriction.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceutical Co., Ltd, Government Support - Non-U.S.

FR-PO419

Green Tea Increases Urinary Excretion of Phosphorus, Magnesium and Calcium in Rats
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Background: The consumption of green tea (GT) is increasing worldwide, and there is a lack of data in the literature regarding its effect on renal tubular function.

Methods: Male Wistar rats were housed in individual cages and randomly assigned to have ad libitum access to GT (Feel Good©) or tap water. On day 8, we moved the rats to metabolic cages and collected 24-h urine samples under oil, in order to evaluate renal function. The rats were then anesthetized, and a catheter was placed in the abdominal aorta to measure blood pressure (BP) and collect blood samples. We quantified creatinine and electrolytes in urine and plasma samples. We removed the kidneys to quantify protein expression (PE) of ion transporters in the cortex and outer medulla (OM), by Western blot. We used unpaired t-test for statistical analyses.

Results: GT increased diuresis,as well as increasing urinary excretion (UV) of phosphorus (P), magnesium (Mg), calcium (Ca) and potassium (K).

	Control (n =11)	Green Tea (n =7)	P-value
Body weight,g	286 ± 7	295 ± 8	0.44
BP, mm Hg	103 ± 2	104 ± 4	0.90
Creatinine Clerance, ml/min.100g^{-1}	0.50 ± 0.05	0.49 ± 0.06	0.83
Liquid intake, ml/day	25 ± 2	29 ± 3	0.30
Urine output, ml/day	20 ± 2	29 ± 2	0.02
UV Na, µmol/day	0.92 ± 0.09	1.16 ± 0.15	0.17
UV K, µmol/day	2.33 ± 0.14	2.73 ± 0.15	0.07
UV Cl, µmol/day	0.61 ± 0.06	0.77 ± 0.16	0.30
UV P, µmol/day	500 ± 53	730 ± 75	0.02
UV Mg, µmol/day	148 ± 19	223 ± 24	0.02
UV Ca, µmol/day	26 ± 2	48 ± 6	0.01

However, plasma concentrations of those ions remained within the normal range, with the exception of K, which was 3.1 ± 0.1 mmol/l in the GT group. The PE of Na-Pi type IIa in the cortex was comparable between the groups. However, in the OM, the PE of ROMK channel was lower in GT rats (n =5) than in control rats (n =3) - 100 ± 13% in GT *vs.* 63 ± 7% ($p<0.02$) - as was that of the Na-K-Cl cotransporter - 100 ± 4% *vs.* 75 ± 8% ($p<0.08$).

Conclusions: Taken together, our findings indicate that GT inhibits ion transporters in the thick ascending limb of Henle's loop, which increases diuresis and ion losses.

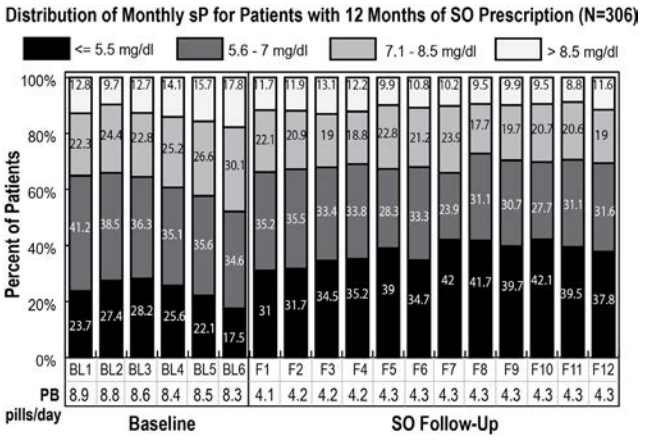
FR-PO420

Serum Phosphorus and Pill Number Per Day in Hyperphosphatemic Hemodialysis Patients (n=306) Prescribed Sucroferric Oxyhydroxide for 12 Months
Linda H. Ficociello, Vidhya Parameswaran, Carly R. Van Zandt, Norma J. Ofsthun, Claudy Mullon, Franklin W. Maddux, Robert J. Kossmann. *Fresenius Medical Care North America (FMCNA), Waltham, MA.*

Background: DOPPS data show that even though phosphate binders (PB) are widely used, 35% of hemodialysis (HD) patients have hyperphosphatemia (serum phosphorus (sP) levels >5.5 mg/dl). This retrospective analysis assesses the real-world effectiveness of sucroferric oxyhydroxide (SO), a chewable iron-based PB, to lower sP to ≤5.5 mg/dl over a one-year period.

Methods: De-identified data was extracted from electronic records for all adult, HD patients with first SO prescription between 3/1/2014- 3/1/2015 and SO prescription for 12 months (F1-F12). Patients on combination PB therapy were excluded. Baseline was defined as the 6 months before SO (BL1-BL6). Descriptive analyses of month to month changes are described and confirmed with linear mixed-effects regression for continuous data and Cochran's Q and McNemar's chi-square test for categorical data.

Results: At BL6, mean sP was 7.1 mg/dl and only 17.5% of patients had sP ≤5.5 mg/dl. During the months of SO follow-up (F1-F12), 31%-42.1% of patients had a sP ≤5.5 mg/dl, a 77%-141% increase (all comparisons $p<0.001$) from BL6. Mean PB pills/day decreased ($p<0.0001$) from 8.3 pills at BL6 to 4.1-4.3 pills during F1-F12. Percent of patients with sP from 5.6-8.5 mg/dl decreased ($p<0.001$) from 64.7% at BL6 to 50.6% at F12.



Conclusions: 82.5% of patients prescribed SO had hyperphosphatemia at baseline compared to a national sample of HD patients (35%). Percent of patients with sP ≤5.5 mg/dl increased from 17.5% at baseline to 31%-42.1% during the year-long follow-up, along with a mean reduction of PB pills/day of 48%-51%.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

FR-PO421

Pill Burden and Serum Phosphorus in Hemodialysis Patients Switched from Calcium Acetate to Sucroferric Oxyhydroxide as Part of Routine Care Linda H. Ficociello, Vidhya Parameswaran, Carly R. Van Zandt, Norma J. Ofsthun, Claudy Mullon, Franklin W. Maddux, Robert J. Kossmann. *Fresenius Medical Care North America, Waltham, MA.*

Background: Although phosphate binders (PB) are widely prescribed, many hemodialysis (HD) patients do not achieve KDOQI recommended serum phosphorus (sP) levels. PB constitute a large proportion of HD patients' overall pill burden and many patients are non-adherent (Chiu et al. 2009). The current retrospective analysis examined PB pills/day and achievement of sP ≤5.5 mg/dl in patients switched from calcium acetate (CaAc) to sucroferric oxyhydroxide (SO).

Methods: Adult, HD patients with first SO prescription between 3/1/2014- 3/1/2015, recorded SO prescription for 10-12 months and CaAc prescription at baseline (previous 6 months) were included (n=139). Patients on combination PB therapy were excluded. Descriptive analyses of quarterly changes were described and linear mixed-effects regression and Cochran's Q/McNemar were used to test for statistical significance.

Results: Mean quarterly PB pills/day and percent of patients with sP ≤ 5.5 mg/dl are presented the table. Using the CaAc2 quarter as the reference (8.5 pills/day), a >47% decrease in number of PB pills/day was observed for each quarter after the switch to SO (4.0, 4.5, 4.2, 4.1 pills/day SO1-SO4, respectively). Percent of patients achieving sP ≤ 5.5 mg/dl increased by 32%, 82%, 132% and 113%, comparing CaAc2 to SO1-SO4, respectively.

	CaAc1	CaAc2 (ref)	SO1	SO2	SO3	SO4	Overall p-value
PB pills/day	8.9	8.5	4**	4.5**	4.2**	4.1**	<0.0001
% pts with sP ≤ 5.5 mg/dl	19.3	15.8	20.9	28.8[a]	36.7**	33.6*	<0.0001

**p-value <0.0001; *p-value <0.001, [a]p-value <0.05. Observation periods include 6 month CaAc and 12 month SO. Each quarter is represented as CaAc# and SO#.

Conclusions: In a cohort of patients switched from CaAc to SO, a >47% reduction in PB pills/day was observed along with improvements in the percent of patients achieving sP ≤ 5.5 mg/dl during SO follow-up.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

FR-PO422

The Effect of Ferric Citrate (Auryxia) on Serum Phosphate Control in Dialysis Patients: Real-World Data Pablo E. Pergola,[1] Debra J. Hain,[2] Meredith Marinaro,[3] David W. Koeper,[4] Melissa A. Rosenthal,[5] Salvatore Chillemi,[6] Jennifer M. Huffman,[9] Teresa Gerbeling,[7] James M. Pritsiolas.[8] *[1]Renal Associates PA, San Antonio, TX; [2]FL Atlantic Uni, Boca Raton, FL; [3]Uni CT, Farmington, CT; [4]Fox Valley Nephrology, Neenah, WI; [5]Los Alamitos HD Clinic, Los Alamitos, CA; [6]N Georgia Kidney Specialists, Marietta, GA; [7]Dialysis Center Lincoln, Lincoln, NE; [8]CarePoint Health Medical Group, Bayonne, NJ; [9]Kidney Associates of KC, Kansas City, KS.*

Background: Ferric citrate (FC) is an approved phosphate binder for use in patients on dialysis. Previous clinical trial data demonstrated FC increased iron stores, but real-world data of FC effects on both bone mineral and anemia parameters are lacking.

Methods: Adult dialysis patients (n=92, 25 peritoneal dialysis, 67 hemodialysis) taking FC for 6 mo and had data as part of routine clinical care were included in a retrospective analysis. Serum phosphate (phos), hemoglobin (Hgb), transferrin saturation (TSAT) and ferritin were extracted from medical records before & during the first 6 mo of FC treatment.

Results: When starting FC, 21 patients (23%) were binder naïve, 36 (39%) were on sevelamer only (average of 11 tablets/day), 20 (22%) were on calcium-based binder only (average of 9 tablets/day) and 15 (16%) on combination (average of 16 tablets/day) or other binder. The mean starting dose of FC was 6 tablets/day increasing to 7 tablets/day at 6 mo of treatment. Before the start of FC, 22% of patients had a serum phos within target range of < 5.5mg/dL increasing to 65% at 6 mo of FC treatment. Phos, TSAT, ferritin and Hgb values are shown in Table 1 (data presented as mean±SEM). 6 patients discontinued FC within 6 mo of treatment.

n=92	Pre-FC	Post FC (months)		
		1	3	6
Serum Phos (mg/dL)	6.5±0.2	5.9±0.2	5.8±0.2	5.4±0.2
TSAT (%)	28.2±1.2	30.3±1.5	34.8±1.5	37.1±2.0
Ferritin (ng/mL)	753±56	841±58	972±62	953±66
Hgb (g/dL)	10.6±0.2	11.0±0.2	11.2±0.1	11.1±0.2
Patients receiving IV iron	53 (47%)			31 (34%)

Conclusions: In a retrospective analysis, switching to FC lowered serum phos and raised TSAT, ferritin and Hgb. Results of serum phos and anemia markers observed in this small retrospective cohort were similar to those in previous FC data.

Funding: Pharmaceutical Company Support - Keryx Biopharmaceuticals

FR-PO423

Serum Calcification Propensity Is Largely Genetically Determined in the General Population Edward Pivin,[2] Matthias Bachtler,[1] Olivier Devuyst,[3,4] Uyen Huynh-Do,[3,5] Murielle Bochud,[3,6] Andreas Pasch.[1,3] *[1]Clinical Research, Univ Bern, Bern, Switzerland; [2]Nephrology, Univ Hosp. Lausanne, Lausanne, Switzerland; [3]NCCR Kidney.ch, Switzerland; [4]Physiology, Univ Zurich, Zurich, Switzerland; [5]Nephrology, Univ Hosp. Bern, Bern, Switzerland; [6]Social and Preventive Medicine, Univ Hosp. Lausanne, Lausanne, Switzerland.*

Background: A novel blood test (T_{50}-Test) quantifies serum calcification propensity by determining the transformation time point T_{50} from amorphous to crystalline calcium phosphate in the presence of human serum. T_{50} is associated with all-cause and cardiovascular mortality in patients with chronic kidney diseases (CKD). Here we investigated T_{50} in the general population.

Methods: T_{50} and fetuin-A were determined in 1033 sera from the Swiss Kidney Project on Genes in Hypertension (SKIPOGH) cohort, the heritability of T_{50} calculated and a genome wide association study (GWAS) and multivariate analysis performed.

Results: T_{50} was normally distributed in the population (mean±SD, 298±58 min.), and the heritability of T_{50} was estimated to be 50±8% (p<0.01). GWAS identified a strong association between T_{50} and SNPs in the *AHSG*/fetuin-A gene locus on Chromosome 3 (e.g. rs2593813 p=7.7e-28). Individuals homozygous for the minor allele had a significantly lower T_{50}-Test than those homozygous for the wildtype allele (254±54 vs. 315±54 min., p<0.01). Serum fetuin-A concentrations were lower in those homozygous for the minor allel (0.33±0.06 vs. 0.43±0.08 g/L, p<0.01). Multivariate analyses identified age, eGFR, and phosphate as determinants associated with worse (i.e. accelerated) and fetuin-A, magnesium and bicarbonate as determinants associated with improved (i.e. delayed) serum calcification propensity.

Conclusions: Serum calcification propensity (T_{50}) is highly heritable in the general population and largely depends on the same determinants as in renal patients. Calcification propensity may reflect a general physiological system of crystalization control inherent in blood.

Funding: Government Support - Non-U.S.

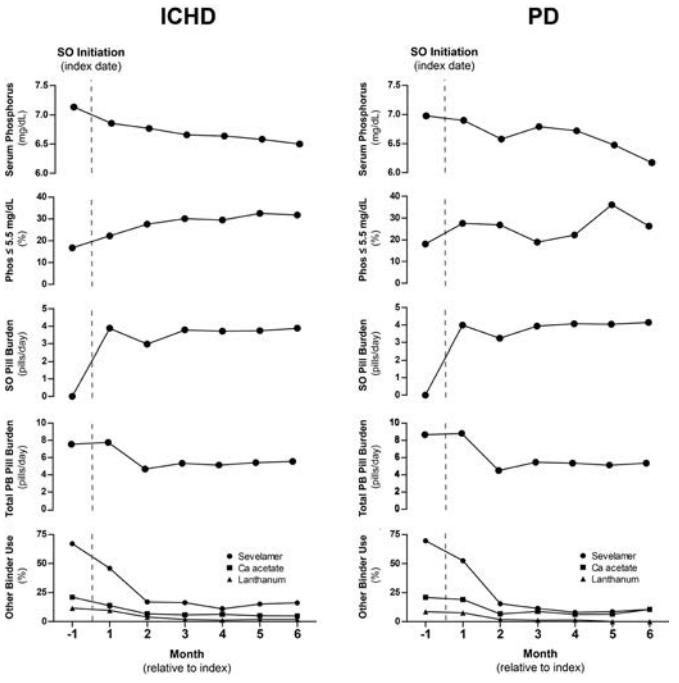
FR-PO424

Phosphorus Control and Pill Burden among In-Center Hemodialysis (ICHD) and Peritoneal Dialysis (PD) Patients Converting to Sucroferric Oxyhydroxide (SO) Kathryn S. Gray,[1] Linda H. Ficociello,[2] Claudy Mullon,[2] Steven M. Brunelli.[1] *[1]DaVita Clinical Research, Minneapolis, MN; [2]Fresenius Medical Care, Waltham, MA.*

Background: SO is a new iron-containing phosphate binder (PB). In developmental studies, SO showed equivalent phosphorus reduction to sevelamer. However, the effects of SO in real-world populations have not been extensively studied. We retrospectively examined SO use among patients who converted from another PB to SO.

Methods: From among ICHD and PD patients at a large dialysis organization (LDO) receiving benefits through the LDO's pharmacy program, we identified those converting to SO from another PB: defined from prescription fill data as having had supply of another PB, receiving a first fill of SO, and subsequently not refilling the initial PB such that supply exhausted for at least 30 days. Longitudinal indices of phosphorus control and PB burden were assessed.

Results: There were 656 ICHD SO converters: mean age, 50 years; 47% female; 45% black; median vintage, 43 months. Prior to SO initiation, mean serum phosphorus was 7.1 mg/dL; during follow-up it fell to 6.6 mg/dL; percentage of patients with phosphorus ≤5.5 mg/dL rose from 17% to 32%. Daily SO pill burden was 3.0-3.9; total daily PB pill burden fell from 7.5 prior to SO initiation to 5.5 during follow-up. There were 105 PD SO converters: mean age, 47 years; 52% female; 29% black; median vintage, 33 months. Prior to SO initiation, mean serum phosphorus was 7.0 mg/dL; over follow-up it fell to 6.2 mg/dL; percentage of patients with phosphorus ≤5.5 mg/dL rose from 18% to 26%. Daily SO pill burden was 3.2-4.0; total daily PB pill burden fell from 8.7 prior to SO initiation to 5.4 during follow-up.



Conclusions: In a real-world population of ICHD and PD patients, conversion to SO coincided with reductions in serum phosphorus, higher percentage of patients with controlled phosphorus, and lower total PB pill burden.

Funding: Pharmaceutical Company Support - Fresenius Medical Care

FR-PO425

The Dietary Adenine Rat Model of Chronic Kidney Disease Produces Hyperphosphatemia in the Absence of High Phosphate Diet

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[1]Biomedical and Molecular Sciences, Queen's Univ, Kingston, ON, Canada; [2]Medicine, Queen's Univ, Kingston, ON, Canada.

Background: Chronic kidney disease (CKD) induces hyperphosphatemia, which associates with cardiovascular events and vascular calcification. Animal models of CKD demonstrate similar pathologies and outcomes to CKD patients. However, a rat adenine model examining the effects of dietary phosphate (PO_4) levels after slow induction of CKD is unknown. This study is a refinement of the dietary adenine model of CKD.

Methods: Male Sprague Dawley rats (15-16 weeks) were fed a 0.25% adenine, 0.5% PO_4 diet to establish stable CKD (creatinine >250 uM), 5 weeks. At 5.5 weeks, rats were then fed 0.5%, 1% or 1.5% PO_4 diet (N=9, 10, 6). Control rats were fed 0.5% PO_4 diet (N=8). Serum creatinine, PO_4, FGF-23, and PTH were measured. At sacrifice, tissue levels of calcium and PO_4 were determined.

Results: Rats in 0.5, 1, and 1.5% PO_4 groups had similar creatinine levels throughout the experiment. From 0-5.5 weeks, all CKD rats were similar in serum PO_4 and significantly higher than control from 2 weeks. At 5 weeks, CKD rats had 3.2±0.6 mM PO_4 versus 2.5±0.3 mM PO_4 Control. When removed from adenine diet, the 0.5% group returned to control PO_4 levels by 6.5 weeks with no calcification or further increase by 7 weeks in FGF-23 (3.1±2.7 vs 0.47±0.15 ng/ml Control) and PTH (0.41±0.18 vs 0.17±0.08 Control ng/ml). The 1.0 and 1.5% groups had significant large increases by 7 weeks in PO_4 (5.0±1.0, 5.8±1.4mM), PTH (2.4±1.3, 3.1±0.6ng/ml), and FGF-23 (47±18, 35±17 ng/ml), aortic calcification in 80% of rats.

Conclusions: These results demonstrate that a high phosphate diet greater than 0.5% is required for mineral bone disorder and calcification in the rat adenine model of CKD. The dietary adenine model of CKD produced a significant increase in serum PO_4 on low PO_4 diet, that returned to normal levels within 1.5 weeks of removal of adenine. Researchers should use caution in comparing serum PO_4 levels in animals on or off adenine-containing diets.

Funding: Pharmaceutical Company Support - OPKO Health, Inc. Renal Division, Government Support - Non-U.S.

FR-PO426

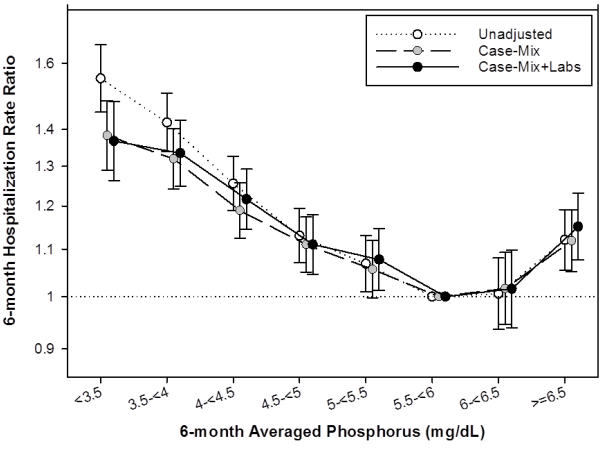
Both Normal and Very High Serum Phosphorous Levels prior to Transition to Dialysis Are Associated with Early Dialysis Hospitalization in U.S. Veterans: A Transition of Care in CKD Study

Amanda R. Tortorici,[1] Elani Streja,[1] Connie Rhee,[1] Melissa Soohoo,[1] Wei Ling Lau,[1] Yoshitsugu Obi,[1] John J. Sim,[2] Daniel L. Gillen,[1] Keith C. Norris,[3] Csaba P. Kovesdy,[4] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Kaiser Permanente SC; [3]UCLA; [4]Univ of Tenn.*

Background: Recent studies suggest that serum phosphorous (Phos) levels are predictors of hospitalization in patients with chronic kidney disease. However, the impact of Phos levels prior to end-stage renal disease (ESRD) on post-ESRD hospitalization is unknown.

Methods: In 85,505 US veterans who transitioned to dialysis between 10/2007 and 3/2014, we identified 19,610 patients with available Phos measurements within the last 6-month prelude period (prior to ESRD). We examined the association of Phos (averaged over 6 months) as a categorical predictor of hospitalization within the first 6 months post transition, using Poisson models adjusted for demographics, comorbidities and laboratory covariates.

Results: The cohort was (mean±SD) 66±11 years old, among whom 34% were African-American, and 50% had diabetes listed as their primary cause of ESRD. The mean±SD Phos of the cohort was 5.1±1.3 mg/dL prior to ESRD. We observed a reverse J-shaped association between pre-ESRD Phos and 6-month post-ESRD hospitalization rate. Patients with Phos levels ≤5.5 mg/dL and ≥6.5 mg/dL demonstrated incrementally higher hospitalization rates compared to the referent group (Phos 5.5-<6 mg/dL).



Conclusions: Both normal and very high Phos levels were associated with higher early post-ESRD hospitalization rates. The finding of normal Phos levels being associated with increased risk was unexpected and suggests further analysis as this could impact existing recommendations of targeting an achieved Phos level to the normal range. Further studies are also needed to determine if using dietary and medication interventions to attain this Phos range confers better early dialysis outcomes in this population.

Funding: NIDDK Support

FR-PO427

Increased Phosphate Burden from Medications Prescribed to In-Center Hemodialysis Patients

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Background: Maintaining phosphorus balance in in-center hemodialysis (IHD) patients is problematic despite dietary restriction (800 – 1000 mg/day if serum P levels ≥5.5 mg/dL), dialysis, and phosphate (P) binder use. High-flux IHD can remove ~30 mmol (900 mg) P/session; P intake should not exceed ~750 mg/day for a 60 kg patient. Rarely is the P in prescribed medications considered part of the diet, but this source should raise concern.

Methods: Data was obtained from the Fresenius Medical Care North America (FMCNA) electronic data warehouse Knowledge Center and MedReview-eRx accessed Surescripts™, housing >80% of prescriptions filled in the US. Adult, FMCNA IHD patients prescribed ≥1 medication in the MedReview-eRx database were analyzed (695,759 prescriptions). Information collected included medication dose, dose unit, dose timing, strength, start and stop dates, refills, patients' demographic information, admission history, and modality type. The number of patients and prescriptions by drug class and individual medication, average dose/day, and phosphate content were analyzed. Average doses/day (# of pills) were calculated for each medication (open order on a randomly selected day-May 1, 2015); medications with >100 orders were reported. P content of medications taken in FMCNA clinics was assessed using routinely used pharmacology references.

Results: The top five prescribed drug classes in FMCNA dialysis patients were calcium-channel blockers (22%), proton pump inhibitors (PPIs; 18%), acetaminophen-opioid (AO; 13%), angiotensin-converting enzyme inhibitors (ACEi; 10%) and α2-agonists (9%). The top five medication orders were amlodipine, lisinopril, clonidine, acetaminophen, and

omeprazole. On average, the additional P added to patients' daily intake was 36.2 mg for amlodipine, 75-148.8 mg for lisinopril, 2.9-7.2 mg for clonidine, 0 mg for AO, and 204.8-234 mg for omeprazole per day.

Conclusions: Increased P content in medications prescribed to IHD patients may contribute to the overall daily P load, requiring more P binders, increasing the daily pill burden and affecting compliance.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America; Fresenius Medical Care Renal Therapies Group

FR-PO428

Pill Burden and Serum Phosphorus in Hemodialysis Patients Switched from Sevelamer to Sucroferric Oxyhydroxide Vidhya Parameswaran, Linda H. Ficociello, Carly R. Van Zandt, Norma J. Ofsthun, Claudy Mullon, Franklin W. Maddux, Robert J. Kossmann. *Fresenius Medical Care North America, Waltham, MA.*

Background: Recent DOPPS data show a trend towards greater phosphate binder (PB) non-adherence and higher number of prescribed PB pills per day. Also, non-adherence was associated with serum phosphorus (sP) >5.5 mg/dl (Fissell et al. 2016). The current retrospective analysis examined PB pills/day and achievement of sP ≤ 5.5 mg/dl in patients switched from sevelamer (Sev) to sucroferric oxyhydroxide (SO) as part of routine care.

Methods: Adult, hemodialysis patients with first SO prescription between 3/1/2014-3/1/2015, recorded SO prescription for 10-12 months and Sev prescription at baseline (previous 6 months) were included (n=277). Patients on combination PB therapy were excluded. Descriptive analyses of quarterly changes were described and linear mixed-effects regression and Cochran's Q/McNemar were used to test for statistical significance.

Results: Mean quarterly PB pills/day and percent sP ≤5.5 mg/dl are presented in the table. Using the Sev2 quarter as the reference (8.9 pills/day), a >50% decrease in number of PB pills/day was observed for each quarter after the switch to SO (4.0, 4.4, 4.3, 4.4 pills/day SO1-SO4, respectively). Percent of patients achieving sP ≤5.5 mg/dl increased by 45%, 93%, 131% and 119%, comparing Sev2 to SO1-SO4, respectively.

	Sev1	Sev2 (Ref)	SO1	SO2	SO3	SO4	Overall p-value
PB pills/day	9.3	8.9	4**	4.4**	4.3**	4.4**	<0.0001
% patients with sP ≤ 5.5 mg/dl	22*	15.4	22.4*	29.7**	35.6**	33.7**	<0.0001

**p-value < 0.0001, *p-value <0.05. Observation periods include 6 month Sev and 12 month SO. Each quarter is represented as Sev# and SO#.

Conclusions: In a cohort of patients switched from Sev to SO, a >50% reduction in PB pills/day was observed along with improvements in the percent of patients achieving sP ≤5.5 mg/dl during SO follow-up.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

FR-PO429

Evidence for Increased Absorption of Phosphate in Experimental Adenine-Induced Chronic Kidney Disease Paul S. Jeronimo,[1] Cynthia M. Pruss,[1] Bruno Svajger,[1] Mandy E. Turner,[1] Kimberly J. Laverty,[1] Emilie C. Ward,[1] Martin P. Petkovich,[1] Rachel M. Holden,[2] Michael A. Adams.[1] *[1]Biomedical and Molecular Sciences, Queen's Univ, Kingston, ON, Canada; [2]Medicine, Queen's Univ, Kingston, ON, Canada.*

Background: Hyperphosphatemia is a common manifestation of chronic kidney disease (CKD) and is a risk factor for cardiovascular morbidity and mortality (e.g. vascular calcification). It is widely acknowledged that the kidney is a primary site of phosphate regulation, but it is poorly understood how other organs, including the gut, contribute to this control. Despite homeostatic mechanisms regulating serum phosphate within a narrow range the gut normally absorbs 70% of dietary phosphate through paracellular and sodium-dependent phosphate cotransporter (NPT2b) mechanisms. The objective of this study was to determine how disposition of phosphate is altered by impaired renal function and uremia in a rat model of CKD.

Methods: Male Sprague Dawley rats (n=42) were fed an adenine containing diet (0.25% adenine with 0.5% phosphate) for 5-6 weeks to establish moderate to severe CKD. Samples of feces (24 hours) and blood samples (1.2 mL) were collected weekly. Fecal and serum levels of phosphate, serum creatinine, FGF-23 and PTH were measured using established colorimetric assays and ELISAs.

Results: The adenine induced a moderate to severe level of CKD (serum creatinine 308 ± 141 μM), but because of the low phosphate diet serum phosphate was not elevated. Total fecal phosphate assessed at 2 time points was significantly lower in the CKD group (p=0.02), despite consuming similar phosphate. Despite the lack of increase in serum phosphate, FGF-23, which can downregulate NPT2b expression and thereby limit gut absorption, was increased in the CKD rats (p=0.02).

Conclusions: These findings demonstrate that despite the phosphate retaining CKD phenotype characterized by elevated levels of FGF-23, absorption of phosphate may be increased. However, the data indicate that the increased absorption of phosphate is not associated with increased serum levels suggesting that a maladaptive deposition of phosphate into the tissues may be enhanced at an early stage of the disease.

Funding: Pharmaceutical Company Support - OPKO Health Renal, Government Support - Non-U.S.

FR-PO430

Warfarin Induced Aorta Calcification and LV Dysfunction in a Remnant Kidney Mouse Model Ying-Ying Chen,[1,2] Szu-Yuan Li,[1,2] Der-Cherng Tarng.[1,2] *[1]Div of Nephrology, Dept of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [2]Faculty of Medicine, National Yang-Ming Univ, Taipei, Taiwan.*

Background: Some studies have suggested that warfarin is beneficial for stroke prevention in dialysis patients with atrial fibrillation. However, consistent with the clinical uncertainty regarding the benefits of stroke prevention with warfarin, the most recent KDIGO recommendations neither supported nor rejected the use of warfarin therapy in dialysis patients. Moreover, warfarin, a vitamin K antagonist, can inhibit γ-carboxylation of glutamic acid residues in matrix Gla protein (MGP) in arterial smooth muscle cells, and is thus involved in the process of arterial calcification.

Methods: Therefore, this study aims to explore the promoting effects of warfarin in aortic calcification *in-vivo* experiments. After 5/6 nephrectomy, B6 mice were divided into four groups: 5/6 NX, warfarin (3 mg/kg/day), Vitamin D3 (100 mg/kg/day), and Vitamin D3 plus warfarin groups (n=10~12 each group) for 4 months.

Results: In the fourth month, only the Vit-D plus warfarin group had micro-CT detectable vascular calcifications and 3-D reconstruction of the micro-CT images illustrated a pipe-like diffused calcified aorta. Histological staining confirmed the severe vascular calcification in the Vit-D plus warfarin group, but no remarkable aorta calcification in the other groups. 5/6 nephrectomy mice had a moderate left ventricular (LV) dysfunction as compared to sham operation group, however, Vit-D plus warfarin is able to induce significant LV dysfunction in remnant kidney mice [figure1].

Conclusions: Warfarin potentially promotes vascular calcification and exaggerates LV dysfunction in CKD mice.

FR-PO431

Analysis of Acidity and Phosphorus Levels in Commonly Consumed Sodas Uma D. Alappan,[1] Raj Alappan.[2] *[1]Science, Brookstone School, Columbus, GA; [2]Nephrology, Renal Associates LLC, Columbus, GA.*

Background: Increased phosphorus intake in CKD patients causes significant morbidity. The purpose of this study is to determine the prevalence of contents in commonly consumed sodas, specifically their pH, titratable acidity, phosphorus (P), phosphoric acid (H_3PO_4) and phosphate levels (PO_4), as this information is not readily available.

Methods: The Metrohm 799 GPT Titrino and the Optima 8x00 Series of ICP-EOS Spectrometers were used to estimate the pH, titratable acidity, and phosphorus content of various sodas respectively. The PO_4 and H_3PO_4 contents were calculated using proportions and the phosphorus number. A survey, inquiring soda preference, weekly intake, possible soda health effects, and consumer demographics, was administered to several high school students and faculty members, as well as to random participants in Columbus, GA.

Results: 124 participants were surveyed (n=124): Male-42 (33.9%), Female-82 (66.1%). The mean age was 31.46 years. 103 (83.1%) consumed sodas and 21 (16.9%) did not. The most frequently consumed sodas were Coca-Cola products, 62 (60.2%), Sprite products, 12 (11.7%), and Dr. Pepper products, 10 (9.7%). The weekly soda can and phosphorus consumption in those aged ≤18 years, 19-49, and 50+, was 5.6, 5.4, and 4.1 cans; and 713.0 mg/L, 748.1 mg/L, and 514.3 mg/L respectively.

	Study Mean	Overall Mean			Overall Mean			Dark Sodas		
		Dark	Light	<0.05 S	Regular	Diet	<0.05 S	Regular	Diet	<0.05 S
pH	2.90	2.75	3.05	0.61NS	2.70	3.10	0.01NS	2.48	3.02	0.01 S
T Acid	16.94	10.59	23.28	0.00 S	16.48	17.40	0.97 NS	11.41	9.77	0.17 NS
Phosphorus	70.13	125.50	6.9	0.00 S	79.00	60.00	0.59 NS	146.00	105.00	0.04 S
H_3PO_4	212.00	397.49	0.00	0.00 S	231.21	190.03	0.54 NS	462.42	332.56	0.04 S
Phosphate	205.24	384.83	0.00		223.85	183.98	0.54 NS	447.70	321.97	0.04 S
Measurements: Phosphorous, H3PO4 & PO4 in mg/L										

Conclusions: The dark regular sodas had the most acidity and phosphorus content, while the light diet sodas had the least. Coca-Cola, the commonest soda consumed, had one of the highest phosphorus contents of all sodas, suggesting high phosphorus intake. Diet Coca-Cola had the least amount of phosphorus of all dark sodas suggesting low phosphorus intake. Fanta, though a light soda, had phosphorus due to a sodium hexametaphosphate preservative. Diet 7-Up had no phosphorus and was the least acidic soda. As the survey results showed, soda intake generally decreases as one gets older.

FR-PO432

Adherence to Bone-Mineral Metabolism Guidelines among Kidney Transplant Candidates Meteb M. AlBugami,[1,2] Fahad Eid Alotaibe,[1,2] Khalid Bel'eed-Akkari.[1] *[1]Multi-Organ Transplant Center, King Fahad Specialist Hospital, Dammam, Saudi Arabia; [2]Dept of Internal Medicine, College of Medicine, Univ of Dammam, Dammam, Saudi Arabia.*

Background: Chronic kidney disease-mineral and bone disorders (CKD-MBD) is linked to cardiovascular disease (CVD). Since CVD is the most common cause of death among kidney transplant (KT) recipients, it would be prudent to optimize CKD-MBD among KT candidates. This study aimed to measure the extent to which KT candidates complied with the National Saudi Bone Biochemistry Guidelines.

Methods: All potential KT recipients evaluated at the Kidney and Pancreas Transplant Department at King Fahad Specialist Hospital-Dammam, between January 2009 and December 2013 were reviewed. Data were collected from electronic database. Blood samples were obtained during patients' initial visit to the pre-transplant evaluation clinic. For patients on hemodialysis, pre-dialysis samples were obtained.

Results: A total of 1014 candidates were evaluated, with a mean age of 43±13.7 years, and 589 (58%) of the subjects were males. Data were missing in 132 (13%) of the cases. Mean phosphorus level was 1.70±0.55 mmol/L, and 44% achieved the guideline target. Mean calcium level was 2.27±0.24 mmol/l, and 42% achieved the guideline target. Median PTH 439.2 pg/ml (IQR 243.4 – 806.75), and 19% only achieved the guideline target. 395 subjects (45%) had a PTH level >500 pg/ml, while 126 subjects (14%) had PTH less than 150 pg/ml. Only 2.3% of patients met all the 3 standards for corrected calcium, phosphorus and PTH.

Conclusions: Substantial proportion of KT candidates referred for pre-transplant evaluation failed to meet the Saudi national guideline targets of CKD-MBD. This should prompt us to place greater and more rigorous emphasis on adherence measures to the guidelines in order to improve the cardiovascular risk of transplant recipients.

FR-PO433

Acid-Base and Phosphorus Homeostasis in Chronic Kidney Disease: Results from the Chronic Renal Insufficiency Cohort (CRIC) Study Pascale Khairallah,[1] Tamara Isakova,[2] John R. Asplin,[3] L. Lee Hamm,[4] Mirela A. Dobre,[5] Mahboob Rahman,[5] Kumar Sharma,[6] Mary B. Leonard,[7] Edgar R. Miller,[8] Bernard G. Jaar,[8] Carolyn S. Brecklin,[9] Wei Yang,[10] Harold I. Feldman,[10] Myles S. Wolf,[2] Julia J. Scialla.[1] *[1]Duke Univ; [2]Northwestern Univ; [3]Litholink Corporation; [4]Tulane Univ; [5]Case Western Reserve Univ; [6]Univ of California San Diego; [7]Stanford Univ; [8]Johns Hopkins Univ; [9]Univ of Illinois; [10]Univ of Pennsylvania.*

Background: Kidneys excrete acid either as ammonium or as titratable acids (TA) that use phosphate as a buffer. In CKD, impaired ammoniagenesis promotes metabolic acidosis. I*n vitro,* acidosis stimulates phosphaturic hormones, parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23), possibly to increase buffer for TA. These *in vitro* findings have not been confirmed in humans.

Methods: In 980 CRIC participants with CKD (eGFR 44±14 ml/min/1.73m^2), we measured net acid excretion (NAE) in 24h urine, potential renal acid load (PRAL) by food questionnaire, and serum bicarbonate. Using adjusted linear and log-linear regression, we modeled associations between acid parameters and 24h urine phosphorus, serum phosphorus, FGF23, and PTH.

Results: 24h urine phosphorus was higher at higher NAE, higher PRAL, and lower bicarbonate (all p-trends<0.05). Serum phosphorus was higher with higher NAE and lower bicarbonate (both p-trends=0.001). Higher NAE or PRAL were not associated with FGF23 or PTH. PTH, but not FGF23 (p=0.2), was 26% higher (P<0.001) when serum bicarbonate was < vs. ≥22meq/L. Results were similar if stratified by eGFR categories, or if adjusted for iothalamate GFR, energy intake, urine urea nitrogen, or dietary phosphorus, where available.

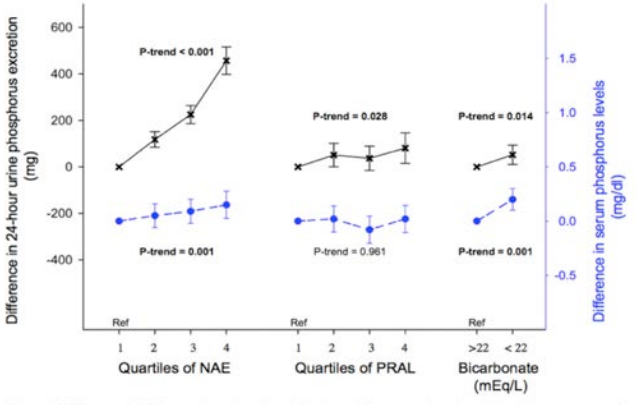


Figure 1. Difference in 24-hour urine phosphorus levels and in serum phosphorus levels by measures of acid loading.
Crosses represent the difference between 24-hour urine phosphorus levels and the reference category. Dots represent the difference between serum phosphorus levels and the reference category. Models are adjusted for age, sex, race, eGFR, 24-hour urine albumin, 24-hour urine creatinine, comorbidities, BMI, and diuretic use. The bars are 95% confidence intervals.

Conclusions: Acid loading may augment phosphaturia in CKD to maintain NAE. Mechanisms may include higher serum phosphorus and not primary increase in FGF23 or PTH. Effect of acid load on phosphorus homeostasis must be tested in trials.

Funding: NIDDK Support

FR-PO434

Novel Non-Absorbed, Calcium-Free, Highly Effective Phosphate Binders Derived from Gum Arabic J. Ruth Wu-Wong, Yung-Wu Chen, Jerry Wessale. *Vidasym, Chicago, IL.*

Background: Inadequate control of serum phosphate in chronic kidney disease can lead to pathologies of clinical importance. Effectiveness of on-market phosphate binders is limited by safety concerns and low compliance (high pill size/burden and gastrointestinal (GI) discomfort).

Methods: We have developed a series of novel, highly effective phosphate binders from metal ions and gum Arabic (GA), ingredients commonly used in food.

Results: In vitro studies show that VS-505 (Fe-GA), VS-605 (Mg-GA) and VS-705 (Zn-GA) have high densities (e.g. 1.95 g/cm^3 for VS-505 vs. 1.27 g/cm^3 for sevelamer) and low swell volumes when exposed to phosphate buffer or simulated gastric fluid (e.g. 0.4 cm^3/0.1g for V-505 vs. 4 cm^3/0.1g for sevelamer). VS-505, VS-605 and VS-705 bind phosphate within a wide physiologically relevant range of pH, enabling them to bind phosphate along much of the GI tract. In normal SD rats, increasing the dietary phosphate led to an increase in serum phosphate, which was prevented in rats treated with VS-505, VS-605, or VS-705 (0.2 - 5% in food). Urinary phosphate increased by >10-fold in the vehicle-treated group; VS-505, VS-605 or VS-705 reduced urinary phosphate, and increased fecal phosphate in dose-dependent manners. No significant changes were observed for serum calcium, while urinary calcium increased from 1.4 ± 0.2 mg/24 hr before dosing to 9.2 ± 1.0 mg/24 hr in the 5% sevelamer group, and to 3.6 ± 0.5, 3.0 ± 0.7, and 5.2 ± 1.6 mg/24 hr in the 5% VS-505, VS-605, and VS-705 groups, respectively. In SD rats made uremic by 5/6 nephrectomy (5/6 NX rats) on a high phosphate diet, urinary and serum phosphate levels were significantly elevated in untreated rats, which were reduced by VS-505 and sevelamer. VS-505 increased fecal phosphate levels in a dose-dependent manner. More aortic calcification was observed in 5/6 NX rats treated with 5% sevelamer, but not in rats treated with VS-505.

Conclusions: These results demonstrate that these novel metal ion-GA phosphate binders effectively control phosphate imbalance in rats by removing phosphate from the GI via the feces. VS-505 is currently being evaluated in a clinical trial in Australia involving hemodialysis patients (ClinicalTrials.gov #: NCT02469467).

Funding: Other NIH Support - NIAMS, Pharmaceutical Company Support - Vidasym

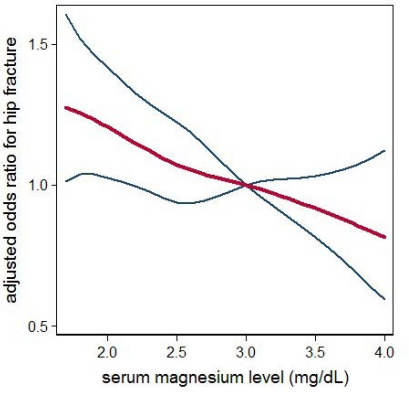
FR-PO435

Lower Serum Magnesium Levels Are Associated with an Increased Risk of Hip Fracture in Hemodialysis Patients - A Nationwide Cohort Study Yusuke Sakaguchi, Takayuki Hamano, Atsushi Wada, Masanori Abe, Eiichiro Kanda, Shunsuke Goto, Takeshi Hasegawa, Junichi Hoshino, Kan Kikuchi, Mariko Miyazaki, Shigeru Nakai, Ikuto Masakane. *Committee of Renal Data Registry, Japanese Society for Dialysis Therapy, Tokyo, Japan.*

Background: Hip fracture is common in dialysis patients, which leads to an increased mortality and substantial economic burden. Although magnesium is an essential mineral for normal bone metabolism, little is known about the relationship between magnesium and a risk of fractures. Here we analyzed the association of serum magnesium levels (sMg) with an incidence of hip fracture in hemodialysis patients.

Methods: We utilized a database of the Japanese Society for Dialysis Therapy-Renal Data Registry that covers nearly all dialysis patients in Japan. We included hemodialysis patients without a prior history of hip fracture. Patients living in a nursing home or aged more than 90 years old were excluded. sMg were divided into quartiles (Q1 to Q4). Primary outcome was the incidence of new hip fractures during 2-year follow-up period.

Results: Among a total of 113,086 hemodialysis patients enrolled in the analysis, a new hip fracture occurred in 2,267 patients (2.00%). The incidence rate of hip fracture decreased as sMg quartiles increased (2.61%, 2.06%, 1.74%, and 1.47% in Q1 to Q4, respectively; p <0.001 for trend) (range of sMg (mg/dL): Q1, -2.3; Q2, 2.4-2.6; Q3, 2.7-2.8, Q4, 2.9-). After an extensive adjustment for demographic and clinically relevant factors including parathyroid hormone levels, patients in Q1 had a 26% higher odds for hip fracture than those in Q4 (p = 0.004). A population attributable fraction analysis indicated that 15.4% (95%CI: 5.6-24.2; p = 0.003) of all hip fractures in this population could have been prevented by increasing sMg to the range of Q4.



Conclusions: Low sMg may be an unignorable risk factor for hip fracture among hemodialysis patients.

FR-PO436

Hypophosphatemia following Hepatectomy and Pancreatectomy: Role of the Phosphaturic Factor NAMPT Jian Zheng, Ilya Glezerman, Eran Sadot, Anjuli J. Mcneil, Vinod Balachandran, Peter Kingham, Michael D'Angelica, Peter Allen, Ronald Dematteo, William Jarnagin, Edgar A. Jaimes. *Memorial Sloan Kettering Cancer Center, New York.*

Background: Clinically significant postoperative hypophosphatemia is common and is associated with a lower risk of liver failure after hepatectomy but a higher rate of complications after pancreatectomy. The mechanisms involved are unclear but presence of

phosphaturia suggests a role for phosphaturic factors such as parathyroid hormone (PTH) or nicotinamide phosphoribosyltransferase (NAMPT). This study evaluates the role PTH and NAMPT have on development of postoperative hypophosphatemia.

Methods: Patients who underwent open liver (n=48) and pancreas (n=30) resections were enrolled, and those deemed unresectable were used as controls (n=21). Serum and urinary phosphate and creatinine were measured preoperatively and on postoperative day (POD)1-7. Serum PTH (immunoassay) and NAMPT (ELISA) were analyzed preoperatively and on POD2.

Results: Phosphate levels significantly decreased from POD1 to POD2 in all 3 groups preceded by an increase in phosphaturia. NAMPT levels were significantly increased from preoperative day to POD2 in resected patients but not in controls. PTH levels did not change in any of the groups.

	Phosphate (mg/dL)		Urine Phos/Cr		NAMPT (ng/mL)		PTH (pg/mL)	
	POD1	POD2	Preop	POD1	Preop	POD2	Preop	POD2
Hepatectomy	3.9 (3.5-4.5)	1.8* (1.5-2.2)	0.4 (0.2-0.6)	1.4** (1-1.7)	1.5 (0.7-2.9)	2.6# (1.5-5)	57 (43-83)	57 (36-76)
Pancreatectomy	4.1 (3.3-4.7)	2.0* (1.6-2.3)	0.4 (0.3-0.5)	1.7** (1.5-2.1)	0.9 (0.5-1.5)	2.5** (1.3-4.2)	47 (39-62)	48 (39-78)
Control	3.0 (2.7-3.8)	1.9* (1.6-2.2)	0.4 (0.3-0.5)	1.2** (1-1.5)	1.3 (0.6-2.9)	1.5 (1.1-3.2)	53 (37-76)	62 (39-93)

Results presented as median (IQR) and compared using Wilcoxon signed rank test (*P<0.001 vs POD1; **P<0.001 vs Preop; #P<0.05 vs Preop).

Conclusions: This study demonstrates that postoperative hypophosphatemia is linked to increased NAMPT. Downregulation of renal sodium-phosphorus co-transporters by NAMPT may be mediating these effects. The mechanisms that upregulate NAMPT and its role on the disparate clinical outcomes in these 2 groups warrant further investigation.

FR-PO437

The Serum Calcification Propensity of Hemodialysis Patients Is Strongly Modified by Serum Phosphate, Magnesium and Bicarbonate

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Background: Serum calcification propensity as measured by the T50 test (Pasch, JASN 2012, 23:1744) has been validated as a strong predictor of morbidity and mortality in hemodialysis patients. We sought to identify biochemical determinants of the T50 test in a prospective cohort of hemodialysis patients.

Methods: 15 chronic hemodialysis patients (12 m, 3 f; mean age 73 ± 14 y.) treated with high volume hemodiafiltration (3 x 4 hr/wk) were studied. T50 was determined monthly over a period of 9 months (n = 122) together with midweek pre-dialysis plasma concentrations of Na+, K+, Calcium, ionized Calcium (ioCa++), Magnesium, Phosphate, Bicarbonate and Albumin. These biochemical parameters were evaluated as continuous predictors of T50 in a generalized regression model.

Results: The mean T50 value in this cohort was 260 minutes (± 72 [SD]; Range 105 - 460). In the linear model, only Magnesium, Bicarbonate, Phosphate and ioCa++ were significant predictors of T50. When the Patient ID was added to the model as a categorical predictor , ioCa++ became nonsignificant:

Parameter		Mean±SD	Beta	B	95% CI for B	p
Na^+	mmol/l	137.6 ± 3.0	-0.026	-0.6	[-4.4 3.1]	0.73
K^+	mmol/l	4.4 ± 0.5	0.013	1.9	[-16.5 20.3]	0.84
Ca^{++}	mmol/l	2.09 ± 0.14	0.456	216.1	[-383.8 816.0]	0.48
Ca^{++}_{corr}	mmol/l	2.30 ± 0.17	-0.360	-148.0	[-743.6 447.6]	0.62
$Ca^{++}_{ionized}$	mmol/l	1.10 ± 0.09	-0.136	-102.1	[-276.3 72.0]	0.25
Mg^{++}	mmol/l	0.94 ± 0.13	0.291	164.2	[83.5 244.9]	0.00012
Bicarbonate	mmol/l	25.3 ± 2.1	0.220	7.6	[2.7 12.5]	0.0027
Phosphate	mmol/l	1.49 ± 0.39	-0.246	-46.2	[-68.3 -24.1]	0.00008
Albumin	g/l	31.4 ± 3.0	0.180	5.2	[-9.9 20.3]	0.49

While Phosphate shortened the T50 precipitation time (promoting calcification), Magnesium and Bicarbonate prolonged T50, inhibiting calcification. Predicted T50 changes when altering these parameters from the minimum to the maximum measured in the study were: Bicarbonate [19 -> 30 mmol/l]: + 84 min. Magnesium [0.61 -> 1.21 mmol/l]: + 99 min. Phosphate [0.72 -> 2.66]: -90 min.

Conclusions: Several easily measurable and modifiable parameters correlate significantly with T50. Serum Phosphate appears to promote, serum Magnesium and Bicarbonate to inhibit calcification propensity. Although the present data may be influenced by individual patients' comorbidities, they constitute a basis for prospectively studying the determinants of T50.

Funding: Pharmaceutical Company Support - Calciscon AG, Bern, Switzerland

FR-PO438

Hepatectomy-Induced Hypophosphatemia: Mechanisms Underlying Downregulation of Phosphate Transport in the Small Intestine

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Background: Several recent clinical studies have explored the potential value of nicotinamide (NAM) in phosphate (Pi) control in dialysis patients. However, the mechanism underlying Pi regulation by NAM has not been fully elucidated. Marked hypophosphatemia is common after major hepatic resection; however, the pathophysiological mechanism remains unknown. Recently, we reported that hepatectomy-induced hypophosphatemia is due to abnormal NAM metabolism. Partial hepatectomy (PH) rats exhibited markedly decreased levels of intestinal NaPi-IIb and Na^+-dependent Pi transport activity. In the present study, we evaluated the roles of nicotinamide phosphoribosyletransferase (Nampt; catalyzes the first rate-limiting step in converting NAM to NAD) on Pi handling in the small intestine.

Methods: We used a PH rat model and $Nampt^{+/-}$ mice to investigate the molecular basis of Pi handling in the small intestine through Nampt activity.

Results: PH rats showed hypophosphatemia and hyperphosphaturia. PH rats also exhibited elevation of plasma NAM concentration and reduction of intestinal Na/Pi transport and NaPi-IIb protein. In addition, cellular Nampt protein and NAD levels were significantly increased in the small intestine. In in vitro analyses using NaPi-IIb-expressing human intestinal epithelial cells (Caco2-BBe), treatment with Nampt and NAM led to a marked decrease in the NaPi-IIb protein levels compared with treatment with NAM alone. In contrast, FK866 (a specific inhibitor to Nampt)-treated mice (C57BL/6J) showed elevated intestinal Na/Pi uptake and NaPi-IIb expression. In PH mice with FK866, urinary Pi excretion was significantly decreased. In addition, $Nampt^{+/-}$ mice showed elevation of intestinal NaPi-IIb and upregulation of intestinal Pi transport activity. These observations suggest that cellular Nampt activation is an important factor for the downregulation of intestinal NaPi-IIb levels.

Conclusions: In PH animals, the downregulation of intestinal Pi transport may be due to Nampt activation. These data suggest that intestinal Nampt is a novel potential tool for treating hyperphosphatemia in CKD patients.

Funding: Government Support - Non-U.S.

FR-PO439

Effect of Antibiotic Treatment on Oxalobacter Formigenes (OF) Colonization and Urinary Oxalate Excretion

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Background: *OF*, a member of the human colonic microbiota, plays a major role in net colonic oxalate absorption and secretion. We now report *OF* colonization rates in a healthy population, the stability of colonization, the effects of antibiotic treatment, and *OF* colonization on urinary oxalate (Uox) excretion.

Methods: We followed 65 healthy subjects tested for *Helicobacter pylori* (HP) gastric colonization. Those who were HP+ were treated with antibiotics (amoxicillin and clarithromycin) for 2 weeks (w) for HP eradication. Using species-specific PCR, we tested for *OF* colonization. Urine samples 3h after a standard meal were analyzed for Uox, factored for creatinine (Cr). Both assessments were done at baseline and at follow-up.

Results: Of the 65 subjects (M/F: 23/42; mean age 25.2 + 5.7y) tested for *OF*, 28 (43%) were positive at baseline. Of 7 *OF*+ subjects at baseline who received antibiotics for HP elimination, 6 became *OF*- at 12 w. Of these, 2 reverted to *OF*+ at week 24, and 4 remained *OF*- at follow up (Mean 22.5 + 4.2w). For 42 untreated subjects, 18 of whom were *OF*+ at baseline, 16 (89%) remained *OF*+ at follow-up (Mean 23.0 +4.2w). Of 24 OF- subjects, only 3 (12%) were *OF*+ at follow up (Mean 20.2+ 6.8w; p=0.001 compared to initial *OF*+). We assessed Uox/Cr in 137 samples from 46 subjects with no antibiotic exposure. *OF*-positivitywas associated with 14% lower Uox/Cr compared with *OF*-negativity (17.0 ±0.0 vs 19.4 ± 0.1mg/g, p=0.04). From 5 antibiotic treated *OF*+ subjects, we assessed Uox/Cr at baseline and 24 weeks following antibiotic exposure and found no significant increase in urine oxalate (16.6 +6.7 vs 18.5 +12.6 mg/g, p=0.5).

Conclusions: We conclude that detectable *OF*-positivity remains stable over several months, but that antibiotic exposure suppresses or eliminates colonization in most subjects. In the absence of a high oxalate content meal, antibiotic exposure did not significantly increase urinary oxalate. Differences in urinary oxalate levels with respect to *OF* status are consistent with protective effects related to calcium oxalate kidney stones.

Funding: Private Foundation Support

FR-PO440

Prevalence of LMWP and CLCN5 Mutations in Proteinuric Cohorts

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Background: Dent disease type 1 (DD1) is a rare X-linked disorder caused by *CLCN5* mutations. Some patients present only with nephrotic range proteinuria leading to erroneous diagnosis and immunosuppressive treatment of focal segmental glomerulosclerosis (FSGS).

Methods: *CLCN5* mutations were screened using specimens from the following cohorts: Chronic Kidney Disease in Children (CKiD; n=112); Multicenter FSGS-Clinical

Trial (FSGS-CT) and Novel therapies for resistant FSGS Trial (FONT) (n=126). The CKiD cohort included patients with FSGS; chronic GN, familial nephritis, congenital nephrotic syndrome, reflux nephropathy, and medullary cystic disease. Urinary α_1-microglobulin (α_1M), albumin (A) and total protein (TP) were assessed in urine from CKiD subjects (n=104); DD1 patients (n=14) and DD1 carriers (DC; n=8).

Results: No *CLCN5* mutations were detected in the screened cohorts. TP/Cr was similar in CKiD and DD1 but lower in DC (P<0.001). A/CR was significantly less elevated in DD1 while α_1M/Cr was higher in DD1 (P<0.001) compared to CKiD cohort. α_1M/TP was similar in DD1 and DC and higher than CKiD (P<0.001), while the A/TP was lower in DD1 but similar in DC and CKiD (P=0.01).

Conclusions: *CLCN5* mutations are rare. Even though TP excretion did not differ, the protein pattern of DD1 could be distinguished from CKiD subjects due to a significantly higher α_1M/Cr and significantly lower A/TP. Although the TP excretion of DC was low, DC had proportionately more α_1M, mirroring DD1. Assessment of urinary LMWP such as α_1M is a good screen for DD1 among male patients with proteinuria. A/TP could also be considered as a simple screening test for Dent since it is readily available and provided good differentiation from other pediatric proteinuric renal diseases.

	TP/Cr (mg/g)	A/Cr (mg/g)	α_1M/Cr (mg/g)	A/TP	α_1M/TP
CKiD	2275 (3917)	1410 (2427)	34 (40)	44 (27)%	5 (5)%
DD1	1589 (837)	247 (120)	195 (91)	18 (8)%	14 (3)%
DC	80 (112)	15 (19)	5 (4)	58 (99)%	11 (6)%

Funding: NIDDK Support, Other NIH Support - NCATS

FR-PO441

Drosophila Model Indicates Role of OSR1/SPAK Signaling in Calcium Oxalate Kidney Stone Formation via Regulation of Slc26a6 Mediated Cl-/Oxalate(2-) Exchange

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Background: Kidney stones (12% male; 6% female) are costly, painful and lead to renal injury. Calcium oxalate (CaOx) are >70% of stones. Oxalate is a metabolic end-product eliminated via the kidneys and intestine. Oxalate-secretion is mediated by Slc26a6 (dPrestin in flies), a Cl^-/$Oxalate^{2-}$ exchanger. Voltage clamping of oocytes expressing dPrestin/Slc26a6 ±OSR1/SPAK indicate that these kinases ↑ Cl^-/$Oxalate^{2-}$ exchange activity. Therefore, we hypothesized that the incidence of CaOx crystals (kidney stones) could be reduced if oxalate excretion was reduced from the Malpighian tubule (MT) and shifted to the gut by reducing oxalate transport via inhibition of OSR1 in MTs.

Methods: Using a *Drosophila* model of CaOx kidney stones [Hirata, PMID22993075], we made tissue specific knockdowns (MT or gut) of *Drosophila* OSR1 (CG7693, *frayed*). Flies were used to investigate the signaling regulation of oxalate secretion , CaOx crystallization, in MTs.

Results: *Ex vivo* CaOx crystallization experiments show a 34% reduction in average crystal count when OSR1 knockdown (via RNAi: 51% knockdown) flies are compared to wildtype. *In vivo* feeding experiments with MT-specific OSR1 knockdown also reduces the crystal count recapitulating *ex vivo* experiments. Preliminary *in vivo* data for gut-specific OSR1 knockdown trends toward increasing average crystal counts.

Conclusions: From this data, we conclude that regulation of oxalate transport via OSR1 signaling is sufficient to reduce average CaOx crystal count. This data also suggests that manipulation of OSR1/SPAK signaling may be a new and important target for the development of therapeutics for the prevention of CaOx kidney stones.

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FR-PO442

Development of Biomimetic Randall's Plaque Using Decellularized Porcine Kidneys

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Background: Idiopathic calcium oxalate stones are commonly found attached to Randall's plaques (RP), calcium phosphate (CaP) deposits in the renal papillae. Plaques originate as concentrically laminated apatitic spherules, and grow by mineralization of interstitial collagen fibrils and vesicles. We hypothesize that such distinct CaP morphologies form by non-classical crystallization mechanisms, the polymer-induced liquid-precursor (PILP) process, in which highly acidic macromolecules sequester ion clusters to induce liquid–liquid phase separation of hydrated, ion-enriched nano-droplets. PILP droplets have fluidic character and thus coalesce into mineral coatings, or infiltrate into the interior of collagen fibrils, producing mineral products which differ from the classical crystallization mechanism.

Methods: Decellularized porcine kidneys were mineralized using a 4.5 mM calcium and 2.1 mM phosphate solution (pH 7.4). The PILP process was induced by addition of 50 μg/ml of poly-L aspartic-acid or osteopontin. At specific intervals, specimens were removed, and characterized using SEM and TEM.

Results: Analysis of the tissues shows features that resemble native Randall's plaques, such as concentrically laminated spherules and collagen fibrils with intrafibrillar mineral, and with differing morphologies in the basement membrane versus interstitium. In contrast, the classical crystallization produced large apatitic spherulites, which is a very different morphology, but one which is also found in some stones.

Conclusions: CaP deposition on decellularized kidney substrate appears to produce biomimetic plaque similar to the native RP with respect to calcification of collagen and production of apatitic spherules. Both classical and non-classical mechanisms might be at play. We are planning to study overgrowth of biomimetic plaques with CaOx in a rat model of hyperoxaluria.

Funding: NIDDK Support

FR-PO443

Nephron-Segment Specific Urinary Extracellular Vesicles Containing MCP-1 and NGAL Associate with Randall's Plaque

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Background: Randall's plaques (RP) are an important precursor of urinary stone formation. However, RP cannot be noninvasively detected. This study investigated urinary EVs as biomarkers of RP.

Methods: RP were assessed by videotape and quantitative image processing in 47 consecutive idiopathic calcium oxalate stone formers undergoing stone removal. Cell-free urinary EVs from different nephron segments carrying protein biomarkers of renal fibrosis and injury were quantified in biobanked urine by digital flow cytometry and fluorophore conjugated antibodies.

Results: Urine from 40 low RP (<5% papillary surface RP) and 7 high RP (≥5% surface RP) patients demonstrated that EVs from multiple nephron segments expressing MCP-1 and NGAL were significantly greater in the low RP group. Osteopontin-positive EVs did not differ.

Nephron Location	Marker 1	Marker 2	Low RP (n=40)	High RP (n=7)	P-value
Proximal	**MCP-1**	**URAT1**	**21.0 (4.8,119.3)**	**3.7 (1.6,9.8)**	**0.05**
Thin Loop	MCP-1	AQ1	11.6 (1.2,46.2)	1.07 (0.6,1.9)	**0.03**
Thick Loop	**MCP-1**	**UROM**	**27.7 (6.5,72.3)**	**5.64 (3.4,29.7)**	**0.05**
Distal	**MCP-1**	**SLC12A3**	**13.1 (2.3,64.5)**	**1.1 (0.5,5.6)**	**0.02**
Collecting Duct	**MCP-1**	**AQ2**	**57.1 (15.2,317.5)**	**1.45 (1.05,24.2)**	**0.003**
Renal Pelvis	**MCP-1**	**CK-19**	**9.5 (2.7,71.8)**	**1.6 (1.2,4.8)**	**0.02**
Proximal	**NGAL**	**URAT1**	**22.4 (5.2,145.0)**	**3.9 (1.6,15.7)**	**0.02**
Thin Loop	NGAL	AQ1	8.1 (2.1,112.0)	2.9 (0.8,14.8)	0.22
Thick Loop	**NGAL**	**UROM**	**201.2 (52.2,689.9)**	**42.1 (20.6,47.6)**	**0.01**
Distal	NGAL	SLC12A3	22.2 (2.7,70.9)	7.0 (1.4,71.6)	0.52
Collecting Duct	**NGAL**	**AQ2**	**118.1 (22.1,421.5)**	**6.3 (1.3,40.0)**	**0.02**
Renal Pelvis	NGAL	CK-19	18.8 (2.0, 63.4)	5.24 (2.9,12.9)	0.50

Conclusions: Urinary EV biomarkers consistent with renal injury (NGAL) and inflammation (MCP-1) were increased in CaOx stone patients with low amounts of RP. These findings may reflect pathologic cellular events that drive stone formation in low RP patients, or perhaps protective responses that limit RP development in this group. Urinary EVs are a promising source of biomarkers for pathogenic events in USD.

Funding: NIDDK Support

FR-PO444

Contribution of Tubular Segments to a Calcium Cortico-Papillary Gradient

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Background: Renal papillary calcification and Randall's plaque formation are largely dependent on urinary calcium excretion. Mathematical models of renal calcium transport predict a cortico-papillary calcium gradient in physiological conditions, but this has not been ascertained in vivo. We aimed at deciphering this gradient and at identifying which part of the nephron may contribute to its formation.

Methods: Small pieces representative of cortex, medulla and papilla were isolated from mouse kidneys, and calcium, phosphate and sodium content were measured, as well as urinary parameters. In experiment 1, C57Bl/6J mouse kidneys were harvested. In experiment 2, mice were previously injected with 1 dose of furosemide (20mg/KgBW), hydrochlorothiazide (25mg/KgBW) or vehicle. In experiment 3, mice were injected daily for 7 days with furosemide (20mg/KgBW). In experiment 4, kidneys of mice with disrupted distal calcium reabsorption (Pax8-LC1-Cre $NCX1^{fl/fl}$ mice) and WT controls were harvested. And in experiment 5, mice were fed daily dihydrotachysterol (1.5mg/kg food) for 7 days.

Results: Results showed higher calcium and sodium content in the papilla of mouse kidney compared to cortex or medulla, but lower phosphate. Acute furosemide treatment disrupted the sodium cortico-papillary gradient, but not the calcium one. Hydrochlorothiazide and disruption of renal NCX1 had no effect on any gradient. Chronic dihydrotachysterol treatment led to hypercalcemia and hypercalciuria, and blunted the calcium cortico-papillary gradient; sodium gradient was unchanged.

Conclusions: We conclude that a calcium cortico-papillary gradient exists in the mouse kidney, with higher calcium concentration in the papilla, while phosphate had a mirror gradient. Distal transepithelial calcium transport does not contribute to the calcium gradient, while thick ascending limb calcium transport may modulate it. Further studies exploring TAL and proximal tubule contribution are warranted.

FR-PO445

Urine Proteomic Analysis Confirms a Higher Degree of Bone Disease in Medullary Sponge Kidney against Nephrolithiasis Alessandra Dalla Gassa,[1] Antonia Fabris,[1] Giovanni Candiano,[2] Maurizio Bruschi,[2] Gianluigi Zaza,[1] Simona Granata,[1] Giovanni Gambaro,[3] Antonio Lupo.[1] *[1]Renal Unit, Univ of Verona, Italy; [2]Laboratory on Pathophysiology of Uremia, Istituto G. Gaslini, Genoa, Italy; [3]Div of Nephrology and Dialysis, Catholic Univ Hospital, Rome, Italy.*

Background: Medullary sponge kidney (MSK) is a genetic malformative disease characterized by cystic formations of the distal ducts, hypercalciuria, nephrocalcinosis and kidney stones. Metabolic bone disease is very frequent in MSK and idiopathic calcium nephrolithiasis (NL). We hypothesized that pathways involved in bone remodeling are more active in MSK than NL.

Methods: In 11 MSK vs 12 NL pts were studied: urine proteins (UP), 24-h urine biochemistry and bone mineral content (BMC). All pts had normal PTH and eGFR>60 ml/min/1.73m^2. UP were analyzed with STRING version 10.0. UP were selected if ≥2-fold difference in spectral counts and ≤0,05 p-value.

Results: Prevalence of F/M was 64/36% and 67/33% in MSK and NL,respectively. Mean age±ds was 53±19 yr in MSK and 54±15 yr in NL. 24-h urine(U) and BMC in MSK and NL pts, mean and (SD) are shown: U.Ca(mg/d)317(107)222(107)p=0,045, U.Na(mEq/d)204.36(49)139(47)p=0.004, Z-ScoreLS -1.4(0.5)-0.76(0.8)p=0.038, T-ScoreLS -1,65(0.45)-1.04(0.67)p=0.018. MSK differed from NL pts in 328 PP. 100 UP were overexpressed in MSK, 228 downexpressed. Some UP are involved in annotated pathways:PPP2CB,LAMB2,HSP90AA1 in PI3K-Akt pathway,CDH15,PTPRM in cell adhesion molecules. PI3K-Akt pathway induces osteoclastogenesis by activating GSK3β/NFAtc1 cascade and also promotes osteoblast differentiation. PI3Kγ was responsible for decreased BMC in a murine model. Down regulated UP: CDH1,CDH3,CDH6,CDH11,CDH13 are involved in Ca-dependent trans-dimerization of cadherin, cadherin/catenin complex; IQGAP1,CD14,RAC3,GNG12 in regulation of actin. Cadherins are linked to the actin cytoskeleton via binding to catenins in adherens junctions; this complex is essential for osteoblast differentiation and osteogenesis by controlling Wnt and PI3K/Akt signaling.

Conclusions: All these findings show that osteogenetic pathways are more active in MSK then in NL confirming their role in nephrocalcinosis and in the more severe BMC observed in MSK.

FR-PO446

Reduced BMD and Bone Quality in GHS Rats Is due to Changes in Osteoblast and Osteoclast Activity Nancy S. Krieger,[1] Hongwei Wang,[2] Murray J. Favus,[2] David A. Bushinsky.[1] *[1]Medicine, Univ of Rochester, Rochester, NY; [2]Medicine, Univ of Chicago, Chicago, IL.*

Background: To study idiopathic hypercalciuria (IH) we developed an animal model, genetic hypercalciuric stone-forming (GHS) rats, whose pathophysiology parallels that in human IH. All GHS rats form kidney stones and have decreased bone mineral density (BMD) and bone quality compared to the founder Sprague-Dawley (SD) rats. To understand this bone defect we have begun to characterize differences in osteoblast and osteoclast activity in the GHS compared to SD.

Methods: Multipotential bone marrow stromal cells (BMSC) and bone marrow monocytes (BMC) were isolated from femurs of GHS and SD rats and cultured to optimize differentiation into osteoblasts or osteoclasts. After treatment of BMSC ±60 ng/mL BMP2 for 7 to 21d, RNA was collected and specific osteoblast gene expression assessed by real time PCR. BMC were treated with 50 ng/ml M-CSF and 100 ng/ml RANKL and resultant osteoclasts were stained for TRAP or cultured in a pit formation assay to assess resorptive activity.

Results: There was increased expression of RANKL and decreased basal expression of RUNX2, alkaline phosphatase (AP), osterix (ostx) and osteocalcin (OC) in GHS compared to SD osteoblasts. Treatment of SD osteoblasts with BMP2 for 7d increased relative expression of RUNX2 (1.8x), AP (3.2x), ostx (3.0x) and OC (2.5x) compared to baseline (P<0.05) while GHS osteoblast gene expressions were unchanged. After 21d of BMP2, SD osteoblasts increased in vitro mineralization to 3.2% of the total area stained with Alizarin Red compared to baseline while only 1% of GHS surfaces were stained (P<0.001). There was increased osteoclastogenesis and increased resorption pit formation in GHS BMC compared to SD BMC cultures (23±7 vs 5±2% of surface resorbed, P<0.05).

Conclusions: These results suggest alterations in baseline characteristics of osteoblasts and osteoclasts in GHS rats that lead to decreased BMD and bone quality, perhaps due to their known increase in vitamin D receptors. Better understanding of the role of GHS bone cells in decreased BMD and bone quality may provide new strategies to prevent or reverse the low bone mass and increased fracture risk found in patients with IH.

Funding: NIDDK Support

FR-PO447

FGF23 and Its Association with Prevalent Hypertension in Calcium Kidney Stone Formers Jie Tang,[1] Michel Chonchol.[2] *[1]Medicine, Univ Medicine, Brown Univ, Providence, RI; [2]Medicine, Univ of Colorado, Aurora, CO.*

Background: As a key regulator of body calcium and phosphorus hemostasis, fibroblast growth factor 23 (FGF23) might be important for the development of hypertension in kidney stone disease.

Methods: We conducted a cross-sectional study of 91 prevalent calcium kidney stone formers, and examined the associations of C-terminal FGF23, vitamin D, intact parathyroid hormone (iPTH) and prevalent hypertension.

Results: The mean serum 25-hydroxy vitamin D [25(OH)D], 1,25-dihydroxy vitamin D [1,25$(OH)_2$D] and plasma FGF23 values were 24 ng/ml, 62 pg/ml, and 223 RU/ml, respectively. These values were different compared to those in published age matched healthy controls (33 ng/ml, 41 pg/ml and 25 RU/ml respectively). Serum iPTH, calcium, and phosphorus values were similar between the two groups, mean MDRD eGFR were both >60 ml/min. Among stone formers, plasma FGF23 had a significant reverse association with eGFR (p=0.04) after adjustment for age, gender, race, body mass index (BMI), history of diabetes, hypertension and dyslipidemia. But it failed to demonstrate significant associations with serum 25(OH)D, 1,25$(OH)_2$D, or iPTH measurements, nor was it associated with urinary fractional excretion of phosphorus. Plasma FGF23 had a strong association with prevalent hypertension from univariate analysis (p=0.002), and the association remained significant (p=0.02) after adjustment for age, gender, race, history of diabetes, dyslipidemia, BMI, eGFR, serum 25D and 1,25D. In 37 stone formers with hypertension, mean plasma FGF23 level was 340 RU/ml, compared to 123 RU/ml in 54 stone formers without hypertension, p<0.0001. In subjects with eGFR≤90 ml/min, FGF23 was a strong predictor of prevalent hypertension, odds ratio (OR) 1.013, 95% confidence interval (CI) 1.004-1.023, p=0.006. However, in subjects with eGFR>90 ml/min, FGF23 was not predictive of prevalent hypertension, OR 0.997, 95% CI 0.985-1.010, p=0.654.

Conclusions: Calcium kidney stone formers have higher plasma FGF23 levels. Plasma FGF23 is strongly predictive of prevalent hypertension among stone formers with GFR≤90 ml/min. Future studies are needed to examine the potential causal relationship and the underlying mechanism.

Funding: Clinical Revenue Support

FR-PO448

Cystine Capacity (CysCap) and Risk of Kidney Stone Events in Cystinuria Frank Modersitzki,[1] Lisa M. Harvey,[2] Dean G. Assimos,[2] David S. Goldfarb.[1,3] *[1]Medicine, NYU Langone Medical Center, New York, NY; [2]Urology, Univ of Alambama, Birmingham, AL; [3]Nephrology, New York Harbor VAMC, New York, NY.*

Background: CysCap values may be important for the treatment of cystinuria and prevention of kidney stones. We studied if greater CysCap values, consistent with undersaturated urine, were associated with fewer stone events.

Methods: Patients were divided into Cyscap+ and Cyscap- groups based on baseline 24h urine. Undersaturated urine takes up cystine from preformed cystine crystals, giving a positive (CysCap+) value; supersaturated urine gives up cystine to added cystine crystals, giving a negative (CysCap-) value. 49 patients from 2 Rare Kidney Stone Consortium sites were enrolled and followed prospectively. Stone activity was defined as radiologic new stone or stone growth, urologic stone removal or spontaneous stone passage.

Results: Participants without 24h urine and information about stone activity were excluded. 26 participants remained: 13 male, 13 female. Mean age was 45y. A total of 17 (10F/7M) participants had a positive CysCap (mean 120 mg/L) and 9 (3F/6M) participants had a negative CysCap (mean -167 mg/L) at baseline. Table shows urine results: CysCap+ had more urine, higher pH, less cystine. Follow-up for the total group was 20 months. We identified 34 stone events that affected a total of 17 participants: fewer events were counted among those with CysCap+ values. Specific data (%) included development of a new stone: CysCap+ 29 vs. CysCap- 44; stone growth: CysCap+ 41 vs. CysCap- 22; urological stone removal: CysCap+ 29 vs. CysCap- 44, stone passage without intervention: CysCap+ 18 vs. CysCap- 33. 9 participants (CysCap+ 41 vs. CysCap- 22), had no events during observation period. Comparing CysCap groups for all stone events, CysCap+ was significantly better (p=.039, McNemar test).

*:P<0.05, Mann-Whitney	CysCap+ mean (SD)	CysCap- mean (SD)
Urine volume*	4279 (1463)	2582 (1045)
24h Cystine excretion*	820 (303)	1128 (223)
pH*	7.24 (0.29)	6.90 (0.34)

Conclusions: CysCap+ values prospectively led to fewer stone events. Achieving better, more positive CysCap values requires greater urine volume, higher urine pH and lower 24h cystine.

Funding: NIDDK Support, Other NIH Support - NCATS

FR-PO449

Selective Protein Enrichment in Calcium Oxalate Stone Matrix Jeffrey Wesson.[1,2] *[1]Medicine/Nephrology, Dept of Veterans Affairs Medical Center, Milwaukee, WI; [2]Medicine/Nephrology, Medical College of Wisconsin, Milwaukee, WI.*

Background: Urine proteins are thought to control calcium oxalate (CaOx) stone formation, but over 1,000 proteins have been reported in stone matrix yielding little insight into their relative importance. We hypothesize that proteins critical to stone formation will be present at increased abundance in stone matrix compared to their urinary abundance, so quantitative proteomic data were acquired and compared for both stone former urine and CaOx stone matrix proteins.

Methods: Urinary proteins were isolated by ultradiafiltration (>10kDa membrane) from random urine samples from 25 CaOx stone forming patients. CaOx stone matrix proteins were isolated from 8 CaOx stone samples (>90% CaOx content) by dissolution in EDTA/SDS solution followed by ultradiafiltration. Proteomic analyses were performed on each

sample independently at the Medical College of Wisconsin Innovation Center using label-free spectral counting mass spectrometry methods. Only proteins with 2 or more peptide matches at >85% confidence were included. Keratin and redundant proteins were removed.

Results: Only 5 proteins were prominently enriched in matrix, accounting for >34% of matrix protein mass, but only 3.4% of urine protein mass. Many highly abundant urinary proteins like albumin and uromodulin were present in stone matrix, but at reduced relative abundance compared to urine. Furthermore, isoelectric point distribution analysis showed that the stone matrix proteome was highly enriched in both highly anionic (pI<5, like osteopontin) and highly cationic (pI>10, like histone) proteins; most of which are normally found in intracellular or nuclear compartments.

Conclusions: Relatively few proteins were enriched and appeared to be critically important to CaOx stone formation, while most highly abundant urine proteins found in matrix were likely included non-selectively. The presence of both highly anionic and highly cationic proteins which aggregate at low concentrations suggests that protein aggregation may trigger CaOx stone formation, while a cell injury process is implicated by the presence of many intracellular proteins. These observations present a new paradigm for CaOx stone research.

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FR-PO450

Risk of Urolithiasis in Anorexia Nervosa: A Population-Based Cohort Study Using the Health Improvement Network

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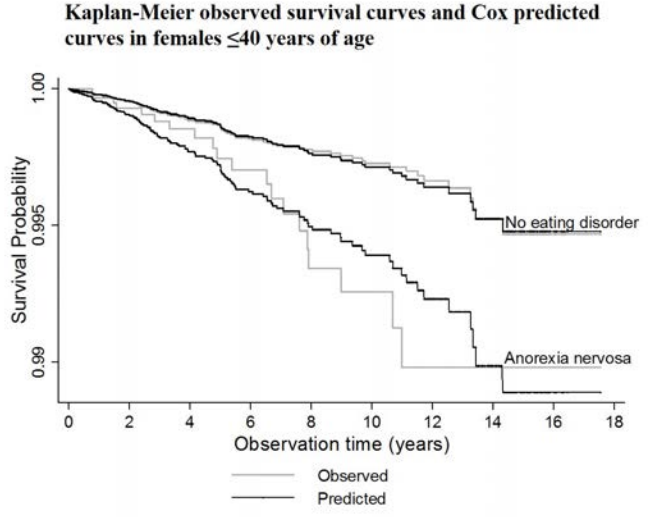
Background: Case reports and uncontrolled studies suggest urolithiasis is a complication of anorexia nervosa (AN). The objective of this large cohort study was to determine if AN is associated with a higher risk of urolithiasis.

Methods: We performed a population-based retrospective cohort study using The Health Improvement Network. The median calendar year for the start of the observation period was 2005. We identified 9302 females <60 years of age with AN and 92,959 randomly selected age- and practice-matched females. Multivariate Cox regression was used to estimate the hazard ratio (HR) for incident urolithiasis.

Results: Median age at start of observation was 29.8 years. 23 participants with AN (0.25%) developed incident urolithiasis compared to 154 unexposed participants (0.17%) over a median observation period of 3.6 years and 3.8 years, respectively. The risk of urolithiasis in AN varied significantly with age (interaction p=0.03). AN was associated with a higher risk of incident urolithiasis in females ≤40 years of age (HR 2.13, 95% CI: 1.32-3.45; p=0.002), but not in females over 40 years.



For participants with AN, the median time from diagnosis of AN to incident urolithiasis was 12.4 years. The distribution of diagnosis codes for urolithiasis differed significantly between the groups (p=0.04), with a higher proportion of codes for uric acid urolithiasis in the AN (16.2%) versus unexposed group (5.0%).

Conclusions: Although urolithiasis is relatively uncommon in women under 40 years of age, we demonstrated a more than two-fold greater risk in those with AN. There were more uric acid based calculi than expected among patients with AN compared to females without eating disorders. We speculate that these were likely ammonium urate stones and related to laxative abuse.

Funding: NIDDK Support, Other NIH Support - UL1 RR024134

FR-PO451

Vitamin D Intake and the Risk of Incident Kidney Stones

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Background: Higher vitamin D intake has been purported to increase the risk of calcium-containing kidney stones, but longitudinal prospective studies of sufficient size on the association between intake of vitamin D and risk of incident kidney stones are lacking.

Methods: We performed a prospective analysis of 193,551 participants of the Health Professionals Follow-up Study (HPFS), Nurses' Health Study (NHS) I and II. Participants were divided into categories of total (<100, 100-199, 200-399, 400-599, 600-999, ≥1,000 IU/day) and supplemental (none, <400, 400-599, 600-999, ≥1,000 IU/day) vitamin D intake with updating over time. During a follow-up of 3,316,846 person-years, there were 6,576 incident kidney stone events. Cox proportional hazards regression models were adjusted for age, BMI, comorbidities, use of medications and intake of other nutrients.

Results: After multivariate adjustment, there was no statistically significant association between total intake of vitamin D and risk of incident stones in HPFS (HR for ≥1,000 vs <100 IU/day 1.08, 95% CI 0.80, 1.47, p-value for trend = 0.92) and NHS I (HR 0.99, 95% CI 0.73, 1.35, p-value for trend = 0.70), whereas there was a suggestion of higher risk in NHS II (HR 1.18, 95% CI 0.94, 1.48, p-value for trend = 0.02). Similar results were found for supplemental vitamin D intake. No interaction was found for total calcium intake.

Conclusions: Total vitamin D intake in typical amounts was not statistically associated with risk of kidney stone formation, though higher risk with substantially higher doses than those studied here cannot be excluded.

Funding: NIDDK Support, Other NIH Support - DK094910, DK91417, CA186107, CA176726 and CA167552

FR-PO452

Proton Pump Inhibitors, Histamine Receptor-2 Blockers and the Risk of Incident Kidney Stones

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Background: Proton pump inhibitors (PPI) and histamine receptor-2 (H_2) blockers are commonly used drugs for the treatment of heartburn, gastroesophageal reflux and peptic ulcer. Although PPI and H2 blockers potentially affect urinary excretions of lithogenic factors such as calcium and magnesium, the association between use of these medications and kidney stone formation has never been explored.

Methods: 187,330 participants of the Health Professionals Follow-up Study (HPFS), Nurses' Health Study (NHS) I and II provided data about chronic PPI use. During a cumulative follow-up of 1,903,725 person-years, there were 3,245 incident symptomatic kidney stone events. Cox proportional hazards regression models were adjusted for age, race, BMI, physical activity, smoking status, comorbidities, use of medications and intake of nutrients. Multivariable linear regression models were used to analyze cross-sectional associations between PPI and H2 blocker use and 24-h urinary excretions in a subgroup of 6,520 participants.

Results: After multivariable adjustment, use of PPI was associated with higher risk of incident kidney stones (HR 1.12, 95% CI 1.02, 1.24, p-value = 0.02). HRs were similar independent of duration of use and after restricting the analysis to incident PPI users and attenuated somewhat employing a 2-year time-lag analysis. Similar results were found for use of H_2 blockers (HR 1.13, 95% CI 1.02, 1.24, p-value = 0.02). Use of PPI was associated with lower urinary excretion of calcium (-18 mg/24h, p-value <0.001), oxalate (-1 mg/24h, p-value = 0.02), citrate (-48 mg/24h, p-value <0.001), and magnesium (-10 mg/24h, p-value <0.001), whereas urine pH was not significantly different.

Conclusions: Use of PPI and H_2 blockers is associated with a small increase in risk of incident kidney stones.

Funding: NIDDK Support, Other NIH Support - DK094910, DK91417, CA186107, CA176726 and CA167552

FR-PO453

Intake of Zinc and Other Trace Elements and the Risk of Incident Kidney Stones

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Background: Recent cross-sectional [Tang J, et al. Am J Nephrol 2012] as well as pre-clinical [Chi T, et al. PLoS One 2015] studies suggest that zinc may play a role in the development of kidney stones. Other studies also hinted at the role of other trace elements such as copper and manganese [Słojewski M, et al. Adv Clin Exp Med 2012]. Longitudinal prospective studies on the risk associated with intake of zinc and other trace metals, however, have not been published.

Methods: We performed a prospective analysis of 193,551 participants of the Health Professionals Follow-up Study (HPFS), Nurses' Health Study (NHS) I and II. During a follow-up of 3,316,846 person-years, there were 6,576 incident symptomatic kidney stone events. Cox proportional hazards regression models were adjusted for age, BMI, comorbidities, use of medications and intake of other nutrients.

Results: After multivariate adjustment, there was no statistically significant association between risk of stones and intake of zinc (HR for highest compared with lowest quintile 0.94, 95% CI 0.77, 1.14, p-value for trend = 0.54), iron (HR 1.04, 95% CI 0.90, 1.20, p-value for trend = 0.48), and copper (HR 1.07, 95% CI 0.97, 1.18, p-value for trend = 0.26). Dietary manganese was associated with lower risk (HR 0.80, 95% CI 0.72, 0.90, p-value for trend < 0.001). For total manganese intake (supplemental plus dietary) the HR was 0.90 (HR 0.90, (95% CI 0.80, 1.02, p-value for trend = 0.06).

Conclusions: Intake of zinc, iron and copper is not associated with risk of kidney stone formation, whereas higher intakes of manganese may be associated with lower risk.

Funding: NIDDK Support, Other NIH Support - DK094910, DK91417, CA186107, CA176726 and CA167552

FR-PO454

Urinary Stones Associates with Arterial Stiffness and Peripheral Artery Disease: A Population Based Study of 10,000 Chinese Participants

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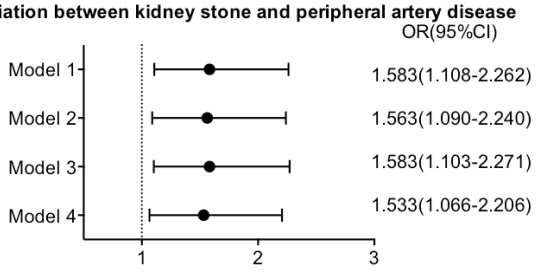
Background: Previous studies investigating cardiovascular health in the context of urinary stone disease (USD) have focused on coronary artery disease and stroke. The risk associated between USD and arterial stiffness and peripheral arterial disease (PAD) has not been examined in detail.

Methods: We performed a cross-sectional study of 10,547 participants in rural China. All underwent renal ultrasound examination to detect USD, brachial-ankle pulse wave velocity (baPWV) measurement to estimate arterial stiffness, and ankle-brachial index examination to detect PAD (defined as ankle-brachial index ≤ 0.9 for at least one side of body). Univariate and multivariate regression analyses were performed to investigate associations between USD and PAD.

Results: Mean age was 55.0±10.4 years and 47.2% were males. Among participants, 5.6% had USD, mean baPWV was 1551 ± 317 cm/s, and 4.0% had PAD. Compared to subjects without USD, subjects with USD had higher baPWV (1548±316 vs. 1610±326 cm/s, p<0.01) and higher prevalence of PAD (3.9 vs. 6.0%, p=0.01). The prevalence of USD was increased with higher quartiles of baPWV (Q4 vs. Q1: 7.0% vs. 4.3%, p<0.01). In univariate and multivariable analyses, USD was associated with increased risk of PAD.



Model 1:bivariable analysis
Model 2:adjusted for age, gender, smoke
Model 3:adjusted for age, gender, smoke, MetS
Model 4:adjusted for age, gender, smoke, BMI,DM, HTN, LDL, hsCRP, CKD

MetS metabolic syndrome; BMI body mass index; DM diabetes mellitus; HTN hypertension; LDL low-density cholesterol, hsCRP hypersensitive C reactive protein; CKD chronic kidney disease.

Conclusions: USD associates with increased risk of arterial stiffness and PAD in a rural Chinese population.

Funding: Government Support - Non-U.S.

FR-PO455

Trends in the Incidence of Symptomatic Kidney Stones among the Residents of Olmsted County, MN from 1984 to 2012

Wonngarm Kittanamongkolchai,[1] Lisa E. Vaughan,[2] Felicity T. Enders,[2] John C. Lieske,[1] Andrew D. Rule.[1] *[1]Nephrology and Hypertesnion, Mayo Clinic, Rochester, MN; [2]Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN.*

Background: Studies have reported increased kidney stone incidence but lack of validation and granular detail regarding stone types.

Methods: Adult incident symptomatic stone formers in Olmsted County, MN from 1984 to 2012 were identified and validated by manual chart review. Available data included stone composition, body mass index (BMI), and medications associated with kidney stones (calcium, vitamin C, vitamin D and Topamax). The incidence rates of kidney stones per 100,000 person-years(100K py) were estimated based on the Olmsted County population census. Poisson regression models were used to calculate incidence rate ratios.

Results: There were 3,338 validated incident symptomatic stone formers (age 45±15 years, 60% male and 89% white). The overall incidence from 1984 to 2012 increased dramatically in women (39 to 118/100K py; p<0.001) and modestly in men (128 to 141/100K py; p=0.01). The increase in incidence was significant in women across all age groups (18-39, 40-59, 60+), with the highest increase observed in those 40-59 y. In men, the increase was significant only in the 18-39 age group. For each stone composition, the relative change in the incidence rate per 5-years was 1.00 (95% CI 0.99-1.01, p=0.9) for calcium oxalate monohydrate, 0.85 (95% CI 0.82-0.88, p<0.001) for calcium oxalate dihydrate, 1.10 (95% CI 1.07-1.13, p<0.001) for hydroxyapatite, 0.90 (95% CI 0.86-0.95, p<0.001) for uric acid and 1.15 (95% CI: 1.14-1.16; p<0.001) for stones of unknown composition. Calcium use, vitamin D use, Topamax use and BMI among incident stone formers increased over the time period, with Vitamin D use rising at a higher rate in women than in men (p=0.01 for interaction).

Conclusions: The incidence of symptomatic kidney stones increased dramatically in women, and more modestly in men over the last 3 decades. The increase was most evident in younger age groups. Obesity and medications associated with kidney stones may be contributing to the increased incidence of kidney stone disease in the general population.

FR-PO456

Risk of Adverse Birth Outcomes Associated with Maternal Hospitalization for Nephrolithiasis during Pregnancy

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Background: Nephrolithiasis is the most common non-obstetric cause of hospitalization among pregnant women, but current information on birth outcomes after hospitalization for nephrolithiasis during pregnancy is conflicting. We sought to determine if maternal nephrolithiasis hospitalization is associated with an increased risk of premature delivery, induction of labor, Cesarean delivery, low birth weight (< 2500 grams), or delivery of a small for gestational age (SGA) infant.

Methods: We conducted a population-based retrospective cohort study in Washington State using a statewide hospitalization discharge database linked to singleton birth certificate data for 2004-2013. Women hospitalized for nephrolithiasis during pregnancy were identified by ICD-9 codes (n=2083) and compared with a cohort of women without documented hospitalization for nephrolithiasis (n=8600) frequency matched 1:4 on birth year. Birth outcomes were assessed using birth certificate data and birth hospitalization ICD-9 codes. Data were analyzed using stratified analysis with Mantel-Haenszel adjustment. Subgroup analyses focused on the influence of trimester of nephrolithiasis hospitalization and procedural intervention.

Results: Nephrolithiasis hospitalization during pregnancy was associated with an increased risk for premature delivery (RR = 1.6, 95% CI 1.3-1.8) and induction of labor (RR = 1.5, 95%CI 1.3-1.6), but a decreased risk of SGA delivery (RR = 0.82, 95% CI 0.70-0.96) compared to women without hospitalization for nephrolithiasis during pregnancy. Nephrolithiasis hospitalization was not associated with low birth weight, nor was it associated with Cesarean delivery after adjusting for prior Cesarean delivery. Trimester of nephrolithiasis hospitalization and procedural intervention did not significantly alter these associations.

Conclusions: This study adds to existing evidence that maternal hospitalization for nephrolithiasis during pregnancy is associated with an increased risk of subsequent preterm delivery and induction of labor. Women hospitalized for nephrolithiasis during pregnancy should be counseled about these risks.

FR-PO457

Low Bone Density and Bisphosphonates and the Association with Kidney Stones and 24-Hour Urine Calcium Excretion

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Background: Previous studies have demonstrated lower bone density in patients with kidney stones (KS). No studies have evaluated KS risk in participants with low bone density. Small studies with short follow-up reported lower 24-hour urine calcium excretion in bisphosphonate users. We examined history of low bone density and bisphosphonate use and the association with incident KS and the association with 24-hour calcium excretion.

Methods: To evaluate the association between history of low bone density and bisphosphonate use and risk of incident KS, we conducted a prospective analysis of 98,078 women participants in the Nurses' Health Study II. We used Cox proportional hazards models to adjust for age, BMI, thiazide use, bisphosphonate use, fluid intake, and dietary factors. We also conducted a cross-sectional analysis of 2567 participants using multivariate linear regression to compare 24-hour urinary calcium excretion between participants with and without a history of low bone density and with and without bisphosphonate use.

Results: The multivariate adjusted relative risk (MVRR) of an incident KS for participants with history of low bone density compared with participants without was 1.35 (95% CI 1.13-1.61 p=0.001). The MVRR for an incident KS for bisphosphonate use was 0.90 (95% CI 0.68-1.20, p=0.47). In the cross-sectional analysis of 24-hour urine calcium excretion, the multivariate adjusted mean difference in 24-hour calcium was 13 mg/day (95% CI 4 to 22, p=0.003) higher for participants with history of low bone density. The multivariate adjusted mean difference in 24-hour calcium was 9 mg/day (95% CI -9 to 27, p=0.31) higher for participants on bisphosphonates. Results of the urine calcium analysis were similar in an analysis limited to participants with history of low bone density.

Conclusions: History of low bone density is an independent risk factor for incident KS and higher 24-hr urine calcium excretion. Bisphosphonates use was not independently associated with KS or 24-hr urine calcium excretion.

Funding: NIDDK Support

FR-PO458

Hyponatremia Is Associated with Increased Kidney Stones in a Large U.S. Health System Population Naoto Tominaga,[1] Stephen Fernandez,[2] Mihriye Mete,[2] Nawar M. Shara,[2] Joseph G. Verbalis.[1] *[1]Div of Endocrinology and Metabolism, Georgetown Univ Medical Center; [2]Dept of Biostatistics and Bioinformatics, MedStar Health Research Inst.*

Background: Kidney stones (KS) impose a large and growing public health burden. Up to 80% of KS is predominately composed of calcium oxalate (CaOx), and urinary oxalate is a major risk factor for CaOx KS formation. Previous studies have shown that hyponatremia (HN) is associated with increased risk for osteoporosis and bone fractures, which are also known to be associated with KS. It is therefore reasonable to hypothesize that HN may be related to the occurrence of KS.

Methods: To assess the potential relationship between HN and KS, we designed a matched case-control study using the electronic health records of the MedStar Health system with more than 3.2 million unique patient records accumulated as of March 2016. Data were extracted via the Explorys tool on clinical factors including labs, medications, and ICD-9 and/or ICD-10 diagnoses for patients with KS (case) and those without KS (control).

Results: Cases (n=21,232) and controls (n=21,232) were matched with a 1:1 ratio on age, sex, race and the duration of encounter window (mean age 44.3 years, 48.4% female, 61.1% Caucasian and mean follow-up days 1345 days). Case and control exposures for each of the HN variables were defined by serum [Na+] laboratory measurements reported within the encounter windows, and divided into 4 categories: prior HN, chronic HN, recent HN, and chronic and recent HN. Bivariate analyses using conditional logistic regression models confirmed increased risk of KS among patients with risk factors such as hypertension (OR=1.77, 95% CI 1.68-1.86). In addition, the risk of KS increased in all of HN categories: prior HN OR, 1.10 [95% CI, 1.03-1.18]; chronic HN OR, 1.43 [95% CI, 1.17-1.75]; recent HN OR, 2.30 [95% CI, 2.02-2.62]; chronic and recent HN OR, 5.18 [95% CI, 3.08-8.70]. Preliminary results of multivariate analyses adjusted for potential confounders confirm independent associations between HN and KS.

Conclusions: These results therefore support the hypothesis that HN is a significant and clinically important risk factor for KS in both inpatients and outpatients in the U.S.

FR-PO459

Racial Differences in Metabolic Risk Factors for Nephrolithiasis Anna L. Zisman, Kristin J. Bergsland, Fredric L. Coe, Elaine M. Worcester. *Dept of Medicine/Nephrology, Univ of Chicago, Chicago, IL.*

Background: Over the past 2 decades, the prevalence of kidney stones in black non-Hispanics has increased by 150%, yet there is a paucity of literature regarding African American (AA) stone-formers. Small studies suggest certain urinary parameters do not significantly differ between racial groups. We asked whether AA stone formers have metabolic differences when compared to Caucasians (C).

Methods: AA patients with known stone composition undergoing metabolic stone evaluation (at least 3, 24 hr urine specimens per patient and paired serum studies) were retrospectively identified by self-reported race from 1995-2016 and sex and age-matched 1:2 to C patients with known stone composition from the same year. Metabolic data were compared between groups by stone type and race using ANOVA. Majority stone type was defined as >50%.

Results: Fifty-five AA (calcium (Ca) oxalate (CaOx) =29, Ca phosphate (CaP)=9, Uric=17) and 125 matched C (CaOx=81, CaP=27, Uric=17) had complete pre-treatment metabolic data. Despite similar supersaturation (SS) for their stone type, AA had significantly lower 24-hr urine volumes than C (1.5 vs. 1.9L, p<0.001). Likewise, 24-hr calcium (Ca) levels, were significantly lower than those for C (135 vs. 225 mg , p<0.0001). Urine oxalate and citrate did not differ by ANOVA. Significant differences between races persisted in volume when analyzed by stone type. CaOx AA had lower urine Ca than C, but oxalate and citrate excretions did not differ. Urine Ca did not differ for CaP stone formers by race. For uric acid stones, AA had lower uric acid excretion and uric acid SS and higher urine pH. Serum phosphate also differed by race, and was significantly lower in AA males than in C males (3.1 vs. 3.45, p<0.001); women did not differ.

Conclusions: While physical chemistry dictates that SS drives risk for stone formation, we demonstrate racial differences in determinants of SS. Previously unknown and significant metabolic differences exist between AA and Caucasian stone formers.

Funding: NIDDK Support, Clinical Revenue Support

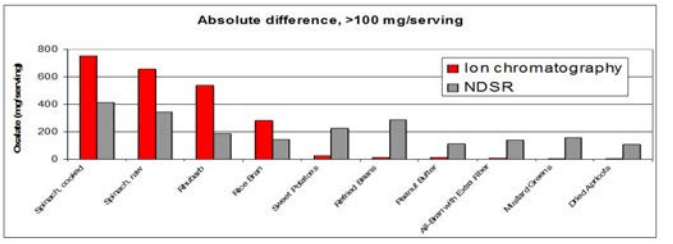
FR-PO460

Variation in Reported Oxalate Content: Implications for Research and Patient Counseling Roy A. Jhagroo,[2] Kristina L. Penniston.[1] *[1]Urology, UW Madison, Madison, WI; [2]Medicine - Nephrology, UW Madison, Madison, WI.*

Background: Hyperoxaluria is a major risk factor for calcium oxalate stone disease. For designing research studies that limit or attempt to standardize the oxalate intake of subjects, and also for the appropriate counseling of patients in the clinic setting, accurate food oxalate values are needed, and agreement on the use of standard food oxalate values is needed.

Methods: Analyze patients' reported oxalate content from 4-day weighed diet records, using standard nutrient analysis software, and compare values with the "gold standard" database for food oxalate. Assess the congruence of food oxalate data of two reputable and - Nutrition commonly-used databases. *Databases:* - Oxalate data from ion chromatography - Maintained by the Harvard School of Public Health; Nutrition Data System Research (NDSR) database, containing oxalate values for 17,820 food items > Nutrition Coordinating Center, University of Minnesota *Diet records:* Consenting patients (n= 78) completing 4-day weighed diet records. Diet records were entered for oxalate intake from the 2 databases used for this study.

Results: The mean daily oxalate intake of patients differs significantly (P = 0.0012) depending on data used. Mean daily oxalate intake assessed by NDSR and by ion chromatography, respectively, was: 108 vs 76 mg for women (min-max, 61-226 vs 40-111 mg) 163 vs 96 mg for men (min-max, 78-324 vs 63-138 mg). Particularly on high oxalate foods differences were seen.



Conclusions: Differences in databases are both clinically- and statistically-relevant(p = 0.0012). Compared to ion chromatographic analyses - the "gold standard" for oxalate analysis of foods - our study showed nearly 40% of patients incorrectly classified above or below a 90 mg oxalate/d cutoff when conventional, research-quality nutrient analysis software was used.

FR-PO461

Oxalate Stones: What Is Most Important for Oxalate Diet Modification? Roy A. Jhagroo,[1] Kristina L. Penniston.[2] *[1]Medicine - Nephrology, UW Madison, Madison, WI; [2]Urology, UW Madison, Madison, WI.*

Background: Dietary oxalate may account for up to 50% of urinary oxalate. In patients with hyperoxaluria, reducing dietary oxalate absorption is a key aspect of medical management. This requires knowledge not only of food oxalate values but also of oxalate bioavailability. Unfortunately, vast differences in the reported oxalate content of foods abound in the literature and media. Moreover, oxalate food values are typically provided in mg/100 g and not as mg per portions actually consumed.

Methods: Calcium stone formers undergoing medical management were trained to provide 4-day weighed diet records. Evaluable records from 83 subjects (M:F, 50:28; 58 and 54 years, respectively) were analyzed using the Nutrition Data System for Research nutrient analysis software (University of Minnesota). Mean oxalate intakes were calculated, and the contribution of oxalate by individual foods were assessed. Discrete food groups were defined; relative contributions to total oxalate intake were calculated.

Results: Mean oxalate intake was 161 ± 16 and 238 ± 22 SE mg/d for women and men, respectively (p = 0.02 for difference); however, when adjusted for kcal intake there was no difference. The calculated calcium:oxalate intake ratio (mg/mg), a surrogate measure for oxalate bioavailability, was 6.5 for both women and men. Nearly two-thirds of oxalate consumed was from 5 specific food groups. These were: nuts, seeds, & nut butters (26.2%); spinach (11.9%); breads, flours, & baked goods (11.0%); ready-to-eat cereals (6.7%); and potatoes & foods made from potatoes (6.3%). Other groups typically included in oxalate-reducing recommendations, e.g., tea, spices, non-spinach leafy vegetables, and fruits, collectively accounted for <10% of total oxalate consumed. The calculated calcium:oxalate ratios were lowest (p < 0.005) for 3 of these groups.

Conclusions: In our efforts to enhance patients' compliance with and the overall efficacy of medical management, dietary recommendations to reduce oxalate intake should focus on the fewest food groups possible, based not only on oxalate concentration per typical portions consumed but also on anticipated oxalate bioavailability.

FR-PO462

Effects of Citrate and Phosphate on Renal Outcomes in Primary Hyperoxaluria Dawn S. Milliner, Lisa E. Vaughan, Felicity T. Enders, Julie B. Olson, Barbara M. Seide, David J. Sas, John C. Lieske, The Rare Kidney Stone Consortium. *Mayo Clinic, Rochester, MN.*

Background: Both citrate (cit) and phosphate (P) inhibit urinary calcium oxalate crystallization and are used for treatment in primary hyperoxaluria (PH). To better understand long term treatment effects, we assessed incidence of NC and ESRD among patients (pts) in the Rare Kidney Stone Consortium (RKSC) PH Registry.

Methods: Pts with PH type 1, 2 or 3 enrolled in the RKSC PH Registry who had presented prior to ESRD were included. Nested cox proportional hazards models were used to assess main and interactive effects of P and cit separately on incident NC and ESRD.

Results: Among 290 pts, 212 had PH1, 40 PH2 and 38 PH3. Median follow-up was 8.8 yrs for ESRD and 6.6 yrs for NC. After adjusting for age at PH diagnosis, prior stone events, and pyridoxine use, neither P nor cit were strong predictors of outcomes when considered as main effects. When an interaction term was added, P use alone had a protective effect on ESRD (HR 0.57, 95% CI: 0.29-1.09), while P and cit use combined was associated with increased risk for incident ESRD (HR 2.37, 95% CI: 0.83-6.81), though results did not achieve statistical significance. Cit alone trended towards increased risk of NC (HR 1.94, 95% CI: 0.98-3.83). Results were consistent in PH1 alone.

			Model 1		Model 2	
Outcome	**Events**	**Medication***	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
ESRD	79	P	0.76 (0.45-1.28)	0.30	0.57 (0.29-1.09)	0.088
		Cit	1.33 (0.70-2.23)	0.27	0.95 (0.47-1.89)	0.88
		P*Cit	--	--	2.37 (0.83-6.81)	0.11
NC	57	P	0.80 (0.43-1.48)	0.48	1.09 (0.54-2.20)	0.81
		Cit	1.45 (0.80-2.61)	0.22	1.94 (0.98-3.83)	0.056
		P*Cit	--	--	0.32 (0.07-1.44)	0.14

Model 1 Adjusted for age at baseline, stone events, and pyridoxine
Model 2 Adjusted as Model 1 with added interaction term for P and cit
*Medications and stone events as time dependent covariates

Conclusions: There is evidence that after adjusting for stone events, P may have a protective effect on renal survival, while cit may increase risk of NC. However, the strength of these associations as well as effect of dose and duration of these medications remains to be established.

Funding: NIDDK Support, Other NIH Support - NCATS, Private Foundation Support

FR-PO463

Changes of Urinary Risk Profile after Short Dietary Intervention in Swiss Kidney Stone Formers Harald Seeger,[1] Pietro Manuel Ferraro,[2] Robert J. Unwin,[3] Carsten A. Wagner,[4] Nilufar Mohebbi.[1] *[1]Div of Nephrology, Univ Hospital Zurich, Zurich, Switzerland; [2]Fondazione Policlinico Univ A. Gemelli, Catholic Univ of the Sacred Heart, Rome, Italy; [3]Centre for Nephrology, Univ College London, London, United Kingdom; [4]Inst of Physiology, Univ of Zurich, Zurich, Switzerland.*

Background: Calcium-containing kidney stones are frequent with high recurrence rates. Several studies have described a significant relation between nephrolithiasis and adverse renal outcomes, including ESRD. While hypercalciuria is a well-known risk factor, restricted intake of animal protein and salt, combined with normal calcium, has been shown to be more effective in stone prevention compared with a low-calcium diet. Notably, the average salt intake in Switzerland is twice as high as the WHO recommends, while surprisingly the intake of milk and dairy products is low. Thus, we wanted to test the effect of a low salt and low calcium diet on the urinary risk profile of recurrent calcium oxalate (CaOx) kidney stone formers (rKSF).

Methods: Standardized metabolic evaluation was performed, including a first 24-hour urine collection (normal diet), followed by a second collection after a 7-day low salt and low calcium diet.

Results: Out of 215 patients, 169 patients had calcium oxalate-containing stones. Of these 169 patients, 49 were hypercalciuric at baseline. Diet produced a highly significant reduction in 24-h urinary sodium and calcium excretions: from 201±89 at baseline to 128±88 mmol/d for sodium ($p<0.0001$), and from 5.67±3.01 to 4.06±2.46 mmol/d ($p<0.0001$) for calcium. Urine volume remained unchanged. Notably, no increase in oxalate excretion occurred on the low calcium diet (0.39±0.26 vs 0.39±0.19 mmol/d, $p=0.277$). Calculated Psf values were only predictive for calcium phosphate stones.

Conclusions: In conclusion, diet low in calcium, as in the wider Swiss population, and here tested as a short intervention did not result in an increase in oxalate excretion in rKSF. The recommendation of a low salt diet in a population with too little dietary milk and dairy products does not seem to increase the risk for CaOx stone formation. However, assessment and correction of low calcium intake in hypercalciuric KSF remains important.

FR-PO464

Absence of miR-146a Increases Risk of Diabetic Glomerulopathy via Upregulation of ErbB4 and Notch-1 in Podocytes Shehryar J. Khaliqdina,[1] Samia Khan,[1] Ha Won Lee,[1] Mehmet M. Altintas,[1] Florian Grahammer,[3] Terese D. Geraghty,[1] Kwi Hye Koh,[1] Nicholas J. Tardi,[1] David J. Cimbaluk,[1] Katalin Susztak,[2] Pierre-Louis Tharaux,[4] Tobias B. Huber,[3] Matthias Kretzler,[5] Markus Bitzer,[5] Jochen Reiser,[1] Vineet Gupta.[1] *[1]Rush Univ; [2]Univ of Pennsylvania; [3]Univ Medical Center Freiburg; [4]INSERM; [5]SGBM.*

Background: MicroRNAs play a significant role in maintaining podocyte health and in glomerular disease pathogenesis. miR-146a is a negative regulator of myeloid cells. It's also expressed in podocytes, but its role is unclear. We examined the role of podocytic miR-146a in diabetic glomerulopathy (DGP). .

Methods: We used qRT-PCR to determine miR-146a expression in isolated glomeruli from a cohort of patients with type 2 diabetes (T2D) and correlated it with kidney function in these patients. We also studied miR-146a target expression levels in T2D patients, $BTBR^{ob/ob}$ mice and miR-146a deficient ($miR\text{-}146^{-/-}$) mice. To investigate the role of miR-146a in glomerular function *in vivo*, we induced hyperglycemia in WT and $miR\text{-}146a^{-/-}$ animals using streptozotocin (STZ) and tested whether ErbB4 inhibition with Erlonitib provides efficacy.

Results: We show that podocytic miR-146a expression decreased in the glomeruli of T2D patients and correlated with increased albuminuria and glomerular damage. miR-146a levels were significantly reduced in the glomeruli of $BTBR^{ob/ob}$ mice that spontaneously develop T2D. $miR\text{-}146^{-/-}$ mice displayed accelerated development of glomerulopathy upon STZ-induced hyperglycemia. miR-146a targets, Notch-1 and ErbB4, were significantly upregulated in the diseased glomeruli, suggesting induction of TGFb signaling. Treatment with Erlotinib significantly suppressed diabetic glomerular injury and albuminuria in WT and $miR\text{-}146a^{-/-}$ mice. TGFb treatment to podocytes *in vitro* resulted in increased levels of Notch-1 and ErbB4, and increased phosphorylation of ErbB4 and its partner EGFR. Increased ErbB4/EGFR signaling also increased levels of MCP-1 and MCP-1 induced protein, a suppressor of miR-146a, suggesting an autocrine loop.

Conclusions: We suggest a novel role for podocytic miR-146a in protecting against DGP. Also, ErbB4 is a novel therapeutic target for DGP intervention, especially since several ErbB4 inhibitors are clinically available.

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FR-PO465

APOL1 Mediated Eukaryotic Cell Injury Involves Disruption of Conserved Intracellular Trafficking Processes Etty Kruzel Davila,[1] Revital Shemer,[2] Ayala Ofir,[1] Ira Bavli,[1] Ilona Darlyuk-Saadon,[2] Pazit Oren-Giladi,[1] Walter G. Wasser,[1,3] Daniella Magen,[1,2] Eid Zaknoun,[2] Maya Schuldiner,[4] Adi Salzberg,[2] Daniel Kornitzer,[2] Zvonimir Marelja,[5] Matias Simons,[5] Karl Leon Skorecki.[1,2] *[1]Nephrology, Rambam Health Care Campus, Haifa, Israel; [2]Rappaport Faculty of Medicine and Research Inst, Technion, Haifa, Israel; [3]Mayanei HaYeshua Medical Center, Bnei Brak, Israel; [4]Dept of Molecular Genetics, Weizmann Inst of Science, Rehovot, Israel; [5]Imagine Inst, Paris Descartes Univ–Sorbonne Paris Cité, Paris, France.*

Background: *APOL1* harbors C-terminus sequence variants (G1 and G2) which account for much of the increased risk for kidney disease in Sub-Saharan African ancestry populations. Expression of the risk variants has also been shown to cause injury to podocytes and other cell types, but the underlying mechanism is not yet understood.

Methods: We used *Drosophila melanogaster* and *Saccharomyces cerevisiae* to help clarify these mechanisms.

Results: Ubiquitous expression of the human APOL1 G1 and G2 disease risk alleles caused near complete lethality in *Drosophila* with no effect of the G0 non-risk *APOL1* allele, corresponding to the pattern of human disease risk. A congruent pattern of cellular damage was also observed with tissue-specific expression of APOL1, consistent with a cell-autonomous effect. Expression of APOL1 risk variants in *Drosophila* nephrocytes caused accumulation of the endocytic tracer ANF-RFP at early stages and nephrocyte loss at later stages. APOL1 variants inhibit endocytic trafficking in *S. cerevisiae.* Differential toxicity and impairment of vacuole acidification of the risk compared to non-risk *APOL1* variants was likewise observed in *S. cerevisiae.* Yeast strains missing key components of endosomal trafficking or acidification, but not of autophagy pathways, resulted in augmented APOL1 toxicity.

Conclusions: The congruency of differential injury by the *APOL1* risk compared to non-risk alleles across evolutionarily divergent species, is most consistent with an impairment of conserved core intracellular endosomal trafficking processes. This should facilitate the identification of specific cell injury pathways and corresponding therapeutic targets of interest in these experimental platforms.

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FR-PO466

The Calcium-Dependent Proteinase Calpain-1 Links TRPC6 Activity to Podocyte Injury Ramon Sonneveld, Jack F. Wetzels, Johan Van der Vlag, Tom Nijenhuis. *Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands.*

Background: Transient Receptor Potential channel C6 (TRPC6) is a calcium-conducting ion channel expressed at the slit-diaphragm of podocytes. TRPC6 gain-of-function mutations and glomerular TRPC6 overexpression are associated with proteinuria. The underlying mechanisms that link TRPC6 to podocyte injury remain elusive. Activation of the calcium-dependent protease calpain-1 was suggested to mediate renal injury through cleavage of the podocyte cytoskeletal protein talin-1. We hypothesized that the calcium-dependent protease calpain-1 is involved in TRPC6-mediated podocyte injury.

Methods: Podocytes, transfected with scrambled, TRPC6 or calpain-1 siRNA, were injured using adriamycin and treated with the TRP channel activator 1-oleoyl-acetyl-sn-glycerol (OAG), calpain inhibitor calpeptin or TRPC channel blocker 2-APB. TRPC6-dependent calcium influx was measured by FURA-2. Calpain activity and talin-1 expression were determined by calpain activity assay and in situ zymography or Western blot. *In vivo*, calpain inhibition was tested in adriamycin induced nephropathy (AN), the model for human FSGS. Urine and kidney biopsies of human FSGS patients were tested for calpain activity as well as talin-1, TRPC6 and nephrin expression.

Results: Adriamycin and OAG increased calpain activity in podocytes, which was prevented in r TRPC6 KD or calpain 1 KD cells, and by 2-APB or calpeptin. TRPC6 KD in podocytes showed that adriamycin-induced calcium influx was TRPC6-dependent. The TRPC6-dependent calpain activation led to talin-1 cleavage. Calpain activity in urine and glomeruli was increased in rat AN and associated with increased proteinuria, which could be prevented by calpain inhibition. Urine and glomeruli from FSGS patients also showed an increased calpain activity, along with increased glomerular TRPC6 and reduced talin-1 and nephrin expression.

Conclusions: We have elucidated a novel mechanism that directly links TRPC6-dependent calcium influx to calpain-1 activation, talin-1 cleavage, subsequent podocyte injury, and proteinuria *in vitro, in vivo*, and in humans. Therefore, calpain-1 and/or TRPC6 inhibition could be a novel therapeutic option to treat FSGS.

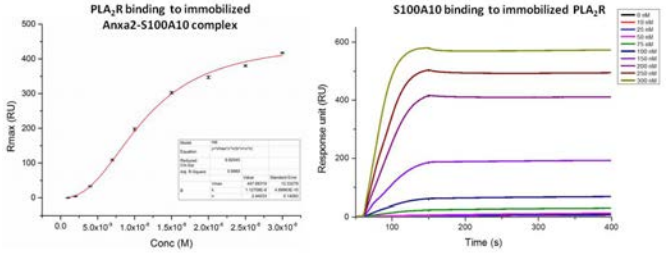
FR-PO467

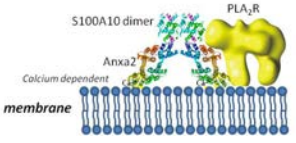
AnnexinA2-S100A10 Complex Is the Binding Partner of PLA2R in Podocytes Maryline Fresquet, Thomas A. Jowitt, Edward A. Mckenzie, Rachel Lennon, Paul E. Brenchley. *Wellcome Trust Centre for Cell-Matrix Research, Univ of Manchester, United Kingdom.*

Background: PLA_2R is the major podocyte antigen targeted by autoantibodies in membranous nephropathy (MN). We have shown that anti-PLA_2R in absence of complement activation induces change in podocyte shape, monolayer permeability, free radical production and apoptosis. How anti-PLA_2R induces these changes and disrupts PLA_2R function is unknown. PLA_2R cannot mediate intracellular signalling implying other receptors are involved. We seek to identify binding partners of PLA_2R in podocytes.

Methods: The PLA_2R binding partners were isolated from human podocytes by immunoprecipitation and analyzed by mass spectrometry. The interactions with the identified candidates were confirmed by surface plasmon resonance (SPR), quartz crystal microbalance with dissipation (QCM-D) and immunofluorescence.

Results: Pull down experiments identified an interaction between PLA_2R and AnnexinA2 (Anxa2). Anxa2 can exist as a heterotetrameric complex (A2t) coupled with S100A10, this complex being the predominant form present at the plasma membrane. We tested the binding by SPR between PLA_2R and A2t complex and found a high affinity interaction with cooperativity. We analyzed these partners individually and showed that PLA_2R interacts with A2t via S100A10 with strong affinity (K_D $8x10^{-11}$M). This is the first evidence that PLA_2R is another receptor interacting with the A2t complex. Moreover we showed using QCM-D that A2t/PLA_2R complex binds to lipids in calcium-dependent manner providing a potential mechanism for PLA_2R trafficking to the cell membrane.





Conclusions: This study describes a novel PLA_2R/A2t complex on the podocyte plasma membrane and identifies S100A10 as a potential mediator of PLA_2R translocation to the cell surface. Blocking PLA_2R expression on the cell membrane may protect the podocyte from the consequences of autoantibody attack in MN.

Funding: Private Foundation Support

FR-PO468

The Transcription Factor Dach1 Is Essential for Podocyte Differentiation and Function Nicole Endlich,[1] Felix Kliewe,[1] Katharina Schmidt,[1] Frances Kindt,[1] Nadine Artelt,[1] Maja Lindenmeyer,[2] Clemens D. Cohen,[2] Franziska Döring,[1] Regina Maciejewski,[1] Andreas W. Kuß,[3] Kerstin U. Amann,[4] Nazanin Kabgani,[5] Marcus J. Moeller,[5] Antje Blumenthal,[1] Karlhans Endlich.[1] *[1]Anatomy and Cell Biology, Univ Medicine Greifswald, Greifswald, Germany; [2]Medical Clinic and Policlinic IV, LMU, Munich, Germany; [3]Human Genetics, Univ Medicine Greifswald, Greifswald, Germany; [4]Nephropathology, Univ Hospital Erlangen, Erlangen, Germany; [5]Internal Medicine II, RWTH Aachen Univ Hospital, Aachen, Germany.*

Background: Dedifferentiation and loss of podocytes are the major causes of chronic kidney disease. The locus of Dach1, a transcription factor, which is essential for cell fate, was found in genome wide association studies to be associated with glomerular filtration rate.

Methods: To investigate the role of Dach1 in transdifferentiation of parietal epithelial cells to podocytes *in vitro*, we transfected murine parietal epithelial cells (PECs) with a plasmid encoding for Dach1 and analyzed the cells by immunocytochemistry, qRT-PCR and Western blot. For studying the function of Dach1 *in vivo*, we used the zebrafish model for morpholino knockdown of dachd, the zebrafish ortholog of Dach1.

Results: We found that podocytes express high levels of Dach1 in mice and humans *in vivo* and to lower extent *in vitro*. PECs, which are able to transdifferentiate into podocytes under certain circumstances, express Dach1 only at low levels. The transfection of PECs with Dach1 induced the expression of synaptopodin, which was located along actin fibers in a punctate pattern, comparable with differentiated podocytes. Moreover, dedifferentiating podocytes of isolated glomeruli showed a significant reduction of the expression of Dach1 together with synaptopodin after 9 days in culture. Knockdown of dachd in zebrafish resulted in morphological changes of the pronephric glomerulus accompanied by a down-regulation of nephrin and a leakage of the filtration barrier. Interestingly, Dach1 and synaptopodin were significantly reduced in biopsies from patients suffering from diabetic nephropathy in contrast to biopsies from healthy controls.

Conclusions: Taken together, Dach1 is a transcription factor that is essential for podocyte differentiation and proper glomerular function.

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FR-PO469

FGF23 Play a Key Role in the Pathogenesis of Podocyte Injury in CKD Junnan Wu, Ying Fan, Niansong Wang. *Dept of Nephrology and Rheumatology, hanghai Jiao Tong Univ Affiliated Sixth People's Hospital.*

Background: Fibroblast Growth Factor 23 (FGF-23) is a bone-derived hormone involved in the regulation of phosphate homeostasis. Substantial clinical evidence has indicated that FGF23 levels extremely elevated in Chronic Kidney Disease (CKD), however, so far FGF23 has only been considered as an early biomarker of renal injury or a key hormone regulating phosphate metabolism, rather than a direct causal role in podocyte function. This research unveil a direct pathological effects of FGF23 on podocytes, providing a novel therapeutic target for podocytopathy.

Methods: Studies were performed with human podocyte cell line, FGF23-treated mice, FGF23 gene transferring *in vivo*, and CKD patients' renal biopsies.

Results: We treated cultured human podocytes with FGF23,and found treatment of FGF23 caused podocyte cytoskeletons dramatic loss and lead to podoycte apoptosis. However,podocyte injury caused by treatment with FGF23 were ameliorated by PD173074(inhibitor of FGFR). We also noticed that FGF23 induced calcium influx, calcineurin activity and NFAT nuclear translocation in podocyte. Moreover, klotho-deficient podocyte exhibited cytoskeletons damage after FGF23 treatment, Suggesting this effect was independent of klotho but via FGF receptor–dependent activation of the calcineurin-NFAT signaling pathway. *In vivo*, Intravenous injection of FGF23 in mice induces a significantly increased in proteinuria, massive foot process effacement, loss of podocin expression. And those phenotype were ameliorated by treatment of PD173074 or calcineurin inhibitor (CSA). Moreover, we injected the lentivirus-expressing FGF23 into the kidneys of mice, we found a similar phenotype as intravenous injection of FGF23.

Conclusions: Taken together, these findings demonstrate a role for FGF23 in the pathogenesis of podocyte injury by targeting calcineurin-NFAT signaling pathway. We believe that these data uncover a novel mechanism underlying podocyte injury and provide a potential target for treating podocytopathy.

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FR-PO470

Loss of APOL1 Induces Autophagy in Podocytes Ahmed Kotb,[1,2] Florian Siegerist,[1] Frank Dombrowski,[3] Kerstin U. Amann,[4] Uwe Zimmermann,[5] Johanna Chluba,[6] Tobias B. Huber,[7] Karlhans Endlich,[1] Nicole Endlich.[1] *[1]Anatomy and Cell Biology, Univ Medicine Greifswald, Germany; [2]Anatomy and Histology, Faculty of Veterinary Medicine, Asyut Univ, Egypt; [3]Pathology, Univ Medicine Greifswald, Germany; [4]Nephropathology, Inst of Pathology, Univ Hospital Erlangen, Germany; [5]Urology, Univ Medicine Greifswald, Germany; [6]INSERM, UMR 866, Univ of Burgundy, Dijon, France; [7]Renal Div, Univ Medical Center Freiburg, Germany.*

Background: *APOL1* codes for a secreted high density lipoprotein, whose variants confer resistance to Trypanosoma in Africans. APOL1 is expressed in several human cells and organs including kidney podocytes. It is known that *APOL1* variants are associated with kidney diseases like focal segmental glomerulosclerosis (FSGS) in African Americans. The aim of our study was to find out which role APOL1 plays for autophagy *in vitro* and *in vivo.*

Methods: To study autophagy *in vitro* we used human podocytes that were transfected with a plasmid encoding GFP-LC3. APOL1 knockdown was performed by siRNA. To study autophagy *in vivo* we used a transgenic GFP-LC3 zebrafish strain (Tg(CMV:EGFP-map1Lc3b)). Live imaging of the expression of GFP-LC3 in the zebrafish pronephros was performed by 2-photon microscopy. Apol1 knockdown was generated by morpholino (MO) injection in zebrafish (standard and *Vivo*-MO). Knockdown efficiencies of siRNA and MO were confirmed by RT-PCR and Western blot. Human kidney sections from FSGS patients were stained with LC3 and APOL1 antibodies.

Results: APOL1 knockdown in cultured human podocytes and in zebrafish larvae induced an increase of LC3 in podocytes. Moreover, ApoL1 knockdown in zebrafish larvae resulted in pericardial edema, a hallmark of kidney disease. Live imaging of zebrafish larvae (4 days post fertilization) that were injected with *Vivo*-MO against Apol1 showed an induction of autophagy independent of a developmental defect. Additionally, in kidney biopsies of patients suffering from FSGS, APOL1 expression was significantly decreased combined with an increase of LC3 spots in podocytes.

Conclusions: APOL1 is important for proper kidney function. Loss of APOL1 induces autophagy in podocytes as determined by an increased LC3 expression *in vitro* and *in vivo*.

Funding: Government Support - Non-U.S.

FR-PO471

Role of Podocyte Receptor Podo-GPCR2 in Diabetic Nephropathy Sonia Zambrano Sevilla, Patricia Rodriguez, Jaakko Patrakka. *Laboratory Medicine, Karolinska Inst, Stockholm, Sverige, Sweden.*

Background: Podocyte injury is associated with progressive kidney disease and correlate with diabetic kidney disease (DKD). However, molecular mechanism leading to podocyte injury in DKD is still poorly understood. By using large-scale expressional profiling we have identified a novel highly podocyte-specific G-protein receptor, podo-GPCR2. Previously, this orphan GPCR has been related with the regulation of Wnt3/

βcatenin pathway in the neocortex. This pathway has been linked previously to podocyte damage in DKD. The aim of this work is to study the function of podo-GPCR2 in podocytes and its role in DKD.

Methods: *In vitro*, we generated a stable cell line of human podocytes over expressing podo-GPCR2. In these cells we carried out studies of gene expression of different component of the Wnt3/βcatenin pathway, as well as luciferase experiment using reporters for activated βcatenin. We used zebrafish and mouse as *in vivo* models. In zebrafish, podo-GPCR2 was inactivated using morpholinos. In mouse podo-GPCRC2 was inactivated using gene targeting. 6 KO and 6 control mice were challenged with LPS that is known to cause podocyte injury and proteinuria.

Results: In cultured cells, we saw that βcatenin was significantly upregulated in human podocytes overexpressing podo-GPCR2. Moreover, the gene expression of Axin3 and DKK2 (two components downstream of wnt3 pathway) was elevated in over expressing podocytes. Using a luciferase reporter we could validate that βcatenin was activated in podocytes overexpressing podo-GPCR2. In zebrafish, the inactivation of podo-GPCR2 resulted in podocyte foot process effacement, glomerular basement membrane abnormalities and proteinuria – all features of human DKD. In mouse, the absence of podo-GPCR2 did not affect normal development and function of the glomerulus. However, KO animals were more prone to LPS-induced podocyte damage as they developed higher albuminuria after LPS injection than control animals.

Conclusions: Podo-GPCR2 is a novel highly podocyte-specific GPCR that seems to be involved in the pathogenesis of podocyte injury through wnt signaling pathway. Podo-GPCR2 may be a new target molecule to treat glomerular diseases.

FR-PO472

Molecular Regulation of the Antifibrotic Protein Follistatin by Caveolin-1 in Mesangial Cells Neel Mehta, Dan Zhang, Renzhong Li, Tony Nuo Wang, Agata Gava, Pavithra Parthasarathy, Bo Gao, Joan C. Krepinsky. *Nephrology, McMaster Univ, Hamilton, ON, Canada.*

Background: Glomerular fibrosis is a key pathologic feature of chronic kidney disease (CKD), with mesangial cells (MC) being a major contributor to the excess extracellular matrix production. We previously showed that caveolin-1 (cav-1) is required for MC synthesis of matrix proteins both basally and in response to several profibrotic stimuli. Here we sought to identify the molecular basis of this protection.

Methods: MC isolated from cav-1 wild-type (WT) and knockout (KO) mice were used and studies conducted using standard molecular biology techniques.

Results: Using microarray, we identified significant upregulation of the antifibrotic secreted glycoprotein follistatin (FST) in cav-1 KO compared with WT MC. We confirmed that KO MC had significantly elevated FST transcript and protein levels. Cav-1 re-expression reduced FST expression and increased basal matrix production, which was similarly increased by FST downregulation with siRNA. The ability of KO MC to respond to Activin A, a TGFβ family member most potently inhibited by FST, was blunted. Activity of a FST mouse promoter (-1.84kb) reporter was higher in KO MC, indicative of higher transcription rates. To identify the promoter region regulated by cav-1, we created and tested a series of deletion constructs. Surprisingly, deletion to -123bp did not eliminate the higher promoter activity in KO cells. This region contains 2 potential binding sites for the transcription factor Sp1, shown to regulate FST promoter activity in intestinal epithelial cells. ChIP studies showed greater Sp1 binding to this region in KO MC, and higher Sp1 transcription activity in KO cells was confirmed using a luciferase reporter assay. Downregulation of Sp1 with siRNA attenuated FST promoter activity, and deletion of both Sp1 sites from this promoter region suppressed activity in KO MC to levels seen in WT MC.

Conclusions: We have identified a novel role for cav-1 in regulating expression of the anti-fibrotic protein FST. These studies lay an important foundation for evaluating FST as a potential novel antifibrotic agent for CKD.

Funding: Government Support - Non-U.S.

FR-PO473

Protein-Tyrosine Kinase Inhibitors as Potential Therapeutic Agents for IgA Nephropathy Zhi Qiang Huang,[1] Xianwen Zhang,[1,2] Zina Moldoveanu,[1] Qi Bian,[1,3] Stacy D. Hall,[1] Joshua Charles Anderson,[1] Rhubell T. Brown,[1] Lea Novak,[1] Christopher D. Willey,[1] Bruce A. Julian,[1] Jan Novak.[1] [1]*Microbiology, Univ of Alabama at Birmingham, Birmingham, AL;* [2]*Long Hua Hospital, Shanghai Univ of Traditional Chinese Medicine, Shanghai, China;* [3]*Changhai Hospital, Second Military Medical Univ, Shanghai, China.*

Background: Immune complexes (ICs) containing galactose-deficient IgA1 (Gd-IgA1) and anti-Gd-IgA1 antibodies play a key role in pathogenesis of IgA nephropathy (IgAN). To explore the mechanism of kidney injury and potential therapeutic targets, we assessed biological activities of circulating ICs (CICs) and engineered ICs (EICs).

Methods: CICs were isolated from sera of IgAN patients. EICs were formed by incubation of Gd-IgA1 with a recombinant antibody anti-Gd-IgA1. Cultured human mesangial cells (MCs) were incubated with ICs with or without several protein-tyrosine kinase (PTK) inhibitors. Cellular proliferation was measured by ^{3}H-thymidine uptake. Cell signaling was determined by changes in PTK activities and phosphorylation using Western blotting and Tyrosine-Kinase PamChips and Bioinformatics analyses. EICs were injected *i.v.* into immunodeficient mice every other day for a week to generate a mouse IgAN model. Mice were daily gavaged with dasatinib. Kidneys were harvested 1 d after last injection and histology was evaluated.

Results: CICs and EICs increased MC proliferation by 3.5±2.5-fold and 2.9±0.7-fold. Western blotting with phospho-tyrosine antibody revealed both ICs increased tyrosine phosphorylation of multiple proteins. Kinomic studies indicated several signaling pathways were activated by both ICs. One PTK inhibitor, dasatinib, inhibited activation of MCs induced by ICs in a dose-dependent manner. In mouse model, dasatinib inhibited MC proliferation and matrix expansion. Analysis of kidney homogenates indicated dasatinib inhibited PDGF pathway and down-stream signals.

Conclusions: Both ICs activated several signaling pathways in MCs, leading to cellular proliferation and matrix expansion. A PTK inhibitor, dasatinib, blocked these pathological changes *in vitro* and in mouse IgAN model. Dasatinib, or similar drugs, may represent a therapeutic agent(s) for IgAN patients.

Funding: NIDDK Support, Private Foundation Support

FR-PO474

APOL1 Confers Cytotoxicity through Alteration of Vesicle pH, Leading to Altered Membrane Homeostasis Jurgen Heymann,[1] Patrick D. Dummer,[1] Michael Kruhlak,[2] Alison B. Hickman,[1] Cheryl Ann Winkler,[2] Jeffrey B. Kopp.[1] [1]*NIH-NIDDK;* [2]*NIH-NCI.*

Background: Apolipoprotein L1 (*APOL1*) C-terminal mutations are risk alleles for glomerular disease in African descent populations. We studied three potential cytotoxicity mechanisms.

Methods: Experiments used HEK293 kidney cells, stably expressing APOL1 common allele G0 and risk alleles G1 and G2.

Results: APOL1 variants displayed different levels of cytotoxicity (G0<G2<G1). We examined whether APOL1 acts as a BH3-only pro-death protein based on the presence of a predicted BH3 domain. We found that the APOL1-BH3 domain is translocated into the endoplasmic reticulum (ER) lumen and, as Bcl2 is cytosolic, there was no APOL1-Bcl2 interaction. We examined APOL1 interactions with vesicle-associated membrane protein (VAMP) 8, a candidate for a functional ortholog of the trypanosomal protein SRA, which binds the APOL1 C terminus and inhibits APOL1 lytic properties. Although APOL1 trafficked to VAMP8(+) late endo-lysosomes, the predicted interaction between the two proteins is unlikely, as we show that the APOL1 C terminus has a luminal orientation, whereas the relevant, N-terminal VAMP8 domain faces the cytoplasm. Cytoplasmically-expressed APOL1 also showed co-localization with VAMP8(+) late endo-lysosomes. Deletion of the APOL1 membrane-addressing domain abolished trafficking to GFP-VAMP8(+) membranes. Together, these findings suggest that APOL1 trafficking relies on lipid interactions rather than on protein interactions. In lipid binding experiments, APOL1 preferentially bound to acidic phospholipids. APOL1 resisted extraction from microsomal membranes by alkaline sodium carbonate, which indicates strong protein-lipid interactions. However, we found that APOL1 does not span the ER membrane, and is unlikely to form pores/channels there. Dextran uptake experiments showed that APOL1 expression increased mean vesicle pH (G0<G2<G1), which would compromise vesicle trafficking. These data suggest that APOL1 toxicity is only acquired later in biogenesis, through membrane insertion.

Conclusions: These data suggest that APOL1 targets cell membranes by lipid binding and that risk alleles compromise vesicle acidification, leading to a general defect in vesicle trafficking.

Funding: NIDDK Support

FR-PO475

Silibinin Improves Mitochondrial Function of Podocytes in Diabetic Mice through Regulation of Sirtuin 3 Expression Zengchun Ye, Meijun Si, Wenbo Zhao, Ming Li, Cheng Wang, Tan-Qi Lou. *Dept of Nephrology, The Third Affiliated Hospital Sun Yat-sen Univ, Guangzhou, China.*

Background: Mitochondrial dysfunction of podocytes plays essential role in diabetic nephropathy. Our previous study shown that expression of Sirtuin 3 (Sirt3) was decreased in diabetic (*db/db*) mice, which lead to reducing mitochondrial complex I activity in podocytes. This study is to investigate the potential protective effect of silibinin and its underlying mechanisms in improving mitochondrial function of podocytes in diabetic mice.

Methods: Diabetic (*db/db*) and non-diabetic (*db/m*) mice were administrated with silibinin for 16 weeks after 8-week old. Moreover, diabetes was induced in Sirt3-knockout mice by streptozotocin (STZ) injection, and silibinin was administrated to these mice for 16 weeks after the induction of diabetes. To assess the expression of Sirt3 and mitochondrial complex I activity, mitochondria were isolated from podocytes of diabetic and non-diabetic mice. The expression of Sirt3 was measured by western blotting. Mitochondrial complex I activity was detected by microplate assay kit purchased from Abcam.

Results: We found that silibinin can increase the expression of Sirt3 in podocytes of *db/db* mice and STZ induced diabetic mice. Administration of silibinin can also ameliorate the mitochondrial function of podocytes in diabetic mice, but had no effect in Sirt3–/– mice. And *in vitro* studies, we also found that silibinin can ameliorate high glucose-induced dysfunction of mitochondria in podocytes by increasing Sirt3 expression, including the increased activity of mitochondrial complex I and the level of mitochondrial DNA.

Conclusions: Collectively, these data suggest that silibinin improves mitochondrial function of podocytes in diabetic mice through regulation of Sirt3 expression.Thus, enhancing Sirt3 by silibinin to improve mitochondrial function in podocytes has potential as a strategy for improving outcomes of renal injury in diabetes.

Funding: Government Support - Non-U.S.

FR-PO476

Expression of Thrombospondin Type 1 Domain-Containing 7A (THSD7A) in Developing Glomeruli Young-Soo Song, Hong Ma, Sudhir Kumar, Weining Lu, David J. Salant, Laurence H. Beck. *Renal Div, Dept of Medicine, Boston Univ Medical Center, Boston, MA.*

Background: Membranous nephropathy (MN) is a common cause of adult nephrotic syndrome. Autoantibodies to the podocyte proteins PLA2R and THSD7A are found in primary MN in approximately 75% and 5% of cases, respectively. Unlike PLA2R which is not expressed by the mouse, THSD7A is expressed on the basal surface of both human and mouse podocytes. The role of THSD7A is unclear, but the protein has been found in focal adhesions in human umbilical vein endothelial cells. We sought to investigate the temporal expression of THSD7A in developing mouse glomeruli to help better understand the role of the molecule.

Methods: We localized THSD7A by confocal immunofluorescence microscopy in developing mouse kidney (E14.5, E17.5, and P1) using serum from a patient with primary MN known to be anti-THSD7A positive. Specificity of the serum for THSD7A was demonstrated using blocking fragments of recombinant human THSD7A. The different stages of glomerular development (cap mesenchyme, C-shaped body, S-shaped body and capillary loop) were identified using differential interference contrast microscopy as well as commercial antibodies to SIX2 (cap mesenchyme), laminin (C-/S-shaped body) and nephrin (capillary loop).

Results: Human anti-THSD7A autoantibody did not detect THSD7A in SIX2-positive cap mesenchyme at E14.5 or in laminin-positive C-/S-shaped bodies at E17.5. However, there was very prominent linear staining of THSD7A along the basal surface of podocytes of capillary loop stage glomeruli (E17.5 and P1), in which THSD7A and nephrin partially colocalized. The specificity of THSD7A staining was shown by the complete inhibition of the glomerular signal after preincubation with the recombinant N-terminal fragment of THSD7A.

Conclusions: THSD7A appears to be first expressed by the podocyte at the capillary loop stage of mouse glomerular development. Further studies are needed to investigate its potential role at the basal surface of the podocyte.

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FR-PO477

Can Extracellular Vesicles Regulate Glomerular VEGF Homeostasis in Chronic Kidney Disease? Sargis Sedrakyan,[1] Stefano Porta,[2] Valentina Villani,[1] Nikita Tripuraneni,[1] Astgik Petrosyan,[1] Stefano Da Sacco,[1] Hasmik Soloyan,[1] Roger E. De Filippo,[1] Benedetta Bussolati,[2] Laura Perin.[1] *[1]Urology, Children's Hospital Los Angeles, Los Angeles, CA; [2]Molecular Biotechnology, Univ of Turin, Turin, Italy.*

Background: Tight regulation of paracrine VEGF signaling between podocytes and glomerular endothelial cells (GEC) is required for maintenance of the glomerular filtration barrier (GFB) structure and function. Disruption of VEGF homeostasis has been implicated in various types of glomerular diseases. However, current therapies neither specifically target the glomerulus nor the VEGF pathway but in addition present multiple side effects. Therefore, identification of new approaches aimed at restoring local VEGF remains a potential therapeutic target to treat glomerular disease. We previously showed that amniotic fluid stem cells (AFSC) are renoprotective in Alport Syndrome (AS), a model of CKD. They home within the diseased glomeruli and secrete extracellular vesicles (EVs). EVs play key role in stem cell mediated paracrine function, including the kidney. Herein, we demonstrate that AFSC derived EVs regulate VEGF/VEGFRs signaling balance in AS GEC via modulation of sFlt1, the soluble isoform of VEGFR1.

Methods: We measured VEGF activity in AS glomeruli by WB. We assessed VEGF/VEGF-Rs activity in GEC, including the sFlt1. We characterized AFSC-EVs cargo by FACS and by miRs arrays and evaluated their potential to affect VEGF biology in GEC.

Results: Glomeruli from AS mice showed increased VEGF activity through increased phosphorylation of VEGFR-2 early on during progression accompanied by modulation of sFlt1. These observations were associated with GEC damage that showed altered VEGFR signaling. Importantly, EVs presented with VEGFRs and angiomodulatory microRNA. These EVs successfully integrated within GEC and modulated VEGF activity. EVs lacking both the full and soluble VEGFR-1 failed to rescue GEC from VEGF inflicted damage.

Conclusions: In conclusion, we demonstrated for the first time the aberration of VEGF signaling within AS glomeruli. We further showed that AFSC derived EVs play important role in maintaining glomerular homeostasis of VEGF signaling, presenting with a potential for new targeted therapies in CKD.

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FR-PO478

Urotensin II Contributes to Hyperproliferation and Extracellular Matrix Accumulation in High Glucose-Challenged Glomerular Mesangial Cells Adebowale Adebiyi, Hitesh Soni. *Physiology, Univ of Tennessee Health Science Center, Memphis, TN.*

Background: Glomerular mesangial cell (GMC) hyperproliferation and matrix expansion are pathological hallmarks of many kidney diseases, including diabetic nephropathy (DN). Although the circulating level of urotensin II (UII) and kidney tissue expression of UII and UII receptors are elevated in DN, it remains unclear whether UII regulates mesangial cell growth and matrix accumulation.

Methods: Using a murine GMC line, we examined the role of UII-induced Ca^{2+} signaling in the mechanisms that underlie mesangial proliferation and matrix accumulation under normal and high glucose ambience.

Results: UII promoted GMC growth and matrix production; effects dependent on TRPC4 channel-mediated store-operated Ca^{2+} entry (SOCE) and sequential activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and Ca^{2+}/cAMP response element-binding protein (CREB) transcription factor. Exposure of GMCs to high glucose (HG) concentration stimulated UII synthesis, proliferation, and type IV collagen (cIV) production in the cells. HG-induced GMC hyperproliferation and cIV synthesis were attenuated by urantide, an urotensin II receptor antagonist, ML204, a TRPC4 channel blocker, BAPTA an intracellular Ca^{2+} chelator, KN-93, a CAMKII inhibitor, and SGC-CBP30, an inhibitor of the transcriptional co-activators CREB binding protein and p300.

Conclusions: UII-induced SOCE via TRPC4 channels stimulates CaMKII/CREB-dependent GMC proliferation and matrix accumulation. Our data also suggest that increased UII synthesis contributes to HG-induced GMC hyperproliferation and matrix production. Conceivably, UII-induced Ca^{2+} signaling is involved in the pathophysiological mechanisms of mesangial matrix expansion in DN.

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FR-PO479

Intermediate Filament Protein Nestin to Wilm's Tumor Suppressor WT1 mRNA Ratio in Urinary Viable Podocyte Correlated with Proteinuria Hoon Young Choi,[1] Mirae Lee,[1] Taeyeon Kim,[1] Seung Kyu Kim,[1] Seok-Hyung Kim,[1] Beom Jin Lim,[2] Jung Eun Lee,[3] Hyunwook Kim,[1] Hyeong Cheon Park.[1] *[1]Dept of Internal Medicine, Gangnam Severance Hospital, Yonsei Univ College of Medicine, Seoul, Korea; [2]Dept of Pathology, Yonsei Univ College of Medicine, Seoul, Korea; [3]Dept of Internal Medicine, Yong-In Severance Hospital, Gyeongi-do, Korea.*

Background: Measurement of mRNA of podocyte proteins in urine sediment has been suggested as a useful tool monitoring glomerular disease activity. Nestin, an intermediate filament protein has been reported to play an important role in maintaining normal podocyte function in the human kidney. Furthermore, nestin is expressed at different stages of kidney development and regulated by the Wilms' tumor suppressor WT1. We performed this study to investigate whether the nestin-to-WT1 mRNA ratio in the urine-excreted viable podocytes could mirror disease activity and be a useful biomarker in proteinuric glomerular disease.

Methods: Fresh urine from patients with nephrotic range proteinuria was collected and urine sediments were cultured for viable podocytes. Viable cells derived from urine cultures were stained for podocyte-specific markers such as podocalyxin and WT-1. The number of cells and the duration at the time of subculture were measured. The total urine podocyte pellet RNA was purified and real-time PCR was performed.

Results: Viable and proliferating podocytes were derived from fresh voided urine. More than 70-80% of viable cells positively stained for podocalyxin and WT-1. The number of podocytes recovered at the time of first subculture was not associated with degree of proteinuria. The urine podocyte WT-1 mRNA expression showed significant negative correlation with proteinuria ($r=-0.622$, $p=0.018$), while nestin mRNA expression was not significantly correlated. Moreover, nestin-to-WT-1 mRNA ratio expression showed a significant correlation with proteinuria ($r=+0.676$, $p=0.011$).

Conclusions: Our results show that nestin-to-WT1 mRNA ratio of the viable podocytes derived from fresh voided urine could be a useful biomarker to predict degree of proteinuria in glomerular disease.

FR-PO480

Reduced ABCA1 and SOAT1 Are Required to Cause Podocyte Injury in Diabetic Kidney Disease Gloria Michelle Ducasa,[1] Christopher E. Pedigo,[1] Mayrin Correa,[1] Tahreem Hashmi,[1] Alla Mitrofanova,[1] Alexis J. Sloan,[1] Armando Mendez,[3] Robert G. Nelson,[2] George William Burke,[4] Sandra M. Merscher,[1] Alessia Fornoni.[1] *[1]Katz Family Center/Div of Nephrology, Univ of Miami, Miami, FL; [2]NIDDK, Phoenix, AZ; [3]Diabetes Research Inst, Univ of Miami, Miami, FL; [4]Surgery, Univ of Miami, Miami, FL.*

Background: Decreased podocyte number and glomerular cholesterol accumulation are associated with albuminuria in diabetic kidney disease (DKD). The contribution of free and esterified cholesterol to podocyte injury remains unknown. We hypothesize that both decreased ATP Binding Cassette A1 (ABCA1) expression and sterol-o acyltransferase 1 (SOAT1) activity are required to cause free cholesterol mediated podocyte apoptosis.

Methods: Patients enrolled in the Pima Indian cohort were separated into progressors and non-progressors (dGFR -97.39±8.2,n=15 and +40.62±8.6, n=16, respectively) based on the change in glomerular filtration rate (dGFR) between enrollment and last examination (10±1.7 years). Human podocytes were treated with patient sera. ABCA1 expression, cholesterol efflux and SOAT1 activity were measured. SiRNA *ABCA1* podocytes (siABCA1p) were analyzed for cholesterol content, efflux and caspase 3 activity in the presence or absence of a SOAT inhibitor (SI) and/or cyclodextrin (CD), a cholesterol sequestering agent. Podocyte specific ABCA1 knockout mice were developed.

Results: Progressor-sera treated podocytes showed reduced ABCA1 expression ($p<0.05$), ABCA1 mediated cholesterol efflux ($p<0.01$) and SOAT1 activity ($p<0.05$). SiABCA1p showed, accumulation of esterified cholesterol and lipid droplets and no increase in apoptosis. Podocyte specific ABCA1 knockout mice did not develop albuminuria. Treatment with SI caused increased caspase 3 activity in siABCA1p ($p<0.05$), which was prevented by pretreatment with CD ($p<0.05$).

Conclusions: Our data indicate that reduced *ABCA1* expression and SOAT1 activity are required to cause podocyte injury. Podocytes with reduced *ABCA1* expression and SOAT1

activity experience free-cholesterol mediated podocyte apoptosis, which is prevented by CD suggesting that strategies to restore ABCA1 and SOAT1 function may be beneficial to inhibit podocyte loss in DKD.

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FR-PO481

Glucocorticoids and Mifepristone Provide Beneficial Effects against Nephrotic Syndrome via Similar and Different Glomerular Expression

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Background: Glucocorticoids (GCs) are the primary therapy for nephrotic syndrome (NS), although GCs have serious side effects and are ineffective in ~20-50% of patients. We previously reported the role of the GC receptor (GR) antagonist/partial agonist mifepristone (Mif) in modulating the GR pathway in podocytes. We hypothesized that Mif could also provide reduction in proteinuria seen with GCs during NS via similar and/or different pathways.

Methods: Proteinuria was induced in Wistar rats by single PAN injections (50 mg/kg). Treatment groups received PAN+Mif (2.5-15 mg/kg) and PAN+high-dose GCs (15 mg/kg). Analyses included proteinuria and glomerular gene expression by RNA-Seq, 11 days after PAN injection. Alignment was performed to the rat reference assembly from NCBI and differentially expressed features calculated using DESeq2.

Results: PAN induced severe proteinuria, which was significantly reduced by high-dose GCs as well as low-dose Mif. PCA plots segregated the PAN-injured glomeruli from control group along the 1st principal component. The global expression pattern shifted robustly towards the control in PAN+GCs group, but only slightly in PAN+Mif group. Moreover, while 673 genes were significantly differentially expressed (fold change > 2) in PAN-inured glomeruli compared to control, and 476 in PAN+GCs compared to PAN, only 151 genes were differentially expressed in PAN+Mif compared to PAN. Furthermore, 627 genes were differentially expressed between GC and Mif treatment groups. Specific genes that were highly differentially expressed upon PAN injury, and either restored by both GCs and Mif or by GCs alone, have also been identified.

Conclusions: GR antagonists/partial agonists such as Mif may provide the same beneficial effects against NS as GCs, although via similar and/or different pathways. This may be helpful as new treatment option if they can circumvent the side effects associated with the use of GCs.

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FR-PO482

The Role of Growth Hormone Action in the Glomerulus: Studies of the Podocyte-Specific Growth Hormone Receptor Gene-Disrupted Mouse

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Background: Growth hormone (GH) has been implicated in the development of kidney disease in animal and human models of both type 1 diabetes (T1DM) and acromegaly. Evidence of increased glomerular size and sclerosis in these conditions suggests that excess GH action exacerbates glomerular damage. The podocyte is a crucial cell in the glomerular filtration barrier and is dysfunctional in many models of nephropathy. This cell is also a target of direct GH action. To explore the mechanisms by which GH impacts the glomerulus, we have developed a transgenic mouse model, the podocyte-specific GHR gene-disrupted mouse (podGHR-/-).

Methods: PodGHR-/- mice were generated on a C57BL/6J background using Cre-Lox transgenic methods. At various time points, urine and blood were collected from these mice and age-matched controls, and numerous measurements were taken, including body composition and tail-cuff blood pressure. Animals were sacrificed at 6, 18 and 30 weeks for histological studies. Supplementary cell culture studies were performed using the MPC-5 immortalized podocyte line exposed to exogenous GH.

Results: PodGHR-/- mice display significant variation in markers of fluid balance, including changes in urinary electrolyte concentration, tail-cuff blood pressure and total body fluid composition. These mice also show differences in the urinary albumin-to-creatinine ratio. Some of these differences are sex-specific and age-dependent. Our *in vitro* studies show that GH action directly increases collagen production from the podocyte.

Conclusions: Our results suggest a novel mechanism for GH action in the podocyte as a determinant of total body fluid balance, possibly through alteration of matrix proteins in the glomerular basement membrane.

FR-PO483

Quantitative Deep Mapping of Podocytes Identifies Proteostatic Shifts during Differentiation

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Background: The renal filtration barrier is maintained by the renal podocyte, an epithelial postmitotic cell. Immortalized mouse podocyte cell lines – both in the differentiated (37 °C) and undifferentiated (33 °C) state - are widely utilized tools to estimate podocyte injury and cytoskeletal rearrangement processes *in vitro*.

Methods: We performed deep proteomic mapping of podocyte proteins from 50µg of protein. The method consists of protein solubilization, tryptic digestion, strong-cation exchange fractionation and analysis of peptides by nLC-MS/MS on a quadrupole-orbitrap mass spectrometer.

Results: We mapped the cultured podocyte proteome at a depth of more than 8800 proteins and quantified 7313 proteins. Copy numbers of proteins mutated in forms of hereditary nephrotic syndrome or focal segmental glomerulosclerosis (FSGS) were assessed. We found that cultured podocytes express abundant copy numbers of endogenous receptors such as tyrosine kinase membrane receptors, the ANP receptor, and several poorly characterized GPCRs. The dataset was correlated with deep mapping mRNA sequencing ("mRNAseq") data from the native mouse podocyte, the native mouse podocyte proteome and staining intensities from the human protein atlas. The generated dataset was similar to these previously published datasets, but several native and high-abundant podocyte-specific proteins were not identified in the dataset. Notably, these data detected perturbations in proteostatic mechanisms as a dominant alteration during podocyte differentiation, with high proteasome activity in the undifferentiated state and markedly increased expression of lysosomal proteins in the differentiated state. Phosphoproteomic analysis at a resolution of more than 3000 sites suggested a preference of phosphorylation of actin-filament associated proteins in the differentiated state.

Conclusions: The dataset obtained here provides a resource and provides the means for deep mapping of the native podocyte proteome and phosphoproteome in a similar fashion. Differentiation of podocytes affects cell cycle, proteostatic mechanism and phosphorylation of the cytoskeleton.

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FR-PO484

Human Mesangial Enriched Transcription in Health and Glomerular Disease

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Background: Mesangial cells are critical players in the initiation and progression of glomerular disease and are an attractive therapeutic target. However, we lack knowledge of specific mesangial cell function. To address this challenge we aimed to identify mesangial cell lineage-enriched transcripts using *in silico* nano dissection (ND), a genome-scale machine learning-based approach. ND leverages high-throughput transcriptomics data from human microdissected kidney biopsy homogenates, for definition of cell type specific mRNA profiles.

Methods: Lists of mesangial- and non-mesangial-specific genes were curated by 5 experts through literature mining and used as positive- and negative-standard-gene inputs for the prediction. Novel human mesangial cell-enriched transcripts were predicted using *ND*. The prediction efficiency was evaluated by AUC and density plot. Genes with a probability score above 0.8 were validated using independent public resources including HPA, GUDMAP, and PUBMED. Mesangial cell–enriched transcript levels were tested for differential regulation in glomerular disease and association with GFR.

Results: 84 genes were predicted with high probability to be novel human mesangial cell-enriched transcripts. GAS2, FHL2, AEBP1, POSTN, THBS2, GUCY1A36, and AGTR1 were genes with confirmed mesangial-enriched expression by at least one independent resource. The expression of the 84 mesangial gene signature showed significant upregulation in mesangial-proliferative glomerular diseases and in aggregate showed a stronger correlation with eGFR than a random gene set.

Conclusions: We identified human mesangial cell-enriched transcripts and reported the association of their expression with impaired kidney function in CKD. Our work can provide starting points to capture the function of this cell lineage in glomerular disease and support the development of novel treatment options.

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FR-PO485

M1 Macrophage-Induced Loss of KLF15 Promotes Chronic Podocyte Injury

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Background: Krüppel-like factor 15 (KLF15), kidney-enriched transcription factor, is known to participate in the differentiation of podocyte. However, the clinical implication of KLF15 in chronic podocyte injury remains uncorroborated particularly in the relationship with the phenotypic influence of macrophage.

Methods: 5/6 nephrectomized and C-C chemokine receptor type 5 $(CCR5)^{-/-}$ mouse models were used to determine chronic podocyte injury and explore exclusive role of M1 macrophage in terms of KLF15 expression, respectively. Human primary podocytes were flow-cytometically isolated and cultured to emulate the injury process in the *in vitro* system. Biopsied kidney tissues were obtained from the patients with diabetic nephropathy (n=21) to elucidate the relationship between glomerular KLF15 expression and subsequent outcomes (i.e., doubling creatinine and end-stage renal disease).

Results: When 5/6 nephrectomy was predisposed to progressive kidney damage, the fibrosis markers (e.g., fibronectin and collagen type I) increased, but the KLF15 expressions decreased in the site of podocytes. Shrinking KLF15 was strengthened by the forced switch of macrophage to M1 subtype using a taking-off for CCR5 and subsequent Th1 milieu, which resulted in more intense fibrosis [Figure 1]. We also observed corresponding trends

in human primary podocytes, such as increase in fibrosis markers and decrease in KLF15 production after 2-day treatment of TGF-β. Baseline glomerular expression of KLF15 was lower in diabetic patients than healthy individuals. When the patients were divided into 3 groups based on the KLF15 expression, the high expression group (n=7) did not suffer any of worse kidney events during the study period (maximum of 2.5 years).

Conclusions: The KLF15 expressions in podocytes are curtailed depending on the inflexible programming of macrophages into M1 subtype, which is a critical step in chronic podocyte injury.

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Both HIV and Interferon (IFN)-gamma Induce APOL1 Expression in Parietal Epithelial Cells through Down Regulation of miR193a Xiqian Lan,[1] Nirupama Chandel,[1] Vinod Sharma,[1] Manoj K. Tembhre,[1] Abheepsa Mishra,[1] Vinita Vishnoi,[1] Ashwani Malhotra,[1] Catherine Meyer-Schwesinger,[2] Karl Leon Skorecki,[3] Pravin C. Singhal.[1] *[1]Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY; [2]Medicine, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3]Medicine, Rambam Health Care Campus, Haifa, Israel.*

Background: Clinical reports indicate that mutation in APOL1 gene contributed to occurrence of a higher rate of glomerulosclerosis in African Americans (AAs). Notably, >50% of HIV infected AAs with the APOL1 2 risk allele genotype develop HIV-associated nephropathy (HIVAN) if not treated with anti-viral therapy. *In vitro* studies show that podocytes over expressing APOL1 risk variants displayed lysosomal injury. We have previously reported that both HIV and IFNγ enhanced podocyte expression of APOL1. Usually, parietal epithelial cells (PECs) do not express APOL1. We hypothesize that both HIV and IFN-γ have the potential to induce APOL1 expression in PECs through down regulation of mR-193a.

Methods: PECs expressing APOL1G0/G1/G2 were transduced with either vector or HIV (NL4-3) and incubated in media for 24 hours (n=4). In parallel sets of experiment, PECs were incubated in media containing variable concentrations of IFN-γ (0, 1, 5, and 10 ng/ml) for 48 hours. RNAs were extracted and cDNAs were probed for APOL1. Subsequently, cDNAs were probed with specific primers for APOL1. To determine whether IFN-γ has potential to modulate miR-193a expression and associated downstream signaling, PECs were incubated in media containing either buffer or IFN-γ (1, 5, 10 ng/ml) for 72 hours. cDNAs were probed for miR-193a, WT1 (transcription factor for podocyte molecular markers), and PAX2 (PEC marker).

Results: HIV enhanced APOL1 mRNA expression in PECs (control vs. HIV, $P<0.05$). IFN-γ also enhanced APOL1 mRNA expression in a concentration dependent manner (control vs. 0 IFN-γ, $P<0.05$; control vs. 1 IFN-γ, $P<0.05$; 1 IFN-γ vs. 5 IFN-γ, $P<0.05$). IFN-γ down regulated miR-193a and PAX2 but up regulated WT1 in PECs.

Conclusions: Since down regulation of miR193a enhances podocyte maturation, HIV/INF-γ might be enhancing APOL1 expression via down regulation of miR193a in PECs.

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FR-PO487

A Role of Autophagy in Regulation of Podocyte Motility Ryusuke Yotsueda,[1] Kumiko Torisu,[1] Kazuhiko Tsuruya,[1,2] Takanari Kitazono.[1] *[1]Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka City, Fukuoka, Japan; [2]Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka City, Fukuoka, Japan.*

Background: Podocyte-specific deletion of autophagy-related gene results in exacerbating nephrotic syndrome in mouse model of podocyte injury. Recent reports revealed that autophagy is essential for regulation of cell motility. However, the role of autophagy in podocyte motility remains poorly understood.

Methods: Cultured mouse podocyte clones (MPCs) are used for all experiments. Autophagy was inhibited by hydroxychloroquine or siRNA targeting autophagy-related 7 (Atg7). Autophagic activity and localization of autophagosome in MPCs were examined by western blot and immunofluorescence. To assess cell motility, we performed scrape motility assay and haptotaxis cell migration assay. β1 integrin expression was examined by flowcytometry and immunofluorescence. To examine signal transduction for motility, we measured small Rho-GTPase activity. The porlymerization of actin monomers into filamentous actin (F-actin) in MPCs was observed by phalloidin staining.

Results: Autophagy-inhibited MPCs became hypermotile both in scrape motility assay and haptotaxis cell migration assay. β1 integrin colocalized with autophagosome in part, within cytoplasm of MPCs. The expression of β1 integrin on cell membrane decreased, whereas increased in cytosol in autophagy-inhibited MPCs. Inhibition of autophagy resulted in the alterlation of small RhoGTPase activities and increment of F-actin.

Conclusions: Autophagy-inhibited MPCs were hypermotile in our assay. In autophagy-inhibited MPCs, β1 integrin was expressed less on cell surface, whereas accumulated in cytoplasm. We also observed colocalization of β1 integrin and autophagosomes. Taken together, our data suggest that autophagy may regulate turnover of β1 integrin in MPCs. Prevention of the decline in autophagy flux observed in podocytes pharmacologically might be beneficial to treat nephrotic syndromes.

FR-PO488

Exogenous Laminin as a Treatment for Pierson Syndrome Meei-Hua Lin, Jeffrey H. Miner. *Div of Nephrology, Dept of Internal Medicine, Washington Univ School of Medicine, St. Louis, MO.*

Background: Pierson syndrome is a congenital nephrotic disorder that targets the glomerular basement membrane (GBM), an important part of the glomerular filtration barrier. We tested the efficacy of exogenous human laminin α5β2γ1 (hLAM-521) in preventing nephrotic range proteinuria in a Pierson syndrome mouse model with a null mutation in laminin β2 (*Lamb2*).

Methods: *Lamb2-/-* mice were infused i.v. with hLAM-521 daily from P12 to P16 by retro-orbital injection. Mice were monitored for proteinuria by urinary albumin to creatinine ratios and for deposition of hLAM-521 in glomeruli, podocyte injury, and immune response by immunofluorescence and histology.

Results: Injected hLAM-521 deposited into all GBM segments of *Lamb2-/-* mice and remained there for at least 2 weeks. hLAM-521 treatment inhibited progression of proteinuria through P18 in mutants with low proteinuria prior to treatment. In contrast, all untreated mutant mice showed moderate or high proteinuria at P18. The inhibitory effect of hLAM-521 treatment on proteinuria was accompanied by reduced injury to podocytes as judged by lack of desmin, a podocyte injury marker. The ectopic deposition of laminin a1 observed in the GBM of *Lamb2-/-* mice was also reduced compared to untreated mutants. While hLAM-521 treatment was able to remedy the proteinuria of *Lamb2-/-* mice until P18, it did not inhibit progression to nephrotic range proteinuria at P25. Injection of hLAM-521 induced production of circulating antibodies against hLAM-521 and accumulation of immunoglobulins in the GBM, which likely counteracted the efficacy of hLAM-521 treatment after P18. The inability of hLAM-521 to maintain glomerular permselectivity was not associated with immune cell infiltration in glomeruli.

Conclusions: hLAM-521 treatment inhibited progression of proteinuria in *Lamb2-/-* mice with low proteinuria until the immune response caused damage to glomeruli. Future studies will include co-injection of an immunosuppressant and the use of immunodeficient *Lamb2-/-* mice. Despite the immune response, this study demonstrates the feasibility of repairing GBM defects using exogenous delivery of macromolecules.

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FR-PO489

Podocyte Injury: Role of Proteinuria, Urinary Plasminogen and Oxidative Stress as "Second Hit" in Glomerular Injury Leopoldo Raij, Runxia Tian, Jenny Wong, John C. He, Kirk N. Campbell. *Nephrology, VAMC, Univ of Miami & SFVAFRE, Miami, FL; Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Podocytes (POD) are a key target of injury in proteinuric glomerular (Glom) diseases that result in progressive POD loss, FSGS and renal failure. In animal and human nephrotic urine aberrant Glom filtration of Plasminogen (Plg) is activated to biologically active Plasmin by urokinase type plasminogen activator (uPA). In vivo, Amiloride a specific inhibitor of uPA mitigates FSGS in several proteinuric models including 5/6 nephrectomy.

Methods: We utilized human podocytes in culture and *Tg26* HIV and *Cd2ap*$^{-/-}$ mice two models of proteinuria, POD injury and FSGS.

Results: Here we show 2-3 fold urine Plg increase in *Tg26* HIV and *Cd2ap*$^{-/-}$ mice respectively and that human POD express uPA and the Plg receptors uPAR, tPA and Plg-RKT. We demonstrate that Plg treatment of POD upregulates NADPH oxidase isoforms NOX2/NOX4 accompanied by increased production of superoxide anion (O_2^-) 35cpm/μg /min +/-5,$p<0.05$). We demonstrate for the first time that Plg via O_2^- 1) augments by 70% POD expression of the B scavenger receptor CD36 with subsequent POD uptake of oxLDL with increased POD apoptosis from 9 to 15%, Plg vs. Plg oxLDL, $p<0.05$ and 2) Promotes synthesis of Endothelin-1 (200%) a molecule implicated in POD-endothelial cell crosstalk and Glom disease progression. The inhibitor of Plg/Plasmin activation EACA significantly prevented all Plg induced actions. Importantly all molecules that reduce oxidative stress (ROS) Apocynin, inhibitor of NADPH oxidase; AICAR, activator of AMPK and Mito Tempo, inhibitor of mitochondria ROS as well as Amiloride, significantly prevented ($p<0.05$) Plg induction of POD CD36 and Endothelin -1.

Conclusions: We demonstrate novel pathophysiological mechanisms suggesting that following disruption of the Glom filtration barrier at the onset of proteinuric disease, POD are exposed to Plg/ Plasmin resulting in further injury mediated by oxidative stress. We propose that chronic exposure to Plg serves as a "second hit" in glomerular diseases and that Plg is potentially an attractive target for therapeutic intervention.

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FR-PO490

p66Shc Regulates Endothelin-1 Induced Calcium Response in Glomerular Mesangial Cells Kevin D. Wright, Bradley S. Miller, Andrey Sorokin. *Dept of Medicine, Div of Nephrology, Cardiovascular Center, Medical College of Wisconsin, Milwaukee, WI.*

Background: In the kidney, glomerular mesangial cells (GMC) function to regulate glomerular filtration area and secrete extracellular matrix. Endothelin-1 (ET-1) is a critical signaling molecule which triggers an influx of calcium (Ca^{2+}) and subsequent contraction of GMC. Our goal was to assess the contribution of the adaptor protein p66Shc, a known ET-1 signal effector, in the regulation of Ca^{2+} handling and contraction in the GMC.

Methods: Primary GMC isolated from either wild type (WT) Dahl Salt-Sensitive (SS) rats, or from p66Shc mutant rats (on the SS genetic background). In these GMC

which either lacked p66Shc (M4) or have the regulatory Ser36 mutated (S36A), we measured ability of the cells to contract when embedded in a collagen matrix upon ET-1 stimulation. Additionally, we measured ET-1-mediated changes in intracellular calcium levels ($[Ca^{2+}]_i$). We also assayed GMC cells for changes in Ca^{2+} dependent signaling upon ET-1 stimulation. Lastly, in vivo assessment of glomerular filtration rate (GFR) was conducted on WT and mutant rats prior to onset of hypertension, on both high salt (1%) and low salt (0.4%) conditions.

Results: We show WT and mutant cells contract collagen disks to the same extent over 15 minutes after treatment with ET-1. There are, however, differences in collagen disks 24 hrs after ET-1 treatment. Additionally, we demonstrate that the loss of p66Shc increases $[Ca^{2+}]_i$ in ET-1 treated cells. Serum starved mutant GMC also exhibit a decreased baseline $[Ca^{2+}]_i$ than WT cells. Furthermore, the S36A GMC do not show increased $[Ca^{2+}]_i$ compared to WT cells and also exhibit a decreased baseline $[Ca^{2+}]_i$. To complement the changes in $[Ca^{2+}]_i$, there is increased phosphorylation of Ca^{2+} dependent p38 MAPK and Pyk2 in the mutant GMC. Analysis of GFR indicates increased filtration in M4 mutant compared to S36A mutant rats on a low salt (0.4%) diet.

Conclusions: These results establish a role for the adaptor protein p66Shc as a negative regulator of calcium homeostasis in GMC in vitro, where loss of p66Shc increases calcium^{2+} mobilization. Analysis of GFR suggests p66Shc may also function similarly in vivo.

Funding: NIDDK Support

FR-PO491

MDM2 Is Implicated in High Glucose Induced Podocyte Mitotic Catastrophe via Numb/Notch1 Signaling Hui Tang, Hua Su, Chun Zhang. *Nephology, Union Hospital, Tongji Medical College, Huazhong Univ of Science and Technology, Wuhan, Hubei, China.*

Background: Podocyte injury and depletion are essential events involved in the pathogenesis of diabetic nephropathy (DN). As a terminally differentiated cell, podocyte is restricted in 'post-mitosis' state and unable to regenerate. Reentering cell cycle will cause podocyte disastrous death which is defined as mitotic catastrophe (MC). Murine double minute 2 (MDM2), a cell cycle regulator, is widely expressed in renal resident cells including podocytes. Here we explore whether MDM2 involved in podocytes MC during hyperglycemia.

Methods: Patients diagnosed with DN were enrolled in this study, and DN model was constructed on C57BL/6 mice by a single intra-peritoneal injection of STZ. In vitro study human podocyte cell line was employed, and exposed to different treatments after differentiation. Nutlin-3a was used as an inhibitor for MDM2-p53 interaction. The expression of MDM2 and Notch1 was suppressed by genetic deletion.

Results: Aberrant mitotic podocytes with multi-nucleation were observed in DN patients as well as DN mice. Simultaneously the expression of MDM2 in podocytes of DN patients and mice was elevated comparing to control group. In vitro, HG exposure upregulated MDM2's abundance and forced podocytes to enter into S phase or transit G2/M phase with enhanced expression of Ki67 and mitotic markers (Aurora B, p-H3) which were partly reversed by MDM2 genetic deletion. Moreover HG-induced podocyte injury was alleviated by MDM2 knocking down but not by nutlin-3a treatment. Interestingly, we found Numb, an antagonist of Notch1, was decreased in glomeruli from DN mice and podocytes exposed to HG. Knocking down MDM2 attenuated Numb reduction and Notch1 activation. Consistently genetic silencing of Notch1 prevented HG-mediated podocyte MC.

Conclusions: Hyperglycemia upregulates MDM2 expression and leads to podocyte MC in vivo and in vitro. Knocking down MDM2 alleviates HG-induced podocyte MC and injury. Interestingly, MDM2 mediates podocyte MC not via classic p53 pathway but through Numb/Notch1signaling.

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FR-PO492

Deiodinase 3 Dysfunction in Thyroid Hormone-Induced Kidney Disease Nicholas J. Tardi,[1] Chuang Chen,[1] Joao Pedro Werneck-de-Castro,[2] Jochen Reiser.[1] *[1]Int. Med., Rush Univ, Chicago, IL; [2]Endocrinology, Rush Univ, Chicago, IL.*

Background: Thyroid hormone (TH) is a circulating, lipid soluble molecule that plays an important role in physiology and development in nearly all cell types. Accordingly, precise control of TH activity is crucial to maintain homeostasis in several tissues, including the kidney where misregulation of TH can lead to tubular dysfunction and organ growth retardation. However, cases of reversible proteinuria and biopsy-proven glomerular disease associated with hyper/hypothyroidism have been reported in children and adults. TH homeostasis is maintained by deiodinases, which turn on/off tri-iodothyronine (T3), the metabolically active TH hormone. While TH regulation via deiodinases has been studied in endocrine tissues, the role of deiodinases in proteinuric kidney disease has not been addressed. Of particular interest is deiodinase 3 (D3); a catabolic enzyme that inactivates T3. We sought to determine if D3 is present and active in podocytes that regulate kidney filtration.

Methods: D3 expression and activity was analyzed in cultured podocytes treated with puromycin aminonucleoside (PAN), and in mice treated with lipopolysaccharide (LPS). qRTPCR, confocal analysis and Western blot were used to study the expression profile of D3. A cleavage assay using a radiolabeled substrate was used to measure the T3 deactivating capacity of D3.

Results: Podocyte D3 expression displays a 20-fold increase in comparison to deiodinase 1 or 2, and was significantly reduced in LPS-induced proteinuric mice up to 72 hrs, indicating persistent downregulation of D3 in injured podocytes. D3 expression and activity was downregulated in response to podocyte injury. Interestingly, D3 expression was greatly diminished at the cell membrane, yet remained concentrated in the golgi and perinuclear region where metabolically active T3 resides. Additionally, D3 is downregulated in glomeruli of kidney biopsies collected from patients with focal segmental glomerulosclerosis and minimal change disease compared to healthy donors.

Conclusions: Our data suggests D3 downregulation is the source of hyperthyroidism in podocytes, and D3 dysfunction may be a mechanism of TH induced kidney disease in humans.

Funding: NIDDK Support

FR-PO493

Mesenchymal Stem Cells Acquire Morphological and Functional Features of Mesangial Cells as They Repair the Damaged Mesangium Jiamin Teng,[1] Chun Zeng,[1] Elba Turbat-Herrera,[1,2,3] Guillermo A. Herrera.[1,3] *[1]Pathology and Translational Pathobiology, Louisiana State Univ Health Sciences Center in Shreveport, Shreveport, LA; [2]Medicine / Feist-Weiller Cancer Center, Louisiana State Univ Health Sciences Center in Shreveport, Shreveport, LA; [3]Cellular Biology and Anatomy, Louisiana State Univ Health Sciences Center in Shreveport, Shreveport, LA.*

Background: Some studies dealing with mesenchymal stem cells (MSCs) have indicated that they only provide paracrine effects when engaged in the process of tissue repair. In order to assess the specific role of MSCs in mesangial repair, a model of mesangial injury by glomerulopathic light chains was used.

Methods: A 6-D live cell imaging system was used as the in-vitro system and to address the issue. Mesangial cells (MCs) were incubated with light chains obtained from the urine of patients of AL-amyloidosis (AL-Am) and light chain deposition disease (LCDD). The light chains were also perfused through the renal artery in the ex-vivo platform. The respective lesions were reproduced in both platforms. Then, tagged MSCs were introduced. Immunofluorescence, immunohistochemistry and electron microscopy were used to evaluate samples obtained at different time frames. Stains for smoothelin, CD68 and CD29 were used to monitor phenotypic transformation of MSCs in the process of repair. Electrical field stimulation to assess the ability of cells to contract was utilized to assess functionality.

Results: MSCs transformed from an undifferentiated to a macrophage phenotype. The process showed transformed MSCs phagocytosing cellular debris resulting from apoptotic MCs, damaged matrix, amyloid, After the cleaning. MSCs acquired morphologic, functional, and immunophenotypic characteristics of MCs as they proceeded to lay down new mesangial matrix.

Conclusions: MSCs manifest great plasticity as they proceed to repair the damaged mesangium. The fact that they transform allows them to perform different crucial functions. The restored mesangium is possible as new MCs derived from MSCs are able to reproduce the normal mesangium and function as normal MCs.

Funding: Private Foundation Support

FR-PO494

Distinct and Overlapping Requirements for Nck1/2 Adaptors in Podocyte Cytoarchitecture Claire E. Martin,[1] Mira Krendel,[2] Nina Jones.[1] *[1]Molecular and Cellular Biology, Univ of Guelph, Guelph, ON, Canada; [2]Cell and Developmental Biology, SUNY Upstate Medical Univ, Syracuse, NY.*

Background: Podocytes contribute to blood filtration selectivity through a network of actin-based projections termed foot processes. The ability of these structures to withstand hemodynamic strain and maintain filtration barrier integrity is proposed to be tied to their unique and flexible cytoarchitecture. However, the molecular mechanisms that regulate such mechanotransduction are not well understood. We have previously established that the Nck1/2 family of actin adaptors is essential in podocytes for both induction and maintenance of foot processes. We have now characterized the cellular basis of this profound phenotype, and further examined the singular roles of these key adaptor proteins.

Methods: Immortalized mouse podocyte cell (MPC) cultures lacking Nck1 and/or Nck2 were generated, and rescue lines were constructed using adenoviral transduction. Complementary mouse lines deficient in Nck1 and/or Nck2 expression were also investigated.

Results: Striking disruptions in actin organization are present in Nck1/2$^{-/-}$ MPCs, characterized by loss of lamellar sheets and radial stress fibres, with remaining stress fibres appearing haphazard, shortened and highly bundled. Consistent with this, Nck1/2$^{-/-}$ MPCs display defects in cell spreading, migration and response to calcium switch injury. Molecular analysis has revealed overexpression of the actin bundling protein alpha-actinin 4 in Nck-deficient cells and animals, and mislocalization of this protein within focal adhesions. Intriguingly, intermediate and distinct phenotypes are present in Nck1$^{-/-}$ and Nck2$^{-/-}$ MPCs, with Nck1$^{-/-}$, Nck2$^{-/-}$ and Nck1$^{-/+}$; Nck2$^{-/+}$ animals all showing increased susceptibility to foot process effacement and proteinuria in multiple acute injury models.

Conclusions: We conclude that Nck proteins regulate podocyte actin bundling and focal adhesion dynamics, and that a threshold level of both Nck1 and Nck2 is required to maintain homeostasis. The ability of Nck to simultaneously associate with proteins both within the slit diaphragm and along the basal compartment positions Nck as a hub to coordinate mechanical signals within the podocyte.

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

FR-PO495

The Kynurenine Pathway in Podocytes and Parietal Epithelial Cells as a Potential Contributor to Kidney Disease Patricia Bolanos-Palmieri,[1,3] Hermann G. Haller,[1,2] Patricia Ann Schroder,[2] Mario Schiffer.[1,2] *[1]Nephrology, Hannover Medical School, Hannover, Lower Saxony, Germany; [2]Mount Desert Island Biological Laboratory, Bar Harbor, ME; [3]HBRS, Hannover Medical School, Hannover, Lower Saxony, Germany.*

Background: The kynurenine pathway (KP) is responsible for the catabolism of tryptophan resulting in the generation of NAD^+ and a series of metabolically active intermediate products that participate in a number of cellular processes. In the kidneys, this pathway remains largely unexplored however an increasing amount of evidence suggests that changes in the activity and expression pattern of KP enzymes, as well as the accumulation of intermediate by-products are associated with disease. This study aims to provide an initial insight to the role played by the KP in the health and function of glomerular cells and its relationship to kidney disease.

Methods: Knock down (KD) of the enzymes in the KP was performed by morpholino injection in transgenic zebrafish Tg(l-fabp:DBP:EGFP). The phenotype of the morphants was determined according to the severity of the yolk sac edema and pericardial effusion. The maximum fluorescence in the retinal vessel plexus was taken as a measure of integrity of the glomerular filtration barrier. To assess the cellular repercussions of KP inhibition we will use UPF480 to block the pathway and analyze variations in oxygen consumption, extracellular acidification rate, as well as changes in actin cytoskeleton and response to stimuli in Podocytes and PEC.

Results: Our initial KD results show a 2-10 fold reduction in mRNA levels of the KP enzymes and by reducing their expression we are able to induce the formation of edema and detect signs of proteinuria in the MO injected fish. The proportion of fish with severe edema is higher, and the fluorescence is lower when the enzymes AFMID, KMO or KYNU are knocked down, indicating problems in the filtration barrier shown by the excretion of the fluorescent protein in the urine.

Conclusions: Taken together these results suggest that the KP is important in the maintenance and proper function of the filtration barrier, however the cellular and molecular mechanisms by which tryptophan metabolites affect cell function are yet to be elucidated.

Funding: Government Support - Non-U.S.

FR-PO496

Elucidation of the Roles of Tissue Transglutaminase in Mesangial Proliferative Glomerulonephritis Akihiro Kato,[1] Tomohiro Mizuno,[2] Kazuo Takahashi,[1] Hideki Tatsukawa,[3] Masashi Mizuno,[4] Kiyotaka Hitomi,[3] Yukio Yuzawa.[1] *[1]Fujita Health Univ School of Medicine, Toyoake, Aichi, Japan; [2]Meijo Univ, Nagoya, Aichi, Japan; [3]Nagoya Univ Graduate School of Pharmaceutical Sciences, Nagoya, Aichi, Japan; [4]Nagoya Univ Graduate School of Medicine, Nagoya, Aichi, Japan.*

Background: Tissue transglutaminase (TG2) is a calcium ion-dependent protein-cross-linking enzyme that plays an important role in fibrosis and inflammation. TG2 is ubiquitously expressed enzyme and mainly distributed intracellularly as a catalytically inactive state due to low calcium concentration in the cells. We have established a method using a TG2-specific FITC-labeled highly reactive substrate peptide for the detection of TG2 activity in renal biopsy tissue. We applied this method to detect active form of TG2 in human renal biopsy tissues (n=241), and found that TG2 activities were high in mesangial areas in patients with IgA nephropathy and lupus nephritis (J Am Soc Nephrol, 2015;26:723A).

Methods: Under normal circumstances, cellular TG2 is catalytically inactive. We hypothesized that the activation of TG2 in mesangial areas may result from its shifting from the intracellular to the extracellular space by complement mediated cell damages. As a complement-mediated stimulus, human glomerular mesangial cells (HGMCs)were stimulated with normal human serum. The levels of TG2 in the culture supernatants as well as those in the intracellular compartment were measured by using ELISA. In addition, human recombinant TG2 and Platelet-Derived Growth Factor (PDGF) were added to HGMCs and cell growth was examined by performing a confluence assay.

Results: Complement-mediated stimulation of HGMCs was accompanied by a significant increase in TG2 levels in the culture supernatant and a decrease in the intracellular TG2 levels. The reaction was not observed in inactivated normal human serum, and was inhibited in the presence of C1 elastase inhibitor. When human recombinant TG2 and PDGF were added to HGMCs, cell growth was significantly promoted.

Conclusions: The extracellular shift and activation of TG2 may be due to complement activation in mesangial cells and could be involved in the progression of mesangial proliferative glomerulonephritis such as IgA nephropathy and lupus nephritis.

Funding: Government Support - Non-U.S.

FR-PO497

Puromycin Aminonucleoside Induces Endoplasmic Reticulum Stress and Apoptosis in Podocyte Tae-Sun Ha. *Pediatrics, Chungbuk National Univ, Cheongju, Chungbuk, Republic of Korea.*

Background: Puromycin aminonucleoside (PAN) is known to be a podocytotoxin, therefore, PAN-induced nephrosis is a widely studied animal model of human idiopathic nephrotic syndrome. Endoplasmic reticulum (ER) stress is the common findings under various pathogenic microenvironments, contributing to the progression of various podocyte diseases. Abnormal protein accumulation associated with ER stress in the ER of podocytes produces structural and functional damage in the cells, which in turn leads to podocyte apoptosis and severe proteinuria. In the present study, we investigated the effect of PAN on ER stress and apoptosis in *in vitro* podocytes.

Methods: We cultured rat and mouse podocytes and treated with various concentrations of PAN and evaluated ER stress markers by western blotting and apoptosis FACS and TUNEL assays.

Results: PANtreatment increased GRP78 protein, an ER chaperone,as early as at 2 hrs, which was not ameliorated by anti-oxidants. PAN also increased ER stress markers, such as, ATF6a and caspase 12 at 12 and 24 hrs, which were improved by ATF6 siRNA and chemical chaperones, such as, sodium 4-phenylbutyric acid (PBA) and TUDCA, however, not by Nox4 siRNA.PAN treatment increased oxidative stress level of podocytes significantly with the induction of Nox4. In addition, PAN induced podocyte apoptosis significantly in concentration- and time-dependent manners in FACS and TUNEL assays, which were improved by Nox4 siRNA, ATF6 siRNA, and chemical chaperones. Therefore, PAN induced ER stress, thereafter, increased oxidative stress, subsequently induced podocyte apoptosis.

Conclusions: Our studies suggest that PAN could induce podocyte ER stress of mainly ATF6a and caspase 12 pathways, which would contribute to the development of podocyte apoptosis via oxidative stress.

Funding: Government Support - Non-U.S.

FR-PO498

RNA Binding Protein Staufen 2 Is Required for Normal Podocyte Adhesion Jessica J. Harris,[1] George J. Cope,[2] Valerie A. Schumacher.[1] *[1]Dept of Urology, Boston Children's Hospital, Boston, MA; [2]Cardiff Univ, Cardiff, United Kingdom.*

Background: Podocytes are critical for the maintenance of the glomerular filtration barrier (GFB) and need to be able to adapt to changes such as variations in pressure or cellular injury, to do so they may need to alter cell-matrix interactions. Failure in the ability to respond to such changes can lead to the irreversible loss of podocytes from the GFB. Our preliminary data supports the novel concept that podocytes store mRNAs in discrete locations in the cell until protein is needed and the mRNAs locally translated to regulate cell adhesion. The localization of mRNAs within a cell can be regulated RNA binding proteins such as Staufen2. Our main focus is to determine how Staufen2 regulates the formation and maintenance of cell-matrix adhesions within the podocyte up on injury and up on adhesion of cells.

Methods: Adriamycin (ADR) treatment was used as a model of injury. siRNA was used to knockdown Staufen2 *in vitro*. Detachment of cells was monitored using a crystal violet assay. Phase contrast microscopy and ImageJ analysis were used to investigate cell spreading and western blotting used to study cell signaling.

Results: Using an *in vivo* model we show that ADR induced injury results in an increase of the phosphorylation of S6 protein indicating an increase in protein. This correlates with an increase of ribosomes within podocyte foot processes. Staufen2 is expressed in podocytes and localizes to focal adhesions *in vitro*. Podocytes lacking Staufen2 detach over time and have smaller paxillin positive focal adhesions compared to control cells. ADR induced cellular injury enhances this decrease in adhesive area. We investigated the role of Staufen2 up on podocyte adhesion to laminin and find that Staufen2 deficient podocytes show a defect in spreading. We also show that glycosylation of integrin beta1 is altered in podocytes lacking Staufen2 and that there is a reduction in phosphorylation of key adhesion related molecules.

Conclusions: Staufen2 is localized to adhesive complexes in podocytes and is required for proper spreading and maintenance of adhesion. Knockdown of Staufen2 leads to defects in glycosylation and signaling.

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FR-PO499

Diet1 Is a Novel Gene Associated with Albuminuria Jessica Ong,[1,3] Laurent Vergnes,[1] Ira Kurtz,[2] Karen Reue.[1,2,3] *[1]Human Genetics, Univ of California, Los Angeles; [2]David Geffen School of Medicine, Univ of California, Los Angeles; [3]Molecular Biology Inst, Univ of California, Los Angeles, CA.*

Background: *Diet1* is a gene previously identified from a naturally occurring null mutation in an inbred mouse strain. Studies in this mouse strain showed that Diet1 plays an important role in bile acid signaling by modulating FGF15/19 secretion. *In situ* hybridization demonstrated *Diet1* expression exclusively in the small intestine and in the renal proximal tubule. At present, nothing is known about the role of *Diet1* in the kidney, but a GWAS study for urinary albumin excretion has revealed a significant association with a polymorphism in *DIET1*.

Methods: To investigate the role of Diet1 in the kidney, we created a congenic mouse strain carrying the *Diet1* null mutation on a C57BL/6J background. Male and female $Diet1^{+/+}$ and $Diet1^{-/-}$ mice were studied on standard mouse chow and an atherogenic diet. Twenty-four hour urine samples were collected and assessed for albumin and creatinine excretion rates. In addition, on the atherogenic diet, blood chemistries and kidney tissue were obtained for histology, electron microscopy, and gene expression studies.

Results: On standard mouse chow, there was no difference in albumin excretion rates of $Diet1^{-/-}$ compared to $Diet1^{+/+}$ mice. However, on the atherogenic diet, $Diet1^{-/-}$ mice exhibited a significantly greater urinary albumin excretion compared to $Diet1^{+/+}$ (77.3% in males and 49.1% in females) without any difference in creatinine clearance. Renal histology and ultrastructural studies of the glomeruli and proximal tubules did not reveal significant differences between $Diet1^{+/+}$ and $Diet1^{-/-}$ mice, suggesting that Diet1 may have a regulatory role in albumin absorption by the kidney.

Conclusions: We have documented for the first time a role for *Diet1* in renal albumin handling in mice. Given the localized expression of *Diet1* in the proximal tubule, our results suggest a new modulatory pathway whereby Diet1 plays a role in proximal tubule albumin absorption depending on the dietary lipid content.

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FR-PO500

The Effects of Diabetes Mellitus on Cell Surface Heparan Sulfate Proteoglycans: The Uncoupling of Syndecan-4 in Podocytes due to Early Loss of N-Sulfated Heparan Deborah J. McCarthy, Kevin J. McCarthy. *Dept of Pathology and Translational Pathobiology, LSU Health Sciences Center, Shreveport, LA.*

Background: Previous work from our laboratory showed that the loss of heparan sulfate (HS) or the depletion of N-sulfated groups (NS) on HS attached to cell surface proteoglycans (PG) led to the development of podocyte (POD) foot process effacement *in vivo* and compromised cell-matrix adhesion *in vitro*, mediated by the "uncoupling" of syndecan-4 (Sdc4) from matrix protein ligands. This study extends this concept to explore the loss of NS in the glomerular basement membrane (GBM) of diabetic animals.

Methods: Control and db/db mice 16 weeks of age were sacrificed, the kidneys removed and processed for paraffin, frozen, and transmission electron microscopy (TEM). Frozen sections were double label immunostained for total HS and N-sulfated HS; Sd4 and either nephrin, synaptopodin, or a-actinin 4. Paraffin sections were stained with PAS/Alcian Blue to demonstrate glomerular hypertrophy and mesangial expansion. Tissue sections were imaged using an Olympus IX-70 microscope equipped for epifluorescent illumination or for TEM, a Hitachi TEM.

Results: PAS/Alcian Blue staining of glomeruli of db/db mice showed glomeruli ranging from normal to glomeruli having glomerular hypertrophy and early mesangial expansion. Immunostaining for NS and HS in glomeruli from control animals revealed glomerular capillaries whose GBMs stained positive for both NS and HS, indicating that the PGs contained normal HS species. GBM staining of diabetic glomeruli showed the presence of PGs lacking NS but whose total HS content remained unchanged. Capillaries in the diabetic glomeruli showed a breakdown in the linear co-distribution of Sdc4 and a-actinin-4 along the length of the GBM.

Conclusions: Our data show that in the early stages of diabetic nephropathy there is a loss of NS on HS associated with Sdc4, one of the cell surface proteoglycans that are now known to be critical in POD-matrix interactions. This change is associated with uncoupling of Sdc4 ectodomain from its GBM ligands which, in turn, leads to disruption of the a-actinin-4 cytoskeleton linkage in PODs and foot process effacement.

Funding: NIDDK Support

FR-PO501

Characterizing the Differential Regulation of Podocyte ANLN Expression by AKT1 and AKT2 Gentzon Hall,[1,3,4] Guanghong Wu,[1,4] Gina E. Kovalik,[1,4] Brandon M. Lane,[2,4] Megan Chryst-Ladd,[4] Robert F. Spurney,[1,3,4] Rasheed A. Gbadegesin.[2,3,4] *[1]Dept of Medicine, Duke Univ Medical Center; [2]Dept of Pediatrics, Duke Univ Medical Center; [3]Div of Nephrology, Duke Univ Medical Center; [4]Duke Molecular Physiology Inst, Duke Univ Medical Center.*

Background: We previously demonstrated that mutations in the F-actin bundling and cell cycle regulatory protein ANLN cause FSGS. Additionally, we have shown that: 1. ANLN expression is upregulated in podocytes in a mouse model of HIV associated nephropathy (HIVAN), 2. ANLN overexpression is sufficient to enhance proliferation and motility of cultured podocytes, and 3. ANLN gene expression is regulated by AKT. These findings suggest that the upregulation of ANLN may play role in the pathobiology of podocyte dysfunction in FSGS. Moreover, therapies that reduce ANLN gene expression might ameliorate the disease. Given the emergence of isoform-specific AKT-antisense therapies (e.g. Archexin), we sought to define the roles of AKT1 and AKT2 in the regulation of podocyte ANLN gene expression.

Methods: We used immunoblotting and cell proliferation assays to evaluate the effects of targeted AKT1 and AKT2 knockdown on ANLN expression and cell proliferation in tetracycline-inducible AKT1-shRNA and AKT2-shRNA podocyte lines.

Results: In AKT2-shRNA-expressing podocytes, ANLN expression and podocyte proliferation were significantly reduced relative to controls. Conversely, ANLN expression was significantly upregulated in AKT1-shRNA-expressing podocytes.

Conclusions: These data suggest an opposing role for AKT1 and AKT2 in the regulation of podocyte ANLN gene expression. Isoform specific modulation of AKT using genetic nanotherapies might be a novel therapeutic strategy for the treatment of FSGS.

Funding: NIDDK Support

FR-PO502

Transcriptional Reprogramming by WT1 in Murine Podocytes Affected by Hereditary FSGS Mahdieh Rahmatollahi, Martin Kann, Maximilian O. Lenz, Bernhard Schermer, Thomas Benzing. *Dept II of Medicine, Nephrology, Rheumatology and Diabetology and Center for Molecular Medicine Cologne, Univ of Cologne, Cologne, Germany.*

Background: Mutations in several podocyte transcription factors (TF) including Wt1 are known to cause hereditary FSGS. However, the gene regulatory networks governed by these TFs in healthy and diseased podocytes are as yet poorly characterized. Here, we investigate Wt1 dependent gene regulatory reprogramming at an early stage of podocyte damage in a mouse model of hereditary FSGS.

Methods: Heterozygous deletion of Wt1 (Wt1het) was chosen as a murine model of hereditary FSGS. Wt1 gene regulatory function was assayed in Wt1het mice and control littermates by ChIPseq for Wt1 at age 4 weeks, an early proteinuric yet not sclerotic stage of glomerular damage. Results were computationally analyzed using standard ChIPseq algorithms.

Results: Wt1het mice showed a consistent phenotype of proteinuria present at age 4 weeks and glomerulosclerosis at age 15 weeks. Wt1 ChIPseq at age 4 weeks identified several thousand conserved Wt1 binding sites (peaks) in both, Wt1het and control animals. Wt1 peaks were reproducible, conserved, predominantly located in putative enhancers, and harbored the established Wt1 DNA binding motif in either condition. In principal component analysis, ChIPseq data clustered according to genotype. Differential binding analysis between Wt1het mice and controls identified changes in binding strengths corresponding to gene regulatory reprogramming events at one third of all Wt1 peaks. Reduction of Wt1 binding strengths was predominant upon glomerular damage with a small cluster of novel Wt1 peaks occurring. The majority of reprogramming events took place at putative enhancers, highlighting their importance to gene regulatory networks. Gene ontology analysis revealed key reprogramming events to be enriched at genes associated with podocyte damage signaling pathways such as Tgf-beta and Wnt, involving Wt1 in transcriptional regulation of such pathways at an early disease stage in this FSGS model.

Conclusions: In a murine model of hereditary FSGS, Wt1 is involved in gene regulatory reprogramming of signaling pathways relevant to podocyte damage at an early stage of disease.

Funding: Government Support - Non-U.S.

FR-PO503

BRAF Signalling Pathway Inhibition Causing Glomerular Injury Luca Perico,[1] Mario Mandala,[2] Arrigo Schieppati,[2] Camillo Carrara,[1] Paola Rizzo,[1] Sara Conti,[1] Lorena Longaretti,[1] Ariela Benigni,[1] Giuseppe Remuzzi.[1,2] *[1]IRCCS - Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy; [2]ASST Papa Giovanni XXIII, Bergamo, Italy.*

Background: The glomerulus is uniquely susceptible to chemotherapeutic injury, though molecular targets have not been fully identified. Dabrafenib and trametinib, BRAF and MEK inhibitors, are effective targeted therapies for malignant metastatic melanoma but less is known about their nephrotoxicity. While initial trials with BRAF inhibitors suggested no renal side effects, recent case reports uncovered significant nephrotoxic events. Whereas most of the published data revealed tubulointerstitial injury as the main renal consequence of these drugs, none depicted nephrotic syndrome (NS) and glomerular damage.

Methods: Starting from the case of a patient with metastatic melanoma who developed NS during dabrafenib and trametinib treatment, we evaluated glomerular ultrastructural changes by electron microscopy analysis and the molecular mechanisms underlying the targeted therapy-induced NS by combining *in vitro* experiment in podocytes and *ex vivo* analysis in the patient biopsies.

Results: Electron microscopy analysis showed diffuse loss of podocyte cytoarchitecture, extensive foot process effacement and glomerular capillary injury in the patient's biopsy during drug treatment. Renal function and glomerular damage recovered after drug withdrawal. *In vitro* experiments documented that BRAF inhibition was the primary culprit in the podocyte slit diaphragm impairment *via* reduction of PLCξ1 and nephrin expression, leading to increased albumin permeability. BRAF and MEK inhibitors jointly altered the overall glomerular functional properties by inhibiting the podocyte VEGF system. The above mechanisms were corroborated *ex vivo* in the patient biopsies.

Conclusions: We demonstrate that MAPK pathway inhibition alters slit diaphragm architecture and we provide direct experimental evidence that this inhibition is a possible novel pathogenic mechanism leading to NS. Besides its implications for NS pathophysiology, we suggest that patients should be monitored closely for potential glomerular damage during follow-up since the dabrafenib and trametinib combination is a standard treatment for melanoma patients.

FR-PO504

The Neonatal Fc Receptor (FcRn) Is Required for IgG but Not Albumin Trafficking in Podocytes In Vitro and In Vivo Evgenia Dobrinskikh,[1] Linda Lewis,[1] Patricia M. Zerfas,[2] Avi Rosenberg,[3] Jeffrey B. Kopp,[3] Judith Blaine.[1] *[1]Medicine, Univ of Colorado Denver, Aurora, CO; [2]ORS, NIH, Bethesda, MD; [3]NIDDK, NIH, Bethesda, MD.*

Background: Proteinuria is strongly associated with kidney disease progression. Podocytes are key constituents of the glomerular filtration barrier (GFB), which determines protein permselectivity. By conservative estimates, 2-9 g of serum proteins pass daily through the GFB. The molecular mechanisms whereby podocytes handle albumin and IgG

remain to be fully determined. Previously, we have shown that transcytosis is the major pathway by which cultured podocytes transport albumin and IgG. In other epithelial cell types, the neonatal Fc receptor (FcRn) is required, thereby salvaging these proteins from degradative pathways.

Methods: Intracellular levels of albumin or IgG in wild type (WT) or FcRn knockout (KO) cultured podocytes were analyzed by Western blot. In vivo effects of FcRn KO on glomerular trafficking of albumin and IgG were examined in control and podocyte-specific FcRn KO mice.

Results: IgG treatment resulted in significantly increased intracellular accumulation of IgG in FcRn KO versus WT cultured podocytes. Densitometric analysis of Western blots showed more intracellular IgG in the KO 0.97 ± 0.16 (KO) compared to WT 0.51 ± 0.06 (mean ± SEM, arbitrary units), $p<0.05$. Surprisingly, FcRn KO had no effect on albumin trafficking in cultured podocytes. There was no difference between WT and KO podocytes in the amount of intracellular albumin remaining 1 h after loading (0.54 ± 0.06 in KO versus 0.38 ± 0.06 in WT, p=NS), suggesting that FcRn is not required for albumin transcytosis. In an in vivo model, there was no significant difference in albuminuria between podocyte-specific FcRn KO and WT mice. Aging resulted in increased intraglomerular accumulation of IgG but not albumin in podocyte-specific FcRn KO compared to WT mice, assessed by immunostaining. Aging also resulted in mesangial expansion in the KO mice, assessed by light and electron microscopy.

Conclusions: These studies indicate that FcRn is required for podocyte transcytosis of IgG but not albumin in vitro and in vivo and suggests that podocytes and proximal tubules handle serum proteins differently.

Funding: NIDDK Support, Private Foundation Support

FR-PO505

Loss of ABIN1 Ubiquitin Binding Function in Podocytes Alters the Exosomal Proteome to a Pro-Inflammatory Phenotype Ryan M. Sheehan, Erik Korte, Michael Merchant, David W. Powell. *Medicine/Nephrology, Univ of Louisville, Louisville, KY.*

Background: Proteomic analysis of urinary exosomes have revealed known markers for podocyte damage and unknown proteins that may play a role in glomerular disease pathogenesis. The formation and packaging of exosomes into multivesicular bodies (MVB) is coordinated by the endosomal sorting complex required for transport (ESCRT) which binds and sorts ubiquitinated proteins. We previous reported that mice with disrupted ABIN1 ubiquitin binding activity develop glomerulonephritis through enhanced pro-inflammatory NF-κB activation. The present study tested a hypothesis that ABIN1[D472N] mutation, lacking ubiquitin binding, alters the proteomic profile within exosomes released from podocytes.

Methods: Expression and secretion proteins within exosomes were assessed in wild type and ABIN1[D472N] expressing human-derived podocytes using protein arrays, qRT-PCR, and SILAC based quantitative mass spectrometry. ABIN1 expression and localization was assessed using confocal microscopy with the early endosomal marker Rab5. The interaction of ABIN1 with exosomal sorting proteins was assessed by co-immunoprecipitation.

Results: Ingenuity pathway analysis of exosomal proteomes revealed an association with kidney damage and immune response in ABIN1[D472N] podocytes. With significant increases in extracellar matrix altering proteins (FN1, SPARC), chemokines (CXCL1, IL-8), actin remodeling proteins (GSN), complement factor (C3), and acute inflammatory maker (SAA1). Two candidates, KU70 and HMGA1, were significantly down regulated in the exosomes from ABIN1[D472N] podocytes, but cytosolic protein and mRNA expression did not differ. The ABIN1 mutation did not affect colocalization with Rab5 at the early endosome, but did alter its interaction with ESCRT accessory protein Alix.

Conclusions: Our findings suggest that ABIN1 ubiquitin binding and localization at the early endosome act as a novel sorting mechanism of exosomal protein packaging. We postulate that podocytes with ABIN1 genetic variants secrete exosomes that enhance glomerular inflammation through intercellular transfer of proteins, providing biomarker candidates and novel mechanistic insight for improved therapeutics.

Funding: Other NIH Support - NIAMS

FR-PO506

Omentin Regulates Podocyte Function and Albuminuria Hidetoshi Kobayashi, Fumihiko Furuya, Kenichiro Kitamura. *Third Dept of Internal Medicine, Univ of Yamanashi, Chuo, Yamanashi, Japan.*

Background: Albuminuria has recently been recognized as the most significant risk factor for end-stage renal disease (ESRD) in diabetics. An adipokine, omeenin, is preferentially produced by visceral adipose tissue compared with subcutaneous adipose tissue. The aim of this study was to elucidate whether serum omentin level is associated with the progression of diabetic nephropathy (DN) and to explore the direct effects of omentin on podocyte injury to determine the mechanisms by which omentin contributes to the development of albuminuria.

Methods: The prospective follow-up study; 114 diabetes patients were followed for 6 years. Patients were divided at baseline into three groups according to their urinary albumin-to-creatinine ratio. To explore the molecular mechanisms of omentin-mediated renoprotective function, we investigated the mouse podocytes with or without recombinant omentin treatment.

Results: Progression either to the next albuminuria level in 16 patients or to end-stage renal disease ESRD occurred in 5 patients. In the patients with microalbuminuria and macroalbuminuria, progression of albuminuria was associated with higher serum omentin levels. When these covariates were inserted in a Cox regression analysis, eGFR and serum omentin levels were independently associated with progression of DN. In cultured podocytes, treatment with omentin significantly increased AMPK activities, and both omentin and AMPK activation reduced podocyte permeability to albumin and podocyte dysfunction, as evidenced by zona occludens-1 translocation to the membrane. Since omentin reduced protein levels of NADPH oxidase Nox4 in podocytes, we speculated that these protective effects of omentin were caused by the reduction of oxidative stress.

Conclusions: In conclusion, increased serum omentin levels predict the progression from microalbuminuria to macroalbuminuria and macroalbuminuria to ESRD in diabetic patients. Our in vitro findings suggest that omentin is a key regulator of albuminuria, likely acting through the AMPK pathway to modulate oxidant stress in podocytes.

FR-PO507

Microtubule and Actin Crosstalk in Podocytes Kamalika Mukherjee, Changkyu Gu, Sanja Sever. *Dept of Medicine/Div of Nephrology, Massachusetts General Hospital/Harvard Medical School, Charlestown, MA.*

Background: Podocyte injury, dysfunction and loss have been implicated in a number of diverse kidney diseases such as focal segmental glomerulosclerosis, diabetic nephropathy and HIV-associated nephropathy. It is known that structural and functional alteration of the podocyte actin cytoskeleton culminates in foot process effacement and proteinuria. The coordinated organization of the cytoskeleton is crucial for maintaining the physiological function of podocytes. The two predominant cytoskeletal proteins present in major processes and foot processes of podocytes are microtubules and actin respectively. We therefore sought to investigate the crosstalk between microtubules and actin in podocytes and identify regulatory proteins that may modulate such interactions.

Methods: Tubulin, actin and paxillin were immunostained to observe the effect of microtubule- and actin- regulating small molecules on podocytes. Dynamin oligomerization was analyzed by monitoring dynamin's ability to hydrolyze GTP over time. Microtubule polymerization and depolymerization in the presence of dynamin or small molecules were monitored using a DAPI based fluorescence assay.

Results: 1. Microtubule active ligands alter actin cytoskeleton and focal adhesion turnover in podocytes. 2. Actin-regulating drugs reorganize microtubule cytoskeleton. 3. Microtubules promote dynamin oligomerization. 4. Dynamin promotes microtubule depolymerization. 5. Dynamin inhibits tubulin polymerization.

Conclusions: Altering microtubule cytoskeleton in podocytes results in reorganization of actin cytoarchitecture and *vice versa*. This finding demonstrates the existence of a crosstalk between the two cytoskeletal proteins in podocytes. There is evidence that dynamin oligomerization promotes actin polymerization. Here, we report that dynamin self-assembles around microtubules and promotes depolymerization of microtubules and inhibits tubulin polymerization into microtubules. Taken together, dynamin oligomerization regulates polymerization activity of both microtubules and actin. Our findings therefore strongly suggest that dynamin may be one of the regulatory proteins that facilitate actin and microtubule crosstalk in podocytes.

Funding: NIDDK Support

FR-PO508

Par3A and Par3B Exhibit Compensatory Roles to Maintain aPKC Mediated Polarity Signaling at the Slit Diaphragm Sybille Köhler,[1] Wilhelm Bloch,[5] Bernhard Schermer,[1,2,4] Thomas Benzing,[1,2,4] Paul T. Brinkkoetter.[1] *[1]Dept II of Internal Medicine and Center for Molecular Medicine, Univ of Cologne, Cologne, Germany; [2]Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Univ of Cologne, Cologne, Germany; [3]Dept of Dermatology and Center for Molecular Medicine Cologne, Univ of Cologne, Cologne, Germany; [4]Systems Biology of Ageing Cologne (Sybacol), Univ of Cologne, Cologne, Germany; [5]Dept of Molecular and Cellular Sport Medicine, German Sport Univ Cologne, Cologne, Germany; [6]Clinical Inst of Pathology, Medical Univ of Vienna, Vienna, Austria.*

Background: Polarity signaling through the aPKC-Par polarity complex is essential for the development and maintenance of the podocyte architecture and the function of the glomerular filtration barrier of the kidney. Despite its well-established role in aPKC-mediated signaling, Par3A appears to be dispensable for the function of the glomerular filtration barrier.

Results: mRNA seq data from primary podocytes revealed high levels of Par3B in podocytes, which were much higher in comparison to Par3A levels. Interestingly, Par3B localized to the slit diaphragm as demonstrated by immunofluorescent stainings and immunogold-labellings suggesting a role of Par3B at the slit diaphragm. To study Par3B function at the slit, we generated a novel podocyte-specific Par3B knockout mouse model. Loss of Par3B did not cause glomerulosclerosis or albuminuria. To study potential compensatory mechanisms between Par3A and Par3B, we generated podocyte-specific Par3A/B double knockout mice. Par3A/B double knockout mice were born following Mendelian rules. Within 8 weeks of age Par3A/B DKO mice developed severe proteinuria in comparison to control mice. To further study the interplay between the different Par3 proteins we utilized *Drosophila* nephrocytes and silenced expression of the Par3A/B homolog *bazooka* which also resulted in disturbed nephrocyte morphology and a severe filtration defect.

Conclusions: Taken together, these findings support the hypothesis of potential compensatory mechanisms between Par3A and Par3B to maintain aPKC mediated polarity signaling at the slit diaphragm.

FR-PO509

Regulation of Canonical Wnt Signaling by the Transcription Factor HNF-1β Siu Chiu Chan,[1] Sachin S. Hajarnis,[2] Patricia Cobo-Stark,[2] Karam S. Aboudehen,[1] Peter Igarashi.[1] *[1]Medicine, Univ of Minnesota Medical School, Minneapolis, MN; [2]Internal Medicine, Univ of Texas Southwestern Medical Center, Dallas, TX.*

Background: Hepatocyte nuclear factor-1β (HNF-1β) is a tissue-specific transcription factor that is required for kidney development and tubular function. Mutations of HNF-1β produce kidney cysts and end-stage kidney failure. Activation of canonical (β-catenin-dependent) Wnt signaling has been implicated in cystic kidney disease and has been detected in HNF-1β mutant kidneys.

Methods: HNF-1β-deficient mIMCD3 cells were produced by gene editing with CRISPR/Cas9. Gene expression was measured by RNA-seq and qRT-PCR. Transcriptional activity was measured with ChIP and luciferase reporter assays.

Results: RNA-seq and Ingenuity Pathway Analysis identified Wnt signaling as one of the most dysregulated pathways in HNF-1β-deficient cells. ChIP-seq analysis identified members of the T-cell factor/lymphoid-enhancer factor (TCF/LEF) family as novel HNF-1β transcriptional targets. Expression of Lef1 was increased in HNF-1β-deficient cells and cells expressing dominant-negative (DN) mutant HNF1β. Knockdown of Lef1 with siRNA decreased β-catenin-dependent transcription and Axin2 mRNA levels in DN-HNF1β-expressing cells. Two functional HNF-1β binding sites were identified in the Lef1 locus by ChIP and luciferase reporter assays. HNF-1β-deficient cells were hyperresponsive to Wnt3a as evidenced by upregulation of canonical Wnt targets Axin2, Sp5 and Lef1. Deletion of the β-catenin-binding domain in Lef1 partially rescued the hyperresponsiveness to Wnt3a. Increased expression of Axin2 and Lef1 was confirmed in vivo by qRT-PCR analysis of kidneys from HNF-1β mutant mice.

Conclusions: Increased expression of Lef1 contributes importantly to the activation of canonical Wnt signaling in HNF-1β mutant cells through a feed-forward mechanism. Characterization of genes that are activated by Wnt in HNF-1β mutant renal epithelial cells may identify new therapeutic targets for the treatment of cystic kidney diseases.

Funding: NIDDK Support

FR-PO510

Inactivation of Transcription Factor HNF-1β with CRISPR/Cas9 Induces Epithelial-Mesenchymal Transition Siu Chiu Chan,[1] Ying Zhang,[2] Sophia M. Vrba,[1] Svetlana Avdulov,[1] Karam S. Aboudehen,[1] Peter Igarashi.[1] *[1]Medicine, Univ of Minnesota, Minneapolis, MN; [2]Minnesota Supercomputing Inst, Univ of Minnesota, Minneapolis, MN.*

Background: Hepatocyte nuclear factor-1β (HNF-1β) is a tissue-specific transcription factor that is essential for the development of the kidney. Mutations of HNF-1β produce autosomal dominant tubulointerstitial kidney disease (ADTKD) characterized by tubular cysts, renal fibrosis, and progressive loss of kidney function. To understand the functions of HNF-1β, we generated HNF-1β-deficient mIMCD3 renal epithelial cells.

Methods: Gene editing with CRISPR/Cas9 was used to delete exon 1 of HNF-1β by non-homologous end joining (NHEJ). HNF-1β-deficient cells were characterized by RNA-seq, western blotting (WB), and assays of proliferation and cell migration.

Results: Three independent HNF-1β-deficient mIMCD3 cell lines and three paired control cell lines were established. qRT-PCR and WB confirmed the complete absence of HNF-1β expression. RNA-seq analysis of HNF-1β-deficient cells showed upregulation of 1,135 genes and repression of 759 genes compared to control cells. ChIP-seq analysis showed that 75% of the differentially expressed genes were direct targets of HNF-1β. Ingenuity Pathway Analysis (IPA) of the HNF-1β targets revealed that fibrosis and epithelial-mesenchymal transition (EMT) pathways were highly activated in HNF-1β-deficient cells. Canonical EMT markers, including vimentin, α-SMA and Zeb2, were up-regulated in HNF-1β mutant cells. HNF-1β mutant cells exhibited loss of contact inhibition and adopted a spindle-shaped morphology. Compared with control cells, HNF-1β-deficient cells had similar growth curves and rates of cell proliferation but exhibited increased cell migration. HNF-1β-deficient cells grown to confluence on Lumox discs produced a multilayered epithelium similar to the phenotype observed in kidneys from HNF-1β mutant mice and humans.

Conclusions: Loss of HNF-1β in renal epithelial cells is sufficient to induce EMT. HNF-1β-deficient mIMCD3 cells created by gene editing will be a useful reagent for unraveling the HNF-1β mutant phenotype.

Funding: NIDDK Support

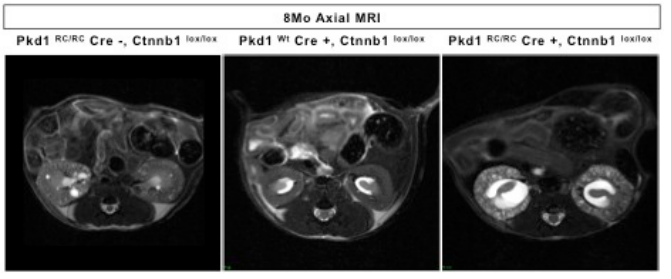
FR-PO511

A Role for Canonical Wnt Signaling in Renal Development, Maintenance, and ADPKD Jennifer Arroyo, Cynthia J. Sieben, Vicente E. Torres, Peter C. Harris. *Nephrology & Hypertension, Mayo Clinic.*

Background: The developmental pathway, Wnt, is important for nephron development, and is suggested to be re-activated post-developmentally in response to injury, cancer and polycystic kidney disease (PKD). Increased Wnt signaling is hypothesized to contribute to increased proliferation in cystogenesis, with a possible direct interaction between Wnt ligands and the PKD1 protein, however assessments of Wnt activity in various PKD mouse models has yielded conflicting results.

Methods: To understand the contribution of Wnt signaling in PKD progression we analyzed the *TCF/Lef:H2B-GFP* transgenic Wnt reporter mouse interbred with the ADPKD mouse model, $Pkd1^{RC/RC}$. We also analyzed $Ctnnb1^{flox\ 2\text{-}6/flox\ 2\text{-}6}$, *Ksp-cadherin16 cre* mice alone and bred with $Pkd1^{RC/RC}$ to determine if loss of b-catenin expression in distal tubular segments could alter cystogenesis.

Results: As expected, *TCF/Lef:H2B-GFP* Wnt reporter mice revealed high levels of Wnt activity in tubules of P0 - P14 mice still undergoing tubule development. Interestingly, sustained Wnt activity within the medullary arrays of adult mice, 1m – 9m, was also observed. This expression was decreased by >75% in $Pkd1^{RC/RC}$, *TCF/Lef:H2B-GFP* mice as early as P2 and remained depressed for 9m. MRI analysis of $Ctnnb1^{flox/flox}$, *Ksp-cre* mice suggested Wnt signaling is needed for appropriate development of the urogenital system since all mice exhibited non-obstructive bilateral renal pelvic urine retention (Fig). This phenotype was markedly more severe in $Pkd1^{RC/RC}$, $Ctnnb1^{flox/flox}$, *Ksp-cre* mice, resulting in loss of medullary tissue. $Pkd1^{RC/RC}$, $Ctnnb1^{flox/wt}$, *Ksp-cre* mice did not exhibit this phenotype, but showed significantly increased cystic burden at 12m, compared to controls.



Conclusions: Our results show that sustained Wnt signaling in the postnatal kidney is necessary for kidney maintenance and reduced Wnt signaling may contribute to cystogenesis in ADPKD.

Funding: NIDDK Support

FR-PO512

Stem/Progenitor Cells in Polycystic Kidney Disease Cyst Formation Timothy A. Fields, Jacqueline D. Peda, Connor J. Grantham, Ransom A. Ellis, Katherine Swenson-Fields. *Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is caused by loss-of-function mutations in polycystins, encoded by *PKD1* (~85%) or *PKD2* (~15%). ADPKD is characterized by expanding renal tubular cysts that damage parenchyma, leading to organ failure by 5th-6th decade. Despite the fact that all cells within the nephron are predicted to contain at least one mutant *PKD1* or *PKD2* allele, only a subset of these cells form cysts. Recent data suggest that cysts form when functional polycystin expression falls below a specific threshold. Factors that may influence expression include second genetic hits, environmental stimuli, or the differentiation state of the cell. Interestingly, cyst lining cells in ADPKD have been shown to express high levels of stem/progenitor cell markers such as CD133. While it may be that CD133 expression is a secondary effect of cyst formation, it is equally possible that CD133+ progenitor cells are particularly susceptible to cystogenesis, potentially due to lowered polycystin expression.

Methods: To investigate potential roles for progenitor cells in cyst formation, we have developed a mouse model in which *Pkd1* can be inducibly deleted in cells expressing the progenitor marker CD133 (CD133-$Pkd1^{cko}$). *Pkd1* knockout was induced in CD133+ cells by tamoxifen given at post-natal day 2 and cystic kidney disease assessed.

Results: All of the CD133-$Pkd1^{cko}$ mice examined (n=9) developed cystic kidney disease by 1 month. Cyst formation was initially limited to outer medulla. Like human ADPKD, disease was worse in males and progressed slowly, involving both cortex and medulla by 2 months in males. Disease progression was characterized by injury and fibrosis, especially adjacent to cysts and areas drained by medullary regions affected by early cysts.

Conclusions: These data indicate that loss of *Pkd1* in CD133+ cells results in cystic kidney disease resembling ADPKD and imply that CD133+ progenitor cells contribute to ADPKD cyst formation. This novel orthologous ADPKD model could be a valuable tool, providing insights about mechanisms that control cystogenesis and disease progression.

Funding: Private Foundation Support

FR-PO513

Six2Frs2a Knockout Mice Are a Novel Model of Renal Cystogenesis Pawan Puri, Daniel S. Bushnell, Caitlin M. Schaefer, Carlton M. Bates. *Div of Nephrology, Dept of Pediatrics, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA.*

Background: *Six2cre*-mediated deletion of Frs2a (*Six2creFrs2aKO*), a docking protein for fibroblast growth factor receptors, in nephron progenitors results in progenitor loss and renal cyst formation. Our objective was to determine the molecular pathogenesis of cystogenesis in *Six2creFrs2aKO* mice.

Methods: We performed histological assays, Western blots, and quantitative PCR (qPCR).

Results: Histologically, embryonic day (E) 18.5 *Six2Frs2aKO* kidneys were hypoplastic but not cystic, P7 kidneys had a mixture of non-dilated tubules and proximal tubular (PT)-derived cysts, and P21 kidneys had cysts virtually replacing the renal parenchyma. We observed higher PT proliferation rates, progressive increases in interstitial fibrosis, and macrophage infiltration in *Six2creFrs2aKO* mutant kidneys versus controls, consistent with other polycystic kidney disease (PKD) models. Mechanistically, *Six2creFrs2aKO* kidneys showed upregulation of Wnt/b-catenin, inflammation, and hedgehog signaling pathways, additional features observed in other PKD models. Interestingly, we observed increased Gli1 (hedgehog effector) in the expanded P7 and P21 *Six2creFrs2aKO* interstitium by in

situ hybridization and aberrant increases in sonic hedgehog (Shh) ligand immunostaining in subsets of *non-dilated* P7 mutant PTs that was likely driving the stromal Gli expression. As ectopic tubular Shh is seen after acute kidney injury (AKI), we examined other AKI markers and found that increases in kidney injury molecular-1 (Kim1) and chemokine Ccl2 (macrophage chemotactic protein-1), also in non-dilated mutant PT cells in vivo. In cysts, we observed many lining cells that had lost expression of PT differentiation markers (e.g. LTL), re-expression of de-differentiation markers such as Pax2 and Ncam (often seen in regeneration after AKI), and inappropriate increases in phospho-Creb staining, a readout of cAMP/protein kinase A activity (a pathway known to drive cyst growth in PKD and that is also active after AKI).

Conclusions: Together, these observations suggest that aberrant early AKI and post AKI regenerative pathways may be driving renal pathogenesis in PKD.

Funding: NIDDK Support

FR-PO514

Smyd2 Regulates Renal Fibrosis via TGF-Beta-Smad2/3 Signaling in ADPKD Xiaoyan Li, Ewud Agborbesong, Xia Zhou, James P. Calvet, Xiaogang Li. *Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS.*

Background: In polycystic kidney disease (PKD), expansion of cysts and loss of renal function are associated with progressive fibrosis, which has been identified as the most significant manifestation associated with an increased rate of progression to ESRD. Anti-fibrotic therapy should be an effective adjunct to treatment of ADPKD. Smyd2, as a SET-domain-containing histone (lysine) methyltransferase, methylates both histone and non-histone proteins, including PKD associated p53, Rb and HSP90, to regulate gene expression and protein function, respectively. We found that Smyd2 promotes renal cyst growth in ADPKD via STAT3 and NF-κB signaling. However, the mechanisms by which Smyd2 regulates renal fibrosis remain unknown.

Methods: To understand the role of Smyd2 in renal fibrosis *in vivo*, we investigated renal fibrosis in *Pkd1* and *Smyd2* double conditional knockout mice (*Pkd1*$^{flox/flox}$:*Smyd2*$^{flox/flox}$:*Ksp-Cre*), and in *Pkd1*$^{nl/nl}$ *mice* and *Pkd1*$^{flox/flox}$:*tamoxifen-Cre* mice treated with a Smyd2 specific inhibitor, AZ505. To explore the pathways underlying Smyd2 mediated renal fibrosis, we also treated renal fibroblasts with AZ505.

Results: We found that knockout of Smyd2 and inhibition of Smyd2 with AZ505 not only delayed cyst growth but also decreased renal interstitial fibrosis in kidneys of *Pkd1* conditional knockout mice as examined by Trichrome Masson and Picrosirus red staining. *Pkd1* and *Smyd2* double knockout mice lived longer, to a mean age of 25 days, while *Pkd1* knockout mice died at a mean age of 17 days ($p < 0.001$). Treatment with AZ505 blocked TGF-β induced upregulation of fibrotic markers, including Col1A1, Col3A1, a-SMA and fibronectin, and decreased the phosphorylation of Smad2/3 in rat kidney interstitial fibroblasts (NRK-49F) as analyzed by qRT-PCR and Western blot. We also found that TGF-β can induce the expression of Smyd2 in a time dependent manner in these cells. Inhibition of Smyd2 with AZ505 decreased NRK-49F cell proliferation.

Conclusions: Smyd2 promotes renal fibrogenesis in ADPKD through the canonical TGF-β-Smad2/3 signaling pathway. Targeting Smyd2 with its inhibitor should not only delay cyst growth but also prevent interstitial fibrosis in ADPKD.

Funding: NIDDK Support

FR-PO515

SAHA Reduced cAMP Levels and Inhibited Renal Cyst Growth through HDAC6 Xin Li, Weiwei Shi, Ming Wu, Changlin Mei. *Dept of Nephrology, Kidney Inst, Shanghai Changzheng Hospital, Shanghai, China.*

Background: Inhibition of cyclic adenosine monophosphate (cAMP) by using Tolvaptan can delay disease progression in patients with autosomal dominant polycystic kidney diseases (ADPKD). However, it has not been approved by USA FDA because of its side effects. Recent study shows that inhibition of Histone deacetylases 6 (HDAC6) reduced cAMP levels and inhibited kidney growth in ADPKD animal models. We therefore hypothesized that treatment with suberoylanilide hydroxamic acid (SAHA), a FDA approved HDAC inhibitor, could retard PKD progression and lower cAMP levels in cystic kidneys.

Methods: Male rats were treated with 50mg/kg/day SAHA or vehicle at 4 weeks of age by gavage for 5 weeks. ADPKD cells were treated with various concentration of SAHA.

Results: Five weeks SAHA treatment reduced BUN and creatinine level by 37.7% (11.50±1.782mmol/L vs 18.15±2.988 mmol/L) and 40.8% (57.62±30.89umol/L vs 97.26±15.60umol/L) respectively in cystic Cy/+ Han:SPRD rats compared with cystic Cy/+ Han:SPRD rats treated with vehicle. Administration of SAHA decreased the two kidney weight/total body weight ratio and cystic volume density in Cy/+ rats by 25.2%(0.02056±0.004799 vs 0.02748±0.004628) and 39.7%(0.3337±0.02054 vs 0.5535±0.02214) respectively. The cell proliferation was inhibited by SAHA in cystic kidneys as shown by Ki-67 staining. SAHA reduced cAMP levels in Cy/+ kidneys, which was correlated with the down-regulation of HDAC6 expression and reduced phosphorylation of CREB. The inhibitory effect of SAHA on HDAC6 expression and cAMP levels was confirmed in ADPKD cells. In addition SAHA reduced protein levels of β-catenin and C-myc in cystic kidneys.

Conclusions: SAHA reduced cAMP levels and inhibited kidney growth in PKD, which may be mediated through HDAC6.

Funding: Government Support - Non-U.S.

FR-PO516

Structural Nephrology: 3D Analysis of Fibrocystin/Polyductin Bound to DNA Naoe Harafuji,[1] Ann C. Varano,[2] Deborah F. Kelly,[2] Lisa M. Guay-Woodford.[1] *[1]Center for Transitional Science, Children's National Health System, Washington, DC; [2]Virginia Tech Carilion Research Inst, Roanoke, VA.*

Background: ARPKD results from mutations in *PKHD1*, a transcriptionally complex gene that encodes a set of secreted and membrane-bound isoforms collectively referred to as FPC. The longest mRNA encodes a membrane-bound FPC that undergoes Notch-like proteolytic cleavage to generate a carboxy terminal domain (CTD-FPC) that translocates to the nucleus. We hypothesize that within the nucleus CTD-FPC assembles into gene regulatory complexes.

Methods: Mouse CTD-FPC was cloned into the modified p3XFLAG-CMV-7.1 vector, sequence-verified, and transfected into mIMCD-3 cells. Cell lysates were prepared and separated into cytoplasmic and nuclear fractions, with the purified nuclear fraction subjected to the "Affinity capture" technique (Sci Rep, 2015) to identify the nuclear assemblies that interact with the CTD-FPC. Captured complexes were examined using single particle Electron Microscopy (EM) methodologies.

Results: We found that Affinity-captured, natively-formed CTD-FPC nuclear assemblies were abundantly integrated into DNA networks (**Fig 1**). In parallel, we examined purified CTD-FPC assemblies using single particle EM. Classification-based computational routines revealed that these assemblies had some degree of heterogeneity, but that most complexes were ~15 nm in diameter. Representative 3D reconstruction of these complexes exhibited a ring-shaped architecture consistent with known DNA-binding motifs.

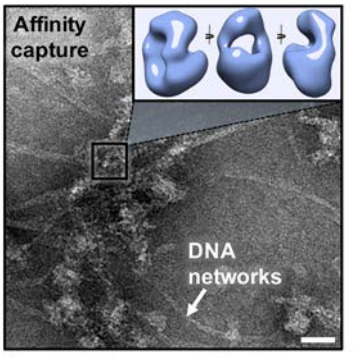


Figure 1. Affinity captured CTD-FPC assemblies integrated into DNA networks. Single particle 3D reconstruction (blue) of purified CTD-FPC assemblies in different orientations (inset). Scale bar, 50 nm.

Conclusions: The "Affinity capture" technique demonstrated that nuclear CTD-FPC is assembled into ring-shaped protein complexes, suggesting that CTD-FPC binds to DNA and plays a role in gene regulation. These initial studies provide a technical framework for elucidating the CTD-FPC nuclear structure-function relationship in renal epithelial cells. Mass spectrometry analysis of these complexes is in progress.

FR-PO517

RNA Sequencing Analysis Reveals Upregulation of Endothelin-MAPK Signaling in Pre-Cystic Kidneys of Thm1 Conditional Knock-Out Mice Luciane M. Silva,[1] Damon T. Jacobs,[1] Bailey A. Allard,[1] Sumedha S. Gunewardena,[2] Pamela Vivian Tran.[1] *[1]Anatomy and Cell Biology, Kidney Inst, Kansas Univ Medical Center, Kansas City, KS; [2]Integrative and Molecular Physiology, Kansas Univ Medical Center, Kansas City, KS.*

Background: Primary cilia are non-motile sensory organelles that mediate signaling pathways and ciliary dysfunction leads to renal cystic disease. In mice, perinatal global deletion of *Thm1,* an intraflagellar transport–A component, causes renal cysts beginning at postnatal day 15 (P15). We aim to identify the molecular events that initiate renal cystogenesis in *Thm1* conditional knock-out (cko) mice.

Methods: We performed RNA sequencing (HiSeq2500, llumina) on whole kidney RNA lysates of pre-cystic P9 and cystic P42 *Thm1* cko mice and of controls (N=6/group), attaining 44X coverage/sample. Sequences were aligned to the mouse genome (GRCm38). Differential gene expression was calculated using Cuffdiff, and P-values were adjusted for false discovery by the Benjamini and Hochberg method. We reasoned that genes with significantly altered expression at both P9 and P42 would represent early initiation events leading to cystogenesis.

Results: We identified 10 genes significantly upregulated at P9 and further upregulated at P42 in *Thm1* cko kidneys. These included *endothelin 1* (*Edn1*), *fos* and *jun*, suggesting EDN1-MAPK signaling may play a role in renal cyst initiation and progression. Endothelial *Vcam1* and immune genes, *C3*, *Egr2* and *Adcy7*, were also upregulated, suggesting simultaneous alteration of signaling in renal epithelial, vascular and immune cells may potentiate renal cyst initiation. At P42, components of MAPK, TGF-β, mTOR, Stat, Wnt, Notch, and Hedgehog pathways were upregulated, suggesting molecular changes similar to those in Autosomal Dominant Polycystic Kidney Disease (ADPKD). These data are being validated *in vivo* in *Thm1* cko renal tissue and *in vitro* using a clonal *Thm1* knock-down collecting duct M1 cell line.

Conclusions: EDN1 is increased in serum of ADPKD patients and *EDN1* polymorphisms are associated with ADPKD severity. Our data suggest misregulation of EDN1-MAPK signaling as an early initiation event in renal cystic disease that merits further exploration.

Funding: NIDDK Support

FR-PO518

Expression of Activated BRAF(V600E) in Collecting Ducts Accelerates Cyst Growth and Fibrosis in Renal Cystic Disease Archana Raman, Stephen C. Parnell, Aditi Khanna, Yuqiao Dai, Grant Aaron Johnson, Gail Reif, Timothy A. Fields, Darren P. Wallace. *Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS.*

Background: In polycystic kidney disease (PKD), aberrant cell proliferation is responsible for the growth of fluid-filled cysts leading to enlarged kidneys and progressive decline in renal function. Mutations in the PKD genes are thought to cause dysregulation of intracellular Ca^{2+}, leading to reduced basal intracellular Ca^{2+} levels in cystic cells compared to normal kidney cells and cAMP-dependent activation of the BRAF/MEK/ERK pathway. This pathway is thought to be important for driving aberrant cell proliferation in PKD.

Methods: To determine the role of BRAF on renal cyst formation, we generated mice that conditionally express $BRAF^{V600E}$, a common activating mutation in BRAF found in cancer. We used *Pkhd1-Cre* to selectively overexpress $BRAF^{V600E}$ in collecting ducts (CD) of wildtype (WT) mice. $BRAF^{V600E}$ was also expressed in cystic epithelial cells by crossing these mice with *pcy/pcy* (*pcy*) mice, a slowly progressive model of PKD that develops predominantly CD-derived cysts.

Results: CD-specific expression of $BRAF^{V600E}$ in WT mice caused hyperproliferation and cystic dilation of CD, formation of small cysts, and prominent interstitial fibrosis. CD-specific expression of $BRAF^{V600E}$ in *pcy* mice caused a striking increase in kidney weight to body weight, cyst number and size, and total cystic area compared to littermate *pcy* mice. There was also a significant increase in phosphorylated ERK and Ki-67 positive cells, consistent with elevated MEK/ERK-dependent cell proliferation. There was extensive infiltration of immune cells and a four-fold increase in interstitial fibrosis that extended through the cortex of the cystic kidneys.

Conclusions: Our results demonstrate that activation of the BRAF/MEK/ERK pathway in renal epithelial cells is sufficient to induce cyst formation and accelerate the progression of cystic disease in PKD mice.

Funding: NIDDK Support

FR-PO519

Genetic Interaction between XBP1 and Pkd1 Modulates Cyst Progression in ADPKD Sorin V. Fedeles, Yasunobu Ishikawa, Rachel Gallagher, Stefan Somlo. *Internal Medicine/Nephrology, Yale School of Medicine, New Haven, CT.*

Background: *Pkd1* is one of the two genes responsible for autosomal dominant polycystic kidney disease (ADPKD). *XBP1* encodes the main chaperone modulator of the ER unfolded protein response. *Sec63* is one of the genes mutated in isolated familial polycystic liver disease (PCLD). *Sec63* and *XBP1* interact genetically to modulate *Pkd1* function in PCLD. In the current work we investigated whether *XBP1* can exhibit a direct genetic interaction with *Pkd1* independently of *Sec63*.

Methods: $Pkd1^{fl/fl}$;*Pkhd1-Cre* (SKO) and$Pkd1^{fl/fl}$;$XBP1^{fl/fl}$;*Pkhd1-Cre*(DKO) mouse models with conditional inactivation of *Pkd1* and *XBP1* alone or together in the collecting duct were evaluated at P24 by morphological and biochemical parameters: kidney to body weight ratio (KW/BW), cystic index, creatinine and rates of apoptosis and proliferation.

Results: Deletion of *Pkd1* using *Pkhd1-Cre* in SKO leads to severe cyst formation at P24. DKO mice display decreased KW/BW as compared to the SKO animals (~2.7 fold decrease in KW/BW, 0.5+/-0.1 vs. 1.4+/-0.2 respectively, ***p<0.001). These changes were accompanied by a ~1.5-fold decrease in cystic index (42+/-1.3 vs. 70+/-1.5, ***p.0.001) and a 2-fold decrease in serum creatinine levels (0.21+/-0.02 vs. 0.45+/-0.05, **p<0.01). These effects were *XBP1* specific as restoration of spliced XBP1 expression via Cre activation of *floxstop-ROSA-XBP1s* led to morphological and functional parameters similar to the SKO mice. The cystic epithelia in the DKO mice displayed extensive apoptosis compared to SKO animals alone (4.7% vs. 0.1%, ***p<0.001) with no changes in proliferation. The level of active *XBP1s* expression was not different between the WT and SKO animals indicating that baseline levels of *XBP1s* are critical for maintaining the viability of *Pkd1* cystic cells *in vivo*.

Conclusions: Our data show that *XBP1* is a novel genetic interactor of *Pkd1* and can modulate the progression of ADPKD in murine models by protecting *Pkd1* cyst cells from apoptosis. Avenues that can reduce homeostatic XBP1 signaling *in vivo* may hold therapeutic potential by selectively promoting apoptosis in *Pkd1* deficient backgrounds.

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FR-PO520

Interaction of Gα12 and Pkd1 in Renal Cystogenesis Jen Xu,[1] Tzongshi Lu,[1] Wassim El-Jouni,[2] Joseph V. Bonventre,[1] Jing Zhou,[1] Bradley M. Denker,[3] Tianqing Kong.[1] *[1]Renal Div, Brigham and Women's Hospital, Boston, MA; [2]Nephrology Div, Massachusetts General Hospital, Boston, MA; [3]Renal Div, Beth Israel Deaconess Medical Center, Boston, MA.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common life-threatening genetic diseases and is characterized by early formation and gradual enlargement of multiple kidney cysts, which eventually results in end-stage renal disease (ESRD). Mutation of PKD1 is responsible for the majority of autosomal dominant polycystic kidney disease (ADPKD). The signaling pathways of PC1 in ADPKD are not fully understood.

Methods: Generation of inducible Pkd1 knockout mice (Mx1Cre+Pkd1flox/flox) were made by exons 2 through 6 were flanked by two LoxP sites. These mice were crossed with the mice of transgenic Cre recombinase under the control of INF-inducible Mx1 promoter (Mx1Cre mice). Gα12-deficient mice (Gα12-/-) were generated by replacement of exon 4 with reverse Neo gene. Double knockout of Pkd1 and Gα12 mice were obtained by crossing Mx1Cre+Pkd1flox/flox mice with Gα12-/- mice. Madin-Darby canine kidney (MDCK) Tet-off inducible Gα12 and Gα12QL cell lines were characterized for three-dimensional cell culture.

Results: Our results provided genetic evidence that Gα12 was essential for the development of kidney cysts induced by Pkd1 knockout. There was no phenotype in mice with deletion of Gα12 (Gα12-/-). Conditional deletion of Pkd1 (Pkd1-/-) in one week old mice resulted in multiple kidney cysts by 9 weeks, but the mice with double knockout of Pkd1 and Gα12 (Pkd1-/-Gα12-/-) had no structural and functional abnormalities in the kidneys. These mice could survive more than one year without kidney abnormalities except multiple hepatic cysts in some mice, which indicates that the effect of Gα12 on cystogenesis is kidney-specific. Furthermore, deletion of Pkd1 increased the activation of Gα12, which subsequently decreased cell-matrix and cell-cell adhesion by affecting the function of focal adhesion, and E-cadherin, respectively.

Conclusions: Our data demonstrate that Gα12 signaling is critical for renal cystogenesis in ADPKD induced by Pkd1 mutation.

Funding: Private Foundation Support

FR-PO521

CU062 Is a Novel Protein That Interacts with Polycystin-1 and Activates Polycystin-2 Channels in Primary Cilia Wendy A. Lea,[1] Steven Kleene,[2] Nancy Kleene,[2] Christopher J. Ward.[1] *[1]Div of Nephrology and Hypertension, Dept of Medicine, Univ of Kansas Medical Center, Kansas City, KS; [2]Dept of Molecular and Cellular Physiology, Univ of Cincinnati, Cincinnati, OH.*

Background: Polycystin-1 (PC1), the product of the *PKD1* gene, has a large 3048 aa extracellular domain, with no known ligands. Over 30% of the protein is composed of PKD β-barrel domains. In an attempt to identify candidate interactors, we compared the proteome of a PC1 rich urine exosomal fraction (PKD-ELVs) from individuals with *PKD1* mutations with that of individuals with normal kidneys. CU062 was identified as a small glycoprotein that was decreased to 44% in *PKD1* versus controls (p = 0.001, q = 0.0001). CU062 is the product of the *C21orf62* gene in the Down syndrome critical region.

Methods: A DNA deletion series for PC1 was produced to map interactions. We also made recombinant C-terminally tandem affinity tagged CU062 in HEK-293 cells for electrophysiological studies. Recordings were performed on the primary cilia of IMCD3 cells on microcarrier beads. Recombinant CU062 was applied to the cilium via the recording pipette and currents measured 2 minutes after application for an 18 minute duration.

Results: CU062 can IP mature PC1 by recognizing PKD domains. CU062 can robustly and reciprocally IP constructs containing PKD repeats 2-17. The terminal three PKD domains (PKD15-17) have a remarkable affinity for CU062, which resists heating to 65ºC and non-reducing SDS-PAGE. CU062 is heavily glycosylated, with a mass of 42 kDa, which decreases to 21 kDa after deglycosylation, and has the ability to oligomerize on non-reducing gels. Applying recombinant CU062 to the primary cilia of IMCD3 cells activates the PC2 channel. At baseline, the current was 100.3 ±119 (SD), while the addition of 10 nM CU062 increased current to 641.1 ±801 (SD) (p = 0.014 (Welch *t*-test), p = 0.0006 (Wilcoxon rank)).

Conclusions: CU062 interacts with the extracellular PKD domains of PC1 and, when applied to primary cilia, increases currents that are due to PC2 channel opening. CU062 will be a useful tool in the investigation of PC1 signaling.

Funding: NIDDK Support

FR-PO522

The Lonidamine Derivative H2-Gamendazole Inhibits Cyst Growth in Pkd1-Deficient Kidneys by Targeting Numerous Cellular Pathways Xia Zhou,[1] Brenda S. Magenheimer,[1] Gunda I. Georg,[2] Joseph S. Tash,[1] Xiaogang Li,[1] James P. Calvet.[1] *[1]Univ of Kansas Medical Center, Kansas City, KS; [2]Univ of Minnesota, Minneapolis, MN.*

Background: Cyst growth and polycystic kidney disease (PKD) progression involve abnormal cellular processes including increases in cell proliferation, fluid secretion, inflammation, and fibrosis. H2-gamendazole (H2-GMZ) is a small molecule indazole carboxylic acid that is well-tolerated in animal studies and is currently under investigation for PKD therapy. H2-GMZ appears to function as an Hsp90 inhibitor, but also targets CFTR chloride channel activity, and the actin cytoskeleton. To better understand the extent to which H2-GMZ is able to improve kidney function we investigated global gene expression by RNA sequencing (RNA-seq) analysis.

Methods: H2-GMZ treatment was carried out on Pkd1 floxed, Pkhd1-Cre mice using daily i.p. injections of 20 mg/kg H2-GMZ from postnatal (PN) day 8 to 18. Total RNA was isolated from PN 19-day wild-type and cystic kidneys that were H2-GMZ treated or vehicle treated. Kidney tissue from three mice (2 males, 1 female) from each group was separately analyzed. RNA was sequenced and analyzed by CLC Genomics Workbench and Ingenuity Pathway Analysis (IPA).

Results: Mice treated with H2-GMZ had significantly reduced cystic index, kidney weight to body weight (KW/BW), and improved blood urea nitrogen (BUN). Continued daily treatment with H2-GMZ extended average survival from 28.8±5 days (n=8) to 67.8±23 days (n=5) (p<0.01). RNA-seq demonstrated that genes up- or down-regulated in

cystic kidneys were normalized by H2-GMZ. Among the most significant changes in cystic kidneys were upregulation of immune pathways and their effectors and downregulation of calcium signaling, among others.

Conclusions: The significant improvement in kidney function and mortality suggests that H2-GMZ may be effective in treating PKD. This was supported by RNA expression analysis which indicated that there were minimal effects on wild-type kidneys and that gene expression pathways were normalized by H2-GMZ. Of particular interest was the observation of a decrease in calcium signaling and a robust acute phase response in cystic kidneys, both of which were normalized by H2-GMZ.

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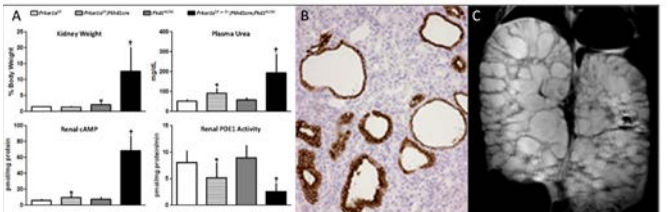
FR-PO523

PRKAR1A Controls Renal Cystogenesis Hong Ye,[1] Xiaofang Wang,[1] Megan M. Constans,[1] Caroline R. Sussman,[1] Maria V. Irazabal,[1] William F. Young,[1] Peter C. Harris,[1] Lawrence S. Kirschner,[2] Vicente E. Torres.[1] *[1]Mayo Clinic, Rochester, MN; [2]Ohio State U, Columbus, OH.*

Background: Although cAMP signaling is thought to be upregulated in PKD, a role for PKA has not been directly demonstrated *in vivo*. PKA exists as an inactive holoenzyme with two catalytic (C) and two regulatory (R) subunits (R inhibiting C). Upon binding of cAMP to R, C subunits are released and activated. The knockout of the RIα encoding gene (*Prkar1a*) is embryonic lethal. *PRKAR1A* mutations cause autosomal dominant Carney complex (a multiorgan tumoral syndrome) which shares features with ADPKD (loss of heterozygosity and haploinsufficiency mechanisms, proliferative response to cAMP).

Methods: To investigate the role of R1α in PKD we created a kidney specific knockout by crossing *Prkar1a*$^{lox/lox}$ and Pkhd1Cre mice. This was also bred into a *Pkd1*$^{RC/RC}$ background. To ascertain whether cystic disease is associated with *PRKAR1A* mutations in humans we reviewed abdominal MR or contrast enhanced CT scans of 9 patients (2 M, 7 F; 39±18 yo, range 12-63) with Carney complex (six with proven *PRKAR1A* mutations).

Results: Kidney specific *Prkar1a* knockout by itself resulted in increased P-CREB and P-ERK levels, epithelial cell proliferation, numerous bilateral cysts (positive for THP, EMA or AQP2), interstitial inflammation and fibrosis, and elevated plasma urea (Figure 1A-B). *Prkar1a*, which contains cAMP response elements in its promoter region,was overexpressed in *Pkd1*$^{RC/RC}$ mice. *Prkar1a* renal homozygous or heterozygousknockout in *Pkd1*$^{RC/RC}$ mice markedly increased renal cAMP (likely due to PKA induced phosphorylation and inhibition of PDE1) and the severity of PKD (Figure 1A,C). Four and 7 of the 9 Carney patients had renal (3.3 per patient, range 1-9) and hepatic (3.9, range 1-8) cysts, respectively.



A) Kidney weights and labs in 16 wk old *Prkar1a*^{lox} (n=10), *Prkar1a*^{lox};Pkhd1cre (n=9) and *Pkd1*$^{RC/RC}$ (n=20) mice, and in 4-6 wk old *Prkar1a*$^{lox+/lox}$;Pkhd1cre; *Pkd1*$^{RC/RC}$ (n=6) mice; B) Immunostaining for AQP-2 in a 16 wk old *Prkar1a*^{lox};Pkhd1cre mouse; C) Coronal MR image in a 5 wk old *Prkar1a*^{lox};Pkhd1cre; *Pkd1*$^{RC/RC}$ mouse.

Conclusions: These observations confirm the importance of PKA in the pathogenesis of PKD and that the expression of *Prkar1a* controls this cystogenic pathway.

Funding: NIDDK Support

FR-PO524

Developing a Mouse Model Better Reflecting ARPKD Renal Disease Severity Rory Olson,[1] Katharina Hopp,[2] Vladimir Gainullin,[1] Peter C. Harris.[1] *[1]Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [2]Div of Renal Diseases and Hypertension, Univ of Colorado, Denver, CO.*

Background: Autosomal recessive polycystic kidney disease (ARPKD) is the most common infantile form of PKD, associated with perinatal lethality and childhood ESRD. The disease is caused by mutations to *PKHD1,* however, the function of the *PKHD1* gene product, fibrocystin/polyductin (FCP), remains unknown. Of note, mouse *Pkhd1* null models have relatively mild renal disease and hence are unsuitable for detailed pathomechanistic analyses.

Methods: Breeding *Pkhd1* null (*Pkhd1*$^{LSL/LSL}$) animals to the *Pkd1* hypomorphic model (p.R3277C; RC) (*Pkd1*$^{RC/RC}$), we generated *Pkhd1*$^{-/-}$;*Pkd1*$^{RC/RC}$ mice, and homozygous/heterozygous combinations. The phenotype was assayed by percent kidney weight to body weight (%KW/BW), cyst index, IF of tubule markers and expression differences analyzed, including by RNA-Seq.

Results: The digenic, homozygous mice (*Pkhd1*$^{-/-}$;*Pkd1*$^{RC/RC}$) died exclusively postnatally (median survival time=P17, p=0.0001) with enlarged kidneys due to rapid expansion of collecting duct-derived cysts, a phenotype similar to human ARPKD, whereas *Pkhd1*$^{-/-}$ or *Pkd1*$^{RC/RC}$ animals presented no or mild disease (%KW/BW at P0: 2.63±0.49 vs 1.0±0.25 or 1.43±0.16, respectively, p<0.0001 [ANOVA]). Interestingly, at 6m the %KW/BW and cyst index of *Pkhd1*$^{-/-}$;*Pkd1*$^{+/RC}$ and *Pkhd1*$^{+/-}$;*Pkd1*$^{RC/RC}$ animals were not significantly different from single homozygote controls (%KW/BW: 1.57±0.12 and 2.01±0.15). These results suggested a threshold effect where 3 mutant alleles did not significantly modulate the disease phenotype, but 4 mutant alleles (no FPC and ~40% PC1) resulted in severe PKD. Targeted analysis of altered pathways in the digenic homozygous animals showed upregulation of c-MYC. To further understand the pathways altered, RNA-Seq analysis was completed, revealing signaling signatures for severe and mild cyst progression.

Conclusions: This mouse model, which reflects the human severity of ARPKD, can be effectively studied to reveal the molecular defects associated with the loss of *Pkhd1*. These results indicate shared signaling events between ARPKD and ADPKD, suggesting that therapeutic intervention for ADPKD may also be beneficial to ARPKD patients.

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FR-PO525

Fibronectin Signaling Modulates Cyst Progression in Models of Autosomal Dominant Polycystic Kidney Disease Ming Ma,[1] Rachel B. Simon,[2] Yasunobu Ishikawa,[1] Xin Tian,[1] Ke Dong,[1] Yiqiang Cai,[1] Chao Zhang,[1] Takao Sakai,[3] Stefan Somlo.[1,4] *[1]Dept of Internal Medicine, Yale School of Medicine, New Haven, CT; [2]Barnard College, Columbia Univ, New York, NY; [3]Dept of Molecular and Clinical Pharmacology, Inst of Translational Medicine, The Univ of Liverpool, Liverpool, United Kingdom; [4]Dept of Genetics, Yale School of Medicine, New Haven, CT.*

Background: Loss of cilia suppresses cyst growth in genetic models of autosomal dominant polycystic kidney disease (ADPKD) suggesting that cilia harbor a signal that stimulates cyst progression when polycystin function is impaired. Integrin receptors for extracellular matrix (ECM) proteins have been shown to be expressed on the cilia membrane and integrin β1 (ItgB1) receptor knockout has been shown to be protective in an early onset mouse model of ADPKD. Moreover, ECM remodeling has been observed in multiple models of cystic kidney disease, including ADPKD models. We investigated whether integrin signaling is one of the drivers of cyst formation in ADPKD.

Methods: We examined expression of integrin signaling pathway components in cilia and inactivated components of integrin signaling in early onset and adult inducible *Pkd1* and *Pkd2* mouse models of ADPKD.

Results: We confirmed that ItgB1, ItgA3 and ItgA5 are expressed in the cilia of LLC-PK1 cells and that loss of ItgB1 in collecting duct cells suppresses cyst growth in an early developmental model. Surprisingly, we found that inactivation of ItgB1 does not protect, and may actually promote, cyst growth in the adult inducible mouse models of ADPKD. In contrast, inactivation of the integrin ligand fibronectin in the kidney tubules suppresses cyst growth and preserves renal function in both the early and adult onset ADPKD models.

Conclusions: ItgB1 exhibits discordant roles for cyst progression in developmental and adult models of ADPKD, excluding a role for ciliary ItgB1 as the cilia dependent signal for cyst formation in ADPKD. Fibronectin produced by kidney tubule cells promotes cyst growth in *Pkd1* and *Pkd2* models suggesting that targeting fibronectin or other ECM molecules may offer therapeutic benefits for the treatment of ADPKD.

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FR-PO526

The AAA ATPase Ruvbl1 Is Essential for the Maintenance of Tubular Architecture and Renal Function In Vivo Claudia Dafinger,[1,2] Markus M. Rinschen,[1,3] Martin Höhne,[1,3,4] Rachel H. Giles,[6] Dorien J.M. Peters,[5] Thomas Benzing,[1,3,4] Bernhard Schermer,[1,3,4] Max Liebau.[1,2] *[1]Dept II of Internal Medicine and Center for Molecular Medicine, Univ Hospital of Cologne, Cologne, Germany; [2]Dept of Pediatrics, Univ Hospital of Tuebingen, Cologne, Germany; [3]Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Univ of Cologne, Cologne, Germany; [4]Systems Biology of Ageing Cologne (Sybacol), Univ of Cologne, Cologne, Germany; [5]Depts of Human Genetics, Leiden Univ Medical Center, Leiden, Netherlands; [6]Dept of Nephrology and Hypertension, Univ Medical Center Utrecht, Utrecht, Netherlands.*

Background: Cystic kidney diseases are among the most common causes of end stage renal disease in childhood and adolescence. Despite the recent progress in the understanding of the underlying molecular mechanisms, the pathogenesis of cystic kidney diseases remains incompletely understood. We recently identified the highly conserved AAA ATPase Ruvbl1 as a cilia-associated protein and could show that targeted deletion of Ruvbl1 in the distal tubule leads to a severe renal phenotype in mice.

Methods: To understand the role of Ruvbl1 for maintenance of tubular function and tubular architecture beyond renal development we generated an inducible tubule-specific Ruvbl1 knockout mouse. To identify components of the Ruvbl1 protein complex we also performed label-free quantitative mass spectrometry after immunoprecipitation of Ruvbl1.

Results: Induced deletion of Ruvbl1 is associated with progressive weight loss and deterioration of kidney function as well as minor cystic tubular changes. Histological and interactome data suggest both non-ciliary and cilia-associated functions of Ruvbl1.

Conclusions: Ruvbl1 is a novel cilia-associated protein required for maintenance of tubular architecture and renal function in mice.

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FR-PO527

Microcrystals Promote Cystogenesis and Exacerbate Polycystic Kidney Disease Jacob A. Torres,[1] Mina Rezaei,[1] Louis Lin,[1] Caroline M. Broderick,[1] Saeed R. Khan,[2] Vicente E. Torres,[3] Benjamin D. Cowley,[4] Thomas Weimbs.[1] *[1]Molecular Cellular Developmental Biology, Univ California Santa Barbara, Santa Barbara, CA; [2]Dept of Pathology, Univ of Florida, Gainseville, FL; [3]Dept of Nephrology, Mayo Clinic, Rochester, MN; [4]Dept of Medicine, Oklahoma Univ, Oklahoma City, OK.*

Background: ADPKD is a slowly progressive disease characterized by the accumulation of fluid-filled cysts that slowly replace normal functioning kidney tissue resulting in renal failure. The rate of disease progression is highly variable amongst individuals suggesting that it is affected by unknown environmental factors. Individuals with ADPKD suffer from a number of renal pathologies including nephrolithiasis. Its thought that occurrences of renal calculi are secondary to ADPKD and are merely a sign of improper kidney function. Microcrystals formed in the urinary filtrate, are usually cleared through luminal passage but may lodge in tubules leading to obstruction.

Methods: Han:SPRD rats were challenged with ethylene glycol leading to CaOx crystal deposition in male rats. To investigate whether PKD progression is specific only to CaOx crystals, PCK rats were fed a high phosphate diet leading to tubular calcium phosphate crystal deposition in renal tubules.

Results: We found that calcium oxalate or phosphate crystal deposition in renal tubules of the Han:SPRD and PCK rats respectively, leads to rapid increases in tubule diameters and activation of mTOR, Src and STAT3 signaling pathways.

Conclusions: Tubule dilation and mTOR, Src and STAT3 signaling pathways are aberrantly activated in ADPKD. We hypothesized that crystal deposition may act as a trigger for cystogenesis in ADPKD. Han:SPRD rats challenged with ethylene glycol led to an increase in cyst size and cyst numbers as did CaP crystals. Together, these results suggest luminal microcrystals may act as triggers of cyst formation in PKD and that environmental factors such as diet that lead to increased crystal burden accelerate progression of PKD. These findings suggest that established therapeutic intervention for reducing renal crystal formation may prove effective in ADPKD patients.

Funding: Private Foundation Support

FR-PO528

Biochemical Changes in Cystic Epithelia of Feline Autosomal Dominant Polycystic Kidney Disease Laurie A. Smith,[1] Sarah E. Moreno,[1] Kelly A. Rogers,[1] Ryan J. Russo,[1] Hyejung Park,[2] Bing H. Wang,[2] Christine M. Adreani,[1] Leslie A. Lyons,[3] Oxana Beskrovnaya,[1] Thomas A. Natoli.[1] *[1]R&D Center, Sanofi-Genzyme, Framingham, MA; [2]Analytical R&D, Sanofi-Genzyme, Waltham, MA; [3]College of Veterinary Medicine, Univ of Missouri, Columbia, MO.*

Background: Human Autosomal Dominant Kidney Disease (ADPKD) is characterized by kidney cyst growth leading to ESRD due to a mutation in the PKD1 or PKD2 gene. Cystic epithelial cells demonstrate hyperplasia, apoptosis, and aberrant fluid secretion that together drives cyst growth. The phenotypic changes are accompanied by dysregulated cell-signaling activities, including activation of the mTOR, MAPK, Wnt, and VEGF signaling pathways, increased intracellular cAMP, glycosphingolipid accumulation, and metabolic alterations resulting in aerobic glycolysis and oxidative stress. Mice with heterozygous germline mutations in Pkd1 or Pkd2 rarely develop cysts. Murine models are widely used to test potential therapies, but testing in a relevant non-murine model of ADPKD could further de-risk clinical trials. Feline ADPKD results from an autosomal dominant nonsense mutation in the PKD1 gene and presents with clinical manifestations that resemble the human disease. However, very little biochemical characterization has been analyzed and reported. Therefore, in this study, we assessed the biochemical changes in the cystic kidneys in feline ADPKD and report analogy to human ADPKD.

Methods: Antibodies to proteins that are dysregulated in human ADPKD were screened for cross-reactivity to feline samples. Immunohistochemistry, immunofluorescence, and western blotting were used to examine protein expression. Glycosphingolipid accumulation was measured by LC/MS/MS.

Results: Cross-reactive antibodies to markers of proliferation, mTOR, MAPK, Wnt and TGFb signaling were identified. Cystic epithelium demonstrated increased proliferation, mTOR activity, MAPK activity, VEGF activation, and oxidative stress compared to surrounding normal tissue by immunohistochemical analysis. Feline cystic kidneys have increased glycospingolipid levels compared with normal.

Conclusions: Biochemical changes in cystic epithelium of feline ADPKD resemble those reported in human ADPKD.

FR-PO529

Quantitative Proteomic and Phosphoproteomic Analyses of Vasopressin V2R Dependent Signaling in Cultured Collecting Duct Cells with and without Primary Cilia Caroline Pahmeyer, Thomas Benzing, Malte P. Bartram, Bernhard Schermer, Markus M. Rinschen. *Dept II of Internal Medicine, Univ Hospital Cologne, Cologne, Germany.*

Background: The role of primary cilia in the pathogenesis of autosomal-dominant polycystic kidney disease (ADPKD) is well established. ADPKD progression is promoted by activation of the vasopressin-V2-receptor and dysregulated downstream kinase pathways. At this point the impact of cilia or ciliary signaling is ambiguous. We analyzed whether ablation of cilia *per se* could interfere with vasopressin signaling in collecting duct cells.

Methods: We generated collecting duct cell lines expressing a dominant negative Kif3A to abrogate ciliogenesis. We analyzed proteomic and phosphoproteomic perturbations of the V2-receptor signaling in both cell lines at different timepoints.

Results: Comparison of the proteome of unciliated Kif3A HL cells with control cells confirmed that membrane proteins and proteins belonging to the ciliary core, the axoneme, were altered. In the control cell line, we found that both long term (proteome) and short term (phosphoproteome) dependent changes in signaling were largely similar to previous studies. In addition, we found that ciliary ablation per se had only minor effects on the long-term response of vasopressin dependent signaling. However, analysis of short-term perturbation of the phosphoproteome revealed that ciliary ablation blunted phosphorylation of polarity dependent proteins, such as Cofilin and Marcks at known regulatory sites, without affecting subcellular localization of Marcks. Using network analysis, we found that phosphorylation sites in the control conditions were mainly present in substrates of Protein kinase A, calmodulin-dependent kinases and ERK-MAP-Kinases, whereas proteins in the ciliary ablated condition were also interactors of Map-kinases-kinases. V2R dependent ERK inhibition, however, was present in both cell lines.

Conclusions: In summary, our data reveal only subtle changes of long-term and short term response of V2R-induced signaling caused by ciliary ablation. Thus, the switch in global vasopressin signaling network which occurs in ADPKD cells might not primarily be modulated by cilia or ciliary signaling.

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FR-PO530

Mitochondrial Dysfunction Contributes to Cyst Proliferation of Autosomal Dominant Polycystic Kidney Disease Yu Ishimoto,[1] Masaomi Nangaku,[1] Masanori Kugita,[2] Shizuko Nagao,[2] Akira Shimizu,[3] Jing Zhou,[4] Reiko Inagi.[1] *[1]Nephrology and Endocrinology, Tokyo Univ, Tokyo, Japan; [2]Education and Research Center of Animal Models for Human Diseases, Fujita Health Univ, Aichi, Japan; [3]Dept of Analytic Human Pathology, Nippon Medical School, Tokyo; [4]Center for Polycystic Kidney Disease Research and Renal Div, Brigham and Women's Hospital, Harvard Medical School, Cambridge.*

Background: Pathological derangements characteristics of autosomal dominant polycystic kidney disease (ADPKD), such as continuous proliferation of cyst epithelial cells, show marked similarities to those of solid tumors. Mitochondria of tumor cells have been reported to differ functionally from those of normal cells and contribute to tumor phenotype. Therefore, we focused on mitochondrial function in ADPKD.

Methods: Comparedmitochondrial DNA (mtDNA) copy number, PGC-1α (a master regulator of mitochondrial biogenesis) expression, and mitochondrial morphology by electron microscopy utilizing ADPKD model rat (Han:SPRD Cy rat) and cultured human ADPKD cyst epithelial cell. To address the molecular mechanism of the mitochondrial alteration, mitochondrial reactive oxygen species (mtROS), ERK1/2 activity, intracellular calcium flux, and calcineurin activity were assessed in vitro. Further, the effect of mitochondria targeted therapy with MitoQ on cyst cell proliferation was evaluated.

Results: Renal mtDNA copy number was decreased with disease progression from early stage of ADPKD and PGC-1α expression was reduced in the cyst lining cells compared with normal tubules ($p<0.05$). These changes were associated with swelling and fragmentation of mitochondria in cyst epithelial cells. Similar results were observed in vitro. Of note, we found that decreased intracellular calcium level reduced PGC-1α expression through inactivation of calcineurin, and thereby deranged mitochondrial biogenesis, which induced cyst cell proliferation via increased mtROS and activation of ERK1/2. Moreover, the reduction of mtROS with MitoQ significantly suppressed the cyst cell proliferation.

Conclusions: Mitochondrial dysfunction contributes to cyst epithelial cell proliferation in ADPKD. Mitochondria may be a new therapeutic target for ADPKD.

FR-PO531

Beta-1 Integrins and Extra-Mitochondrial Electron Transport Contribute to Aerobic Glycolysis in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Wassim El-Jouni,[1] Brian D. Adair,[1] Wondong Kim,[1] Rachid Akiki,[2] Eugene P. Rhee,[1] Georges El Fakhri,[2] M. Amin Arnaout.[1] *[1]Dept of Medicine/Nephrology, Massachusetts General Hospital, Boston, MA; [2]Dept of Radiology, Massachusetts General Hospital, Boston, MA.*

Background: Increased cell proliferation in ADPKD imposes a critical requirement for nutrients, a demand achieved by increasing glucose uptake and diverting cell metabolism away from mitochondrial oxidative phosphorylation towards aerobic glycolysis. This metabolic switch converts pyruvate into lactate in the cytoplasm despite the presence of oxygen and a functional mitochondrial TCA cycle. Little is known about the cellular pathways leading to this metabolic switch in ADPKD.

Methods: We analyzed cultured DBA^+ mouse embryonic kidney cells isolated from *Pkd1*$^{-/-}$ E15.5 embryos and wild type littermates using [^{18}F]Fluoro-2-deoxy-D-glucose ([^{18}F]FDG) single cell positron emission tomography (SCPET) imaging, metabolomics, and real time measurements of cellular respiration (oxygen consumption rate, OCR, extracellular acidification rate, ECAR).

Results: We made the following observations. 1) [^{18}F]FDG SCPET revealed increased glucose uptake at the single cell level. 2) LC-MS-based metabolomics profiling of *Pkd1*$^{-/-}$ vs. WT cells showed increased glycolytic intermediates, associated with significant increases in pentose phosphate pathway metabolites and decreases in several TCA cycle intermediates in the *Pkd1* null cells. 3) An extra-mitochondrial redox pathway, located in the plasma membrane and blocked by a specific inhibitor, makes a major contribution to glucose-

driven cellular oxygen consumption and proliferation of *Pkd1*$^{-/-}$cells. 4) Stable silencing of integrin β1 inhibited OCR in *Pkd1*$^{-/-}$cells, suggesting a critical role for β1 integrin signaling in aerobic glycolysis in these cells.

Conclusions: These studies elucidate important mechanisms underlying abnormal cell metabolism in murine ADPKD, and identify potential targets for therapeutic intervention.

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FR-PO532

Suppressing Both Renin and Angiotensinogen Synthesis Slows Acceleration of Cystogenesis Induced by Unilateral Nephrectomy in Pkd1 Mice Takamitsu Saigusa,[1] Yujing Dang,[1] Catalin F. Baicu,[2] Michael Zile,[2] Adam E. Mullick,[4] Wayne R. Fitzgibbon,[1] P. Darwin Bell.[3] *[1]Div of Nephrology, Medical Univ of South Carolina (MUSC), Charleston, SC; [2]Div of Cardiology, MUSC, Charleston, SC; [3]Div of Nephrology, Univ of Alabama at Birmingham, Birmingham, AL; [4]Ionis Pharmaceutical, Carlsbad, CA.*

Background: Intrarenal renin angiotensin system (RAS) is activated in polycystic kidney disease. We have recently shown in *Pkd1* mouse, that Gen 2 antisense oligonucleotide (ASO) which suppresses angiotensinogen (Agt) synthesis, is efficacious in slowing kidney cyst formation compared to lisinopril. The suppression of Agt was notable for a compensatory increase in kidney renin content. Therefore, inhibiting both Agt and renin might further suppress intrarenal RAS and slow kidney cyst formation. Here we compared aliskiren+Agt ASO (Ali/Agt) to AgtASO or control in an accelerated cystic mouse model induced by unilateral nephrectomy (PMID:21493775) to test whether AgtASO slows the progression of a severe form of PKD.

Methods: Adult *Pkd1*conditional floxed allele mice expressing cre were administered tamoxifen resulting in global knockout of *Pkd1*. Two weeks after tamoxifen injection, mice underwent left unilateral nephrectomy. Mice were then treated with AgtASO (66mg/kg/wk), aliskiren (20mg/kg/d)+Agt or control (no drug) for total of 8 wks.

Results: Both AgtASO and Ali/Agt treatment significantly reduced plasma and urinary Agt levels. Compared to control mice, those receiving AgtASO had reduced Agt mRNA (liver: 80% kidney: 50%). BP was lowest in Ali/Agt among all treatment groups and control group had the highest BP. All mice developed kidney cysts at 8 wks after nephrectomy but Ali/Agt group had lower kidney/body weight, fewer kidney cysts compared to control or AgtASO. Renal pAkt, pS6 levels and apoptosis were significantly suppressed in Ali/Agt compared to AgtASO alone or control.

Conclusions: These results indicate that suppressing Agt alone is insufficient to slow an accelerated form of PKD induced by nephrectomy in *Pkd1* mice. However, concomitant use of aliskiren and AgtASO, was efficacious in slowing cyst expansion compared to AgtASO alone, likely resulting from intensive intrarenal RAS inhibition and suppression of the mTOR pathway.

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FR-PO533

Loss of Primary Cilia Increases Polycystin-2 and TRPV4 Resulting in the Appearance of a Non-Selective Cation Channel at the Apical Membrane of Mouse Cortical Collecting Duct Principal Cells Takamitsu Saigusa,[1] Marlene Amjad Bunni,[1] Qiang Yue,[3] Tiffany L. Thai,[3] P. Darwin Bell,[2] Douglas C. Eaton.[3] *[1]Div of Nephrology, Medical Univ of South Carolina; [2]Div of Nephrology, Univ of Alabama at Birmingham; [3]Dept of Physiology, Emory Univ.*

Background: Polycystic kidney disease (PKD) is a ciliopathic disorder, which results in numerous kidney cyst mostly arising from the collecting duct. The mechanism by which the loss of the primary cilium promotes cyst formation is unknown. There are several TRP channels in cilia/apical membrane including polycystin (PC) 2 and TRPV4; what happens to these channels with the loss of cilia is presently unknown.

Methods: To further study ion channel activity in PKD, we measured channel activity, using the patch clamp technique, from isolated split-open collecting ducts (CCD) from adult conditional knockout mice with (*Ift88*$^{+/+}$) or without (*Ift88*$^{-/-}$) cilia. In addition, single tubules were isolated for measurements of mRNA for PC1, PC2, TRPV4, and ENaC subunits.

Results: Apical membrane channel activity from control (*Ift88*$^{+/+}$) mice had the biophysical characteristics for ENaC (5pS Na^+ selective channels with long mean open times (475.7±83.26 ms) and open probability (P_o) >0.2. However, the predominant channel activity, after the loss of cilia was a 21pS non-selective cation channel (reversal potential near 0) with short mean open time (72±17 ms), P_o <0.08 and a characteristic flickery opening. The biophysical properties of this channel in CCD's (*Ift88*$^{-/-}$) are similar to a previously reported 23pS non-selective cation channel found in mouse CCD cell line derived from an *Ift88* hypomorph (PMID:23977387). In the absence of cilia, there was over a 2-fold increase in mRNA for PC2 and TRPV4 from single isolated CCD compared to mRNA levels present in tubules with intact cilia, but there were no differences in mRNA for PC1 and ENaC subunits.

Conclusions: We interpret these results to suggest that an early event in ciliary loss is the appearance of a non-selective cation channel in the apical membrane. Whether this channel, found in freshly isolated CCD's, is a multimer of TRPV4 & polycystin 2 and the same as that identified in immortalized CCD's, remains to be determined.

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FR-PO534

Increased Salt Intake Does Not Deteriorate Renal Cystic Disease Progression in High Water Loaded PCK Rats Masanori Kugita,[1] Tamio Yamaguchi,[2] Yoichi Nagamura,[2] Harold M. Aukema,[3] Shizuko Nagao.[1] *[1]Education and Research Center of Animal Models for Human Diseases, Fujita Health Univ, 1-98 Dengakugakubo Kutsukake Toyoake, Aichi, Japan; [2]Dept of Clinical Nutrition, Suzuka Univ of Medical Science, Suzuka, Mie, Japan; [3]Dept of Human Nutritional Sciences, Univ of Manitoba, Winnipeg, MB, Canada.*

Background: We reported that high water intake (HWI) reduced the kidney/body weight ratio (KB%), improved renal function and limited serum AVP levels in PCK rats (Nagao et al: JASN 2006). However, HWI in ADPKD patients resulted in higher total kidney volume, urine sodium and urine volume, which could be a consequence of high salt intake (Higashihara et al: NDT 2014). In the current study, we loaded high salt in PCK rats with HWI.

Methods: PCK rats, an orthologous model of human autosomal recessive polycystic kidney disease, were randomly assigned to the control group (CONT: distilled water), high water intake group (HWI: 5% glucose) or high water intake with high salt group (HWS: 5% glucose+0.45% NaCl) and treated from 4 to 20 wk of age.

Results: Total water intake during the experimental period was 1.86 and 2.37 times higher in HWI (P=0.00) and HWS (P<0.01), respectively, compared with CONT, whereas total food intake was not different between all groups. Sodium intake in HWS was 5.71 or 5.94 times higher than CONT (P=0.00) or HWI (P=0.00), respectively. Systolic blood pressure (SBP) started to increase in HWS compared with HWI (P<0.05) at one week after high salt loading. SBP became significantly higher in HWS (164 ± 2 mmHg) compared with CONT (146 ± 1 mmHg, P<0.05), or HWI (146 ± 1 mmHg, P<0.05) at 20 wk of age. KB% was significantly lower in HWI (1.33 ± 0.05) compared with CONT (1.79 ± 0.11, P<0.01), and this beneficial effect was not affected by the overload of high salt in HWS (1.31 ± 0.10, HWI vs HWS: NS).

Conclusions: Although high blood pressure was induced by high NaCl intake, the effect of HWI was not adversely affected by salt in renal cyst expansion in PCK rats. This work was supported by Japan Society for the Promotion of Science Grants-in-Aid for Scientific Research.

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FR-PO535

Effects of Sodium-Deficient and High Salt Diets on Cysts Formation in ARPKD Daria Ilatovskaya, Vladislav Levchenko, Jessica L. Barnett, Tengis S. Pavlov, Alexander Staruschenko. *Physiology, Medical College of Wisconsin, Milwaukee, WI.*

Background: Polycystic kidney diseases (PKD) are a group of nephropathies marked with the formation of fluid-filled cysts along the nephron. Generally, patients with PKD restrict their dietary sodium intake to 100 mmol/day or less, as it is expected to reduce blood pressure and albuminuria. We have shown that inhibition of Epithelial Na^+ Channel (ENaC) with benzamil aggravates cyst formation in PCK rat, a model of ARPKD. Here we hypothesize that general manipulation with sodium content in the diet can alter cyst formation.

Methods: Immunohistochemistry, Western blotting, GFR measurements in conscious animals, and routine molecular biology approaches were utilized to assess renal function in PCK rats fed a normal, high salt, and sodium-deficient (0.4% (NS), 4% (HS), and 0.01% (SD) NaCl, respectively) diets for 8 weeks (starting at 6 weeks of age).

Results: Compared to NS, both HS and SD diets resulted in a dramatic increase in the cyst formation: SD and HS diet groups exhibited 43.6% and 39.8% of cystic area compared to 28.5% in NS group). However, the development of cysts was different between HS and SD diets. HS diet provoked cyst enlargement in a manner seen in NS group. In contrast, SD diet caused extensive growth of small cysts in the cortex, and hypertrophy of the renal tissue (2K/BW ratio was 15.9 ± 0.7 when fed SD diet vs 11.5 ± 0.9 and 13.7 ± 0.8 in NS and HS). SD diet-fed PCK rats had reduced body weight (324 ± 11 compared to 517 ± 6 and 496 ± 5 g in NS and HS groups). Urinary output was significantly higher in the HS animals compared to both SD and NS groups; interestingly, food intake did not differ. GFR levels were 3.9 ± 0.5, 6.5 ± 0.3, and 9.8 ± 1.1 uL/min/BW in SD, NS and HS fed rats, respectively. Plasma electrolytes (K^+, Na^+, Cl^-, and Ca^{2+}) were significantly lower in PCK rats fed SD diet and not different between NS and HS groups. Consistent with other data, BUN was almost 130 mg/dL in the SD group compared to < 20 mg/dL in NS and HS animals.

Conclusions: Both HS and SD diets significantly increase cystic area in PCK rats, although cyst formation and its effects on kidney function are different between these two groups.

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FR-PO536

The Recessive PKD Proteins, Fibrocystin/Polyductin and Cystin, Act Independently to Regulate Myc Expression Maoqing Wu,[1] Chaozhe Yang,[1] Naoe Harafuji,[1] Jacob A. Watts,[1] Candice Wolf,[1] Avi Rosenberg,[2] Lisa M. Guay-Woodford.[1] *[1]Center for Translational Science, Children's National Health System, Washington, DC; [2]Dept of Pathology, Children's National Health System, Washington, DC.*

Background: *Myc* overexpression in renal epithelia has been reported in several PKD mouse models, as well as human ADPKD. Transgenic mice overexpressing *Myc* develop renal cystic disease. Therefore, Myc has been proposed as an inducer of cystogenesis, but little is known about *Myc* expression in recessive PKD. In previous studies, we have shown 1) cystin, encoded by *Cys1*, the gene disrupted in the *cpk* mouse, undergoes regulated nuclear trafficking; 2) cystin downregulates *Myc* expression; and 3) the *PKHD1* gene product FPC undergoes proteolytic cleavage with nuclear translocation of the carboxy terminus (CTD-FPC). In the current study, we evaluated *Myc* expression in recessive PKD kidneys and cell lines, assessed whether CTD-FPC regulated *Myc* expression, and determined the role of cystin.

Methods: Lysates and sections prepared from the *Cys1^{cpk}*, *Bicc1^{bpk}*, *Pkhd1^{cl}* mouse kidneys and lysates from wild-type and *Cys1^{cpk}* collecting duct cells were examined by immunoblotting and immunofluorescence using standard protocols. Luciferase reporter assays were conducted per our published protocol (PLOS ONE, 2013).

Results: When compared to controls, *Myc* is overexpressed in *Cys1^{cpk}* and *Bicc1^{bpk}* cystic kidneys, as well as the *Cys1^{cpk}* cell line. In addition, we observed variable levels of *MYC* upregulation in ARPKD kidneys. In contrast, *Myc* expression was not upregulated in kidneys from the spontaneously occurring *Pkhd1^{cl}* mutant, which does not express a renal cystic phenotype. In CTD-FPC overexpressing cell lines, *Myc* was upregulated and the luciferase reporter assay demonstrated that the CTD-FPC significantly enhanced the activity of *Myc* P1 promoter, a functional effect that was cystin-independent.

Conclusions: Our data demonstrate that *Myc* overexpression is a common signature of renal cystic epithelia in recessive PKD. Further, we show that in *in vitro* assays, the CTD-FPC and cystin act independently to regulate *Myc* expression. The absence of *Myc* overexpression in *Pkhd1^{cl}* kidneys may explain the absence of a renal cystic phenotype.

FR-PO537

Differential Expressions of miR-378a-3p/ADAMTS1 in cpk Mice, a Model of ARPKD Masashi Sato,[1] Koichi Nakanishi,[1] Taketsugu Hama,[1] Hironobu Mukaiyama,[1] Hiroko Togawa,[1] Yuko Shima,[1] Masayasu Miyajima,[2] Kandai Nozu,[4] Shizuko Nagao,[5] Hisahide Takahashi,[5] Kazumoto Iijima,[4] Norishige Yoshikawa,[3] Hiroyuki Suzuki.[1] *[1]Pediatrics, Wakayama Medical Univ, Wakayama City, Wakayama Prefecture, Japan; [2]Laboratory Animal Center, Wakayama Medical Univ, Wakayama City, Wakayama Prefecture, Japan; [3]Clinical Research Center, Wakayama Medical Univ, Wakayama City, Wakayama Prefecture, Japan; [4]Pediatrics, Kobe Univ, Kobe City, Hyogo Prefecture, Japan; [5]Education and Research Center of Animal Model for Human Disease, Fujita Health Univ, Toyoake City, Aichi Prefecture, Japan.*

Background: The pathophysiology of cystic epithelia in polycystic kidney disease (PKD) is characterized by altered proliferative activity, secretory rather than absorptive function and abnormal matrix microenvironment. miRNA is reported to contribute to the pathophysiology in PKD, however, the details are still unknown.

Methods: To assess roles of miR-378a-3p, previously identified by our miRNA microarray, as well as ADAMTS1, a target molecule of miR-378a-3p, we investigated the expression levels of those molecules using real-time PCR, western blotting and immunohistochemistry in kidney and urine of *cpk* mice.

Results: Real-time PCR confirmed that miR-378a-3p expression was significantly down-regulated in *cpk* kidney (day 14, n=14, 20%, p<0.01; day 21, n=12, 11%, p<0.01) and that ADAMTS1 mRNA was significantly up-regulated in *cpk* kidney (day 14, n=20, 1.4-fold, p=0.01; day 21, n=12, 3.5-fold, p<0.01) compared to control. Western blotting revealed that ADAMTS1 expression was increased in *cpk* kidney (day14, n=4, 2.7-fold, p=0.02; day 21, n=4, 2.4-fold, p=0.02). Immunohistochemistry for ADAMTS1 supported these findings. Urinary miR-378a-3p expression by real-time PCR was significantly down-regulated in cpk (day 14, n=8, 15%, p<0.01).

Conclusions: Recently, dysregulation of miR-378a-3p axis is a topic in various carcinomas. Elevated ADAMTS1 promotes pro-tumorigenic changes such as increased tumor cell proliferation and altered extra cell matrix environment. Our results suggest that miR-378a-3p/ADAMTS1 axis is involved in *cpk*, and give us a rationale for future intervention studies for disease-specific treatments. Moreover, urinary miR-378a-3p might be a potential biomarker for PKD.

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FR-PO538

Deregulation of Long Non-Coding RNAs in Autosomal Dominant Polycystic Kidney Disease Karam S. Aboudehen,[1] Mohammed Shabbir Kanchwala,[2] Shayan A. Farahani,[1] Sophia M. Vrba,[1] Siu Chiu Chan,[1] Svetlana Avdulov,[1] Vishal Patel,[3] Chao Xing,[2] Peter Igarashi.[1] *[1]Dept of Medicine, Univ of Minnesota Medical School, Minneapolis, MN; [2]McDermott Center for Human Growth and Development, UT Southwestern Medical Center, Dallas, TX; [3]Dept of Internal Medicine, UT Southwestern Medical Center, Dallas, TX.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) represents the most common monogenic cause of kidney failure in humans. ADPKD is characterized by progressive cyst formation in renal tubules and is caused by mutations in *PKD1* or *PKD2*. Long non-coding RNAs (lncRNA), defined by a length >200 nucleotides and absence of a long open reading frame, have been implicated in a range of diseases. However, the role of lncRNAs in PKD has not been reported.

Methods: We performed deep RNA sequencing to identify alterations in the expression of lncRNAs in cystic kidneys from conditional *Pkd1* and *Pkd2* mutant mice. We also performed *de novo* transcriptome assembly to discover novel lncRNAs.

Results: We identified 66 known lncRNAs and 80 non-annotated transcripts that were commonly deregulated in both mouse models. The majority of the 66 annotated lncRNAs were located in intergenic regions or were antisense transcripts. Five lncRNAs were sense transcripts, and four localized to gene introns. Characterization of 44 highly deregulated lncRNAs revealed that 82% displayed developmental changes in expression between embryonic, newborn, and adult mouse kidney. Comparison of the expression in the kidney to other organs in the mouse revealed that 17 lncRNAs were widely expressed and four lncRNAs were kidney-specific. RNA fractionation experiments showed that 80% of the lncRNAs were predominantly located in the nucleus, suggesting that ADPKD-associated lncRNAs may be involved in transcriptional regulation. Consistent with this role, a subset of lncRNAs showed alterations in the expression of neighboring protein-coding genes in both mouse models.

Conclusions: Collectively, these studies identify a subset of developmentally regulated and tissue-specific lncRNA that may be involved in the pathogenesis or progression of ADPKD.

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FR-PO539

The Intron 40 Transcript from the HmPKD1 Gene Induces Major Changes in Protein Expression of NIH 3T3 Cells Robert L. Bacallao,[1] Takashi Hato,[1] Xianyin Lai,[2] Frank Witzmann.[2] *[1]Medicine, Indiana Univ, Richard Roudebush VAMC, Indianapolis, IN; [2]Cellular and Integrative Physiology, Indiana Univ School of Medicine, Indianpapolis, IN.*

Background: Informatic analysis of the HmPKD1 gene identifies 46 transcripts produced from this gene. One small transcript expressed from intron 40 of HmPKD1 is the subject of this communications. The intron 40 transcript , begins at intron 40, runs into exon 41 and then spices the 3' end of intron 41 to the 5' end of exon 43. Thereafter the sequence uses the standard splices site from full-length polycystin-1 (PC-1).

Methods: The sequence from the intron 40 cDNA was performed to confirm the identify of the clone relative to its identification in the UC Santa Cruz genome browser. To confirm the reading frame we cloned the construct into pRSET and used the proprietary XPRESS antibody to determine in frame expression. Based on sequence analysis we found significant homology between the amino acid sequence of the itron 40 transcript and 200 amino acids from the c-terminal of PC-1. Antibodies raised against c-terminal sequences of human PC-1 confirmed expression of the intron 40 transcript in NIH 3T3 cells. MS MS mass spectroscopy was performed on cell lysates obtained from mock transfected NIH 3T3 cells and intron 40 cDNA transfected NIH 3T3 cells.

Results: Immune blot analysis reveals a 40 kDA protein whose molecular weight is in agreement with the predicted open reading frame. Mas spectroscopy and 2D DIGE studies revealed over 200 proteins whose expression is changed by expression of the intron 40 transcript. Major pathways down regulated include glutathione biosynthesis, colanic acid biosynthesis, GDP-mannose biosynthesis, phagasome matureation and NRF2-mediated oxidative stress response. Upregulated pathways include cysteine degradation, glutathione biosynthesis and fatty acid oxidation.

Conclusions: Intron 40 of HmPKD1 expresses a 1200 bp message that produces a 40 kDa protein. Transfection of the intron 40 produced cDNA into NIH 3T3 cells results in significant changes in expression levels of 200 proteins .

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FR-PO540

The Roles and Mechanisms of ADP Ribosylation Factor-Like GTPase 13B in Mouse Kidney Yuanyuan Li,[1] Xin Tian,[2] Ming Ma,[2] Stephanie Jerman,[1] Stefan Somlo,[1,2] Zhaoxia Sun.[1] *[1]Genetics, Yale Univ School of Medicine, NewHaven, CT; [2]Internal Medicine, Yale Univ, NewHaven, CT.*

Background: ADP ribosylation factor-like GTPase 13B (Arl13b) encodes a small GTPase essential for cilia biogenesis in multiple model organisms. In zebrafish inactivation of arl13b leads to ventral body curvature and kidney cysts, typical phenotypes resulted from ciliary defects. In mouse null mutation of Arl13b results in disrupted neural tube patterning and defective hedgehog signaling. In human mutations of ARL13B lead to a classical form of Joubert Syndrome (JS) or retinal impairment and obesity linked by JS. However, ARL13B mutations in patients do not cause kidney cysts.

Methods: To investigate the roles of Arl13b in mammalian kidneys, we generated Arl13bFlox/Flox, Ksp-Cre mice in which Arl13b was depleted in the distal nephron at the perinatal stage.

Results: We detected rapid kidney cyst formation in the Arl13b conditional knockout model, collagen deposition and α-SMA accumulation in late stage indicative of renal fibrosis. In our model, we detected significantly upregulated Wnt7a expression as early as collecting duct dilation, before cyst formation. Valproic acid, a histone deacetylase inhibitor, inhibited the early rise of Wnt7a expression, ameliorated fibrosis, slowed cyst progression and improved kidney function.

Conclusions: Previous studies showed that, Wnt7a expression is upregulated in Pkd1-/- and unilateral ureteral obstruction (UUO) mouse model. Moreover, TGF-β activate collagen synthesis and leads to renal fibrosis through activating Wnt7a expression. In addition, NF-κB expression is upregulated significantly in folic acid induced acute kidney injury in mice. Inhibition of NF-κB activation in the UUO model reduced interstitial collagen IV deposition and α-SMA accumulation. To tease out the relationship between the different pathway in disease progression of the Arl13b model, we will investigate the roles of TGF-β and NF-κB pathway in both knockout mice and MEFs.

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FR-PO541

Centrosome Amplification Disrupts Kidney Development and Causes Cystic Kidney Disease Moe Mahjoub,[1,2] Kyuhwan Shim,[1] Lai Kuan Dionne,[1] Masato Hoshi,[1] Veronique Marthiens,[3] Amanda Knoten,[1] Renata Basto,[3] Sanjay Jain.[1] *[1]Div of Nephrology, Dept of Medicine, Washington Univ in St. Louis, MO; [2]Dept of Cell Biology and Physiology, Washington Univ in St. Louis, MO; [3]Inst Curie, Paris, France.*

Background: Cystic kidney diseases are characterized by hyperproliferation of normally quiescent renal epithelial cells, which profoundly alter the organ architecture and impair renal function over time. It is well established that defects in two essential microtubule-based organelles, the centrosome and cilium, contribute to the cystic transformation of renal epithelial cells. The centrosome-cilium complex acts as a cellular signaling center to organize and regulate the activity of various developmental signaling pathways. Recent studies have noted the presence of ectopic centrosomal structures (meaning too many centrosomes per cell) in renal epithelial cells isolated from patients and animal models of polycystic kidney disease. Surprisingly, this phenotype has been mostly ignored, and considered a potential secondary effect of cystic cell transformation and proliferation. However, we hypothesize that abnormal centrosome biogenesis may play an important causal role in the pathogenesis of the disease.

Methods: In this study, we make use of novel genetic mouse models with which we can alter centrosome biogenesis *in vivo.* We induce the formation of ectopic centrosomes in progenitor cells of the metanephric mesenchyme and the ureteric bud epithelium. Kidneys are analyzed at various stages of embryonic and postnatal development.

Results: We demonstrate, for the first time, that the formation of ectopic centrosomes disrupts embryonic kidney development and results in rapid cystogenesis. We also find that ectopic centrosomes sensitize kidneys in adult mice, causing cystogenesis following renal injury.

Conclusions: These results indicate that ectopic centrosome biogenesis alone is sufficient to trigger cyst formation and growth, even in the absence of mutations in cystic genes. These studies further our understanding of the fundamental cellular events that trigger cystogenesis, and characterize a potentially new therapeutic target for treatment of cystic kidney disease.

Funding: NIDDK Support

FR-PO542

Depletion of Ciliary Gate Protein FBF1 Promotes Cystogenesis in Pkd1RC/RC Mice Tao Xu.[1,2,3,4] *[1]Nephrology and Rheumatology, Shanghai Jiao Tong Univ Affiliated Sixth People's Hospital, Shanghai, China; [2]Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [3]Mayo Translational PKD Center, Mayo Clinic, Rochester, MN.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic disorder resulting from mutations in either *PKD1* or *PKD2* and characterized by massive bilateral renal cyst formation. Dysfunction of sensory organelle cilia has been tightly correlated with the pathogenesis of cystogenesis. Renal cyst is a common manifestation in various ciliopathies, but intriguingly, removal of cilia also suppressed cyst growth in ADPKD rodent model, suggesting cystogenesis mechanism between ciliopathies and ADPKD may be distinctly different. We previously discovered that FBF1 is a key component of the poorly understood transition fibres (TFs), which regulates ciliogenesis initiation and selective gating of various ciliary proteins.

Methods: By combining genetics, cell biology, and model organisms, we study the conserved role of TFs in regulating polycystin pathway across ciliates species.

Results: Surprisingly, we found that *Fbf1*$^{tm1a/tm1a}$ knockout mice show negligible cystogenesis in the kidney or liver. Notably, combining *Fbf1*$^{tm1a/tm1a}$with *Pkd1*$^{RC/RC}$results in aggressive and accelerated cystogenesis in both kidney and liver. By using genetic model *C. elegans*, cultured mammalian kidney cells, and isolated MEFs from knockout mice, we demonstrated that FBF1 and its homologue play a highly conserved role in regulating the proper homeostasis of ciliary polycystins across ciliated species.

Conclusions: The defective ciliary trafficking of polycystins upon depletion of FBF1 explains the severe renal and liver manifestations of *Fbf1*$^{tm1a/tm1a}$; *Pkd1*$^{RC/RC}$double mutants, and also reveal an important role for TF-mediated cilia gating in the pathogenesis of cystogenesis.

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FR-PO543

Suppressed Autophagy Leads to Increased Apoptosis in Pkd1 Knockout Models Kameswaran Ravichandran, Katharina Hopp, Andrew Thorburn, Charles L. Edelstein. *Univ Colorado Denver.*

Background: Increased proliferation and apoptosis play a role in cyst growth. The link between autophagy and apoptosis in PKD is not known. When autophagy is suppressed, there is accumulation of p62 that results in activation of caspase-8 and subsequent activation of caspase-3, the major mediator of apoptosis.

Methods: 90 (early PKD) and 150 d old mice with a kidney specific tamoxifen-inducible *Pkd1* knockout or Human *Pkd1*-/- (WT 9-12) RCTE cells with a homozygous mutated *Pkd1,* were treated with the lysosomal inhibitors, bafilomycin (Baf) or chloroquine (C), to measure autophagic flux. LC3-II (autophagic flux), cleaved caspase-3 (CC-3), cleaved caspase-8 (CC-8), p62 (autophagy/apoptosis crosstalk) were measured by immunoblot. Annexin-V staining (apoptosis) was measured by flow cytometry.

Results: Baf resulted in an increase in LC3-II in +/+ and a decrease in LC3-II in *Pkd1*-/- kidneys (decreased autophagic flux) associated with increased p62, CC-3 and CC-8. C resulted in an increase in LC3-II in control RCTE (+/+) cells but not in *Pkd1* -/- cells suggesting decreased autophagic flux. Decreased autophagic flux and increased p62 in *Pkd1* -/- cells was associated with increased apoptosis (annexin V staining), increased CC-8 and increased CC-3.

KIDNEYS	+/+	+/+ Baf	90 d old -/-	90 d old -/- Baf	150 d old -/-	150 d old -/- Baf
LC3-II	++	+++	++	+	++	+
CC-3	+	+	+++	+++	+++	+++
CC-8	+	+	+++	+++	+++	+++
p62	+	+	+++	+++	+++	+++
CELLS	+/+	+/+ C	-/-	-/- C		
LC3-II	++	+++	++	+		
CC-3	++	+	+++	+++		
CC-8	+	+	+++	+++		
p62	+	+	+++	+++		
Annexin-V (%)	9.5	6.3	15.5 *	15.9 *		
	Baf=bafilomycin	C=chloroquin	*P<0.05 vs +/+	+ - +++= density of protein expression (n=3)	+/+ = wild type	-/- = Pkd1 -/-

Conclusions: The lack of effect of the lysosomal inhibitors to increase LC3-II in *Pkd1* -/- kidneys and *Pkd1* -/- cells suggests a defect in autophagy resulting from a block of autophagosome-lysosome fusion and degradation. Suppressed autophagy is associated with increased apoptosis and apoptosis/autophagy crosstalk. Autophagy inhibition with Baf or Chloroquin leads to increased apoptosis in *Pkd1* -/- models.

Funding: Pharmaceutical Company Support - IC-Meditech

FR-PO544

Identification of a Novel Ciliary Targeting Sequence in Polycystin-1 Chong Luo,[1,2] Xuefeng Su,[1] Maoqing Wu,[1] David Verkaik,[1] Jianghua Chen,[2] Jing Zhou.[1] *[1]Harvard Center for Polycystic Kidney Disease Research and Renal Div, Dept of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Kidney Disease Center, The First Affiliated Hospital, School of Medicine, Zhejiang Univ, Hangzhou, Zhejiang Province, China.*

Background: Mutations of *PKD1* cause 85% autosomal dominant polycystic kidney disease (ADPKD) cases. Previous studies by us and others have shown that many pathogenic mutations result in defective ciliary localization of polycystin-1 (PC1), suggesting that the ciliary trafficking of PC1 might be a functional assay for ADPKD. However, how PC1 traffics to primary cilia remains poorly understood. A ciliary targeting sequence (CTS) is thought to be involved in this process. The VxP motif present in the C-terminal tail of PC1 was reported to function as a CTS through an Arf4/ASAP1 dependent manner similar to rhodopsin trafficking to the primary cilia. However, this motif is dispensable for full-length PC1 targeting to cilia. The ciliary targeting motif(s) in PC1 is to be identified.

Methods: A set of chimeric constructs with different motifs in PC1 including mutations that correspond to human ADPKD patients were made. These constructs were transiently transfected into IMCD3 cells, and the ciliary trafficking ability of these constructs was evaluated by immunofluorescent staining.

Results: Here we show that an ~ 40 amino acid sequence is sufficient to drive chimeric proteins to the primary cilia. This region consists of several highly conserved motifs. Multiple deletion and point mutation analyses further led to the discovery of an eight amino acid sequence that functions at an efficiency similar to the 40 amino acid sequence in ciliary trafficking. Another motif in this region also has a milder effect on targeting chimeric protein to the primary cilia. Effects of amino acid substitutions found in ADPKD patients were analyzed.

Conclusions: Through a systemic analysis, we have identified a novel ciliary targeting motif in PC1 responsible for targeting chimeric proteins into the primary cilia. Ongoing studies include testing its function and its regulation in full-length PC1.

Funding: NIDDK Support

FR-PO545

Primary Cilia Regulate Kupffer Cell/Resident Macrophage Activation, Monocyte Recruitment, and Hepatic Fibrosis in a Mouse Model of PKD

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Background: Patients with hepatorenal fibrocystic diseases (HRFD)(including PKD) develop extra-renal complications including biliary cysts and periportal fibrosis. While many HRFD genes are known, the underlying processes that drive liver cyst formation and fibrosis are not well understood.

Methods: To better define mechanisms involved in HRFD liver disease, we used an *Ift88*^{orpk} mouse model with an insertional mutation in the IFT88 gene leading to reduced IFT88 protein, short dysfunctional cilia, and severe cysts in the kidney and liver by 4 weeks.

Results: Our data indicate that 4 week old *Ift88*^{orpk} cilia mutant mice overexpress the pro-fibrotic genes *Col1a1* and *Col3a1* and have increased collagen protein in periportal regions as indicated by picrosirius red stain. In addition, livers from these mice show an accumulation of F4/80 positive macrophages in periportal regions containing smooth muscle actin positive cells. Fluorescent activated cell sorting (FACS) data indicate that a majority of the macrophages present in 4 week cilia mutant mice are the pro-fibrogenic Ly6c^{hi} monocytes. Whole liver transcript analysis shows a substantial increase in multiple pro-inflammatory and pro-fibrotic cytokines in cilia mutant mice including TGF-β, PDGF-bb, TNF-α, IL-1β and MCP-1. Preliminary data using FACS analysis of sorted liver cell populations from 4 week mutant mice show that resident macrophages/kupffer cells are the major cell type responsible for hepatic MCP-1 production whereas infiltrating monocytes are the major source of TGF-β. Importantly, resident macrophages isolated from *Ift88*^{orpk} cilia mutant mice demonstrated increased proliferation at 4 weeks compared to controls. This observation suggests that resident macrophages become activated in late stage disease progression and may be a driving force in HRFD.

Conclusions: In conclusion, we demonstrate that primary cilia defects alter hepatic immune responses including resident macrophage/kupffer cell activation. We show that activated kupffer cells overexpress MCP1, a known chemoattractant, that triggers the influx of Ly6c^{hi} pro-fibrogenic monocytes leading to development of periportal fibrosis.

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FR-PO546

Unilateral Nephrectomy in Adult Pkd1 Knockout Mice Accelerates Kidney Cystogenesis

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Background: One explanation for the variability in disease progression in patients with polycystic kidney disease (PKD) can be attributed to "third hit" signaling. We reported that unilateral nephrectomy induces hypertrophic signaling and accelerates kidney cyst formation in adult *Ift88* mice, a model of recessive PKD (PMID: 21493775). Whether this applies to other PKD mouse models and the mechanism of how unilateral nephrectomy accelerates cystogenesis are both unknown. Therefore, we tested the effects of unilateral nephrectomy on cystogenesis in autosomal dominant PKD mice.

Methods: Adult *Pkd1*conditional floxed allele mice (C57B6 background) without cre (*Pkd1*$^{+/+}$) and with cre (*Pkd1*$^{-/-}$) were administered tamoxifen. Some mice underwent left unilateral nephrectomy (1K) and others retained both kidneys (2K). Kidneys from all 4 groups (1K&2K *Pkd1*$^{+/+}$and 1K&2K *Pkd1*$^{-/-}$) were examined for cystic development. High-throughput RNA sequencing (RNAseq) (SE50) were performed on kidney RNA extracted using an Illumina HiSeq2500.

Results: Four weeks after nephrectomy, 1K *Pkd1*$^{-/-}$ mice had increased kidney/body weight and became cystic compared to 2K *Pkd1*$^{-/-}$ mice. Both 1K and 2K *Pkd1*$^{+/+}$ mice had no cyst in kidney and liver. Analysis of the RNAseq data from the 1K vs 2K *Pkd1*$^{+/+}$mice revealed no differences in gene regulation. However, *Pkd1*$^{-/-}$mice revealed, 1,335 significantly differentially expressed transcripts (q <0.4) when 1K was compared to 2K kidney. Gene ontology analysis demonstrated significant enrichment of terms including cell migration and regulation of cell motility (Bonferroni adjusted $p < 4.003^{E-36}$). Pathway analysis, revealed significant enrichment of genes involved in the extracellular matrix pathway (79/264 genes, Bonferroni adjusted $p< 5.560^{E-22}$).

Conclusions: In summary, unilateral nephrectomy in adult *Pkd1* conditional knockout mice results in accelerated kidney cyst formation compared to 2K *Pkd1*$^{-/-}$mice. Analysis of kidney RNAseq data demonstrated that, unilateral nephrectomy in *Pkd1*$^{-/-}$ mice, significantly enriched and upregulated transcripts and genes compared to 2K *Pkd1*$^{-/-}$ mice.

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FR-PO547

Acute Kidney Injury and Polycystic Kidney Disease Share Common Signaling Mechanism

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Background: Acute kidney injury (AKI) and autosomal dominant polycystic kidney disease (ADPKD) are considered separate entities that both frequently cause renal failure. ADPKD kidneys develop multiple cysts that arise from dosage dependent mechanism with mutations in *PKD1* and *PKD2* encoding PC1, PC2. Since ischemia-reperfusion injury (IRI), a model of AKI, can promote earlier cyst formation in *Pkd1* dosage-reduced mice, we questioned whether cystogenesis could be accelerated in *Pkd1* dosage-increased and mutant mouse models via a similar mechanism.

Methods: Mice with mild overexpression of full-length *Pkd1* gene in Pkd1$_{TAG}$ dosage-increased mouse model and with a human *PKD1* mutation Pkd1$_{extra}$ develop slow progressive PKD. These transgenic mice and control littermates were subjected to unilateral renal IRI at 3-months and sacrificed at different timepoints following reperfusion. IRI kidneys were evaluated by histo-morphometry, proliferation, fibrosis and cilia length analyses. Renal transcript and protein expression was monitored by qPCR and immunoblot.

Results: All non-transgenic (n=63) and transgenic (n=36) mice relative to sham-operated (n=20) reproducibly develop moderate to severe tubular cysts and typical PKD cellular defects that is epithelial hyperplasia, immune interstitial infiltrates and fibrosis within 23 days to 3 months post-IRI. Similar onset and severity of IRI induced-cystogenesis in mice independently of their genotype revealed that IRI is sufficient to promote cyst formation and was not amplified by the transgene. IRI non-transgenic and transgenic kidneys showed from 16 days post-IRI, strikingly increased and sustained *Pkd1*/Pc1 (>3-fold) and *Pkd2*/Pc2 (>8-fold) expression that each can be cystogenic in mice. Long-term and important stimulation of *Hif1a* expression was induced as in ADPKD. While mTOR signaling is activated, stimulation of the Wnt pathway, with markedly increased active ß-catenin and c-Myc expression in IRI renal epithelium, uncovered a similar regulatory cystogenic response shared by IRI and ADPKD.

Conclusions: Our study demonstrates that AKI induces long-term cystogenesis in wild-type mice and crosstalks with ADPKD pathogenic and/or repair signaling mechanism.

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FR-PO548

Activation of Notch3 Signaling Pathway in Polycystic Kidney Disease

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Background: Polycystic kidney disease (PKD) is a genetic disease associated with fluid filled renal cysts and causes complications such as pain, hypertension and aneurysms and ultimately end stage renal disease. Despite recent advances, there is no approved treatment for PKD in United States. Notch signaling plays a key role in many chronic kidney diseases. Since the cellular processes such as proliferation and dedifferentiation are common between PKD and other kidney pathologies, we hypothesized that Notch signaling may play a critical role in PKD.

Methods: Protein expression profile of Notch pathway members in autosomal recessive PKD (ARPKD) and Autosomal dominant PKD (ADPKD) mouse models as well as patients with ADPKD was evaluated using immunolabeling techniques and Western blots. The effect of Notch inhibitor was evaluated on cysts grown on collagen gels from cells obtained from ADPKD patients.

Results: We show that Notch pathway, particularly Notch3 (N3) pathway is consistently activated in cystic cells from all the mouse models and human ADPKD samples studied. Among the ligands, only Delta like 4 (Dll4) was found to be consistently increased in all the models. N3 was expressed and upregulated in both collecting duct and proximal tubular cysts. The expression of N3 and Dll4 was maximum when the cysts were rapidly growing at earlier stage of the disease. In a slow progressing mouse model of PKD (RC/RC), there was no N3 expressed in cystic cells which had lost their structure due to de-differentiation, however N3 was found to be expressed in few cells that had retained their structure. Notch3 expression co-localized with proliferation marker, PCNA. Moreover Notch inhibition using Gamma secretase inhibitor ameliorated cyst formation when primary cells from ADPKD patients were allowed to form cysts in collagen gels.

Conclusions: We conclude that Notch3/Dll4 pathway is activated in PKD and that inhibition of Notch signaling may prevent cyst formation in PKD setting most likely by inhibiting cell proliferation.

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FR-PO549

CRISPR-Mediated Knockdown of Arl3 Implicates the Functional Sequestration of Cystin as the Mechanism Underlining the Recessive PKD Phenotype in Arl3-/- Mice

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Background: The *cpk* mouse, which arose spontaneously from a frameshift mutation in *Cys1*, phenocopies human ARPKD and is considered the best-characterized mouse model of recessive PKD. The overexpression of c-Myc at both the transcript and protein level is a signature of recessive PKD epithelia (Abstract No. 2290, this meeting). We have previously shown that cystin, the protein product of *Cys1*, regulates the expression of *Myc* through its nuclear interaction with necdin.

Methods: Using tandem affinity purification, we identified the ciliary GTPase Arl3 as a putative interacting partner of cystin. Previously published data demonstrated that 1) Arl3 regulates the UNC119b-mediated ciliary localization of myristoylated proteins, specifically cystin (*Genes Dev*, 2011) and 2) *Arl3*$^{-/-}$ mice express a renal cystic phenotype that closely resembles that observed in the *cpk* mouse (*Am J Pathol*, 2006). Using CRISPR technology, we generated stable *Arl3* knockdown cell lines with a Cas9 expression vector containing RNA guides targeted to the translational start site of mouse *Arl3* that were nucleofected into mIMCD-3 cells. Cells were synchronized at G_0/G_1 using simvastatin treatment.

Results: Immunoblotting confirmed that the Arl3 protein level was substantially decreased in the *Arl3*^{CRISPR} cells and c-Myc was overexpressed in these cells compared to control cell lines. The elevated c-Myc expression was rescued by over-expression of cystin$_{G2A}$, a myristoylation-deficient variant that has decreased ciliary membrane association but preserved nuclear localization and function.

Conclusions: We propose that the renal cystic phenotype observed in the *Arl3*$^{-/-}$ mouse results from functional sequestration of cystin by UNC119b due to the absence of Arl3. Our data implicate cystin-UNC119b-Arl3 in a functional complex that is required to maintain normal ciliary signaling and renal epithelial homeostasis. In this functional model, loss of either Arl3 or cystin results in renal cystic disease.

FR-PO550

Cystin, the Protein Disrupted in the cpk Mouse, Is Implicated in Pkhd1 Transcriptional Regulation Jacob A. Watts, Candice Wolf, Chaozhe Yang, Maoqing Wu, Naoe Harafuji, Lisa M. Guay-Woodford. *Center for Translational Science, Children's National Health Systems, Washington, DC.*

Background: ARPKD results from mutations in *PKHD1*. However, gene-targeted *Pkhd1* mouse models and the spontaneous *Pkhd1*^{cl} mutant express limited or no kidney disease. In contrast, the *cpk* mouse with defects in *Cys1* phenocopies human ARPKD. This cross-species phenotypic similarity suggests that cystin (*Cys1*) and FPC (*Pkhd1*) may function in common pathway(s) that are differentially regulated in mouse and human renal epithelia. In the current study, we sought to identify cystin-binding partners, elucidate the nuclear function of cystin, and define a potential functional interaction between cystin and FPC in mouse renal epithelia.

Methods: Cystin$_{G2A}$, a myristoylation deficient variant that preferentially targets to the nucleus was cloned into a tandem affinity purification (TAP) vector. The cystin$_{G2A}$-TAP construct, double-tagged with Strep and FLAG at the N-terminus, was stably transfected into mIMCD-3 cells. Following the TAP procedure, mass spectrometry (MS), informatics analysis (STRING v10), and targeted co-IP studies were performed. Minigene assays and RT-PCR were conducted as described (*J Mol Med, 2014*).

Results: MS identified several putative cystin interacting partners, including the nuclear-entry regulatory proteins, importin α1, α2, and β2, as well as several splicing-related proteins. Our previous studies demonstrated that *Pkhd1* is transcriptionally complex and implicated the splicing regulator Srsf5 as a major factor in *Pkhd1* alternative splicing. We now show that 10 of the 12 *Srsf* genes, including *Srsf5*, are expressed in mIMCD-3 cells. Co-IP studies indicate that cystin and Srsf5 interact. In minigene assays, a construct containing *Pkhd1* exons 6-7-51 (the latter with an Srsf5 binding motif) is differentially expressed in wild-type versus *Cys1*^{cpk} collecting duct cells.

Conclusions: Our data: 1) indicate that cystin localizes to the nucleus via importin-regulated pathways and 2) implicate a role for cystin in the transcriptional regulation of *Pkhd1*. These data provide the first experimental evidence functionally linking cystin and FPC in mouse renal epithelia.

FR-PO551

Four-Jointed Knock-Out Causes a Delay in Kidney Failure in an Autosomal Dominant Polycystic Kidney Disease Model with Renal Injury Chiara Formica,[1] Hester Happé,[1] Kimberley Veraar,[2] Sandra Kunnen,[1] Marion Scharpfenecker,[2] Dorien J.M. Peters.[1] [1]*Human Genetics, Leiden Univ Medical Center, Netherlands;* [2]*Pathology, Leiden Univ Medical Center, Netherlands.*

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is characterized by the development of fluid-filled cysts, which leads to renal failure. In the majority of cases the disease is caused by a mutation in the *PKD1* gene. In a previous study, we demonstrated that injury-induced tubular epithelial cell proliferation accelerates cyst formation in kidneys of inducible *Pkd1*-deletion (iksp*Pkd1*^{del}) mice (Happé *et al.*, Hum. Mol. Genet. 2009). In particular, our results suggested a role for the Planar Cell Polarity (PCP) regulator Four-jointed (Fjx1), in the injury/repair mechanism. Therefore, we studied the role of Fjx1 in cyst formation and PKD progression.

Methods: We generated several mouse models, i.e. *Fjx1*$^{-/-}$mice, iKsp*Pkd1*^{del} mice as well as *Fjx1*$^{-/-}$;iksp*Pkd1*^{del} mice (double knock-out mice). After *Pkd1*-gene inactivation, we induced nephrotoxic injury using 1,2-dichlorovinyl-cysteine (DCVC) or PBS as control, and characterized tissue-repair and cyst formation in the different models.

Results: We confirmed that nephrotoxic injury is able to accelerate cyst formation in iksp*Pkd1*^{del} mice, while this was not observed in the *Fjx1*$^{-/-}$; iksp*Pkd1*^{del} mice, which showed longer survival (median survival: 14 weeks vs 20 weeks; p. value < 0.05). PCP, assessed by measuring Golgi position, was comparably aberrant in both iksp*Pkd1*^{del} and *Fjx1*$^{-/-}$;iksp*Pkd1*^{del} mice, already early after DCVC. This suggests a more complex regulation of PCP, and excludes a causal role for this pathway in prolonged survival. Also proliferation, Hippo signalling and cystic indices were comparable. However, fibrosis was significantly less in the double knock-out mice, consistent with the delayed kidney failure observed in this genotype.

Conclusions: Our data suggest that in PKD, *Fjx1* disruption is protective against renal failure by delaying fibrosis. Further analyses to unveil the mechanism are ongoing.

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FR-PO552

Ouabain Induced Differences in [Ca2+]i Response in NHK and ADPKD Cells Depend on L-type Calcium Channels Jessica D. Venugopal,[1,3] Gail Reif,[2,3] Darren P. Wallace,[2,3] Gustavo Blanco.[1,3] [1]*Molecular and Integrative Physiology, Kansas Univ Medical Center;* [2]*Internal Medicine, Kansas Univ Medical Center;* [3]*The Kidney Inst, Kansas Univ Medical Center, Kansas City, KS.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the progressive growth of renal cysts that alter the structure and function of the kidney. We have shown that the hormone ouabain enhances cell proliferation in cystic kidney epithelial cells from patients with ADPKD (ADPKD cells); but does not affect normal human kidney epithelial cells (NHK cells). The mechanisms involved in this dissimilar response are unclear. Due to the essential role of intracellular calcium concentration ($[Ca^{2+}]_i$) in ADPKD, we explored the effect and mechanisms of ouabain action on $[Ca^{2+}]_i$ levels in NHK and ADPKD cells.

Methods: We used the calcium dye Fura-2AM as a reporter to follow $[Ca^{2+}]_i$ changes in primary cultures of NHK and ADPKD cells, after treatment + 3 nM ouabain.

Results: Ouabain increased $[Ca^{2+}]_i$ in NHK cells, but not in ADPKD cells. Ouabain-induced $[Ca^{2+}]_i$ elevation in NHK cells was blocked by Ca^{2+} removal from the medium, suggesting that plasma membrane ion channels are involved in the response. Ouabain induced Ca^{2+} increase in NHK cells was abrogated by the L-type calcium channel (LTCC) inhibitor verapamil. Moreover, LTCC agonists restored the ouabain-dependent $[Ca^{2+}]_i$ increase in ADPKD cells to levels similar to those of NHK cells. LTCC agonists also blocked ouabain induced proliferation of ADPKD cells. Protein expression levels of full-length LTCC were lower in ADPKD cells than NHK cells. Concomitantly, ADPKD cells contained higher amounts of LTCC cleavage products and greater activity of calpain, a protease involved in LTCC cleavage.

Conclusions: Our data shows that ouabain stimulates $[Ca^{2+}]_i$ increase in NHK cells by facilitating its uptake from the extracellular space via LTCC. Instead, ouabain cannot elevate $[Ca^{2+}]_i$ in ADPKD cells, due to low LTCC levels, which may be secondary to enhanced LTCC cleavage by calpain. The lack of $[Ca^{2+}]_i$ response to ouabain in ADPKD cells helps enhance ADPKD proliferation, an event that exacerbates the ADPKD phenotype.

Funding: NIDDK Support

FR-PO553

Characterization of a P2RX7 Knockout in PCK Rats, a Model of ARPKD Tengis S. Pavlov,[1,2] Daria Ilatovskaya,[1] Vladislav Levchenko,[1] Aron M. Geurts,[1] Melinda R. Dwinell,[1] Alexander Staruschenko.[1] [1]*Physiology, Medical College of Wisconsin, Milwaukee, WI;* [2]*Hypertension and Vascular Research, Henry Ford Health System, Detroit, MI.*

Background: Over the last decade, accumulating evidence suggests that the autocrine and paracrine effects of ATP (through P2 receptors) could be detrimental for the progression of PKD. High ATP release and concentrations were reported in cystic fluid. P2X family receptors are non-selective ion channels, permeable for Ca^{2+} ions; these channels are characterized by high affinity to extracellular ATP, which makes them critical for controlling calcium dependent intracellular mechanisms. $P2X_7$ (*P2RX7* gene) is expressed in the collecting ducts (CD), as well as in cysts formed from CDs in ARPKD. We hypothesize that interfering with $P2X_7$ signaling precludes cystogenesis. To study this hypothesis we generated the knockout of the *P2RX7* gene in PCK rat strain, an established model of ARPKD characterized by a mutation in the *PKHD1* gene.

Methods: *P2RX7* knockout was performed with a CRISPR/Cas9 approach targeting exon 2 that resulted in a single base insertion of a 'T' which induced a frameshift. F2 and further litters were used to establish the colony and run pilot experiments. For characterization of the new strain, 8-weeks old animals were anesthetized and the kidneys were flushed with phosphate buffer and collected with other organs. Western blotting analysis of total kidney lysate was performed to evaluate $P2X_7$ expression. To assess severity of ARPKD, H&E histological staining of central kidney slices were analyzed to calculate cyst area as percentage of total slice area.

Results: Western Blotting revealed lower $P2X_7$ expression in heterozygous compared to wild type rats (44.7%), and lack of the protein in homozygous animals. Homozygous animals were viable and born at Mendelian ratios from intercrosses between heterozygotes. Initial characterization of the first litters showed reduction in cyst area in the homozygous compared to wild type or heterozygous male animals.

Conclusions: $P2X_7$ signaling might be involved in cystogenesis in the ARPKD rodent model.

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FR-PO554

Comprehensive Metabolomics Analysis Shows Evidence of TCA Cycle Dysregulation in a Rat Model of Polycystic Kidney Disease Ivan Vuckovic, Song Zhang, Petras Dzeja, Slobodan Macura, Peter C. Harris, Vicente E. Torres, Maria V. Irazabal. *Mayo Clinic.*

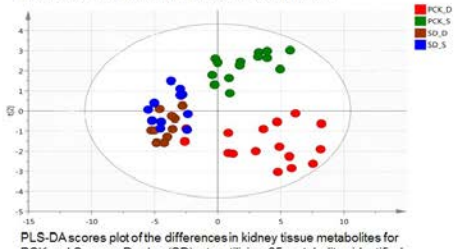
Background: Autosomal Dominant Polycystic Kidney Disease is a leading cause of end-stage renal disease. Many of the metabolic dysregulations contributing to cystogenesis remain to be elucidated. Using a comprehensive metabolomics approach (proton nuclear magnetic resonance,^{1}H-NMR and gas chromatography-mass spectrometry, GC-MS) we investigated the metabolic pathways associated with cystogenesis in the kidney of PCK compared to Sprague-Dawley (SD) wild-type rats.

Methods: We included male and female, PCK and SD rats, treated with dDAVP (PCK_D, n=16 or SD_D, n=12) to aggravate the cystic phenotype or saline solution (PCK_S, n=16 or SD_S, n=12) as controls. Kidney metabolites were identified from tissues collected at euthanasia (P37) and correlated with kidney volume byabdominal MRI (P35).

Results: Partial least squares-discriminant analysis (PLS-DA) score plots showed a significant separation between the groups (Fig 1A). Sixty five metabolites were identified by GC-MS and 42 by ^{1}H-NMR of which 30 were significantly different between PCK_S and SD_S, and 10 of the 30 remained significant ($p<0.05$) between PCK_S and PCK_D. The resulting metabolic profiles demonstrated significantly increased tissue and urine levels of most TCA cycle metabolites, including citrate, isocitrate, α-ketoglutarate, succinate, fumarate and malate in PKD (Fig 1B). Moreover, tissue TCA cycle metabolites levels correlated directly with kidney volumes (Fig 1C).

Conclusions: Comprehensive metabolomics analysis showed significant increases in TCA cycle metabolites in PCK rats. Furthermore, these levels were even higher in PCK dDAVP treated rats. Studies with state of the art stable isotope (^{13}C, ^{18}O) labeling techniques are ongoing to investigate metabolite fluxes and carbon sources, and will aid in determining dysregulations in metabolic pathways for therapeutic interventions.

Figure 1A – Partial least squares-discriminant analysis (PLS-DA) of kidney tissue metabolites in PCK and Sprague Dawley (SD) rats



PLS-DA scores plot of the differences in kidney tissue metabolites for PCK and Sprague Dawley (SD) rats, utilizing 65 metabolites identified by GC-MS and four classes (PCK_D, PCK_S, SD_D and SD_D) to build the model.

Figure 1B – Increased TCA cycle metabolites in PCK vs Sprague Dawley Rats

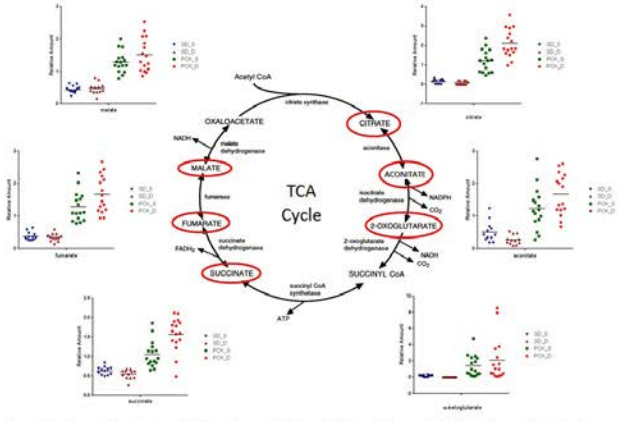
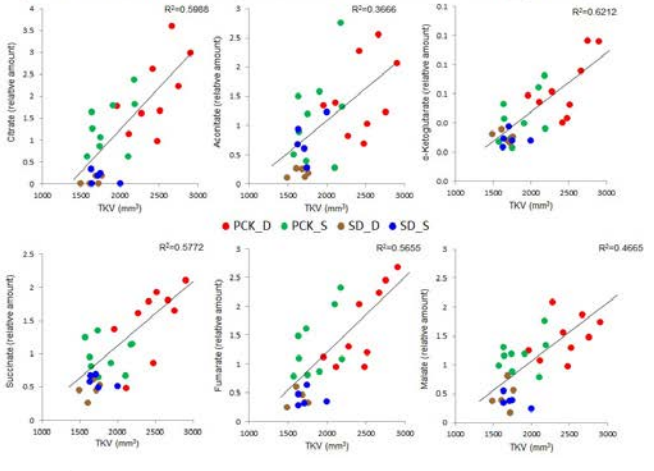


Figure 1C – Correlations between TCA cycle metabolites and Kidney Volumes in PCK vs Sprague Dawley Rats



Funding: NIDDK Support

FR-PO555

Characterization of Two Pkd1 Rat Models Megan M. Constans,[1] Diana L. Escobar,[1] Jessica M. Smith,[1] Aron M. Geurts,[2] Vicente E. Torres,[1] Peter C. Harris.[1] *[1]Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [2]Genome Editing Rat Resource Center, Medical College of Wisconsin, Milwuakee, WI.*

Background: Rats are well established as an experimental model of renal physiology but to date no ADPKD rat model exists. In mice, Pkd1 nulls are embryonic lethal with clear PKD at ~E14.5, while heterozygotes develop few cysts, but the V2 receptor agonist dDAVP aggravates cystic disease. The CRISPR/Cas9 system allows mutants to be generated in alternative model organisms, including rats, such that novel gene knockout models can be generated which may be more experimentally tractable. Here we describe the generation and characterization of two *Pkd1* rat models.

Methods: A plasmid expressing Cas9 and short guide RNAs targeting exon 29 of the *Pkd1* gene were injected into Lewis strain embryos and founder animals with putative Pkd1 mutations were identified. Breeding to wildtypes determined germline transmission, and two mutant lines were aged to 6 months. MRI and histology characterized the heterozygous phenotype and these animals were also treated with dDAVP daily from P7 to P35.

Results: *Pkd1* models were generated with either an inframe, c.9790_9801del12; p.S3273_T3276del (del12), or a frameshifting, c.9793_9800del8, p.R3274fs (del8), deletion. Analysis for homozygotes showed no live born pups for either model from 3 litters, with embryonic analysis at E14.5 not identifying any live embryos. Heterozygotes showed no significant renal enlargement at 6 months, but MRI and histological analysis showed multiple renal cysts in the cortex and medulla (median 7, range 4 to 15) are evident at P21 from a cohort of heterozygous animals. dDAVP aggravated the development of cyst number and size by ~2-fold.

Conclusions: Analysis of these new models shows heterozygous *Pkd1* rats having more kidney cysts than the corresponding mice, which are aggravated by dDAVP as in the PCK rat model of ARPKD. Embryonic analysis suggests earlier lethality in the rat compared to mouse models. These new models will enhance the understanding of slowly progressive ADPKD in a rodent model.

Funding: NIDDK Support

FR-PO556

Microvascular Endothelial Dysfunction in a Rat Model of Autosomal Recessive Polycystic Kidney Disease David M. Pollock,[1] Anthony K. Cook,[1] Chunhua Jin,[1] Robert A. Kesterson,[3] Bradley K. Yoder,[2] Michal Mrug,[1] Edward W. Inscho.[1] *[1]Div of Nephrology, Dept of Medicine, Univ of Alabama at Birmingham, Birmingham, AL; [2]Dept of Cell, Developmental & Integrative Biology, Univ of Alabama at Birmingham, Birmingham, AL; [3]Dept of Genetics, Univ of Alabama at Birmingham, Birmingham, AL.*

Background: Hypertension is a common early complication of polycystic kidney diseases (PKDs) including the autosomal recessive PKD (ARPKD). Hypertension is often associated with endothelial dysfunction, that is a lack of endothelial-dependent relaxation and an inability to buffer vasoconstriction. Thus, we hypothesized that the ARPKD rat should display impaired endothelial function.

Methods: Male, 2-month old ARPKD (PCK/CrljCrl-*Pkhd1*^{pck}/Crl) and control [Crl:CD(SD)] rats from Charles River were maintained on normal salt (NS 0.49% NaCl) diet prior to study. Rats were anesthetized and afferent arterioles (AA) visualized using the blood-perfused juxtamedullary nephron technique. AA diameters were measured in response to different concentrations of the endothelial dependent vasodilator, acetylcholine (ACH; 10^{-8}-10^{-4} M), or the endothelial independent vasodilator, sodium nitroprusside (SNP; 10^{-8}-10^{-4} M). An additional series of experiments were conducted in anesthetized rats surgically prepared to determine renal blood flow (RBF) responses to intravenous angiotensin II (ultrasonic flow probe).

Results: As expected, both ACH and SNP (1.0 mM) significantly increased AA diameters in kidneys from control rats (134±2% and 133±2%, respectively, n=4, $p<0.05$). The vasodilator response to ACH was significantly attenuated in ARPKD vessels (118±2%) compared to controls while the relaxation in response to SNP was similar between strains (123±2%). Decreases in RBF following intravenous bolus of angiotensin II in ARPKD rats were significantly greater in ARPKD rats compared to controls (ΔRBF -47.5±4.6% vs -27.4±3.8%, $p<0.05$).

Conclusions: These results support the hypothesis that renal microvascular dysfunction in ARPKD results from endothelial dysfunction and may contribute to vascular complications in PKDs.

Funding: Private Foundation Support

FR-PO557

A Novel Aldosterone Synthase Inhibitor Ameliorates Polycystic Kidney Disease in the PCK Rat Bert Oehlen, Ping Zhou, Bin Duan, Xiaokang Zhu, Kai Jiang, Latha Paka, Itzhak D. Goldberg. *Angion Biomedica Corp., Uniondale, NY.*

Background: The renin-angiotensin-aldosterone system (RAAS) plays a critical role in renal physiology and pathology. Inhibitors of RAAS, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are commonly used in the management of polycystic kidney disease (PKD). However, despite initial success in reducing aldosterone, concentrations return to pretreatment levels in 30-40% of patients. This "aldosterone escape" significantly limits the therapeutic effectiveness of current RAAS

inhibitors. An attractive novel alternative approach to target RAAS is to inhibit aldosterone synthase (AS), the enzyme encoded by the CYP11B2 gene, which is directly responsible for aldosterone production. We identified a promising new series of inhibitors of AS. Lead compound ANG3586 has potent AS inhibitory activity, has excellent selectivity against other P450 enzymes, is orally bioavailable in rodents and appears to be generally well tolerated.

Methods: Male PCK rats (PCK/CrljCrl-Pkhd1pck/Crl) were treated with ANG3586 (25 mg/kg, po, bid) from the age of 6 weeks to the age of 10 weeks. A comprehensive panel of renal and liver endpoints was evaluated to assess the effect of compound treatment.

Results: Male PCK rats at the age of 6 weeks showed markedly enlarged kidneys and livers, with evident cyst formation in both organs, indicating the establishment of polycystic kidney and liver disease by this age. When these animals were treated for 4 weeks with ANG3586, the kidney weight as a percentage of body weight was reduced compared to vehicle treated animals. Progression of renal cyst formation and renal fibrosis, as well as readouts of renal function such as proteinuria were also improved. Liver fibrosis was similarly ameliorated by ANG3586 treatment.

Conclusions: In preclinical experiments, the novel aldosterone synthase inhibitor ANG3586 shows promise as a possible treatment for PKD.

Funding: NIDDK Support

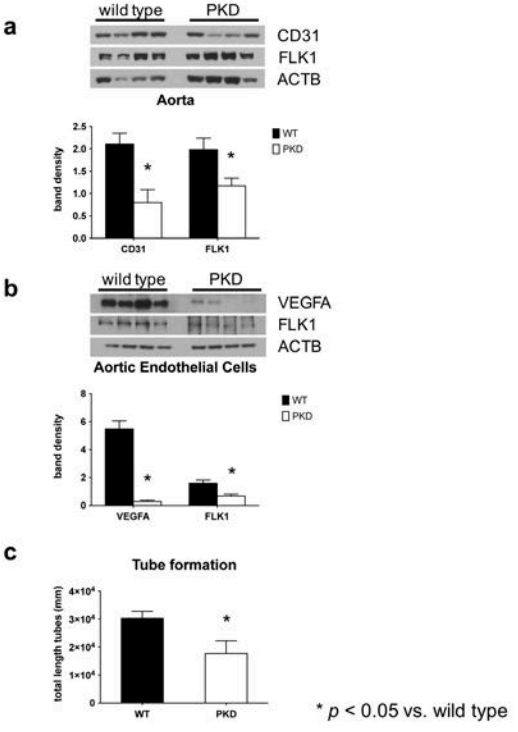
FR-PO558

The Role of Fibrocystin in the Vascular Pathophysiology of Polycystic Kidney Disease Federico Franchi,[1] Karen M. Peterson,[1] Katherine L. Quandt,[1] Peter C. Harris,[2] Martin G. Rodriguez- Porcel.[1] *[1]Cardiovascular Diseases, Mayo Clinic, Rochester, MN; [2]Nephrology and Hypertension, Mayo Clinic, Rochester, MN.*

Background: We have previously reported that Polycystic Kidney Disease (PKD) has abnormalities in vascular structure and function even in the early stages of the disease. Here, we hypothesized that normal fibrocystin is essential for the normal function of endothelial cells.

Methods: We assessed the angiogenic profile of non-cystic organs (lung, aorta) in young (4-week old) PCK rats (model of autosomal recessive PKD – ARPKD), prior to changes in blood pressure or renal function. Then, to study the role of endothelial cells in the vascular abnormalities seen in PKD, we isolated aortic endothelial cells (AEC) from young PCK rats and characterized their angiogenic profile. Lastly, to determine if fibrocystin is responsible for the abnormal function of these cells, we used small interfering RNA (siRNA) to knockdown (KD) the expression of fibrocystin in wild type AECs and study their angiogenic profile.

Results: The aorta (fig. 1a) and lung of PCK rats had decreased expression of the vascular endothelial growth factor (VEGF) receptor, FLK1, and the endothelial marker CD31 compared to wild type, showing a significant vascular impairment of non-cystic organs in PKD. Furthermore, studies in PCK-AECs revealed a reduced expression of endothelial markers and angiogenic factors compared to wild type AECs (fig. 1b). Importantly, KD of fibrocystin in wild type AECs led to a protein expression profile similar to that observed in PCK-AECs, together with inhibition of tube formation potential (fig. 1c).



Conclusions: Here we provide evidence that ARPKD may have a primary defect in vascular function and that an intact fibrocystin is critical for the normal biology of endothelial cells. Novel interventions to reduce vascular dysfunction should be evaluated to prevent cardiovascular risk in PKD.

Funding: NIDDK Support

FR-PO559

Does the Copy Number Variation of APOL1 Gene Associate with the Susceptibility or Clinical Manifestations of Focal Segmental Glomerulosclerosis Guisen Li, Li Wang. *Renal Div and Inst of Nephrology, Sichuan Provincial People's Hospital, Chengdu, Sichuan, China.*

Background: Focal segmental glomerulosclerosis (FSGS) is a primary glomerular disease characterized by diffuse fusion or effacement of podocyte foot processes.Lots of studies demonstrated that genetic mutations can be sufficient to cause or increase susceptibility to FSGS by combining the effects of environmental factors. APOL1 gene mutation (G1 and G2) in African individuals show strongly association with FSGS, but it was not replicated in Chinese FSGS patients. The copy number variation (CNV) is another type of important genetic variations. In this study, we examined the APOL1 gene copy number in chinese FSGS, and analyzed the relationship between CNV of APOL1 gene and the susceptibility to FSGS as well as clinical manifestations.

Methods: The copy number assay was custom designed to amplify and detect a 142bp region in the last exon of APOL1. The assay was performed using Applied Biosystems 7900HT quantitative real time PCR system by using 3μl of genomic DNA (50ng/μl). The results were analyzed using Copycaller software version 2. We analyzed 127 FSGS patients and 123 individuals without kidney disease for the presence of APOL1 gene duplication.

Results: The Copycaller results show that in case group and control group, 14 cases and 12 controls with one copys of APOL1, 91 cases and 92 controls with two copys of APOL1, 20 cases and 17 controls with three copys of APOL1, both cases and controls is only one sample with four copys of APOL1 and one sample didn't be detected. There was no statistical significance between the case group and control group upon the APOL1 gene copy number (p=0.34). The serum creatinine and urine proteinuria in the patients with three or four copies was obviously higher than patients with one or two copy of APOL1 gene.

Conclusions: In this study, the CNV of APOL1 gene does not associate with the susceptibility to Chinese Han FSGS patients. But the patients with high copy have higher serum creatinine and urine proteinuria.

FR-PO560

APOL1 Nephropathy Risk Variants Alter PON1 Activity in African Americans Orlando M. Gutierrez, Tamara Keenum, G.m. Anantharamaiah. *UAB.*

Background: *APOL1* nephropathy risk variants are associated with higher risk of kidney function decline and cardiovascular disease in African Americans (AA). The reasons for these associations are unclear. We reported that greater numbers of APOL1 risk variants were associated with higher circulating concentrations of small HDL subfractions linked to increased cardiovascular disease risk in population-based studies. Whether this has an impact on HDL function by *APOL1* genotype is unclear.

Methods: We recruited 11 AA with two *APOL1* risk variants (G1/G1, G2/G2, or G1/G2) and matched them by age and sex with 11 AA with one risk variant (G1 or G2) and 11 AA with zero risk variants. Participants provided plasma for HDL extraction and assessment of PON1 activity, indexed by paraoxonase/arylesterase enzymatic activity, and anti-oxidative capacity indexed by production of lipid hydroperoxides (LOOH) via dichlorofluorescein diacetate (DCFA) assay. We also measured these outputs in 11 European Americans (EA). All participants were healthy and free of kidney disease.

Results: AA participants with 2, 1 or 0 risk variants did not differ by age (33±10 vs. 36±11 vs. 35±13 years, respectively) or percentage of men (27% for each). Paraoxonase/arylesterase activity significantly increased with increasing numbers of *APOL1* risk variants in AA participants (Figure 1A). In contrast, LOOH levels did not differ by number of *APOL1* risk variants in AA participants (Figure 1B). Mean paraoxonase/arylesterase activity was lower and LOOH levels were higher in EA vs. AA participants irrespective of *APOL1* genotype status.

Figure 1A

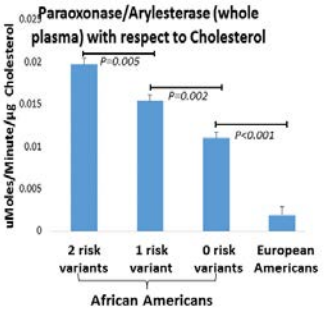
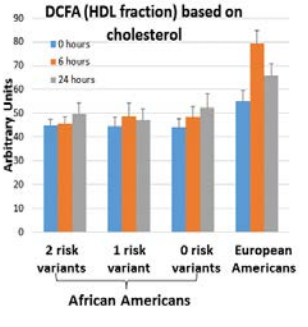


Figure 1B



Conclusions: Greater numbers of *APOL1* risk variants associate with higher PON1 activity but no difference in LOOH levels in healthy AA. These data suggest potential resistance to the anti-oxidative action of PON1 in AA with higher numbers of *APOL1* risk variants. EA had lower PON1 activity and greater LOOH levels than AA irrespective of APOL1 risk status.

Funding: Private Foundation Support

FR-PO561

APOL1 Risk Genotype in a Cohort of French FSGS Patients Aude Servais,[1,2] Olivier Gribouval,[2] Marie-Josèphe Tête,[2] Olivia Boyer,[2,3] Corinne Antignac.[2] *[1]Nephrology Unit, Necker Hospital; [2]Inserm U1163, Inst Imagine, Univ Paris Descartes; [3]Pediatric Nephrology Unit, Necker Hospital, Paris, France.*

Background: Apolipoprotein L1 (*APOL1*) G1 and G2 coding risk variants are strongly associated with sporadic FSGS in either the homozygous or compound heterozygous state in populations with African ancestry. The aim of our study was to determine the frequency of G1/G2 variants in a cohort of French steroid resistant FSGS patients with African or French West Indies origin and to analyze associations with clinical outcome.

Methods: Direct Sanger sequencing allowed the detection of three SNPs: the two missense variants p.Ser342Gly and p.Ile384Met called G1 risk allele and the 6 bp deletion p.del Asn388/Tyr389 called G2.

Results: We studied 152 patients in 139 families: 75 patients originated from French West Indies (49.0%) and 77 (51.0%) from Africa. The two risk allele (HR) genotype was considered any combination of G1 and G2 and was found in 43.1% of subjects. Patients in the HR group were more likely to originate from French West Indies than from Africa [45 (68.2%) vs 30 (34.5%), p<0.0001]. At diagnosis, patients in the HR group were more often older than 18 years than in the low risk (LR) group [34 (51.5%) vs 22 (25.6%), p=0.001] and had a lower eGFR (78.9 vs 95.2 ml/min/1.73m² by MDRD, p=0.03). All patients had similar evolution to end stage renal disease (ESRD) but patients were older at ESRD in the HR group (27.9±13.8 vs 16.6±12.3 years, p=0.007). There were more familial cases in the HR group than in the LR group [28 (42.4%) vs 13 (15.1%), p=0.0002]. Causative mutation in known monogenic steroid-resistant nephrotic syndrome genes was found in only one individual in the HR group (*NPHS1*-compound heterozygous mutation associated with G1/G1 two risk allele) and in 7 patients in the LR group. In two families, only 3/4 and 1/2 patients, respectively, had the two risk allele genotype.

Conclusions: The two risk allele genotype is found in 43% of French FSGS patients with African ancestry, compared to 13% in other population-based studies of blacks. It is more frequent in adult FSGS patients than in children and is usually not associated with other causative mutation in known monogenic steroid-resistant nephrotic syndrome genes.

Funding: Government Support - Non-U.S.

FR-PO562

APOL1 G1/G2 Down Regulates Maturation of Parietal Epithelial Cells and Immature Podocytes Xiqian Lan,[1] Nirupama Chandel,[1] Ashwani Malhotra,[1] Catherine Meyer-Schwesinger,[3] Karl Leon Skorecki,[2] Pravin C. Singhal.[1] *[1]Medicine, Rambam Health Care Campus, Haifa, Israel; [2]Medicine, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany.*

Background: Loss of critical numbers of podocytes contributes to the initiation and progression of focal segmental glomerulosclerosis (FSGS). Recently, a subset of parietal cells has been demonstrated to act as progenitor cells to replace injured podocytes in adverse milieus. Since FSGS risk is estimated to be ~17-fold higher in African Americans with compared to 0/1 copies of the APOL1 risk variants (G1, G2), we hypothesize that expression of APOL1 variants might compromise either parietal epithelial cellc (PECc) transit to podocytes or maturation of immature podocytes.

Methods: Immortalized parietal epithelial cells (PECs) were characterized by expression of PAX2, claudin 1, and notch 1 and immortalized podocytes (PDs) were characterized by expression of nephrin. These cells proliferate at 33°C and stop growing at 37°C. Both PECs and PDs differentiate at 37°C. PECs were transduced with APOL1G0/G1/G2 and incubated for 10 days at 37°C. Protein blots were probed for nephrin and reprobed for actin. Protein blots were stripped and reprboed for notch 1. Similarly, immortalized podocytes (PDs) stably expressing vector, G0, G1, and G2 were transduced with either vector with GFP or NL4-3 (HIV) with GFP. All cells were incubated at 37°C for 10 days. Protein blots were probed for nephrin and reprobed for actin.

Results: PECs expressing G1/G2 (differentiated for 10 days at 37°C) displayed attenuated expression of nephrin. Moreover, PECs expressing APOL1G0 displayed low levels of Notch 1 expression but PECs expressing APOL1 G1 and G2 displayed moderate expression of Notch 1. Differentiated APOL1G1 and G2 expressing podocytes displayed lower expression of nephrin both in the presence of vector or HIV when compared to APOL1G0. These findings indicate that expression of APOL1 G1/G2 compromises transition of PECs as well as maturation of podocytes.

Conclusions: Expression of APOL1 variants compromises transit of PECs and immature podocytes to matured podocytes.

FR-PO563

Effect of APOL1 Disease Risk Variants on APOL1 Gene Product Shabirul Haque,[1] Xiqian Lan,[1] Seyedeh Shadafarin Marashi Shoshtari,[1] Judith Eng,[1] Vinita Vishnoi,[1] Ashwani Malhotra,[1] Karl Leon Skorecki,[2] Pravin C. Singhal.[1] *[1]Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY; [2]Medicine, Rambam Health Care Campus, Haifa, Israel.*

Background: Gene sequence mutations may alter mRNA transcription, transcript stability, protein translation, protein stability, and protein folding. APOL1 has two sets of sequence variants which are risk factors for kidney disease development, APOL1G1 (substitution mutation) and APOL1G2 (deletion mutation). Our present study focuses on the impact of these variants on APOL1 mRNA transcription and translation.

Methods: APOL1 plasmids (EV, G0, G1, and G2) were transfected into HEK 293T cells. Podocyte cell lines stably expressing APOL1 transgenes (vector, G0, G1, and G2) were evaluated for APOL1 expression by immunoblotting (using three different commercially available antibodies) as well as FACS analysis. To determine the effect of reticulum stress or misfolded protein on APOL1 variant expression, podocytes stably expressing APOL1 and APOL1 variants were analyzed for the expression of GRP78. To determine the stability of APOL1 proteins, bioinformatics analysis (MUPro and I-Mutant 2.0) was carried out. APOL1 mRNA transcript stability was tested after actinomycin D pulsing.

Results: APOL1 variant expression was observed to be significantly lower than that of APOL1G0. Podocyte cell lines stably expressing APOL1 transgenes also showed lower levels of APOL1 expression of APOL1 variants (G1 and G2) compared to APOL1G0. The enhanced expression of GRP78 by podocytes expressing APOL1 variants suggested ongoing ER stress. Bioinformatics evaluation predicted that APOL1 variants are less stable than APOL1 G0. APOL1G1 mRNA transcript decayed 10–15 % within 0.5 to 3 hours and APOL1G2 mRNA transcript decayed 15–20% within 0.5 to 3 hours.

Conclusions: Attenuated APOL1 protein expression of APOL1 variants are due to compromised transcription and decay of the APOL1 variant transcripts.

Funding: NIDDK Support

FR-PO564

Mother and Baby APOL1 High Risk Alleles in Births Complicated by Preeclampsia Rebecca C. Hjorten,[1] Stacy Rosenblum,[4] Joseph Myrie,[7] Bianca Lyzette Ruiz,[7] Masako Suzuki,[5] Sandra E. Reznik,[6] Cheryl Ann Winkler,[2] Jeffrey B. Kopp,[2] Frederick J. Kaskel,[1] Kimberly J. Reidy.[1] *[1]Pediatrics, Nephrology, Albert Einstein College of Medicine (AECOM), Bronx, NY; [2]Genetic and Epidemiology Studies Section, National Insts of Health, Frederick, MD; [3]Kidney Disease Section, National Insts of Health, Frederick, MD; [4]Pediatrics, Neonatology, AECOM, Bronx, NY; [5]Genetics, AECOM, Bronx, NY; [6]Pathology, AECOM, Bronx, NY; [7]AECOM, Bronx, NY.*

Background: Increased prevalence of APOL1 high-risk alleles was associated with adverse perinatal outcomes in children with chronic kidney disease. The goal of this study is to determine if APOL1 risk status is associated with risk or severity of preeclampsia, a major cause of adverse perinatal outcomes, which is more prevalent and severe in women of African Ancestry.

Methods: Clinical Looking Glass, a clinical data extraction tool, was used to identify mothers who identify as Black or African American with births complicated by preeclampsia. DNA from mothers and babies was then extracted from their placental and umbilical cord tissues and genotyped for *APOL1* SNPs (rs73885319 and rs60910145) and the G2 indel (rs717185313) by TaqMan assay.

Results: Of the 19 mothers genotyped, 2 had high-risk alleles (11%) a proportion not dissimilar to general population. Of the 24 babies genotyped, 7 were had the high-risk alleles (29%), which is significantly different from the general population (p-value 0.01, chi-square). When comparing birth outcomes, births with babies with APOL1 high-risk status have a lower gestational age, 32 versus 37 weeks gestation (p-value 0.02, Mann–Whitney test) and lower Apgar scores at 1 and 5 minutes, 5 and 7 versus 8 and 9 (p-value 0.1 and 0.02 respectively, Mann–Whitney test). They also had a lower mean birth weight, 1.8 kg versus 2.5 kg, however this difference was not statistically significant (p-value 0.21, Mann–Whitney test).

Conclusions: While limited by small sample size in this preliminary study, our results suggest that high-risk APOL1 status may be present at a higher proportion in babies born from births complicated by preeclampsia and that they are more likely to have poorer perinatal outcomes.

Funding: NIDDK Support

FR-PO565

Detection and Validation of Epithelial-to-Mesenchymal Transition (EMT) with Increased Expression of Axl and MMP-14 in Renal Cell Carcinoma Lea Landolt,[1] Oystein Solberg Eikrem,[1] Gro Gausdal,[5] Lavina Ahmed,[5] Christian Beisland,[1,2] Kenneth Finne,[1] Andreas Scherer,[4] Mohammad Madani Ibrahim,[1] Hans-Peter Marti.[1,3] *[1]Dept of Clinical Medicine, Univ of Bergen, Bergen, Hordaland, Norway; [2]Dept of Urology, Haukeland Univ Hospital, Bergen, Hordaland, Norway; [3]Dept of Medicine, Univ of Bergen, Bergen, Hordaland, Norway; [4]Inst for Molecular Medicine Finland (FIMM), Univ of Helsinki, Helsinki, Finland; [5]Bergenbio AS, Bergen, Hordaland, Norway.*

Background: EMT is an important feature in cancer and can be used for therapeutic interventions. Recently, we described overabundance of vimentin, and underrepresentation of E-cadherin on mRNA level *(O. Eikrem, PLOS One 2016)* in clear cell renal cell carcinoma (ccRCC). In the present study, we wanted to further document and validate presence of EMT and two of its mediators or inducers, namely Axl receptor tyrosine kinase and matrix metalloproteinase 14 (MMP-14).

Methods: We have obtained perioperative core biopsies from ccRCC patients: detection cohort (n=16) and subsequent validation cohort (n=12). Paired kidney biopsies from each patient with ccRCC and adjacent non-tumorous tissue were formalin-fixed and paraffin-embedded. Next generation transcriptome sequencing (NGS), immunohistochemistry (IHC), and proteomics were performed as described *(O. Eikrem, PLOS One, 2016; K. Finne, NDT, 2014)*.

Results: In both of our NGS datasets, we found up-regulation of EMT genes, including an approx. 3-fold increased abundance of Axl tyrosine kinase and an approx. 2.7-fold overabundance of MMP-14 in ccRCC samples compared to the adjacent non-malignant tissue. Increased expression of Axl was confirmed by IHC. Up-regulation of vimentin

as well as down-regulation of E-cadherin in ccRCC were validated on mRNA level and confirmed on protein level by proteomics and IHC. Proteomic data confirmed presence of EMT, including a 3.4 fold up-regulation of vimentin and a 2.7 fold down-regulation of E-cadherin in our ccRCC samples. Proteomics, IHC and RT-PCR also confirmed up-regulation of MMP-14 in ccRCC.

Conclusions: Evidence for EMT in conjunction with up-regulation of Axl receptor tyrosine kinase and MMP-14 is a prominent feature in our ccRCC patients and offers potential therapeutic targets.

Funding: Pharmaceutical Company Support - Bergenbio AS, Bergen, Norway, Government Support - Non-U.S.

FR-PO566

An Increased Incidence of Idiopathic Membranous Nephropathy and Gene-Environment Analysis in Northern Part of China: A Cross-Sectional Study Sufang Shi,[1] Wanyin Hou,[1] Ying Li,[2] Shu Xia Fu,[3] Ming Hui Zhao.[1] *[1]Renal Div, Peking Univ First Hospital, Beijing, China; [2]Renal Div, the 3rd Hospital of Hebei Medical Univ, Shijiazhuang, China; [3]Renal Div, the 2nd Hospital of Hebei Medical Univ, Shijiazhuang, China.*

Background: Idiopathic membranous nephropathy (IMN),more common in elderly male in developed country,is becoming the most popular primary glomerula disease in China.The reason is not clear. Phosphlispase A2 receptor,PLA2R1and HLA-DQA1 genes contribute the most to IMN. It is presumed gene and air pollution were associated with the incidence of IMN. In this study, we performed a multi-center cross-sectional study in Hebei province (north China, near Beijing), to validate the increased trend of MN and the roles of gene-environment interaction.

Methods: 5785 IMN patients out of 16981 who accept renal biopsy from 28 hospitals in 11 cities since 2009 to 2013 were enrolled.374 MN and 239 controls were available of DNA samples. We classified MN patients according to age (≤20,20-40, ≥40)and air pollution level(non-risk northeast, mid-risk northwest and high-risk middle south).SNPs were genotyped by TaqMan assays. Rs4664308 within PLA2R1 and rs 2187668 within HLA-DQA1 were to validate gene roles in IMN. Gene-environment interaction was performed by epinet-calculation.

Results: From 2009 to 2013,proportion of IMN in primary glomerular disease(PGN) were 27%(258/955),36.9%(474/1283),45.6(681/1492),54.7%(1048/1917),62.6%(1409/2250) ,respectively. Younger patients (≤20) was increasing greatly from 13.9% to 31.8%. In terms of geographic and pollution level,IMN accounted for 38.6%,25.3%and23.4% of PGN in middle south(high risk), northwest (mid-risk)and northeast(non-risk)region, with the middle south mostly increased.Genetically,rs4664308 and rs2187668 were significantly associated with MN($p=4.8\times10^{-16}$ and1.0×10^{-3}, respectively),but not for rs2187668 in northwest MN(p=0.11).For PLA2R1, gene-environment interaction showed a 38 times [OR=38.72,95%CI 12.0-125.5,p<0.01,RERI 25.0(-3.4-53.4),AP 0.8(0.7-0.9),S 6.9(2.9-16.5)]of risk for developing MN.

Conclusions: IMN is the leading cause of glomerular disease in northern China. PLA2R1 gene and environment interaction might contribute to the increased MN incidence.

FR-PO567

Comprehensive RNA Sequencing Analysis of Human Diabetic and Hypertensive Kidney Disease Chengxiang Qiu,[1] Matthew Palmer,[2] Mendy Liang,[1] Melanie Sweeney,[1] Julie Hawkins,[3] Jonathan Hill,[3] Paolo Guarnieri,[3] Gregory R. Warnes,[3] Carine Boustany,[3] Steven S. Pullen,[3] Katalin Susztak.[1] *[1]Dept of Medicine, Renal Electrolyte and Hypertension Div, Univ of Pennsylvania, Philadelphia, PA; [2]Pathology and Laboratory Medicine at the Hospital, Univ of Pennsylvania, Philadelphia, PA; [3]Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT.*

Background: One in ten people in the United States suffers from chronic kidney disease (CKD). Progress in CKD research and drug development has been limited, and no drugs have been registered for the last 15 years. One key limitation has been that animal models do not recapitulate common forms of CKD (diabetic and hypertensive kidney disease). The aim of the current study was to collect and analyze a large number of human kidney tissue samples and identify transcript level changes in microdissected human glomeruli and tubules.

Methods: Human kidney tissue samples were collected in RNAlater from non-neoplastic regions of tumor nephrectomies. Detailed clinical information was collected using an "honest broker" system. Histologic sections were scored for 19 independent pathological parameters reflecting glomerular, tubulointerstitial, and vascular compartments. RNA sequencing of 256 human kidney tissue samples (154 control and 102 CKD) was performed on glomeruli and tubules separately using Illumina Trueseq v3 library kits and Hiseq2000 instruments. Reads were aligned using STAR aligners and annotated using Gencode human genome (GRCh37). Data analysis was performed with R/Bioconductor using a regression model.

Results: Glomerular filtration rate was best associated with tubulointersitial fibrosis. Using statistical modeling, a large number of genes showed correlation with fibrosis and glomerulosclerosis. In addition, we applied weighted gene co-expression network analysis (WGCNA) to identify key transcriptional nodules that correlate with structural and functional changes. Both analyses highlighted pathways associated with immune system activation and dysmetabolism (eg. oxidoreductase) in CKD.

Funding: NIDDK Support, Pharmaceutical Company Support - Boehringer Ingelheim Pharmaceuticals

FR-PO568

The Association between Genotypes of Urate Transporter-1, Serum Uric Acid, and Mortality in the Community-Based Population Soichiro Kon, Keita Kamei, Hiroko Sato, Kazunobu Ichikawa, Tsuneo Konta, Isao Kubota. *Dept of Cardiology, Pulmonology, and Nephrology, Yamagata Univ School of Medicine, Yamagata, Japan.*

Background: Hyperuricemia is a risk factor for renal and cardiovascular diseases, and serum uric acid level is affected by genetic predisposition. The function of urate transporter-1 (URAT1:SLC22A12), an important transporter in the reabsorption of uric acid in renal tubules is regulated by several single nucleotide polymorphisms (SNPs) within URAT1 gene. However it is unknown whether the genotypes in URAT1 is associated with the mortality in the community-based population.

Methods: The participants of this study were 1596 subjects (male 45%, mean age 61 years) that were registered at health checkup in Takahata, Japan and were followed up for 7 years. The association between the genotypes of SNPs (rs505802, rs475688, rs476037) in URAT1 gene, serum uric acid levels and the mortality were examined.

Results: The serum uric acid levels at baseline were significantly different between the genotypes of rs505802 (G/G: 5.1±1.3 [mean±SD] mg/dL, AG: 5.0±1.4, AA: 4.7±2.0, P=0.02), but not rs475688 and rs476037. Multiple regression model showed that the genotypes of rs505802 was independently associated with serum uric acid levels after the adjustment with confounders including gender, renal function, and comorbidities. Kaplan-Meier analysis showed that the mortality was higher in the subjects with the G/G genotypes of rs505802 than those with the A/G and the A/A genotypes. Cox proportional hazard model with the adjustment for confounders showed that the G/G genotype was an independent predictor for the mortality (hazard ratio [HR] 2.17, 95% confidence interval [CI] 1.07-5.02, [vs. A/G+A/A genotypes]). This significant association was unchanged in the analysis model adjusted with above mentioned confounders and serum uric acid levels (HR 2.16, 95%CI 1.06-5.00).

Conclusions: This study showed that the genotypes of rs505802 in URAT1 gene was independently associated with serum uric acid levels and the mortality in the community-based population. However, the link between this genotypes in URAT1 and the mortality might be due to serum uric acid-independent mechanism.

Funding: Government Support - Non-U.S.

FR-PO569

Translatability of the ZSF1 Rat to Human Diabetic Nephropathy Kathleen A. Lincoln,[1] Holly Clifford,[1] Jonathan Hill,[1] Mark Mchugh,[1] Hu Sheng Qian,[1] Steven S. Pullen,[1] Chengxiang Qiu,[2] Katalin Susztak,[2] Julie Hawkins,[1] Carine Boustany.[1] *[1]Cardiometabolic Diseases Research, Boehringer-Ingelheim Pharmaceuticals, Ridgefield, CT; [2]Perelman School of Medicine, Univ of Pennsylvania, Philadelphia, PA.*

Background: The ZSF1 rat is utilized for preclinical screening of drug candidates due to its similarities to human diabetic nephropathy. To explore pathways dysregulated in this model, we investigated longitudinal changes in renal biomarkers, histological measures, and transcriptomics, and identified similarities with human disease. Furthermore we determined whether losartan would repair dysregulated pathways.

Methods: ZSF1 obese rats were treated with either vehicle or losartan and compared to aged-matched lean counterparts. Mean arterial pressure and urine were collected weekly. Histologic quantification of glomerular and interstitial lesions and transcriptomics were performed at 10, 25 and 41 weeks of age. For comparison to human disease we utilized transcripts derived from sequencing of human nephrectomy samples from patients with/without diabetic nephropathy.

Results: By 10 weeks of age, ZSF1 rats were obese and diabetic compared to aged-matched leans. Proteinuria preceded the onset of hypertension and was reduced by losartan treatment. The incidence of glomerulosclerosis and interstitial lesions increased with age in obese ZSF1 vs leans and was reduced by losartan at 41 weeks. Histological lesions were accompanied with increases in urinary markers of tubular damage and inflammation that were only partially reduced by losartan. Transcriptomics performed at 10, 25 and 41 weeks of age revealed 2500 genes upregulated in obese vs lean that were indicative of inflammation. In contrast, only 350 genes were downregulated in obesity and reflected dysmetabolism and oxidative stress. Losartan treatment restored a subset of these dysregulated genes. Comparison of differentially expressed genes in ZSF1 rats with those differentially expressed between healthy and diabetic nephropathy patients revealed overlapping inflammatory pathways.

Conclusions: In conclusion the ZSF1 rat displays key hallmarks of diabetic nephropathy and shares common pathways with human disease.

Funding: Pharmaceutical Company Support - Boehringer-Ingelheim Pharmaceuticals

FR-PO570

A Single Nucleotide Polymorphism in Kidney Anion Exchanger 1 Gene Causes Incomplete Type 1 Renal Tubular Acidosis Takumi Takeuchi. *Urology, Japan Organization of Occupational Health and Safety Kanto Rosai Hospital, Kawasaki, Japan.*

Background: Various conditions including distal renal tubular acidosis (dRTA) can induce stone formation in the kidney. dRTA is characterized by an impairment of urine acidification in the distal nephron. dRTA is caused by variations in genes functioning

in intercalated cells including SLC4A1/AE1/Band3 transcribing two kinds of mRNAs encoding the $Cl^-/HCO3^-$ exchanger in erythrocytes and that expressed in α-intercalated cells (kAE1).

Methods: Sixty-eight unrelated Japanese urolithiasis patients who had previously undergone lithotripsy were investigated regarding their capacity for renal tubular acidification during hospitalization. For genomic DNAs of patients who showed urine acidification abnormality, the SLC4A1/AE1/Band3 gene was amplified in fragments encompassing all exons except exon 1 and directly sequenced. Erythroid introns 3, 7, and 17 of participants (n=13 for incomplete dRTA and n=29 for non-dRTA) were further amplified and directly sequenced. Intron 3 of the AE1 gene of an incomplete dRTA case and a non-dRTA control were amplified and subcloned into pGL4.17 [luc2/Neo] reporter vector. Those tester constructs as well as pNL1.1.TK [Nluc/TK] control vector were used to transfect MDCK and HEK293 cells. The normalized strength of the firefly luciferase activity was calculated by the firefly luciferase activity of each well divided by the NanoLuc® luciferase activity of the same well.

Results: With the acid-loading test, 25% of urolithiasis patients were diagnosed with incomplete dRTA. In erythroid intron 3 containing the promoter region of kAE1, rs999716 SNP showed a significantly higher minor allele A frequency in incomplete dRTA compared with non-dRTA patients. The promoter regions of the kAE1 gene with the minor allele A at rs999716 downstream of the TATA box showed reduced promoter activities compared with that with the major allele G.

Conclusions: Patients with the A allele at rs999716 may express less kAE1 mRNA and protein in the intercalated cells, developing incomplete dRTA. This relatively common polymorphism can cause urolithiasis frequently in population.

FR-PO571

Will Exome Sequencing Increase the Number of Patients Referred to Nephrology Clinics? Hila Milo Rasouly, David Fasel, Adele Mitrotti, Simone Sanna-Cherchi, David B. Goldstein, Ali G. Gharavi. *Medicine, Columbia Univ, New York, NY.*

Background: A growing number of individuals are undergoing whole exome sequencing (WES) for diagnosis of kidney or non-kidney disorders. We studied the prevalence of variants in genes associated with kidney diseases in healthy individuals to assess the potential for **I**ncidental **F**indings related to these disorders.

Methods: Using OMIM and Pubmed, we identified 355 genes associated with genitourinary disorders. We investigated 788 individuals of European ancestry, without any known medical issues, who had undergone WES using the Roche exome capture kit at the Institute of Genomic Medicine at Columbia University, as controls for non-kidney diseases. We used the in-house software, ATAV, to filter by minor allele frequency (MAF range 0-0.01 in ExAC and EVS databases), perform functional annotation, and select likely deleterious variants as predicted by Polyphen2 and CADD scores. We also investigated prior reports of pathogenicity in ClinVar and HGMD.

Results: 414 individuals (52.5%) carried at least 5 rare, predicted deleterious variants in the 355 kidney genes (MAF<0.01, CADD>10, Polyphen > 0.9). In 199 genes causing recessive disorders, 37 individuals (4.7%) were homozygous or potentially compound heterozygous for rare predicted deleterious variants. In 126 genes causing dominant disorders, 55% of individuals carried at least 2 such variants. Furthermore, 114 individuals (14.5%) carried **novel** predicted deleterious variants (absent in ExAC and EVS, CADD>20) and 37 individuals (4.7%) carried variants reported in HGMD and in ClinVar as **pathogenic** for dominant diseases associated with kidney diseases.

Conclusions: WES interpretation based solely on MAF and in-silico prediction algorithms may lead to misdiagnosis or erroneous assignment of multiple renal disorders to patient with nephropathy and also generate many referrals for incidental findings for individuals with no kidney disease. These data suggest the need for robust genetic criteria and consideration of prior clinical context for interpretation of genetic variants for renal disorders.

Funding: NIDDK Support, Other NIH Support - NHGRI

FR-PO572

Tissue-Specific MicroRNA Expression Patterns in Four Types of Kidney Disease Maria Angeles Baker,[1] Seth J. Davis,[1] Pengyuan Liu,[1] Kevin R. Regner,[2] Yong Liu,[1] Kenneth A. Iczkowski,[3] Mingyu Liang.[1] *[1]Center of Systems Molecular Medicine, Dept of Physiology, Medical College of Wisconsin; [2]Div of Nephrology, Dept of Medicine, Medical College of Wisconsin; [3]Dept of Pathology, Medical College of Wisconsin.*

Background: MicroRNAs (miRs) are small RNAs that primarily bind to target mRNA to reduce protein abundance. Several miRs have been shown to contribute to the development of kidney disease. However, previous analyses of miR expression in human kidney diseases were limited by the tissue heterogeneity of biopsy samples or the inclusion of only one pathology type.

Methods: In the present study, laser-capture microdissection was used to obtain glomeruli and proximal tubules from human needle kidney biopsies for miR expression analysis using deep sequencing.

Results: Nearly 100 patients with four different types of kidney diseases including diabetic nephropathy (DN), focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN) and membranoproliferative glomerulonephritis (MPGN) and a control group with minimal kidney injury were analyzed. The deep sequencing analysis detected 205 known human miRs and 173 potentially new miRs. A miR was considered differentially expressed if the adjusted p value was less than 0.05 according to an edgeR2 analysis. In the glomeruli, 21, 17, 5, and 25 known human miRs were respectively differentially expressed in DN, FSGS, IgAN, and MPGN compared to control. Fewer than 5 miRs were differentially expressed between any two of the four disease conditions. Nevertheless, miR-3182 was significantly downregulated in IgAN compared to all other conditions tested, and a combination of miRs 146a-5p and 30a-5p distinguished DN from all other conditions. In the proximal tubules, 18, 23, 11, 8 miRs were respectively differentially expressed in DN, FSGS, IgAN, and MPGN compared to control. No miR was differentially expressed in the proximal tubules between any two of the disease conditions.

Conclusions: In conclusion, we have identified tissue-specific miR expression patterns associated with several types of kidney pathologies. The identified miRs could serve as biomarkers of kidney diseases and might be involved in the disease mechanisms.

Funding: Other NIH Support - NHLBI

FR-PO573

Mutations of Upper Tract Urothelial Carcinoma in Chronic Kidney Disease in Taiwan Chih-Chuan Yu, Daw-Yang Hwang. *Div of Nephrology, Kaohsiung Medical Univ, Kaohsiung, Taiwan.*

Background: Urothelial carcinoma is the most common malignant tumor of the urinary tract. In Europe and the USA, the occurrence in the bladder account for more than 85% of all urothelial carcinoma with a male to female ratio of about 2.5:1. However, the upper tract urothelial carcinoma (UTUC) accounts for 40% of all kidney cancers, and the male to female ratio was 1:1.3 in Taiwan. Furthermore, dialysis patients had more urothelial carcinoma than renal cell carcinoma in Taiwan.

Methods: Sixty-four paired cancer and normal tissues of chronic kidney disease patients who were diagnosed of upper tract urothelial carcinoma were examined. Target re-sequencing was performed by using Fluidigm 48.48. Access Array and MiSeq. The panel included 1) oncogenes (TXNIP, ELF, CDKN1A, MDM2, KLF5, ERCC, KDM6A, RUNX, NRAS, ARID1A, TP53, PIK3CA, CDKN2A, FBXW7, CTNNB1, KRAS, PTEN, FGFR1, FGFR3, NFE2L2, HRAS) and 2) potential actionable receptor tyrosine kinase (FGFR1, FGFR2, GFR3, ALK, ROS1, NTRK1, NTRK3, RET, PDGFRA, PDGFRB, FLT3). CLCbio Genomic Workbench was used to analyzed data and compared with dbSNP database and COSMIC database.

Results: A high mutation rate in TP53 (45%), RET (34%), FGFR2 (30%), FGFR3 (22%), ARID1A (21%), and FBXW7 (17%) were found in our cohort, which is in accordance to previous bladder cancer and UTUC studies. However, several tyrosine kinase mutations, including ROS1, ALK, NTRK1, ELF3, and PDGFRA, were found with relative high mutation incidence in our UTUC cohort.

Conclusions: Our study showed that the UTUC mutation profiles in Taiwan were similar in many well-known oncogenes as in the bladder cancer.However, differences existed in the possible actionable tyrosine kinases between bladder cancer and UTUC.This high throughput method provided mutation detection, drug applications, and cancer follow up.

Funding: Government Support - Non-U.S.

FR-PO574

Characterization of Coding Variation in the Urate Transporter GLUT9, a Key Determinant of Serum Uric Acid: Absence of Gain-of-Function Phenotypes Asim Mandal,[1] Hyon Choi,[3] Tony Merriman,[2] David B. Mount.[1] *[1]Renal Div, Brigham and Women's Hospital, Boston, MA; [2]Dept of Biochemistry, Univ of Otago, Dunedin, New Zealand; [3]Div of Rheumatology, Massachusetts General Hospital, Boston, MA.*

Background: Genetic variation in *SLC2A9* encoding the GLUT9 urate transporter is the single biggest genetic contributor to serum uric acid (SUA) and hyperuricemia; loss-of-function mutations also cause genetic "renal hypouricemia". Transcriptional initiation at different promoters generates GLUT9 isoforms with different N-termini and membrane targeting; the GLUT9a protein traffics to the basolateral membrane of epithelia whereas GLUT9b traffics to the apical membrane. Multiple common coding single nucleotide polymorphisms (cSNPs) in *SLC2A9* affect SUA, with considerable population heterogeneity.

Methods: We assessed the phenotypic transport function of 30 *SLC2A9* cSNPs, generating point mutants in GLUT9a/b and measuring urate transport activity in *Xenopus* oocytes under both depolarized and non-depolarized conditions. We also resequenced *SLC2A9* in ~800 subjects with extremes in SUA, i.e. hyper/hypouricemia.

Results: We identified 14 cSNPs that generated a loss-in-function, including variants in several transmembrane domains. However, mutants corresponding to five other cSNPs were no different from wild-type. Other cSNPs reduced the urate uptake activity of GLUT9a without affecting GLUT9b, i.e. isoform-specific effects. Several variants in a large intracellular loop exhibited loss of function in non-depolarized conditions that was rescued by depolarization, suggesting a voltage-sensitive conformation effect. Finally, loss-of-function mutations were detected by resequencing of subjects with very low SUA (renal hypouricemia); however, no gain-of-function mutants were discovered in hyperuricemics. No variants affected expression or N-glycosylation of GLUT9 proteins, as assessed by Western blotting.

Conclusions: In summary, "protective" cSNPs in *SLC2A9* that reduce SUA can have loss-of-function transport phenotypes, with no gain-of-function phenotypes that would explain hyperuricemia; this highlights the dominance of non-coding variation in *SLC2A9* in determining SUA.

Funding: Other NIH Support - NIAMS, Pharmaceutical Company Support - Astra Zeneca

FR-PO575

Creation of Complement Factor H Mutations in Human C5a-Receptor Knock-In Mice as a Model to Assess the Effects of C5aR Antagonism in Complement-Mediated Renal Diseases

Chris Li, Linda Ertl, Pirow Bekker, Israel Charo, Thomas J. Schall. *ChemoCentryx, Mountain View, CA.*

Background: C3 glomerulopathy (C3G), and atypical hemolytic uremic syndrome (aHUS) are complement-mediated renal diseases. Mutations of complement factor H (CFH), a negative regulator of alternative complement activation, are associated with these diseases. In mouse, CFH deficiency results in a phenotype that resembles C3G, and C-terminal truncation of CFH leads to spontaneous development of aHUS. In this study, we aimed to generate these CFH mutations in mice whose complement C5a receptor (C5aR) was replaced with its human homolog, in order to assess the effects of C5aR antagonism using an inhibitor that is specific for human C5aR.

Methods: Using CRISPR technology, guide RNAs targeting the start codon (for complete deficiency) and Cysteine 937 (for C-terminal truncation) were injected into fertilized oocytes from human C5aR knock-in mice. Mutations were identified by PCR and DNA sequencing.

Results: gRNAs targeting the start codon lead to small deletions of this region and completely ablated CFH expression. In these CFH deficient mice, the C3 concentration in the circulation was dramatically reduced due to over-consumption, and renal function was impaired as evidenced by modest increase of urine albumin/creatinine ratio (UACR), even at young age. Effects of hC5aR antagonists in both spontaneous and accelerated disease settings are currently being investigated. The gRNA targeting Cys937 generated a larger deletion and unexpectedly resulted in the deletion of exon 17 of CFH, and produced a mutant CFH protein lacking amino acid 880-949. C3 levels in CFH exon 17 deletion mice are not significantly changed, and the functional consequence of this deletion is being further investigated.

Conclusions: These mice represent a new tool for assessing the contribution of C5a/C5aR signaling to the underlying pathophysiology for complement mediated renal diseases, and will allow assessment of the therapeutic potential of specifically blocking the C5a receptor in destructive diseases such as C3G and aHUS.

Funding: Pharmaceutical Company Support - ChemoCentryx

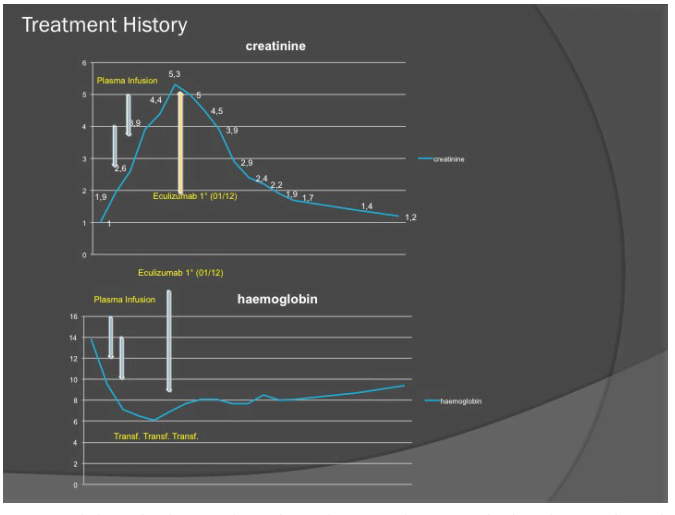
FR-PO576

New Complement Factor H (CFH) Mutations in a Patient with Pregnancy Associated aHUS

Domenico Santoro,[1] Anna Perri,[2] Renzo Bonofiglio.[2] *[1]Univ of Messina, Messina, Italy; [2]Hospital Cosenza, Cosenza, Italy.*

Background: Pregnancy-associated thrombotic microangiopathy (P-TMA) is a rare disorder associated with a significant perinatal or maternal morbidity and mortality. P-TMA may be related to acquired or constitutional deficiency in ADAMTS13, a von Willebrand factor (vWF)-processing enzyme and gene mutations for proteins involved in regulation or activation of the alternative pathway of complement. The last one can safely and successfully treated with an anti-C5 therapy (eculizumab) to induce terminal complement blockade.

Methods: S.T. 39 years female. First pregnancy (twin pregnancy) after assisted reproduction. No therapy before pregnancy. At 32 week she referred strong pain in the epigastrium. Serum analysis showed: elevated live enzymes, acute hemolitic anemia, elevation of lactate dehydrogenase, thrombocitopenia. Twin delivery was induced (2.190Kg e 2.050 Kg). Plasma infusion and steroid therapy was started. Since no improvement was achieved , at day 5 she started Eculizumab 900 mg/week followed by 1200 every other week. Renal and clinical improvement started the day after the first infusion of eculizumab leading to complete resolution in 2-3 weeks.



Genetic investigations on alternative pathway regulatory proteins have been performed. The screening of the CFH gene showed a splicing mutation on SCR11 domain in +1G/A position of the exon 12-13, not yet described in the literature.

Conclusions: Our case show the identification of a new gene mutations coding for complement factor H (CFH). Moreover, it emphasizes the importance of a early diagnosis of aHUS for a prompt start of therapy with eculizumab in order to avoid dialysis and induce a rapid renal recovery. Future studies will help to understand how long such therapy needs to be prolonged.

FR-PO577

Apobec-1 Complementation Factor: A Novel Mediator of Renal Function

Jennie Lin, Xiao Wang, Alanna Strong, Kiran Musunuru. *Medicine, Perelman School of Medicine at the Univ of Pennsylvania, Philadelphia, PA.*

Background: A recent genome-wide association study identified rs10994860 as a genetic variant associated with higher eGFR in non-diabetic humans. This variant is located in the 5' untranslated region of *A1CF* (apobec-1 complementation factor), a RNA binding protein known to facilitate the editing of apolipoprotein B (apoB) mRNA into different isoforms in other organ systems. With little known about A1CF in the renal context, we used an unbiased approach to investigate its role in the kidney.

Methods: *A1cf* knockout (KO) mice were generated through the CRISPR/Cas9 system, with embryonic microinjection of (1) guide RNAs to target exon 9 of *A1cf* and (2) RNA encoding Cas9 nuclease. Plasma was collected for KO and wildtype (WT) male mice 12-20 weeks of age, and whole kidneys were processed for histopathology and tissue lysate immunoblotting. In addition, RNA from whole kidneys of mice from both groups was processed for RNA sequencing (N = 6 per group).

Results: *A1cf* KO mice had over 90% decrease in A1cf mRNA expression compared to their WT littermates (FDR adjusted $P < 0.01$). Mean plasma Cr values for KO (N = 10) and WT (N =14) mice were 0.84 mg/dL and 0.66 mg/dL, respectively ($P = 0.05$), although no significant differences in tissue fibrosis were observed by trichrome or Sirius red staining. Immunoblot for apoB revealed low renal apoB expression and no differences in apoB-100/apoB-48 isoform abundance between *A1cf* KO and WT mice despite elevated plasma triglycerides in the KO mice (138.4 vs. 83.4 mg/dL, $P < 0.01$). RNA-seq of whole kidneys revealed 229 differentially expressed (DE) genes (FDR adjusted $P < 0.05$) between *A1cf* KO and WT mice. We identified top canonical cell pathways enriched within these DE genes as retinoid X receptor signaling ($P = 4.8E-05$), insulin growth factor-1 signaling ($P = 6.4E-05$), and acute phase response ($P = 6.5E-05$). The top scoring gene networks for the DE genes included renal tubular injury, embryonic development, and lipid metabolism.

Conclusions: A1CF may have causal roles in renal function through metabolic pathways independent of apoB. Further studies in renal injury models are warranted.

Funding: Other NIH Support - KL2TR00013910

FR-PO578

Low Copy Numbers of FCGR3A and FCGR3B Associated with Chinese Patients with Lupus Nephritis and Anti-Neutrophil Cytoplasmic Antibody-Associated Renal Vasculitis

Yuan-Yuan Qi,[1,2] Xujie Zhou,[1,2] Ping Hou,[1,2] Jicheng Lv,[1,2] Hong Zhang.[1,2] *[1]Renal Div, Peking Univ First Hospital; [2]Peking Univ Inst of Nephrology.*

Background: Low copy number (CN) of *FCGR3B* had been implicated in systemic lupus erythematosus (SLE). However, conflicting results were reported for anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. And the genetic role of CN of *FCGR3A* had seldom been addressed for these two autoantibody-mediated diseases. Here, we aimed to determine whether CNs in *FCGR3A* and *FCGR3B* were associated with lupus nephritis (LN) and ANCA-associated renal vasculitis in Chinese individuals.

Methods: A total of 1118 individuals were enrolled, including 320 LN, 95 SLE without renal involvement, 139 ANCA-associated renal vasculitis and 564 healthy controls. *FCGR3A* and *FCGR3B* CNs were determined by both paralogue ratio test and TaqMan quantitative PCR assay. The *FCGR3A* and *FCGR3B* CNV genotypes were compared between controls and cases and among patients stratified according to clinical characteristics.

Results: By comparison of results from >800 DNA samples with CN measurements by two different methods, we validated the reliability of method at first (*FCGR3A* $r=0.903$, $p<0.001$; *FCGR3B* $r=0.837$, $p<0.001$). And in susceptibility associations, a low *FCGR3B* CN was significantly associated with both LN ($p= 3.68*10^{-4}$, OR 2.02, 95% CI 1.37-2.99) and ANCA-associated renal vasculitis ($p= 0.04$, OR= 1.72, 95% CI 1.02-2.88). And a low *FCGR3A* CN was also significantly associated with both LN ($p=1.29*10^{-3}$, OR 3.26, 95%CI 1.53-6.94) and ANCA-associated renal vasculitis ($p=0.042$, OR 2.64, 95%CI 1.00-6.93). No similar associations were observed in lupus patients without nephritis. Further sub-phenotype analysis showed that lower *FCGR3A* CN associated with presence of antinuclear antibody ($p= 0.036$) and lower *FCGR3B* CN associated with anti-dsDNA and low complement ($p = 0.013$, $p = 0.035$, respectively).

Conclusions: In a large case-control study with Chinese ancestry, we identified that low CNs of *FCGR3A* and *FCGR3B* were common risk factors for LN and ANCA-associated renal vasculitis.

Funding: Government Support - Non-U.S.

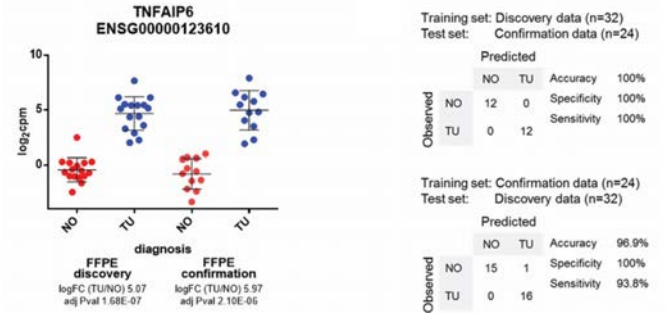
FR-PO579

Development and Confirmation of Gene Classifiers of Human Clear Cell Renal Cell Carcinoma Using Next-Generation Sequencing Oystein Solberg Eikrem,[1] Andreas Scherer,[2] Lea Landolt,[1] Hans-Peter Marti,[1] Philipp Strauss.[1] *[1]Dept of Clinical Medicine, Univ of Bergen, Bergen, Norway; [2]Spheromics, Kontiolahti, Finland.*

Background: We recently reported on the feasibility of RNAseq technology for capturing disease biology of clear cell renal cell carcinoma (ccRCC) and presented initial results for CA9 and TNFAIP6 as possible biomarkers of ccRCC ("discovery set"). To confirm these results we included another, independent cohort of 12 patients ("confirmation set") with biopsies from both cancer and peritumoral normal renal tissue.

Methods: From each of 12 patients undergoing nephrectomy, two core biopsies were obtained with a 16g needle. RNA sequencing libraries were generated with Illumina TruSeq® Access library preparation protocol. Comparative analysis was done using linear modeling (voom/limma; R Bioconductor).

Results: The FFPE discovery and confirmation data yielded 8957 and 11047 detected transcripts, respectively. Each of these two datasets shared 1193 of differentially expressed genes with each other. The average expression and the log2 fold changes of differentially expressed transcripts in both datasets correlated with R^2=0.95, and R^2=0.94, respectively. Among transcripts with the highest fold changes in both datasets were carbonic anhydrase 9 (CA9), neuronal pentraxin-2 (NPTX2) and uromodulin (UMOD). The diagnostic accuracy of CA9 was 100% and 93.9% when using the discovery set as training and the confirmation data as test set, and vice versa, respectively. Our data further support TNFAIP6 as a novel biomarker of ccRCC. On the average, TNFAIP6 had an accuracy of 98.5%. TNFAIP6 and CA9 expression abundance on the protein level was confirmed by immunohistochemistry.



Conclusions: We provide confirmatory data of potential use of CA9 and TNFAIP6 as biomarkers of ccRCC. This enables the investigation of well defined retrospective cohorts for transcriptomic analyses from FFPE kidney biopsies.

FR-PO580

Value of Genome Copy Number Variation in Predicting Responses to a Prescribed Chinese Herbal Medicine in the Treatment of Idiopathic Membranous Nephropathy(IMN) Lin Wang,[1] Shihui Li,[2] Xianwen Zhang,[1] Jianhui Tian,[1] Minping Qian,[2] Lin Wan,[3] Yiping Chen.[1] *[1]Nephrology, Longhua Hospital, Shanghai Univ of Traditional Chinese Medicine, Shanghai, China; [2]School of Mathematical Sciences, Peking Univ, Beijing, China; [3]Academy of Mathematics and Systems Science, Chinese Academy of Sciences, Beijing, China.*

Background: IMN is one of the leading causes of nephrotic syndrome. Current treatment of IMN is far from satisfactory. ShenQi Granule (SQ) is a prescribed Chinese herbal medicine used to treat IMN in China for decades with significant efficacy but different clinical responses among patients. Clinical responses to IMN treatment may be genetically co-determined. To explore this hypothesis, we assessed a correlation between genome-wide copy number variation (CNV) and the clinical responses to SQ treatment in a cohort of IMN patients.

Methods: 80 patients were divided into 4 groups:complete remission (CR) of SQ(SCR, n=36); no remission (NR) of SQ (SNR, n=11); CR of the immunosuppressive agent (IA) (ICR, n=18); NR of IA (INR, n=15). Genomic DNA was extracted from peripheral-blood lymphocytes and genotyped with the Affymetrix Genome-Wide Human SNP Array 6.0. Samples from 270 healthy people were used as control. We analyzed a possible association of CNV and responses to IMN treatment.

Results: CNV partition called 921 CNV regions, among which 654 are gained regions, 267 are lost regions. The lengths of the CNV regions ranged from 310 bp to 3,248,859 bp, with the median size 50,365 bp. The 3 most significant CNVs regions ($p<0.05$) are located on chromosomes 5, 6 and 8, on which SCR group showed fewer loss (2, 0, and 1 on chromosomes 5, 6, and 8) while SNR group showed more loss (6, 3 and 5 on chromosomes 5, 6, and 8). The CNV of HLA gene family, located on chromosome 6, showed gain in IMN patients of SCR group, but loss on patients of SNR group. There were no significant differences in CNVs between ICR and INR groups.

Conclusions: The differences in genetic background of IMN patients may explain some of the different clinical responses to SQ treatment. The CNVs of HLA gene family may serve as a predictive factor of the response to SQ treatment.

Funding: Government Support - Non-U.S.

FR-PO581

PER1 Coordinates Kidney-Specific Sodium Trafficking and Liver-Specific Lipid Metabolism via Timing System in Nephropathy Rats Peipei Chen, Ruiyu Zhang, Lijun Mou, Xuemei Li, Yan Qin. *Renal Div, Peking Union Medical College Hospital, Beijing, China.*

Background: The circadian gene *Per1* regulates various genes involved in sodium transport in kidney and metabolism processes in liver. We have identified the circadian rhythm of blood pressure(BP) and urine sodium excretion synchronized with the core clock genes oscillating in normal rats kidney. The present study was to explore the potential role of *Per1* in communications between the peripheral organs in nephropathy rats.

Methods: Adriamycin(ADR) rats and Sprague-Dawley (SD) rats were housed in a 12:12 hour light/dark cycle and sacrificed in six time points(ZT=2,6,10,14,18,22) for 24-hr, respectively. The circadian expression of kidney and liver genes involved with clock gene *per1* evaluated by the real-time quantitative PCR and the data were analyzed by a stepwise regression.

Results: 1.*Per1* gene showed 24-hr and 4.8-hr rhythm in kidney and liver of SD rats, respectively. It is more significant difference in rhythmic features compared with other core clock genes(*Clock*, *Bmal1*, *Cry1*, *Cry2* and *Per2*) with a robust 24-hr period in both two tissues ($p<0.05$);2.The oscillated expression of *Per1* was completely disappeared in both two tissues of ADR rats. Moreover, liver presented a high level of *Per1* expression and kidney showed a low level(MESOR 5.29 vs. 0.81, $p<0.05$);3.Kidney-specific sodium trafficking genes(*αENaC*, *NCC* and *NHE3*)regulated by *Per1* with 24-hr rhythm in SD rats. However, ADR rats lost all oscillations of above clock and clock-controlled genes which were coupled with the disturbed circadian rhythm of BP and urinary sodium excretion in the nephrotic syndrome model($p<0.05$);4.In ADR rats, the disruption of rhythmic expression of liver-specific sterol regulatory element binding protein-1c (*SREBP-1c*) and ATP binding cassette transporter A1(*ABCA1*) were regulated by *Per1* involved with lipid metabolism in nephrotic syndrome.

Conclusions: The clock gene *Per1* plays a coordinating role in regulating sodium trafficking via *αENaC*, *NCC* and *NHE3* in kidney and lipid metabolism processes in liver via *SREBP-1c* and *ABCA1* genes. It shed new light on the molecular mechanisms of communications between the peripheral organs via circadian timing system in renal diseases.

Funding: Government Support - Non-U.S.

FR-PO582

Mendelian Randomization Study of HDL and LDL Cholesterol as Risk Factors for Chronic Kidney Disease Matthew Lanktree,[1] Sébastien Thériault,[2,4] Michael Walsh,[1,3,4] Guillaume Pare.[1,2,3,4] *[1]Dept of Medicine, McMaster Univ, Hamilton, ON, Canada; [2]Dept of Pathology and Molecular Medicine, McMaster Univ, Hamilton, ON, Canada; [3]Dept of Clinical Epidemiology & Biostatistics, McMaster Univ, Hamilton, ON, Canada; [4]Population Health Research Inst, McMaster Univ, Hamilton, ON, Canada.*

Background: Dyslipidemia is a risk factor for vascular disease, but its role in progression of chronic kidney disease is unclear. We sought to utilize Mendelian randomization (MR) analysis of public datasets to assess a causal role for dyslipidemia in chronic kidney disease.

Methods: Using data from the Global Lipid Genetics Consortium (n = 173,000) and 1000 genomes project, the effect of independent polymorphisms ($r^2 < 0.01$) on inverse normalized high-density lipoprotein (HDL) (124 polymorphisms) and low-density lipoprotein (LDL) (97 polymorphisms) cholesterol was obtained. The effect of those same polymorphisms on log transformed eGFR (ml/min/1.73m^2), and chronic kidney disease (CKD) outcome was obtained from the Chronic Kidney Disease Genetics (CKDGen) Consortium (n = 133,000). Using a conventional MR approach, we assessed the causal effect of HDL and LDL on eGFR and CKD.

Results: A genetic increase in HDL was associated with higher eGFR ($\beta = 0.008$; P = 0.0001) and decreased CKD risk (OR = 0.68; 95% CI: 0.58 - 0.81; $P = 7.4 \times 10^{-6}$) per 1 unit increase in inverse normalized HDL. A 17 mg/dl genetic increase in HDL corresponded to a 2% increase in eGFR and 32% reduced risk of CKD. A genetic increase in LDL was weakly associated with higher eGFR ($\beta = 0.005$; P = 0.01), but no effect was seen for CKD risk (OR = 1.00; 95% CI: 0.85 - 1.17; P = 0.97) per 1 unit increase in inverse normalized LDL. Observed effects were similar if diabetic patients were excluded from analyses.

Conclusions: MR analysis supports a genetic increase in HDL as causally associated with eGFR and CKD risk. Genetically increased LDL did not change risk of CKD.

FR-PO583

HLA-DQA1 Variants and Risk of Steroid Sensitive Nephrotic Syndrome in Children Rasheed A. Gbadegesin, Christopher Esezobor, Larry A. Greenbaum, Mahmoud Kallash, Cynthia J. D'Alessandri-Silva, Tracy E. Hunley, Nilka deJesus-Gonzalez, Gentzon Hall, Brandon M. Lane, Megan Chryst-Ladd, Guanghong Wu, Adebowale A. Adeyemo. *Pediatircs, Div of Nephrology, Duke Univ Medical Center, Durham, NC.*

Background: There is relatively little known about the genetic variants underlying the risk of developing steroid sensitive nephrotic syndrome (SSNS) in children. Recently, the first exome array association study identified the missense variants C34Y (rs1129740) and F41S (rs1071630) in *HLA-DQA1* as significantly associated with SSNS in South Asian and European ancestry children. The objective of this study is to further refine this locus and evaluate its role in other ethnicities.

Methods: We screened for the C34Y and F41S in a cohort of 68 African American children with SSNS by direct sequencing. Imputation of classical alleles and amino acids of *HLA-DQA1* was done in 363 South Asian children to further refine the association.

Results: We extend our original findings to African American children (C34Y p=5.7 X 10^{-11}, OR=3.53, 95% CI 2.33,5.42; F41S p=1.23 X 10^{-13}, OR=4.08, 95% CI 2.70, 6.28). Both variants are significant *cis*-eQTLs for HLA-DQA1 in lymphoblastoid cells. Imputation of classical HLA alleles and amino acids in SA children revealed that *HLA-DQA1*0201*,*HLA-DQB1*0201,* and *HLA-DRB1*0701* (p=1-5.4 X 10^{-6}) are the most significant classical HLA-alleles. The most significantly associated amino acid positions are *HLA-DQA1* positions 56 (2.83 X 10^{-7}), 76 (p=2.83 X 10^{-7}) and 69 (p=8.11 X 10^{-7}), which are in the functional a domain of the protein and are located on the dimer interface of the structural model of the protein. Conditional analysis revealed that there was no residual association after conditioning on *HLA-DQA1* positions 56 and 76, indicating that these are most likely the functional amino acids accounting for the observed association.

Conclusions: We have demonstrated that *HLA-DQA1* is an important locus for SSNS in children of European, Asian and African ancestries and further refined the association to the critical amino acid positions of the *HLA-DQA1* molecule.

Funding: NIDDK Support, Private Foundation Support

FR-PO584

Integrative Analysis of Disease-Associated and Gene-Expression-Driving Genetic Variants Highlights Genes Likely Mediating Chronic Kidney Disease Development

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Background: Genome-wide association studies (GWAS) identified single nucleotide polymorphisms (SNPs) significantly associated with chronic kidney disease (CKD). These variants are localized to non-coding genomic regions and how they cause CKD is not understood. Expression quantitative trait loci (eQTL) is a method to identify gene-expression changes driven by genetic variations. We hypothesized that an integrative analysis of eQTL and GWAS could identify target genes of GWAS studies.

Methods: eQTL analysis was performed in 99 CEU control human kidney samples by correlating genotype with RNAseq gene expression levels. Genetic variants passed genome-wide significance and associated with CKD were manually curated. Other disease-trait GWAS signals were obtained from the National Human Genome Research Institute GWAS Catalog. Enrichment analysis was performed using *coloc*, a Bayesian colocalization method. Linkage disequilibrium and p-values from both GWAS and kidney eQTL were integrated in the analysis.

Results: Integrating eQTL analysis with GWAS signals identified target genes for several non-coding GWAS loci. The overlap between the kidney eQTL dataset and CKD GWAS was greater than for other disease traits (immune, cardiovascular, metabolic and other diseases), indicating variants driving CKD development are functional in the kidney. Using *coloc*, we identified 4 regions corresponding to 4 target genes for CKD-associated genetic signals, including a previously published gene, CASP9, and others including MANBA and ALMS1P. To examine the functional role of the newly identified gene MANBA, we used *Danio rerio* as a model system. eQTL analysis showed decreased MANBA expression in kidneys of subjects with risk alleles. Expression of MANBA was also decreased in kidneys of patients with CKD. Manba knockdown in zebrafish resulted in pericardial edema, a phenotype seen with kidney developmental defect.

Conclusions: Integrative analysis of genetic and transcript level data is critical to understand genes causally related to specific trait development.Our integrative analysis identified novel genes for CKD.

Funding: Private Foundation Support

FR-PO585

Rare Genetic Variants That Segregate with Familial IgA Nephropathy Belong to a Single Aberrantly Modulated Immune-Related Network

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Background: The pathogenesis IgA nephropathy (IgAN) is still not clear but familial clustering demonstrates a strong genetic involvement. Aim of our study was to find rare, high penetrant risk variants, combining family-based linkage analysis (LA) with whole exome sequencing (WES).

Methods: Genotyping and LA were performed on 16 families of South Italian ancestry. Eight informative IgAN families containing 2 affected individuals and the most genetically discordant unaffected control were selected for WES. Variant calling and annotation were performed with GATK high standard procedures. High-priority variants in linked regions were identified and validated using Sanger sequencing. Their frequency was evaluated in external databases and with TaqMan Assays on an independent cohort of 240 IgAN patients and 113 controls. The connectivity between genes containing variants was evaluated with IPA network analysis.

Results: We found suggestive linkage signals to multiple loci. Our WES study identified 24 validated linked variants segregating with IgAN status. They were confirmed to be private or extremely rare (MAF<0.0003) and were present within coding or regulatory regions of 23 genes that merged into a IgAN-related network. The genes were interconnected by AKT, CTNNB1, NFKB, MYC and UBC, key modulators of WNT-β-catenin and PI3K/AKT pathways, notably implicated in IgAN pathogenesis. Overlaying publicly available expression data onto this network, genes/proteins whose expression is notably altered in IgAN were also included. A central role in this network was ascribed to the glucocorticoid receptor, the target of corticosteroid therapy and recommended by the KDIGO guidelines in the treatment of IgAN.

Conclusions: Our study suggests that disease could be influenced by multiple rare variants acting in a common immune related network. The analysis of IgAN related network could identify novel drug-targets for personalized therapy.

Funding: Government Support - Non-U.S.

FR-PO586

rs2576178 in Renalase Gene Is Associated with Hypertension in Type 2 Diabetic Nephropathy with Overt Albuminuria Patients

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Background: The renalase expression is related to plasma norepinephrine, systolic blood pressure (SBP) and proteinuria and renalase gene (RNLS) polymorphism is correlated with essential hypertension, type 2 diabetes and heart failure have been reported. We performed a case-control study to investigate if the rs2576178 in *RNLS* is associated with hypertension in type 2 diabetic nephropathy (DN) with overt albuminuria patients in Chinese.

Methods: The study population consists of unrelated 226 type 2 diabetic nephropathy with overt albuminuria patients (DN group) and 251 diabetes without nephropathy control subjects (Control group). According to if the hypertension (HTN) exists, the DN group was further divided into DN-HTN(+) group (n=169) and DN-HTN(-) group (n=56). Genotypic and allelic frequencies of rs2576178 as well as clinical characteristics were compared among groups. Taqman PCR assay was performed for the genotyping of all subjects.

Results: 1) Three genotypes (GG, GA and AA) of rs2576178 (G/A) were detected. The genotype distribution of rs2576178 (G/A) was in consistent with Hardy-Weinberg equilibrium. AA genotypic and A allelic frequencies were decreased in DN group when compared with Control group (P<0.05 for each). 2) AA genotype of rs2576178 is significantly associated with preventing hypertension in all subjects, by multiple logistic regression analysis, adjusted for sex, age, and BMI with OR(95% CI) of 0.48 (0.28~0.81). 3) Compared with DN-HTN (-) group, GG genotypic and G allelic frequencies were significantly increased in DN-HTN (+) group (P<0.05 for each). 4) Adjusted for sex, onset age of diabetes and BMI, AA genotype of rs2576178 is significantly associated with preventing hypertension in DN patients with OR of 0.37 (0.17~0.80) by multiple logistic regression analysis.

Conclusions: AA genotype carriers of rs2576178 in *RNLS* may decrease the risk of hypertension in overt albuminuria of type 2 diabetic nephropathy when adjusted for sex, onset-age and BMI.

Funding: Government Support - Non-U.S.

FR-PO587

O-Glycosylation of IgA1 Is Associated with Genetic Variation of C1GALT1

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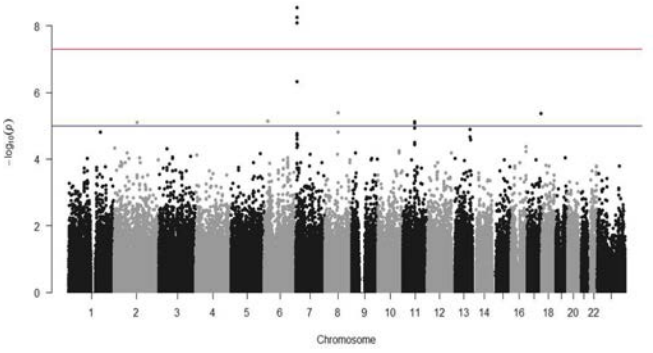
Background: IgA nephropathy (IgAN) is associated with abnormal glycosylation of the IgA1 molecule. We sought factors determining IgA1 glycosylation in cohorts of patients and healthy controls.

Methods: Levels of Galactose-deficient IgA1 (Gd-IgA) were measured by lectin-binding assay in a discovery cohort of 503 UK patients with biopsy-proven IgAN with >5 year follow-up data and 250 of their healthy parents in 137 complete trios, all genotyped using a 300,000-marker array. Findings were replicated in 309 UK patients with Membranous Nephropathy (MN) genotyped on a different 330,000-marker array. Further replication was performed in 690 Chinese patients with biopsy-proven IgAN genotyped at 38 markers across the locus.

Results: Gd-IgA levels were higher in IgAN patients with progressive kidney damage (p<0.01). Heritability (h^2) was 0.28. Linear regression genome wide association study in 613 founder members of the discovery cohort identified alleles at a single locus, spanning the *C1GALT1* gene, that were strongly associated with Gd-IgA level (p<10^{-8}), with no other hits across the genome.



C1GALT1 encodes an enzyme important in galactosylation of *O*-linked glycoproteins. The association was replicated in separate cohorts of UK patients with MN ($p<10^{-6}$; combined cohorts $p<10^{-14}$) and Chinese patients with IgAN ($p<10^{-6}$). The same extended haplotype was associated with elevated Gd-IgA levels in all cohorts studied, with a frequency of 0.26 in Caucasians but only 0.02 in Chinese people.

Conclusions: In addition to providing robust validation of the assay, we conclude that genetic variation at *C1GALT1* affects Gd-IgA level in the population.

Funding: Government Support - Non-U.S.

FR-PO588

Linking Tagging SNPs with Regulatory Information in Idiopathic Membranous Nephropathy Sebastian Martini,[1] Maja Lindenmeyer,[1] Clemens D. Cohen,[1] Viji Nair,[2] Detlef Bockenhauer,[3] Paul E. Brenchley,[4] Hanna Debiec,[5] Pierre M. Ronco,[5] Jack F. Wetzels,[6] Robert Kleta,[3] Matthias Kretzler.[2] *[1]Medizinische Klinik IV, Klinikum der Univ München, Germany; [2]Dept of Internal Medicine, Univ of Michigan, Ann Arbor; [3]Centre for Nephrology, Univ College London, UK; [4]School of Biomedicine, Univ of Manchester, United Kingdom; [5]Inst National de la Santé et de la Recherche Médicale, Univ Pierre et Marie Curie Univ-Paris, France; [6]Dept of Nephrology, Radboud Univ Nijmegen Medical Centre, The Netherlands.*

Background: Genome-wide association studies have identified an association of two single nucleotide polymorphisms (SNPs) in the introns of PLA2R1 and HLA-DQA1 with idiopathic membranous nephropathy (iMN, Stanescu et al., 2011). We hypothesize that iMN SNPs with below genome wide significances can provide information on iMN disease mechanism.

Methods: An integrative strategy was devised linking less stringently ($p<10^{-5}$) selected SNPs associated with iMN to underlying mechanism. Utilizing ENCODE, HaploReg and RegulomeDB potentially regulatory SNPs (rSNPs) patterns were evaluated for their cis-transcript impact using Genomatix variant analyzer and mRNA levels from 28 iMN and 6 living donor biopsies.

Results: Starting with 525 SNPs genome-wide suggestive variants associated with iMN HaploReg identified 7,956 SNPs in linkage disequilibrium. RegulomeDB retrieved 512 potential rSNPs overlying TF binding sites. In proximity to these 512 rSNPs we identified 127 transcripts. Nineteen of those 127 genes were differentially regulated in glomeruli of iMN patients versus 6 living donors. A strong functional concept among these 19 genes was the Antigen-*presentation* pathway with non-classical human leukocyte antigens (HLA-F, HLA-G) and superfamily receptors modulating T cell function (BTN3A). Consistent with this concept several members of Antigen-*processing* pathways like PSMB9, an immunoproteasome subunit or CLIC1 regulating macrophage phagosomal functions were identified.

Conclusions: A systems genetics approach can generate a testable hypothesis of additional molecular mechanisms in iMN by integrating GWAS and gene expression information.

Funding: NIDDK Support

FR-PO589

Bi-Ethnic GWAS Refines Genetic Architecture of Membranous Nephropathy Nikol Mladkova,[1] Jingyuan Xie,[2] Justin A. D'Addario,[1] Monica Bodria,[1] Robert A. Ledesma,[1] Nicole Lester,[1] Valeria Matta,[4] Carlo Sidore,[4] Magdalena Zoledziewska,[4] Francesco SCOLARI,[3] Antonello Pani,[4] Francesco Cucca,[4] Nan Chen,[2] Krzysztof Kiryluk.[1] *[1]Columbia U *equal contribution; [2]Ruijin Hospital *Equal Contribution; [3]U of Brescia; [4]U of Monserrato, Cagliari.*

Background: Idiopathic membranous nephropathy (MN) is the leading cause of nephrotic syndrome worldwide. Common variants at PLA2R1 and HLA loci have previously been associated with MN in Europeans, but these signals have not yet been fine-mapped. Notably, PLA2R (encoded by PLA2R1) represents a known target of pathogenic autoantibodies in up to 70% of MN cases.

Methods: We performed a GWAS discovery in 1,465 East Asians and 1,685 Sardinians (654 cases & 2,496 controls). The Asian cohort was genotyped with the OmniZhongHua-8 chip while the Sardinian cohort with OmniExpress. Following stringent QC, genotype data were imputed using 1000G reference. Imputation of classical HLA alleles was performed with SNP2HLA. Ethnicity-specific results were meta-analyzed using METAL.

Results: We replicated the *HLA* signal on chr.6p21 (OR=5.56, P=9.6E-65) and *PLA2R1* locus on chr.2q23 (OR=3.23, P=2.1E-24). We also confirmed a significant genetic interaction between these loci (P=1.4E-3). We next performed conditional haplotype analyses and defined a single genome-wide significant *PLA2R1* haplotype and 3 independent *HLA* haplotypes. The analysis of classical HLA alleles revealed that the HLA signal is entirely explained by *HLA-DRB1*1501* (OR=5.34, P=7.3E-47), Arg at position 233 of *DRB1* (OR= 5.24, P=1.6E-07) and Arg at position 74 of *DRB1* (OR= 9.0, P= 2.2E-19). After conditioning on the *HLA* and *PLA2R1* loci, we identified a number of new suggestive loci across the genome that are presently being tested for replication in >1,200 additional cases.

Conclusions: We confirmed the previously implicated variants with large effects on the risk of MN, fine-mapped the MHC signal to a single gene, demonstrated that the association at the *PLA2R1* locus can be explained by a single risk haplotype, and identified several novel suggestive signals. Our genetic results confirm that the interaction between the antigen (PLA2R) and HLA-DRB1 is critical for the development of MN, confirming strong autoimmune component to the disease pathogenesis.

Funding: NIDDK Support

FR-PO590

GWAS for Serum Galactose-Deficient IgA1 Implicates Critical Genes of the *O*-Glycosylation Pathway Krzysztof Kiryluk,[1] Yifu Li,[1] Zina Moldoveanu,[2] Hitoshi Suzuki,[3] Ping Hou,[4] Jingyuan Xie,[5] Nikol Mladkova,[1] Colin Reily,[2] Robert A. Ledesma,[1] Drew A. Bradbury,[1] Frank Eitner,[9] Thomas Rauen,[6] Jürgen Floege,[6] Nan Chen,[5] Hong Zhang,[4] Francesco SCOLARI,[7] Robert J. Wyatt,[8] Bruce A. Julian,[2] Jan Novak,[2] Ali G. Gharavi.[1] *[1]Columbia U; [2]U of Alabama at Birmingham; [3]Juntendo U; [4]Peking U; [5]Ruijin Hospital; [6]U of Aachen; [7]U of Brescia; [8]U of Tennessee; [9]Bayer Pharma.*

Background: IgA1 *O*-glycosylation defects are universally detected among patients with IgA nephropathy (IgAN). Serum level of galactose-deficient IgA1 (Gd-IgA1) represents a known heritable biomarker for IgAN, but specific genetic factors involved in its determination are not known.

Methods: We performed a quantitative GWAS for serum Gd-IgA1 in 2,633 individuals (IgAN cases and controls). In the discovery phase, we used HAA-lectin ELISA to profile sera of 1,195 individuals of Asian and European ancestry genotyped with Illumina 610q and 550v3 platforms. The association analysis of each cohort was adjusted for age, sex, ancestry and case status. Suggestive loci were followed by targeted genotyping in 1,438 additional individuals. Subsequently, all cohorts were meta-analyzed to identify novel genome-wide significant loci.

Results: The strongest association signal was mapped to chr.7p21.3 ($P=3x10^{-11}$). The top SNP intersects a B-cell specific enhancer of C1GALT1, the key enzyme of the *O*-glycosylation pathway. This variant exhibits a significant cis-eQTL effect in which the Gd-IgA1-increasing allele is associated with lower C1GALT1 mRNA levels ($P=4x10^{-23}$). The second significant locus mapped to chr.Xq24 containing C1GALT1C1 ($P=3x10^{-8}$). This gene encodes Cosmc, the molecular chaperone of C1GalT1 protein. We confirmed the role of these two genes in the production of Gd-IgA1 by iRNA knock-down experiments in IgA1-secreting cell lines. Jointly, the new loci have large effects and explain up to 7% of the overall variability in the circulating level of Gd-IgA1.

Conclusions: In the first GWAS for serum levels of Gd-IgA1, we discovered two genome-wide significant loci encoding enzymes involved in the key step of *O*-glycosylation. Our findings provide new insights into the genetic regulation of *O*-glycosylation and are relevant to IgAN as well as other human diseases, including IBD, hematologic disease, and cancer.

Funding: NIDDK Support

FR-PO591

Genome Wide Association of Blood Pressure in Individuals of African Ancestry Identifies Novel Loci Enriched for Renal, Immune and Cardiovascular Pathways Nora Franceschini.[1,2] *[1]COGENT-BP Consortium of African Ancestry; [2]Epidemiology, Univ of North Carolina at Chapel Hill, Chapel Hill, NC.*

Background: Hypertension is a leading cause of global mortality and disability, with a large burden on African Americans, who also are more likely to develop kidney and cardiovascular complications. Genetic studies in African populations can help to identify underlying biological pathways contributing to hypertension.

Methods: We used data from 21 genome wide association studies of blood pressure (BP) comprising of 31,968 African Americans and Africans. Studies used high density imputed genotypes from the 1000 Genomes Project and followed standardized protocols for analyses. We combined association summary statistics across studies using fixed effects meta-analysis, and the evidence across BP traits using the cross phenotype association analysis. We validated our significant results in additional 54,395 multi-ethnic samples of individuals of African, European, Hispanic and East Asian ancestries. Functional annotation and cell type enrichment analysis were performed using the LD score method.

Results: We identified 11 independent variants at 9 loci reaching genome wide significance ($P < 5.0\times10^{-8}$) for systolic BP, diastolic BP or hypertension. Four loci were novel (*TCF21, GPR20, FRMD3* and *LLPH/TMBIM4*), and two loci (*CDH17* and *IGFBP3*) have been reported in European ancestry but not previously replicated in African ancestry. *FRMD3* has previously been associated with diabetic nephropathy. Functional annotation identified super enhancer ($P_{Enrich} = 6.6\times10^{-6}$ for diastolic BP), enhancer ($P_{Enrich} = 3.8\times10^{-4}$ for systolic BP) and H3K27ac ($P_{Enrich} = 9.0\times10^{-4}$ for hypertension) that were significantly enriched. Cell types enrichment analysis identified immune ($P_{Enrich} = 1.4\times10^{-9}$ for diastolic BP), kidney ($P_{Enrich} = 2.4\times10^{-6}$ for diastolic BP) and cardiovascular ($P_{Enrich} = 2.3\times10^{-5}$ for systolic BP) as the three most significantly enriched pathways.

Conclusions: Our study provides new links between BP and immune, kidney and cardiovascular pathways, and illustrates the advantage of using hypertension susceptible populations of African ancestry to identify novel pathways for BP regulation.

Funding: Other NIH Support - NHLBI, NIEHS

FR-PO592

Pregnancy Outcomes in a Racially Diverse Patient Cohort with Lupus Nephritis Meghan A. Jobson,[1] Michelle M. O'Shaughnessy,[2] Katy Sims,[1] Scarlett Murphy,[1] William Franklin Pendergraft.[1] *[1]Div of Nephrology and Hypertension, UNC Kidney Center, Univ of North Carolina, Chapel Hill, NC; [2]Div of Nephrology, Stanford Univ, Palo Alto, CA.*

Background: Prior studies examining pregnancy outcomes in patients with lupus nephritis are generally restricted to white, non-US populations.

Methods: We examined maternal and fetal outcomes among patients enrolled in the Glomerular Disease Collaborative Network who received obstetric care at the UNC Hospitals between 1995 and 2015, either within the year prior to or any time after their lupus nephritis diagnosis, prior to end-stage renal disease. Our primary outcome was fetal loss (stillbirth at > 20 weeks). Secondary outcomes included: premature birth (<37 weeks), fetal weight and maternal outcomes (e.g. pre-eclampsia, disease flare). Categorical variables were compared using Fisher exact testing and continuous variables using Wilcoxon rank sum testing.

Results: We identified 32 pregnancies in 24 women with lupus nephritis. Forty-two percent were black, 34% were white and the remaining 25% were other. Mean age was 25 (SD 5.4) with black mothers being younger than white mothers ($p<0.001$). At baseline, mean serum creatinine was 0.92 mg/dL (SD 1.2) and urine protein 1.4 gm/24hrs (SD 2.2). There were 4 fetal losses, all between 20-24 weeks of gestation, 3 spontaneous and one elective due to disease severity. There were differences based on race for multiple variables including low birth weight (<0.01), preeclampsia (0.007), prematurity (0.037), having a pediatrician present at birth (0.01), NICU admission (0.004), renal flares in pregnancy (0.008) and IUGR (0.04), which were seen more often in black mothers compared to other racial groups. The median gestation was 35 weeks (IQR 34 to 37). Sixteen pregnancies (50%) developed pre-eclampsia, 8 were black, and 88% were non-white. Four required dialysis during pregnancy (3 black).

Conclusions: We identified a high frequency of adverse fetal and maternal outcomes in women with lupus nephritis, especially in black patients. We plan to evaluate this further in a multi-site study that includes lupus patients without nephritis as a control for effects seen in black and other non-white pregnancies.

FR-PO593

A Clinical Research of the Effect of Leflunomide as an Induction Treatment for Proliferative Lupus Nephritis Fei Deng, Daqing Hong, Li Wang. *Renal Div and Inst of Nephrology, Sichuan Provincial People's Hospital, Chengdu, Sichuan, China.*

Background: To assess the efficacy and safety of leflunomide (LEF) as an induction treatment for proliferative lupus nephritis (PLN).

Methods: Thirty biopsy-proven PLN patients were included and randomized to LEF combined with prednisolone (LEF group) or cyclophosphamide (CTX) combined with prednisolone (CTX group) for 24 weeks. Urine routine, blood routine, blood biochemistry, quantitation of anti-ds-DNA, compliment C3, T-cell subsets and SLEDAI scoring were measured and all adverse reactions were assessed during the study.

Results: Proteinuria and SLEDAI score was reduced, and hemoglobinuria, serum albumin was increased significantly after 24-week treatment ($p<0.001$). At week 8, the efficacy was better in the CTX group than LEF group ($P<0.05$). However, at the end of treatment, there was no significant difference in efficacy between the two groups ($P>0.05$). ALT, WBC and hemoglobin were not significantly changed ($P>0.05$) in either group while T-cell subset was decreased in both groups ($P<0.001$) Although the CTX group manifested higher adverse effects in all measurements than the LEF group did, there was no statistical significance between the two groups.

Conclusions: LEF has a good efficacy as an induction treatment for PLN. LEF has the equivalent efficacy to that of CTX at the end of the induction treatment but lower adverse reactions and better patient compliance than that of CTX, indicating its further use in the treatment of PLN patients.

FR-PO594

Comparison of Clinical and Histologic Changes in Kidney Biopsies for Lupus Nephritis (LN) Repeated Early and Late after Induction Therapy Ana Malvar,[1] Valeria Gabriela Alberton,[2] Cecilia Recalde,[1] Bruno Jorge Lococo,[1] Brad H. Rovin.[3] *[1]Nephrology, Fernandez Hospital, Buenos Aires, Argentina; [2]Pathology, Fernandez Hospital, Buenos Aires, Argentina; [3]Nephology, Ohio State Univ, Columbus, OH.*

Background: Repeat kidney biopsies (Bx) done 6-9 months after starting treatment for LN often show persistence of inflammation despite complete clinical response(CR). We postulated that expanding the interval between repeat Bx may demonstrate more complete histologic resolution and a better correlation to clinical findings. To test this hypothesis we examined histologic and clinical responses at 7 and 14 months after initiating LN therapy.

Methods: SLE patients(n=53) were biopsied at first presentation of kidney involvement(Bx1) and again (Bx2) either 7 (n=30) or 14 months (n=23) after starting therapy with steroids+MMF. NIH activity(AI) and chronicity(CI) indices, proteinuria (prot, g/d) and serum creatinine (SCr) were compared.Complete Response was defined as normal SCr and prot ≤ 0.5 g/d.

Results: Clinical and histologic data are shown in the Table presented as median(range). Final prot was determined after a mean follow-up of 55±12 months.

Re -Bx months/ response	AI Bx1	CI Bx1	Prot Bx1	AI Bx2	CI Bx2	Prot Bx2	Final prot
7/CR	7.5(3-15)	3(0-6)	2.8(0.6-8)	3.5(05)	4(2-6)	0.2(1-0.5)	0.2(0.1-0.4)
7/NR	8.5 (3-13)	3(0-5)	3.6(0.7-8)	4(0-7)	4(1-7)	1.9(0.6-3.6)	0.3(0.1-1)
P(CRvsNR)	0.33	0.55	0.21	0.51	0.38	0.001	0.3
14/CR	8(4-14)	3.5(0-5)	3.1(1-7.5)	1.5(0-4)	4(3-7)	0.3(0.1-0.7)	0.2(0.1-0.8)
14/NR	7(6-12)	3(0-6)	3.4 (2-2.6)	4(0-6)	4(3-8)	0.0(0.6-3)	0.7(0.2-1.5)
P(CRvsNR)	0.83	0.68	0.99	0.16	0.9	0.001	0.007

Conclusions: Response to therapy in LN takes a long time. Even though the difference between AI-Bx2 in CR vs AI-Bx2 in NR was not significant, perhaps because of the small N, there was a tendency for AI-Bx2 in NR to be higher than AI-Bx2 in CR when the biopsy was repeated at 14 versus 7 months. Conversely, proteinuria at Bx2-7 months did not reflect long-term outcome, but at 14 months the association appeared to be better.

FR-PO595

Characteristics and Outcomes of Males with Lupus Nephritis in a Racially Diverse Patient Cohort Stephen A. Proctor, Meghan A. Jobson, Caroline J. Poulton, Keisha L. Gibson, William Franklin Pendergraft. *Div of Nephrology and Hypertension, UNC Kidney Center, Univ of North Carolina, Chapel Hill, NC.*

Background: Prior studies examining lupus nephritis (LN) in males have been limited to small racially homogenous cohorts or cohorts outside of the US. Little information exists on the differences between disease in males and females and in white males compared to black males.

Methods: We evaluated disease history and outcomes among patients enrolled in the Glomerular Disease Collaborative Network who were diagnosed with biopsy proven LN. Our primary outcome was end stage renal disease. Secondary outcomes include death and time to death from biopsy. Categorical variables were compared using Fisher exact testing and continuous variables using a Mann Whitney test.

Results: A total of 125 male patients with biopsy proven LN were included in the study. Forty-two percent were black, 39% were white and 19% were other. Sub-stratification by race revealed black race to be associated with positive anti-RNP ($p=0.004$), SSA ($p=0.006$), SSB ($p=0.03$), and Smith ($p=0.01$) antibodies, and present with serositis at presentation ($p=0.05$) compared to white males. White males had more intense C1q staining compared to black males ($p=0.05$) and males had more intense C1q staining compared to females ($p=0.001$). There was no difference in rates of ESRD, time from biopsy to ESRD and mortality in black patients when compared to white male counterparts; however, males time to ESRD from biopsy was shorter compared to females (2.8 vs 4.2 years, $p=0.05$). Males were more likely to die (0.008) compared to females, but time to death was similar between the two groups (males 6.2 vs females 4.7 years after biopsy, $p=0.24$).

Conclusions: We identified that male patients with lupus nephritis have higher mortality rates compared to females. Further understanding of why male presentation and serological markers vary by race and why males have a higher mortality rate need to be elucidated further to provide optimized interventions and therapeutic plans.

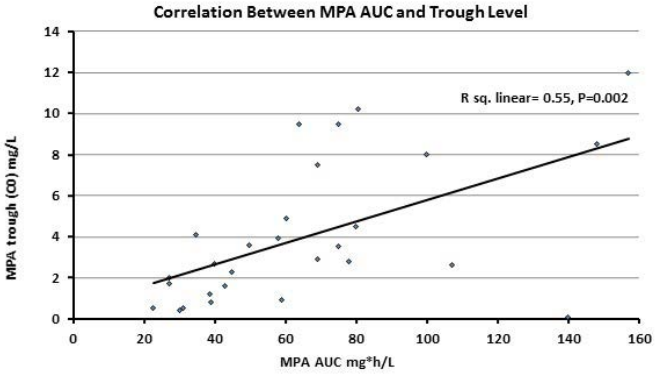
FR-PO596

Correlation between Trough Levels of Mycophenolic Acid and Area under the Curve in Patients with Lupus Nephritis Negiin Pourafshar, Rajesh Mohandas, Eric S. Sobel, Westley Reeves, Xuerong Wen, Mark S. Segal. *Univ of Florida, Gainesville, FL.*

Background: Mycophenolate mofetil is the mainstay of induction as well as maintenance therapy for lupus nephritis. Therapeutic drug monitoring appears to be particularly important in this population of patients for effective dosing and prevention of toxicity due to the high pharmacokinetic variability, however whether trough levels are the acceptable method of monitoring, remains debatable. We hypothesized that trough levels of MPA might be a poor predictor of Area Under the Curve (AUC) of mycophenolic acid in patients with lupus nephritis.

Methods: 31 patients with lupus nephritis were included in this study. We measured fasting trough levels of mycophenolic acid. Patients were then given the usual dose of oral mycophenolate mofetil. Mycophenolic acid levels were measured at 0 (C0), 1 (C1) and 2 (C2) hours. The MPA-AUC values were calculated using the linear trapezoidal rule. Pearson or Spearman correlations were used to look for correlations. Multiple linear regression and logistic regression analyses were employed to examine significant predictors of continuous and categorical dependent variables, respectively.

Results: There was a statistically significant correlation between trough levels of mycophenolic acid and area under the curve ($P=0.002$). However linear regression showed an R^2 of only 0.55. Demographic, clinical or laboratory variables did not identify subgroups in which trough levels were predictive of AUC. We were able to show that MPA trough level has a significant but moderate correlation ($r^2 = 0.55$, $P = 0.002$) and a positive linear relationship with MPA AUC.



Conclusions: Trough levels of mycophenolic acid does not show strong correlation with AUC. In clinical situations where mycophenolic acid levels are essential to guide therapy, an AUC would be a better indicator of adequate treatment.

FR-PO597

Treating Lupus Nephritis with Rituximab and Mycophenolate Mofetil (RituxiRescue Regimen) without Increasing Maintenance Oral Steroids Leads to Sustained Disease Remission and Steroid Reduction Camilla Pillay, Megan Griffith, Jeremy B. Levy, Tom Cairns, Liz Lightstone. *Imperial College Lupus Centre, London, United Kingdom.*

Background: To ↓ the morbidity caused by high-dose and long-term steroids we have used rituximab as a steroid-sparing agent in patients on maintenance steroids who develop active lupus nephritis (LN). The RituxiRescue regimen (2 x 1g rituximab ± 125-500mg methylprednisolone on d1 and 15, maintenance mycophenolate mofetil + **no** ↑ in b/line steroid dose) led to steroid ↓/cessation at 1 year in 18 patients with LN (NDT, 2009). Outcomes are now reported on 38 patients with ≥ 5 years f/up.

Methods: Inclusion: 38 patients with class III/IV/V LN on biopsy, on steroids ≥ 4 weeks at b/line, f/up ≥ 5 years, Dec 2005-Mar 2016. **Exclusion**: Requirements for dialysis ± cerebral/other life-threatening lupus features. **Remission**: **Complete** (CR): uPCR ≤ 50, eGFR ≥ 60 or ≤ 20% ↓ if > 60 at b/line. **Partial** (PR): uPCR < 50% + eGFR ↓ ≤ 20% (not nephrotic) + uPCR < 300 (if nephrotic) from b/line. **Relapse** (from CR/PR): uPCR ≥ 50% ↑ from CR/PR + >100 ± eGFR ≥ 20% ↓ from b/line.

Results: Outcomes in 38 patients by 1 and 5 years, 4 lost to f/up.

	1 year n=37(%)	5 years n=33(%)	Median time to event (months)
CR/PR	23(62.2)	31(93.9)	13.0(4.8-33.5)
No response	12(32.4)	8(24.2)	
Relapse from CR/PR	2(5.4)	7(21.2)	28.4(11.0-40.8)
↓ in eGFR ≥ 50%	3(8.1)	1(3.0)	13.2(7.1-54.6)
Mean steroid dose (mg)	7.5	5.9	
Off oral steroids	7/37(18.9)	15/33(45.5)	

1 death (28 y/o male, non-adherent) at 21.9 months. 2/37 with ↓ eGFR ≥ 50% at 1 year progressed to ESRD (from no response). By 5 years: 13/33 had not responded/relapsed before CR/PR with **no** recommencement/↑ in oral steroid dose from baseline. **Median time to steroid cessation**: 21.4 months (10.4-46.8). **Adverse events**: 19/21 episodes of infection (21 patients) required hospitalisation, 23.8% by 1 year. 42% (16/38) patients had evidence of steroid toxicity, 62.5% (10/16) bone related.

Conclusions: The RituxiRescue regimen led to sustained disease remission and a significant ↓ in steroid dose/cessation by 5 years. Poor renal outcomes were rare + adherence related. The data suggest that it is safe not to ↑ baseline oral steroids at relapse.

FR-PO598

Effect of Cyclophosphamide versus Mycophenolate Mofetil in Induction Therapy of Lupus Nephritis in Nepalese Population Arun Sedhain, Rajani Hada, Rajendra Kumar Agrawal, Anil Baral, Gandhi R. Bhattarai. *Nephrology, National Academy of Medical Sciences (NAMS), Kathmandu, Nepal.*

Background: Management of SLE and lupus nephritis (LN) comprises timely and coordinated management consisting of induction phase followed by maintenance phase. This study aimed to evaluate and compare the effectiveness and safety profile of mycophenolate mofetil and intravenous pulse cyclophosphamide in induction therapy of proliferative LN in Nepalese population.

Methods: A prospective open label randomized control trial was conducted in a tertiary hospital at Kathmandu, Nepal for a period of one and half year from January 2014 to June 2015. Fifty two patients with biopsy proven proliferative lupus nephritis were screened and 49 patients were randomized out of which only 42 patients could complete the study period of six months. Monthly intravenous injection of pulse cyclophosphamide (CYC) was given to one group and daily oral mycophenolate mofetil (MMF) to the other. Participants were followed up monthly and the results were analysed at the end of 6 months.

Results: At 6 months, serum creatinine (mg/dL) decreased from 1.73 to 0.96 in CYC and from 1.24 to 0.91 in the MMF group. Twenty four hour urinary protein (gm/1.73 m^2) reduced from 4.47 to 0.94 in CYC and from 4.5 to 0.62 in the MMF group. 19% patients in CYC and 28.6% patients in MMF group achieved partial remission (primary end point) and equal proportion (67% in each group) achieved complete remission (secondary end point). 14.3% of patients in CYC group and 4.8% in MMF group did not respond to treatment.

Efficacy measurement	CYC	MMF	P Value
Achieved partial remission (Primary end point)	4 (19%)	6 (28.6%)	0.572
Achieved complete remission (Secondary end point)	14 (66.7%)	14 (66.7%)	
Did not respond to treatment	3 (14.3%)	1 (4.8%)	

The occurrence of adverse events was higher in the CYC than in MMF group (56 vs. 15 non-infection related and 10 vs. 7 infection related events).

Conclusions: Present study found that MMF is equally effective in inducing remission with reduction of proteinuria and improvement of kidney function with lesser adverse events than CYC in proliferative lupus nephritis in 6 months therapy.

FR-PO599

Steroid-Treatment Promotes a M2 Pro-Fibrotic Macrophage Phenotypic in Lupus Nephritis Yohei Ikezumi,[1] Yuji Matsumoto,[1] Takeshi Yamada,[2] Hiroya Hasegawa,[2] Ichiei Narita,[3] David J. Nikolic-Paterson.[4] *[1]Dept of Pediatrics, Fujita Health Univ School of Medicine, Toyoake, Japan; [2]Dept of Pediatrics, Niigata Univ Medical and Dental Hospital, Niigata, Japan; [3]Dept of Nephrology, Niigata Univ Medical and Dental Hospital, Niigata, Japan; [4]Dept of Medicine, Monash Univ, Clayton, Victoria, Australia.*

Background: M1 pro-inflammatory macrophages (MQ) promote glomerular injury in lupus nephritis (LN). However, it is unclear whether steroid therapy affects macrophage phenotype in these patients. We examined the effect of steroid treatment on MQ phenotype in LN.

Methods: 46 patients with LN were divided in 2 groups; N group, underwent biopsy before steroid-treatment (N=24, 20.0±9.2 years at biopsy); S group, underwent steroid treatment (2 to 6 months) before biopsy (N=19, 20.1±9.2 years at biopsy). Macrophage number and phenotype was assessed by immunofluorescence. In vitro studies used monocyte-derived MQ from healthy human volunteers.

Results: Urine findings were comparable between the two groups, but the S group had a significantly lower eGFR (104±34 vs 125±22 ml/min/1.73m^2; p<0.05). Biopsies revealed les endocapillary proliferation (p<0.05) and greater glomerular matrix expansion (p<0.001), glomerulosclerosis (p<0.001) and interstitial fibrosis (p<0.05) in the S group. The total $CD68^+$ MQ infiltrate was comparable between N and S groups. However, the N group had fewer M1 MQ ($CD68^+CD86^+$ cells) (p<0.05) and more M2 MQ ($CD68^+CD163^+$ cells) (p<0.05), giving a 6-fold increase in the M2/M1 ratio in S vs N groups. In addition, M2 MQ correlated with glomerular matrix expansion and interstitial fibrosis (p<0.001). Steroid (dexamethasone) treatment of cultured MQ induced up-regulation of CD163 expression, increased production of anti-inflammatory (IL-10) and pro-fibrotic factors (TGF-β1, CTGF), and up-regulated the scavenger receptor, stabilin-1. We confirmed up-regulation of stabilin-1 in $CD163^+$ M2 MQ in biopsies from the S group.

Conclusions: Initial steroid treatment induces a MQ phenotypic change from pro-inflammatory M1 to pro-fibrotic M2 in LN with acute/active lesions. Promotion of fibrotic lesions via M2 MQ is a potential downside of steroid single therapy in LN.

Funding: Government Support - Non-U.S.

FR-PO600

Clinical Features of Metabolic Indices Patients with Lupus Nephritis Hua Zhou, Lizhi Li, Congcong Jiao, Di Lu, Kong Weiwei, Lining Wang. *The First Hospital of China Medical Univ, China.*

Background: Lupus Nephritis (LN) is an autoimmune mediated disease. Metabolic disorders often occur in chronic kidney diseases. We aim to investigate clinical features of metabolic indices in LN patients.

Methods: 194 patients with LN proven by renal biopsy were treated with steroid and immunosuppressants at China Medical University from 2007 to 2015. 24hr total urinary protein (uTP), hematuria (uRBC), estimated glomerular filtration rate (eGFR-EPI), systemic lupus erythematosus disease activity index (SLEDAI), compliments (C), immunoglobulin (Ig), and serum metabolic indices including uric acid (UA), low-density lipid cholesterol (LDL-C), and calcium (Ca) were observed up to 18 months. The correlations between pretreated metabolic indices and severity of LN before and after treatment were analyzed.

Results: After 18 months' treatment, uTP, uRBC, SLEDAI, and IgG decreased (uTP 4.3±0.3 vs 0.7±0.2 g/24hr, p<0.01; uRBC 50±10 vs 5±2/hp, p<0.01; SLEDAI 17.3±0.6 vs 5.3±0.9, p<0.01; IgG13.2±0.6 vs 9.9±0.4 g/L, p<0.01). sAlb, C3, and C4 increased (sAlb 24.7±0.6 vs 40.1±0.9 g/L, p<0.01; C3: 0.5±0.02 vs 0.9±0.04 g/L, p<0.01; C4: 0.11±0.01 vs 0.20±0.02 g/L, p<0.01). The pretreated metabolic indices significantly correlated with the activity of systemic and renal disease before and after treatment (table).

		Pretreated		
		UA	LDL	Ca
Pre-treated	uTP	r=0.2(p<0.05) n=119	r=0.34(P<0.01) n=151	r=−0.5(p<0.01) n=161
	eGFR	r=-0.4(p<0.01) n=118		r=0.2(p<0.01) n=159
	SLEDAI	r=0.3(p<0.05) n=82		r=−0.3(p<0.01) n=108
	C4		r=0.2(p<0.05) n=141	
	IgG		r=−0.4(p<0.01) n=137	
Post-treated	uRBC	r=0.4(p<0.05) n=42 (9m)		
	eGFR			r=0.4(p<0.05) n=40 (12m)
	SLEDAI	r=0.6(p<0.05) n=18(9m)		
	C4		r=0.6(p<0.01) n=31(18m)	
	IgG		r=−0.4(p<0.05) n=30(9m)	

Conclusions: The level of pretreated serum UA, LDL-C, and Ca correlated with the changing activity of lupus and LN. Our data suggest that the changes of pretreated metabolic indices might be additional biomarkers for the severity and management of LN. Thus, early correction of metabolic disorders might improve LN outcome.

Funding: Government Support - Non-U.S.

FR-PO601

Urinary Levels of TWEAK as a Biomarker of Lupus Nephritis in Hispanic Populations Fabiola Reyes,[1] Monserrat M. Perez-Navarro,[1] Adrian Rodriguez Matias,[1] Virgilia Soto,[2] Gabriela Gutierrez,[3] Zaira Medina,[3] Rafael Valdez-Ortiz.[1] *[1]Servicio de Nefrología, Hospital General de México, México, Mexico; [2]Dept of Pathology, Hospital General de México, México, Mexico; [3]Dept of Experimental Medicine, Univ Nacional Autónoma de México, México, Mexico.*

Background: Urinary levels of TWEAK (uTWEAK), may be correlated with the degree of lupus nephritis (LN) activity. Our objective was to determine the sensitivity and specificity of uTWEAK in Hispanic patients with active lupus nephritis.

Methods: A clinical study was performed. Four groups of patients were analyzed as follows: 1) patients with systemic lupus erythematosus (SLE) without renal activity (SLE-LN), 2) patients with SLE with renal activity (SLE+LN), 3) patients with other types of glomerulopathies (GMN), and healthy patients (controls).

Results: In all, 44 patients, with an average age of 35.9±11.5 years, were evaluated. uTWEAK levels were higher in patients with SLE+LN compared with patients in the other groups: SLE+LN 12.88±8.33, SLE-LN 3.12±2.31, GMN 4.36±2.31 and controls 2.41±1.94 pg/mgCr (p=0.007). A total of 72.7% of the cases had renal activity index scores above 12, and 90.9% of the cases had scores of chronicity below 6 points. Receiver Operating Characteristic (ROC) curve analysis revealed that uTWEAK levels above 2.0 pg/mgCr had a sensitivity of 90 % and a specificity of 60% for the diagnosis of renal activity due to lupus, with an area under the curve of 0.876 (IC 0.75 - 0.99). However, a significant correlation was not observed between the levels of uTWEAK and the histological findings specific to the activity and chronicity associated with SLE.

Conclusions: Our study revealed that uTWEAK can adequately distinguish renal activity due to lupus, but cannot predict the degree of histological activity in Hispanic patients with active lupus nephropathy.

FR-PO602

Using Hazard Functions to Predict Outcomes in Lupus Nephritis: A Novel Way to Assess New Therapies Brad H. Rovin,[1] Meggan Mackay,[2] Joanna Stein Fishbein,[2] Kenneth Kalunian,[4] Maria Dall'Era.[3] *[1]Ohio State Univ, Columbus; [2]Feinstein Inst; [3]UCSF; [4]UCSD.*

Background: The goal of therapy in lupus nephritis (LN) is long-term preservation of renal function. In clinical trials of drugs for LN, treatment success is evaluated by the proportion of patients achieving complete remission 6-12 months after starting therapy. However, short-term remission does not necessarily equate to sustained long-term kidney function. The present work was undertaken to establish novel endpoints for LN clinical trials that predict long-term kidney health.

Methods: A database of 944 patients with extended follow-up was established from 15 clinical centers/trials. This analysis sought predictors of new or worsening CKD, defined as a sustained decrease in eGFR ≥30%. Associations between CKD and clinical data at LN flare (baseline) through month 12 of treatment were determined using univariate Cox regression. Explanatory variables considered were: gender, age, race/ethnicity, ISN class, absolute levels of proteinuria, serum creatinine (SCr) and urine RBCs at baseline and 12 months, and % change in proteinuria and SCr from baseline through month 12. Variables significantly (p<0.10) associated with CKD were then tested by Cox proportional hazards regression, and using stepwise selection methods included in a final multivariable model if p<0.05.

Results: A total of 558 LN patients had all the required data and were included in the analysis. Variables significantly associated with CKD on univariate screen were race (binary variable, Black/non-Black), urine RBCs at baseline and 12 months, proteinuria at 12 months, SCr at baseline and 12 months, and %Δ in proteinuria and SCr from baseline to 12 months. The final multivariable model included log (%Δ proteinuria, p<0.0001), log (SCr at 12 months, p<0.0001) and race (p=0.04). The hazard ratios (HR) for CKD were 1.86 (95% CI: 1.52, 2.65) for log (%Δ proteinuria), 5.11 (3.04, 8.58) for log SCr and 1.65 (1.003, 2.70) for race. These variables were combined into a hazard function (HF) for CKD. HF=0.062*log(%Δ proteinuria)+1.63*log(SCr)+0.49*X_3, where X_3=1 if black, 0 if non-Black.

Conclusions: The HF can be used to evaluate new LN drugs for superiority in preventing future development of CKD.

Funding: Private Foundation Support

FR-PO603

Medication Adherence, Depression, and Disease Activity among Patients with Systemic Lupus Erythematous Abdulkareem Alsuwaida,[1] Nada S. Alsowaida,[2] Meshael M. Alrasheed,[2] Ahmed Y. Mayet,[3] Mohammed A. Omair.[1] *[1]Dept of Medicine, King Saud Univ, Riyadh, Saudi Arabia; [2]College of Medicine, King Saud Univ, Riyadh, Saudi Arabia; [3]Dept of Clinical Pharmacy, King Saud Univ, Riyadh, Saudi Arabia.*

Background: There are only a few studies that correlate adherence problems to disease progression among systemic lupus erythematosus (SLE) patients. The aim of this study is to assess the prevalence of medication adherence and depression among Saudi SLE patients, and to explore the impact of depressive symptoms on patient's adherence to the treatment regimen.

Methods: In a cross sectional study of 140 outpatients with SLE, we assessed the prevalence of medication non-adherence and severity of depression using paper questionnaires that contain a number of questions based on Morisky Medication Adherence Scale (MMAS-4) and Beck's Depression Inventory (BDI). The disease activity was assessed using the SLE Disease Activity Index (SLEDAI).

Results: None adherences were reported in 62.1 % and depression was noted 35% (49 patients). Moderate and severe depression were significantly associated with medium and high non adherence (p = 0.04) but not with disease activity. There is a significant correlation between disease activity and severity of depression (r=0.31, p=0.003). The logistic regression showed only moderate to severe depression is associated with non-adherence (OR 2.62; 1.02-6.71) and disease activity is the predictor of depression.

Conclusions: SLE patients should be routinely assessed for medication non-adherence and the factors behind that especially depression. Interventions aimed at alleviating depressive symptoms, which are quite common, could result in significant improvements in patient adherence and disease response in patients with SLE.

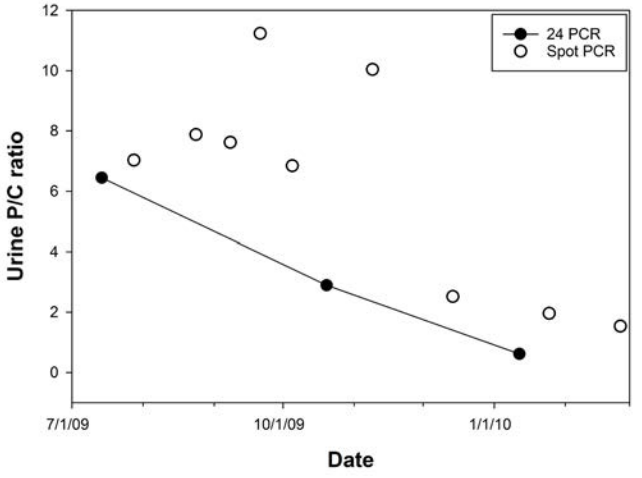
FR-PO604

24 Hour Protein:Creatinine Ratio (24 PCR), Not Spot PCR (Spot PCR), Should Be Used to Monitor the Treatment of Severe Lupus Nephritis (LN): The Experience of ACCESS Ganesh B. Shidham, Daniel J. Birmingham, Brad H. Rovin, Lee A. Hebert. *Nephrology, Ohio State Univ Wexner Medical Center, Columbus, OH.*

Background: It is well established that in proteinuric renal disease urine PCR varies greatly during any given 24 hour period. Spot urine (single void) PCR reveals this variability; 24 hour urine (24 PCR) conceals this variability because it represents the average of the PCRs during the urine collection. Here we estimated the extent to which using spot PCR, rather than 24 PCR, might lead to serious errors in management of LN because spot PCR are unreliable.

Methods: ACCESS (phase 2 trial of abatacept in severe LN) measured spot PCR monthly and 24 PCR each 3 months for up to 12 months in 103 patients. To assess the ability of spot PCR to correctly identify proteinuria trends during LN treatment, in each patient we displayed their spot PCRs in relationship to their proteinuria trend line (the line formed by the sequential 24 PCRs). Using a semiquantitative approach in each patient, spot PCR was adjudicated as either Reliable, Generally Reliable (problematic), or Unreliable in identifying proteinuria trend.

Results: The figure shows a representative patient in whom spot PCR was deemed Unreliable. Overall spot PCR was Unreliable in 35%, problematic in 24% and Reliable in only 41%. Baseline demographics and clinical measures did notdistinguish between Reliable/Unreliable. However, those with Unreliable PCRs were more likely to experience Treatment Failure and less likely to experience Complete Remission than those whose spot PCRs were Reliable (p = 0.024).



Conclusions: Compared to 24 PCR, spot PCR results are often highly and consistently misleading and likely would lead to management errors if relied upon for clinical decision making.

Funding: Other NIH Support - National Institute of Allergy and Infectious Diseases

FR-PO605

Molecular Imaging of Treatment Naïve and Treatment-Experienced Kidneys in Lupus Nephritis Samir Parikh,[1] Ana Malvar,[2] Huijuan Song,[1] Valeria Gabriela Alberton,[2] Jianying Zhang,[1] Lianbo Yu,[1] Brad H. Rovin.[1] *[1]Nephrology, The Ohio State Univ Medical Center, Columbus, OH; [2]Nephrology, Hospital Fernandez, Buenos Aires, Argentina.*

Background: Lupus nephritis (LN) frequently relapses, and often shows the same histologic class at each flare. It is not clear whether the kidneys of patients who have LN flares after successful treatment show a similar molecular profile as kidneys from the first presentation of LN. This study was done to investigate the similarities and differences in LN flares at the molecular level.

Methods: Molecular profiling of the kidney was done on one SLE patient who had a biopsy at their first presentation of LN (Bx1, treatment naïve), and a second biopsy when the disease relapsed on maintenance immunosuppression after 1.5years of remission. Both biopsies showed class IV LN. RNA was extracted from each biopsy and the expression of 511 immune-response genes was compared using Nanostring technology.

Results: Bx1 and Bx2 showed significant differences in pro-inflammatory transcript profiles. Genes with increased expression at Bx2 compared to Bx1 included: *CD79a* (12.7-fold >Bx1), *CCL19* (10.3-fold), *CXCR6* (4.5-fold), *CXCL12* (3.6-fold), *IL17F* (3.1-fold), *CXCL11* (2.6-fold), *CCL13* (2.3-fold), and *CXCL10* (2.2-fold). Transcripts with increased expression at Bx1 compared to Bx2 included: *CCL23* (3.5-fold), *CCL16* (3-fold), *CCRL2* (2.7-fold), and *CCBP2* (2.7-fold).

Conclusions: These data show that LN flares of the same class and within the same patient can demonstrate different renal molecular profiles. Despite similar histology, the dominant inflammatory signature, especially among chemokine family member genes, is different in a treatment naïve flare compared to a flare that occurs on immunosuppression. These data suggest that relapses of LN may need to be treated differently than the first flare, and may explain why relapses often are more treatment resistant.

Funding: NIDDK Support

FR-PO606

Refractory Lupus Nephritis: Results of a Multi-Dimensional Survey on Real-Life Clinical Practice among International Lupus Experts Julia Maria Eder, Marc J. Weidenbusch, Hans J. Anders. *Nephrologisches Zentrum, Klinikum der Univ München, Munich, Bavaria, Germany.*

Background: Refractory lupus nephritis (RLN) is associated with poor long-term outcome in systemic lupus erythematosus (SLE). There is no consensus on how to define and manage RLN.

Methods: After review of international guidelines regarding LN and a literature search, a 27-item questionnaire was created in adherence to data privacy regulations by experts of the Lupus Nephritis Trials Network (LNTN). This survey was sent in March 2016 to LNTN members via email and given to attendees of two conferences (ISN Nexus Berlin 2016 and ERA-EDTA Vienna 2016). Statistical analyses were performed by means of the chi-square test (significance at $p<0.05$).

Results: The survey reached 293 nephrologists and rheumatologists, the response rate was 42.3%. 92.7% of the participants used persisting proteinuria as a diagnostic criterion for RLN, followed by serum creatinine (S-Cr) (71.7%) and an abnormal urine sediment (U-Sed) (61.2%). 60.4% of the participants performed re-biopsies when RLN is suspected. Experienced physicians (>20 yr practice) relied more on S-Cr (p=0.01). Nephrologists considered clinical SLE symptoms more relevant (p=0.002), while non-nephrologists outranked the U-Sed (p=0.004). RLN was believed to be due to persisting SLE disease activity (95.2%), drug non-compliance (77.4%) and renal scarring (56.5%). Non-compliance was addressed by asking the patient (80.6%) and usage of IV-medication (73.4%). 61.5% of all study participants administered a drug for at least 6 months before classifying LN as refractory, experienced physicians reassessed earlier (p=0.03). 1st line LN therapy is often MMF (61.6%), 2nd line therapy cyclophosphamide (total 42%, 36.8% Euro-Lupus, 5.2% NIH regimen). Rituximab is used as a 2nd and 3rd line treatment (23.1% and 13.3%, respectively).

Conclusions: There is a no consensus on when and how to assess treatment response in LN and a definition of RLN. Many causes can underly lack of efficacy, but often persistent disease activity is assumed and immunosuppressive therapy is escalated, while the awareness for other causes of RLN is limited. There is an unmet need for a consensus on definition and management of RLN.

FR-PO607

Lupus Podocytopathy: Comparison of Clinical Features and Renal Outcomes with Primary Forms Eduardo J.D. de Sa Carneiro Filho, Mariana Pigozzi Veloso, Marcella Martins Frediani, Lectícia Jorge, Cristiane B. Dias, Luis Yu, Viktoria Woronik. *Nephrology Div, Univ of São Paulo, Brazil.*

Background: Lupus podocytopathy (LP) is characterized by diffuse foot process effacement without peripheral capillary wall immune deposits and glomerular proliferation. It has been described in Systemic Lupus Erythematosus (SLE) patients with distinct features from classic proliferative nephritis, sharing similar characteristics with primary podocytopathies. This study aimed to compare clinical–morphologic features and renal outcomes between primary and lupus forms of Focal Segmental Glomerulosclerosis (LP/FSGS).

Methods: Retrospective unicentric analysis of 24 SLE patients who fulfilled the following 3 criteria were included as LP:[1] morphologic pattern resembling minimal change disease, mesangial proliferation or FSGS by light microscopy with negative immunofluorescence or only mesangial immune deposition;[2] absence of LN class III, IV or V; [3] presence of nephrotic syndrome. Sixteen LP/FSGS cases were randomly matched with 32 primary FSGS, NOS variant, according to age, gender and eGFR baseline clearance (MDRD simplified formula). Baseline, one year and final follow-up results were analyzed in both groups. Treatment proposed was based on KDIGO guidelines.

Results: At baseline LP global group showed an average age of 35 years, proteinuria 4.2±2 g/day, albumin 2.3±0.8 g/dL, Hb 11.8 g/L, C3 103 mg/dL, C4 20 mg/dL, creatinine 1.1±0.5 mg/dL and MDRD 84.9±38.8 mL/min/1,73 m2. FSGS subgroups clinical features and renal outcomes are summarized below.

	Primary FSGS (32)	LP/FSGS (16)
Baseline Features		
Age (y)	31± 14.9	34.8±11
Proteinuria (g/day)	8.31±0.98	4.6±0.79*
Cr (mg/dL)	1.28±0.9	1.28±0.93
Alb (g/dL)	2.08±0.9	2.1±0.9
Hb (g/L)	13.1±0.3	11.4±0.3*
Follow-up (months)	98	117
Remission		
Complete(%)	16(51)	8(57)
Parcial(%)	8(25)	2(14)
No response(%)	7(22)	4(28)
***p<0.05**		

Conclusions: Despite there was no difference regarding age, sex, fibrosis, albumin or treatment between subgroups, primary forms presented higher proteinuria (8.3g±0.9vs4.6g±0.7 p0.01), while LP subgroup lower Hb levels (11.4±0.3vs13.1±0.3 p0.004) with similar renal outcomes.

FR-PO608

Retinal Drusen in Patients with IgA Glomerulonephritis or SLE Judith A. Savige,[1] Peter D. Hughes,[3] Kathleen M. Nicholls,[3] Deb J. Colville.[1] *[1]Medicine and Nephrology, Univ of Melbourne, Melbourne, VIC, Australia; [2]Nephrology, Northern Health, Melbourne, VIC, Australia; [3]Nephrology, Royal Melbourne Hospital, Melbourne, VIC, Australia.*

Background: Drusen are deposits in the retina of immunoglobulins and Complement, that have an identical composition to glomerular deposits, and are associated with mutations in the Complement genes. Complement is implicated in the pathogenesis of IgA gn and SLE. We have found drusen in occasional patients with IgA gn or SLE and this study investigated how often they occurred in IgA gn and SLE, and any association with ESRD and common drusen-associated SNPs.

Methods: All subjects underwent non-mydriatic retinal imaging, and photographs were examined for drusen (more than 10 within 2 disc diameters of the macula). Control groups had FSGS or structural renal disease. Subjects also provided DNA for drusen-related SNP analysis, using the SEQUENOM iPLEX Assay at the Australian Genome Research Facility. SNPs included variants in genes in the Complement pathway (C2, C3, CFB, CFH, CFI and CD46), the purinergic system (P2RX4, P2RX7, PANX1) and other genes (TIMP3, APOE and ARMS). Statistical analysis was performed using SPSS.

Results: Thirty–nine subjects with IgA disease were studied including 32 with ESRD. Fifteen (38%) had central drusen. Thirty-two with SLE were studied including 17 (55%) with SLE nephritis and 6 (19%) with ESRD. Eighteen (58%) had drusen. Drusen were more common in subjects with IgA gn and SLE than with FSGS (3/38, 8%) or structural

renal disease (2/20, 10%) (p<0.0001). In IgA disease, drusen occurred more often in ESRD. One CFH SNP (p=0.03) and the CD46 S13F variants (p<0.01) were more common in IgA gn and ESRD than a normal cohort. In SLE the A353V variant in CD 46 was more common than in the normal cohort (p=0.03). There were trends for increased occurrence of the I272V variant in PANX1 (p=0.08) and the TIMP3 variants (rs9621532) (p=0.09) too.

Conclusions: Drusen are more common in IgA gn and SLE than in FSGS or structural renal disease. There is a possible increase with ESRD in IgA gn. GWAS suggest associations with Complement loci, and a CFH SNP was more common in patients with IgA disease and ESRD. Other drusen-associated SNPs may be important too.

Funding: Clinical Revenue Support

FR-PO609

Genetic Markers to Predict Progression of IgA Nephropathy in Caucasians
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Background: Genome–wide association studies indicate that IgA Nephropathy (IgAN) has a complex genetic architecture. In this study, we aimed to evaluate 4 tag single-nucleotide polymorphisms (tSNPs) in 129 patients with IgAN. Although these SNPs were found to be associated with risk of IgAN in Chinese cohort, the association signal has not been uniformly replicated in Turkish population.

Methods: A total of 129 IgAN patients (77 (59.7%) male, mean age: 36±13 years, median follow up of 25 months) were evaluated. The relationship between genetic markers (tSNPs; rs3803800, rs2738048, rs2412971, rs6677604) in 4 IgAN-associated genes (TNFSF13, DEFA, HORMAD2, CFH, respectively) and progression to kidney failure [category G5 chronic kidney disease (CKD)] were assessed.

Results: Kidney failure developed in 34 (26.4%) patients after a median follow up time of 25 months. Using the recessive model, we found that the genotype "AA" rs3803800 in TNFSF13 was associated with an increased risk of kidney failure in IgAN (OR = 2.52, 95% CI = 1.1-5.7, p = 0.018). Although not reaching statistically significance, the genotypes "GG" rs6677604 and "GG" rs2412971 were also associated with increased risk of kidney failure. The genotype "GG" rs6677604 was also found to be associated with higher T scores according to Oxford-MEST classification (p=0.04). The genotype "AA" rs3803800 was also found to be associated with higher S scores (p=0.04).

Conclusions: A new progression risk score for IgAN can be calculated based on these genetic markers including tSNPs in TNFSF13 and CFH genes to predict the risk of progression to kidney failure.

FR-PO610

Serum IgA/C3 Ratio: A Marker of Disease Activity in Patients with IgA Nephropathy
Kazuo Torikoshi,[1] Tomomi Endo,[1] Hiroyuki Suzuki,[1] Tatsuo Tsukamoto,[1] Eri Muso,[1] Takashi Yasuda,[2] Yoshinari Yasuda,[2] Tetsuya Kawamura,[2] Seiichi Matsuo.[2] *[1]Nephrology and Dialysis Center for Nephrology and Urology, Kitano Hospital, Tazuke Kofukai Medical Research Inst, Osaka, Japan; [2]Study Group of The Nationwide Retrospective Cohort Study in IgAN.*

Background: Serum levels of high IgA and low C3 through lectin and alternative pathway activation might relate the progression and exacerbation of IgA nephropathy (IgAN). The aim of this study were to examine 1) whether the serum IgA/C3 ratio serve as a marker of the progression in patients with IgAN and 2) the effect of tonsillectomy on the ratio.

Methods: 1) This nationwide multi-center retrospective study included 718 patients with biopsy-proven IgAN in Japan (mean follow-up of 6.5±2.9 years). The patients with doubling of serum creatinine at the time of renal biopsy were defined as progression. 2) After excluding those with insufficient serum IgA and C3 data at the end of observation period, 63 patients were subdivided either into 4 groups by therapy (control, tonsillectomy, steroid, and tonsillectomy and steroid pulse (TSP) group) or into 2 groups according to the change of IgA/C3 ratio from at the biopsy to the end of observation (6.1±2.8 years) (<15% decrease (non-improved) and ≥15% decrease (improved)).

Results: 1) Kaplan-Meir analysis of the patients with IgAN revealed that the group with high serum IgA/C3 (3.3 and above) had a significantly poorer renal outcome (p<0.05, log-rank test). In multivariate analysis of more than 4.45 years observation periods, renal end point of IgAN was significantly predicted by proteinuria≥1g/day (relative risk (RR)=2.11, 95% confidence interval (CI) 1.09-4.08), eGFR<60 (RR=7.30, 95% CI=3.40-15.6) and serum IgA/C3 ratio≥3.3 (RR=2.07. 95% CI=1.02-4.22). 2) Among the 4 groups divided by therapy, the serum IgA/C3 ratio and proteinuria were reduced only in the TSP group at the end of observation. The 2 groups divided along the change of ratio showed significantly higher percentage of complete remission of proteinuria in improved group than in non-improved (log rank=0.035).

Conclusions: The levels of serum IgA/C3 might reflect the disease activity and be a potent surrogate marker of the therapeutic efficacy in patients with IgAN.

Funding: Government Support - Non-U.S.

FR-PO611

IFI27/ ISG12A in Peripheral White Blood Cells Is a Useful Marker for IgA Nephropathy
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Background: IgA Nephropathy is most common primary glomerular nephritis not only in Asian, but also in Caucasians. The methods to identify IgA nephropathy without hospitalization had been required. DNA microarray analysis is useful to comprehensively identify up- or down-regulated genes in PBMCs of patients. To identify a useful marker for IgA nephropathy, we explore the peripheral white blood cells by DNA microarray methods.

Methods: Sequential 137 patients who underwent kidney biopsy and blood samples were collected from Osaka University Hospital or Kitano Hospital. These patients had been diagnosed totally by kidney biopsy, medical history and blood examinations. Peripheral white blood cells samples from first fifteen IgAN and eight MN patients were provided for DNA microarray compared with healthy volunteers. And other samples were provided for extended qRT-PCR analysis. The study was reviewed and approved by the Research Ethics Committee of Osaka University and Kitano Hospital.Written informed consent was obtained from all participants.

Results: IFI27(interferon (IFN)-alpha-inducible protein 27 gene = interferon-stimulated gene 12a protein (ISG12A))gene was identified as the gene which decreased in all 15 IgA nephropathy patients along with 8 membranous nephropathy (See Figure1). Then, extended quantitative RT-PCR revealed the gene expression decreased in 44 IgA patients out of 48 IgA nephropathy patients. Median expression levels of IFI27 gene in IgA nephropathy patients (see Figure group 2) significantly reduced than those in immune disorder diseases (group 3) including myeloma kidneys(p=0.019). The expression levels in IgA nephropathy patients were marginally less than those in other primary glomerular nephritis patients (group 2) ($P = 0.079$). These results suggest that reduced IFI27 mRNA level is a useful gene marker that can be measured using RNA from PMBCs.

Conclusions: We propose that IFI27 may serve a useful genetic marker to diagnose IgA nephropath using peripheral blood.

FR-PO612

Successfull Rituximab Treatment for Adult Patients with Severe IgA Vasculitis - Henoch-Schoenlein Purpura Nephritis (HSPN)
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Background: Corticosteroids alone or in combination with Immunosuppressive agents has been suggested to be effective in IgA vasculitis (IgAV)- Henoch-Schoenlein Purpura Nephritis (HSPN). However, optimal treatment remains controversial. Due to the putative role of B lymphocytes in the pathogenesis of IgAV, Rituximab (RTX) appears a potential therapeutic tool. We report a monocentric experience on the use of RTX in severe adult IgA-vasculitis with biopsy-proven nephritis.

Methods: Our series includes 5 adult patients (3 males and 2 females), age 21-70 years.

Patients (n°)	Gender	Age at diagnosis	Organ involvement	Follow-up
1	F	70	S, K, J°	8 years
2	M	21	A, K, S*	33 months
3	M	43	A,K, S, J°	18 months
4	F	26	K, S*, J	7 months
5	M	55	K, A, J, S	3 months

CS=corticosteroids, MMF= mycophenolate mophetil, IGIV=intravenous Immunoglobulins, Cyp= cyclophosphamide, CyA=cyclosporine, AZA=azathioprine, S=skin with (*) necrotic ulcers, A=abdomen, K=kidney, J=joint involvement with (°) frank arthritis

The diagnosis was achieved according to EULAR criteria. RTX (lymphoma protocol) was administered as a rescue therapy in 3 patients, previously given a conventional immunosuppressive therapy without benefits. Two patients received RTX as a front-line treatment. All had a severe cutaneous and kidney involvement (diffuse intra and extracapillary proliferation with fibrinoid necrosis). Three patients had abdominal pain (in two cases associated with bleeding) and 2 severe arthritis.

Results: All patients achieved a complete renal remission. One needed a maintenance RTX therapy due to cutaneous relapses. The follow-up ranged from 6 months to 8 years. No clinically relevant adverse events have been observed.

Conclusions: This is the first case series describing successful RTX treatment of adult HSPN, and underlines the role of B lymphocytes in the pathogenesis of IgAV. This is consistent with previously reported benefits of RTX in other forms of vasculitis, and emphasized the role of B lymphocytes in the pathogenesis of IgAV.

FR-PO613

Can Serum Levels of Galactose-Deficient IgA1 and IgG Autoantibodies Predict the Course of Disease in Czech Patients with IgA Nephropathy? Dita Maixnerova,[1] Chunyan Ling,[2,3] Stacy D. Hall,[3] Colin Reily,[3] Rhubell T. Brown,[3] Michaela Neprasova,[1] Jelena Skibova,[4] Miloslav Suchanek,[5] Jan Novak,[3] Vladimir Tesar.[1] *[1]Dept of Nephrology, General Univ Hospital, 1st Faculty of Medicine, Charles Univ, Prague, Czech Republic; [2]Longhua Hospital, Shanghai Univ of Traditional Medicine, Shanghai, China; [3]Depts of Microbiology and Medicine, Univ of Alabama at Birmingham, Birminghan, AL; [4]Statistical Unit, Inst of Clinical and Experimental Medicine, Prague, Czech Republic; [5]Univ of Chemical Technology, Prague, Czech Republic.*

Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis with serious prognosis leading to end-stage renal disease in 30-50% of patients. The diagnosis requires renal biopsy. Due to its inherent risks, non-invasive approaches are needed.

Methods: We examined 95 patients with biopsy-proven IgAN who were assessed at the time of diagnosis for renal function, proteinuria, microscopic hematuria, and hypertension, and followed-up clinically since then. Using serum samples collected the time of diagnosis, we determined levels of galactose-deficient IgA1 (Gd-IgA1) and IgG autoantibodies specific for Gd-IgA1 (IgGAb) using lectin and immunodetection methods. Spearman correlation coefficient was used for statistical analysis.

Results: Higher serum levels of Gd-IgA1 were associated with worse renal function (elevated serum creatinine) at the time of renal biopsy and during follow up ($r=0.223$ and $r=0.246$, respectively; $p<0.05$ for both). Higher serum levels of IgGAb correlated with higher degree of microscopic hematuria at the time of renal biopsy ($r=0.244$, $p<0.05$) and with worse renal function during the follow-up and at the end of the follow-up ($r=0.254$ and $r= 0.338$, respectively; $p<0.05$ for both).

Conclusions: Elevated serum levels of Gd-IgA1 and IgGAb may serve as markers of disease activity and/or decline of renal function and, thus, unfavorable prognosis in Czech patients with IgAN. Future tests in larger cohorts will determine whether these markers may provide diagnostic as well as prognostic information, enable monitoring of disease activity, and/or responses to treatment.

FR-PO614

IgA Nephropathy Is Associated with Elevated Levels of Renal BAFF and APRIL Deepak Kumar,[1] Rui Chang,[1] Chia Chi Sun,[1] Ivy A. Rosales,[2] A. Bernard Collins,[2] Rex Neal Smith,[2] Herbert Y. Lin,[2] Ravi I. Thadhani,[2] Julie Demartino.[2] *[1]TIP Immunology, EMD Serono Inc, Billerica, MA; [2]Div of Nephrology, Massachusetts General Hospital, Boston, MA.*

Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis, with up to 40% of patients progressing to end stage renal disease. Studies have shown that elevated levels of serum BAFF (B cell activating factor) and APRIL (A Proliferation Inducing Ligand) in IgAN are associated with severity of clinical and pathological disease features. Biologically, these cytokines also play a role in IgA class switch recombination in B cells. Further, a recent report showed that sera from IgAN patients can induce proliferation of renal mesangial cells, providing a mechanism for the pathogenesis of IgAN. However, the expression levels of BAFF and APRIL and their cognate receptors in the kidney during IgAN is not known.

Methods: Immunofluorescence (IF) staining was performed on kidney biopsies from 15 IgAN, 3 diabetic glomerulopathy (DG), 4 Minimal Change Disease (MCD) and 1 with no diagnostic abnormality (NDA).

Results: We report increased expression of APRIL by IF staining in both the glomerulus and tubular epithelial cells, and for BAFF in the glomerulus in kidney biopsies showing IgAN compared to biopsies showing DG, MCD and NDA. APRIL and BAFF staining in IgAN was also evident in interstitial CD68+ macrophages. Moreover, IF analysis of cognate receptors for BAFF and APRIL, such as B-cell maturation antigen (BCMA), transmembrane activator and CAML interactor (TACI) and BAFF-R, also showed increased expression in both tubular epithelial cells and glomerular parietal epithelial cells in IgAN compared to MCD. BCMA, TACI and BAFF-R staining was also evident in the interstitial CD20+ B cells.

Conclusions: Taken together, these data show increased tissue expression by immunohistochemical studies of BAFF, APRIL and their cognate receptors in kidney biopsies showing IgAN. Given the roles of BAFF and APRIL in autoantigen and/or autoantibody production in IgAN, this demonstrates the potential of BAFF and APRIL blockade in the treatment of IgAN.

Funding: Pharmaceutical Company Support - EMD Serono Research and Development Inst. Inc.

FR-PO615

Long Term Renal Survival in IgA Nephropathy with Crescents Kendral R. Knight, Dustin J. Little, Stephen W. Olson. *Walter Reed National Military Medical Center, Bethesda, MD.*

Background: The Oxford Classification (MEST criteria) established the impact of mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T) histopathology on renal survival for IgA nephropathy (IgAN). Outcomes have been reported for Asian patients with >50% crescents, but the prognostic implications of glomerular crescents (including 1-50% crescents) in an ethnically diverse population have not been reported.

Methods: We performed a retrospective cohort study of 136 biopsy confirmed IgAN cases identified in the military electronic medical record system from 2000 - 2015. The renal survival, defined by the absence of renal replacement therapy (RRT), of IgAN with 1-50% crescents was compared to both IgAN with >50% crescents, and IgAN without crescents. For secondary analysis, the incidence of a >25% decline in eGFR and progression to stage IV CKD were compared between IgAN cases with 26%-50% crescents and IgAN cases with 1-25% crescents .

Results: Renal survival of IgAN with 1-50% crescents was superior to IgAN with >50% crescents (89%; 49/55 vs. 25%; 3/12, $p<0.001$), and equivalent to IgAN without crescents (89% vs. 87%; 60/69, $p=0.79$) over a median (IQR) follow up period of 61 (24,110) months. There was no statistically significant difference between these groups for any component of the MEST criteria. A greater proportion of subjects with 26-50% crescents experienced a ≥25% decline in eGFR (44%; 7/16 vs. 13%; 5/39, $p=0.02$) and progressed to stage IV CKD (50% vs. 13%, $p=0.006$) than those with 1-25% crescents.

Conclusions: In this comprehensive analysis of the prognostic value of crescents, independent of MEST criteria, for renal outcomes in IgAN patients followed for median 5 years, IgAN with1-50% crescents had a renal survival superior to IgAN with >50% crescents and similar to IgAN without crescents. The subgroup of IgAN with 26-50% crescents experienced a more rapid decline in GFR and more often reached stage IV CKD than IgAN with 1-25% crescents. Future prospective immunosuppression therapy trials could be considered for IgAN patients with 26-50% crescents.

Funding: Other U.S. Government Support

FR-PO616

Renal Outcomes in Patients with IgA Nephropathy (IgAN) Undergoing Liver Transplant (LT) Musab S. Hommos, Ziad El-Zoghby. *Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.*

Background: Liver cirrhosis is the most common cause of secondary IgAN. Renal IgA deposition is thought to be a consequence of impaired removal of IgA-containing immunocomplexes by Kupffer cells in the failing liver. If this hypothesis is correct, IgAN should have favorable renal outcomes following liver transplant.

Methods: Included are 11 patients (9 males) with biopsy proven IgAN. 6 patients underwent LT and 5 patients underwent combined liver-kidney transplant (CLKT) with a mean age of 50 at transplant time (Tx). We collected the level of proteinuria, hematuria, GFR at time of transplant, 12 and 60 months after Tx. We also reviewed any kidney biopsy done after Tx.

Results: Results are summarized in Figure 1. All patients had hematuria prior to Tx. Patient 2 progressed to end stage renal disease 5 years post Tx. Patient 9 had histological recurrence of IgAN found on protocol kidney allograft biopsy done 4 months post CLKT without clinical features of IgAN. Patient 10 had recurrent IgAN 2 months post CLKT associated with heavy proteinuria of 2640 mg/day, but that resolved with the addition of angiotensin-converting enzyme inhibitor (ACEi) and GFR remained stable at last follow up.

ID	Tx Type	GFR at Tx	Proteinuria (mg/day) prior to Tx	Hematuria at 1 year post TX	Proteinuria (mg/day) at 1 year post Tx	Hematuria at 5 years post Tx	Proteinuria (mg/day) at 5 years post Tx
1	LT	66	91	Yes	197	No	184
2	LT	110	95	No	3570	No	4343
3	LT	17	450	No	715	No	1096
4	LT	31	459	No	44	No	227
5	LT	35	855	No	422	N/A	N/A
6	LT	54	1147	No	356	No	58
7	CLKT	17	7784	No	44	No	35
8	CLKT	12	206	No	120	No	66
9	CLKT	19	558	No	94	N/A	N/A
10	CLKT	14	46	Yes	374	Yes	95
11	CLKT	21	217	No	211	No	143

Conclusions: Previous reports suggest that IgAN in liver cirrhosis patients has a benign course following LT. However, our data shows that IgAN can progress to end stage renal disease following LT and can have early recurrence in kidney allograft following CLKT. It is possible that some patients with progressive disease have primary rather than secondary IgAN. Persistent hematuria and/or proteinuria > 1000 mg/day post-transplant may indicate recurrent or persistent IgAN and may identify patients who would benefit from aggressive supportive therapy, including treatment with ACEi to prevent poor renal outcomes.

FR-PO617

Clinical Presentation of IgA Nephropathy Is Changing Toward More Aggressive Forms Affecting Older Patients: Data from the Spanish Registry of Glomerulonephritis Eduardo Gutierrez-Martinez,[1] Manuel Praga,[1] Francisco Rivera,[2] Juan Manuel Lopez Gomez.[3] *[1]Nephrology, Hospital Univ 12 de Octubre, Madrid, Spain; [2]Nephrology, Hospital General de Ciudad Real, Ciudad Real, Spain; [3]Nephrology, Hospital Gregorio Marañón, on Behalf of All Members of the Spanish Registry of Glomerulonephritis, Madrid, Spain.*

Background: IgA nephropathy (IgAN) is the most common glomerulonephritis in the world, but there are few epidemiological data about possible changes in its presentation over the years. Also, available infomation about the influence of age on the form of clinical presentation is scarce.

Methods: Aim of the study was to analyze all renal biopsies performed between 1994 and 2013 and recorded in the Spanish Registry of Glomerulonephritis with histological diagnosis of IgAN. The study was divided into five 4 year-periods (1994-97, 1998-2001, 2002-2005, 2006-2009 and 2010-2013) and patients were divided into 4 age groups: children (<17 years), adults: (17-45 years) and (46-65 years), and elderly (>65 years).

Results: From 20,974 renal biopsies recorded, 2961 (14.1%) corresponded to IgAN. The prevalence of IgAN remained stable, but a significant increase in age [from 37.6 (17.7) in 1994-97 to 44.9 (16.8) years in 2010-13; p0.001] and worse renal function at presentation from [1.9 (1.9) to 2.3 (2.1) mg/dl; p 0.001] was observed over the years. Nephrotic range proteinuria and acute kidney injury (AKI) as forms of presentation were significantly more commmon among elderly patients (17.7 and 35.3%) as compared to adult patients (12.7 and 9.5%) and children (11.3 and 4.9%). AKI in elderly patients correlated with a significant increase in the frequency of gross haematuria over time (54.5% in 1994-97 to 70.6% in 2010-13; p 0.001). Blood pressure, serum creatinine, proteinuria and the incidence of CKD were also significantly higher at presentation among elderly patients.

Conclusions: Although the prevalence of IgAN in Spain has remained stable over the years, patients are significantly older and present with a significantly worse renal function. Elderly patients with IgAN have a remarkable incidence of nephrotic range proteinuria (17.7%) and gross-haematuria-related AKI (70.6%).

FR-PO618

Association of Recurrent Proteinuria Related to IgA Nephropathy with the Mesangial Hypercellularity Score and Grade of Proteinuria at Diagnosis Takayuki Fujii, Satoshi Suzuki, Mizuki Shinozaki, Kaiji Saito, Mayu Morimoto, Noriko Terasaki, Tanaka Hiroaki. *Kidney Center, Seirei Sakura Citizen Hospital, Sakura City, Japan.*

Background: The grade of proteinuria is important for predicting the renal prognosis of patients with IgA nephropathy. The renal prognosis of those with the remission of proteinuria is favorable. However, even when treatment leads to the remission of proteinuria, recurrence is often observed. Currently, there are no global guidelines defining the remission or recurrence of IgA nephropathy. We examined recurrence-associated factors, regarding patients with a urinary protein level of <0.3 g/day as achieving remission and those in whom remission could not be maintained for 6 months or more as showing recurrence.

Methods: Of 313 patients who were diagnosed with IgA nephropathy based on kidney biopsy findings, with an eGFR of ≥30 mL/min/1.73 m^2 and a urinary protein level of ≥0.5 g/day, and could be followed-up for 2 years or more, we conducted a retrospective cohort study in 155 with the remission of proteinuria. Regarding recurrent proteinuria as an outcome, we examined recurrent proteinuria-associated clinical/histopathological data and treatment using Cox's proportional hazard model.

Results: The mean follow-up period was 16.5±8.7 years. The mean daily urinary protein level on kidney biopsy was 1.0±0.9 g. The mean eGFR was 78.1±23.2 mL/min/1.73 m^2. Of the 155 patients with remission of proteinuria, recurrent proteinuria was noted in 68. Recurrent proteinuria was associated with a urinary protein level of ≥1 g/day (HR: 2.78, 95%CI: 1.40-5.37) and mesangial hypercellularity score (M) =1 according to the Oxford classification (HR: 1.99, 95%CI: 1.06-3.58). On the other hand, steroid therapy was useful for maintaining the remission of proteinuria (HR: 0.37, 95%CI: 0.18-0.75).

Conclusions: Recurrent proteinuria in patients with IgA nephropathy was associated with a urinary protein level of ≥1 g/day at diagnosis and M1 according to the Oxford classification.

FR-PO619

The Clinical and Histopathological Difference of IgA Dominant Infection-Related Glomerulonephritis from Those of IgA Nephropathy: A Single Center Study Takaya Handa, Hiroyuki Suzuki, Eri Muso, Tatsuo Tsukamoto. *Nephrology, Kitano Hospital, The Tazuke Kofukai Medical Research Inst, Osaka, Japan.*

Background: IgA dominant infection-related glomerulonephritis (IgA-IRGN) is a unique form of IRGN histologically resemble to IgA nephropathy (IgAN). However, IgA-IRGN should be discriminated because of the difference of the clinical course. We compared both using a database of our hospital.

Methods: We extracted 15 patients with IgA-IRGN, whose clinical and pathological findings were matched the previous paper (Kidney Int2013;83,792-803), and 122 patients with IgAN as control from 1788 patients who underwent kidney biopsy from 2000 to 2015 in our hospital. To rise the characteristic surface of IgA-IRGN, we took several clinical and pathological parameters, including age, laboratory findings, and histological observation with light microscopy, immunofluorescence, and electron microscopy, and compared with those of IgAN. We further examined the prognosis of IgA-IRGN by the all-cause mortality and end stage renal disease.

Results: IgA-IRGN showed higher proportion of elderly (26.7vs 5%;p<0.05), lower eGFR (53.8±25.7 vs 74.7±24.9 ml/min/1.73m2;p<0.05), heavier proteinuria (5.1±6.0 vs 1.1±2.1 g/day;p<0.05),and lower serum albumin (3.1±0.7 vs 3.9±0.4 g/dl;p<0.05). Endocapillary proliferation was common(93%vs36%,p<0.05),and immunogloburines(IgG, IgA ,IgM) and complements(C3c,C1q and C4c) were detected along the glomerular capillary more frequently(p<0.05) consistent with the dense deposits at both subendtohelial and subepithelial sites more frequently (p<0.05) .IgA-IRGN patients were more susceptible to acute kidney injury (54% vs 4%; p<0.01).The prognosis of IgA-IRGN patients was poorer (p<0.05). Using univariate analysis, the risk factors of IgA-IRGN were past history of diabetic mellitus, heavy proteinuria (>3.0g/day), IgG and C1q deposition along the glomerular capillary.

Conclusions: IgA-IRGN and IgAN showed different clinical course and histological findings in immune complex deposition. Involvement of glomerular capillary lesion and activation of multiple complement pathway might influence on the prognosis in IgA-IRGN.

FR-PO620

Complement Factor H Gene Polymorphism rs6677604 and the Risk, Severity and Progression of IgA Nephropathy: A Systematic Review and Meta-Analysis See Cheng Yeo, Xinyang Liu, Adrian Liew. *Renal Medicine, Tan Tock Seng Hospital, Singapore.*

Background: Several studies reported an association between rs6677604 polymorphism and susceptibility to IgA nephropathy (IgAN), but attempts at validating this finding yielded inconsistent results.

Aim: We seek to clarify the association between complement factor H gene rs6677604 polymorphism and IgAN susceptibility, severity and progression.

Methods: Eligible studies were identified by a comprehensive database search. Meta-analyses were performed for rs6677604 allele frequency and the association with IgAN susceptibility. Subgroup analyses, publication bias, and sensitivity analyses were also conducted.

Results: 10 studies were included in the systematic review. Among them, four studies containing 10 datasets (15,617 IgAN-cases and 31,947 controls) were included in the quantitative meta-analysis. The pooled frequency of the minor allele (A) was significantly higher in Europeans than in Asians both in IgAN-cases (15.3% vs. 5.2%) and controls (21.3% vs. 6.4%), and the frequency in IgAN-cases was significantly lower than that in controls in both Europeans and Asians. Overall, a significant association was detected between rs6677604 and risk of IgAN – AA vs. GG: odds ratio (OR)=0.58, 95% confidence interval (CI) [0.48, 0.69]; AG vs. GG: OR=0.77, 95% CI [0.73,0.81]). In stratification by ethnicity, significant association between AA vs. GG and IgAN susceptibility was observed in Europeans (OR=0.56, 95%CI: 0.46-0.69) but not in Asians (OR=0.66, 95%CI: 0.46-1.04). No publication bias was observed. Systematic review did not reveal any association between rs6677604 polymorphism and IgAN severity/progression.

Conclusions: rs6677604-A allele was more prevalent in Europeans than in Asians. The presence of rs6677604-A allele significantly decreased IgAN susceptibility in Europeans, but this association was not confirmed in Asians. Not enough clinical evidence was found between rs6677604 polymorphism and IgAN severity/progression. Further functional studies are needed to validate the findings.

FR-PO621

First 1-Year GFR Decline Slope Can Identify High-Risk Patients in IgA Nephropathy Kyungho Lee, Eun Jeong Lee, Jung-Ho Shin, Hye Ryoun Jang, Jung Eun Lee, Wooseong Huh, Yoon-Goo Kim, Dae Joong Kim, Ha Young Oh. *Div of Nephrology, Dept of Medicine, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Korea.*

Background: IgA nephropathy (IgAN) is the most frequent primary glomerular disease and the leading cause of end-stage renal disease. This study investigated clinical and histologic predictors for renal survival in patients with IgAN with a focus on glomerular filtration rate (GFR) decline slope.

Methods: We screened all patients who diagnosed with primary IgAN between 1995 and 2012. Renal progression was defined as creatinine doubling. Using serial measurements of serum creatinine during the first 1 year, we calculated the GFR decline slopes. Then, we defined the patients with the steepest quartile of GFR slope as rapid decliner, those with the 2nd quartile of GFR slope as slow decliner and the others as non-decliner.

Results: Among 214 subjects, the age was 37 (28, 46), and baseline GFR was 81 (62, 100) mL/min/1.73 m^2. Both of them did not differ between the 3 groups. Rapid decliner and slow decliner had higher levels of protein/creatinine ratio (0.88, 0.89, and 0.58 g/g Cr respectively, P < 0.001) and higher score of tubular atrophy/interstitial fibrosis compared with non-decliner; 20.8%, 16.7 %, and 6.5 % in each groups showed score ≥1 (P = 0.007). Renal progression at 5 year was 76 % in rapid decliner, 91 % in slow decliner, and 100 % in non-decliner (P < 0.001, rapid or slow decliner vs non-decliner). After adjustment for sex, blood pressure, GFR, proteinuria, and histologic findings, slow decliner was associated with a 7.3-fold higher risk of progression (P = 0.017) and rapid decliner was associated with a 9.6-fold increased risk of progression (P = 0.006) compared with non-decliner. GFR slope value was also negatively associated with renal progression after adjustment for aforementioned covariates (P = 0.005).

Conclusions: First 1-year GFR slope was a predictor of renal progression, independently of proteinuria amounts and histologic findings. GFR slope can be incorporated to identify high-risk patients who need more aggressive treatment.

FR-PO622

Clinical Usefulness of the Oxford Classification in Determining Immunosuppressive Treatment in IgA Nephropathy Min-Uk Cha, Chang-Yun Yoon, Changhwan Seo, Hae-Ryong Yun, Seung Hyeok Han. *Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.*

Background: Although the Oxford classification has been widely used in IgA nephropathy, its clinical usefulness of determining immunosuppression is unknown. Here, we conducted an observational study to investigate whether the Oxford-MEST could predict the development of persistent proteinuria and worsening kidney function. We also evaluated the clinical effectiveness of corticosteroid treatment by the Oxford classification.

Methods: We studied 377 patients with early-stage IgA nephropathy who had proteinuria <1.0 g/g Cr and estimated glomerular filtration rate (eGFR) ≥50 ml/min/1.73m^2. The study endpoints were the development of a random urine protein-to-creatinine ratio of ≥1 g/g Cr and a 30% decline in eGFR during follow-up.

Results: The results showed that among the Oxford-MEST lesions, only M1 predicted the risk of the development of proteinuria ≥1.0 g/g Cr compared to other lesions in a

time-varying Cox model adjusted for multiple confounding factors. In addition, the risk of reaching a 30% decline in eGFR was significantly higher in patients with M1 than in those with M0. Furthermore, patients with M1 had a greater decline of eGFR than patients with M0. However, steroid treatment in M1 lesion was not associated with improving clinical outcomes in the unmatched and propensity score matched cohort.

Conclusions: The results showed that among the Oxford-MEST lesions, only M1 predicted the risk of the development of proteinuria ≥1.0 g/g Cr compared to other lesions in a time-varying Cox model adjusted for multiple confounding factors. In addition, the risk of reaching a 30% decline in eGFR was significantly higher in patients with M1 than in those with M0. Furthermore, patients with M1 had a greater decline of eGFR than patients with M0. However, steroid treatment in M1 lesion was not associated with improving clinical outcomes in the unmatched and propensity score matched cohort.

FR-PO623

Response of Patients with IgA Nephropathy to High Doses of Lisinopril and Omacor Ronald J. Hogg,[1] Ralph C. Bay,[2] Gerald B. Appel,[3] Daniel C. Cattran,[4] Fernando C. Fervenza,[5] Debbie S. Gipson,[6] Robert J. Wyatt.[7] *[1]Baylor, Scott & White Health, Temple, TX; [2]A.T. Still Univ, Mesa, AZ; [3]Columbia Univ, New York, NY; [4]Toronto General Hospital, Toronto, ON, Canada; [5]Mayo Clinic, Rochester, MN; [6]Univ of Michigan, Ann Arbor, MI; [7]Univ of Tennessee, Memphis, TN.*

Background: Treatment for patients (pts) with IgA nephropathy (IgAN) using angiotensin converting enzyme inhibitors (ACEi) or omega-3 fatty acids (O3FA) has been described previously, but there are limited data describing results obtained when the two are combined in high doses.

Methods: Lisinopril 10-80mg, as tolerated, and O3FA (Omacor®) 4gm (EPA 1.88 g., DHA 1.48 g.), were given daily to 79 IgAN pts with urine protein to creatinine ratios (UP/C) ≥0.6 (males) or ≥0.8 (females) who were enrolled in a multicenter prospective clinical trial. We evaluated the efficacy of the therapy after 3-6 months in 29 pts who were not receiving pre-study ACEi and/or O3FAs. Complete remission (CR) of proteinuria = UP/C ≤ 0.20 g/g. Partial remission (PR) = UP/C < 0.6 (males), < 0.8 (females).

Results: The UP/C fell from 1.94±1.13 to 0.88±0.75 in the 29 pts. The decrease in UP/C was correlated with decrease in systolic BP (r=.441, p=0.02) and diastolic BP (r=.483, p=0.01). Seventeen of the 29 pts had a CR (n=5) or PR (n=12) after 3 months; an additional 3 pts had a PR after 6 months. The UP/C fell from 1.91±1.26 to 0.42±0.15 in these 20 pts. Three of the pts who did not have a PR at 3 months were randomized to mycophenolate and subsequent UP/C results were censored. The overall rate of CR or PR after 3 or 6 months was therefore 76.9% (20/26 pts). The UP/C fell by at least 50% in 18 of the 20 pts, giving an adjusted CR/PR rate of 69.2% of pts who fulfilled both of the criteria for a PR.

Conclusions: Based on this small sample size, high doses of Omacor® and lisinopril for 3-6 months induced at least a PR in 69.2-76.9% of IgAN pts depending on how PR is defined. These results appear to be better than those described in other recent trials of non-immunosuppressive therapy and suggest that a further trial of the combination therapy described herein should be considered.

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FR-PO624

Clinicopathological Features and Outcomes of IgA Nephropathy with Mild Proteinuria Xiang-Mei Chen. *Dept of Nephrology, Chinese PLA General Hospital, Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing.*

Background: Information about the outcomes of IgA Nephropathy is mostly based on patients in whom proteinuria are higher than 1–2 g/d at renal biopsy time. The clinicopathological features and outcomes of IgAN patients presenting with mild proteinuria are not well described. Therefore we conducted a study to investigate the clinicopathological features and outcomes of IgAN patients with mild proteinuria.

Methods: Primary IgAN patients with proteinuria less than 1g/d in our hospital from January 1995 to December 2014 were retrospectively reviewed. The clinical and pathological data at renal biopsy and follow-up informations were collected and analyzed.

Results: 510 IgAN patients with mild proteinuria were enrolled in this study. At biopsy, 32.7% of the patients were found to have hypertention and 32.3% had a history of macroscopic hematuria.Lee's Grade III was observed in 73.1% of the patients. Lee's Grade IV-V was observed in 7.7% of the patients. Of the Oxford Classification, M1 was observed in 30.4% of the patients, E1 was observed in 5.1% of the patients, S1 was observed in 69.6% of the patients, T1 was observed in 14.9% of the patients, and T2 was observed in 1.6% of the patients. After a median follow-up of 50 months, 4(0.8%)patients developed ESRD, 22 (5.85%) presented proteinuria levels >1 g/24 h, 31(6.1%)patients had eGFR decline ≥30% of the basline(not including ESRD). 45(8.8%) patients presented proteinuria ≥1g/d, only 82(16.1%) patients had complete clinical remisssion. Logistic regression revealed that time average-proteinuria(TA-P)(RR31.85, P=0.000) was the risk factor of renal function dererioration and ESRD. Age(RR1.53, P=0.022) and proteinuria(RR11.61, P=0.001) were the risk factors of sustained proteinuria ≥1g/d after biopsy.

Conclusions: Severe renal pathological lesions may be observed in some IgAN patients with mild proteiunuria. Renal outcome is dismal in IgAN patients with mild proteinuria. Life-long follow-up with regular monitoring of proteinuria ,blood pressure and renal function is important especially for older patients with more proteinuria.

FR-PO625

Mycophenolate Mofetil Treatment for Henoch-Schonlein Purpura Nephritis with Nephrotic Range Proteinuria Dmitry V. Samsonov,[1] Anna Zolotnitskaya,[2] Praveen N. Chander,[3] Robyn G. Matloff,[1] Tanya E. Pereira.[1] *[1]Pediatrics, New York Medical College, Valhalla, NY; [2]Pediatric, The Children's Hospital at Montefiore, Bronx, NY; [3]Pathology, New York Medical College, Valhalla, NY.*

Background: We present our experience with Mycophenolate Mofetil (MMF) as an adjuvant agent for treatment of severe childhood HSP nephritis with nephrotic range proteinuria.

Methods: A retrospective chart review was performed on all patients (N=65) referred to our clinic for HSP Nephritis 01/01/2001 - 12/31/2015. Patients with confirmed nephrotic range proteinuria (> 3 mg/mg creatinine) who were treated with MMF (N=9) were included in analysis. Biopsies were classified according to Oxford MEST-scores. MMF mean dosage was 1251 mg/m^2/day, median follow up was 115 weeks.

Results: Demographic characteristics, treatment, and response to therapy are summarized below

N	Age/ Gender	Biopsy	Treatment	Up/c at onset	Laboratory findings prior to MMF initiation / at last visit		
	yr.mo/ gender	Oxford Class	1 Solumedrol pulse 2 Oral steroids 3 MMF 4 Cyclophosphamide	mg/ mg	Up/c mg/ mg	Albumin g/dl	eGFR by CKID Schwartz ml/min/1.73m2
1	4. 8/M	M1E1S0T0	2,3	10.7	4.2 / 0.12	3.5 / 3.6	> 75 / >75
2	6.5/M	M1E1S0T0	1,2,3	8.5	5.9 / 0.18	3.8 / 4.0	> 75 / >75
3	6.8/F	M1E1S0T0	1,2,3	27	8.6 / 0.26	2.9 / 3.9	> 75 / >75
4	8.0/M	M1E1S0T0	1,2,3	22.3	26 / 0.22	1.8 / 4.6	50.3 / 75
5	10.10/M	M1E1S0T0	1,2,3	8.4	8.7 / 0.14	2.6 / 4.5	> 75 / >75
6	5.10/M	M0E1S1T0	2,3	4.6	2.5 / 0.11	3.7 / 4.5	> 75 / >75
7	6.3/F	M1E1S1T0	2,3	3.8	2.1 / 0.19	3.7 / 4.4	> 75 / >75
8	5.6/M	M1E1S0T0	1,2,3,4	19.9	18.2 / 0.35	1.6 / 4.6	57 / >75
9	7.6/F	M1E1S0T0	1,2,3	13.2	3.9 / 0.13	2.7 / 4.4	> 75 / >75

All patients had normal eGFR and up/c at last follow up. Mean duration of MMF therapy was 36 weeks. MMF was successfully withdrawn in 7 out of 9 patients at last follow up. Degree of proteinuria on presentation was correlated with time needed to achieve remission.

Conclusions: Our results indicate that MMF may be an attractive adjunctive agent for treatment of HSP nephritis with nephrotic range proteinuria.

FR-PO626

A Global Platform for Prediction Modeling in 4915 Patients with IgA Nephropathy from Asia, Europe and the Americas Sean Barbour,[1,7] Gabriela Espino-Hernandez,[8] Heather N. Reich,[2,7] Yusuke Suzuki,[5,7] Zhihong Liu,[6,7] Rosanna Coppo,[4,7] Daniel C. Cattran.[2,7] *[1]Univ of BC; [2]Univ of Toronto; [3]Oxford Univ Hospital; [4]Torino Univ Hospital; [5]Juntendo Univ; [6]Nanjing Univ; [7]For the International IgAN Collaboration; [8]BC Renal Agency.*

Background: Predicting renal outcome in IgA nephropathy (IgAN) is very challenging. A comprehensive prediction model is needed to guide clinical management, facilitate trial design and test the prediction benefit of new biomarkers. The lack of a sufficiently large and diverse cohort with standardized data collection have limited previous efforts in this area, and no current prediction model has been validated for use in diverse ethnic and age groups worldwide.

Methods: We merged 10 datasets from collaborators worldwide to create a large international database designed to derive and validate a comprehensive prediction model in IgAN. All patients have biopsy-proven disease with Oxford MEST histology scores, and detailed baseline and longitudinal clinical, medication and laboratory data.

Results: The dataset includes 4915 patients from research groups in China, Japan, Europe and North/South America. This includes 1734 Caucasian, 1654 Chinese and 1338 Japanese patients. Across datasets, median follow-up time ranges from 3.3-7.2 years, mean baseline eGFR from 64-120 ml/min/1.73m^2, proteinuria from 0.9-2.6 g/d and age from 13-40 years. The frequency of MEST scores is: M1 12-94%, E1 11-58%, S1 31-83%, T1 6-30% and T2 1-12%. 870 patients experienced a 50% reduction in eGFR or ESRD.

Conclusions: We have created the largest and most diverse dataset in IgAN to date based on a collaboration of international researchers. The size and granularity of data captured in this dataset will enable development of the first ever prediction model in IgAN (similar to a Framingham score) that will be valid across different age and ethnic groups, and can be implemented in clinical practice worldwide. While each of the individual datasets will be governed locally, the merged database has been standardized for use by the collaborative group for multiple research purposes. This approach serves as a prototype for international collaboration and generation of merged datasets to study other types of glomerular diseases.

FR-PO627

Clinicopathological Characteristics and Prognosis of IgA Nephropathy Patients with Hepatitis B Virus Infection Hongrui Shi, Mengjun Liang, Jiafan Zhou, Ning Su, Jiang Zongpei. *Dept of Nephrology, The Six Affiliated Hospital, Sun Yat-sen Univ, Guangzhou, China.*

Background: Some studies had found HBV played an important role in IgA nephropathy(IgAN).The aim of our study is to investigate clinicopathological characteristics and prognosis in IgAN patients with HBV infection.

Methods: We conducted a cohort study enrolling primary IgAN patients diagnosed by renal biopsy in our Hospital from Jan 2013 to Feb 2016.We compared clinicopathological characteristics between IgAN patients with or without HBV infection.Then the HBV-IgAN group was followed for a median of 14.2 months.Primary outcome was the decline of eGFR>25%.Secondary outcomes were remission of proteinuria and hematuria (defined as decline of proteinuria or hematuria>50%) and reactivation of HBV replication.

Results: There were146 patients eligible in our study,including 29 patients with HBsAg positive(19.9%).Patients in HBV-IgAN group were older (40.90±10.05yr vs.34.50±12.05yr, p=0.007),and had higher ALT level (26.38±14.72U/L vs.22.90±21.91U/L,p= 0.020),higher AST level (21.21±7.82U/L vs.18.64±9.90U/L, p=0.010),worse pathological grade (Lee IV+V,72.8% vs. 49.4%,p=0.040) and more thickness of vessel wall (100% vs. 81.9%,p=0.040).23 HBV-IgAN patients were followed up.10 patients (43.5%) had met the primary outcome,who had more serious renal injury (CKD4-5,50% vs. 0, p=0.007),more proteinuria in 24h(2.60±1.98g vs. 1.19±1.10g, p=0.017) and more interstitial infiltration (Oxford classification T2,66.7% vs.9.1%,p=0.028).Among 23 patients,9 of them got glucocorticoid or immunosuppressant therapy (GC group) and 14 of them received conservative therapy (CV group).In GC group,33.3% had met primary outcome;55.6% got remission of proteinuria;100% arrived remission of hematuria,while the ratio in CV group was 50.0%(p=0.67),30.8%(p=0.38) and 42.9%(p=0.018),respectively.The reactivation rate of HBV replication in GC group and CV group were 44.4% and 57.1% (p=0.68).

Conclusions: HBV-IgAN patients were 19.9% in our center.After follow-up,43.5% of the HBV-IgAN patients had met primary outcome.Glucocorticoid or immunosuppressant therapy may improve renal outcome of HBV-IgAN patients without obvious effect on reactivation of HBV replication.

FR-PO628

Long-Term Study of Cyclophosphamide, Leflunomide, Glucocorticoids and ACE-Inhibitors Treatment in IgA Nephropathy Shasha Chen, Li Wang, Guisen Li. *Renal Div and Inst of Nephrology, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, Chengdu, Sichuan, China.*

Background: Few studies are currently available about the efficiency and renal survival of IgA nephropathy (IgAN) treated with immunosuppressive agents.We retrospectively analyzed data from Chinese patients with IgAN to study long-term efficacy with different therapies, and explore the prognostic factors for recovery of renal function in patients with declining renal function.

Methods: 311 cases of biopsy-proven IgAN were retrospectively studied in this study. Outcome was renal function recovery (defined as improvement of creatinine by at least 30% or back to normal range). declining renal function.

Results: Cyclophosphamide group had a higher level of Scr (P<0.001), a lower level of eGFR(P<0.001), higher mesangial hypercellularity score (P<0.001), higher proportion of global and segmental glomerularsclerosis (P<0.001), more severe tubular atrophy/interstitial fibrosis lesions (P<0.001), severe interstitial lymphocyte and monocyte infiltration and most prominent vascular lesions (P<0.001) than other groups. Leflunomide group, Steroids+ACEI/ARB group and especially cyclophosphamide group had higher annual increase rate and value of eGFR, higher proportion of renal function recovery than ACEI/ARB group(P<0.001). 58.5%, 58.1%, 65.3% and 52.4% of cyclophosphamide group, leflunomide group, steroids+ACEI/ARB group and ACEI/ARB achieved renal function recovery. Multivariate regression analysis indicated that only eGFR (HR 1.094, P=0.027), gross hematuria (HR 0.045, P=0.016) and crescents (HR 0.677, P=0.049) were predictors for renal recovery.

Conclusions: Immunosuppressants (cyclophosphamide and leflunomide) played an important role in increasing renal recovery in IgA nephropathy patients with impaired renal function, especially in patients with crescents, vasculitic lesions on renal biopsy or massive proteinuria.

FR-PO629

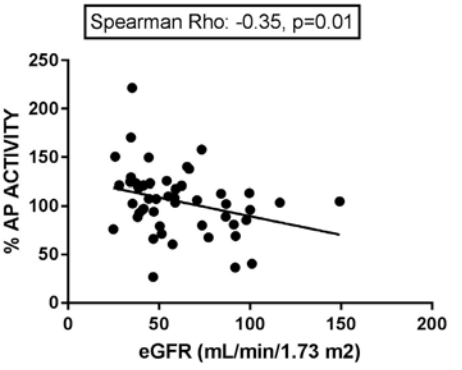
Alternative Pathway Activity in IgA Nephropathy Raad B. Chowdhury,[1] Magdalena Riedl,[5] Ping Lam,[1] Jennifer Gommerman,[1] Jan Novak,[2] Krzysztof Kiryluk,[3] Stuart Yang,[1] Sean Barbour,[4] Daniel C. Cattran,[1] Michelle A. Hladunewich,[1] Rulan S. Parekh,[5] Elisa Porfilio,[1] Bryan Coburn,[1] David Guttman,[1] Scott Gray-Owen,[1] Harindra Rajasekeran,[1] Christoph Licht,[5] Heather N. Reich.[1] *[1]UHN, Univ of Toronto; [2]Univ of Alabama; [3]Columbia Univ; [4]Univ of British Columbia; [5]Hospital for Sick Children.*

Background: A hallmark of IgA nephropathy (IgAN) is mesangial and circulating immune complexes containing aberrantly glycosylated IgA1 an anti-glycan antibody and C3. Recent GWAS suggest a common deletion of *CFHR1* and *CFHR3* as protective variant in IgAN. Deficiency of CFHRs results in functional surplus of CFH, a key regulator of the complement alternative pathway (AP), suggesting a functional role for the AP in IgAN pathogenesis. We evaluated functional differences in systemic AP activity in patients with IgAN hypothesizing that AP activity is increased in IgAN due to CFH dysfunction.

Methods: 52 IgAN and 38 healthy subjects were examined. AP activity was quantified via ELISA (Wieslab) detecting terminal C5b-9 generation after pathway-specific activation. CFH function was evaluated via hemolysis assay using sheep erythrocytes. Complement activity was correlated with clinical measures of disease activity including proteinuria and renal function.

Results: We did not observe an increase in systemic AP activity in IgAN compared with healthy controls with the Wieslab ELISA nor the hemolysis assay (p>0.05). In IgAN AP activity was inversely correlated with renal function (eGFR) (Spearman r=-0.35, p=0.01). There was no correlation with proteinuria.

Conclusions: We did not observe increased systemic AP activity in our IgAN cohort although we did find an inverse correlation with kidney function. If studies in a larger cohort confirm these results it is possible that AP dysregulation in IgAN is more important locally (at the cell surface) than systemically (fluid phase). Genotype and measures of AP proteins will be evaluated next.



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

FR-PO630

Altered Expression of *O*-Glycan Biosynthetic Enzymes in IgA1-Producing Cell Lines from Patients with IgA Nephropathy (IgAN) and Their Family Members Hiroyuki Ueda,[1,2] Yoshimi Ueda,[1,2] Colin Reily,[1] Zina Moldoveanu,[1] Stacy D. Hall,[1] Karen Hart,[1] Dana Rizk,[1] Krzysztof Kiryluk,[3] Ali G. Gharavi,[3] Takashi Yokoo,[2] Bruce A. Julian,[1] Jan Novak.[1] *[1]Univ of Alabama at Birmingham; [2]The Jikei Univ School of Medicine, Japan; [3]Columbia Univ College of Physicians and Surgeons.*

Background: Familial (F) and sporadic (S) IgAN patients (IgANP) have elevated levels of serum galactose-deficient IgA1 (Gd-IgA1). Moreover, 50% of the first-degree relatives of F-IgANP have high serum Gd-IgA1 levels, ≥95th percentile of healthy controls (HC) without any clinical sign of IgAN. These serum Gd-IgA1 levels are longitudinally stable in most individuals. We have previously generated immortalized IgA1-producing cell lines (IgAPC) from S-IgANP and HC as a model system for analysis of IgA1 *O*-glycosylation pathways. Cells from IgANP secrete more Gd-IgA1 than do the cells from HC; this aberrant *O*-glycosylation is associated with aberrant expression of key glycosyltransferases (GTs) involved in the biosynthesis of *O*-glycans. Here, we generated IgAPC from a pedigree with F-IgAN and characterized their gene-expression patterns for C1GalT1 and *O*-glycan branching enzymes (GCNTs).

Methods: The pedigree includes 4 IgANP. We generated IgAPC from blood relatives with serum Gd-IgA1 levels >95th percentile of HC (high-Gd-IgA1 relatives; n=8), IgANP (n=2), and marry-ins (n=7). Expression levels of selected genes were determined by qRT-PCR.

Results: IgAPC from high-Gd-IgA1 relatives and IgANP secreted more Gd-IgA1 compared to those from marry-ins; Gd-IgA1 serum levels correlated with the degree of galactose deficiency of IgA1 secreted by the cell lines of corresponding donors. qRT-PCR analysis revealed that expression levels of *C1GALT1*, *COSMC*, and *GCNT1, 3,* and *4* in cells from high-Gd-IgA1 relatives and IgANP were lower compared to those in cells from marry-ins. Moreover, expression levels of *C1GALT1* and *GCNT1, 3,* and *4* negatively correlated with serum Gd-IgA1 levels.

Conclusions: Our studies revealed abnormal expression of multiple GT genes in IgAPC from IgANP and their relatives at risk of IgAN. These aberrancies affected *C1GALT1* as well as genes of *GCNT* family. Expression of these GTs correlated with the degree of IgA1 galactose deficiency.

FR-PO631

Clinical Significance of Histopathology in C3 Glomerulopathy (C3G) Pietro A. Canetta,[1] Dominick Santoriello,[2] Andrew S. Bomback,[1] Rupali S. Avasare,[1] Vivette D. D'Agati,[2] Glen S. Markowitz,[2] Gerald B. Appel.[1] *[1]Nephrology Div, Columbia Univ, New York, NY; [2]Renal Pathology Div, Columbia Univ, New York, NY.*

Background: C3G is defined by glomerular lesions containing C3 with little or no immunoglobulin (Ig). The relationship between histology, clinical features, and prognosis has not been studied in a large US series.

Methods: We examined histologic and clinical features of 66 patients (pts) with biopsy (bx) and followup data at our center. Each initial bx was re-scored for light microscopic

(LM) pattern of injury, immunofluorescent (IF) staining, and deposit location by electron microscopy (EM). A combined endpoint of 2x creatinine, GFR <15 or transplant was studied by logistic regression.

Results: Median GFR at bx was 62 ml/min (IQR, 39-135) and proteinuria was 2.8 g/gCr (1.2-5.4). LM patterns included membranoproliferative (MPGN, 55%), mesangioproliferative (MesGN, 23%), diffuse proliferative (12%), and diffuse sclerotic (11%). MPGN pts were youngest (22±16y); MesGN pts were older (45±25y, P<0.01) and had the least proteinuria (median 1.3 *vs* 3.2 g/gCr, P<0.01). By IF, C3 was the only immunoreactant in 47%; these pts were older than pts with any Ig (37±23 *vs* 23±14y, P=0.01) and had lower GFR (median 41 *vs* 106, P=0.01). By EM, 28% had dense deposit disease (DDD) and 72% had C3 glomerulonephritis (C3GN). DDD pts were older than C3GN (39±21 *vs* 26±18 y, P<0.01) and had a suggestion of lower GFR (P=0.07) but similar proteinuria. Rare variants of *C3*, *CFH*, *CFHR5*, or *CFI* were found in 11/48 and were not associated with LM/IF/EM pattern. A paraprotein was found in 12/25 and when present was associated with DDD (OR 6.7, P<0.05). Over a median 38 months (13-117), 35% reached the endpoint. Univariable outcome predictors included GFR at bx, global and segmental glomerulosclerosis, and IFTA. Achieving a 50% fall in proteinuria lowered risk of the endpoint (OR 0.11, P<0.01). MesGN had marginally significant lower risk (OR 0.22, P=0.07). In multivariable analysis, only GFR was significant.

Conclusions: C3G histology had important associations with age onset, disease severity, and other clinical features (such as DDD with paraproteins), but for predicting prognosis the effect of GFR dominated.

FR-PO632

Recurrent C3GN and Dense Deposit Disease (DDD) in the Renal Allograft Wooin Ahn, Renu Regunathan-Shenk, Rupali S. Avasare, Pietro A. Canetta, Andrew S. Bomback, Gerald B. Appel. *Internal Medicine, Columbia Univ Medical Center, New York, NY.*

Background: C3 glomerulopathy (C3G) is a GN associated with dysregulation of the alternative complement pathway, histologically categorized as either DDD or C3GN. There are few studies of transplantation in C3G, none comparing C3GN to DDD, and little data on the effect of eculizumab in recurrent C3G.

Methods: We retrospectively reviewed the charts of 19 patients (pts) with biopsy-diagnosed C3G evaluated at Columbia University Medical Center, who'd received a renal transplant (txp). We analyzed their clinical and laboratory presentation, and post-txp outcomes.

Results: Of the 19 pts receiving allografts 12 had C3GN and 7 DDD. There were 14 males and 5 females with a median age at diagnosis of 27(range 7-60) and at transplantation of 30 (range 17-70). Mean time from biopsy to ESRD was 64 months (range 5-191). 2/17 pts evaluated for genetic defects had variants in *MCP* or *CFHR5*. 3 had C3 nephritic factor and 3/7 tested had a monoclonal protein. 15 pts received allografts from live donors (10 related). Prior to txp 9 pts were on HD (mean 31 mo) and 2 on PD (mean 5 mo). Available HLA typing revealed 4/9 pts had DR17-DQ2, known to be associated with autoimmune disease. Pts were followed for a mean of 82 mo post txp. Total graft failure was 3/12 (25%) in C3GN and 6/7 (86%) in DDD. 1 DDD pt had immediate graft failure. For-cause biopsy revealed recurrence in all 6 remaining (100%) DDD pts by 15 mo (range 2-32) and in 10/12 (83%) C3GN pts by 42 mo (range 0-212).Graft failure occurred in 3/10 (30%) recurrent C3GN pts at a mean of 62 mo and 5/6 (83%) of recurrent DDD pts at a mean of 47 mo. Graft failure was attributed to recurrence in 67% of recurrent C3GN pts and 60% of the DDD pts. 5 pts with recurrence (4 C3GN and 1 DDD) were treated with eculizumab, of which 3 had graft failure attributed to recurrence.

Conclusions: Our data confirm the frequent post-txp recurrence of C3G, despite immunosuppression. We also show similar recurrence rates and graft failures rates due to recurrence in C3GN and DDD. Total graft failure rate was higher in DDD. The potential beneficial effects of eculizumab for recurrent C3G await larger studies.

FR-PO633

C3 Glomerulonephritis and Dense Deposit Disease Share Similar Clinical Features, Genetics, and Disease Course Rupali S. Avasare,[1] Andrew S. Bomback,[1] Pietro A. Canetta,[1] Maddalena Marasa,[1] Yifu Li,[1] Ali G. Gharavi,[1] Richard J. Smith,[2] Dominick Santoriello,[3] Vivette D. D'Agati,[3] Glen S. Markowitz,[3] Gerald B. Appel.[1] *[1]Div of Nephrology, Columbia Univ Medical Center; [2]Molecular Otolaryngology and Renal Research Laboratories, Univ of Iowa; [3]Div of Renal Pathology, Columbia Univ Medical Center.*

Background: C3 glomerulopathy (C3G) includes both dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). Few large series, and no large US study, have defined the course of these entities. We reviewed our center's experience with C3G to compare the clinical presentations, genetics, and outcomes of patients with DDD and C3GN.

Methods: We reviewed charts of 100 patients with a diagnosis of C3G followed at Columbia University. The primary outcome was doubling of creatinine, ESRD, or death. Patients with C3GN and DDD were compared by two-tailed T test or Mann-Whitney U test (continuous variables) and Fisher exact test (categorical variables).

Results: Of 100 patients, 78 had C3GN and 22 had DDD. There were 63 men and 37 women with 66 non-Latino whites, 20 Latinos, 8 Asians, 5 Blacks and 1 other. Median age was 24 yrs (15 – 43). Median creatinine was 1.27 mg/dl (0.8 – 2.0). Median proteinuria was 2.8 g/gCr (1.5 – 5.1). Of 74 patients with whole exome sequencing or complement-cascade specific testing, 14 (19%) had rare variants in *C3*, *CFH*, *MCP*, *CFHR5*, or *CFI* genes, although some variants were of unknown significance. Seven of 35 (20%) and two of 24 (8%) patients had C3 nephritic factor and CFH Ab, respectively. Nineteen of 32 (58%) patients had a monoclonal protein. Median follow-up time was 3.2 yrs (1.3 – 8.5). Therapies included steroids (n=65) and other immunosuppression (n=49). Forty-two patients reached the primary endpoint of doubling SCr, ESRD, or death: 32/78 (41%) in the C3GN group and 10/22 (45%) in the DDD group (p=0.6).

Conclusions: In 100 US patients, we found no major differences in clinical presentation, diagnostic workup, or outcomes between C3GN and DDD. Our detection rate for mutations and autoantibodies was lower than in previous reports. C3GN and DDD share not only a common pathogenesis but also a common course. The value of distinguishing between the two should be examined in future studies.

FR-PO634

Clinicopathological Features in Patients with Amyloidosis and Low Serum C3 Level Bernardo V. Reichert, Lectícia Jorge, Precil Diego Miranda de Menezes Neves, Cristiane B. Dias, Luis Yu, Viktoria Woronik. *Nephrology, Univ of São Paulo, São Paulo, SP, Brazil.*

Background: The complement system play an important role in the pathogenesis of different glomerulopathies. Recently, we have observed patients with amyloidosis and low serum C3 level. As far as we know, no study have specifically studied the complement levels in patients with amyloidosis. The aim of this study was to describe subjects with kidney amyloidosis and low serum C3 as well as compare them with those who present normal levels of C3.

Methods: We performed a retrospective study by reviewing clinical and histological data of amyloidosis patients submitted to renal biopsy at our center from 1999-2016. Decreased serum C3 levels (hypoC3) was defined as C3<90mg/dl. Of 47 patients, 9 were excluded by insufficient data.

Results: Of the patients, there were 9 patients with hypoC3(24%). In hypoC3, the type of amyloid was Ig amyloidosis in 6 patients(67%), AA amyloidosis (secondary b hepatitis) in 1(11%), familiar amyloidosis in 1(11%) and unclassified in 1(11%). In normalC3, the type of amyloid was Ig amyloidosis in 20 patients(69%), AA amyloidosis in 2(7%), familiar amyloidosis in 2(7%) and unclassified in 5(17%). The data are summarized in table 1.

Clinical and Histological Features		
	HypoC3(n=9)	NormalC3(n=29)
Age(y)	53.6±14.1	55.4±12.8
Male	5 (56%)	12 (42%)
Creat In(mg/dl)	4.1±2.9	1.6±0.7*
CKD EPI in	28±34	68±35*
Albumin(g/dl)	2.4±0.9	1.8±0.7
Proteinuria(g/day)	5.5±2.3	8.9±5.2*
C3 Level(mg/dl)	62±14	144±57*
Hemoglobin(g/dl)	10.4±0.5	12.6±2.3*
Hematuria n(%)	2(22%)	6(20%)
Mesangial C3 Deposition n(%)	6(75%)	7(25%)*
Follow up(y)	0.6±0.9	2.3±2.4*
ESRD	6(67%)	5(25%)*
*p<0.05		

Interestingly, hypoC3 was significantly associated with a lower CKD EPI, lower hemoglobin and a higher rate of mesangial C3 deposition, suggesting a more severe manifestation of the disease in hypoC3 subjects.

Conclusions: In our study, the presence of hypocomplementemia was associated with a worse renal prognosis and a greater mesangial deposits of C3 in renal biopsies in patients with amyloidosis. More studies are needed to clarify the role of the complement system in amyloidosis.

Funding: Government Support - Non-U.S.

FR-PO635

Mycophenolate Mofetil in C3 Glomerulopathy: Is It Really Effective? Ege Sinan Torun,[1] Tarik Onur Tiryaki,[1] Aysegul Oruc,[2] Yasemin Ozluk,[3] Halil Yazici,[1] Mehmet S. Sever,[1] Yasar Caliskan.[1] *[1]Dept of Internal Medicine Div of Nephrology, Istanbul Univ Istanbul Faculty of Medicine, Istanbul, Turkey; [2]Dept of Internal Medicine Div of Nephrology, Uludag Univ Faculty of Medicine, Bursa, Turkey; [3]Dept of Pathology, Istanbul Univ Istanbul Faculty of Medicine, Istanbul, Turkey.*

Background: This study aimed to evaluate the effect of immunosuppressive treatment on C3 glomerulopathy (C3G) progression.

Methods: A total of 68 patients [37 male, mean age:36±16 years] with C3G were enrolled. Patients with a baseline GFR value ≥30 mL/min and a minimum follow up of 6 months were assigned to mycophenolate mofetil (MMF) based (n=22) or non-MMF based (cyclophosphamide or azathioprine) (n=18) or conservative care (ACE inhibitors or ARBs) (n=12) treatment groups. The study groups were similar regarding age, gender, systolic blood pressure (BP), hemoglobin, serum albumin, proteinuria and eGFR at the time of biopsy. Patients in the MMF or non-MMF based groups received low-dose daily corticosteroids. The relationship between study groups and composite kidney failure events (defined as ESRD or a two-fold increase in serum creatinine level as compared to baseline) was assessed.

Results: Composite kidney failure events developed in 13 (25%) and ESRD developed in 10 (21.2%) patients after a median time of 40 months. The number of patients developing composite kidney failure events were similar among the study groups (MMF based group: 22.7%, non-MMF based group: 16.7%, conservative care group: 41.7%, p=0.29). In Cox

regression analysis, age (HR:0.863, p=0.003), proteinuria at the time of biopsy (HR:1.86, p=0.005) and eGFR (HR:0.923, p<0.001) at baseline were the clinical markers and the presence of crescents was the histopathological marker (HR 1.41, p=0.002) which predicted the composite kidney failure events.

Conclusions: In the present study, immunosuppressive treatment, particularly MMF based regimen was not found to be superior to conservative care in delaying the progression of C3G. Age, proteinuria and eGFR at the time of biopsy as clinical markers and the presence of crescents as a histopathological marker predicted the progression to ESRD.

FR-PO636

Progression of Chronic Kidney Disease in Alport Syndrome: Interim Data from the Athena Study Oliver Gross,[1] Gerald B. Appel,[2] James F. Simon,[3] Bertrand Knebelmann,[4] Paul C. Grint,[5] Jacqueline Blem,[5] Michael Huang,[5] Michelle N. Rheault.[8] *[1]Univ Medicine Goettingen, Goettingen, Germany; [2]Columbia Univ Med Center, NY; [3]Cleveland Clinic, Cleveland; [4]Hopital Necker, Univ Paris Descartes, Paris, France; [5]Regulus Therapeutics, San Diego; [6]Regulus Therapeutics, San Diego; [7]Regulus Therapeutics, San Diego; [8]Univ Minnesota Masonic Children's Hosp, Minneapolis.*

Background: Alport syndrome (AS) is a genetic kidney disorder resulting in capillary glomerular basement membrane defects, leading to end stage renal disease. The natural progression of chronic kidney disease (CKD) in AS is not well studied and biomarkers to predict CKD progression are lacking. The current study characterizes the natural decline in renal function in AS patients over 120 weeks.

Methods: ATHENA (NCT02136862) is a non-interventional, global, multicenter study enrolling 250 AS patients. Eligibility criteria include: age ≥12 years, confirmed diagnosis of AS, and glomerular filtration rate (GFR) between 30-90 ml/min/1.73m2. Patients with previous renal transplantation are excluded. Renal biomarkers and estimated GFR (eGFR) are assessed at baseline and every 12 weeks. mGFR is assessed at baseline and every 24 weeks.

Results: Interim analysis included 113 enrolled patients, with 69 and 33 patients through 24 and 48 weeks of follow-up, respectively. At baseline, mean age was 44.8 years (SD 15.2), 65% of patients were female, and 82% were white. Genetic analysis revealed 65% had X-linked AS. Baseline mean mGFR and eGFR (MDRD) were 55.2 and 58.5 ml/min/1.73m^2, respectively. At week 24 and 48, mean mGFR change from baseline was -0.61 and -2.19 ml/min/1.73m^2 and mean eGFR (MDRD) change from baseline was -1.27 and -2.83 ml/min/1.73m^2, respectively, compared to baseline. No clear trends in other blood or urine biomarkers were observed during 24 and 48 weeks of follow-up.

Conclusions: In this first prospectively designed natural history study of AS, interim data show a measurable decline in GFR by 24 and 48 weeks. With no currently approved therapies for AS, these data may have important implications for the design of future therapeutic clinical trials. Enrollment and analysis of ATHENA is ongoing.

Funding: Pharmaceutical Company Support - Regulus Therapeutics

FR-PO637

Rates of Kidney Transplantation across Glomerulonephritis Subtypes in the United States Michelle M. O'Shaughnessy,[1] Sai Liu,[1] Maria E. Montez-Rath,[1] Richard A. Lafayette,[1] Wolfgang C. Winkelmayer.[2] *[1]Stanford Univ, Palo Alto, CA; [2]Baylor College of Medicine, Houston, TX.*

Background: Whether access to kidney transplantation differs by cause of ESRD, and specifically by glomerulonephritis (GN) subtype, has rarely been explored.

Methods: Using the US Renal Data System, we identified all adult patients with ESRD attributed to 1 of 6 GN subtypes or 1 of 2 non-GN comparator groups (see table) who initiated dialysis in the US (1996-2011). Using Cox proportional hazards regression, with death as a competing risk and follow-up to end of 2011, we estimated hazard ratios [HRs (95% confidence intervals)] for first kidney transplantation (IgAN=reference). Models were adjusted for baseline demographics, comorbidities, and socioeconomic factors, as well as Organ Procurement Organization (OPO; actual or geographically most proximate).

Results: Among 632,908 patients, considerable heterogeneity in transplant rates across GN subtypes existed:

	Median f/u, yrs	Deceased Donor TX, %	Living Donor TX, %	Death before TX, %	Censored, %
FSGS, n=27,036	2.7	22.1	11.7	32.6	33.7
IgAN, n=9,828	2.8	26.9	24.2	17.3	31.6
MN, n=5,356	2.0	17.9	11.3	38.2	32.7
MPGN, n=3,977	2.7	19.3	12.7	39.6	28.4
LN, n=14,161	2.4	17.6	11.7	36.7	34.0
Vasculitis, n=5,277	2.4	10.7	8.8	47.2	33.4
DN, n=540,753	2.4	6.0	3.0	61.4	29.6
ADPKD, n=26,520	2.5	30.0	11.8	26.8	31.4

FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; MN, membranous nephropathy; MPGN, membranoproliferative GN; LN, lupus nephritis; DN, diabetic nephropathy; ADPKD, autosomal dominant polycystic kidney disease; TX, transplant.

After adjusting for case-mix and OPO, patients with FSGS, LN, vasculitis, or DN had lower rates of kidney transplantation than those with IgAN [HRs 0.83 (0.76-0.90), 0.70 (0.63-0.78), 0.70 (0.59-0.82), and 0.48 (0.44-0.53), respectively], whereas those with MN, MPGN, or ADPKD had similar rates [HRs 1.07 (0.93-1.23), 0.88 (0.75-1.02), and 0.96 (0.87-1.04), respectively].

Conclusions: Identifying underlying reasons for these apparent disease-specific barriers to kidney transplantation may improve pre-transplant patient counseling, recipient selection procedures, and organ allocation policy.

FR-PO638

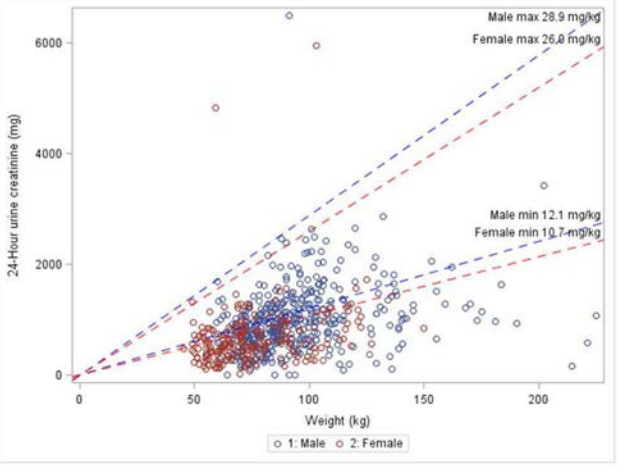
Unexpectedly Low 24-Hour Creatinine Excretion amongst Patients with Biopsy-Proven Glomerular Diseases Marie C. Hogan, Heather N. Reich, Peter J. Nelson, Sharon G. Adler, Daniel C. Cattran, Gerald B. Appel, Debbie S. Gipson, Matthias Kretzler, Jonathan P. Troost, John C. Lieske. *Nephrotic Syndrome Study Network Consortium (NEPTUNE).*

Background: Urine creatinine excretion (UCrE) is often used to assess accuracy of timed urine collections. Urinary analytes are also often normalized to UCr concentration.

Methods: Data from 666 unique 24 hr urine collections of 226 adults collected at protocol visits in the NEPTUNE cohort were available for analysis (minimal change 60, Focal sclerosis 91, membranous 60, other 91). UCr was analyzed in batches in a centralized laboratory by enzymatic creatinase assay.

Results: Total UCrE was systematically lower than typical reference ranges independent of weight (Figure). Overall among NEPTUNE adult patients, the measured UCrE was systematically 50% lower than predicted by a recently published equation (Ix and Wassel; CJASN 6:184-191,2011). A model using repeated measures ANOVA for 48 patients with 3 or more available values supported internal consistency of UCrE by subject (P=0.50). CKD stage influenced creatinine excretion with 37% at CKD stage 1 within the predicted UCrE range while only 24% were at CKD stage 4 (P<0.001). UCrE did not associate with serum albumin, but correlated with baseline steroid exposure (OR=1.5; p=0.02). However, when UCrE was stratified by exposure (on steroids one, both, or neither collection) intra-patient correlations did not vary.

Figure. Correlation of individual patients' 24-hour urine creatinine excretion (mg/ weight kg) for all adult NEPTUNE samples (n=226 patients/ 666 observations). Reference lines denote published 95% reference ranges for UCrE (Junge et al. Clin Chim ACTA 344: 137-148, 2004).



Conclusions: Patients with these biopsy proven glomerular diseases appear to have reduced creatinine generation. The reasons are unclear, but reduced muscle mass related to CKD likely plays some role. These results have implications for interpretation of both random and timed urine collections.

Funding: NIDDK Support, Private Foundation Support

FR-PO639

Glomerular Disease Frequency Distributions by Continent - Results from the International Kidney Biopsy Survey Michelle M. O'Shaughnessy,[1,2] Susan L. Hogan,[2] Bawana Donna Thompson,[2] Rosanna Coppo,[3] Agnes B. Fogo,[4] J. Charles Jennette.[2] *[1]Stanford Univ, Palo Alto, CA; [2]Univ of North Carolina, Chapel Hill, NC; [3]Regina Margherita Hospital, Turin, Italy; [4]Vanderbilt Univ Medical Center, Nashville, TN.*

Background: Large-scale studies comparing glomerular disease frequencies across continents are lacking.

Methods: We surveyed 29 nephropathology laboratories in 4 continents using a standardized form to obtain kidney biopsy diagnosis frequencies in recent consecutive years, along with population demographics for each diagnosis. If a specimen had multiple diagnoses, each was coded separately. This report focuses on glomerular disease frequencies by region and race/ethnicity. Cooperation was received from ASN-GDAG, RPS, and ERA-EDTA Immunonephrology Working Group.

Results: Diagnosis frequencies differed significantly by continent:

Glomerular disease frequencies by continent (n=41,527). Numbers represent %.				
	USA/Canada (10 centers) n=23,189	**Europe (14 centers) n=15,042**	**Asia (2 centers) n=1,609**	**Latin America (3 centers) n=1,687**
Focal Segmental GS[1]	19.2	14.9	6.9	21.8
IgA nephropathy[1]	11.7	22.1	39.5	6.8
Diabetic GS[1]	19.0	7.0	10.7	3.3
Membranous GP[1]	11.7	12.5	10.1	14.1
Lupus GN[1]	9.7	10.1	16.8	26.2
Pauci-immune GN[1]	5.2	8.0	2.5	2.5
Minimal change disease[1]	4.2	6.4	3.4	10.0
MPGN/C3GP[1]	2.6	3.7	1.1	3.1
Amyloidosis[1]	2.2	4.4	0.9	1.7
Thrombotic microangiopathy[1]	2.8	2.2	0.8	1.1
Thin basement membrane GP[1]	2.2	1.4	3.1	0.7
Other[1]	9.5	7.3	4.2	8.7
[1]Chi-square p<0.004 (0.05/12). GS, glomerulosclerosis; GP, glomerulopathy; GN, glomerulonephritis.				

After stratifying by race/ethnicity, diabetic GS was more (17% *vs* 2%, p<0.001) and lupus GN less (16% *vs* 28%, p<0.001) frequent among Latinos in USA/Canada *vs* Latin America, while focal segmental GS was more (13% *vs* 7%, p<0.001) and IgA nephropathy less (27% *vs* 41%, p<0.001) frequent among Asians in USA/Canada *vs* Asia.

Conclusions: Glomerular disease frequencies differed by continent, even among patients of similar race. Environmental factors or local biopsy policy may influence regional glomerular disease epidemiology independently from race.

FR-PO640

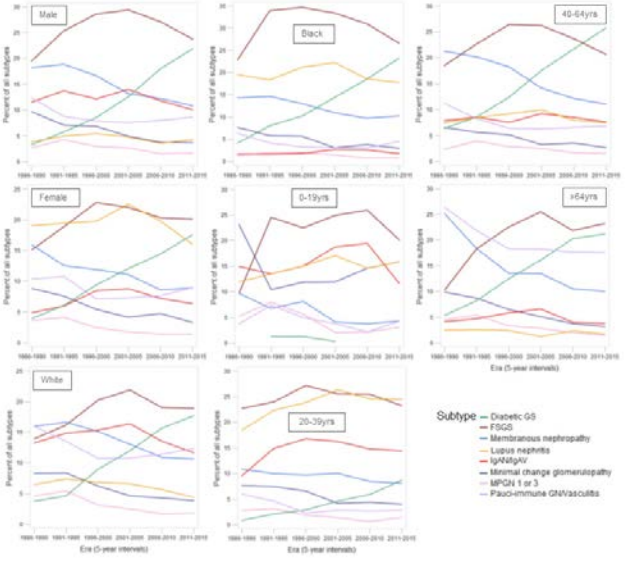
Temporal and Demographic Trends in Glomerular Disease Epidemiology in the United States, 1986-2015

Michelle M. O'Shaughnessy,[1,2] Susan L. Hogan,[2] Caroline J. Poulton,[2] Ronald J. Falk,[2] Harsharan Kaur Singh,[2] Volker Nickeleit,[2] J. Charles Jennette.[2] *[1]Stanford Univ, Palo Alto, CA; [2]Univ of North Carolina, Chapel Hill, NC.*

Background: Large-scale, contemporary, US studies exploring temporal trends in glomerular disease epidemiology by patient age, sex, and race are lacking.

Methods: In this cross-sectional, observational study, we examined glomerular disease subtype frequencies among all patients whose native kidney biopsy specimen was referred to the University of North Carolina (UNC), Chapel Hill, Nephropathology Laboratory (1986 to 2015), and who received a first biopsy confirmed diagnosis of a primary or secondary glomerular disease. Biopsy era (1986-1995, 1996-2005, 2006-2015) was the primary predictor. Patient age, sex, and race were secondary predictors. Relative biopsy frequencies were the primary outcomes.

Results: Among 23,959 cases of biopsy confirmed glomerular disease, the frequency of diabetic glomerulosclerosis increased dramatically over the 3 decades (4.4%, 10.0%, and 17.6% of cases, respectively, p<0.002). The frequency of FSGS increased initially but subsequently declined (18.0%, 23.8%, and 22.1%, respectively, p<0.002), whereas that of other common glomerular disease subtypes remained stable (IgA nephropathy, pauci-immune glomerulonephritis, lupus nephritis) or declined (minimal change disease, membranous nephropathy). These temporal trends were observed within all major sex, race, and age groups, with the exception of children, although substantial variation in glomerular disease subtype frequency distributions were observed across demographic groups cross-sectionally, **Figure 1**.



Conclusions: We identified significant changes in the relative frequencies of many glomerular disease subtypes over the past 30 years. We propose that exploration of behavioral and environmental exposures that likely underlie these findings should be the focus of future hypothesis-driven studies.

FR-PO641

B7.1 and suPAR Fail as Potential Biomarkers to Detect Podocyte Injury and Focal Segmental Glomerulosclerosis in Kidney Biopsies

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Background: The mechanism of injury to podocytes in focal segmental glomerulosclerosis (FSGS) remains unclear. Both B7.1 (CD80) and suPAR have been proposed to cause FSGS but the findings have not been validated. To survey these markers as potential mediators of podocyte injury and as an aid to histologic diagnosis of FSGS we evaluated the expression of B7-1 and uPAR in native and transplant (Tx) kidney biopsies (Bx), and the expression of uPAR in mice injected with suPAR.

Methods: Study groups included Bx with FSGS (n=10), early post-Tx recurrent FSGS prior to (n=15) and post-plasmapheresis (n=7). Native Bx with membranous nephropathy (MN) (n=10) and minimal change disease (MCD (n=5), and normal 6 month post-Tx protocol Bx [n=10] served as controls. Immunostains were performed on formalin-fixed paraffin-embedded (FFPE) and frozen tissues for B7.1 and uPAR. B7.1 mRNA expression was also assessed by next generation *in situ* hybridization (ISH) on FFPE. Signal co-localization was evaluated via co-stain with the podocyte marker synaptopodin. In addition, uPAR immunohistochemical expression was also evaluated in the kidneys of wild type and uPAR -/- mice infused with recombinant suPAR. Electron microscopy was used in the mouse kidneys to assess foot process effacement in conjunction with renal functional studies.

Results: B7.1 protein and mRNA were not expressed in native kidneys with FSGS or MCD or in transplant kidneys with recurrent FSGS. In MN, B7.1 was localized only to the immune deposits. No apparent uPAR immunoreactivity was present in native kidneys or recurrent FSGS. suPAR infusion did not produce proteinuria or effacement of podocytes in wild type or uPAR deficient mice. uPAR was detected along the glomerular endothelial cells but not in podocytes in wild type mice while uPAR stain remained negative in uPAR deficient mice even after suPAR injection.

Conclusions: The data suggest that B7.1 and suPAR may not play a significant role in podocyte injury in native and transplant kidneys with FSGS. B7.1 and suPAR immunostains and ISH seem to have a limited value as diagnostic markers in kidney Bx with FSGS and recurrent FSGS post-transplant.

Funding: Pharmaceutical Company Support - AbbVie

FR-PO642

Urinary Monocyte Chemotactic Protein 1 as a Predictive Marker of Steroid Responsiveness in Children with Idiopathic Nephrotic Syndrome

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Background: We have previously reported that CD36 (low-density lipoprotein scavenger receptor)$^+$ macrophage (MQ) contributed in the pathogenesis of refractory nephrotic syndrome (NS). To elucidate the mechanism of MQ accumulation and to identify a predictive biomarker of steroid responsiveness, we compared differences in cytokine and chemokine levels in serum and urine between steroid-sensitive (SSNS) and steroid-resistant (SRNS) children.

Methods: In this study, 20 children with NS (7.1 ± 4.3 years; male-to-female ratio, 13:7) were enrolled. They were divided into a steroid-sensitive group (SSNS; n = 15) and a steroid-resistant group (SRNS; n = 5) according to their clinical course. Serum and urinary samples were collected at the time of onset and remission. Control serum and urine samples were also collected from age-matched healthy children (n = 15). Cytokines and chemokines were measured by using a cytometric bead array kit.

Results: The levels of several cytokines and chemokines in the urinary samples were significantly higher at onset than at remission (IP-10: p < 0.001, MCP-1: p < 0.001, MIG: p = 0.012, RANTES: p = 0.003) and those in the control samples (IL-6: p = 0.026, IP-10: p < 0.001, MCP-1: p = 0.032, MIG: p = 0.001, RANTES: p = 0.005). However, serum cytokine and chemokine levels did not significantly differ among the three groups. At onset, the urinary MCP-1 level was significantly higher in the SRNS group than in the SSNS group (p = 0.044).

Conclusions: The present study demonstrated that urinary cytokines and chemokines might be associated with the pathogenesis of NS. In particular, increased urinary excretion of MCP-1 in SRNS children was a potent predictive biomarker of steroid responsiveness in idiopathic NS. MCP-1, a chemokine recruiting macrophage, may play an important role in the pathogenesis of steroid resistance. Further histological studies warrant elucidation of the mechanisms of steroid resistance in refractory NS.

Funding: Clinical Revenue Support

FR-PO643

Biomarkers to Predict the Development of Glomerulosclerosis

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Background: Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are two common causes of the nephrotic syndrome. Some patients with biopsy-proven MCD have been shown to progress to FSGS. Early biomarkers indicating potential development of glomerulosclerosis before it becomes detectable by histology could help to discriminate between MCD patients that do or do not progress to FSGS. We previously described early changes in nephrin and segmental changes in desmin and podoplanin in a rat model for proteinuria and glomerulosclerosis (MWF rats). The aim of this study was to investigate whether changes in these markers are predictive for the development of glomerulosclerosis in MWF rats and patients with MCD.

Methods: 20 kidney sections of MWF rats and the non-proteinuric SHR strain were stained for desmin, podoplanin and nephrin at 4, 8 and 24 weeks of age. Quantification was performed using ImageJ. For a pilot study, renal biopsy samples of 10 MCD patients and 15 primary FSGS patients, diagnosed between 2001 and 2016, were stained for desmin, podoplanin and nephrin.

Results: In MWF rats, desmin expression in glomeruli was significantly increased at 8 and 24 weeks of age ($p<0.0001$), whereas it remained stable in SHR. Moreover, at 8 and 24 weeks, MWF rats showed segmental loss of podoplanin, which co-localized with *de novo* expression of desmin in podocytes. At 24 weeks of age, MWF rats developed segmental sclerosis. Glomeruli with segmental sclerosis displayed strong *de novo* desmin expression in podocytes and loss of podoplanin at the site of sclerosis. Confirming other studies, in biopsies of patients with MCD, the expression pattern of nephrin was granular and in FSGS, segmental loss of nephrin was observed. However, we also detected segmental loss of nephrin in patients with MCD.

Conclusions: Loss of podoplanin expression and *de novo* expression of desmin in podocytes predict development of segmental sclerosis in MWF rats. We also show segmental loss of nephrin in patients with MCD, which suggests that this marker may predict progression to FSGS.

FR-PO644

Minimal Change Disease and Focal Segmental Glomerulosclerosis Patient Subgroups Using Cluster Analysis of Morphologic Descriptors: Early Findings from the Nephrotic Syndrome Study Network

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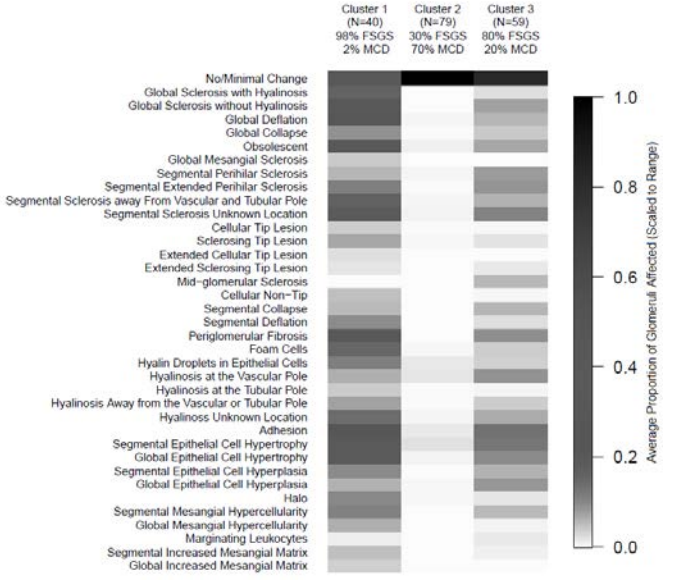
Background: Conventional classification of minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) is based on qualitative interpretative pathology and does not capture disease heterogeneity. To overcome this problem, the descriptor-based NEPTUNE Digital Pathology Scoring System (NDPSS) was developed to assess multi-level, annotated whole slide images of renal biopsies.

Methods: To explore whether the NDPSS can identify patient subgroups, we used unsupervised cluster analysis of 68 MCD and 110 FSGS patients using the percent of glomeruli affected by 37 morphologic glomerular descriptors. We compared demographics, clinical characteristics, time to remission, and time to the composite of 40% reduction in estimated glomerular filtration rate (eGFR) or end-stage renal disease (ESRD) across the clusters.

Results:



3 clusters were found. Patients with a conventional diagnosis of MCD and FSGS were distributed across all 3 clusters, although FSGS patients represented the majority in Cluster 1. Cluster 1 patients had the highest rates of the composite outcome and lowest remission rates compared to the other two ($p<0.001$). Cluster 2 patients had higher rates of remission compared to Cluster 3. Cluster 2 patients were younger, had higher baseline eGFR, and lower baseline urine protein creatinine ratio ($p's<0.001$).

Conclusions: Clusters of patients with similar glomerular descriptor profiles had different clinical characteristics and outcomes. Therefore, given that the clusters do not match conventional morphologic classifications, there may exist previously undiscovered proteinuric disease subtypes that can now be identified using the NDPSS. The NDPSS is thus a useful methodology for diagnostic and prediction medicine.

Funding: NIDDK Support, Other NIH Support - ORDR/NCATS

FR-PO645

Simple and Rapid Identification of Podocyte (Podo) Injury Using Anti-Podocalyxin (PCX) Antibody-Bound Latex Beads and Urine Sediments

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Background: The urine sediments from patients with Podo injury contain numerous PCX positive strucures as a form of granules trapped in the casts, in addition to Podo(es). In the current study we developed a simple and rapid light microscopic procedure to detect Podo injuries using latex beads bound with an anti-PCX antibody and urine sediments.

Methods: In order to get the antibody-bound latex we have newly developed monoclonal antibodies designing to trap the PCX positive granules or Podo(es). PCX expressing cell line (NCCIT) was used as positive control to search for the optimal reacting condition or requirements. Various approaches were tried and examined for requirements to get better discriminatory appearance of cells by light microscopic examination. The optimal conditions in the assay using NCCIT were checked also using human urine samples. Finally the new assay was applied to human urine samples with 34 diabetic patients (10 with microalbuminuric and 24 macroalbuminuric) and compared with the standard assay of conventional IF method.

Results: The optimal assay condition for the identification of PCX positive casts or Podo(es) in the sediments were as follows; 1) the mixture of 4 different antibodies (clones; 4A2, 4A7, 4D2 and 4E5) was required. 2) size and color of the latex should be 1.0 um and blue, 3) the sediments after centrifugation of starting urine volume of 1.5ml was mixed with 10 ul of 0.2 % antibody-bound latex and centrifuged using swing type at 1500 G for 15minutes and then the mixtures was gently suspended and served for light microscopic examination. The presence of latex-bound cells or casts was evaluated as positive for Podo injury in this assay. The time needed for entire procedures including microscopic examination was ~30 minutes. The good sensitivity (0.71) and specificity (0.96) was obtained.

Conclusions: We have developed a new method to detect podocyte injuries using antibody-bound latex beads and urine sediments that is simple and rapid without use of immunofluorescent microscope. This new approach might offer great advantages for the screening of podocyte injury in the practice of clinical nephrology.

FR-PO646

Proteomic Analysis Identifies Candidate Biomarkers of Steroid Resistance in Pediatric Glomerular Disease

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Background: Glomerular disease is the third leading cause of ESRD in the US. Immunosuppressive drugs are the primary therapies for most glomerular diseases, but ~20-50% of patients fail to achieve a remission and can be deemed steroid resistant. No biomarkers exist to predict treatment responsiveness, leaving patients at high risk for both toxic side effects and disease progression. Prognostic biomarkers to prevent drug-induced toxicity, and to identify more targeted and effective treatments for glomerular disease represents an urgent need.

Methods: Paired plasma samples (n=30) were collected from 15 patients with nephrotic syndrome (NS) (steroid sensitive, SSNS; n=7 and steroid resistant, SRNS; n=8) and low abundant serum proteins were enriched by FPLC based immunodepletion of high abundant proteins. These paired samples were collected 6-8 weeks apart and corresponded to entry into the study (pre-steroid treatment) and a follow-up period at which time the clinical determination of steroid responsiveness was known. Samples were trypsinized, LCMS data (Orbitrap ELITE) collected and analyzed with Mascot/Sequest search strategy. Scaffold 4 was used for false discovery rate control, and ANOVA analysis was used to determine differences in protein abundances between SSNS and SRNS patient samples at pre- and follow-up time points.

Results: 45 of 223 protein clusters were differentially expressed (p-value <0.05) by ANOVA. 21 proteins remained significantly different following Benjamini-Hochberg multiple comparison correction (*p-value< 0.003). Unique protein abundance observations for SSNS were 4 increased pre-treatment and 3 increased post-treatment. 8 proteins decreased and 5 increased with steroid treatment in both SSNS and SRNS sample groups. One protein absent in SSNS pre-treatment was abundant in SSNS post-treatment and both SRNS pre-/post-treatment.

Conclusions: SSNS patients have plasma proteins that correlate with the response to steroid therapy. These proteins may have utility as prognostic biomarkers in pediatric patients.

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FR-PO647

Regulatory T-Cells Dynamics Predicts Clinical Response to Rituximab in Patients with Severe Primary Membranous Nephropathy
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Background: Little is known about cellular immune responses in primary membranous nephropathy (PMN). We aimed to characterize lymphocyte populations and cytokines/chemokines in patients with severe PMN at baseline and after rituximab infusion added to non-immune-suppressive anti-proteinuric treatment (NIAT) or under NIAT alone in the first rituximab-based RCT.

Methods: Twenty-five patients were enrolled in this study as well as 27 age-matched healthy donors. We investigated the dynamic changes of 33 lymphocyte subpopulations and 26 cytokines/chemokines in patients' peripheral blood.Twenty-one patients had PLA2R-related MN and one had anti-THSD7 antibodies.

Results: At baseline, the most significant changes between PMN patients and controls were (i) increased percentages of naive B-cells with decreased switched and non-switched memory B-cells; ii) overall decrease of NK cells percentage, contrasting with an increase of the $CD56^{bright}CD16^{-/lo}$ NK subset; (iii) decreased percentage of regulatory T cells (Tregs). This was associated with an increase of the plasma concentration of TNF-alpha, IL-5 and IL-2RA. After rituximab treatment, B-cell recovery was still incomplete at 6 months, with persistent alterations of B-cell subsets, overall increase of Treg and NK cell percentages and decrease of $CD56^{bright}CD16^{-/lo}$ NK subset and TNF-alpha levels. Noteworthy, the patients who responded to rituximab had the lower percentage of Tregs at baseline and a significant Treg increase at day 8 after rituximab. In contrast, Tregs remained unchanged in non-responders and in patients not treated with rituximab.

Conclusions: Altogether, Tregs delineate subgroups of PMN patients and is a potential predictive biomarker of rituximab efficacy.

Funding: Pharmaceutical Company Support - Hoffmann-La Roche

FR-PO648

Rituximab Residual Levels and Neutralizing Anti-Rituximab Antibodies (Ab) Are Associated with Response to Treatment in Patients with PLA2R-Related Membranous Nephropathy (MN)
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Background: The anti-CD20 monoclonal antibody rituximab can induce remission in patients with MN but apart from PLA2RAb titer, no predictor of clinical response has yet been identified.

Methods: In this pilot study, we measured residual rituximab serum levels and anti-rituximab antibodies at months 3 and 6 after each rituximab course, and searched for a neutralizing effect of anti-rituximab antibodies in 15 patients from Nice (1g at day 0 and day 14) and 27 patients from the French cohort GEMRITUX (375 mg/m^2 at day 0 and day 7; Dahan et al, JASN in press).

Results: Rituximab induced 10 remissions at month 6 in patients from Nice. Residual rituximab levels at month 3 were highly variable but significantly higher in patients who achieved remission at month 6 (p=0.003) while baseline proteinuria and PLA2RAb titer were not different (p=0.83 and p=0.09, respectively). Eight patients from the GEMRITUX trial were in remission at month 6. The rate of remission was higher in patients from Nice (p=0.03) and associated with higher residual rituximab level at month 3 (p=0.002) and lower CD19 count at month 6 (p<0.0001) while baseline proteinuria and PLA2RAb titer did not differ between the two cohorts (p=0.08 and p=0.53 respectively). Anti-rituximab antibodies were detected after 8 courses at month 6 in the two cohorts. Using competition assays, we showed that in 6 patients, rituximab antibodies could bind rituximab in the fluid phase and block in vitro rituximab cytotoxicity on B-cells whereas in the 2 other patients, antibodies were not neutralizing. The presence of neutralizing anti-rituximab antibodies in 6 among the 29 patients from the two cohorts in remission at month 12 (p=0.02) and PLA2RAb titers at month 6 (p=0.03) were both significantly associated with subsequent clinical relapses (n=6).

Conclusions: Monitoring of rituximab and neutralizing anti-rituximab antibodies may predict response and relapse in patients with MN associated with anti-PLA2R antibodies.

Funding: Government Support - Non-U.S.

FR-PO649

Circulating Antibodies against Thrombospondin Type I Domain-Containing 7A in Chinese Patients with Idiopathic Membranous Nephropathy
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Background: Prevalence of anti THSD7A antibodies in Chinese membranous nephropathy and its effect on prognosis were unknown. The present study is designed to assay the prevalence of anti THSD7A antibodies in Chinese idiopathic MN patients and explore its effects on prognosis.

Methods: 578 consecutive patients with biopsy-proven idiopathic MN diagnosed between years 2008 and 2016, and followed up at our center were enrolled. Anti PLA2R antibodies and anti THSD7A antibodies were assayed in circulation and in glomeruli. Clinical features and outcomes were compared between MN patients with and without anti THSD7A antibodies.

Results: Among 578 consecutive patients with idiopathic MN, 8 (1.4%) had anti THSD7A antibodies in circulation and in glomeruli. Among them, 2 patients had dual antibodies and two antibodies had no cross-reaction. Only one patient was female. Mean age of these patients was 58.4 ± 15.4 years. Patients with anti THSD7A antibodies had higher level of fibrinogen compared to anti PLA2R antibodies positive alone and dual antibodies negative patients (P=0.023, P=0.008). Other clinical features were comparable to MN patients without anti THSD7A antibodies (P>0.05). Patients with anti PLA2R antibodies positive had higher level of D-dimmer than those of dual antibodies negative (P=0.005). PLA2R and THSD7A expressed on the same position of podocyte by immunofluorescence. Patients received corticosteroids combined immunosuppressive therapy similar to that in patients without anti THSD7A antibodies (P>0.05). Clinical and renal prognosis among patients of anti THSD7A antibodies positive patients and antibodies negative patients had no significant differences (P>0.05).

Conclusions: MN patients with anti THSD7A antibodies had higher level of fibrinogen, which might be related with thrombogenesis. Patients with positive anti PLA2R antibodies seemed more likely to thrombus than patients with dual antibodies negative. Clinical and renal prognosis had no difference among patients with anti THSD7A antibodies positive and negative patients.

Funding: Government Support - Non-U.S.

FR-PO650

Clinical and Pathological Spectrum of THSD7A Positive Membranous Glomerulopathy
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Background: Thrombospondin type-1 domain containing 7A (THSD7A) is a recently described antigenic target in primary membranous glomerulopathy (MG). In the initial series, approximately 10% of the patients negative for PLA2R had antibodies against THSD7A.

Methods: All non-SLE associated MG cases (n=1070) were stained for PLA2R and THSD7A in our laboratory for a 30 month period. THSD7A-positive MG cases were selected for study. Serum samples were available from 18 THSD7A positive cases at the time of biopsy and tested by IFA for the presence of THSD7A antibodies (Euroimmun).

Results: The cohort consisted of 28 patients (17 males and 11 females). The mean age was 62 years (range 17 to 91 years). Twenty five (25) patients presented with full nephrotic syndrome and 3 patients with proteinuria with a mean proteinuria of 10 grams/day (range: 1.1-15 grams/day). The mean serum creatinine was 1.3 mg/dL(range: 0.6-3.3; n=25) and mean serum albumin was 2.0 g/dL(range: 1-3.2; n=18) . On renal biopsy, all the cases had positive THSD7A staining and two cases were also positive for PLA2R. Serum samples from all 18 patients available for study at the time of biopsy were positive (titer 1:10 to 1:500) for THSD7A antibodies. Follow up data was available in 18 patients. The mean proteinuria on follow up was 7.5 grams/day (range: 0.06 – 9.9; n=13), creatinine was 1.3 mg/dL (range 0.5-3.2; n= 17) and albumin was 2.5 g/dL (range 1.2-4.1; n=14).

Conclusions: We present the largest cohort to date of THSD7A-associated MG. In our patient population, THSD7A-associated MG accounts for 2.6%of non-SLE associated MG. Biopsy staining correlates well with the presence of serum antibodies at the time of diagnosis. Ongoing studies are underway examining the prognostic significance of serum antibody level.

FR-PO651

Analysis of PLA2R Sequence Variants in Japanese Patients with Idiopathic and Secondary Membranous Nephropathy
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Background: Phospholipase A2 receptor (PLA2R) was found to be the major target antigen of autoantibodies in idiopathic membranous nephropathy (iMN) [N Engl J Med. 361: 11-21, 2009]. The prevalence of anti- PLA2R antibodies in Japanese patients with iMN is lower than those of any other countries [Clin Exp Nephrol. 19: 653-60, 2015]. Several reports showed PLA2R sequence variants are associated with iMN. However, genetic background of PLA2R in Japan has not been studied. Also genetic backgrounds of PLA2R in secondary MN (sMN) are unclear in Japan.

Methods: A total of 50 patients with iMN, 23 patients with sMN, and 50 patients with other renal diseases as a control admitted to our hospital and affiliated hospitals between 1990 and 2013 were enrolled in this study. Since Coenen et al. reported that single nucleotide polymorphisms (SNPs) in exon 1, 2, 5, 16 and 24 of PLA2R gene are significantly associated with iMN [J Am Soc Nephrol. 24: 677-83, 2013], we selected reported six SNPs, and then sequenced directly five exons of PLA2R, using genomic DNA prepared from peripheral lymphocytes in patients with iMN, sMN, and controls. The differences in these SNPs allele frequency among three groups were analyzed by Kruskal-Wallis test or χ^2 test. We also analyzed the relationship between clinical parameters (urinary protein, serum albumin, and serum creatinine) and genotypes of PLA2R by Kruskal-Wallis test.

Results: Four of six SNPs, rs3747119, rs3749117, rs35771982, and rs2715918 were significantly associated with iMN (p=0.0366, p<0.0001, p<0.0001, and p<0.0001, respectively). Only rs35771982 was significantly but weakly associated with sMN (p=0.0405). Between iMN and sMN, there were significant differences in allele frequency in rs3749117 and rs2715918 (p=0.0439 and p<0.0291, respectively). There were no correlations between PLA2R genotypes and clinical parameters.

Conclusions: This study showed for the first time the genetic background of PLA2R in Japanese iMN patients. The difference in these SNPs allele frequency may influence the lower prevalence of anti-PLA2R antibodies in Japan. We also showed that PLA2R sequence variants were not closely related with sMN.

FR-PO652

Changes of Lymphocytes Profile in Patients with Severe Systemic Lupus Erythematosus Treated with an Intensified B-Cell Depletion Therapy with Rituximab Dario Roccatello, Savino Sciascia. *Nephrology Dept, San Giovanni Bosco Hospital.*

Background: In this study we aim to prospectively investigate the differentiation and phenotypic changes of peripheral B cells and T regulatory lymphocytes (Treg) in patients with systemic lupus erythematosus (SLE) after an intensified B-Cell depletion therapy with Titiximab (RTX).

Methods: Ten patients with sever SLE [2males, mean age 41.6 yrs (25–57)] with severe multiorgan involvement have been prospectively treated with IBCDT protocol due to their resistance or intolerance to previous therapy. Protocol:RTX 375 mg/sm on days 1,8,15,22, and 2 more doses after 1 and 2 months, associated with 2 IV administrations of 10 mg/kg of cyclophosphamide and 3 methylprednisolone pulses (15mg/kg) followed by oral prednisone (0.8 mg/kg/day, rapidly tapered to 5mg/day by the end of the 3rd month after RTX). No further immunosuppressive maintenance therapy has been given. Circulating B cells and Treg in the peripheral blood were investigated by flow-cytometry (with monoclonal antibodies against CD45,CD3,CD4,CD19,CD20,CD25,FOXP3) at baseline, month 1, month 2, and every other month thereafter up to 1 year. Response was evaluated by assessing the changes in clinical/laboratory parameters and SLEDAI score.

Results: All patients had complete peripheral blood-B cell depletion after IBCDT and the CD20+B cells were not detectable in the circulation by the 12th month (detection limit of 0.005x109 /l). Upon detection of B cell depletion, we observed in 12 months a 4-fold increase in the circulating Treg (CD4+CD25+FOXP3+) (2% at baseline, 3% after 1 month, 4,5% at 6 month, 8% at 12 months). All patients achieved clinical remission after IBCTD and no flare were observed during the one-year follow-up. IBCDT resulted in a decrease of median global SLEDAI from 14.6 [11–23] to 4 [1–5] at 12 months ($p<0.01$).

Conclusions: Our results suggest a phenotypic change of peripheral T lymphocytes as a result of B cells depletion obtained with IBCTD. Treg considered being essential in the maintenance of peripheral self-tolerance, progressively increased after B cell depletion. Such immunological re-assessment was observed in association with clinical remission in the absence of further disease flare.

FR-PO653

Monocyte Chemotactic Protein-1, Fractalkine, and Receptor for Advanced Glycation End Products in Different Pathological Types of Lupus Nephritis and Their Value in Predicting the Treatment Prognosis Lan Lan, Jianghua Chen. *Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China.*

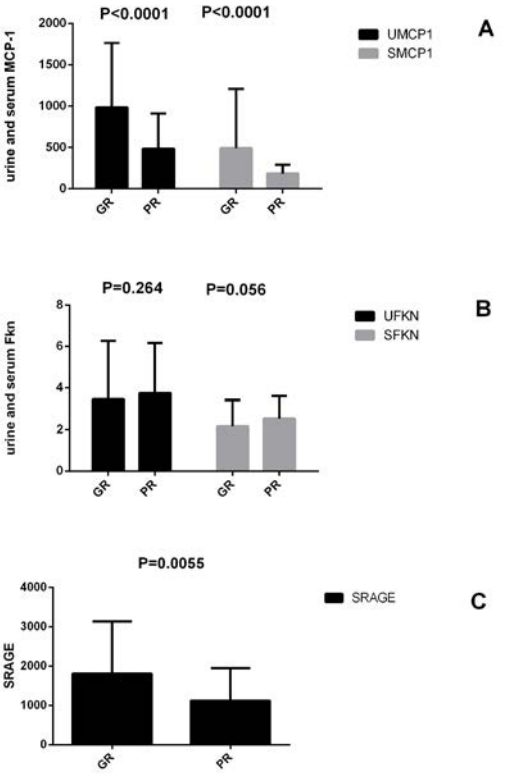
Background: Early diagnosis is important for the outcome of lupus nephritis (LN), and the pathological type of LN is closely related to the clinical manifestations and treatment prognosis.

Methods: In the patients included in this study, through renal biopsy, class III and class IV were defined as proliferative group, class V as nonproliferative group, class V+III and class V+IV as mixed group. During the follow-up, 40 of the 178 enrolled patients were found to have poor response to standard immunosuppressant therapy. The level of urine and serum MCP-1,Fractalkine, RAGE in the different groups was tested.

Results: The levels of urine and serum MCP-1, urine and serum Fkn, and serum RAGE were higher in the proliferative group, and lower in the nonproliferative group, and the difference was significant.

	Urine MCP-1 (pg/ml creatinine)	Serum MCP-1 (pg/ml creatinine)	Urine Fkn (ng/mmol creatinine)	Serum Fkn (ng/mmol creatinine)	Serum RAGE (pg/mL.)
proliferative group	1240.65 ±876.38	354.49 ±598.60	4.44 ±3.05	2.53 ±1.24	2020.74 ±1421.27
nonproliferative group	544.47 ±430.63	200.40 ±171.83	2.37 ±1.88	2.07 ±1.19	1257.94 ±862.83
mixed group	595.20 ±603.42	273.31 ±429.31	3.42 ±2.45	2.28 ±1.05	1707.85 ±1383.43

The levels of urine and serum MCP-1 and serum RAGE were lower in the poor response group; the difference was significant.



The relationship between urine MCP-1, urine and serum Fkn with the Systemic Lupus Erythematosus Disease Activity Index was proved.

Conclusions: The concentration of cytokines MCP-1, Fkn, and RAGE may be correlated with the nuclear factor-kappaB pathway. The cytokines may help in predicting the prognosis before standard immunosuppressant therapy.

Funding: Clinical Revenue Support

FR-PO654

Zonal Cortical Scarring and Tubular Thyroidization in Biopsies of Patients with SLE - Indicator for Anti-Phospholipid Antibodies? Anjali A. Satoskar,[1] Robin Shah,[2] Sergey V. Brodsky,[1] Lee A. Hebert,[2] Brad H. Rovin,[2] Tibor Nadasdy.[1] *[1]Pathology, Ohio State Univ Wexner Medical Center, Columbus, OH; [2]Internal Medicine Nephrology Div, Ohio State Univ Wexner Medical Center, Columbus, OH, United Kingdom.*

Background: Anti-phospholipid antibody syndrome (APS) can be primary or secondary to other autoimmune diseases, most commonly systemic lupus erythematosus (SLE). Among SLE patients, prevalence of anti-phospholipid antibodies (aPL) ranges from 30 to 40% and approximately 50% of these develop APS sometime during their disease course. Thrombotic microangiopathy (TMA) is a well-known complication of APS. We have encountered many kidney biopsies in SLE patients with zonal scarring and tubular thyroidization and positive aPL without evidence of ongoing TMA. Therefore we systematically studied the relevance of this association.

Methods: We searched our Pathology database for kidney biopsies from patients with SLE. Laboratory testing results for aPL were assessed based on a combination of tests (Staclot, dilute Russel viper venom test [DRVVT], and anti-cardiolipin antibodies). Biopsies were screened for presence/absence of zonal cortical scarring with tubular thyroidization.

Results: We identified 114 patients with SLE and kidney biopsy over a period of 9 years and 46 (40%) had at least one laboratory test indicating presence of aPL. Of the 46 patients with aPL, 15 (33%) had zonal scarring, 31(67%) did not. Of the 68 patients without aPL,only 5 (7.3%) had zonal scarring and 63 (92%) did not. Therefore, sensitivity was calculated to be 33%, specificity 92%, positive predictive value 75% and negative predictive value 67%. TMA-like changes were seen only in 7/15 biopsies with zonal cortical scarring and aPL.

Conclusions: Presence of zonal scarring and tubular thyroidization in kidney biopsies from patients with SLE, is a specific indicator for presence of aPL. Sensitivity of this feature is expectedly low because of its zonal nature and biopsy sampling issue. It may be the only morphologic indicator for the presence of aPL because TMA changes are frequently absent. The association of zonal renal cortical scarring with aPL isimportant to recognize because anti-coagulation therapy may be warranted.

FR-PO655

Proteome Analysis for Identification of Biomarkers for Accurate Diagnosis and Classification of Lupus Nephritis Patients in Saudi Arabia
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Background: Lupus Nephritis (LN) is one of the most common causes of renal failure in Saudi Arabia. Treatment and prognosis in lupus nephritis are based mainly on the findings in renal histopathology obtained by renal biopsy, which is non-specific, invasive and does not account for disease mechanism. Most proteomic studies to date used either serum or urine samples in studying potential biomarker, making identifying potential biomarkers cumbersome and difficult to trace back to its site of origin.

Methods: Kidney tissue biopsy, urine and Peripheral Blood Plasma (PBP) samples from biopsy proven lupus nephritis patients were subjected to expression-proteomics using quantitative label-free liquid chromatography tandem mass-spectrometry (LC-MS/MS).

Results: Approximately 785 & 225 differentially expressed proteins were identified from kidney tissues & peripheral blood samples respectively. About 5% of the identified proteins from the plasma samples were also among the identified proteins from the tissue samples. Some of the differentially expressed proteins in kidney as well as peripheral blood are LGALS3BP, IGKC, FN1, IGHM, GHG1, and HBB". This indicates the likelihood to identify disease-associated biomarkers seen in kidney tissue as well as in plasma. This would subsequently allow monitoring of such biomarker proteins in peripheral blood, demanding less invasive procedures against kidney biopsy for objective classification and prognostic monitoring of LN patients.

Conclusions: The result demonstrates the potential of proteomics as a powerful tool for discovery of reliable diagnostic markers for lupus nephritis and other kidney diseases. The proteins with differential expression in both kidney tissues and corresponding plasma are potential targets for biomarker discovery in larger sample cohorts.

Funding: Government Support - Non-U.S.

FR-PO656

Clinical and Histopathologic Determinants of Renal Outcome in Lupus Nephritis - Starting from Scratch
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Background: Controversy surrounds the prognostic significance of various lesions forming the basis of the ISN/RPS 2003 classification of lupus nephritis (LN). To improve evidence-based patient prognostication, we analyzed individual clinical and histopathologic parameters for their potential to predict renal outcome in LN outside the framework of the classification.

Methods: We included 105 patients with LN biopsied between 1987-2011. Fifty histopathologic and 10 clinical variables were determined as candidate predictors of outcome. We tested these baseline variables for their potential to predict eGFR trajectories during follow-up (registrations at 1, 5, and 10 years) in mixed and linear regression models, and progression to renal flare and end-stage renal disease (ESRD) in Cox regression models.

Results: The mean adjusted decline in eGFR was -0.75 (95% CI -1.46, -0.04) mL/min per year. A change in the level of eGFR decline was best predicted by %normal glomeruli (+2.67 mL/min/10%; 95% CI 0.52, 4.81), %cellular/fibrocellular crescents (-3.76 mL/min/10%; 95% CI -6.26, -1.25), %fibrous crescents (-13.47 mL/min/10%; 95% CI -24.20, -2.75), interstitial fibrosis/tubular atrophy (IF/TA) >25% (-39.26 mL/min; 95% CI -21.70, -56.82), age (-0.67 mL/min/y; 95% CI -0.26, -1.09) and non-Caucasian ethnicity (-13.85 mL/min; 95% CI -2.06, -25.63). Renal flare was best predicted by %fibrinoid necrosis (HR 1.48 per 10%; 95% CI 1.00, 2.16) and non-Caucasian ethnicity (HR 2.26; 95% CI 1.25-4.10). The end-point ESRD was predicted by %fibrinoid necrosis (HR 2.16 per 10%; 95% CI 1.34, 3.71) %fibrous crescents (HR 2.50 per 10%; 95% CI 1.20, 5.19), IF/TA >25% (HR 3.64; 95% CI 1.18, 11.25), eGFR at baseline (HR 0.98 per mL/min; 95% CI 0.96, 1.00); and non-Caucasian ethnicity (HR 7.21; 95% CI 2.33, 22.27).

Conclusions: Prognostication in LN may benefit from the assessment of specific lesions currently obscured in the classification. These prognosticators necessitate validation in future studies.

FR-PO657

Idiopathic Non-Lupus Full House Nephropathy Is Associated with Poor Renal Outcome
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Background: Full house immunofluorescence in combination with various histopathologic lesions in the renal biopsies of patients without overt systemic lupus erythematosus (SLE) poses a diagnostic challenge. In this setting, the biopsy findings are sometimes termed non-lupus "full house nephropathy" (FHN). It is presently unknown whether non-lupus FHN is distinct from lupus FHN.

Methods: We included non-lupus FHN patients and controls with lupus FHN according to ≥4 ACR or SLICC criteria that were biopsied between 1968–2014 at the Leiden University Medical Center. The clinicopathologic characteristics and renal outcome of non-lupus FHN patients were compared to lupus FHN.

Results: Of 149 included patients, 32 had non-lupus FHN. Twenty of the non-lupus FHN patients had idiopathic non-lupus FHN, and the remainder had membranous nephropathy (anti-PLA2R-positive, n=1; paraneoplastic, n=3), IgA nephropathy (n=4), infection-related glomerulonephritis (n=2), and ANCA-associated vasculitis (n=2) with FHN. Idiopathic non-lupus FHN patients were more often male (P<0.001) than lupus FHN, and their renal biopsies more often showed a mesangial (P=0.04) or membranous pattern of injury (P=0.02), and less intense C1q staining (P=0.002). Clinically, they presented with significantly lower-range erythrocyturia (P=0.04), more proteinuria (P<0.01), and less complement consumption in the classical pathway (P<0.001) than lupus FHN patients. During the median follow-up of 20 years, no non-lupus FHN patients developed SLE. By multivariable Cox regression analysis of patients with a lupus nephritis class III/IV (±V) pattern of injury, idiopathic non-lupus FHN compared to lupus FHN was an independent risk factor for end-stage renal disease (hazard ratio 5.31, P=0.01).

Conclusions: Our results show that idiopathic non-lupus FHN is clinically and histopathologically distinct from lupus FHN. Importantly, idiopathic non-lupus FHN is associated with a poor renal outcome, warranting (early) recognition and urging future studies to elucidate therapeutic options.

FR-PO658

Validation of Systemic Lupus International Collaborating Clinics' Classification Criteria in a Cohort of Patients with Full House Glomerular Immune Deposits
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Background: In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) presented a new classification for systemic lupus erythematosus (SLE). In this classification, biopsy-confirmed lupus nephritis with positive antinuclear or anti-double stranded DNA antibodies became a stand-alone criterion. In light of the increased weight of renal lupus in the classification, we aimed to test the validity of the SLICC classification as compared with the American College of Rheumatology (ACR) classification in patients with a lupus nephritis(-like) renal biopsy showing full house immunofluorescence.

Methods: All patients with a full house renal biopsy between 1968-2014 and clinical follow-up in our center were included. After independent review of clinical records and re-evaluation of biopsy findings, clinicians and a pathologist reached a consensus on the reference-standard clinical diagnosis of SLE. Fulfilment of ACR and SLICC criteria at the time of renal biopsy, diagnostic performance, and net reclassification improvement (NRI) were assessed.

Results: We included 149 patients with a renal biopsy showing full house immunofluorescence, 117 of whom had clinical SLE. Compared with the ACR classification, the SLICC classification had better sensitivity (100 vs. 94%); although, this was at the expense of specificity (91 vs. 100%; NRI= -0.034, P=0.563). Excluding the stand-alone renal criterion, the specificity of the SLICC classification reached 100%, with an NRI of 0.06 (P=0.008) compared with the ACR classification.

Conclusions: The SLICC classification proved to be useful with regard to diagnostic sensitivity among patients with a full house renal biopsy, whereas the stand-alone renal criterion had no additional value and compromised the specificity.

FR-PO659

PEARL: Pathway Exploration and Analysis in RenaL Disease in the Accelerating Medicine Partnership (AMP) Lupus Network
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Background: Despite treatments, a substantial proportion of lupus nephritis (LN) patients progress to end stage renal disease and death. Detailed transcriptomic analyses of LN kidneys may identify new therapeutic targets. Our goal is to demonstrate the feasibility of single cell and low-input transcriptomic analyses of LN kidney and urine cells.

Methods: Cells from urine and renal biopsies performed for clinical diagnosis from inform-consented patients (1 class III, 3 class IV+V, 1 class V) and 1 control (healthy part of tumor nephrectomy) were isolated, frozen into Cryostor solution, sorted and analyzed by RNAseq.

Results: Bulk flow sorted cell populations (CD45, epithelial) from kidney samples can separate LN from controls based on gene expression. Differential expression of IFN stimulated genes was detected in renal CD45 LN cells. Analysis of single cells sorted from 4 LN kidney biopsies revealed major differences in infiltrates composition, with 2 samples demonstrating a high percentage of B cells (average of 18% compared to no B cells in the other 2 samples) and CD4 T cells (18% vs 8%), and low percentage of CD8 T cells (9% vs 23%). A high transcriptomic lupus interferon signature was detected in urine CD45 cells. Distinct infiltrates and distinct expression profiles were detected across patients.

Conclusions: The PEARL-Phase 0 project shows the feasibility of single cell isolation and transcriptomic analysis from LN kidney and urine. Analyses at a bigger scale in the two next phases of the project will accelerate discovery of new therapeutic targets and identification of biomarkers to guide therapeutic decisions in lupus nephritis and integrate the treatment effect.

Funding: Other NIH Support - NIAMS UH2 AR067688-01

FR-PO660

Comprehensive Aptamer-Based Screening of 1,129 Proteins Reveals Novel Urinary Biomarkers of Lupus Nephritis Samantha Stanley,[1] Huihua Ding,[1] Claudia Pedroza,[2] Ramesh Saxena,[4] Michelle Petri,[3] Chandra Mohan.[1] *[1]Biomedical Engineering, Univ of Houston, Houston, TX; [2]Center for Clinical Research, UT Health Science Center, Houston, TX; [3]Rheumatology, John Hopkins Univ Medical School, Baltimore, MD; [4]Clinical Research and Evidence-Based Medicine, Univ of Texas Health Science Center, Houston, TX.*

Methods: An aptamer-based screen of 1129 proteins in 24 human urine samples (8 active lupus nephritis (LN), 8 inactive LN, 8 healthy controls (HC)) revealed 281 proteins were significantly elevated in both SLE patients relative to healthy controls and in active LN relative to inactive LN.

Results: Ingenuity Pathway Analysis revealed the upregulated proteins belong to known inflammatory, fibrosis and chemokine/cytokine networks. In an independent cohort of 93 subjects (16 active LN, 52 inactive LN, 25 HC), urine ALCAM, BFL1, calpastatin, hemopexin, PRX6, PF4, properdin, sE-selectin, TFPI and VCAM1 were ELISA-validated and shown to be once again significantly elevated in active LN compared to disease/HC (Fig 1); they also correlated strongly with many clinical/laboratory parameters, including renal-SLEDAI, PGA, eGFR, ESR and C3/C4. In ROC curve analysis, several proteins exhibited significant AUC in distinguishing active LN: ALCAM [0.89], calpastatin [0.82], FcgRIIBC [0.70], hemopexin [0.76], PRX6 [0.67], PF4 [0.77], properdin [0.71], TFPI [0.77], and VCAM1 [0.81]. Lasso logistic regression analysis identified a 4-marker-panel (PF4, TFPI, PRX6, VCAM1) as the best discriminator of active LN, with an AUC value of 0.93. A longitudinal cohort study of 18 LN patients with an average of 3 visits per patient showed these markers to vary substantially in their ability to track conventional disease indices.

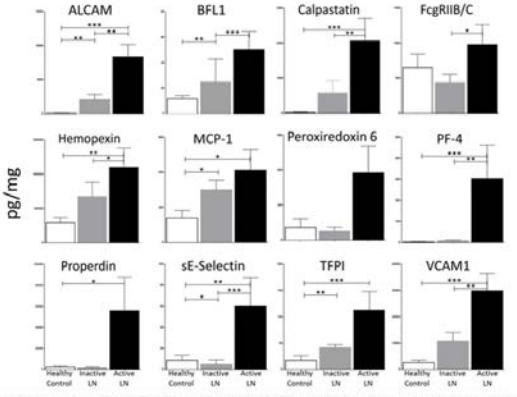

Fig 1: Creatinine-normalized ELISA units of 12 urine proteins in 93 subjects (16 active LN, 52 inactive LN, 25 healthy controls)

Conclusions: Urine ALCAM, BFL1, calpastatin, FcgRIIBC, hemopexin, MCP1, PRX6, PF4, properdin, sE-selectin, TFPI and VCAM1 arise as potential urinary biomarkers of LN; further studies are needed to establish their biomarker potential and pathogenic role.

Funding: NIDDK Support

FR-PO661

Cryofibrinogen Associated Glomerulonephritis Mariam P. Alexander,[1] Ralph Yachoui,[2] David L. Murray,[1] Jai Radhakrishnan,[3] Sanjeev Sethi.[1] *[1]Mayo Clinic, Rochester, MN; [2]Marshfield Clinic, Marshfield, WI; [3]Columbia Univ Medical Center, New York, NY.*

Background: Cryofibrinogen is a cryoprotein that precipitates after refrigeration of plasma, but not serum. While cryofibrinogenemia (CF) maybe asymptomatic it can manifest with thrombi, often involving skin. Renal involvement by CF is rarely reported. We present 2 cases of CF related membranoproliferative glomerulonephritis (CFGN)that were initially misdiagnosed as immunotactoid glomerulopathy (IG) and cryoglobulinemic GN (CGN).

Methods: The clinical presentation, lab results, renal biopsy (BX) morphology as assessed by light (LM), immunofluorescence (IF) and electron microscopy (EM) of 2 patients (pt) is presented. The cryoprecipitate (CRP) was isolated and studied ultrastructurally. The proteomic profile of the CRP was determined by mass spectrometry.

Results: Pt 1 was a 66yr old man who had cold induced skin eruptions. An initial BX due to hematuria & proteinuria was diagnosed as CGN. He was rxed with cyclophosphamide & high-dose steroids. A second BX a few yrs later for declining renal function was also diagnosed as CGN. Lab investigations: CF, present; CG, negative; normal complements, negative viral and autoimmune serology. Pt 2 was a 70yr old man with hematuria & proteinuria. He was a Hepatitis B carrier. He had no cutaneous eruptions. A BX was diagnosed as immunotactoid GN. Lab investigations: creatinine, 2.2mg/dL;24 hr urine protein, 8 g; SPEP, negative; CG, negative; CF, positive. Both biopsies showed a membranoproliferative GN (MPGN) with rare subendothelial & intraluminal deposits. IF showed no immunoglobulin deposition. EM showed intraluminal, subendothelial and rare subepithelial deposits which had a multilayered tubular structure. The mean luminal diameter was 158 nm. CRP isolated from the plasma showed identical ultrastructure. Mass spectrometry confirmed the peptide profile of the CRP was fibrinogen. Both BX diagnoses were revised as CFGN. Appropriate therapy was initiated.

Conclusions: Familiarity with the unique ultrastructural appearance of CFGN averts erroneous diagnosis, prompts appropriate evaluation for CF & permits accurate & timely initiation of therapy.

FR-PO662

Renal Dysfunction and Pathology Evaluation with Contrast-Enhanced Ultrasound Yao Xu,[1] Hongli Li,[2] Shan Mou.[1] *[1]Nephrology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong Univ, Shanghai, China; [2]Ultrasound, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong Univ, Shanghai, China.*

Background: The number of people with renal dysfunction due to CKD is increasing worldwide. The potential application of CEUS in nephrology has been proposed as a novel non-invasive imaging technique. We performed a prospective study to evaluate the predictive ability of contrast-enhanced ultrasound (CEUS) in chronic kidney disease (CKD) progression and its correlation with renal pathological changes.

Methods: CEUS was performed after an intravenous bolus injection of 1.5 ml SonoVue (BR1; Bracco Milan, Italy). Time-intensity curves (TICs) and quantitative indexes were created using QLAB quantification software. Risk factors related to kidney survival were investigated using a binary logistic regression model. All biopsies were analyzed with Masson's trichrome stain and α-SMA immunohistochemistry. Spearman correlation analysis was used to determine correlations.

Results: A total of 167 patients with CKD were enrolled in the study and followed for a mean period of 13.95 months. In total, seven (4%) patients exhibited composite kidney failure events (glomerular filtration rate (GFR) halving or end-stage renal disease (ESRD)). A significant difference in derived peak intensity (DPI) was noted among groups in different CKD stages. Multivariate logistic regression analysis revealed that the DPI was independently associated with progression of kidney disease. Patients with a DPI<9.63 db were less likely to recover from kidney disease progression. DPI levels were highly correlated with the degree of renal fibrosis. The area under the curve (AUC) for DPI and pathology combined was 0.874 (P<0.05), with a sensitivity of 75% and a specificity of 81%, which is greater than the AUC of pathology alone (0.829, P<0.05).

Conclusions: In patients with CKD, a high correlation exists between the DPI value and renal fibrosis. The DPI might be the most valuable CEUS parameter for the evaluation of renal function and fibrosis. It could be rapidly and continuously used for the diagnosis and prognosis of renal dysfunction.

Funding: Government Support - Non-U.S.

FR-PO663

Urinary miR-21 Abundance Increases with Decreasing Renal Function Markus Bitzer,[1] Klaas E.A. Max,[4] Jian Shi,[1] Iddo Z. Ben-Dov,[4] Beatrice Goilav,[3] The Neptune Consortium,[1] Thangamani Muthukumar.[2] *[1]Univ of Michigan; [2]Weill Cornell Medicine, Cornell Univ; [3]Albert Einstein College of Medicine; [4]The Rockefeller Univ.*

Background: MicroRNAs (miRs) are implicated as regulators and markers of kidney disease. We explored the role of urinary miRs as candidate markers for clinical outcomes in samples of two independent clinical studies.

Methods: Cell-free urine supernatant from 99 subjects with glomerular disease collected at time of enrollment into the Nephrotic Syndrome Study Network (NEPTUNE) was used to isolate RNA using a novel protease/nuclease-based isolation method which allows extraction of RNA tightly bound to proteins, including Argonautes. Small RNA-sequencing was performed using Illumina platform, sequence reads were mapped to the human genome and relative read-frequencies were associated with clinical, laboratory and structural parameters. 161 cell-free and equally processed urine samples of kidney transplant recipients enrolled in the Clinical trials in Organ Transplantation (CTOT) study were used for validation.

Results: Small-RNAs that were detected included microRNAs, tRNAs, ribosomal RNA, mRNA fragments and non-human RNAs. The 300 miRs with the highest mean abundance across all samples were used for further analysis. After correction for multiple testing, only miR-21 was significantly inversely associated with cross-sectional eGFR (r=-0.60; Bonferroni-adjusted p<0.01), and future development of ESRD (Bonferroni-adjusted p<0.05). Urinary miR-21 abundance was positively associated with scores for interstitial fibrosis (IF; r=-0.50; Bonferroni-adjusted p<0.01) and tubular atrophy (TA; r=-0.47; Bonferroni-adjusted p<0.01) but not with future eGFR decline in 77 samples for which these data were available. No association of urinary miR abundance with diagnosis, age, albuminuria or BMI was detected. In the independent CTOT cohort, miR-21 was also negatively correlated with cross-sectional eGFR (r=-0.42; Bonferroni-adjusted p<0.01), but not with other available parameters.

Conclusions: The association of higher urinary miR-21 abundance with increased IF/TA scores and lower renal function suggests that urinary miR-21 is a marker of renal fibrosis independent from disease category.

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FR-PO664

Negative Staining for COL4A5 Correlates with Worse Prognosis and More Severe Ultrastructural Alterations in Alport Syndrome Samar M. Said,[1] Mary E. Fidler,[1] Anthony M. Valeri,[2] Lynn D. Cornell,[1] Mariam P. Alexander,[1] Ahmed Mansour Alkhunaizi,[3] Anne S. Salyer,[4] Carl H. Cramer,[1] Marie C. Hogan,[1] Samih H. Nasr.[1] *[1]Mayo Clinic, Rochester, MN; [2]Columbia Univ, New York, NY; [3]Johns Hopkins Aramco Healthcare, Dhahran, MN, Saudi Arabia; [4]Permanente Medical Group, Oakland, CA.*

Background: Alport syndrome (AS) is a genetic disorder characterized by progressive hematuric nephropathy with or without sensorineural hearing loss and ocular lesions. Previous studies on AS included mostly children. In this renal biopsy-based study, we seek

to determine the prognostic value of loss of staining for COL4A5, its value in elucidating the mode of inheritance and its relationship with the ultrastructural glomerular basement membrane (GBM) alterations.

Methods: We performed direct immunofluorescence using a mixture of FITC-conjugated and Texas-red conjugated antibodies against COL4A5 and COL4A2, respectively, on renal biopsies of 58 patients with a pathologic diagnosis of AS (including 38 who were diagnosed in adulthood).

Results: The cohort consisted of 60% males and 40% females. All patients showed normal positive staining of GBM and tubular basement membranes for COL4A2. Of the 58 patients, 17 (29%) had loss of staining for COL4A5, with an expression pattern consistent with X-linked AS in 65% of cases and autosomal AS in 35% of cases. The remaining 41 (71%) had intact staining for COL4A5. Compared to patients with intact staining for COL4A5, those with loss of staining had more prominent ultrastructural GBM alterations, were younger at biopsy, were more likely to be males, and had a higher incidence of gross hematuria. By Kaplan-Meier survival analysis and Cox regression analysis, loss of staining for COL4A5 predicted earlier progression to overt proteinuria, CKD stage 2 or worse, and ESRD. By multivariate Cox regression analysis, loss of staining for COL4A5 and the severity of ultrastructural GBM alterations were independent predictors of the development of overt proteinuria and CKD stage 2 or worse.

Conclusions: COL4A5 expression pattern has an important prognostic value, it can unravel the mode of inheritance, and it correlates with the severity of ultrastructural GBM alterations.

FR-PO665

Podocyte Detachment Rate in Alport Syndrome Larysa T. Wickman,[1] Fangrui Ding,[2] Su Qing Wang,[1] Roger C. Wiggins,[1] Jie Ding.[2] *[1]Univ of Michigan, Ann Arbor, MI; [2]Peking Univ First Hospital, Beijing, China.*

Background: Alport Syndrome (AS) is an important cause of End Stage Kidney Disease recognized as a contributor to global disease burden. We previously reported that podocyte detachment rate measured in urine is increased and degree of podocyte depletion in renal biopsies is related to degree of proteinuria and glomerulosclerosis in AS. Podocyte detachment play a role in progressive loss of kidney function in AS. Podocyte detachment rate assay might therefore help guide treatment and assess novel therapies.

Methods: Alport Syndrome Prevention of Progression Project is an integration of a large well-characterized cohort of genetically-defined AS patients managed at Peiking University First Hospital in Beijing with novel podometric technology developed to identify and prevent progression of glomerular diseases at University of Michigan in Ann Arbor. Podocyte detachment rate was measured as the urine pellet podocin mRNA in ng/g creatinine using TaqMan assay.

Results: A total of 169 urine samples were collected for cross-sectional analysis, including from 132 AS patients with a clinical phenotype ranging from hematuria alone through hematuria with proteinuria with and without abnormal kidney function, and 37 age-matched controls. Control values from China and the US were not different. Urine samples from all AS patients contained an average 21-fold elevated amounts of podocin mRNA vs controls ($P<0.01$), comparable with 23-fold increase previously reported for AS patients in the US. AS patients with hematuria alone (without proteinuria) as a group had a 4.1-fold (range undetectable to 230-fold) increased rate of podocyte detachment vs controls ($P<0.01$), suggesting that individuals with high levels may be identifiable at an early stage as at risk for progression while those with normal levels may be identifiable as at low risk for progression.

Conclusions: Initial cross-sectional data in a large Chinese AS cohort are compatible with the concept that podocyte detachment rate measured non-invasively in urine might contribute useful information towards AS management. Further longitudinal studies are therefore warranted.

FR-PO666

Characteristics of Podocytes in the Urine in Pregnancy Using Flow Cytometry Bairbre A. McNicholas, Susan K. Anderson, Kimberly A. Muczynski. *Div of Nephrology, Univ of Washington, Seattle.*

Background: Podocyturia may be useful to predict high risk pregnancy. Detection of podocyturia is currently technically complex requiring a high level of expertise for interpretation. Flow cytometry is a sensitive technique that allows immediate study of cells shed into the urine. We describe the characteristics of podocytes detected in the urine of high-risk pregnancies using flow-cytometry and how they differ from non-pregnant individuals.

Methods: Urine cell pellets from 11 patients attending high-risk obstetric clinic and 2 healthy subjects at various stages of pregnancies was compared with 7 non-pregnant individuals (4F, 3M) using 7-color flow cytometry. Podocytes were identified as $DAPI^{-}$ $CD45^{-}$ cells positive for human Nephrin and/or podocalyxin. Appropriate isotype and fluorescence minus one was used for controls. Expression of CD80 and HLA-DR on podocytes was assessed. Immunofluorescence for nephrin and CD80 on urine cell pellets was used to confirm flow-cytometric findings.

Results: Podocytes were detected in the urine of all subjects. Podocytes per ml of urine was higher in high-risk pregnancy compared to healthy pregnancy and non-pregnant individuals (21.9±9 vs. 2.5±0.2 vs. 1.1±0.2 cell/ml urine, $p=0.05$ and $p<0.0001$ vs. high risk pregnancy). Two distinct population of podocytes were identified, $nephrin^{+}podocalyxin^{-}$ and $nephrin^{+}podocalyxin^{+}$. CD80 and HLA-DR was expressed only on $nephrin^{+}$ $podocalyxin^{-}$ cells. The proportion of $CD80^{+}nephrin^{+}podocalyxin^{-}$ cells was lower in high risk pregnancy compared to non-pregnant individuals (4.4±1.8 vs. 36.4±13 % of $nephrin^{+}podocalyxin^{-}$, $p=0.007$). The number of podocytes as a proportion of viable cells did not differ but number of viable cells was higher in high risk pregnancy compared to healthy controls (46101 vs 3745 cells/sample, $p=0.002$).

Conclusions: Podocytes can be detected in the urine using flow cytometry. Low levels of podocytes were detected in non-pregnant individuals suggesting turnover of podocytes occurs in healthy individuals. The number of $nephrin^{+}podocalyxin^{+}$ cells was higher and the proportion co-expressing CD80 was lower in high-risk pregnancy. Alteration in phenotype of detached podocytes may be a feature of high-risk pregnancies.

Funding: Private Foundation Support

FR-PO667

Localization of Kidney Injury Markers TIMP-2 and IGFBP7 in Human Kidney Biopsies Martin Kimmel,[1] Moritz Schanz,[1] Mark Dominik Alscher,[1] Kerstin U. Amann,[2] Christoph Daniel.[2] *[1]Internal Medicine, Robert-Bosch Hospital, Stuttgart, Germany; [2]Nephropathology, FAU Erlangen-Nürnberg, Erlangen, Germany.*

Background: Tissue inhibitor of matrixmetalloproteases 2 (TIMP-2) and Insulin-like growth factor-binding protein 7(IGFBP7) are markers of cell cycle arrest and urinary [TIMP-2]*[IGFBP7] was recently cleared by the FDA for risk assessment of acute kidney injury. However, studies describing the localization or expression profiles of TIMP-2 and IGFBP7 in human renal tissue in patients with glomerular or tubular damage are lacking.

Methods: We analyzed n=38 kidney biopsies of patients with renal disease and n=10 control biopsies immunohistochemically. Changes in glomerular morphology were evaluated by a semi-quantitative glomerulosclerosis score (GSI) and tubular interstitial changes were graded by the tubular injury score (TSI) using PAS-stained paraffin sections and interstitial fibrosis and tubular atrophy (IF/TA) was graded according to BANFF classification. In addition, co-localization studies were performed using confocal laser scanning microscopy.

Results: In healthy control biopsies both TIMP-2 and IGFBP7 are rarely expressed within the tubular and glomerular compartment. However, compared to these controls both antigens are at least 2-fold significantly upregulated in biopsies from patients with kidney disease. TIMP2 is predominantly expressed in aquaporin 2 positive collecting ducts and to a lesser degree in the glomeruli. In contrast, IGFBP7 is expressed in both the glomerular and tubular compartment with comparable intensity. IGFBP7 expression could be detected in glomerular endothelial cells and podocytes as well as distal tubules and parts of the thick ascending limb. There were significant correlations for the tubular injury score (TSI) with tubular TIMP-2 ($r=0.403$; $p<0.005$) and IGFBP7 ($r=0.521$; $p<0.0002$). In addition, glomerular sclerosis score (GSI) correlated with glomerular TIMP-2 ($r=0.347$; $p<0.02$) and IGFBP7 ($r=0.341$; $p<0.03$).

Conclusions: The immunohistological examinations of TIMP-2 and IGFBP7 in human kidney biopsies underline the role of these markers especially in tubular damage.

FR-PO668

A New Therapeutic Strategy in IgA Nephropathy with CKD Using Methylprednisolone Pulse Therapy and Autologous Adipose Derived Stem Cells (Stromal Vscular Fraction) Byoung-Soo Cho,[1] Hyaejin Yun,[1] Sung Min Jung,[2] Kyung-Min Lee,[1] Wang Kwang Hong.[3] *[1]MIRAE ING Kidney Center, Seoul, Korea; [2]EWha Women's Medical College, Seoul, Korea; [3]ByulE Plastic Surgery, Seoul, Korea.*

Background: As yet there is no specific therapeutic means to treat IgAN especially when associated with CKD, but giving RAAS blocker etc., almost all cases of IgAN with CKD eventually progress to ESRD and need RRT.

Cell therapy is extensively evaluated as an alternative therapeutic modality for many kinds of diseases with no other options. Recently human MSCs prevent podocyte apotosis and injury and other reports have shown to reduce glomerulosclerosis and oxidative stress in animal model. We tried MP pulse therapy and autologous SVF in IgAN with CKD or with moderate degree glomerulosclerosis and followed up for 2 years.

Methods: Case 1: A 26-year-old male was diagnosed as IgAN with 24% glomerulosclerosis. Follow up renal biopsy showed markedly decreased immune deposits without lesions of glomerulosclerosis. Laboratory results showed BUN/Creatinine 6.9 mg/dl / 1.08 mg/dl, IgA 363 mg/dl, C3 159 mg/dl. urine protein/creatinine ratio 0.974, CCr 82 ml/mn. Follow up laboratory data showed BUN/creatinine 9.2 mg/dl/ 0.75 mg/dl, normal urinalysis, GFR, spot urine protein/creatinine ratio 0.090, GFR 131 ml/min. Case 2: A 44 years old female was diagnosed as IgAN stage IV(HSLee class.) with 61% glomerulosclerosis. Follow up renal biopsy showed 41% sclerosis with disappearance of IgA and C3 deposits. serum creatinine and GFR before therapy was 1.77 mg/dl and 35 ml/min, however follow up after 27 months was 0.99 mg/dl and 65 ml/min. Case 3: A 35 years old female was diagnosed as IgAN grade V with 67% glomerulosclerosis. Follow up renal biopsy showed IgAN stage IV with 33% glomerulosclerosis. Initial creatinine was 1.39 mg/dl and GFR was 43 ml/min. and follow up serum creatinine 1.21 mg/dl and GFR 53 ml/min.

Conclusions: Although further studies are needed, MP pulse therapy and autologous SVF therapy in intractable severe IgAN showed dramatic improvement not only laboratory data but also pathological findings. Therefore MP pulse therapy followed by autologous SVF therapy might be a promising new therapeutic strategy without noticeable side-effects or complications.

FR-PO669

Value of Biological Markers for Kidney Involvement and Outcome in Henoch Schonlein Purpura Nephritis: A Prospective Cohort Study
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Background: Henoch–Schönlein purpura (HSP) is a systemic vasculitis characterized by immunoglobulin A (IgA) deposits in skin, joints, kidneys and other organs. The current diagnosis and prognosis markers used in HSP assessment lack accuracy to estimate the risk of nephritis occurrence and its long-term outcome.

Methods: This French multicenter study prospectively enrolled 135 patients at the time of HSP diagnosis. All patients were evaluated for clinical and biological parameters: cytokines, immunoglobulins, Neutrophil Gelatinase Associated Lipocalin (NGAL), immune complexes and IgA glycosylation in serum and urine. They were followed 1 year for renal outcome. Poor renal outcome was defined as proteinuria/creatinine ratio >0.5g/g and/or decrease of eGFR or death.

Results: Among the 135 HSP patients, 93 had HSP-related nephritis (HSPN) and 42 did not. At the time of diagnosis, patients HSPN, compared to HSP without nephritis, exhibited higher serum levels of Galactose-deficient IgA1 and higher urinary concentrations of IgA, IgG, IgM, NGAL, IL-1β, IL-6, IL-8, IL-10, IgA-IgG and IgA-sCD89 complexes. Among those, urinary IgA had the highest AUC. After one year of follow-up, 23/93 patients showed a poor renal outcome. Clinical factors associated with poor renal outcome were age, diabetes, hypertension and eGFR decline. Among all biological parameters, determinants of poor renal outcome were urinary IgA, IgM, IgA-IgG and IgA-sCD89 complexes. They showed an accurate discrimination performance to identify patients with poor renal outcome.

Conclusions: This large prospective cohort study, with both adults and children, included at the onset of the disease, bring a better understanding of the pathophysiology of HSP. We defined new biomarkers able to segregate patients initially with or without nephritis, some of them provide an accurate discrimination of HSP-nephritis patients with poor 1-year renal outcome. This allowed us to define promising tools for clinicians that could be helpful in the diagnostic and follow-up of HSPN.

Funding: Government Support - Non-U.S.

FR-PO670

Antibody-Mediated Depletion of Galactose-Deficient IgA1 Secreted by Specific Subset of Tonsillar B Cells: A Novel Potential Pharmaceutical Concept for IgA Nephropathy
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Background: Galactose-deficient IgA1 (Gd-IgA1) has been proposed as one of the important effector molecules in IgA nephropathy (IgAN). In IgAN multi-hit hypothesis, Gd-IgA1 secretion from tonsillar B cells is the primary step for pathogenesis of the disease. Serum Gd-IgA1 level is significantly high in patients with IgAN, approved by Gd-IgA1 ELISA. It might be possible that specific depletion of Gd-IgA1-producing tonsillar B cells enables descending serum Gd-IgA1 level and consequent IgAN treatment. Several reports have suggested the involvement of glycosylation enzymes such as galactosyltransferase and sialyltransferase in Gd-IgA1 secretion from mucosal B cells; we hypothesized that *O*-link glycans were broadly aberrant in various proteins expressed in tonsillar B cells of patients with IgAN due to dysfunction of those enzymes under pathophysiological condition.

Methods: CD27, which has *O*-link glycan sites, was chosen as a target membranous molecule in B cells. Anti galactose-deficient CD27 (Gd-CD27) monoclonal antibody (mAb) was established. Target cells of anti Gd-CD27 mAb were examined by flow cytometry using tonsillar cells and peripheral blood mononuclear cells (PBMCs) derived from patients with IgAN. Anti Gd-CD27 mAb was subjected to antibody dependent cytotoxicity (ADCC) assay against tonsillar Gd-CD27-positive cells under NK cells to evaluate their viability by flow cytometry and supernatant Gd-IgA1 level by enzyme-linked immunosorbent assay (Gd-IgA1 ELISA).

Results: Gd-CD27-positive cells were predominantly observed in tonsil derived from patients with IgAN. ADCC assay with NK cells revealed dose-dependent depletion of Gd-CD27-positive cells and consequent decrease of supernatant Gd-IgA1 level.

Conclusions: This study suggested the possibility to remedy IgAN by targeting tonsillar B cells that produce Gd-IgA1, based on the multi-hit hypothesis. Anti Gd-CD27 mAb may be one of the candidate therapeutic agents for IgAN.

Funding: Pharmaceutical Company Support - Kyowa Hakko Kirin Co., Ltd.

FR-PO671

Galactose-Deficient IgA1 Monoclonal Antibody Specifically Discriminate IgA Nephropathy and Henoch-Schönlein Purpura Nephritis
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Background: Galactose-deficient IgA1 (Gd-IgA1) has been proposed as an important effecter molecule in patients with IgA nephropathy (IgAN) and Henoch-Schönlein purpura nephritis (HSPN). Our previous study revealed that Gd-IgA1-specific monoclonal antibody KM55 (KM55 mAb) could be a new tool for detecting circulatory Gd-IgA1 in patients with IgAN, which enabled us to study molecular roles of Gd-IgA1. In this study, we further examined pathophysiological significance of Gd-IgA1 in glomerular deposits of patients with IgAN and HSPN by immunohistochemical analysis with KM55 mAb.

Methods: Renal biopsy specimens were obtained from 2013 to 2015 at Juntendo University Hospital with the informed consent from patients. Double Immunofluorescentstaining of Gd-IgA1 with KM55 mAb and anti-human IgA antibody was performed in paraffin embedded sections of renal biopsy specimens from patients with IgAN (n=45), and other renal diseases (n=30); such as lupus nephritis, HCV-related nephropathy and Henoch-Schönlein purpura nephritis (HSPN).

Results: Glomerular Gd-IgA1 was specifically detected in all patients with IgAN, but not in those with other renal diseases. Gd-IgA1 could not be detected even in patients with lupus nephritis accompanied by glomerular IgA deposition. In patients with IgAN, Gd-IgA1 was localized predominantly in the mesangial region as IgA deposition. Importantly, KM55 mAb was also positive in patient with HSPN as similar to those in IgAN.

Conclusions: This is the first observation to clearly indicate that Gd-IgA1 could be specifically deposited in glomeruli of IgAN and HSPN, strongly suggesting the pathophysiological function of Gd-IgA1 in those diseases. Further studies are necessary to clarify the underlying mechanisms of Gd-IgA1 deposition and induction of renal injuries in IgAN and HSPN. Novel monoclonal antibody KM55 mAb against Gd-IgA1 could be a powerful tool to detect nephritogenic IgA in patients with IgAN and HSPN.

Funding: Pharmaceutical Company Support - Kyowa Hakko Kirin Co., Ltd., Government Support - Non-U.S.

FR-PO672

Production of Aberrantly-Glycosylated IgA1 and the Corresponding Autoantibodies Is Elevated in Patients with Henoch- Schönlein Purpura Nephritis
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Background: Patients with Henoch-Schöenlein purpura with nephritis (HSPN) and IgA nephropathy (IgAN), but not with Henoch-Schoenlein purpura without nephritis (HSP) have elevated serum levels of galactose-deficient IgA1 (Gd-IgA1). Gd-IgA1 is recognized by Gd-IgA1-specific IgG autoantibodies and, thus, forms immune complexes that are pathogenic, as they activate mesangial cells to proliferate of overproduce components of mesangial matrix. Mucosal infections are often associated with clinical presentation and exacerbation of HSPN and IgAN. In IgAN, some Gd-IgA1 and autoantibodies originate from tonsillar immunoglobulin-secreting cells; IL-6 may enhanceproduction of Gd-IgA1. Here, we assessed whether the common pathogenic features of IgAN are found also in patients with HSPN.

Methods: Serum and immunoglobulin-secreting cells from patients with HSPN and HSP and healthy controls were used for analysis of IgA1 glycosylation and Gd-IgA1-specific IgG. Serum Gd-IgA1 and Gd-IgA1-specific IgG were measured before and after tonsillectomy in adult HSPN patients.

Results: IgA1 secreted by cells from HSPN patients had Gal-deficient *O*-glycans, whereas IgA1 from HSP patients and healthy controls was normally galactosylated. This finding was consistent with lower expression of ß1,3-galactosyltransferase observed in cells from HSPN patients compared to cells from HSP patients. Levels of Gd-IgA1-specific IgG in sera and cell-culture supernatants of IgG-secreting cells were higher in HSPN than in HSP patients or healthy controls ($P<0.01$). Serum levels of Gd-IgA1 and Gd-IgA1-specific IgG were elevated in HSPN patients with active disease, manifested by hematuria/proteinuria ($P<0.01$). Tonsillectomy in HSPN patients reduced proteinuria and hematuria was accompanied by reduction of serum levels of Gd-IgA1 and Gd-IgA1-specific IgG ($P<0.001$).

Conclusions: Gd-IgA1 and Gd-IgA1-specific autoantibodies are elevated in patients with HSPN, supporting the hypothesis that HSPN and IgAN have common pathogenetic components.

Funding: NIDDK Support

FR-PO673

Regional Variations in the Clinical Characteristics at Diagnosis in Japanese Patients with IgA Nephropathy: An Analysis of the Japan Renal Biopsy Registry (J-RBR)
Yusuke Okabayashi,[1] Nobuo Tsuboi,[1] Yoichi Miyazaki,[1] Tetsuya Kawamura,[1] Makoto Ogura,[1] Ichiei Narita,[2] Toshiharu Ninomiya,[3] Hitoshi Yokoyama,[4] Takashi Yokoo.[1] *[1]Div of Nephrology and Hypertension, The Jikei Univ School of Medicine, Tokyo, Japan; [2]Div of Clinical Nephrology and Rheumatology, Niigata Univ Graduate School of Medical and Dental Sciences; [3]Center for Cohort Studies, Kyushu Univ; [4]Dept of Nephrology, Kanazawa Medical Univ School of Medicine.*

Background: Older age, hypertension, renal impairment, and heavy proteinuria at diagnosis are known to be poor prognostic indicators of immunoglobulin A nephropathy (IgAN). Previous studies have shown the remarkable regional differences in the incidence of ESRD within Japan, which has an ethnically homogeneous population (JAMA, 2000). This study examined the regional differences in these clinical features at biopsy and the relevant factors associated with such differences among Japanese IgAN patients.

Methods: The Japan Renal Biopsy Registry registration facilities were divided into 10 regions. The clinical features at biopsy were compared among the groups, which was divided based on the factors that may be associated with regional differences.

Results: A total 7177 patients were analyzed. In each region, the sex ratio was almost the same, but there were significant regional variations in age, eGFR, and urinary protein excretion. Distributions of clinical features were closely associated with the number of the Japanese Society of Nephrology (JSN) members per population, while, the regional variations in the clinical features did not correlate with the distributions of the elderly populations.

Variables	Category of JSN members ratio			P-value *
	Highest 3 areas (n=2458)	Intermediate 4 areas (n=1977)	Lowest 3 areas (n=2742)	
JSN members /10,000 populations	0.89	0.76	0.58	<0.001
Elderly IgAN patients (%)	9.4	8.7	10.4	0.127
Hypertension (%)	38.6	41.7	46.9	<0.001
eGFR (ml/min/1.73 m^2)	76.7±30.1	76.3±30.8	70.7±28.6	<0.001
UPE (g/day)	0.86±1.52	1.00±1.41	1.54±1.79	<0.001
Urinary RBC (%Grade3-4)	65.3	66.8	68.0	0.123
C-grade Ⅲ (%)	18.7	24.7	32.0	<0.001

UPE: urinary protein excretion, RBC: red blood cell,
Urinary RBC: Grade 1: 0-4/HPF, Grade 2: 5-10/HPF, Grade 3: 10-30/HPF, Grade 4: >30/HPF,
Continuous variables were expressed as mean±S.D. * : Kruskal-Wallis test

Conclusions: There are significant regional differences in the clinical features at diagnosis among Japanese IgAN patients. Social factors, such as an uneven distribution of nephrologists, may influence the timing of diagnosis and contribute to such differences.

FR-PO674

Prognostic Impact of Deleted Variants in Complement Factor H-Related Protein Genes, CFHR3 and CFHR1, in IgA Nephropathy on a Caucasian Population Perrine Jullien, Blandine Laurent, Christopher R. Mariat, Eric Alamartine, Nicolas Maillard. *Nephrology, Dialysis, Transplantation, CHU de Saint Etienne, Saint-Etienne, France.*

Background: Activation of complement through the alternative pathway plays a key role in the pathogenesis of IgA nephropathy. Large international genome–wide association studies have identified a deletion of complement factor H–related genes 1 and 3 (ΔCFHR1/3) associated with a lower risk of IgA nephropathy, but the prognosis value of these deletions in IgA nephropathy in Caucasian remains unknown. This study aims to compare the renal outcomes according to the ΔCFHR1/3 genotype.

Methods: This study was retrospective monocentric including only caucasian patients with biopsy proven primary IgA nephropathy since 1979, with available DNA samples and informed consent. Quantitative PCR was used to determine the presence of deletions of the genes CFHR1/3 (CFHR3-1Δ), standardized on the RNAse P gene. Clinical and biological data were collected by reviewing subject's medical records.

Results: A total of 727 patients were included, with an age of (median [IQR]) 38 [28-51] years at diagnosis and a follow up of 11,4 [5-18,1] years. So far, copy number analysis has been performed for 425 patients for CFHR1 gene only. Thirty-four percents of patients were heterozygous and 2% were homozygous for CFHR1Δ. Association between CFHR1Δ and age, eGFR, urinary protein excretion or pathologic measures at diagnosis was not significant (Welch t-test, p=0.99, p=0.1, p=0.35 and p=0.72 respectively). No significant association was found between CFHR1Δ and evolution toward stage III (167/425 patients) and stage V chronic kidney disease (CKD) (89/425 patients) (log rank test, p=0.62 and p=0.37 respectively).

Conclusions: There is no trend of association between CFHR1 gene deletion and renal outcomes in this intermediate analysis. Complete results concerning CFHR1/3 genotype of the whole cohort and evolution of renal function will be available for the ASN meeting.

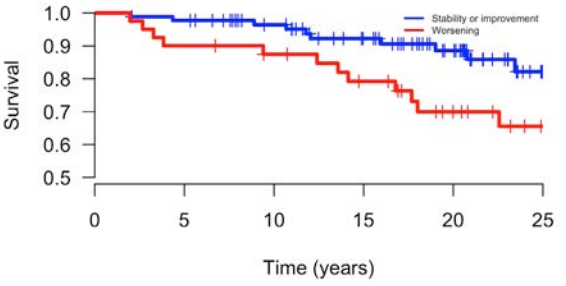
FR-PO675

Repeat Renal Biopsy Improves Oxford Classification-Based Prediction of IgA Nephropathy Outcomes Perrine Jullien, Blandine Laurent, Christopher R. Mariat, Eric Alamartine, Nicolas Maillard. *Dept of Nephrology, Dialysis, Transplantation, CHU Saint Etienne, Saint Etienne, France.*

Background: The prognosis of IgA nephropathy is heterogeneous, and its prediction is crucial to refine patient's treatment. It remains unknown whether a repeat pathological evaluation can be useful to refine renal death prediction. The aim of this study was to evaluate the prognostic impact of an Oxford classification-based repeat kidney tissue evaluation to predict end stage renal disease (ESRD).

Methods: Patients with biopsy-proven primary IgAN who underwent 2 renal biopsies in our center were analyzed retrospectively. Renal biopsies were scored blinded to the clinical data and according to the Oxford classification. Multivariable cox models were generated to evaluate the prognosis impact of the Oxford classification score progression on ESRD. This histological progression was defined as the difference in the sum of M,E,S,T variables between two biopsies (ΔMEST).

Results: A total of 131 patients were included, with an age of (median, [IQR]) 33 [23-45] years at diagnosis and a follow up of 19 [11-25] years. The second biopsy was performed after a time of 64 [59-78] months. ΔMEST was predictive of ESRD univariately (Cox, Hazard Ratio[IC95%] 1.38[1.06;1.81]).



This predictive capability remained significant after adjustment on clinical data at diagnosis and on initial Oxford classification score (M,E,S,T separately) (HR 2.37[1.55;3.62]). ΔMEST was still predictive of renal death after adjustment on previous variables and on evolution of proteinuria, evolution of hypertension and GFR slope between biopsies (HR 1.91[1.16 ;3.14]).

Conclusions: The evolution of Oxford classification, assessed by a second biopsy, is an efficient tool to predict ESRD in IgA Nephropathy. This prediction is independent from the histo-clinical evaluation at baseline and even from the clinical evolution between two biopsies.

FR-PO676

Comparison of Urinary Protein Levels in IgA Nephropathy Patients with or without Streptococcus Mutans Strains with cnm Gene Encoding Collagen-Binding Protein in the Oral Cavity Taro Misaki,[1] Shuhei Naka,[2] Rina Hatakeyama,[2] Akiko Fukunaga,[3] Ryota Nomura,[2] Taisuke Isozaki,[1] Kazuhiko Nakano.[2] *[1]Div of Nephrology, Seirei Hamamatsu General Hospital, Hamamatsu, Shizuoka, Japan; [2]Div of Oral Infections and Disease Control, Osaka Univ Graduate School of Dentistry, Suita, Osaka, Japan; [3]Dept of Dentistry, Seirei Hamamatsu General Hospital, Hamamatsu, Shizuoka, Japan.*

Background: Immunoglobulin (Ig)A nephropathy (IgAN) is the most common primary chronic glomerulonephritis, but the precise initiating pathogenesis remains unclear. *Streptococcus mutans* is a major pathogen for human dental caries, and *S. mutans* strains with the *cnm* gene encoding the Cnm collagen-binding protein reportedly contribute to the development of several systemic diseases. We have previously found that the rate of *cnm*-positive *S. mutans* strains harbored in the oral cavity was significantly higher in an IgAN patient group (32.1%) than in healthy controls (14.0%, p<0.05), as reported atASN Kidney Week 2014 and in *Clinical and Experimental Nephrology* in 2015. We therefore investigated the relationship between dental caries status and IgA nephropathy.

Methods: Saliva specimens from IgAN patients (n=109) were collected and *S. mutans* strains were isolated. The *cnm* gene was detected using PCR techniques. A total of 49 patients who agreed to dental visits were evaluated for dental caries status (DMFT score: decayed, missing, or filled teeth).

Results: The rate of *cnm*-positive *S. mutans*strains detected in IgAN patients was 27.5%. Mean (±standard error of the mean) DMFT score was significantly higher in the *cnm*-positive group (16.3±1.3) than in the *cnm*-negative group (11.9±1.2, p=0.04). Urinary protein levels were significantly higher in the *cnm*-positive group (1.6±0.5 g/gCr) than in the *cnm*-negative group (0.4±0.1 g/gCr, p=0.0021). Moreover, urinary protein levels were significantly higher in the high DMFT score group (score >15; 0.9 ± 0.3 g/gCr) than in the low DMFT score group (score <15; 0.3 ±0.05 g/gCr, p=0.0246).

Conclusions: The *cnm*-positive *S. mutans* strains could be associated with urinary protein levels as well as dental caries status in IgAN patients.

FR-PO677

Identification of Micro-RNAs Associated with IgAN Progression Izabella Z.A. Pawluczyk,[1] Robert H. Jenkins,[2] Karen Molyneux,[1] Donald Fraser,[2] Jonathan Barratt.[1] *[1]Infection, Immunity and Inflammation, Univ of Leicester, Leicester, Leicestershire, United Kingdom; [2]Inst of Molecular and Experimental Medicine, Univ of Cardiff, Cardiff, Wales, United Kingdom.*

Background: MicroRNAs (miRs) are small non-coding RNA molecules that post transcriptionally regulate gene expression and control many physiological and pathological processes. The aim of this study was to identify miRs associated with the risk of IgAN progression.

Methods: The miRnomes of renal biopsies from IgAN progressors (IgANp)(100% increase in serum creatinine post diagnosis) and non progressors (IgANnp) (<10% increase in serum creatinine over 10 years) were compared. To rule out differences due to generic proteinuric renal disease IgAN profiles were compared with those from membranous nephropathy (MN). Thin membrane nephropathy (TM) biopsies were used as 'normal' controls. Next Generation Sequencing was performed on RNA from 6 frozen biopsies from each of the 4 cohorts.

Results: 13 miRs were differentially expressed in IgANp compared to IgANnp, MN and TM and selected for validation by qPCR (20 biopsies per cohort). Validation identified 5 dysregulated miRs. Cortical localisation studies revealed that miR-150 exhibited a trend towards higher glomerular levels in IgANp (p=0.054), and significantly raised glomerular levels in MN (p=0.02). No differences in distribution were seen in IgANnp and TM. miR-155 expression was raised in the glomeruli of IgANp (P=0.025) and showed a similar trend

in IgANnp (p=0.057). Expression levels were comparable in the MN and TM. miR135a displayed higher interstitial expression in IgAnp (p=0.02) while IgANp, MN and TM showed no statistical difference in distribution.

Conclusions: These data suggest that a glomerular preference for miR-150 may indicate progressive disease, raised glomerular levels of miR155 may be associated with the IgAN phenotype and increased interstitial expression of miR135a may indicate a lower risk of progression. In conclusion these data provide us with a platform to robustly test miRs 150, 155 and 135a as potential biomarkers of IgAN progression and to investigate in vitro and in vivo the functional roles of these miRs in the pathogenesis and progression of IgAN nephropathy.

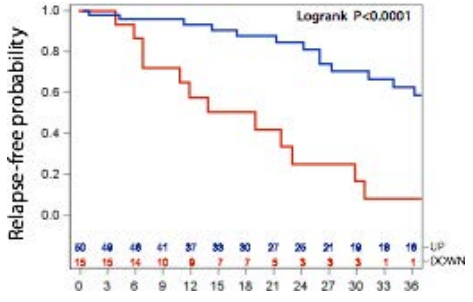
FR-PO678

Gene-Specific DNA Methylation Changes Predict Stable Remission in ANCA-Associated Vasculitis Patients Britta E. Jones,[1,2] Jia Jin Yang,[1] Akhil Muthigi,[1] Susan L. Hogan,[1] Yichun Hu,[1] Joshua Starmer,[1,3] Caroline J. Poulton,[1] William Franklin Pendergraft,[1] J. Charles Jennette,[1,2] Ronald J. Falk,[1] Dominic J. Ciavatta.[1,3] *[1]UNC Kidney Center, Dept of Medicine, UNC, Chapel Hill, NC; [2]Dept of Pathology and Laboratory Medicine, UNC, Chapel Hill, NC; [3]Dept of Genetics, UNC, Chapel Hill, NC.*

Background: Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) is an autoimmune condition characterized by vascular inflammation and organ damage. Pharmacologically induced remission is complicated by relapses. Potential triggers of relapse are immunological challenges and environmental insults, both of which are associated with changes in epigenetic silencing modifications.

Methods: To establish a link between DNA methylation, a model epigenetic gene silencing modification, and autoantigen gene expression and disease status in AAV, we measured gene-specific DNA methylation of the autoantigen genes, myeloperoxidase (*MPO*) and proteinase 3 (*PRTN3*), in leukocytes of AAV patients followed longitudinally (n=82) and healthy controls (n=32).

Results: Patients with active disease demonstrated hypomethylation of *MPO* and *PRTN3* and increased expression of the autoantigens. Longitudinal analysis divided AAV patients into two groups based on DNA methylation change from active disease to remission. In patients with increased DNA methylation, *MPO* and *PRTN3* expression correlated with DNA methylation. Patients who increased DNA methylation at the *PRTN3* promoter had a significantly greater probability of a relapse-free period, independent of ANCA serotype; patients with decreased DNA methylation were more likely to relapse with a hazard ratio of 4.55 (95% CI, 2.09 to 9.91).



Conclusions: Changes in the DNA methylation status of the *PRTN3* promoter predict likelihood of stable remission and may explain autoantigen gene regulation.

Funding: NIDDK Support

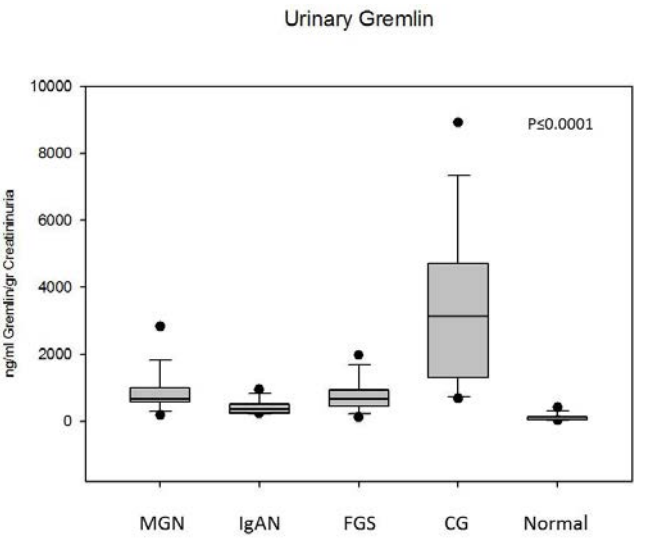
FR-PO679

Gremlin, a New Potential Urinary Biomarker of Crescentic Glomerulonephritis Alejandra Droguett,[1] Daniel Carpio,[1] Carolina Lavoz,[1] Maria Eugenia Burgos,[1] Graciela Valderrama,[1] Jesus Egido,[2] Marta Ruiz-Ortega,[2] Sergio A. Mezzano.[1] *[1]Nephrology, Univ Austral, Valdivia, Chile; [2]Fundación Jiménez Díaz, Univ Autónoma, Madrid, Spain.*

Background: Crescentic glomerulonephritis (CG) require immediate accurate diagnosis and appropriate therapeutic decisions. The pathogenesis of crescent formation still is debated. We have previously described that Gremlin, a BMP antagonist, is highly expressed both in cellular and fibrocellular crescents, corresponding to proliferating parietal epithelial cells (PECs) and monocytes and we proposed that Gremlin could act as a mediator of this damage and be a urinary biomarker of crescent formation.

Methods: We here studied urinary Gremlin by ELISA test in samples from 94 patients who simultaneously undergoing renal biopsy. 43 of them with CG (23 Pauci-immune, 17 Systemic Lupus and 3 IgA Nephropathy), 51 patients with other non crescentic GN and 16 healthy controls. CD163 and CCL18 have been recently described as monocytes-macrophages secreted proteins associate to crescent formation, therefore we also examined the potential colocalization of Gremlin with these proteins by immunohistochemistry and in situ hybridization.

Results: Urinary Gremlin levels were markedly augmented in patients with crescentic glomerulonephritis compared with healthy donors and with patients with other glomerular diseases (CG: 347.8 ug/grCr vs 91.6 in non-crescentic GN and 11.3 in healthy controls; P<0.001) (figure 1), and were correlated with the percentage of crescents (R= 0.5, P<0.004) and tubulointerstitial fibrosis (R=0.5, P<0.02).



Moreover, we confirmed a strong expression of Gremlin protein and mRNA in cellular glomerular crescents and this expression was co-located with CD163 and CCL18.

Conclusions: Overall, our results further extend the concept that Gremlin plays a role in the genesis of crescent formation and suggest that urinary Gremlin could be a non-invasive biomarker in CG. Fondecyt 1160465.

Funding: Government Support - Non-U.S.

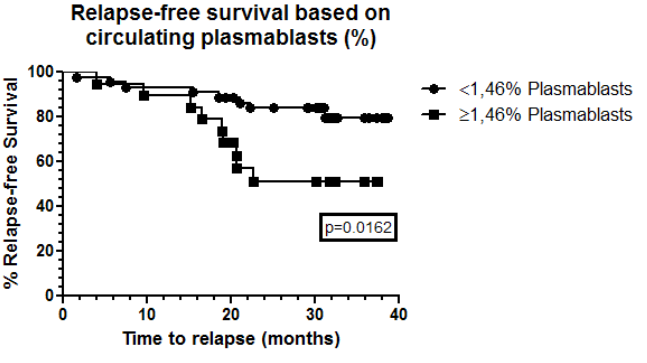
FR-PO680

Percentage of Circulating CD19+CD27+/hiCD38hi Plasmablasts in Granulomatosis with Polyangiitis Patients Predicts Relapse-Free Survival Anouk von Borstel,[1] Judith Land,[2] Abraham Rutgers,[2] Wayel H. Abdulahad,[2] Coen A. Stegeman,[1] Peter Heeringa,[3] Jan-Stephan Sanders.[1] *[1]Internal Medicine, Nephrology, UMCG, Groningen, Netherlands; [2]Rheumatology and Clinical Immunology, UMCG, Groningen, Netherlands; [3]Pathology and Medical Biology, UMCG, Groningen, Netherlands.*

Background: Granulomatosis with polyangiitis (GPA) is a small vessel vasculitis characterized by the presence of ANCA. Patients with GPA suffer from frequent disease relapses. Currently no reliable method to predict relapse in individual patients is available. B cells have both pro- and anti-inflammatory functions and are precursors of plasma cells that produce ANCA. We investigated the proportion of circulating plasmablasts (PB) in relation to relapse-free survival.

Methods: A cohort of 83 GPA patients was monitored for 19.4-38.8 months (median 32.7 months). By flow cytometry, the whole blood B cell phenotypes were determined from remission patients at time of inclusion. PB were defined as $CD27^{+/hi}CD38^{hi}$ within $CD19^{+}$ B cells. Patients with <2% B cells were excluded from analysis (n=20). Relapse-free survival was analyzed by Log-rank test and Cox proportional hazards analysis.

Results: During follow-up 17 patients relapsed 1.7-31.2 months (median 18.7) after inclusion. Relapsing patients had a significantly increased percentage of PB (median 1.46; range 0.73-3.88) compared to 46 non-relapsing patients (median 1.01; range 0.12-4.94; p=0.0436). Relapse-free survival during follow-up was significantly (p=0.0162) worse in patients with more than 1,46% PB (51.3%; n=44) in the circulation, 47.4% of these patients suffered from a relapse compared to 18.2% of patients with less than 1.46% PB (relapse-free survival 79.4%; n=19).



Conclusions: In conclusion, GPA patients that have a higher percentage of PB are at increased risk to experience a disease flare. The percentage of PB might be a potential biomarker for relapse and a novel monitoring and therapeutic target in AAV.

Funding: Government Support - Non-U.S.

FR-PO681

International Validation Study for the Histopathological Classification of ANCA-Associated Glomerulonephritis (AAGN) Emma Van Daalen,[1] Laure-Helene Noel,[3] Kensuke Joh,[4] Yayoi Ogawa,[5] Suzanne Wilhelmus,[1] Andreas Kronbichler,[6] Renate Kain,[7] Steven Salvatore,[8] Xavier Puéchal,[9] Wladimir M. Szpirt,[10] Jan A. Bruijn,[1] Ingeborg M. Bajema.[1] *[1]Pathology, Leiden Univ Medical Center; [2]Nephropathology, San Gerardo Hospital, Monza; [3]Pathology, Hôpital Necker, Paris; [4]Pathology, Tohoku Univ Sendai; [5]Renal Pathology Center, Hokkaido; [6]Internal Medicine, Medical Univ of Innsbruck; [7]Pathology, Medical Univ of Vienna; [8]Pathology and Laboratory Medicine, Weill Cornell Medical College, New York; [9]Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Paris; [10]Nephrology, Rigshospitalet, Copenhagen.*

Background: In the original validation study for the histopathological classification of AAGN, the order of classes from focal to sclerotic corresponded to increasing severity of renal function loss. Subsequent validation studies (N=15) disagreed on outcomes in crescentic and mixed class. We here present an international validation study driven by the original investigators.

Methods: This interim analysis included 104 patients from centers in the U.S., Europe, and Asia. Each case was scored at a secured website by 2 pathologists from a group of 6; a 3rd pathologist gave the final conclusion in case of disagreement. Outcome at 1 and 5 years follow-up was based on KDOQI classification (eGFR>60/15-60/<15 or on dialysis/death). Renal survival was expressed as ESRD-free survival.

Results: The distribution of the histopathological classes was 41% focal, 18% crescentic, 27% mixed, 14% sclerotic. Mean $eGFR_{baseline}$ differed between classes (P<0.001), but was similar in crescentic and mixed class. The order of classes corresponded to outcome at 1 and 5 years (P<0.001, resp. P=0.016). Renal survival after 5 years was 95% in focal, 89% in crescentic, 96% in mixed, and 71% in sclerotic class. In the original study, renal survival after 5 years for respective classes was 93%, 76%, 61%, and 50%.

Conclusions: In this international validation study for the histopathological classification of AAGN, the classification predicted outcome at 1 and 5 years with crescentic and mixed class lumped together. Interestingly, in all classes renal survival was much higher than in the original report, possibly due to improvements in therapy.

FR-PO682

Measuring Complement Activation in ANCA-Associated Vasculitis Sonia Brigitte Boyer,[1] Eve Wu,[1] Elizabeth Alderman McInnis,[1] Lydia Aybar,[1] Carmen E. Mendoza,[1] Yichun Hu,[1] Susan L. Hogan,[1] Ronald J. Falk,[1] Patrick H. Nachman,[1] J. Charles Jennette,[2] Donna O. Bunch.[1] *[1]UNC Kidney Center, Chapel Hill, NC; [2]Pathology, Univ of North Carolina, Chapel Hill, NC.*

Background: Investigating complement activation in ANCA-associated vasculitis (AAV) remains important. Cleavage of complement proteins *in vitro* despite using EDTA has been reported, thus accurate measurement of complement activation requires careful sample processing to avoid *in vitro* complement activation. We studied the effect of futhan (FU), a broad-specificity protease inhibitor, on measured complement activation in patients with AAV and healthy controls (HC).

Methods: 61 blood samples (15 active, 26 remission and 20 HC) were drawn into EDTA tubes and put on ice immediately. Paired samples were processed without or with 100mg/ml FU within 30 minutes and stored at -80°C until use. Plasma concentrations of properdin (Hycult), Bb, C3a, C5a and sC5b-9 (Quidel) were measured by ELISA. Differences in quantitative parameters between groups were assessed using a paired signed rank test. The relationship between two continuous variables was analyzed using Pearson's correlation.

Results: Bb plasma levels were higher in samples processed without FU than with FU (p<0.0001) for all sample groups (Table); however, the difference was systematic (r^2=0.83). Levels of sC5b9 also consistently trended higher (r^2=0.8) in samples processed without FU than with FU, but were different only in one group (p=0.02). C3a, C5a and properdin did not differ with or without FU (data not shown). C3a and C5a in samples with FU strongly correlated with those without FU (r^2 0.94 and 0.94 respectively).

Analyte	Group	No FU (median)	+FU (median)	P
Bb (µg/ml)	Act	0.88	0.69	<.0001
	Rem	0.85	0.69	<.0001
	HC	0.70	0.58	<.0001
sC5b9 (ng/ml)	Act	203.2	181.3	0.07
	Rem	134.7	126.5	0.02
	HC	123.6	114.5	0.29

Conclusions: Addition of FU may be required to accurately measure Bb and sC5b-9, but not properdin, C3a, or C5a. Further study is required, but our data suggests standardized processing methods including FU will improve measurement of complement activation.

Funding: NIDDK Support

FR-PO683

Significance of Immune Complex Deposition in Antineutrophil Cytoplasmic Antibody Associated Glomerulonephritis Ravi Agrawal,[1,2] James R. Taylor,[3] Pranay Kathuria.[1] *[1]Div of Nephrology, Univ of Oklahoma, School of Community Medicine, Tulsa, OK; [2]Northeast Pennsylvania Nephrology Associates, Scranton, PA; [3]Pathology Laboratory Associates, Tulsa, OK.*

Background: Antineutrophil Cytoplasmic Antibody(ANCA) associated glomerulonephritis is characterized by findings of a pauci-immune necrotizing and crescentic glomerulonephritis. In a small percentage of cases, immune complex deposition may be seen and in various studies have been associated with more severe disease.

Methods: A retrospective study of 43 ANCA positive patients with necrotizing/crescentic glomerulonephritis. Using data from the electron microscopy, patients were categorized into those with deposits and those without deposits. The presence and absence of deposits was correlated with age, ethnicity, clinical data, histologic (percentage of crescents and glomerular cellularity score) and immunofluorescence findings.

Results: Thirteen patients (30.2%) had immune deposits on electron microscopy. Immune deposits were seen significantly more in males (p=0.019) and in African-American ethnicity (p=0.023). The presence of immune deposits was associated with significantly more crescents (52.9±19.8 % Vs 31.9±27.4%, p=0.017) and more glomerular cellularity score (p=0.020). The mean serum creatinine but not the eGFR(calculated using Modification of Diet in Renal Disease equation) was significantly higher in the group with immune complex deposits. There was no significant difference between the two groups in terms of comorbid conditions and the amount of proteinuria. Immunoglobulins IgG and IgA were significantly more in patients with immune deposits (p=0.0004 and p=0.025, respectively).

Conclusions: Immune complex deposition in ANCA glomerulonephritis is seen significantly more in males and in African-American ethnicity. It is associated with significantly more crescents and higher glomerular cellularity score indicating more glomerular damage.

FR-PO684

Thrombotic Microangiopathy Associated with a Monoclonal Gammopathy Aishwarya Ravindran, Ronald Go, Fernando C. Fervenza, Sanjeev Sethi. *Mayo Clinic, Rochester, MN.*

Background: Thrombotic microangiopathies (TMA) comprise a heterogenous set of conditions linked by a common histopathologic finding of endothelial damage resulting in microvascular thrombosis. Monoclonal gammopathy may act as a potential trigger in the pathogenesis of TMA. We performed a retrospective, single institution study to determine the prevalence of monoclonal gammopathy in patients with TMA.

Methods: We included adults (≥18 years) from 2000-2016 with a clinical diagnosis of TMA who met the following criteria: i) microangiopathic hemolytic anemia and thrombocytopenia or histologic evidence of TMA ii) absence of a coagulopathy and a negative direct antiglobin test, iii) screened for monoclonal gammopathy. Monoclonal gammopathy was defined as the presence of monoclonal Ig in the serum/urine.

Results: 146 patients met the study criteria. Monoclonal Ig was detected in 20 patients (13.7%). The median age at diagnosis of TMA in patients with monoclonal Ig was 63 years (range: 19-80) and the majority were males (12; 57.1%). Among patients >50 years, the prevalence of monoclonal gammopathy was 19.7% (n=16), which is approximately 5-fold higher than the expected rate in this population (4.2%). Among the 20 patients with monoclonal gammopathy, 2 (10%) were classified as thrombotic thrombocytopenic purpura (ADAMTS13 activity <10%), 10 (50%) as atypical hemolytic uremic syndrome (clinicopathologic findings), and the remaining 8 (40%) could not be classified. The median serum creatinine at time of TMA diagnosis was 3.5 mg/dL (range: 0.7-14). Renal biopsy was performed in 15 cases, of which 8 showed glomerular thrombi, 11 showed mesangiolysis, and all 15 showed double contours along glomerular capillaries. Acute tubular injury was present in all biopsies. 8 biopsies also showed arterial thrombi. None of the biopsies showed monoclonal Ig on IF microscopy. 12 patients (60%) required dialysis during the course of the disease.

Conclusions: Similar to C3 glomerulopathy, our study shows an unexpectedly high prevalence of monoclonal gammopathy in patients with TMA suggesting a potential association of TMA with monoclonal gammopathy. Further studies are required to determine the underlying mechanisms of TMA associated with monoclonal gammopathy.

FR-PO685

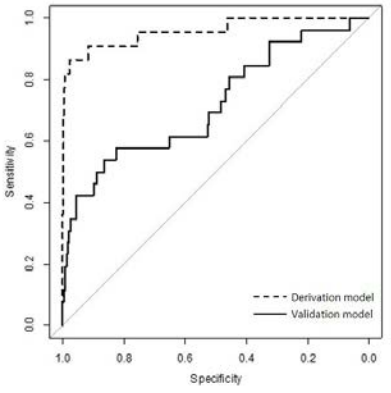
A Prediction Model for the Diagnosis of Thrombotic Microangiopathies at Hospital Admission Pietro Manuel Ferraro, Gianmarco Lombardi, Alessandro Naticchia, Antonio Sturniolo, Giovanni Gambaro. *Fondazione Policlinico Univ A. Gemelli, Rome.*

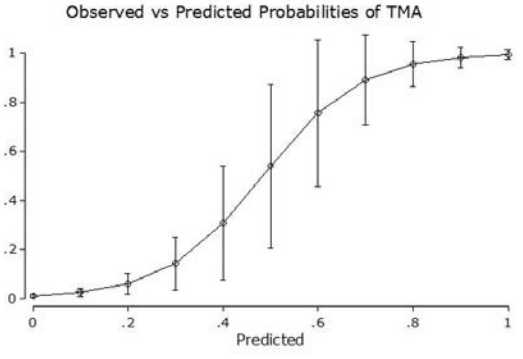
Background: Thrombotic microangiopathies (TMA) are a heterogeneous group of conditions characterized by microangiopathic hemolytic anemia, thrombocytopenia and several degrees of renal and other organs impairment. We developed a prediction model for the timely diagnosis of TMA in hospitalized patients based on easily obtained laboratory measurements.

Methods: We retrospectively collected data from all adult patients admitted at our Hospital from January 2010 to December 2014. ICD9 codes from primary diagnoses were used to determine whether a patient had TMA. Demographic and laboratory characteristics at admission of TMA patients were then compared with a sample of 476 patients who received other diagnoses. The model was externally validated in a cohort from another Hospital.

Results: Overall, 23 out of 696,438 patients received a primary diagnosis of TMA (prevalence rate 3.3 per 100,000). In univariate analyses, indirect bilirubin (odds ratio

[OR] for 1 mg/dL 2.68, 95% confidence interval [CI] 1.85, 4.02), lactate dehydrogenase (LDH) (OR for 100 IU/L 1.57, 95% CI 1.38, 1.85), hemoglobin (OR for 1 g/dL 0.56, 95% CI 0.45, 0.68), and platelet count (OR for 1,000 platelets/uL 0.97, 95% CI 0.96, 0.98) were significantly associated with TMA. In multivariate models, only LDH (OR 1.26, 95% CI 1.05, 1.63) and platelet count (OR 0.96, 95% CI 0.94, 0.98) were associated with TMA. The final regression model had an area under the ROC (AUROC) of 0.96 (95% CI 0.91, 1.00) and showed good calibration. External validation on 26 patients with and 500 without a diagnosis of TMA showed an AUROC of 0.72 (95% CI 0.60, 0.84).





Conclusions: We derived and externally validated a simple prediction model for the diagnosis of TMA in hospitalized patients. The model shows good performance and can help the clinician in identifying patients at high risk of TMA.

FR-PO686

Detection of Amyloidogenic Immunoglobulin Light Chain in AL Amyloidosis with Urinary Exosomes Nelson Leung,[1,2] David R. Barnidge,[3] Angela Dispenzieri,[2] Christopher J. Dick,[4] Shawna A. Cooper,[4] Samih H. Nasr,[3] Christopher J. Ward,[5] Marina Ramirez-Alvarado.[4,6] *[1]Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [2]Hematology, Mayo Clinic, Rochester, MN; [3]Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; [4]Biochemistry and Molecular Biology, Mayo Clinic, Rochester, MN; [5]Nephrology and Hypertension, Kansas Univ Medical Center, Kansas City, KS; [6]Immunology, Mayo Clinic, Rochester, MN.*

Background: Immunoglobulin light chain (AL) amyloidosis is a fatal disease caused by the overproduction of monoclonal immunoglobulin light chain (LC). Diagnosis currently requires tissue biopsy. Urinary exosomes (UEX) are the smallest extracellular vesicles excreted by cells of the nephron. This study explores the use of UEX to assess for amyloidogenic LC.

Methods: A patient with no clinically detectable monoclonal LC in the serum or urine had UEX collected and evaluated by Western Blot. Identification of the monoclonal LC was performed by a combination of accurate molecular weight determination and topdown tandem mass spectrometry (MS) on the UEX and serum. Bottom-up proteomics was performed on a tryptic digest of amyloid deposits from the kidney isolated by laser dissection and then analyzed by tandem mass spectrometry (LSMS). cDNA was obtained from plasma cells clones from the bone marrow biopsy.

Results: Characteristic oligomeric LC bands were identified in the UEX. The same 2 monoclonal λ LC found in the UEX by MS were also found in the blood. LSMS identified tryptic peptides from a monoclonal LC in the IGLV6 gene family, same as the cDNA from the plasma cell clones which had the same amino acid sequences as the tryptic peptides. The molecular mass of the IGLV6 LC predicted by cDNA was identical to accurate molecular mass of the monoclonal λ LC observed in the serum and UEX. Finally, the relative abundance of the IGLV6 LC was conserved compared to the other non-amyloidogenic LC in the serum and UEX.

Conclusions: These results suggest that UEX can discriminate amyloidogenic LC from non-amyloidogenic LC. This could contribute significantly to the understanding of the pathogenicity of monoclonal LC.

Funding: Private Foundation Support

FR-PO687

Assessment of Renal Response in Immunoglobulin Light Chain (AL) Amyloidosis by Urinary Exosomes Nelson Leung,[1,2] David R. Barnidge,[3] Angela Dispenzieri,[2] Christopher J. Dick,[4] Shawna A. Cooper,[4] Samih H. Nasr,[3] Christopher J. Ward,[5] Marina Ramirez-Alvarado.[4,6] *[1]Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [2]Hematology, Mayo Clinic, Rochester, MN; [3]Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; [4]Biochemistry and Molecular Biology, Mayo Clinic, Rochester, MN; [5]Nephrology and Hypertension, Kansas Univ Medical Center, Kansas City, KS; [6]Immunology, Mayo Clinic, Rochester, MN.*

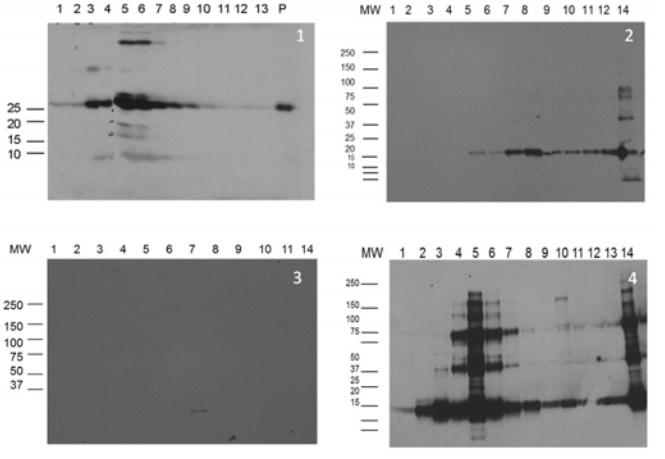
Background: Immunoglobulin light chain (AL) amyloidosis is a fatal disease caused by the overproduction of a monoclonal immunoglobulin light chain (LC). Accurate assessment of response is crucial for successful treatment. Urinary exosomes (UEX) have demonstrated different characteristics in AL amyloidosis vs multiple myeloma. This study explores the use of UEX to assess the renal response after treatment in AL amyloidosis.

Methods: Western blot was performed on the UEX of 4 patients with different hematologic status.

Patient	Hematologic status	Current proteinuria (g/d)	Proteinuria reduction	Renal outcome
1	ND	9.7	n/a	n/a
2	Treated to CR	0.7	91.6%	CR
3	Treated to CR	3.4	61.2%	CR
4	Treated to CR	3.4	76.5%	ESRD

From newly diagnosed (ND) patients to those treated to a hematologic complete response (CR).

Results:



The UEX of Patient 1 showed oligomeric LC bands > 25 kDa. Patient 2 and 3 had only monomeric LC bands (~25 kDa) often seen in multiple myeloma. Oligomeric (50 - 250 kDa) bands (similar to patient 1) were present in the UEX of patient 4 indicating active amyloid formation despite achieving a hematologic CR.

Conclusions: The oligomeric LC bands in UEX appear to be a good marker of renal response in AL amyloidosis. If confirmed, UEX may offer a great advantage over proteinuria in the assessment of renal response in AL amyloidosis.

Funding: Private Foundation Support

FR-PO688

Intra-Tubular Amyloid: A Significant Pathological Finding during Myeloma Cast Nephropathy Jean-Baptiste Gibier,[1] Viviane Gnemmi,[1] Marie-Christine Copin,[1] Francois Glowacki,[3] Raymond Azar,[4] Maxime Hoffmann,[7] Thomas Guincestre,[5] Xavier Leleu,[6] David Buob.[2] *[1]Pathology, CHRU Lille, Lille, France; [2]Pathology, Tenon Hospital, Paris, France; [3]Nephrology, CHRU Lille, Lille, France; [4]Nephrology, Dunkerque General Hospital, Dunkerque, France; [5]Nephrology, Hopital Victor Provo, Roubaix, France; [6]Hematology, CHU Poitiers, Poitiers, France; [7]Nephrology, La Louvière Hospital, Lille, France.*

Background: Cast nephropathy (CN) is the most common form of kidney disease in patients with multiple myeloma. Occasionally, casts may show amyloid staining properties i.e. green birefringence in Congo red. The frequency and signification of such intra tubular amyloid (ITAM) are poorly understood. In particular the link between ITAM and systemic amyloidosis has never been investigated.

Methods: A retrospective analysis with clinico-pathological correlation was performed of all cases of CN diagnosed at our institution between 2002 and 2012. Renal pathological findings and Congo red staining status were reviewed. Each patient was also screened for extra renal samples and if available a Congo red staining was performed. Treatment and clinical follow up data were obtained.

Results: Among 66 patients diagnosed with CN, 18 (27,2%) showed ITAM. There was no differences in clinical characteristics between patients with or without ITAM at time of biopsy. ITAM was associated with overrepresentation of λ light chain (14 out 18) whereas patients without ITAM showed balanced κ/λ ratio. Renal amyloid was found in 3 patients: 1 with ITAM and 2 without. Extra renal amyloid was found in 6 patients in the ITAM group and in only one patient in the "no ITAM" group. All in all, ITAM was significantly associated with systemic amyloidosis (7/18 vs 3/48 p=0,003).

Conclusions: This study reports for the first time an association between the existence of ITAM in kidney biopsies with CN and systemic amyloidosis. Our study highlights the importance of the systematic search of Congo red staining of casts in such context. Moreover it suggests that the detection of ITAM should lead to an exhaustive screening for other localizations of amyloidosis, as associated systemic amyloidosis is an adverse factor in myeloma patients.

FR-PO689

Beta Trace Protein Does Not Outperform Cystatin C or Creatinine in Estimating GFR in Older Adults

Natalie Ebert,[1] Peter Martus,[2] Camilla Koep,[1] Olga Jakob,[3] Elke Schaeffner.[1] *[1]Inst of Public Health, Charité, Berlin, Germany; [2]Inst for Med. Biometry, Eberhard Karls Univ Tübingen, Germany; [3]Clinical Epidemiology and Biostatistics, Charité.*

Background: Despite a lot of research the optimal endogenous biomarker for GFR estimation in the elderly has not been identified. We sought to analyse if beta trace protein (BTP) improved GFR estimation in older adults.

Methods: In 570 older adults with iohexol clearance measurement (BIS) creatinine, cystatin C, and BTP were measured. In a double logarithmic linear model prediction of mGFR by BTP was assessed. Analyses with BTP only and combined with serum creatinine and cystatin C were performed (all analyses adjusted for age and gender).

Results: Table 1 documents seven regression models including either single biomarkers or combinations.

	corrected R^2
Regression Modell (including age and gender)	
- BTP	0.671
- CysC - CysC + BTP	0.781 0.799
- Crea - Crea + BTP	0.739 0.787
- Crea + CysC - Crea + CysC + BTP	0.840 0.845

In terms of best r^2 the combination of all three biomarkers shows the best prediction of mGFR (r^2=0.828), although the combination of creatinine and cystatin C provided only a minimally diverging result (0.82). The single usage of BTP showed the worst prediction (r^2=0.671) within the models with one biomarker. In subgroup analysis (AHT, DM, BMI≤23 and BMI>30) there was no relevant additional benefit of including BTP into the prediction model (data not shown).

Conclusions: BTP alone or the addition of BTP does not outperform current biomarkers such as creatinine and cystatin C for GFR-estimation in older adults. Especially the use of cystatin C renders the addition of BTP unnecessary. Also, BTP did not show additional benefit in hypertensive, diabetic, lean or obese elderly patients.

Funding: Private Foundation Support

FR-PO690

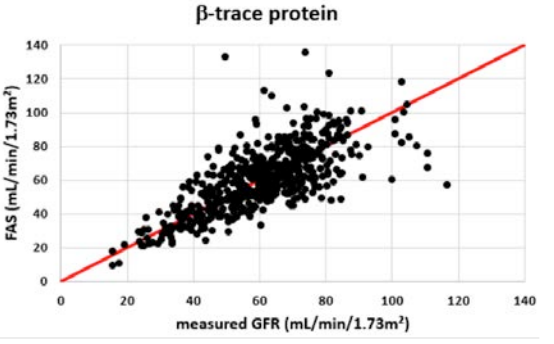
Diagnostic Value of Normalized Beta Trace Protein for Estimating GFR in Older Adults

Natalie Ebert,[1] Elke Schaeffner,[1] Hans Pottel.[2] *[1]Pub. Health, Charite, Germany; [2]Pub. Health, KU Leuven, Belgium.*

Background: BTP as a novel biomarker has emerged as alternative to creatinine (Scr) and cystatin C (Scys). The recently published Full Age Spectrum (FAS) eGFR equation has been developed by normalizing Scr with mean Scr of large healthy cohorts. We investigate whether this concept is also valid for BTP in elderly indiv. and compare it to Scr and Scys.

Methods: We used data from the Berlin Initiative Study (BIS), a pop-based cohort with mGFR (iohexol) examining KF in indiv. aged ≥70y. The fixed form of the FAS-equation was applied with normalized single (Scr, Scys, BTP) or combined (average of Scr and ScysC or Scr, Scys and BTP) biomarkers and performance statistics were calculated: constant bias (FAS - mGFR), proportional bias (FAS/mGFR), root mean square error of prediciton (rmse), Lin's concordance corr. coefficient, P10 and P30 (percentage of predictions within 10% or 30% of mGFR).

Results: Based on the distribution of BTP in n=566 BIS participants (mean age 78.5y), the peak-value is ±0.60 mg/L. Using the fixed form of the FAS equation and rephrasing it with BTP leads to: $FAS_{BTP} = 107.3 / [BTP/0.60] \times 0.988^{(Age-40)}$. Fig 1 shows FAS-prediction of single BTP versus mGFR.



BTP shows equivalent bias but less precision (P10, P30) as compared to Scr and Scys.

	Scr	Scys	BTP	Scr/sCys	Scr/Scys/BTP
bias	-0.4	0.6	0	-0.3	-0.6
prop	1.01	1.02	1.01	1.01	1.00
lin	0.826	0.832	0.728	0.873	0.863
rmse	9.5	9.6	11.1	8.0	8.4
P10	51	49	40	57	58
P30	94	94	87	96	97

The added value for the combination of three biomarkers (BTP/Scr/Scys) compared to Scr/Scys FAS is very small (Tab 1).

Conclusions: Normalizing renal biomarkers to make them independent of age and gender and building them into the FAS equation holds also true for BTP in our elderly cohort. Adding BTP to the combined Scr/Scys FAS equation has only limited effect on precision of GFR estimation.

Funding: Private Foundation Support

FR-PO691

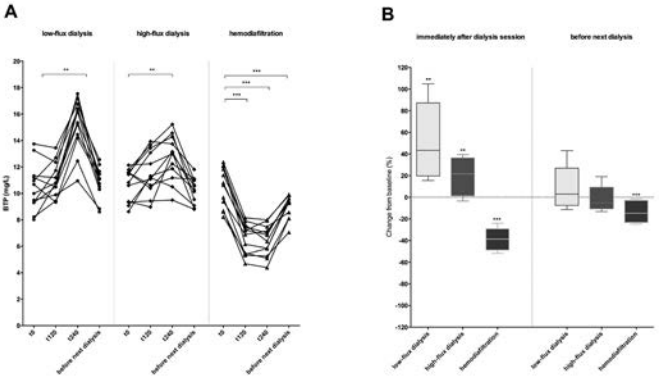
Plasma Beta-Trace Protein (BTP) as a Marker of Residual Renal Function (RRF): The Effect of Different Hemodialysis (HD) Modalities and Intraindividual Variability over Time

Amaryllis H. Van Craenenbroeck,[1,2] Ann-Christin Bragfors Helin,[1] Abdul Rashid Tony Qureshi,[1] Bengt Lindholm,[1] Björn Anderstam,[1] Peter Stenvinkel,[1] Peter F. Barany.[1] *[1]Divs of Renal Medicine and Baxter Novum, Dept of Clinical Science, Intervention and Technology, Karolinska Inst, Stockholm, Sweden; [2]Dept of Nephrology, Antwerp Univ Hospital, Antwerp, Belgium.*

Background: BTP is a low-molecular-weight molecule which may be used to assess RRF in dialysis patients (pts). Here we evaluated the influence of HD and hemodiafiltration (HDF) on plasma BTP, and analyzed the intra-individual variability of plasma BTP over time in HD and peritoneal dialysis (PD) pts.

Methods: In 12 prevalent HD pts, the effect of a single session of low-flux HD, high-flux HD and HDF on plasma BTP was studied. Blood samples were taken at baseline, after 120 and 240 minutes, and at the start of the next dialysis session. In 13 HD pts and 10 PD pts, intra-individual variability over three months was studied (monthly and weekly, respectively). Plasma BTP was measured using a nephelometric test (Siemens).

Results: No significant decrease in plasma BTP was seen following HD. HDF resulted in significant reduction of BTP levels already after the first half of dialysis time with a median reduction of 39% at the end of the session. A significant reduction of the molecule persisted and a significant decrease (-15%) was still found immediately before the start of the next dialysis session.



In both HD and PD pts, the reproducibility over time was excellent with intraclass correlation coefficient of 0.962 (0.928-0.995) and 0.923 (0.858-0.987) respectively.

Conclusions: BTP-based equations are a promising tool for estimations of RRF in pts on conventional HD or PD while in pts receiving HDF, plasma levels of BTP should be interpreted with care.

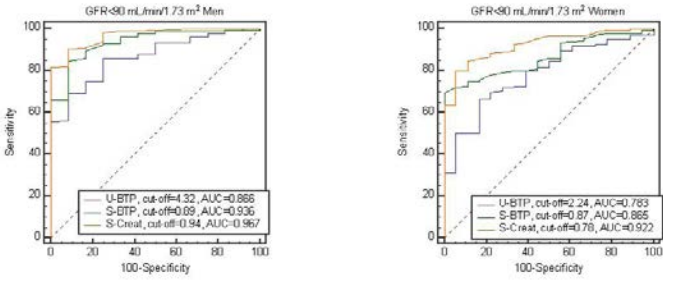
FR-PO692

Urinary β-Trace Protein – A Unique Biomarker to Screen Early Glomerular Filtration Rate Impairment Carlo Donadio. *Clinical and Experimental Medicine, Univ of Pisa, Pisa, Italy.*

Background: The screening for chronic kidney disease (CKD) patients needs the measurement of serum markers. Our previous results indicated that urinary excretion of β-trace protein (BTP) (23-29 kDa), is increased in CKD patients from stage 2. **The aim of this study t**o assess the major determinants of urinary excretion of BTP and to evaluate its feasibility as non invasive marker of glomerular filtration rate (GFR) impairment.

Methods: We studied 355 CKD patients (198 males), 15-83 years, in stable clinical conditions, at the different stages of CKD on the basis of GFR (^{99m}Tc- DTPA). At the same time, we measured serum and urinary creatinine and BTP, and urinary albumin. Urinary excretion of BTP and albumin were expressed as mg/g creatinine. Fractional clearance of BTP was calculated as ratio of BTP clearance to creatinine clearance (%).

Results: Urinary excretion of BTP is mainly determined by its serum concentration and by the level of GFR, and to a lower extent by urinary albumin excretion. In fact, U-BTP and fractional clearance of BTP progressively and significantly increased along with the reduction of GFR and the concurrent rise in serum BTP. The relationship of U-BTP with GFR was very similar to that of S-BTP with GFR: urinary BTP mirrors serum BTP. The accuracy of U-BTP to screen patients with GFR<90 ml/min/1.73 m² was good (AUC 0.833), its sensitivity was 76.9%, specificity 80% and PPV 84.9%. Sensitivity of U-BTP was similar to that of S-BTP and S-Cr.



Conclusions: The major determinants of urinary excretion of BTP are S-BTP and GFR. U-BTP may be a suitable non invasive marker to screen the general population for detection of GFR<90 ml/min/1.73m².

Funding: Government Support - Non-U.S.

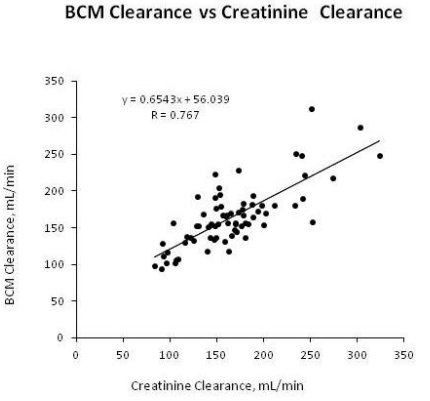
FR-PO693

Urinary Creatinine Excretion and Creatinine Clearance Can Be Predicted in Severely Obese Patients by the Measurement of Body Cell Mass Carlo Donadio. *Clinical and Experimental Medicine, Univ of Pisa, Pisa, Italy.*

Background: In obese patients the accuracy of prediction of renal function by formulas based on serum creatinine (PCr) and anthropometric data is quite low. The aim of this study was to evaluate if the value of body cell mass (BCM) allows to predict urinary creatinine excretion (UCr) and creatinine clearance (CCr).

Methods: Seventy-four patients (54 women), 19-66 years, BW 82.5-210 kg; BMI 35.2-73.6 kg/m², PCr (0.57-1.06 mg/dL). Measured parameters: PCr; UCr (urine collection 2 hrs); CCr measured (m-CCr) with the standard formula; CCr predicted by CG formula (CG-CCr) and by Salazar&Corcoran formula (S&C-CCr). GFR was predicted using MDRD formula (IDMS) and CKD-EPI formula. BCM was measured using a single frequency impedance analyzer. Renal dimensions were evaluated by bydimensional ultrasound scanning.

Results: 24h-UCr was 976-3684 mg, m 1809; BCM was 25-74 kg (m 49.3 kg men, 31.6 kg women). A strict linear correlation was found between 24h-UCr and BCM (r=0.79), closer than between 24h-UCr and BW (r=0.65). 24h-UCr and CCr were predicted from the individual values of BCM (BCM-CCr) (Donadio C. Kidney Int 63: S166-S168, 1997). Total renal volume was 425±103 mL; right kidney 211±63, left kidney 219.66 mL. The difference between BCM-CCr (165±41 mL/min) and m-CCr (167±44 mL/min) was insignificant. Quite different estimates were given by the other prediction formulas: C&G-CCr (199±72 mL/min), S&C-CCr (149±47mL/min), MDRD-GFR (122±34 mL/min), CKD-EPI-GFR (131±32 mL/min). BCM-CCr values showed also a good correlation with m-CCr (r=0.767, p<0.0001) and the concordance was similar for all values of renal function.



Correlation between predicted creatinine clearance (BCM Clearance) and measured Creatinine Clearance

Conclusions: In severely obese patients urinary creatinine excretion and creatinine clearance can be more accurately predicted from the measurement of body cell mass combined with serum creatinine, than with other formulas.

Funding: Government Support - Non-U.S.

FR-PO694

Do Cystatin C Based Estimates of GFR Add Value in CKD Management in Primary Care? Adam Shardlow,[1,4] Natasha Juliette Mcintyre,[1] Simon D.S. Fraser,[2] Paul J. Roderick,[2] Richard J. Fluck,[1] Christopher W. McIntyre,[3] Maarten W. Taal.[1,4] *[1]Renal Medicine, Royal Derby Hospital, Derby, United Kingdom; [2]Univ of Southampton, Southampton, United Kingdom; [3]Univ of Western Ontario, London, ON, Canada; [4]Centre for Kidney Research and Innovation, Univ of Nottingham, Nottingham, United Kingdom.*

Background: Cystatin C has been proposed as a filtration marker and a risk factor in people with CKD. KDIGO guidelines suggest using a cystatin C based estimate of GFR ($eGFR_{cys}$) in defining those with disease. Cystatin C has not yet been widely adopted in clinical practice and to do so would require significant expense and education. We investigated the use of $eGFR_{cys}$ in 5 year follow-up of people with CKD stage 3 prospectively recruited from primary care.

Methods: 1741 people were recruited from primary care. All participants had an eGFR 30-60 ml/min on two occasions more than 90 days apart prior to study entry. Participants were assessed at baseline, 1 and 5 year follow-up visits. CKD EPI equations were used to calculate creatinine-based ($eGFR_{creat}$), cystatin C-based ($eGFR_{cys}$) and combined ($eGFR_{creat-cys}$) estimates of GFR. Multivariable regression models were used to predict CKD progression and mortality.

Results: At baseline, mean $eGFR_{creat}$ was 53.5, mean $eGFR_{cys}$ 45.1 and mean $eGFR_{creat-cys}$ was 48.3 ml/min (p<0.001 for all). Of 784 participants with $eGFR_{creat}$ 45-60ml/min, only 57 (7%) had $eGFR_{cys}$ >60 ml/min and 488 (62%) had $eGFR_{cys}$ <45ml/min. Greater difference between $eGFR_{creat}$ and $eGFR_{cys}$ was associated with higher eGFR, BMI, age, smoking and CRP. Over 5 years, correlation between the percentage change in $eGFR_{creat}$ and $eGFR_{cys}$ was moderate (r=0.49). Multivariable models to predict progression and mortality did not show significant difference using $eGFR_{creat}$, $eGFR_{cys}$ or $eGFR_{creat-cys}$.

Conclusions: In this cohort, use of $eGFR_{cys}$ resulted in minimal reclassification from CKD 3a to disease free. Baseline estimates of eGFR were significantly different and there was only moderate correlation in the change in renal function using $eGFR_{creat}$ and $eGFR_{cys}$. Whilst $eGFR_{cys}$ may have a place in selected patients with extremes of body habitus, these results do not show significant benefit to support its widespread application in primary care.

Funding: Private Foundation Support

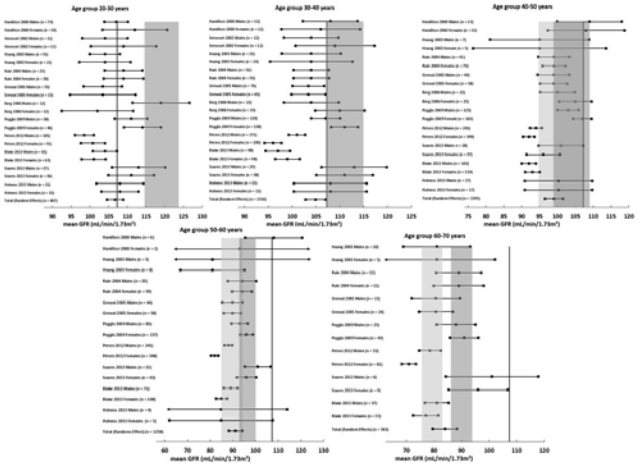
FR-PO695

Glomerular Filtration Rate in Healthy Living Potential Kidney Donors: A Meta-Analysis Hans Pottel,[2] Liesbeth Hoste,[2] Pierre Delanaye.[1] *[1]Nephrology, Univ of Liège, CHU Sart Tilman, Liege, Belgium; [2]Dept of Public Health and Primary Care, KU Leuven Campus Kulak, Kortrijk, Belgium.*

Background: Normal kidney function, or more specifically, normal glomerular filtration rate (GFR), in males and females, and its decline with age, is still much debated today. Most estimating GFR-equations have gender (and etnicity) multiplication factors, account for a decline that starts at very young age, and assume that GFR is as high as 120-130mL/min/1.73m² at young age, a reference value that dates back to the work of Homer Smith in the 1950s. The aim of this research study was to give more insight into 'normal' GFR-levels and the physiological decrease of kidney function with age and to test if the mathematical construction of eGFR-equations holds true in healthy kidney donors.

Methods: We conducted a meta-analysis of published GFR-measurements in healthy living potential kidney donors (n=5476, 46.7% males). Only publications dating from after the year 2000 were selected to avoid the possible influence of body surface area changes in the last decades on the indexed GFR, expressed in mL/min/1.73m², and involving only Caucasian subjects.

Results: We found that the mean GFR~107mL/min/1.73m² up to the age of 40 years, but beyond 40 years renal decline begins.



No evidence could be found for a difference between males and females in the separate age-groups.

Conclusions: A new mean GFR of 107mL/min/1.73m² can be set as opposed to the value of 120-130mL/min/1.73m² which was considered the reference value until now. It is advisable that the mathematical properties of estimating GFR-equations reflect the gender and age-independency (up to 40 years of age).

FR-PO696

Associations between Iohexol Clearance Measurement and Outcomes

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Background: In Sweden, the preferred method to determine GFR is measuring plasma iohexol clearance (IC). However, the safety of IC measurement has been questioned. We aimed (1) to evaluate which demographic and medical factors play a role in the decision to perform an IC measurement, and (2) to assess the associations between IC measurement and timing of start of RRT for ESRD, and all-cause mortality.

Methods: We included adult patients from the Swedish Renal Registry of Chronic Kidney Disease with a first visit between 2005-2011. By logistic regression we assessed which factors influenced the likelihood of IC measurement. To analyse time until start of RRT and death, Cox regression was performed. All multivariate models included age, sex, primary renal disease, and eGFR at inclusion in the registry. Propensity score matching was applied to control for confounding by indication in the comparison of patients with and without IC measurement.

Results: From a total of 13,570, there were 1,705 patients (12.6%) with IC measurement at least once during follow-up. The likelihood of receiving an IC measurement was significantly lower in patients aged ≥75 years (Odds Ratio [OR]: 0.79, 95% confidence interval [CI]: 0.69-0.91) when compared to those aged 45-64 years, in those with a higher eGFR (OR: 0.98, 95%CI: 0.97-0.98 for every ml/min/1.73m² increase) or with glomerulonephritis (OR: 0.64, 95% CI: 0.51-0.79) compared to those with diabetes as cause of renal failure. Cox regression based on the propensity matched cohort (N=2,966) showed that the risk of starting RRT was not different between patients with and without an IC measurement (Hazard Ratio [HR]: 0.90, 95%CI: 0.80-1.02). Also the risk of death was similar (HR: 1.04, 95%CI: 0.91-1.18).

Conclusions: We found that the oldest patients, those with higher eGFR and with glomerulonephritis were least likely to receive an IC measurement. Exposure to IC measurement was neither associated with higher risk of starting RRT for ESRD, nor with higher mortality risk. Based on these findings IC measurement seems to be safe for assessing GFR. Nevertheless, further research in other study populations is warranted to confirm our findings.

FR-PO697

Measurement of Glomerular Filtration Rate by Plasma Iohexol Clearance: Single versus Multiple Samples Method

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Background: Iohexol plasma clearance is considered as a reference method to measure glomerular filtration rate (GFR). However, different methodologies, have been developed regarding the number of plasma samples needed. In the current study, we tested the concordance between the simple single sample (SS) versus the multiple samples (MS) method.

Methods: We considered the patients referred to our university center for GFR measurement. In all patients, 5 mL of iohexol (Omnipaque™240; 240 mg/mL) are intravenously injected. Iohexol was measured by High Performance Liquid Chromatography. MS plasma clearance were obtained by calculating the clearance from slope calculated with four samples at 120, 180, 240 and 300 min. The result was then corrected by the Brochner-Mortensen equation. SS plasma clearance was calculated at every time with only one concentration and applying the Jacobsson equation. We studied the concordance within ±10%. We tested if the concordance was influenced by the timing of the SS method.

Results: One hundred and twelve patients have been included in the study (52 females): mean age 53±13 years, BMI 27±7 kg/m², GFR 84±29 mL/min (range from 17 to 158 mL/min). If the MS method is considered as the reference, results with SS method at 120, 180, 240 et 300 min had a concordance ±10% of 73, 91, 92 and 70%, respectively. For patients with GFR<50 mL/min (n=13), concordances were 15, 54, 77 and 92%, respectively. For patients with GFR>50 mL/min (n=99), concordances were 80, 96, 94 et 67%, respectively. If the timing of the SS method is chosen according to the expected GFR, i.e. SS at 180 min for patients with GFR>50 and SS at 300 min for patients with GFR<50 mL/min, the concordance will be of 96%.

Conclusions: We showed a good concordance between iohexol plasma clearance obtained with two methodologies, (MS and SS). This is especially concordant if the timing of the SS method is adapted to the expected GFR (180 min if normal GFR and 300 min if lower GFR). In large epidemiological studies, iohexol plasma clearance with SS is a validated and simplified alternative to measure GFR. The timing of this SS strongly influences the results and must be adapted to the GFR level.

FR-PO698

Systematic Renal Function Evaluation Using Iohexol or Inuline Clearance before Lung Transplantation in Adult Cystic Fibrosis Patients

Etienne Novel,[1] Solenne Pelletier,[1] Raphaële Nove-Josserand,[2] Quitterie Reynaud,[2] Stephane Durupt,[2] Laurence Dubourg,[3] Isabelle Durieu,[2] Maurice Laville,[1] Denis Fouque.[1] *[1]Nephrology, Univ Center Hospital – Lyon-Sud, Lyon - Pierre Benite, France; [2]Cystic Fibrosis Adult Center, Univ Center Hospital – Lyon-Sud, Lyon - Pierre Benite, France; [3]Nephrology, Univ Center Hospital – Edouard Herriot, Lyon, France.*

Background: Cystic fibrosis (CF) patients are at risk for kidney injury even before undergoing lung transplantation, because of prolonged exposure to aminoglycoside and complications of diabetes mellitus. The usual equations estimating the glomerular filtration rate (GFR) are not adapted in CF population due to patients low body weight. The aim of our study was to measure precisely the GFR of CF adult patients before lung transplantation.

Methods: Iohexol or Inuline clearance was realized in 21 adult CF patients, when they entered the lung transplant waiting list (n=17) or when the patient was considered by the clinician at high risk for renal disease (n=4). No patient was treated with aminoglycoside at the time of GFR measurement. BMI, history of diabetes mellitus were recorded. Exposure to IV aminoglycoside within the 5 years before GFR measurement was calculated. Urines samples were collected to check for proteinuria and albuminuria.

Results: 57% of CF patients were male, 43% were diabetic. Mean age at GFR measurement was 31 years old. Mean BMI was 19kg/m². 14% of patients had albuminuria of more than 30mg/L and none of them had proteinuria. Mean days of exposure to IV aminoglycoside therapy within the 5 years before GFR evaluation was 169 days (Ranging from 60 to 280 days). Tobramycin was the most used aminoglycoside at the mean posology of 7.6mg/kg/day. GFR was measured using iohexol for 15 patients and inuline was used for the remaining 6 patients. Mean measured GFR was 107mL/min/1.73m². Only 2 patients had a measured GFR between 60 and 90mL/min/1.73m². For these 2 patients, GFR estimation using CKD EPI was unable to detect the moderate decline in kidney function (estimated GFR >90mL/min/1.73m²).

Conclusions: Despite prolonged exposition to high dose of aminoglycoside associated with a high prevalence of diabetes mellitus, no major decline in GFR was observed in our cohort.

FR-PO699

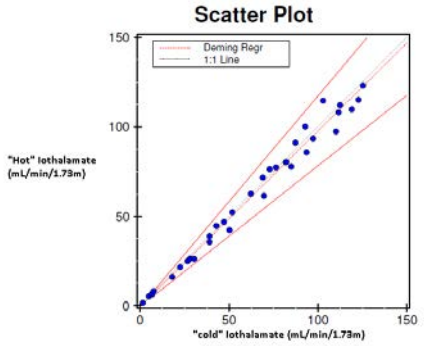
Measurement of Glomerular Filtration Rate by Clearance of Non Radiocative Iothalamate

Yvonne El Kassis,[1] Joe M. El-Khoury,[2] Sihe Wang,[3] Emilio D. Poggio,[1] Georges Nakhoul.[1] *[1]Nephrology and Hypertension, Cleveland Clinic Foundation, Cleveland, OH; [2]Laboratory Medicine, Yale Univ, New Haven, CT; [3]Laboratory Medicine, Cleveland Clinic Foundation.*

Background: Assessment of kidney function is best reflected by the Glomerular Filtration Rate (GFR). While GFR can be estimated using creatinine and cystatin-based equations, measurement using exogenous substances is more accurate and often necessary, particularly when precise assessment of renal function is desired (kidney donation). Radioactive iothalamate has commonly been used as a tracer for GFR measurement but the handling of radioactive material is cumbersome and challenging. The goal of our study is to compare the renal clearance (GFR measurement) of radioactive "hot" and non-radioactive "cold" iothalamate.

Methods: Patients received simultaneous sub-cutaneous injections of "hot" ^{125}I Sodium Iothalamate and "cold" Iothalamate Meglumin 60%. Analysis of the marker concentration in serum/urine samples was done by gamma counting (GAMC) of the ^{125}I and by liquid chromatography-tandem mass spectrometry (LCMS) of the "cold" iothalamate. GFR was measured as the renal clearance of "hot" and "cold" Iothalamate. We used scatter plots, regression analysis, correlation coefficient and bias.

Results: Between Oct 2011 and Jan 2013, 36 patients were enrolled. 18 were males (50%). Mean age was 50.9±15.8 years. GFR measurements ranged from 1.67-125.33 ml/min/1.73m² with a mean of 62.87±38.42 ml/min/1.73m² for the "hot" iothalamate and 1.45-122.96 ml/min/1.73m² with a mean of 61.07±37.85 ml/min/1.73m² for the "cold" iothalamate. The correlation coefficient of the 2 measurement methods was 0.99 with a bias of -1.81 ml/min/1.73m² (-2.9%) and an accuracy of 95%.



	Deming
Slope	0.985 (0.942 to 1.028)
Intercept	-0.854 (-4.023 to 2.315)
Std Err Est	4.755

Regression analysis - 95% Confidence Interval are shown in parenthesis

Conclusions: Renal clearance of "cold" iothalamate by LCMS is comparable to renal clearance of "hot" iothalamate by GAMC and offers a safer, less cumbersome option for GFR measurement.

FR-PO700

Creatinine-Based Renal Function Assessment Underestimates Chronic Kidney Disease (CKD) Prevalence: The Northern Manhattan Study (NOMAS) Syed Ali Husain,[1] Joshua Z. Willey,[1] Yeseon Park Moon,[1] Mitchell S.V. Elkind,[1] Ralph L. Sacco,[2] Myles S. Wolf,[3] Ken Cheung,[1] Clinton Wright,[2] Sumit Mohan.[1] *[1]Columbia Univ; [2]Univ of Miami; [3]Northwestern Univ.*

Background: Accurate glomerular filtration rate estimation (eGFR) informs drug dosing, risk stratification, and prognosis. Body composition heterogeneity influences creatinine production and the precision of creatinine-based eGFR ($eGFR_{cr}$) in the elderly. We compared CKD categorization using $eGFR_{cr}$ and cystatin C-based eGFR ($eGFR_{cys}$) in an elderly cohort.

Methods: NOMAS is a predominantly elderly, multi-ethnic cohort (n=3298) with a primary aim to determine stroke and vascular disease risk factors. We included participants with concurrent measured creatinine and cystatin C. $eGFR_{cr}$ was calculated using CKD-EPI 2009 and $eGFR_{cys}$ used CKD-EPI 2012 (cystatin). Logistic regression was used to estimate odds ratios (OR) for correlates of reclassification from $eGFR_{cr}$≥60 to $eGFR_{cys}$<60mL/min.

Results: Participants (n=2988, mean age 69±10yrs) were predominantly >65 years old (61%), Hispanic (53%), female (63%), former/current smokers (53%), and overweight/obese (BMI >25Kg/m^2: 69%). $eGFR_{cys}$ was lower than $eGFR_{cr}$ by mean 23 mL/min, and only 27.7% had a concordant CKD class by both measures.

Table 1: Reclassification of CKD Class by GFR-estimating Equation

$eGFR_{cr}$	$eGFR_{cys}$					Total
	<15	15-29	30-59	60-89	≥90	N
<15	11	1	0	0	0	12
15-29	19	14	0	1	0	34
30-59	10	172	385	41	1	609
60-89	2	48	1181	379	19	1629
≥90	0	8	256	402	38	704
Total	42	243	1822	823	58	2988

Most (78%) had $eGFR_{cr}$≥60 mL/min; of those, 64% had $eGFR_{cys}$<60 mL/min. Among participants with $eGFR_{cr}$ ≥60 mL/min, discordant cystatin C-based CKD diagnosis ($eGFR_{cys}$<60 mL/min) was more likely in those with age >65 (OR 5.68, 4.61-6.99), obesity (OR 2.06 vs BMI≤30, 1.64-2.59), current smokers (OR 1.87 vs non-smokers, 1.41-2.48) and females (OR 1.47, 1.19-1.92).

Conclusions: In a large, multiethnic, elderly cohort with a high BMI, we found a higher prevalence of CKD using $eGFR_{cys}$. Use of $eGFR_{cr}$ may underestimate CKD prevalence, particularly among the elderly, obese, smokers and women. Determining the best method to estimate renal function in elderly populations needs further study.

Funding: Other NIH Support - National Institute of Neurological Disorders and Stroke

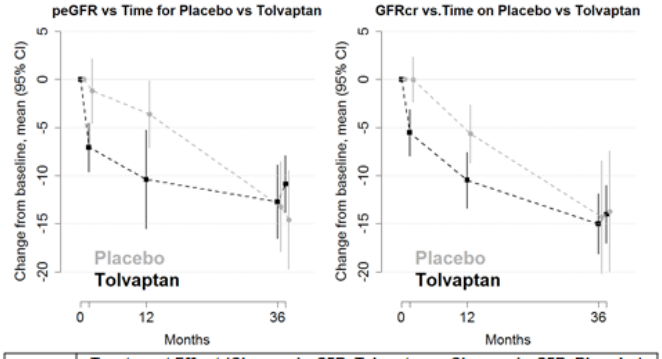
FR-PO701

Precise Estimation of GFR from Multiple Markers in Clinical Trials Lesley Inker,[1] Ronald D. Perrone,[1] Andrew S. Levey,[1] Hocine Tighiouart,[1] Frank S. Czerwiec,[2] Jaime Blais,[2] Sharin Roth,[2] Lucas Westcott-Baker,[2] Regis Perichon,[3] Josef Coresh.[4] *[1]Tufts Medical Center; [2]Otsuka Pharmaceuticals; [3]Metabolon; [4]Johns Hopkins Univ.*

Background: We showed that a panel of filtration markers (peGFR) can improve precision of estimated GFR compared to creatinine (eGFRcr). Improved ascertainment of endpoints can enhance conduct of clinical trials. As proof of concept, we evaluated the use of peGFR to detect treatment (Tx) effects of tolvaptan in a subset from the TEMPO3:4 pivotal trial (Torres NEJM 2012) compared to eGFRcr.

Methods: 42 (21 tolvaptan and 21 placebo) subjects matched by CKD stage, Mayo imaging classification, sex, age, race, region, hypertension status, and total kidney volume were included. Samples were assayed by Metabolon using LCMS methods for targeted metabolites. eGFRcr was computed using CKD-EPI equation. We examined treatment effects in acute phase after Tx initiation (baseline-week 3), chronic phase on Tx (week 3-month 36), and acute phase after Tx discontinuation (month 36-6 weeks post discontinuation). Tx effect was assessed as the difference in the slope of eGFR between Tx arms using a random effect mixed model with a three piece wise linear spline with knots at week 3 and month 36.

Results: The mean age was 39y and 48% were female. Mean baseline eGFRcr was 78 mL/min/1.73m^2. In the acute phases before or after Tx initiation, there were no differences between tolvaptan and placebo using peGFR or eGFRcr. In the chronic phase, tolvaptan slowed the decline in GFR compared to placebo using peGFR but not using eGFRcr.



	Treatment Effect (Change in GFR Tolvaptan – Change in GFR Placebo)					
	Acute phase on treatment (per month)		Chronic slopes (per year)		Acute phase off treatment (per month)	
	Tx effect (SE)	p	Tx effect (SE)	p	Tx effect (SE)	p
peGFR	-9.8 (3.4)	0.007	2.2 (0.9)	0.03	2.9 (2.5)	0.3
eGFRcr	-8.3 (2.6)	0.003	1.1 (1.1)	0.4	0.7 (2.0)	0.7

Conclusions: In a small subset of TEMPO trial, peGFR appears to enhance discrimination of the treatment effect seen in the overall population. This example provides preliminary support for test of the hypothesis that more precise estimates of GFR could increase efficiency of clinical trials.

Funding: Pharmaceutical Company Support - Otsuka

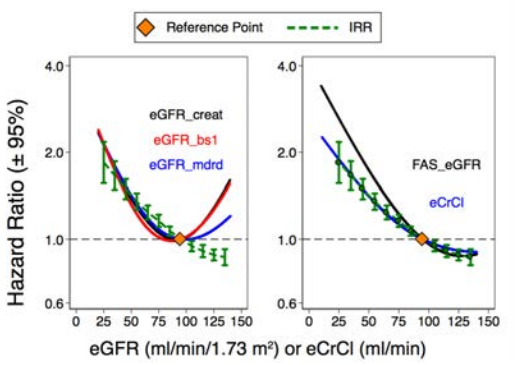
FR-PO702

Comparisons of Estimated GFR and Cockcroft Gault Equations: Calibration against Relative Risk for All-Cause Mortality David G. Warnock,[1] Jan A.J.G. van den Brand,[5] Pierre Delanaye,[2] Richard J. Glassock,[3] Hans Pottel.[4] *[1]Medicine, UAB, Birmingham, AL; [2]Nephrology-Dialysis-Transplantation, Univ of Liege, Liege, Belgium; [3]Medicine, Geffen School of Medicine, Los Angeles, CA; [4]Public Health, KU Kulak, Kortrijk, Belgium; [5]Nephrology, Radboud Univ, Nijmegen, Netherlands.*

Background: The Cockcroft-Gault estimated creatinine clearance (eCrCl) equation has poorer precision and accuracy than the creatinine-based estimated GFR (eGFR), but still outperforms these equations in describing the risks of all-cause mortality. The full age spectrum equation (FAS_eGFR) has better accuracy than other creatinine-based eGFR equations, but its performance in assessing mortality risk has not yet been described.

Methods: Multivariable adjusted Cox analyses were done with the REGARDS cohort to assess the hazards for death using eGFR (CKD_EPI (eGFRcreat), MDRD (eGFRmdrd), Berlin Study Initiative (eGFRbs1), FAS_eGFR) and eCrCl as continuous variables. Hazard ratios were compared to Incident Rate Ratios mapped on to the eGFR scale, with a reference value set at 90 ml/min/1.73 m^2 or 90/ml/min.

Results:



The eGFRcreat, eGFRmdrd and eGFRbs1 equations had increased hazards for mortality above the reference eGFR ("J-curve"). This was not seen with eCrCl or FAS_eGFR equations, which were better calibrated with the Incident Rate Ratio curve above the reference eGFR, while eCrCl was better calibrated than FAS_eGFR below the reference eGFR value.

Conclusions: None of the current models optimize both estimation of measured GFR and risk assessment. The FAS_eGFR equation parallels the Relative Risk curves below the reference eGFR; a simple linear adjustment should improve its calibration. In contrast, the "J-curves" for the other eGFR equations cannot be resolved with simple linear adjustments of the hazard ratios above the reference eGFR value.

Funding: Other NIH Support - This research project is supported by a cooperative agreement U01 NS041588 from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Department of Health and Human Service

FR-PO703

Formulas Do Not Reflect Renal Function Decline in CKD: The Nephrologist in the Mist

Ana Aldea Perona, Sergio Luis Lima, Natalia Negrín, Federico J. Gonzalez-Rinne, Armando Torres, Esteban Porrini, Victor Lorenzo. *Hospital Univ de Canarias, La Laguna, Spain.*

Background: The error of estimated GFR (eGFR) may jeopardize clinical trials designed to prevent CKD. However, the agreement between eGFR and measured (mGFR) decline has been seldom analyzed.

Methods: NEFROVID clinical trial (NCT01442272) evaluates the impact of calcifediol,paricalcitol or standard therapy in reducing proteinuria in CKD. mGFR was assessed in a subgroup of 13 patients by the clearance of iohexol and by 52 formulas every 3-m during 12 months. The agreement between mGFR and eGFR-derived declines was tested by the Concordance Correlation Coeficient (CCC).

Results: CCC ranged from 17 to 60 (~42%), indicating that 90% of eGFR showed an error of ±42% compared with mGFR. In some cases the error was severe for all formulas (case 12); indicated false slow (case 6) or faster decline (case 10) or improvement in GFR decline (case 8), (similar results were observed for all equations).

mGFR decline (ml/min/y)		Creatinine			Cystatin-c			Creatinine +cystatin-c		
Patient	**mGFR**	aMDRD	CKD_ EPI	RuleMC	Hoek	RuleCysc	CKD_ EPI	Stevens	Ma	CKD_ EPI
1	**-6**	-6	-6,3	-4,6	-8	-6,5	-8	-7	-8	-6
2	**-9**	-10,6	-11	-11	0,1	0,1	0	-6	-6	-4,4
3	**-3,5**	-5,4	-5,8	-7,5	-1,8	-1,6	-2	-4	-4	-3
4	**-0,6**	2,5	2,4	1,9	4	3	3,2	3	3,4	2,4
5	**-8,3**	-8	-8,4	-6	-3	-2,2	-2,7	-6	-6,5	-5
6	**-3**	-1	-1,2	-1	-1,2	-1	-1	-1	-1,3	-1
7	**-4,3**	-4	-4,5	-3,5	-1	-0,8	-1	-3	-3,4	-2,5
8	**-4,3**	1	0,9	1,3	10,6	9,5	11,4	5,6	6,8	5,7
9	**-2**	-5,5	-5,5	-4,7	-0,2	-0,1	-0,2	-3,1	-3	-2
10	**-9**	-13,5	-14	-12	-5	-4	-5	-10	-11	-8,4
11	**-24**	-18	-20	-28	-21	-22,6	-27	-22	-26	-21
12	**2**	-15	-16	-23	-10,6	-10,4	-12,5	-14,4	-16	-13
13	**-2**	-0,6	-0,6	-0,5	-38	-38	-41	-9	-12	-10

Conclusions: Formulas should not be used in clinical research.

Funding: Government Support - Non-U.S.

FR-PO704

When Creatinine Clearance and Estimated GFR Do Not Agree: The Use of a Gold Standard Method to Measure Renal Function in Clinical Practise

Esteban Porrini, Sara Estupiñan, Patricia Delgado Mallen, Marian Cobo, Aurelio Rodriguez, Rosa Miquel, Sergio Luis Lima, Natalia Negrín, Armando Torres. *Hospital Univ de Canarias, La Laguna, Spain.*

Background: Estimated GFR by formulas (eGFR) has a wide error in reflecting renal function in patients with diabetes, Chronic Kidney Disease (CKD), renal transplantation, polycystic disease and in healthy subjects. However, the impact of this error in day-to-day clinical practice has not been properly studied.

Methods: We studied 31 subjects who had a relevant dissociation between creatinine clearance (CrCl) and eGFR (MDRD), which limited the evaluation of renal function. We defined a relevant dissociation as a difference ≥20% between CrCl and eGFR. Also, GFR was measured (mGFR) in all patients by a gold standard, th iohexol plasma clearance. Subjects were divided in those with proven evidence of renal disease, from the outpatient clinic, and those without evidence of renal disease, referred from general practitioners.

Results: 20 subjects had no evidence of renal disease and 11 had CKD of diverse causes: unknown (n=1), CKD (n=5), lupus nephropathy (n=1), tubulointerstitial nephriis (n=1), diabetic nephropathy (n=3).

	No history of renal disease	History of CKD
N	20	11
Age	46.7±17.8	47.8±16.8
Gender (male)	20 (100%)	8 (73%)
Serum creatinine mg/dl	1.36±0.14	2±0.72*
eGFR-MDRD (ml/min)	66.3±13.2	46.1±21.8*
CrCl (ml/min)	108.3±23.2	73.8±32.9*
Diff. CrCl vs MDRD (%)	37.7±10.2	35.7±22.2*
mGFR (ml/min)	88.6±17.0	49.9±19.4*

The difference between eGFR and CrCL was about 40%, and CrCL was frequently higher than eGFR. Of note, mGFR showed values in between eGFR and CrCL. Renal ecography was normal in subjects with no history of renal disease.

Conclusions: mGFR is restricted to clinical research. However, the use of mGFR may be considered in especial clinical conditions, like these patients in whom standard methods do not allow an accurate and precise diagnosis of real renal function. The error of eGFR may have important consequences in clinical practice, which needs further study. *$p<0.05$.

Funding: Government Support - Non-U.S.

FR-PO705

Prevalence of Chronic Kidney Disease According to eGFR Derived from Standardized Serum Creatinine: A Population-Based Study

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Background: Standardization of serum creatinine measurements (SCr) has improved the utility of SCr-based equations for estimating glomerular filtration rate (eGFR). The purpose of this study was to estimate the prevalence of chronic kidney disease (CKD) in Iceland based on eGFR derived from standardized SCr.

Methods: In this retrospective study, we obtained all SCr values from all clinical laboratories in Iceland for the years, 2008-2013. Information on age and sex was also obtained. Using computerized algorithms, we exclued SCr values during episodes of acute kidney injury. eGFR was calculated using the CKD-EPI equation. CKD was defined as eGFR <60 mL/min/1.73 m^2 for more than 3 months and staged according to the KDIGO classification system. Period prevalence of CKD stages 3-5 was calculated based on the population of individuals aged 18 years or above in Iceland, which numbered 245,631 on December 31, 2013.

Results: We retrieved 1,523,914 SCr values for 198,289 individuals aged 18 years and older. The median age was 60 years and 46% were male. The crude prevalence was in men and í women, The age-adjusted prevalence rate per 100,000 in men was 975 for CKD 3A, 269 for CKD 3B, 86 for CKD 4, and 33 for CKD 5. In women, the age-adjusted prevalence rate per 100,000 was 1314 for CKD 3A, 382 for CKD 3B, 86 for CKD 4, and 21 for CKD 5. The prevalence of CKD stages 3-5 increased with advancing age, from 31/100,000 in the age group 18-39 years, 261/100,000 in the age group 40-59 years, 1761/100,000 in the age group 60-69 years, 6003/100,000 in the age group 70-79 years and 12116/100,000 in those who were 80 years of age or older.

Conclusions: This nationwide study, which included standardized SCr measurements and comprises a large proportion of the Icelandic population, demonstrates lower prevalence of CKD stages 3-5 compared with previous studies in Iceland.

Funding: Government Support - Non-U.S.

FR-PO706

Effect of Large Weight Reductions on Measured and Estimated Kidney Function Bernt Johan Illum von Scholten,[1] Frederik I. Persson,[1] Maria S. Svane,[2] Tine Hansen,[1] Sten Madsbad,[2] Peter Rossing.[1] *[1]Steno Diabetes Center; [2]Hvidovre Hospital.*

Background: In patients undergoing gastric bypass surgery and subsequently experiencing fast and large weight loss, muscle mass may be affected followed by changes in plasma creatinine (pCr). The MDRD and CKD-EPI equations for eGFR include creatinine. Serum cystatin C levels provide alternative GFR estimates not linked to muscle mass. We determined the effects of large weight loss after gastric bypass surgery on measured GFR and compared these changes with changes in eGFR.

Methods: Prospective, intervention study including 19 patients. All attended a baseline visit before gastric bypass surgery followed by a visit 6 months post-surgery. Renal function (mGFR) was assessed during four hours plasma ^{51}Cr-EDTA measurement by standard methods. PCr and cystatin C (cysC) were measured and GFR estimated by four different equations (MDRD, CKD-EPI-pCr, CKD-EPI-cysC and CKD-EPI-pCr-cysC) (ClinicalTrials.gov,NCT02138565).

Results: Patients were (mean±SD) 40.0±9.3 years, 14 (74%) were female and 5 (26%) had type 2 diabetes. Baseline weight was 127±21 kg, BMI 42±6 kg/m^2 and mGFR 88±17 ml/min/1.73m^2. At baseline, mGFR correlated with all estimates of GFR (R>0.50;$p\leq$0.025), except MDRD (p=0.093). Six months post-surgery weight loss was 27 (95% CI: 23; 31) kg, mGFR changed -9 (-17; -2) from 122 to 113 ml/min (p=0.024); adjusted for body surface area (BSA) mGFR was insignificantly changed +2 (-5; 9) ml/min/1.73m^2 (p=0.52). CKD-EPI-pCr eGFR increased by 12 (6; 17) (p<0.001) and MDRD eGFR by 13 (8; 18) (p<0.001), while CKD-EPI-cysC eGFR was changed by -2 (-8; 4) ml/min/1.73m^2 (p=0.51). Post-surgery mGFR correlated with all GFR estimates (R>0.60;$p\leq$0.008). Change in mGFR correlated with change in MDRD eGFR (R=0.50,p=0.030), but not with changes in other eGFR measures ($p\geq$0.08).

Conclusions: A weight loss of 27 kg achieved after gastric bypass surgery was associated with a reduction in mGFR of 9 ml/min but unchanged after adjustment for BSA. CKD-EPI-pCr and MDRD eGFR were increased, whereas CKD-EPI-cysC eGFR reflected the unchanged mGFR. eGFR equations based on creatinine should be carefully interpreted in patients experiencing large weight reductions, likely due to muscle mass change affecting creatinine.

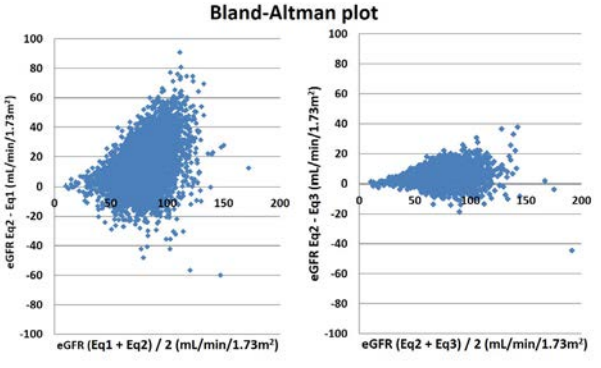
FR-PO707

Clinical Impact of Nutritious Status to Estimate GFR among Japanese Health-Check Subjects Yoshinari Yasuda, Shoichi Maruyama. *CKD Intiatives/ Nephrology, Nagoya Univ, Nagoya, Japan.*

Background: Accurate estimation of GFR is essential in diagnosis and severity classification of CKD. Utility of various GFR equations based on sCr and cystatin-C (Cys) were analyzed in this study.

Methods: The study subjects were 6,635 health-check subjects (3,234 females) in a single center in Aichi prefecture, Japan. IDMS-traceable sCr values were measured by enzymatic method and standardized Cys values were measured by immunonephelometry. Estimated GFR was calculated by Japanese GFR equations based on age, gender and sCr (Eq1) or Cys (Eq2), and by Eq3 based on age, gender, sCr, albumin and UN, eGFR=142×sCr$^{-0.923}$ ×Age$^{-0.185}$ ×Alb$^{0.414}$ ×UN$^{-0.233}$×0.772 (if female) (AJKD2009).

Results: Baseline characteristics (mean ± SD) of study subjects in male and female were 66.0 ± 11.5 and 63.4 ± 11.2 years old (yo), 166.4 ± 6.4 and 154.1 ± 6.1 cm, 63.7 ± 9.5 and 51.6 ± 7.8 kg, sCr: 0.91 ± 0.21 and 0.65 ± 0.13 mg/dL and Cys: 0.94 ± 0.23 and 0.81 ± 0.17 g/L. Both sCr and Cys increased as age developed, but exceeding upper-limit value rate was significantly high in Cys among elderly compared to sCr (male: 29.6 vs 7.3% in 60-69 yo, 50.5 vs 12.3% in 70-79 yo and 80.5 vs 16.7% in 80- yo, female: 21.3 vs1.5% in 60-69 yo, 43.5 vs 2.0% in 70-79 yo and 76.7 vs 21.1% in 80- yo), suggesting body muscle mass effect in sCr. CKD prevalence (GFR category 3a/3b and above) in Eq1 was significantly high compared to Eq2 and Eq3 (male: 23.3/3.9, 9.2/7.0, 14.7/2.5%, female: 16.5/1.5, 4.5/0.1, 8.7/0.9%). Bland-Altman plot revealed a systemic error between Eq1 and Eq2 especially in cases with high GFR values, but not between Eq2 and Eq3, suggesting considerable underestimation of GFR by Eq1.



Conclusions: Different GFR equations seriously affected CKD prevalence. Cys based equation and sCr based equation evaluating nutritious status would be more accurate among health-check subjects, probably because of high body muscle mass.

Funding: Government Support - Non-U.S.

FR-PO708

Coronal Sectional Areas of the Kidney Components Measured by Noncontrast-Enhanced Steady-State Free Precession Magnetic Resonance Imaging with Spatially Selective Inversion Recovery Pulse and Their Association with Chronic Kidney Disease Tadashi Otsuka,[1] Ryohei Kaseda,[2] Yoshikatsu Kaneko,[2] Ryuzi Aoyagi,[1] Ichiei Narita.[2] *[1]Nephrology, Tachikawa General Hospital, Japan; [2]Nephrology, Niigata Univ, Japan.*

Background: Kidney imaging by magnetic resonance imaging (MRI) has been expected as a powerful tool to diagnose renal lesions. However, without contrast agents, it has been difficult to distinguish renal compartments clearly such as renal cortex or medulla region. Recently, noncontrast-enhanced steady-state free precession (SSFP) MRI with spatially selective inversion recovery (IR) pulse was reported to improve the visibility of renal corticomedullary differentiation in patients with renal insufficiency. Using this method, we investigated the correlations between renal function and segmental areas of the kidney compartments.

Methods: A total of 85 patients (aged 64±17 years) with CKD (mean estimated glomerular filtration rate [eGFR], 54.0 ± 24.5 ml/min/1.73 m^2) were recruited for this study. CKD patients were classified into four groups: The chronic glomerulonephritis group (CGN; n=34), the diabetic nephropathy group (DN; n=19), the nephrosclerosis group (BNS; n=15), and others (n=17). All patients underwent noncontrast-enhanced SSFP MRI with spatially selective IR pulse. The coronal sectional areas of kidney cortex, medulla and the maximum and minimum cortical thickness were measured.

Results: eGFR was positively correlated with coronal sectional areas of kidney cortex (R^2=0.53, P<0.001), medulla (R^2=0.28, P<0.001), and maximum cortical thickness (R^2=0.36, P<0.001) and minimum cortical thickness (R^2=0.47, P<0.001). Among DN and BNS, the correlation efficiency of eGFR with area of medulla (R^2=0.66, P<0.001; R2=0.63, P<0.001) was significantly higher than with other compartments. By contrast, in CGN, eGFR had no correlation with the area of medulla (R^2=0.06, P=0.07) and highest correlation was observed with the area of cortex (R^2=0.44, P<0.001).

Conclusions: Two-dimensional quantitative assessment of kidney compartments by noncontrast-enhanced SSFP MRI with spatially selective IR pulse significantly correlates with renal function and could provide specific information for differentiating the etiology of CKD.

FR-PO709

Surveillance of CKD Epidemiology in the U.S. – A Joint Analysis of NHANES and KEEP Orrin Myers, V. Shane Pankratz, Mark L. Unruh, Christos Argyropoulos. *Internal Medicine, Univ New Mexico, Albuquerque, NM.*

Background: Chronic kidney disease (CKD), although a growing public health issue, lacks a nationwide surveillance system. Large voluntary, community based detection programs (e.g. KEEP) have been used but have limitations due to self-selection. Surveillance with representative samples (e.g. NHANES) is limited because they do not capture sufficiently detailed data. We applied selection models to assess whether KEEP data can be adjusted to reflect trends in CKD prevalence from 2001-2012 as observed in NHANES.

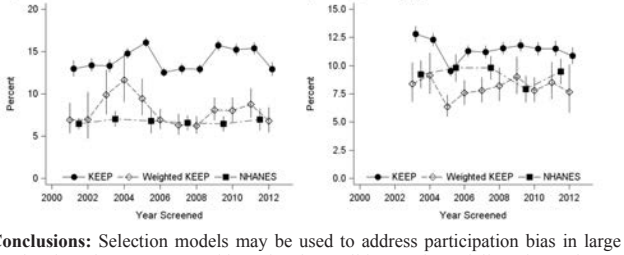
Methods: Selection models to predict KEEP participation were based on data collected 2001-2012 by KEEP and NHANES. Variables included demographic, socio-economic, and health-related indicators. Prevalence of CKD endpoints, eGFR<60 mL/min/1.73m^2, and ACR≥30 mg/g, were estimated by weighted logistic regression analyses that included random effects to account for state-level variation in recruitment practices.

Results: NHANES and KEEP samples included 27,565 and 127,149 participants, respectively. Participation bias was dramatically reduced after accounting for participation. KEEP (eGFR<60) estimates dropped from 14.3% to 8.0% when defining CKD as eGFR<60, and from 11.4% to 8.1% when defined as ACR≥30. NHANES estimates were 6.7% and 9.2%, respectively. Weighted CKD prevalence by year showed very good agreement with NHANES.

Table 1. Prevalence of eGFR<60 and ACR≥30.

	eGFR<60		ACR≥30	
Data and Model	**%**	**95% CI**	**%**	**95% CI**
NHANES	6.72	6.29 - 7.16	9.25	8.73 - 9.77
KEEP Unweighted	14.31	13.19 - 15.50	11.35	10.75 - 11.98
KEEP Weighted	8.01	7.02 - 9.12	8.07	7.25 - 897

Figure 1. Prevalence of eGFR < 60 ml/min/1.73 m^2 (A) and ACR ≥ 30 mg/g (B) by year for KEEP and NHANES.



Conclusions: Selection models may be used to address participation bias in large community detection programs. This makes it possible to substantially enhance inputs for future CKD surveillance systems that provide spatio-temporal maps of CKD hotspots in the US.

Funding: Private Foundation Support

FR-PO710

Secular Trends in Increase in the Prevalence of CKD in Diabetes Tracks the Secular Trends in Lower Systolic and Diastolic Blood Pressures in the U.S. Srini Beddhu,[1,2] Alfred K. Cheung,[1,2] Guo Wei,[1] R. E. Boucher,[1] Rabia Nadeem Kiani,[1] Tom Greene.[1] *[1]Univ of Utah, SLC, UT; [2]VA, SLC, UT.*

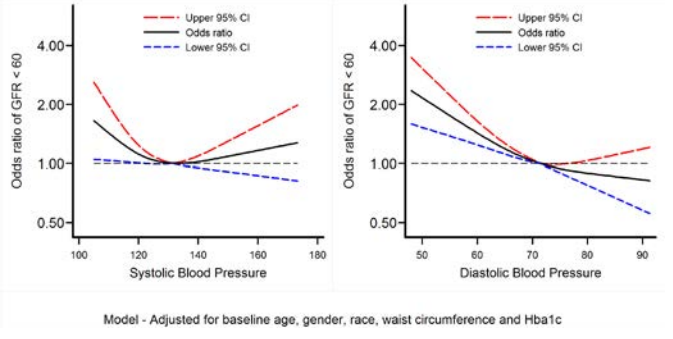
Background: Recent studies indicate intensive BP control might ↑ the incidence of CKD, yet ↓ the risk for mortality in those with established CKD. Hence, greater BP control might result in ↑ prevalence of CKD at the population level.

Methods: Using 1988-1994 (National Health And Nutrition Examination Survey) NHANES III as the reference, survey weight adjusted secular trends in prevalence of CKD (eGFR < 60 ml/min/1.73 m^2) in diabetics in 1999-2002, 2003-2006 and 2007-2010 NHANES were examined. Similarly, trends in SBP and DBP in diabetics with and without CKD were examined. Using median SBP or DBP as the reference, the odds of CKD in diabetics in the entire cohort were related to SBP or DBP in natural cubic spline regression models in svy suite using STATA 14.

Results: The prevalence of CKD in diabetics in the US has increased. In parallel, there has been a drop in SBP and DBP in diabetics without and with CKD but the drop has been more pronounced in CKD.

Diabetics in Survey	CKD prevalence in diabetics (%)	Non-CKD diabetics		CKD diabetics	
		SBP	DBP	SBP	DBP
NHANES III (N =1842)	13.3	133 ± 25	76 ± 13	146 ± 30	74 ± 16
1999-2002 (N=1078)	16.7	132 ± 18	73 ± 13	144 ± 25	61 ± 21
2003-2006 (N=1170)	18.1	131 ± 17	71 ± 12	139 ± 24	61 ± 18
2007-2010 (N=1793)	17.4	128 ± 19	70 ± 13	133 ± 24	60 ± 17

In spline regression analyses, lower SBP and DBP were associated with higher odds of CKD in diabetics.



Conclusions: Secular trends in increase in the prevalence of CKD in diabetics track the secular trends in drop in both SBP and DBP in the US population. This might reflect hemodynamic effects of intensive BP lowering that increases CKD incidence, practice patterns of more intensive BP lowering in CKD or decreased mortality with intensive BP lowering in CKD.

Funding: NIDDK Support, VA Support

FR-PO711

Prediction of Pathologic Proteinuria by Dipstick Albuminuria and the Specific Gravity Hajeong Lee,[1] Hee Gyung Kang.[2] *[1]Internal Medicine, Seoul National Univ Hospital, Korea; [2]Pediatrics, Seoul National Univ College of Medicine, Korea.*

Background: Proteinuria is essential to diagnose kidney disease. Urine dipstick test is easy to recognize pathologic proteinuria with lower cost, so usual health examination programs use it for screening of kidney diseases. However, spot urine dipstick albumin (DSA) is affect by urine specific gravity (USG). The impact of USG on estimation of proteinuria remains obscure.

Methods: We included patients who were tested DSA, spot urine protein to creatinine ratio (UPCR) and spot urine albumin to creatinine ratio (UACR) in the same day from 2010 to 2013. Pathologic proteinuria was defined as UPCR ≥0.2 g/g creatinine. Albuminuria was divided as microalbuminuria (UACR 0.03~0.30 g/g) and macroalbuminuria (UACR >0.30 g/g). A random 60% of the cohort was used to generate a development model, which was validated in the remaining 40%. Samples were stratified according to DSA and SG values. A DSA versus SG matrix was created, and each sample was allocated to a discrete DSA-SG category. Proportions of samples with pathologic proteinuria, microalbuminuria, macroalbuminuria were calculated for all 42 cells.

Results: A total of 86,874 cases of UPCR and 52,459 cases of UACR were collected. Associations between DSA and UPCR/UACR was different according to the USG. In the diluted urine with USG ≤1.010, more than 80% of patients with dipstick albumin 1+ had pathologic proteinuria. However, in the concentrated urine with USG ≥1.025, it was less than 5%. Using DSA-SG combination, we developed pathologic proteinuria, microalbuminuria, and macroalbuminuria prediction model. Optimum correlation between DSA-SG cells and UPCR/UACR were determined for development model. Accuracy for pathologic proteinuria, microalbuminuria, and macroalbuminuria were 90.1%, 84.0%, and 95.8%, respectively. Moreover, positive predictive values were 93.7%, 74.9%, and 89.2%.

Conclusions: A novel algorism to predict pathologic proteinuria and proteinuria quantitation using USG and DSA may be helpful to screening kidney disease more precisely.

FR-PO712

A Stochastic Model for the Waiting Time of Creatinine Rise to a Critical Level in Post Renal Transplant Period Chandra M. Pandey,[1] Sonam Bedi,[1] Raj K. Sharma,[2] Sada Nand Dwivedi.[3] *[1]Biostatistics and Health Informatics, Sanjay Gandhi Postgraduate Inst of Medical Sciences, Lucknow, Uttar Pradesh, India; [2]Nephrology, Sanjay Gandhi Postgraduate Inst of Medical Sciences, Lucknow, Uttar Pradesh, India; [3]Biostatistics, All India Inst of Medical Sciences, New Delhi, Delhi, India.*

Background: Elevated creatinine is a signal to poor functioning of allograft. There is a need to estimate the risk of rise in creatinine to a critical level, which is not observable directly.

Methods: A stochastic model with varied risk of creatinine rise is proposed to estimate the above risk. The underlying assumptions are: time to achieve the critical level in days was taken as random variable. Π and $(1-\Pi)$ is the proportion of transplant cases whose creatinine rise to critical level in a small length of time t to Δt is $\lambda_1\Delta t$ and $\lambda_2\Delta t$; where $\lambda_1<\lambda_2$. The probability density function of duration derived follows multinomial distribution with parameters λ_1, λ_2 and Π. The parameters are estimated using Maximum Likelihood Estimation method. The pilot values were given as an initial input. The estimates produced by previous iteration was given as input for subsequent iteration. The iteration process was repeated till the convergence was achieved and output at this level was taken as final estimate of these parameters. The variances and co-variances of the estimates are also obtained. The model was applied to 430 transplants performed at SGPGIMS during Jan 2008 to Dec 2013. The creatinine level within 20 days of discharge was considered as baseline. A rise of at least 30% to this baseline was considered as critical level of creatinine. The model has been applied to recipients within the first year of follow up.

Results: The model explained the data set ($\chi 2$=0.90). The estimate of parameters is: Π=0.5797, λ_1=0.0403 and λ_2=0.2427. About 40% of transplant cases belonged to high risk group, while 60% to low risk group.

Conclusions: The frequency and pattern of creatinine rise may help in formulating more precise and patient centric management strategy in post-transplant period.

Funding: Government Support - Non-U.S.

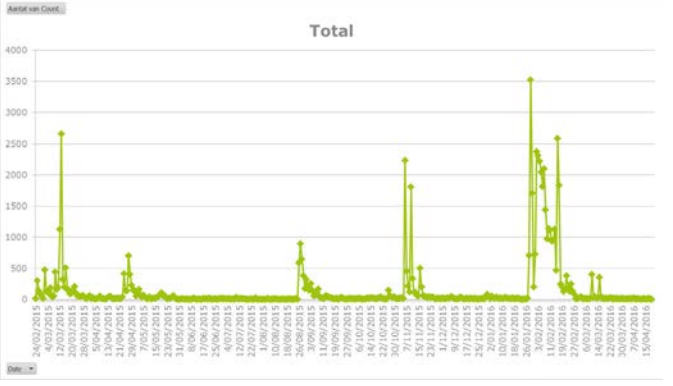
FR-PO713

Facebook® Can Be Used to Reach a Target Audience to Screen for CKD Risk Using the QKidney®-2014 Risk Calculator Eric E. Gheuens, Koenraad Peter Bouman, Ronald Daelemans. *ZNA Kidney Clinic, Ziekenhuis Netwerk Antwerpen, Antwerpen, Belgium.*

Background: On World Kidney Day (WKD) 2015 we launched the QKidney®-2014 risk calculator (www.Qkidney.org) to screen for CKD risk in the general population, aged between 35 and 75 years.

Methods: A webpage was created (wereldnierdag.zna.be) and launched on WKD 2015 using different traditional campaigns. In February 2016 we launched a Facebook® advertising campaign targeting users in the desired age group.

Results: The first weeks after the launch the risk calculator was used by about 5000 people. In the proceeding year a steady activity on the website created about 30.000 records. In February 2016, almost a year after the launch, the Facebook advertising campaign was active during two weeks. The website was viewed almost 600.000 times by about 350.000 unique users. 329.000 views were on desktops and 270.000 on mobile devices. Around 30.000 new records were created in this short time span.



There was a need to monitor the Facebook® page on a daily basis, since many messages were posted and discussions ensued that needed to be moderated. All in all the atmosphere on the page was very positive and very few negative reactions were posted.

Conclusions: Screening for CKD risk with an online risk calculator (QKidney®-2014) targeted to a specific audience via a Facebook® advertising campaign was highly effective. The use of social media in order to reach a specific target population to deliver a health related message should be explored more often.

FR-PO714

Chronic Kidney Disease(CKD) in HIV-Infected Patients: Relation to Viral Load Justine Johnson,[1] Eric Joseph Lai,[1] Wadi N. Suki,[1] Duc T.M. Nguyen,[2] Edward Graviss.[2] *[1]Dept of Medicine, Houston Methodist Hospital, Houston, TX; [2]Pathology, Houston Methodist Hospital, Houston, TX.*

Background: Since the advent of HAART, HIV-associated nephropathy has evolved from a disorder characterized by proteinuria and glomerulosclerosis to one with clinical characteristics more suggestive of tubulo-interstitial disease . The object of this study was to investigate the prevalence of CKD in a large HIV-infected population and viral load and CD4 counts as indices of effective HAART.

Methods: Electronic Medical Records of 3858 HIV-infected patients at a community health clinic were reviewed. Demographic characteristics and laboratory values for serum creatinine (SCr), CD4 count, and viral load were collected. Estimated GFR (eGFR) was calculated from the SCr by the CKD-Epi equation. CKD was considered as eGFR <60 ml/min/1.73m^2. Differences across kidney function stages were compared using Chi-square or Fisher's exact tests for categorical variables and Kruskal-Wallis test for continuous variables as appropriate. Univariate and multivariate ordinal logistic regression models were used to examine the relationship between kidney function stages and potential comorbidities. Representative comorbdities included hypertension, diabetes, cardiovascular disease. All analyses were performed on Stata version 13.1 (StataCorp LP, College Station, TX). A p-value of <0.05 was considered statistically significant.

Results: Patients with CKD represented 4.1% of the population; they were older, and had a higher representation of females. On ordinal logistic regression analysis, there was a highly significant association of CKD with viral load <50 copies/ml (OR+1.73, CI1.46 to 2.05, p<0.001), but not with the CD4 count.

Conclusions: Low or undetectable HIV viral load is generally indicative of a high degree of HAART medication compliance. The association of CKD with very low or undetectable viral load indicates that HAART medications are responsible for the high prevalence of CKD in these patients.

FR-PO715

Identification of Chronic Kidney Disease in the Veterans Affairs Healthcare System Rajiv Saran,[1] Anca Tilea,[1] Vahakn B. Shahinian,[1] Aaron Pearson,[1] Jennifer L. Bragg-Gresham,[1] Hal Morgenstern,[1] Brenda W. Gillespie,[1] Alan B. Leichtman,[1] Ann M. O'Hare,[2] John R. Hotchkiss,[2] Daniel F. Balkovetz,[2] Susan T. Crowley.[2] *[1]Univ of Michigan; [2]VA Healthcare System.*

Background: The strict application of the KDIGO definition for CKD surveillance in the VA HCS may miss cases; a more liberal case definition may improve sensitivity. We estimated VA CKD prevalence using two different definitions in existing operational data in the VA Renal Information System (VA REINS).

Methods: CKD prevalence was examined using laboratory data and ICD-9 codes from 2006-2014. Proteinuria was hierarchically categorized using any urine tests for albumin excretion rate (AER), albumin- creatinine ratio (ACR), protein excretion rate (PER), protein-creatinine ratio (PCR), or urine dipstick. GFR was estimated from outpatient serum creatinine. CKD prevalence was assessed using both strict KDIGO-specific criteria (evidence of persistent lab abnormality) and 'liberal' definitions of CKD. The denominator was defined operationally as the population of VA HCS 'users' (with ≥1 contact with VA in that or 2 previous yrs).

Results: Among 6,932,278 VA users in 2014, CKD prevalence using KDIGO criteria was 16.4%, whereas the liberal definition increased prevalence to 36.3% (Table). Only 3.2% had an ICD-9 diagnosis of CKD, while 74% had at least 2 eGFR measurements available and 74.5% had urinary protein assessment (29.4% with quantitative evaluation).

Liberal CKD Definition	N=6,932,278	%
Any eGFR <60ml/min/1.73m2	1,869,755	27
Proteinuria moderate or worse	1,342,435	19.4
CKD ICD-9 diagnosis	220,666	3.2
Total CKD	2,516,475	36.3
Strict CKD Definition		
Persistent eGFR <60 ml/min/1.73m2	713,068	10.2
ACR/PCR/AER/PER moderate or worse	555,778	8.0
CKD ICD-9 diagnosis	220,666	3.2
Total CKD	1,140,382	16.4

Conclusions: In the VAHCS there are substantial differences in CKD prevalence depending on the stringency of definition applied. The definition of CKD has implications for VA CKD population health management to ensure Veteran access to CKD care.

Funding: VA Support

FR-PO716

Prevalence of Chronic Renal Disease in Afro-Brazilian Isolated Communities in Brazilian Northeast Natalino Salgado Filho, Joyce S. Lages, Dyego José Araujo Brito, Laisson De Moura Feitoza, Francisco Monteiro Jr, Denizar Vianna, Gyl Barros-Silva, Elton Jonh Freitas Santos. *Federal Univ of Maranhão, Brazil.*

Background: In Brazil, *there are no consistent studies* investigating the prevalence of chronic renal disease in its Afro-descendant population. The objective was to investigate the prevalence of chronic renal disease (CRD) in 32 isolated Afro-descendant communities existing in the state of Maranhao, Northeast of Brazil.

Methods: This study included 1539 individuals living in rural areas. Epidemiological, clinical, and laboratory and anthropometric aspects were evaluated. The glomerular filtration rate (GFR) was estimated using CKD-EPI Creatinine (CKD-EPIcr), CKD-EPI Cystatin C (CKD-EPIcy), CKD-EPI Creatinine-Cystatin C (CKD-EPIcc) e MDRD. For the diagnosis and classification of CRD, the KDIGO (2012) criteria were applied.

Results: The gender most frequent was female (50,5%). The average age was 44,4 (±17,3) years, 616 (42,5%) without fixed income, 592(40,9%) have less than three years of study, 159 (10,98%) were smokers, 611 (42,2%) consumed alcohol regularly, diabetes was diagnosed in 91 (6,29%), hypertension in 427 (29,51%) and overweight and obesity in 653(45%). The evaluation of GFR for the stages 3A, 3B and V was respectively: 0.76, 0.14 and 0 (MDRD); 0.97, 0.14 and 0 (CKD-EPIcr); 3.32, 1.31 and 0.07 (CKD-EPIcy). It was not found individual with these stages when we used CKD-EPIcc equation.

Conclusions: The prevalence of CRD in Brazilian Afro-descendant communities, with low average age and socially vulnerable, was less than previously reported for others populations and presented wide variation of results according to the GFR measurement method used.

FR-PO717

Ovarian Reserve and Fertility Hormonal Profiles in Women with Chronic Kidney Disease Kate Bramham,[1,2] Aasmita Gautam,[1] Kate S. Wiles,[1] Lucy C. Chappell.[1] *[1]Div of Women's Health, King's College London, London, United Kingdom; [2]Dept of Renal Sciences, King's College London, London, United Kingdom.*

Background: Fertility is reported to be reduced in women with increasing severity of chronic kidney disease (CKD). Improved understanding of fertility assessment in women with impaired renal function will enable women with CKD to make informed choices about planning future pregnancy. Previous studies of reproductive hormones in women with CKD are small and the relationship between the novel biomarker of ovarian reserve, Anti-Mullerian Hormone (AMH) and renal function has not been explored. The objective of this study was to define the relationships between glomerular filtration rate (GFR) and i) reproductive hormones (follicle stimulating hormone (FSH), luteinising hormone (LH), oestradiol, progesterone and prolactin) ii) AMH, in women with CKD and healthy controls.

Methods: 94 women with CKD (Stage 1: 24 (23.1%); Stage 2: 23 (22.1%); Stage 3:35 (31.8%); Stage 4 and 5: 14 (13.5%) and 10(9.6%) healthy female controls were recruited. Participants provided a single blood sample for analysis. Fertility hormones were quantified by standard laboratory assays and their relationship with GFR assessed.

Results: AMH was not affected by GFR after adjustment for age. However there was a strong association between maternal age and AMH in women with CKD (R= -0.474, value p<0.005). No significant relationships were identified between GFR and FSH, oestradiol, progesterone after adjustment for age. However, there were significant negative correlations between LH and GFR despite correction for age (R= -0.231, p= 0.020), and between prolactin and GFR (R= -0.271, p= 0.005).

Conclusions: CKD does not appear to be associated with reduced ovarian reserve, thus AMH could be a useful tool in the assessment of ovarian reserve in women with CKD as its quantification is not affected by renal function. Serum prolactin increases with worsening GFR which is likely to reflect reduced excretion. Another novel finding was the increase in LH with reduced GFR and requires confirmation in a larger cohort.

Funding: Government Support - Non-U.S.

FR-PO718

Antiretroviral Treatment and Chronic Kidney Disease in Urban Zambia: Cohort Characteristics and Association with Chronic Kidney Disease Martin G. Zeier. *Div of Nephrology, Heidelberg Univ Hospital, Heidelberg, Germany.*

Background: The widespread use of antiretroviral-treatment (ART) increases life spans in Sub-Saharan-Africa (SSA). This goes along with an increase in non-communicable diseases, e.g. chronic kidney disease (CKD).

Methods: Study design Retrospective cohort study **Setting & Participants** Routine data of 1119 HIV patients were assessed for CKD in Lusaka/Zambia between 2011 and 2013 in a quasi-random sample. Inclusion criteria were at least one serum creatinine measurement and 90 days on ART. **Predictor OR Factor** HIV-infection, high blood pressure, ART-medication **Outcomes** We compared patients' conditions prior to ART initiation and at the last observation and applied multivariate models to assess the association between ART and eGFR. The CKD-EPI equation was used to estimate the glomerular filtration rate (eGFR) without the correction factor for African Americans.

Results: Ultimately, 28.2% of patients had eGFR category 2-5 (5.5% < 60 ml/min), compared to 24.8% (4.8%) prior to ART initiation. Hypertension was recorded in 26% of patients. 83% ever received Tenofovir (TDF). 12% of patients who later switched to TDF-free ART (TscART) had baseline eGFR categories3-5. eGFR deteriorated in 41% of

TscART patients, compared to 20% in the rest. Overall, 93% of patients with initial eGFR category 3-5 kept eGFR constant or improved. 20% newly developed high blood pressure, 40% of those with eGFR category 3-5 at baseline. Multivariate models revealed a negative effect of TDF on GFR. **Limitations** One creatinine measurement, 45% baseline creatinine values missing, no assessment of proteinuria.

Conclusions: Impaired renal function including CKD is a relevant health problem in HIV patients in SSA, growing with treatment duration. Patients with initially no/mild renal impairment experienced a loss of eGFR, in particular if receiving TDF. Baseline moderately/severely impaired patients retain or improve renal function on ART. Kidney monitoring is recommended, but should not delay access to ART.

Funding: Private Foundation Support

FR-PO719

Glomerular Filtration Rate Is Low in the Inflammatory Arthritis Diseases Compared to Healthy Population: Essential Role of Inflammation

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Background: Inflammatory diseases are associated with subclinical renal impairment. **We** aimed at investigating the associations between estimated glomerular filtration rate(eGFR), traditional cardiovascular risk factors, and markers of inflammation and oxidative stress in inflammatory arthritis patients compared to healthy controls.

Methods: Participants were recruited from January 2013 to2016. Healthy subjects recruited from the community. MDRD formula was used to get eGFR. ttest was used to compare the laboratory values and renal function parameters between two groups. Linear regression analysis used to look for the correlation between GFR and each of traditional cardiovascular risk factors and inflammatory markers.

Results: Age mean(SD) was 49(13) yrs. Mean GFR of the inflammatory arthritis patients was 118 ± 30 ml/min (range 60 - 227) and 128 ±37 ml/min for the control. Inflammatory arthritis patients had lower GFR, albumin(P<0.001), and total protein (p=0.03), and higher ESR(P<0.001), CRP (P<0.001), and uric acid (p=0.01). Among patients and control groups, there was a negative linear relationship between GFR and age of the participants Controls (p=0.01,CI: -1.82,-0.26), patients (p<0.001,CI: -1.24,-0.40), SBP: controls (p= 0.04,CI: -0.61, -.00), patients(p=0.022 ,CI: -0.61, -0.05). Among the inflammatory arthritis group, GFR has a negative linear relationship with age of participants, age at disease onset (p=0.002,CI: -1.18, -0.29), DBP(p=-2.14, CI: -1.24, -0.05), ESR(p=0.04,CI:-0.24,-0.01), CRP(p=0.02, CI: -0.47, -0.04), uric acid(p<0.001,CI -0.18, -0.05), total protein (p= 0.01,CI: -0.91, -0.16). GFR positively associated with albumin level (p=0.03, p= 0.14, 2.35).

Conclusions: Untraditional risk factors such as oxidative stress and inflammation is associated with progression of renal injury. Study indicates that in inflammatory arthritis inflammation is involved in the early stages of impaired kidney function. Whether anti-inflammatory therapies are effective in slowing down the deterioration of kidney function in the arthritis diseases remain to be established.

FR-PO720

Chronic Kidney Disease of Unknown Origin-Possible Link to Mesoamerican Nephropathy in Guatemala

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Background: Several epidemiological studies have described a high prevalence of Chronic Kidney Disease of unknown etiology (CKDu) along the Pacific Coast of Central America. This particular disease presentation is known as Mesoamerican Nephropathy (MeN). A definitive study has not been conducted to confirm the presence of MeN in Guatemala.

Methods: This cross sectional study was conducted in the largest referral center in Guatemala. All the patients who presented with ESRD during a period of 6 months were interviewed. We looked for "traditional" risk factors (diabetes and/or hypertension) and lack of "traditional" risk factors of CKD.

Results: A total of 249 patients were interviewed. 51% were males and 49% females, 54% of the patients lived in Guatemala City and 16.8% along the Pacific Coast. A total of 68% of the subjects had hypertension (HTN), 41% had diabetes mellitus (DM), and 25% did not present with DM or HTN. The subjects without DM and HTN were younger (35 ± 18.5) than the subjects with DM and/or HTN (50±17.3, p<0.001).

Table 1. Demographic Characteristics (n=249)

Gender	Frequency	Percentage %	
Male	128	51	
Female	121	49	
Origin	Frequency	Percentage %	
Guatemala	136	55	
Pacific Coast	42	19	

Table 2. Risk factors for ERSD (n=249)

Risk factor	Frequency	Percentage %	p
Diabetes	103	41	<0.001
Hypertension	170	68	
Diabetes and hypertension	85	34	
None	61	25	

Table 3. Age difference between those without traditional risk factors and those with traditional risk factors

	Without traditional risk factors	With traditional risk factors	p
Age,Mean±SD	35±18.5	50±17.3	<0.001

Conclusions: 25% of the subjects had neither DM nor HTN, a 16.8% came from three towns located on the Pacific Coast and the mean age was statistically significantly different between both groups, these findings may indicate evidence of MeN in Guatemala. Additional studies are recommended to establish the extent of MeN in Guatemala.

Funding: Private Foundation Support

FR-PO721

Rapid Loss of Kidney Function amongst Apparently Healthy Young Adults from Communities at Risk of Mesoamerican Nephropathy

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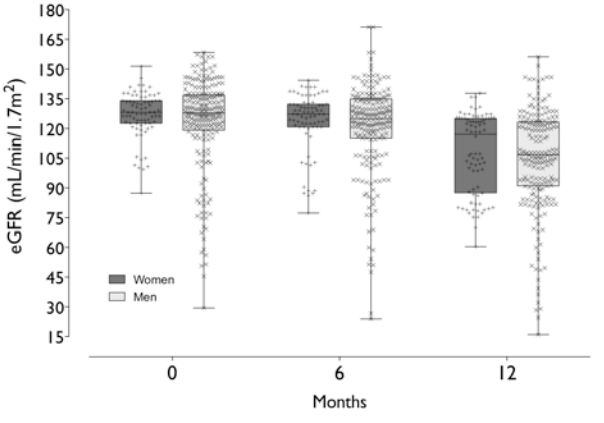
Background: Mesoamerican Nephropathy (MeN) is killing thousands of young adults across rural Central America, where intensive agricultural work is the dominant occupation. MeN is a form of chronic kidney disease (CKD) characterised by minimal proteinuria and interstitial scarring on biopsy. The aetiology and natural history of MeN are unknown.

Methods: In partnership with 9 affected communities in Leon and Chinandega regions, Nicaragua, we are (to our knowledge) undertaking the first community-based longitudinal study investigating MeN. We invited all men and a random sample of women (ratio 3:1), aged 18-30, without a history of CKD to take part. Questionnaire data and biosamples have been collected at baseline and at 6-monthly intervals. Estimated glomerular filtration rate (eGFR) was calculated by $CKD\text{-}EPI_{creat}$ and the slope estimated using a multilevel model. This abstract describes the eGFR decline to the halfway point of the 2-year study.

Results: 16 potential participants had a diagnosis of CKD and were not included. 350 of 360 eligible participants consented to take part and 94% have attended ≥2 of the 3 study visits to date. Mean baseline eGFR was 125mL/min/1.72m^2 and mean decline in eGFR was 19.0mL/min/1.73m^2 (95%CI: 16.5-21.5) over the first year with no difference between sexes (Figure).



Individual eGFR values with overlying box and whisker plot over the first year of follow-up (all communities). Boxes: interquartile range; Whisker: range.

Conclusions: The average annualised loss of >15% of kidney function in unselected, apparently healthy, young adults is consistent with the devastating effects of this disease that are reported. Questionnaire data and biosamples should allow us to go on to uncover associations between potential causal exposures and eGFR decline in MeN.

Funding: Private Foundation Support

FR-PO722

A Comparision between the First-Degree Relatives of IgAN Patients and General Population: Prevalence, Risk Factors and Relative Risk of Chronic Kidney Disease Yi Bao, Xin Wei, Jing Zhou. *Nephrology, The First Affiliated Hospital of Nanchang Univ, Nanchang, China.*

Background: Primary IgA nephropathy (IgAN) is the commonest type of primary glomerulonephritis worldwide,which is a major cause of leading to ESRD in china. However,it is well unclear whether the first-degree relatives (FDRs)of IgAN patients underwent a higher risk with CKD or renal damage than the general population.The aim of our study was to investigate the familial clustering of IgAN in southern China, and estimated the relative risk of CKD comparing with mached controls.

Methods: A total of 634 FDRs of 295 IgAN patients were reviewed from November 2007 to March 2009 in southern China,and a random sample of 1167 age-, gender-, and region-matched controls without family history of CKD were included.Information on questionnaire,anthropometric measurements, laboratory examination results and health history were recorded. CKD risk factors, including age, gender, BMI, hypertension and etc were investigated.The odds ratio (OR) was used to estimate the relative risk of CKD between FDRs of IgAN patients and controls.

Results: There was a significant difference in prevalence of CKD (31.3% vs. 11.3%, P < 0.001)between the FDRs of IgAN patients and matched controls.After adjusting confounders, female gender (OR=2.02, P=0.008), hypertension (OR=2.14, P<0.001) and etc were independently associated with increased risk of CKD.The adjusted relative risk of 4.03 for CKD was obtained among the FDRs of IgAN patients and matched controls,and the adjusted relative risk for hematuria, albuminuria and reduced eGFR were 6.61 , 3.32 and 4.00, respectively.

Table1 The risk analysis of CKD, haematuria,albuminuria and reduced eGFR in IgAN patients' first-degree relatives comparing with controls

	Adjusted[a] OR	P	Adjusted[b] OR	P
CKD	3.71 (1.07, 1.84)	0.013	4.03 (3.08, 5.27)	<0.001
Haematuria	6.59 (4.60, 9.43)	<0.001	6.61 (4.59, 9.53)	<0.001
Albuminuria	3.05 (2.10, 4.43)	<0.001	3.32 (2.26, 4.88)	<0.001
Reduced eGFR	2.92 (1.65, 5.16)	<0.001	4.00 (2.17, 7.37)	<0.001

Table 2 Multivariate logistic regression analysis of associated risk factors of CKD in the first degree relatives with IgAN patients

Variable	Adjusted ORs	P
Age(years)		
20 – 39	1.00	
40 – 59	1.13 (0.73-1..73)	0.586
60 – 69	2.33 (1.07-5.05)	0.033
70 –	6.42 (2.26-18.26)	<0.001
Gender (female vs male)	2.02 (1.20-3.40)	0.008
BMI		
Nomal[a]	1.00	
Over weight[b]	1.30(0.81-2.10)	0.281
Obese [c]	1.91 (1.07-3.41)	0.028
Hipertrigliceridemia	1.81 (1.11-2.96)	0.018
Hypercholesterolemia	0.89 (0.52-1.52)	0.675
Hyperuricemia	0.91 (0.55-1.52)	0.721
Diabetes	1.84 (1.20-3.40)	0.159
Hypertension	2.14 (1.25-3.79)	0.006
Smoking	2.00 (1.11-3.60)	0.021

Conclusions: The study revealed the FDRs of IgAN patients experienced a higher risk with CKD than the general population.Furthermore, hypertension,female gender, hypertriglyceridemic and overweight are independent risk factors of CKD for this special population .

FR-PO723

Renal Interstitial Fibrosis: An Imperfect Prognostic Indicator in Chronic Kidney Disease Hanni Menn-Josephy,[1] Carol S. Lee,[1] Angela Nolin,[1] Marta Christov,[2] Denis Rybin,[1] Janice Weinberg,[1] Joel M. Henderson,[1] Ramon G. Bonegio,[1] Andrea Havasi.[1] *[1]Medicine- Renal Section, Boston Univ School of Medicine, Boston, MA; [2]Renal Div, New York Medical College, Valhalla, NY.*

Background: The extent of interstitial fibrosis on kidney biopsy is regarded as a prognostic indicator and guide to treatment. Patients with extensive fibrosis are assigned to supportive treatments with the expectation that they have advanced beyond the point at which immunosuppressive or other disease modifying therapies would be of benefit. Our study highlights some of the limitations of using interstitial fibrosis to predict who will develop ESRD.

Methods: Analysis of 434 consecutive renal biopsies performed between 2001-2012 at a single center. We assessed the influence of various clinical factors along with fibrosis as predictors of ESRD and dialysis free survival in various patient groups.

Results: Interstitial fibrosis performed well overall as a predictor of progression to dialysis and on average patients with >50% fibrosis progressed more rapidly than those with either 25-49% or 0-24% fibrosis with a median time to dialysis of 1.2 years, 6.5 and >10 years respectively. In contrast, interstitial fibrosis was of less value as a predictor of disease progression in a subset of cases that included patients over the age of 70 and those with diabetic nephropathy on biopsy. Surprisingly, 13.9% of patients with normal renal function had 25-49% fibrosis and 5% had more than 50% fibrosis on biopsy, and 5 years after undergoing biopsy 21% of patients with >50% fibrosis still remained dialysis free.

Conclusions: Renal fibrosis is an imperfect prognostic indicator for the development of ESRD and caution should be exercised in applying it too rigidly, especially in elderly or diabetic patients.

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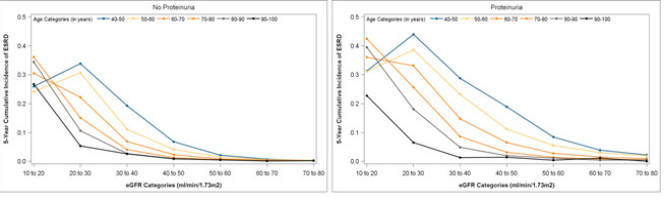
FR-PO724

Age-Dependent Thresholds of Kidney Function and Progression to End Stage Renal Disease in the Veterans Affairs Healthcare System Jennifer L. Bragg-Gresham,[1] Anca Tilea,[1] Hal Morgenstern,[1] Vahakn B. Shahinian,[1] Ann M. O'Hare,[2] Daniel F. Balkovetz,[2] Linda F. Fried,[2] Susan T. Crowley,[2] Rajiv Saran.[1] *[1]Univ of Michigan; [2]Veterans Affairs Healthcare System.*

Background: Normal aging has been linked to GFR decline; however, the definition of CKD does not take age into consideration. The VA Healthcare System (HCS) manages an aging population with many enrollees meeting CKD criteria using the standard fixed eGFR threshold. Whether age is a modifier of ESRD risk amongst Veterans with CKD has agency relevance for population health management, thus we examined existing data in the VA Renal Information System (REINS) to understand this issue.

Methods: 5,913,070 VA 'users' (defined by ≥1 contact with VA HCS in past 3 yrs) were identified in 2006 and followed through 2013. Cox regression estimated the effects of baseline eGFR by age and proteinuria [based on urine tests: Urine Albumin Excretion Rate (mg/24h), UACR (mg/g), Urine Protein Excretion Rate (mg/24h), UPCR (mg/g), Dipstick], on the 5-yr cumulative incidence of ESRD, adjusting for sex, race, BMI, blood pressure, and comorbidities at baseline. Patients were censored at death.

Results: The mean age of users was 61 yrs with 9.3% females. Veterans with eGFR <60 ml/min/1.73m^2 were older with more comorbidities. Adjusted 5-yr cumulative incidences of ESRD were higher for Veterans with albuminuria and for each incremental category of lower eGFR regardless of albuminuria, except for the youngest individuals at the lowest eGFR range. The risks of ESRD were highly dependent on age, with younger Veterans reaching a 5-yr ESRD risk of 10% at much higher levels of eGFR than older Veterans.



Conclusions: For Veterans with CKD, the risk of ESRD is highly dependent on age in addition to eGFR and albuminuria. When forecasting future VA operational and business needs related to ESRD, the VA HCS should consider age as a modifier of the current fixed eGFR definition of CKD.

Funding: VA Support

FR-PO725

Low Serum Magnesium and Incident Chronic Kidney Disease in the Dallas Heart Study Javier A. Neyra, Silvia Ferrè, Xilong Li, Beverley Adams-Huet, Orson W. Moe. *UT Southwestern, Dallas, TX.*

Background: CKD is highly prevalent in the US adult population and carries increased mortality risk. Low magnesium has been associated with higher inflammatory cytokines in endothelial cells, which may contribute to kidney function decline. In this study, we aim to examine the association of serum magnesium (SMg) with incident CKD in the multiethnic population-based Dallas Heart Study (DHS) cohort.

Methods: DHS participants without prevalent CKD (eGFR-EPI ≥60 and absence of microalbuminuria) were included in the study (n =3146). The independent variable was SMg measured at the beginning of the study period, both as a continuous variable and divided into tertiles (low-medium-high). The primary outcome was incident CKD, defined as eGFR <60 and ≥25% reduction from baseline and/or de novo microalbuminuria (doubling of urinary albumin-to-creatinine ratio [ACR] from <10 mg/g to >10 mg/g). Multivariable Cox regression hazard models included demographics; comorbidity; anthropometric and biochemical parameters including albumin, phosphorus, and PTH; use of diuretics; and their interactions.

Results: Mean (SD) age was 44 (10) years, eGFR 102 (18) ml/min/1.73 m², and ACR 4.4 (4.4) mg/g. 44% were men; 52% African American, 29% Caucasian and 17% Hispanic. Mean SMg was 2.07 (0.18) mg/dl. Incident CKD occurred in 123/467 (26%) in the low, 177/884 (20%) in the medium, and 83/619 (13.4%) in the high SMg tertile groups, after a median follow-up of 7.1 years. SMg was independently associated with incident CKD: adjusted HR 1.5 (95% CI, 1.1–2.0) for low vs high tertile. Every 0.2 mg/dl increase in SMg reduced the adjusted hazard for incident CKD by 63%. There was a negative correlation between SMg and high-sensitivity C-reactive protein (hs-CRP) at the time of CKD diagnosis (r -0.11, p <0.001).

Conclusions: Low SMg was independently associated with incident CKD and had an inverse correlation with hs-CRP in the DHS cohort. Whether Mg deficiency contributes to CKD progression, and Mg supplementation attenuates inflammation and therefore retard the occurrence of CKD require further investigation.

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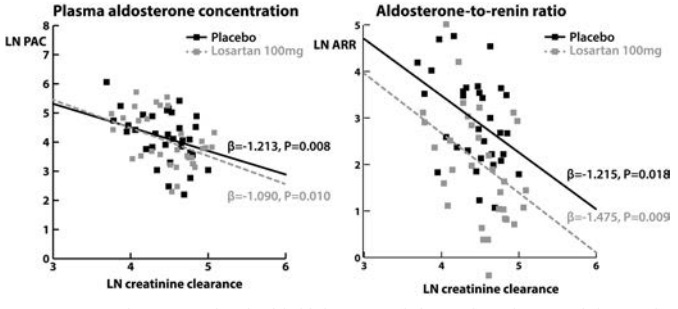
FR-PO726

Lower Renal Function Is Associated with Higher Aldosterone and High Blood Pressure in Chronic Kidney Disease, Irrespective of RAAS Inhibition Christina M. Gant,[2,1] Gozewijn Dirk Laverman,[1] Liffert Vogt,[3] Hiddo Jan Lambers Heerspink,[4] Marc H. Hemmelder,[6] Gerjan Navis,[2] Femke Waanders.[5] *[1]Internal Medicine, ZGT Hospital, Almelo, Netherlands; [2]Nephrology, Univ Medical Centre Groningen, Groningen, Netherlands; [3]Nephrology, Academic Medical Centre Amsterdam, Amsterdam, Netherlands; [4]Clinical Pharmacy and Pharmacology, Univ Medical Centre Groningen, Groningen, Netherlands; [5]Internal Medicine, Isala Hospital, Zwolle, Netherlands; [6]Internal Medicine, Medical Centre Leeuwarden, Leeuwarden, Netherlands.*

Background: Aldosterone is elevated in chronic kidney disease (CKD) and may be involved in hypertension. The determinants of aldosterone and its association with blood pressure (BP) are not well studied in CKD patients. We studied the determinants of the plasma aldosterone concentration (PAC) and its association with BP in CKD, untreated and during renin-angiotensin-aldosterone system inhibition (RAASi).

Methods: We performed a post-hoc analysis on data from a randomized controlled cross-over trial in non-diabetic CKD patients (n=33, creatinine clearance (CrCl) 85 (75-95) ml/min, proteinuria 3.2 (2.5-4.0) g/d). The 6-week study periods were placebo, losartan 100mg (ARB) and ARB+hydrochlorothiazide 25mg (HCT), during both a normal (200±10 mmol Na+/d) and low (89±8 mmol Na+/d) dietary sodium intake (LS).

Results:



Lower CrCl was correlated with higher PAC (left panel) and ARR (right panel), similarly during placebo (black line) and during ARB (grey dotted line; ARR line shifted down). Patients with baseline PAC above the median had higher BP during most study periods. Only during maximal treatment with ARB+HCT+LS, BP was no longer different.

Conclusions: In CKD patients with mild renal function impairment, lower CrCl is associated with higher PAC, irrespective of RAASi. Also, high PAC is associated with higher BP. It is important to test the implications of our study on BP treatment in patients with renal function impairment.

Funding: Pharmaceutical Company Support - Merch Sharp & Dohme

FR-PO727

Glomerular Filtration Rate Declines after Adrenalectomy in Patients with Primary Aldosteronism: Identification of Predictors for Decreased Renal Function Il Young Kim,[1] Jong Man Park,[2] Harin Rhee,[2] Sang Heon Song,[2] Eun Young Seong,[2] Dong Won Lee,[1] Soo Bong Lee,[1] Ihm Soo Kwak.[2] *[1]Dept of Internal Medicine, Pusan National Univ Hospital, Busan, Republic of Korea; [2]Dept of Internal Medicine, Pusan National Univ Yangsan Hospital, Yangsan, Republic of Korea.*

Background: Glomerular filtration rate (GFR) has been reported to decrease after unilateral adrenalectomy in patients with primary aldosteronism (PA). The aim of this study was to identify clinical predictors for decreased GFR after adrenalectomy in patients with PA.

Methods: The records of 187 patients (98 patients with PA and 89 patients with non-PA adrenal disease) who were followed for 6 months after unilateral adrenalectomy were retrospectively analyzed. Estimated GFR (eGFR) at 1, 3, and 6 month after operation were investigated. Preoperative predictors for eGFR % decrement at 1 month [(preoperative eGFR - eGFR at 1 month)/preoperative eGFR×100] were investigated.

Results: In baseline preoperative characteristics, PA group showed higher levels of systolic/diastolic blood pressure (SBP/DBP), aldosterone to renin ratio (ARR), and lower levels of potassium than non-PA group. There was no difference of baseline eGFR between two groups. The eGFR declined by 18.0 ± 22.1 ml/min/1.73 m² (16.8 ± 19.6% decline, P < 0.001) within 1 month of operation, then remained stable in PA group. However, there were no significant changes of eGFR in non-PA group throughout 6 months. In PA group, univariate analysis showed that SBP (r = 0.291, P = 0.004), DBP (r = 0.359, P < 0.001), ARR (r = 0.572, P < 0.001), and preoperative eGFR (r = 0.309, P = 0.002) correlated with eGFR % decrement at 1 month. Multiple linear regression analysis revealed that higher preoperative eGFR (β = 0.286, P = 0.001) and ARR (β = 0.464, P < 0.001) were independent predictors for eGFR % decrement at 1 month.

Conclusions: Renal function seems to deteriorate significantly after unilateral adrenalectomy in patients with PA. Clinicians need to pay attention to postoperative renal function in patients with PA, particularly who showed higher preoperative eGFR and ARR.

FR-PO728

Hyperuricemia as a Risk Factor for Proteinuria in Japanese General Population Tadashi Toyama, Shinji Kitajima, Akinori Hara, Yasunori Iwata, Norihiko Sakai, Miho Shimizu, Kengo Furuichi, Takashi Wada. *Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Ishikawa, Japan.*

Background: Chronic kidney disease (CKD) is a risk factor for end-stage kidney disease and cardiovascular disease. Proteinuria consists the definition of CKD and is a known risk factor for progression of kidney dysfunction. Recent studies showed that hyperuricemia is one of the risk factors for loss of GFR and end-stage kidney disease; however, few studies have focused on the relationships of the development of proteinuria.

Methods: A historical Japanese cohort who underwent annual medical check-up between 1998 and 2007 and met the eligible criteria were included in the analysis. Participants aged ≥ 18 years and without CKD (eGFR was ≥60 ml/min/1.73 m² and urinary protein was minus or trace) were included in the analysis. Participants with CKD at baseline, without baseline status, or aged < 18 years were excluded from the analysis. Hyperuricemia was defined as uric acid ≥ 7 mg/dL for male and ≥ 6 mg/dL for female. Outcome was defined as development of dipstick proteinuria 1+ or more. Cox proportional hazards model was used to estimate risks for proteinuria.

Results: A total of 58,563 subjects were satisfied inclusion criteria. Mean follow-up period was 4.4 years. During the follow-up period, 2,285 (3.90%) subjects developed proteinuria. Compared with reference group, hyperuricemia was a significant risk factor for development of proteinuria (hazard ratio [HR] 1.64, 95% confidence interval [CI] 1.19 – 2.26) in female. These relationships were not found in male (HR 0.98, 95% CI 0.83 – 1.16). Analysis treating uric acid as a continuous variable showed the same trends (hazard ratio 1.16 [1.07 – 1.25], 95% CI 1.07 – 1.25 for female; HR 1.03, 95% CI 0.99 – 1.08 for male).

Conclusions: Stratified with male and female, hyperuricemia was a significant risk factor for development of proteinuria in females in the general Japanese population. Interventional studies are required to define the relationships.

Funding: Government Support - Non-U.S.

FR-PO729

Hyperuricemia out of Proportion to Renal Dysfunction in a Hotspot of Mesoamerican Nephropathy Joseph Kupferman,[1] Juan Jose Amador,[2] Katherine E. Lynch,[1] Rebecca L. Laws,[3] Damaris A. Lopez Pilarte,[2] Daniel R. Brooks,[2] David J. Friedman.[1] *[1]Dept of Medicine, Beth Israel Deaconess Medical Center, Boston, MA; [2]Dept of Epidemiology, Boston Univ School of Public Health, Boston, MA; [3]Dept of Environmental Health, Boston Univ School of Public Health, Boston, MA.*

Background: An epidemic of CKD of unknown etiology, termed Mesoamerican Nephropathy (MeN), is a major cause of morbidity and mortality in parts of Central America. Previous research has found hyperuricemia in some patients, and suggested that uric acid may play a role in disease pathogenesis. To probe deeper into this question, we compared the relationship between uric acid and kidney function in MeN cases to that in patients with CKD of traditional etiologies.

Methods: In a community in northwestern Nicaragua with very high CKD prevalence, we identified 24 families with multiple members affected by MeN. We also studied unrelated

former sugarcane workers with CKD of unknown cause. We compared the relationship of serum uric acid and eGFR between males with CKD from 3 NHANES cycles (n=253) and MeN patients from each of our two groups (n=99 and 237 for related and unrelated cases, respectively).

Results: Hyperuricemia, often severe, was common among MeN patients, whose uric acid levels were higher than those of NHANES participants despite more frequent use of uric acid-lowering medications in the Nicaraguan subjects (mean 9.8 and 9.6 mg/dL in unrelated and related patients, respectively, vs. 7.2 mg/dL in NHANES subjects). In multivariable linear mixed-effects regression analysis, uric acid levels were 2.0 mg/dL (95% CI, 1.0-3.0; p<0.001) higher in MeN cases with familial clustering compared to NHANES subjects, adjusting for age, eGFR, and hypouricemic therapies. Mean serum uric acid was higher in unrelated MeN cases than in the NHANES group by 1.8 mg/dL (1.0-2.6; p<0.001), after adjustment for age and eGFR.

Conclusions: In CKD patients from a MeN hotspot in Nicaragua, hyperuricemia out of proportion to the degree of renal dysfunction was common. Our results support the notion that, rather than being simply a consequence of impaired kidney function, hyperuricemia may be important in MeN pathogenesis.

Funding: Pharmaceutical Company Support - Comite Nacional de Productores de Azucar (Nicaragua); Genzyme Corporation, Private Foundation Support

FR-PO730

Heart Rate Variability and Its Relation to Renal Disease: Longitudinal Results from the PREVEND Study Chris H.L. Thio,[1] Arie M. Van Roon,[2] Ron T. Gansevoort,[3,4] Harold Snieder.[1] *[1]Epidemiology, Univ Medical Center Groningen (UMCG), Groningen, Netherlands; [2]Vascular Medicine, UMCG; [3]Nephrology, UMCG; [4]Prevention of REnal and Vascular ENdstage Disease (PREVEND) Cohort Study, Groningen, Netherlands.*

Background: In the general population, autonomic dysfunction (reflected by low heart rate variability, HRV) has been associated with cardiovascular disease. However, little is known about its relation to renal disease. We therefore examined the association between low HRV and renal outcomes.

Methods: In the population-based PREVEND Cohort Study, HRV measures (among which SDNN, standard deviation of normal-to-normal RR-intervals) were calculated from time-series of beat-to-beat blood pressure recordings at baseline. The lowest quartile was considered the risk group of interest and compared to the upper three quartiles combined. Cox-regression was performed to assess difference in incidence of chronic kidney disease (CKD de novo: eGFR<60ml/min/1.73m^2 and/or urinary albumin excretion, UAE≥30mg/24h). Using mixed effects modelling we examined the effect of SDNN on levels and slopes of eGFR and UAE in the total population and in CKD patients.

Results: Included were 4605 subjects (49% males, age range 33-80). During a median follow-up time of 7.3 years we identified 341 new cases of CKD. Low SDNN was associated with higher risk of CKD (unadjusted HR:1.66, 95%CI [1.30;2.12], p<0.001). After adjustment for age, sex, mean heart rate, and cardiovascular risk factors this association was no longer significant (fully adjusted HR:1.13, 95%CI [0.86;1.48], p=0.40). Association with de novo eGFR<60 or UAE≥30 was similarly non-significant. We found no effect of SDNN on levels and slopes of eGFR or UAE in the total population. In those with baseline CKD (N=939) low SDNN was related to lower level of eGFR (fully adjusted β=-3.73 ml/min/1.73m^2, 95%CI [-6.70;-0.75], p=0.014) but not to steeper eGFR decline.

Conclusions: In our study, low SDNN was not associated with de novo CKD. We found low SDNN to be associated with levels but not with steeper decline of eGFR in a subgroup of subjects with baseline CKD. Our findings suggest that autonomic dysfunction is a complication of CKD rather than a causal factor.

FR-PO731

Progression of Kidney Disease in Stage 3 and 4 Chronic Kidney Disease Elderly Patients Pradeep Arora,[1] Kabir Jalal,[2] Anu Gupta,[3] James W. Lohr.[3] *[1]Div of Nephrology, Richmond VA Medical Center, Richmond, VA; [2]Dept of Biostatistics, SUNY at Buffalo, Buffalo, NY; [3]Div of Nephrology, Buffalo VA Medical Center, Buffalo, NY.*

Background: The prevalence of chronic kidney disease is rising in the elderly population. We studied the rate of progression of CKD in this population and the factors associated with progression of CKD.

Methods: 4,562 patients > 65 years with 2 outpatient eGFRs <60 ml/min/1.73m^2, at least 90 days apart with no intervening eGFR > 60 ml/min/1.73m^2 (March 1, 2001 and March 31, 2008) in VISN2 network. Patients with eGFR<15 ml/min/1.73m^2 were excluded. Data obtained included demographics, comorbidities, and laboratory variables. Patients were stratified based on annual rate of decline of eGFR in 3 categories: < 1 ml/min/1.73 m^2, 1 to 4 ml/min/1.73 m^2, and > 4 ml/min/1.73 m^2 A mixed effects model with an unstructured covariance structure was used to model eGFR over time, measured quarterly. Two-way interactions of time by all comorbidities, time by lab scores, time by proteinuria status, as well as time by stage and time by age were included.

Results: Mean age was 77.2 years. 24.3% were diabetics. 4.3% had proteinuria. In univariate comparison of different rates of progression, 54.2% patients had an annual rate of progression < 1 ml/min/1.73 m^2. Multivariable Mixed Model analyses revealed that increasing age, BMI, presence of CVD, DM and proteinuria were associated with significantly increased rate of progression of CKD. Serum albumin and hemoglobin level were inversely associated with progression of CKD.

Model Effect	Estimate	P- Value
Time	0.086	0.054
Age	-0.119	<.001
Gender	1.087	0.041
BMI	-0.042	0.0267
Time * Albumin	0.101	<.001
Hemoglobin	0.436	<.001
Triglycerides	-0.005	<.001
CVD	-0.461	0.019
COPD	0.423	0.194
Time * Diabetes	-0.140	<.001
Stage 3a	24.159	<.001
Stage 3b	12.025	<.001
Time * Proteinuria	-0.7326	0.010
Systolic Pressure	-0.0135	0.001
Time * Systolic pressure * Proteinuria	0.004	0.047

Conclusions: CKD generally progresses at a slower rate in the elderly population.

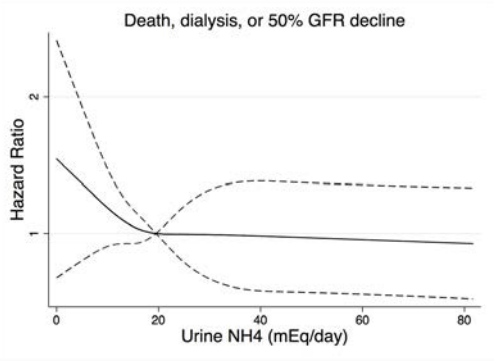
FR-PO732

Association of Urine Ammonium with Death and Kidney Outcomes in Hypertensive Chronic Kidney Disease Kalani L. Raphael,[1] David J. Carroll,[1] Jennifer L. Murray,[2] Thomas H. Hostetter,[3] John R. Asplin,[4] Srini Beddhu.[1] *[1]Univ of Utah; [2]Colorado College; [3]Case Western Reserve; [4]Litholink, Inc.*

Background: High renal NH_3 promotes tubulointerstitial fibrosis in animal models of chronic kidney disease (CKD), however, low NH_4^+ excretion was associated with CKD progression in a prior clinical study. We examined the association between urine NH_4^+ excretion, CKD progression, and death in the African American Study of Kidney Disease (AASK).

Methods: Baseline urine [NH_4^+] (mEq/L) was measured by the glutamate dehydrogenase method (n=1057). Participants were divided into tertiles of urine NH_4^+ excretion (mEq/day). Cox and spline regression models related baseline urine NH_4^+ excretion to the AASK primary composite outcome (death, dialysis or GFR reduction by 50%). Models were adjusted for demographics, randomized group, protein intake, urine potassium excretion, body mass index, measured GFR (mGFR), proteinuria, and [bicarbonate] at baseline. The lowest tertile served as the reference group in Cox model. The median NH_4^+ excretion value was the reference in the spline model.

Results: Baseline characteristics were: age 54 years, 61% male, mGFR 47 ml/min per 1.73m^2, median proteinuria 81 mg/gm, and urine NH_4^+ excretion rate 19.5 (95%, CI 6.5-44.3) mEq/day. After adjustment, the hazard ratios of the composite outcome were 0.93 (95% CI, 0.71-1.22) in the middle tertile and 0.89 (95% CI, 0.65-1.21) in the highest tertile compared to the lowest tertile of NH_4^+ excretion. The results were similar after including blood pressure, heart disease, and smoking status at baseline in the model. Adjusted spline regression models showed a trend towards higher risk of the composite outcome with urine NH_4^+ excretion below the median value.



Conclusions: Lower urine NH_4^+ excretion may associate with death and CKD progression among African Americans with hypertensive CKD, however, this did not reach statistical significance.

Funding: VA Support, Private Foundation Support

FR-PO733

Glycosuria and Renal Outcomes in Patients with Nondiabetic Chronic Kidney Disease - Is Glycosuria or Proximal Tubulopathy Renoprotective? Chi-Chih Hung, Shang-Jyh Hwang. *Internal Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung Medical Univ.*

Background: Sodium glucose cotransporter 2 inhibitors have shown a potential for renoprotection beyond blood glucose lowering. Glycosuria in nondiabetic patients with chronic kidney disease (CKD) is sometimes noted. Whether glycosuria in CKD implies a

channelopathy or proximal tubulopathy is not known. Theoretically, proximal tubulopathy could prevent protein reabsorption and damage in proximal tubular cells. The consequence of glycosuria in CKD is also not studied.

Methods: We performed a cross-sectional study for the association between glycosuria and urine electrolyte excretion in 208 nondiabetic patients and a longitudinal study for the consequence of glycosuria, defined by dipstick, in 783 nondiabetic patients with stage 4-5 CKD and urine protein-to-creatinine ratio >500 mg/g.

Results: In the cross-sectional study, fractional excretion (FE) of glucose >4% was 3.4%, 6.3% and 62.5% in CKD stage 3, 4 and 5, respectively.Log-transformed FE glucose correlated with FE sodium, FE potassium, FE uric acid, and log-transformed eGFR in multivariate linear regression. In the longitudinal study, 279 (35.6%) patients had glycosuria. Glycosuria was associated with a decreased risk for end-stage renal disease (adjusted hazard ratio: 0.77; CI=0.62-0.97; *p=0.024*) and for rapid renal function decline (adjusted odds ratio: 0.63; CI=0.43-0.95; *p=0.032*); but glycosuria was not associated with all-cause mortality or cardiovascular events. The results were consistent in the propensity score matched cohort.

Conclusions: Glycosuria or proximal tubulopathy becomes frequent with renal function decline and is related to favorable renal outcomes in nondiabetic patients with stage 4-5 CKD.

Funding: Private Foundation Support

FR-PO734

Health Literacy and Clinical Outcomes in Adults with Chronic Kidney Disease Claudia M. Lora, Ana C. Ricardo, Jesse Yenchih Hsu, Xue Wang, Eunice Carmona, Elisa J. Gordon, James H. Sondheimer, Jing Chen, Eva Lustigova, Edward J. Horwitz, Anne M. Slaven, Michael J. Fischer, James P. Lash. *The Chronic Renal Insufficiency (CRIC) Study Group.*

Background: In the general population, limited health literacy has been associated with increased risk for hospitalization and death. These associations have not been well evaluated in pre-dialysis chronic kidney disease.

Methods: We conducted a prospective study of 2,392 non-Hispanic white and black adults enrolled in the CRIC Study to examine the association between health literacy and clinical outcomes including incident end-stage renal disease (ESRD, dialysis, transplantation), atherosclerotic events (myocardial infarct, stroke, and peripheral arterial disease), hospitalizations, and all-cause death. Health literacy was measured once using the Short Test of Functional Health Literacy (STOFHLA) starting in 2008 (median: 4.7 years post-CRIC enrollment). Limited health literacy was defined as STOFHLA score ≤22.

Results: Five percent of non-Hispanic whites and 28% of non-Hispanic blacks had limited health literacy. Compared to participants with adequate health literacy, individuals with limited health literacy were more likely to be older (66 vs. 61 years), have income <$20,000 (51 vs. 19%), and less than high school education (44 vs. 7%). Over a median follow-up of 3.5 years, 229 developed ESRD, 206 experienced an atherosclerotic event, the overall hospitalization rate was 64 per 100 person-years, and 265 died. Table 1 summarizes multivariable analyses.

Table 1. Adjusted* Hazard Ratio or Rate Ratio for Participants with Limited vs. Adequate Health Literacy (N=2,392)

Outcome	HR or RR (95% CI)
Incident ESRD	1.09 (0.74, 1.60)
Atherosclerotic event	1.68 (1.10, 2.58)
Hospitalization rate	1.40 (1.28, 1.53)
Death from any cause	1.10 (0.72, 1.67)

*Adjusted for clinical center, age, gender, race, education, smoking, body mass index, systolic blood pressure, diabetes, HgA1c, baseline eGFR, urine protein, ACEi/ARB use

Conclusions: Limited health literacy was associated with higher risk of atherosclerotic events and hospitalization rates, but not with incident ESRD or death. Future work is needed to better understand these associations.

Funding: NIDDK Support

FR-PO735

T2* Values Are Better Than ADC Values for Functional MRI Evaluation to Accurately Predict CKD Progression Kei Sugiyama,[1] Tsutomu Inoue,[1] Eito Kozawa,[2] Masahiro Ishikawa,[3] Naoki Kobayashi,[3] Hirokazu Okada.[1] *[1]Nephrology, Saitama Medical Univ, Iruma-gun, Saitama, Japan; [2]Radiology, Saitama Medical Univ, Iruma-gun, Saitama, Japan; [3]Biomedical Engineering, Saitama Medical Univ, Hidaka, Saitama, Japan.*

Background: Blood oxygen level-dependent (BOLD) and diffusion-weighted (DW) magnetic resonance imaging (MRI), can non-invasively assess oxygen bioavailability and fibrosis in the kidney (Inoue T, et al. JASN 22: 1429, 2011). To extend their clinical utility, in this study, we investigated the relationships among the parameters from these two functional MRI modalities and the clinical course of chronic kidney disease (CKD).

Methods: This was a single center, retrospective observational study. Participants consisted of CKD stage G1-4 patients who had regularly visited our outpatient clinic. MRI was performed using a 1.5T imager. Age, gender, history of diabetes, proteinuria level, estimated glomerular filtration rate (eGFR), as well as T2* and apparent diffusion coefficient (ADC) values from both BOLD and DW MRI, were examined. Multiple regression analysis was performed to identify independent predictors of the annual rate of change in eGFR.

Results: Sixty-six cases (age 53.3 ± 16.4 years, eGFR 53.6 ± 28.8 mL/min/1.73 $m^{2)}$ were enrolled. Mean observation period was 5.5 ± 1.9 years. At the start point, ADC values, but not T2* values, were significantly correlated with eGFR ($p<0.05$; Spearmans). Univariate analyses, however, showed that T2* values, eGFR and proteinuria level, but not ADC values, were significantly correlated with annual decline in eGFR. These factors were still significant after adjustment for all independent variables in the multiple regression analysis (T2* values and eGFR $p<0.005$, proteinuria $p<0.001$).

Conclusions: ADC values, which are indices of tissue fibrosis, are significantly correlated with the current remaining renal function. On the other hand, T2* values, which are indices of tissue oxygenation, predict the future progression of CKD. In addition to traditional risk factors such as proteinuria and low GFR, we reconfirmed that hypoxia is another risk factor for CKD progression. Therefore, functional MRI can be a useful tool in assessing the pathophysiological and prognostic aspects of CKD.

FR-PO736

Optimization and Measurement of Urinary C3a Levels in the CRIC Cohort Venkata Sabbisetti,[1] Chi-Yuan Hsu,[2] Kathleen D. Liu,[2] Emily Christie,[1] Sushrut S. Waikar,[1] Joseph V. Bonventre.[1] *[1]Brigham & Women's Hospital, Harvard Medical School, Boston, MA; [2]Univ of California San Francisco School of Medicine, San Francisco, CA; [3]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Complement activation plays a vital role in the pathogenesis of renal fibrosis. We have found limitations of the available assays when performed on urine samples due to interference by urine proteins. We modified and validated a commercially available serum C3a assay (Quidel) to accurately measure urinary C3a (uC3a) levels and applied this method to measure uC3a from individuals in the Chronic Renal Insufficiency Cohort (CRIC) study.

Methods: We measured urinary C3a in 388 participants in the CRIC cohort in a nested, frequency matched case:control study design. Inclusion criteria for cases and controls included followup time of >3 years and baseline proteinuria <3.5 gm/d. We identified 194 randomly selected cases with eGFR slope <-3 ml/min/1.73m^2 per year and 194 randomly selected controls with eGFR slope of -1.5 to + 2.5 ml/min/1.73m^2 per year. C3a was measured using Quidel assay after urine protein was precipitated using acidified acetone followed by re-suspension of the pellet in sample diluent buffer. Unadjusted and multivariable-adjusted logistic regression models were fit to test the association of uC3a with subsequent CKD progression.

Results: Optimized protocol markedly improved assay performance with excellent linearity of dilution and spike recovery and eliminated the interference in urine matrix. Among 388 CRIC participants, uC3a was above the detection limit (0.026 ng/mL) in 45%. In logistic regression models adjusted for age, sex, race, clinical center, proteinuria, and eGFR, we detected no association between tertiles of uC3a and risk of CKD progression (tertile 2 vs tertile 1: odds ratio 0.96, 95% CI 0.55 – 1.66; tertile 3 vs tertile 1: odds ratio 1.24, 95% CI 0.64 – 2.40).

Conclusions: Readily implemented modifications of a commercial C3a assay eliminated analytical interference when implemented in urine. We found no evidence that uC3a levels can be used to identify CKD progression among CRIC Study participants.

Funding: NIDDK Support

FR-PO737

The Ambulatory Arterial Stiffness Index Is an Independent Predictor of Accelerated Age-Related GFR Decline in the General Middle-Aged Population Bjorn Odvar Eriksen, Vidar T.N. Stefansson, Trond G. Jenssen, Ulla Dorte Mathisen, Jørgen Schei, Marit D. Solbu, Toralf Melsom. *Metabolic and Renal Research Group, UiT The Arctic Univ of Norway, Tromso, Troms, Norway.*

Background: Arterial stiffness measured as aortic pulse wave velocity predicts cardiovascular disease and incident chronic kidney disease. However, the role of arterial stiffness as a predictor of age-related GFR decline in the general population is unresolved due to the difficulty of measuring arterial stiffness and GFR with sufficient precision in population studies. The ambulatory arterial stiffness index (AASI) is a validated indicator of arterial stiffness easily calculated from ambulatory blood pressure measurements. We investigated whether AASI could predict iohexol clearance decline in a cohort representative of the general population.

Methods: We calculated the AASI from baseline ambulatory blood pressure measurements and measured iohexol clearance at baseline and follow-up in the Renal Iohexol Clearance Survey Follow-Up Study (RENIS-FU). The AASI was defined as 1 minus the regression slope of diastolic over systolic blood pressure. The RENIS cohort included a representative sample of the general middle-aged population without self-reported diabetes, cardiovascular, or kidney disease at baseline (n=1627). The age was 50 to 62 years at baseline, and the median observation time was 5.6 years.

Results: The mean (standard deviation) of the GFR decline rate was 0.95 (2.23) ml/min/year and of the AASI 0.38 (0.13). Baseline ambulatory or systolic blood pressure did not predict a steeper GFR decline. In multivariable adjusted linear mixed regression analysis, one standard deviation increase in baseline AASI was associated with a 0.12 (95% confidence interval 0.01 – 0.24) ml/min/year steeper GFR decline. This effect was independent of baseline ambulatory systolic and diastolic blood pressure and antihypertensive medication. The same finding was made in a subgroup without baseline hypertension ($p<0.05$).

Conclusions: We conclude that increased arterial stiffness, measured with the AASI, is an independent risk factor for accelerated age-related GFR decline in the general middle-aged population.

Funding: Government Support - Non-U.S.

FR-PO738

Serum FGF21 and FGF23 Are Associated with the Diastolic and Systolic Functions, Respectively, in Patients with Non-Diabetic Chronic Kidney Disease Masashi Kitagawa, Hitoshi Sugiyama, Akifumi Onishi, Keiko Tanaka, Toshio Yamanari, Tatsuyuki Inoue, Jun Wada. *Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama Univ Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.*

Background: Fibroblast growth factor (FGF) 19/21/23 is an endocrine FGF. Besides regulating mineral metabolism, FGF23, with the co-receptor Klotho, plays an important role in cardiovascular conditions including left ventricular hypertrophy. FGF21, a metabolic hormone that is crucial in glucose and lipid homeostasis, also has cardioprotective effects. The mechanisms by which FGF23, Klotho and FGF21 influence the systolic and diastolic functions in chronic kidney disease (CKD) patients remain unclear.

Methods: This cross-sectional study included 160 non-diabetic CKD patients. The serum levels of FGF23, Klotho and FGF21 were measured by a sandwich ELISA and the relationship between these biomarkers and the echocardiographic data was examined. Echocardiography was performed to measure the left ventricular mass index (LVMI), peak early diastolic mitral filling velocity (E), peak early diastolic mitral annular velocity (E'), and E/E' and ejection fraction (which represent the diastolic and systolic functions, respectively).

Results: The median or mean serum FGF23, Klotho and FGF21 levels were 48 (30-97), 617±236 and 356 (95-520) pg/mL, respectively. A univariate analysis showed that the natural logarithms of the FGF23 and FGF21 concentrations were negatively and positively correlated with E' and positively correlated with E/E' and LVMI. The serum FGF23 levels were associated with the EF. In a multivariate analysis, serum FGF21 and FGF23 were significant predictors of E' and EF, respectively (adjusted for age, gender, systolic blood pressure, HDL-cholesterol, hemoglobin, albumin, eGFR, proteinuria, phosphate, B-type natriuretic peptide, FGF21/23 and Klotho). Serum Klotho was significantly correlated with E', E/E' and LVMI in the univariate analysis but not in the multivariate analysis.

Conclusions: The serum FGF21 and FGF23 concentrations were independently associated with the diastolic and systolic functions, respectively in patients with non-diabetic chronic kidney disease.

Funding: Government Support - Non-U.S.

FR-PO739

Predicting Treatment Response and Renal Survival in Crescentic ANCA Associated Glomerulonephritis Xia Liu, Ying-Hua Chen, Haitao Zhang, Zheng-Zhao Liu, Zhihong Liu, Weixin Hu. *National Clinical Research Center of Kidney Diseases, Research Inst of Nephrology, Jinling Hospital, Nanjing, Jiangsu, China.*

Background: Patients with crescentic ANCA associated glomerulonephritis (cre-AAGN) received intensive immunosuppressive therapy still have poor long-term renal survival. In this study, we analyze the factors, which may predict treatment response and long-term renal outcome in Chinese patients with cre-AAGN.

Methods: Sixty patients with biopsy-proven cre-AAGN were included and classified into renal replacement therapy (RRT, n=30) and non-RRT groups (n=30). Treatment response was recorded as good response (GR, the patients got rid of RRT in RRT group, or Scr declined ³25% of the baseline in non-RRT group) and non- response (NR, the patients needed maintenance RRT in RRT group, or Scr declined <25% of the baseline in non-RRT group) at three months of induction treatment.

Results: At three months treatment, GR was achieved in 53.3% and 80% of patients in RRT and non-RRT groups, respectively. In RRT group, renal disease duration, total crescent percentage, circumferential crescent ratio (circumferential/total crescents) and sclerotic glomeruli ($p<0.01$) were significantly lower in GR than that in NR cases. By multivariate Cox regression analysis, the circumferential crescent ratio was the only risk factor predicting not being GR, with the circumferential crescent ratio ³50% been the high risk for not being GR(HR 22.2, CI 2.17-200, P=0.002). In non-RRT group, the normal glomeruli percentage was markedly higher in GR patients than in NR patients (median: 20.4(12.3,29.0)% vs 5.3(2.3,11.5)%, p=0.022), with the normal glomeruli >7% being more likely to be GR (HR 13.3, CI 1.7-107.4, P=0.006). During a median follow-up of 19 (6- 58) months, 18 (30%) patients developed to ESRD, the five-year renal survival rate was 56.0%. The need of RRT(HR7.09, CI 2.32-21.65, P=0.006) and presence of nephrotic range proteinuria(HR5.9, CI 1.35-25.88, P=0.019) were the two independent risk factors for the development of ESRD.

Conclusions: In crescentic AAGN, the extent of circumferential crescent and normal glomeruli predicts treatment response, while the need for renal replacement therapy and proteinuria predict long-term renal survival.

FR-PO740

Urine Citrate Excretion Might Identify Eubicarbonatemic CKD Patients with Acid Retention and Assess Their Response to Therapy Nimrit Goraya,[1,2] Jan Simoni,[3] Jessica Pruszynski,[4] Nicolaos E. Madias,[5] Donald E. Wesson.[1,2,6] *[1]Internal Medicine, Baylor Scott and White Healthcare, Temple, TX; [2]Texas A&M HSC College of Medicine, Temple, TX; [3]Surgery, Texas Tech Univ HSC College of Medicine, Lubbock, TX; [4]Biostatistics, Baylor Scott and White Healthcare, Temple, TX; [5]Internal Medicine, St. Elizabeth's Medical Center and Tufts Univ School of Medicine, Boston, MA; [6]Diabetes Health and Wellness Inst, Dallas, TX.*

Background: Some CKD stage 2 (eGFR 60-89 ml/min/1.73 m^2) patients without metabolic acidosis nevertheless have acid retention and dietary acid reduction slows their eGFR decline. Urine excretion of citrate, a pH-sensitive metabolite, might identify eubicarbonatemic CKD patients with acid retention and assess response to therapy.

Methods: We measured acid retention and urine citrate excretion in CKD stage 2 (n=40) and stage 1 (eGFR >90 ml/min/1.73 m^2, n=26) eubicarbonatemic patients (TCO_2 ≥ 24.5 mM) before and after 30 days of dietary acid reduction with base-producing fruits and vegetables (F+V). Acid retention was measured by comparing observed to expected increase in plasma [TCO_2] in response to retained HCO_3 (dose - $U_{HCO3}V$) 8 hours after an oral $NaHCO_3$ bolus (0.5 meq/Kg bw), assuming 50% bw HCO_3 space distribution.

Results: Baseline acid retention was higher in CKD 2 than CKD 1 (28.1±9.4 vs. 5.2±12.0 mmol, respectively, $p<0.01$) but baseline 8 hour urine citrate excretion was lower in CKD 2 than CKD 1 (187±40 vs. 335±125 mg, $p<0.01$). Thirty days of F+V reduced acid retention in CKD 2 (to 18.4±17.4 mmol, $p<0.01$) but not in CKD 1 (to 4.7±15.6 mmol, p=0.88) and acid retention remained higher in CKD 2 than CKD 1 ($p<0.01$). By contrast, 30 days of F+V increased urine citrate excretion in both CKD 2 (to 245±70 mg, $p<0.01$ vs. baseline) and CKD 1 (to 369±125 mg, $p<0.02$, vs. baseline) yet urine citrate excretion remained lower in CKD 2 than CKD 1 ($p<0.01$).

Conclusions: Acid retention in eubicarbonatemic CKD patients was associated with low urine citrate excretion which increased after dietary acid reduction with F+V. Low urine citrate excretion might identify eubicarbonatemic CKD patients with acid retention and assess their response to therapy.

FR-PO741

Apolipoprotein L1 Genetic Variants Are Associated with Evidence of Early Kidney Injury in Sickle Cell Disease Divya G. Moodalbail, Joshua Zaritsky, Robert S. Mathias, Carlos E. Araya, Bonita E. Falkner. *Nemours.*

Background: Apolipoprotein L1 (APOL1) renal-risk variants prevalent in African-ancestry populations are associated with chronic kidney disease (CKD). CKD is a major cause of morbidity and mortality in sickle cell disease (SCD) in adults; yet the prevalence and significance of APOL1 renal-risk variants in this population remains unknown. Our objective was to determine expression of biomarkers of early kidney disease in African American youth with SCD, based on their APOL1 genotype.

Methods: We enrolled 40 African American subjects between 5 to 21 years of age with SCD (Hb SS or Hb S $ß^0$ thalassemia). Blood and concurrent urine samples were collected. All enrolled subjects underwent APOL1 genotyping by PCR analysis of DNA extracted from whole blood. Presence of two renal-risk variants qualified for APOL1 High Risk (HR) genotype, while presence of zero or one copy of renal-risk variants qualified for APOL1 Low Risk (LR) genotype. Only two subjects (both in APOL1 LR group) were on ACEi/ARB therapy at baseline.

Results:

Table 1. Characterization of Clinical Variables Based on APOL1 Genotype (total n=40)

Variables	APOL1 LR Group (n=30)	APOL1 HR Group (n=10)	p-value
Female Gender (%)	60	50	N/A
Age (Years)	12.0±4.28	11.1±4.63	0.596
BMI z-score	-0.18 (±1.19)	-0.53(±1.54)	0.466
Serum Cystatin C(mg/L)	0.71 (±0.114)	0.69 (±0.059)	0.633
BUN (mg/dL)	9.8 (±4.3)	10.6 (±3.9)	0.608
Serum Creatinine (mg/dL)	0.45 (±0.19)	0.42 (±0.08)	0.594
Bedside Schwartz eGFR (ml/min/1.73m^2)	150.67 (±46.8)	144.30 (±29.8)	0.690
Cystatin C eGFR (ml/min/1.73m^2)	102.36 (±17.0)	106.90 (±13.8)	0.474
Urine Osmolality (mOsm/Kg H_2O)	458.0 (426.0-514.0) *	417.0 (247.0-457.0) *	0.394
Urine Albumin Excretion Rate (mg/g creatinine)	**9.5 (8.0-16.0) ***	**19.5 (11.7-51.7) ***	**0.040**
ACEi/ARB Use (%)	6.7	0	N/A

*Median (IQR)

APOL1 HR genotype was expressed by 25% of our subjects; this is comparable to 23% reported prevalence of APOL1 HR genotype in African American adults with CKD (AASK study). Both groups were similar with respect to distribution of age, BMI z-scores, renal function and urine osmolality. Hyperfiltration was noted in both groups based on low serum creatinine for age, and elevated eGFR based on creatinine clearance. However, median urine albumin excretion rate was significantly higher in HR group vs. LR group.

Conclusions: Preliminary data in this cohort of 40 children and adolescents with SCD detected greater urine albumin excretion rate in the presence of APOL1 HR genotype. Screening SCD youth for heightened CKD risk may be an avenue to initiate targeted preventive interventions to preserve renal function and reduce progression of kidney disease.

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FR-PO742

Blood Monocyte Subsets and Neutrophils Increase with CKD Stage and Correlate with Both Renal Function and Inflammatory Cytokines

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Background: Chronic kidney disease (CKD) is associated with systemic inflammation which may contribute to cardiovascular complications and progression of renal injury. The aims of this study were to examine the relationships between specific circulating leukocyte populations and CKD stage/eGFR as well determine the correlations between circulating leukocytes and specific innate cytokines.

Methods: Blood samples were collected from outpatients with CKD stage 2-5 (n=188) and from healthy adult volunteers (Ctrl, n=42). Total lymphocyte, monocyte and neutrophil counts were quantified in whole blood aliquots by flow cytometry. Peripheral blood mononuclear cells were prepared and were analyzed immediately by 8-colour flow cytometry to quantify individual monocyte subsets. Serum cytokines levels were quantified by multi-plex assay. Statistical analyses were performed using GraphPad Prism© software.

Results: Total blood monocyte and neutrophil (but not lymphocyte) numbers increased progressively from Ctrl through CKD stages 2-5 and correlated strongly with serum creatinine, eGFR and blood urea nitrogen (BUN). Among the monocyte subsets, intermediate ($CD14^{++}/CD16^{+}$) monocytes demonstrated the strongest relationship with CKD stage, eGFR and BUN. Intermediate monocyte numbers also correlated strongly with neutrophil numbers. Among the serum cytokines analyzed, interferon gamma (IFNγ) and IL-18 were most significantly increased in a CKD stage-dependent manner and also correlated with intermediate monocyte numbers as well serum creatinine, eGFR, BUN and serum albumin levels. Serum concentrations of IFNγ and IL-18 correlated strongly with each other.

Conclusions: Our results demonstrate relationships between circulating innate immune cells (neutrophils/monocytes) and severity of CKD as determined by eGFR. Selective expansion of intermediate monocytes and increases in specific innate cytokines indicate that CKD-associated inflammation has distinct characteristics that may be amenable to intervention.

Funding: Government Support - Non-U.S.

FR-PO743

Implication of the White Blood Cell Count (WBC) in the Progression of IgA Nephropathy

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Background: Inflammatory markers such as serum or urinary interleukin-6 (IL-6) and serum albumin have been shown predicted effect for renal progression in patients with IgA nephropathy (IgAN)**,** however, there are limited data regarding on the relationship between the white blood cell count (WBC) and renal progression in IgAN patients.

Methods: We conducted a retrospective cohort study in 543 biopsy proven IgAN patients in our center to evaluate the association between the WBC and the clinical characteristics and the pathological features in IgAN patients, and analyzed the predictive effect of the WBC on long-term renal progression. The renal progression endpoint was defined as end stage renal disease (ESRD) or the doubling of the baseline serum creatinine concentration. Patients were divided into four groups according to the quartiles of the WBC. The Cox's proportional hazards regression models were used to assess the association of WBC with long-term renal progression.

Results: Compared to patients with lower quartiles of the WBC, those with higher quartiles of the WBC were with higher systolic blood pressure, diastolic blood pressure, and higher levels of neutrophils, lymphocytes, eosinophils, triglyceride, total cholesterol, low-density lipoprotein (LDL) cholesterol, 24 hours proteinuria, complement component 3 and complement component 4, as well as a lower level of estimated glomerular filtration rate (eGFR) ($P<0.05$). In addition, patients with higher quartiles of the WBC were with higher proportion of sclerosis in renal biopsy ($P<0.05$). During a median follow up of 50 months, 47 (8.7%) patients were found to achieve renal progression endpoint. The highest quartile of WBC was associated with higher risk of long-term renal progression (HR, 3.90; 95% CI, 1.23 – 12.4) after adjusting for potential confounding factors, and this result was still significant when using WBC as a continuous variable (HR, 1.13; 95% CI, 1.03 – 1.23).

Conclusions: Our results suggest that the higher baseline level of the WBC is associated with the long-term renal progression in IgAN patients.

FR-PO744

Urinary Activin A: A Novel Biomarker Reflecting the Severity of Tubular Damage in IgA Nephropathy

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Background: Activin A, a member of TGF-β superfamily, is known to regulate cell growth and differentiation in various tissues. It has been reported that activin A modulates ureteric bud branching in kidney development, inhibits tubular regeneration after renal ischemia, and acts as a potent inducer of renal fibrosis in rodents. However, the role of activin A in kidney diseases remains unknown in human. To address this issue, we analyzed renal biopsy specimens and urine from patients with IgA nephropathy (IgAN).

Methods: Ninety-two patients with biopsy-proven IgAN who were treated in our department from 2011 and 2015 were included in this study. Patients were categorized into 4 groups according to estimated GFR (≥60 versus <60 mL/min/1.73 m^2) and proteinuria (≥ 0.5 versus <0.5 g/gCr). Serum and urinary activin A were measured by ELISA. Correlation of urinary activin A with urinary N-gal, urinary KIM-1, renal functions and urinary protein levels were analyzed. The localization of activin A in renal biopsy specimens from IgAN patients was examined by immunostaining. Normal kidney specimens from patients who underwent nephrectomy were used as controls.

Results: Urinary activin A was almost undetectable in healthy volunteers, but was significantly increased in IgAN patients categorized into high-risk group (eGFR<60, U-P/Cr≥0.5 g/gCr) (9.6 ± 2.3 vs. 37.5 ± 9.6 pg/mgCr, $p<0.001$). There was a significant correlation of urinary activin A level with urinary N-gal and KIM-1. Urinary activin A level was negatively correlated with eGFR, but not with urinary protein level. Activin A was localized in the cytoplasm of distal tubules of normal kidneys. In contrast, activin A was present not only in distal tubules, but also in the apical lumen of proximal tubules in patients with IgAN.

Conclusions: These data suggest that urinary activin A is a new biomarker reflecting the severity of tubular damage in IgAN.

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FR-PO745

The Development and Progression of Renal Disease in Aboriginal People in a Remote Aboriginal Community: A Probable Model of Oligonephronia

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Background: Kidney disease, marked by albuminuria, is very common in remote-living Australian Aboriginal people. Biopsy and autopsy findings are compatible with low nephron endowment. We describe renal profiles followed longitudinally in one high risk community, and interpret them in terms of disease "incidence" and "progression".

Methods: Urine ACR and EGFR were measured at a "baseline' community screen, (>80% participation), and measured or imputed (for renal failure) a mean 10.6 years later, in 1031 persons. Changes in ACR and EGF R over time were evaluated. Rates of two definitions of new onset or "incident" albuminuria (ACR>1 gm/mol, and ACR >3.4 gm/mol) developing over follow up were calculated for people with "normal" ACR levels at the first screen (ACR <1 or ACR <3.4).

Results: Birthweights were low (45% of older and 20% of younger subjects were low birthweight, <2.5 kg). On both screens high urine ACR and lower EGFR were common and were more marked at higher ages. Additionally, ACR rose and EGFR fell in many individuals over the follow up interval. Among 453 subjects with ACR <1 at the first screen, 55.9% developed ACR>1, and among 691 with ACR <3.4 at the first screen, 30.4% had developed ACR >3.4, by the second screen. From age >10+ years onwards, lower birthweight and lower baseline EGFR, independently, predicted new onset albuminuria by both incident expressions. Additional predictors included female sex, and, for those age>18+ years, the previous level of ACR (even those within the "normal" ranges). "Progression" (>25% loss of baseline EGFR) over the follow up in subjects age 18+ years was predicted by baseline ACR, age and diabetes.

Conclusions: The data support a model of nephron deficiency. Lower birthweight and lower previous EGFR are surrogates for relative nephron deficiency. Female sex is also constitutionally associated with lower nephron numbers. Once such a deficit is marked by high ACR, albuminuria is the most powerful predictor of further loss of GFR. Beyond continued attention to birthweights, interventions should target progression of albuminuria.

Funding: Pharmaceutical Company Support - Amgen Australia, Private Foundation Support, Government Support - Non-U.S.

FR-PO746

Low White Blood Cell Count Is Independently Associated with the Progression of Chronic Kidney Disease in the Elderly: The CKD-ROUTE Study Yohei Arai,[1] Eiichiro Kanda,[2] Soichiro Iimori,[1] Shotaro Naito,[1] Yumi Noda,[3] Sei Sasaki,[1] Eisei Sohara,[1] Tomokazu Okado,[1] Tatemitsu Rai,[1] Shinichi Uchida.[1] *[1]Dept of Nephrology, Graduate School of Medicine, Tokyo Medical and Dental Univ, Tokyo, Japan; [2]Dept of Nephrology, Tokyo Kyosai Hospital, Tokyo, Japan; [3]Dept of Nephrology, Nitobe Memorial Nakano General Hospital, Tokyo, Japan.*

Background: Elevated white blood cell (WBC) count is a well-known predictor of the progression of chronic kidney disease (CKD). However, particularly in elderly patients, it is not uncommon for them to present with low WBC count rather than developing high WBC count in response to various morbidity states. Therefore, we hypothesized that not only high WBC count but also low WBC count may be associated with the progression of CKD in the elderly.

Methods: A prospective cohort derived from three-year follow-up data of the CKD Research of Outcomes in Treatment and Epidemiology (CKD-ROUTE) study was conducted. In thepresent study, participants aged over 60 years with pre-dialysis CKD stage G2-G5 were eligible. They were stratified into three groups based on WBC count using tertiles (T). The primary outcome was a composite of end-stage renal disease (ESRD) and 50% reduction in estimated glomerular filtration rate (eGFR). Data were analyzed using Cox proportional hazards model with adjustments for baseline characteristics.

Results: We enrolled 761 patients (males, 69%). Median WBC count was 6100 cells / high-power field (T1: <5400, n = [thinsp]248; T2: 5400-6900, n = [thinsp]250; T3: ≥6900, n = 263). During a median follow-up of 854 days, the primary outcome was observed in 181 patients (ESRD, 91; 50% reduction in eGFR, 90), whereas 61 patients died. Not only T3 but also T1 had significantly higher hazard ratios (HR) for the primary outcome than T2 (T1: HR 1.66, 95% confidence interval 1.12-2.45; T3: HR 1.78, 95% confidence interval 1.22-2.62). After adjusting for baseline characteristics, T1 had significantly higher adjusted hazard ratio (aHR) for the primary outcome than T2 (aHR 1.54, 95% confidence interval 1.02-2.33).

Conclusions: Low WBC count is independently associated with the progression of CKD in the elderly.

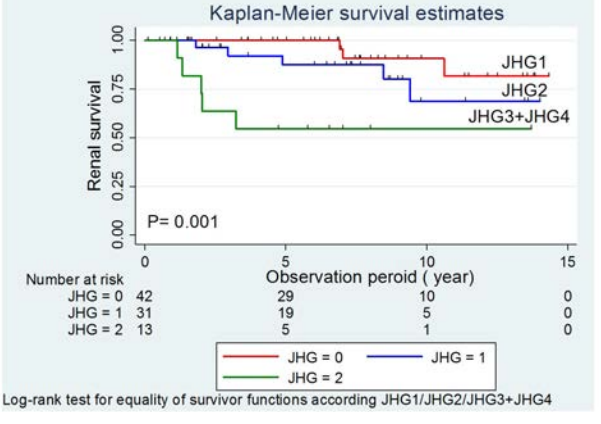
FR-PO747

Japanese Histologic Grade but the Oxford Classification Could Predict Renal Outcome in Japanese IgA Nephropathy Patients Ahmad Baseer Kaihan, Yoshinari Yasuda, Takayuki Katsuno, Shoichi Maruyama. *Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya City, Aichi Prefecture, Japan.*

Background: The Oxford classification (Oxford) is globally used, however it has not been fully validated among Japanese patients with IgA Nephropathy (IgAN). The aim of this study is to elucidate utility of Oxford and Japanese histologic grade (JHG), used in nationwide renal biopsy registry by Japanese Society of Nephrology, to predict renal outcome in Japanese IgAN patients.

Methods: This is a retrospective cohort study of 91 adult IgAN patients diagnosed in Nagoya University Hospital between 2001-2009 and followed up >1 year. Five cases with <8 glomeruli were excluded. Oxford and JHG were evaluated by 6 independent specialists. In JHG, glomerular lesions (cellular/fibrocellular/fibrous crescents, global/segmental sclerosis) percentage score in total obtained glomeruli was assessed and categorized into HG1 (<25%), HG2 (25-49%), HG3 (50-74%) and HG4 (≥75%). Renal outcome was 50% increase in sCr.

Results: Baseline characteristics (median, IQR) of study subjects were 36 (24-46) years old, 41 female, proteinuria: 1.2 (0.7-1.8) g/day and sCr: 0.9 (0.7-1.1) mg/dL. During a median follow-up period of 6.8 years, 15% of patients reached renal outcome. Pathological features were M0/1:79/21%, E0/1:59/41%, S0/1:33/67%, T0/1/T2:86/6/8% and crescent-/+:55/45% in Oxford and HG1:49%, HG2:36%, HG3:13% and HG4:2% in JHG. As compared to Oxford validation paper (KI2014) E1 and crescent were high and T1/2 was low in this study. Proteinuria, sCr, eGFR, UA, T score and JHG were significantly associated with renal outcome, but M/E/S scores nor crescent were not. In multivariate analysis, only JHG was a significant predictor for renal outcome.



Conclusions: JHG was superior to Oxford to predict renal outcome in Japanese IgAN patients, probably because Japanese patients are diagnosed at earlier and active phase.

Funding: Private Foundation Support

FR-PO748

Clinico-Pathological Characterization and Outcome of IgAN with Crescent Dong-Rong Yu,[1] Qi-Ce Sun,[2] Yun-Qin Hu,[3] Fei Jiang,[4] Jun Wu,[5] Yong-Jun Wang.[6] *[1]Hangzhou Hospital of Traditional Chinese Medicine; [2]Zhejiang Chinese Medical Univ.*

Background: We examined the relations of crescent with clinic-pathological features and loss of renal function in IgAN.

Methods: 1054 patients with IgAN in Hangzhou hospital of traditional Chinese medicine between 2001 and 2007 were retrospectively studied. We divided 1054 patients who were diagnosed with IgAN into three groups based on their having mild (≤10%; n = 271),moderate (>10% and ≤25%, n = 182), or severe (>25%; n = 46) proportion of crescent lesion at diagnosis, compared with 555 cases without crescent formation as control group comparison.Ratios of decline in renal function was compared among the four groups during a median follow-up of 90.0 months(IQR=62.1-113.7).Loss of renal function was defined as ≥50% loss of GFR from baseline,doubling of serum creatinine,Dialysis or death. Multivariable associations between crescent and loss of renal function were examined by Cox proportional-hazards regression. Renal survival curves were generated with the Kaplan–Meier method.

Results: Of the 1054 subjects (59.3% women, mean age (33.4±9.94) years, mean proportion of crescent (13.2%±15.7%), mean GFR (98.0±35.5). Pathological indicators of activity indexes such as mesangial proliferation, glomerular sclerosis, tuft necrosis and chronic pathological changes such as tubular atrophy/interstitial fibrosis showed statistical difference in four groups,with the increasing of crescent proportion, degree of pathological further aggravate (P<0.05).(3)There were significant difference in the Lee's classification and the Oxford classification(P<0.05).Progression to renal failure was observed in 106(10.3%) patients.After multivariable adjustment, crescent(≥25%) was significantly associated with an increased risk of developing the loss of renal function (P=0.03), A Kaplan-Meier plot showed statistical difference in four groups in survival rate (P = 0.004) .

Conclusions: There is a certain correlation between the crescent lesion and the clinic-pathological features ,which can reflect the degree of disease progression to a certain extent. Higher proportion of crescent lesion (≥25%)is an independent risk factor for progression to Loss of renal function in IgAN.

FR-PO749

Associations of Echocardiographic Measures with Rapid Kidney Function Decline among African-Americans: The Jackson Heart Study Leila R. Zelnick,[1] Ronit Katz,[1] Bessie A. Young,[1] Adolfo Correa,[2] Bryan R. Kestenbaum,[1] Ian H. De Boer,[1] Nisha Bansal.[1] *[1]Univ of Washington; [2]Univ of Mississippi.*

Background: Heart failure (HF) is common in African-Americans. Structural cardiac abnormalities precede its clinical presentation, including greater left ventricular mass (LVM), greater pulmonary artery systolic pressures (PASP) and lower ejection fraction (LVEF). These subclinical measures, measured by echocardiogram, may also be associated with longitudinal kidney function decline.

Methods: We studied 2,405 African-American participants in the Jackson Heart Study (JHS) who had available echocardiograms at baseline and longitudinal measures of kidney function. LVM, LVEF and PASP were quantified from baseline echocardiograms. Estimated glomerular filtration rate (eGFR) was calculated from the creatinine-based CKD-EPI equation. Rapid kidney function decline (RKFD) was defined as >30% over a mean of 8 years, and incident CKD was defined as development of eGFR<60 mL/min/1.73m^2 and eGFR decline >1 mL/min/1.73m^2/year among CKD-free participants at baseline. Logistic regression models were adjusted for demographics, physical characteristics, comorbidities and medication use.

Results:

Associations of exposures with rapid kidney function decline (N = 2405)

	N at risk	N event	Unadjusted IR (per 1000 pys)	Adjusted odds ratio (95% CI)
Left ventricular hypertrophy				
No LVH	1846	78	5.3	1.0 (Ref)
LVH	559	57	12.5	1.31 (0.87, 1.97)
Per 25 g increment in LVM				1.18 (1.04, 1.34)
p-value				0.01
Left ventricular ejection fraction:				
LVEF < 60%	672	39	7.4	1.0 (Ref)
LVEF ≥ 60%	1720	96	6.9	0.83 (0.55, 1.25)
Per 5% increment				0.95 (0.83, 1.08)
p-value				0.40
Pulmonary artery systolic pressure:				
PASP < 30 mmHg	1146	52	5.6	1.0 (Ref)
PASP ≥ 30 mmHg	469	43	11.3	1.18 (0.75, 1.84)
Per 5 mmHg increment				0.97 (0.85, 1.10)
p-value				0.59

Left ventricular hypertrophy was defined as a left ventricular mass ≥ 150g for women and a left ventricular mass ≥ 200g for men. Rapid kidney function decline defined as >30% decline between exam 1 and exam 3. Adjusted model includes age, sex, education (HS/some college/college), height, weight, SBP, DBP, current smoking, history of diabetes, history of cardiovascular disease (MI and HF), and antihypertensive use

Mean (SD) age and eGFR were 52.2 (11.9) years and 87.4 (17.1); 37% of participants were male. Higher LVM was significantly associated with RKFD and incident CKD; a sex/LVM interaction was not significant in continuous models. The association with RKFD, but not incident CKD, remained statistically significant after multivariable adjustment. There was no association of LVEF or PASP with either RKFD or incident CKD in multivariable models.

Conclusions: Among African-Americans in a community-based cohort, greater LVM was significantly associated with RKFD. Further studies are needed to determine whether treating risk factors for left ventricular hypertrophy may also reduce risk of progression of kidney disease in this high-risk population.

Funding: NIDDK Support, Other NIH Support - The Jackson Heart Study is supported by contracts HHSN268201300046C, HHSN268201300047C, HHSN268201300048C, HHSN268201300049C, HHSN268201300050C from the National Heart, Lung, and Blood Institute and the National Institute on Minority Health and Health Disparities, VA Support

FR-PO750

Moderate Elevated Blood Selenium Is Associated with Reduced Risk of Renal Function Decline

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Background: Although the benefit of selenium (Se) supplement for patients with end-stage renal disease was supported by many studies, it is not clear whether elevated blood Se could or not improve renal function among general people. The purpose of this study is to examine the relationship between Se states and glomerular filtration rate (GFR) among general adults.

Methods: We conducted a cross-sectional analysis using 2011-2012 National Health and Nutrition Examination Survey (NHANES), and a total of 4885 persons 20 years or older were included. Whole blood Se were measured with inductively coupled plasma mass spectrometry. Renal function decline was defined as estimated GFR (CKD-EPI) <60 mL/min/1.73m^2. Logistic regression was applied to assess the association between blood Se levels and risk of renal function decline.

Results: The mean of blood Se of the all the 4885 participants was 193.3±27.5 μg/L, and all of them were above the criteria of Se deficiency, i.e. 98 μg/L. The mean Se concentrations for persons with eGFR≥90, 60-89, 30-59 and <30 mL/min/1.73m^2 were 193.8±28.1, 194.5±25.8, 186.8±28.5 and 177.3±24.0 μg/L, respectively. Compared to the lowest quintile of blood Se, the age-, gender- and race- adjusted odds ratios (ORs) were 0.88 (95% confidence interval 0.63-1.22) for the 2nd quintile, 0.61 (0.43-0.87) for the 3rd quintile, 0.60 (0.42-0.85) for the 4th quintile and 0.59 (0.41-0.85) for the highest quintile.

Blood Se (μg/L)	OR (95% CI)	*P*
Quintile 1 (105.39-172.96)	Reference	
Quintile 2 (172.98-185.64)	0.88 (0.63-1.22)	0.44
Quintile 3 (185.65-197.33)	0.61 (0.43-0.87)	<0.01
Quintile 4 (197.39-212.23)	0.60 (0.42-0.85)	<0.01
Quintile 5 (212.25-692.52)	0.59 (0.41-0.85)	<0.01

Conclusions: Even for the persons with relatively low but normal Se levels, moderate elevated blood Se was associated with reduced risk of renal function decline, but further elevated Se concentration, e.g. > 200 μg/L, may not have additional benefit for renal function.

Funding: Government Support - Non-U.S.

FR-PO751

Elevated Bilirubin Level Is Associated with Better Renal Prognosis

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Background: Protective effect of bilirubin on kidney injury was reported in patients with diabetes mellitus or Gilbert syndrome, and its role as an antioxidant was claimed as the reason. However, whether mildly elevated bilirubin is related to renal prognosis in more generalized population was scarcely described.

Methods: We assessed a cohort with reference range value of total bilirubin who visited for screening coronary artery CT scans. Patients who had major adverse cardiovascular events and follow-up duration less than 1 month were excluded from the study. The primary outcome was 30% reduction of eGFR from baseline, and the secondary outcome was a composition of doubling of serum creatinine, eGFR halving and a start of dialysis. Next, *in vivo* experiment with C57BL/6 mice was done to investigate the protective effect of intraperitoneal bilirubin treatment on kidney fibrosis by unilateral ureteral obstruction (UUO) model. The relationship between bilirubin treatment and activation of the HIF-1 pathway was also evaluated.

Results: A total number of 1,128 patients were included in our cohort. The study group who had relative hyperbilirubinemia (total bilirubin 0.8-1.2mg/dL) showed better renal prognosis in terms of the primary outcome (adjusted hazard ratio (HR) 0.332, 95% CI 0.162-0.679, *P*=0.003) and the secondary outcome (adjusted HR 0.114, 95% CI 0.026-0.791, *P*=0.026). Moreover, mice treated with bilirubin showed less fibrosis in UUO model (*P*<0.05) and decreased fibrosis markers such as TGF-β or FSP1 (*P*<0.01). Lastly, intraperitoneal bilirubin treatment led increment in HIF1a (*P*<0.01) and HIF1b (*P*<0.05).

Conclusions: Relative hyperbilirubinemia even within reference range level showed a protective effect on renal dysfunction progression. Intraperitoneal bilirubin treatment decreased kidney fibrosis and upregulated HIF-1 pathway in *in vivo* experiment. Therefore, bilirubin could be a potential therapeutic target to ameliorate kidney fibrosis by reducing oxidative stress injury.

FR-PO752

Differential Effects of Nicotine on the Cortical Production of Prostaglandins in Rats with Chronic Kidney Disease

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Background: Cigarette smoking is a risk factor in the progression of CKD. Nicotine (N), a major component of tobacco, worsens renal injury in 5/6 nephrectomy rats (Nx), a well-validated model of CKD (AJP'12). As we have shown, COX2 inhibition reduces renal injury in Nx rats on nicotine (ASN'13). In these studies we determined the effects of nicotine on the cortical production of prostaglandins (PGs) in normal rats and in rats with CKD.

Methods: Male SD rats were divided in five groups (n=7): Sham (S), S+N (0.1 gm/L, DW), S+N+COX-2 inhibitor (NS, 1.5 mg/Kg/day, SQ), Nx, Nx+N, Nx+N+NS, Nx+NS for 12 weeks. Rats were euthanized after 12 weeks and kidney cortex snap frozen and saved for PGs measurement by mass spectrometry (ng/g wet weight).

Results: Nicotine increased production of PGE_2 and PGI_2 in sham rats that was inhibited by NS. Nx resulted in increases in the cortical production of all PGs studied. Nicotine significantly reduced the production of PGE_2, PGI_2 and $PGF_{2\alpha}$ in Nx rats but not of TXB2 (Table). NS reduced the production of PGs in Nx groups suggesting COX2 as the is the main source of PGs in this model.

	S	S+N	S+N+NS	Nx	Nx+N	Nx+N+NS	Nx+NS
PGE_2	9.7±1.3	37.8±5*	20.3±3.2#	52.1±13.4*	29±4.6*,#	24.4±1.9#	18.5±3.6#
PGI_2	3.7±0.8	14.3±1.5*,#	5.5±0.7#	108.4±28.4*	40.6±10.7*,#	3.2±0.9#	2.4±0.5#
TXB_2	2.6±0.3	5.3±0.3	0.7±0.1#	9.4±2.8*	10.7±3.3*	1.4±0.3#	1.2±0.3#
PGF2α	5.3±0.9	10±1.2#	5±0.3#	26±6.8*	14.1±2.6*,#	6.6±0.5#	6.4±1#

* P < 0.05 vs Sham, # P < 0.05 vs Nx.

Conclusions: This study demonstrates that nicotine increases the production of PGs via COX2 in normal rats but reduces the production of all PGs studied except TXB_2 in rats with CKD. These findings suggest that differential effects on the production of specific PGs could explain at least in part the deleterious effects of nicotine in the progression of CKD, by downregulating some PGs (PGE_2, PGI_2 and $PGF_{2\alpha}$) while having no effect on others (TXB_2). Future studies will investigate the effects of nicotine on specific PG synthases.

Funding: Other NIH Support - NIEHS

FR-PO753

Association between Gestational Diabetes and Maternal Chronic Kidney Disease

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Background: Gestational diabetes mellitus (GDM) is associated with subsequent type 2 diabetes mellitus, metabolic syndrome, and cardiovascular disease for affected women. We analyzed whether GDM is associated with incident chronic kidney disease (CKD), controlling for pre-pregnancy risk factors for both conditions.

Methods: A total of 820 women without diabetes enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) Study who were nulliparous at baseline in 1985-86 and reported at least one pregnancy during 25 years of follow-up were studied. GDM was self-reported. CKD was defined as development of estimated glomerular filtration rate < 60 ml/min/1.73m^2 or urine albumin to creatinine ratio ≥ 25 mg/g. Hazard ratios (HR) for developing CKD were compared between women with and without history of GDM using complementary log log models, beginning with first pregnancy and adjusting for pre-pregnancy age, systolic blood pressure, high density lipoprotein cholesterol, body mass index, smoking, education, kidney function, fasting glucose, and physical activity level as well as race and family history of diabetes. Interaction between race and GDM was also tested.

Results: Over mean follow-up of 20.8 years, N=101 women reported GDM and N=105 (58 black, 47 white) developed incident CKD, predominately manifested by increased albumin excretion in the urine. The unadjusted HR (95% confidence interval (CI)) for CKD was 1.46 (0.87, 2.45) for women with GDM compared to parous women who did not report a pregnancy with GDM. There was evidence of a GDM-race interaction (Wald interaction p=0.07 in the fully adjusted model). The HR (95% CI) for CKD in the fully adjusted model was 1.96 (1.04, 3.67) for black women with GDM compared to those without GDM. Among white women, the HR (95% CI) was 0.65 (0.23, 1.83).

Conclusions: GDM may be associated with subsequent development of CKD among black women.

FR-PO754

Advanced CKD Is Associated with Higher Use of Insulin, Independent of Hemoglobin (Hb) A1C Levels and Duration of Type 2 Diabetes Mellitus (T2DM) R. E. Boucher,[1] Debra Lynn Simmons,[1] Rabia Nadeem Kiani,[1] Guo Wei,[1] Tom Greene,[1] T. S. Bjordahl,[1] Linda F. Fried,[2] Srini Beddhu.[1] *[1]Univ of Utah; [2]VA Pittsburgh.*

Background: Need for insulin in T2DM might reflect decreased insulin secretion (beta cell dysfunction) and/ or insulin resistance. Longer duration of T2DM might also result in exhaustion of beta cell insulin secretion. We hypothesize that more advanced CKD reflects a state of ↓ insulin secretion and/or ↑ insulin resistance, so that need for use of insulin is higher in more advanced CKD after accounting for T2DM duration and HbA1C.

Methods: We examined a cohort of 592,491 veterans with a diagnosis for T2DM (defined by ICD9 codes) and outpatient serum creatinine measured between 1/1/2010 and 12/31/2013. Data on filled medications were obtained from outpatient pharmacy database. Laboratory data were obtained from routine clinical labs. DM duration was obtained by identifying the first instance of ICD9 codes for DM or HbA1c>6.5% or use of diabetes medications in the preceding 12 years. In a logistic regression model, eGFR stages, duration of DM and HbA1C levels were related to the use of insulin as the dependent variable adjusted for age, gender, race, CHF, lung disease, cancer, atherosclerotic conditions, SBP, DBP and BMI.

Results: Mean age was 67 ± 11 yrs. 96.6% were males and 16.9% were black. 28.0% were on insulin. Mean BMI was 32 ± 6 kg/m^2, mean eGFR was 74 ± 22 ml/min/1.73 m^2, mean HbA1c was 7.4 ± 1.7%, and mean diabetes duration was 5.8 ± 3.8 yrs.

Associations of eGFR groups, duration of diabetes and Hb1C with the use of insulin in veterans (N = 592,491)

	Adjusted Odds Ratio (95% CI)
eGFR groups	
≥90	Reference
60-89	1.21 (1.19, 1.23)
45-59	1.85 (1.81, 1.89)
30-44	2.84 (2.76, 2.92)
<30	4.26 (4.09, 4.45)
Diabetes Duration (yrs)	
<5	Reference
5-9	2.05 (2.02, 2.08)
≥10	4.00 (3.92, 4.07)
HbA1c (%)	
<7	Reference
7-8.4	3.49 (3.44, 3.55)
≥8.5	9.90 (9.73, 10.07)

Conclusions: Worsening renal function is associated with greater use of insulin. This is observed even at eGFR levels (> 45) at which metformin use is not contraindicated.

Funding: NIDDK Support

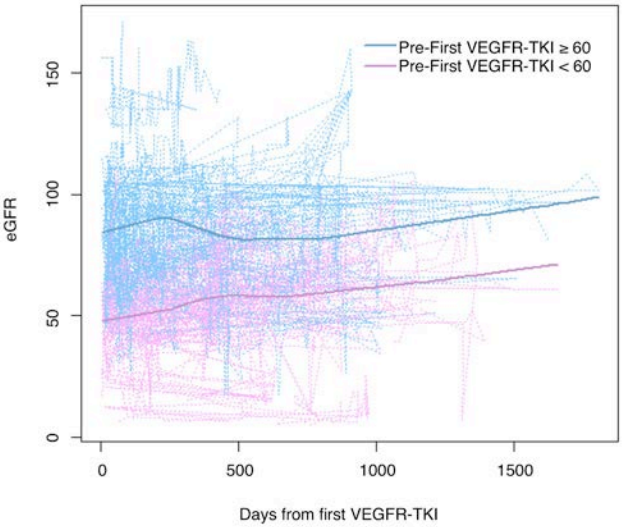
FR-PO755

Renal Function in Kidney Cancer Patients: Effects of Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitors Brian Charles Boursiquot,[1] Emily C. Zabor,[2] Ilya Glezerman,[3,4] Edgar A. Jaimes.[3,4] *[1]Stanford Univ School of Medicine, Stanford, CA; [2]Dept of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; [3]Dept of Medicine, Div of Nephrology & Hypertension, Weill Cornell Medical College, New York, NY; [4]Dept of Medicine, Renal Service, Memorial Sloan Kettering Cancer Center, New York, NY.*

Background: VEGFR tyrosine kinase inhibitors (TKIs) have become first line therapy for metastatic renal cell carcinoma (mRCC). Their use leads to hypertension (HTN) in ~30% of patients, but their effects on long-term renal function are not known. In addition, it has been suggested that the development of HTN is linked to treatment efficacy. The main objective of this study was to determine whether TKIs affect long-term renal function and the role of HTN on these effects.

Methods: This is a retrospective study of 130 mRCC patients who were treated with TKIs at MSKCC. Longitudinal measurements of serum creatinine were used to calculate the eGFR for each patient over time, for a median of 1.5 years among survivors. New or worsening HTN was defined by documented start or addition of antihypertensives.

Results: Overall, the use of TKIs in patients with eGFR < 60 ml/min or eGFR ≥ 60 ml/min did not result in significant changes in long term renal function.



During follow up, 41 patients (31.5%) developed new/worsening HTN within 30 days from first TKI use and this was not linked to further reductions in eGFR. These patients appeared to survive longer than those who did not develop HTN within 30 days, although this was not statistically significant (P=0.07).

Conclusions: Our findings suggest that the use of TKIs does not adversely affect renal function even in the setting of new onset HTN or reduced eGFR at baseline. However prospective long-term studies will be needed to better assess the effects of TKIs on long-term renal function.

Funding: Other NIH Support - NIH National Cancer Institute grant nos. R25 CA020449 (BCB) and P30 CA008748 (ECZ, IGG, EAJ), Private Foundation Support

FR-PO756

Histopathological Findings for Renal Progression Are More Pronounced in Upper Tract Urothelial Carcinoma Than in Renal Cell Carcinoma after Unilateral Nephrectomy Sheng-Wen Niu,[1] Peir-In Liang,[2] Ming-Yen Lin,[1] Wei-Ming Li,[3,4] Chun-Nung Huang,[3,4] Wen-Jeng Wu,[3,4] Li-Tzong Chen,[5] Shang-Jyh Hwang.[1,4] *[1]Nephrology, Kaohsiung Medical Univ Hospital; [2]Pathology, Kaohsiung Medical Univ Hospital; [3]Urology, Kaohsiung Medical Univ Hospital; [4]National Inst of Cancer Research; [5]Faculty of Medicine, Kaohsiung Medical Univ.*

Background: Patients with upper urinary tract urothelial carcinoma (UTUC) had high risk of chronic kidney disease or entering dialysis than renal cell carcinoma (RCC). We studied the pathological changes of renal tissue from nephrectomized kidney of UTUC and RCC, and compared the correlation between renal histopathology and progression to end-stage renal disease in these two groups of cancer patients.

Methods: This study included 132 cases of UTUC post ipsilateral nephrectomy and 61 cases of RCC post radical nephrectomy(RN). All of them were not yet on dialysis before surgery. The renal histopathology was read by 3 specialists: nephrologists or pathologist, independently. Clinical and laboratory data before surgery, whether entering into dialysis eventually, and dialysis-free days from surgery until December 31, 2014 were collected. We used logistic regression for tubulointerstitial (TI) nephropathy score and global glomerular sclerosis(GGS) rates respectively, and Cox regression to investigate which factors affect renal survival.

Results: There were significantly higher TI nephropathy scores and greater abnormal GGS rates from nephrectomized kidneys of UTUC than from RCC. Kaplan-Meier survival curve showed five-year dialysis-free survival rate was 0.863 in UTUC group and 0.967 in RCC group. There were two major pathological factors, hypertension [HR(95%CI): 3.03(1.02-9.02), p=0.046] and abnormal GGS rate [HR(95%CI):2.88(1.01-8.17), p=0.047], for dialysis-free survival in UTUC group; but no factor in RCC group.

Conclusions: There were two major pathological factors, hypertension and abnormal GGS rate, for dialysis-free survival within 5 years in UTUC patients post ipsilateral NUx; but no specific risk factor in RCC patients.

Funding: Government Support - Non-U.S.

FR-PO757

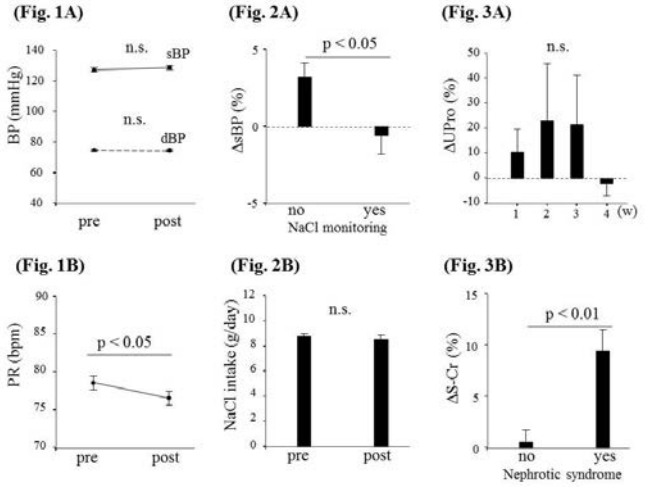
The Impact of the Kumamoto Earthquake on Renal Parameters in CKD Patients Yushi Nakayama, Masataka Adachi, Hideki Inoue, Takashige Kuwabara, Yuichiro Izumi, Yutaka Kakizoe, Masashi Mukoyama. *Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan.*

Background: Disasters inevitably affect a number of diseases such as hypertension and kidney disease. A series of strong earthquakes attacked Kumamoto in central Kyushu, a southwest part of Japan, in April 2016. In this study, we evaluated the impact of the seismic disaster on CKD states during an early phase.

Methods: We analyzed blood and urine data from 225 out-patients with CKD (58±1.2 years), who visited our hospital during four weeks after the main shock. Systolic and diastolic blood pressures (sBP and dBP), pulse rate (PR), and body weight were also evaluated. These data were compared with preceding ones.

Results: Percentage of diabetic nephropathy (DN) was 12% and that of nephrotic syndrome was 14%. sBP and dBP did not change significantly (Fig. 1A). However, PR significantly reduced after the disaster (Fig. 1B). In sub-analyses evaluating the changes of each parameter between groups, sBP significantly increased only in patients whose daily NaCl intake was not monitored (Fig. 2A). For patients under monitoring, NaCl intake before and after the disaster was almost equivalent (Fig. 2B). dBP significantly reduced in DN (–9.5±3.0% vs non-DN; +1.2±1.1%, p<0.01). Urine protein excretion (U-Pro) tended to increase during three weeks (Fig. 3A). U-Pro also tended to increase in male (+22.5±12.3% vs female; -8.7±5.2%, p=0.086) or patients who experienced evacuation (+33.9±24.9% vs no; +5.7±5.2%, p=0.089). Serum creatinine significantly increased in patients with nephrotic syndrome (Fig. 3B).

Conclusions: Regular monitoring of urinary NaCl excretion might ameliorate the increase of BP during disaster. Sex, evacuation, and nephrotic syndrome could affect renal parameters after the earthquake. Further analyses are needed to evaluate the long-term impact of earthquake on CKD.



FR-PO758

Care of Chronic Kidney Disease Patients by General Practitioners Dunia Diaz, Ileana Farrada, Felix Hernandez, Rute C. Paixao. *Cleveland Clinic Florida.*

Background: The prevalence of patients with chronic kidney disease (CKD) in the United States has been steadily rising. While there is reasonable evidence that specific activities can be implemented to delay its progression and reduce mortality, CKD is under-recognized and undertreated in primary care offices.

Methods: We conducted a quality improvement (QI) project at Cleveland Clinic Florida by assessing the rate of recognition and proper staging of CKD and whether or not KDOQI guidelines for CKD care were being followed by general practitioners. The data was analyzed pre and post practitioner education (current CKD guidelines were taught at several conferences).

Results: A total of 99 patients were evaluated in the pre education (pre) and 107 in the post education (post). In the pre, no patients were followed by nephrology. In the post, 62/107 patients were established with a nephrologist. In terms of demographics there was no statistical difference for age, gender, or Caucasian ethnicity. Comorbidities such as DM and HLD were comparable but more patients in the post had HTN (82% vs 65%; p=0.007). General practitioners recognized and properly staged CKD more often in the post than in the pre (71% vs 23% for CKD recognition and 76% vs 22% for proper staging respectively; p<0.0001). There was no statistical difference for blood pressure control, ACEi/ARB, statin, and Metformin use among the groups. Better glucose control (HbA1c < 7.5) was achieved in the post when compared to the pre (84% vs 55%; p<0.05). Measurement of vitamin D also improved in the post (76% vs 25%; p<0.05). No statistical difference was noted in terms of NSAID use, anemia work up/treatment, and measurement of proteinuria, PTH, and phosphorus in the pre and the post unless the patient was followed by nephrology.

Conclusions: In this QI project, we found that education of general practitioners improved some but not all parameters. We also noted that patients followed by nephrologists were more likely to have measurement of proteinuria and bone mineral disease, anemia work up/treatment, and less NSAID use. No difference was noted for blood pressure control, ACEi/ARB, statin, or Metformin use. Further studies are needed to determine the long term significance of these differences.

FR-PO759

Haptoglobin Genotype among Patients with IgA Nephropathy: Impact on Disease Progression and Response to Treatment Zaher Armaly,[1] Nayef Mohamed Habbashe,[2] Kamal Hassan,[3] Rawi Ramadan,[4] Raymond Farah.[5] *[1]Nephrology, E.M.M.S. Hospital, Bar Ilan Univ, Nazareth, Israel; [2]Nephrology, HaEmeq Medical Center, Afula, Israel; [3]Nephrology, Western Galilee Hospital-Nahariya, Nahariya, Israel; [4]Nephrology, Rambam Health Campus, Haifa, Israel; [5]Internal Medicine, Ziv Medical Center, Safed, Israel.*

Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis, may progress to ESRD. Although the pace of decline in kidney function in IgAN is affected by proteinuria, hypertension, and low eGFR at the time of the diagnosis, the exact mechanisms underlying the pace of deterioration is still largely unknown. Recently, the role of genetic risk factors in the pathogenesis of IgAN is being elucidated. However, the impact of haptoglobin (Hp) genotype on the progression of IgAN, was not studied yet. Therefore, the current study examines whether Hp genotype influences disease progression and response to treatment.

Methods: The present study included 28 patients with IgAN (42.5±2.5 years old), 26 non-IgAN chronic kidney disease (CKD), 54 patients on hemodialysis, and 150 healthy subjects. Blood and urine samples were collected at baseline and 6 months after initiation therapy. Serum creatinine (SCr) and total proteinuria, were determined in all IgAN patients. Blood analysis for Hp genotype was performed for all subjects.

Results: Twenty nine percent of IgAN patients were Hp 1-1, 36% Hp 2-1, and 36% Hp 2-2. In contrast, in patients with non-IgAN chronic kidney disease the prevalence of Hp 1-1, Hp 2-1, and Hp 2-2 was 8%, 19%, and 73%, respectively. In hemodialytic patients, prevalence of Hp 1-1, Hp 2-1, and Hp 2-2 was 19%, 28%, and 54%, respectively. In healthy subjects, the distribution of Hp 1-1, Hp 2-1, and Hp 2-2 was 7%, 39%, and 54%, respectively. Interestingly, IgAN Hp 2-2 patients were more stable and responded better to treatment with routine therapy (RAS inhibitors or steroid) than other Hp genotype, as was evident by the extent of proteinuria and SCr.

Conclusions: Hp 1-1 genotype is more common in IgAN patients as compared with general population in Israel, and even more than CKD patients or subjects on HD. Patients with Hp 2-2 responded better to appropriate therapy. The mechanisms underlying this phenomenon remain to be explored.

FR-PO760

Effects of Uric Acid and Inflammation on the Risk of Developing Chronic Kidney Disease in Female Rheumatoid Arthritis Patients Masako Kochi,[1] Kentaro Kohagura,[2] Yusuke Ohya.[1] *[1]Dept of Cardiovascular Medicine, Nephrology and Neurology, Univ of the Ryukyus School of Medicine, Nishihara, Okinawa, Japan; [2]Dialysis Unit, Univ Hospital of the Ryukyus, Nishihara, Okinawa, Japan; [3]Dept of Cardiovascular Medicine, Nephrology and Neurology, Univ of the Ryukyus School of Medicine, Nishihara, Okinawa, Japan.*

Background: Inflammation is a risk factor for progression of chronic kidney disease in the patients with in patients with rheumatoid arthritis as well as general population.Uric acid (UA) is suggested to promote inflammation. However, the combined effects of UA and inflammation on the risk of developing CKD are not known in RA. This study aims to examine the relationship between UA, C-reactive protein (CRP; a marker of inflammation), and the incidence of CKD in female RA patients.

Methods: We retrospectively examined a total of 284 female RA patients. The outcome of interest was incidence of CKD which was defined as an eGFR<60 mL/min/1.73 m^2 and/or positive dipstick testing for proteinuria for ≥3 months. High UA was defined >5.0 mg/dL, based on more than the highest quartile value at baseline and high CRP was defined as > 4.9 mg/L, based on more than median value for the baseline CRP.Patients were categorized into four subgroups by the presence of high UAand high CRP at baseline: lowUA and low CRP, lowUA and high CRP, highUA and low CRP, and high UA and high CRP.

Results: Mean baseline patient age was 57 years, and mean eGFR was 86 ml/minute/1.73 m^2. Over a median follow-up of 8 years, 41 (14%) patients developed CKD. High UA and high CRP were independently associated with the incidence of CKD, respectively. Subgroup analysis showed that the cumulative incidence of CKD was the highest in patients with high UA and high CRP group compared with all other groups (P = 0.002, log-rank test). In a multivariate analysis, high UA and high CRPwas significantly associated with increased risk for incident CKD (adjusted HR, 3.91; 95% confidence interval, 1.40–11.71; $p = 0.009$) independent of age, eGFR at baseline, classical risk factors and anti-RA drug uses.

Conclusions: Independent of confounding risk factors, high UA had an inflammation-augmented association with increased risk of CKD in female RA patients.

FR-PO761

Predictive Factors of Renal Outcome after Heart Transplantation Hee Jin Kwon, Subin Hwang, Jae Shin Choi, Jung Eun Lee, Wooseong Huh, Yoon-Goo Kim, Dae Joong Kim, Ha Young Oh, Hye Ryoun Jang. *Nephrology Div, Dept of Medicine, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Korea.*

Background: Cardiorenal syndrome (CRS) frequently occurs in end-stage heart failure patients waiting for heart transplantation (HT) and combined heart kidney transplantation (HKT) is required in some patients. However, there have been few reports investigating predictive factors of renal outcome in patients receiving HT with no consensus for indication

of HKT. In this study, we investigated the factors predicting renal outcome after HT in end-stage heart failure patients, focusing on changes in renal function and chronic kidney disease (CKD) evaluated 1 year after HT.

Methods: A single–center retrospective cohort study of 182 patients receiving HT from 1996 to 2015 was conducted. A total of 160 patients were followed for at least 1 year after HT. Primary outcomes were eGFR, %ΔeGFR [100 X (post-HT eGFR - pre-HT eGFR)/ pre-HT eGFR], and CKD (eGFR < 60 ml/min/1.73m^2) prevalence at 1 year after HT. The results of pre-transplant kidney ultrasound (US) images were scored as follows: normal (0), increased echogenicity (1), findings suggestive underlying CKD (2).

Results: Perioperative renal replacement therapy (RRT) group (n=45) had more frequent proteinuria (p=.003) and mechanical circulating support (p<.001). Although mortality within 1 year was higher in RRT group than in non-RRT group (p<.001), there was no difference in CKD at post-HT 1 year. Higher eGFR at post-HT 1 year was associated with young age, high preoperative eGFR, and high ejection fraction (EF) at 1 year. High %ΔeGFR (significant improvement of renal function) at post-HT 1 year was associated with young age, preexisting CKD, preoperative RRT, low preoperative eGFR, and high preoperative EF. Old age, preexisting CKD, and high kidney US image score were identified as independent risk factors of CKD at post-HT 1 year.

Conclusions: Although RRT group showed higher mortality than non-RRT group, there was no difference in CKD at post-HT 1 year in survivors. Closer monitoring and careful management are required in HT patients with old age, preexisting CKD, high kidney US image score, and low postoperative EF for improving renal outcome.

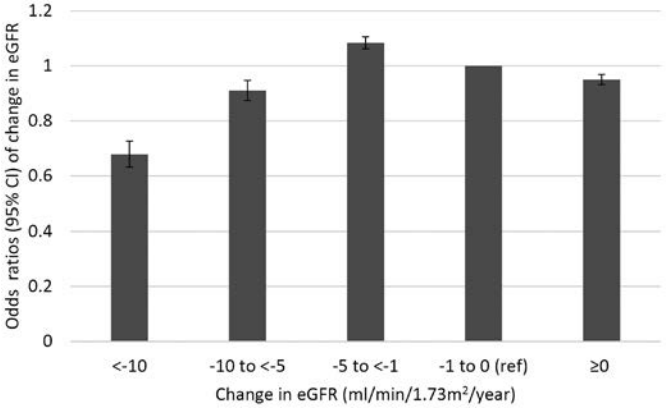
FR-PO762

Testosterone Replacement Therapy Is Associated with Less Progression of Chronic Kidney Disease Praveen Kumar Potukuchi,[1] Keiichi Sumida,[1] Miklos Zsolt Molnar,[1] Jun Ling Lu,[1] Fridtjof Thomas,[1] Connie Rhee,[2] Melissa Soohoo,[2] Elani Streja,[2] Kamyar Kalantar-Zadeh,[2] Csaba P. Kovesdy.[1,3] *[1]Univ of Tennessee Health Science Center, Memphis, TN; [2]Univ of California, Irvine, CA; [3]VA Medical Center, Memphis, TN.*

Background: Testosterone levels decrease with reduced renal function. Testosterone replacement therapy (TRT) has putative cardiovascular and metabolic benefits, but its effects on kidney function are unknown.

Methods: In a nationwide cohort of 827,582 U.S. male veterans with an eGFR ≥60 mL/ min/1.73 m^2 and available total testosterone level, we examined the association of incident TRT with kidney function changes (slopes of eGFR calculated from serum creatinine levels measured over 8-year follow up period) in five groups of chronic kidney disease (CKD) patients, using logistic and multinomial logistic regression models with adjustment for sociodemographics, comorbidities, medications, and clinical variables.

Results: The mean (SD) age of the cohort was 57.8 (11.3) years; 19% were African American and 27% were diabetic. Patients who received (vs. those who did not receive) TRT had experienced significantly lower risk of fast and very fast eGFR decline (logistic odds ratio[95% CI] for eGFR slope <-5 vs. >=-5 mL/min/1.73 m^2/year, 0.84 [0.81-0.87]) (multinomial odds ratios [95% CI] for eGFR slope <-10, -10 to <-5, -5 to <-1, and ≥ 0, vs. -1 to <0 mL/min/1.73 m^2/year, 0.68 [0.63-0.73], 0.91 [0.87-0.95], 1.08 [1.06-1.11] and 0.93 [0.93-0.97], respectively) (Figure).



Conclusions: TRT is associated with lower risk of rapid eGFR decline. Further studies are needed to elucidate the underlying mechanisms and to determine whether testosterone replacement therapy could indeed be renoprotective.

Funding: NIDDK Support, VA Support

FR-PO763

Diuretic Use and Type on Progression in Chronic Kidney Disease Claudia S. Cabrera,[1] Jingrong Yang,[2] Thida Tan,[2] Bergur V. Stefansson,[1] Peter J. Greasley,[1] Alan S. Go.[2] *[1]AstraZeneca; [2]Kaiser Permanente Northern California.*

Background: Few studies have systematically evaluated medical therapies as potential risk factors for accelerated progression of CKD in "real world" populations. Conflicting data exist about the impact of diuretics outside clinical trials. In a large community-based Stage 3/4 CKD cohort, we evaluated the association between diuretic use and type with CKD progression and development of ESRD.

Methods: Within Kaiser Permanente Northern California, we identified adults with eGFR 15-59 min/1.73m^2 by CKD-EPI between 2008-2012 who had no prior diuretic use or ESRD. Through 2012, we calculated the rate (per 100 P-Y) of the composite outcome of ESRD, reaching eGFR <15 ml/min/1.73m^2, or >50% reduction from baseline eGFR. New initiation of diuretic therapy and type was identified from comprehensive pharmacy data. Demographics, clinical risk factors and longitudinal medical therapies were obtained from electronic medical records. We used marginal structural models (MSM) with inverse probability weighting (IPW) to evaluate the impact of loop or thiazide diuretics on CKD progression after adjusting for baseline and time-dependent confounders (including heart failure episodes). IPW's were calculated for treatment and censoring for each 30-day period of follow-up and integrated into pooled logistic regression models to estimate the effect of new use of loop or thiazide diuretics.

Results: In 117,728 eligible adults with eGFR 15-59 min/1.73m^2, mean age was 72 years, 57% women, 24% persons of color and 25% with diabetes. Over mean follow-up of 3.7±1.3 years, the overall rate of the renal composite outcome was 1.47 per 100 P-Y (95% CI: 1.43-1.50). In MSM models, initiation of diuretics was independently associated with higher rates of CKD progression even after accounting for use of other cardiovascular and renal-related medications and time-dependent confounders: thiazide diuretic (adjusted odds ratio [OR] 2.95, 95% CI:2.11-4.12) and loop diuretic (OR 1.47, 95% CI:1.23-1.74).

Conclusions: In a large, diverse, community-based Stage 3/4 CKD population, use of diuretics was independently associated with a higher risk of CKD progression, especially thiazide diuretics.

Funding: Pharmaceutical Company Support - AstraZeneca

FR-PO764

Long Term Kidney Outcomes among Proton Pump Inhibitors Users with and without Acute Kidney Injury Yan Xie,[1] Benjamin Charles Bowe,[1] Tingting Li,[1,2] Hong Xian,[1] Yan Yan,[1] Ziyad Al-Aly.[1,2,5] *[1]Clinical Epidemiology Center, VA Saint Louis Health Care System, Saint Louis, MO; [2]Dept of Medicine, Washington Univ School of Medicine, Saint Louis, MO; [3]Renal Section, Medicine Service, VA Saint Louis Health Care System, Saint Louis, MO.*

Background: Proton Pump Inhibitor (PPI) use is associated with increased risk of acute kidney injury (AKI), incident chronic kidney disease (CKD), CKD progression, and end stage renal disease (ESRD). PPI-associated CKD is presumed to be secondary to incomplete recovery of AKI. Whether long term adverse renal outcomes are mediated solely by occurrence of AKI is not known.

Methods: We used the Department of Veterans Affairs national databases to build a cohort of 158,574 incident users of acid suppression therapy: 137,310 PPI and 21,264 Histamine H2 receptor antagonists (H2 blockers) users with no history of AKI. Logistic regression models were built to examine the association of PPI exposure and odds of incident CKD, CKD progression, and ESRD within cohort participants with and without AKI during follow up.

Results: After a follow-up of 5 years, among those who developed AKI, and compared to new users of H2 blockers, new users of PPI had 1.29 (1.20, 1.38), 1.24 (1.17, 1.32), and 1.19 (1.03, 1.39) odds of having incident CKD, eGFR decline >30%, and 50% decline in eGFR or ESRD, respectively. Among cohort participants without AKI, and compared to new users of H2 blockers, new PPI users had 1.34 (1.25, 1.42), 1.30 (1.23, 1.37), and 1.31 (1.15, 1.50) odds of having incident CKD, eGFR decline >30%, and 50% decline in eGFR or ESRD, respectively.

Conclusions: Our results demonstrate that PPI use is associated with significant higher odds of adverse long term renal outcomes in incident users of acid suppression therapy with and without intervening AKI. The findings suggest that association of PPI use and long term renal outcomes may not be solely mediated by occurrence of AKI. Other possible pathways may include chronic indolent renal damage caused directly by PPI or mechanisms related to PPI-induced hypomagnesemia. Further investigation is necessary to elucidate the mechanisms linking PPI use and CKD.

Funding: VA Support

FR-PO765

Red Cell Indices Are Not Indicative of Iron Deficiency in Children with Pre-Dialysis Chronic Kidney Disease Abdullahi Mudi,[1,2] Cecil S. Levy.[1] *[1]Div of Paediatric Nephrology, Univ of the Witwatersrand, Johannesburg, South Africa; [2]Dept of Paediatrics, Bayero Univ, Kano, Nigeria.*

Background: Iron deficiencyis common in children with chronic kidney disease (CKD). Clinicians in developing countries often rely on red cell indices (MCV, MCHC, RCDW) as a screening tool for iron deficiency because serum iron parameter tests are either expensive or not readily available. We aimed to evaluate the use of red cell indices in screening for iron deficiency in a group of children with pre-dialysis CKD.

Methods: Ninety-four children with CKD stage 1–4 were reviewed for age, sex and current medications. Each patient had blood samples sent for FBC and Iron Studies. CRP was simultaneously sent to exclude inflammation.

Results: Eleven of the children were on oral iron supplement and were excluded from the analysis. None of the children had received blood transfusion within the last four months. Median age 10 years (IQR:7-13 years); male to female ratio 1.96:1; 9/83 had low Hb (< 12g/dl); 43/83 had a low TSAT (<20%); 32/83 had a low ferritin (<30µg/l) and 20/83 had absolute iron deficiency (low TSAT and low ferritin); 23/83 had functional iron deficiency (low TSAT and normal ferritin). There was no statistically significant difference in the mean values of the haemoglobin and red cell indices between patients with deplete (low TSAT and/or low ferritin) and replete iron stores. CRP was not significantly associated with ferritin levels (p=0.093).

	Deplete Iron stores (n=55)	Replete Iron stores (n=28)	P value
Hb (g/dl)	13.41 ± 1.28	13.56 ± 1.33	0.619
MCV (Fl)	83.97 ± 5.55	83.78 ± 5.24	0.883
MCH (pg)	27.60 ± 2.19	27.69 ± 1.71	0.842
MCHC (g/dl)	32.81 ± 1.11	33.12 ± 0.93	0.211
RCDW (%)	14.13 ± 1.57	13.79 ± 0.95	0.297

Conclusions: A large number of children with CKD are iron deficient. The use of red cell indices to screen for iron deficiency among such patients may be misleading. We emphasise the use of serum iron parameters, rather than red cell indices to assess for iron deficiency in CKD as recommended by the KDIGO guidelines.

FR-PO766

Anemia Prevalence and Treatment in Patients with Non-Dialysis-Dependent Chronic Kidney Disease Wendy L. St. Peter,[1] Haifeng Guo,[1] Shaum Kabadi,[2] Sean Zhao,[2] David T. Gilbertson,[1] Louise Janice Sargent Heuer,[2] Yi Peng,[1] Trudy Pendergraft,[2] Suying Li.[1] *[1]Chronic Disease Research Group, Minneapolis Medical Research Foundation, Minneapolis, MN; [2]AstraZeneca, Wilmington, DE.*

Background: Relatively little is known about the burden of anemia in stage 3-5 non-dialysis-dependent chronic kidney disease (NDD-CKD) patients. We evaluated anemia prevalence, treatment patterns, and cardiovascular (CV) outcomes in adults with stage 3-5 NDD-CKD.

Methods: We used Medicare and MarketScan® (commercial) claims data (10/1/2011 to 9/30/2012) to identify "older" (65+ yrs) and "younger" (18-64 yrs) CKD-NDD patients, respectively. During the baseline year from 10/1/2011-09/30/2012, anemia status (defined by diagnosis codes), patient demographics, and comorbidities were determined. We evaluated anemia treatment patterns [erythropoiesis-stimulating agents (ESAs), intravenous (IV) iron, and red blood cell (RBC) transfusions] after baseline anemia diagnosis. CV outcomes were identified during the 1-yr follow-up period.

Results: There were 148,550 (52%) older and 15,716 (28%) younger patients with anemia among stage 3-5 NDD-CKD patients in Medicare and MarketScan databases, respectively. Prevalence increased as CKD stage and age increased and was generally higher among women. The most common form of treatment (at least 1 administration) for anemia was RBC transfusions (22.2% older, 11.7% younger) followed by ESA (12.7% older, 10.8% younger) and IV iron (6.7% older, 9.4% younger). Treatment across all modalities increased by CKD stage and age. Comorbidity burden and inflammatory conditions were more commonly observed among older patients relative to younger patients. Major adverse cardiac events and thromboembolic events (unadjusted) increased by CKD stage and were higher among patients with anemia versus those without.

Conclusions: Approximately half of Medicare stage 3-5 NDD-CKD patients have anemia; RBC transfusion was commonly used to treat anemia. Anemia treatment patterns differ by age; older patients received twice as many RBC transfusions as younger patients and were also more likely to receive treatment with ESAs. Investigation into effects of anemia treatment patterns on CV outcomes is warranted in this population.

Funding: Pharmaceutical Company Support - AstraZeneca

FR-PO767

Anemia Treatment Pattern Changes in Non-Dialysis-Dependent Chronic Kidney Disease Patients before and after Revised Food and Drug Administration Label and New Anemia Guidelines for Erythropoiesis-Stimulating Agents Wendy L. St. Peter,[1] Haifeng Guo,[1] Shaum Kabadi,[2] Sean Zhao,[2] David T. Gilbertson,[1] Louise Janice Sargent Heuer,[2] Yi Peng,[1] Trudy Pendergraft,[2] Suying Li.[1] *[1]Chronic Disease Research Group, Minneapolis Medical Research Foundation, Minneapolis, MN; [2]AstraZeneca.*

Background: In June 2011, the US Food and Drug Administration (FDA) added more Black Box warnings to erythropoiesis stimulating agent (ESA) labels; in 2012, KDIGO released new anemia treatment guidelines. Our study aimed to examine changes in anemia treatment patterns from 2008 to 2012 in stage 3-5 non-dialysis-dependent chronic kidney disease (NDD-CKD) patients.

Methods: Stage 3-5 NDD-CKD patients with anemia (defined by diagnosis codes) were selected from a 20% Medicare random sample. Two study cohorts were created,"2008" and "2012", consisting of patients identified from 2007-2009 and 2011-2013 claims, respectively. ESA, intravenous (IV) iron, and red blood cell (RBC) transfusion use and time to use were evaluated after anemia diagnosis during baseline year. Consistent ESA treatment was defined as at least 1 ESA monthly administration in at least 80% of 12 follow-up months.

Results: There were 71,744 and 109,251 stage 3-5 NDD-CKD patients with anemia in 2008 and 2012 cohorts, respectively. Treatment with ESAs declined from 2008 to 2012, while IV iron use and RBC transfusions remained stable. Consistent ESA treatment was low among these NDD-CKD patients and declined further by 2012. Median time to ESA treatment increased by a week, remained stable for IV iron, but decreased for transfusions (59 to 34 days).

Anemia Treatment	2008 cohort (n=71,744) % Patients Treated	2012 cohort (n=109,251) % Patients Treated
ESA	29.4	12.7
IV iron	6.3	6.7
RBC transfusion	21.3	22.2
Any Anemia Treatment	45.1	34.0
ESA Treatment Patterns	**% Patients with ESA Treatment Pattern**	
Untreated	70.6	87.3
Not consistently treated	19.7	9.3
Consistently treated	9.7	3.4

Conclusions: ESA use decreased by 57% from 2008 to 2012; IV iron use and RBC transfusions remained stable. Patients received transfusions sooner, corresponding to decline in ESA use. This is the first study to report on the impact of FDA and KDIGO action on anemia treatment patterns in stage 3-5 NDD-CKD patients.

Funding: Pharmaceutical Company Support - AstraZeneca

FR-PO768

Cost-Effectiveness Analysis of Intravenous Ferumoxytol for Treatment of Iron Deficiency Anemia in Adult Patients with Non-Dialysis Dependent Chronic Kidney Disease (ND-CKD) Naomi V. Dahl,[1] William Strauss,[1] Robert F. Kaper,[1] Frank A. Corvino,[2] Marko Zivkovic.[2] *[1]AMAG Pharmaceuticals, Inc., Waltham, MA; [2]Genesis Research, Hoboken, NJ.*

Background: Treatment of iron deficiency anemia (IDA) in CKD patients requires oral or IV iron replacement therapy, with or without simultaneous use of erythropoietin stimulating agents (ESAs). Ferumoxytol (FER) has demonstrated superior efficacy to oral iron in clinical trials.

Methods: This analysis studied the cost-effectiveness (CE) of treating IDA in ND-CKD patients with FER compared to oral iron, alone or in combination with ESA. A decision-analytic model was developed to compare health outcomes and costs associated with a 5-week outpatient treatment of IDA in ND-CKD patients with FER±ESA or oral iron±ESA in the US. Direct costs included: drug acquisition and administration, serious adverse events (AEs), and medical management. Treatment efficacy was determined as mean increase in g/dL hemoglobin (Hb) from baseline over a 5-week period. Clinical inputs were derived from patient-level data from 2 Phase 3 trials of FER vs oral iron in ND-CKD patients. Cost inputs were retrieved from RED BOOK and Centers for Medicare and Medicaid Services data. One-way sensitivity analysis to identify cost drivers and probabilistic sensitivity analysis utilizing Monte Carlo simulations to assess stability of results were performed.

Results: The cost of 5-week IDA treatments were $2,489, $5,216, $1,298, and $4,263 for FER, FER+ESA, oral iron, and oral iron+ESA patients, respectively. Over this period, increases in Hb were 0.76g/dL (FER), 1.42g/dL (FER+ESA), 0.19g/dL (oral iron), and 0.53g/dL (oral iron+ESA). Incremental cost per g/dL increase in Hb, compared to FER alone, was $398 for FER+ESA, $3,558 for oral iron, and $4,768 for oral iron+ESA. Efficacy was the main driver of CE for all treatments. AE and medical management costs were major components of oral iron monotherapy costs, as were drug acquisition costs for the other treatments.

Conclusions: FER was found to be the more cost-effective treatment strategy for IDA in ND-CKD patients over a 5-week study period compared to oral iron with or without ESA, and that FER as monotherapy was more cost-effective than in combination with ESA.

Funding: Pharmaceutical Company Support - AMAG Pharmaceuticals, Inc.

FR-PO769

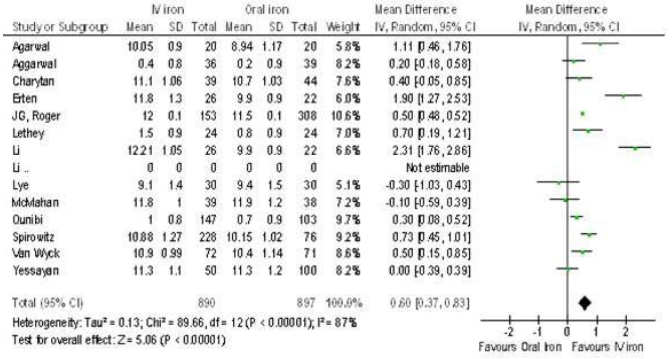
Intravenous versus Oral Iron Supplementation for the Treatment of Anemia in CKD: An Updated Systematic Review and Meta-Analysis Xavier Perez Hernandez,[1] Sumeet Munjal,[1] James W. Lohr,[1,2] Pradeep Arora,[3] Irfan Ahmed Moinuddin.[3] *[1]Medicine, SUNY at Buffalo, Buffalo, NY; [2]Nephrology, VA Medical Center, Buffalo, NY; [3]Nephrology, VA Medical Center, Richmond, VA.*

Background: Iron supplementation is essential for the treatment of patients with anemia of chronic kidney disease (CKD) not on dialysis. It is not clear which is the best method of iron administration. A previous meta-analysis which included studies through 12/2010 showed a significant improvement in transferrin saturation (Tsat), ferritin, and hemoglobin (Hgb) levels with the use of intravenous (IV) iron. However, further studies addressing this have been inconsistent in showing a benefit of IV iron over oral iron supplementation. In view of this, we performed an updated meta-analysis using the recent articles published after the original meta-analysis.

Methods: A search was performed from January 2011 of trials published in Medline. We included trials that included patients with CKD (stages III to V), were published in English, and the interventions were IV iron preparations versus oral iron supplementation. Primary outcomes assessed: percent of patients reaching their target Hgb, absolute Hgb level, ferritin level, and Tsat levels. Data was analyzed using Review Manager 5.1 using random effect modeling.

Results: 19 trials were identified (14 from prior trial and 5 from the updated search). Compared with oral iron, there was a significantly greater Hgb level in CKD patients treated with IV iron (weighted mean difference, 0.6 g/dL; 95% CI, 0.37 to 0.83), target

Hgb level (RR, 1.44; 95% CI, 1.13 to 1.82), ferritin level (weighted mean difference, 224.18 ng/dL; 95% CI, 157.24 to 291.12), and Tsat level (weighted mean difference, 2.99 %; 95% CI, 1.49 to 4.49).



Conclusions: Our review shows that CKD patients not on hemodialysis therapy have better Hgb level response when treated with IV iron.

FR-PO770

Serum Level of Soluble Fas Is a Predictor of Need for Red Blood Cells Transfusion in Patients with Chronic Kidney Disease Krissia K.S. Wallbach,[1] Luiza Pego Silva,[1] Marcos A. Meniconi,[1] Maria Dalboni,[1] Maria Eugenia F. Canziani,[1] Miguel A. Goes.[1,2] *[1]Nephrology, Federal Univ of Sao Paulo, Sao Paulo, SP, Brazil; [2]Nephrology, Hospital Israelita Albert Einstein, Sao Paulo, SP, Brazil.*

Background: Anemia related to chronic kidney disease (CKD) is associated with inflammation, impaired erythropoietin (Epo) production, iron status, soluble Fas (sFas) and PTH levels. Red blood cells (RBCs) transfusion as a consequence of severe anemia might be harmful, and predicting it remains a challenge.

Methods: We conducted a prospective study with 56 pre-dialysis patients for 144 months (Jan/2004-Dec/2015). Need for RBCs transfusion was the primary outcome. Serum sFas, IL-6, PTH, Epo level, EPI-CKD, Hb, Hct, iron status and use of rHuEPO were analyzed at baseline. Correlation between the variables and multivariate regression with Hb-dependent variable were performed on admission and binary logistic regression for RBCs transfusion was performed at the end of 144 months with sFas, EPI-CKD, transferrin saturation(Trs), IL-6 and Epo.

Results: Our population at baseline was 56+13 yo, 65,5% (35) males; diabetes and hypertension were the leading causes of kidney failure; Hb 12.5+2.3g/dL, Hct 37+7%, Trs 23+ 14%, ferritin 123+110ng/ml, EPI-CKD 34+14mL/min, sFas 3121+1249pg/ml, Epo 11+10pg/ml, IL-6 7.0 ± 6.4pg/mL, PTH 200 + 178pg/ml. There was a positive correlation between Hb and EPI-CKD (r=0.35; p=0.009), Hb and Trs (r=0.14; p=0.09) and a negative correlation between Hb and sFas (r=-0.35; p=0.008) and Hb and PTH (r=-0.32; p=0.03). Independent association between Hb and sFas (b=-0.378, p=0.02) was found. Four patients (7%) used rHuEPO and 8 (14%) required RBCs transfusion (3+1,5 units). We observed lower IL-6 (4.3+1.8, 7.4+6.8; p=0.08), EPI-CKD (22+9, 36+13; p=0.008) and Trs (18+7, 23+14; p=0.09) but higher sFas (5067+1015,2797+960, p<0.001), Epo (15.8+13.4, 10.6+9.7; p=0.08) and PTH (313+277,189+170; p=0.1) levels in the RBCs transfusion group. After binary logistic regression, sFas levels were independently associated to RBC transfusion (b=1.001 95% CI 1.000-1.001; p=0.01).

Conclusions: Serum sFas level is associated with anemia and is an independent predictor of need for RBC transfusion in CKD patients.

FR-PO771

Achieving Target Haemoglobin with Single High-Dose Iron Infusion: Predicting the Optimal Approach in Non-Dialysis Chronic Kidney Disease Christopher Brown, David Jackson, Reuben Morgan, Jennifer Williams, Ashraf I. Mikhail. *ABMU Health Board, United Kingdom.*

Background: The UK National Institute for Health and Care Excellence (NICE) have updated their guidelines for managing anaemia of CKD. These recommend a high-dose, low-frequency (HDLF) IV iron strategy for treating iron-deficiency for 1. patients receiving ESA and 2. patients not receiving ESA if intolerant of oral iron or Hb levels are not reached within 3 months. We analysed the Hb response in a non-dialysis CKD cohort to HDLF IV iron with a target Hb of 110g/L whose iron requirements were determined from the Ganzoni equation.

Methods: This retrospective analysis of 197 patients examined the Hb response to a single infusion of iron isomaltoside. Individual doses were calculated from the Ganzoni equation (with a target Hb set at 110g/L and iron stores set at 500mg) to a maximum single dose of 20mg/kg.

Results:

			Pre-treatment			Post-treatment		
			ESA group	Non-ESA group	Combined	ESA group	Non-ESA group	Combined
Parameter	Number of patients	n	96	101	197	96	101	197
Hb	Mean (Min:Max)	g/L	94.2 (45:124)	92.2 (70:127)	93.3 (45:127)	104.5 (76:144)	103.1 (69:145)	103.8 (69:145)
	% achieve target (>110)	%	12%	7%	9%	34%	29%	32%
	% above lower range (>100)	%	31%	25%	28%	52%	58%	55%
	% above upper range (>120)	%	2%	3%	3%	13%	10%	12%
Ferritin	Mean (Min:Max)	mcg/L	224 (7:690)	154 (6:1112)	190 (6:1112)	445 (31:1568)	419 (5:1820)	433 (5:1820)
TSAT	Mean (Min:Max)	%	13 (3:79)	12 (3:39)	13 (3:79)	20 (6:66)	20 (3:44)	20 (3:66)
IV iron doses	Mean (Min:Max)	mg	819 (300:1400)	837 (500:1300)	828 (300:1400)	*	*	*
	Doses >1 g in single infusion	%	10%	9%	10%	*	*	*
Treatment effect	Change in Hb (Min:Max)	g/L	*	*	*	10.2 (12.5%) (-9:55)	10.8 (12.7%) (-13:52)	10.5 (12.6%) (-13:55)
	Change in Hb per gram iron (Min:Max)	g/L/g	*	*	*	13 (15.1%) (-50:60)	12.2 (14.0%) (-35:56)	12.6 (14.6%) (-50:60)
Indicative	Additional dose needed to achieve target Hb	mg	*	*	*	424	570	494
	Additional dose needed to achieve target Hb	%				35%	48%	41%

Of the 197 patients analysed who received high-dose iron infusion between Oct 2012 and Apr 2016, one patient developed an adverse drug reaction (ADR); rash. Subsequent doses in this cohort resulted in 264 infusions with no further reported ADR. No patients had angioedema or required stopping the infusion, hospitalisation or medical intervention. Both ESA and non-ESA treated patients equally achieved aspirational Hb range. We calculated an indicative adjustment to the iron dose that may improve Hb target achievement to direct future dosing decisions. The higher indicative dose in the non-ESA group reflects the lower baseline iron stores (ferritin and TSAT).

Conclusions: A high-dose,low-frequency approach to IV iron can effectively achieve aspirational Hb levels in non-dialysis CKD patients. This is equally achievable in both ESA and non-ESA treated patients. Further analysis of dosing strategies are needed to predict the appropriate IV iron dose to achieve Hb levels and to evaluate the long-term safety of a HDLF approach.

FR-PO772

The Mortality Risk Associated with Functional Iron Deficiency in the U.S. Veterans with CKD Monique E. Cho, Jared Hansen, Celena B. Peters, Tao He, Brian C. Sauer. *Univ of Utah and George E. Wahlen Dept of Veterans Affairs Medical Center.*

Background: The clinical significance of functional iron deficiency (FID) has not been investigated in a large CKD population.

Methods: We performed a historical cohort study using the Veterans Affairs Informatics and Computing Infrastructure. We identified a CKD cohort (MDRD eGFR <60 mL/min/1.73m^2) with at least one set of iron indices between 2006-2015. The clinical characteristics were determined from the ICD-9 codes and laboratory data during the *baseline period*, defined as the year preceding the first available iron indices. Patients with baseline hematologic disorders, ESRD, organ transplantation, and cancer were excluded. The cohort was divided into 4 iron groups based on the joint quartiles (Q) of transferrin saturation (Tsat) and ferritin: FID, 1st Tsat Q + 3rd-4th ferritin Qs; Low Iron (LI), 1st Tsat+ferritin Qs; High Iron (HI), 4th Tsat+ferritin Qs; and Reference (R), 2nd-3rd Tsat+ferritin Qs. Mortality among iron groups was assessed using Cox proportional hazard models.

Results: Of the 1,126,184 Veterans with CKD, 249,705 met the inclusion criteria. The mean±SD for age and eGFR were 72±11 years and 47±19 mL/min/1.73 m^2, respectively. The median (IQR) Tsat and ferritin values were 21 (15, 28)% and 118 (56, 232)ng/mL. Of the study cohort, 43% could not be categorized. In the remaining 142,832 Veterans, the prevalence for FID, HI, LI, and R were 14%, 14%, 20%, and 52%, respectively. FID had the greatest baseline prevalence for arrhythmia (36%), diabetes (62%), heart failure (35%), hypertension (91%), stroke (18%), and peripheral arterial disease (20%). During the mean±SD follow-up period of 4.1±2.7 years, FID group exhibited the highest risk of all-cause mortality compared to R [hazard ratio, 95% CI: 1.46 (1.43, 1.50)], followed by HI [HR 1.23 (1.20, 1.26)], and LI [HR 1.17 (1.15,1.20)], after adjusting for age, sex, race, diabetes, cardiovascular (CV) risk factors, albumin, and hemoglobin.

Conclusions: FID is significantly more prevalent in patients with diabetes and CV disease and is strongly associated with all-cause mortality risk in CKD.

Funding: Private Foundation Support

FR-PO773

Lowering Diastolic Blood Pressure Was Associated with Higher Incidence of Chronic Kidney Disease in General Population Only in Those Using Antihypertensive Medication Daisuke Uchida,[1] Ryo Kido,[2] Hiroo Kawarazaki,[1] Masaru Murasawa,[1] Shouichi Fujimoto,[3] Kunitoshi Iseki,[3] Toshiki Moriyama,[3] Kunihiro Yamagata,[3] Kazuhiko Tsuruya,[3] Tsuneo Konta,[3] Ichiei Narita,[3] Masahide Kondo,[3] Masato Kasahara,[3] Koichi Asahi,[3] Tsuyoshi Watanabe,[3] Yugo Shibagaki.[3] *[1]Dept of Nephrology, Inagi Municipal Hospital, Inagi, Tokyo, Japan; [2]Dept of Examination Center, Inagi Municipal Hospital, Inagi, Tokyo, Japan; [3]Steering Committee of Research on Design of the Comprehensive Health Care System for Chronic Kidney Disease (CKD) Based on the Individual Risk Assessment by Specific Health Checkup, Japan.*

Background: Whether diastolic blood pressure (DBP) is associated with developing chronic kidney disease (CKD) in the general population is not examined well.

Methods: Using national health check-up database from 2008 to 2011 in the general Japanese population aged 39 to 74 years, we evaluated the association between DBP and incidence of CKD 2 years later in 128,005 participants without CKD (proteinuria and/or eGFR <60, ml/min/1.73m2). DBP was categorized by every 5mmHg from the lowest

(<60mmHg) to the highest category (>100mmHg), and was further stratified into those with (meds+) and without antihypertensive medication (meds-). We calculated odds ratio (OR) for estimating adjusted risk of developing CKD using logistic regression model.

Results: Participants including 62% of female and 25.9% of med+ had mean age of 63 years, with mean eGFR of 78.2±13.4 and DBP of 76±11mmHg. Two years later, 12,379 (9.7%) developed CKD. Compared to meds- with DBP 60-64mmHg as reference, multivariate analysis showed no difference in risk of developing CKD among meds-, but significant difference in most DBP category of meds+, especially in the lowest category showing the highest risk (OR 1.51, 95%CI 1.14 to 1.99). The risk decreased as the DBP rose up to 90-94mmHg (p for trend 0.05). In subgroup analysis, meds+ similarly showed CKD risk reduction as DBP rose (p for trend 0.02), with significant difference among categories in part, but no difference was seen among any DBP in meds-.

Conclusions: Lower DBP was associated with higher risk of developing CKD in general population only in those taking antihypertensive medication.

FR-PO774

The Minimum Clinically Important Difference in the Incremental Shuttle Walk Test following a 12 Week Exercise Intervention in Chronic Kidney Disease

Thomas James Wilkinson,[1] Soteris Xenophontos,[1] Douglas W. Gould,[1] Emma L. Watson,[1] Alice C. Smith,[1] Joao L. Viana.[2] *[1]Leicester Kidney Exercise Team, Univ of Leicester, Leicester, Leicestershire, United Kingdom; [2]Univ Inst of Maia.*

Background: Chronic kidney disease (CKD) patients have poor cardiorespiratory capacity which limits physical performance and is strongly associated with outcome. The incremental shuttle walk test (ISWT) is a popular and well-defined field test to assess this but has not been validated in CKD. For clinical and research outcome measures, the minimum clinically important difference (MCID) is 'the smallest change important to patients' and is more relevant than 'statistically significant' changes which merely indicate that a change did not occur by chance. We aimed to establish the MCID in the ISWT after an exercise intervention in non-dialysis CKD.

Methods: 23 CKD patients (10 male, mean age 59 (27–80) years, eGFR 25 (8–41) mL/min/1.73m^2) undertook 30 minutes supervised aerobic and resistance exercise training thrice weekly for 12 weeks. Patients completed the ISWT at baseline and end of study. MCID was estimated using a patient centred *anchor*-based approach. Patient's perception of their ISWT change was assessed using the 36-Item Short Form Survey. After completing the exercise programme, patients were asked to identify, on a 5-point Likert scale, their perceived change in general health ('much better' to 'much worse').

Results: Mean baseline ISWT was 431 (SD: 232) m, which increased to 474 (SD: 227) m (+43m (CI: 17–68)) after the exercise intervention (P = .002). Using an *anchor*-based analysis, for participants who rated their general health as *'somewhat better'*, the mean improvement in the ISWT was 60m (CI: 27–93), or 14%. Conversely, in the participants who rated their general health as *'somewhat worse'*, the mean difference was -25m.

Conclusions: The MCID in the ISWT following an exercise intervention in CKD is 60m. This corresponds well with the ISWT MCID in patients completing cardiac (70m) and pulmonary rehabilitation (48m). This value will inform the design of clinical trials, and aid clinicians in the interpretation of meaningful ISWT changes in CKD after medical and lifestyle interventions in both clinical and research settings.

Funding: Private Foundation Support

FR-PO775

Charlson Comorbidity Index - Impact on Hospitalization and Mortality in Chronic Renal Disease

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Background: Chronic kidney disease (CKD) is a known risk factor for increased morbidity and mortality. Charlson comorbidity index (CCI) is the most extensively studied comorbidity index for predicting mortality and may help improving outcomes by identifying and treating patients earlier and more effectively. In this study we evaluated the correlation between CCI and hospital admissions in patients with chronic kidney disease and the influence of CCI on their mortality.

Methods: We included, in a retrospective observational study, 693 patients, with an eGFR< 30 ml/min/1.73m^2, followed in a pre-dialysis clinic between 2008-2012. Four groups were created, according to the CCI. G1 (n=172)-CCI ≤ 5.2; G2 (n=162)-CCI – 5.4-6.4; G3 (n=177)-CCI – 6.5-7.4 and G4 (n=182)-CCI ≥7.5. Descriptive statistics, ANOVA and chi-square tests were used for comparison between groups. *Bonferroni* test was used as a post-hoc test. *Kaplan-Meier* analysis was used to evaluate mortality in each group and *Log Rank* test for comparison between groups. To evaluate the relationship between CCI and the other variables we used a multivariate logistic regression.

Results: The mean age of our population was 70.09 years, 54% (371) male, with a mean eGFR (MDRD) of 20.2±9.2 ml/min. G1 patients were younger (p<0.001) and showed higher hemoglobin (p<0.001), eGFR (p=0.025), calcium (p=0.033) and albumin (p<0.001). In a multivariate logistic regression model ajusted to gender, age, haemoglobin, phosphorus, parathormone, eGFR, albumin and blood pressure, CCI is a risk factor of hospitalization (OR=1.362, Cl 95% 1.175-1.580, p<0,0001) and death (OR=1.243; CI 95% 1.053-1.467; p=0.010).Survival at 85 months was progressively shorter with higher CCI (G1= 86.7%, G2= 65.9%, G3=59.35 % and G4= 30.4%, log Rank =34.465, p=0.0001.

Conclusions: CCI provides a simple and valid method for classifying comorbidities and can be used as an instrument to predict patient's survival/mortality as their kidney disease progresses.

FR-PO776

Waist Circumference and LDL-Cholesterol and the Incidence of Chronic Kidney Disease in the Healthy Young- to Middle-Aged Working Men in Japan

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Background: Identifying modifiable risk factors is crucially important for reducing the burden of chronic kidney disease (CKD) in the working age population. We aimed to examine the association of lifestyle-related clinical parameters with kidney function decline over 5 years in a cohort of healthy young- to middle-aged men with preserved estimated glomerular filtration rate (eGFR).

Methods: We enrolled 10,668 adult Japanese men (<60 years) who had worked at the two companies in a retrospective fashion. We selected the subjects whose basal eGFR (mL/min/1.73m^2) range was from 60 to 90. We analyzed medical checkup data 5 years later, and examined changes of those data between the 2 time points. We defined the cut-off values of waist circumference (WC) as below 85 cm and serum LDL-cholesterol (LDL-C) as below 120 mg/dL according to the definition of the metabolic syndrome in JapanMinistry of Health, Labour and Welfare.

Results: Mean age and eGFR were 40.9±10.3 years and 76.2±7.8 at baseline. The 773 males (7.2 %) had developed newly to CKD at 5 years later. There was a significantly higher risk of CKD in men whose WC (OR=1.63, p<0.001) or LDL-C (OR=1.78, p<0.001) remained elevated at the two points. In addition, healthy men whose WC or LDL-C had become elevated over the cut-off value at 5 years later had a higher risk for CKD development (WC: OR=1.53, p=0.001, LDL-C: OR=1.38, p=0.008). There was also a significantly lower rate of eGFR decline in men whose WC and LDL-C levels had been concomitantly normalized at 5 years later than those whose levels had been still elevated (-1.1±7.1 vs. -3.6±6.5, p= 0.012).

Conclusions: These findings show that both WC over 85 cm and LDL-C over 120 mg/dL were risk factors for CKD development in adult men with 60-90 in eGFR. Because normalization of WC and LDL-C were related to a slower rate of eGFR decline, abdominal fatness and disturbed lipid profile could be a potentially modifiable risk factor in preventing CKD development in healthy young- to middle-aged working men.

FR-PO777

eGFR Agreement and Mortality Discrimination in Community Dwelling Obese Individuals

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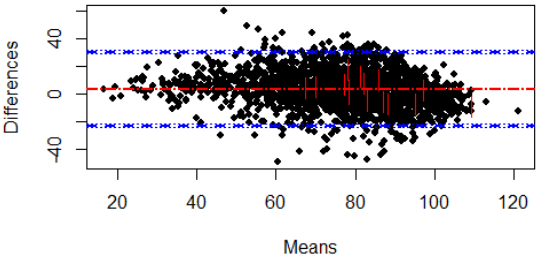
Background: Obesity is increasing worldwide and is a risk factor for chronic kidney disease. The relative performance of eGFR equations in obesity has not been fully characterised.

Methods: We analysed data from the first wave (2009-2011) of The Irish Longitudinal Study on Ageing with mortality follow up through wave 3 (2015). TILDA is a nationally representative prospective cohort study of community dwelling individuals in Ireland aged 50 years and over. Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) were used to compare the additive discrimination of each eGFR equation in comparison to MDRD within the obese subgroup.

Results: Mean (se) (Obese N=1805 vs 3554 non-obese individuals): SBP 138.6(0.49) mmHg vs 135.4(0.39) mmHg, Waist:hip ratio 0.95(0) vs 0.89(0), BMI 34(0.1) kg/m2 vs 26(0.04) kg/m2, all P<0.001. Mean difference 95% limits of agreement between eGFR equations included (ml/min/1.73m2): (vs MDRD) -3.53(-13.2 to 6.09) for CKD EPI Creatinine, -0.26 (-29.4 to 28.9) for CKD EPI Cystatin, and -1.82(-19.5 to 15.82) for CKD the combination equation. When comparing CKD EPI Creatinine to CKD EPI Cystatin we found 3.28 (-23.5 to 30.01) (**Bland-Altman plot Figure 1**).

Conclusions: eGFR equations do not appear to be interchangeable in obese community dwelling individuals, cystatin based eGFR equations may not provide improved mortality discrimination in this subgroup.



eGFR equation (vs MDRD)	Continuous NRI (se)	P value	IDI (se)	P value
Cystatin CKDEPI	0.0809 (0.06)	0.19	1083980 (0.0)	0.12
Creatinine CKDEPI	0.0099 (0.03)	0.77	0.000071 (0.0)	0.61
Combination Creatinine & Cystatin	0.0953 (0.06)	0.10	0.000585 (0.0)	0.24

Funding: Government Support - Non-U.S.

FR-PO778

Association between Weight, Abdominal Obesity, and Albuminuria: Results from NHANES 2003-2014 Anawin Sanguankeo,[1] Sikarin Upala,[1] Eric L. Knight.[2] *[1]Internal Medicine, Bassett Medical Center, Cooperstown, NY; [2]Nephrology, Bassett Medical Center, Cooperstown, NY.*

Background: Many conditions are related to albuminuria. However, the relationship between obesity and albuminuria is controversial. We aim to determine the prevalence of albuminuria by obesity status based on multiple complementary measures of adiposity in U.S. adults and examine the association between weight, abdominal adiposity, and albuminuria.

Methods: We analyzed data from U.S. adults aged 18 years and older examined in the National Health and Nutrition Examination Survey (NHANES) from 2003–2014. We excluded participants who were pregnant or had estimated GFR<15 ml/min per 1.73 m^2. We determined the prevalence of albuminuria (urine albumin-to-creatinine ratio (UACR)≥30 mg/g) among the total sample, and separately within the two BMI classes: normal weight (18.5≤BMI<25) or obesity (BMI≥30), and abdominal obesity status: defined by gender criteria of waist circumference. Relationship between albuminuria, obesity, and abdominal obesity were evaluated using multivariate logistic regression.

Results: Among 28,468 adults who met inclusion criteria, 8.75% had UACR≥30 mg/g and 1.14% had UACR≥300 mg/g. Prevalence of having UACR≥30 mg/g in obesity, normal BMI, abdominal obesity, and normal waist are 11.43%, 7.32%, 8.75%, and 6.54%, respectively. In univariate model, obesity increases odds of having UACR≥30 mg/g (OR=1.63; 95%CI: 1.43-1.87), and UACR≥300 mg/g (OR=1.79; 95%CI: 1.38-2.31). Abdominal obesity also increases odds of having UACR≥30 mg/g (OR=1.72; 95%CI: 1.56-1.90), and UACR≥300 mg/g (OR=1.93; 95%CI: 1.53-2.45). After adjusting for age, gender, race, history of hypertension, history of diabetes mellitus, SBP, and DBP, being obese does not having UACR≥30 mg/g (OR=1.05; 95%CI: 0.91-1.20) or UACR≥300 mg/g (OR=0.87; 95%CI: 0.67-1.14). After adjusting for these factors and obesity, abdominal obesity increases odds of having UACR≥30 mg/g (OR=1.14; 95%CI: 1.01-1.28), but not UACR≥300 mg/g (OR=1.04; 95%CI: 0.73-1.47).

Conclusions: Abdominal obesity defined by waist circumference is an independent predictor of having UACR≥30 mg/g. Obesity defined by BMI is not associate with albuminuria after adjusting for confounders.

FR-PO779

Sedentary Time and Chronic Kidney Disease: A Cross Sectional Analysis of the Canadian Health Measures Study Tamara Glavinovic,[1] Thomas W. Ferguson,[1,2] Paul Komenda,[1,2] Claudio Rigatto,[1,2] Navdeep Tangri,[1,2] Clara Bohm.[1,2] *[1]Univ of Manitoba, Winnipeg, MB, Canada; [2]Chronic Disease Innovation Centre, Winnipeg, MB, Canada.*

Background: Low physical activity (PA) levels are associated with adverse outcomes, including mortality in individuals with CKD. To determine the association between PA behavior and CKD using accelerometry data in a Canadian population, we conducted a cross-sectional analysis of data in the Canadian Health Measures Survey (CHMS). We hypothesized that lower kidney function would be associated with low PA levels and increased sedentary time.

Methods: The CHMS, a national survey, collects health information about Canadians. Data from adults (>18 years old) in the first three cycles (2007-2013) were analyzed (n=8444). PA monitoring was performed using Actical™ accelerometers. Primary outcome was proportion of sedentary time by activity quartiles (n=2111 per quartile). Multivariate logistic and linear regression incorporating key modifiers of PA behavior was used to assess the association between kidney function and sedentary time.

Results: Mean proportion of weekly sedentary time ranged from 81% (most sedentary quartile) to 58% (least sedentary quartile). CKD prevalence was highest in the most sedentary quartile (6.5%). CKD Stages 3b or higher had a 4.2-fold higher likelihood (95%CI 2.5-7.3) of being in a more sedentary quartile in comparison to eGFR>60ml/min/1.73m^2. CKD Stage 3a was associated with a 1.7-fold (95%CI 1.2-2.3) higher likelihood of being increasingly sedentary. Age, female sex, diabetes, heart disease and increased pulse pressure were significantly associated with increased sedentary time. Linear regression identified that the presence of CKD Stage 3b or higher was associated with an additional 5.41% (95%CI 3.8-7.0) of sedentary time vs. those with eGFR>60ml/min/1.73m^2. Stage 3b CKD was associated with an additional 3.58% (95%CI 1.6-5.6) of sedentary time compared with CKD 3a.

Conclusions: In this analysis more advanced CKD was strongly associated with increased sedentary time as measured by accelerometry. The effect of PA promotion and exercise programming on long-term improvement of sedentary behavior and associated adverse outcomes in this population warrants further investigation.

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

FR-PO780

Associations of Unintentional versus Intentional Weight Loss with Mortality in CKD in the U.S. Shweta Bansal,[1] Guo Wei,[2] R. E. Boucher,[2] Rabia Nadeem Kiani,[2] Tom Greene,[2] Srini Beddhu.[2] *[1]UTHSC at San Antonio, SA, TX; [2]Univ of Utah, SLC, UT.*

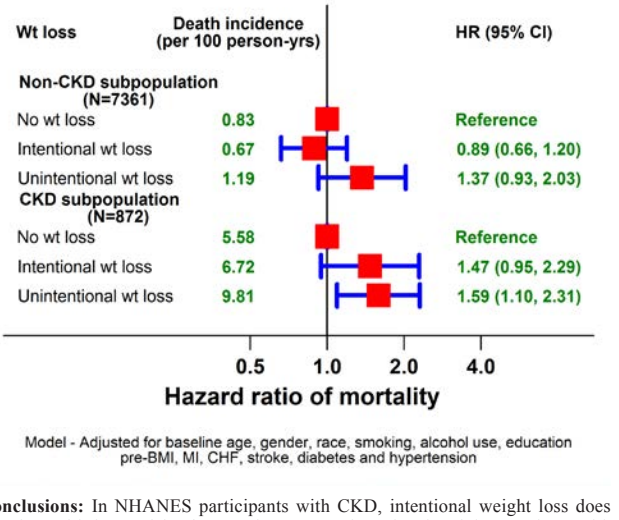
Background: Associations of weight (wt) loss with all-cause mortality (ACM) in moderate CKD is unclear. We hypothesize that intentional wt loss is associated with lower risk whereas unintentional wt loss is associated with increased risk of ACM in CKD.

Methods: We examined this hypothesis in 8233 participants with age>20yrs and BMI>25kg/m^2 in 1999-2004 NHANES. In this survey, subjects were asked about their current and 1yr prior wt; if the wt loss was >10lbs, whether it was intentional or unintentional. CKD was defined as CKD-EPI eGFR<60ml/min/m^2. Mortality until 2011 was obtained by probabilistic linkage to vital statistics by NHANES.

Results: Baseline characteristics are given in the table

	Non-CKD Subpopulation (N=7361)			CKD subpopulation (N=872)		
	No wt loss	Intent wt loss	Unintent wt loss	No wt loss	Intent wt loss	Unintent wt loss
	80.7%	14.2%	5.1%	82.8%	8.4%	8.8%
Wt loss(lb)	4.3±9	-26.9±14	-25.1±16	2.8±9	-25.7±14	-26.8±16
Age(yr)	47±12	44±11	44±14	71±11	67±10	73±10
Male(%)	55	48	53	44	33	35
AA race(%)	11	11	17	8	14	15
Smoking(%)	50	50	56	49.5	38	51
High School(%)	79.6	84	68.8	67	63.6	51
eGFR(ml/min)	95±14	97±13	97.8±16	47.8±10	46.8±10	44.7±14
CAD(%)	3.3	3	4.7	16.1	19.4	16
CHF(%)	2	1.4	2	12	24	18
Stroke(%)	2	2.7	3.3	10.7	20.8	10.8
DM(%)	10.4	15.5	14	25.6	38	30
HTN(%)	35	37	31	76	82	70
Wt 1yr ago(lb)	193±30	222±37	205.8±35	182.8±34	214.7±52	196.1±39
Current wt(lb)	197.2±31	195±33	180.6±33	185.5±36	189±50	169.4±36
PreBMI(kg/m^2)	30.3±4	34.8±5	32.3±5	30.2±4	35.7±7	32.5±6.0

There were 1253 ACM events over mean 8.3yrs of follow-up.



Conclusions: In NHANES participants with CKD, intentional weight loss does not associate with lower risk of ACM; however, unintentional weight associates with increased risk.

FR-PO781

Coffee, Tea, Caffeine and Risk of End Stage Renal Disease Quan Lan J. Lew,[1] Tazeen H. Jafar,[2] Jin Ai Zhen,[3] Khuan Yew Chow,[3] Woon-Puay Koh.[2] *[1]Singhealth Polyclinic, Singhealth Polyclinic, Asian, Singapore; [2]Duke-NUS Medical School; [3]Health Promotion Board, Singapore.*

Background: Previous studies have reported increased estimated glomerular filtration rate with coffee drinking, but no study has examined the relationship with end stage renal disease (ESRD) risk.

Methods: We examined the relationship between coffee, tea and caffeine consumption, and ESRD incidence in the Singapore Chinese Health study, a prospective cohort of 63,257 men and women aged 45-74 years during recruitment (1993-1998). Baseline information on consumption of caffeinated beverages, dietary and lifestyle factors were collected via in-person interviews. ESRD incidence was linked with the Singapore Renal Registry.

Results: After average 16.8 years, 1,143 incident ESRD cases were identified. Compared with <1 cup/day, regular coffee consumption reduced ESRD risk, the adjusted hazard ratio (HR) (95% CI) was 0.91 (0.79-1.05) for 1 cup/day and 0.82 (95% CI: 0.71-0.96) for >2 cups/day, P_{trend}=0.012. In men, the HR (95% CI) was 0.81 (0.66-1.00) for 1 cup/day and 0.71 (0.57-0.87) for >2 cups/day (P_{trend}=0.001). In contrast, in women, the results were 1.01 (0.83-1.21) for 1 cup/day and 0.97 (0.78-1.19) for >2 cups/day (P_{trend}=0.75); $P_{interaction}$=0.026. No association was observed with caffeinated tea or soda. The weak association between caffeine consumption and ESRD risk was nullified after adjusting for coffee. Results limited to participants with >4 years follow-up were similar.

Conclusions: Daily drinking of two or more cups of coffee may reduce ESRD risk, and this effect is not mediated by the caffeine content. The much stronger association in men suggests that the effect of coffee may be mediated via estrogen-receptors and is more apparent in estrogen deficiency.

Funding: Other NIH Support - National Institutes of Health, USA (R01 CA144034 and UM1 CA182876

FR-PO782

Prevalence of Medication Non-Adherence and Factors Affecting It in Patients of Chronic Kidney Disease at a Tertiary Care Public Teaching Hospital: A Cross Sectional Study Sanjay D'Cruz,[1] Rajiv Ahlawat,[2] Pramil Tiwari.[2] *[1]General Medicine, GMCH, Chandigarh, India; [2]Pharmacy Practice, NIPER, SAS Nagar, Punjab, India.*

Background: Medication non-adherence in CKD patients leads to adverse outcomes. The two important factors leading to non-adherence to medications are inability to afford the treatment and poor knowledge of the patient. The present study was carried out to study the prevalence of medication non-adherence and the factors influencing it in patients of CKD.

Methods: A cross sectional study was carried out in 600 CKD patients over a period of 20 months from Sept 2014 to April 2016 at our tertiary care hospital. CKD definition of the KDIGO was used. The proportion of days covered (PDC=total days all drug(s) available/days in follow-up period) algorithm was used to assess medication adherence in CKD patients. PDC varies between 0 and 1; and it can be converted to percentages. PDC value over 80% is considered adherent. Multivariate logistic regression was used to analyse factors affecting medication compliance.

Results: Out of 600 patients, 69% were non-adherent to prescription. Forgetfulness in 30% was found to be most common reason for non-adherence to drug therapy. It was followed by high cost of medications (21%), casual attitude (15%), lack of information (12%) and others in 22%. Medication non-adherence was found highest towards antihypertensive drugs (27%) followed by oral hypoglycemic drugs (21%), insulin (19%), iron injection (11%) and others in 23%. Non-adherence to drug therapy was found significantly higher with pill burden over 5 (OR 1.32,95% CI 0.84-3.12; P=0.043), medication by caregivers (OR 2.04, 95% CI 0.93-6.83; P=0.021), age > 60 (OR 2.17, 95% CI 1.06-3.21; P=0.047), illiteracy (OR 3.43, 95% CI 1.43-6.65; P=0.035) and lack of reimbursement (OR 2.17, 95% CI 1.31-3.26; P=0.012). Gender, dialysis, GFR, and duration of CKD did not have any influence on adherence.

Conclusions: 69%of patients were found non-adherent to drug therapy. Medication adherence was found to decrease with increased pill burden, drugs given by caregiver, increased age, lack of reimbursement and illiteracy.

FR-PO783

Effectiveness of Multifaceted Care Approach on Adverse Clinical Outcomes in Non-Diabetic CKD: A Systematic Review and Meta-Analysis Aminu K. Bello,[1] Bilal Qarni,[1] Arian Samimi,[1] Julius Oluoch Okel,[1] Trish Chatterley,[2] Branko Braam.[1] *[1]Medicine, Univ of Alberta; [2]Library Sciences, Univ of Alberta.*

Background: The impact of multifaceted interventions as compared to the usual care (ie. single risk factor control) in patients with non-diabetic CKD is unclear. We reviewed the evidence on the impact of multiple interventions on reducing adverse clinical outcomes in non-diabetic patients with CKD.

Methods: We searched MEDLINE, EMBASE, CINAHL and the Cochrane Library databases for published studies up to May 2016 on adult patients in a community or specialty care setting, with >2 CKD risk factors, treated with a combination of two or more interventions. We included randomized controlled trials (RCTs) and observational studies with at least 100 participants. The intervention of interest was treatment with a combination of two or more interventions compared to the usual care. The primary outcomes were reduction in the risk of adverse events (renal replacement therapy; RRT, all-cause hospitalizations, all-cause and cardiovascular mortality). Secondary outcomes were optimal risk factor control (blood pressure, proteinuria, smoking cessation).

Results: We identified 5 studies (2 RCTs and 3 cohort studies). In comparison to the usual care, multifaceted interventions were associated with a lower risk of all-cause mortality: (Risk ratio; [RR] 0.81, 95% confidence interval [CI] (0.63-1.03) and progression to kidney failure requiring dialysis- RR (95% CI): 0.57 (0.35-0.94). Multifaceted interventions did not impact risk of all-cause hospitalization- RR (95% CI): 0.93 (0.71-1.23) and blood pressure control- mean difference (95% CI): -0.48 (-2.5 to 1.55). Only a small number of studies met inclusion criteria. Heterogeneity, small sample sizes, and suboptimal study quality hampered the internal validity and generalizability.

Conclusions: Multifaceted interventions targeting multiple risk factors appeared to reduce the risk for major adverse clinical outcomes in patients with CKD. There is a need for high quality studies that can rigorously evaluate a set of interventions targeting multiple domains of CKD management in the population with non-diabetic CKD.

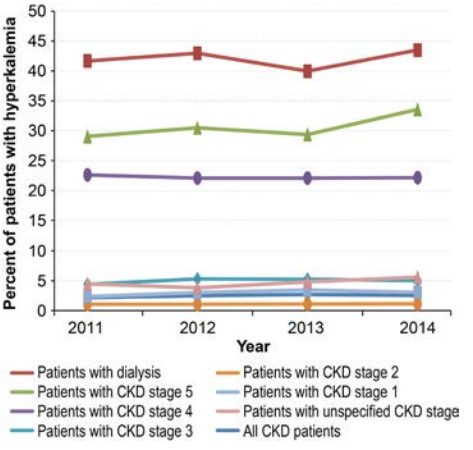
FR-PO784

Prevalence of Hyperkalemia among Patients with Chronic Kidney Disease Keith Betts,[1] J. Michael Woolley,[2] Fan Mu,[1] Evangeline McDonald,[1] Wenxi Tang,[1] Eric Wu.[1] *[1]Analysis Group, Inc., Boston, MA; [2]ZS Pharma, San Mateo, CA.*

Background: There are limited published data on the epidemiology of hyperkalemia among patients with chronic kidney disease (CKD). This study estimated the prevalence of hyperkalemia among patients with CKD.

Methods: Adult patients with CKD were selected from a large US commercial claims database (01/01/2011-12/31/2014). CKD and CKD stage were identified by ICD-9 diagnosis codes or estimated by glomerular filtration rate. Dialysis was identified by procedure codes. Patients were required to have at least one calendar year of data with continuous enrollment throughout the year and at least one potassium lab result. Hyperkalemia was defined as having at least two serum potassium measurements >5.0 mEq/L or one diagnosis code of hyperkalemia (ICD-9, 276.7) or one prescription fill of a sodium polystyrene sulfonate. Prevalence of hyperkalemia for each calendar year (2011-2014) was calculated as the number of patients with hyperkalemia divided by the total number of eligible patients within the year.

Results: A total of 847,604 CKD patients were included in the analysis. Among all CKD patients, the prevalence of hyperkalemia ranged from 2.2% to 2.7% across calendar years (Figure 1). When stratified by CKD stage, the prevalence of hyperkalemia across calendar years ranged from 40.0% to 43.5% among patients on dialysis, 29.0% to 33.6% for stage 5, 22.1% to 22.6% for stage 4, 4.4% to 5.3% for stage 3, 1.0% to 1.1% for stage 2, 2.3% to 3.4% for stage 1. Among patients with unspecified CKD stage, the prevalence ranged from 3.8% to 5.6%. Figure 1. Prevalence of Hyperkalemia Among Patients with CKD.



Conclusions: The study provided estimates of prevalence of hyperkalemia among CKD patients, stratified by CKD stages across different calendar years. Hyperkalemia is common among CKD patients, and its prevalence generally increased at more advanced CKD stages.

Funding: Pharmaceutical Company Support - ZS Pharma

FR-PO785

Cost of Hyperkalemia in Patients with Chronic Kidney Disease Keith Betts,[1] J. Michael Woolley,[2] Fan Mu,[1] Cheryl Q. Xiang,[1] Wenxi Tang,[1] Eric Wu.[1] *[1]Analysis Group, Inc.; [2]ZS Pharma.*

Background: Healthcare costs in patients with hyperkalemia (HK) have not been well characterized. This study estimated the healthcare costs of HK in patients with chronic kidney disease (CKD).

Methods: Adult patients with CKD, with or without HK (cases vs. controls), were selected from a large US commercial claims database (1/1/2010-12/31/2014). Patients were required to have serum potassium lab results. CKD was identified by ICD-9 diagnosis codes or estimated glomerular filtration rate. Dialysis was identified by procedure codes. HK was defined as having at least two serum potassium measurements >5.0 mEq/L or one diagnosis code of HK (ICD-9, 276.7) or one prescription of sodium polystyrene sulfonate. The index date was a randomly selected claim date indicating HK for cases and a randomly selected claim date for controls. Continuous enrollment of at least 6 months before the index date and 12 months after the index date was required. Controls were exactly matched one-to-one to cases on age group, CKD stage, heart failure, and Renin-Angiotensin-Aldosterone-System inhibitor use. 30-day and 1-year total healthcare costs (2015 USD) from the third-party perspective were compared between cases and controls.

Results: A total of 14,689 CKD patients with HK were matched to 14,689 CKD patients without HK. Among all CKD patients, cases had $4,379 higher 30-day costs ($7,241 vs. $2,862) and $19,589 higher 1-year costs than controls ($45,172 vs. $25,583) (both p<0.01). The 30-day cost difference was $6,983 between cases and controls in patients on dialysis, $9,685 for CKD stage 5, $3,730 for CKD stage 4, $3,880 for CKD stage 3, $3,113 for CKD stage 2, $3,075 for CKD stage 1 and $6,706 for unspecified CKD stage (all p<0.01, except for stage 1). The 1-year cost difference was $25,097 in patients on dialysis, $52,795 for CKD stage 5, $16,736 for CKD stage 4, $16,474 for CKD stage 3, $13,964 for CKD stage 2, $6,072 for CKD stage 1 and $27,459 for unspecified CKD stage (all p<0.01, except for stage 1).

Conclusions: Patients with HK had higher healthcare costs across all CKD stages, with generally higher costs in more advanced disease, supporting the hypothesis that HK imposes a large economic burden on US payers and the healthcare system.

Funding: Pharmaceutical Company Support - ZS Pharma

FR-PO786

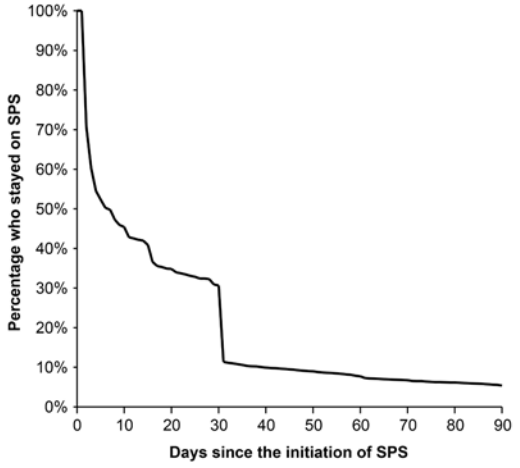
Real-World Treatment Discontinuation of Sodium Polystyrene Sulfonate

Keith Betts,[1] J. Michael Woolley,[2] Lihao Chu,[1] Fan Mu,[1] Wenxi Tang,[1] Eric Wu.[1]
[1]Analysis Group, Inc., Boston, MA; [2]ZS Pharma, San Mateo, CA.

Background: Sodium polystyrene sulfonate (SPS) has been studied in the context of clinical trials, but there is limited information regarding SPS treatment patterns in the real-world. This study describes the persistence of SPS treatment over time.

Methods: Adult patients who had at least one SPS prescription fill were identified from a large US commercial claims database (01/01/2010-12/31/2014). Patients were required to have at least 31 days of continuous enrollment post SPS prescription fill. SPS discontinuation was defined as having no subsequent SPS prescription refills within 30 days after the end of days of supply of their previous SPS prescription. Patients who did not discontinue SPS treatment were censored at the end of their continuous eligibility. SPS discontinuation was evaluated using the Kaplan-Meier estimator.

Results: A total of 4,559 patients initiated SPS therapy and met the eligibility criteria. Among these patients, the average number of SPS fills was 2.3 and the median time to discontinuation of SPS was 7 days (Figure 1). 49.8% of patients remained persistent with SPS through 7 days, 42.0% through 14 days, 30.7% through 30 days, 7.7% through 60 days, and 5.4% through 90 days, and 2.6% of patients were censored (not observed to discontinue). Figure 1. Kaplan-Meier curve of SPS persistence.



Conclusions: Patient persistence with SPS treatment was low, as the majority of patients discontinued treatment within 7 days and less than 10% remained persistent through 60 days.

Funding: Pharmaceutical Company Support - ZS Pharma

FR-PO787

No Association of Serum Potassium Level with Mortality in Patients with Optimized Chronic Kidney Disease Care - The NephroTest Study

Sandra Wagner,[1,2] Marie Metzger,[1] Martin Flamant,[3] Pascal Houillier,[4,5] Jean-Philippe Haymann,[6] Francois Vrtovsnik,[3] Eric Thervet,[5,7] Jean-Jacques Boffa,[6] Ziad Massy,[1,2] Benedicte Stengel,[1,2] Patrick Rossignol.[2,8]
[1]INSERM U1018, Villejuif, France; [2]F-CRIN INI-CRCT; [3]Bichat APHP; [4]INSERM U1138; [5]HEGP APHP; [6]Tenon APHP; [7]INSERM UMRS970; [8]INSERM CIC 1433, Nancy, France.

Background: Low and high serum potassium (S_K) values are often associated with chronic kidney disease (CKD) or its treatments, and with poor outcomes, but their prognostic value in patients with optimized CKD care is uncertain.

Methods: We studied the prevalence of hypokalemia (hypoK) (<4 mmol/L) and hyperK (>5 mmol/L) in 1993 nondialysis patients with stage 1 to 5 CKD who underwent extensive renal tests during a 5-h in person visit (mean age: 59±15 yrs, 66% men). All had baseline S_K and GFR measurements (mGFR; ^{51}Cr-EDTA renal clearance) and 60% at least two. Cox models were used to estimate adjusted hazard ratios (HRs) of end-stage kidney disease (ESKD) and mortality prior to ESKD associated with baseline and time-dependent S_K levels.

Results: At baseline, median mGFR was 38.4 ml/min/1.73m² (IQR, 26.9-53.0); prevalence of hypoK was 26% (3.9% for Sk<3.5), and of hyperK, 6.4%; ACEi or ARBs was used in 77% of patients, thiazide or loop diuretics in 48%, potassium-sparing diuretics in 4%, K-binding resins in 6%, bicarbonates in 4%. At the initial and 2nd visits, 67.1% and 63.9% of the patients were normokalemic. After excluding 94 patients with stage 5 CKD at baseline, there were 376 ESKD events and 219 deaths prior to ESKD (36% from CV cause) over a median follow-up of 5 years. As compared to patients with S_K within [4-5] mmol/L, HRs [95%IC] of ESKD, all-cause and CV mortality prior to ESKD for those with hypoK were 1.32[0.99,1.76], 0.73[0.5,1.06] and 0.73[0.31,1.7], and for those with hyperK, 1.08[0.78,1.51], 0.70[0.39,1.27] and 1.59[0.63, 4.0], respectively. Considering time-varying S_K did not materially change these findings.

Conclusions: In this cohort of patients with optimized CKD care (per cohort protocol scheduled repeated measurements of S_K, GFR, treatment review after renal tests), mild hypoK was common and hyperK uncommon. Neither of them appeared to be associated with excess ESKD or mortality.

FR-PO788

Prevalence of Hyperkalemia among U.S. Adults

J. Michael Woolley,[1] Derek Weycker,[2] Mark Atwood,[2] Gerry Oster.[2] *[1]ZS Pharma; [2]Policy Analysis Inc.*

Background: While the underlying causes and clinical consequences of hyperkalemia (HK) are well understood, relatively little is known about the epidemiology of the condition among US adults, especially persons with comorbidities that may predispose them to high potassium (K) levels.

Methods: A retrospective study was undertaken using data from the National Health and Nutrition Examination Survey (NHANES), a large, multi-year, cross-sectional, nationally representative survey of the health and nutritional status of US adults and children based on both interview and physical exam. We identified all persons in NHANES, aged ≥18 years, with valid serum K values between 1999 and 2014; observations across years were pooled to increase precision of analyses. We estimated the point prevalence of HK (serum K level ≥5.0 mEq/L) on an overall basis and within subgroups defined on the basis of age, gender, comorbidity profile, and medication use. Multivariable logistic regression was employed to evaluate the relationship between the demographic and clinical characteristics of study participants and the presence of HK.

Results: We identified a total of 42,083 persons, aged ≥18 years, with valid serum K values between 1999 and 2014. Mean (SD) age of study subjects was 46 (17) years, 52% were women, 29% had hypertension, 10% had diabetes, 7% had chronic kidney disease (CKD), and 13% were taking a RAASi. Prevalence of HK increased approximately 9-fold with age, from 278 per 100,000 persons aged 35-49 years to 2394 per 100,000 persons aged ≥75 years; on an overall basis, the rate was 564 per 100,000 persons. In multivariable analyses, age, CKD, heart failure, and use of RAASi were important predictors of HK (Table).

Conclusions: Prevalence of hyperkalemia in the US increases substantially with age, and is especially high among persons with CKD or heart failure, and those taking RAASi.

Table. Prevalence of hyperkalemia among US adults aged ≥18 years in NHANES

	Prevalence of Hyperkalemia (≥5.0 mEq/L)	
	Rate per 100,000 (95% CI)	Odds Ratios (95% CI)*
Overall	564 (482 - 646)	---
Age, years		
18-34	146 (67 - 225)	---
35-49	278 (152 - 404)	1.8 (0.9 - 3.6)
50-64	689 (469 - 909)	3.5 (1.8 - 6.6)
65-74	1,150 (800 - 1,500)	3.8 (1.9 - 7.6)
≥75	2,394 (1,935 - 2,854)	5.5 (2.7 - 10.8)
Sex		
Male	597 (480 - 714)	1.3 (0.9 - 1.7)
Female	533 (417 - 648)	---
Comorbidities		
Chronic Kidney Disease		
Yes	3,479 (2,769 - 4,190)	---
No	354 (282 - 425)	---
By Stage		
eGFR: ≥60	361 (290 - 432)	---
eGFR: ≥45 - <60	2,015 (1,297 - 2,734)	2.5 (1.6 - 4.0)
eGFR: ≥30 - <45	5,133 (3,139 - 7,127)	5.4 (3.0 - 9.8)
eGFR: ≥15 - <30	11,459 (7,110 - 15,808)	13.0 (7.4 - 23.0)
eGFR: <15	22,075 (10,003 - 34,147)	45.3 (21.5 - 95.1)
Heart Failure		
Yes	3,387 (2,192 - 4,581)	1.5 (0.9 - 2.4)
No	498 (419 - 578)	---
Hypertension		
Yes	1,101 (902 - 1,300)	1.0 (0.7 - 1.3)
No	347 (264 - 430)	---
Diabetes		
Yes	1,451 (1,057 - 1,844)	1.1 (0.8 - 1.5)
No	461 (381 - 541)	---
Medication Use		
RAASi		
Yes	1,733 (1,337 - 2,129)	1.9 (1.3 - 2.6)
No	402 (327 - 478)	---

*Based on multivariate logistic regression regressing presence of hyperkalemia on age, sex, comorbidity profile, and use of renin inhibitors

Funding: Pharmaceutical Company Support - ZS Pharma

FR-PO789

Higher Phosphorus Is Associated with Lower Hemoglobin in CKD Stages 3-5: Early Results from the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps)

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Background: High phosphorus (P) and low vitamin D levels, typical manifestations of mineral and bone disorder (MBD), are common in patients with advanced CKD. MBD has been associated with increased inflammation, which may affect normal erythropoiesis. In order to better understand the link between phosphorus and hemoglobin (Hb) levels, we tested this association in the international CKDopps.

Methods: We evaluated early data from CKDopps, a prospective study of CKD patients with eGFR <60 mL/min/1.73m² from national samples of nephrology clinics in Brazil, France, Germany, and US. Linear mixed models were used to estimate the effect of P on hemoglobin (Hb), with different levels of adjustment for potential confounders and mechanistic variables.

Results: Data were available from 5,040 patients (mean age: 69 years; 40% female; median eGFR: 28.8 mL/min/1.73m²). eGFR was associated positively with Hb and inversely with P. Higher serum P was strongly associated with lower Hb even after adjustment for demographics, comorbidities, eGFR, labs, and vitamin D therapy (Table 1).

Table 1. Associations of serum phosphorus (per 1 mg/dL higher) with hemoglobin level, by level of adjustment

	Effect (95% CI) on Hb(g/dL) per 1 mg/dL higher serum P
Model 1	-0.64 (-0.70, -0.58)
Model 2	-0.39 (-0.45, -0.33)
Model 3	-0.36 (-0.42, -0.30)
Model 4	-0.36 (-0.42, -0.30)

Model 1 : adjust for age, gender, black, BMI, diabetes, hypertension, country
Model 2: Model 1 + eGFR
Model 3: Model 2 + albumin
Model 4: Model 3 + PTH + Vit D levels + Vit D therapy

Conclusions: In this multinational CKD cohort, higher P was associated with lower Hb, independent of kidney function and other MBD markers/treatments. Further studies will need to explore the possible mechanisms (inflammatory, endocrine) for this association and may generate important advances in the management of both anemia and MBD.

Funding: Pharmaceutical Company Support - AbbVie, Amgen, Baxter Healthcare, F. Hoffmann-LaRoche, Hexal, Keryx, Kyowa Hakko Kirin, Merck, Proteon, Relypsa, Sanofi, Shire, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, WiNe Institute, Societies for Nephrology in Germany, Italy, & Spain

FR-PO790

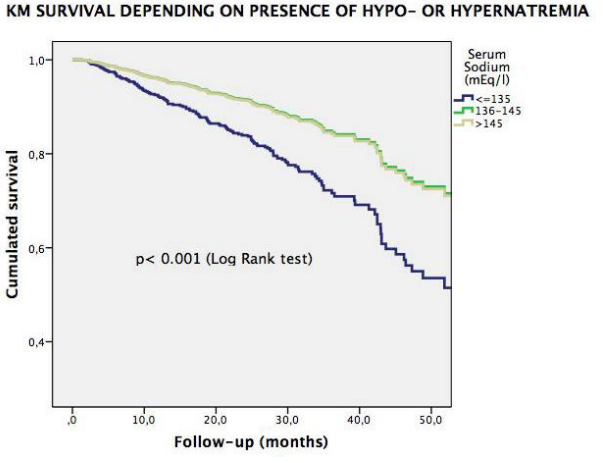
Prognostic Significance of Dysnatremia in the Survival of Chronic Kidney Disease Patients Not on Dialysis

Cristina Castro, Pablo Molina, Ana Avila, Veronica Escudero, Mercedes Gonzalez, Irina Sanchis, Jonay Pantoja Perez, Sandra Beltrán, Luis M. Pallardo, Jose L. Gorriz. *Nephrology, Hospital Univ Dr Peset, Valencia, Spain.*

Background: Patients with chronic kidney disease (CKD) show a high prevalence of comorbid conditions that could predispose to dysnatremias. The assessments of dysnatremias are scarce, being less in case of outpatients. In this study, we analyze the prevalence of dysnatremias in patients with CKD not on dialysis and its effect on survival and renal progression.

Methods: Post-hoc analysis of PECERA study(a 3-year follow-up prospective observational multicenter study, in Spanish Nephrology clinics), which included 882 patients, CKD stages 4-5 not on dialysis: 61,6% male, mean age:68±13 years. Baseline data: serum creatinine:3.1±1.1mg/dl; estimated glomerular filtration rate (eGFR) (MDRD):20±5ml/min/1.73m2. Mean follow-up:47±30 months.

Results: The prevalence of hyponatremia was 4.1% and hypernatremia 9.6% The univariate analysis found no differences in age, BMI, GFR, presence of liver disease or use of diuretic therapy among those with hyponatremia and normonatremia. The history of congestive heart failure (CHF)(p=0.034) and proteinuria (p=0.038) were more prevalent in patients with hyponatremia. After adjustment for age, sex, eGFR, CHF, diuretics, phosphatemia and serum albumin, the presence of hyponatremia was independently associated with worse survival (HR 1.97,95% CI:1.06-3.67;p=0.033)



Hypernatremia was not associated with increased mortality rate (p=0.862). In the multivariate analysis, dysnatremia was not associated with renal progression (p=0.219) nor hospitalization (p=0.739).

Conclusions: In patients with CKD not on dialysis, abnormalities water homeostasis, manifested as hypo- or hypernatremia, are common clinical findings. Hyponatremia was independently associated with an increased mortality, whereas hypernatremia is not associated with poor prognosis.

FR-PO791

Impact of Pill Burden on Adherence and Patient-Reported Quality of Life - An Analysis of a Real-World Non-Dialysis Chronic Kidney Disease Patient Population

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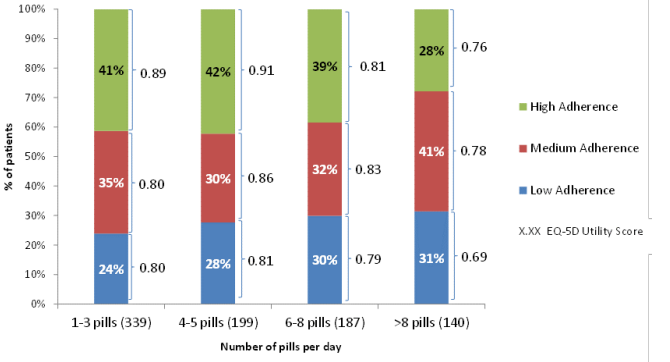
Background: Pill burden is a common problem facing Chronic Kidney Disease (CKD) patients trying to manage complications caused by their CKD. The objective of this analysis is to determine if there is a link between increased pill burden and poorer adherence and whether this has an additional impact on patient quality of life (QoL).

Methods: Data were drawn from the Adelphi CKD Disease Specific Programme (DSP), a real-world, cross-sectional survey of consulting CKD patients conducted between July-October 2015 in the US and 5EU. Patients were grouped into those reporting to take 1-3, 4-5, 6-8 and >8 pills per day in total and descriptively analysed. Adherence was assessed using the Morisky Medication Adherence scale (MMAS-8) and QoL was a measured using the EuroQol-5D-3L (EQ-5D).

Results: Results from 865 non-dialysis CKD (stage 3-4) patient-completed questionnaires showed an increase in polypharmacy was associated with an increase in the proportion of patients with low adherence (24% among patients taking 1-3 pills rising to 31% among those taking >8 pills per day (figure 1). A clinically significant reduction was observed in the mean EQ-5D score for patients taking >8 pills per day compared with those taking 1-3,4-5 or 6-8 pills per day (figure 1). Patients with high adherence consistently reported higher EQ-5D scores, regardless of pill burden (figure 1).

Figure 1. MMAS-8 and associated EQ-5D scores for non-dialysis CKD patients receiving daily oral therapy



Conclusions: Increased polypharmacy has a negative impact on patient adherence. Low adherence is associated with a poorer quality of life compared with patients who have high adherence. Physicians should therefore aim to prescribe drug regimens with a lower pill count as this could lead to an increase in patient adherence and improved patient outcomes.

FR-PO792

Barriers to Dietary Adherence in Chronic Kidney Disease

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Background: Dietary restriction is essential to multidisciplinary chronic kidney disease (CKD) care. Barriers to dietary adherence are poorly understood.

Methods: English and Spanish speaking patients with Stage 4 and 5 CKD were enrolled in a cross sectional study and completed 1) a Short Assessment of Health Literacy (SAHL) screen, 2) Newest Vital Sign (NVS), a numeracy screen, 3) a survey evaluating barriers to adherence, 4) a food frequency questionnaire (FFQ), and 5) a knowledge assessment of high potassium and phosphorus foods.

Results: The majority of patients (37/52, 71%) had limited health literacy and numeracy defined as a SAHL score of ≤ 8 or a NVS score ≤ 3. These patients were more likely to be older (p=.006), Hispanic (p=.014), have lower educational attainment (p=.003), and primarily Spanish speaking (p=.009). Most patients (81%) reported receiving dietary counseling. Patients who received counseling were more likely to report changing their diet since CKD diagnosis (p=.024) and improved compliance with kidney dietary restrictions (p=.002). Dietary sodium, potassium, phosphorus and protein intake as measured by the FFQ was not different among patients with and without limited literacy and numeracy, or patients who did and did not receive dietary counseling. In the total cohort, the mean number of correct answers in identifying the four high potassium and four high phosphorus foods was 2.4 and 1.5, respectively. These numbers were not different among patients with and without limited literacy and numeracy, or patients who did and did not receive dietary counseling.

Conclusions: Limited health literacy and numeracy is common among patients with CKD 4 and 5 but there was no difference in dietary intake of restricted nutrients, or knowledge of restricted foods in subjects with and without limited literacy and numeracy. Dietary counseling did not result in better knowledge of restricted foods or differences in intake of restricted nutrients. Methods to improve the efficacy of dietary counseling need to be explored further.

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FR-PO793

Pharmacological Treatment for Chronic Kidney Disease (CKD) and Associated Outcomes in Medicare Part D Enrollees

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Background: Few studies have assessed the effects of different pharmacological treatment regimens in hypertensive CKD patients. This study aimed to assess the effects of monotherapy with ACEIs/ARBs versus the combination therapies of ACEIs/ARBs plus other blood pressure/ lipid lowering agents among Medicare Part D enrollees with hypertension and CKD in the United States.

Methods: We used the Medicare 5% sample claim data (2006-2013) in this retrospective cohort study. Eligible cases were hypertensive patients newly diagnosed with CKD and continuously enrolled in Medicare Part D from 2008-2013. Pharmacologic therapies were assessed using a 3-month period after the date of the first CKD diagnosis. Multivariate Cox proportional hazards regression was used to assess effects of different pharmacologic therapies on progression to end stage renal disease (ESRD) and death.

Results: About 44% of CKD patients used ACEIs/ARBs within three months after the diagnosis of CKD. Compared to therapies without ACEIs/ARBs, combination therapy of ACEIs/ARBs plus statins showed the largest beneficial effect on reducing the risk for ESRD (HR: 0.53, p<0.0001). Combination of statins, ACEIs/ARBs, and other concomitant antihypertensive agents was most significantly associated with reducing the risk for all-cause mortality (HR: 0.45, p<0.0001).

Table 1.1 Descriptive Statistics of individual characteristics among elderly patients with hypertension and incident chronic kidney disease (CKD) by status of ACEIs/ARRs use (n=66,315)*#

Variable	*ACEIs/ARBs user (n=29,280)*		*non-ACEIs/ARBs user (n=37,035)*		*All(n=66,315)*	
Baseline characteristics	***Mean/%***	***SD***	***Mean/***	***SD***	***Mean/%***	***SD***
Age (yrs)	78.3	7.1	80.3	7.5	79.4	7.4
<70	13.5		9.8		11.5	
70-75	23.8		18.6		20.9	
75-80	23.4		20.9		22	
>80	39.3		50.7		45.7	
Charlson Index $	1	1.6	1.3	1.7	1.2	1.7
Male	37.6		38.8		38.3	
Race						
While	87.1		87.9		87.6	
Black	9.5		9		9.2	
Asians	1.6		1.5		1.6	
Others	1.7		1.4		1.5	
Unknown	0.1		0.1		0.1	
Prescription coverage at baseline						
Part D without LIS	64.5		62.9		63.6	
Part D with non-deemed L	2.3		2		2.1	
Part D with deemed LIS	33.2		35.1		34.3	
Diabetes mellitus (DM)	42.7		34.1		37.9	
Cardiovascular Comorbidities and Procedures ^						
ASHD	45.2		44.5		44.8	
AMI	9.6		9		9.3	
CHF	26.8		28.5		27.7	
CVA-TIA	27.1		29.6		28.5	
PAD	31.7		35.2		33.6	
AFIB	18.1		21.1		19.8	
SCA/VA	4.6		4.7		4.6	
Other Cardiovascular diseases	41.7		41.8		41.7	
PCI	3.3		2.5		2.8	
CABG	0.8		0.8		0.8	
ICD/CRT-D	0.6		0.5		0.5	
Medication-related characteristics &						
ACEIs/ARBs window categories						
none	NA		37.22		20.79	
using after CKD diagnosis	5.06		9.69		7.65	
using before CKD	94.94		53.09		71.57	
Other common medications						
Statins user	77.19		43.22		35.96	
Calcium channel blockers	49.96		24.9		20.51	
Beta blockers user	28.51		14.19		37.62	
Diuretics user	48.59		28.95		24.98	
Anti-hypertension agents user	38.19		14.53		58.22	
Pharmacologic Therapeutic strategies						
None	NA		49.18		27.47	
Statins only	NA		7.6		4.24	
Anti-hypertension agents only	NA		25.91		14.47	
ACEIs/ARBs only	13.08		NA		5.78	
Anti-hypertension agents+Statins	NA		17.31		9.67	
ACEIs/ARBs+Statins	9.73		NA		4.3	
ACEIs/ARBs +Anti-hypertension agents	36.96		NA		16.32	
ACEIs/ARBs +Anti-hypertension	40.22		NA		17.76	
Follow-up characteristics						
Follow-up period (yrs)	5	1.5	4.1	2	4.5	1.8
Died	40.8		63.3		53.4	
End Stage Renal Disease (ESRD)	1.1		0.9		1	

Medication use was defined as having at least one pharmacy claim within each pharmacologic therapy during a three-month period after the date of first diagnosis of CKD

* Continuously enrolled in Medicare A&B from 2006/1/1 and continuously enrolled in Medicare Part D from 2007 to end of 2013/date of death were required. A two-year look-back period was applied (2006-2007) to evaluate baseline characteristics, and a one-year look-back period (2007) was used to examine medication use history.

$ Adapted Charlson comorbidity index was calculated by excluding diabetes, kidney diseases and cardiovascular diseases

^ Abbreviations: ASHD, atherosclerotic heart disease; AMI, acute myocardial infarction; CHF, congestive heart failure; CVA/TIA, cerebrovascular accident/transient ischemic attack; PAD, peripheral arterial disease; AFIB, atrial fibrillation; SCA/VA, sudden cardiac arrest and ventricular arrhythmias; PCI, percutaneous coronary interventions; CABG, coronary artery bypass grafting; ICD/CRT-D, implantable cardioverter defibrillators/cardiac resynchronization therapy with defibrillator devices.

& ACEIS/ARBs window is defined as time distance between first observed date of refilling ACEIs/ARBs and first observed date of CKD diagnosis. Anti-hypertension agents user defined as having any pharmacy claim of calcium channel blockers, beta blockers or diuretics.

Conclusions: Therapies including ACEIs/ARBs were preferred as initiation therapy in hypertensive CKD Medicare patients more than non-ACEIs/ARBs therapies. Combination therapies of ACEIs/ARBs and statins were associated with reduced risk of ESRD, while treatment regimens including ACEIs/ARBs plus statins and other antihypertensive agents were associated with decreased risk of death. These findings may provide additional evidence for the effectiveness of treatment regimens including ACEIs/ARBs in treating elderly patients with hypertension and CKD.

Funding: NIDDK Support

FR-PO794

Intake of Proton Pump Inhibitors Is a Significant Risk Factor for Bacterial Pneumonia in CKD Patients

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Background: CKD is a well-known risk factor for cardio- and cerebrovascular diseases, thus many of CKD patients are treated with oral antiplatelet agents together with proton pump inhibitors (PPIs). Recently, an association between the intake of PPIs and pneumonia has received a good deal of attention, particularly among the elderly. In this study, therefore, we investigated whether PPI intake increases the incidence of pneumonia in CKD patients.

Methods: The study was designed as a single center, observational and longitudinal study. Subjects consisted of patients with renal insufficiency equal to or more than CKD stage G3a, who had visited our outpatient clinic. Multivariable logistic-regression models were employed to estimate the risk of hospitalization due to bacterial pneumonia. Independent variables included age, gender, serum albumin, the presence of diabetes mellitus, and the administration of immunosuppressants, statins, PPIs, and H2-receptor blockers (H2RB).

Results: A total of 410 CKD patients were enrolled. Mean age was 60.0 ± 13.1 years, mean estimated GFR was 34.1 ± 16.0 ml/min/1.73^2, and rates of PPI and H2RB intake were 18.0% and 17.8%, respectively. Adjusted odds ratio (aOR) of PPI and H2RB were 7.81 (p<0.01) and 1.01 (p=0.99), respectively. Intake of PPIs was found to be a significant risk factor for hospitalization due to bacterial pneumonia. Additionally, lower serum albumin, the presence of diabetes mellitus, and the administration of immunosuppressants were also significant risk factors, while intake of statin decreased the incidence of pneumonia (aOR 0.28, p=0.04).

Conclusions: Intake of PPIs was a marked risk factor for pneumonia. Since there was a significant difference in the incidence of pneumonia between patients receiving PPIs and those receiving H2RBs, mechanisms unique to PPIs, such as their effect on the pH of respiratory secretions, likely contribute to the episodes of pneumonia. We should, therefore, pay attention to the deterioration of defense mechanisms against bacterial infection in CKD patients when we prescribe PPIs with or without antiplatelet agents.

FR-PO795

Increased Urinary Angiotensinogen in CKD Patients with High Salt Diet and Hypertension

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Background: Urinary angiotensinogen is known to be related with intra-renal renin-angiotensin system (RAS) activity. High sodium diet is associated with volume expansion and hypertension. Increased RAS activity is suggested as its common pathomechanism of hypertension. We investigate the clinical determinant of urine angiotensinogen and determine the relationship between high salt intake and increased urinary angiotensinogen in patients with high blood pressure.

Methods: In total, 969 CKD patients were included and divided into four groups according to quartile of their 24hr - urine sodium excretion to creatinine ratio and 24-hr urine sodium-to-creatinine ratio (24HUNa/Cr): The urine angiotensinogen-to-creatinine ratio (UAGT/Cr) was specifically assayed with a commercially available enzyme-linked immunosorbent assay kit.

Results: Urine angiotensinogen was significantly higher in patients with increased 24hr - urine sodium excretion to creatinine ratio. Univariate linear regression analysis showed that the urine angiotensinogen concentrations were correlated with systolic blood pressure, the albumin-to-creatinine ratio, and 24-hr urine sodium-to-creatinine ratio. Whereas they were negatively correlated with waist hip ratio, the estimated glomerular filtration rate, serum albumin and hemoglobin levels and 24-hr urine potassium-to-creatinine ratio. Multiple regression analysis revealed that 24-hr urine sodium-to-creatinine ratio, the estimated glomerular filtration rate and waist hip ratio were independently associated with the logarithm of urine angiotensinogen levels (r = 0.35, p =0.021).

Conclusions: Urine angiotensinogen concentrations are higher in patients with increasing 24hr - urine sodium excretion to creatinine ratio. In a group of 4th quartile systolic blood pressure and 4th quartile 24h urine-sodium excretion to creatinine ratio, the level of urine angiotensinogen was highest in a total cohort study. Urine angiotensinogen was significantly independent determinant in high blood pressure concomitant with high salt diet after adjusting other clinical factors in CKD patients.

FR-PO796

Detection of Early Nephropathy and Risk Factors in Patients with Essential Hypertension in the Primary Health Care Jorge Lopez-Leal, Laura Cortes-Sanabria, Edgar U. Tellez-Agraz, Roxana Marquez-Herrera, Maria Alejandra Guzman, Alfonso M. Cueto-Manzano. *Unidad Investigacion Medica en Enfermedades Renales, IMSS, Guadalajara, Mexico.*

Background: Hypertension (HTN) is the second most common cause of ESRD. There is scarce information about prevalence of early nephropathy (EN) in patients with essential HTN. **Aim:** To determine the prevalence of EN and associated risk factors in patients with essential HTN of 9 primary health care units (PHC) in Guadalajara.

Methods: Cross-sectional study in patients with essential HTN, ≥18 yrs, any HTN vintage. Patients with transient albuminuria, diabetes, secondary HTN, other CKD causes and previously known CKD were excluded. Sociodemographic, clinical and biochemical data were collected. Albuminuria/Creatinuria ratio (ACR) in a first void urine sample and eGFR (CKD-EPI) were determined. Kidney function was classified (KDIGO) as normal (NF): eGFR ≥90mL/min/1.73m^2 and ACR <30mg/g; EN: CKD stages 1 and 2, and overt nephropathy (ON) stage ≥3.

Results: Prevalence of CKD was 18% (6% EN and 12% ON). Main results are shown in the table.

Variable	NF (N871)	EN (N66)	ON (N125)
Age *yrs*	59±11	62±14	69±11[ab]
Male sex *N(%)*	267(31)	29(44)[a]	56(45)[a]
Smoking *N(%)*	222(25)	20(30)	43(34)
<6 school yrs *N(%)*	503(58)	43(65)[a]	90(72)[a]
Systolic blood pressure *mmHg*	131±16	135±17	137±20[a]
HTN vintage *yrs*	7(3-14)	9(4-12)	10(5-17)
>140/90 mmHg *N(%)*	330(38)	34(51)[a]	63(50)[a]
Body mass index *kg/m^2*	30±5	30±6	29±5
Antihypertensives *N(%)*	1.5±0.7	1.5±0.7	1.7±0.7[ab]
ACE inhibitors *N(%)*	488(56)	40 (61)	66(53)
Uric acid *mg/dL*	5.4±1.1	5.6±1.4	6.4±1.3[ab]
Creatinine *mg/dL*	0.80±0.16	0.82±0.20	1.32±0.49[ab]
eGFR *mL/min/1.73m^2*	88±14	88±14	47±10[ab]
ACR *mg/g*	7(3-12)	51(34-117)[a]	8(1-20)
[a]p<0.05 vs NF, [b]p<0.05 vs EN			

Older age (≥60 yrs) (OR 2.5, p<0.001), hyperuricemia (OR 2.1, p=0.001), uncontrolled HTN (OR 1.8, p=0.001), male (OR 1.6, p=0.007), <6 school yrs (OR 1.4, p=0.032) predicted the presence of nephropathy.

Conclusions: Overall prevalence of CKD was 18% in patients with essential HTN of the PHC. Modifiable and non-modifiable risk factors associated to nephropathy are very common in this population.

FR-PO797

The Association of Midlife Uric Acid with Kidney Function in the General Population after 26 Years of Follow-Up Anny Ros Gudmundsdottir,[1] Thor Aspelund,[2,3] Bjorn Odvar Eriksen,[4] Rafn Benediktsson,[1,5] Margret B. Andresdottir.[1,5] *[1]Faculty of Medicine, Univ of Iceland; [2]The Icelandic Heart Association, Iceland; [3]Puplic Health Sciences, Univ of Iceland; [4]Metabolic and Renal Research Group, The Arctic Univ of Norway; [5]Div of Endocrinolgy, The National Univ Hospital of Iceland; [6]Div of Nephrology, The National Univ Hospital of Iceland.*

Background: Hyperuricemia has been associated with decline in kidney function. Proving causation is a challenge because of the renal elimination of serum uric acid (SUA) in addition to the association between SUA and other metabolic factors. In this study we used inverse probability of treatment weighting (IPTW) as an approach to limit confounding.

Methods: Data from 5141 volunteers in the AGES/Reykjavik study who had been followed prospectively for a median of 26 years, were analyzed to examine the association between SUA in midlife and GFR in late life. Estimated GFR (eGFR) was calculated with CKD-EPI creatinine equation. First, a multivariable linear regression model was conducted with SUA as exposure of interest and eGFR as outcome. We adjusted for age, hypertension, erythrocyte sedimentation rate, triglycerides, glucose, BMI and $eGFR_{midlife}$. Second, a propensity score was calculated based on the variables above. IPTW was used which is based on the propensity scores. The effect on eGFR was then studied with linear regression analysis, with hyperuricemia as exposure.

Results: Average eGFR in late life was 64.6 ml/min per 1.73m^2 in men and 63.2 ml/min per 1.73m^2 in women with mean age 76.5 (±5.1) and 76.1 (±5.1), respectively. Patients with hyperuricemia were 364 in total. Results of the statistical models are shown in table:

Multiple linear regression				
	Coef. of interest	β	95% CI	P-value
Men	SUA (per 100 µmol/L)	-0.30	-1.3 to 0.71	0.6
Women	SUA (per 100 µmol/L)	-1.61	-2.6 to -0.60	0.002
IPTW				
Men	Hyperuricemia	-3.54	-4.87 to -2.22	<0.0001
Women	Hyperuricemia	-7.62	-8.77 to -6.48	<0.0001

Conclusions: Higher SUA in midlife was independently associated with lower eGFR in late life especially in women.The association was confirmed with IPTW which supports causal effect of SUA.

Funding: Private Foundation Support

FR-PO798

The Effect of Early Urate Lowering Therapy on Renal Disease Progression in Hyperuricemic Patients with Chronic Kidney Disease Sung Joon Shin,[1] Kwanghoon Lee.[2] *[1]Nephrology, Dongguk Univ Ilsan Hospital, Goyang-si, Gyeonggi-do, Korea; [2]Rheumatology, Dongguk Univ Ilsan Hospital, Goyang-si, Gyeonggi-do, Korea.*

Background: This study aimed to determine whether urate lowering therapy (ULT) could delay renal disease progression in hyperuricemic patients with chronic kidney disease (CKD) according to the baseline stage of CKD.

Methods: We retrospectively reviewed the medical records of patients who were diagnosed as stage 3 and 4 CKD and concurrent hyperuricemia (> 7.0 mg/dL for males and > 5.7 mg/dL for females) from September 2005 to October 2015. The duration of follow-up should be longer than 6 months and the duration of treatment longer than 6 months for ULT group. We defined renal disease progression as follows; decline of eGFR greater than 30% compared to the baseline value, initiation of dialysis or eGFR < 15 mL/min/1.73m^2. To determine whether the baseline stage of CKD has an impact on the effect of ULT on renal disease progression, we analyzed the association of baseline stage of CKD with renal disease progression by binary logistic regression analysis.

Results: The uric acid levels markedly decreased from baseline (from 9.2±1.9mg/dL to 7.5±3.0mg/dL, p=0.028) and the degree of decrease was significantly greater in the ULT group (-1.9±4.2 mg/dL vs. -0.6±1.8 mg/dL, p=0.037). The mean decrease of eGFR from baseline tended to be smaller in the group that achieved target uric acid level (-2.81±9.4 mL/min/1.73m^2 vs. -8.57±10.0 mL/min/1.73m^2) and the rate of renal disease progression tended to be lower in the ULT group (33.9% vs. 44.1%). Subgroup analysis showed that the benefit of ULT was most apparent in CKD patients with stage 3a. In the multivariate analysis, the baseline stage of CKD was significantly associated with renal disease progression (p for trend <0.001) and the adjusted odds ratio for renal disease progression with stage 3a as a reference was 6.5 (95% confidence interval (CI) 3.419 ~ 12.357).

Conclusions: The ULT delayed renal disease progression significantly in hyperuricemic patients with CKD. The baseline stage of CKD was an independent risk factor for renal outcomes in ULT group. So, patients with early CKD stage might gain more benefit from ULT than those with late stage.

FR-PO799

Uric Acid in Chronic Kidney Disease Patients: The Role of Villain on Inflammation Denise Mafra, Juliana Saraiva Anjos, Ana Paula Black Dreux, Ludmila F.M.F. Cardozo, José Carlos Carraro-Eduardo. *Federal Univ Fluminense.*

Background: Hyperuricemia has been suggested to be involved in progression of chronic kidney disease (CKD), inflammation and developing cardiovascular disease. However, the mechanisms by which uric acid acts have not yet been fully elucidated. Researchers have shown that uric acid induces renal inflammation via activation of NF-κB signaling. Then, uric acid might be the new mechanism that activates the NF-κB and consequently, inflammation.The aim of this study was to evaluate a possible association between uric acid plasma levels and NF-κB mRNA expression in non-dialysis CKD patients.

Methods: Thirty-seven non-dialysis CKD patients (20 men, 58.0 ± 12.3 yr, BMI 29.0 ± 6.2 kg/m^2, glomerular filtration rate 34.8±13.6mL/min/1.73m^2) were evaluated. The peripheral blood mononuclear cells (PBMC) were isolated and Quantitative Real-Time PCR analysis were performed to evaluate the expression levels of mRNA encoding NF-κB (*7500 Real-Time PCR* System, *Applied Biosystems*). Routine laboratory parameters were measured by standard techniques and body mass index (BMI) was calculated.

Results: The biochemical parameters are shown in Table 1.

Parameters	Values
Creatinine (mg/dL)	2.2 ± 0.9
Blood urea nitrogen (mg/dL)	73.9 ± 30.8
C-Reactive Protein (mg/dL)	4.9 (1.1-5.8)
Potassium (mEq/L)	4.4 ± 0.5
Albumin (mg/dL)	3.7 ± 0.4
Uric acid (mg/dL)	6.3 ± 1.3
Cholesterol (mg/dL)	170 ± 48
Triglycerides (mg/dL)	129 ± 58
LDL (mg/dL)	91.4 ± 41.9
HDL (mg/dL)	53.1 ± 17.3
NF-κB mRNA expression	0.83 (0.66 – 1.5)

Only 33% of patients presented high uric acid levels. Linear regression showed that uric acid was an independent predictor for NF-κBmRNA expression (β = 0.35, p= 0.04) after adjustment on age, gender, BMI, GFR and CPR levels.

Conclusions: The results suggest that uric acid levels, even in the normal range, are associated with increased NF-κB expression in CKD patients.

FR-PO800

Uric Acid and Disease Progression and Mortality in CKD

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Background: Various observations associate hyperuricemia (HU) with progression of CKD and mortality. We examined the association of HU with ESRD and mortality in the Cleveland Clinic CKD Registry.

Methods: We included 1,676 patients with CKD stages 3 and 4 from Ohio, without malignancy who had uric acid (UA) measurements a year prior to second eGFR<60ml/min per 1.73 m^2, and some follow up eGFR, between 2005 and 9/15/2009. We ascertained ESRD from the USRDS and mortality from the State Department of Health mortality files. We fitted Cox models of pre-ESRD mortality and competing risks model of ESRD with death as a competing risk adjusted for demographics, comorbidities, and laboratory measures including eGFR. Time-dependent uric acid lowering therapy (UALT) was adjusted on mortality models, and baseline UALT on ESRD models.

Results: 95 patients reached ESRD and 201 reached pre-ESRD death during a median follow up of 2.8 years. In the adjusted models, neither UA level nor UALT were significantly associated with mortality or ESRD.

Table 1. Associations between uric acid and UALT and pre-ESRD mortality and ESRD

	Pre-ESRD Mortality*** HR (95% CI)	ESRD* SHR (95% CI)
Model 1 (high/low UA)		
High UA (M>8, F>7) vs. low	1.15 (0.85, 1.55)	1.25 (0.76, 2.04)
UALT vs. No	0.81 (0.60, 1.09)	1.41 (0.92, 2.16)
Model 2 (Quartiles of UA)		
Q1 (1.1-5.9)	Ref	Ref
Q2 (6.0-7.3)	1.07 (0.68, 1.67)	0.52 (0.19, 1.42)
Q3 (7.4-8.8)	1.24 (0.80, 1.93)	1.59 (0.72, 3.50)
Q4 (8.9-16.6)	1.28 (0.84, 1.95)	1.43 (0.65, 3.14)
UALT vs. No	0.82 (0.61, 1.11)	1.48 (0.97, 2.24)
Model 3 (continuous UA)		
Uric Acid (per 1 mg/dL higher)	1.05 (0.98, 1.12)	1.06 (0.97, 1.16)
UALT vs. No	0.81 (0.60, 1.10)	1.39 (0.91, 2.13)

*Adjusted for age, sex, race, BMI, SBP quartiles, DM, ACEI/ARB, diuretics, eGFR
**Above variables plus log triglycerides, log cholesterol, CAD

Conclusions: In contrast to some prior reports we found no evidence that hyperuricemia is associated with increased risk of mortality or CKD progression to ESRD in patients with CKD stages 3 and 4, in the adjusted models.

Funding: Pharmaceutical Company Support - Pharmaceutical Company Support-CCF CKD Registry creation was supported by an unrestricted grant from Amgen to the Department of Nephrology and Hypertension at the Cleveland Clinic

FR-PO801

Urinary Calcium Excretion and Risk of Chronic Kidney Disease in the General Population

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Background: Calcium and vitamin D are essential nutrients for human health, and are recommended as part of a healthy diet. However, high urinary calcium excretion (UCaE) has been shown to lead to accelerated renal function decline in individuals with renal tubular diseases. It is not known whether this association also exists in the general population. Therefore, we investigated whether high UCaE is associated with risk of developing chronic kidney disease (CKD) in community dwelling subjects.

Methods: Urine samples of 5,491 subjects who were free of CKD at baseline and participated in the PREVEND study (a prospective, observational, general population based cohort of Dutch men and women aged 28-75 years), were examined for UCaE. UCa concentration was measured in two 24h urine samples at baseline (1997-1998) by indirect potentiometry. UCaE was treated both as a continuous variable and as a categorical variable grouped according to sex-specific quintiles for UCaE. UCaE was compared to *de novo* development of eGFR <60 ml/min/1.73m^2 and/or albuminuria >30 mg/24h.

Results: Baseline median UCaE was 166 mg/24h for men (interquartile range [IQR]: 117-220 mg/24h), and 141 mg/24h for women (IQR: 96-193 mg/24h). During a median follow-up of 10.3 years (IQR: 6.2-11.4 yrs), 899 subjects developed CKD. After multivariable adjustment for non-modifiable and modifiable covariates, every 40 mg/24h higher baseline UCaE was associated with a 6% lower risk for incident CKD during follow-up (HR: 0.94 [0.88-0.99], p=0.02). The association showed to be significantly non-linear, with highest risk of CKD in the lowest quintile for UCaE (HR: 1.28 [0.97-1.68], p=0.09). There was no association between UCaE and mortality or cardiovascular health during follow-up, indicating that this association was not a reflection poor nutritional intake due to bad health.

Conclusions: These findings indicate that high levels of UCaE do not increase risk of CKD, but rather that low levels of UCaE may be harmful.

Funding: Private Foundation Support

FR-PO802

Optimal End Stage Renal Disease Starts Are Associated with Less Sepsis, Lower Mortality and Fewer Inpatient Days

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Background: Endorsed by the National Quality Forum, the Optimal End Stage Renal Disease (ESRD) Starts measure assesses the proportion of patients who receive a preemptive kidney transplant or initiate maintenance outpatient therapy on peritoneal dialysis or hemodialysis [HD] via arteriovenous fistula or arteriovenous graft. Six Kaiser Permanente Regions have tracked the measure since 2011; this study compares outcomes for patients with and without an optimal ESRD start.

Methods: 2089 patients with an optimal ESRD start were propensity score-matched by demographics, comorbidities, BMI, eGFR before ESRD, and alcohol and tobacco use to 2089 patients starting outpatient HD with a central venous HD catheter. Outcomes included sepsis, mortality and inpatient days for the first 12 months after starting renal replacement therapy. Logistic regression and Cox proportional hazard regression, adjusted for propensity score, were used to calculate odds ratios for sepsis and mortality and the hazard ratio for mortality. The rate ratio for inpatient days was adjusted for prior inpatient use and propensity score.

Results: Among patients with optimal ESRD starts, mean sepsis and mortality rates per person-year were 0.14 and 0.09; mean annual inpatient days were 9.8. Comparable rates and days for patients with nonoptimal starts were 0.49, 0.31, and 25.8, respectively. Odds ratios for sepsis and mortality were 0.29 (95% confidence interval [CI], 0.24 to 0.34) and 0.28 (95% CI, 0.23 to 0.35), respectively, compared to patients with nonoptimal starts; the mortality hazard ratio was 0.36 (95% CI, 0.30 to 0.43). Patients with optimal ESRD starts had 62% fewer inpatient days (rate ratio 0.38, 95% CI 0.31 to 0.46). All ratios were significant at $p < 0.001$.

Conclusions: Optimal ESRD Starts were associated with substantial reductions in morbidity, mortality, and inpatient days. While it was not possible to match for all patient characteristics, this study supports the use of the Optimal ESRD Starts measure within the U.S. health care system to evolve a more systematic approach to identifying, educating and supporting patients at high risk for ESRD.

Funding: Clinical Revenue Support

FR-PO803

Prediction Model and Risk Stratification Tool of Survival in Patients with CKD

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Background: CKD patients have an increased risk of death. A simple prediction model of CKD patient mortality would be useful. To improve the accuracy and streamline such predictions, we used the Woodpecker™ approach to construct models from reported risks in the literature. The goal of this project was to develop a risk scoring system and prediction model of two-year mortality of patients with CKD of stage 2 and greater.

Methods: A risk indicator (*R*) was calculated by starting with 0, add 0.039 for every year of age, add 0.4 for male sex, add 0.4 for every stage of CKD over stage 2, add 0.9 for presence of proteinuria, add 0.6 for smoking history, and add 0.3 for each significant comorbidity up to 5. The result is multiplied by 1.257 to scale *R* from 0 to 10. We developed 4 different equations (one linear, two exponential, and a combined one) to estimate the probability of two-year mortality. We used NHANES 1999-2004 data for validation (n=6,057 subjects with CKD stage 2 or above).

Results: The predictions were compared to actual NHANES mortality outcomes by R alone and in patient groups divided by R (0-2, >2-3, >3-4, >4-5, >5-6, >6). This prediction yielded a satisfactory area under an ROC curve of 0.84. We compared the predicted probability of death based on R with the actual two-year mortality using each of the prediction formulae. The combined expression offered predictive results closest to the actual outcomes, particularly in the higher risk groups (R>4).

Conclusions: We propose a practical prediction model that allows estimation of a CKD patient's relative risk of two-year mortality on a 1 to 10 scale, and a probability of death. This equation can be used in clinical practice to target subjects at risk as well as in clinical research, e.g., to help designing clinical trials.

Funding: Clinical Revenue Support

FR-PO804

eGFR Decline of 40% as an Alternative Endpoint in Clinical Trials: Experience from EMPA-REG OUTCOME

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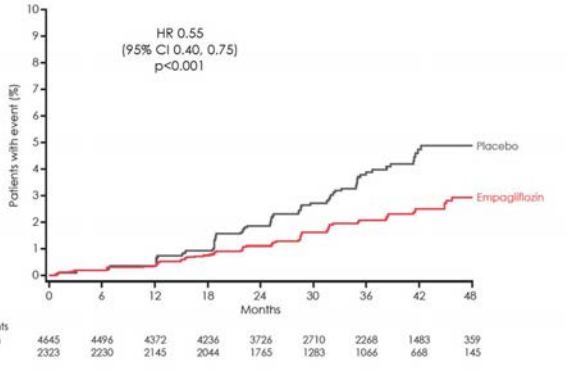
Background: Doubling of serum creatinine (DSC) is highly predictive of ESRD but its use as an endpoint in clinical trials requires long duration of follow-up and large sample sizes. The National Kidney Foundation and FDA have proposed the utility of lower thresholds in eGFR decline as alternative renal endpoints.

Methods: In EMPA-REG OUTCOME, 7020 patients with type 2 diabetes and high cardiovascular risk were randomized 1:1:1 to receive empagliflozin (EMPA) 10 mg, 25 mg, or placebo in addition to standard of care. Treatment group differences in the time to first DSC (accompanied by eGFR [MDRD] of ≤45 mL/min/1.73m^2) and sustained (defined as 2 consecutive measurements ≥4 weeks apart) eGFR decline of 40% from baseline were assessed for EMPA pooled vs placebo using a Cox proportional hazards model.

Results: Incidence rates of DSC were 9.7 and 5.5 events per 1000 person-years with placebo and EMPA, respectively. EMPA reduced DSC risk by 44% *vs* placebo (p<0.001). Incidence rates of sustained eGFR decline of 40% were 12.4 and 7.0 events per 1000 person-years with placebo and EMPA, respectively. The risk of sustained eGFR decline of 40% was reduced by 45% with EMPA *vs* placebo (p<0.001, Figure).

Figure. Time to first sustained decline in eGFR of 40% from baseline



Data from patients treated with ≥1 dose of study drug.
Sustained decline in eGFR of 40% from baseline: defined as 2 consecutive measurements with decline in eGFR of 40% from baseline that were ≥4 weeks apart.

Conclusions: EMPA significantly lowered the risk of sustained eGFR decline of 40% and the overall effect size was consistent with the harder endpoint of DSC. Our data support the consideration of a lower threshold in eGFR decline as an alternative renal endpoint for assessing CKD progression in clinical trials.

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

FR-PO805

Effect of Empagliflozin on Albuminuria in Patients with Type 2 Diabetes and High Cardiovascular Risk

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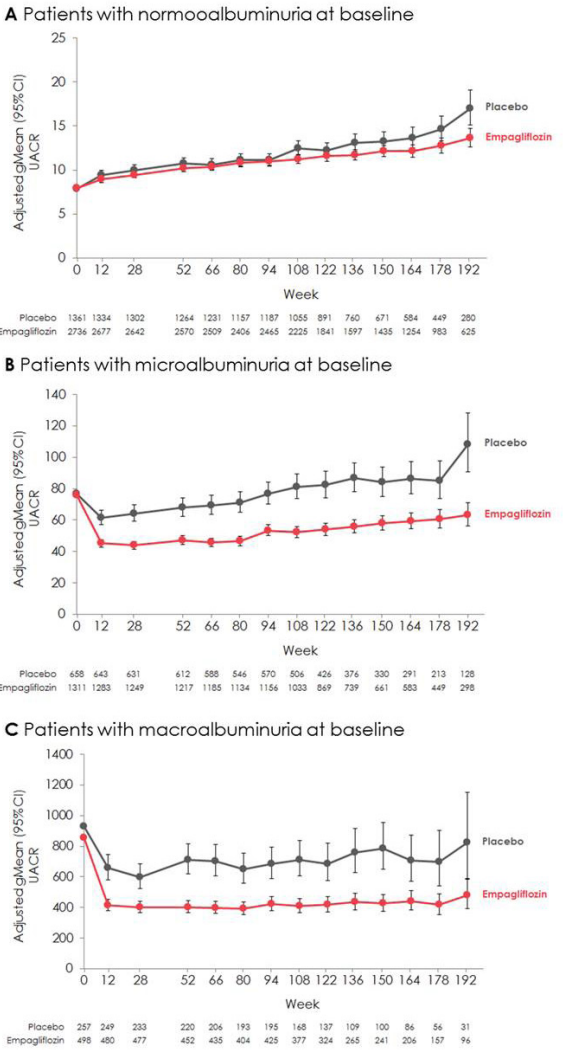
Background: Short-term treatment with empagliflozin (EMPA) reduced albuminuria in patients with type 2 diabetes (T2D). The present analysis aimed to explore short- and long-term effects of EMPA on albuminuria in EMPA-REG OUTCOME.

Methods: Patients with T2D and high cardiovascular (CV) risk were randomized (1:1:1) to EMPA 10 mg, 25 mg or placebo in addition to standard of care. Changes in urinary albumin-to-creatinine ratio (UACR, log-transformed) from baseline were analyzed for EMPA pooled vs placebo using a mixed model repeated measures analysis.

Results: 7020 patients were treated. At baseline, 59.4%, 28.7% and 11.0% had normo-, micro- and macroalbuminuria, respectively. At Week 12, placebo-adjusted geometric mean ratio of UACR change from baseline with EMPA pooled was -7% (95%CI -12 to -2; p=0.01), -25% (95%CI -31 to -19; p<0.001) and -32% (95%CI -41 to -23; p<0.001) in patients with normo-, micro- or macroalbuminuria at baseline, respectively. At Week 192, placebo-adjusted geometric mean ratio of UACR change from baseline with EMPA pooled was -21% (95%CI -31 to -9; p=0.001), -40% (95%CI -51 to -27; p<0.001) and -38% (95%CI -58 to -9; p<0.05) in these subgroups, respectively (Figure).

Figure. UACR over time.



Mixed model repeated measures analysis using all data up to individual trial completion in treated patients who had a baseline and post-baseline measurement.
Normoalbuminuria defined as UACR <30 mg/g.
Microalbuminuria defined as UACR ≤300 mg/g
Macroalbuminuria defined as UACR >300 mg/g.

Conclusions: In patients with T2D and high CV risk, EMPA led to sustained reductions in UACR from as early as Week 12, regardless of baseline albuminuria status. These results support both short- and long-term renal effects of EMPA on UACR.

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

FR-PO806

Rapid Onset of Renal Effects with Empagliflozin in Type 2 Diabetes: A Cumulative Renal Event Analysis over Time in EMPA-REG OUTCOME

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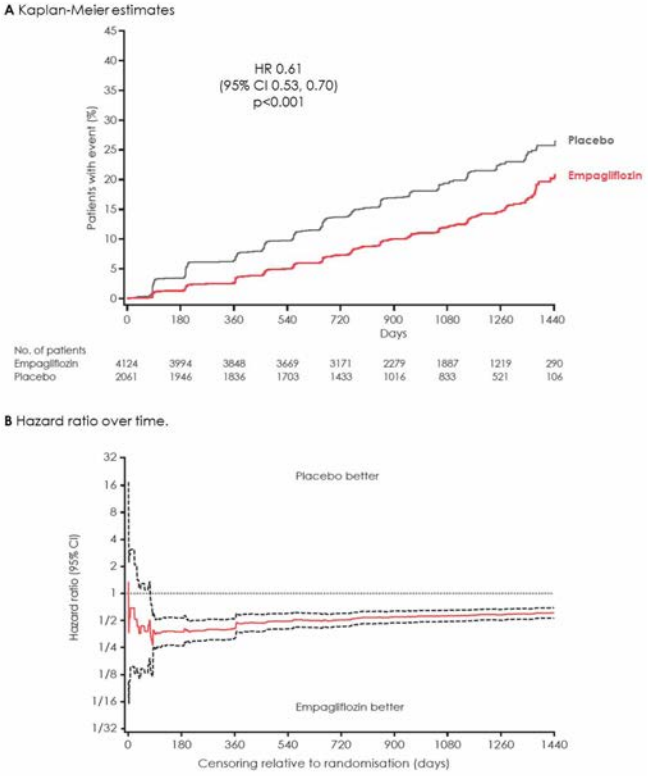
Background: Patients with diabetes are at high risk of developing CKD. In EMPA-REG OUTCOME, empagliflozin (EMPA) significantly slowed CKD progression in patients with type 2 diabetes and high cardiovascular risk. To further explore the onset of the observed renal effects with EMPA we investigated hazard ratios (HRs) over time for the composite outcome of incident or worsening nephropathy.

Methods: Patients were randomized to receive EMPA 10mg, 25mg or placebo in addition to standard of care. The cumulative probabilities of experiencing incident or worsening nephropathy (i.e. progression to macroalbuminuria, doubling of serum creatinine

accompanied by eGFR [MDRD] ≤45 mL/min/1.73m^2, initiation of renal replacement therapy or death due to renal disease) were analyzed for pooled EMPA *vs* placeboin patients treated with ≥1 dose of study drug. HRs and 95% CIs (obtained from Cox regression analyses) were derived at each time point following randomization until the last observation of the last patient. All events until the respective cut-off day were considered and patients without events were censored at that day.

Results: A significantly lower risk for the composite renal outcome with EMPA *vs* placebo was observed within the first 3 months and this effect was maintained throughout the trial (Figure). HRs stabilized as the number of patients with events increased over time.

Figure. Incident or worsening nephropathy. (**A**) Kaplan-Meier estimates (**B**) Hazard ratio over time.



Conclusions: Renal effects of EMPA occurred within the first 3 months of treatment. This rapid onset of action may reflect renal hemodynamic changes and reduction of glomerular hypertension.

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

FR-PO807

Effects of Canagliflozin versus Glimepiride on eGFR Based on Serum Creatinine and Cystatin C in Patients with Type 2 Diabetes

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Background: Canagliflozin (CANA), an SGLT2 inhibitor, has shown durable glycemic improvement and weight loss versus glimepiride (GLIM) over 104 weeks in patients with type 2 diabetes mellitus (T2DM) on background metformin; CANA showed a transient estimated glomerular filtration rate (eGFR) reduction that stabilized over time versus a progressive decline with GLIM. Accurate assessment of eGFR (typically calculated using serum creatinine [Cr]) is important as efficacy of SGLT2 inhibitors is impacted by renal function, and cystatin C (CysC)-based equations have been proposed but not confirmed as an alternative, less variable measure of eGFR. We assessed the effects of CANA 300 mg versus GLIM on eGFR based on serum Cr and combined Cr/CysC.

Methods: This post hoc analysis used data for CANA 300 mg (n=252) and GLIM (n=215) from patients in the overall study who completed 104 weeks of treatment without rescue therapy. Correlation in baseline (BL) eGFR using Cr and Cr/CysC equations was measured, and mean change from BL in eGFR at Week 104 was evaluated for CANA 300 mg versus GLIM.

Results: There was a modest correlation in BL eGFR calculated using Cr and Cr/CysC equations (R^2=0.38). Similar eGFR reductions were seen with CANA 300 mg and GLIM after 104 weeks using the Cr/CysC equation, whereas eGFR reduction was larger with GLIM compared to CANA 300 mg using the Cr-based equation (**Table**).

Conclusions: Differences in eGFR over 2 years were seen with CANA and GLIM when assessed based on serum Cr but not Cr/CysC. SGLT2 inhibitors are a newer class of antihyperglycemic agents with hemodynamic effects and ongoing, long-term, renal outcome trials will determine the potential for renoprotection in patients with T2DM.

Table. Change in eGFR at Week 104 Using Cr- and Cr/CysC-based Equations

	eGFR (Cr)*		eGFR (Cr/CysC)	
	GLIM (n = 215)	CANA 300 mg (n = 252)	GLIM (n = 215)	CANA 300 mg (n = 252)
Mean (SD) baseline, mL/min/1.73 m^2	87.5 (16.7)	91.7 (18.1)	88.7 (18.6)	92.2 (17.9)
LS mean change (SE) at Week 104	–6.2 (1.0)	–2.7 (0.9)	–4.4 (1.0)	–4.5 (1.0)
Difference (95% CI) vs GLIM		3.5 (1.3, 5.8)		–0.1 (–2.4, 2.3)

SD, standard deviation; LS, least squares; SE, standard error; CI, confidence interval; MDRD, Modification of Diet in Renal Disease.
*MDRD equation.

Funding: Pharmaceutical Company Support - Janssen Scientific Affairs, LLC

FR-PO808

Effects on Renal Function, Renal Protection and Glucose Metabolism of Sitagliptin to Type 2 Diabetes with Moderate or Severe Renal Dysfunction

Renal Effect and Safety of Sitagliptin (REAL) Trial Koichi Kanozawa,[1] Shigehiro Katayama,[2] Satoko Nakamura,[1] Rika Kono,[1] Yuichi Noguchi,[2] Yuta Kogure,[1] Hiroaki Hara,[1] Minoru Hatano,[1] Tomonari Ogawa,[1] Hajime Hasegawa.[1] *[1]Div of Nephrology and Hypertension, Saitama Medical Center, Saitama Medical Univ, Kawagoe, Saitama, Japan; [2]Dept of Endocrinology and Diabetes, Saitama Medical Univ, Moroyama, Saitama, Japan.*

Background: Recently, many studies suggested renoprotective effects by the DPP-4 inhibitor (DPP-4i). Clinically, while maintaining renal function, and performing the medical economically efficient glycemic control is important. A multicenter study aimed to investigate the maintenance and protection of renal function, and an efficient glycemic control by the DPP-4i, sitagliptin for the patients with type 2 diabetes (T2DM) with moderate or severe renal impairment.

Methods: Objects: Japanese adult patients with T2DM, have renal dysfunction less than eGFR 60mL / min / 1.73m2, and treat with different characteristic DPP-4i (one of the vilda-, alo- or linagliptin) more than two months. Study Design: Patients have been switched administration a dose of sitagliptin according to renal function (group A: 25-50mg in 30 <eGFR ≤ 60 mL / min / 1.73 m2, group B: 12.5-25mg in eGFR ≤ 30 mL / min / 1.73m2) from the other DPP-4i, and follow after three and six months. The primary endpoints are, eGFRcreat, eGFRcys, urinary liver type fatty acid binding protein, urinary albumin to creatinine ratio, urinary type IV collagen, urinary β2-microglobulin, and urinary 8-isoprostane. Secondary endpoints are HbA1c, postprandial blood glucose, postprandial c- peptide, and postprandial active GLP-1. In addition, it was also examined drug prices.

Results: 49 patients of seven centers (group A: 26 , group B: 23 patients) were analyzed. By changes to sitagliptin from other DPP-4i, there was no change in any of the primary endpoints also to secondary endpoints. On the other hand, drug prices per day had been reduced even 76.7 Japanese yen.

Conclusions: Switching from other DPP-4i to sitagliptin had maintained good glycemic control, renal function or renoprotection, and it was considered to be beneficial in terms of cost-effectiveness for patients with T2DM, had moderate or severe renal impairment.

Funding: Private Foundation Support

FR-PO809

Clinical Characteristics of Patients with Bullous Pemphigoid Associated with Dipeptidyl Peptidase-4 Inhibitors: Is Chronic Kidney Disease a Risk Factor?

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Background: Bullous pemphigoid (BP) is the most commonly acquired autoimmune blistering dermatosis. Its etiology is usually idiopathic but may occasionally be drug-induced. This study assessed the incidence of BP induced by dipeptidyl peptidase 4 inhibitors (DPP4Is) and the factors associated with DPP4Is-induced BP.

Methods: The present study was a single-center retrospective cohort studythat reviewed and examined all patients who were histologically diagnosed with BP at our hospital between 2005 and 2015. We analyzed the incidence of DPP4Is-associated BP and compared the characteristics of BP patients who were and were not treated with DPP4Is.

Results: Of the 66 patients diagnosed with BP during the study period, 19 were diagnosed during the 5 years before the introduction of DPP4Is and 47 during the 6 years after the introduction of DPP4Is. Of the latter, nine had been taking DPP4Is at diagnosis. There were no significant differences in age, sex, prevalence of anti-BP180 antibody, and BP treatment and outcomes between patients who were and were not treated with DPP4Is. In contrast, the prevalence of chronic kidney disease (CKD) was higher in patients who were than were not treated with DPP4Is, with rates of stage 5 CKD being 44% (4 of 9) and 4% (2 of 57), respectively.

Conclusions: The incidence of DPP4Is-associated BP appears to be increasing. CKD may increase the risk of DDP4Is-associated BP. Further large cohort studies and case-control studies are required to identify the interactions between CKD and DPP4Is-associated BP.

FR-PO810

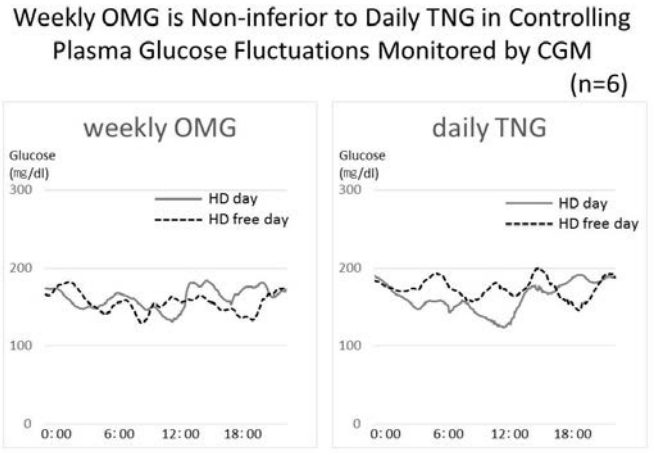
Omarigliptin, a Novel Once-Weekly Oral Dipeptidyl Peptidase-4 Iinhibitor, Is Non-Inferior to Daily Teneligliptin in Controlling Plasma Glucose Fluctuations and Exerts Better Medication Adherence in Hemodialysis Patients with Type 2 Diabetes in a Crossover Study: An Assessment by Continuous Glucose Monitoring

Sayuri Watanabe,[1] Rei Moriyama,[1] Chigusa Fukagawa,[1] Kenta Tsukuda,[1] Jyunichiro Hashiguchi,[1] Satoshi Funakoshi,[1] Takashi Harada,[1] Yoko Obata,[2] Tomoya Nishino.[2] *[1]Nagasaki Kidney Center, Japan; [2]Nagasaki Univ Hospital, Japan.*

Background: During hemodialysis (HD), plasma glucose (PG) level drops due to various factors including clearance gap between glucose and insulin, and then rebounds to hyperglycemic state after HD. These PG fluctuations can induce cardiovascular events in HD patients with type 2 diabetes mellitus (T2D). Omarigliptin (OMG) is a novel long-acting oral dipeptidyl peptidase-4 inhibitor (DPP-4I)used in the treatment of T2D patients with or without renal impairment.

Methods: In this study we compared once-weekly OMG to once-daily teneligliptin (TNG) on PG control in a crossover study assessed by continuous glucose monitoring (CGM) in a crossover study. Six adult HD patients with T2D who had been treated with 40mg of daily TNG were switched to once-weekly 12.5mg of OMG for 8 weeks, then to previous dose of daily TNG. All patients were monitored for PG control by 5-day CGM, and the mean amplitude of glycaemic excursions (MAGE) calculated before and after switching. OMG was given right after HD treatment in the presence of HD staff, and the medication adherence (total actual number of tablets taken during a period / number of tablet expected to be taken during a period x 100) was calculated at the end time point of each arm.

Results:



As shown in figure 1, there was no significant difference between once-daily TNG and once-weekly OMG in PG at the start of HD or MAGE. The medication adherence was 100% in OMG and 87% in TNG, respectively.

Conclusions: Our results indicate the effects of OMG are non-inferior to TNG, and OMG exerts better medication adherence.

Funding: Private Foundation Support

FR-PO811

Linagliptin and Changes in Novel Urinary Biomarker Panels in Type 2 Diabetes: A Predefined Substudy from the MARLINA-T2D™ Trial

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Background: The DN_Score is a composite score derived from DNlite, a novel urinary biomarker panel composed of alpha2-HS-glycoprotein precursor, alpha-1-antitrypsin and acid-1-glycoprotein. Previous evidence showed that the DN_Score significantly correlated with stages of kidney disease in both, type 1 diabetes (T1DM) and type 2 diabetes (T2DM). In this predefined substudy from MARLINA-T2D™, we applied the DN_Score to evaluate the renal effects of linagliptin in patients with T2DM and prevalent albuminuria.

Methods: MARLINA-T2D™ is a Phase IIIb, multicenter, multinational, randomized, double-blind, placebo (PBO) controlled, parallel group study to evaluate the glycemic and renal efficacy of linagliptin 5 mg QD for 24 weeks in T2DM patients, with micro- (30-300 mg/g creatinine) or macroalbuminuria on top of current treatment with ACE inhibitor or ARB. The percent change from baseline in the DN_Score at Week 24 was analyzed by an analysis of covariance (ANCOVA) based on the full analysis set, with baseline DN_Score as the prespecified covariate.

Results: Out of 360 patients in MARLINA-T2D™, urine samples for this biomarker study were available for 157 and 161 individuals receiving PBO and linagliptin, respectively. Linagliptin significantly reduced the DN_Score (%) from baseline to Week 24 vs PBO ($p<0.05$). Moreover, adjusted mean changes in the DN_Score (%) were consistently reduced with linagliptin in subgroups of patients with baseline UACR<300, eGFR-C ≥median, HbA1C <8.5%, and age <65 (all $p<0.05$).

Conclusions: Linagliptin significantly improved the DN_Score in T2DM patients and this effect was mainly driven by the early renal damage subgroup. The potential of linagliptin in diabetic kidney disease with concomitant albuminuria warrants further research, including longer-term observation and studies of linagliptin in T2DM patients with more advanced CKD.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim Pharma GmbH & Co. KG, Germany

FR-PO812

Non-Insulin Glycemia-Lowering Strategies and Mortality in Patients on Chronic Hemodialysis-A EURODOPPS Study

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Background: Patients with type 2 diabetes mellitus on chronic hemodialysis may be at an increased risk for hypoglycemia associated mortality. We hypothesized that in this patient group, this risk may be higher with insulin vs non-insulin glycemia-lowering treatment strategies and that a strategy of maximal oral therapy is better than that of starting/adding insulin.

Methods: Clinical data were obtained from the European Dialysis Outcomes and Practice Patterns Study (EURODOPPS) phases 1-4 (1998-2011) for 5437 diabetic patients (age 40-104 years) on hemodialysis from 7 European countries (Belgium, France, Germany, Italy, Spain, Sweden, and United Kingdom). Patients on non-insulin glycemia-lowering strategies (all classes) were compared with those on insulin containing strategies (all types) for all-cause and cardiovascular mortality. Multivariate Cox regression analysis was conducted in the total sample.

Results: After adjusting forage, gender, dialysis vintage, comorbidities, country, DOPPS phase, body mass index, albumin, glycated hemoglobin (HbA1c), smoking, Kt/V, residual renal function, and diabetes as a cause or as a comorbidity, patients on non-insulin vs insulin containing glycemia-lowering strategies had a reduced risk of all-cause mortality (HR:0.74;95%CI:0.57-0.96) but not of cardiovascular mortality.

Conclusions: Our results suggest a reduced risk of death in patients with diabetes on hemodialysis when on non-insulin vs insulin based glycemia-lowering strategies. However, these findings may be subject to residual confounding and require further investigation.

Funding: Other NIH Support - "The EURODOPPS Initiative is supported by the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) and the DOPPS Program. The DOPPS Program is principally supported by Amgen, Kyowa Hakko Kirin, Baxter Healthcare. Additional support for specific projects is also provided by Vifor Pharma, Ltd. Hexal, Deutsche Gesellschaft fur Nephrologie (DGfN), and Shire in Germany, the Societa Italiana di Nefrologia (SIN) in Italy, Keryx, Japanese Society for Peritoneal Dialysis (JSPD) and Genzyme Corporation. Public support is provided by National Health & Medical Research Council (NHMRC) in Australia, Canadian Institutes of Health Research (CIHR) and Ontario Renal Network in Canada, Agence Nationale de la Recherche in France, National Institute for Health Research (NIHR) via the Comprehensive Clinical Research Network (CCRN) in the United Kingdom, and National Institutes of Health (NIH) and Patient-Centered Outcomes Research Institute (PCORI) in the United States. All support is provided without restrictions on publications. The authors alone are responsible for the reporting and interpretation of EURODOPPS data used in the publication and they do not necessarily represent the decisions or policies of the ERA-EDTA or the DOPPS Program"

FR-PO813

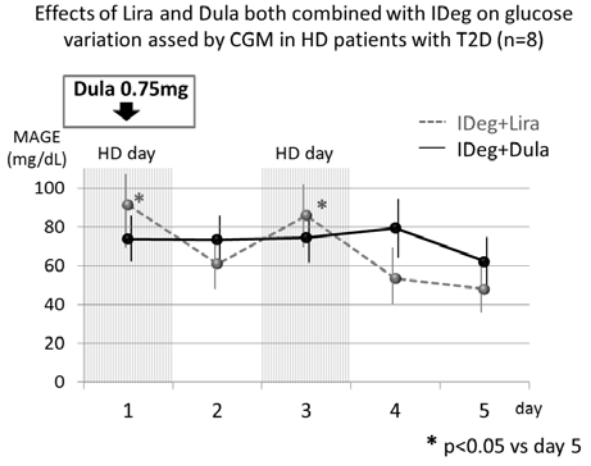
Dulaglutide, a Once-Weekly Glucagon-Like Peptide Receptor-Antagonist, Is Superior to Daily Liraglutide in Reducing Plasma Glucose Fluctuations in Hemodialysis Patients with Type 2 Diabetes Receiving Insulin Degludec: An Assessment by Continuous Glucose Monitoring

Satoshi Funakoshi,[1] Jyunichiro Hashiguchi,[1] Takashi Harada,[1] Kenji Sawase,[1] Hiroshi Ichinose,[1] Osamu Sasaki,[1] Chigusa Fukagawa,[1] Rei Moriyama,[1] Kenta Tsukuda,[1] Yoko Obata,[2] Tomoya Nishino.[2] *[1]Nagasaki Kidney Center, Japan; [2]Nagasaki Univ Hospital, Japan.*

Background: Plasma glucose (PG) levels are shown to drop during the course of hemodialysis (HD) but to rebound to a hyperglycemic state following HD. These PG fluctuations place HD patients with type 2 diabetes (T2D) at risk of cardiovascular events. Dulaglutide (Dula) is a novel, long-acting glucagon-like peptide receptor antagonist (GLP-1RA) used in the treatment of T2D patients with or without renal impairment. We previously reported the superiority of liraglutide (Lira) + insulin degludec (IDeg) to basal-bolus insulin therapy in controlling PG fluctuations in HD patients with T2D. In this study we compared by using CGM once-daily Lira and once-weekly Dula, each combined with daily IDeg.

Methods: Eight adult HD patients with T2D who had been treated with once-daily Lira (0.6-0.9 mg) combined with daily IDeg (5-74 units) (Lira + IDeg) were switched to once-weekly Dula 0.75 mg combined with daily IDeg (Dula + IDeg), where Dula was injected on Wednesday or Thursday (day 1 in Figure). All patients were monitored for PG control by CGM for 5 days, and the mean amplitude of glycaemic excursions (MAGE) calculated before and after switching.

Results:



As shown in figure 1, a significant difference was observed in MAGE between on-HD and off-HD days with IDeg + Lira, whereas this difference was cancelled out 2 to 4 weeks after switching to IDeg + Dula. Four out of 8 patients reported mild gastrointestinal adverse events with IDeg + Dula, which, however, were thought to be transient.

Conclusions: Thus, Dula appears to be potentially superior to Lira in reducing PG fluctuations in HD patients with T2D receiving IDeg.

Funding: Private Foundation Support

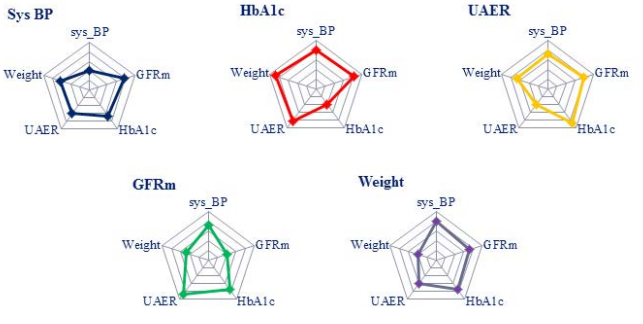
FR-PO814

Pleiotropic Effects of GLP-1 Treatment on Renal Risk Factors in Type 2 Diabetes: Individual Effects of Treatment Emilie Hein Zobel, Bernt Johan Illum von Scholten, Morten Lindhardt, Frederik I. Persson, Tine Hansen, Peter Rossing. *Steno Diabetes Center.*

Background: Management of diabetic nephropathy includes reduction of albuminuria, blood pressure, glucose and weight. The GLP-1 receptor agonist liraglutide may possess these pleiotropic effects. We aimed to elucidate the individual treatment response on multiple renal risk factors and determined if high responders (highest reduction) in each risk factor also had the highest response in other renal risk factors (cross-dependency).

Methods: We treated 31 type 2 diabetics with liraglutide for 7 weeks followed by 3 weeks washout. 23 re-started treatment and were followed for 1 year. We evaluated changes in HbA_{1c}, weight, SBP, UAER and mGFR (^{51}Cr-EDTA). Changes in high (Q4) vs. low responders (Q1-Q3) were compared for each outcome measure. The effects of treatment/off treatment/re-treatment (the off-on/off-on effect) was evaluated to account for random effects.

Results: After 7 weeks HbA_{1c} was reduced by 6 (95%CI: 3;9) mmol/mol, weight 2.5 (1.8;3.2) kg, SBP 4 (-1;9) mmHg and UAER 30 (12;44) %. mGFR was reduced 11 (7;14) ml/min/1.73m^2, previously shown reversible and considered haemodynamic. High responders in mGFR had a reduction in weight compared to low responders (4.3 *vs.* 1.9 kg; p=0.002). High responders in weight and SBP had a tendency of higher reduction in UAER compared to low responders (47 *vs.* 23%, p=0.14). No cross-dependency was observed in the other outcome measures (p≥0.16). The treatment response (the off-on/off-on effect) did not differ after 7 weeks and 1 year of liraglutide treatment (p≥0.12).



Conclusions: Liraglutide possesses pleiotropic effects on renal risk factors. On the patient-level, the effect on the individual risk factor cannot be anticipated based on response in other risk factors. The patients experienced same response when re-starting treatment, indicating that our primary findings are not caused by random effects.

FR-PO815

Renal Effects of Liraglutide in Type 2 Diabetic Patients with Albuminuria: A Randomized Clinical Trial Bernt Johan Illum von Scholten,[1] Frederik I. Persson,[1] Signe Rosenlund,[1] Tine Hansen,[1] Peter Rossing.[1,2,3] *[1]Steno Diabetes Center; [2]Univ of Copenhagen; [3]Aarhus Univ.*

Background: Patients with type 2 diabetes and albuminuria have high cardiorenal morbidity and mortality despite multifactorial treatment. We evaluated the renoprotective effect of glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide on top of multifactorial care, including renin angiotensin system (RAS) inhibition.

Methods: Randomized, double-blind, placebo-controlled, cross-over trial including patients with type 2 diabetes and persistent albuminuria (urinary albumin to creatinine ratio [UACR] > 30 mg/g in at least two of three consecutive morning spot urine samples), estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2, and prescribed stable antidiabetic treatment and RAS inhibition > 4 weeks before inclusion. Patients received liraglutide (1.8 mg/day) and matched placebo for 12 weeks in random order. Primary endpoint was change in 24-h urinary albumin excretion rate (UAER) (ClinicalTrials.gov, NCT02545738).

Results: We screened 40 patients, 32 were randomized and 27 completed the study. After placebo treatment, geometric mean (IQR) UAER was 199 (81-531) mg/24-h, mean (SD) measured GFR (^{51}Cr-EDTA) was 75 (36) mL/min per 1.73 m^2, 24-h blood pressure 145/80 (15/8) mmHg and HbA_{1c} 61 (11) mmol/mol. Liraglutide treatment reduced HbA_{1c} by 8 (95% CI: 5; 11) mmol/mol (p<0.001) and weight by 1.8 (95% CI: 0.2; 3.4) kg (p=0.032) when compared to placebo. In addition liraglutide treatment reduced UAER by 32 (95% CI: 7; 50) % (p[thinsp]=[thinsp]0.017) compared with placebo. Seven patients (26%) had a reduction in UAER > 50%. Change in GFR (^{51}Cr-EDTA) was -5 (95% CI: -11; 2) mL/min/1.73 m^2 (p=0.15), and change in 24-h systolic blood pressure was -4 (95% CI: -9; 2) mmHg (p=0.16). Change in UAER was associated with change in 24-h systolic blood pressure (p=0.006) but not with change in HbA_{1c}, weight or GFR (p>0.06), overall model R^2=0.54.

Conclusions: Our placebo-controlled randomized trial suggests that liraglutide treatment has renoprotective effects on top of multifactorial treatment, including RAS inhibition, in patients with type 2 diabetes and albuminuria.

Funding: Pharmaceutical Company Support - Novo Nordisk A/S

FR-PO816

Delayed-Release Metformin Targeting the Lower Small Intestine Elicits Minimal Systemic Exposure in Patients with Severe Renal Impairment: Results of Pharmacokinetic Simulation George L. Bakris,[1] Adekemi Taylor,[2] Brandon Walsh,[3] Colleen Burns,[3] Ralph A. DeFronzo,[4] Mark Fineman.[3] *[1]Univ of Chicago; [2]Certara Strategic Consulting; [3]Elcelyx Therapeutics; [4]Univ of Texas.*

Background: Initiation of metformin is not recommended in patients with chronic kidney disease (CKD) Stage 3B or greater due to lactic acidosis risk secondary to increased systemic metformin exposure. A delayed-release metformin (Met DR) that targets the L-cell in the lower bowel is in development and results in improved potency (e.g., equivalent fasting glucose reduction at daily doses of 600 mg Met DR vs. 1000 mg current metformin), with ~50% less systemic exposure at identical daily doses. Thus, Met DR may provide an alternative to current metformin in subjects with CKD Stage 3B/4. To select appropriate Met DR doses in various CKD stages, we developed a population PK model capable of predicting metformin plasma exposure based on formulation, dose, and CKD stage.

Methods: Metformin exposure predictions from simulations of 3 doses of Met DR (600, 900, 1200 mg) were compared to 1000 and 2000 mg metformin immediate-release (Met IR) in patients with CKD Stage 3A, 3B, or 4. Each simulation consisted of 1000 subjects with varying body weight and eGFR values.

Results: Across CKD Stages 3 and 4, all Met DR doses elicited lower systemic exposure than 2000 mg daily Met IR in Stage 3A patients. In Stage 3B CKD, 1200 mg of Met DR (a dose predicted to elicit similar glycemic effects to 2000 mg Met IR) elicits 40% lower mean exposure than the suboptimal, but recommended, 1000 mg daily Met IR dose.

Conclusions: We conclude that Met DR at doses up to 1200 mg daily may provide a useful alternative for subjects receiving ≤1000 mg Met IR with CKD Stage 3B, or as an option to initiate metformin for patients with CKD Stage 3B/4.

	Plasma Metformin Steady State $AUC_{0\text{-}24}$ (µg•h/mL; mean [CI: 5%-95%])				
	Met IR (BID) Total Daily Dose		Met DR (QD) Total Daily Dose		
CKD Stage	2000 mg	1000 mg	1200 mg	900 mg	600 mg
3A	33 (19-55)*	20 (4-22)	12 (5-27)	9 (4-22)	7 (3-15)
3B	42 (24-72)	25 (15-43)*	15 (6-37)	12 (5-29)	9 (4-20)
4	58 (33-102)	35 (20-62)	21 (8-51)	17 (7-40)	12 (5-28)
*=labeled/recommended use					

Funding: Pharmaceutical Company Support - Elcelyx Therapeutics

FR-PO817

Metformin Misuse in Chronic Kidney Disease: A Cohort Study Vladimir Coliche, Laetitia Koppe, Louis De Laforcade, Maurice Laville, Solenne Pelletier, Pierre Trolliet, Denis Fouque. *Nephrology, Centre Hospitalier Lyon Sud, Lyon, France.*

Background: Metformin is the most widely prescribed oral antidiabetic treatment, and the only one that showed a survival benefit including in chronic kidney disease (CKD) patients. However, metformin has side effects, particularly in these patients. Yet, there is no consensus on metformin optimal dose and withdrawal necessity in severe CKD stages. The aim of our study is to describe the use of metformin in routine practice in patients with CKD.

Methods: We followed 581 patients with type 2 diabetes in the Departement of Nephrology at the University Hospital between March 2014 and March 2016. Pts were classified into 6 CKD stages: 45 pts (eGFR-CKD EPI > 90 ml/min, stage 1), 72 (stage 2), 117 (stage 3a), 187 (stage 3b), 124 (stage 4), and 36 (stage 5ND). All antidiabetic treatments were gathered. Glycated hemoglobin (HbA1c) was recorded in 376 patients. Comparisons were performed by Student's T test.

Results: Results are shown in Table 1. There was no statistical difference between Met+/- groups for HbA1c. One lactic acidosis episode was recorded over 2 yrs.

CKD Stage	1	2	3a	3b	4	5
Metformin+: patients (%), HbA1c	40(89%), 7.3 ±1.5%	42(58%), 7.6 ±1.5	61(52%), 7.2 ±1.5	39(21%), 7.3 ±1.2	9(7%), 8.4 ±1.8	0
Metformin-: patients (%), HbA1c	5(11%), 7.2 ±0.3	30(42%), 7.6 ±2.0	56(48%), 7.4 ±1.3	148(79%), 7.5 ±1.4	115(93%), 7.4 ±1.8	36(100%), 6.8±1.8
Daily dose (mg)	1907 ±574	1786 ±705	1535 ±602	1423 ±649	1400 ±555	0

Conclusions: Except in stage 5, there was a gradual increase in HbA1c with the severity of CKD, whereas metformin use was limited (50% pts only, stages 2 and 3a) and dosage low (stages 2 and 3a). By contrast, metformin dose was above recommendation in stage 3b, and still prescribed in few patients in stage 4 despite theoretical contraindication. The better diabetes control in stage 5 is probably explained by the concomitant insulin treatment (75% pts). Thus, the use of metformin in CKD seems to be inadequate both in terms of dose adjustment and metabolic control. Dosage should be better adapted to the CKD stage. There is an urgent need for randomized studies of metfomin use on survival in stages 4 and 5 CKD.

FR-PO818

HbA1C, ESRD and Death in Chronic Kidney Disease Sankar D. Navaneethan,[1] Stacey Jolly,[2] Jesse D. Schold,[2] Susana Arrigain,[2] Wolfgang C. Winkelmayer,[1] Joseph V. Nally.[2] *[1]Baylor College of Medicine; [2]Cleveland Clinic.*

Background: Diabetic nephropathy is the leading cause of end stage of renal disease and contributes to mortality in chronic kidney disease (CKD). Ideal HbA1C level in CKD is unclear. We studied the associations of HbA1C with ESRD and death among non-dialysis dependent CKD patients.

Methods: We included 6,165 diabetic patients with eGFR <60 ml/min/1.73 m^2 and/or having CKD diagnosis, and on oral hypoglycemic agents and/or insulin in this analysis. Time dependent Cox proportional hazards models and competing risk analyses were used to study the associations between HbA1C, and all-cause mortality and ESRD while adjusting for demographics, comorbid conditions, use of relevant medications and kidney function measures.

Results: During a median follow-up of 2.4 years, 957 patients died (887 pre-ESRD deaths) and 205 patients reached ESRD. In the Cox proportional hazards model with time dependent repeated measures, after covariate adjustment, lower HbA1C level (<6% vs 6-6.9%) was associated with higher risk of death (HR 1.41, 95% CI 1.16, 1.71).

Outcome	<6%	6-6.9%	7-7.9%	8-8.9%	>9%
Mortality [HR, 95% CI)	**1.41(1.16, 1.71)**	Ref	0.89(0.74,1.06)	0.94(0.76, 1.19)	1.22(0.96, 1.55)
ESRD [SHR, 95% CI)	0.56(0.31, 1.01)	Ref	0.85(0.57,1.27)	0.59(0.35, 1.01)	1.20(0.78, 1.84)

Even though there was a trend, higher levels of HbA1C were not associated with death. When examining HbA1c as a continuous variable, the relationship was non-linear, with very low levels of HbA1c having the highest risk of mortality, and risk being lowest at about HbA1c 7-8%. In the competing risk models, both lower and higher HbA1C levels were not associated with ESRD when compared to HbA1c 6-6.9%. Sensitivity analyses by excluding those with malignancy and type 1 diabetes yielded qualitatively similar results.

Conclusions: Among non-dialysis dependent CKD population, HbA1C <6% was associated with higher risk of death. Associations between HbA1C and ESRD appears to be non-linear with lowest risk at 7-8%. Further studies examining causes of death in those with lower HbA1C are needed.

Funding: Pharmaceutical Company Support - Development of Cleveland Clinic CKD registry was supported by an unrestricted educational fund from Amgen to the Department of Nephrology and Hypertension, Cleveland Clinic

FR-PO819

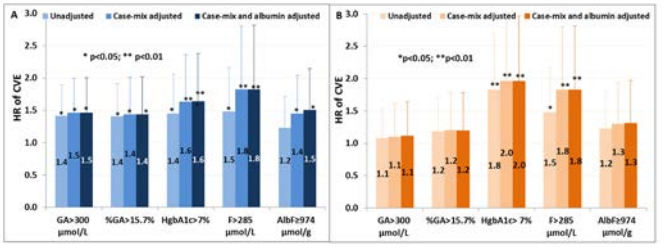
Glycemic Markers and Cardiovascular Events in Hemodialysis Patients from the GIDE Study Mark E. Williams,[1] Neal Mittman,[2] Lin Ma,[3] Julia I. Brennan,[4] Ann Mooney,[3] Chinu M. Jani,[4] Curtis D. Johnson,[4] Eduardo K. Lacson,[5] Norma J. Ofsthun,[3] Franklin W. Maddux.[3] *[1]Joslin Diabetes Center, Boston, MA; [2]Kidney Care of Brooklyn and Queens, Brooklyn, NY; [3]Fresenius Medical Care North America, Watham, MA; [4]Spectra Laboratories, Rockleigh, NJ; [5]Tufts Univ School of Medicine, Boston, MA.*

Background: The GIDE (Glycemic Indices in Dialysis Evaluation) study is evaluating several glycemic indices including HgbA1c, albumin-adjusted and unadjusted fructosamine (AlbF; F), and glycated albumin (GA) or percent GA (%GA) in hemodialysis (HD) cohorts with and without diabetes. Since cardiovascular events (CVE) are associated with diabetes, we examined the associations between each glycemic indices and CVE risks.

Methods: A combined cohort of 2,501 active HD patients (1,478 with diabetes, 1023 without) from 26 FMCNA facilities had baseline indices measured Jan-Mar 2013 and monthly until March 2016. Poor glycemic controls were based on: HgbA1c >7%, F>285µmol/L, AlbF≥974µmol/g, GA>300µmol/L, and %GA>15.7%. CVE included acute myocardial infarction (AMI), cerebrovascular accident (CVA), and peripheral vascular disease (PVD) which were diagnosed from hospital discharges in 3-years follow up. Times to the first CVE were used for the survival analysis. Standard and time-dependent (TD) Cox models with adjustments for case-mix and albumin level at baseline were utilized to determine associations between each glycemic indices and CVE risks.

Results: In 2,501 HD patients, 179 (7.1%) had at least one CVE during the 3-years follow-up periods; 125 (8.5%) in diabetes and 54 (5.3%) in non-diabetes. The hazard ratios of CVE from standard and time-dependent Cox models were shown in Figure 1.

Figure 1. Hazard Ratios (HR) of Cardiovascular Events (CVE) from Standard (A) and Time-dependent (B) Cox Models



Conclusions: While most studies in ESRD evaluated for a relationship between poor glycemic control and mortality, the GIDE study also demonstrates an increased risk for CVE associated with elevated levels of multiple glycemic indices.

FR-PO820

Glycemic Control and All-Cause Hospitalization in an Urban Hemodialysis Population Jeffrey I. Silberzweig,[1,2] Thomas Parker,[1] Daniel Levine.[1] *[1]The Rogosin Inst, New York, NY; [2]Nephrology and Hypertension, Weill Cornell Medicine, New York, NY.*

Background: Data suggests a U-shaped association of mortality with glycemic control in patients with diabetes mellitus treated by hemodialysis (Ricks[1], Ramirez[2], Rhee[3]) but limited published data suggest that poor glycemic control is associated with increased risk of hospital admission (Toida[4]).

Methods: We evaluated time-averaged glycemic control in a population of 346 in-center hemodialysis patients and assessed its relationship with all-cause hospitalization between January 1, 2014 and July 30, 2015. Data were analyzed using t tests and a multifactorial model of the number of hospitalizations per patient.

Results: We observed close fits between time-averaged serum glucose levels and hemoglobin A1c (r^2=0.56). While the risk of hospital admission associated with the diagnosis of diabetes ($p < 0.05$), it did not associate with either measure of glycemic control (p=0.4 for serum glucose, p=0.7 for mean hgbA1c). These relationships were not changed by inclusion of race, gender, age, duration of dialysis or tobacco use. Both serum albumin ($p<0.05$) and ferritin ($p<0.05$) were associated with increased risk of hospital admission.

Conclusions: Glycemic control does not associate with increased risk of hospital admission despite an association with the presence of diabetes. The relationships with markers of inflammation and nutrition suggest that improved glycemic control may associate with poor nutrition, a known risk factor for poor outcomes among patients treated by hemodialysis.

FR-PO821

Associations between Mortality and Glycemic Control with Glycated Albumin and Hemoglobin A1c in Diabetic Patients on Hemodialysis
Junichi Hoshino,[1,2] Masanori Abe,[1,3] Takeshi Hasegawa,[1,4] Takayuki Hamano,[1,5] Atsushi Wada,[1,6] Yoshifumi Ubara,[2] Kenmei Takaichi,[2] Shigeru Nakai,[1,7] Masaaki Inaba,[8] Ikuto Masakane.[1,9] *[1]The Committee of Renal Data Registry, The Japanese Society for Dialysis Therapy, Tokyo, Japan; [2]Nephrology Center, Toranomon Hospital, Tokyo, Japan; [3]Nihon Univ School of Medicine, Tokyo, Japan; [4]Showa Univ Fujigaoka Hospital, Kanagawa, Japan; [5]Osaka Univ Graduate School of Medicine, Osaka, Japan; [6]Kitasaito Hospital, Asahikawa, Japan; [7]Fujita Health Univ, Aichi, Japan; [8]Osaka City Univ Graduate School of Medicine, Osaka, Japan; [9]Yabuki Hospital, Yamagata, Japan.*

Background: For glycemic control in diabetic HD patients, it remains unclear what level of glycated albumin (GA) was associated with lower mortality. Here we examined the difference in association between GA and hemoglobin A1c (HbA1c) with 1-year mortality in a cohort of the Japanese Society for Dialysis Therapy.

Methods: We followed 84,282 diabetic patients on maintenance hemodialysis (mean age 67.3±11.2 years; mean dialysis vintage, 6.4±4.5 years) for a year, 2013-2014, using Cox regression to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (95% CI) for 1-year mortality after adjusting for all such potential confounders as age, sex, smoking, diabetes type, etc.

Results: The adjusted HRs of mortality with baseline GA <12.5, 12.5-<15, 15.0-<17.5, 17.5-<20.0, 20.0-<22.5, 22.5-<25.0, 25.0-<27.5, 27.5-<30.0, and ≥30.0% were, respectively, 2.53 (95% CI, 1.10-5.80), 1.06 (0.68-1.66), 1.00 (reference), 1.22 (0.93-1.58), 1.09 (0.84-1.43), 1.40 (1.07-1.85), 1.31 (0.96-1.79), 1.77 (1.26-2.49), and 1.64 (1.20-2.23); and with A1c <4.5, 4.5-<5.0, 5.0-<5.5, 5.5-<6.0, 6.0-<6.5, 6.5-<7.0, 7.0-<7.5, 7.5-<8.0, and ≥8.0%, respectively, 1.57 (1.03-2.37), 1.34 (0.97-1.84), 1.16 (0.87-1.55), 1.11 (0.83-1.47), 1.09 (0.82-1.45), 1.14 (0.84-1.54), 1.00 (reference), 1.30 (0.89-1.88), and 1.55 (1.11-2.18). Lowest mortality**:** 12.5-22.5% for GA, 5.0-7.5% for HbA1c. U-shape association of both GA and HbA1c was consistent regardless of albumin level, although weakened in cardiovascular patients.

Conclusions: Both GA and Hb1c levels showed U-shape associations with 1-year mortality in diabetic HD patients, lower mortality with GA 12.5-22.5% and HbA1c 5.0-7.5%.

FR-PO822

Associations between Glycemic Control and Infections among U.S. Hemodialysis Patients with Diabetes Mellitus
Jinnie J. Rhee,[1] Yuanchao Zheng,[1] Maria E. Montez-Rath,[1] Wolfgang C. Winkelmayer.[2] *[1]Div of Nephrology, Stanford Univ School of Medicine, Palo Alto, CA; [2]Section of Nephrology, Baylor College of Medicine, Houston, TX.*

Background: Little is known about any associations between glycemic control and hospitalized or fatal infections in hemodialysis (HD) patients with diabetes mellitus (DM).

Methods: We used data from the US Renal Data System and electronic health records data from a large US dialysis provider merged at the patient level. Socioeconomic status was estimated using area-level US census data. Adult Medicare-insured patients with DM aged ≥18 years who initiated in-center maintenance HD treatment from 2006 to 2011 and survived >90 days were included. The exposure was time-averaged HbA1c and quarterly mean HbA1c values were categorized as follows: <6.5% (reference), 6.5-<7.5%, 7.5-<8.5%, and ≥8.5%. We used Medicare claims to ascertain infection-related hospitalizations and the ESRD Death Notification (CMS-2746) to identify death from infectious cause as study outcomes. We used Cox proportional hazards models to estimate multivariable-adjusted hazard ratios (HR) and 95% CI for the associations between time-averaged HbA1c category and these infectious events, adjusting for baseline demographics, updated comorbidities from claims, and time-averaged vital signs and laboratory results.

Results: Among 16,387 eligible patients, 6585 infection-related hospitalizations occurred and 887 deaths were linked to infection. Compared with patients with HbA1c <6.5%, the HRs for infection-related hospitalization were 0.99 (CI, 0.93, 1.06), 1.03 (CI, 0.95, 1.13), and 1.12 (CI, 1.02, 1.22) for patients with HbA1c 6.5-<7.5%, 7.5-<8.5%, and ≥8.5%, respectively (*P*-trend=0.02). The corresponding HRs for death from infection were 0.88 (CI, 0.70, 1.10), 0.82 (CI, 0.61, 1.09), and 0.74 (0.52, 1.04) for patients with HbA1c 6.5-<7.5%, 7.5-<8.5%, and ≥8.5%, respectively, compared with those with HbA1c <6.5% (*P*-trend=0.08).

Conclusions: In summary, while time-averaged HbA1c was not clearly associated with the risk of infection-related mortality, there was a significant trend toward higher rates of infection-related hospitalizations with increasing HbA1c levels.

Funding: NIDDK Support

FR-PO823

Changes in Health-Related Quality of Life over Time and Effect of Losartan Treatment in Patients with Type 2 Diabetes Mellitus and Nephropathy
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Background: Patients with chronic kidney disease have low health-related quality of life (HRQOL), and in general females report lower HRQOL than males. However, there is limited data about longitudinal changes in HRQOL in these patients. Additionally, the effect of angiotensin receptor blockers on HRQOL is unknown. We explored these issues in patients with type 2 diabetes mellitus (T2DM) and nephropathy who participated in the RENAAL trial.

Methods: The RENAAL trial assessed the effect of losartan versus placebo on renal outcomes in 1513 patients with T2DM and nephropathy. Analysis of HRQOL was pre-specified for the 635 U.S. participants (42% of total cohort). HRQOL was assessed with the Short Form-36 survey and is reported as the mental health component summary (MCS) and physical health component summary (PCS). The general population reference values for both MCS and PCS are 50.0 (SD 10.0). HRQOL was measured at baseline and every 3 months until end of follow-up. Mixed-effects models were used to assess changes in MCS and PCS over time and to determine the effect of losartan on MCS and PCS.

Results: Participants (mean age 59.7 (SD 7.8) years; 64.3% males; mean eGFR 42.0 (SD 12.5) mL/min/1.73m^2; median UACR 1060 [Q1–Q3 502–2259] mg/g) were followed for a median of 3.3 [Q1–Q3 2.7-3.8] years. Mean baseline MCS was 51.4 (SD 10.1) and PCS was 38.6 (SD 10.8). In the placebo arm, MCS and PCS decreased by 0.8 (95%CI -1.04, 0.46; p<0.01) and 1.1 (95%CI -1.74, 0.83; p<0.01) per year, respectively. Losartan compared to placebo did not change MCS (-0.96 (95%CI -3.00, 1.09; p=0.36) or PCS -0.80 (95%CI -2.81, 1.22; p=0.44). At baseline, males reported higher MCS and PCS compared to females, but there were no gender differences in changes in MCS and PCS over time.

Conclusions: MCS and PCS decreased over time in patients with T2DM and nephropathy. Furthermore, losartan did not appear to have an effect on MCS and PCS, although it previously showed effect on other clinical parameters in this group of patients. Both men and women reported similar declines in MCS and PCS over time.

FR-PO824

Urinary Metabolomics Predict Albuminuria Response to Spironolactone Therapy in Type 2 Diabetes
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Background: Spironolactone, a mineralocorticoid blocker, significantly reduces albuminuria (UACR) in patients with type 2 diabetes (T2DM) albeit with a large betweeen-individual variability in response. Finding new biomarkers that predict UACR response to spironolactone may tailor optimal therapy. We tested an *a priori* defined set of metabolites to predict UACR response to spironolactone.

Methods: Samples were used from a randomized placebo controlled double blind trial of patients with T2DM and resistant hypertension assigned to spironolactone 25-50mg/day (n=50) or placebo (n=50) for 16 weeks adjunct to RAS inhibition. We used a systems medicine approach to select *a priori* 14 plasma metabolites (oxidative stress, biogenic amines) and 18 urine metabolites (biogenic amines, organic acids) to predict UACR response to spironolactone. Metabolites were chosen by matching a diabetic kidney disease molecular model with a spironolactone mechanism of action molecular model. We performed plasma and urinary metabolomics by LC-MS at baseline. We used linear regression to develop separate baseline plasma and urine metabolite scores and tested if these scores could predict UACR response to spironolactone by analysis of covariance.

Results: Spironolactone reduced UACR relative to placebo by median -42% with large variability (5th–95th percentile -93 – +212). The urine metabolite score was inversely correlated with baseline UACR (Pearson's r -0.37 p<0.01). The plasma metabolite score was not correlated with baseline UACR. The urine metabolite score predicted UACR response to spironolactone (p=0.03 urine score*treatment interaction). The plasma score*treatment interaction was not significant. Analyzed by tertiles of urine metabolite score, placebo-adjusted UACR reduction was significant only in the lowest tertile (-61% (95%CI -86 – -36) p<0.01).

Conclusions: An *a priori* defined set of 18 urinary biogenic amines and organic acids predicts UACR response to spironolactone, suggesting that this urine metabolite score may be a tool to tailor optimal therapy in T2DM.

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FR-PO825

Angiotensin Converting Enzyme Inhibitors versus Angiotensin Receptor Blockers for Control of Moderately Increased Albuminuria in Hypertensive Type 2 Diabetic Patients
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Background: Studies on head to head comparison of angiotensin-converting enzyme inhibitors(ACEi) or angiotensin receptor blockers (ARBs) with reduction of albuminuria as a primary outcome in patients with type 2 diabetes mellitus (DM) and hypertension are limited.

Methods: This was a single centre, prospective, randomized, open label, active controlled study carried out in patients with well controlled type 2 DM with hypertension and urinary albumin excretion rate (UAER) of 20-200µg/min. Exclusion criteria included pregnancy, renal artery stenosis, serum creatinine>1.5 mg/dl , blood pressure more than 180/110 mm Hg, coronary artery disease, congestive heart failure, cerebrovascular accident. Sixty patients were recruited from January 2013 to December 2014 and followed for 52 weeks. Patients were randomized to receive enalapril (n=30, group A) or losartan (n =30, group B) which were titrated to the maximum of 20 mg and 100 mg respectively. Patients with blood pressure of >150/95 mm of hg at the end of 8 weeks, were started on other antihypertensive drugs. Albumin excretion rate was calculated in a 24 hr sample using EIA.

Results: The mean age(years) was 56±11.2 in group A and 54.10.8 in group B . Ratio of male to female was 16:14 in group A and it was 15:15 in group B. The mean SBP(mm of hg) , DBP(mm of hg) and UAER (µg/min)in group A were 167.73±10.58, 99.20±4.16 and 133.33±45.79 respectively and in group B were 159.13±10.49, 100.33±6.33 and 117.80±34.0 respectively. After 52 weeks of follow up there was significant decrease in mean SBP, DBP and UAER in both groups (p<0.0001, <0.0001 and 0.001 respectively for group A and P<0.0001, <0.0001 and <0.0001 respectively for group B).On comparison there was no significant difference between enalapril and losartan on control of hypertension and UAER (p- 0.32 , 0.28 and 0.06 for SBP and DBP and UAER respectively).

Conclusions: In patients with type 2 DM and hypertension, treatment with ACEi or ARBs is equally effective in reducing blood pressure and albuminuria.

FR-PO826

High Salt Intake Is an Independent Predictor for Diabetes Mellitus in Japanese Adults: 5 Year Cohort Study Masanari Kuwabara,[1,2,3] Miguel A. Lanaspa,[1] Thomas Jensen,[1] Ana Andres-Hernando,[1] Carlos Alberto Roncal-Jimenez,[1] Tamara Milagres,[1] Christina Cicerchi,[1] Richard J. Johnson.[1] *[1]Div of Renal Diseases and Hypertension, Univ of Colorado Denver; [2]Toranomon Hospital, Tokyo, Japan; [3]St. Luke's International Hospital, Tokyo, Japan.*

Background: Diabetes mellitus (DM) is a strong risk factor for cardiovascular disease. Type 2 DM develops in the setting of excess caloric intake. This clinical study was conducted to clarify whether high salt intake may be independent of caloric intake as a risk factor for developing DM.

Methods: This was a large-scale retrospective cohort study using Japanese medical check-up data in St. Luke's international hospital, Tokyo, Japan between 2004 and 2009. We analyzed 12,456 subjects without DM between 30 and 85 years old in 2004. We evaluated risk factors for developing DM in 2009 by adjusted logistic analysis and propensity score matching analysis by age, gender, body mass index, smoking habit, hypertension, dyslipidemia, hyperuricemia, chronic kidney disease, total calorie and salt intake. This study divided the two groups as total calories (cutoff level: 2150 kcal/day) and salt intake (cutoff level: 11g/day) and compared with two-by-two groups.

Results: The group with high calorie and high salt intake had a significantly higher risk for developing DM compared with low calories and low salt intake group (p=0.001) and high calories and low salt intake group (p=0.013). After multiple adjustment, salt intake of >11g/day was an independent risk factor for developing DM [odds ratio (OR) per 1 year increased: 1.330, 95% confidence interval (CI): 1.023-1.730], as was aging (p<0.001), higher body mass index (p<0.001), smoking habit (p=0.029), and dyslipidemia (p=0.002). Gender, hypertension, hyperuricemia, chronic kidney disease and high calorie intake (>2150 kcal/day) did not predict development of DM. After adjustments for propensity score, salt intake of > 11g/day was an independent risk factor for developing DM as compared with salt intake of ≤ 11 g/day (OR: 1.35, 95% CI: 1.017-1.795).

Conclusions: Salt intake of > 11 g/day is an independent predictor of DM. Restricting salt intake in addition to other life style modifications may be important in preventing the development of DM.

Funding: Private Foundation Support

FR-PO827

Renal Effects of Intravitreal Bevacizumab Injection for Diabetic Retinopathy Jiahua Li,[1] Min Zhuo,[1] Christine Joy C. Junia,[1] Ferah Diba Ciftci,[1] Carolyn S. Brecklin.[2] *[1]Internal Medicine, John H. Stroger Jr. Hospital of Cook County, Chicago, IL; [2]Nephrology, John H. Stroger Jr. Hospital of Cook County, Chicago, IL.*

Background: Vascular endothelial growth factor (VEGF) inhibitors, including the humanized monoclonal antibody bevacizumab, are widely used to treat forms of pathologic angiogenesis, such as metastatic carcinomas and proliferative diabetic retinopathy. Patients who receive systemic bevacizumab for malignancy may develop renal insufficiency, hypertension, and proteinuria. However, the renal effects of intravitreal bevacizumab injection among diabetic patients are unclear.

Methods: In this single-center retrospective study, patients who received intravitreal bevacizumab injection for diabetic retinopathy from September 2014 to October 2015 were identified. Patients were selected by the following criteria: received ≥2 standard doses (2.5mg) of intravitreal injection; had a basic metabolic panel, spot urinary protein/creatinine ratio (UPCR), hemoglobin A1c, and blood pressure records before the first injection and after the last injection within a defined period. The comparisons of serum creatinine (SCr), estimated GFR (eGFR), UPCR, blood pressure were performed with the use of paired t-test and multivariate regression.

Results: 75 out of 472 patients were included. On average, patients received 3.1 (95% confidence interval [CI], 2.9 to 3.5) intravitreal bevacizumab injections. The changes of SCr (mg/dl) and eGFR (ml/min/1.73m^2) were insignificant (1.19 to 1.38 and 67.4 to 66.4 respectively). The diastolic blood pressure (DBP) (mmHg) significantly increased from 72.6 to 75.2 (p=0.05) while the systolic blood pressure (SBP) and mean arterial pressure (MAP) did not change significantly. The UPCR (mg/mg) significantly increased from 545 to 720 (p=0.05). The change of proteinuria is positively correlated with the number of injections (R^2=0.214, p=0.019) after adjusting for age, black race, baseline eGFR, change of MAP, change of HbA1c, and use of ACEi/ARBs.

Conclusions: Our study shows that intravitreal bevacizumab injection associated with an increase of proteinuria in a dose-dependent fashion.

FR-PO828

The Renoprotective Role of Paracalcitol on Type 2 Diabetic Chronic Kidney Disease Filipa B. Mendes,[1] Isabel Almeida,[2] Luisa H. Pereira,[1] Ana Paula Silva,[1,2] Ana Marreiros,[3] Pedro Neves.[1,2] *[1]Dept of Nephrology, Algarve Hospital Centre; [2]Dept of Biomedical Science, Algarve Univ; [3]Algarve Univ.*

Background: Chronic kidney disease (CKD) is a public health problem and Diabetes is the number one causing it, worldwide. Albuminuria is an important sign of CKD progression, cardiovascular disease and death. Therefore, many drugs have been tested in order to reduce the albuminuria. One of those drugs have been the vitamin D analogues. In this study we analyzed the role of paricalcitol in the reduction of the urinary albumin-to-creatinine ratio (UACR) in patients with type 2 diabetes and CKD. We also verified the impact of baseline vitamin D in that ratio.

Methods: In an observational retrospective study, 42 patients with CKD secondary to type 2 diabetes were treated with paricalcitol, 1 µ daily during at least 3 months. We analysed patients data and laboratorial parameters at baseline (T0) and 12 weeks after treatment with paricalcitol (T1). We also divided our population in 2 groups accordingly the vitamin D level (G 1 – vitamin D <10 ng/mL and G 2 - vitamin D ≥ 10 ng/mL). We used descriptive statistics, *Wilcoxon* test, Sign test, *Student's t* test and the geometric average growth rate.

Results: After paracalcitol treatment (T1) we found a reduction of UACR (p=0.001) and PTH (p=0.001), whereas the vitamin D level increased (p < 0,0001). G1 showed higher levels of UACR (p=0,002) at baseline. After 12 weeks (T1) of paricalcitol treatment, according to the geometric average growth rate, it was found a reduction of in the UACR (1.78 %) and in the PTH (3,85%). On the other hand, Vitamin D and eGFR showed an increase of 3,38% and 0,10%, respectively.

Conclusions: In our study paricalcitol showed renoprotective effects in type 2 diabetes, promoting a reduction in the urinary albumin-to-creatinine ratio. Moreover, there is an inversely proportional association between vitamin D and UACR at baseline.

FR-PO829

PBI-4050 Reduces Cardiovascular and Renal Biomarkers in Type II Diabetic Patients with Metabolic Syndrome Pierre Laurin, Brigitte Grouix, Alexandre Laverdure, Boulos Zacharie, Lyne Gagnon. *ProMetic BioSciences Inc., Laval, QC, Canada.*

Background: PBI-4050 is an orally active drug candidate with anti-fibrotic efficacy in multiple preclinical models of fibrosis in kidney, liver, lung, heart and pancreas. PBI-4050 has been shown to protect against pancreatic fibrosis in db/db and db/db eNOS-/- mice by reducing macrophage and lymphocyte infiltration, ER stress and increasing autophagy.

Methods: A phase II, open label, single center, single arm study in twenty type 2 diabetes patients with metabolic syndrome was undertaken. The objectives were to evaluate the efficacy safety and tolerability of PBI-4050 following oral administration of 800 mg doses once daily for 12 weeks; and to demonstrate pharmacological activity and translation of efficacy from preclinical studies to humans by monitoring early evidence of changes in cardiorenal disorders biomarkers.

Results: PBI-4050 was demonstrated to be safe and well tolerated without SAEs. PBI-4050 treatment reduced HbA1c (average ΔHbA1c of -0.80, p=0.003 with HbA1c baseline of >7.5%, average ΔHbA1c of -1%, p=0.003 with HbA1c baseline of >7.5%,) in twenty patients. In same patients IL-18 was reduced in the urine (p<0.05). Pentraxine-3 and resistin were reduced in blood (p<0.01).

Conclusions: PBI-4050 was safe and well tolerated in type II diabetic patients with metabolic syndrome. PBI-4050 was efficacious in reducing HbA1c, waist circumference, BMI and weigh, and reduced cardio renal biomarkers Il-18, Pentaxine-3 and resistin. These results demonstrated that PBI-4050 may be an efficacious therapy for chronic kidney disease patients with type II diabetes.

FR-PO830

Structured Exercise in Obese Diabetic Patients with Chronic Kidney Disease: A Randomized Controlled Trial David J. Leehey,[1,2] Eileen Collins,[1] Holly J. Kramer,[1,2] Cheryl Cooper,[1] Jolene Butler,[1] Conor Mcburney,[1] Christine Jelinek,[1] Domenic Reda,[1] Lonnie Edwards,[1] Anne Garabedian,[1] Susan Oconnell.[1] *[1]Medicine and Research, Hines VA Hospital, Hines, IL; [2]Medicine, Loyola Univ Medical Center, Maywood, IL.*

Background: Patients with type 2 diabetes mellitus (DM), obesity, and chronic kidney disease (CKD) are generally physically inactive and may benefit from exercise. Our objective was to determine the effects of structured exercise on physical fitness, kidney function, endothelial function, inflammation, and body composition in such patients.

Methods: In this randomized, controlled trial, 36 male patients (age 49-81) were randomly assigned to exercise + diet management (n=18) or diet alone (n=18). Participants were eligible if they had type 2 DM, body mass index (BMI) > 30 kg/m^2, CKD stage 2-4, and persistent proteinuria (> 200 mg/g creatinine for > 3 months). The exercise intervention was a 12-week (3 days per week) program of aerobic and resistance training followed by 40 weeks of home exercise. The primary outcome measure was change from baseline in urine protein to creatinine ratio (UPCR) at 12 weeks and 52 weeks.

Results: 32 participants completed the study (14 exercise + diet, 18 diet alone group). Change from baseline in UPCR was slightly greater in the diet alone group at 12 weeks but not at 52 weeks. Changes in both symptom-limited and constant-workrate treadmill times were significantly higher in the exercise + diet group at 12 weeks but not at 52

weeks. There were no significant differences in urine albumin to creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), endothelial function, inflammation, or body composition between the groups.

Conclusions: In obese diabetic subjects with CKD, structured exercise improved exercise capacity but not body composition or renal function.

Funding: VA Support

FR-PO831

Renal Sympathetic Activity Assessed by 123I-MIBG Scintigraphy Is Associated with Clinical Measures of Cardiac Autonomic Function

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Background: Scintigraphy with ^{123}I-metaiodobenzylguanidine (MIBG) can assess functional sympathetic innervation in organs. The relation between renal ^{123}I-MIBG uptake and measures of cardiac autonomic function has never been investigated.

Methods: In 25 patients with type 2 diabetes and 14 non-diabetic controls we performed three cardiac autonomic reflex tests (CARTs) and five time- and frequency domain heart rate variability (HRV) indices. We quantified functional renal sympathetic innervation by planar scintigraphy performed 15 min (early) and 4 hours (late) after administration of ^{123}I-MIBG. Regions of interest (ROI) were drawn over left kidney (avoiding the pelvis) and the upper mediastinum (avoiding the thyroid gland) in the planar posterior view, andlate kidney/mediastinum-ratio was calculated from mean counts per pixel within each ROI.

Results: Late kidney/mediastinum ratio correlated positively with all time- and frequency domain HRV indices ($p \leq 0.02$). For the CARTs, the late kidney/mediastinum ratio correlated positively with the deep breathing test (a measure of parasympathetic function) ($p=0.04$), but not with response to standing or the Valsalva test ($p \geq 0.70$). All significant associations persisted after adjustment for age and heart rate ($p \leq 0.02$). After further adjustment for sex, HbA1c and urinary albumin excretion rate one of the HRV indices, low frequency power, reflecting a combination of sympathetic and parasympathetic tone remained significantly correlated to late kidney/mediastinum ratio ($p=0.02$). Late kidney/mediastinum ratio did not correlate with urinary albumin excretion rate, eGFR or systolic blood pressure ($p \geq 0.19$).

Conclusions: We demonstrate a relationship between renal ^{123}I-MIBG uptake and cardiac autonomic function. This indicates that ^{123}I-MIBG scintigraphy of renal sympathetic tissue could be a valid measure of autonomic function in the kidneys and warrants further research in larger study populations.

FR-PO832

Comparative Effectiveness of a Multifactorial Patient-Centered Intervention in Type 2 Diabetes (T2D)

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Background: The STOP-DKD study is an ongoing clinical trial evaluating the impact of a multifactorial pharmacist telehealth intervention on renal complications of T2D. We sought to explore expected costs, improvements in quality-adjusted survival and cost-effectiveness of implementing such an intervention on a population level in T2D when varying program costs and age eligibility.

Methods: The Archimedes Model is a mathematical simulation model which represents physiological processes using data incorporated from the National Health and Nutrition Survey (NHANES) to generate population-level estimates. We used Archimedes modeling to simulate and compare costs and outcomes over a 20-year (yr) period amongst individuals with T2D receiving usual care and a multifactorial intervention consisting of statin therapy, smoking cessation, blood pressure reduction (systolic blood pressure 139 mmHg if > 140), weight reduction (5% if BMI >30 and <35; 10% if BMI ≥35) and HbA1c reduction (target 8% if >8%), each modeled at 50% effectiveness. We varied annual program costs from $200 to $800 per individual and assessed four age-based subgroups (45-64, <65, 65-74 and ≥65 yrs).

Results: Among individuals ages 20 to 80 yrs, 9.4% are diagnosed with T2D (mean age 60.2yr). Simulated, undiscounted quality-adjusted life-years (QALYs) with usual care and QALY gains expected with the multifactorial intervention were estimated at 3.93+ 0.02 at 5yr, 7.26+ 0.06 at 10yr and 12.09+ 0.22 at 20yr. At 20yr, all programs ranging from $200 to $800 per yr per individual demonstrated good value: $200/yr, cost-saving; $400/yr, $7025 per QALY; $600/yr, $18,461 per QALY; and $800/yr, $33,784 per QALY. The program was more economically-attractive when targeting older individuals with incremental cost-effectiveness ratios of $23,299 per QALY in ages 65-74 and $23,362 per QALY in ages ≥65.

Conclusions: Dissemination of a population-based, moderately-effective, low-cost, patient-centered intervention in T2D could increase quality-adjusted life expectancy more efficiently than standard medical therapies used to treat complications of T2D, particularly among older individuals.

Funding: NIDDK Support

FR-PO833

Referral to a Multi-Disciplinary Diabetic Renal Clinic Is Associated with Improved Renal Functional Course in Type 2 but Not Type 1 Diabetics with Chronic Kidney Disease

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Background: Diabetic patients with chronic kidney disease (CKD) may benefit from combined Diabetology and Nephrology care. The study aim was to examine the impact of a multi-disciplinary Diabetic Renal Clinic (DRC) on slope of MDRD eGFR and metabolic indices of type 1 (T1D) and type 2 (T2D) diabetics with CKD.

Methods: Patients attending a DRC at a tertiary referral center from 2008 to 2012 were identified. Serial renal and metabolic indices were recorded from 2004 to 2014, and compared pre- and post-first DRC attendance using SPSS v22.

Results: 200 subjects were identified (44 (22.0%) T1Ds and 156 (78.0%) T2Ds). Median [IQR] number of eGFR measurements was 31 [18, 56] per subject over 8.70 [6.34, 10.31] years. Age, n (%) female, eGFR, and urinary albumin:creatinine ratio of the two subgroups at the time of first DRC attendance were: 44.71 ± 15.71 vs. 68.94 ± 10.53 years ($p < 0.001$); 19 (43.2%) vs. 46 (29.5%) ($p = 0.126$); 57.98 ± 29.92 vs. 46.10 ± 20.57 mL/min/SA/year ($p = 0.018$); and 33.30 [4.00, 147.50] vs. 13.20 [3.20, 91.10] mg/mmol ($p = 0.321$). An additional etiology for CKD was found in 2 (4.5%) T1D and 34 (21.8%) T2D subjects. Results for eGFR decline are shown in the Table.

	T1D (n = 44)				T2D (n = 156)			
	Pre-DRC Attendance	Post-DRC Attendance	n (%)	p	Pre-DRC Attendance	Post-DRC Attendance	n (%)	p
Rate of eGFR decline (mean ± SD; mL/min/SA/yr)	-2.06 ± 4.37	-2.77 ± 3.33	28 (63.6%)	0.476	-3.22 ± 4.52	-2.21 ± 3.14	105 (67.3%)	0.049
Mean $HbA1_c$ (mean ± SD; mmol/mol)	79.22 ± 19.82	71.81 ± 17.73	42 (95.4%)	0.001	62.23 ± 14.37	60.73 ± 13.13	143 (91.7%)	0.171
Mean total cholesterol (mean ± SD; mg/dL)	197.22 ± 50.27	180.59 ± 41.38	40 (90.9%)	0.012	157.77 ± 35.19	152.36 ± 36.74	127 (81.4%)	0.065

Conclusions: Referral to a combined care DRC resulted in slower eGFR decline in T2D but not T1D subjects with CKD.

Funding: Government Support - Non-U.S.

FR-PO834

Impact of the Medical Care by Diabetologists, Non-Diabetlogists and Home Doctors before Nephrology Referral on Renal Prognosis in Patients with Diabetic Nephropathy

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Background: Although it has been recognized that early referral to nephrologists is crucial for the protection of kidney function, it is hard to say that in the current clinical practice in Japan, nephrology referral (NR) is early enough for nephrologists to offer specialized care to patients with diabetic nephropathy (DN). Thus, we conducted single center retrospective study to compare the impact of the medical care by diabetologists, non-diabetologists and home doctors before NR on clinical status at NR and renal outcome.

Methods: We enrolled 469 patients with DN referred to our nephrology division from October 2010 to September 2014. Clinical status at NR were compared among the three groups and the impact of the medical care by the different specialties before NR on renal outcome (initiation of renal replacement therapy; RRT) was analyzed by multivariate Cox proportional hazards model.

Results: Mean age and eGFR at NR were 67.1±12.3 years and 31.2±19.6 ml/min/1.73m^2, respectively and 70.5% were male. The number of patients referred from diabetologists (Group A), non-diabetologists (Group B) and home doctors (Group C) were 140, 184, and 145, respectively. A total of 105 patients started RRT: 33, 45 and 27 in Group A, B and C, respectively ($P = 0.416$). The cumulative incidence of renal outcome was not significantly different between the groups ($P = 0.392$). The median duration from NR to the renal outcome was 16.7 months (IQR : 6-25.3). Multivariate Cox proportional hazards model showed that eGFR (HR 0.90; 95%CI 0.86-0.94), proteinuria (HR 1.03; 95%CI 1.01-1.05), and systolic blood pressure (HR 1.01; 95%CI 1.00-1.03) were independently associated with renal outcome; however, pre-nephrology care by non-nephrologists including diabetologists did not have any impact on renal outcome.

Conclusions: In the current clinical practice in Japan, NR may be too late to offer specialized care by nephrologists to protect kidney function in patients with DN.

FR-PO835

Patients' Perspectives of Diabetes Management in the Haemodialysis Unit Katey Atkins, Adam Kirk. *Wessex Kidney Centre, Queen Alexandra Hospital, Portsmouth, United Kingdom.*

Background: Patients with diabetes and established renal failure on haemodialysis pose unique challenges for the nephrologist. Individualised care is recommended with the aim to improve outcomes without added hypoglycaemic risk. Patient understanding will underpin this process. We performed a survey to establish the current practices and opinions of our haemodialysis patients managing diabetes.

Methods: A questionnaire was distributed to all patients with diabetes that are on regular maintenance haemodialysis.

Results: 110 returned questionnaires, 101 in-centre HDF and 9 from the Home HD programme. Of these 20% report having Type 1 diabetes, 73% Type 2 diabetes and 7% were unclear. 97/110 (88%) have had diabetes for over 5 years. 93/110 (84%) of all respondents considered themselves to be either very or quite confident in managing their diabetes. Surprisingly 52/110 (47%) were unaware of the HbA1c test. 85/110 (77%) were on insulin therapy. One person reported having no home monitor. In the 84 remaining 6% did not check their blood sugars, a further 5% did not check on a daily basis. 6/110 respondents had either no access to a home monitor or did not have blood sugar levels checked at dialysis. The remaining 104 provided opinions on glucose control and corrective actions. For some answers more than one response was given, this was reflected in the totals. 29/104 (28%) considered only a reading of ≤ 3 to be low, 8 (8%) did not know what a low reading was. On having a low reading 7/108 (6%) did nothing or did not know what to do, only 2 commented on adjusting medication and 1 on re-checking. 17/104 (16%) did not consider a reading to be high until it was ≥20, 9/104 (9%) did not know what a high reading was. Following a high level 22/110 (20%) of all answers stated they either did nothing or did not know what to do. Of those on insulin 49/85 (58%) adjust insulin dose in their actions. 10/110 (9%) managed hyperglycaemia with water or exercise.

Conclusions: There is significant variation in practices and opinions within the cohort of patients that responded. Despite the high level of perceived confidence many issues with understanding and safety has been highlighted. To address this we propose targeted education programme.

FR-PO836

Timing of Renal Replacement Therapy in Acute Kidney Injury: A Systematic Review and Meta-Analysis Rhea Bhargava,[1] Saiprasad Narsingam,[1] Himmat Grewal,[3] Mohamed A. Omer,[1] Reem Mustafa.[2] *[1]Internal Medicine, Univ of Missouri - Kansas City School of Medicine, Kansas City, MO; [2]Nephrology, Univ of Missouri - Kansas City School of Medicine, Kansas City, MO; [3]Internal Medicine, Saint Vincent Hospital, Worcester, MA.*

Background: Acute Kidney Injury (AKI) is common in critically ill patients and has been associated with increased mortality. The timing of initiation of renal replacement therapy (RRT) has been controversial in patients with AKI.

Methods: We searched the Cochrane Central Register, OVID MEDLINE, EMBASE and PubMed until May 15th 2016. We reviewed the reference lists of relevant reviews, registered trials, as well as relevant conference proceedings. We included all randomized controlled trials that evaluated the effect of timing of initiation of renal replacement therapy in adult patients with AKI. We followed the GRADE approach to assess confidence in the estimates of effect (i.e. the quality of evidence). We conducted meta-analyses using random effects models on review Manager Version 5.3.

Results: Nine randomized control trials were included consisting of a total of xxx pts. Compared to "Late RRT", "early RRT" had a non-significant decrease in mortality with a Risk Ratio (RR) of 0.92 (95% confidence interval (CI) 0.82-1.04, p=0.18, I^2=51%). However, "early RRT" significantly decreased the number of patients who were dialysis dependent with a RR of 0.55 (95% CI 0.32-0.95,I^2=0%). Intensive care unit length of stay (LOS) decreased with a mean difference (MD) of 1.41 days (95% CI 0.24-2.59 ,I^2=0%) and hospital LOS also decreased with a MD of 5.15 days (95% CI 3.0-7.3 ,I^2=87%) in the early versus late RRT group. There was no difference in the adverse events between the two groups.

Conclusions: In critically ill patients with AKI, early initiation of RRT may decrease dependence on long-term dialysis. It may also shorten the ICU and hospital LOS. Additional studies are needed to determine the true effect on mortality although it appears to be decreased.

FR-PO837

Implementation of a Decision Making Algorithm for Acute Kidney Injury Requiring Renal Replacement Therapy Mallika L. Mendu, David M. Charytan, Joseph V. Bonventre, Sushrut S. Waikar. *Brigham and Women's Hospital, Harvard Medical School, Boston, MA.*

Background: Acute kidney injury (AKI) is a common and devastating complication in hospitalized patients. AKI requiring renal replacement therapy (RRT) is associated with in-hospital mortality rates exceeding 40%. Clinical decision tools related to RRT initiation for AKI patients in the ICU have yet to be elucidated.

Methods: We conducted a 1-year prospective cohort study in a medical ICU of an academic medical center involving the implementation of an AKI Standardized Clinical Assessment and Management Program (SCAMP), a decision making algorithm. The SCAMP algorithm provided recommendations about optimal indications for initiating and discontinuing RRT based on various clinical parameters. We collected information on clinicians' adherence or non-adherence to the SCAMP recommendations as well as clinical outcomes.

Results: Patients whose providers adhered to the SCAMP recommendation to start RRT had lower in-hospital mortality (42% vs. 63%, p<0.01) than those whose providers did not. The difference in mortality persisted after multivariable logistic regression analysis adjusting for age, albumin and severity of disease. In pre-specified subgroup analyses, adherence was associated with lower risk of death only in patients with severity of disease scores below the median (adjusted odds ratio 0.21, 95% CI 0.08 – 0.54).

-	Univariable OR (95%)	p-value	Multivariable OR (95% CI)	p-value
Adhered to recommendation to start RRT	0.42(0.22, 0.81)	0.01	0.43 (0.21, 0.85[a]	0.02
By Risk Group				
High risk[c]	1.09(0.40, 2.95)	0.86	1.06 (0.38, 2.95)[b]	0.91
Low risk[d]	0.22(0.09, 0.55)	<0.01	0.21 (0.08, 0.54)[b]	<0.01
Age at enrollment	1.02 (1.00,1.04)	0.12	1.02 (1.00, 1.04)	0.1
Albumin at enrollment	0.49 (0.29,0.82)	<0.01	0.49 (0.27, 0.89)	0.02

a. Main effects for risk group and adherence b. Incorporates interaction term between risk group and adherence, p-value= 0.02 c. High ATN risk- >50% predicted mortality risk d. Low ATN risk- <50% predicted mortality risk.

Conclusions: Algorithms like the AKI SCAMP may assist in complex clinical decision making and potentially improve outcomes.

FR-PO838

Analysis of Mortality Predictors in Acute Kidney Injury Requiring Continuous Renal Replacement Therapy after Cardiac Surgery Young Lee Jung,[1] Jae Young Kang,[2] Soo Youn Lee,[3] Dong Jin Kim.[4] *[1]Dept of Internal Medicine, ; [2]Div of Nephrology, ; [3]Div of Cardiology, ; [4]Dept of Cardiothoracic Surgery, Sejong Hospital, Korea.*

Background: Since the postoperative AKI contributes to high mortality,several risk factors have been reported to be associated with AKI after cardiac surgery.Despite the advances of CRRT and surgery techniques using cardiopulmonary bypass as the management of AKI,the mortality of postoperative AKI requiring CRRT increased.The purpose of this study was to determine the predictors of mortality in AKI requiring CRRT after cardiac surgery,and to contribute to reducing mortality through correction of the determined risk factors.

Methods: The retrospective analysis included a total of 3623 patients underwent cardiac surgery;CRRT was required in 125patients between March 2011 and March 2016. Variables predicting mortality were selected from those proven as available risk factors of postoperative AKI in the previous studies.The variables were analyzed in two groups:non-survivor group who died within 30days,and survivor group.We used a logistic regression model to assess the relationship between predictors and mortality,while adjusting for other risk factors.

Results: The mortality rate was 44.1% for 125 patients with postoperative AKI requiring CRRT.Univariate analysis identified the following as significant risk factors:Extracardiac vascular disease,eGFR,EuroSCORE,IABP before surgery,Combined operation,Operation time,Time of bypass,Aortic cross clamp time,CRP level at CRRT,the use of ECMO(P<0.05). In multivariate analysis,mortality was significantly correlated with extracardiac vascular disease,eGFR,combined operation,CRP level at CRRT,the use of ECMO(P<0.05).

Conclusions: These findings demonstrated that the statistically strong predictors of the mortality following cardiac surgery were proved to be the presence of extracardiac vascular disease,preoperative renal dysfunction,concomitant surgery,the use of ECMO,and high CRP level at CRRT initiation.The identification of predictors associated with mortality would help to better manage such patients with AKI requiring CRRT after cardiac surgery. Also,preventive strategy using these predictors remains the mainstay to reduce the mortality.

FR-PO839

Predictors of AKI and Renal Outcome in Adult Patients on Extra Corporeal Membrane Oxygenation (ECMO) Venkata Buddharaju, Maureen E. Brogan, Rudrick V. Ledesma, Savneek S. Chugh. *Nephrology, New York Medical College, Valhalla, NY.*

Background: ECMO is increasingly being used in critical care units for patients with cardiogenic shock or respiratory failure. In spite of advances, mortality associated with it is very high. Acute Kidney injury (AKI) requiring renal replacement therapy (RRT) is very common and is associated with increased mortality. There is paucity of data about the predictors of AKI needing RRT and of poor outcome among these patients. Previous studies have been mostly in pediatric population and data is lacking in adults.

Methods: We performed a chart based retrospective study analyzing all the adult patients admitted to our hospital receiving ECMO.

Results: Charts on 40 patients reviewed which showed high in-hospital mortality (45% or 18/40) and the incidence of AKI was 50% (20/40). The Etiology of AKI was documented to be from Acute Tubular Necrosis (ATN). Out of 20 patients with AKI, 18 patients required RRT with 16 patients requiring CVVHD (Continuous Veno-venous hemodialysis) and 2 required Hemodialysis (HD) as the initial modality of renal support. Out of 18 patients who died, 10 patients had AKI requiring RRT. The data also showed that 16 patients had new onset proteinuria on dipstick and was associated with the development of AKI. We found an interesting relationship between the flow on ECMO and development of AKI. Low flow less than 2-2.5L and high flow more than 4-4.5L are associated with more AKI. This relationship has to be studied using statistical analysis at the conclusion of the data

collection. Out of 20 patients who developed AKI, 10 patients died, another 4 went on to End Stage requiring HD at the time of discharge and the remaining 6 patients left with significant renal injury and progressed to chronic kidney disease.

Conclusions: What is clear from our study so far is that patients, who require ECMO, regardless of the indication, have a higher mortality and AKI requiring RRT. The flow parameters are also very interesting as very low (less than 2.5L/min) and higher flows (more than 4-4.5L) are associated with kidney injury which supports the hypothesis that AKI in these patients are mainly due to ischemic ATN.

FR-PO840

Intraoperative Hemodialysis during Liver Transplantation Cary H. Paine,[1] Terra Pearson,[2] James D. Perkins,[2] Raghu V. Durvasula.[1] *[1]Dept of Medicine, Div of Nephrology, Univ of Washington, Seattle, WA; [2]Dept of Surgery, Div of Transplant Surgery, Univ of Washington, Seattle, WA.*

Background: With the introduction of the Model for End-Stage Liver Disease (MELD) in 2002 the percentage of liver transplant recipients (LTRs) with acute kidney injury (AKI) has increased. Intraoperative hemodialysis (IHD) during liver transplantation has been shown to be safe, but it is unknown whether this procedure improves perioperative outcomes.

Methods: We conducted a retrospective analysis of all LTRs at the University of Washington between 2003 and 2014. We compared all LTRs that received IHD with LTRs that had preoperative AKI but did not undergo IHD. AKI was defined as serum creatinine ≥1.5mg/dL. Outcomes included postoperative serum potassium, arterial base deficit, alanine aminotransferase (ALT) (a marker of early graft function), ventilator days, ICU length of stay (LOS), and hospital LOS.

Results: Among 1,191 LTRs, 146 received IHD (12.3%) compared to 164 patients who had AKI but did not receive IHD (13.8%). IHD patients had higher MELD scores (mean 34.6 vs. 24.9) and were more likely to require mechanical ventilation and vasoactive medications preoperatively. ALT and arterial base deficit were lower in the IHD group, and there was no difference in serum potassium, ventilator days, or ICU LOS. Hospital LOS was longer in the IHD group (Table 1).

Table 1: Postoperative Outcomes

	IHD [n=146]	non-IHD [n=164]	P
Mean (SD) Potassium (mEq/L)	4.5 ± 0.7	4.6 ± 0.8	0.11
Mean (SD) Arterial Base Deficit (mEq/L)	6.98 ± 4.2	9.9 ± 3.8	<0.0001
Mean (SD) ALT (units/L)	799 ± 1044	1061 ± 1012	0.02
Mean (SD) Ventilator days	1.86 ± 3.67	1.78 ± 5.37	0.9
Mean (SD) ICU LOS (days)	4.35 ± 5.2	3.28 ± 6.2	0.17
Mean (SD) Hospital LOS (days)	37 ± 33.6	19 ± 16	<0.0001

Conclusions: Our data indicate that, despite an overall higher level of acuity among LTRs who received IHD, there was no difference in postoperative electrolyte concentrations, ventilator days or ICU LOS when compared to LTRs with AKI who did not receive IHD. However, LTRs who received IHD had lower ALT levels, which may suggest better early graft function. Clinical trials are needed to further determine the efficacy of IHD in LTRs to improve perioperative and long-term outcomes.

FR-PO841

Use of Novel Phosphate-Containing Replacement Solution for Treating Hypophosphatemia in Continuous Renal Replacement Therapy (CRRT): Predictions from a Mass Balance Model Farah N. Ali,[1,2] Mary Gellens,[1] Baris U. Agar,[1] J. Ken Leypoldt.[1] *[1]Baxter Healthcare; [2]Northwestern Univ.*

Background: Hypophosphatemia is a common consequence of CRRT that often requires treatment with intravenous infusion of phosphate-containing solutions. Conventional replacement solutions (RS) do not contain any phosphate, but phosphate-containing replacement solutions (RS+P) now exist; however, there is limited data on optimal use of such solutions. Our objective was to predict the changes in serum phosphate concentration for hypophosphatemic patients when using RS+P in various CRRT prescriptions.

Methods: A mass balance model was used to predict increases in serum phosphate concentration for patients treated with CRRT when using varying ratios of conventional dialysate/replacement fluid with zero phosphate concentration and RS+P (1 mmol/L or 3.097 mg/dL phosphate). CRRT assumptions included: solution rates of 20-40 mL/min, starting serum phosphate concentrations of 1.5, 2.0, or 2.5 mg/dL, and CVVHDF modality.

Results: Use of RS+P alone or as both replacement fluid and dialysate increased serum phosphate concentrations in all 3 starting concentration groups; increases in serum phosphate concentrations ranged from 1.24 to 2.95 mg/dL. For starting phosphate values of 1.5 mg/dL, any studied combination of fluids normalized the serum phosphate (normal range 2.5-4.5 mg/dL). For starting phosphate values of 2.5 mg/dL, only use of RS+P as both replacement and dialysate resulted in values of serum phosphate higher than 5.0 mg/dL. Use of RS+P post-filter resulted in modestly higher values than pre-filter infusion.

Conclusions: Normalization of serum phosphate using RS+P in CRRT may be achieved through a variety of prescription techniques. High phosphate levels only occurred with higher baseline serum phosphate values when RS+P was used as both replacement and dialysate. Varying the proportion of RS+P as replacement fluid and dialysate during CVVHDF may allow individualization of therapy to normalize serum phosphate, while maintaining CRRT dose.

FR-PO842

A Comparison of Two Different Dialysate Phosphate Supplementation Approaches for Continuous Renal Replacement Therapy Michael Heung,[1] Alex Ryan Shaw,[2] Weerachai Chaijamorn,[2] Bruce A. Mueller.[2] *[1]Internal Medicine-Nephrology, Univ of Michigan, Ann Arbor, MI; [2]College of Pharmacy, Univ of Michigan, Ann Arbor, MI.*

Background: Hypophosphatemia is a common and clinically significant complication of continuous renal replacement therapy (CRRT). To decrease risk of hypophosphatemia, we routinely supplement CRRT solutions with phosphate (1.5mmol/L). Recently, a commercially-available phosphate-containing (P-C) CRRT solution (1.0mmol/L) has become available in the US.

Methods: We performed a time-limited substitution trial of P-C CRRT solution and compared biochemical parameters to our baseline standard approach of phosphate-added (P-A) solutions. CRRT was otherwise prescribed at discretion of treating team. Outcomes were daily serum phosphate and bicarbonate concentrations, incidence of hypophosphatemia and acidosis, and need for phosphate supplementation.

Results: We analyzed data from 127 patient CRRT-days using P-C solutions and compared to baseline experience with 256 CRRT-days using P-A solutions (Table). Mean daily phosphorus levels were in the normal range for both groups, but lower in the P-C compared to P-A groups; there was no difference in incidence of hypophosphatemia. The P-C group did receive more exogenous phosphate administration but at a low overall rate. No CRRT solution-related complications occurred during either period of the pilot.

Variables	Phosphate Containing Dialysate (4 K/1 Phos/22 HCO_3)	Phosphate Added Dialysate (4 K/1.5 Phos/25 HCO_3)	P-Value
Minimum daily phosphorus, mean (SD)	3.41 (0.87)	3.78 (0.98)	<0.05
Maximum daily phosphorus, mean (SD)	4.27 (1.34)	4.61 (1.11)	<0.05
Phosphorus <2.7mg/dL (% of days)	14.29	13.67	0.87
Phosphate supplementation (% of days)	5.51	1.56	<0.05
Daily serum bicarbonate, mean (SD)	28.56 (6.32)	29.60 (6.06)	0.16
Serum bicarbonate <22mEq/L (% of days)	12.60	8.59	0.22
Daily pH, mean (SD)	7.39 (0.06)	7.36 (0.06)	<0.05

Conclusions: Overall, hypophosphatemia was uncommon when using phosphate-enriched CRRT solutions, and occurred at a similar rate between the P-A and P-C groups. Commercially available P-C dialysate has the potential advantage of eliminating the risks associated with compounding errors, such as contamination or incorrect additives. Additional analyses examining clinical outcomes and cost effectiveness are needed.

FR-PO843

Cost Savings and Quality Improvement in an Independent Pediatric CRRT Program Katherine Twombley. *Pediatrics, Medical Univ of South Carolina.*

Background: CRRT is a complex method of providing dialysis to critically ill patients. Lack of education and hands on training specific to pediatric patients can lead to inadequate therapy. The goal of this project was to implement a pediatric specific CRRT education program for nurses and ICU physicians.

Methods: Pediatric specific education, protocols, clinical algorithms, and policies were developed. Direct care nurses completed an 8 hour learning session that included hands on practice using high fidelity simulation. Additionally, a core pediatric CRRT resource team comprised of nurses with advanced training in CRRT was formed to provide additional support for therapy initiation, sophisticated pump management, and additional staff needs. We also developed a pediatric ICU physician class that focused on the importance of starting CRRT before a patient is fluid overloaded to decrease treatment time. Pre and post education tests were given to asses comprehension. After one year, we compared filter life and dose of CRRT received.

Results: Pre education CRRT knowledge for RN and MD/DOs was 73% and post was 93%. Our average Filter life before training was 8.9 hours. Our average filter life post is 55.81 hrs. Pre-education we did 7272 hours of CRRT=17.8days/pt=427hrs/pt. At 8.9hrs/filter=817 filters X $210/filter=$171,586 .Assume 4 bags of fluid/day @$28.21/bag=$34,190.52 **Total=$239,967.04** Post-education we did 2352 hour of CRRT=7days/pt=168hrs/pt. At 55.81hrs/filter=42 filters X $210/filter=$8850 Assume 4 bags of fluid/day @$28.21/bag=$11,058.32 **Total=$19,908.32 Total Savings since new education initiative=$220,028.72** on filters and fluids alone. Pre education, the unintended time off therapy was 9 hrs, and the patients received only 81% of prescribed dose. Post education, the unintended time off therapy was 0.9hrs, the patients received 98% of the prescribed dose.

Conclusions: An independent pediatric CRRT education program and resource team were instrumental in creating a baseline for all caregivers. Pediatric CRRT algorithms established a standard of care for all patients. In addition, interactive education and ongoing support improved delivery of therapy and reduced time off therapy overall. This resulted in a huge cost savings in just one year.

FR-PO844

Effect of Continuous Renal Replacement Therapy on Carnitine Levels and Acyl to Free Carnitine Ratio in Children Kl Sgambat, Asha Moudgil. *Children's National, Washington DC.*

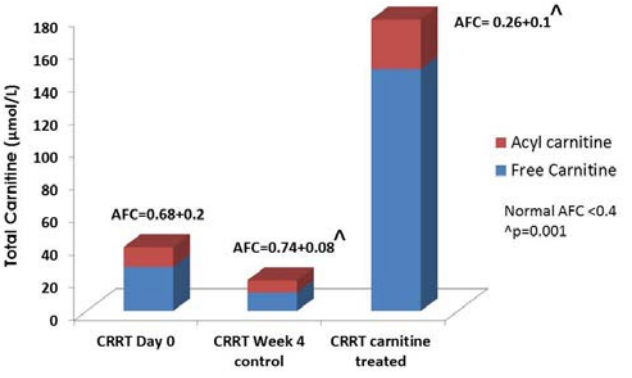
Background: Carnitine is essential for energy production in myocardium and removal of toxic acylcarnitines. We recently showed carnitine is rapidly depleted by continuous renal replacement therapy(CRRT), however effect of CRRT on acylcarnitine and response to therapy have not been investigated. We report effect of CRRT and carnitine therapy on carnitine homeostasis in critically ill children with acute kidney injury(AKI).

Methods: We conducted a retrospective study of children(0-26 years) who underwent CRRT at Children's National between 2011-2015. Patients with serial total(TC) and free carnitine(FC) levels were included and acyl to free carnitine ratio(AFC) calculated. TC, FC, and AFC of patients who received intravenous carnitine during CRRT were compared with unsupplemented controls by Student's t-test, prevalence of abnormal TC, FC, and AFC(≥0.4) by Chi-squared.

Results: The study group comprised of 49 children(9.2± 0.9 years); 6 received carnitine supplementation, 43 controls did not. At initiation of CRRT, 41.1% were TC and FC deficient, and 64.7% had elevated AFC. Prevalence of abnormal TC, FC, and AFC increased to 100% by week 4 of CRRT in controls. In comparison, 100% of those treated with carnitine while on CRRT became TC and FC replete, and only 16.6% had abnormal AFC(p=0.003). TC and FC of treated patients(179+108 and 148.5+93.1 µmol/L) were higher vs. controls(27.1+2.3 and 18.7+1.8 µmol/L), p=0.0001. Mean AFC at CRRT initiation was elevated (0.68±0.16), and increased to 0.74±0.08 within 4 weeks in controls; FC negatively correlated with AFC(r= -0.4,p=0.003). In those treated with carnitine, AFC normalized to 0.26+0.06 at 4 weeks of CRRT(p=0.001),see Figure.

Conclusions: CRRT is associated with disturbed carnitine homeostasis, resulting in TC and FC deficiency with concurrent elevation of AFC. This is the first study to show TC, FC, and AFC normalize in children on CRRT who receive carnitine supplementation.

Figure. Mean total and free carnitine levels decrease while Acyl:free carnitine ratio (AFC) increases with time on CRRT in controls. Mean AFC is normal in those receiving carnitine supplementation on CRRT.



FR-PO845

High Cut-Off Dialysis Is Efficient with HCO Membrane Markus Storr, Ulrike Haug, Adriana Boschetti-de-Fierro, Bernd Krause. *Research & Development, Gambro Dialysatoren GmbH, Hechingen, Germany.*

Background: High cut-off (HCO) membranes are indicated for enhanced removal of 20-50kDa toxins [Gondouin, Adv Chronic Kidney Dis 2011]. Applications include myeloma kidney treatment, sepsis and rhabdomyolysis. Though a classification for HCO membranes is available [Boschetti-de-Fierro, Int J Artif Organs 2013], some high-flux dialyzers are used for high cut-off dialysis. We compare the performance of two dialyzers offered for high cut-off treatment of myeloma kidney, and which, according to the mentioned classification, are categorized as high cut-off dialyzer (Theralite) and as high-flux dialyzer (APS-21EH).

Methods: High cut-off treatments were simulated with Q_B=250ml/min, Q_D=500ml/min and Q_{UF}=10ml/min for Theralite (HCO, Gambro) and APS-21EH (APS, Asahi). In each experiment (HCO n=7, APS n=2), 1L of human plasma (octaplasLG, protein conc. 60g/L) was recirculated for 60min followed by 60min treatment. Markers were spiked into the plasma at 55min of recirculation: β2-m (5 mg), myoglobin (500 µg), λ-FLC (150 mg), interleukin 6 was comprised in plasma. Samples were taken from plasma pool and dialysate at various times. Clearances were calculated from first order kinetics of pool concentration (measured by nephelometry) over time.

Results:

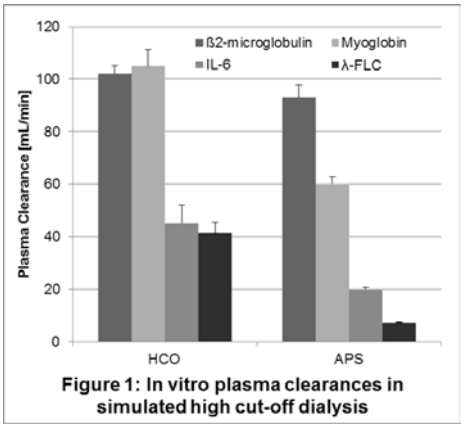


Figure 1: In vitro plasma clearances in simulated high cut-off dialysis

The HCO membrane showed higher clearances than the APS high-flux membrane for the middle molecules investigated. High differences were found for myoglobin (105 vs. 60ml/min), relevant when treating rhabdomyolysis, and for λ-FLC (41 vs. 7ml/min), which is relevant in the myeloma treatment.

Conclusions: Based on the plasma clearances observed, an efficient high cut-off dialysis treatment with the expected removal of middle molecules is only possible with dialyzers comprising a membrane categorized as high cut-off (HCO) membrane. Results indicate that a high-flux membrane does not offer the efficient removal required in acute cases.

Funding: Pharmaceutical Company Support - All authors are employees of the Gambro Dialysatoren GmbH, Hechingen (Germany). Gambro AB (including all direct and indirect subsidiaries) is now part of Baxter International Inc. Baxter is a manufacturer of dialysis devices. None of the authors has proprietary interest. All experimental information is given in great detail to exclude any bias on the results

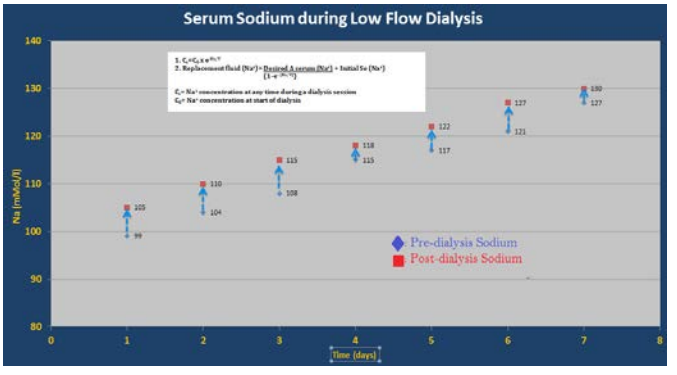
FR-PO846

Use of Logarithmic Constant of Exponential Decay to Control Sodium Conductivity and Kinetics in a Patient with End Stage Renal Disease and Severe Hyponatremia Hormaz Dara Dastoor,[1] Chandra Mauli Jha,[2] Ken J. Donaldson,[3] Thalakunte Muniraju,[3] Samra Abouchacra,[1] Hatem Mohyeldin Ebeid.[4] *[1]Div of Nephrology, Rahba Hospital- Johns Hopkins International, United Arab Emirates; [2]Div of Nephrology, Burjeel Hospital, United Arab Emirates; [3]Div of Nephrology, Dumfries and Galloway Royal Infirmary, United Kingdom; [4]Div of Nephrology, Al Noor Hospital, United Arab Emirates; [5]Div of Nephrology, Tawam Hospital, United Arab Emirates.*

Background: We present a case of a patient with severe renal failure and Hyponatremia who was treated by Renal Replacement Therapy. Sodium (Na^+) Kinetics and Conductivity were regulated using a complex algorithm created using a logarithmic constant "*e*" as measure of Exponential Decay of Na^+ transfer, resulting in a controlled and predictive rise in Plasma Sodium (PNa^+).

Methods: A 25-year-old male presented with renal failure and PNa^+ 99 mmol/l, urea 58 mmol/l, Creatinine 1551 umol/l with altered mental status and seizures.The patient was initially placed on CVVHD followed by conventional HD. Over the next few days his PNa^+ had a gradual and steady rise and had a complete recovery without any neurological sequelae .

Results: Using the below formulas we can predict expected post dialysis Serum Na concentration and determine Na concentration of Replacement fluid required to achieve desired post dialysis Na concentration.



Conclusions: Understanding the principles of Sodium Transfer, Conductivity and Kinetics in renal failure, allows for use of complex Logarithmic equations using Mathematical constant of Logarithmic Decay "e" as measure of exponential transfer of Sodium and Urea.By controlling the transfer of Sodium during a Hemodialysis session we can control the rate of rise in Plasma Na^+ for patients with severe Hyponatremia and renal failure. This can result in a steady rise in PNa^+ concentrations and avoid potentially fatal ODS.

FR-PO847

OPTIMAL Selection for and Timing to Start Renal Replacement in Critically Ill Older Patients with Acute Kidney Injury (OPTIMAL-AKI): A Prospective Observational Cohort Study

Ron Wald,[1] Josee Bouchard,[2] Jean-Francois Cailhier,[2] James William Barton,[3] Sean M. Bagshaw.[4] *[1]St. Michael's Hospital, Canada; [2]Univ de Montreal, Canada; [3]Univ of Saskatchewan, Canada; [4]Univ of Alberta, Canada.*

Background: Older patients represent approximately half of those who receive renal replacement therapy (RRT) in intensive care unit (ICU) settings. We have limited information on the optimal circumstances for starting or withholding RRT in older patients with AKI.

Methods: Prospective observational cohort study performed at 16 centers from across Canada, September 2013 and July 2015. Inclusion criteria: 1) >= 65 y, 2) admitted to ICU, and 3) KDIGO Stage 2-3 AKI. Exclusions: 1) received urgent RRT for drug overdose and 2) receiving any RRT in preceding 4 weeks. Primary exposure was receipt of RRT. Primary outcome was 90-day mortality. Secondary outcomes included reasons for not receiving RRT and changes to goals-of-care (GOC).

Results: 499 patients were enrolled. Mean age was 75 (SD 7.2) y, 204 (41%) were female, and mean Charlson comorbidity score was 3.0 (SD 2.3). Median Clinical Frailty Score (CFS) was 4.0 (IQR 3.0-5.0), 95 (20%) had cognitive impairment and 192 (39%) and has been hospitalized in the preceding 6 months. Mean APACHE II score was 28.0 (SD 8.8). Of the cohort, 361 (72%) of patients would have been offered RRT if indicated while 229 (46%) actually received RRT. Leading indications for RRT included oligo-anuria (74%), fluid overload (35%) and acidemia (33%). Reasons for not starting RRT included: kidney recovery (67%), not aligned with goals-of-care (25%) and active limitation-of-medical-therapy (11%). Factors independently associated with not receiving RRT included: age, CFS, peak serum creatinine at admission, vasoactive support and APACHE II score. 90-day mortality was 45% (n=113) for those receiving RRT and 56% (n=141) for those not receiving RRT (OR 0.91; 95% CI, 0.64-1.31). In total, 201 patients (42%) had a change in GOC; change in GOC was not associated with the receipt of RRT.

Conclusions: The majority of older adults in the ICU with AKI would be offered RRT and approximately half received RRT. Clinical need, as well as underlying frailty and severity of illness, influence decision-making regarding RRT.

Funding: Government Support - Non-U.S.

FR-PO848

Temporal Trends of Dialysis Requiring Acute Kidney Injury after Orthotopic Cardiac and Liver Transplant Hospitalizations

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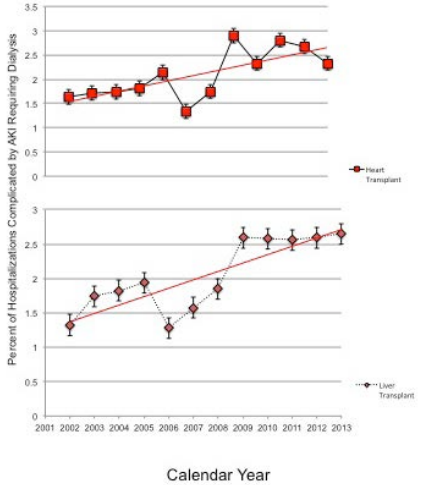
Background: We sought to assess the national epidemiology of acute kidney injury requiring dialysis (AKI-D) in stable orthotopic cardiac and liver transplant.

Methods: We used the Nationwide Inpatient Sample to evaluate the yearly trends (2002 to 2013) of AKI requiring dialysis (AKI-D) in cardiac and liver transplant. We excluded the postoperative period. We defined AKI by ICD9 code 584.xx and dialysis procedure by presence of procedure code of 39.95 or diagnosis code of v45.11, v56.0 or v56.1. We used survey logistic regression to assess AKI-D impact on hospital mortality and adverse discharge and calculated adjusted odds ratios (aOR).

Results: We identified 130,143 hospitalizations with cardiac transplant of which 2776 (2.13%) had AKI-D and 266,987 hospitalizations with liver transplant of which 5689 (2.14%) had AKI-D. There was 45% increase in AKI-D in cardiac transplant, from 1.63% in 2002 to 2.33% hospitalizations in 2013; p<0.01 and a two-fold increase in AKI-D in liver transplant admissions, from 1.32% in 2002 to 2.65% hospitalizations in 2013; p<0.01.

Figure 1. Temporal Trends of Orthotopic Heart and Liver Transplant Hospitalizations Complicated by Acute Kidney Injury Requiring Dialysis



This increase was attenuated after adjustment for temporal changes in demographics, comorbidities and procedures. AKI-D in cardiac transplant recipients was associated with three-fold mortality (aOR 2.85; 95% CI 2.11-3.80) and two-fold adverse discharge (aOR 1.97; 95% CI 1.53-2.55). Similarly, AKI-D in liver transplant recipients was associated with two fold mortality (aOR 1.95; 95% CI 1.53-2.55) and adverse discharge (aOR 1.91; 95% CO 1.57-2.30).

Conclusions: This study highlights the growing burden of AKI-D in non-renal solid organ transplant recipients and its impact, and emphasizes the need to develop strategies to reduce the risk of AKI.

FR-PO849

Timing of Renal Replacement Therapy and Risk of Death: A Pooled Observational Analysis of 5 Randomized Trials

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Background: There is uncertainty regarding the effect of timing of RRT initiation on patient outcomes in AKI. We sought to assess the relationship, in acute kidney injury (AKI) patients, between the timing of initiation of renal replacement therapy (RRT) and death at 28 days.

Methods: We collected data on timing of RRT initiation from 5 randomized trials (originally assessing dialysis intensity) defined as the time from intensive care unit (ICU) admission to RRT initiation (or trial randomization as a proxy to RRT initiation). We used Cox regression, stratified by study, using baseline demographic, disease-severity, and laboratory information. Follow up for death started at RRT initiation (or proxy).

Results: 3150 patients were included. The median time between ICU admission and RRT initiation (or proxy) was 2 days. Patients were grouped into 4 categories of increasing time from ICU admission to RRT initiation (quartiles: ≤0.62 [reference], 0.63-2, 2.1-4.25, ≥4.26 days). The effect of the timing of RRT initiation was not constant over time (i.e. proportional hazards violation) and thus the association between timing of RRT initiation and death was assessed across 2 time-bands (0-7 and 8-28 days). Patients in the first time-band (who did not survive to be included in the second) had higher APACHE2 scores, which indicated greater disease severity (31.9 vs 27.2). The timing of RRT initiation was not associated with the risk of death at 7 days during the first week of follow-up (HR[95% CI] for groups 0.63-2, 2.1-4.25, ≥4.26 days: 0.93[0.74-1.16], 1.01[0.78-1.30], and 0.94[0.72-1.24], respectively. For those who survived to 8 days, delayed RRT initiation was associated with an increased 28-day death risk (1.19;[0.90-1.57], 1.41;[1.04-1.90], 1.55;[1.15-2.09], respectively).

Conclusions: In our pooled analysis, the effect of RRT initiation timing varied with the duration of follow up. Delayed RRT initiation was associated with an increased risk of death among patients who survived more than 7 days.

FR-PO850

TORCH: How a Small Charity Can Effect Significant Improvement in Kidney Care in Haiti

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Background: Though the ISN 0 by 25 initiative to avoid preventable deaths from AKI by 2025 is desirable, kidney disease care in Haiti was almost non-existent. Renal replacement therapy (RRT) was available to only a few patients in Port-au-Prince. In a World Kidney Forum (AJKD Mar 2016), Haiti was not even mentioned with the 20 Latin American countries providing some RRT.

Methods: In 2014, The Organization for Renal Care in Haiti, TORCH, Inc, a 501(c)(3) tax exempt Massachusetts charity, was formed with the mission to 'provide education, medical equipment, training and other resources to medical professionals and facilities in Haiti so that they can provide treatments to individuals with kidney disease who would otherwise not receive such treatments'. We realized that TORCH could not obtain enough monetary support to accomplish such a task by itself.

Results: TORCH served as a focus to obtain help from multiple partners. TORCH brought medical residents and nurses from the Partners in Health/Zanmi Lasante hospital in Mirebalais (HUM) to Hanover and Boston for training to perform hemodialysis (HD). Then, using equipment and supplies donated by NxStage, Bridge of Life and Sustainable Kidney Care Foundation, HUM initiated HD treatments for patients with AKI. To date, 26 patients have undergone a total of 70 HD treatments with 12 complete recoveries, 2 improved, 2 ongoing treatments, 1 CKD and 9 deaths. TORCH has sent 2 advanced practice nurses from the USA to Port-au-Prince to teach peritoneal dialysis techniques to 30 professionals. With Bridge of Life, we plan a prevention program to diagnose Haitians with undetected hypertension, diabetes and proteinuria. TORCH will provide expenses to train Haitian professionals in the USA in basic nephrology care and later in kidney transplantation.

Conclusions: With dedicated volunteers, a group of charitable partners, and only limited funds, a small charity can effect large improvements in kidney care in Haiti. The success of this effort to save lives may engender future support from government and other deep pockets.

FR-PO851

A Single-Center Retrospective Study of the Effect of Residual Renal Function plus Continuous Renal Replacement Therapy (CRRT) Dose on the Prognosis of Patients with Acute Kidney Injury (AKI) Xiang-Mei Chen. *Dept of Nephrology, Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing.*

Background: Pre-CRRT residual renal function differs among patients with AKI, and "uninjured healthy nephrons" still work. "Exogenous" replacement function provided by CRRT and residual renal function were considered total renal function, whose levels may affect the prognosis and renal function recovery of AKI patients.

Methods: We conducted a retrospective analysis of patients treated at our hospital between January 2010 and December 2014. A total of 215 AKI patients who received CRRT met the inclusion and exclusion criteria and were included in this study. Pre-CRRT residual renal function, CRRT dose, and pre-CRRT residual renal function plus CRRT dose were calculated. Moreover, the patients were divided into "high" groups and "low" groups based on the mean values of pre-CRRT residual renal function plus CRRT dose, and inpatient mortality and the 90-day renal recovery rate were compared between the two groups.

Results: Residual renal function and CRRT dose were calculated for 215 patients, and the patients were divided into a high group (55.72 ± 6.53 mL/h/kg, n = 104) and a low group (30.89 ± 7.69 mL/h/kg, n = 111) on the basis of their total renal function (pre-CRRT residual renal function plus CRRT dose). whereas inpatient mortality was significantly higher in the low group than in the high group (53.15% vs 39.39%, P = 0.021). Moreover, the 90-day renal recovery rate was higher in the high group than in the low group (67.21% vs 50.00%, P = 0.044). A multivariate regression analysis that controlled for confounding factors showed that renal function was an independent factor for inpatient mortality (HR 0.802; 95% CI 0.570-0.983; P = 0.013) and renal recovery rate (OR 0.817; 95% CI 0.556-0.984; P = 0.017).

Conclusions: Exogenous "renal function" with CRRT provided on the basis of pre-CRRT residual renal function may have improved the survival and renal recovery of AKI patients and was more effective in the high group than in the low group.

FR-PO852

Early Continuous Renal Replacement Therapy in Septic Acute Kidney Injury Could Be Defined by Its Initiation within 24 Hours of Vasopressor Infusion Seung Don Baek,[1] Eun Kyoung Lee,[2] Jai Won Chang.[1] *[1]Dept of Internal Medicine, Asan Medical Center, Seoul, Korea; [2]Dept of Internal Medicine, Dankook Univ College of Medicine, Cheonan-si, Korea.*

Background: Although institution of early continuous renal replacement therapy (CRRT) reduces morbidity and improves outcomes in patients with septic acute kidney injury (AKI) by removing inflammatory cytokines, the optimal timing for the initiation of early CRRT is uncertain and requires a practically feasible definition with acceptable evidence.

Methods: We investigated the clinical impacts of three time interval parameters on the morbidity and mortality of 177 patients with septic AKI: (1) time from vasopressor initiation to CRRT initiation ($T_{vaso\text{-}CRRT}$), (2) time from ICU admission to CRRT initation ($T_{ICU\text{-}CRRT}$), and (3) time from endotracheal intubation to CRRT initiation ($T_{endo\text{-}CRRT}$).

Results: The proportion of the patients with $T_{vaso\text{-}CRRT}$ less than 24 hours (median 14 hours, interquartile range [IQR] 5–30 hours) was significantly higher in the survival group than in the non-survival group (84.3% vs. 58.5%, $p < 0.001$). $T_{vaso\text{-}CRRT}$ less than 24 hours and SOFA score were independent factors associated with 28-day mortality (hazard ratio [HR], 0.449; 95% confidence interval [CI], 0.211–0.956; $p = 0.038$; and HR, 1.587; 95% CI 1.339–1.880; $p < 0.001$, respectively) and 90-day mortality (HR, 0.369; 95% CI, 0.165–0.825; $p = 0.015$; and HR, 1.566; 95% CI, 1.320–1.858; $p < 0.001$, respectively). $T_{ICU\text{-}CRRT}$ (median 17 hours, IQR 5–72 hours) and $T_{endo\text{-}CRRT}$ (median 13 hours, IQR 4–48 hours) were significantly correlated with both the length of ICU stay ($p < 0.001$) and mechanical ventilation duration ($p < 0.001$).

Conclusions: Considering the possible therapeutic measurement by physician on the basis of the results in this study, early CRRT could be defined by a $T_{vaso\text{-}CRRT}$ less than 24 hours. The $T_{ICU\text{-}CRRT}$ and $T_{endo\text{-}CRRT}$ are associated with morbidity and not mortality.

FR-PO853

Early Mortality on Continuous Renal Replacement Therapy (CRRT): The Prairie CRRT Study Bhanu Prasad. *Nephrology, Regina Qu Appelle Health Region, Regina, SK, Canada.*

Background: Patients with acute kidney injury (AKI) requiring renal replacement therapy (RRT) have an increased short-term and long-term risk of mortality. In most north american intensive care units (ICU), these patients receive continuous renal replacement therapy (CRRT). Some patients once initiated on CRRT may not survive more than 24 hours. For these patients the rationale for the use of this invasive and cost intensive therapy and its appropriateness has been debated. We were interested in identification of risk factors for early mortality.

Methods: We conducted a prospective cohort study of patients undergoing CRRT for AKI in three ICUs of the Regina Qu'Appelle Health Region (RQHR) from April 2013 to September 2014. We collected data on demographic, laboratory and clinical measures and followed patients from admission to 9 months post discharge. The primary outcome was: <24 hour mortality after CRRT initiation. Other secondary outcomes included mortality, and renal outcomes post discharge for 90 days. A stepwise multiple variable logistic regression model was created using death within 24 hours of starting CRRT as the dependent variable, with significant variables derived from univariate analysis as covariates.

Results: 269/2634 patients admitted to the ICUs in the study period had stage III AKI. 106/269 were started on CRRT. 66/106 died in ICU whilst on CRRT. 17/66 (26%) died within 24 hours of initiating therapy. Patients who died within 24 hours had a higher FiO2 (0.8 ± 0.2 vs. 0.6 ±0.2, p= 0.011); higher epinephrine (32.0 ± 29.9 vs. 6.5 ± 9.3, p= 0.005); higher norepinephrine levels (39.4 ± 23.5 vs. 19.6 ± 14.2, p=0. 005); lower pH (7.1 ± 0.2 vs. 7.3 ± 0.1, p= 0.005) when compared to those who survived the first 24 hours of admission.

Conclusions: 26% of the patients died within the first 24 hours of starting CRRT. In stepwise multivariate logistic regression analysis, patients appear to be at high risk of early mortality if they have a high FiO2 (>0.7) and high norepinephrine > 20 ug. However, we were unfortunately unable to identify any specific clinical and biochemical indicators that suggested early mortality with a high degree of statistical confidence.

FR-PO854

Pre-Emptive CRRT Is Associated with Improved Outcome of Dialysis-Requiring Severe Acute Kidney Injury: Multicenter Prospective Study Tetsushi Yamashita,[1] Eisei Noiri,[1] Daisuke Sanada,[2] Takayuki Tsuji,[3] Hideo Yasuda,[3] Masaomi Nangaku,[1] Kent Doi.[1] *[1]The Univ of Tokyo, Tokyo, Japan; [2]Showa Univ, Tokyo, Japan; [3]Hamamatsu Univ School of Medicine, Hamamatsu, Japan.*

Background: It is controversial when to start RRT for AKI patients without life-threatening complications and pre-emptive RRT is frequently considered especially in ICUs. This study was conducted to reveal the characteristics of patients with pre-emptive CRRT compared with classic CRRT.

Methods: This study enrolled 146 patients who needed CRRT as the initial method of RRT in the adult mixed ICUs of 3 university hospitals. CRRT initiation was determined by the attending physicians based on each patient condition. We considered the following factors as conventional indications for RRT according to the previous study (CJASN 2014;9:1577): hyperkalemia, severe acidosis, severe azotemia, oliguria, and fluid overload with pulmonary edema. CRRT without conventional indications was defined as pre-emptive CRRT and CRRT with one or more conventional indications was defined as classic CRRT.

Results: Fifty-nine patients (40%) fulfilled at least one conventional indication before initiation of CRRT (classic CRRT). Patients with pre-emptive CRRT had similar baseline conditions evaluated by eGFR, SOFA score on ICU admission, SOFA score at CRRT initiation. However, they had lower serum creatinine (p<0.001) and plasma NGAL (p=0.03) at CRRT initiation, less in-hospital mortality (p=0.04), and more often renal recovery (p=0.006) which was defined as being alive and independent from dialysis on discharge with a less than 50% decrease in eGFR than patients with classic CRRT.

	Pre-emptive	Classic	*p* value
Age	69	72	0.27
Baseline eGFR	74.5	66.8	0.17
Cre	2.47	3.53	<0.01
Plasma NGAL	449	609	0.03
SOFA score on ICU admission	8	8	0.97
SOFA score at CRRT initiation	10	10	0.71
ICU mortality	29%	32%	0.71
In-hospital mortality	37%	54%	0.04
Renal recovery	54%	31%	<0.01

Conclusions: This observational study suggests pre-emptive CRRT could provide better outcomes of in-hospital mortality and renal recovery. Measures to distinguish the patients for whom RRT is beneficial is necessary to improve the performance of CRRT on AKI treatment.

Funding: Government Support - Non-U.S.

FR-PO855

Initiation Time of Renal Replacement Therapy on Patients with Acute Kidney Injury: A Systematic Review and Meta-Analysis of 7746 Participants Caixia Wang,[1] Linsheng Lv,[2] Xun Liu,[1] Shaomin Li,[1] Yanni Wang,[1] Tan-Qi Lou.[1] *[1]Div of Nephrology, The Third Affiliated Hospital of Sun Yat-sun Univ, Gaungzhou, China; [2]Operation Room, The Third Affiliated Hospital of Sun Yat-sun Univ, Guangzhou, China.*

Background: Early initiation of renal replacement therapy (RRT) is recommended to improve clinical outcomes in patients with acute renal failure (ARF) in some studies, but its effects on mortality and renal recovery are unknown.

Methods: Randomized controlled trials (RCTs) and cohort comparative studies comparing early RRT with late RRT in patients with AKI were identified through PubMed, Embase, the Cochrane library and references of related papers. The primary outcome was all-cause mortality. Secondary outcomes were renal recovery, hospital mortality, duration of hospitalization and mechanical ventilation. Data were analyzed by Random effects model.

Results: We evaluated 52 studies (including nine RCTs) with 7746 patients with AKI. Analysis of the trials included showed that patients receiving early RRT had a 25% reduction in all-cause mortality compared to those receiving late RRT (risk ratio [RR] 0.75, 95% CI [0.69, 0.81]). We noted a 22% increase in renal recovery (RR 0.75, 95% CI [1.02, 1.45]) and 4.26 days (mean difference [MD], 95% CI [-7.99, -0.53]) reduction in duration of hospitalization and 2.33 days (MD, 95% CI [-3.40, -1.26]) reduction in duration of mechanical ventilationin patients assigned to early RRT.

Conclusions: Early initiation of RRT was associated with a decreased risk of all-cause mortality compared with late initiation of RRT in patients with AKI. The findings need to be interpreted with caution given the heterogeneity between studies. Further studies are needed to identify the causes of mortality and to assess whether mortality differs by dose of dialysis.

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FR-PO856

Phase Angle Is Associated with Hospital Mortality Risk in Acute Kidney Injury Patientes Irrespective of Clinical Severity Francisco Javier Lavilla,[1] Maria Jose Molina Higueras,[1] Pelayo Moiron Fdez-Felechosa,[1] Nuria Garcia-Fernandez,[1] Paloma L. Martin Moreno,[1] Pedro Errasti,[1] Jorge M. Nunez-Cordoba.[2] *[1]Nephrology, Clínica Univ de Navarra, Pamplona, Navarra, Spain; [2]Research Support Service, Central Clinical Trials Unit, Clinica Univ de Navarra, Pamplona, Navarra, Spain.*

Background: The phase angle (PA) is a novel marker of functional status that is determined by bioelectrical impedance analysis (BIA). A low PA has been suggested to be an adverse prognostic marker of survival, although no study has evaluated its prognostic influence on acute kidney injury (AKI) patients, independently of clinical severity. We evaluated the association between PA and hospital death in AKI patients adjusting for individual severity index (ISI), which is a validated proxy of clinical severity.

Methods: Clinical and analytical factors, PA, and hospital death were prospectively registered in 97 AKI patients. ISI formula includes age decade, sex, nephrotoxic, oliguria, hypotension, jaundice, coma, consciousness, and assisted respiration. We evaluated c-reactive protein (CRP- mg/dL) and albumin (mg/dL) levels. Also we evaluated ECOG and Karnofsky index. Clinical and analytical variables were assessed when the nephrologist saw the patient the first time.

Results: Patients characteristics: mean age, 67.4 (SD: 14.9) years; men (72.2%); AKI etiology (Prerenal 67.6%, Renal 9.5%, Pre-renal 14.3%, Postrenal 3.8%, others 4.8%); mean ISI, 0.24 (SD: 0.12); and mean PA, 3.99 (SD: 1.35). Hospital deaths: 10 (10.31%). We evaluate association of PA with ISI (r=-0.210 p=0.031), CRP (r=-0.209 p=0.039), Albumin (r=0.362 p=0.003), ECOG (r=-0.374, p=0.003) and Karnofsky index (r=0.456, p<0.001). The OR (95% CI) for PA (per degree increase) was 0.33 (0.14; 0.78) after adjusting for age, sex, and clinical severity.

Conclusions: PA was associated with protein metabolism and chronic health status The PA appears to be a prognosis index of hospital mortality in AKI patients irrespective of clinical severity.

FR-PO857

Extracellular Hypervolemia Evaluated with Bioimpedance, as a Prognostic Marker in Acute Kidney Injury Francisco Javier Lavilla, Maria Jose Molina Higueras, Pelayo Moiron Fdez-Felechosa, Paloma L. Martin Moreno, Nuria Garcia-Fernandez, Pedro Errasti. *Nephrology, Clínica Univ de Navarra, Pamplona, Navarra, Spain.*

Background: The bioelectrical impedance analysis (BIA) is a noninvasive and painless technique is easy to perform, which is used for determining body composition . Can offer information about membrane cell integrity, volemia and clinical status. We evaluate use of BIA to measure extracellular watter with extracelular/intracelular watter ratio –ECW/ICW- and extracelular/total body watter –ECW/TBW-) as a prognostics markers in acute kidney injury (AKI).

Methods: We include a cohort of 159 patients (médium age 66 years SD 1.8, and male 73 % with AKI, and BIA. We evaluate clinical prognostic index (individual severity index –ISI-), analitical inflammatory parameters (C-reactive protein –mg/dL-) and chronic health index (Karnofsky –K-). We use SPSS 20.0.

Results: Exitus 9.4%. ECW/ICW p=0.004, OR 2.247 CI 95%1.266-3.98 was associated with risk mortality better than ECW/TBW p= 0.018 OR 5.539 CI 95% 1.33-23.0. The AUC to mortality with ECW/TBW was 0.734 (p=0.003, CI 95% 0.625-0.844) and with ECW/ICW was 0.778 (p=0.001, CI 95% 0.678- 0.879). ECW/ICW was associated with prognosis, inflammatory and chronic health state in AKI, better than ECW/TBW. ECW/ICW with ISI (r=-0.271, p=0.001), CRP (r=0.248, p=0.004) and Karnofsky (r=-0.253, p=0.003) and ECW/TBW with ISI (r=-0.115, p=0.148), CRP (r=0.124, p=0.131) and Karnofsky (r=0.242, p<0.002). ECW/ICW is also better associated (p=0.014) with respiratoy failure (No failure 1.45 EE 0.05, moderate 1.57 EE 0.16, severe 2.33 EE 1.17) than ECW/TBW (p=0.082).

Conclusions: Higher ECW are associated with prognosis in AKI. ECW/ICW was associated better with mortality than ECW/TBW. ECW/ICW is associated better with prognostic index, c-reactive protein levels, Karnofsky index and respiratory failure.

FR-PO858

Bioimpedance Analysis Guided Volume Expansion for the Prevention of Contrast Induced-Acute Kidney Injury Sarassawan Kananuraks, Arkom Nongnuch. *Renal Unit, Dept of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol Univ, Bangkok, Thailand.*

Background: Periprocedure fluid administration is a cornerstone for prophylaxis of contrast-induced acute kidney injury (CI-AKI). Recent trials showed the benefit of personalized larger amount of fluid administration categorized by fluid status accessed by left ventricular end diastolic pressure (LVEDP) compared with conventional protocol. However, the LVEDP is invasive procedure leading to limited clinical application. Bioimpedance analysis (BIA) is non-invasive tool for determining fluid status in CKD. This study aim to prove personalized fluid administration categorized by BIA may lower incidence of CI-AKI comparing with conventional protocol (NCT02449317).

Methods: In this randomized controlled trial, we personalized isotonic bicarbonate administration categorized by total body water/extra cellular water (ECW/TBW) comparing with conventional bicarbonate protocol for preventing CI-AKI in 56 CKD patients undergoing coronary angiography (CAG). For the BIA group, patients would receive fluid rate 3 ml/kg for 1 hour before CAG and 1ml/kg/h, 2 ml/kg/h and 4 ml/kg/h for 6 hours after CAG if ECW/TBW was >0.4, 0.36-0.4 and <0.36 respectively. In the conventional group, they received fluid rate 3 ml/kg for 1 hour before CAG and 1 ml/kg/h for 6 hours after CAG. CI-AKI was defined as an increased in serum creatinine more than 0.3 mg/dL with in 48-72 hours after CAG.

Results: Baseline characteristics were comparable between two groups except periprocedure volume, which was significantly greater in BIA group.

	BIA-guided hydration group (N=27)	Control group (N=29)	P Value
Age (years)	72.9 ± 7.1	71.4 ± 8.0	0.44
Female sex, n (%)	12 (44.4)	13 (44.8)	0.98
BMI (kg/m^2)	25.3 ± 4.7	26.1 ± 4.5	0.52
Blood pressure (mmHg)			
Systolic	138.1 ± 19.4	139.8 ± 11.4	0.70
Diastolic	74.1 ± 11.3	76.3 ± 8.3	0.42
Renal function			
Serum creatinine (mg/dl)	1.3 ± 0.3	1.4 ± 0.4	0.44
Serum blood urea nitrogen (mg/dl)	19.8 ± 1.2	19.9 ± 1.3	0.95
Estimated GFR (ml/min/1.73m^2)	48.7 ± 11.3	47.3 ± 12.3	0.66
Extracellular water/total body water	0.4	0.4	0.14
Extracellular water/total body water category, n (%)			0.15
< 0.36	0	0	
0.36-0.40	19 (70.4)	15 (51.7)	
> 0.40	8 (29.6)	14 (48.3)	
Left ventricular ejection fraction (%)	61.5 ± 12.3	56.1 ± 8.4	0.09
NYHA, n (%)			0.25
I	7 (25.9)	4 (13.8%)	
II	20 (74.1)	25 (86.2)	
Underlying disease, n (%)			
Diabetes mellitus	10 (37.0)	15 (51.7)	0.27
Hypertension	26 (96.3)	29 (100)	0.48
Congestive heart failure	3 (11.1)	5 (17.2)	0.71
Previous percutaneous coronary intervention	11 (40.7)	10 (34.5)	0.63
Previous coronary artery bypass graft	0	2 (6.9)	0.49
Medications			
RAS blocking agents	16 (59.3)	15 (51.7)	0.57
Diuretic	4 (14.8)	10 (34.5)	0.09
HMG-CoA reductase inhibitors	22 (81.5)	27 (93.1)	0.24
Procedural details			
Contrast volume (ml)	52.3 ± 34.5	63.3 ± 51.2	0.35
Procedure duration (min)	49.8 ± 31.7	55.4 ± 40.1	0.56
Percutaneous coronary intervention, n (%)	7 (25.9)	11 (37.9)	0.34
Number of vessel disease > 1, n (%)	10 (37.0)	16 (55.2)	0.17
Left ventricular end-diastolic pressure (mmHg)	23.7 ± 6.9	20.4 ± 6.6	0.08
Total risk score category			0.48
Low risk (0-5)	5 (18.5)	3 (10.3)	
Moderate risk (6-10)	13 (48.1)	19 (65.5)	
High risk (11-16)	9 (33.3)	7 (24.1)	
Total fluid volume (ml)	871.1 ± 247	597.7 ± 129.2	<0.001

The incidence of CI-AKI was 3.7% in BIA group and 6.9% in conventional group. Relative risk for CI-AKI of conventional group was 1.86 (0.18-19.37, p=0.6).

Conclusions: The larger amount of isotonic bicarbonate administration guided by BIA was not show additional benefit for prevention CI-AKI when compared with conventional protocol.

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FR-PO859

Fluid Overload Masks AKI Diagnosis and Associated Outcomes in Critically Ill Children David T. Selewski,[1] Katja M. Gist,[2] Erin K. Stenson,[3] Shina Menon,[4] Stuart Goldstein,[3] Rajit K. Basu.[3] *[1]Univ of Michigan, Ann Arbor, MI; [2]Univ of Colorado, Aurora, CO; [3]Cincinnati Children's Hospital, Cincinnati, OH; [4]Univ of Washington, Seattle, WA.*

Background: Acute kidney injury (AKI) occurs commonly in critically ill children and is associated with adverse outcomes. Fluid overload (FO) has been shown to mask the diagnosis of AKI in select populations (adults, congenital cardiac surgery). This study aims to evaluate the impact FO has on the diagnosis of AKI in a general pediatric intensive care unit (PICU) population.

Methods: Secondary analysis of The Acute Kidney Injury in Children Expected by Renal angina and Urinary Biomarkers (AKI-CHERUB) study, a single center prospective observational study conducted in a tertiary care PICU. The primary outcome was severe AKI at 48 hrs, utilizing the SCr based KDIGO definition Stage 2-3 AKI. AKI was also recalculated using SCr corrected for FO (Cr_{corr} = SCr x [1 + (net fluid balance/total body water)]). FO was calculated daily by fluid balance from PICU admission. Secondary outcomes: length of mechanical ventilation (MV), PICU LOS, hospital LOS.

Results: 181 patients were in the cohort (166 with complete outcome data). Mortality was 5%. 57 patients (31%) had 10-20% FO and 28(15%) ≥20% FO at 48 hrs. The incidence of all AKI was 14.9%(n=29) and increased to 27.7%(n=50) with Cr_{corr}. Using Cr_{corr}, 34.5%(N=10) had an increased AKI stage, with 5 additional cases of severe AKI diagnosed. Severe AKI by Cr_{corr} was associated with adverse outcomes (Table).

	Severe AKI by Cr(N=163)		p	Severe AKI by Cr_{corr}(N=166)		p
	Yes(N=12)	No(N=151)		Yes(N=17)	No(N=149)	
Length of MV*	3(0.5,8)	1(0,5)	0.16	3(0.5,8)	1(0,5.5)	0.18
ICU LOS*	8(3.8,15)	4(3,11)	0.15	10(6,16)	4(3,11)	0.02
Hospital LOS*	16(10,56)	14(8,29)	0.37	18(10,55)	14(8,25)	0.06
Organ Failure*	8.5(3.3,14.8)	2(0,6)	0.002	7(2.5,10.5)	2(0,6)	0.008
*days, Med(IQR)						

Conclusions: We show FO masks the diagnosis of over 40% of patients with AKI and should be accounted for when monitoring for AKI. Furthermore the failure to correct SCr measure for FO dilutes the impact of AKI on outcomes.

FR-PO860

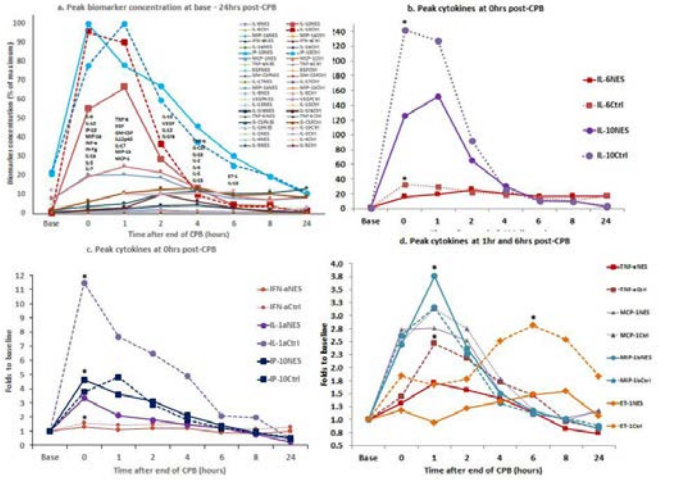
Nesiritide Modulates Inflammatory Response during Cardiac Surgery Thomas M. Beaver,[1] Jessica A. Cobb,[1] Abhilash Koratala,[2] A. Ahsan Ejaz.[2] *[1]Div of Thoracic and Cardiovascular Surgery, Univ of Florida; [2]Div of Nephrology, Hypertension & Renal Transplantation, Univ of Florida.*

Background: The study was performed to investigate the effects of NES on inflammatory response during cardiac surgery.

Methods: N=29 cardiac surgery patients were randomized to an infusion of NES versus placebo (Ctrl). The effect of NES on inflammatory response was investigated by measuring a panel of candidate biomarkers and clinical parameters at predetermined time points.

Results: There were no significant differences between the groups with regards to the early biomarkers of AKI: urine NGAL (NES 230.3+71.5ng/mL vs. Ctrl 554.4+263.3ng/mL, p=0.253) and urine IL-18 (NES 29.9+4.8pg/mL vs. 254.5+118.3pg/mL, p=0.090). A concerted biomarker kinetic pattern of time-differentiated peak concentrations was observed. IL-10, IP-10, IL-6, IL-10, IP-10, MIP-1a, INF-a, INF-g, IL-1a, IL-3 and IL-7 reached peak concentration at 0hr following end of CPB; TNF-a, EGF, GM-CSF, IL-12p40, IL-17, MIP-1b and MCP-1 at 1hr; IL-18, VEGF, IL-13 and IL-1ra at 2hrs, TNF-b, G-CSF, IL-1b, IL-2, IL-4, IL-5 and IL-15 at 2hrs; and ET-1 and IL-18 at 6hrs. A generalized trend towards lower levels of biomarker concentration in the NES group compared to the Ctrl group could be observed. At 0hr, the NES group exhibited significant reduction of peak concentrations of IL-6 (p=0.009), IL-10 (p=0.009), IL-1a (p= 0.020), IP-10 (p= 0.001) and IFN-a (p=0.032) compared to the Ctrl group. Significant reduction in peak concentrations of TNF-a (p=0.007) and MIP-b (p=0.027) at 1hr and ET-1 (p=0.020) at 6hrs were observed in the NES group compared to the Ctrl group.

Conclusions: Our study demonstrated a concerted inflammatory response in cardiac surgery that was modulated by nesiritide. Furthermore nesiritide attenuated ET-1 response thus suggesting that previously observed favorable renal effect may be linked to attenuated renal vasoconstriction.



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FR-PO861

Pulsatile Portal Flow and Acute Kidney Injury after Cardiac Aurgery William Beaubien-Souligny,[1] Josee Bouchard,[2] Yoan Lamarche,[1] Jean-Francois Cailhier,[3] André Denault.[1] *[1]Intensive Care, Montreal Heart Inst, Montreal, QC, Canada; [2]Nephrology, Hôpital Sacré-Coeur de Montréal, Montreal, QC, Canada; [3]Nephrology, Chum, Montreal, QC, Canada.*

Background: Acute kidney injury (AKI) is frequent following cardiac surgery and venous congestion of the kidneys may play a role in the development of AKI. We assessed whether portal flow pulsatility (PP), a sign of portal hypertension from congestive heart failure which could reflect elevated venous pressure in kidneys, may independently predict AKI, as well as risk factors for PP.

Methods: We conducted a retrospective cohort study including patients who had at least one assessment of portal flow during the week following cardiac surgery between May 2015 and February 2016 at our institution. We excluded patients with stage V CKD, AKI before surgery or liver cirrhosis. PP was defined as a pulsatility fraction ≥ 50%. We assessed AKI over the week after surgery according to the KDIGO serum creatinine criteria and performed logistic regression analyses to identify independent risk factors of AKI and PP.

Results: We screened 136 patients and included 102 patients with a mean age of 69. 37.3% of patients underwent CABG while 58.8% had valvular or complex surgeries. 21.6% had stage III CKD and 2% had stage IV CKD. PP was detected in 35% of patients. AKI developed in 60.8% of patients with 13.7% progressing to severe AKI (stage 2 or higher). The detection of PP was associated with a significant increase in the risk of AKI (OR: 6.0 CI: 2.2-16.4) and severe AKI (OR: 5.4 CI: 1.5–18.6).The association with AKI was significant in a multivariate model including baseline creatinine and the SOFA cardiovascular score during the first two days after surgery (OR: 5.7 CI: 1.9-16.8). Maximal pulmonary artery pressure (44 vs 39 mmHg p = 0.03) and percentage of cumulative fluid balance over body weight (4.9% vs 3.6% p = 0.04) were associated with PP.

Conclusions: In our study, the detection of PP during the first week after cardiac surgery was independently associated with an increased risk of AKI after adjustment for baseline serum creatinine and SOFA cardiovascular score after surgery. Further studies are required on the role of PP as a marker of venous congestion of the kidneys to predict AKI.

Funding: Private Foundation Support

FR-PO862

The Timing of Eculizumab Therapy Predicts Renal Survival in Atypical Hemolytic Uremic Syndrome Salem Almaani, Udayan Y. Bhatt, Jason Prosek, Brad H. Rovin, Samir Parikh. *Ohio State Univ, Columbus, OH.*

Background: Atypical hemolytic uremic syndrome (aHUS) is a life threatening disease instigated by alternative complement pathway dysregulation and often results in acute renal failure from thrombotic microangiopathy. Treatment with eculizumab, a terminal complement blocker, is effective, but some patients are still left with significant renal impairment. This work aims to determine whether the timing of eculizumab treatment predicts renal survival in patients with aHUS.

Methods: We conducted a retrospective analysis of clinical data from 22 aHUS patients treated with eculizumab. Demographics are summarized in the table. Median follow up time was 22 months (IQR 13-43.75). The time to treatment initiation was tested as a predictor of adverse renal outcomes by univariate and multivariate analysis. Outcomes were defined as a ≥50% increase in serum creatinine (SCr), end-stage renal disease, or a composite endpoint of either. Other variables were tested but only age and sex met inclusion criteria for multivariate analysis.

Age at presentation (Avg ±SD)	41.7±17.2
Sex (men/women)	5(20.8%) / 19 (79.2%)
Race (White/Black/Other)	19(79.2%) / 4 (16.6) / 1 (4.2%)
Patients requiring dialysis	15 (62.5%)
Time on dialysis (months, Median, IQR)	2 (0.6-12)
Time to Eculizumab (days, Median, IQR)	9 (6-34)
Baseline Creatinine (mg/dl, Avg±SD))	1.31±0.54
Patients with identified mutation	13 (59%)

Results: A delay in eculizumab initiation >10 days after clinical presentation was predictive of a ≥50% increase in SCr (OR=10.5, 95% CI: 1.11 to 98.91, p=0.040), and was 100% predictive of dialysis dependence by univariate analysis. Time to treatment was a significant predictor of the composite outcome by univariate analysis (OR=22.5, 95% CI: 2.60 to 194.51, p=0.005) and multivariate analysis (OR=50.14, 95% CI: 2.67 to 942.29, p=0.005).

Conclusions: The delayed administration of eculizumab is associated with an increased risk of poor renal outcomes in aHUS. Initiation of terminal complement blockade within 10 days of clinical presentation is essential for long-term preservation of renal function in patients with aHUS.

FR-PO863

Free Hepatic Venous Pressure as a Marker of Renal Venous Congestion: Is There a Correlation with Hemodynamic Renal Dysfunction in Patients with Cirrhosis? Neel Desai, Ladan Golestaneh. *Nephrology, Albert Einstein College of Medicine - Montefiore Medical Center, Bronx, NY.*

Background: Intra-abdominal hypertension (IAH, abdominal cavity pressure >/= 12 mmHg) correlates with renal disease. The pathophysiology of this relationship is not clearly understood - IAH is thought to cause renal venous congestion by increasing venous pressure and impairing venous drainage. We hypothesize that in patients with cirrhosis elevated abdominal venous pressure, as represented by an elevated Free hepatic venous pressure (FHVP, routinely measured during Transjugular Intrahepatic Portosystemic Shunt or TIPS procedures), correlates with hemodynamic renal dysfunction when adjusted for other pertinent clinical factors.

Methods: We used our institution's electronic health record based database to search for patients who underwent TIPS procedures between 2008-2015. Information collected included demographics, FHVP, other co-morbidities and markers of parenchymal renal disease. Patients with End Stage Renal Disease (ESRD) +/- missing race information were excluded. Calculated GFR using the MDRD formula was used in all data analyses which was done using the STATA 14.0 software.

Results: A total of 122 patients were included in the study based on the criteria listed above. The mean FHVP was 13.9mmHg and mean EF was 65%. 16.8% of the patients had evidence of parenchymal renal disease on the renal sonogram which correlated with a 19.2cc/min decrease in baseline GFR (P=0.02). 12.4% of the patients had proteinuria which correlated with a 19.4cc/min decrease in baseline GFR (P=0.04). Every 1mmHg increase in the FHVP was associated with a 0.49cc/min decrease in baseline GFR which was not statistically significant (P=0.35).

Conclusions: Our data suggests that in patients with cirrhosis an increase in FHVP is not associated with a statistically significant decrease in baseline GFR. It is possible that the presence of hyper-dynamic cardiac function is compensating to maintain GFR in this sample by increasing cardiac output and renal perfusion. Our study is also not adequately powered. The association of elevated venous pressure and hemodynamic renal dysfunction needs to be explored further in patients with cirrhosis.

FR-PO864

Efficacy of Eculizumab in Gemcitabine-Induced Thrombotic Microangiopathy: Analysis of a Retrospective Study Cohort Steven Grange,[1,7] Maximilien Grall,[1,7] Francois Provot,[2,7] Coindre Jean-Philippe,[3,7] Claire Pouteil-Noble,[4,7] Dominique Guerrot,[5,7] Paul Coppo.[6,7] *[1]Medical Intensive Care Unit, Rouen Univ Hospital, France; [2]Nephrology, Lille Univ Hospital, France; [3]Nephrology, Le Mans General Hospital, France; [4]Nephrology, E.Herriot Hospital, Lyon I Univ, France; [5]Nephrology, Rouen Univ Hospital, France; [6]Hematology, St. Antoine Univ Hospital, AP-HP, Paris, France; [7]French TMA Reference Center, St. Antoine Univ Hospital, AP-HP, Paris, France.*

Background: Gemcitabine is a broadly prescribed chemotherapy with renal adverse events, including thrombotic microangiopathy (TMA). This study evaluated the efficacity of eculizumab in patients with gemcitabine-induced TMA.

Methods: We conducted an observational, retrospective, multicentric study including all patients with gemcitabine-induced TMA treated by eculizumab in 4 French centers, between 2011 and 2014. Patients with TMA attributed to cancer and to allogenic stem cell transplant were excluded.

Results: 7 patients were included (6 women, 1 man). Gemcitabine was prescribed for pancreatic (n=3, 43%), ovarian (n=3, 43%) and pulmonary (n=1, 14%) cancer. TMA occured after a median of 5 months (range 1.7-8.4) and a median cumulative dose of 23.7g (range 0.9-48.0). The main characteristics were hemolytic anemia (100%), acute renal failure (100%, including 57% stage 3 AKI and 28% renal replacement therapy), hypertension (71%) and diffuse edema (57%). Eculizumab was started after a median of 27 days (range 7-44) following TMA diagnosis. A median of 4.5 injections of eculizumab was performed (range 3-22). Hematological remission was achieved in 5 patients (71%) and blood transfusion significantly decreased after one injection of eculizumab (median of 2 packed red blood cells (range 0-10) vs 0 (range 0-1), p=0.047). Complete nephrologic remission was achieved in 1 patient (14%), and partial remission in 4 patients (57%). Three patients (42%) died during follow up, 1 from a septic and hemorrhagic shock, 2 from cancer evolution (3 and 13 months after eculizumab initiation).

Conclusions: This study suggests that eculizumab is efficient on hemolysis and reduces transfusion requirement in gemcitabine-induced TMA. The benefit of eculizumab on the revovery of kidney function remains uncertain.

FR-PO865

Design of the STOP-AKI Trial: Safety, Tolerability, Efficacy and Quality of Life of Human Recombinant Alkaline Phosphatase in Patients with Sepsis-Associated Acute Kidney Injury Jacques Arend,[1] Esther Peters,[2] Ravindra L. Mehta,[3] Patrick T. Murray,[4] Jurgen Hummel,[5] Michael Joannidis,[6] John A. Kellum,[7] Peter Pickkers.[2] *[1]AM-Pharma, Bunnik, Netherlands; [2]Dept of Int Care Med, Radboudumc, Nijmegen, Netherlands; [3]Div of Nephrol, Dept of Med, Univ of California, San Diego, CA; [4]School of Med, Univ Coll Dublin, Dublin, Ireland; [5]PPD, Bellshill, United Kingdom; [6]Div of Int Care and Emerg Med, Dept of Int Med, Medical Univ Innsbruck, Innsbruck, Austria; [7]Ctr for Crit Care Neph, Dept of Crit Care Med, Univ of Pittsburgh, Pittsburgh, PA.*

Background: Acute Kidney Injury (AKI) occurs in ~60% of critically ill patients, and sepsis is the most common underlying cause. No pharmacological treatment options are licensed to treat sepsis-associated AKI (SA-AKI). Administration of *bovine* intestinal alkaline phosphatase (AP) improved renal function in critically ill sepsis patients. To build on these observations, a *human recombinant* AP (recAP) was developed and is currently tested for safety and efficacy in patients with SA-AKI.

Methods: This is a randomized, double-blind, placebo-controlled, dose-finding adaptive phase IIa/IIb study, conducted in critically ill patients with SA-AKI (NCT02182440). A minimum of 290 patients will be enrolled at ~50 sites in the European Union and North America. The study involves 2 parts. Patients enrolled during Part 1 will be randomly assigned to receive placebo (n=30) or 1 of 3 different doses of recAP (n=30 per group) once daily for 3 days (0.4 mg/kg, 0.8 mg/kg, or 1.6 mg/kg). In Part 2, patients will be randomly assigned to receive the most efficacious dose of recAP (n=85), selected by an independent data safety monitoring board during an interim analysis, or placebo (n=85). Treatment must be administered within 24 h after SA-AKI is first diagnosed and within 96 h from first diagnosis of sepsis. The primary endpoint is the area under the time-corrected endogenous creatinine clearance curve from days 1-7. The key secondary endpoint is the incidence of renal replacement therapy during day 1-28.

Results: The estimated study enrollment completion date is February 2017.

Conclusions: Results of this study will reveal the safety and efficacy of recAP to treat SA-AKI in critically ill patients.

Funding: Pharmaceutical Company Support - AM-Pharma

FR-PO866

How Is Acute Kidney Injury Defined and Represented in Critically Ill Patients in Randomized Controlled Trials? Rogerio Passos, Zilma Regia de Sousa Barreto, Roseanne Ferreira de Freitas Euzebio, Luis Miranda Conceição, Ana Carolina E. Cattony, Camila Magalhães Brandão, Fabiana Gois Sousa, Gerlane Araujo Luz, Laryssa Passos Santos, Paulo Benigno Pena Batista. *Intensive Care Unit, São Rafael Hospital, Salvador, Bahia, Brazil.*

Background: Acute kidney injury (AKI) is a prevalent condition in critically ill patients and it is associated with increased mortality in this population. Targeted analysis of this subgroup in randomized clinical trials is essential to guide an accurate conduct and lead to better outcomes. The primary goal of the present study was to quantify the representation of patients with AKI and to assess the criteria used to define it in multicenter randomized clinical trials.

Methods: A sensitive search strategy for randomized controlled trials published from 2006 to 2016 was conducted in MEDLINE using the PubMed interface selecting the keywords "sepsis", "mechanical ventilation", "ARDS" and "critically ill patients". All publications of adult, randomized controlled trials carried out in the intensive care unit, with mortality as primary outcome were included and reviewed independently.

Results: A total of 379 articles were reviewed. We identified 60 elegible studies, 41 (68%) were multicenter, 51 (85%) included patients with renal dysfunction at baseline and in 14 (23%) the population with renal impairment underwent a subgroup analysis. None of studies reported the proportion of enrolled patients with acute kidney injury. In the follow up of the patients during these studies, generic scores as APACHE II, SAPS II and SOFA were used in 44 (73%) of studies to define AKI, specific AKI scores as RIFLE and the Brussels score were used in 6% and 3% respectively, and 18% of the studies did not describe any criteria to define AKI.

Conclusions: In multicenter randomized clinical trials assessing mortality as primary outcome there is an underrepresentation of AKI patients in the enrollment of the patients and no consensus in AKI definition during the follow up of the patients during studies. The consequence is that we lack evidence on interventions for this growing high-risk population.

FR-PO867

Serum Free Light Chain Level at Diagnosis and Patient Outcomes in Myeloma Cast Nephropathy-A Multicentre Study Punit Yadav,[1] Insara Jaffer Sathick,[2] Nelson Leung,[2] Elizabeth E. Brown,[3] Mark Cook,[1] Paul W. Sanders,[3] Paul Cockwell.[1] *[1]Queen Elizabeth Hospital, Birmingham, United Kingdom; [2]Mayo Clinic, Rochester; [3]Univ of Alabama at Birmingham.*

Background: Myeloma cast nephropathy (MCN), a consequence of excess monoclonal immunoglobulin free light chain (FLC) production, is a common cause of severe renal impairment in multiple myeloma (MM). However, the threshold of FLC level in serum that is associated with the development of MCN is uncertain.

Methods: In a multicentre cohort of MM patients presenting with biopsy-confirmed MCN between 2002-2014, we evaluated prospectively measured serum FLC levels obtained using a single nephelometric assay. We report renal outcome and overall survival (OS) relative to serum FLC level at diagnosis controlling for demographic factors.

Results: 103 patients were enrolled from 3 tertiary centres. Median age at diagnosis was 63 years (IQR 57-69). The majority were male (58.2%) and of white race (88.3%). Light chain only MM was the predominant paraprotein type (47.6%). The median involved FLC level at diagnosis was 753 mg/L (range 107-114600). Serum creatinine was 6.0 mg/dL (IQR 4.6-9.8), eGFR 7 ml/min (IQR 5-11), calcium 9.4 mg/dL (IQR 9.0-10.8) and haemoglobin 9.0 g/dL (IQR 7.8-10.1). 67% of patients received dialysis treatment, of which 52.1% recovered independent renal function. Median duration on dialysis for those who recovered renal function was 36 days (IQR 22.7-89.7). 2 patients had a monoclonal FLC level <500 mg/L; one was hypercalcaemic, while the other patient had high-normal serum calcium level and received NSAIDs. 67.3% died with a median OS of 515 days (95% CI 293-736). In a multivariable analysis, age, serum calcium level and high cut-off haemodialysis treatment were associated with recovery of independent renal function. Age at diagnosis and serum calcium level were inversely correlated with OS.

Conclusions: This is the largest reported cohort of patients with biopsy-confirmed MCN and serum FLC levels. Only 2 patients had a serum FLC level <500 mg/L at diagnosis; both of whom had risk factors known to promote the development of MCN. Elevated serum calcium level at diagnosis was associated with lower rates of renal function recovery and poor OS.

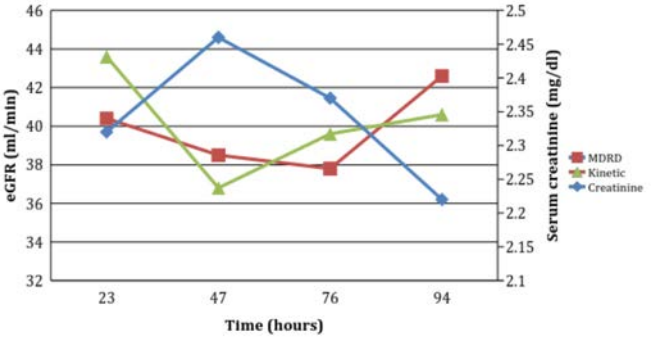
FR-PO868

Renal Function Assessment in the Setting of Acute Kidney Injury Applying the Kinetic GFR Formula Jose S. Lopez Gil,[2] Luis Antonio Garcia,[2] Javier Zúñiga-Varga,[1] Juan Pablo Herrera Felix.[1] *[1]Nephrology Dept, American British Cowdray, Mexico, Mexico City, Mexico; [2]Postgraduate, UNAM, Mexico, Mexico City, Mexico.*

Background: There is no reliable method to estimate or asses kidney function in acute kidney injury (AKI), therefore, we applied the kinetic GFR formula proposed by Chen (JASN 24:2013) to estimate changes in GFR, evaluate renal outcomes and value the accuracy of this formula.

Methods: This is a retrospective study. 30 patients with AKI were randomly selected from 763 admissions between 2010 and 2016. Serum creatinine (SCr) values from previous years to admission were collected to establish baseline SCr. Admission SCr and the four subsequent SCr were collected. GFR was estimated by Kinetic (kGFR) and MDRD formulas.

Results: Mean age was 70.6 ± 15.9 years. Males represented 56.6% (17). Admission diagnosis was infectious disease in 26.6% (8), heart disease in 13.3% (4) and neoplasms in 10% (3). Mean baseline SCr was 1.15±0.44mg/dl and the admission SCr was 2.46 ± 1.9mg/dl. The mean SCr in the first sample was 2.32±1.8mg/dl, eGFR MDRD 40.4±25.1ml/min and kGFR 43.6±22.5ml/min. In sample 2, mean SCr was 2.46±2.1mg/dl, MDRD 38.5±24.4ml/min and kGFR 36.8±25.5ml min. In sample 3, SCr was 2.37±1.9mg/dl, MDRD 37.8 ± 21.3ml/min and kGFR 39.6± 25.5ml/min. In sample 4, SCr was 2.22±1.9mg/dl, MDRD 42.6 ± 30.7ml/min and kGFR 40.6±27.4ml/min. Mean SCr increased 6% from sample 1 to sample 2 and MDRD GFR decreased only 4.7% while kGFR decreased by 15.6%. From sample 2 to sample 3 mean SCr decreased 3.7% and MDRD GFR declined by 1.8%, while the kGFR improved by 7.6%. Even when the SCr remains constant between samples, the kGFR formula demonstrates a recovery of GFR of 2.3 ml/min while the MDRD remains unchanged.



Conclusions: The kGFR formula seems to be more reliable than MDRD to accurately estimate kidney function in AKI. Renal function recovery is identified earlier by kGFR.

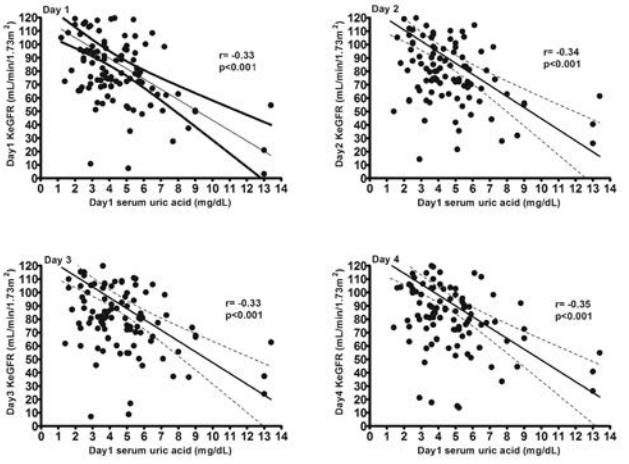
FR-PO869

Relationship of Serum Uric acid and Kinetic Estimated Glomerular Filtration Rate in Acute Myeloid Leukemia Patients Abhilash Koratala,[1] Kawther Farouk Alquadan,[1] Girish Singhania,[2] Michiko Shimada,[3] Richard J. Johnson,[4] A. Ahsan Ejaz.[1] *[1]Univ of Florida; [2]Univ of Utah; [3]Hirosaki Univ, Japan; [4]Univ of Colorado.*

Background: We investigated the relationship between SUA and renal function using kinetic eGFR (KeGFR) in a unique patient cohort wherein SUA levels fluctuate during the course of standard care.

Methods: Data from patients undergoing treatment for acute myeloid leukemia (AML) were analyzed retrospectively. Correlations between SUA and serum creatinine (SCr) and KeGFR were investigated. Statistically significant and clinically relevant determinants were studied in multivariate regression models.

Results: N=126 patients. Baseline SUA was associated with an increased risk for AKI (OR 1.27, 1.1-1.5, p=0.003) and tumor lysis syndrome (OR 1.26, 1.1-1.5, p=0.005). Prophylactic uric acid-lowering therapy and hydration resulted in lower SUA values from baseline in 88.1% of the patients, 20.4% reduction was observed on post-induction day 1. Significant linear correlations were observed between SUA and SCr (r=0.35, p<0.001) and inverse correlation was also observed between SUA and KeGFR on day 1 (r= -0.33, p<0.001) that persisted through day 4. By subgroup analysis, patients with primary AML (r= -0.49, p<0.001), baseline SUA >5.5mg/dL (r= -0.41, p=0.002) and baseline eGFR >60mL/min/1.73m2 (r= -0.51, p<0.001) demonstrated robust relationships between SUA and KeGFR. The relationship was more robust when the groups were combined (primary AML + baseline SUA>5.5mg/dL + baseline eGFR >60mL/min/1.73m2, r= -0.52, p<0.001).



Conclusions: The study demonstrated a linear relationship between SUA and SCr and an inverse relationship between SUA and KeGFR in a dynamic clinical situation.

FR-PO870

Subarachnoid Hemorrhage Induces Neuro-Cardio-Renal Interactions in the Acute Phase Naoki Ikegaya,[1] Kiyoshi Mori,[2] Takuya Yoshida,[5] Hiromichi Kumagai,[5] Yasuhiro Yamamura,[4] Mamoru Tomida,[4] Seiya Takehara,[4] George Seki,[3] Akira Hishida.[3] *[1]Dept of Medicine, Yaizu City Hospital, Yaizu, Japan; [2]School of Pharmaceut Sci, Univ of Shizuoka, Shizuoka, Japan; [3]Dept of Nephrology, Yaizu City Hospital, Yaizu, Japan; [4]Dept of of Neurosurgery, Yaizu City Hospital, Yaizu, Japan; [5]Dept of Clin Nutrition, School of Food and Nutritional Sci, Univ of Shizuoka, Shizuoka, Japan.*

Background: Subarachnoid hemorrhage (SAH) is known to induce acute cardiovascular stress as reflected by ECG changes, and renal dysfunction is associated with poor prognosis in SAH. However, the precise mechanisms of extra-brain injury in SAH have not been fully understood.

Methods: We prospectively analyzed ECG, urinary albumin, and NGAL, and serum NT-proBNP, endothelin and inflammatory cytokines such as IL-6 and TNF-alpha in 24 consecutive SAH patients without known kidney disease on day1, 2, and 14.

Results: ECG abnormalities were observed in 13 out of 24 patients with SAH at baseline. SAH patients with ECG abnormalities showed increased levels of albuminuria (Mean±SD, 627.9±1441.5 vs. 88.0±88.6 mg/g Cr), NT-proBNP (1033.8±2121.2 vs. 95.1±111.6 pg/ml) and endothelin (2.21±0.80 vs. 1.88±0.5 pg/ml), but no differences in IL-6 and TNF-alpha compared to patients without ECG abnormalities at baseline. Urinary NGAL significantly increased in patients with ECG abnormalities on day 2. Serum endothelin decreased towards normal values on day 2 and 14, and IL-6 and TNF-alpha increased on day 2 and 14 in both groups.

Conclusions: ECG abnormalities were associated with elevated levels of endothelin and albuminuria early after SAH, suggesting interactions among heart, brain and kidneys through increased endothelin in the acute phase.

FR-PO871

Inverse Interaction between Diuretics and Renin-Angiotensin Blockers in Contrast-Induced Nephropathy after Coronariography Lucero Salgado Ambrosio, Armando Vazquez-Rangel. *Nephrology, Inst Nacional de Cardiologia Ignacio Chavez, Mexico, Mexico City, Mexico.*

Background: Prevention of contrast-induced nephropathy(CIN)is limited mostly to hydration, while some other interventions as diuretics and renin-angiotensin blockers seem to be counter intuitive. Nevertheless, patients with cardiovascular disease are usually under these drugs,and sometimes hydration is difficult to implement if heart failure or chronic fluid overload is present.

Methods: A retrospective cohort of patients undergoing coronary angiography in our National Institute of Cardiology in Mexico City from January 2011 to December 2011. Patients with ambulatory or short-stay procedures were excluded. Clinical and biochemical characteristics were obtained through medical records. Specifically, the use of loop diuretics, angiotensin converting enzyme inhibitors(ACEI) or angiotensin receptor blockers (ARB) was assessed from 24 hours before to 24 hours after coronariography. CIN was defined by KDIGO criteria by serum creatinine.

Results: 515 patients were analyzed. Baseline characteristics included:male 398 (77.3%), diabetes 201 (39.0%),hypertension 273 (53.0%), cardiogenic shock 2 (4.3%), chronic heart failure 72 (14.0%), previous myocardial infarction 60 (11.6%), acute coronary syndrome 460 (89.3%), emergency procedure 178 (34.5%). Of the total, 168 (32.6%) received loop diuretics, and 420 (81.5%) received ACEI/ARB peri-procedure.CIN was present in 61 (11.8%) patients. There was a significant difference between patients receiving loop diuretics for CIN (34 [20.2%]) vs patients without loop diuretics (27 [7.8%]) (p<0.05). Within patients receiving loop diuretics, the incidence of CIN for those receiving ACEI/ARB was 21 (16.7%) vs 13 (30.9%) without ACEI/ARB.Multivariate analysis confirmed this observation adjusted for fluid balance.

Conclusions: For high risk cardiovascular population, mostly with acute coronary síndrome, the use of diuretics increased the incidence of CIN, nevertheless, the concomitant use of ACEI/ARB protected partially from this risk. In patients with adequate fluid status or fluid overload because of heart failure, with the need of loop diuretics, reducing local vasoconstriction with ACEI/ARB could reduce the risk of CIN.

FR-PO872

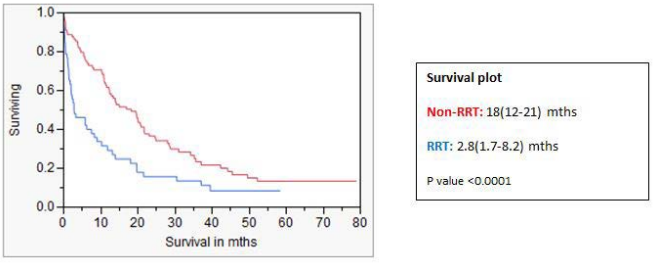
Renal Replacement Therapy after Ventricular Assist Device Implantation, a Single-Center Study Insara Jaffer Sathick,[1] M. Lourdes Gonzalez Suarez,[1] Kianoush Banaei-Kashani,[1,3] Karl A. Nath.[1] *[1]Nephrology, Mayo Clinic, Rochester, MN; [2]Critical Care, Mayo Clinic, Rochester, MN; [3]Mayo Medical School, Rochester, MN.*

Background: We evaluated heart failure patients receiving ventricular assist device(VAD)implantation who developed severe acute kidney injury(AKI) requiring renal replacement therapy(RRT).

Methods: We included patients≥18 years undergoing VAD implantation at Mayo Clinic between 2007 to 2015. We assessed overall survival in patients with or without AKI requiring RRT.

Results: 326 patients underwent VAD implantation. 71/326 patients required RRT after implantation.Serum creatinine at implantation,pulsatile device, duration of surgery,higher APACHE and SOFA scores,blood transfusion,positive fluid balance were associated with AKI requiring RRT. RRT group had worse survival (Odds ratio (CI) = 4.5 (2.5-8.2) p value <0.0001) and less likelihood of receiving cardiac transplant (Odds ratio (CI)= 0.47 (0.2-0.98), p value 0.03). At 2year follow up, median survival was 2.8 months in the RRT group vs 18 months in the nonRRT group.

N=326	RRT N=71	Non RRT N=255	p value
Median age	59	62	0.05
Pre-existing CKD %	60	56	0.4
Creatinine at implantation, mg/dl	1.8 (1.3-2.3)	1.3 (1.1-1.7)	0.0003
Continuous vs pulsatile device(%)	83:17	96:4	<0.0001
Median duration of surgery, mins	368	288	0.0002
Median RBC transfusion, units	36	12	<0.0001
Fluid balance on day 1, liter	+1.9	+1.4	0.01
Median follow up, days	180	680	<0.0001
Median survival, mths	2.8(1.7-8.2)	18(12-21)	<0.0001
Cardiac transplant	14%	25%	0.03



Conclusions: Patients who sustain severe AKI requiring RRT after VAD implantation have worse outcomes. Blood transfusion and positive fluid balance are predictors of severe AKI in addition to kidney function at implantation and severity of illness.

FR-PO873

Comparing Left Ventricular Assist Device Implantation and Inotropes for Renal Function and Outcomes Sean Verma,[1] Emmanuel Bassily,[1] Shane Leighton,[1] Igor Sunjic,[1] Angel Iran Martin,[1] Tambi Jarmi,[2] Claude Bassil.[2] *[1]Internal Medicine, Univ of South Florida; [2]Nephrology, Univ of South Florida.*

Background: Left Ventricular Assist Device (LVAD) implantation and inotropes serve as a bridge to heart transplantation or as destination therapy in those who aren't heart transplant candidates. Little is known about renal function and outcomes with LVAD placement, and a study comparing LVAD recipients versus solely inotrope treatment has not been previously performed.

Methods: 169 patients with continuous flow LVAD implantations and 20 patients with solely inotrope therapy with dobutamine or milrinone were analyzed. Mann-Whitney U Testing and chi-squared analysis compared the groups for long term renal outcomes after LVAD or continuous inotrope therapy was started (baseline), 3, and 6 months later. We also compared incidence of AKI, defined as an increase in creatinine of 0.3 mg/dL in 48 hours or 1.5 times the baseline in the last 7 days, need for renal replacement therapy (RRT), brain natriuretic peptide (BNP), and death during 6 months following LVAD or inotrope implementation.

Results: The groups had the same age, race, gender, BMI, tobacco use, diabetes, CKD, and hypertension distribution. The median creatinine in the groups was not statistically different (p-values 0.552, 0.081 and 0.469 at baseline, 3, and 6 months respectively). The median estimated glomerular filtration rate, calculated with the modified diet renal disease equation, was not statistically different between the groups (p-values 0.822, 0.644, and 0.507 at baseline, 3 and 6 months respectively). The incidence of AKI, RRT, and mortality in the groups over 6 month follow up after treatment were not significantly different. The median BNP at 6 months in the LVAD and inotrope groups was 216 pg/dL (range 14 to 2995 pg/dL) and 497 pg/dL (range 147 to 1242 pg/dL), with p-value statistically significant at 0.005.

Conclusions: The sole use of inotropes in patients with end-stage heart failure is non-inferior for outcomes in survival, incidence of AKI, need for RRT, and renal function within 6 months when compared to LVAD placement. More studies are needed to compare inotropes and LVAD implantation on renal function and outcomes over a longer time period.

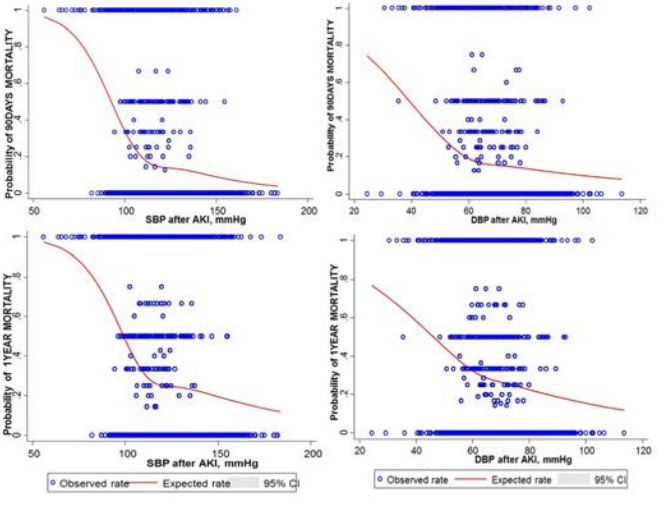
FR-PO874

Optimal Blood Pressure in Acute Kidney Injury: What and When? Seon Ha Baek, Ki Young Na, Sejoong Kim. *Internal Medicine, Seoul National Univ Bundang Hospital, Seongnam, Republic of Korea.*

Background: Blood pressure (BP) is an important target for kidney injury, but few data showed optimal BP in patients with acute kidney injury (AKI) relative to mortality.

Methods: We performed a retrospective cohort study of 2304 patients who had their creatinine levels measured (≥ 1 measurement) during admission for a period of 1 year (January 1, 2013 through December 31, 2013) at tertiary hospital and were diagnosed with AKI by Kidney Disease Improving Global Outcomes (KDIGO) definition based on serum creatinine criteria. Average BP (systolic [SBP] and diastolic [DBP]) was categorized into 10-mmHg increments (at early period of admission within 48hr and at 48hr after development of AKI).

Results: The overall 90-day and 1-year mortality for patients were 17.6 % (405/2304) and 29.0% (669/2304). The relationship between BP (SBP and DBP) followed a J-shaped curve association with increased 90-day and 1-year mortality at low BP value in univariable analysis (SBP <120mmHg and DBP <60mmHg at admission and after AKI).



However, SBP at 48hr after AKI was only a predictor for 90-day mortality after adjustment for baseline variables (reference systolic BP ≥ 140mmHg, <100mmHg, Hazard ratio [HR] 4.528, P <0.001; 100-110mmHg, HR 2.177, P = 0.005; 110-120mmHg, HR 1.764, P = 0.033; 120-130mmHg, HR 1.415, P = 0.215; 130-140mmHg, HR 1.656, P = 0.088). This trend also remained in the relationship between average SBP after AKI and 1-year mortality.

Conclusions: After AKI, a J-shaped curve association existed between SBP at 48hr after AKI and 90-day/1-year mortality, which suggests that too low of a pressure (especially <120mmHg) may be dangerous. SBP after AKI was only a predictor for mortality rather than SBP/DBP at admission or DBP after AKI.

FR-PO875

Identification of Acute Kidney Injury Using a Novel Electronic Urine Flow-Rate Device Mor Grinstein,[1] Aliza D. Goldman,[2] Hagar Azran,[2] Dafna Willner.[2] *[1]Massachusetts General Hospital; [2]Anesthesiology and CCM, Hadassah-Hebrew Univ Hospital, Israel.*

Background: Criteria for identifying acute kidney injury (AKI) include measurements of serum creatinine (SCr) and urine output (UO). Current clinical practice for UO measurement involves manual recording of data, subject to human errors, including time errors and inaccurate urine drainage bags. A novel electronic device used in this study provided timely and accurate data for hourly urine output. We validated this device and analyzed it for the ability to identify AKI according to the AKIN (Acute Kidney Injury Network) criteria. We compared UO measured electronically to manual nursing staff records, as well as to SCr values.

Methods: Study Population: 40 hospitalized patients in the General ICU at Hadassah Hospital, Jerusalem, Israel with a urinary catheter Materials: The RenalSense *Clarity RMS™ sterile sensor kit* for electronic monitoring of UO. For this study, the RenalSense drainage bag included a standard urinometer for the nursing staff to record UO as per standard practice. The drainage bag was placed on a scientific scale (gold standard) to validate the sensor measurements. Sensor data and nursing staff manual records of UO were compared to the scale data. Daily SCr, urea, and creatinine clearance were collected from patient records up to 7 days following the drainage bag removal. Relevant fluids and medication were recorded.

Results: Our observations have shown that electronically recorded data of UO is more consistent, reliable and accurate than nursing records. Moreover, our study has highlighted the weakness of SCr as an accurate measurement of kidney function. Most patients showed a steady decrease to very low levels of SCr, even below normal range, possibly due to fluid overload. We found an average length of stay in the ICU of 14 days in patients with low UO as defined by the AKIN criteria versus 10 days in patients that had normal UO.

Conclusions: Close urine monitoring during this study has provided observation of diuretic response in real-time. This study has highlighted applications of a novel electronic device for measuring UO such as identifying AKI, decisions as to timely fluid and diuretic administration, and dose response.

Funding: Pharmaceutical Company Support - RenalSense

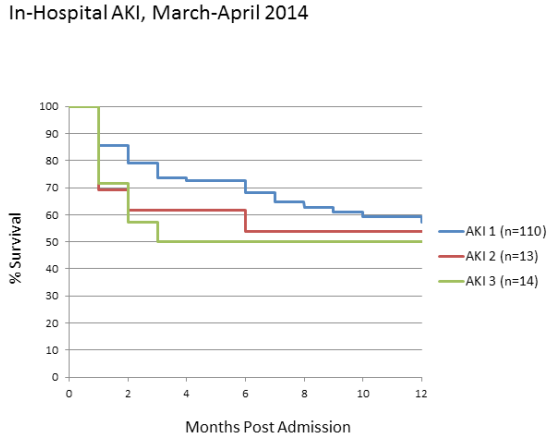
FR-PO876

Poor Survival 12 Months after In-Hospital AKI e-Alert Regardless of Stage Nina Gerdes, Clare Morlidge, Kate Berresford, Catherine J. Marshall, Suresh Mathavakkannan, Andrew Findlay. *Dept of Nephrology, Lister Hospital, East & North Hertfordshire NHS Trust, Stevenage, Hertfordshire, United Kingdom.*

Background: Acute kidney injury (AKI) is an emerging national and global health imperative. Here we review 12 month survival amongst patients following in-hospital AKI e-alert.

Methods: Data was retrospectively evaluated from secondary care hospital AKI e-alerts between 28/03-28/04/2014. Patient contact episodes (PCE) over the same period were recorded to calculate incidence. PCE were defined as adult elective and emergency attendances to the hospital. AKI e-alerts were staged by a nephrologist for accuracy along KDIGO guidelines. In-hospital AKI was defined as an e-alert generated >24 hrs after admission. Age adjusted co-morbidity was obtained from electronic patient record. Patients were followed up for one year.

Results: There were 412 AKI e-alerts generated from 19,530 patient contact episodes (PCE). On nephrologist review 299 (72.5%) were genuine AKI. 137 AKI e-alerts were in-hospital AKI with 110 AKI 1; 13 AKI 2 and 14 AKI 3. This gave AKI event rates of 7.01/1000 PCE for total in-hospital AKI, 5.63/1000 PCE for AKI 1, 0.67/1000 PCE for AKI 2 and 0.72/1000 PCE for AKI 3. Patient survival 12 months after AKI e-alert for in-hospital AKI was 57.27% for AKI 1, 53.85% for AKI 2 and 50% for AKI 3. Timing of death differed between AKI stages with 37.8% of AKI 1, 67.74% of AKI 2 and 81.82% of AKI 3 in-hospital AKI dying whilst inpatients.



Mean age adjusted Charlson co-morbidity scores of all in hospital AKI, Stage 1, 2 and 3 were high (5.71, 5.51, 6.85, 6.51 respectively).

Conclusions: In-hospital AKI, regardless of stage, is associated with poor survival at 12 months. High age-adjusted co-morbidity scores for AKI 1 may explain why a relatively minor AKI is associated with poor 12 month survival. Minor AKI may be a marker of underlying physiological frailty and increased risk of death.

FR-PO877

Reduction of In-Hospital AKI Incidence Using a Multidisciplinary Model and Intelligent Data Analysis Nina Gerdes, Clare Morlidge, Kate Berresford, Catherine J. Marshall, Suresh Mathavakkannan, Andrew Findlay. *Nephrology, Lister Hospital, East & North Herts NHS Trust, Stevenage, Hertfordshire, United Kingdom.*

Background: In-hospital acute kidney injury (AKI) is associated with poor survival at 1 year regardless of stage. A multidisciplinary AKI service was developed to reduce in-hospital AKI incidence.

Methods: A specialist nurse interrogated daily AKI e-alerts and prioritized deteriorating AKI above severity. A daily working week ward round consisting of Nephrology consultant, Renal pharmacist and AKI specialist nurse started in February 2016 to review patients with deteriorating AKI. AKI incidence was measured retrospectively 2 months prior to the introduction of AKI team and 2 months afterwards. All AKI e-alerts from December 2015-March 2016 were staged along KDIGO guidelines. In-hospital AKI was defined as an e-alert generated >24hrs post admission. To measure incidence the number of patient contact episodes (PCE) defined as adult emergency and elective attendance to a secondary care hospital was calculated per week. The number of AKI alerts over a week was divided by the number of PCE and multiplied by 1000 to give number of AKI events per 1000 PCE per week.

Results: There was a significant reduction in total in-hospital AKI, AKI 1 and AKI 2 but not AKI 3 incidence following the introduction of the AKI team (February+March 2016) compared to the 2 months prior to introduction.

	Pre-AKI team	Post AKI team	P - value
Total in-hospital AKI	7.07* (1.14)	5.25 (1.31)	0.015
In-hospital AKI 1	5.56 (0.84)	4.25 (1.24)	0.034
In-hospital AKI 2	0.87 (0.33)	0.21 (0.14)	0.0016
In-hospital AKI 3	0.44 (0.49)	0.51 (0.26)	0.92
* Incidence - No of AKI events / 1000 PCE / Week			
Data not normally distributed - Median (SD) shown, P value refers to Mann-Whitney U-test.			

Conclusions: A model of daily AKI e-alert review, data analysis and prioritization of declining AKI over severity followed by targeted clinical multidisciplinary review of the patients with AKI has been associated with a significant reduction of in-hospital total AKI, AKI 1 and 2 incidence reduction. A preventative approach targeting early deteriorating AKI rather than severe established AKI may reduce in-hospital AKI.

FR-PO878

Telenephrology: A 2 Year (1978 Visits) Experience Caring for Hospitalized Patients in a Rural Community Hospital Brenda R.C. Kurnik, Jerome S. Tannenbaum. *Sanderling Renal Services, Nashville, TN.*

Background: Telemedicine has been utilized for over 30 years. Early applications included "store and forward" technology and tele-monitoring. The limited literature in telenephrology is primarily focused on outpatients. We report a two year experience using real-time audio video technology to perform nephrology consultations, follow up visits and dialysis on in-patients in a rural hospital.

Methods: A retrospective study of inpatients requiring nephrology care between April 2014 and April 2016. Consultations were requested by the on-site physicians and were performed by reviewing the patient's hospital EMR and performing a real-time history and physical exam with audio-video technology and Littman electronic stethoscope.Notes were typed into the hospital EMR and local physicians were contacted by phone as needed.

Results: A total of 427 consults and 1551 follow up visits were performed. Population characteristics: 213 females, 214 males; age range 25-99 yrs. old. Patient location: ICU 154, PCU 36, floor 237. Average LOS of 6.8 days. Disposition: home/rehab 360, transferred to tertiary care hospital 28, hospice 21, and deceased 18. Consults were performed on 186 patients with ESRD (165 HD/21 PD) and 241 pts for: ARF (193) Overdose (2) CKD (26) and electrolyte disorders (20). The pts with ESRD received 405 hemodialysis treatments and 70 peritoneal dialysis treatments. We did 123 acute dialysis treatments in 31 pts. (15 pts received 45 HD for ARF, 15 pts received 77 HD for CKD which progressed to ESRD, and one pt/ 1 HD for an overdose. Dialysis complications were few, 5 pts had shortened HD for hypotension and 2 treated for hypertension. There were no access issues. Disposition for ESRD pts: home/rehab 171, transfer 7, hospice 3, deceased 5. Disposition for Non-ESRD pts: home/rehab 189, transfer 21, hospice 18, deceased 13. Of the 15 pts requiring HD for ARF, 12 regained renal function, 1 was made hospice and 2 were transferred on HD.

Conclusions: Telenephrology for the co-management of patients in a rural hospital is both feasible and safe. Our care included pts with both ESRD and ARF requiring dialysis.

FR-PO879

A Bedside Clinical Tool Using Creatinine Kinetics to Predict Additional Renal Injury and Early Recovery Maurice I. Khayat,[1] Jonathan Deeth,[2] Jonathan Sosnov.[3] *[1]Internal Medicine, San Antonio Military Medical Center, Fort Sam Houston, TX; [2]Anesthesiology, Evans Army Community Hospital, Fort Carson, CO; [3]Nephrology, San Antonio Military Medical Center, Fort Sam Houston, TX.*

Background: The characteristics of changing creatinine concentrations during acute renal failure are often confusing to clinicians and can cloud the patient's true current state of renal injury. By modifying the formula for kinetic estimate of glomerular filtration rate, a simple bedside clinical tool can be used to identify subtle changes in renal function.

Methods: The kinetic estimate of glomerular filtration rate was rewritten to instead calculate a predicted peak creatinine after each assumed renal injury. By comparing the changes in predicted peak creatinine at two or more subsequent time intervals, the patient's current state of renal injury can be determined: early recovery, a single ongoing renal insult, or multiple simultaneous renal injuries.

Results: Three case examples are provided using the equation for predicted peak creatinine. In each case, the creatinine concentration has continued to rise at three sequentially-measured times. However, the change in predicted peak creatinine is analyzed for each case, demonstrating scenarios involving (a) multiple simultaneous renal injuries, (b) a single, ongoing renal injury, and (c) a renal process with early intervention and recovery.

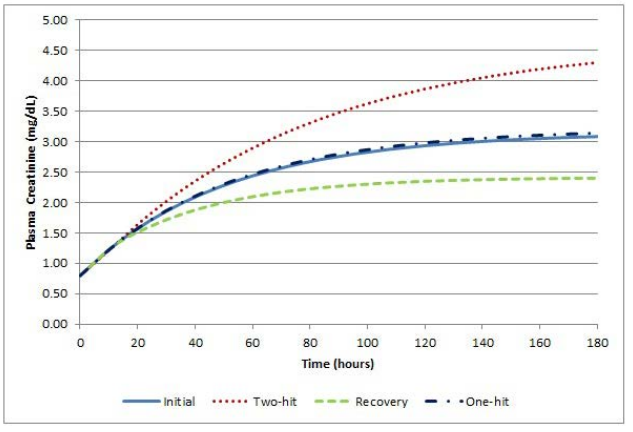


Figure 1 – Plot of the projected plasma creatinine versus time describing three different clinical case scenarios. The initial projected creatinine based on the plasma creatinine values at t1 and t2 (common to all example cases) is demarcated by the solid line above. The projected creatinine curves based on the amended peak creatinine after recalculation at t3 for each case (two injuries, one injury and early recovery) are superimposed as marked.

Conclusions: The use of this model may provide the clinician with an easy bedside tool to assess a patient's state of acute kidney injury. Reassessment of how the creatinine is changing is already a non-quantitative part of a nephrologist's approach to acute kidney injury. Providing an assessment of the patient's changing renal function would be a useful addition to detect early renal recovery or additional renal injuries in order to appropriately adjust treatment strategies.

Funding: Other U.S. Government Support

FR-PO880

Computerized Algorithms Compared to a Nephrologists Diagnosis of Acute Kidney Injury Arnar Jan Jonsson,[1,2] Sigrun Helga Lund,[2] Runolfur Palsson,[1,2] Olafur S. Indridason,[2] Ingibjorg Kristjansdottir.[2] *[1]Univ of Iceland; [2]Landspitali - the National Univ Hospital of Iceland, Reykjavik, Iceland.*

Background: Although the recent consensus criteria for acute kidney injury (AKI) is a step forward, the lack of reliable baseline serum creatinine (SCr) still hampers epidemiological studies. The aim of this study was to examine AKI diagnosis based on different computerized algorithms compared to AKI determined by a nephrologist in patients visiting an emergency department (ED) of a university hospital.

Methods: In this retrospective study, we used electronic medical records at the University Hospital in Reykjavik to identify all patients aged ≥18 years, who upon arrival to the ED in the year 2010 had an elevated SCr level. All available SCr values were reviewed and a nephrologist determined whether AKI was present using the KDIGO criteria, together with clinical data. Computerized algorithms based on the KDIGO SCr criteria, accounting for various time intervals for baseline SCr and changes in follow-up SCr were constructed in R.

Results: At 47,558 ED visits, SCr was measured in 15,623 patients for a total of 24,594 measurements. An elevated SCr was observed in 2,878 (18.4%) patients. Strict adherence to the KDIGO criteria (SCr increase of 0.3 mg/dl over 48 hrs or 50% increase over 7 days) yielded a 63% sensitivity, 94% specificity, 96% positive predictive value (PPV) and 49% negative predictive value (NPV) for the diagnosis of AKI. Allowing for longer time frame (365 days) for baseline SCr, yielded 75% sensitivity, 89% specificity, 94% PPV and 58% NPV. The algorithm with the highest sensitivity consisted of strict adherence to the KDIGO criteria together with the addition of 50% increase from baseline SCr from the previous year or 33% decrease in SCr within 7 days of the index SCr. This algorithm yielded a sensitivity of 86% but only 46% specificity. PPV and NPV were 81% and 57%, respectively.

Conclusions: Computerized algorithms for detection of AKI in patients visiting the ED, perform variably compared to a nephrologists (gold standard). Incorporating a measure of reduction in SCr following the visit may confer benefit at the risk of decreased specificity.

Funding: Government Support - Non-U.S.

FR-PO881

Acute Kidney Injury Electronic Alert Triggered Intervention Improves Length of Stay Rhodri Pyart, Craig D. Beaton, Afza L. Sadiq, Harsha P. Reddy, Benjamin J. Thomas, Chris P. Subbe, Vijaya Bharath P. Ramasamy. *Nephrology, BCUHB, Wrexham, United Kingdom.*

Background: Acute kidney injury (AKI) in hospital can be alerted electronically (e-alert) to clinicians using software that tracks creatinine changes. It is unclear however if any clinical intervention at this stage has a beneficial outcome. The aim of this study was to establish whether nephrology or critical care outreach team (CCOT) review of patients identified with AKI by e-alerts resulted in improved clinical outcomes and length of hospital stay.

Methods: Patients with AKI e-alerts were reviewed by nephrologists (grade 2 and 3 AKIs) and CCOT (grade 1 AKIs) on the same day. This was carried out for 30 consecutive days. Information on outcomes was prospectively collected for a follow up period of 80 days. A comparator group was formed 6 months earlier, made up of patients with an AKI e-alert generated over 60 consecutive days who were followed up with no intervention.

Results: 398 genuine AKIs were identified from all generated AKI e-alerts, 273 patients had no intervention while 125 patients were reviewed based on grade of AKI as above. There were no differences between the groups in mean age (75.0 ±14.9 vs 75.2 ±14.4 years, p = 0.909) and baseline creatinine (97.0 ±52.6 vs 99.7 ± 57.7 µmol/L, p = 0.467). The proportion of patients discharged home by 30 days post AKI was significantly higher in the intervention group (56.0% vs 44.7%, p = 0.018). The death censored median length of hospital stay was also significantly lower in the intervention group (13 vs 8 days, p = 0.034). The mortality rate trended towards being lower in the intervention group as compared to the comparator group at 80 days (32.0 % vs 38.5%, p = 0.108). The rate of progression of grade 1 and 2 to grade 3 AKIs also trended towards being lower in the intervention group (10.3% vs 6.3%, p = 0.115). There were no statistically significant differences in the need for renal replacement therapy, use of ICU beds and renal recovery at 80 days.

Conclusions: Our study supports the use of intervention in patients triggered with AKI e-alert. In particular it suggests that there is significant benefit in terms of shorter length of hospital stay. Larger studies are needed to support these findings.

FR-PO882

Irisin and Inflammatory Biomarkers in End Stage Renal Disease Patients Submitted to Remote Ischemic Pre Conditioning Marcelo Rodrigues Bacci, Mariana Carvalho Gouveia, Fernando Luiz Affonso Fonseca. *General Practice, ABC Medical School, Santo Andre, São Paulo, Brazil.*

Background: Irisin is a muscle-secreted protein released into the circulation by cleavage of fibronectin type III domain containing protein 5.It has been studied as a biomarker of myocardial injury. Areas submitted to remote ischemic cardiac preconditioning in experimental models have less occurrence of necrosis.The purpose of this study is to determine serum irisin levels and its association with troponin in patients with chronic kidney disease undergoing hemodyalisis submitted to RIPC.

Methods: It is a double blind randomised trial with two groups:intervention;submitted to RIPC in the right arm with sphygmomanometer with 200mm/Hg of pressure with three-5 minute rounds alternating with deflation totalling 30 minutes and control group;without RIPC.Intervention group received RIPC in three consecutive hemodialysis sessions.Blood samples were taken before the first session and after the third consecutive dialysis session. BUN for calculation of single pool Kt/v, ultra sensitive I troponin and irisin were measured to evaluate dialysis adequacy and myocardial injury.To evaluate inflammatory profile were measured TNF, selenoprotein, tioredoxin, NF kB.

Results: A total of 14 patients were selected with 50% of men. About 64.3% had diabetes. Troponin levels were not affected by the RIPC intervention with a p=0.281. The difference between the moments of blood collection of each biomarker was not affected by the RIPC . Spearman's correlation test showed a p value of 0.558 between irisin and troponin.

Inflammatory biomarkers did not have statistical difference between the time of collection of the sample and neither between RIPC and control group. Only interleukin 6 showed a p= 0.039 analysing the moments of collection and the occurrence or not of RIPC.

Conclusions: In conclusion despite being a promising myocardial injury biomarker, irisin was not affected by hemodialisys in end stage renal disease. Moreover, RIPC did not affect its levels independently of the moment of the collection (before or after).

FR-PO883

Prognostic Significance of Hemodynamic Parameters in Hemodialysis Patients Ferruh Artunc,[1] Bjoern Friedrich,[2] Nils Heyne,[1] Stefanie Haag.[1] *[1]Internal Medicine, Div of Nephrology, Univ Hospital, Tuebingen, Germany; [2]Nephrology Center, Leonberg, Germany.*

Background: Hemodialysis (HD) patients have a high mortality that mainly results from cardiac impairment. Using an ultrasound dilution device various hemodynamic parameters can be measured during a HD session. So far, there is no data regarding the prognostic significance of these parameters.

Methods: We conducted a prospective cross-sectional study in 185 stable HD patients and measured cardiac index (CI), access flow (AF) and central blood volume

index (CBVI) using the Transonic HD03 monitor at the beginning and end of a single HD session. In addition, we calculated systemic CI (SCI=CI-AF) and oxygen delivery index (DO_2I=SCI*hemoglobin*1.34). Survival analysis was performed after a median follow-up of 606 (interquartile range 593;621).

Results: During follow-up 33 patients (18%) died. Compared to the survivors, deceased patients tended to have a lower CI (P=0.09) and had a significantly reduced SCI and DO_2I (P=0.02 and 0.002, resp.). Drop in CI, SCI and DO_2I at the end of HD (ΔCI, ΔSCI und ΔDO_2I) was significantly higher in deceased patients. In contrast, AF, CVBI and hemoglobin was not different between survivors and deceased patients. Receiver-operator-characteristic (ROC) analysis revealed area-under-the-curve (AUC) values for the endpoint death of 0.68 for DO_2I (P=0.001) and 0.65 for SCI (P=0.013). AUC for ΔCI, ΔSCI and ΔDO_2I ranged between 0.62 and 0.63 (P=0.02-0.03). The combination of two parameters such as CI with ΔCI or SCI with ΔSCI or DO_2I with ΔDO_2I increased AUC values substantially (0.71-0.75). In addition, cox regression confirmed significant survival benefit at higher DO_2I and lower ΔCI, ΔSCI and ΔDO_2I.

Conclusions: This study is the first to show a prognostic significance of hemodynamic parameters in HD patients. Systemic CI and oxygen delivery index at rest as well as drop of these parameters at the end of HD were associated with increased mortality. The results underscore the prognostic relevance of cardiac function for the survival of HD patients.

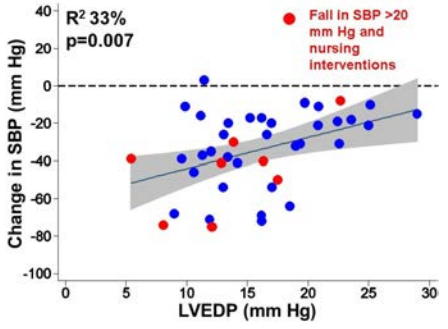
FR-PO884

Non-Invasive Left Ventricular End-Diastolic Pressure Measurement in Hemodialysis Patients and Intradialytic Hypotension Tariq Shafi, Bernard G. Jaar, Luis F. Gimenez, Chloe F. Knight, Seungyoung Hwang, Naya El Hage, Surekha Uma Mullangi, Josef Coresh, Harry A. Silber. *Johns Hopkins Univ.*

Background: Assessment of volume status remains highly subjective and is a major challenge in managing dialysis patients. We tested a novel hand-held device that provides non-invasive assessment of left ventricular end-diastolic pressures (LVEDP), an important indicator of left ventricular volume/pressure overload. We hypothesized that a low LVEDP at the start of hemodialysis (HD) will be associated with intradialytic hypotension.

Methods: We recruited HD patients from 4 Baltimore area dialysis units. Baseline data collected includes demographics, medical history, KDQOL-36, NYHA dyspnea scale, intra/post dialysis symptoms, predialysis metrics [LVEDP, bioimpedance, blood pressure (BP)] and echocardiogram. We assessed the association of predialysis LVEDP with change in systolic BP (SBP) during dialysis (lowest SBP – predialysis SBP) and hypotension episodes requiring nursing interventions.

Results: In the first 45 participants (mean age 60 years, 58% male, 87% Black), median [25th, 75th percentiles] for predialysis LVEDP was 16 mmHg [2, 20], interdialytic weight gain (IDWG) was 1.8 kg (1.1, 2.7) and SBP was 147 mmHg [134, 162]. Significant fall in SBP (≥20 mmHg) was common and occurred in 32 (71%) patients of whom 7 (16%) also required nursing interventions. Predialysis LVEDP was associated with fall in SBP during dialysis (p=0.007) and intradialytic hypotension requiring nursing interventions (p=0.04). Predialysis SBP (p=0.3), IDWG (p=0.4) or bioimpedance water measurement (p=0.5) were not associated with intervention requiring intradialytic hypotension.



Conclusions: Our findings suggest that non-invasive LVEDP measurement can provide an objective assessment of volume status and identify HD patients at risk of intradialytic hypotension.

Funding: NIDDK Support

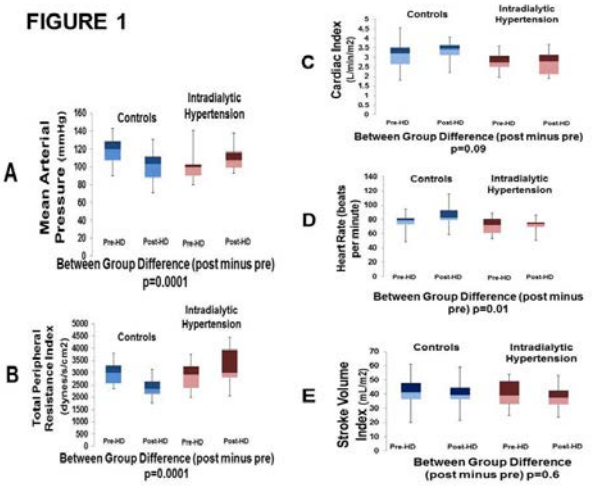
FR-PO885

Measurements of Extracellular Volume and Cardiovascular Hemodynamics in Patients with Recurrent Intradialytic Hypertension Peter N. Van Buren, Javier A. Neyra, Robert D. Toto. *UT Southwestern.*

Background: Intradialytic hypertension (IH) is a recurrent phenomenon in some hemodialysis (HD) patients and is associated with increased mortality. Both extracellular volume overload and vascular resistance surges have been separately observed in patients with intradialytic blood pressure (BP) increases. We simultaneously compared pre-HD, post-HD, and changes in body fluid and hemodynamics in patients with recurrent IH and HD controls.

Methods: We used whole-body bioimpedance spectroscopy and impedance cardiography to compare pre-HD, post-HD, and intradialytic changes in total body water (TBW) and extracellular water (ECW), as well as cardiac index (CI) and total peripheral resistance index (TPRI) in 18 patients with recurrent IH and 18 hypertensive HD controls with intradialytic BP decreases.

Results: During screening, the mean systolic BP before and after HD was 165 (18) and 138 (2.1) mmHg in controls and 141 (17) and 162 (16.2) mmHg in IH patients. During the study, there were between group differences in the change in MAP, TPRI and heart rate from pre to post dialysis, but not in CI or stroke volume index.



The ECW/TBW ratio was higher in IH patients before and after dialysis.

	Controls (n=18)	IH (n=18)	p-value
PRE-HD			
TBW (L)	48.2 (11)	46.5 (10)	0.6
ECW (L)	21.6 (5)	22.0 (5)	0.8
ECW/TBW	0.453 (0.05)	0.478 (0.03)	0.05
POST-HD			
TBW (L)	45.2 (11)	43.6 (9)	0.7
ECW (L)	19.1 (4)	20.1 (5)	0.5
ECW/TBW	0.427 (0.04)	0.461 (0.03)	0.01

There was a trend for changes in ECW and ECW/TBW from pre- to post-dialysis to be smaller in IH patients than controls (p= 0.06 and 0.1, respectively).

Conclusions: Recurrent IH is associated with higher post-HD extracellular volume and TPRI. Intradialytic TPRI surges likely account for the vasoconstrictive state post-HD, but intradialytic fluid shifts may contribute to the volume expanded state post-HD.

Funding: NIDDK Support

FR-PO886

Adrenal Insufficiency (AI) Is Highly Prevalent and May Be Associated with Intradialytic Hypotension(IDH) in Hemodialysis(HD) Patients Eunjung Kim,[1] Myung Jin Choi,[2] Jung-Woo Noh,[3] Dong Ho Shin,[4] Ja-Ryong Koo.[1] *[1]Hallym Univ, Dongtan; [2]Chuncheon; [3]Kangnam; [4]Gangdong.*

Background: Many maintenance HD patients had been chronically exposed to pharmacologic dose of steroid for the underlying kidney disease or various coexisting disease. We evaluated prevalence, risk factor and clinical impact of AI as a possible cause of IDH in HD patients.

Methods: Among 106 HD patients, 10 patients on current steroid treatment were excluded and remaining 96 patients were studied. Adrenal function was evaluated during HD by high dose ACTH stimulation test. AI was defined by baseline serum cortisol<10 μg/dL and ACTH stimulated maximal serum cortisol<18 μg/dL. Status of previous steroid exposure was identified through the evaluation of medical record and history about underlying, coexisting disease, medications and injections. IDH was defined by symptomatic decrease in systolic BP≥20 mmHg and the mean IDH event during 6 consecutive HD sessions was calculated. In selected patients with IDH and AI who agreed to steroid replacement, change in the incidence of IDH before and after steroid treatment was ascertained.

Results: The prevalence of AI was 36.5% (73.5% in 34 patients with previous steroid exposure vs 16.1% in 62 patients without steroid exposure). There was no difference in the prevalence of AI according to the type of underlying kidney disease (diabetes 32.0%, glomerulonephritis 40.5%). However, the patients with coexisting disease (gout, osteoarthritis, connective tissue disease)had significantly higher prevalence of AI as compared with the patients without coexisting disease (81.3% vs 20.6%). 33 (34.4%) patients had one or more(mean 2.30±1.13) IDH events during 6 consecutive HD sessions. The proportion of patient with IDH event was significantly higher in the patients with AI as compared with the patients without AI(48.6% vs26.2%). Moreover,in 10 IDH patients with AI who treated by steroid, IDH occurred in only 3 patients after 4weeks of steroid replacement(mean 1.90±0.74vs0.30±0.48).

Conclusions: In HD patients, careful evaluation of medical record and history about coexisting disease, medications, and injections is required to find out underlying AI. Steroid replacement may be a therapeutic option in IDH patient with AI.

FR-PO887

Pneumatic Compression during Hemodialysis May Avoid Hypotension
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Background: Intradialytic hypotension (IDH) is still the most common complication during chronic hemodialysis (HD), and is associated with increased mortality. As the main source of extracellular fluid removed during HD is the legs, we hypothesized that exercise and pneumatic compression during the first hour of HD would reduce IDH, by providing higher venous return and preserving central blood flow.

Methods: We prospectively studied 21 patients (13 men) who were submitted to a baseline cicloergoespirometry and undergone three consecutive random first-week HD session: control, pneumatic compression and intradialytic exercise (cicloergometry). Data from segmental bioelectrical impedance and blood pressure measurement each hour during HD were assessed. IDH was defined as a drop in mean arterial pressure (MAP) ≥20 mmHg with symptoms.

Results: When comparing control, exercise and pneumatic compression, we found no difference in ultrafiltration rate (p=0.628), delta of weight (p=0.415), and percentage of urea reduction (p=0.941). Maximum oxygen uptake (VO_2 peak) was 23.0 ± 6.2mL/kg/min. MAP pre dialysis was similar in the three conditions (p=0.245). The delta of total body water, intra and extracellular volume was similar in control, exercise and pneumatic compression (p=0.209, p=0.348 and p=0.467, respectively). The delta of legs and trunk water content was also similar among conditions (p=0.235 and p=0.817, respectively). The delta of MAP was -5.9 ± 17.2, -9.6 ± 18.0 and -0.2 ± 13.7 mmHg in control, exercise and pneumatic compression, respectively (p=0.152). IDH occurred in 9 (43%), 8 (38%) and 5 (24%) patients in control, exercise and pneumatic compression, respectively (p=0.014);post test revealed that pneumatic compression presented less IDH than control and exercise.

Conclusions: Pneumatic compression during the first hour of dialysis was associated with less IDH, albeit no effect on fluid parameters, including preservation of central fluid was observed. Further studies are required to better understand physiological and hemodynamic changes in patients during HD.

FR-PO888

The Effects of Intradialytic Volume Changes on Cardiovascular Hemodynamics
Nathan W. Levin,[1] Marcia H.F. Goulart de Abreu,[2] Lucas Espíndola Borges,[2] Helcio Antonio Tavares Filho,[2] Rabia Sarwar,[3] Surendra K. Gupta,[3] Shaul Lev,[4] Caroline Williams.[3] *[1]Mt Sinai School of Medicine, NY; [2]Biocor Hospital Belo Horizonte MG, Brazil; [3]Queens Artificial Kidney, NY; [4]Rabin Medical Center, Israel.*

Background: Intradialytic hypotension (IDH) is a major clinical problem in chronic hemodialysis. A novel noninvasive regional impedance cardiography device was used to evaluate IDH in a quality improvement project.

Methods: The device (NICaS, NI Medical, Israel) provided repeated cardiac power index (CPI) and total peripheral resistance index (TPRI) measurements over 4-5 treatments.

Results: N=52 patients. In 184 non-IDH treatments/ 237, SBP decreased from 141±24 to 130±20 mmHg. CPI and TPRI decreased by 18±19% and 2±27% respectively. IDH occurred in 53 (22%) treatments with mean SBP decreasing from 134±20 to 92±11 (P>0.001). IDH treatments were divided into 3 subgroups according to hemodynamic trends: **1)** ***Solitary cardiac power reduction*** (n=26, 49% of treatments): CPI decreased 42±11%, (0.64±0.14 to 0.37±0.07 [w/m^2]) (P>0.001) with insignificant TPRI reduction. SBP decreased from 130±23 to 89±12 (P>0.001). **2)** ***Solitary vasodilatation*** (n=11, 21% of treatments): TPRI decreased 31±6% (3,155±962 to 2,168±639) [dyn*sec/cm^5/m^2]) (P>0.001 with insignificant change in CPI. SBP decreased from 134±16 to 102±7 (P>0.001). **3)** ***Mixed hemodynamics*** (n=16, 30% of treatments): CPI decreased 34±9% (0.66±0.13 to 0.44±0.10 (P>0.001) and TPRI decreased 32±7% (2,431±547 to 1,645±306 (P>0.001). SBP decreased from 140±17 to 90±10 (P>0.001). The proportion of diabetic patient treatments was greater in the low TPRI than in the low CPI groups (81% vs 42%, P<0.005).

Conclusions: 1) This technology provides quantitative insights into the major proximate causes of IDH, which are reductions in CPI and/or in TPRI**. 2)** *Potential actions*before onset of hypotension include lowering UFR to maintain falling cardiac preload and CPI, and using vasopressors (e.g.midodrine) or cooling, to increase TPRI. These approaches could prevent occurrence of IDH. **3)** The apparent effect of diabetes with presumed autonomic dysfunction, in the low TPRI subgroups (2 and 3), warrants the investigative use of prophylactic vasoconstriction.

FR-PO889

Oxygen Extraction Ratio (OER): A Marker of Haemodynamic Stress in Haemodialysis (HD)?
Sandro Mazzaferro,[1] Silverio Rotondi,[2] Maria Luisa Muci,[2] Lida Tartaglione,[1] Luciano Carbone,[2] Marzia Pasquali.[3] *[1]Scienze Cardiovascolari, Respiratorie, Nefrologiche, Anestesiologiche e Geriatriche, Sapienza Univ, Rome, Italy; [2]Nephrology and Dialysis Unit, ICOT Hospital, Latina, Italy; [3]Nephrology and Dialysis Unit, Policlinico Umberto I, Rome, Italy.*

Background: Cardiovascular stress and symptoms occurr in HD sessions. Monitoring Blood Volume (BV) allows prevention but does not measure the stress entity. The OER (n.v.25-30%), used to estimate tissue oxygenation, mirrors adaptation to hypoxia/hypoperfusion. We hypothesized that, if detectable, its changes during HD could reflect hemodynamic stress.

Methods: OER (periferal O_2 saturation (SO2)/central venous SO_2, respectively measured with an oxymeter and a gas analyser) was measured in patients with CVC. We sampled OER before, 15', 30', 60', 120' and at the end of HD in each patient in three consecutive HD (long and short intervals) with an UF rate <10 ml/kg/h. We recorded BP, HR, UF, BV and symptoms.

Results: In the 10 patients enrolled (age 72±14 y, M/F=2/8, HD since 38±41 months) we observed overlapping changes in OER (p=n.s.) in the 3 consecutive sessions and thus averaged the values. OER increased progressively from 35±7% to 47±8% (p<.0002), in front of UF (-2,2±0,79 Kg, BV reduction (-8±4%, p<.0001), no change in BP or HR (table 1), no symptoms.

	Basal (M±SD)	15' (M±SD)	30 '(M±SD)	60' (M±SD)	120' (M±SD)	End of HD(M±SD)	ANOVA
O.E.R., %	35±7	40±9	42±7	42±7	43±9	47±8	.0002
SBP, mmHg	121±16	126±21	126±19	128±18	121±16	122±22	n.s.
DBP, mmHg	69±13	68±12	73±16	73±15	70±13	71±14	n.s.
HR, bpm	67±10	65±10	65±15	66±11	67±10	70±10	n.s.
BV, %	0	-2±1	-3±2	-5±2	-6±3	-8±4	.0001
UF, Kg	0	0.2±0.08	0.3±0.12	0.6±0.21	1.2±0.4	2.2±0.79	.0001
OER= Oxygen extration ratio; SBP= Systolic blood pressure; DBP= Dyastolic blood pressure; HR= Heart rate; BV= Blood volume; UF= Ultrafiltration							

Conclusions: OER, already increased before HD, showed a progressive increment during session, reflecting haemodynamic adaptation. With stable BP and no symptoms, OER significantly increases during HD and could represent a useful tool to monitor hemodynamic stress.

Funding: Private Foundation Support

FR-PO890

Pre-Dialysis IVC Diameter Predicts Ultrafiltration Goal in Hospitalized ESRD Patients
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Background: Estimates of hemodialysis(HD) ultrafiltration(UF) goals are based on volume status. Usually UF goals are empiric, with hypotension on HD indicating "dry weight." Bedside ultrasonography can determine inferior vena caval diameter(IVCD) which may predict right ventricular (RV) pre-load. We theorized that IVCD may enhance assessment of volume status and help guide UF goals for HD.

Methods: ESRD inpatients without known RV failure were studied. Prior to HD, hypertension(HTN) (BP> 140mmHg) and presence of edema were recorded and UF goal assigned. A nephrology fellow, trained to assess IVCD using a GE Sonosite machine, measured IVCD at its entry into the right atrium prior to and following HD. Linear regression(LR) was used to examine the association between pre-IVCD and volume removal.

Results: 20 patients were studied from Jan-May 2016. Physical findings:edema(65%), HTN(70%) and both(45%). Groups were defined as euvolemic (no edema, no HTN N=3) or hypervolemic(edema and HTN N=10).

Group	Pre SBP	Post SBP	Pre IVCD	Post IVCD	Change in IVCD	UF removed
Euvolemic	113±13	114±9	1.47±0.3	1.33±0.4	0.1±0.1	0.3±0.6
Hypervolemic	168±23	142±16*	2.44±0.4	2.01±0.4*	0.4±0.2	2.07±0.5
All patients	152±27	133±17*	1.74±0.4	2.07±0.5*	0.3±0.2	3.75±0.98
*p < 0.05 when compared to pre-dialysis levels						

Table 1 shows pre and post-dialysis SBP(mmHg), IVCD (cm), change in IVCD (cm) and UF removed (L). For all patients, a correlation between pre-SBP and IVCD (r=0.7801) and pre-SBP and volume removed (r=0.7719) was found. In edematous patients LR showed for every 1 cm change in pre IVCD the amount of volume removed increased by 1.43 kg controlling for edema and pre-SBP.

Conclusions: IVCD is a non-invasive, objective marker of pre-load in hypervolemic HD inpatients, is well tolerated, and correlates with UF removal. IVCD augments volume assessment and may help guide determination of UF goals in HD.

FR-PO891

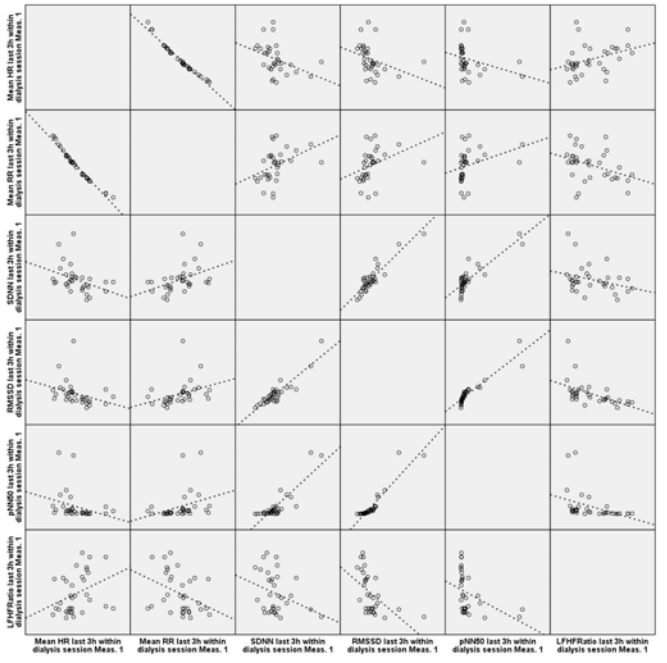
Heart-Rate-Variability in Haemodialysis
Joachim H. Beige. *Nephrology and Dialysis, Hospital St. Georg, Leipzig, Germany.*

Background: Heart rate variability (HRV) is a measure of time intervalls between heartbeats and characterizes the ability to adapt to (patho)physiological conditions. It can be used hypothetically to assess the sympathetic acitivity during haemodialysis (HD). Because only sparse infomation about HRV during HD is available we investigated the course of HRV during and after HD and it´s correlation to anthropometrical and HD data.

Methods: Continous measurement of five recognized HRV measures (meanRR-dist., SDNN, RMSSD, pNN50, LF/HF Ratio) in time slots of 3 hours during and immediately after HD at 2 consecutive HD sessions of 34 patients by long-term ECG including artifact flattening. During these 68 sessions, no intradialytic morbid events (IME) appeared.

Computation of descriptive statistical analyses (ANOVA, linear regression, population discrimation) was done by SPSS vs. 21 package including analysis of HRV precision by repeated measures by paired t-test.

Results: The highest correlation between HRV markers (all p<0.0001) in consecutive HD sessions (i.e. the best precision) was found for RMSSD during HD (T=0,856) and PNN50 after HD (T=0,929). Correlation of HRV Marker with each other was highest for pNN50 and RMSSD.



Linear regression analyses of pNN50 und RMSSD with age, gender, dialysis vintage, comorbidities, ESA index, PO4, Hbg, KtV, ultrafiltration (UF), dry weight and blood pressure yielded only one weak association between UF and pNN50 during HD (T=2,72, p=0,035).

Conclusions: All HRV markers showed high measurement precision and no interdependency with anthropometrical data. Dialysis-related HRV showed similarity to data from 695 healthy individuals (Sammito et al.). Relationship with (not appeared) IME was not studied and no conclusion about predictibility of HRV against IME can be drawn. However, the relationship with UF points to a thinkable usefullness of HRV as HD biofeedback measure. Further investigations of time courses and patterns will be conducted.

FR-PO892

On-line Hemodiafiltration: Which Mode for Better Cost Effectiveness

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Background: According to the latest studies there are benefits from the use of on line hemodiafiltration (olHDF), especially in the postdilution mode. Generally, this advantage is due to the fact that postdilution olHDF results in better removing of low and medium molecular weight substances. However for successful and uncomplicated postdilution olHDF, high blood flow rates (typically >350 mL/min) are needed. This study aimed to assess the efficacy of removal of low and medium molecular weight substances when blood flow rates<350 ml/min are used, combining various modes of online hemodiafiltration / hemofiltration (olHF).

Methods: We studied 30 patients who were subjected to 4 different dialysis modes. The duration of all dialysis sessions was 4 hours and a high flux filter (PEPA membrane, surface 2,1m^2) was used with blood flow rates from 320 to 350 ml/min. The blood flow rates were the same in each mode for each patient. The 4 groups were: A) a combination of predilution olHDF (2 hours) and predilution olHF (2hours) by giving replacement fluid (RF) at a replacement rate (RR) of 80%, B) predilution olHDF by giving RF at RR of 80%, C) a combination of postdilution olHDF (2 hours) and postilution olHF (2 hours) by giving RF at a RR of 20%, D) postdilution olHDF by giving RF at a RR of 20%. The percentage of change of β2 microglobulin and urea during every session was measured.

Results: No statistical significance in β2 microglobulin for all methods (percentage of change per method A: 75% B: 70% C: 72.5%; D: 78.7%) was found. Instead the percentage of change of urea was statistically significant lower (p <0.01) in method A and C relatively to others. No statistically significant difference for urea in method B and D was found.

Conclusions: Thus, for patients with blood rate <350 ml/min, the use of predilution olHDF by giving RF at a RR of 80% is effective, providing sufficient removal of uremic toxins (low and medium molecular weight substances) without the disadvantage of filter malfunction (increased transmembrane pressure, filter clotting etc.),as seen usually in olHDF postdilution in these blood flow rates.

FR-PO893

Clinical Effectiveness of Intermittent Infusion Hemodiafiltration Using Backfiltration of Ultrapure Dialysis Fluid Compared with Predilution On-Line Hemodiafiltration: A Prospective, Multicenter, and Controlled Trial

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Background: Intermittent Infusion Hemodiafiltration (I-HDF) has been introduced to improve the peripheral circulation of dialysis patients and to reduce the occurrence of hypotension during a hemodialysis treatment. The clinical effectiveness of I-HDF, however, has not been clarified in comparison with those in other on-line HDF therapies.

Methods: A prospective, multicenter, parallel group comparative trial was carried out to reveal the clinical effectiveness of I-HDF compared with predilution on-line HDF (Pre-HDF) that is the most popular on-line HDF therapy in Japan at present. Patients were allocated to two groups after matching for age(±5y.o.), dry weight(±5kg) and with/without diabetes. After obtained informed consent, 36 patients, namely 18 pairs, participated in this clinical trial. During the trial, we evaluated the clinical condition and quality of life (QOL) of the patients and solute removal characteristics.

Results: The results showed no difference in clinical condition and QOL scores between two groups. Reduction ratio of the systolic blood pressure originally showed no difference between two groups but it decreased slightly as the trial proceeded after changing from hemodialysis therapy. There was also no difference in the number of treatments by medical staff, but this also significantly decreased as the trial proceeded in both groups. On the other hand, the Pre-HDF group demonstrated significantly higher removal rates of β2-microglobulin and α1-microglobulin than in the I-HDF group. As the same time, albumin leakage amount in a treatment was also significantly larger in Pre-HDF than that in I-HDF.

Conclusions: In conclusion, the clinical condition and QOL of the patients undergoing I-HDF was not inferior to those having Pre-HDF. Furthermore, Pre-HDF demonstrated a significantly higher removal rate in the middle and larger solutes and larger albumin leakage in comparison with I-HDF.

FR-PO894

Beta-2 Microglobulin Removal by Convective Dialysis: A Meta-Analysis

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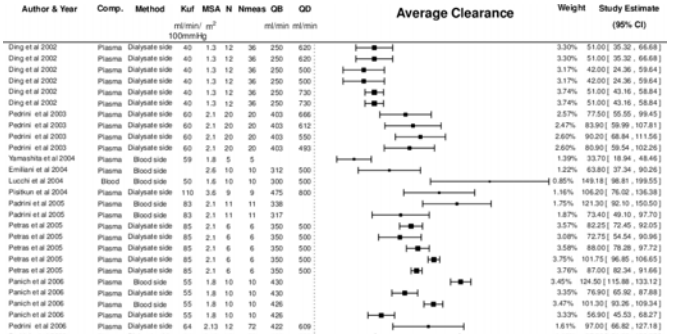
Background: Accumulation of Beta-2 Microglobulin (B2M) in ESRD patients is associated with cardiovascular and infectious mortality. We conducted a meta-analysis of data about the efficacy of convective dialysis therapies (CDT) i.e. (hemodiafiltration, HDF or hemofiltration, HF) in removing B2M.

Methods: We used ProQuest to search EMBASE and MEDLINE, for randomized controlled trials and observational studies in CDT between 2001-2013. Clearance measurements at blood side and/or dialysate side were included and reported via random effects meta-analysis.

Results: We identified 36 HDF and 4 HF studies. Average clearance was 90 ml/min with substantial heterogeneity among studies.



In meta-regression (table 1) we found that whole blood and dialysate side clearances were higher and lower respectively compared to plasma clearance. Higher blood and substitution flow rates were significantly associated with higher clearance of B2M.

	estimate	se	p-value
Intercept	26.2	26.7	0.3
Membrane Kuf (ml/min/100mmHg)	0.3	0.2	0.1
Clearance Type (ref=blood side)			
Average Dialysate+Blood Side	34.2	27.3	0.2
Dialysate	-36.9	6.9	**<0.001**
Blood vs. plasma clearance	57.7	8.2	**<0.001**
Blood flow (ml/min)	0.2	0.1	**0.02**
Treatment Duration (min)	-0.05	0.03	0.1
Substitution fluid rate (ml/min)	0.1	0.04	**<0.001**
Secular trend (year)	-0.2	2.04	0.9

Conclusions: There is substantial heterogeneity in the middle molecule clearance by CDT related to both methodological (type of measurement) and operational characteristics (flow rates). Future studies should standardize methodology for these measurements to highlight clinically important differences related to the dialysis technique.

Funding: Clinical Revenue Support

FR-PO895

The Standardization of Convective Volume to Body Water Predicts the Efficacy of Convective Transport in On-Line Hemodiafiltration

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Background: Online hemodiafiltration(OL-HDF) with high convective volumes(CV) has been associated with improved patient survival compared to conventional hemodialysis, explained by better removal of middle-sized uremic toxins. The purpose of this study was to determine the corporal composition parameters influencing the efficacy of CV in the removal of different molecular weight(MW) molecules.

Methods: Demographic data, corporal composition with bioimpedance, dialysis features and reduction rates of different MW-molecules (urea–60Da–, beta-2microglobulin(B2M)–11.8KDa–, cystatin C–13KDa–, myoglobin–17.2KDa–, prolactin–23KDa– and alpha-2macroglobulin–725KDa–) in a 4-hour postdilution OL-HDF session were collected in 61 patients.

Results: The mean of CV was 30.6 ± 4.7 L/session. We observed a significant negative correlation of B2M, cystatin-C, myoglobin and prolactin reduction rates with body surface area, weight, total body, extracellular(ECW) and intracellular water (ICW), lean tissue mass and body cellular mass. The multivariable regression analysis identified ECW and ICW as the only corporal composition factors independently associated to the relative elimination of B2M (Beta:-.801, p0.002 for ECW and Beta:-1.710, p0.001 for ICW), cystatin-C (Beta:-.656, p0.010 for ECW and Beta:-1.511, p0.004 for ICW) and myoglobin (Beta:-.745, p0.014 for ECW and Beta:-2.103, p0.001 for ICW), in addition to CV. Only the ratio CV/ECW was an independent predictor for higher elimination of B2M (Beta:.866, p<0.001), cystatin-C (Beta:.745, p0.001) and myoglobin (Beta:.662, p0.008). The standardization with total body water(TBW) as the ratio CV/TBW showed similar significant results with weaker association.

Conclusions: Extracellular and intracellular water are independently associated to the reduction of medium-sized molecules. The ratio "convective volume/extracellular water" predicts higher efficacy of convective transport. Adjust the convective volume to patient features could be useful to monitor the efficacy of OL-HDF and to prescribe individualized therapies.

FR-PO896

Impact of Different Low Molecular Weight Heparin Administration Routes in High-Flux Hemodialysis and Online Hemodiafiltration

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Background: Pre-filter administration of low molecular weight heparin(LMWH) in the arterial line of hemodialysis(HD) circuits during high-flux HD(HF-HD) and online hemodiafiltration(OL-HDF) can lead to clearance of LMWH. The aim of this study was to evaluate whether different administration routes of enoxaparin can affect its efficacy.

Methods: 15 patients, 13 on OL-HDF and 2 on HF-HD. All sessions were done with 1.8 m2 helixone dialyzer and each session lasted 4 hours. Baseline dialyzer and venous chamber clotting were evaluated by administration of enoxaparin through the arterial line(AL) at the start of HD, and for 3 consecutive weeks by administration of enoxaparin through the venous line 2 minutes before connection with the following dosing schedule: Week 1 with 100% of the AL dose(V100), week 2 with 75% of the AL dose(V75), week 3 with 50% of the AL dose(V50). In each session filter clotting was assessed with a semiquantitative visual scale (0= no clotted capillaries, 1= <5% clotted capillaries, 2= 5-25% clotted capillaries, 3= >25% clotted capillaries). Anti-Xa levels were measured at 0, after 60 and 240 minutes of HD. In each session we determined KT, processed blood volume(PBV), and infusion volume in patients with OL-HDF.

Results: There were no significant differences in dialyzer clotting between AL (0=46.7%, 1=40%, 2=13.3%, 3=0%), V100 (0=73.3%, 1=20%, 2=6.7%, 3=0%)(p=0.155) and V75 (0=66.7%, 1=20%, 2=6.7%, 3=6.7%)(p=0.388). Dialyzer clotting was significantly higher with V50 than with AL, V75 and V100 (0=0% 1=26.7%, 2=53.3%, 3=20%) (p<0.001). Similar differences were observed regarding venous chamber clotting. Anti-Xa levels were significantly higher with V100 (60 min=0,525, 240 min= 0,262 IU/mL) than with AL (60 min=0,784, 240 min=0,428 IU/mL)(p=0,02). There were no differences in Anti-Xa levels between AL and V75 or V50. There were no differences in KT, PBV and infusion volume in OL-HDF between the different forms of LMWH administration.

Conclusions: Administration of LMWH through the venous line before the start of hemodialysis allows for a 25% reduction in the dose compared to administration through the arterial line, both in HF-HD and OL-HDF.

FR-PO897

Protein-Bound Toxin Removal with Novel High Cut-Off Membrane Dialyzer in Limited Blood Flow Online Hemodiafiltration (OL-HDF) versus High-Efficiency OL-HDF with High-Flux Dialyzer

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Background: Protein-bound toxins especially p-cresol (pCS) which could not be removed by hemodialysis (HD) are obviously correlated with high mortality in HD patients. High-efficiency post-dilution online hemodiafiltration (OL-HDF) using high-flux dialyzer which requiring high blood flow rate has been reported to enhance pCS removal and improve patient survival. Unfortunately, the majority of patients could not reach that high blood flow because of the limitation of their arteriovenous access. Herein, we innovated the effective OL-HDF modality for this situation by integrating the novel high cut-off membrane dialyzer (HCM) into pre-dilution OL-HDF.

Methods: This randomized crossover control study was conducted in 9 OL-HDF patients to compare the two week periods between the new modality (limited blood flow OL-HDF with HCM) and the control (high-efficiency OL-HDF). The removals of small and middle molecular weight uremic toxins as well as protein-bound uremic toxin were determined and compared. The pCS was measured by high performance liquid chromatography. The dialysate albumin loss and patient safety were also monitored.

Results: This new modality, OL-HDF with HCM, was safe and no adverse event was recorded. Its pCS removal in term of pCS reduction ratio (RR) was comparable with high efficiency OL-HDF [59.5 (IQR; 49.1, 62.6) vs. 54.7 (IQR; 48.6, 58.2) %, p=0.441]. The β2-microglobulin removal was significant higher in this new modality. Two techniques provided adequate and comparable small molecule removal. No patients developed hypoalbuminemia despite the higher dialysate albumin loss in the new modality.

Conclusions: This new OL-HDF with HCM which could apply to every dialysis patients provided effectively protein-bound uremic toxin removal comparable with high efficiency OL-HDF and could potentially provide the comparable good long-term survival.

FR-PO898

Immersion Can Enhance Fluid Redistribution and Prevent Intradialytic Hypotension- A Prospective, Randomized, Crossover Clinical Trial

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Background: Intradialytic hypotension (IDH) is an important cause for morbidity among hemodialysis (HD) patients. IDH occurs mainly when the ultrafiltration (UF) rate exceeds fluid redistribution from the extravascular to the vascular bed. Water immersion can be an effective method for hydrostatic pressure induced transfer of volume from the interstitium to the intravascular space. This randomized, crossover study evaluated the physiological and clinical effects of immersion on the occurrence of IDH.

Methods: Ten male HD patients, who had frequent IDH, defined as symptomatic hypotension occurring in more than 20% of the sessions were randomized to a 3 hour mid-week "wet" and "dry" HD session, in a crossover manner. The wet session was performed while immersed up to the neck in a 34ºC-35ºC bath, and the dry session was standard HD. UF goals were determined as the mean UF during the 10 sessions preceding the study ±10% according to body weight at admission, and the dialysis time was shortened to 3 hours instead of the usual 4. Symptoms, blood pressure (BP), atrial natriuretic peptide (ANP) and aldosterone blood levels were measured during the sessions. .

Results: Mean UF did not differ between the two sessions (2.99±0.64kg vs. 2.96±0.74kg in wet and dry sessions respectively). Symptomatic hypotension did not develop in any of the patients during the wet session, compared to 4 (40%) during the dry session. Systolic BP adjusted to UF was stable during the wet session, 0.22 (95% CI -0.27 to 0.70), P=0.38, but significantly decreased during the dry session, -0.68 (95%CI -1.24 to-0.11), P=0.02. Diastolic BP did not change during the sessions. Mean ANP significantly increased in the wet session, by 31.36 (95%CI 8.73 to 53.99), P=0.07, and slightly and insignificantly decreased in the dry session, by -21.66 (95% CI -52.59 to 9.25), P=0.167. Aldosterone blood levels did not change.

Conclusions: Delayed fluid redistribution during HD can be effectively reversed by immersion, with improved blood pressure stability and symptoms.

FR-PO899

Utility of Plasma b2-Microglobulin Levels for Estimating Residual Kidney Function without Urine Collection Yoshihiro Matsumoto, Kimitoshi Shiratori, Youichi Nojima, Yasushi Shimada. *Dept of Nephrology and Dialysis, Shizuoka City Hospital, Japan.*

Background: Residual kidney function (RKF) is associated with survival benefits in hemodialysis (HD) patients but cannot be assessed without urine collection. Plasma β2-microglobulin and cystatin C levels have been used to estimate kidney function in patients with renal insufficiency before dialysis therapy. We investigated the ability of these markers to estimate RKF in patients on HD.

Methods: Seventy-one patients undergoing incremental low-flux HD in a single center during 2008–2015 were enrolled. Blood was sampled before the first HD session of the week to estimate β2-microglobulin and cystatin C. Urine was collected 24 hours before the first HD session of the week. We assumed that creatinine and urea secretion per day divided by body weight before HD (Ucr and Uurea, respectively) corresponded to RKF regardless of their plasma levels, which are known to change significantly during urine collection. The relationships between plasma β2-microglobulin/cystatin C levels and Ucr/Uurea were explored.

Results: The average HD duration and urine volume were 17 (1–58) months and 1280 (350–3000) mL, respectively. Ucr and Uurea were closely correlated (r = 0.84). Ucr was more closely correlated with plasma β2-microglobulin levels (r = -0.74) than with cystatin C levels (r = -0.61) and urine volume (r = 0.62). Urea was also correlated with β2-microglobulin levels (r = -0.69), cystatin C levels (r = -0.51) and urine volume (r = 0.73).

Conclusions: Plasma β2-microglobulin levels before HD may provide better estimates of RKF than cystatin C. β2-microglobulin may be clinically useful for determining individual dialysis doses without the need for frequent urine collection in HD patients with RKF.

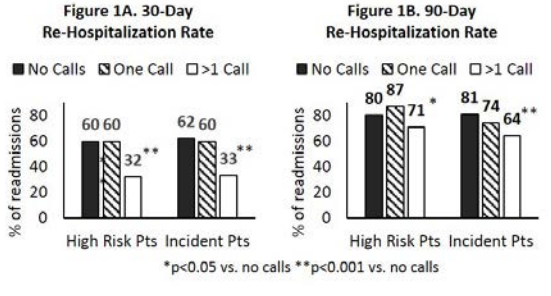
FR-PO900

Post-Hospital Case Management of Incident and High Risk Prevalent Hemodialysis Pts Reduces 30- and 90-Day Readmission Rates Rebecca L. Wingard,[1] Kathryn A. McDougall,[1] Billie Axley,[1] Andrew D. Howard,[2] Joelle Heilemann,[1] Sharon Deluca,[1] Sheetal Chaudhuri,[1] Hao Han,[1] Len A. Usvyat,[1] Franklin W. Maddux.[1] *[1]Fresenius Medical Care, Waltham, MA; [2]Metropolitan Nephrology Associates, Clinton, MD.*

Background: 30-day readmission rates for West Virginia (WV) Fresenius HD incident pts (IPs, n=384, 1st 120 days of HD) and high risk prevalent pts (HRPPs, n=159, >=6 hospitalizations/yr) were high in 2014 at 55% and 60%, respectively. 90-day readmission rates were 80% for IPs and 85% for HRPPs. The Right TraC™ (RT) Program used post-hospital case management to reduce readmissions for IPs and HRPPs.

Methods: 26 Fresenius WV HD clinics were in RT 2/1/15 to 2/29/16. IPs, and HRPPs with high likelihood of >=6 hospitalizations/year (identified by an internally validated predictive model) were included. A telephonic RT case manager (RTCM) attempted contact with pt or caregiver weekly during 30 days post-hospital discharge (DC) to discuss DC instructions, facilitate follow-up appointments, and review strategies to manage medications, nutrition, dry weight, access issues, and anemia. For pts alive for 90 days post-hospital (n=205 IPs, 369 DCs; 310 HRPPs, 605 DCs), 30- and 90-day readmission rates were compared for pts who received no RTCM calls (29% for IPs; 27% for HRPPs) vs. one call (13% for IPs; 18% for HRPPs) or >1 call (58% for IPs; 55% for HRPPs) using two sample t-test.

Results: 30-day readmission rates for pts with no calls vs. >1 call were 60% vs. 32% for HRPPs (p<0.001) and 62% vs 33% for IPs (p<0.001) (Figure 1A). 90-day readmission rates for pts with no calls vs. >1 call were 80% vs. 71% for HRPPs (p<0.05) and 81% vs 64% for IPs (p<0.001) (Figure 1B). 30- and 90-day readmission rates for no calls vs 1 call were not significantly different.



Conclusions: Post-hospital telephonic case management was associated with fewer readmissions for IPs and HRPPs who received >1 phone call in the 30-day post-hospital period.

FR-PO901

Effect of Dialysis Potassium Bath on QT Interval during Hemodialysis Aamir Zuberi, Hafsa Z. Zuberi, Hassaan Patel, Maggie Dickens, Fatima Zuberi. *Nephrology, Wise Health System, Decatur, TX.*

Background: Sudden death accounts for nearly half of all cardiac deaths in dialysis patients.QT prolongation has been associated with cardiac arrhythmias that could lead to sudden cardiac death. Of interest is the question of effect of potassium concentration in dialysis solution on QT interval. This study was conducted to assess the effects of 2K and 3K dialysis baths on QT interval in stable hemodialysis patients in an outpatient dialysis facility.

Methods: Study was approved by the Institutional Review Board. Funding was provided by the dialysis provider, Wise Health System. EKGs were checked at the beginning and end of dialysis sessions. The following parameters were noted: age, gender, presence or absence of comorbidities including coronary artery disease and diabetes , dialysis treatment time, dialysis K concentration, pre-dialysis plasma K concentration, pre & post-dialysis corrected QT intervals (QTc), and pre- and post-dialysis change in QTc.

Results: We enrolled 79 patients, with a mean age of 62 years (range: 21-88 years). Male gender dominated the cohort 46/79 (58%). 50 (63%) patients had CAD. 48 (61%) had DM. Dialysis treatment time ranged from 2.75-4.5 hours with an average of 3.7 hours. Pre-dialysis QTc ranged from 408-574 milliseconds. Post- dialysis QTc ranged from 413-665 milliseconds. Pre-dialysis mean K was 4.7 mmol/L (range: 3.1 to 7.5 mmol/L). Of the 31 patients dialyzed with a 2K dialysis solution, mean QTc change was 202 milliseconds as opposed to 160 milliseconds in the 48 patients dialyzed with a 3K dialysis solution (p=NS). Subgroup analyses for duration of dialysis (>3.5 hours), pre-dialysis K (>4.5 mmol/L), CAD, DM and age>60 did not reveal any significant trends. Men were more likely to have a prolonged QTc (p=0.03). We observed an inverse relationship between pre-dialysis K and QTc (p=0.04).

Conclusions: Patients dialyzed with a 2K dialysis solution had longer QTc compared to patients dialyzed with a 3K dialysis solution. Men were more likely to have a longer QTc compared to women. Patients with lower pre-dialysis K were more likely to have longer QTc. Adjustments in dialysis solution K concentration could limit risk of life threatening arrhythmia in patients at risk of sudden cardiac death.

FR-PO902

Aiming for the Optimal Bicarbonate Prescription for Maintenance Hemodialysis Therapy in End-Stage Renal Disease Andreas Bozikas, Iliana Kiriakoutzik, Ioannis Petrou, Pinelopi Pisanidou, Theodoros Tourountzis, Nikolaos Georgilas, Panagiotis Pangidis, Sofia Spaia. *Nephrology, General Hospital, Thessaloniki, Greece.*

Background: Due to the gradual depletion of the body's buffers and rapid repletion during hemodialysis, many problems arise as a result of current treatment routine since both acidemia and alkalemia can be associated with adverse consequences. We compared the effect of higher doses of [HCO3] based dialysate to standard [HCO3] bath plus oral bicarbonate therapy.

Methods: 60 HD patients were evaluated according to their predialysis acid-base status before the 1st and the 2nd session of the week with a standard [HCO3] based dialysate of 35 mEq/l. Those with predialysis[HCO3]< 22 mEq/l were assigned against dialysis bath with[HCO3] levels (+2 mEq/l) for 2weeks (period A) and subsequently to the standard dialysate bath plus oral sodium bicarbonate (5gr/t.i.d) for 2 more weeks (period B). Records of pre/post dialysis acid base status after each period,with evaluation of different parameters were recorded.

Results: Predialysis acid base didn't present significant differences, between the 1st and 2nd dialysis session. 25 patients predialysis pH was <7.35, while 42 presented predialysis HCO3 <22 mEq/L. 18 patients had pH >7,45 after HD session.Comparing the 2 study periods, patients appeared with predialysis [HCO3] in accordance with quidelines, after 2 weeks of oral bicarbonate, while post dialysis HCO3 were increased during the 1st study period.

	Period A	Period B	p
$HCO3^-$ predialysis	21.51 ± 2.5	23.02 ± 2.8	0.03
$HCO3^-$ post dialysis	27.6 ± 1.7	26.4 ± 1	0.03
pH predialysis	7.36 ± 0.05	7.36 ± 0.05	ns

Conclusions: This study shows that conventional dialysate [HCO3] concentrations of 35 mEq/l results in a considerable degree of predialysis acidemia. Increasing [HCO3] dialysis bath results in more prominent postdialysis alkalemia, but it is not sufficient to maintain acid base balance in the interdialytic period. On the contrary, oral bicarbonate therapy at a dose of 5gr/d results in more balanced acid base status, avoiding post dialysis alkalemia.Potential solutions include a multifaceted approach of oral and individualized delivery of HCO3.

FR-PO903

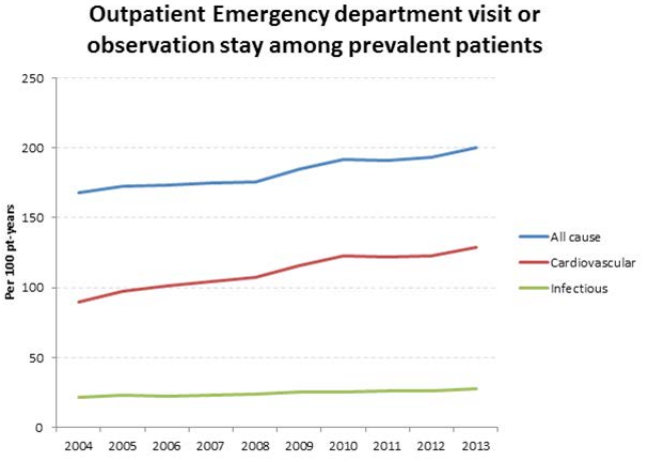
Growth of Cardiovascular and Infection Emergency Room and Observation Stays in the Dialysis Population Allan J. Collins,[1] Peer Kidney Care Initiative Investigators.[2] *[1]Chronic Disease Research Group, MMRF, Minneapolis, MN; [2]Peer Kidney Care Initiative.*

Background: Recent efforts by CMS to incentivize hospitals to reduce readmissions have focused on acute myocardial infarction, congestive heart failure, and pneumonia. While traditional readmissions of dialysis patients have declined, little is known about changes in the use of alternative forms of acute care, namely emergency department encounters (EDE) and observational stays (OBS), following an index hospitalization.

Methods: We studied prevalent (>1 year on dialysis) and incident (<1 year on dialysis) Medicare patients dialyzing in freestanding US units for the cohort years 2004-2013. EDE and OBS (occurrence and hours) were identified from revenue codes and the place of service on Part A hospital claims. Because clinical symptoms commonly occupy the first position, we used the first 5 diagnosis codes to define disease areas by organ system.

Results: Overall, EDE or OBS increased 19.2% 2004-2013. The increase in EDE (alone) was 3.8% and in OBS (alone) 58.5%. The combination of EDE or OBS for cardiovascular disease (CVD) causes increased 43% and for infections 29.3%, 2004-2013. After stabilizing from 2010 to 2012, EDE or OBS increased 3.4% overall, 4.6% for CVD and 6.8% for infection, 2012-2013.

Conclusions: While EDEs have changed only modestly in the past 10 years, there is evidence of marked increases in the use of OBS. Data suggest that hospitals are shifting the site of care away from traditional inpatient admissions, but how this affects morbidity and mortality is unknown.



Funding: Pharmaceutical Company Support - Financial support for the Peer Kidney Care Initiative is provided by the following participating provider organizations: American Renal Associates, Atlantic Dialysis Management Services, DaVita HealthCare Partners, Dialysis Clinic, Inc., Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Satellite Healthcare, The Rogosin Institute, U.S. Renal Care, and Wake Forest University, Private Foundation Support

FR-PO904

Low Vitamin D as a Modifying Factor in the Relationship between Obesity and Vascular Calcification in Hemodialysis Patients Jwa-Kyung Kim,[1] Sun Ryoung Choi,[2] Jae-Won Lee,[3] Sung Gyun Kim.[1] *[1]Internal Medicine, Kidney Research Inst, Hallym Univ Sacred Heart Hospital, Anyang, Korea; [2]Internal Medicine, Sahmyook Medical Center, Seoul, Korea; [3]Internal Medicine, G Sam Heart Hospital, Anyang, Korea.*

Background: Obesity is a risk factor for increased cardiovascular disease. Whether vitamin D deficiency modifies this association is unclear. Here, we examined the association of obesity and vitamin D deficiency with vascular calcification score (VCS) in incident end-stage renal disease (ESRD) patients.

Methods: A cross-sectional study was conducted with 213 ESRD patients who newly started hemodialysis. Vitamin D deficiency was defined as serum 25-hydroxyvitamin D (25(OH)D) levels below 10 ng/mL, and levels below 3 ng/mL was considered very low. Obesity was defined as a percentage of body fat (PBF) higher than the sex-specific median value in the cohort (>26.8% for men, >36.2% for women). VCS was measured by plain radiographic film of the lateral abdomen in the standing position.

Results: Mean age was 63.7±13.4 years and 31.9% were women. Most ESRD patients (76.6%) had 25(OH)D deficiency at the start of dialysis, and 44.7% of them had very low levels of 25(OH)D. The prevalence of 25(OH)D deficiency was much higher in obese patients than non-obese patients, and it had significant inverse association with PBF (r=-0.315, p< 0.001). Abdominal aortic calcification was identified in 104 (48.9%) patients. VCS was significantly higher in obese population; 2.6 (0-23) for all patients, 4.2 (0-23) for obese and 1.0 (0-12) for non-obese patients (p<0.001). Interestingly, serum 25(OH)D affected the relationship between obesity and the risk of vascular calcification, such that vitamin D deficiency was associated with greater risk of a high VCS, especially in obese population [odds ratio (OR) 3.02, 95% confidence interval (CI) 1.09-9.38)], but not with non-obese patients (OR 1.82, 95% CI 0.56-5.60).

Conclusions: The magnitude and direction of the association between obesity and the risk of vascular calcification may depends on an individual's 25(OH)D level, a possible representative marker of cardiometabolic disturbance in ESRD patients.

FR-PO905

Association of Vitamin K and Matrix Gla Protein with Subclinical Cardiovascular Disease in Incident Hemodialysis: Predictors of Arrhythmic and Cardiovascular Risk in End-Stage Renal Disease (PACE) Study Esther D. Kim,[1] Stephen M. Sozio,[2] Michelle M. Estrella,[2] Bernard G. Jaar,[2] Lucy A. Meoni,[2] Joao A.C. Lima,[2] Rulan S. Parekh.[1,2] *[1]U of Toronto; [2]Johns Hopkins U.*

Background: Recent studies suggest repletion of low vitamin K levels in HD patients may have a beneficial effect in reduction of circulating inactive desphosphorylated-uncarboxylated matrix Gla protein (dp-ucMGP) and vascular calcification; however, the independent associations of vitamin K and dp-ucMGP with subclinical measures of cardiovascular disease are unknown.

Methods: In a prospective study of 231 incident HD patients in the PACE study with available biomarker data, we examined the association of dietary vitamin K and baseline dp-ucMGP with total coronary artery calcium (CAC) score and longitudinal measures of pulse wave velocity (PWV). Vitamin K status was estimated using self-reported phylloquinone intake from 24-hour dietary recall. Baseline and longitudinal associations were examined using modified Poisson regression and mixed-effects model, respectively.

Results: The mean age of the cohort was 55±13 years, and the majority were African-American (68%), had diabetes (57%), and coronary artery disease (39%). Compared to lower vitamin K (<31mcg) intake, moderate intake was associated with lower prevalence of CAC at baseline and higher intake was associated PWV longitudinally independent of dp-ucMGP and potential confounders. Dp-ucMGP was not associated with CAC or PWV.

Association of vitamin K and dp-ucMGP with subclinical cardiovascular outcomes

	CAC score >0 (reference score=0) (n=231)	Longitudinal PWV* (n=108)
	Prevalence ratio (95% CI)	Difference (95% CI), log-m/s
Dietary vitamin K in tertiles		
Low (<31 mcg)	*ref*	*ref*
Moderate (31-74 mcg)	**0.78 (0.63, 0.97)**	-0.01 (-0.11, 0.09)
High (>74 mcg)	0.91 (0.74, 1.11)	**-0.10 (-0.20, -0.01)**
dp-ucMGP, per 1 log-pm	0.98 (0.86, 1.11)	-0.01 (-0.06, 0.05)

Adjusted for dietary vitamin K, dp-ucMGP, age, sex, race, Charlson comorbidity index, C-reactive protein, warfarin use
* p- trend<0.05

Conclusions: Higher dietary vitamin K intake is not consistently associated with lower prevalence of coronary calcification but is associated longitudinally with less arterial stiffness. This suggests that dietary vitamin K supplementation may be beneficial in reducing vascular stiffness but requires further study.

Funding: NIDDK Support

FR-PO906

FGF-23 and IL-6 Are Associated with Progression of Coronary Arterial Calcification (CAC) in Patients New to Dialysis Qijun Wan,[1,2] Sylvia E. Rosas.[2] *[1]Nephrology Dept, The First Affiliated Hospital of Shenzhen Univ, Shenzhen, China; [2]Kidney and Hypertention, Joslin Diabetes Center, Boston, MA.*

Background: Inflammation stimulates production of fibroblast growth factor 23 (FGF23). We have shown that elevated FGF23 levels are associated with CAC progression in individuals initiating dialysis. Our aim was to determine if inflammation was responsible for the association of FGF23 with CAC progression.

Methods: One hundred initial dialysis patients were enrolled. CAC were measured by multi-slice computed tomography. CAC was calculated using Agatston score (AS) and calcium volume score (VS). CAC progression was measured by the annualized difference in score AS and by the square root volume difference. Sixty-seven study participants had repeat CAC measures at one year. Linear regression was used to assess the association of IL-6 and FGF23 with CAC progression adjusting for potential confounders. The participants were also divided into 3 groups (mild, moderate and high) based on their IL-6 and FGF23 levels.

Results: The mean age of participants was 50.6 ± 12.8 years. 33 % were women, and 64.7 % were black. The baseline median IL-6 level was 3.07 mg/L [interquartile range (IQR), 1.98-5.75] and was associated with the baseline CAC [coefficient (standard error), 0.57 (0.24), $p = 0.02$] after adjustment for known risk factors for CAC. IL-6 was associated with CAC progression both by AS [158.1 (68.99), $p = 0.03$]. When FGF23 was included in the model there was only mild change of the coefficient [135.42 (66.67), $p = 0.047$]. FGF remained significant in this model [171.12 (70.1), $p = 0.02$]. Similar results were found using the VS. Participants in the high group had increased CAC progression [AS 122.41 (9.40-447.69) and VS 3.62 (1.87-14.73)] compared to mild [AS 5.64 (0-70.89) and VS 0.97 (0-2.58)] and moderate groups [AS 18.75 (0-125.21) and VS 1.66 (0-3.11)]. This association persisted in multivariate models [AS 497.19 (168.21), $p = 0.005$ and VS 6.93 (1.72), $p < 0.001$].

Conclusions: IL-6 is strongly associated with CAC presence. Both serum IL-6 and FGF23 are independently associated with CAC progression. Individuals new to dialysis with both elevated IL-6 and FGF23 are at highest risk for CAC progression.

FR-PO907

Vascular Calcification and Left Ventricular Hypertrophy in Hemodialysis Patients: Interrelationship and Clinical Impact Yu Ah Hong, Hye Eun Yoon, Yoon-Kyung Chang, Chul Woo Yang, Suk Young Kim, Hyeon Seok Hwang. *Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Korea.*

Background: Vascular calcification (VC) and left ventricular hypertrophy (LVH) is a morphological marker of vascular disorders and a significant indicator of cardiac pathology in hemodialysis (HD) patients. However, their relationship and combined effects on clinical outcomes remain undetermined.

Methods: We included 341 HD patients, who were examined with plain chest radiographs for aortic arch VC and with echocardiography for LVH.We investigated the relationship between VC and LVH, and their clinical significance for cardiovascular events (CVE) and death.

Results: VC was found in 100 HD patients (29.3%). LVH was more prevalent in patients with VC compared with those without VC (70.0% vs. 50.2%; $P = 0.001$). VC was independently associated with a 2.42-fold increase in the incidence of LVH (95% confidence interval [CI], 1.26–4.65).In multivariate analysis, compared with patients with neither VC nor LVH, the coexistence of VC and LVH was independently associated with CVE (hazard ratio [HR], 2.01; 95% CI, 1.09–3.72), whereas VC or LVH alone was not. Patients with both VC and LVH had the highest risk for a composite event of death and CVE (HR, 1.88; 95% CI, 1.15–3.06). Significant synergistic interaction was observed between VC and LVH (P for interaction = 0.039).

Conclusions: VC was independently associated with LVH. Coexistence of VC and LVH was associated with higher risk of CVE and composite event than either factor alone. There was a synergistic interaction between VC and LVH for the risk of a composite event.

FR-PO908

Factors Affecting Vascular Calcifications in Peritoneal Dialysis Sofia H. Marques, Rute Carmo, Luís Mendonça, Ana Teresa Nunes, Ana Beco, Ana Oliveira, Manuel Pestana. *Nephrology, Centro Hospitalar São João, Porto, Portugal.*

Background: Vascular calcifications are associated with mortality in dialysis patients. Correlations with serum markers, therapy and dialysis modalities are not constant across the studies. We aimed to study clinical and laboratory data to determine factors influential to a higher vascular calcification index (VCI) in peritoneal dialysis (PD) patients.

Methods: 109 patients in our PD unit in December 2015 entered this retrospective analysis. VCI was determined using the Adragao score, counting the presence of vascular calcifications in a plain X-ray of the pelvis and hands (0 to 8) dating from the last 12 months. Current clinical and analytical data were collected.

Results: Mean age was 53.8 (±14.0) and 52.3% were men. Concerning the VCI, 51 patients had 0; 20 had 1-2; 14 had 3-4 and 24 had > 4. Compared to 71 patients with score ≤2, patients with VCI >2 (n=38) were significantly older (60.2±13.0 vs. 50.3±13.4; p=0.00), more often men (73.7% vs. 42.3%; p=0.00), diabetic (60.5% vs. 14.3%; p=0.00), hypertensive (55.6% vs. 34.8%; p=0.04), with higher extracellular/intracellular water ratio (0.65±0.03 vs. 0.60±0.04; p=0.00) by bioimpedance and higher BMI (27.5±4.6 vs. 25.4±4.3; p=0.04). They had more often a weekly Kt/V < 1.7 (29.7% vs. 10.1%; p=0.01) and were more often on automatic peritoneal dialysis (APD) vs. continuous ambulatory peritoneal dialysis (57.9% vs. 35.3%; p=0.02). In addition, they had lower albumin (3.4±0.47 vs. 3.8±0.50 g/dL; p=0.00), lower potassium (4.0±0.68 vs. 4.4±0.68 mEq/L; p=0.01) and higher protein losses (24.5±12.7 vs.17.5±9.8 g/day; p=0.00). No differences were found in dialysis vintage, residual renal function, icodextrin use, serum calcium, phosphate, parathyroid hormone, hemoglobin or current use of phosphate-binder, vitamin D analogs, cinacalcet, erythropoiesis-stimulating agent, renin-angiotensin system blockers or statins.

Conclusions: In PD patients, VCI was associated with traditional biomarkers such as increased age, masculine gender, diabetes and hypertension as well as with other non-traditional factors such as less efficient dialysis, APD, higher extracellular water content and serum parameters suggestive of malnutrition.

FR-PO909

Serum Fibroblast Growth Factor 21 Predicts All-Cause Mortality in End-Stage Renal Disease Marina Kohara,[1] Takahiro Masuda,[1] Kazuhiro Shiizaki,[2] Tetsu Akimoto,[1] Yuko Watanabe,[1] Sumiko Honma,[3] Chuji Sekiguchi,[4] Yasuharu Miyazawa,[4] Eiji Kusano,[5] Yasushi Asano,[3] Makoto Kuro-o,[2] Daisuke Nagata.[1] *[1]Div of Nephrology, Dept of Medicine, Jichi Medical Univ, Shimotsuke, Tochigi, Japan; [2]Center for Molecular Biology, Jichi Medical Univ, Shimotsuke, Tochigi, Japan; [3]Japanese Red Cross Koga Hospital, Koga, Ibaraki, Japan; [4]Nasu-Minami Hospital, Nasukarasuyama, Tochigi, Japan; [5]JCHO Utsunomiya Hospital, Utsunomiya, Tochigi, Japan.*

Background: Fibroblast growth factor (FGF) 21 is an anti-aging hormone which is secreted from liver in response to fasting. Circulating FGF21 concentration is increased in end-stage renal disease (ESRD) that may be survival response to accelerated aging. However, the impact of an increase in circulating FGF21 levels on prognosis remains unknown.

Methods: ESRD patients receiving chronic hemodialysis (HD) were included in this study. Serum FGF21 levels were measured by a sandwich ELISA. The patients were grouped into the high and low FGF21 groups by the median value. The primary outcome was cardiovascular events and all-cause death. The Kaplan–Meier method and Cox proportional hazard model were used for survival analyses.

Results: Of 107 participants (age 65.3±13.0 years, male 59.8%, HD duration 5.7±5.3 years, diabetes mellitus [DM] 41.1%), 17 (15.9%) patients died during a median follow-up of 44 months (interquartile range [IQR] 21–66 months). Median serum FGF21 levels were 1701 pg/mL (IQR 867–2957 pg/mL). Smoking rates and serum uric acid (UA) in the high FGF21 group were significantly higher than in the low FGF21 group. Kaplan–Meier analysis with log-rank test revealed that the high FGF21 group had a higher rate of all-cause mortality (P=0.040) than the low-FGF21 group, but the association between FGF21 levels and cardiovascular events was not found (P=0.795). In the multivariate Cox regression model including age, gender, DM, smoking and serum UA, high serum FGF21 remained an independent predictor for increased mortality (hazard ratio, 4.05; 95% confidence interval, 1.34 to 15.27; P=0.012).

Conclusions: These results suggest that high serum FGF21 levels are associated with increased mortality in ESRD patients. Further studies are required to evaluate a mechanistic link between FGF21 elevation and poor outcome.

Funding: Government Support - Non-U.S.

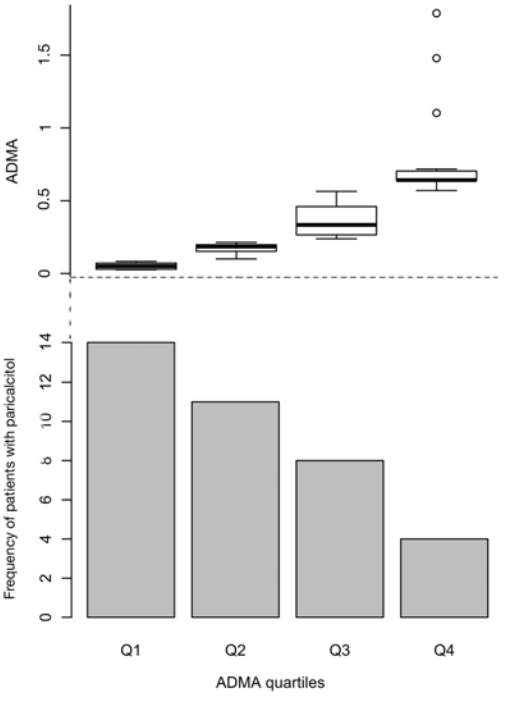
FR-PO910

Asymmetric Dimethylarginine Levels Are Lower in Hemodialysis Patients Treated with Paricalcitol Nestor Oliva-Damaso,[1,4] Elena Oliva-Damaso,[2] Francisco Javier Rodriguez-Esparragon,[3] Juan Payan Lopez,[1] Alberto Maranes,[4] Eduardo Baamonde,[2] Yanet Parodis Lopez,[2] Nicanor Vega-Diaz,[2] Jose C. Rodriguez-Perez.[2] *[1]Nephrology, Hospital Costa del Sol, Marbella, Malaga, Spain; [2]Nephrology, Hospital Univ de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria, Las Palmas, Spain; [3]Unidad de Investigación, Hospital Univ de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria, Las Palmas, Spain; [4]Nephrology, Hospital Quirón, Marbella, Malaga, Spain.*

Background: Chronic Kidney Disease (CKD) is associated with an inflammatory condition involving an increased risk of cardiovascular (CV) morbimortality. Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase and may be an independent risk factor for CV disease in HD patients.

Methods: We performed a cross sectional observational study in 93 randomly selected patients on chronic HD to evaluate the association between ADMA levels and CV medication.

Results: Patients (62.4% male) had an average age of 64.7±13.1 years. 45.2% were diabetic with a median of 53.1 months (IQR 31.8-89.7) in HD. Patients treated with paricalcitol had significantly lower ADMA levels (0.21±0.19 µmol/L) than the rest (0.42±0.35 µmol/L) (**p=0.00027**).



Patients treated with paricalcitol were less likely to have very high ADMA levels (**p=0.014**) with no significant differences with other medications. Higher dose of paricalcitol was related with lower levels of ADMA showing a significant negative dose-response relationship (–0.46; **p=0.001**).

Conclusions: HD patients treated with paricalcitol presented significantly lower ADMA levels. Beneficial effects in terms of CV morbidity and mortality have been demonstrated by paricalcitol in HD patients but its association with ADMA has not been reported. Studies to confirm this effect and determine the underlying pathophysiological mechanism are necessary.

FR-PO911

Oral Calcitriol and Cardiovascular Events in Hemodialysis Patients Lin Ma,[1] Ravi I. Thadhani,[2] Norma J. Ofsthun,[1] Amanda Stennett,[1] Jeffrey L. Hymes,[1] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Massachusetts General Hospital, Boston, MA.*

Background: A large clinical pilot began at Fresenius Medical Care North America (FMCNA) in December of 2013 to examine the feasibility of administering oral calcitriol (OC) rather than intravenous Vitamin D (IVD) for in-center hemodialysis (IHD) patients. We conducted a retrospective cohort study to compare the survival and hospitalization risks associated with OC and IVD treatments.

Methods: Among FMCNA IHD adult patients, 6,689 who started OC and 128,890 who received only IVD between December 1, 2013 and June 30, 2014 were followed up to 1 year. The index date was set to the OC start date or a random date within the study period for those patients receiving IVD. Cardiovascular events (CVE) including acute myocardial infarction (AMI), congestive heart failure (CHF), cerebrovascular accident (CVA), peripheral vascular disease (PVD), and cardiorespiratory arrest (CPA) were examined. These were all newly diagnosed from hospital discharges in the first year following the start date. Months from the index date to the first CVE were used for the survival analysis. Kaplan-Meier and Cox proportional hazards regression models were used to compare the CVE risks.

Results: Baseline characteristics between 2 groups were clinically comparable. Incident rates were: AMI 1.2% in OC vs. 1.4% in IVD, p=0.2; CHF 1.8% in OC vs. 2.3% in IVD, p=0.004; CVA 0.3% in OC vs. 0.9% in IVD, p<0.0001; PVD 0.9% in OC vs. 1.2% in IVD, p=0.03; CPA 1.3% in OC vs. 1.6% in IVD, p=0.05. Compared with IVD, crude CVE risk for OC was 26.3% lower (2.1% vs. 2.8%, p=0.0003); unadjusted hazard ratio (HR) was 0.73 (95% CI: 0.62, 0.87), p=0.0004; case-mix adjusted HR was 0.80 (95% CI: 0.67, 0.95), p=0.009; and case-mix & lab adjusted HR was 0.78 (95% CI: 0.66, 0.93), p=0.005.

Conclusions: There was no overall increase cardiovascular events seen in the oral calcitriol group at 1 year, and outcomes may have been slightly better compared with intravenous vitamin D group.

FR-PO912

Outcome Predictors in Maintenance Hemodialysis Patients with Cerebral Hemorrhage Mineaki Kitamura,[1,2] Tadashi Uramatsu,[2] Yoko Obata,[2] Yohei Tateishi,[3] Masaharu Nishikido,[1] Takayuki Matsuo,[4] Akira Tsujino,[3] Tomoya Nishino.[2] *[1]Div of Blood Purification, Nagasaki Univ Hospital, Nagasaki, Japan; [2]Dept of Nephrology, Nagasaki Univ Hospital, Nagasaki, Japan; [3]Dept of Neurology, Nagasaki Univ Hospital, Nagasaki, Japan; [4]Dept of Neurosurgery, Nagasaki Univ Hospital, Nagasaki, Japan.*

Background: Cerebral hemorrhage is life-threatening and adversely affects activities of daily living (ADLs). However, factors contributing to poor outcomes in maintenance hemodialysis patients with cerebral hemorrhage remain unknown. Accordingly, we retrospectively studied hemodialysis patients with cerebral hemorrhage.

Methods: After excluding traumatic and subarachnoid hemorrhage, 91 hemodialysis patients with cerebral hemorrhage admitted to Nagasaki University Hospital during 2007-2015 were enrolled. We collected data on hemodialysis status, laboratory data, and medication from medical referral letter. We also evaluated hematoma volume, National Institutes of Health Stroke Scale (NIHSS) score on admission, and ADLs on discharge from the hospital.

Results: The patients were aged 65±11 years old, and male:female = 60:31. Hemorrhage area: putamen, 31; subcortical, 24; thalamus, 20; cerebellum, 10; pons, 3; and others, 2. Severe outcomes: 29 died and 31 were severely disabled. Large volume of hematoma and high NIHSS score predicted poor prognoses. Antiplatelet use was an independent risk factor for death and severe disability by multivariate analysis. Pre-onset low serum albumin was also an independent risk factor for death. Age, dialysis duration, sex, anticoagulant use, pre-onset blood pressure, and diabetes history did not influence the prognosis. The relationship between prognosis and amount of fluid removal per unit body weight in pre-onset hemodialysis showed a U shape, e.g., Quintile 1 (lowest) and Quintile 5 (highest) for the fluid removal rate in pre-onset hemodialysis had a significantly higher risk for death (odds ratio 11.9; p<0.01 and 10.8; p=0.012, respectively; reference = Quintile 3).

Conclusions: To prevent the progression of cerebral hemorrhage, we should be aware of the use of antiplatelet drugs and weight gain caused by malnutrition or dietary noncompliance.

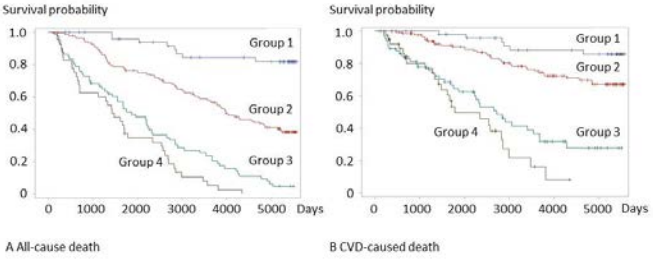
FR-PO913

A New Risk Scoring System for Prediction of Long-Term Mortality in Patients on Maintenance Hemodialysis Eiichiro Kanda,[1] Hiroshi Kawaguchi,[2] Yoichiro Tabata,[3] Noriyoshi Murotani,[4] Tomoko Maeda,[5] Hidetaka Itoh,[6] Haruki Itoh.[7] *[1]Tokyo Kyosai Hospital; [2]Tokiwa-kai Medical Corporation; [3]Meysey-kai Medical Corporation; [4]Japan Community Health Care Organization Chiba Hospital; [5]Sakakibara Heart Inst Clinic; [6]Toranomon Mutual Aid General Hospital; [7]Sakakibara Heart Inst.*

Background: It has been reported that the survival of hemodialysis (HD) patients is poor, and the leading cause of death is cardiovascular disease. To identify high-risk patients and treat them carefully, we developed a scoring system to evaluate their 15-year prognosis in a prospective cohort study.

Methods: We analyzed data from 312 and 310 patients to develop and validate the prediction model, respectively. The association of potential risk factors with death was tested by Cox proportional-hazards analysis, and a risk scoring model was developed. Then, the model was validated.

Results: Two hundred patients (64.1%) in the cohort for model development died. Six independent prognostic factors were retained in the final model, and each was assigned a score proportional to its regression coefficient: 65 years or older, 3; diabetic nephropathy, 3; hypotension, 1; pre-HD cardiothoracic ratio ≥50%, 1; pre-HD BNP ≥250 pg/mL, 1; and pre-HD numbers of abnormal findings on electrocardiograms=0, 1, 2 or larger, 0, 1, 5. The patients were categorized as follows with their scores: Group 1 (low risk), 0; Group 2, 1 to 3; Group 3, 4 to 5; and Group 4 (high risk), 6 and higher. In the cohort for model validation, Groups 2 to 4 showed a higher risk than Group 1: Group 2, hazard ratio 4.66 (95% confidence interval 2.25, 9.64); Group 3, 13.62 (6.48, 28.63); and Group 4, 20.86 (9.60, 45.31).



Conclusions: A new risk scoring system for predicting 15-year mortality was developed. This system may be useful for evaluating HD patients' prognosis.

FR-PO914

High Interleg Systolic Blood Pressure Difference and Protein-Energy Wasting (PEW) Increase Risk of Cardiovascular Events and Mortality in Incident Dialysis Patients Sawako Kato,[1] Bengt Lindholm,[2] Shoichi Maruyama,[1] Yukio Yuzawa,[3] Yoshinari Tsuruta,[4] Kaoru Yasuda.[5] *[1]Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Japan; [2]Baxter Novum & Renal Medicine, Karolinska Inst, Stockholm, Sweden; [3]Nephrology, Fujita Health Univ Hospital, Toyoake, Japan; [4]Meiyo Clinic, Toyohashi, Japan; [5]Masuko Memorial Hospital, Nagoya, Japan.*

Background: While high interarm blood pressure (BP) difference is a marker of arterial stiffness, PEW is linked to atherosclerosis. Here we analyzed if high interleg systolic BP difference (ISBPD) used instead of interarm BP difference (as most hemodialysis patients had arm AV fistula), and concomitant PEW associates with cardiovascular (CV) events and mortality in dialysis patients.

Methods: In 125 incident Japanese dialysis pts (aged 59 ± 11 years; 84 men), ISBPD and subjective global assessment (SGA) as a marker of PEW were measured. Pts were divided into 4 groups according to median ISBPD, 6 (range, 0-98) mmHg, and if they were well-nourished (SGA A; n=28) or malnourished (SGA B; n= 79, and SGA C; n=18). During follow-up for median 46.4 (range, 1–95) months, 20 deaths and 76 CV events occurred and their corresponding relative risks (RRs) were analyzed.

Results: In Kaplan-Meier, high ISBPD and malnutrition associated with the highest mortality (Log rank 8.65, P = 0.034), while there was no difference between high ISBPD/well-nourished pts and low ISBPD/malnutrition pts. In Cox, pts with high ISBPD and malnutrition had increased RR of death (RR of high vs low ISBPD, 3.14, 95% CI; 1.21-9.15; RR of SGA category B and C vs A, 2.94, 95% CI; 0.71-20.8 and 12.3, 95% CI; 1.81-120.7, respectively) after adjustments for age and diabetes. For SGA categories A, B, and C, the cumulative number of CV events per 100 pts year in high-ISBPD pts were 4.6, 29.1, and 91.9, and in low-ISBPD pts 3.0, 5.7, and 0, respectively.

Conclusions: In incident dialysis pts, higher ISBPD associated with increased risk of mortality, and with CV events which however occurred almost exclusively in pts with higher ISBPD and severe PEW, suggesting that pts with arterial stiffness have increased susceptibility to onset of CV events especially in presence of severe PEW.

Funding: Government Support - Non-U.S.

FR-PO915

Periodontitis and Early Mortality among Adults Treated with Hemodialysis: A Multinational Propensity-Matched Cohort Study Marinella Ruospo,[1,2] Suetonia Palmer,[3] Giovanni F.M. Strippoli.[1,4,5] *[1]Diaverum Medical Scientific Office; [2]Amedeo Avogadro Univ of Eastern Piedmont; [3]Univ of Otago Christchurch; [4]Univ of Sydney; [5]Univ of Bari, on behalf of the ORALD Investigators.*

Background: Periodontitis, a multifactorial disease that involves inflammation of the structures supporting teeth, is common, treatable, and may be associated with mortality in the general population and adults with chronic diseases. However, it is unclear whether periodontitis is associated with survival in the setting of kidney failure.

Methods: ORAL-D was a multinational cohort study involving 3338 dentate adults with end-stage kidney disease treated in a hemodialysis network in Europe and South America. ORAL-D was designed to examine the associations between oral health and all-cause and cardiovascular-related mortality in people on long-term hemodialysis. Propensity score methods were used to assemble a matched cohort of participants with moderate to severe periodontitis with characteristics similar to patients with no or mild periodontitis. Periodontal disease was assessed using the World Health Organization Community Periodontal Index. A random-effects Cox proportional hazards model was fitted with shared frailty to account for clustering of mortality risk within countries.

Results: Among the 3338 dentate participants, 1355 (40.6%) had moderate to severe periodontitis at baseline. Moderate to severe periodontitis was associated with a lower risk of all-cause (9.1 versus 13.0 per 100 person years, hazard ratio 0.74, 95% confidence interval 0.61 to 0.90) and cardiovascular (4.3 versus 6.9 per 100 person years, hazard ratio 0.67, 0.51 to 0.88) mortality. These associations were not changed substantially in sensitivity analyses restricted to participants with 12 or more natural teeth or when analyses accounted for competing causes of cardiovascular death.

Conclusions: Periodontitis does not appear to be associated with an increased risk of all-cause and cardiovascular mortality in adults treated with hemodialysis.

FR-PO916

Accelerated Aging-Associated Immune Changes Are Associated with Cardiovascular Disease in End-Stage Renal Disease Patients

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Background: Patients with end-stage renal disease (ESRD) exhibit accelerated aging of the immune system and increased risk for cardiovascular diseases, but the contribution of "immune system aging", or "immunosenescence" to cardiovascular disease is not clear.

Methods: We performed comprehensive lymphocyte and monocyte immunophenotyping in 199 ESRD patients on maintenance hemodialysis and age-matched 57 healthy individuals. Peripheral blood were sampled before hemodialysis session and processed immediately for mononuclear cell isolation and staining. Using multicolor flow cytometry, lymphocytes were separated into subpopulations including naive T cells (CCR7+CD45RA+), central memory (CCR7+CD45RA-), effector memory (CCR7-CD45RA-), terminal effector (CCR7-CD45RA+) and memory stem cells (naive cells with high CD28 and CD95). Monocytes were separated into classical (CD14++CD16-), intermediate (CD14++CD16+) and non-classical monocytes (CD14+CD16+).

Results: Compared to healthy individuals, ESRD patients showed decreased numbers of naïve CD4+ and CD8+ T cells and increased numbers of intermediate monocytes (CD14++CD16+), and these changes significantly correlated with age. Lymphocyte and monocyte aging also correlated with other established cardiovascular risk factors, including hemoglobin and high-sensitivity C-reactive protein. In a multivariate-adjusted logistic regression model, a low naïve CD8+ T cell level in combination with a high intermediate monocyte level was independently associated with the existence of coronary artery disease (OR=3.58, 95% CI=1.2~10.4, p=0.019) as well as cardiovascular diseases including stroke and peripheral arterial occlusive disease (OR=3.98, 95% CI=1.5~10.8, p=0.007).

Conclusions: These results indicate that cardiovascular disease burden in the ESRD population might be enhanced by the presence of accelerated immunosenescence, or aging-related immune changes.

Funding: Government Support - Non-U.S.

FR-PO917

Serum Magnesium Level Can Predict Mortality in Chinese Hemodialysis Patients: A Cohort Study and 3-Year Follow-Up

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Background: To analysis serum magnesium level and its risk factors in Chinese hemodialysis.and whether serum magnesium level is associated with mortality.

Methods: MHD patients were treated in Ruijin Hospital affiliated to Shanghai Jiaotong University School of Medicine in July 1,2012. All patients were consistently treated by 4-hour hemodialysis three times per week, with dialyzer magnesium concentration 0.5 mmol/L. All clinical data, biochemical data and medication were collected at baseline. 3 years follow up and record with the combination of death or withdrawal from dialysis therapy leading to death as the primary outcome. Reference range of magnesium in our laboratory is 0.74-1.03mmol/L.

Results: 230 MHD patients were enrolled, with 63.0% male, 11.3% diabetes. Mean age was 56.67±14.48yrs-old and median dialysis vintage 41(IQR 20.75-72.25) months. Mean magnesium was 1.12±0.16mmol/L. 34.8% patients was in normal range and 65.2% with hypermagnesemia, no one was hypomagnesemia. Pearson correlation showed that age, weight, spKt/V, RBC, Hb, Hct, pre-ALB, pre-dialysis BUN, SCR,UA,Na, K,P, ALB, LDL, 25(OH)D is associated with serum magnesium level(Fig 1). In multiple stepwise liner regression,BUN, Hct, Ca, spKt/V, SCR, K, Na and weight are independent factors of magnesium(Table 1). Follow 36 months, totally 54 patients died. 15 patients died of heart disease, 13 cerebral disease. Kaplan-Meier analysis showed lower magnesium level is associated with higher all-cause mortality and cardiovascular motality (Fig 2).Cox regression hazard analysis identified hypomagnesemia as a significant predictor for all-cause mortality in MHD patients(Table 2).

Table 1. Independent factors of Mg in multiple stepwise liner regression

	beta	P	95.0% CI	
Constant		0.115	-1.578	0.172
BUN	0.166	0.025	0	0.007
Hct	0.184	0.003	0.212	1.044
Ca*	0.161	0.01	0.022	0.158
spKt/V**	0.146	0.034	0.015	0.39
SCR	0.278	0	0	0
K	0.216	0.001	0.016	0.06
Na	0.143	0.02	0.001	0.014
weight	-0.153	0.034	-0.004	0

Model R square=0.396, model ANOVA P<0.001.
Variable with P<0.1 in single liner regression were included into multiple stepwise regression.
*Calcium level is adjusted by serum albumin.
**spKt/V is log transformed.

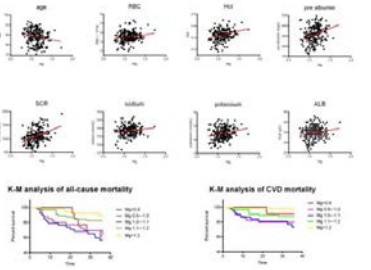

Table 2. Hazard ratios with 95% confidence intervals for all-cause mortality according to different Mg levels

	Model 1				Model 2				Model 3				Model 4			
	P	HR	95.0% CI		P	HR	95.0% CI		P	HR	95.0% CI		P	HR	95.0% CI	
			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper
	0.004				0.016				0.055				0.059			
Mg<1.0mmol/L	0.004	3.901	1.557	9.771	0.042	2.64	1.036	6.726	0.399	1.52	0.575	4.018	0.331	1.623	0.611	4.308
Mg 1.0-1.17mmol/L	0.004	3.884	1.551	9.728	0.01	3.361	1.337	8.45	0.054	2.534	0.986	6.515	0.044	2.652	1.028	6.839
Mg 1.17-1.37mmol/L	0.322	1.667	0.606	4.587	0.608	1.306	0.471	3.621	0.753	0.838	0.278	2.524	0.887	0.923	0.305	2.792
Mg>1.37mmol/L(Ref)	-	1	-	-	-	1	-	-	-	1	-	-	-	1	-	-

Model 1:Unadjusted Model 2:age, sex, dialysis vintage adjused Model 3:Model 2+kt/V, Hb, ALB, Ca, P, iPTH
Model 4:Model 3+TG, TC, HDL,LDL

Conclusions: A high prevalence of hypermagnesemia is in MHD patients. Serum magnesium level can predict the mortality in Chinese dialysis patients.

FR-PO918

High suPAR Is Strongly Associated with Adverse Outcomes in Patients with End-Stage Renal Disease on Dialysis

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Background: Soluble urokinase plasminogen activator receptor (suPAR) is associated with adverse outcomes in various populations, and is implicated in the pathogenesis of kidney disease. SuPAR concentrations often increase as eGFR decreases, and it is unclear whether they remain predictive of outcomes in patients with end-stage renal disease (ESRD).

Methods: We measured serum suPAR at enrolment in 1175 hemodialysis patients with type 2 diabetes mellitus (54% male, mean age 66±8 years old), participating in the German Diabetes and Dialysis Study (4D Study). Patients were followed for 4 years for death and cardiovascular events. We examined the association between suPAR tertiles and outcomes using Cox regression analyses, adjusting for clinical characteristics.

Results: Median suPAR was 10521 pg/ml (IQR 9105–12543 pg/ml). Patients with suPAR > 11633 pg/ml (third tertile) had an almost 2-fold higher mortality compared to those with suPAR < 9599 pg/ml (first tertile) (adjusted HR 1.9; 95% CI 1.5-2.3). The risks of sudden death and stroke were strongly increased (adjusted HR_{SD} 2.2; 95% CI 1.4-3.5, and adjusted HR_{stroke} 2.2; 95% CI 1.3-3.6, respectively, third versus first tertile), together accounting for the higher incidence of cardiovascular events combined (adjusted HR 1.7; 95% CI 1.4-2.2). In contrast, there was no association between suPAR and the risk of non-fatal myocardial infarction.

Conclusions: SuPAR is strongly associated with poor cardiovascular outcomes in patients with ESRD which may reflect pathologic processes beyond decreased renal function. Further studies are needed to determine whether suPAR is a modifiable risk factor and a potential therapeutic target.

FR-PO919

Plasma Betaine and Cardiovascular Outcomes in Hemodialysis Patients

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Background: Betaine (trimethylglycine) is a precursor for gut microbiome-derived trimethylamine-N-oxide (TMAO), a uremic toxin, but is also biochemically active, enhancing very-low-density lipoprotein (VLDL) activity and affecting serum homocysteine concentration.

Methods: We measured plasma betaine levels in 1276 patients of the NIDDK sponsored, Hemodialysis (HEMO) Trial and analyzed their relation over time to CV death, sudden cardiac death (SCD) and first CV event adjudicated by an outcomes committee. We used Cox proportional hazards models adjusted for potential confounders (demographics, clinical characteristics, comorbidities, residual kidney function, albumin and TMAO). We also examined interactions by race and dialysis interventions (high flux or dose).

Results: Mean age of the patients was 58 years, 63% were Black and 42% were male. Median (interquartile range) betaine concentration was 53 μM (41, 65). Median follow-up

was 2.3 years. In unadjusted and full adjusted models (including adjustment for TMAO), higher betaine concentrations were associated with a higher risk of CV outcomes. Subgroup analyses did not show significant interactions with race or dialysis intervention.

Association of Betaine with Cardiovascular Outcomes in 1276 Patients of HEMO Study**			
Outcomes	Events	HR (95% CI)	*P*
CV Mortality	220	1.52 (1.15-2.02)	0.003
Sudden Cardiac Death	126	1.55 (1.17-2.05)	0.002
First CV Event	644	1.15 (0.98-1.35)	0.09
**Adjusted HR per 2-fold increase in solute			

Conclusions: Plasma betaine is a risk factor for CV outcomes in hemodialysis patients and this association appears to be statistically independent of serum TMAO concentrations.

Funding: NIDDK Support

FR-PO920

P-Cresol Sulfate, Indoxyl Sulfate, Hippurate and Phenylacetylglutamine and Cardiovascular Outcomes in Hemodialysis Patients

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Background: We recently reported that a large increase in Kt/Vurea in the Hemodialysis (HEMO) Study failed to achieve significant reduction in p-cresol Sulfate (PCS), indoxyl sulfate (IS), hippurate (HIPP) and phenylacetylglutamine (PAG). The goal of this study was to determine the association of these solutes with cardiovascular (CV) outcomes.

Methods: We measured PCS, IS, HIPP and PAG in HEMO Study samples (N=1276) and analyzed their association with CV death, sudden cardiac death (SCD) and first CV event, using Cox model adjusted for potential confounders [demographics, clinical characteristics, comorbidities, albumin, residual kidney function (RKF)].

Results: Mean age of the patients was 58 years, 63% were Black and 42% were male. None of the solutes were associated with any CV outcomes (Table 1). Trial interventions (which did not reduce solute concentration) did not modify the association between the solutes and CV outcomes. In pre-specified subgroup analyses, total HIPP and PAG were associated with CV death only in patients with RKF (n=433; p-interaction <0.05).

Association of Solutes with CV Outcomes in 1276 Patients of HEMO Study**						
	CV Death (n=220)		**SCD (n=126)**		**First CV Event (n=644)**	
	HR	P	HR	P	HR	P
PCS	0.98 (0.90-1.07)	0.7	0.98 (0.88-1.10)	0.8	0.98 (0.94-1.01)	0.1
IS	0.96 (0.81-1.14)	0.6	0.94 (0.75-1.18)	0.6	0.99 (0.92-1.07)	0.8
HIPP	1.09 (0.98-1.21)	0.1	1.03 (0.91-1.17)	0.6	0.98 (0.94-1.03)	0.5
PAG	1.09 (0.94-1.26)	0.2	1.08 (0.90-1.30)	0.4	0.99 (0.92-1.05)	0.6
** Adjusted HR per 2-fold increase in solute						

Conclusions: In prevalent hemodialysis patients participating in a large U.S. hemodialysis trial, PCS, IS, HIPP and PAG were not associated with CV outcomes. Dialysis interventions to reduce the burden of CV disease are unlikely to be successful without better knowledge of solute toxicity.

Funding: NIDDK Support

FR-PO921

Adipokines, Blood Pressure and Arterial Elasticity in Dialysis Patients

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Background: Previous studies have suggested that adipokines, a group of hormones and cytokines released by white adipose tissue, may exert potent and inconsistent effects on cardiovascular (CV) system. There remains a paucity of data regarding theirs associations with CV parameters in patients on maintenance hemodialysis.

Methods: This is a cross-sectional analysis of midterm baseline data from a cohort study. Two-hundred and twenty eight dialysis patients from dialysis centers of four tertiary hospitals in East China were recruited. Blood pressure level and arterial elasticity were evaluated by ambulatory blood pressure monitoring and pulse wave velocity measurement on a nondialysis day, respectively. Adipokines (adiponectin, resistin, PAI-1, Leptin, MCP-1, adipsin) were detected using pre-dialysis plasma samples by multiplex assays. Associations of adipokines with ambulatory systolic blood pressure (A-SBP) and carotid-to-femoral pulse wave velocity (cfPWV) were determined using generalized linear models.

Results: For blood pressure, in a basic age- and sex-adjusted model, adiponectin is positively associated with A-SBP (p=0.004) while resistin, PAI-1, leptin and adipsin are inversely associated with A-SBP (p≤0.001 for resistin, PAI-1 and leptin; p=0.021 for adipsin).In more extensive adjusted models, adiponectin is still positively associated with A-SBP while resistin, PAI-1, leptin are inversely associated with A-SBP (p<0.01 for all). For arterial elasticity, only adiponectin is inversely associated with cfPWV (p<0.01 for all models).

Conclusions: Circulating adipokines are associated with blood pressure and arterial elasticity in dialysis patients, suggesting their diverse effect on cardiovascular system in these patients.

Funding: Government Support - Non-U.S.

FR-PO922

Additive Prognostic Utility of Serum ST2 Level as a Predictor of Cardiovascular Outcomes in Incidental Hemodialysis Patients

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Background: ST-2 concentration is known to be a predictor for cardiovascular (CV) mortality and hospitalization due to CV disease in patients with heart failure. This study was to evaluate the prognostic value of serum ST-2 level in incident dialysis patients, in terms of mortality and CV events.

Methods: A total 182 ESRD patients starting maintenance dialysis were enrolled. We measured the pre-dialysis serum ST-2 level at the start of dialysis. Patients were divided into two groups according to the median ST-2 level. Factors associated with serum ST-2 level were analyzed. The associations between serum ST-2 level and mortality and CV events were investigated.

Results: Median follow up duration was 628 days (interquartile range 382 to 1,052 days). There was no significant difference in baseline demographic characteristics and comorbidity between the two groups. The high ST-2 group showed higher levels of C-reactive protein (CRP), phosphorus, and calcium-phosphorus product, and lower albumin and calcium levels than those of the low ST-2 group. Serum ST-2 level showed significantly positive correlations with levels of phosphorus, calcium-phosphorus product, and CRP, and the ratio of peak early to late diastolic filling, while it showed significantly negative correlations with serum albumin level and ejection fraction, after age- and sex-adjustment. The patient survival rate was significantly lower in the high ST-2 group compared with that of the low ST-2 group after 3 years follow up (69.2% vs. 86.9%, P= 0.023). The event free survival rate for death and non-fatal CV event was significantly lower in the high ST-2 group compared with the low ST-2 group (59.4% vs. 80.3%, P =0.008). In multivariate Cox regression analysis, the ST-2 level was also a significant predictor for composite of end-points after adjustments for traditional CV risk factors and laboratory parameters (HR = 1.011, P = 0.003).

Conclusions: This study showed that serum ST-2 level independently predicted mortality and non-fatal CV events in ESRD patients. High ST-2 concentration could be an additive predictor for adverse CV outcomes in incident dialysis patients.

Funding: Private Foundation Support

FR-PO923

A Lower Serum Uric Acid Is Associated Not Only with All-Cause Mortality but also Cardiovascular Mortality among Patients Receiving Hemodialysis in Japan

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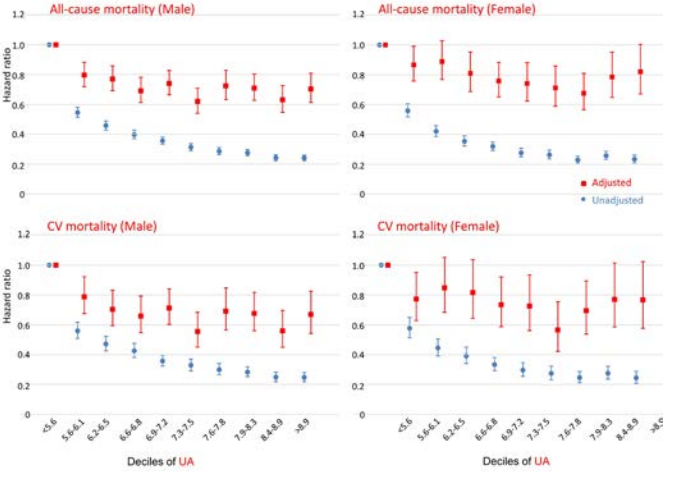
Background: High level of serum uric acid is prevalent in chronic kidney disease (CKD), however it has a controversy whether high or low serum uric acid level appears to be a risk factor of cardiovascular event and mortality in the patients of receiving renal replacement therapy.

Methods: We collected the baseline data of 222,434 patients receiving HD thrice weekly (males: 63.0%, 66 ±12 years, median HD vintage of 60 months, females: 68 ±13 years, median HD vintage of 72months) extracted from a nationwide dialysis registry at the end of 2011 in Japan. Then we evaluated the patient survival and development of complication using the registry at the end of 2012.

Results: During one-year follow-up, 18775 (8.4%) died of all causes including 8094 (3.6%) cardiovascular death. All-cause mortality, and cardiovascular mortality were lower in line with the increase of baseline uric acid. In a multivariable logistic regression analysis (figure 1), patients of the highest quartile of uric acid had lower all-cause, and cardiovascular mortality compared with those of the lowest quartile (males: OR, 0.745; 95% CI, 0.6753 to 0.8207, females: OR, 0.8333; 95% CI, 0.7206 to 0.9636, and males: OR, 0.7202; 95% CI, 0.6266 to 0.8278, females: OR, 0.8575; 95% CI, 0.7029 to 1.0462, respectively).



Conclusions: In this large observational cohort study, lower levels of serum uric acid were independently associated not only with all-cause mortality but also cardiovascular mortality among Japanese HD patients. Close monitoring of serum uric acid is thought to be necessary for the management of HD patients.

FR-PO924

Menopause Status Is Associated with Mortality in Women on Hemodialysis Sharanya Ramesh,[1] Matthew T. James,[1,2,3,4] Stephen B. Wilton,[1,2] Jayna M. Holroyd-Leduc,[1,3] Marcello Tonelli,[1,2,3,4] Brenda Hemmelgarn,[1,2,3,4] Sofia B. Ahmed.[1,2,4] *[1]Cumming School of Medicine, Univ of Calgary; [2]Libin Cardiovascular Inst of Alberta; [3]Dept of Community of Health Sciences, Univ of Calgary; [4]Alberta Kidney Disease Network; [5]Brigham and Women's Hospital, Harvard Univ.*

Background: Young women with end-stage kidney disease (ESKD) have low survival compared to age-matched men. Women with ESKD have an abnormal hypothalamic pituitary gonadal axis, characterized by low estradiol. We hypothesized that premature menopause is associated with death in women with ESKD.

Methods: Women who initiated hemodialysis (HD) between Feb 2005 and Nov 2012 in 3 centers were classified as premenopausal, perimenopausal and postmenopausal using the Women's Ischemia Syndrome Evaluation (WISE) criteria based on serum estradiol, follicle stimulating hormone levels and age. The associations between menopausal status and all cause, cardiovascular(CV) and non-cardiovascular(non-CV) mortality were determined by survival curves and Cox regression.

Results: Four hundred eighty-two women (60±16years, 53% diabetic) were followed for 2.9 years (IQR=3.47 years) with 241 deaths (31% CV). Thirty percent of women had a premenopausal sex hormone profile (estradiol: 196±187 pmol/L), while 7% and 58% had a perimenopausal (estradiol: 230±335 pmol/L) and postmenopausal (estradiol: 55±38 pmol/L) sex hormone profile respectively. In comparison to postmenopausal women, peri- and premenopausal women had higher all-cause mortality after adjustment for covariates (hazard ratio(HR)[95% confidence interval (CI)]:1.87[1.17-2.99] and 1.8[1.32-2.46] respectively), and higher CV mortality after adjustment (HR: 2.72[1.30-5.70] and 1.81[1.03-3.17], respectively). In comparison to postmenopausal women, premenopausal women had higher non-CV mortality after adjustment (HR: 1.71[1.07-2.73]).

Conclusions: Using the WISE classification,peri- and premenopausal women with ESKD on HD have a higher risk of all-cause and CV mortality compared to postmenopausal, and premenopausal women have a higher non CV mortality compared to postmenopausal women. Further studies are required to determine the pathophysiology leading to increased mortality risk in young women with ESKD.

FR-PO925

Long-term Serial Measurements of High-Sensitivity Troponin T in Stable Hemodialysis Patients: The Effect of Angiotensin II Blockade and Associations with Clinical Variables The Safir Study Group. *Depts of Renal Medicine and Cardiology, Aarhus Univ Hospital, Aarhus, Denmark.*

Background: For the interpretation of high-sensitivity troponin T (TnT) levels in hemodialysis (HD) patients, it is important to know the expected range, variation over time, and the impact of clinical and HD specific factors.

Aim To study the effect of angiotensin II receptor blockade (ARB), short and long-term variation in TnT, and associations with cardiac status in stable HD patients.

Methods: 81 HD patients (urine output >300 mL/day, HD-vintage <1 year, and left ventricular (LV) ejection fraction (EF) >30%) were randomized double-blind for placebo (n=40) or ARB treatment (n=41) with irbesartan (150-300 mg) and followed for 12 months with serial measurements of TnT using Roche (Elecsys STAT) high-sensitivity assay.

Results: Baseline TnT medians with ranges (placebo/ARB) were: 45(14-295)/46(10-343)ng/L. ARB treatment did not significantly affect mean TnT levels over the 12-month study period ($P \geq 0.19$ in all tests for parallel curves, equal levels, and constant levels). Week-to week individual variation was median(95% range) 0(-24-19)ng/L corresponding to a median (95% ref. range) TnT-ratio (1 week/baseline) of 1.0(0.7-1.4); $P=0.9$. Individual amplitude (max-min) over 12 months was median 13(0-114)ng/L corresponding to range/median 29(0-208)%. In univariate analysis, baseline TnT was positively correlated with diabetes, ultrafiltration, arterial stiffness, and N-terminal brain natriuretic prohormone (NT-proBNP) and negatively correlated with hematocrit and residual renal function. Higher TnT levels at baseline were associated with a higher risk of admission and cardiovascular events during follow-up with natural log-transformed TnT odds-ratios (95% CI): 2.62(1.22-5.64) and 2.25(1.04-4.86). Increase in TnT over time was significantly associated with increase in LV mass and NT-proBNP and decrease in LV EF and late intradialytic stroke volume (30 minutes before end of HD).

Conclusions: There was no significant effect of ARB treatment. Week-to-week variation was low, yet over 12 months individual patients had considerable TnT fluctuations. Rise in TnT over time was significantly correlated with deterioration of cardiac status.

Funding: Government Support - Non-U.S.

FR-PO926

High-Sensitivity Troponins in Clinically Stable Dialysis Patients: Variation and Prognostic Value Sunna Snaedal,[1,2] Peter F. Barany,[1] Sigrun Helga Lund,[3] Abdul Rashid Tony Qureshi,[4] Olof Heimburger,[1] Peter Stenvinkel,[1] Christian Löwbeer,[5,6] Karolina Szummer.[7] *[1]Dpt of Clinical Science, Intervention and Technology, Karolinska Inst, Stockholm, Sweden; [2]Nephrology Dpt, Landspitali Univ Hospital, Reykjavik, Iceland; [3]Faculty of Medicine, Univ of Iceland, Reykjavik, Iceland; [4]Dept of Baxter Novum, Karolinska Inst, Stockholm, Sweden; [5]Dept of Laboratory Medicine, Karolinska Inst, Stockholm, Sweden; [6]Dept of Clinical Chemistry, Aleris Medilab, Täby, Sweden; [7]Dept of Cardiology, Karolinska Inst, Stockholm, Sweden.*

Background: Cardiac troponins are elevated in dialysis patients even without signs of cardiac ischemia.The study aim was to assess variation and prognostic value of serial high sensitivity cardiac Troponin I (hs-cTnI) and T (hs-cTnT) in prevalent, stable dialysis patients.

Methods: In 198 prevalent hemodialysis (HD) and 78 peritoneal dialysis (PD) patients 4 monthly hs-cTnI and hs-cTnT measurements were obtained. Variability was assessed with reference change values and mixed models. Cox regression models were used for survival analyses, maximal follow-up 50 months.

Results: Troponin levels were similar in HD and PD patients (median [IQR] hs-cTnI; 25ngL [14–43] vs 21ng/L [11–37], hs-cTnT; 70ng/L [44–129] vs 67ng/L [43–123]). 42% of hs-cTnI and 98% of hs-cTnT were above the decision limit of myocardial infarction (MI). Variability of troponins associated with age, male sex, protein-energy wasting and congestive heart failure, not with ischemic heart disease or dialysis form. The reference change values were +68/-41% (hs-cTnI) and +29/-23% (hs-cTnT), index of individuality 0.07 for both. Constantly high hs-cTnT (above 108 ng/L) predicted death [HR 2.09 95% CI 1.03-4.26] while hs-cTnI did not.

Conclusions: A large proportion of stable dialysis patients have troponins levels above the decision limit for MI. Large intra-individual differences support the use of reference change values when assessing dialysis patients with possible acute cardiac events. A constantly high level of hs-cTnT and not hs-TnI predicted a doubled risk of death.

Funding: Pharmaceutical Company Support - Amgen, Government Support - Non-U.S.

FR-PO927

High Sensitive Troponin-I Level and Hemodialysis-Induced Myocardial Injury in Chronic Hemodialysis Patients Khajohn Tiranathanagul,[1] Tanawat Tarapan,[2] Khrongwong Musikatavorn,[2] Piyarat Phairatwet,[3] Paweena Susantitaphong,[1] Kriang Tungsanga,[1] Somchai Eiam-Ong.[1] *[1]Medicine-Nephrology, Faculty of Medicine, Chulalongkorn Univ, Bangkok, Thailand; [2]Emergency Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [3]Nephrology, Bhumirajanakarindra Kidney Inst Hospital, Bangkok, Thailand.*

Background: High-sensitivity Troponin I (hsTnI) is the best biomarker for myocardial injury. The current cut-off point for diagnosis of acute myocardial infarction (MI) was derived from general population. The reduction in renal clearance and the removal by hemodialysis (HD) affected the level and utility of this marker in HD ESRD patients. Unfortunately, there was unavailable well-designed study that determined the appropriated level of hsTnI in this specific population. Moreover, the HD process itself might cause undesirable myocardial injury and enhance post HD hsTnI level.

Methods: This comparative study was conducted to compare the hsTnI level between 100 HD ESRD patients (age 64.5 ± 13.8 years) and their 107 matched population with good renal function (age 63.8 ± 9.97 years). Moreover, the pre- and post-HD hsTnI levels were also compared to determine the effect of HD on hsTnI.

Results: The hsTnI levels in the HD ESRD group were higher than in the control group [median (IQR): 54.3(20.6-152.7) vs. 18 (6.2-66.1) ng/L, p< 0.001).The hsTnI levels reduced after HD process from 54.3 (20.6-152.7) ng/L in pre-HD to 27.1(12.3-91.4) ng/L in post-HD (p=0.015). Of interest, 25% of HD ESRD patients had increment of hsTnI after HD and represented HD-induced myocardial injury. The significant risk factors were high HbA1C, high blood flow rate, and high dialysate flow rate.

Conclusions: In HD ESRD patients, the baseline hsTnI levels are approximately three times significantly higher than in general population. As such, the cut point for acute MI diagnosis in HD ESRD patients should be three times of reference level in general population. However, the dynamic change of hsTnI overtime was still recommended for the final acute MI diagnosis. Hemodialysis could reduce hsTnI level. Certain numbers of HD ESRD patients had HD-induced silent myocardial injury and should be aggressively investigated to prevent further cardiovascular mortality.

FR-PO928

Native T1 Mapping Is a Highly Reproducible Measure of Myocardial Fibrosis in Hemodialysis Patients Independent of Hydration Status
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Background: Myocardial fibrosis occurs frequently in hemodialysis (HD) patients and is associated with poor prognosis. Native T1 mapping is a novel cardiac MRI (CMR) technique that measures longitudinal proton relaxation to characterize tissue with great specificity. Native T1 mapping correlates well with myocardial fibrosis in many diseases, but concerns remain about its use in HD patients due to the potential impact of changes in hydration status on T1 time. We examined the inter-study reproducibility of native T1 mapping in HD patients and the effects of hydration on native T1 time.

Methods: 3T CMR was performed twice on non-dialysis days for 10 patients (median interval 7 days) to assess reproducibility of native T1 mapping. Changes in left ventricular end-diastolic volume (ΔLVEDV) and changes in weight (Δweight) between scans were used as surrogates of hydration status and the effects these on change in native T1 (ΔT1) between scans was assessed.

Results: There was no interval difference between mean native T1times (1267.8ms±35.4 vs 1270.7ms±30.5, P=0.6) with an inter-study co-efficient of variation of 0.7%. Bland-Altman analysis showed narrow limits of agreement with no systematic bias. LVEDV and weight were different between scans (mean change LVEDV 11.7ml±8.7, mean change weight 0.5kg±0.5) and there was a significant correlation between ΔLVEDV and Δweight (r=0.682, P=0.03). There were no correlations between ΔT1 and ΔLVEDV or Δweight (r=-0.14, P=0.7 and r=0.2, P=0.6). Linear regression confirmed ΔT1was unaffected by ΔLVEDV and Δweight (F(1,8)=0.15, adj R^2=0.1, P=0.71 and F(1,8)=0.31, adj R^2=0.08, P=0.59).

Conclusions: These results show for the first time that native T1 time is unaffected by hydration status. The outstanding test-retest, inter-study, reproducibility demonstrated for native T1 mapping make it an attractive imaging biomarker for clinical trials to assess changes in myocardial fibrosis.

FR-PO929

Insights from Speckle Tracking Echo in Detecting Differences in Myocardial Function in End-Stage Renal Disease
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Background: Hemodialysis (HD) is capable of inducing subclinical myocardial dysfunction and this phenomenon is primarily related to hemodynamic instability. In contrast, peritoneal dialysis (PD) has until recently been considered to exert little, if any, significant hemodynamic effects. The aim of the current study was to assess whether speckle tracking echocardiography, by measuring global longitudinal strain (GLS), could assess differences in early myocardial dysfunction between patients with end stage renal disease (ESRD) who have undergone PD and those who are treated with HD.

Methods: Thirty-nine patients with ESRD and with no known coronary artery disease were enrolled. Patients were stratified into two groups according to the dialysis modality (i.e. 23 on HD and 16 on PD). All patients underwent comprehensive 2D echocardiographic study. Apart from standard 2D and Doppler measurements, GLS was measured using the obtained apical views. Cross-sectional comparisons of the derived parameters were made between the two groups.

Results: There was no difference in mean age (65.5 ± 9.9 vs. 57.7 ± 7.9, p= 0.07) and dialysis duration (mean 85 ± 106.7 vs 50.63 ± 57.2 months, p=0.4) between the two groups. Moreover, mean left atrial (40.1 ± 6.4 vs 41.6 ± 8.9mm, p=0.5), intra-ventricular septum (10.7 ± 1.8 vs. 9.9 ±1.9mm, p=0.4), EF (48.5 ± 12.3 vs. 45,6 ± 8.7%, p= 0.4) and E/Em (9.7 ± 4.5 vs. 10.1 ± 4.8, p=0.7) measurements were not statistically different. However, GLS was less negative in the HD group (-11.6± 3.8 vs. -15.4 ± 4.5, p=0.04).

Conclusions: Patients, in HD, exhibit less negative GLS values, in comparison to those in PD. It must be mentioned that less negative GLS is proven to be associated with an early myocardial dysfunction and an increased cardiovascular mortality. This could be attributed to different hemodynamic effects of each dialysis modality on myocardial function.

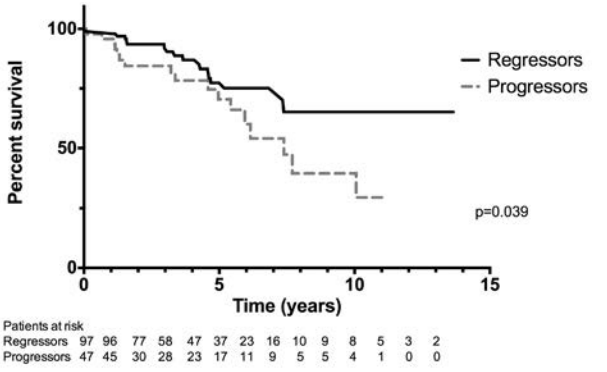
FR-PO930

Impact of Left Ventricular Hypertrophy Regression after Initiation of Intensive Hemodialysis on Clinical Outcomes
Emilie Trinh, Christopher T. Chan. *Nephrology, Univ Health Network, Toronto, ON, Canada.*

Background: Left ventricular hypertrophy (LVH) is an independent risk factor for mortality and cardiovascular events in patients with end-stage renal disease. Multiple studies have shown that frequent hemodialysis leads to LVH regression. However, the impact of left ventricular mass (LVM) regression on clinical outcomes in the setting of intensive hemodialysis remains unknown.

Methods: This observational cohort study assessed the impact of LVH regression on the composite outcome of time to all-cause mortality, technique failure or cardiovascular hospitalization. LVH regression was defined as either a reduction of more than 10% in LVM in patients with LVH at baseline or prevention of LVH in those without LVH at baseline. Risk factors associated with regression or progression of LVM were also examined.

Results: We studied 144 intensive hemodialysis patients at a single center between 1999 to 2012 with a mean follow-up of 4.7 years. 97 patients (67.4%) had LVH regression or prevention and 47 patients (32.6%) had LVH progression. In a multivariate analysis, smoking history (OR 3.007, 95% CI 1.073-8.427, p=0.036) and presence of LVH at baseline (OR 3.654, 95% CI 1.506-8.868, p=0.004) were significant predictors for LVM progression. 18 patients (18.6%) in the regressors groups as compared to 17 patients (36.2%) in the progressors group developed the composite end-point. When adjusted for age and diabetes, LVH regression was significantly associated with a decreased risk (HR 0.422, 95% 0.214-0.835) for the composite end-point. On the basis of mortality alone, LVH regression was also significantly associated with a decreased risk of death in the adjusted analysis (HR 0.211, 95% CI 0.069-0.645).



Conclusions: Regression of LVH with intensive hemodialysis is associated with favorable clinical outcomes in patients with end-stage renal disease.

Funding: Pharmaceutical Company Support - Baxter extramural grant

FR-PO931

Left Ventricular Geometry in Peritoneal Dialysis Patients: Predictive Factors
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Background: Left ventricular hypertrophy (LVH) is an independent risk factor of morbidity and mortality in chronic kidney disease (CKD). Concentric hypertrophy remains the main culprit. The aim of this study was to identify factors that could be associated with different geometric patterns of LVH on a PD population.

Methods: We evaluated 114 CKD patients who underwent both echocardiography and Peritoneal Dialysis (PD) for more than 2 months, since 1999 until 2015. LVH (LV mass >95 g/m(2) [women] and >115 g/m(2) [men]) and relative wall thickness (RWT) were used to define LV geometry: no LVH, LVH and RWT≤0.42 (eccentric), and LVH and RWT>0.42 (concentric). Descriptive statistics and multinomial logistic regression analysis were done.

Results: Baseline demographics included age (54.6±17.6 years), gender (56.1% males), diabetes prevalence (33.3%) and clinical parameters included systolic blood pressure (143±25mmHg), renal residual function (RRF - 6.0±5.6 ml/min), kt/V (2.7±1.0), normalized protein catabolic rate (nPCR - 0.99±0.32g/kg) hemoglobin (11.9±1.8g/dL), phosphorus (4.9±1.6mg/dL), PTH (656.0±641.8pg/mL), high sensitivity C-reactive protein (hs-CRP - 12.7±21.9mg/L), total cholesterol (208.6±58.1mg/dL). Vintage on PD was of 33.8±24.2 months and regarding LV geometry, 38 patients presented with concentric LVH and 11 with eccentric LVH.

In our population, higher phosphorus (p=0.043) and PTH (p=0.017) levels, higher systolic blood pressure (p=0.029) and lower nPCR (p=0.030) were predictive of concentric LVH, and hsCRP was predictive of eccentric LVH (p=0.048), when adjusting for gender, age, RRF, kt/V diabetes, cholesterol and hemoglobin levels and using the group without LVH as reference.

Conclusions: Modifiable factors, in this population, were conditioning concentric LVH, namely higher systolic blood pressure, worse mineral metabolism and nutrition parameters. Ameliorating these variables would we diminish cardiovascular mortality in CKD patients? Larger studies are needed, but worth attempting in daily practice.

FR-PO932

Relation between Different Blood Pressure Measurements and Left Ventricular Hypertrophy in Peritoneal Dialysis Patients
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Background: Hypertension is prevalent in end stage renal disease (ESRD) and is associated with left ventricular hypertrophy (LVH), which is an independent predictor of cardiovascular mortality. Although hypertension is an important and modifiable risk factor for cardiovascular events, the optimal approach to monitor blood pressure (BP) in peritoneal dialysis (PD) patients for therapeutic guidance is unclear. In this study, we compared different methods of BP measurement and evaluated the relationship between different BP measurements and LVH in PD patients.

Methods: Fifty two prevalent PD patients were enrolled at a single dialysis center. We measured ambulatory BP, office BP, home BP, and central BP. The ambulatory BP was recorded for 24 hours, office BP was measured at least in two visits, and home BP was measured for one week. The central BP was estimated using radial artery tonometry. Left ventricular mass index (LVMI) was measured using echocardiography and the presence of LVH was ascertained.

Results: LVH was best predicted by ambulatory systolic BP (area under the curve (AUC), 0.811; 95% CI, 0.691-0.931) and home systolic BP (AUC, 0.786; 95% CI, 0.658-0.915). The office systolic BP (AUC, 0.643; 95% CI, 0.488-0.799) and central systolic BP (AUC, 0.662; 95% CI, 0.514-0.840) were inferior to ambulatory and home BP in predicting LVH. The adjusted odd ratio (OR) for home systolic BP (OR, 1.066; 95% CI 1.018-1.117) was higher than those for ambulatory (OR, 1.052; 95% CI 1.010-1.096) and central systolic BP (OR, 1.032; 95% CI 1.021-1.173) in LVH prediciton. The office systolic BP did not significantly predict LVH (OR, 1.026; 95% CI 0.986-1.068).

Conclusions: Home and ambulatory systolic BP were the strongest predictors of LVH suggesting that treatments targeting these BP measurements may prevent end organ damage in PD patients.

FR-PO933

Tallium-201 Washout Rate of Stress Myocardial Perfusion Imaging as a Predictor of Mortality in Diabetic Kidney Disease Patients Undergoing Hemodialysis: An Observational, Follow-Up Study

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Background: Thallium-201 (^{201}Tl) washout rate of stress myocardial perfusion imaging (MPI) has been reported to correlate with coronary flow reserve which is a parameter of myocardial microcirculation and be useful to detect coronary artery disease and evaluate the severity. However, the evidence for its use in diabetic kidney disease (DKD) has been lacking, and the association between thallium-201 washout rate and adverse outcomes including death is unknown. Therefore, a hospital-based, prospective, cohort study was conducted to evaluate the predictive ability of thallium-201 washout rate for mortality in DKD patients undergoing hemodialysis.

Methods: A total of 96 DKD patients who had been started on maintenance hemodialysis undergoing pharmacologic or exercise stress MPI with thallium-201 within 1 year, 72 men and 24 women, with a median age of 67 years, were studied. The endpoint was defined as all-cause death. The Cox proportional hazards model was used to calculate hazard ratios (HR) and 95 % confidence intervals (CI).

Results: During the mean follow-up period of 3.1 ± 2.4 years, 18 (18.8 %) deaths occurred. Cumulative survival rates during the follow-up period, with thallium-201 washout rate levels in the lowest tertile (3.1 - 36.2 %), the middle tertile (36.5 - 46.3 %), and the highest tertile (46.4 - 66.2 %) were 47.7 %, 85.7 %, and 84.2 %, respectively (Figure).

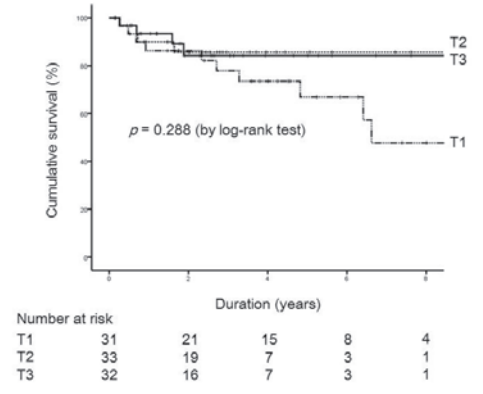

Figure. Cumulative survival in diabetic patients undergoing hemodialysis (n = 96) among three groups classified into tertiles by baseline tallium-201 washout rate levels.
Abbreviations: T1, lowest washout rate tertile (washout rate; 3.1 - 36.2 %); T2, middle washout rate tertile (washout rate; 36.5 - 46.3 %); T1, highest washout rate tertile (washout rate; 46.4 - 66.2 %).

Overall, the multivariate Cox regression analysis revealed that thallium-201 washout rate remained an independent predictor of death after adjusting by confounding variables (HR 0.92, 95 % CI 0.87 to 0.98).

Conclusions: Among DKD patients undergoing hemodialysis, thallium-201 washout rate seems to be useful for predicting death.

FR-PO934

Myocardial Perfusion Imaging in Renal Transplant Candidates

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Background: There is a high prevalence of coronary heart disease in patients with end stage renal disease (ESRD) with estimates ranging from 30-60% based on various screening modalities such as history, laboratory tests, myocardial imaging and cardiac catheterization. We studied the outcome of perfusion imaging as an indicator of coronary heart disease in African American patients with ESRD awaiting renal transplantation.

Methods: A retrospective analysis was done on patients with ESRD who were candidates for renal transplant and consecutively referred for a pre transplant cardiac evaluation. All patients had a thorough history and physical examination, standard laboratory tests,12 lead EKG, chest x-ray, echocardiogram and stress myocardial perfusion imaging. Patients with a positive perfusion test were considered to have ischemic heart disease and referred for cardiac catheterization.

Results: A total 289 patients were evaluated most of whom were African American; 62%(178) were male and 38%(111) females patients; mean age was 54.5 years; 75%(218) were on renal replacement therapy; mean duration of dialysis was 4.2years; Hypertension was present in 82%(238) and diabetes in 42%(121) of patients. Stress radionuclide myocardial perfusion imaging was suggestive of ischemic heart disease in 164(56.7%) patients and 125(53%) tested negative.

Conclusions: Although this subset of ESRD patients had less comorbidities, the prevalence of coronary heart disease was high at 57% in pre-transplant ESRD patients based on myocardial perfusion imaging. Further risk stratification is recommended to confirm coronary heart disease.

FR-PO935

Early Mortality and Late Outcomes for Coronary Revascularisation in End Stage Renal Disease - A Systematic Review and Meta-Analysis

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Background: Despite the high prevalence of coronary artery disease in patients with end-stage renal disease (ESRD), the optimal method of coronary revascularisation remains unclear. We conducted a systematic review and meta-analysis of the available literature comparing outcomes after percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) in ESRD patients.

Methods: We reviewed contemporary studies, conducted after the year 2000 as PCI therapy have improved, comparing PCI to CABG in ESRD patients, using Review Manager 5.1 for statistical analysis and PRISMA guidelines for reporting. Clinical end-points compared were early (in-hospital or 30-day) and late (> than 1 year) mortality; repeat revascularisation, occurrence of major adverse cardiovascular events (MACE) and myocardial infarction (MI) after revascularisation.

Results: In 12 studies investigating early mortality, the analysis demonstrated less early deaths for PCI compared to CABG (4% v 8%, p<0.001, Figure 1a). Late mortality was reported in 10 studies with late deaths similar for CABG and PCI (44% v 50%, p=0.32). Repeat revascularisation was reported in 9 studies. CABG was less likely to require revascularisation compared to PCI (12% v 41%, p<0.001, Figure 1b). The occurrence of MACE was reported in 3 studies. CABG was associated with less events compared to PCI (16% v 57%, p<0.001, Figure 1c). Similarly, MI alone occurred less often with CABG than PCI (5% v 11%, p=0.003, Figure 1d). There existed a selection bias with PCI preferred to CABG in single vessel disease and CABG for multivessel or left main disease.

Conclusions: The results demonstrate better early mortality in patients with ESRD undergoing PCI, however the results favoured CABG for repeat revascularisation, MACE and MI. CABG was only marginally beneficial for late mortality.

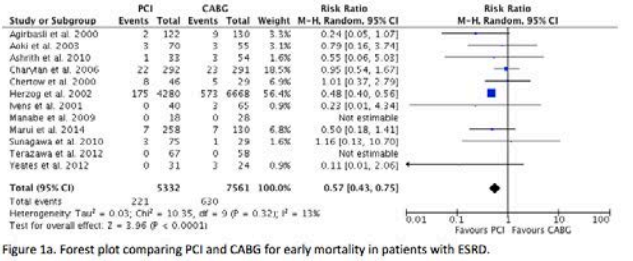


Figure 1a. Forest plot comparing PCI and CABG for early mortality in patients with ESRD.

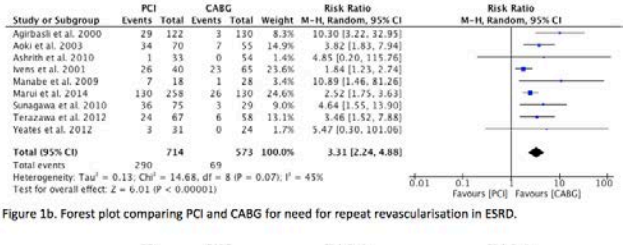


Figure 1b. Forest plot comparing PCI and CABG for need for repeat revascularisation in ESRD.

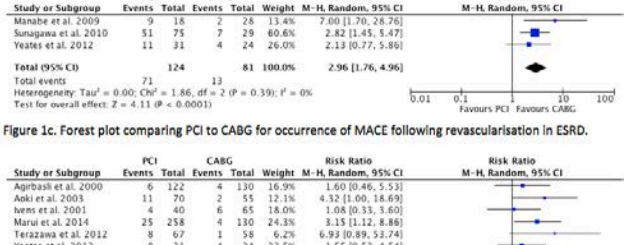


Figure 1c. Forest plot comparing PCI to CABG for occurrence of MACE following revascularisation in ESRD.

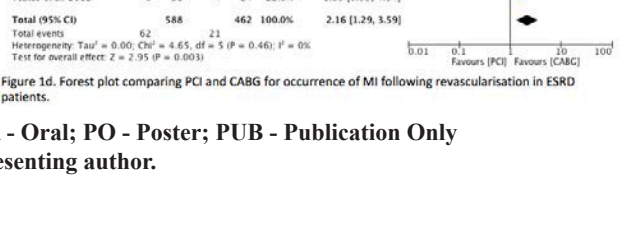


Figure 1d. Forest plot comparing PCI and CABG for occurrence of MI following revascularisation in ESRD patients.

FR-PO936

Use of Eliquis (Apixaban) in Atrial Fibrillation Patients Undergoing Hemodialysis Bobby Rajesh Malik, Anjali Om, Prabal K. Guha. *Cardiology, McLeod Regional Medical Center, Florence, SC.*

Background: Hemodialysis (HD) patients with multiple other cardiovascular (CV) risk factors are at high risk for development of atrial fibrillation (AFib). Most of these patients have high CHA2D2-VASc scores requiring anticoagulation treatment. For almost fifty years, warfarin has been the gold standard treatment, but with significant limitations, especially in its interaction with antibiotics that HD patients often require. In the last few years, non vitamin K oral anticoagulation (NOAC) has emerged as a new class of drug for reducing thromboembolic complications in these patients. However, out of 4 NOACs, only apixaban is approved for use in HD patients based solely on its pharmacokinetic data.

Methods: Medical records of 65 patients on HD with history of AFib treated with apixaban were retrospectively reviewed for any thromboembolic events and any bleeding. Average follow up was 150 days with minimum follow up being 30 days.

Results: There were 65 patients (47% male) age 43 to 85 with an average age of 68. There were no clinical thromboembolic events noted. Only one patient had epistaxis that was self-limiting, not requiring hospitalization or transfusion.

Conclusions: In this small retrospective study, apixaban was found to be well tolerated and effective with no significant bleeding complications. If supported in larger studies, apixaban could be an alternative in HD patients with a history of AFib.

FR-PO937

Utilization of Statin Medications in U.S. Veterans Receiving Maintenance Dialysis Arouna Senthilkumar, Talar Markossian, Nicholas Burge, Benjamin Ling, Kevin Stroupe, Vinod K. Bansal, David J. Leehey, Holly J. Kramer, Julia Schneider. *Hines VA Hospital, Hines, IL.*

Background: The Kidney Disease Improving Global Outcomes (KDIGO) guidelines do not recommend stopping statin medications when patients initiate dialysis. Guidelines state that statins should not be initiated for dialysis patients as large trials did not demonstrate mortality or cardiovascular benefits in dialysis population. The objective of this study was to examine current statin use and both initiation and discontinuation of statin medications in U.S. veterans receiving maintenance dialysis.

Methods: Retrospective analysis of U.S. Department of Veterans Affairs Healthcare System (VA) national databases to determine statin use in dialysis. Medications acquired with the VA system were obtained from the Managerial Cost Accounting National Data Extracts. Medications acquired outside the VA were obtained from the Corporate Data Warehouse (CDW). Statin medication use was ascertained from pharmacy dispensing records during years 2012 and 2013. The dialysis patients were identified using the CPT, ICD-9, and VA dialysis procedure codes at VA outpatient centers.

Results: A total of 17,883 veterans dialysis patients were evaluated. 97% were male, 55% aged ≥60-75 years and 18% aged ≥ 75 years; 38% were African-American. Diabetes and coronary artery disease were present in 59% and 32.3%, respectively. During fiscal year 2012, 63.3% of patients were using statins, and 57.7% were using statins in 2013. Of the 17,883 patients, 53.0% used statins continuously and 10.3% discontinued statin use during year 2013. Statin initiation was noted in 4.7% during 2013.

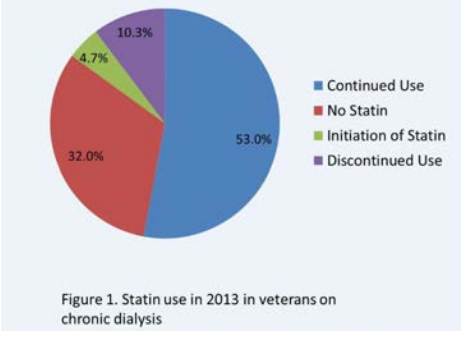


Figure 1. Statin use in 2013 in veterans on chronic dialysis

Conclusions: A large proportion of U.S. veterans on hemodialysis use statin medications. Very few discontinue statins and even fewer initiate them. Future studies should determine patient need for statin medication in dialysis patients considering large pill burden and financial costs.

Funding: VA Support

FR-PO938

Facility Use of Low Dialysate Temperature for Prevention of Intra-Dialytic Hypotension Is Associated with Lower Cardiovascular Mortality in the DOPPS Indranil Dasgupta,[1] G. Neil Thomas,[2] Joanne L. Clarke,[2] Alice Sitch,[2] Angelo Karaboyas,[3] Brian Bieber,[3] Manfred Hecking,[4] Bruce M. Robinson,[3] Hugh C. Rayner.[1] *[1]Heartlands Hospital, United Kingdom; [2]Univ of Birmingham, United Kingdom; [3]Arbor Research; [4]Medical Univ of Vienna, Austria.*

Background: Intra-dialytic hypotension (IDH) occurs during 20-30% of haemodialysis (HD) sessions and is associated with cardiovascular (CV) mortality and events. Aim was to investigate associations between HD facility practices related to the management of fluid volume and hypotension and adverse events.

Methods: Data on 8807 patients from 232 HD facilities across 12 countries in DOPPS phase 4 (2009-12) were analysed. Multi-level survival models assuming a Weibull distribution (allowing for clustering of data within facilities) were used to estimate associations between facility practices reported by MDs and patient all-cause and CV mortality, CV events and hospitalizations, adjusted for country**,** age, gender, vintage, pre-dialysis systolic BP, CV comorbidities, diabetes (model 1) plus BMI, smoking, residual renal function, Kt/V, vascular access (model 2). We tested 10 practices: (1) protocol for fluid volume management, (2) routine orthostatic BP measurement, (3) blood volume monitor (BVM), (4) bio-impedance device (BID), (5) BVM and BID, (6) limit to fluid removal, (7) isolated ultrafiltration and use of (8) a protocol, (9) routine sodium profiling and (10) low dialysate temperature for managing IDH.

Results: Among the 10 HD facility practices studied, routine use of low temperature dialysate for patients prone to intradialytic hypotension (47% of facilities vs. infrequent or no use) was associated with lower CV deaths in both models.

Low dialysate temperature for managing IDH	Model 1 Hazard ratio (99% CIs)	Model 2 Hazard ratio (99% CIs)
Hospitalization	1.02 (0.87-1.20)	1.02 (0.84-1.23)
All cause deaths	0.82 (0.65-1.02)	0.91 (0.67-1.22)
CV events	0.80 (0.64-0.99)	0.86 (0.67-1.10)
CV deaths	0.56 (0.39-0.79)	0.55 (0.35-0.85)

Conclusions: The HD facility practice of routinely using low dialysate temperature to limit or prevent IDH is associated with lower CV mortality. This merits further investigation in a randomised trial.

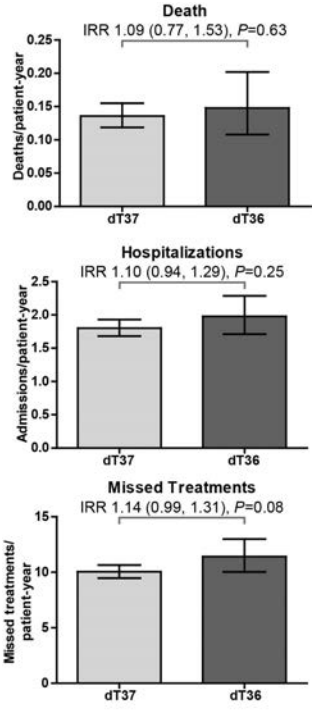
FR-PO939

Standardized Dialysate Temperature of 36 Degrees Celsius: Association with Clinical Outcomes Kathryn S. Gray, Dena E. Cohen, Steven M. Brunelli. *DaVita Clinical Research, Minneapolis, MN.*

Background: Hemodynamic insults may contribute to poor outcomes among hemodialysis (HD) patients. Individualized dialysate cooling based upon patient body temperature can improve intermediary outcomes but is difficult to operationalize. Here, we sought to test whether a standardized dialysate temperature of 36°C (dT36), which is easier to enact, might be a viable strategy to improve clinical outcomes.

Methods: Because patients with known hemodynamic instability may be selectively prescribed dT36, we minimized selection bias by considering incident adult in-center HD patients who (between Jan 2011-Dec 2013) received their first-ever HD treatment at a large dialysis organization and based exposure status on the order for this first-ever treatment (so that knowledge of intradialytic hemodynamics could not have factored into clinical decision-making). dT36 patients were propensity-score matched (1:5) to controls prescribed a temperature of 37°C (dT37). Outcomes (death, hospitalization, missed HD treatments) were considered from the date of first-ever HD treatment until death, loss to follow-up, crossover (month in which prescribed temperature was consistent with exposure group for <80% of treatments), or study end (Jun 2015).

Results: 313 dT36 patients were matched to 1565 dT37 controls; groups were balanced on all matched covariates at baseline. During follow-up, rates of death, hospitalization, and missed HD treatments were not significantly different between groups; nominal risk of each outcome was greater (IRR>1) for dT36 patients.



Conclusions: These data fail to demonstrate benefit of dT36 versus dT37; our results do not favor conversion to a default dialysate temperature of 36°C. These data do not pertain to other standardized or individualized cooled dialysate temperatures; further study of the latter should be advanced over study of standardized 36°C dialysate.

Funding: Pharmaceutical Company Support - DaVita, Inc

FR-PO940

Effect of Spironolactone on Heart Rate Variability in Hemodialysis - A Randomized Crossover Study

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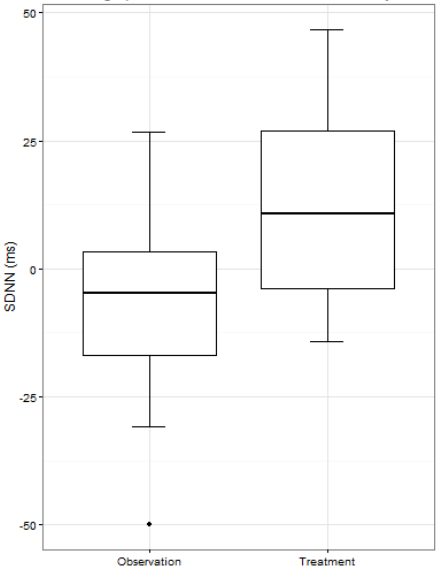
Background: Cardiac autonomic function is decreased and the risk of sudden cardiac death (SCD) is increased in hemodialysis (HD) patients. Spironolactone reduces the risk of SCD in congestive heart failure (CHF) and is associated with improvement of cardiac autonomic function as measured by heart rate variability (HRV). The effect of spironolactone on HRV in HD has rarely been studied and with varying results. This study measured HRV in HD patients treated with spironolactone.

Methods: This was a two center, open, randomized crossover study. Primary endpoint was the frequency of premature ventricular contractions (PVC) and this sub-study represents a secondary hypothesis. Subjects on HD (n = 30) were randomly allocated into two arms with either treatment with spironolactone 50 mg daily or observation for twelve weeks, then a six week wash-out period followed by cross-over for twelve weeks. HRV (time domain and frequency domain analysis) was measured by ambulatory 24-hour Holter electrocardiogram (LTECG). Differences in change of HRV parameters during the two periods were analyzed using confidence intervals (CI).

Results: Complete LTECG data could be analyzed for 16 participants, due to drop outs. The difference of differences (dod) for SDNN (the change during treatment with spironolactone minus the change during the observation period) was 20.98 ms (CI 3.21-38.74). The dod for SDANN was 19.14 (CI 0.78-37.49). Other HRV variables did not change significantly.

Fig 1: Change in heart rate variability during spironolactone treatment in hemodialysis



Conclusions: HRV was reduced and spironolactone treatment in HD patients increased time-domain HRV variables SDNN and SDANN, indicating a possible improvement in cardiac autonomic function. This may have an impact on SCD and mortality which needs to be studied in a larger randomized study.

FR-PO941

Utilization Pattern and Clinical Outcomes of Mineralocorticoid Receptor Blockers in U.S. Dialysis Patients: A National Registry Study

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Background: Mineralocorticoid receptor blockers (MRB) are important therapies for resistant hypertension and for congestive heart failure (CHF). These are common problems in ESRD patients treated with hemo- or peritoneal dialysis (HD-PD), yet MRB use is limited in HD-PD patients. The current study sought to determine the utilization pattern and clinical outcomes of MRB use in HD-PD treated patients.

Methods: We conducted a retrospective cohort study with new user design using United States Renal Data System data and Medicare Part D claims data. The study cohort was adult patients initiating HD-PD between 7/1/2006-12/31/2011. MRB use was defined as filling more than one consecutive MRB prescription following HD-PD initiation. We compared outcomes to patients either with filled prescriptions for ACE-I/ARB alone or with both MRB and ACE-I/ARB. Subjects were followed until first occurrence of each endpoint: hyperkalemia (ICD-9 276.7), all-cause mortality, composite cardiovascular disease (CVD, ICD 410, 430, 431, 433.x1, 434.x1, and 436) mortality or CVD hospitalization.

Results: 516 patients used MRB alone, 183 used MRB+ACE-I/ARB, and 26,974 used ACE-I/ARB alone. Baseline differences included race (AA: 16%, 21%, 29%; P<.001), female sex (37%, 46%, 51%; P<.001), and history of CAD (65%, 70%, 57%; P<.001), CHF (45%, 41%, 36%; P<.001), diabetes mellitus (46%, 57%, 59%; P<.001), hypertension (83%, 93%, and 89%; P<.001), and hyperkalemia prior to dialysis (20%, 21%, 29%; P<.001). Multivariate Cox proportional hazard analyses showed MRB use alone was associated with reduced risk of hyperkalemia (aHR (adjusted hazard ratio): 0.68; 95%CI: 0.59-0.80; P<.0001), all-cause death (aHR: 0.79; CI: 0.70-0.90; P<.001), and composite CVD death and events (aHR: 0.72; CI: 0.65-0.80; P<0.001) as compared to ACE-I/ARB use.

Conclusions: MRB use alone was associated with decreased risk of hyperkalemia, CVD composite outcome, and all-cause mortality as compared to ACE-I/ARB use alone. These findings suggest MRB use may have substantial clinical benefits in ESRD HD-PD patients.

Funding: NIDDK Support, VA Support

FR-PO942

The Use of Beta-Blockers in Hemodialysis Patients: A Systematic Review and Meta-Analysis

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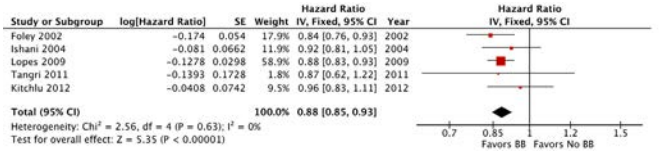
Background: Beta-blockers reduce mortality in patients with heart failure and after myocardial infarction. However, dialysis patients have been excluded from all large randomized trials of beta-blockers. Limited evidence of their efficacy and safety has led to inconsistent use in this population. We conducted a systematic review and meta-analysis on the use of beta-blockers in hemodialysis patients to analyze the existing evidence and inform and encourage future research.

Methods: A medical librarian designed a search strategy. We included studies of hemodialysis patients comparing those on beta-blockers vs. placebo or active control. Randomized controlled trials of any size, prospective cohort studies with at least 100 patients, and retrospective studies with at least 500 patients were included. All cause mortality was the primary outcome and a meta-analysis was pre-specified for this outcome.

Results: Of 465 articles screened, 16 met inclusion criteria and two were randomized trials, both small with intermediate outcomes and considerable opportunity for bias. One showed a significant mortality benefit in dialysis patients with ejection fraction <35% on carvedilol compared to placebo. Of the 14 observational trials, seven reported all cause mortality and five were included in the meta-analysis; hemodialysis patients on beta-blockers had lower mortality (HR 0.88, 95% CI 0.85-0.93, I^2=0%).



Conclusions: Evidence supporting the use of beta-blockers in hemodialysis patients is limited and randomized control trial data is particularly sparse. Existing evidence suggests a significant mortality benefit with carvedilol in those with reduced ejection fraction and possibly a modest benefit with beta-blockers in the general population of hemodialysis patients.

FR-PO943

Effect of Carvedilol on B-Type Natriuretic Peptide and High-Sensitivity Cardiac Troponin I in Dialysis Patients

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Background: Beta-blocker therapy may modify left ventricular (LV) stress [measured by B-type natriuretic peptide (BNP)] and myocardial damage [measured by high-sensitivity cardiac troponin I (hs-TnI)]. We aimed to demonstrate the effects of the beta-blocker carvedilol on BNP and hs-TnI in adult dialysis patients.

Methods: Patients were randomized to carvedilol or placebo. BNP and hs-TnI (Abbott assays) were measured from samples collected at baseline (T0) and 12 months (T12). Change in biomarker levels was analyzed using ANCOVA adjusted for baseline values. Associations between T0 echo measures and biomarkers were assessed by Pearson's correlation coefficient.

Results: At T0, median (IQR) LV global strain was -14.27 (-11.93 to -22.07) and LV ejection fraction 61.0% (56.5 to 65.0). BNP was associated with LV global strain (r=0.30, p=0.04) and LV ejection fraction (r=-0.28, p=0.04). 16/26 and 18/23 participants randomized to carvedilol and placebo, respectively, had serum and plasma samples at T12. Change in BNP and hs-TnI was similar for the two groups (Table).

	Carvedilol	Placebo	P
BNP T0 (ng/L)	94 (50-154)	70 (25-208)	
BNP T12 (ng/L)	168 (101-314)	168 (86-275)	
BNP Change	+76 (+8 to +228)	+44 (-20 to +129)	0.64
hs-TnI T0 (ng/L)	11.2 (7.8-19.7)	20.1 (9.0-31.6)	
hs-TnI T12 (ng/L)	10.3 (6.3-13.6)	16.3 (7.8-36.8)	
hs-TnI Change	-0.5 (-2.7 to +1.9)	-0.6 (-6.8 to +7.9)	0.39

Conclusions: BNP was positively associated with global longitudinal strain and inversely associated with ejection fraction. Carvedilol therapy did not improve levels of biomarkers of LV stress or myocardial damage after 12 months of therapy. Sample size was a limitation.

Funding: Government Support - Non-U.S.

FR-PO944

Higher End-Stage Renal Disease (ESRD) Star Ratings Are Associated with Lower Mortality, Hospitalization, and Readmission Ratios

Andrea C. Besharat, Stephen A. Valderrama, Mahesh Krishnan, Allen R. Nissenson, Steven M. Brunelli. *DaVita Inc, Denver, CO.*

Background: The Centers for Medicare & Medicaid Services (CMS) Star rating system for ESRD was introduced in January 2015 to inform patient choice by creating transparency with respect to dialysis facility performance. Facilities are assigned a Star rating on a forced bell curve (1-5) based on 9 quality metrics that include standardized hospitalization and mortality ratios (SHR and SMR). We sought to assess whether facilities with higher Star ratings had lower SHR, SMR, and standardized readmission ratio (SRR; proposed for inclusion in future Star ratings), and whether change in current Star rating was associated with commensurate change in these metrics.

Methods: Data for calendar years 2013 and 2014 were derived from the CMS Dialysis Facility Compare website. Facilities with Star ratings and SHR (N=4896), SMR (N=4842), and SRR (N=4852) reported for both years were considered. Associations of Star rating in each year and change in rating from 2013 to 2014 with SHR, SMR, and SRR were assessed using generalized linear models.

Results: Mean SHR was 1.00 and SRR was 0.99 for both years, SMR was 1.031 and 1.026 (*P*-difference=0.02) for 2013 and 2014, respectively. In each year, higher Star rating was associated with lower SHR, SMR, and SRR (*P*-trend<0.001 for each; figure shows SHR). There were dose-dependent associations of change in Star rating from 2013 to 2014 with changes in SHR, SMR, and SRR (figure shows SHR).

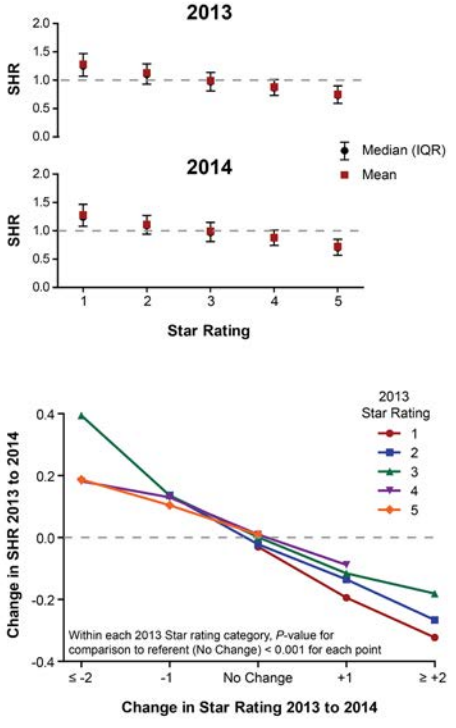

Figure. Association between Star Rating and SHR:
(top) 2013 and 2014 Star Rating each with contemporaneous SHR
(bottom) change in Star Rating from 2013 to 2014 with change in SHR from 2013-2014

Conclusions: Facilities with higher Star ratings perform better in key clinical outcomes SHR, SMR, and SRR than those with lower ratings. Moreover, year-over-year Star rating improvement is associated with like improvements in these metrics. Our study confirms that Star ratings reflect care quality and improvements in quality—as indicated by SHR, SMR, and SRR—and can be used by patients to inform dialysis care choices.

Funding: Pharmaceutical Company Support - DaVita Inc.

FR-PO945

Comparing Original and Updated Dialysis Facility Compare (DFC) Star Ratings

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Background: Starting January 2015, CMS implemented star ratings for dialysis facilities using quality measures reported on DFC. CMS revised the methodology based on technical expert panel and stakeholder feedback. The changes focus on measure scoring techniques and use of a baseline year. This study compares star ratings given by the original and updated methodologies.

Methods: The original methodology calculates facility scores and assigns facilities 1-5 stars (10%, 20%, 40%, 20%, 10%). The updated methodology sets measure and rating category thresholds using a baseline year and applies these to a current year. The original methodology applied to year 2014 is compared to the updated methodology with 2013 as the baseline year and 2014 as the current year. Both methods use DFC measures currently included in the star rating.

Results: The updated methodology results in 5% more facilities in each 4 and 5 star category and a decrease in facilities with 1 and 2-stars as compared to the original methodology. The different measure scoring methods are consistent as indicated by the high correlation (.90) of the final scores.

Original Method	Updated Method					
Cell=Facility N	1	2	3	4	5	Total(%)
1	369	218	0	0	0	587 10%
2	6	677	491	0	0	1174 20%
3	0	12	1719	619	0	2350 40%
4	0	0	23	850	301	1174 20%
5	0	0	0	10	577	587 10%
Total	375 6%	907 15%	2233 38%	1479 25%	878 15%	5872 100%

Conclusions: Scoring against a baseline year lets consumers directly observe each facility's longitudinal improvement since scoring criteria remain fixed over a period of time, while the original method rates facilities relative to each other in the same year. There are tradeoffs with each method. The original method does not permit tracking improvement over time while the updated method using a baseline may allow more facilities to be rated 4 and 5 stars but could obscure meaningful differences between facilities. The new methodology is responsive to the TEP recommendations.

Funding: Other U.S. Government Support

FR-PO946

Evaluation of Missing Data Methods for Prevalent-Comorbidity-Adjusted Standardized Mortality Ratio

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Background: The standardized mortality ratio (SMR) for dialysis facilities is adjusted for prevalent comorbidities from prior year Medicare claims. In year 2013, 43% dialysis pts had <12 month of claims in 2012, 16% had 0, and 27% had 1-11 months, possibly yielding missing comorbidities. The current method includes all pts, but only adjusts for comorbidities for pts with ≥6 month of claims in prior year. The new method imputes comorbidities for pts with missing data.

Methods: We use the 57% pts in 2013 with 12 month of claims in 2012 as "full data", and randomly generate missing months to yield 100 analytic datasets mimicking the distribution of months with claims. We use logistic regression to impute the probability of comorbidity in pts with missing claims and no observed comorbidity in prior year. We calculated 3 versions of SMR using a facility-stratified Cox model adjusted for age, race, ethnicity, sex, DM, yrs of ESRD, nursing home status, BMI, and incident and prevalent comorbidities. 1)Gold standard uses "full data". 2)Current method applies 6-month cutoff to analytic datasets. 3)Imputation method uses analytic datasets with imputed comorbidities. SMR and facility classifications (better than, worse than or as expected based on DFC method) from methods 2 & 3 are compared to those from gold standard.

Results: Analyses of the 100 analytic datasets show that both methods are reasonably precise, but imputation is slightly better. The correlation of gold standard SMRs with imputation SMRs is improved from .957 (±.001) to .964 (±.001), and the MSE is improved from .017 (±.0004) to .014 (±.0004). Compared to the gold standard, 2.7% of facilities were classified differently in current method compared to 2.44% in imputation method, a 10% reduction.

Conclusions: The current method provides reasonably precise comorbidity-adjusted SMR. The precision can be improved slightly by imputation with a minimal increment of computing cost.

FR-PO947

Achievement of Quality Indicator Targets and Survival of Incident Hemodialysis Patients in Iceland Thordur P. Palsson,[1] Olafur S. Indridason,[2] Runolfur Palsson,[1,2] Helga K. Mogensen.[2] *[1]Univ of Iceland; [2]Landspitali - the National Univ Hospital of Iceland, Reykajvik, Iceland.*

Background: The use of clinical practice guidelines and treatment targets in the care of dialysis patients has been emphasized over the past decade. The aim of this study was to investigate the quality of hemodialysis (HD) care at the University Hospital in Reykjavik with respect to common quality indicators (QI) and to assess patient survival in relation to these QI.

Methods: This was a retrospective study of all incident HD patients in Iceland during 2003-2014, who received treatment for at least 3 months. Data was obtained from medical records. The QI included hemoglobin (target range, 100-120 g/L), iron saturation (>20%), URR (>65%), calcium (2.2-2.6 mmol/L), phosphate (0.85-1.78 mmol/L), PTH (130-585 pg/mL), CO_2 (>21 mmol/L) and albumin (>35 g/L), and the mean value of each QI for each patient was employed. Patients were assigned to 3 groups depending on how many QI targets they achieved; 1-3, 4-5 or 6-8. Kaplan-Meier plots were used to assess survival and groups were compared using the log-rank test. Cox regression was used to assess independent association of variables with survival.

Results: A total of 160 patients were included in the study, of whom 101 were males (63%). The median age at onset of HD was 68 (17-92) years. Sixteen patients (10.1%) achieved 1-3 QI targets, 56 (35.2%) achieved 4-5 targets and 87 (54.7%) achieved 6-8 targets. There was no significant difference in age or sex distribution between the three groups. Patient survival was significantly better when a greater number of QI targets was achieved ($p<0.001$) and this difference remained significant in multivariable analysis and if albumin was used as covariate rather than as a QI. One- and 3-year survival of patients achieving 1-3, 4-5 and 6-8 QI targets was 58.0% (95% CI, 35.2-95.7) and 34.8% (14.5-83.4), 84.3% (74.8-94.9) and 47.5% (34.0-66.3%), and 96.1% (91.8-100.0) and 78.5% (68.7-89.8), respectively.

Conclusions: A survival advantage is associated with a greater number of treatment goals achieved in HD patients. Thus, greater emphasis should be placed on achievement of treatment targets for established QI in HD care.

Funding: Government Support - Non-U.S.

FR-PO948

Attaining the Standards Proposed in Guidelines - Results from EURODOPPS Sophie Liabeuf,[1] Karlijn J. Van Stralen,[2] Fergus J. Caskey,[3] Francesca Tentori,[4] Ronald L. Pisoni,[4] Ayesha Sajjad,[2] Kitty J. Jager,[2] Ziad Massy.[5] *[1]INSERM U1088, CRC, Amiens Hospital Univ, Amiens, France; [2]ERA EDTA Registry, Amsterdam Medical Center, Amsterdam, Netherlands; [3]UK Renal Registry, Southmead Hospital, Bristol, United Kingdom; [4]Arbor Research Collaborative for Health, Ann Arbor; [5]INSERM U 1018 and Div of Nephrology, Univ of Versailles Saint Quentin en Yvelines, Boulogne Billancourt, France.*

Background: In the field of chronic kidney disease (CKD), global clinical practice guidelines have been developed and implemented with a view to improving patient care and outcomes. We sought to measure and compare the extent to which various European countries have adopted and attained the targets set in international guidelines, with a focus on factors that can be modulated by pharmacological agents.

Methods: The EURODOPPS study is the European part of an international, prospective study of a cohort of adult, in-centre, haemodialyzed patients. For the current project, 6317 patients from seven European countries were included between 2009 and 2011. The mean follow-up period was 1.5 years. Data on laboratory test results and medication prescriptions were extracted from patient records, in order to determine the overall percentage of patients treated according to the international guidelines on anaemia, dyslipidaemia, metabolic acidosis and mineral bone disease (MBD).

Results: Attainment of the targets set in international guidelines was far from complete; only 34.1% of the patients attained their target blood pressure, and 31.2% attained their target haemoglobin level. Overall, only 3% of the patients attained all the relevant targets set in the guidelines. Levels of guideline uptake/application and the use of pharmacological agents varied from one European country to another.

Conclusions: The results of this first ever large-scale, European study of attainment of targets and drug prescription in haemodialyzed patients highlighted the low overall levels of target attainment and emphasized the marked disparities between European countries in this respect.

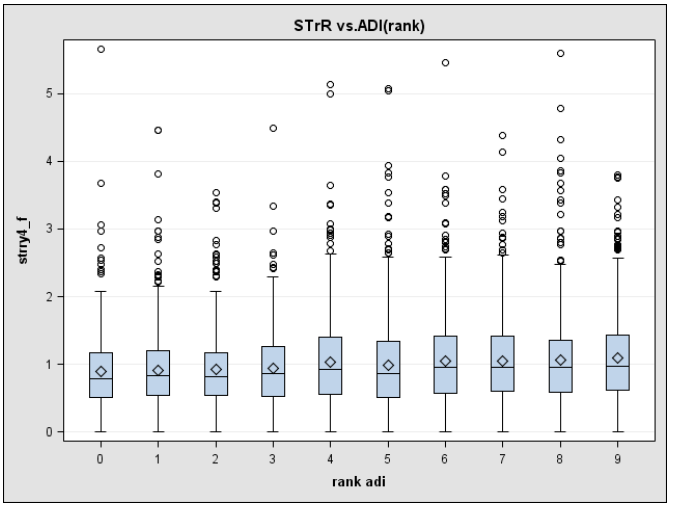
FR-PO949

Transfusion Practices by Area-Level Socioeconomic Deprivation C. Dahlerus, Shu Chen, Douglas E. Schaubel, Bin Nan, Jennifer Sardone, J. M. Messana. *Univ of Michigan Kidney Epidemiology and Cost Center.*

Background: The standardized transfusion ratio (STrR) is reported by CMS on Dialysis Facility Compare and will be implemented in the ESRD Quality Incentive Program. Stakeholders raised concerns that the STrR unfairly characterizes facility performance because of geographic variation, possibly related to area socioeconomic status (SES). This concern is buttressed by studies reporting geographic differences in SES influence many other health outcomes. In another abstract, we describe a revised, more conservative definition for defining transfusion events in STrR that results in reduced variation due to geographic-based differences. This abstract assesses the contribution of SES to the remaining geographic variation.

Methods: 2014 Medicare claims data are used to calculate STrR across SES deciles. SES is measured by deciles of mean zipcode-level Area Deprivation Index (ADI) scores with 2000 Census data from HIPxChange.org. We plotted mean STrR by deciles of ADI indicating least to most deprived areas.

Results: As reported in the companion abstract, mean STrR based on the new transfusion definition still shows some variation by geographic region. In contrast, differences in STrR across deciles of area deprivation vary in a non-monotonic pattern. Interquartile range values overlap substantially between deciles of lower vs higher deprivation scores (figure). Extreme values of STrR were observed in both the lowest and highest SES deciles.



Conclusions: We observed overall minimal differences in STrR by levels of area deprivation suggesting SES does not directly impact transfusions or drive regional differences in outcomes. Extreme values of transfusions in the lowest/highest categories of deprivation suggest SES works in concert with other characteristics that determine health care access along with provider practices that impact outcomes.

Funding: Other U.S. Government Support

FR-PO950

Effects of Patient Sociodemographics (SDS) versus Comorbidities on Hospitalization and Mortality C. Dahlerus, John Wheeler, Tempie H. Shearon, Yang Jiao, John Stephen, Deanna Chyn, Minling Zhang, Yifan Wu, Jennifer Sardone, J. M. Messana. *Univ of Michigan Kidney Epidemiology and Cost Center.*

Background: Risk factor adjustment for hospitalization and mortality outcomes can increase measure validity. Public reporting of outcomes measures has raised interest in adjusting for SDS. Studies observe black and Hispanic ESRD patients typically have lower hospitalization and mortality while lower SDS is predictive of higher hospitalization and mortality. Prevalent comorbidities may attenuate the impact of SDS on outcomes. We examine the relationship of SDS to hospitalization and mortality w/ and w/o comorbidity adjustment.

Methods: 2014 Medicare claims data for readmission; 2011-14 for hospitalization and mortality. Analyses are limited to the Medicare population; prevalent comorbidities are claims based. We fit Cox models stratified by facilities. One set of models adjusts for patient clinical and demographic characteristics including age, sex, race, ethnicity and dual Medicare/Medicaid status. The second adds comorbidities. Analyses include main effects only for race and ethnicity. Hazard ratios (admission, mortality) and odds ratios (readmission) are calculated.

Results: Black patients had lower admissions, readmissions and mortality. The effect of black race decreased nominally when adjusting for comorbidities. Hispanic patients had lower likelihood of hospitalization, readmission, and mortality; all effects diminished w/ comorbidities. Dual status increased likelihood of all outcomes but the effects declined w/ comorbidities. Statistical significance and direction of covariates were consistent across models.

	Black	Hispanic	Dual
Admissions HR			
w/o comorb	0.92	0.87	1.13
w/comorb	0.94	0.93	1.08
Readmissions OR			
w/o comorb	0.94	0.88	1.11
w/comorb	1.00	0.94	1.04
Mortality HR			
w/o comorb	0.69	0.70	1.06
w/comorb	0.72	0.76	1.03

(all $p<0.01$).

Conclusions: The relationships among outcomes, SDS, and comorbidities are complex. Prevalent comorbidities may attenuate effects of SDS on outcomes. Caution is warranted in attributing outcomes directly to SDS when comorbidities may be a key driver.

Funding: Other U.S. Government Support

FR-PO951

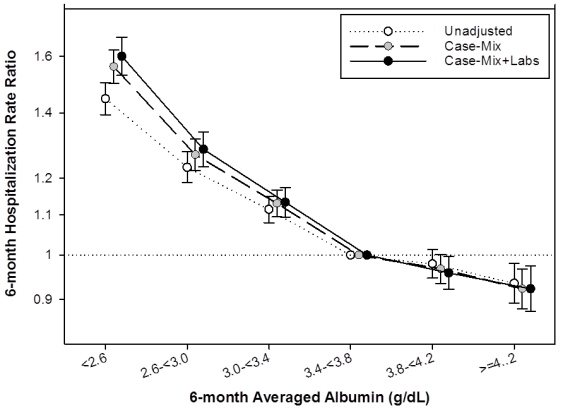
Low Albumin Levels prior to Transition to Dialysis and Early Dialysis Hospitalization among U.S. Veterans: A Transition of Care in CKD Study

Amanda R. Tortorici,[1] Elani Streja,[1] Melissa Soohoo,[1] Connie Rhee,[1] Rieko Eriguchi,[1] Yoshitsugu Obi,[1] Daniel L. Gillen,[1] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Univ of Tenn.*

Background: Previous studies have shown the importance of albumin (Alb) as a predictor for a number of adverse outcomes including mortality and hospitalization in chronic kidney disease patients. However, the impact of Alb levels prior to end-stage renal disease (ESRD) on post-ESRD hospitalization is not known.

Methods: In 85,505 US veterans who transitioned to dialysis between 10/2007 and 3/2014, we identified 30,781 patients with available Alb measurements within the last 6-month prelude period (prior to ESRD transition). We examined the association of Alb (averaged over 6 months) as a categorical predictor of hospitalization within the first 6 months post transition, using Poisson models adjusted for demographics, comorbidities and 6-month prelude averaged laboratory covariates.

Results: The mean±SD age of the cohort was 68±11 years, among whom 30% were African-American, 8% were Hispanic, and 48% had diabetes listed as their primary cause of ESRD. The mean±SD Alb in the 6 months prior to transition was 3.4±0.6 g/dL. We observed a linear association between pre-ESRD Alb and 6-month post-ESRD hospitalization rate [Figure]. Patients with Alb levels < 3.4 g/dL demonstrated higher rate of post-ESRD hospitalization compared to the referent group (Alb 3.4-<3.8 g/dL), whereas patients with Alb levels ≥4.2 g/dL experienced a lower rate.



Conclusions: Among veterans transitioning to dialysis, higher Alb levels are associated with lower rate of early post-ESRD hospitalization. Additional studies are needed to examine if nutritional interventions in the predialysis period can lower post-ESRD hospitalization incidence.

Funding: NIDDK Support

FR-PO952

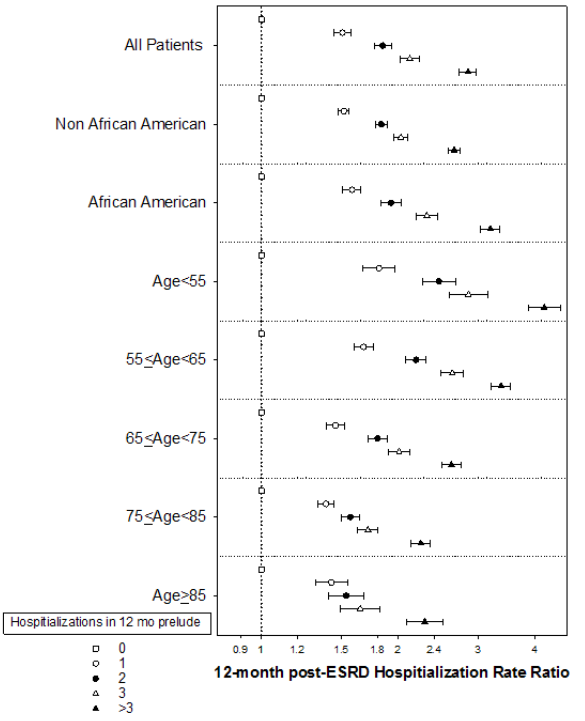
Disparities in Age and the Association of Number of Hospitalizations Pre-ESRD and after Dialysis Transition among U.S. Veterans: A Transition of Care in CKD Study

Melissa Soohoo,[1] Elani Streja,[1] Alpesh Amin,[1] Anna Mathew,[2] Danh V. Nguyen,[1] Csaba P. Kovesdy,[3] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Northwell Health; [3]Univ of Tenn.*

Background: A previous study showed that younger African American(AfAm) dialysis patients are more frequently hospitalized during the first year of end-stage renal disease(ESRD), compared to older whites. It is unknown if more frequent hospitalizations within the last year pre-transition to ESRD is associated with hospitalization frequency within the first year post-transition. We seek to examine the impact of age and race on the relationship of pre and post ESRD hospitalization frequency.

Methods: In 85,505 US veterans who transitioned to ESRD between 10/2007 and 3/2014, we identified 41,241 patients who utilized VA or CMS resources during the last 12 months prior to ESRD and remained on dialysis for at least 1 year. We examined the association of the number of hospitalizations within the 12 month prelude period as a predictor of the number of hospitalizations in the first 12 months post transition, using Poisson models adjusted for demographics and comorbidities. Models were also stratified by incidence age and race.

Results: The cohort was 71±11(mean±SD) years and 23% were African American. Across all strata of age and race, we observed a direct relationship of hospitalization frequency pre and post-ESRD. However, the relationship between pre- and post-ESRD hospitalizations were stronger in AfAm patients (p-for-interaction<0.0001) and across in increasing age strata (p-for-trend<0.0001).



Conclusions: Patients who experience at least 1 hospitalization pre-ESRD have a higher risk of hospitalization post-transition. This association is more pronounced among younger patients who were hospitalized multiple times. Further studies are needed to understand the reasons why age and race exacerbate the impact of pre-ESRD hospitalizations on post-transition hospitalizations.

Funding: NIDDK Support

FR-PO953

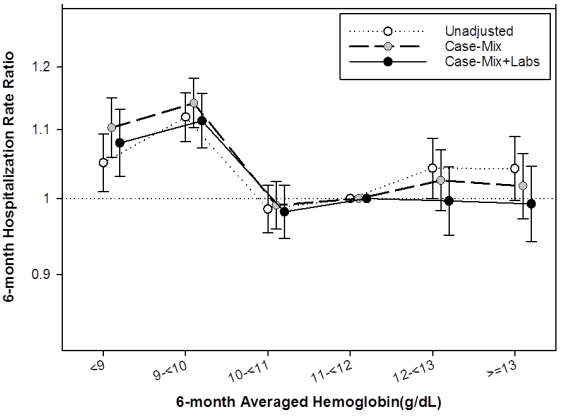
Hemoglobin Levels prior to Transition to Dialysis and Early Dialysis Hospitalization among U.S. Veterans: A Transition of Care in CKD Study

Melissa Soohoo,[1] Elani Streja,[1] John J. Sim,[2] Connie Rhee,[1] Danh V. Nguyen,[1] Csaba P. Kovesdy,[3] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Kaiser Permanente SC; [3]Univ of Tenn.*

Background: Patients with advanced chronic kidney disease (CKD) are often afflicted with anemia. Previous studies have found that both lower and higher hemoglobin (Hgb) levels were associated with worse outcomes in dialysis and non-dialysis dependent CKD patients. However, the association between Hgb levels in the immediate period preceding dialysis (prelude) and early post-dialysis hospitalization remains unknown.

Methods: In 85,505 US veterans who transitioned to dialysis between 10/2007 and 3/2014, we identified 31,303 patients with available Hgb measurements within the last 6 month prelude period (prior to transition). We examined the association of Hgb (averaged over 6 months) as a categorical predictor of hospitalization within the first 6 months post transition, using Poisson models adjusted for demographics, comorbidities and laboratory covariates.

Results: The mean±SD age of the cohort was 68±11 years, among whom 30% were African-American, 8% were Hispanic, and 48% had diabetes listed as their primary cause of end-stage renal disease (ESRD). The mean±SD Hgb for the cohort was 10.7±1.6 g/dL. Across all levels of adjustment, patients with Hgb ≤10 g/dL demonstrated a higher rate of hospitalization post transition to ESRD compared to the referent group (Hgb 11-<12 g/dL).



Conclusions: Among patients transitioning to dialysis, lower pre-ESRD Hgb levels were associated with a higher rate of early post-transition to ESRD hospitalization. Clinical trials to examine the impact of anemia management during prelude on post-ESRD outcomes are indicated.

Funding: NIDDK Support

FR-PO954

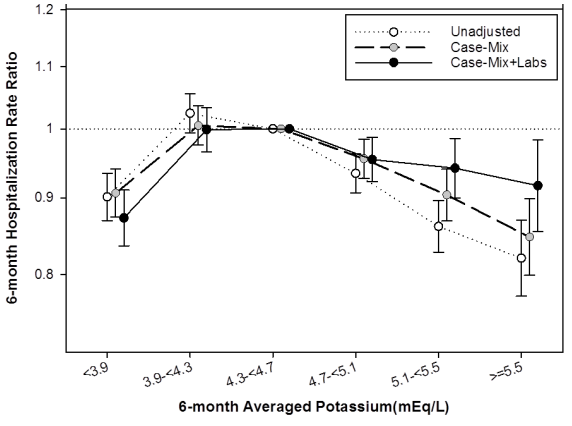
Association of 6-Month Pre-ESRD Potassium with Immediate Post-Dialysis Hospitalization among U.S. Veterans: A Transition of Care in CKD Study

Melissa Soohoo,[1] Elani Streja,[1] Connie Rhee,[1] Alpesh Amin,[1] Danh V. Nguyen,[1] Miklos Zsolt Molnar,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Univ of Tenn.*

Background: Recent studies have shown that both high and low potassium (K) were associated with higher rates of hospitalization in non-dialysis dependent chronic kidney disease (CKD) patients. However, the impact of potassium measured in the immediate period prior to dialysis (prelude) and hospitalization post transition remains understudied.

Methods: Among 85,505 US veterans who transitioned to dialysis between 10/2007 and 3/2014, we identified 33,499 patients with available K measurements within the last 6-month prelude period (prior to transition). We examined the association of K (averaged over 6 months) as a categorical predictor of hospitalization within the first 6 months post transition to end-stage renal disease (ESRD), using Poisson models adjusted for demographics, comorbidities and laboratory covariates.

Results: The cohort was (mean±SD) 68±11 years old, and included 29% African-Americans, 7% Hispanics, and 48% had diabetes listed as their primary cause of ESRD. The mean±SD K of the cohort prior to transition was 4.5±0.6 mEq/L. Low serum K <3.9 mEq/L was associated with lower rate of hospitalization compared to the reference (K 4.3-<4.7 mEq/L). Furthermore, patients with higher K≥4.7 mEq/L were associated with a lower rate of hospitalization post transition to ESRD.



Conclusions: Among veterans transitioning to dialysis, both low (<3.9 mEq/L) and high (>4.7 mEq/L) K levels were associated with lower rate of early post-ESRD hospitalization. These results differ from the K-hospitalization association observed in patients with non-dialysis dependent CKD. Additional studies are needed to investigate the K-hospitalization relationship in this population.

Funding: NIDDK Support

FR-PO955

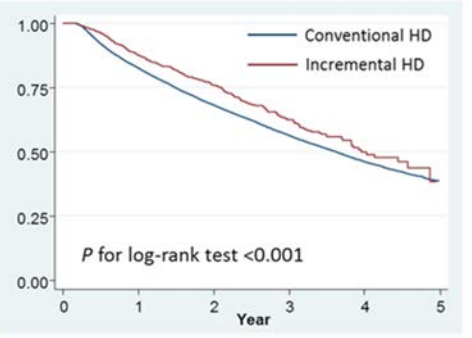
Twice Weekly Hemodialysis and Mortality in the United States

Anna Mathew,[1] Yoshitsugu Obi,[2] Connie Rhee,[2] Joline L.T. Chen,[3] Gaurang M. Shah,[2] Wei Ling Lau,[2] Csaba P. Kovesdy,[4] Rajnish Mehrotra,[5] Kamyar Kalantar-Zadeh.[2] *[1]Northwell Health; [2]UC Irvine; [3]VA Long Beach; [4]Univ of Tenn.; [5]Univ of Wash.*

Background: Most end stage renal disease patients in the United States are treated with a thrice-weekly hemodialysis(HD) regimen upon initiation of renal replacement therapy. Hemodialysis patients have the highest mortality during the first six months after HD initiation. Understanding the risk factors associated with the transition to HD is necessary to improve the outcomes of HD patients. We hypothesized that incremental transition to HD with a twice-weekly regimen does not compromise survival compared to a thrice-weekly schedule.

Methods: In a longitudinal national cohort of 1,124 incremental (twice-weekly) and 116,266 conventional (thrice-weekly) incident HD patients enrolled over five years (2007-2011), Cox regression analysis compared survival between these groups, with additional survival analyses after matching groups based on baseline and demographic parameters using coarsened exact matching methods.

Results: The matched cohort included 1,120 incremental and 54,633 conventional HD patients.In both the unmatched and cohort and matched cohorts, the incremental patients had a mean ± SD age of 70 ± 13 years, among whom 52% were male. The incremental group had lower mortality rates compared to the conventional group in both unmatched and matched cohorts, with case-mix adjusted HRs of 0.75 [95% CI, 0.66 to 0.86], and 0.76 [95% CI, 0.67 to 0.86], respectively. Data on residual kidney function was limited, and we were thus unable to incorporate this variable into our analysis.



Conclusions: Among incident HD patients, initiation with twice-weekly HD, non-inferior survival was observed with twice-weekly compared to thrice-weekly transition to HD. Randomized controlled trials are indicated to examine the effect of residual kidney function and dialysis treatment frequency on survival and other relevant outcomes.

Funding: NIDDK Support

FR-PO956

Gender Disparities in Hospitalization among Maintenance Hemodialysis Patients in the United States

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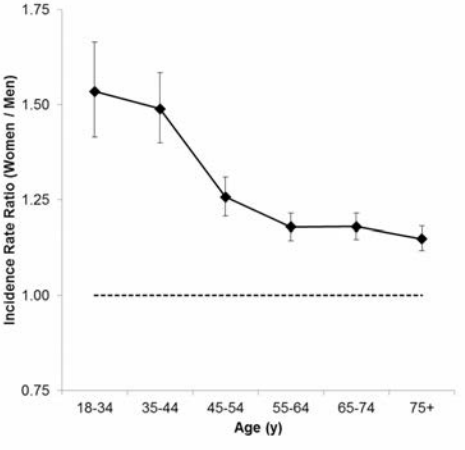
Background: Hospitalization is a major burden among maintenance hemodialysis patients; reducing hospitalizations and readmissions is a target of healthcare policy in the US. We sought to detail subgroups of patients undergoing maintenance dialysis at highest risks of hospitalization and readmission.

Methods: We analyzed data from a cohort of 111,653 adult hemodialysis patients in the US (2007-2011). Rates of hospitalization and 30-day readmission were compared by gender, age, and race, adjusting for other case-mix and laboratory/clinical variables.

Results: There were 333,756 hospitalizations over 4 years of follow-up. The overall rate of hospitalization was 1.85 per person-year (1.68 among men and 2.08 among women). Hospitalization rates were higher for women than men of the same age and race; for example, women ages 35-44 y had a 49% (95% CI: 40% to 58%) higher hospitalization rate than men of the same age and race (Figure). The gender disparity in hospitalization risk decreased with older age, and was attenuated with adjustment for serum albumin. The probability of 30-day readmission followed similar patterns to hospitalization rate. The probability of readmission was strongly associated with previous admissions, rising from 27.0% (95% CI: 26.5% to 27.4%) following a patient's first hospitalization, to 38.6% (95% CI: 38.1% to 39.2%) following a patient's fifth hospitalization.

Conclusions: Women undergoing maintenance hemodialysis experience excess risk of hospitalization and 30-day readmission compared to men. Additionally, patients with multiple prior hospitalizations are at particularly high risk of readmission. Interventions focused on these groups may be of benefit in reducing hospitalization and readmissions among dialysis patients.

Figure:



Funding: NIDDK Support

FR-PO957

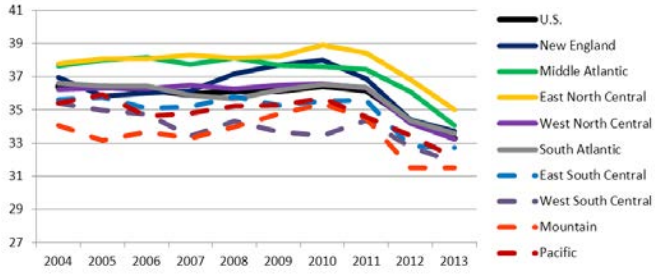
Geographic Variation in Hospital Readmissions Allan J. Collins,[1] Peer Kidney Care Initiative Investigators.[2] *[1]Chronic Disease Research Group, MMRF, Mpls, MN; [2]Peer Kidney Care Initiative.*

Background: Reducing 30-day hospital readmissions is a major CMS policy objective. Readmissions have fallen for both targeted and non-targeted diseases. USRDS reports show readmissions for the dialysis population almost twice those of the general Medicare population (35% versus 17%). We studied geographic trends over time in 30-day hospital readmissions, comparing the US census divisions.

Methods: The 2004-2013 prevalent dialysis population was assessed yearly from January 1 to November 30 to determine 30-day hospital readmission patterns. The index hospitalization, used to define a primary cause of hospitalization, was categorized by organ system and included causes targeted by CMS (MI/acute coronary syndrome, CHF/fluid overload, pneumonia), and causes not targeted (GI bleeding, hyperkalemia, vascular access complications, bacteremia/sepsis, Clostridium difficile infections). We assessed how readmission rates changed over time by US census division, a marker of geography.

Results: Overall, the relative decrease in readmission rates, 2011-2013, was 8%, greater than reported in the general Medicare population. The greatest decline was in the Mid-Atlantic division, 9.1%, and the least in the Pacific division, 7.2%. Overall, divisions with the greatest declines also had the highest admission rates. Index hospitalization causes leading to the highest percentage of 30-day readmissions were C. diff infections followed by MI/acute coronary syndrome, CHF/fluid overload, and bacteremia/sepsis.

Conclusions: The dialysis population, although not specifically targeted by CMS, has experienced a greater reduction in readmissions than the general Medicare population across broad geographic regions and index causes of hospitalization.



Funding: Pharmaceutical Company Support - Financial support for the Peer Kidney Care Initiative is provided by the following participating provider organizations: American Renal Associates, Atlantic Dialysis Management Services, DaVita HealthCare Partners, Dialysis Clinic, Inc., Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Satellite Healthcare, The Rogosin Institute, U.S. Renal Care, and Wake Forest University, Private Foundation Support

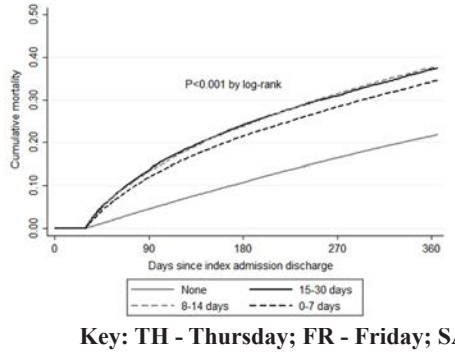
FR-PO958

Mortality by Hospital Readmission Window among U.S. Hemodialysis Patients Laura Plantinga,[1] Janice P. Lea,[1] Rachel E. Patzer,[1] Bernard G. Jaar.[2] *[1]Emory Univ, Atlanta, GA; [2]Johns Hopkins Univ, Baltimore, MA.*

Background: U.S. dialysis facilities will be accountable for hospital readmissions in 2017, but whether the 30-day window defined by pay-for-performance predicts poor outcomes as well as earlier windows is unknown. We examined the prevalence of hospital readmissions within 7 or 14 days of discharge and compared 1-year mortality by readmission window.

Methods: We identified 153,349 U.S. hemodialysis (HD) patients from a national registry (United States Renal Data System) who had at least one hospitalization in 2010 (first=index) and survived on HD for at least 30 days. Readmissions were defined by admissions within windows of 0-7, 8-14, or 15-30 days after discharge from the index admission. Kaplan-Meier analyses and multivariable Cox proportional hazards models were used to estimate the association between readmission window (referent=no readmission in 30 days) and time to mortality, censored at 1 year.

Results: Overall, 13.1%, 5.9%, and 9.6% of patients had readmissions within 0-7, 8-14, and 15-30 days of discharge from index admission; 45.8% of readmissions were within 7 days. Regardless of readmission window, patients with readmissions had about twice the risk of death within 1 year, compared to those with no readmissions; this effect was attenuated after 6 months.



Adjustment for age, sex, race/ethnicity, dialysis vintage and comorbid conditions made little difference: 15-30 days, HR=2.05 (95% CI, 1.98-2.12); 8-14 days, HR=2.06 (95% CI, 1.97-2.15); and 0-7 days, HR=1.80 (95% CI, 1.74-1.86).

Conclusions: Nearly half of 30-day readmissions occurred within the first 7 days after discharge, suggesting that opportunities for dialysis providers to prevent readmission may be limited. These results also suggest that readmission, regardless of timing, is associated with about 2-fold increased risk of mortality in the following year among U.S. HD patients.

Funding: Other NIH Support - NIMHD

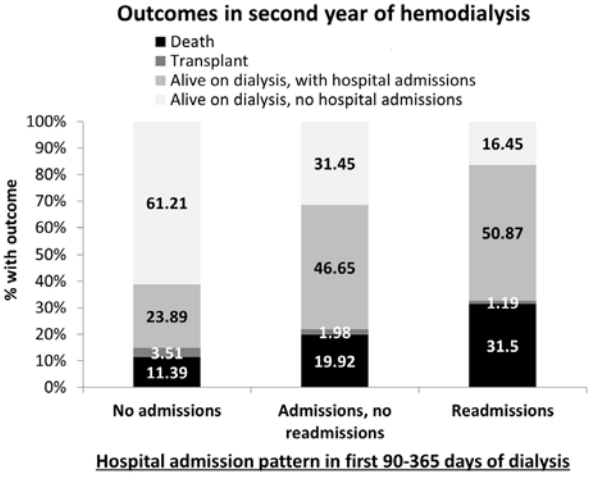
FR-PO959

Long-Term Outcomes among Hemodialysis Patients Readmitted in the First Year of Dialysis Bernard G. Jaar,[1] Rachel E. Patzer,[2] Janice P. Lea,[2] Laura Plantinga.[2] *[1]Medicine - Nephrology, Johns Hopkins Univ, Baltimore, MD; [2]Medicine - Nephrology, Emory Univ, Atlanta, GA.*

Background: Readmissions are common among hemodialysis (HD) patients and may predict poor outcomes. We examined long-term outcomes among incident in-center HD patients readmitted in their first year of treatment.

Methods: We categorized 275,475 U.S. incident patients from a national registry (USRDS) who started HD between 9/2005 and 9/2009 and remained on HD alive for at least 1 year as having no admissions, admissions but no readmission (within 30 days), and 30-day readmissions in the 90-365 days after HD start. Outcomes (mortality, transplantation, and hospital admissions) were examined between 366 and 730 days. Multivariable Cox proportional hazards and Poisson models were used to estimate hazard ratios (HRs) and incidence rate ratios (IRRs).

Results: Overall, 15.8%, 25.0%, and 59.1% of patients had readmissions, hospital admissions but no readmission, and no admissions, respectively, in the first 90-365 days of HD. Patients with readmissions in year 1 were more likely to die and be hospitalized, and less likely to be transplanted in their year 2 of HD, compared to their counterparts with no readmission or no admission.



With adjustment for age, sex, race/ethnicity and comorbid conditions, those with readmissions and those with admissions but no readmission remained far more likely than those without admission in year 1, to have poor outcomes in their year 2: mortality, HR=2.84 (95% CI, 2.77-2.90) and 1.61 (95% CI, 1.51-1.65); and hospital admissions, IRR=5.02 (95% CI, 4.97-5.06) and 2.66 (95% CI, 2.64-2.68), respectively.

Conclusions: Having hospital readmissions (within 30 days) early in the course of HD, even beyond having hospital admissions alone, is highly predictive of poor long-term subsequent outcomes, including death, not being transplanted, and further hospital admissions.

Funding: Other NIH Support - National Institute on Minority Health and Health Disparities

FR-PO960

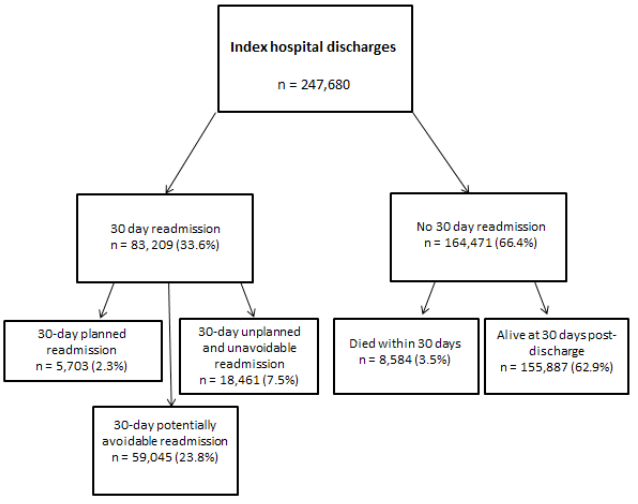
Potentially Avoidable Readmissions in United States Hemodialysis Patients Anna Mathew,[1] Lisa M. Rosen,[1] Renee Pekmezaris,[1] Andrzej Kozikowski,[1] Daniel W. Ross,[1] Thomas Mcginn,[1] Kamyar Kalantar-Zadeh,[2,3] Steven Fishbane.[1] *[1]Hofstra Northwell School of Medicine, Northwell Health, Great Neck, NY; [2]Harold Simmons Center for Kidney Disease Research, Div of Nephrology, Orange, CA; [3]Fielding School of Public Health, UCLA, Los Angeles, CA.*

Background: Patients with end stage kidney disease have a high risk of 30-day readmission after hospital discharge, associated with excessive financial cost and poor quality of life. Whereas all-cause readmissions have been described, potential avoidability of readmissions has not been previously analyzed. We aimed to analyze the frequency, causes and predictors associated with 30-day potentially avoidable readmission to hospital in maintenance hemodialysis patients.

Methods: In this historical cohort study using the United States Renal Data System, 107,940 prevalent HD patients with 248,680 index hospital discharges were assessed for the main outcome of 30-day potentially avoidable readmission after an index hospital discharge, as identified by a computerized algorithm.

Results: Of 83,209 thirty-day readmissions, 59,045 (70% of all readmissions and 24% of all hospital discharges) resulted in a 30-day potentially avoidable readmission.

Figure 1: Index hospital discharge outcomes and frequencies



Characteristics associated with 30-day potentially avoidable readmission included younger age, shorter time on dialysis, greater number of hospitalizations in preceding 12 months, black race, unemployed status, treatment at a for-profit facility, longer length of index hospital stay, and index hospitalizations which involved a surgical procedure.

Conclusions: Maintenance hemodialysis patients are at high risk for 30-day readmission to hospital, with over two-thirds (71%) of all 30-day readmissions potentially avoidable. Research is warranted to develop cost-effective and transferrable interventions to improve care transitions from hospital to outpatient dialysis facility and reduce readmission risk for this vulnerable population.

FR-PO961

Effect of a Medication Intervention on Acute Care Utilization after Hospitalization in Patients with ESRD Katherine R. Tuttle,[1,2] Radica Z. Alicic,[1,2] Robert Short,[1] Sterling McPherson,[1,3] Brad Dieter,[1] Joshua J. Neumiller,[3] Brian J. Gates,[3] Celestina Barbosa-Leiker,[3] Naomi Chaytor,[3] Cynthia F. Corbett.[1,3] *[1]Providence Health Care, Spokane, WA; [2]Univ of Washington, Spokane, WA; [3]Washington State Univ, Spokane, WA.*

Background: Hospital readmission rates in patients with end-stage renal disease (ESRD) exceed that of most chronic health conditions. Strategies to improve care are urgently needed.

Methods: The **E**nd **S**tage **R**enal **D**isease-**M**edication **I**ntervention **T**rial (ESRD-MIT) (www.clinicaltrials.gov NCT01459770) was a randomized, controlled clinical trial conducted between 2013 and 2015. Participants were patients with ESRD (treated by hemodialysis or peritoneal dialysis) acutely hospitalized at Providence Health Care. They were randomized to usual care or the intervention, a single home visit for medication management by a study pharmacist within 7 days of discharge. Acute care utilization (hospital readmission, emergency department or urgent care visits) for 90 days after hospital discharge was the primary outcome.

Results: Study participants (n=39) were 61±16, mean±SD, years of age and 41% (16/39) women. Hypertension and diabetes were present in 51% (20/39) and 59% (23/39), respectively. Duration of dialysis was 22 (3-71), median (IQ range), months. The most common primary diagnoses for index hospital admission included: infections 23% (9/39), cardiovascular diseases 15% (6/39), and vascular access procedures 18% (7/39). Length of stay was 3 (1.5-7) days. The primary outcome, analyzed as time-to-first event, occurred in 40% (8/20) of participants in the intervention group and in 47% (9/19) of those in usual care (p=0.64). Rates for each type of acute care event were similar between groups. For total hospital readmissions, the most common primary diagnoses included: infections 24% (5/21), respiratory diseases 19% (4/21), vascular access procedures 14% (3/21) and cardiovascular diseases 14% (3/21).

Conclusions: Acute care utilization after hospital discharge in patients with ESRD was not reduced by a medication management intervention. Comprehensive strategies to enhance care pre- and post-discharge may be needed to improve health outcomes.

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

FR-PO962

Hospitalization Rates before and after the Initiation of a Fluid Management Quality Improvement Project Using Crit-Line Monitors during In-center Hemodialysis Paul Balter,[1] Ludmila Anderson,[2] Alice Topping,[1] Claudy Mullon,[2] Robert J. Kossmann,[2] Linda H. Ficociello.[2] *[1]Renal Research Inst, New York, NY; [2]Fresenius Medical Care North America, Waltham, MA.*

Background: Patients on hemodialysis (HD) are at high risk for hospital admissions, especially fluid-related admissions. A fluid management quality improvement (QI) project utilizing Crit-Line monitors® (CLM) was conducted by the Renal Research Institute. CLM non-invasively assess intra-dialytic relative blood volume and provide real-time data that allow for ongoing fluid monitoring by clinical staff. The aim of this analysis was to determine whether fluid-related admission rates decreased during the year-long QI project. All-cause hospital admissions and mortality rates were also assessed.

Methods: Data were de-identified and extracted from routinely collected electronic data. Crude rates and rate ratios (RR) were calculated to compare baseline (BL; 12 months before the QI project) to follow-up (12 months during the QI project, after 1 month of CLM transition). To ensure complete outcome ascertainment, all outcomes occurring within 7 days of the last HD treatment were captured for each period. Patients treated in 2 or more centers during baseline and/or follow-up were excluded.

Results: Overall, 2,673 adult patients at 16 HD centers were eligible for analysis. Demographic characteristics varied minimally between study periods (p>0.05); although, a difference in reported congestive heart failure was noted (BL: 18.8% vs. 15.5%, p=0.02). Fluid-related hospitalization rate declined by 19% from 0.21 to 0.17 per patient-year (PY); RR: 0.81 (95% confidence interval: 0.67-0.97), and all-cause hospitalization rate declined by 10% from 1.88 to 1.70 per PY; RR: 0.90 (0.85-0.96). A non-significant decline in mortality rate was observed (16% decrease from 0.19 to 0.16 per PY; RR: 0.84 (0.69-1.01)).

Conclusions: Fluid-related and all-cause hospitalization rates decreased by 19% and 10%, respectively, during a year-long QI project utilizing CLM in 16 HD centers.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

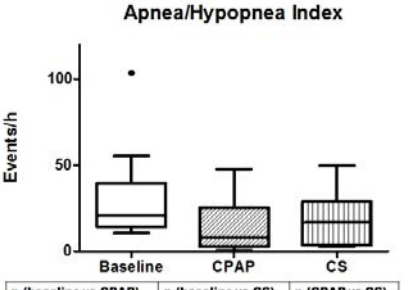
FR-PO963

Compression Stockings Improve Sleep Apnea in Hemodialysis Patients Bruno C. Silva,[1] Roberto S.S. Santos,[1] Luciano F. Drager,[1] Fernando Coelho,[2] Rosilene M. Elias.[1] *[1]Univ de São Paulo, Brazil; [2]UNIFESP, Brazil.*

Background: Sleep apnea (SA) is prevalent in edematous states, such as in hemodialysis (HD) patients. As nocturnal rostral fluid shift from the legs is implicated in its physiopathology, we hypothesized that avoiding fluid retention in the legs during the day, by wearing compression stockings (CS), would improve SA in HD patients.

Methods: We included 14 HD patients with SA (AHI)>5 events/hour) by polysomnography exam (PSG). Pts were submitted to another two PSGs: one for continuous positive airway pressure (CPAP) titration and another 1-week after daytime use of medium (20-30 mmHg) CS. Neck circumference (NC) and bioimpedance analysis (BIA) were performed before and after PSG.

Results: Mean age was 53±9 years (57% men), body mass index was 30±7 Kg/m², and dialysis vintage was 60±62 months. Dry weight and total week ultrafiltration volume were similar in the three exams. AHI decreased from 20.8 (14.2;39.6) at baseline to 16.7 (3.5;28.9) after CS use (p=0.017) and to 7.9 (2.8;25.4) events/hour with CPAP (p=0.004).



p (baseline vs CPAP)	p (baseline vs CS)	p (CPAP vs CS)
0,004	0,017	0,017

Overnight NC variation increased at baseline (0.7±0.4 cm), but decreased after CS use (-0.4±0.8 cm), p=0.001 and after CPAP (-1.0±0.4), p<0.0001. BIA revealed displacement of fluid from the legs to the intracellular compartment of trunk after wearing CS: comparing baseline, CPAP and CS, nocturnal lower limbs water content (relative to body water) was 34.1±2.1%, 34.3±2.3% and 33.5±2.3%, respectively (p=0.04), while nocturnal intracellular trunk water (relative to body water) as 61.8±1.5%, 61.6±1.5% and 62±1.6 %, respectively (p=0.03).

Conclusions: Wearing compression stockings in HD pts during the day avoided fluid retention in the legs, leading to lower nocturnal rostral fluid shift and, consequently, attenuated SA. Even though CPAP remains the mainstream treatment for SA, this study highlights an alternative treatment to such syndrome in HD patients.

FR-PO964

Asymptomatic Sleep Apnea Syndrome in End-Stage Renal Disease: Implications of Volume Overload for Obstructive Sleep Apnea Syndrome Toshiki Kano, Hitoshi Suzuki, Masao Kihara, Yusuke Suzuki, Satoshi Horikoshi. *Div of Nephrology, Dept of Internal Medicine, Juntendo Univ Faculty of Medicine, Bunkyo-ku, Tokyo, Japan.*

Background: Sleep apnea syndrome (SAS) has been reported in up to 50% to 70% of patients with end-stage renal disease (ESRD). It is hypothesized that SAS in patients with ESRD is caused by narrow upper airway due to volume overload. SAS is considered an independent risk factor for hypertension, congestive heart failure, acute coronary syndromes, pulmonary hypertension, arrhythmias, and cerebrovascular events. To improve the prognosis of patients with ESRD, management of appropriate body fluid in reference to degree of obstructive sleep apnea syndrome (OSAS) is essential. The aim of present study is to evaluate the association between severity of OSAS and volume overload in patients with ESRD.

Methods: The apnea-hypopnea index (AHI) and its severity were measured in fourteen patients with ESRD (CKD stage 5) using a portable sleep monitoring device. Body weight (BW), cardio thoracic ratio (CTR), serum levels of BNP, AHI were measured during the therapeutic course of hemodialysis. The association of AHI with age, gender, body mass index (BMI), history of smoking and complication of ESRD were analyzed.

Results: In fourteen patients with ESRD, 92.8 % were diagnosed as asymptomatic SAS. Those patients were divided according to AHI scores into mild (AHI 5-14.9, 21.4%), moderate (AHI 15-29.9, 21.4%), and severe OSAS (AHI≥30, 50.0%) groups. Age, gender, BMI, smoking and complication of ESRD were not associated with AHI. Improvement of AHI due to modification of volume overload was associated with decreased BW and BNP (P=0.032, P=0.026, respectively).

Conclusions: Present study suggested that the OSAS is a major complication in patients with ESRD. The OSAS is caused by narrow upper airway due to volume overload. Assessment of AHI using a portable sleep monitoring device is useful tool to evaluate the appropriate body fluid in patients with ESRD.

FR-PO965

Visual Changes in Response to Haemodialysis Huda Mahmoud,[1,2] Philip Wright,[1,3] Laurence Hodierne,[1] Andrew B. Newsham,[1] Simon E. De Sousa,[1] Patrick Richardson,[3] Nicholas M. Selby,[1,2] Oliver R. Smith.[1] *[1]Dept of Renal Medicine, Royal Derby Hospital, United Kingdom; [2]Centre for Kidney Research and Innovation, Univ of Nottingham, United Kingdom; [3]Dept of Opthamology, Royal Derby Hospital, United Kingdom.*

Background: Haemodialysis (HD) patients report visual disturbances associated with dialysis sessions although causes for these symptoms are poorly documented and understood. We performed an observational study to describe and assess the change in visual acuity (VA) in response to HD therapy.

Methods: All patients receiving chronic HD at our centre were invited to participate. VA of each eye was assessed before and after a single HD session. The Snellen result was converted to Logarithm for Minimal angle of resolution (LogMar) score for comparative analyses and categorized according to the World Health Organisation (WHO) classification of visual loss into normal, mild, moderate and severe. Patients' subjective perceptions of visual disturbances and HD treatment details were recorded.

Results: 148 (281 eyes) patients participated. The WHO classification of visual impairment based on best eye pre-dialysis results; 34% of patients had normal vision, 40% mild, 21% moderate and 5% severe visual impairment. This incidence of moderate and severe visual impairment was higher than would be expected from general population data. 44% of patients experienced a deterioration in VA in one or both eyes by the end of HD, equivalent to one row on Snellen chart. Looking at each eye separately, there was a significant deterioration in mean LogMar score comparing pre-dialysis (mean 0.4±0.2) and post-dialysis measurements (0.44±0.2,p=0.01). 17% of patients reported visual disturbances during HD, most commonly blurring of vision or difficulty reading. Of these 29% dropped a VA category across HD.

Conclusions: This study illustrates that HD patients have a high prevalence of visual impairment, and a subgroup experience significant decline in VA in response to dialysis treatment. This may pose a significant risk in this vulnerable population who often experience high levels of comorbidity and physiological frailty. Further work is required to understand the mechanisms, associated factors and impact of this problem.

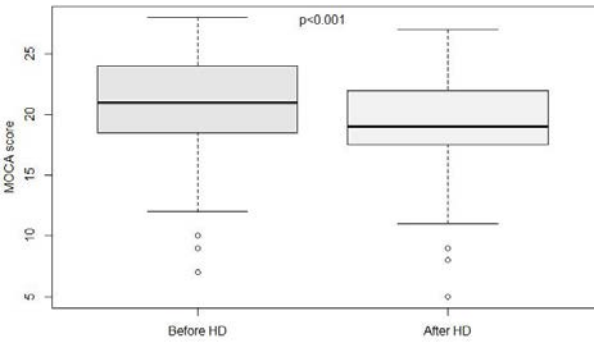
FR-PO966

Change in Cognitive Function over a Single Haemodialysis Session Indranil Dasgupta,[1] Nuredin Ibrahim Mohammed,[2] Mitesh Patel,[1] Jyoti B. Baharani,[1] Thejasvi Balaji Subramanian,[1] G. Neil Thomas,[2] George Tadros.[1] *[1]Birmingham Heartlands Hospital, United Kingdom; [2]Univ of Birmingham, United Kingdom.*

Background: Cognitive impairment (CI) is 3 times more common among haemodialysis (HD) patients compared with the general population, it declines progressively and is associated with increased mortality and reduced functional capacity. The effect of a single HD session on cognition is unclear. We aimed to assess change in cognitive function over a single HD session and risk factors associated with it.

Methods: All patients ≥50 years, on HD for ≥3 months, from 2 satellite HD units were selected. Patients with known CI and those unable to read and write English were excluded. Cognitive function was assessed before and after a single HD session using 2 parallel versions of the Montreal Cognitive Assessment (MOCA) tool and compared using a paired t-test. Linear regression was used to examine factors associated with CI including age, change in weight and BP, electrolytes, albumin, sedative drugs, depression score and comorbidity score.

Results: Of 176 patients, 100 met the inclusion criteria; 83 were able to complete both tests. Median age was 73 years (52 – 91), 59% male, dialysis vintage 41 months (3 – 388). 69 patients (83%) had mild CI at base line(MOCA score <26) with 13 (16%) severe CI (MOCA <17). Cognitive function declined significantly over a dialysis session (p<0.001, Figure1). All domains of cognitive function were affected except visuo-spatial and naming. No association was observed between change in MOCA score and putative risk factors.



Conclusions: Cognitive function declines significantly over a single HD session which has significant clinical implications including for self management advice given during HD and tasks requiring cognition following HD like driving. More research is needed to find the underlying cause of cognitive decline during HD and measures to prevent this.

FR-PO967

High Serum 25-Hydroxyvitamin D, Fibroblast Growth Factor 23, and Interleukin-6 Levels Are Associated with Self-Reported Sleep Quality in the HEMO Study Cohort Anna Jeanette Jovanovich,[1] Morgan E. Marcuccilli,[1] Jessica B. Kendrick,[1] Alfred K. Cheung,[2] Zhiying You,[1] Michel Chonchol,[1] Kristen L. Nowak.[1] *[1]Univ of Colorado; [2]Univ of Utah.*

Background: Although sleep problems are thought to be prevalent among patients who undergo chronic hemodialysis, there is limited information on the relationship between sleep quality with markers of mineral metabolism and inflammation.

Methods: This report uses data from the HEMO Study which was a randomized multicenter study evaluating the effects of high-dose versus standard-dose and high-flux versus low-flux hemodialysis. Twelve-hundred two patients aged 18-80 years were randomized and completed the Kidney Disease Quality of Life Long Form (KDQOL-LF) at baseline. Sleep quality was assessed using the sleep subscale from the KDQOL-LF and a binary outcome of sleep disturbance was defined. Logistic regression models were used to investigate the association between presence and absence of sleep disturbances with markers of mineral metabolism and inflammation.

Results: Mean age (SD) was 58±14 years, 44% were male, 64% were Black, 37% had diabetes, and 32% had hypertension. The median (IQR) 25-hydroxyvitamin D (25(OH)D), fibroblast growth factor 23 (FGF23) and interleukin-6 (IL-6) levels were 19.1 (14.2-26.6) ng/mL, 3118 (726-12,928) pg/mL and 3.1 (1.6-5.7) pg/mL, respectively. After adjustment for potential confounders available in the database, the highest tertile of FGF23 (OR: 1.51, 95% CI 1.05-2.16; p=0.02) and IL-6 (OR: 1.54, 95% CI 1.10-2.16; p=0.01) were associated with an increased odds of sleep disturbance. In contrast, the highest tertile of 25(OH)D was associated with a decreased odds of sleep disturbance (OR: 0.65, 95% CI 0.47-0.90; p=0.04) when compared to the lowest tertile.

Conclusions: Decreased serum levels of vitamin D and increased circulating levels of FGF23 and IL-6 were associated with poor sleep quality in chronic hemodialysis patients. Future work should examine the link between sleep quality with abnormalities of mineral metabolism and inflammation.

Funding: NIDDK Support

FR-PO968

Parathyroid Hormone as a Novel Risk Factor of Hemodialyzer Clotting Kyohei Ogawa,[1] Keita Hirano,[1] Izumi Yamamoto,[2] Yukio Maruyama,[2] Ichiro Ohkido,[2] Nobuo Tsuboi,[2] Takashi Yokoo.[2] *[1]Nephrology, Ashikaga Red Cross Hospital, Ashikaga, Tochigi, Japan; [2]Kidney and Hypertension, Jikei Univ School of Medicine, Minato, Tokyo, Japan.*

Background: Hyperparathyroidism gives rise to low levels of HDL-cholesterol (HDL-C), and hence imposes a cardiovascular risk (Clin Endocrinol 2002;56:253). However, it is unknown whether parathyroid hormone (PTH) level also represents a risk factor for dialyzer clotting.

Methods: All outpatient dialysis sessions performed at Ashikaga Red Cross Hospital in 2015 were examined as a historical cohort. Blood remaining in more than 10 hollow fibers at the end of each session was taken as significant dialyzer clotting.

Results: Out of 4,207 dialysis sessions derived from 36 patients, significant dialyzer clotting was observed in 144 sessions (3.4%). Sessions were then stratified by the median of alkaline phosphatase (ALP) to 2,094 sessions as low ALP group and 2,113 sessions as high ALP group, because there was a significant interaction for the risk of clotting between PTH and ALP. On multivariate analysis adjusted with hemoglobin, albumin and APTT, PTH was associated with the risk of clotting especially in low ALP group (OR 2.10, 95%CI 1.43-3.06, per 100pg/ml of intact PTH), but the association was not observed in high ALP group (OR 1.17, 95%CI 0.87-1.58, P>0.2). Of note, although PTH was proportional to HDL-C in high ALP group (B 3.592, SE 0.279, P<0.001), it was inversely proportional to HDL-C in low ALP group (B -2.108, SE 0.441, P<0.001).

Conclusions: PTH is associated with dialyzer clotting especially in hemodialysis sessions with low ALP level. Consequently, it should deserve more attention when working towards more biocompatible dialysis with reduced dialyzer clotting.

Funding: Private Foundation Support

FR-PO969

Polymorphisms of Vitamin D Signaling Pathway Genes and Calcium Sensing Receptor Gene in Respect to Survival of Hemodialysis Patients – A Prospective Observational Study (Part I) Alicja E. Grzegorzewska, Monika K. Swiderska, Adrianna Mostowska, Wojciech J. Warchol, Pawel P. Jagodzinski. *Poznan Univ of Medical Sciences, Poland.*

Background: Studies on associations of single nucleotide polymorphisms (SNPs) of vitamin D signaling pathway genes and calcium-sensing receptor gene (*CASR*) with survival of hemodialysis (HD) patients are scarce. We evaluated whether SNPs of abovementioned genes are determinants of mortality in HD patients.

Methods: Prevalence HD patients without history of renal transplantation (n = 532, men 56%, RRT vintage prior to the study 2.2, 0.0 - 24.7 years, age at the start of the study 61.2, 14.6 - 89.3 years, diabetic nephropathy 25.8%, dyslipidemia 41.0%) were enrolled in the 7-year prospective observational study at January 30, 2009. HRM analysis was used for *GC*rs2298849, *GC* rs1155563, *RXRA* rs10776909, *RXRA* rs10881578, and *CASR* rs7652589 genotyping. *GC* rs7041, *RXRA* rs749759, *VDR* rs2228570, and *VDR* rs1544410 were genotyped using PCR-RFLP analysis. Survival analyses were conducted using the Kaplan-Meier method and the Cox proportional hazard model.

Results: *GC* rs2298849 was associated with all-cause mortality in dominant model of inheritance (log rank test P = 0.02), and *VDR* rs2228570 - with cardiovascular mortality in additive model of inheritance (log rank test P = 0.04). Subjects bearing the minor allele in rs2298849 demonstrated the higher risk of death during 7 years on HD than the major allele homozygotes (OR 1.81, 95%CI 1.13 - 2.92, P = 0.02). Cardiovascular mortality was associated with major homozygosity (CC) in rs2228570 (HR 1.90, 95%CI 1.16 – 3.09, P = 0.01). The CC genotype patients were more often dyslipidemic compared to the TT genotype subjects (46 vs 31%, P = 0.03). Dyslipidemic HD patients showed higher frequency of the rs1544410_rs2228570 haplotype AC than non-dyslipidemic subjects (26 vs 18%, P_{corr} = 0.005), whereas the TT genotype patients were at lower risk of dyslipidemia compared to patients with CC/CT genotypes (HR 0.59, 95%CI 0.37 – 0.96, P = 0.04).

Conclusions: *GC*rs2298849 and *VDR* rs2228570 SNPs are associated with survival of HD patients. *VDR*-related cardiovascular mortality may occur due to connections of rs2228570 with dyslipidemia.

FR-PO970

Polymorphisms of T Helper Cell Cytokine-Associated Genes in Respect to Survival of Hemodialysis Patients – A Prospective Observational Study (Part II) Alicja E. Grzegorzewska, Monika K. Swiderska, Adrianna Mostowska, Wojciech J. Warchol, Pawel P. Jagodzinski. *Poznan Univ of Medical Sciences, Poland.*

Background: We evaluated in the 7-year prospective study whether variants in T helper cell cytokine-associated genes are determinants of mortality in hemodialysis (HD) patients (n=532).

Methods: HRM analysis was used for *IFNL3*, *IL12A*, *IL13*,and *IL4R* genotyping. *CCL2*, *IL12B*, and *IL18* were genotyped using PCR-RFLP analysis. Survival analyses were conducted using the Kaplan-Meier method and the Cox proportional hazard model.

Results: *IFNL3* rs8099917 was associated with all-cause mortality in recessive model of inheritance (log-rank test P = 0.044), *IL12A* rs568408 - in dominant model (log-rank test P=0.029). Minor homozygotes (GG) in rs8099917 showed shorter survival than major allele (T) bearers (3.6, 1.0–7.0 years vs 4.7, 0.1–7.0 years, P = 0.009), although their RRT vintage prior to the onset of the study was also shorter (1.4, 0.0-6.8 years vs 2.3, 0.0-22.2 years, P=0.010). The rs8099917 GG patients demonstrated higher risk of death than the remaining patients (GT+TT) (OR 1.94, 95%CI 1.11-3.40, P = 0.020). Major homozygosity (GG) in rs568408 was associated with higher mortality than that shown in bearers of the minor allele (AA+AG) (HR 1.31, 95%CI 1.02–1.69, P = 0.035). There were less responders to HBV vaccination in the genotype GG patients compared with the rs568408 minor allele bearers (84.6% vs 94.3%, P = 0.019). However, significant predictors of 7-year survival in multivariate analysis were only coronary artery disease (HR 1.685, 95% CI 1.297–2.191, P = 0.0001), age (HR 1.016, 95% CI 1.006–1.026 per each 1-year increase, P = 0.002), RRT vintage prior to the study onset (HR 1.053, 95% CI 1.013–1.093 per each 1-year increase, P=0.008), and serum PTH (HR 1.028, 95% CI 1.001–1.057 per each 100 pg/mL decrease, P=0.046). There were no associations of tested polymorphisms with cardiovascular, infection- or neoplasm-related mortalities, and no gene-gene interactions between tested polymorphisms in the 7-year survivors and non-survivors.

Conclusions: Polymorphisms of *IFNL3* rs8099917and *IL12A* rs568408 are associated with survival on HD, however, they are not significant predictors of all-cause mortality.

FR-PO971

Parathyroidectomy (PTX), KDOQI Targets and Mortality in a Cohort of Italian Dialysis (D) Patients: A Multicenter Observational Study Sandro Mazzaferro. *On Behalf of the Italian Study Group of Mineral Metabolism; Sapienza Univ of Rome, Dept of Cardiovascular, Respiratory, Nephrology, Anesthesiology and Geriatric Sciences, Rome, Italy.*

Background: Secondary hyperparathyroidism (SHP) plaques patients with ESRD on D negatively affecting survival. Achieving even once KDOQI target levels for Ca, P and PTH associates with lower risk of mortality. PTX, possibly by improving biochemical control, may improve survival. Aim of this study was to evaluate the impact of PTX on biochemical control and survival of Italian HD patients in the medium term.

Methods: Data were collected from 149 HD units spread throughout the Country, by means of a data sheet filled by a reference physician.

Results: We collected 524 living PTX cases (age: 57.90±12.52 y.o; D time: 14.57±8.37 y; sex: 231M/296F), out of a total 12515 receiving D (=4,2%). Time from surgery was 6,0 y (3,0-9,0; M, IQR). A control group was identified (432 cases, 58.9±16.5 y.o.; on D since 11.7±2.6 y; 192M/240F). Data were then collected on a yearly basis for 3 consecutive years. At enrollment, compared to the control group, PTX patients had lower Ca (8.76±0.87 vs 9.05±0.73 mg/dl; p <.05), P mg/dl (4.90±1.36 vs 5.10±1.34 mg/dl; p<.05) and PTH (181.9±292.5 vs 333.7±293.7 pg/ml; p<.01). At enrollment the percentage of patients at target was lower in the PTX group: P = 55,3% vs 58,8 (p<.05); Ca = 50,9% vs 57,6 (p<.001); PTH =17% vs 35% (p<.001). PTH, but not Ca and P, was confirmed to be more frequently at target in the control group (35% vs 21%, p<.05) during 1 and 2 years of follow-up. In multivariate adjusted analysis, sHR for all-cause mortality was 0,843 (CI 0,783-0,908; p<.0001) for PTX patients.

Conclusions: In conclusion, in D patients PTX associates with lower risk of mortality regardless of achievement of Ca,P or PTH targets.

Funding: Pharmaceutical Company Support - Unrestricted Funds from Amgen

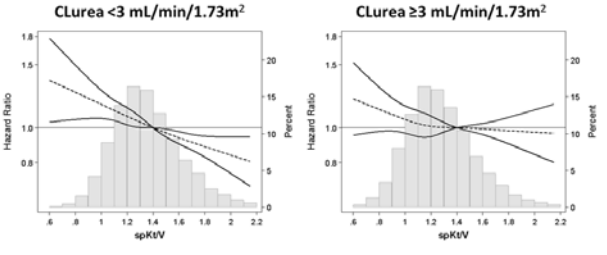
FR-PO972

Residual Kidney Function Modifies the Association between Dialysis Dose and Mortality in Hemodialysis Patients Yoshitsugu Obi,[1] Mengjing Wang,[1] Connie Rhee,[1] Elani Streja,[1] Csaba P. Kovesdy,[2] Rajnish Mehrotra,[3] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Univ of Tenn.; [3]Univ of Wash.*

Background: Recent studies have suggested that frequent hemodialysis is associated with faster decline in residual kidney function (RKF) and higher mortality among hemodialysis patients with substantial RKF. We hypothesized that dialysis dose is associated with better survival only in those with little or no RKF.

Methods: We identified 34,076 incident hemodialysis patients with measured residual renal urea clearance (CLurea) in a large dialysis organization in the U.S. between 2007 and 2011. The associations ofspKt/Vduring the first 91 days of dialysis with all-cause mortality were examined across two strata of baseline CLurea using Cox models with adjustment for case-mix characteristics and 9 laboratory variables associated with nutritional and inflammatory status.

Results: The mean age of the cohort was 63±15 years and included 43% females, 53% diabetics, and 29% African Americans. Median spKt/V andCLurea at baseline were 1.42 (IQR, 1.24–1.64) and 3.2 (IQR, 1.8–5.6) mL/min/1.73m^2, respectively. Lower spKt/V was associated with higher mortality among patients with low CLurea (i.e., <3 mL/min/1.73m^2, left panel); adjusted HRs (95%CIs) of mortality associated with spKT/V of 1.0 and 1.8(reference: 1.4) were 1.16 (1.06–1.27) and 0.89 (0.83–0.95), respectively. However,there was no significant association between spKt/V and all-cause death among patients with high CLurea (i.e., ≥3 mL/min/1.73m^2, right panel); adjusted HRs (95%CIs) of mortality associated with spKT/V of 1.0 and 1.8(reference: 1.4): 1.05 (0.97–1.15) and 0.98 (0.90–1.07), respectively.



Conclusions: Dialysis dose was not associated with mortality among patients with high CLurea. Further studies are needed to validate these findings and determine how they could be used to improve patient-centered outcomes without compromising survival if patients have substantial RKF.

Funding: NIDDK Support

FR-PO973

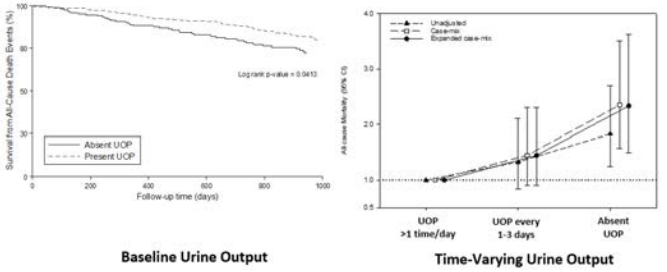
Residual Urine Output and Mortality in a Prospective Hemodialysis Cohort Amy Seung You, Kamyar Kalantar-Zadeh, Danh V. Nguyen, Alpesh Amin, Elani Streja, Yoshitsugu Obi, Tracy Nakata, Lidia Lou, Mary Veliz, Daniel L. Gillen, Csaba P. Kovesdy, Connie Rhee. *UC Irvine.*

Background: Assessment of residual urine output (UOP) is an important aspect of native kidney function evaluation in hemodialysis (HD) patients given its associations with better survival and quality of life. As frequent measurement by 24-hour urine collection may be cumbersome, self-reported UOP may be used as an adjunctive method of routine assessment in the clinical setting. We examined the association of patient-reported UOP with all-cause mortality in a prospective HD cohort.

Methods: Among 670 HD patients from the prospective *Malnutrition, Diet, and Racial Disparities in Kidney Disease* study, we examined the association of patient-reported UOP with all-cause mortality. Patients underwent protocolized surveys querying about presence and frequency of UOP (absent, every 1-3 days, >1 time/day) every 6 months over 2011-16. We examined the association of baseline and time-varying UOP with all-cause mortality using unadjusted, case-mix, and expanded case-mix Cox models.

Results: In baseline and time-varying analyses, absence of UOP was associated with higher mortality risk in expanded case-mix models (ref: presence of UOP): HR (95%CI)

1.78 (1.16-2.72) and 2.01 (1.35-2.99), respectively. In baseline and time-varying analyses of UOP frequency, point estimates suggested a graded association between lower UOP frequency and higher mortality, although estimates for UOP every 1-3 days did not reach statistical significance: HR (95%CI) 1.29 (0.82-2.05) and 1.97 (1.24-3.12) for absence of UOP and UOP every 1-3 days, respectively (ref: UOP >1 time/day).



Conclusions: In HD patients there is a graded association between higher frequency of self-reported UOP and lower mortality. Further studies are needed to validate self-reported UOP as an alternative metric of residual kidney function, and to determine optimal approaches for preserving UOP.

Funding: NIDDK Support

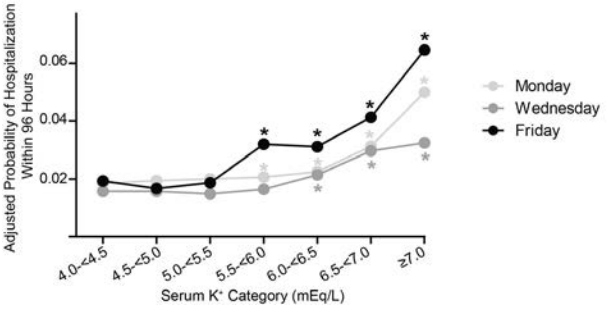
FR-PO974

Serum Potassium and Clinical Outcomes among Hemodialysis Patients: Impact of the Long Interdialytic Interval Steven M. Brunelli,[1] Charles Du Mond,[2] Nina Oestreicher,[2,3] Viatcheslav Rakov,[4] David M. Spiegel.[2] *[1]DaVita Clinical Research, Minneapolis, MN; [2]Relypsa Inc, Redwood City, CA; [3]Univ of California San Francisco, San Francisco, CA; [4]Vifor Pharma, Glattbrugg, Switzerland.*

Background: Hyperkalemia among hemodialysis (HD) patients is associated with morbidity and mortality. Among those who dialyze thrice-weekly, adverse outcomes peak after the 2-day interdialytic interval. Here, we estimated the independent association between serum potassium (K) concentration and outcomes among HD patients, and estimated how these associations were impacted by day of week.

Methods: This retrospective (2010-2011) study considered patient-interval data, defined as a routine K measurement made among adult Medicare Parts A & B enrollees receiving in-center HD on Monday/Wednesday/Friday (Mon/Wed/Fri) at a large US dialysis organization. Outcomes considered over the day of K measurement and the next 3 days were: hospital admissions, deaths, and emergency department (ED) visits.

Results: The association between high serum K and hospitalization risk was present on all days but most potently on Fri (*P*-interaction=0.008). Adjusted odds ratios (OR) for K5.5-<6, 6-<6.5, 6.5-<7, ≥7 (ref: 4-<4.5) were respectively: 1.68, 1.63, 2.19 and 3.51 on Fri; 1.04 (*P*=0.43), 1.37, 1.91 and 2.09 on Wed; and 1.12, 1.22, 1.70, 2.78 on Mon. Associations of high serum K with death and ED visit were significant but did not differ by day of week. Adjusted ORs for K 6-<6.5, 6.5-<7, ≥7 were 1.52, 2.42, 3.37 for death, and 1.19, 1.48, 2.62 for ED visit (for all, *P*<0.05 except as noted).



Conclusions: Higher serum K is associated with greater risk of hospitalization, death, and ED visit. The effect on hospitalization is modified by day of week, suggesting an enhanced burden of high K over the long interdialytic interval. Further work is needed to determine whether directed intervention ameliorates this risk.

Funding: Pharmaceutical Company Support - Relypsa Inc

FR-PO975

Oral Sodium Bicarbonate Reduces Inter-Dialytic Potassium Gain - The BicHD Trial Stella Kourtellidou, Damien Ashby, Lina Johansson. *Imperial College Healthcare NHS Trust, United Kingdom.*

Background: The intermittent nature of haemodialysis (HD) has adverse effects on clinical outcomes, with excess mortality associated with long intervals. High potassium contributes to this, but low levels post-HD can cause arrhythmias: a treatment reducing inter-HD potassium gain, would therefore be useful. Acidosis develops during each interval causing extracellular potassium shift - oral bicarbonate replacement may therefore limit potassium gains.

Methods: Prevalent in-centre HD patients with pre-HD bicarbonate <22mmol/l were randomly assigned to oral sodium bicarbonate or no treatment for 12 weeks. Starting dose was 2g/day with titration up to 4g/day. Electrolyte and blood pressure data are presented by paired testing in the intervention group. ECG and nutritional outcome analysis is in process.

Results: Forty-two patients were recruited, of which 16 (aged 27–74, 75% male) were randomised to and started the intervention. Average sodium bicarbonate dose after titration was 3.7g/day. On final doses, inter-HD bicarbonate loss was reduced from 6.42 to 3.72mmol/l (p<0.001), due mostly to an increase in pre-HD bicarbonate from 18.21 to 20.64mmol/l (p<0.001), although 75% of patients still fell below the target pre-HD bicarbonate. Inter-HD potassium gain was reduced from 1.89 to 1.70mmol/l (p=0.060), due mostly to a modestly significant reduction in pre-HD potassium by 0.15mmol/l (p=0.132). In the 11 responders whose pre-HD bicarbonate increased by at least 2.0mmol/l, pre-HD potassium was reduced by 0.29mmol/l (p=0.028). Pre-HD potassium was reduced by roughly 0.1mmol/l for every 1mmol/l increase in pre-HD bicarbonate, and the frequency of clinically relevant hyperkalaemia (>6.0mmol/l) was reduced from 12.1 to 4.9% of measurements (p=0.056). Systolic/diastolic blood pressures were increased by 6/4mmHg (p=0.021) without change in fluid gains.

Conclusions: Oral sodium bicarbonate is a well-tolerated treatment that reduces inter-HD potassium gain, hence lowering pre-HD levels. The effect size is modest, with achievable reductions in pre-HD potassium around 0.3mmol/l, but the impact on relevant hyperkalaemia and clinical events may be more substantial.

Funding: Government Support - Non-U.S.

FR-PO976

Persistent and Episodic Hyponatremia Are Prevalent in Hemodialysis Patients and Associated with Increased Mortality Ryan A. Brenneis,[1,2] Darcy R. Visscher,[2] Branko Braam.[1] *[1]Univ of Alberta, Edmonton, AB; [2]The King's Univ, Edmonton, AB, Canada.*

Background: Hyponatremia is common in many patient populations and has been linked to increased mortality and undesirable outcomes. Limited information about hyponatremia in hemodialysis (HD) patients indicates a high prevalence, yet, information is lacking regarding outcome. The hypothesis of the current study was that both persistent and episodic hyponatremia in HD patients is prevalent and associated with increased mortality.

Methods: Hyponatremia (Na < 135 mmol/L) of 2473 patients on in-center HD was evaluated using monthly plasma Na over a median of 4.6 years. Prevalence of 10 patterns was studied: persistent hyponatremia, and combining episodic low (1-3 episodes), medium (4-7 episodes) or high (>=8 episodes) frequency with short (1-2 month), medium (>2-<=4 months) and long duration (>4 months). Mortality was assessed for persistent and episodic hyponatremia compared to normonatremia.

Results: Of the patients 34% had normal sodium (no hyponatremia), 1% had stable hyponatremia and 65% had an episodic sodium pattern. Frequencies of episodic hyponatremia and mortality are displayed in the table.

	Duration (Avg. months/episode)					
Frequency	Short 1 -2 months/episode		Average >2-<=4 months/episode		Long >4 months/episode	
	%	% mortality	%	% mortality	%	% mortality
High >8 episodes	9	20	4	14	1	9
Medium 3-7	13	26	3	42	2	40
Low <3	18	33	2	51	1	54

Both persistent hyponatremia and average and long duration, low and medium frequency were associated with decreased survival compared to patients without hyponatremia. High frequency hyponatremia episodes did not predict mortality compared to normonatremia.

Conclusions: In this HD cohort, episodic hyponatremia is highly prevalent implying that a cross-sectional analysis of hyponatremia underestimates prevalence. Moreover, average and long duration with low and medium frequency hyponatremia is associated with increased mortality. Factors that are associated to episodic hyponatremia need further study.

FR-PO977

Predicting Clinical Outcomes Using Phase Angle in Maintenance Hemodialysis Patients Chae Rim Kim, Jung-Ho Shin, Jin Ho Hwang, Su Hyun Kim. *Dept of Internal Medicine, Chung-Ang Univ Hospital, Seoul, Korea.*

Background: Protein-energy wasting is common in hemodialysis patients, and it is an independent risk factor for major adverse events. Recently, bioelectrical impedance analysis (BIA) has been widely used as a non-invasive method to estimate nutritional status. We retrospectively investigated whether nutritional markers measured by BIA can predict clinical outcomes in end-stage renal disease (ESRD) patients receiving hemodialysis.

Methods: ESRD patients who had been treated with outpatient hemodialysis were recruited. Using BIA, phase angle (PA), a nutritional marker, was obtained every 6 months, and patients were divided into two groups according to baseline PA: group A included those with PA ≥4.5°; and group B included those with PA <4.5°.

Results: A total of 142 patients (77 [54.2%] in group A and 65 [45.8%] in group B) were included and were followed for 29 (12, 42) months. The baseline PA was 4.6 ± 1.0°. We found that a decrease in the PA was associated with an increased risk for death, but it was disappeared after the adjustment for age, sex and comorbidity (HR 0.58, 95% CI 0.34–1.00; P = 0.051). Cardiovascular event was not associated with PA (P = 0.685). However, we found that PA predicted the occurrence of infection, independent of age, sex and comorbidity (HR 0.65, 95% CI 0.45–0.94; *P* = 0.20). Although the levels of hemoglobin did not differ between two groups during the study period, patients in group B received higher doses of erythropoiesis-stimulating agents and intravenous iron, compared with those in group

A (P = 0.004 and 0.044, respectively). In longitudinal analyses, patients who had mean Kt/V≥1.4, protein catabolic rate ≥1.2 g/kg/day, total carbon dioxide levels ≥22 mmol/L, or intact parathyroid hormone <300 pg/mL did not have the increases in PA over time.

Conclusions: Nutritional status can be simply assessed using BIA and those provide important information to predict clinical outcomes in ESRD patients with maintenance hemodialysis.

FR-PO978

Obestatin Predicts Clinical Outcomes in Hemodialysis Patients: A Prospective Cohort Study Ilia Beberashvili,[1] Inna Sinuani,[2] Ada Azar,[3] Leonid Feldman,[1] Shai Efrati.[1,4] *[1]Nephrology, Assaf Harofeh Medical Center, Zerifin, Israel; [2]Pathology, Assaf Harofeh Medical Ceneter, Zerifin, Israel; [3]Nutrition, Assaf Harofeh Medical Center, Zerifin, Israel; [4]Research & Development, Assaf Harofeh Medical Center, Zerifin, Israel.*

Background: Obestatin, an anorexigenic gut peptide, has been reported as involved in appetite and energy homeostasis.It is not clear, however, if elevated levels of this hormone in maintenance hemodialysis (MHD) patients contribute to the protein-energy wasting and consequently adverse clinical outcomes.

Methods: A prospective cohort study on 261 MHD outpatients (39% women, mean age 68.6±13.6 years) with median follow-up - 28 months (interquartile range - 19-34 months). We measured obestatin, acyl-ghrelin (AG) levels, appetite, nutritional and inflammatory markers, prospective all-cause and cardiovascular (CV) mortality.

Results: Obestatin positively correlated with AG (r=0.25, p<0.001) and negatively correlated with BMI (r=-0.14, p=0.03) and lean body mass (r=-0.15, p=0.01). During follow-up, 109 patients died, 51 due to CV causes. For each 1.0 ng/ml increase in baseline obestatin levels, multivariable adjusted all-cause death HR was 0.85 (95% CI, 0.75 to 0.96, P=0.01) and CV death HR was 0.82 (95% CI, 0.69 to 0.97, P=0.02). Adjusted models included age, sex, vintage, diabetes, smoking, co-morbidity index, vascular access type, Kt/V, residual renal function, malnutrition-inflammation score and IL-6. Associations between obestatin and mortality risk continued to be significant in analyses that additionally accounted for AG levels. Cubic spline survival models confirmed linear trends.

Conclusions: Higher obestatin level is associated with lower death risk in MHD patients independent of nutritional status and inflammation.Future studies are needed to elucidate underlying mechanisms associated with improved outcomes in MHD population.

FR-PO979

Metabolically Abnormal Non-Obese Phenotype Is Significantly Associated with Increased Mortality in Incident Dialysis Patients Hae-Ryong Yun,[1] Youn Kyung Kee,[1] Changhwan Seo,[1] Seonghun Kim,[2] Tae-Hyun Yoo.[1,2] *[1]Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea; [2]Dept of Internal Medicine, College of Medicine, Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ, Seoul, Korea.*

Background: Metabolically abnormal obesity is associated with high all-cause mortality in general population. However, paradoxical inverse association between obesity and mortality was observed in dialysis population. Therefore, to investigate whether the concept of metabolic unhealthiness with obesity might be applicable in dialysis patients, we performed the post hoc analysis of a prospective cohort study.

Methods: During 2009 and 2015, Total 1,141 Patients who started dialysis were recruited from the Clinical Research Center for End Stage Renal Disease data set. Metabolic abnormality was determined by the presence of 2 or more of the following: 1) HbA1c ≥6.5% or history of diabetes, 2) Triglyceride ≥150 mg/dL, 3) HDL-C ≤40 mg/dL in men or ≤50 mg/dL in women, 4) hs-CRP ≥3 mg/L. Obesity was defined by BMI ≥25.0 kg/m². Patients were divided into four groups [metabolically healthy obesity (MHO), metabolically healthy non-obesity (MHNO), metabolically abnormal obesity (MAO), and metabolically abnormal non-obesity (MANO)].

Results: A 63 (5.5%), 316 (27.7%), 240 (21.0%), and 522 (45.7%) patients were classified into MHO, MHNO, MAO, and MANO group, respectively. All-cause mortality was observed with 5 (7.9%), 43 (13.6%), 35 (14.5%), and 148 (28.3%) patients in each groups, respectively. In Cox proportional hazard analysis, MANO group showed significantly higher all-cause mortality events (hazard ratio, 2.700; 95% confidence interval, 1.09-6.64; P=0.031) even after adjustment for age, sex, smoking status, systolic blood pressure, diastolic blood pressure, serum albumin, calcium, phosphate, uric acid, and total cholesterol and intact-PTH.

Conclusions: MANO group was significantly associated with higher mortality compared to other groups in dialysis patients. Obese phenotype stratified metabolic abnormality is substantially different from that in general population.

FR-PO980

Natural Course of Muscle Mass Change and Related Factors in Patients Undergoing Hemodialysis Hyoungnae Kim,[1] Su-Young Jung,[1] Changhwan Seo,[1] Boyoung Nam,[2] Dae-Suk Han.[1] *[1]Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea; [2]Dept of Internal Medicine, College of Medicine, Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ, Seoul, Korea.*

Background: Muscle wasting is a common feature found in patients undergoing dialysis. Although measurement of muscle mass has been noticed as a prognostic factor in hemodialysis (HD) patients, the natural course of muscle mass change over time and related factors are not fully elucidated in this patient group. Therefore, muscle mass alteration was evaluated and the relationship with demographic and clinical variables was investigated in patients undergoing HD.

Methods: Ninety-three prevalent HD patients were enrolled. The patients were followed-up from January 2011 to December 2015. Total skeletal muscle index (SMI) was evaluated by multifrequency bioimpedance using a four-paired electrode bioimpedance device (InBody 720; Biospace, Seoul, South Korea). Bioimpedance analysis was performed after dialysis on a mid-weak dialysis session every 3 months during the study duration, Biochemical and clinical data were also collected.

Results: The mean age of the enrolled patients was 62.2 ± 13.3 years, and 52 (55.9%) patients were male. Diabetes was accompanied in 34 (36.6%) patients. At baseline, the mean SMI was 9.2 ± 1.2 kg/m^2. During the mean follow-up duration of 49.2 ± 9.9 months, the rate of SMI change was –0.43 kg/m^2/year. SMI decrease was found in 62 (66.7%) patients, while SMI increased in 31 (33.3%) patients over time. Multiple linear regression analysis revealed that baseline CRP (β = 0.25, P < 0.001) and albumin (β = –0.60, P < 0.001) levels were significantly associated with the rate of SMI change after adjusting for confounding factors. However, no significant relationship was found with normalized protein catabolic rate (β = –0.20, P = 0.94), urea reduction ratio (β = –0.01, P = 0.06).

Conclusions: The rate of SMI change over time differs among patients. Chronic inflammation and nutritional status may affect SMI change while the amount of protein intake or dialysis adequacy may not.

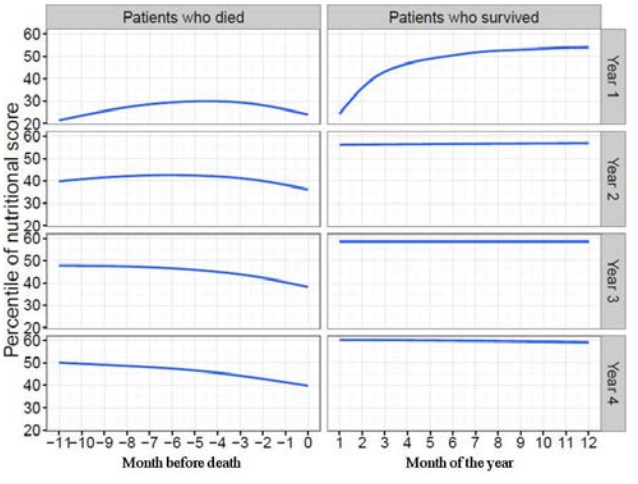
FR-PO981

Dynamics of Nutritional Status in Chronic Hemodialysis Patients before Death Xiaoling Ye,[1] Stephan Thijssen,[1] Jeroen Kooman,[2] Frank van der Sande,[2] Len A. Usvyat,[3] Peter Kotanko,[1,4] Franklin W. Maddux.[3] *[1]Renal Research Inst, New York, NY; [2]Maastricht Univ Medical Center, Maastricht, Netherlands; [3]Fresenius Medical Care North America, Waltham, MA; [4]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Previous studies in chronic hemodialysis (HD) patients(Pts) indicated a decline in nutritional competency up to a year(yr) before death (Thijssen et al., CJASN 2015), but the relationship with HD vintage has not been addressed.

Methods: The goal of this study was to assess nutritional competency in vintage-matched cohorts of HD Pts. We included all Pts who started HD in FMCNA clinics between 01/2006 and 12/2011. Nutritional competency was quantified monthly using a nutritional score that comprised of mean serum albumin, creatinine, phosphate, enPCR, and IDWG. In Pts who died (cases), the score was calculated in the 12 months(mo) before death. Vintage-matched survivors served as controls.

Results: We studied 67,752 HD pts, 26,057 cases (mean age 68; 58% males; 28% Blacks) and 41,695 controls (mean age 61; 56% males; 38% Blacks). Across vintage groups, the number of Pts were distributed as follows: yr1, 13,300 cases & 41,308 controls; yr2, 6,546 cases & 23,216 controls; yr3, 3,872 cases & 11,798 controls; yr4, 2,339 cases & 4,446 controls. In both cases and controls scores increased with longer vintage, we observed distinct differences between cases and controls.



First, across all groups, scores were lower in cases. Second, in controls, the scores either increased (yr 1) or remained stable (yr 2 to 4), whereas in cases scores declined in the final 12 mo. This terminal decline was more pronounced in yr 3 & 4, compared to yr 1 & 2.

Conclusions: Our study shows that nutritional competency is stable in survivors but declines in cases before death. This may indicate a deteriorating nutritional status and may alert health care workers.

Funding: Pharmaceutical Company Support - Renal Research Institute

FR-PO982

Low Body Mass Index and All-Cause Mortality in Patient with Hemodialysis
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Background: Malnutrition is common in patients with hemodialysis and is a major risk factor of mortality. The Korean Society of Nephrology (KSN) collected data of end-stage renal disease registry since 1985. We evaluated whether body mass index (BMI) can affect mortality in patient with hemodialysis.

Methods: From 2004 to 2015, a total of 32,163 patients starting hemodialysis were included. The patients were divided into four groups according to quartiles of BMI measurement.

Results: At baseline, mean age was 59.0 ± 14.3 years old, and 60.0% were men. The 5-year mortality of hemodialysis patients was 16.9 % (N=5,435) and ratio of unknown state was 24.9 % (N=7,996). The mean of BMI in each quartiles were 18.2 ± 1.2, 20.8 ± 0.5 22.8 ± 0.6, 26.4 ± 2.6 kg/m^2 respectively. The mean of BMI between survivor and non-survivor were different (22.3 ± 3.3 vs. 21.5 ± 3.2 kg/m^2). Cox-proportional regression multivariate analysis revealed that the 5-year all-cause mortality was associated with age (HR 1.04, CI 1.03-1.05), diabetes (HR 1.34, CI 1.07-1.7), coronary heart disease or heart failure (HR 1.3, CI 0.9-1.7), 2nd BMI quartile (HR 0.7, CI 0.5-0.9), 3rd BMI quartile (HR 0.6, CI 0.46-0.88), 4th BMI quartile (HR 0.59, CI 0.43-0.82), hypoalbuminemia (HR 2.9, CI 2.3-3.7) and anemia (HR 1.6, CI 1.2-2.0).

Conclusions: Higher quartiles of BMI was significantly associated with better survival rate in hemodialysis patients in Korea. Traditional risk factors of malnutrition, such as hypoalbuminemia, anemia were also independent risk factors for mortality. This result suggests that hemodialysis patients require nutritional support.

FR-PO983

Body Mass Index and Causes of Death in Incident Hemodialysis Patients in Korea
Sejoong Kim,[1] Shin-Young Ahn,[2] Jong Cheol Jeong,[3] Ki Young Na.[1] *[1]Seoul National Univ Bundang Hospital, Republic of Korea; [2]Korea Univ Medical Center Korea Univ Guro Hospital, Republic of Korea; [3]Ajou Univ School of Medicine, Republic of Korea; [4]The Catholic Univ of Korea, Republic of Korea.*

Background: In dialysis patients, higher body mass index (BMI) leads to better survival, so called "reverse epidemiology". However, distribution of BMI in Korea is different from western countries, and cause-specific death is still unknown. We examined 10,299 incident hemodialysis patients from Korean Society of Nephrology registry.

Methods: We evaluated whether various causes of death (cardiovascular disease, malignancy renal disease, diabetes, infection and others related deaths) may be associated with the BMI range using Cox proportional hazards analysis.

Results: During a median follow up of 9.1 years, 5,425 (52.7%) patients died. In multivariable model, a negative association was noted between BMI and all-cause mortality. Compared with the normal BMI group (18.5–24.9 kg/m^2), low BMI group (BMI < 18.5 kg/m^2) had higher mortality with hazard ratio 1.288 (95% C.I. 1.201 – 1.381, p<0.001) and obese group (BMI ≥ 30.0 kg/m^2) had lower mortality with hazard ratio 0.776 (95% C.I 0.588 – 1.023 , p=0.135). Low BMI group had higher kidney disease-specific mortality with hazard ratio 1.382 (95% C.I 1.243 – 1.537, p<0.001) and higher diabetes specific mortality with hazard ratio 1.310 (95% C.I 1.114 – 1.500, p<0.001).

Conclusions: This registry data showed that higher BMI group may be lower risk of all cause mortality, and that low BMI group may be at the higher risk of all-cause mortality, especially kidney specific and diabetes specific mortality.

FR-PO984

L-Carnitine Improves Gastrointestinal Disorders and Altered Intestinal Microbiota in Hemodialysis Patients
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Background: Patients receiving hemodialysis also manifest gastrointestinal symptoms such as constipation, by restriction of water intake and the loss of body water balance. Because dietary carnitine deficiency is supposed to cause smooth muscle dysmotility of the gastrointestinal tract similarly to skeletal muscles, carnitine deficiency in hemodialysis patients may be one cause of gastrointestinal discomfort and dysfunctions.

Methods: We performed a multicenter nonrandomized single-arm prospective clinical trial. 15 Japanese patients receiving hemodialysis were administered L-carnitine tablets (900 mg) for 3 months, and clinical and biochemical analyses were performed before and after the treatment.

Results: Serum total carnitine level increased significantly by the supplementation of L-carnitine for 3 months (from 40.9 ± 2.6 μmol/L to 172.3 ± 19.0 μmol/L, P < 0.05). The myasthenia score decreased significantly by the supplementation (from 1.3 ± 0.3 to 0.8 ± 0.2, P < 0.05). The frequency of passing stool tended to increase with the treatment for 3 months (from 4.2 ± 0.5 times to 4.8 ± 0.5 times). The phyla-level analysis of microbiota showed that the composition of individual microbiota was not different between before and after the supplementation. The genus-level analysis, however, revealed that the genus Clostridium subcluster 4 significantly decreased in number by the supplementation (from 7.7 ± 1.9% to 4.7 ± 1.3%, P < 0.05).

Conclusions: Oral supplementation of L-carnitine to the patients receiving hemodialysis improved not only their muscle discomfort but also their gastrointestinal disorders and microbiota, although its effect on the prognosis of hemodialysis patients should be further investigated.

FR-PO985

Albumin Values with C-Reactive Protein Taken into Account Can Be a Good Predictor of Dialysis Patient Survival
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Background: Albumin is often used for the markers of wasting or malnutrition. However, albumin can also be affected by inflammation. We speculated that albumin values with the inflammatory status taken into account would be a better index in assessing albumin index, namely "C-reactive protein considered albumin". We investigated the association of this index with mortality, and compared the power of prediction of this index with other albumin indices.

Methods: In total, 397 patients were included into this study. Baseline data were obtained in July 2012. The survival until the end of August 2014 (follow up period of 25 months at most) was investigated. Firstly, the regression line was obtained from the entire population between albumin and CRP. Thereafter, the CRP-considered albumin levels were determined as a dichotomous variable; the patients with the albumin values above the regression line were considered high, vice versa. We investigated the association of three albumin indices (the actual values, the dichotomous index by median, and CRP-considered values) and mortality by Cox proportional hazard models.

Results: Among total population, albumin and CRP were correlated reciprocally and weakly significantly; albumin (g/dl) = 3.438 – 0.215 logCRP (log mg/dl), R2=0.126. During the observational period, 73 patients deceased. In univariate Cox analysis demonstrated that all three indices were associated with survival; HR 0.40 (95%CI 0.25 – 0.68), 0.41 (95%CI 0.25 – 0.68), and 0.46 (95%CI 0.28 – 0.74) for each increase of actual albumin, the higher dichotomous albumin by median, and the higher CRP-considered albumin, respectively. On the other hand, only the higher CRP-considered albumin related to the better survival (HR 0.51, 95%CI: 0.30 – 0.85). The degree to which the deviation of albumin was attributable to that of CRP was 12.9%.

Conclusions: CRP-considered albumin was shown to be a better predictor of mortality among dialysis population. In assessing albumin values, inflammatory status should be taken into account.

Funding: Private Foundation Support

FR-PO986

Individualized Prediction of Mortality Using Multiple Inflammatory Markers in Patients on Dialysis: A Prospective Multicenter Cohort Study
Sun-Hee Park, Hee-Yeon Jung, Kyu Yeun Kim, Min Jung Kim, Wonseok Do, Youngae Yang, Taehoon Yim, Inryang Hwang, Sukyung Lee, Ji-Young Choi, Jang-Hee Cho, Chan-Duck Kim, Yong-Lim Kim. *Internal Medicine, Kyungpook National Univ Hospital, Daegu, Republic of Korea.*

Background: This study was aimed to evaluate whether the incremental combination of inflammatory markers captured on routine clinical practice could improve predictive powers for mortalities in patients on dialysis and to develop a predictive model for mortality according to dialysis modality.

Methods: Inflammatory markers obtained at the time of enrollment from 3,309 patients on dialysis from a prospective multicenter cohort were used. Cox proportional hazards regression methods and time dependent ROC curves were constructed and net reclassification index and integrated discrimination improvement were calculated. Cox proportional hazards regression analysis was used to derive a prediction model of mortality.

Results: Addition of the three predictors (WBC, hsCPR, and albumin) one by one to the conventional risk factors had more predictive powers than conventional risk factors alone for all-cause and infection-related mortality in entire population. hsCRP and albumin had additional predictability for cardiovascular mortality in entire population and for infection-related mortality in HD patients. The incremental combination of WBC, hsCRP, and albumin improved predictive powers for all-cause mortality in entire population. hsCRP and albumin gradually increased predictive powers for all-cause and infection-related mortalities in HD patients. Cox multivariate analysis showed age, sex, presence of diabetes, history of coronary artery disease and dialysis vintage were statistically significant predictors of all-cause mortality. The prediction model using multiple inflammatory markers stratified mortality according to dialysis modality.

Conclusions: Multi-marker approaches using multiple inflammatory markers practically available in clinic provided higher predictive power for all-cause mortality in dialysis patients. The predictive model for mortality based on different combinations of inflammatory markers according to dialysis modality enables a stratified risk assessment in this population.

FR-PO987

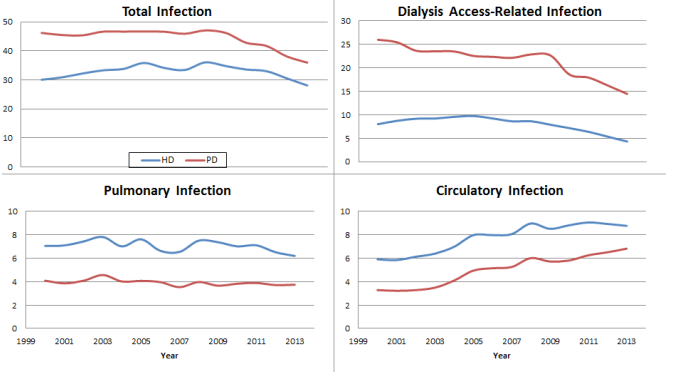
Infection Hospitalization Trend among Hemodialysis and Peritoneal Dialysis Patients

Jiannong Liu,[1] Peer Kidney Care Initiative Investigators.[2]
[1]CDRG, MMRF, Mpls, MN; [2]Peer Kidney Care Initiative.

Background: Infections are a major cause of morbidity and mortality in maintenance dialysis patients (pts). Previous work has shown that peritoneal dialysis (PD) pts are at higher risk for dialysis access (DA)-related infections and hemodialysis (HD) pts for most other infections. However, whether and how infectious hospitalization (IH) rates have changed over time, especially in recent years, is unknown.

Methods: Using the 2000-2013 CMS ESRD database, we identified pts and modalities on January 1 of each year. Pts were followed from January 1 to the earliest of death, transplant, loss of Medicare coverage, or year end. IHs were identified from medical claims and classified as circulatory, pulmonary, DA-related, or other based on the primary diagnosis code. A Poisson regression model was used to test the trend in IH rates and the trend differences between HD and PD pts, 2008-2013.

Results: Before 2008, the overall IH rate was stable among PD pts at approximately 46 per 100 patient-years, but increased among HD pts from 30.1 in 2000 to 36.0 in 2008. Rates then decreased by an average of 5.4% per year for PD and 4.6% per year for HD pts (P=0.001, PD-HD decrease rate comparison).



PD pts had much higher rates of DA-related IH than HD pts; rates decreased since 2008, on average 12.4% per year for HD and 9.1% per year for PD pts (P<0.001). Pulmonary, circulatory, and other IH rates were higher for HD pts. Since 2008, pulmonary IH rates decreased by 3.7% and 0.7% per year for HD and PD pts, respectively (P<0.001); circulatory IH rates increased by 0.2% and 3.3% per year for HD and PD pts, respectively (P<0.001); IH rates for other infections decreased 3.4% per year for HD and remained unchanged for PD pts (P<0.001).

Conclusions: Overall, IH rates decreased for both HD and PD pts in recent years, but more improvement is needed, especially for PD pts and for DA-related infections.

Funding: Pharmaceutical Company Support - Financial support for the Peer Kidney Care Initiative is provided by the following participating provider organizations: American Renal Associates, Atlantic Dialysis Management Services, DaVita HealthCare Partners, Dialysis Clinic, Inc., Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Satellite Healthcare, The Rogosin Institute, U.S. Renal Care, and Wake Forest University

FR-PO988

Associations between Apolipoproteins and Infection, Cardiovascular Events and Mortality in Patients Receiving Dialysis

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Background: Lipid lowering therapy may not be beneficial in the dialysis population. Lipoproteins play a role in the innate immune system, providing a potential link to infection that may counterbalance cardiovascular (CV) effects.

Methods: We examined the associations between serum concentrations of apolipoproteins A1, B, C2, and C3 and all-cause mortality, CV- and infection-related hospitalization or death in 442 participants in the ACTIVE/ADIPOSE study of prevalent HD patients recruited 2009-2011, followed through March 2014. We examined associations between each lipoprotein and outcomes using Cox models with time-varying apolipoprotein concentrations (q 6 mos).

Results: In univariate models, higher levels of each of the apolipoproteins were associated with statistically significantly lower risk of infectious events and, except for apo A I, with lower all-cause mortality. Apolipoproteins were not associated with CV events. In multivariable models, higher Apo A1 concentration was associated with lower risk of infection and higher Apo B was associated with lower risk of all-cause mortality.

Analyte	Mortality		Infection		CV Outcome	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
	Multivariable Analysis					
Apo A1 10 Units	0.96 (0.89-1.04)	0.35	0.94 (0.88-0.99)	0.030	0.94 (0.86-1.03)	0.18
Apo B 10 Units	0.91 (0.82-1.00)	0.047	0.95 (0.88-1.02)	0.17	0.93 (0.80-1.08)	0.34
Apo C2	0.95 (0.87-1.03)	0.23	0.95 (0.97-1.03)	0.19	0.99 (0.89-1.11)	0.88
Apo C3	0.96 (0.92-1.01)	0.13	0.97 (0.94-1.01)	0.18	1.01 (0.95-1.06)	0.82

Conclusions: Lipoproteins were associated with lower risk of infection-related outcomes and death but were not associated with CV outcomes. These results may help explain the unclear benefit of lipid lowering in the dialysis population.

Funding: NIDDK Support

FR-PO989

Association between Plasma Macrophage Stimulating Protein Levels and Risk of All-Cause Mortality in Hemodialysis Patients

Tetsu Miyamoto,[1] Mika Matsumoto,[2] Yumi Furuno,[3] Kenichiro Bando,[1] Junichi Nakamata,[1] Yoko Fujimoto,[3] Ken Otsuji,[1] Ikutaro Furuno,[1] Yutaka Otsuji,[1] Masahito Tamura.[3] *[1]2nd Dept of Internal Medicine, Univ of Occupational and Environmental Health School of Medicine, Kitakyushu, Japan; [2]Yukuhashi Clinic, Yukuhashi, Japan; [3]Kidney Center, Univ of Occupational and Environmental Health School of Medicine, Kitakyushu, Japan.*

Background: Persistent low-grade inflammation, a condition observed in a majority of hemodialysis patients, is a major driving force of the uremic phenotype which leads to increased morbidity and mortality. Macrophage stimulating protein (MSP), also known as Hepatocyte Growth Factor-like protein (HGFL), has been demonstrated to play a key role in regulating inflammation in the peripheral tissues of multiple disease models.

Methods: In this multicenter prospective cohort study comprising 236 maintenance hemodialysis patients (37% female; median age, 66 years; age range, 21-92 years), we investigated the effect of MSP levels, measured by enzyme-linked immunosorbent assay, on all-cause mortality, with a particular focus on inflamed patients. We used Kaplan-Meier analyses and multivariate Cox regression analyses to estimate mortality risk.

Results: During the observation time (median observation time, 25 months), a total of 31 patients died during the observation period. Patients were categorized into two groups according to serum C-reactive protein (CRP) levels. In the inflamed patient group (CRP > 0.5 mg/dL, n=49), Kaplan-Meier analysis comparing the survival rate between lower and higher plasma MSP levels, showed that patients with lower MSP levels, defined as the lowest tertile of plasma MSP (<223 ng/mL), had an significantly higher mortality risk (Log rank X^2=8.0, P = 0.005). When adjusting for age, sex, dialysis vintage, diabetes mellitus and cardiovascular disease, lower MSP levels was independently related to increased mortality (Hazard ratio [HR]:3.8, 95%CI:1.3-11.1;P=0.01). Conversely, no association was observed in patients in the non-inflamed patient group (CRP < 0.5 mg/dL).

Conclusions: Plasma MSP levels may be a useful biomarker for assessing 2-year mortality risk in maintenance hemodialysis patients with high CRP levels.

FR-PO990

B-Lymphocytes Depletion, a New Mortality Risk Factor in Hemodialysis

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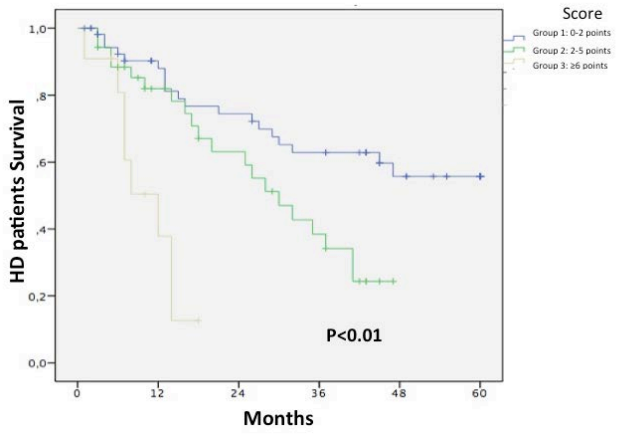
Background: Acquired quantitative disturbances in immunity system are known in hemodialysis patients (HDP). It could explain the deaths for infection events, and a effect on the atherosclerosis process is discussed. The aim of this study was to analyze the effect of immune cell subsets (ICS) in the mortality of HDP.

Methods: Prospective observational single centre study in HDP from 2011-12. Total and ICS (CD3, CD4, CD8, CD56, CD19) were measured. We used a new score of mortalility with this variables: Charlson's index ≥7=2 points (p), Kt/V <1.2=3p, previous failed transplantation=-2p, low CD19 with normal serum albumin (SA)=3p, low SA with normal CD19 lymphocytes=6p and low SA with low CD19 lymphocytes=2p.

Results: We included 104 patients, 51% male, with mean age 64±15 years old. The mean Charlson's index was 6.5±2.7 and the mean time with renal replacement therapy was 57±76 months. The distribution of ICS was 45% low total lymphocytes (<1200cells/mm^3), 40% CD3 (<850cells/mm^3), 37% CD4 (<500cells/mm^3), and 58% CD19 (<100cells/mm^3) of the HDP. The mean of the follow-up was 23.8±17 months. Forty-eight (46%) patients died. The causes of death were 40% for cardiovascular disease, 31% infection disease and 13% oncology disease. The death risk factors showed in the univariable analysis were Charlson's index ≥7 (OR=2.5 (1.3-4.6), p<0.01), Kt/V <1.2 (OR=3.8 (1.6-9.4), p<0.01), previous failed renal transplantation (OR=0.4 (0.2-0.8), p<0.01), low CD19 (OR=2.2 (1.1-4.3), p=0.01) and SA <3.5 g/dL (OR=2.5 (1.3-4.8), p<0,01). We classified HDP according their punctuation in score: Group 1 with 0-2 points, Group 2 with 3-5 points and Group 3 with > 6 points. Survival is shown on the graphic.



Conclusions: Lower CD19 lymphocyte is a new independent mortality risk factor in HDP. Our score could be a new tool to predict the risk of death in HD patients. Our score needs to be validated in other populations for be generalized.

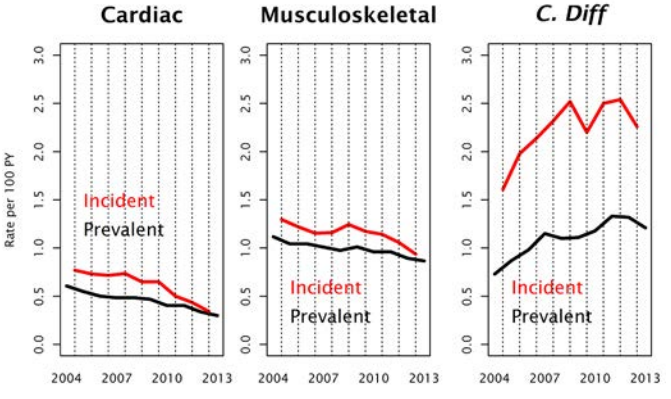
FR-PO991

Cardiac, Musculoskeletal, and *C. diff* Infections in Hemodialysis Patients David T. Gilbertson,[1] Peer Kidney Care Initiative Investigators.[2] [1]*Chronic Disease Research Group, Minneapolis Medical Research Foundation, Minneapolis, MN;* [2]*Peer Kidney Care Initiative.*

Background: Dialysis patients are at significantly increased risk of hospitalization due to infection. Trends in overall infection rates have been well described, but less is known about cause-specific infections. We assessed trends in cardiac (e.g., endocarditis), musculoskeletal (e.g., osteomyelitis, septic arthritis), and *C. diff* (e.g., colitis) infections in dialysis patients, 2004-2013.

Methods: We used the Centers for Medicare & Medicaid Services End-Stage Renal Disease database to examine rates of hospitalization with a primary cause of cardiac, musculoskeletal, or *C. diff* infection among dialysis patients. Analyses were performed separately for prevalent patients (> 1 year on dialysis) and incident patients (≤ 1 year on dialysis).

Results: For all three infection types, rates were higher in incident than in prevalent patients, particularly for *C. diff* infections. While rates of cardiac and musculoskeletal infections declined from 2004-2013, *C. diff* infections increased ~ 40% among incident and prevalent patients.



Conclusions: While overall hospitalized infection rates were relatively constant from 2004-2013 despite decreasing all-cause hospitalization rates, trends varied by infection type. These infections comprise only a modest percentage of all-cause infections, but the decrease in hospitalizations for cardiac and musculoskeletal infections is encouraging. However, dialysis patients with *C. diff* infections are at increased risk for morbidity and mortality, and interventions to reduce risk are needed.

Funding: Pharmaceutical Company Support - Financial support for the Peer Kidney Care Initiative is provided by the following participating provider organizations: American Renal Associates, Atlantic Dialysis Management Services, DaVita HealthCare Partners, Dialysis Clinic, Inc., Fresenius Medical Care, Independent Dialysis Foundation, Northwest Kidney Centers, Satellite Healthcare, The Rogosin Institute, U.S. Renal Care, and Wake Forest University

FR-PO992

Infective Endocarditis in Dialysis-Dependent Chronic Kidney Disease: One Centre's Experience Andrew Nixon, Naeem Desai, Ajay Prabhakar Dhaygude. *Renal Medicine Dept, Royal Preston Hospital, Preston, Lancashire, United Kingdom.*

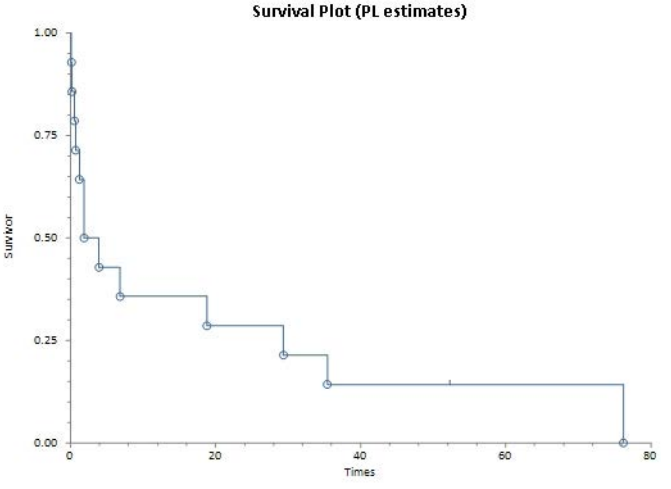
Background: Infective Endocarditis (IE) is a devastating complication of dialysis-dependent chronic kidney disease (CKD).[1,2] One-year survival rates were reported to be as low as 38.4% over a decade ago.[2] We wished to establish if there had been any improvement in outcomes in recent years.

Methods: The local echocardiogram database was reviewed to identify all reports suggesting a valve vegetation between August 2002 and March 2016. Clinical records were then reviewed to identify all those with dialysis-dependent CKD diagnosed with IE.

Results: Fourteen patients were identified (15 episodes). The median age was 65 years (range 32-84 years). The male:female was 1:1. The median dialysis vintage was 9 months (range 1-46 months). Table 1 demonstrates patient clinical characteristics.

Clinical Characteristics	Number of Episodes (%)
Haemodialysis	13 (87)
Central Venous Catheter	6 (40)
Pre-existing Valve Lesion	9 (60)
Previous Valve Surgery	2 (13)
Valve Affected -Mitral -Aortic -Tricuspid ->1 Valve	 10 (67) 4 (27) 4 (27) 3 (20)
Causative Organism(s) -*Staphylococcus Aureus* -*Enterococcus sp.* -*Other*	 8 (53) 5 (33) 3 (20)

Valve surgery was performed for 3 patients (21%). Survival rates were as follows: 30-day: 71% (n=10); 90-day: 50% (n=7); 1-year: 36% (n=5). Figure 1 demonstrates Kaplan-Meier survival analysis (months).



Conclusions: Dialysis-dependent CKD patients, irrespective of dialysis access and pre-existing valve disease, are at risk of IE. Survival rates remain low for patients with dialysis-dependent CKD diagnosed with IE. **References:** 1. Doulton T et al. Infective endocarditis in dialysis patients: new challenges and old. Kidney Int. 2003 Aug;64(2):720-7. 2. Shroff GR et al. Long-term survival of dialysis patients with bacterial endocarditis in the United States. Am J Kidney Dis. 2004 Dec;44(6):1077-82.

FR-PO993

Urinalysis in the Diagnostic Workup of Dialysis Patients with Possible Infection Katerina Oikonomou, Adib Alhaddad. *Internal Medicine, NYU Lutheran Medical Center, Brooklyn, NY.*

Background: Data on the role of urinalysis (UA) in the diagnostic workup of dialysis patients with possible infection are limited, and there is also variability in the coexistence of urinary tract infection (UTI).

Methods: A retrospective study was conducted to assess the sensitivity, specificity, and positive, and negative predictive values of urinalysis parameters in dialysis patients who were hospitalized between 9/2008 and 8/2015 with an admitting diagnosis of fever, sepsis or urinary tract infection. Characteristics of patients were recorded, and their associations with urinalysis parameters were assessed with Fisher's exact test. Receiver operating characteristic (ROC) analysis of urinalysis parameters was also performed.

Results: 275 dialysis patients (141 males, mean age 73±14.9 years) were assessed. Pyuria of different cut-offs (>10, >50 WBC/HPF) was associated with urine culture positivity (P< 0.001), and growth ≥10^5 CFU/ml (P=0.039), but not with presence of fever or sepsis. There was also association with urinary catheter use (P=0.001). Pyuria >10 WBC/

HPF had a sensitivity of 86%, and a specificity of 35% for identification of a positive urine culture with growth $\geq 10^5$ CFU/ml (P=0.025). Pyuria > 50 WBC/HPF had a sensitivity of 66% and a specificity of 58% (P=0.032). Bacteriuria, and leukocyte esterase (LE) positivity were associated with positive urine culture but not with growth $\geq 10^5$ CFU/ml. LE was also associated with presence of urinary catheter (P=0.031). No difference was found in patients with or without fever or sepsis in terms of bacteriuria, LE or nitrite positivity.

Conclusions: In the absence of adequate specificity and positive predictive value of urinalysis in dialysis patients with fever, sepsis or suspected UTI, a urine culture should be obtained to guide further treatment. Physicians should be vigilant for sources of infection other than the genitourinary tract.

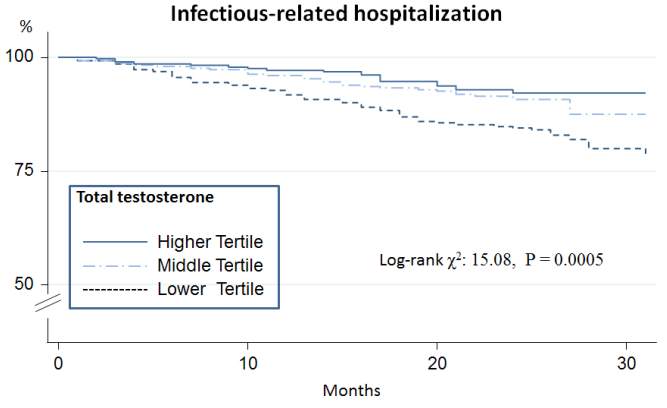
FR-PO994

Association between Low Serum Testosterone and All-Cause Mortality and Infection-Related Hospitalization in Male Hemodialysis Patients: Prospective Cohort Study Akio Nakashima, Ichiro Ohkido, Keitaro Yokoyama, Takashi Yokoo. *Div of Nephrology and Hypertension, Dept of Internal Medicine, Jikei Univ School of Medicine, Tokyo, Japan.*

Background: Infectious diseases are the second-highest cause of death in patients on dialysis. In addition, testosterone deficiency is prevalent in dialysis. However, no studies have investigated the association between testosterone levels and infection-related hospitalization (IRH). We aimed to evaluate whether serum testosterone levels are associated with IRH and mortality in male hemodialysis patients.

Methods: We divided the study population into three groups based on serum testosterone levels. Associations between testosterone levels and the clinical outcomes of IRH, and all-cause mortality were analyzed using the Cox proportional hazard model after controlling for important clinical covariates.

Results: 902 male patients were enrolled and followed up for a median of 24.7 months. Their mean age (±SD) was 63.4 (± 11.8) years.123 participants died during follow-up. IRH occurred in 116 patients. IRHs were significantly more frequent in the lower than higher testosterone tertile (hazard ratio [HR], 2.12; 95% confidence interval [CI], 1.18-3.79) in adjusted models.



Moreover, all-cause mortality was significantly greater in the lower groups (HR, 2.26; 95%CI, 1.21-4.23).

Conclusions: These results suggest that low levels of testosterone are associated with higher rates of IRH and all-cause mortality in male hemodialysis patients.

FR-PO995

Nasal Methicillin-Resistant *Staphylococcus aureus* Carriage in Hemodialysis Patients: Hospital-Based versus Separate Dialysis Centers Georg Schlieper, Werner Kleophas. *MVZ DaVita Rhein Ruhr, Duesseldorf, Germany.*

Background: Methicillin-resistant Staphylococcus aureus (MRSA) colonization in hemodialysis patients is associated with higher risk for systemic infection. Recent hospitalization and temporary dialysis access are known risk factors for MRSA colonization. Whether MRSA colonization rates in hospital-based dialysis centers differ from separate dialysis centers is unknown.

Methods: Nasal swab cultures for MRSA were performed regularly according to the local health authority. MRSA-positive patients were decolonized according to a standardized protocol (intranasal mupirocin, tooth brush, oral and body octenidine). Results of positive swab cultures for MRSA were assessed in 358 hemodialysis patients of two separate dialysis centers (n=185) and four hospital-based dialysis centers (n=173) in February 2015 and February 2016.

Results: The rate of positive nasal swab cultures for MRSA of all centers were 4.8% in 2015 and with 1.4% significantly lower in 2016 (p=0.002). The MRSA rates of single centers ranged from 0% to 7.5%. The positive MRSA rate in hospital-based dialysis centers was higher than in separate dialysis centers (3.9% vs. 2.5%, p<0.001).

Conclusions: Despite significant differences of positive nasal swab cultures for MRSA in different years hospital-based dialysis centers had a higher positive MRSA rate compared to separate dialysis centers. Whether in-depth analysis of transmission ways may reduce MRSA rates in dialysis patients remains to be investigated in future studies.

FR-PO996

Efficacy and Safety of Sofosubuvir-Based Treatment in Patients with Chronic Hepatitis-C Infection and End Stage Renal Disease Haresh N. Savani. *Nephrology, Savanikidney Care, Surat, Gujarat, India.*

Background: treament for hepatitis-c infection for patients of end stage renal disease on regular haemodialysis is difficult, treatment option are limited.we have treated hepatitis-c infected patients on regular hemodialysis ,genotype-1 postive patients treated with fix dose combination of sofosbuvir and ledipasvir on alternate day,and genotype-3 positive patients with sofosbuvir and daclatasvir [alternate day].

Methods: in haemodialysis unit total 14 patients were infected with hepatitis-c, 11 patients of genotype-1, and 3 patients of genotype-3.genotype-1 infected patients were treated with fix dose combination tablet containg ledipasvir 90mg and sofosbuvir 400mg administered orally alternateday for 12 weeks.genotype-3 infected patients treated with tablet of sofosbuvir 400mg and tablet of daclatasvir 60 mg ,given orally alternate day for 12 weeks.routine clinical and laboratory data were collected at base line and during treatment.the primary out come was sustained virological response at week 12(SVR12).

Results: totlal 14 patients,10 male ane 4 female,of various age group between 34 to 71 years were included in this study.therapy was well tolereted. no patient discontinued treatment because of side effects.comparsion of lab at baseline and nadir level during treatment revealed no significant change in haemoglobin ,platletcount,ALT,and billirubin.all 14 patients had undetectable HCV RNA at the end of treatment.no cardiac or hepatobiliary toxicity observed during treatment.one patient had nausea,one patient had drop in haemoglobin by 1 gm/dl.other wise no side effects at all.

Conclusions: alternate day fix dose sofosbuvir and ledipasvir for HCV genotype-1 infection , and also alternate day sofosbuvir and daclatasvir for HCV genotype -3 infection ,was highly effective in previously untreated hepatitis-c infection in patients of end stage renal disease, on regular dialysis.treatment was safe,no significant adverse events were observed during the period of treatment.

FR-PO997

Sofosbuvir and Ribavirin Is Safe and Effective Therapy in Chronic Hepatitis C Patients with End-Stage Renal Disease and GFR (30 ml/min) Suman Nayak.[1] [1]*Nephrology, Inst of Liver and Biliary Sciences, New Delhi, Delhi, India;* [2]*hepatology, Inst of Liver and Biliary Sciences, New Delhi, Delhi, India.*

Background: Direct acting antiviral (DAAs) have been very effective in chronic hepatitis C. However, treatment of HCV in patients with advanced CKD on HD and low GFR (30ml) remains a major challenge due to the lack of reported efficacy and safety data of DAAs in this population. We investigated the efficacy and safety of Sofosbuvir (SOF) and Ribavirin (RBV) in chronic HCV infected CKD patients on HD and CKD stage 3 and 4 **Patients and methods:** Patients with CKD on HD and GFR (30 ml/min) having chronic HCV infection, were prospectively enrolled between September 2015 –June 2016 to receive SOF with RBV for 24 weeks. Patients were started on SOF 400 mg daily and RBV at 200 mg once to thrice weekly (as per tolerability of patients and serial Hb values). Safety and efficacy data were collected; including SVR12 and SVR24 data for all patients after completing therapy. **Results:**48 patients have been enrolled, with mean age of 44.99 ±11.99 yrs. 39(81.3%) patients were on dialysis and 7(14.6%) in stage 4, 2(4.1%) with stage 2 . 4 out of 48 patients were having Chronic liver disease and one patient was post liver transplant. The mean viral load at baseline was 5.78±1.4log (median =6 varies from 1.0-7.8 copies). HCV genotype 1 was present in 28(58.3%) and genotype 3 in 20 (41.7%) patients. 39 %(19) patients have completed 24 weeks of therapy. The virological cure was achieved in 19/19 (100%) of patients who have completed 24 weeks. Those who have reached 12 weeks & 24 weeks post-treatment had 100 % SVR at 12 & 24 Wk. 34% patients required adjustment in ribavirin dosage and increase in erythropoietin dose. **Conclusions**: Sofosbuvir plus ribavirin therapy, given for 24 weeksappears to be well tolerated in patients with advanced renal failure and carries good efficacy results with 100% SVR at 12 weeks.

Funding: Government Support - Non-U.S.

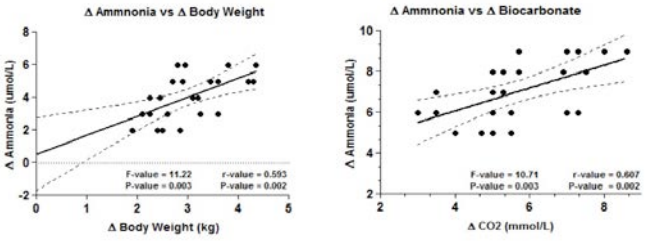
FR-PO998

Effects of End-Stage Renal Disease (ESRD) and Dialysis Modalities on Blood Ammonia Level Madeleine V. Pahl, Mahyar Khazaeli, Ane C. Nunes, Kevin T. Harley, Hyder Said, Wei Ling Lau, Nosratola D. Vaziri. *Nephrology and Hypertension, Univ of California, Irvive, Orange, CA.*

Background: ESRD results in increased urea levels in gastrointestinal and glandular secretions. In the gut, bacterial hydrolysis of urea results in formation of ammonia and increased intestinal permeability. In the breath, nasopharyngeal bacterial hydrolysis and exhalation of circulating blood ammonia by the lungs contribute to ammonia levels. A direct correlation between breath ammonia and blood urea levels exits in ESRD, and hemodialysis (HD) treatments result in reduction of breath ammonia. The effects on blood ammonia are unknown and are explored here.

Methods: Blood from 23 HD (pre and post HD), 11 peritoneal dialysis (PD) and 6 controls (CNT) individuals were assayed for ammonia, urea, and bicarbonate.

Results: Baseline urea was significantly higher in HD (52.0 ± 21.1 mg/dL) and PD (44.8± 13.4 mg/dL) when compared with CNT groups (14.9 ± 4.5 mg/dL). No difference was found in baseline blood ammonia between HD (19.0 ± 1.4 umol/dL), PD (20.2 ±1.4 umol/dL) and CNT groups (25.3 ± 0.3 umol/dL). HD resulted in reduction in urea concentration (P<0.001) and a rise in blood ammonia level (28.8 ± 2.1 umol/dL; p<0.05). This was inversely related to the change in body weight and directly related with the change in bicarbonate concentration.



Conclusions: The post-HD fall in blood urea levels is paradoxically accompanied by a rise in breath ammonia. This rise is directly related to the extent of ultrafiltration and inversely related to the rise in bicarbonate concentration. Ultrafiltration may result in an acute reduction of hepatic perfusion limiting the liver's ability to convert gut-derived ammonia to urea. Additionally, the acute correction of mild acidosis in which ammonia is held as a nonvolatile ammonium, to a normal or alkalotic state can result in increased levels of volatile ammonia.

Funding: Other NIH Support - Univ. Calif., Irvine Institute Clinical Translational Science: Grant UL1 TR001414

FR-PO999

Quantification of Risk Factors for Progression of Medial Arterial Calcification W. Charles O'Neill,[1] Syed Mustafa Ahmed,[1] Shumila Manzoor,[1] Ioannis Sechopoulos,[2] Baowei Fei.[2] *[1]Renal Div, Dept of Medicine, Emory Univ, Atlanta, GA; [2]Dept of Radiology, Emory Univ, Atlanta, GA.*

Background: The relative effects of risk factors for medial arterial calcification are unknown because of the difficulty in quantifying it and distinguishing it from atherosclerotic calcification. Calcification of breast arteries is exclusively medial, readily apparent on mammograms (MGs), and correlates with peripheral arterial calcification and clinical outcomes. We hypothesized that progression and the effect of putative risk factors could be measured by routine mammography.

Methods: Women with breast arterial calcification (BAC) and the following single risk factors were identified: end-stage renal disease (ESRD) on hemo- or peritoneal dialysis, diabetes, warfarin therapy, or no risk factors (eGFR>90 ml/min/1.73 m2, no diabetes or warfarin). Lengths of calcified arterial segments were summed and compared between MGs in a blinded fashion, with BAC rate expressed as mm/yr per breast (+/- SE). Breast CT scanning was used to validate the measurements.

Results: Intra- and interobserver correlations were 0.99 (n=28) and 0.98 (n=31). Interstudy variability, determined by averaging residuals of the linear regression of 5 successive MGs, was 9.8 +/- 1.2%. The correlation between CT and MG was 0.92 (n=10 breasts). In subjects with no risk factors, BAC was rare before age 65 and the rate increased by 1.1 mm/yr each decade (mean 3.4 +/- 0.7 mm/yr; n=32; age: 78.8 +/- 1.2). BAC rate increased to 6.1 +/- 1.6 mm/yr in diabetics ($p<0.01$, n=15; age: 75.7 +/- 2.3) and 8.9 +/- 2.5 mm/yr in ESRD ($p<0.01$, n=18; age: 57.4 +/- 3.1) but the ESRD effect is greater considering the younger age. ESRD + diabetes resulted in very high rates (53.4 +/- 10.9 mm/yr; n=23; age: 61.1 +/- 1.4). In MGs before and during warfarin, progression increased 10-fold from 1.7 +/- 0.7 to 16.4 +/- 5.4 mm/yr (age: 78.7 +/- 3.6; n=11). BAC rate did not correlate with baseline BAC (r=0.08).

Conclusions: Mammography is a convenient and reliable method to measure progression of medial arterial calcification. Age, diabetes, ESRD, and warfarin are all risk factors for progression, with warfarin, ESRD, and ESRD + diabetes being the strongest.

Funding: Clinical Revenue Support

FR-PO1000

Residual Renal Function Is Associated with Vascular Calcification and Valvular Calcification in Hemodialysis Patients Dong Ho Shin, Eunjung Kim, Jung-Woo Noh, Ja-Ryong Koo. *Hallym Univ College of Medicine.*

Background: Vascular calcification (VC) and cardiac valvular calcification (CVC) are common and may contribute to cardiovascular mortality in hemodialysis patients. Although there are multiple risk factors associated with VC and CVC in hemodialysis patients, little is known about the potential influence of RRF on VC and CVC in hemodialysis patients. Thus, we investigated VC and CVC according the degree of RRF in hemodialysis patients.

Methods: A total of 144 patients with RRF on maintenance hemodialysis for > 3 months were recruited between January 2014 and February 2016 at Kangdong Sacred Heart Hospital, Kangnam Sacred Heart Hospital, and Dontan Sacred Heart Hospital. Abdominal aortic calcification (AAC) score was measured on lateral lumbar radiographs and arterial stiffness was assessed by brachial-ankle pulse wave velocity (baPWV). Additionally, CVC was assessed using echocardiogram. Univariate and multivariate logistic regression were conducted to ascertain the potential influence of RRF on VC and CVC.

Results: Themean patient age and dialysis duration were 56.4 ± 10.8 years and 36.3 ± 11.2 months, respectively. The median RRF was 1.2 ml/min/1.73 m^2 (interquatile range 0.4 - 2.1 ml/min/1.73 m^2). AAC score [9 (3 - 22) vs. 5 (0 - 17), p = 0.04] and baPWV [1895.0 (1707.0 - 2155.5) cm/s vs. 1785.0 (1558.0 - 1983.0) cm/s, p = 0.003] were significantly higher in patients with RRF < 1.2 ml/min/1.73 m^2. CVC was common in patients with RRF < 1.2 ml/min/1.73 m^2 (45.1% vs. 23.1 %, p = 0.04). In multivariate analysis, RRF was identified as factors affecting AAC scoring (β = -0.210, P = 0.03) and baPWV (β = -0.146, P = 0.04), after adjusting for age, diabetes, smoking history, C-reactive protein, total cholesterol, and calcium-phosphate product.

Conclusions: This study showed that RRF in hemodialysis patients contributes significantly to the VC and CVC. Therefore, continuous monitoring of RRF may be useful to predict the risk of cardiovascular event in hemodialysis patients.

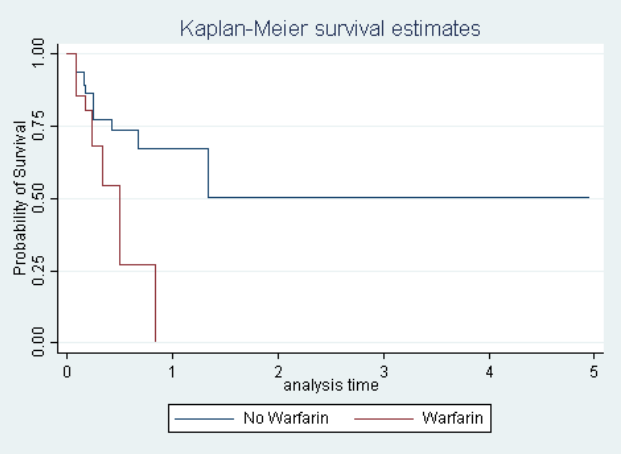
FR-PO1001

The KUMC Calciphylaxis Registry-Clinical Characteristics and Factors Associated with Mortality Peter W. Santos,[1] Jianghua He,[2] Ahmad M. Tuffaha,[2] James B. Wetmore.[3] *[1]AKDHC, Phoenix, AZ; [2]Univ of Kansas Medical Center, Kansas City, KS; [3]Hennepin County Medical Center, Minneapolis, MN.*

Background: We sought to describe clinical characteristics, methods of diagnosis, treatments prescribed, and mortality in CUA patients using cases reported in the University of Kansas Medical Center Calciphylaxis Registry (KUMC CR), a voluntary web-accessible registry.

Methods: Descriptive was reported as percents or means. Univariate analysis using the Cox survival model was conducted to estimate the hazard ratios (HRs) for factors associated with mortality. Kaplan-Meier survival curves of subgroups with different risk burdens were compared with log-rank tests.

Results: Of 117 patients, mean age was 58.5 years, females comprised 63.8%, and 63.8% were white. Mean BMI was 31.9 kg/m^2. DM was present in 66.7% and cardiovascular disease (CVD) in 62.2%. Warfarin was used in 40.2%. The mean iPTH level was 459 pg/ml, P was 6.3 mg/dl, uncorrected Ca was 9.0mg/dl, and Alb was 3.1 g/dl. Clinical suspicion (56.7%) was the most common diagnostic approach, while 32.5% had a histological diagnosis; only 9.4% underwent a bone scan. While nonspecific wound care was initiated in 70.9% of patients, debridement was undertaken in only 42.6% of cases. Sodium thiosulfate (STS) was initiated in 54.7% of patients, with the majority (74.1%) receiving ≥ 12.5 mg of STS, most often for <3 months (79.7%). In univariate analysis higher mortality was observed in patients with CVD (HR=10.47; 95% CI, 1.40 to 78.38), and those taking warfarin (HR=2.74; 95% CI, 1.16 to 6.51).



Conclusions: In real-world clinical practice, there is substantial heterogeneity in the diagnosis and treatment of CUA. Bone and mineral parameters were not often strikingly abnormal. The presence of CVD and use of warfarin appear to be mortality risk factors.

FR-PO1002

UK Calciphylaxis Study: Interim Analysis Abby Leah Huckle, Helen Alderson, Smeeta Sinha, Philip A. Kalra. *Vascular Research Group, Inst of Population Health, The Univ of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom.*

Background: Calcific uraemic arteriopathy (CUA or calciphylaxis) is a rare condition associated with a high mortality. It predominantly affects dialysis patients and is characterised by debilitating skin ulceration and calcification of cutaneous arterioles.

Methods: The UK calciphylaxis Study is a UK wide prospective observational internet-based study of CKD associated calciphylaxis. Data including demographics, laboratory results, medication use and therapeutic interventions are collected from enrolled patients on a 4 monthly basis.

Results: Data was available for 63 patients enrolled between 2012 and 2016. 76.2% were on renal replacement therapy (peritoneal or haemodialysis). 52.4% were female, median age was 57.5 years (IQR 52-66). 58.2% had a BMI >30 and 80.8% a BMI of >25. Prior to lesion development 66.7% (n=42) were prescribed a phosphate binder, 36.5% (n=23) a vitamin K antagonist. Baseline mean corrected calcium was 2.41 (SD±0.209) mmol/l, phosphate 1.68 mmol/l (SD±0.58) and iPTH median was 91.1 (IQR=29.6-189.8) mmol/l. The majority of lesions were on the lower extremities (57.1%), followed by the thighs (28.6%) and abdomen (15.9%). The treatment used varied considerably between patients.

Conclusions: 80.8% of patients in this study were overweight in comparison to the average dialysis population. Vitamin K antagonist use was highly prevalent in keeping with the literature; both may be important risk factors for the development of CUA. Therapeutic strategies varied greatly identifying a need for more research and consensus on the management of this condition.

FR-PO1003

Direct Links between Coronary Artery Calcification, Abnormal Cardiac Function, and Mortality in CKD-5D Paul Anaya,[1,2] Gustav A. Blomquist,[3] Daniel Davenport,[4] Marie-Claude M. Faugere,[5] Vincent L. Sorrell,[1,2] Hartmut H. Malluche.[5] *[1]Div of Cardiovascular Medicine; [2]Dept of Internal Medicine; [3]Dept of Radiology; [4]Dept of Surgery; [5]Div of Nephrology, Bone & Mineral Metabolism, Univ of Kentucky, Lexington, KY.*

Background: Coronary artery calcification (CAC) is common in patients with chronic kidney disease on hemodialysis (CKD-5D) and is an important predictor of mortality, but cardiac functional links between CAC and mortality have not been well-established. This study tested the hypothesis that CAC increases mortality by adversely affecting cardiac function.

Methods: Patients were recruited from 37 regional dialysis centers. 2-D and Doppler echocardiographic (Echo) analyses were performed and CAC was measured using 64-slice computed tomography. Relationships between CAC and Echo measures of left ventricular (LV) function were analyzed. Survival was assessed with median follow-up of 37 months.

Results: There were 157 patients: 59% men, 46% Caucasian, 48% diabetic. Median age was 55 years and median duration of CKD-5D was 45 months. Agatston CAC scores >100 were found in 69% of patients with 51% having a score >400. CAC was associated with measures of LV systolic and diastolic function (global longitudinal strain [GLS; rho=0.270, p=0.004]), mean LV systolic velocity (rho= -0.259, p=0.004), and estimate of LV filling pressure (E:E'; rho=0.286, p=0.001). Multivariate regression confirmed these relationships after adjustment for age, gender, ejection fraction and coronary artery disease. Valvular calcification varied linearly with CAC (p<0.05). Both LV diastolic and systolic functional measures were significant predictors of mortality; the strongest of which was LV diastolic dysfunction.

Conclusions: These findings show a link between CAC, cardiac function, and mortality in CKD-5D. LV diastolic function (E:E'), peak LV systolic velocity, and GLS are independent predictors of mortality. Valvular calcification may be an important marker of CAC in CKD-5D. These effects on cardiac function likely explain the high mortality with CKD-5D and describe a potentially valuable role for Echo in the routine management of these patients.

Funding: NIDDK Support

FR-PO1004

Clinical Significance of Vascular Calcification Volume Assessed by 3D Imaging Software Kaori Takaori,[1] Hirotsugu Iwatani,[1] Yuta Asahina,[1] Shintaro Koizumi,[1] Yoko Tomiyama,[1] Ikue Nagayama,[1] Takahito Ito,[2] Masafumi Yamato.[1] *[1]Nephrology, Osaka National Hospital, Osaka, Japan; [2]Nephrology, Kataguilli Medical Center, Shibata, Niigata, Japan.*

Background: Vascular calcification (VC) is closely associated with cardiovascular events and mortality. Quantification methods of VC vary among studies. We studied clinical significance of vascular calcification volume (VCV) assessed by 3D imaging software.

Methods: This is a retrospective cross-sectional observational study. Out of 69 patients undergoing thoracoabdominal computed tomography from May 2014 to December 2015 in our department of Osaka National Hospital, 65 patients were subjected to the analysis. The patient characteristics were as follows; 71 ± 11y.o., 36 males, eGFR 20.4 (8.94-40.0) ml/min/1.73m^2, P 3.8±1.1 mg/dl, hypertension 55 (85%), diabetes 27 (42%), macroangiopathy 19 (29%), use of ACE-I/ARB 28 (43%), use of phosphate-binder 6 (9.2%), and Brinkman Index (BI) 130 (0-750). Four patients were excluded because of the treatment history of aortic aneurysm. Using the Hounsfield Unit more than 130 as the cut-off level, VCV of the entire aorta was measured with 3D imaging software. Statistical analysis was performed by JMP and p-value less than 0.05 was considered significant.

Results: VCV was 6.6 (2.7-18.1) ml. Univariate analysis showed that log(VCV) was significantly associated with age, sex, log(eGFR), log(BI), use of phosphate-binder, use of ACE-I/ARB, hypertension, and macroangiopathy. Use of warfarin was marginally significant. Multivariate analysis for log(VCV) by these 9 parameters indicated that age (b 0.053, p 0.026), log(BI) (b 0.57, p 0.035) and use of ACE-I/ARB (b 0.53, p 0.0042) were independent positive predictors and log(eGFR) (b -0.69, p 0.015) was an independent negative predictor of high aortic VCV.

Conclusions: The quantification method of VC using 3D imaging software is visible and clinically useful. Our results are consistent with the already known risk factors of VC. Unexpectedly, ACE-I/ARBs seemed to promote VC. Our results are, however, compatible with a recent report that angiotensin II prevents phosphate-induced calcification in human aortic smooth muscle cells.

FR-PO1005

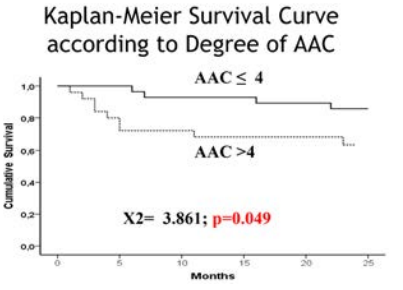
Abdominal Aortic Calicifications as a Prognostic Factor of All Cause Mortality in Hemodialysis Patients Kyriaki Stamatelou,[1] Dimitra Bacharaki,[2] Ioannis Griveas,[3] John Kyriazis,[4] Dimitrios V. Vlahakos.[2] *[1]Nephrology, Galinos Hospital, Athens, Greece; [2]Nephrology, Atticon Hospital, Chaidari, Greece; [3]Dialysis, NEFROIATRIKI, Athens, Greece; [4]Nephrology, General Hospital, Chios, Greece.*

Background: Vascular calcification has been associated with adverse clinical outcomes in hemodialysis patients. In this prospective study we examined the role of abdominal aortic calcification (AAC) in predicting all cause mortality in HD patients.

Methods: We studied 53 HD patients, 26 men, 27 women. After assessing the degree of AAC with Leena Kauppilla score (range 0-24) in lateral abdominal X-rays, patients were prospectively followed for two years, while recording fatal events. Kaplan-Meier survival analysis and univariate and multivariate Cox model were used.

Degree of AAC	≤4	>4	SS(p)
Age (y)	60±16	74±12	0.001
Dialysis Vintage (m)	26(16-58)	55(17-125)	0.011

Results: Median follow-up was 19.8 months, 13 deaths recorded, of which 11(27.3%) due to cardiovascular causes. Kaplan Meier survival analysis showed that patients with AAC score higher than the median score of 4, had worse survival compared to patients with AAC score ≤ 4 (17.6 versus 23.6 months; p <0.05).



Univariately, patients with advanced age, low diastolic blood pressure, history of coronary heart disease, high Ca X P product and high AAC score had an increased risk of death. In multivariate (stepwise) Cox regression analysis, only the degree of AAC emerged as an independent predictor of worse outcome. For each increment of the AAC by 1 degree, the risk of death increased by 10%(adjusted HR= 1.10, CI95%, 1.02-1.20). The area under the ROC curve for predicting mortality was 0.717(p=0.022) and at an optimal AAC score cutoff of 7.5, the sensitivity and specificity of AAC score in predicting all-cause mortality were 69% and 80% respectively.

Conclusions: The degree of AAC is a reliable indicator for estimating the risk of death in hemodialysis patients.

FR-PO1006

Aortic Calcification Area Index Predicts Increased Mortality in Peritoneal Dialysis Patients Fumiko Kuwahara, Saeko Miura, Kenji Harada, Hidetoshi Kanai. *Nephrology, Kokura Memorial Hospital, Kitakyushu, Japan.*

Background: Patients with end-stage renal disease have a high prevalence of vascular calcification, and cardiovascular diseases are an important cause of deaths. Here, we investigated the relationship of aortic calcification area index(ACAI) and mortality using the aortic calcification rate as an indicator of arteriosclerosis.

Methods: 76 patients (50 men and 26 women) who initially started peritoneal dialysis(PD) therapy and who took an abdominal computed tomography(CT) scan between Febuary 2010 and November 2013 were included. We calculated the calcification rate(%Area) for abdominal aortic vascular volume by using the abdominal CT. Patients were divided into two groups; low ACAI<11.7%(low ACAI group) ,n=43, and high ACAI≥11.7%(high ACAI group), n= 33. We analyzed the abdominal aortic calcification and mortality in PD patients using the Kaplan-Meier method.

Results: Median follow up period was 47.7±13.1 months. Median patient age was 63.6±11.7. Median value of ACAI was 11.7±10.5. High ACAI group were significantly older, higher ALP value and higher calcification rate of change than low ACAI group. Calcium, phosphorus, whole parathyroid hormone, uric acid, albumin, hemoglobin A1c, blood pressure, residual renal Kt/V and urine volume were not significantly differences in the two groups. In the Kaplan-meire method, high ACAI group was increased mortality (log-rank test; p= 0.0348). In the univariate Cox proportional hazards model, ACAI was a significant predictor of survival (hazard ratio 1.056 per 1.0% increment ACAI, 95% CI 1.007-1.108, P<0.05). However, in the multivariate Cox proportional hazards model, we could not show that ACAI was prognostic factor for survival.

Conclusions: In this study, we found that high ACAI group was associated with increased mortality by Kaplan-meire method. However, non cardiovascular death such as infection and cancer death is in the majority, therefore we could not show ACAI was prognostic factor for survival. We suggest that ACAI might be associated with mortality in PD patients.

FR-PO1007

Phosphorus and Panthotenic Acid Intake Are Related to Vascular Calcification in Class III and IV CKD: The PROGREDIR Study
Alisson Diego Machado,[1] Fernanda Silva Nogueira dos Anjos,[1] Maria Alice Muniz Domingos,[1] Maria del Carmen B. Molina,[2] Dirce Marchioni,[3] Rosa M.A. Moyses,[1] Paulo Lotufo,[4] Isabela M. Bensenor,[4] Silvia M. Titan.[1] *[1]Nephrology Div, School of Medicine, Sao Paulo Univ, Sao Paulo, Brazil; [2]Nutrition Dept, Federal Univ of Espirito Santo, Vitória, Espírito Santo, Brazil; [3]Nutrition Dept, School of Public Health, Sao Paulo Univ, Sao Paulo, Brazil; [4]Epidemiological and Clinical Research Center, Univ Hospital, Sao Paulo Univ, Sao Paulo, Brazil.*

Background: Vascular calcification (VC) is a widespread condition in CKD. Diet may be a determinant, but its role is not clear. We analysed the association between nutrient intake and VC in class III and IV CKD.

Methods: Data from 454 participants (Progredir Study) was used. A validated food frequency questionnaire was applied and nutrient intake was estimated using the USDA Database, adjusted for energy. Agatston Score (CAC) was obtained and those with coronary stent were excluded (artifact), leaving 372 people, which were classified by CAC (≥100).

Results: Median CAC was 165, with 50% of values >100. Age, male sex, race, diabetes, hypertension and smoking were related to CAC. While macronutrient intake was not different, a higher intake of phosphorus, calcium, vitD, vitB2, pantothenic acid (vitB5), potassium and magnesium was observed in the CAC>100 group. In logistic regression, all micronutrients except vitB2 remained related to CAC, even after adjustment for age, sex, diabetes, smoking, and protein intake. Lastly, we added micronutrient intake to the adjusted model and phosphorus intake remained significantly related to CAC [OR=1.002, 95%CI 1.000-1.003, p=0.01], whereas vitB5 showed a nearly significant relation [OR=1.286, 95%CI 0.98-1.70, p=0.07).

Conclusions: Our results show that (1) phosphorus intake is independently associated to VC in CKD, responsible for the major effect among nutrients related to CAC; (2) pantothenic acid intake may be related to CAC. This last finding raises questions about vitB5 in VC, considering its role in coenzyme A, fatty acids and cholesterol synthesis, metabolic pathways which have been related to the osteogenic differentiation of the vascular smooth muscle cell.

Funding: Government Support - Non-U.S.

FR-PO1008

Serum Bicarbonate Concentration and Arterial Stiffness: The Health ABC Study
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Background: Arterial calcification contributes to arterial stiffness. Animal studies suggest that metabolic acidosis protects against arterial calcification. The relationship between serum bicarbonate and arterial stiffness in community-living older individuals is unknown.

Methods: We performed cross-sectional analyses in 1,698 participants aged 70-79. Serum bicarbonate was measured by arterialized venous blood gas at the point of care and categorized into <23 (low), 23-27.9 (ref) and ≥28mEq/L (high). Arterial stiffness was assessed by pulse wave velocity (PWV) and by high ankle-brachial index (ABI; >1.3/non-compressible vs. 0.91-1.3). We used linear and logistic regression to evaluate association of bicarbonate with PWV and high ABI respectively.

Results: The mean age was 76 years (52% women, 35% black). Mean bicarbonate was 25.2± 2.1mEq/L; 4.6% had low and 10.5% had high bicarbonate. Median PWV was 793 cm/s (IQR 632-1033), 5% had high ABI, 19% had diabetes and mean eGFR was 80±17mL/min/1.73m^2. High bicarbonate was not associated with high PWV or high ABI in either demographic or fully adjusted models. Results were similar among participants with and without CKD (p for interactions >0.05).

Association of bicarbonate categories with PWV and high ABI			
	<23	23-27.9	≥28
Log-PWV (n=1698) [β (95% CI)]			
M1	0.071 (0.012, 0.130)	ref	-0.015 (-0.074, 0.045)
M2	0.021 (-0.044, 0.085)	ref	-0.033 (-0.095, 0.030)
High ABI (n=1434) [OR (95% CI)]			
M1	1.81 (0.98, 3.35)	ref	0.95 (0.42, 2.15)
M2	1.34 (0.65, 2.77)	ref	0.88 (0.36, 2.17)
M1: adjusted for age, sex, race, clinical site M2: adjusted for covariates in M1 + eGFR, albuminuria, DM, systolic BP, diuretics, RAAS blocker, smoking status, heart rate			

Conclusions: These findings do not support an independent association between high bicarbonate and arterial stiffness in community-living elders.

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FR-PO1009

Sodium Thiosulfate Intervenes Coronary Artery Calcification in Maintenance Hemodialysis Patients
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Background: The purpose is to investigate the factors correlated to coronary artery calcification in maintenance hemodialysis (MHD) patients, further to observe the effect of sodium thiosulfate (STS) on the progression of vascular calcification and its safety.

Methods: All subjects underwent coronary artery CT scan using Philip's spiral CT and the calcification degree was evaluated by calcification scores. First, the MHD patients were divided into coronary artery calcification group(CAC scores <10)and non-coronary artery calcification group (CAC scores >10). The differences of age, duration of dialysis and other hematological indexes between the two groups were analyzed. Then, those with coronary artery calcification (CAC scores >50) received intravenous 0.18g/kg STS (dissolved in 100ml saline) in 30 minutes after each dialysis for 3 months (n=15) or received conventional treatment (n=10). The changes of vascular calcification imaging, CAC scores, biochemical and bone mineral density were compared between two groups before and after the treatment. Besides, adverse reactions were observed during the treatment of STS.

Results: 27 in 38 patients (71.05%) had coronary artery calcification, The patients with coronary artery calcification had significantly higher age, duration of dialysis, phosphate, the product of calcium and phosphate, PTH and hsCRP and lower serum albumin (P<0.05) than patients without coronary artery calcification. There was no significant difference in the baseline characteristics between STS treatment group and the conventional treatment group. CAC score was unchanged in the STS treatment group (P=0.053), but increased significantly in the conventional treatment group (P=0.021). Difference of calcification score parameters before and after treatment showed statistically significant difference between the two groups (P= 0.004). After STS treatment, hsCRP and $HCO3^-$ levels decreased, and serum calcium levels increased (P<0.05).

Conclusions: Coronary artery calcification is commonly present in MHD patients. STS treatment seems to be feasible, safe and may decrease the rate of progression of vascular calcification, reduce inflammation in MHD patients.

Funding: Government Support - Non-U.S.

FR-PO1010

AKt/mTOR Signalling Is Involved in VSMC Calcification Induced by High Phosphate
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Background: The aim is to characterize the possible role of AKt/mTOR signalling in the vascular smooth muscle cells (VSMC) calcification induced by high phosphate.

Methods: Passage 3 to 5 of VSMC were used for experiments. VSMC were divided into two groups: normal phosphate group (Pi 1.3 mmol/L) and high phosphate group (Pi 2.6 mmol/L). Cbfα1 and OPN mRNA levels were determined by Real-Time PCR. p-AKt (ser473), p-mTOR (S2448), Cbfα1 and OPN protein expressions were quantified by Western Blot. When p-Akt and p-mTOR expression of VSMC were enhanced by high phosphate, Akt/mTOR inhibitors were respectively added in high phosphate group. VSMC then were divided into seven groups: high phosphate group (Pi 2.6 mmol/L); high phosphate+ Wortmannin(10, 50, 100 nmol/L); high phosphate+rapamycin (1, 10,100ng/ml). After 24-48h, Cbfα1 and OPN mRNA levels were determined, and p-AKt, p-mTOR, Cbfα1 and OPN protein expressions were quantified. All experiments were repeated 3 times.Calcium deposition was visualized by Alizarin stain method at day 7-14.

Results: After 7 days, compared with normal phosphate group, calcium deposition was obvious in high phosphate group. Cbfα1 and OPN mRNA expressions were significantly increased and the expressions of p-Akt/p-mTOR, Cbfα1 and OPN protein were significantly increased in high phosphate group (P<0.05). Cultured for another 7 days, calcium deposition was significantly decreased in high phosphate+ Wortmannin(50, 100nmol/L) groups and high phosphate +rapamycin(100ng/ml)group, compared with high phosphate group. After 24 -48hours, Cbfα1 and OPN mRNA expressions were significantly decreased; p-AKt, p-mTOR, Cbfα1 and OPN protein expressions were significantly decreased in high phosphate+ Wortmannin(50, 100nmol/L) and high phosphate+rapamycin(10, 100ng/ml) groups(P<0.05) compared with high phosphate group.

Conclusions: AKt/mTOR inhibitors, may suppress VSMC calcification and expressions of p-AKt/p-mTOR, Cbfα1 and OPN. Akt/mTOR is involved in VSMC calcification induced by high phosphate.

Funding: Government Support - Non-U.S.

FR-PO1011

SNF472 - A Potential Novel Calcification Inhibitor in CKD-MBD
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Background: Chronic kidney disease (CKD) is associated with cardiovascular calcification (CVC) in response to mineral and bone disorder. SNF472 (an intravenous formulation of the hexasodium salt of myo-inositol hexaphosphate) directly inhibits calcification by binding to growth sites of the hydroxyapatite crystal. We investigated the effects of SNF472 upon vascular smooth muscle cell (VSMC)-mediated calcification triggered by high calcium (Ca) and phosphate.

Methods: The anti-calcific effects of SNF472 or sodium thiosulfate (STS) were analyzed on primary VSMC from rat aorta treated with 3 mM calcium phosphate (CaPO).

Ca content, apoptosis rate and gene expression were measured. Dose Finding: Calcifying VSMCs were treated with 1, 10, 30 and 100 µM of SNF472 and 25, 50, and 100 mM of STS for 5 days. Apoptosis was measured by TUNEL assay, gene expression by Taqman real-time PCR. Time dependency: Using the most efficient anti-calcification dosage, treatment with SNF472 was started 3, 5, and 7 days after the beginning of the calcification experiment until day 10.

Results: SNF472 significantly reduced Ca concentrations compared to untreated VSMCs (maximum inhibition of 97%). CaPO treatment increased apoptosis rate compared to the control group after 7 days (control group: 0.09% vs. CaPO group: 1.5%). SNF472 treated cells showed an apoptosis rate of 0.8% at 30 µM. STS was most effective at 100 mM in reducing calcification (96% inhibition) but increased apoptosis rate by 77%. SNF472 (30 µM) is also effective in lowering the Ca content in later calcification stages. SNF472 treatment prevented CaPO-induced downregulation of SMA and also prevented upregulation of Alk Phos and cbfa1.

Conclusions: SNF472 decreased the calcium deposition in the ECM of rodent VSMC in a high CaPO microenvironment without inducing apoptosis. Moreover, it prevented upregulation of genes indicating switch form contractile VSMC to osteoblast-like cells. SNF472 qualifies as a promising research target to inhibit cardiovascular calcification in CKD patients undergoing dialysis.

Funding: Pharmaceutical Company Support - Sanifit

FR-PO1012

Safety, Pharmacokinetics and Pharmacodynamics of SNF472 in Hemodialysis Patients: New Data from a Phase 1b/2a Randomised Placebo-Controlled Clinical Trial

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Background: SNF472 (an intravenous formulation of inositol hexaphosphate) inhibits calcification by binding to the growing sites of hydroxyapatite (HAP). SNF472 is being developed for the prevention of vascular calcification in patients with end-stage renal failure on hemodialysis (HD). Non-clinical investigations and a single dose study in healthy volunteers and HD patients supported proceeding to a repeated dose trial in HD patients.

Methods: A double-blind, randomized, repeated dose study was performed in two cohorts of eight HD patients on three HD sessions per week. SNF472 was administered by a 4-hour infusion during the HD sessions. Doses of 1, 3, 5, 12.5, and 20 mg/kg were given during three consecutive HD sessions, with a 3-week washout period between doses. A second cohort received 10 mg/kg during 12 consecutive HD sessions. Standard safety parameters, serum bio element concentrations, pharmacokinetics, and calcification pharmacodynamics (PD) were determined.

Results: No adverse events, systemic side effects or local irritation related to SNF472 administration were reported. Dose linearity was observed in terms of C_{max} and AUC between 3 and 20 mg/kg. No SNF472 accumulation was observed after 1 month of administration at 10 mg/kg. Serum P, Mg^{2+}, and K^{+} were decreased as a consequence of HD, but SNF472 did not affect these changes. Ionized calcium was unaffected by SNF472 administration. The doses of 5, 12.5, and 20 mg/kg were on a PD plateau and reduced the HAP formation propensity by 80%. The EC_{50} using this assay was 2.18 mg/kg.

Conclusions: The findings support continuation of the clinical development program, namely a phase 2 three-month study in calciphylaxis assessing wound healing and a phase 2 one-year dose-finding study in HD patients evaluating coronary artery calcification progression. Supported by RETOS COLABORACIÓN: RTC-2014-2460-1 ISCIII grant.

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FR-PO1013

Warfarin-Induced Vascular Calcifications: Underlying Cellular Mechanisms and Effects on Bone Mineralization

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Background: Vascular calcification (VC) is considered to be an important risk factor for cardiovascular morbidity and mortality in CKD patients. Loss of calcification inhibitors is one of the mechanisms responsible for the development of VC in the media of the vessel wall. Matrix gla protein (MGP) is a strong inhibitor of VC and its activity depends on vitK-mediated γ-carboxylation. As warfarin interferes with vitK recycling, active (carboxylated) MGP is depleted and VC consequently develop. Here, we investigated cellular mechanisms underlying warfarin-induced VC as well as its effects on the bone.

Methods: Calcifications were induced in rats by daily administration of a warfarin-supplemented diet (3mg warfarin/g diet + 1.5mg vitK1/g diet). Rats receiving a standard diet, served as controls (CTR). At sacrifice at 4, 6, 8 and 10 wk, VC, aortic mRNA expression and bone status were assessed by bulk calcium (Ca) analysis, q-rt PCR and bone histomorphometry.

Results: Aortic Ca concentration gradually increased and significantly differed from CTR in 4-wk treated rats (p=0.0286), reaching a 50-fold increase in 10-wk treated rats, (p=0.0061 vs CTR). mRNAs of osteochondrogenic transdifferentiation markers were upregulated, among which the transcription factor Sox9 and β-catenin, an important protein in the anabolic Wnt/β-catenin bone signaling pathway (p=0.0317 and 0.0159, resp.). Interestingly also the mRNAs of the Wnt/β-catenin pathway inhibitor sclerostin as well as the Wnt/β-catenin upstream protein activin receptorIIA were significantly up-regulated (p=0.0159 and 0.0317, resp.). A mild decrease in bone area, trabecular number and -thickness (p=0.0095 vs CTR for each) was observed in rats treated for 10 wk.

Conclusions: The current study allows to suggest that, Wnt/β-catenin signaling in concert with or in addition to transdifferentiation of vascular smooth muscle cells, also plays a crucial role in warfarin-induced VC. Findings may lead to identifying e.g. upstream proteins/inhibitors of the Wnt/β-catenin pathway as new targets for treating VC. Furthermore, it became clear that warfarin induces a mild reduction of mineralized bone volume by a currently unknown mechanism.

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FR-PO1014

Characterization and Comparison of Vascular Calcification in Two Mouse Strains with Adenine-Induced CKD

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Background: Medial vascular calcifications (VC) are frequently observed in patients with chronic kidney disease (CKD) and are associated with increased morbidity and mortality. Until now, our and other laboratories studied these CKD-induced VC in a rat model of adenine-induced CKD. However, because of the availability of knockout mice that lack expression of proteins potentially playing a role in the development of these VC, the development of a CKD-induced mouse model of VC is highly desirable.

Methods: Two mice strains, C57Bl6 (n=10) and DBA2 mice (n=10), received alternately a 0.30% and 0.15% adenine supplemented diet, containing 1% phosphate. Serum creatinine and phosphate levels were monitored in the animals in order to follow-up the development/progression of CKD. At sacrifice (C57Bl6 at 8 weeks, DBA2 at 12 weeks), VC were assessed by bulk calcium analysis and von Kossa staining and compared to control mice with normal renal function.

Results: The adenine-supplemented diet led to a clear induction of CKD in C57Bl6 and to a lesser extent in DBA2 mice, as reflected by increased serum creatinine and phosphate levels. Due to mortality (4/10 mice), C57Bl6 mice were sacrificed after 8 weeks of treatment. One animal of this group developed obvious VC in the aorta, confirmed by bulk calcium analysis (9.9 mg Ca/g wet tissue vs 0.16 mg Ca/g wet tissue in controls) and von Kossa staining (6.6% calcified tissue vs 0.008% in controls). Less mortality was observed in DBA2 mice (1/10). All DBA2 mice developed severe media calcifications in the aorta (average: 20.2mg Ca/g wet tissue, 12.4% calcified tissue). Furthermore because calcification of the heart was macroscopically visible at sacrifice, von Kossa staining was performed on cardiac tissue. All DBA2 animals seemed to have developed severe cardiac calcification of which quantification is ongoing.

Conclusions: In this study we managed to develop a mouse model of CKD-induced medial VC. DBA2 mice however, seemed to be more prone to the development of VC compared to C57Bl6 mice.

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FR-PO1015

Inhibition of Nephritis and the CKD-MBD in Alports Syndrome by an ActRIIA Ligand Trap

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Background: To examine the role of ActRIIA signaling in interstitial nephritis and the CKD-MBD, we used the murine Alport's homolog (Col4α5 deficiency) with CKD and 70% reduction in GFR at 200 days of life, we found the CKD-MBD to be characterized by marked reductions in renal klotho, elevated FGF23 and PTH levels, normophosphatemia, cardiac hypertrophy and vascular calcification.

Results: Plasma activin levels and aortic p-smad 2/3 levels were increased in Alport's, $p<0.01$, and decreased by treatment with RAP-011, an ActRIIA ligand trap 10mg/kg SC twice weekly from day 75 to 200. Aortic Ca levels were 0.27mg/g in 200do wild type littermates, 0.59 in Alport's and 0.36 in Alport's mice treated RAP-011, $p<0.05$ versus Alport's. Aortic micro CT and histology showed the calcium apatite deposits to be advential abutting the muscularis. The vascular smooth muscle levels of sm22α and αSMA (transcriptional targets of p-smad 2/3) were actually increased in Alport's mice, and Runx2 (a marker of osteoblastic transition of VSMC) was not expressed. However, osterix, a second osteoblastic transcription factor was expressed in advential cells adjacent to the calcium deposits. Heart weight was 6.2mg/mm (weight/tibial length) in Alport's and corrected to normal (4.9mg/mm) by RAP-011 treatment. In the Alport's kidney, activin expression, elevated p-smad 2/3, Col1, fibronectin and interstitial fibrosis were inhibited by RAP-011 treatment. Glomerular sclerosis was diminished and GFR was increased by RAP-011 treatment, $p<0.01$.

Conclusions: In conclusion, the results are consistent with renal production of activin stimulating ActRIIA signaling and driving fibrosis and glomerular sclerosis, and contributing to the vascular and cardiac components of the CKD-MBD. ActRIIA signaling may be a therapeutic target in Alport's syndrome.

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FR-PO1016

Reducing Dietary Phosphate in Experimental CKD Is Sufficient to Attenuate Vascular Stiffness and the Associated Left Ventricular Hypertrophy
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Background: Impaired renal function in CKD causes hyperphosphatemia and alters hormonal regulators (calcitriol, FGF-23). One hypothesis is that the increased phosphate (PO_4) pool combined with elevated FGF-23 and the generation of vascular calcification (VC) cause cardiovascular disease (CVD). Understanding this mechanism is important as CVD-related outcomes in CKD patients account for over half of all CKD mortality. To determine the importance of dietary PO_4 on CKD-based CVD we sought to determine the effects of low versus high dietary PO_4 in a rat model of CKD.

Methods: 16 wk male SD rats were fed a CKD-inducing diet (0.25% adenine, 0.5% PO_4, n=35) for 4 wks, were taken off adenine and separated into 3 diet grps: 0.5% PO_4 (n=14), 1% PO_4 (n=11), and 1.5% PO_4 (n=10). Non-CKD control groups on 0.5% PO_4 (n=8) or 1.5% PO_4 (n=5) were compared. After 4 wks, hemodynamic changes were measured and the rats sacrificed.

Results: Low PO_4 (0.5% diet) in CKD rats did not change serum PO_4 or aortic VC vs. controls; while high PO_4 (1% and 1.5% diets) led to increased serum PO_4 (6.2±2.1 vs 2.1±0.2mM, $p<0.05$) and VC compared to controls (413.0±525.6 vs 4.1±0.76 & 6.1±2.8 mmol/mg). PWV was elevated in high PO_4 compared to controls and low PO_4 (0.13±0.1 vs 0.06±0.02 m/s*mmHg, $p<0.05$). CKD induction increased serum FGF-23 ($p<0.05$) with significant elevations in high PO_4 groups compared to low PO_4 (30±28.4 vs 2±1.6 ng/mL, $p<0.05$). High PO_4 groups have significant LVH compared to control and low PO_4 groups ($p<0.05$).

Conclusions: Increasing dietary PO_4 in CKD leadsto greater propensity for VC and this appears to directly contribute to the development of CVD. Our findings show that maintaining low dietary PO_4 protects vessels against VC and vascular stiffening, ultimately reducing the extent of LVH in CKD. These findings support the value of dietary PO_4 regulation for CKD patients and the use of dietary PO_4 binders to help improve CVD complications in CKD patients.

Funding: Pharmaceutical Company Support - OPKO, Government Support - Non-U.S.

FR-PO1017

In Vivo Effect of Indoxyl Sulfate (IS) and p-Cresyl Sulfate (PCS) on the Development of Vascular Calcification in Rats with Adenine-Induced Uremia
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Background: Vascular calcification (VC) is frequently seen in patients with chronic kidney disease (CKD). Recently uremic toxins, IS and PCS, have been postulated as novel promoters for VC development. To provide further evidence for this, a rat model with adenine-induced uremia was used to define whether IS and PCS are major contributors to VC development during CKD.

Methods: To induce CKD, rats were treated with adenine sulfate during 10-days via daily oral gavage (600 mg/kg/day). Simultaneously, rats were continuously exposed to either (i)IS or (ii)PCS via the drinking water until wk2 followed by oral gavage at a dose of 150 mg/kg/day until sacrifice at wk7. Control animals received vehicle. Calcium(Ca), phosphorus(P) and creatinine were determined in serum and urine samples. Serum IS and PCS levels were analyzed by LC MS/MS. As uremic toxins may interfere with glucose(Glu) metabolism serum Glu was measured at the start and end of the study. At sacrifice, VC was evaluated by bulk calcium(Ca) and Von Kossa staining.

Results: CKD was present in all groups as indicated by a significant reduction of the creatinine clearance and increasing serum P levels. CKD rats exposed to IS showed a significantly higher creatinine clearance and lower serum P levels as compared to vehicle treated CKD rats. Induction of CKD resulted in significantly increased serum IS and PCS levels which were comparable to levels in CKD patients. Glu levels were significantly elevated at the end of the study in both IS and PCS treated rats. No calcification had developed in the aorta, femoral or carotid arteries in CKD rats exposed to vehicle. Development of moderate to severe VC as indicated by a distinct Von Kossa positivity and significant increase in Ca content was observed in the aorta and peripheral vessels of CKD rats exposed to IS and PCS.

Conclusions: IS and PCS induced vascular calcification in the aorta and peripheral vessels of CKD rats and thus can be considered as vascular toxins. Further research will explore the mechanisms by which both toxins affect the vascular wall.

Funding: Government Support - Non-U.S.

FR-PO1018

Indoxyl Sulfate Promotes Aortic Calcification through Notch Signaling Pathway Activation in Vascular Smooth Muscle Cells
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Background: Vascular calcification is common in chronic kidney disease (CKD), and recognized as surrogate marker for cardiovascular disease (CVD). Indoxyl sulfate (IS) is a protein bound uremic toxin to exacerbate vascular calcification in CKD patients, and its therapeutic target has been searched for. We hypothesized that Notch signal pathway alterations caused by IS is involved in vascular calcification because Notch signal activation increase cell survival of vascular cells in developmental and pathological status.

Methods: IS (200 mg/kg/day in drinking water) administered Dahl rat and vehicle rat were used to evaluate vascular calcification. Human arterial smooth muscle cells (HASMCs) was culture under various concentration of IS, and the expression of Notch 1 and 3, and apoptosis were assessed with RT-PCR, caspase activity assay, and TUNEL staining.

Results: Aortic calcification was observed solely in IS-administered rats. The expression of Notch1 and 3 was slightly increased in aortic SMCs from IS- administered rats compared to vehicle rat. Notably the expression of Notch1 and 3 was fainted in vascular calcification in IS-treated rats. In cultured HASMCs, the expression of Notch1 and 3 was peaked at 24h after administration of IS (1000μM), and fainted within 72h. Exposure to IS increased TUNEL positive cells and caspase3/7 activity in a dose- and time-dependent manner. IS and Notch signal inhibition accelerated inorganic phosphate-induced calcification in HASMCs, and the effect was canceled by pharmacological inhibition of apoptotic signaling.

Conclusions: IS transiently activates Notch signal in vascular smooth muscle cells, but the effect was fainted getting along with higher concentration and longer duration of exposure to IS. The decreased Notch activity induced formation of apoptotic body and calcified lesions. Thus Notch signal would be a novel therapeutic target for vascular calcification in CKD patients.

FR-PO1019

Metformin Prevents from Severe Kidney Failure, Vascular Calcification and High Bone Turnover Disease
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Background: Chronic renal impairment causes systemic dysregulation of the mineral metabolism and coincides with vascular calcification and bone disorders which is called 'Chronic Kidney Disease-Mineral and Bone Disorder' (CKD-MBD). Metformin, an oral anti-hyperglycemic agent used for type II diabetes mellitus as a standard treatment, has been shown to have beneficial effects on kidney fibrosis and atherosclerosis. This study aims to investigate the effect of metformin on renal function and structure, arteries and the bone in CKD-MBD.

Methods: To induce CKD, rats received a 0.25% adenine/low vitamin K diet for 8 weeks. Animals were daily treated with 200 mg/kg metformin or vehicle by oral gavage from 1 week after CKD induction onwards until week 8. Renal function, histology, fibrosis and inflammation were assessed. The calcium content in the arteries was determined and static and dynamic bone parameters were measured.

Results: Severe, stable CKD along with serious hyperphosphatemia and hypocalcemia had developed in vehicle treated rats which led to calcification in the arteries and high bone turnover disease. Metformin treatment protected adenine dosed rats from the evolution towards severe CKD and serum phosphorus and calcium concentrations remained within the normal range. The kidney of the metformin group showed significant less cellular infiltration, fibrosis and inflammation. Metformin also prevented the development of vascular calcification and inhibited the progression towards high bone turnover disease.

Conclusions: In conclusion, metformin treatment protected against the development of severe renal failure and preserved the calcium phosphorus homeostasis which presumably prevented the onset of vascular calcification and development of high bone turnover disease.

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FR-PO1020

High Dose Vitamin D-Induced Vascular Calcification Is Attenuated in TLR4 Deficient Mice Jianheng Zhou,[1] Yuan Min Wang,[1] David C. Harris,[2] Heather J. Medbury,[3] Helen Williams,[3] Anne M. Durkan,[1] Grahame J. Elder,[2] Steven J. Chadban,[4] Huiling Wu,[4] Stephen I. Alexander,[1] Vincent W.S. Lee.[2] *[1]Centre for Kidney Research, Children's Hospital at Westmead, Westmead, NSW, Australia; [2]Centre for Transplantation and Renal Research, Westmead Inst of Medical Research, Westmead, NSW, Australia; [3]Vascular Biology Research Centre, Westmead Hospital, Westmead, NSW, Australia; [4]Renal Medicine, Royal Prince Alfred Hospital, Kidney Node Laboratory, Charles Perkins Centre, Univ of Sydney, NSW, Australia.*

Background: Vascular calcification is strongly associated with cardiovascular morbidity and mortality. Several studies have suggested that monocytes/macrophages are involved in arterial vascular calcification, while the involvement of the TLR4 pathway in vascular calcification has also been proposed.

Methods: WT C57BL/6 and TLR4-/- mice aged 8 weeks were injected with a high dose of vitamin D (500000IU/kg/day) subcutaneously at 0, 24 and 48 hours. All mice were sacrificed 4 days after the final injection. Kidneys were collected for examination of injury by histochemistry. Whole aortas were dissected. Macrophage infiltration, TLR4 expression and vascular calcification were examined by immunohistochemistry and histology.

Results: High dose vitamin D treated WT mice demonstrated significantly higher calcium deposition in their aortas (15.5% of vessel area) than did WT and TLR4-/- mice without injection (0.5% $p<0.001$, 0.2% $p<0.001$). Aortic calcium deposition was significantly attenuated in TLR4-/- mice with vitamin D injection (1% $p<0.001$) as compared to vitamin D treated WT mice. This was accompanied by a lower level of macrophage infiltration and TLR4 expression in aortas of high dose vitamin D treated TLR4 -/- mice compared to high dose vitamin D treated WT mice, whilst untreated mice had minimal aortic macrophage infiltration. High dose vitamin D treatment did not induce kidney fibrosis or tubular injury in WT and TLR4-/- mice, as assessed by GT fibrosis score and PAS tubular damage score.

Conclusions: Accelerated vascular calcification and macrophage infiltration with high dose vitamin D treatment was reduced in TLR4 -/- mice compared to WT mice. These data suggest a potential role for macrophages and the TLR4 pathway in vascular calcification.

FR-PO1021

Effect of Pioglitazon on Calcification of Rat Vascular Smooth Muscle Cells through the Down-Regulation of Wnt/β-Catenin Signaling Pathway Huijuan Mao. *Nephrology, First Affiliated Hospital of Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: To investigate the effect and possible mechanism of Pioglitazon(PIO) on calcification of rat vascular smooth muscle cells (VSMCs)in vitro.

Methods: β-glycerophosphate (10mmol/L) was used to induce calcification of VSMCs, with different concentrations(5,10,15,20μmol/L)of PIO to intervene for 12d.Calcium deposits were tested by Alizarin red staining. Extracellular calcium content was detected by Calcium Assay Kit. Western Blot was used to measure the expressions of α-smooth muscle actin (α-SMA), runt-related transcription factor 2 (Runx2),bone morphogenetic protein-2 (BMP2),β-catenin,GSK-3β,p-GSK-3β and cyclin-D1. On the basis of 10mmol/L β-glycerophosphate and 20 μmol/L PIO, 20 μmol/L PPARγ antagonist GW9662 was added to the cell culture media. The changes of the above indexes were observed.

Results: 1.The calcium content in calcification group increased significantly compared with the control's($P<0.05$),and all different concentrations of PIO reduced extracellular calcium content($P<0.05$).Alizarin red staining was strong positive in calcified VSMCs, and PIO(20μmol/L) intervention group was almost negative. 2.The expressions of Runx2,β-catenin,p-GSK-3β,BMP2 and cyclin-D1increased significantly in calcification group, and 20μmol/L PIO group obviously down-regulated the expressions of all the above proteins, while up-regulated the expression of α-SMA. 3. PPARγ antagonist GW9662 could partly block the effect of PIO on calcified VSMCs.

Conclusions: PPARγ agonist PIO can alleviate rat aortic VSMCs calcification induced by β-glycerophosphate via inhibiting the activity of Wnt/β-catenin signaling pathway.

Funding: Government Support - Non-U.S.

FR-PO1022

Vascular Calcification Induced by High Extracellular Phosphate Imply Activation of Aldosterone Receptor and Transactivation of Epidermal Growth Factor Receptor Victor Manuel Barrientos,[1] Rodrigo Alzamora,[1] Luis F. Michea.[1,2] *[1]Facultad de Medicina, ICBM, Univ of Chile, Chile; [2]Millennium Inst on Immunology and Immutherapy, Univ of Chile, Chile.*

Background: Vascular calcification (VC) is a mayor mortality risk factor in CKD patients. During VC the vascular smooth muscle cells (VSMC) of the tunica media transdifferentiate into osteoblast-like cells. High extracellular phosphate (HP) promotes VC through the induction of the sodium-dependent phosphate cotransporter (Pit1) activity. Recent studies indicate that spironolactone (mineralocorticoid receptor antagonist) ameliorated VC in Klotho-deficient mice. However, the potential activation of mineralocorticoid receptor (MR) and the potential mechanisms that could mediate the activation of the MR are unknown. MR activation produces transactivation of epidermal growth factor receptor (EGFR), a mechanism that could participate in VC. We analyzed if HP, via sodium-dependent phosphate transport, activates MR leading to EGFR transactivation and VC.

Methods: A7r5 VSMC cells were switched from normal to HP medium. We analyzed the time course of receptor activity and the dependence on sodium-dependent phosphate cotransport by using buffers with/without sodium (sodium replaced by choline and potassium). We determined the role of MR and EGFR with pharmacological antagonists (spironolactone and AG1478 respectively) and the intracellular signaling pathways: ERK1/2 and MR genomic effect on an early response gene, the Neutrophil Gelatinase-Associated Lipocalin (NGAL).

Results: HP (2.5mM, sodium buffer) induced a time-dependent activation of ERK (2.7 times, 10 min *vs*. 0 min; $P<0.05$; n=4). The incubation of VSMC with no-sodium HP buffer did not cause ERK activation (n=4). Spironolactone (10uM) or AG1478 (10uM) in the culture medium suppressed HP-induced activation of ERK ($P<0.05$ vs. 0 min; n=4). Finally, HP induced NGAL mRNA expression (1.67 times *vs.* NP; $P<0.05$; n=4). Spironolactone prevented the induction of NGAL. In contrast, AG1478 did not prevent NGAL induction by HP (n=4).

Conclusions: We conclude that HP activates the MR via sodium-dependent phosphate transport, leading to EGFR transactivation in VSMC. Funding: FONDECYT 1130550-1151423, IMII P09-016-F.

FR-PO1023

Inhibiting Post-Translational Core Fucosylation Prevents Vascular Calcification in Chronic Kidney Disease Wen Xin Yu. *Nephrology, The First Affiliated Hospital of Dalian Medical Univ, Dalian, Liaoning, China.*

Background: Vascular calcification (VC) is an independent risk factor for cardiovascular disease and mortality in chronic kidney disease. Post-translational core fucosylation is implicated in a number of pathological processes.

Methods: We investigated the role of core fucosylation and key receptors of TGF-β1 pathway on calcified arteries *in vivo*. To determine whether blocking core fucosylation effectively inhibited vascular calcification and TGF-β/Smad signaling pathway, we established an *in vitro* model of phosphate-induced calcification in rat vascular smooth muscle cells (VSMCs) to assess the role of core fucosylation in VC.

Results: Core fucose could be detected at markedly higher levels in calcified VSMCs than control. *Fut8* (α-1,6 fucosyltransferase), the only enzyme responsible for core fucosylation in humans, was significantly upregulated by high phosphate. Exposed to high phosphate condition, blocking core fucosylation in VSMCs by knocking down *Fut8* using a siRNA markedly reduced calcium and phosphorus deposition and Cbfα1 expression (osteoblast-specific transcription factor), and increased α-SMA expression (smooth muscle cell marker). The TGFβ/Smad2/3 signaling pathway is involved in VC. *Fut8* siRNA significantly inhibited TGF-β/Smad2/3 signaling activation in VSMCs cultured in high phosphate media.

Conclusions: This study provides evidence to suggest core fucosylation plays a major role in the process of VSMCs calcification and appropriate blockade of core fucosylation may represent a potential therapeutic strategy for treating VC in end-stage renal disease.

Funding: Government Support - Non-U.S.

FR-PO1024

The Anti-Calcific and Anti-Apoptotic Effects of GSK-3 Inhibitors in Cultured Human Aortic Smooth Muscle Cells Narihito Tatsumoto,[1,2] Masaki Arioka,[2] Shunsuke Yamada,[1] Masanori Tokumoto,[3] Kazuhiko Tsuruya,[1,4] Takanari Kitazono,[1] Toshiyuki Sasaguri.[2] *[1]Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; [2]Dept of Clinical Pharmacology, Faculty of Medical Sciences, Kyushu Univ, Fukuoka, Japan; [3]Dept of Internal Medicine, Fukuoka Dental College, Fukuoka, Japan; [4]Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.*

Background: Vascular calcification is an active, cell-mediated, and complex pathology that includes apoptosis of vascular smooth muscle cells (SMCs). Recent experimental studies showed that Wnt/β-catenin signaling pathway is involved in the pathogenesis of vascular calcification. However, it still remains unclear whether or not inhibition of glycogen synthase kinase (GSK)-3, a critical downstream component of Wnt/β-catenin signaling, affects the calcification process of vascular SMCs.

Methods: Human aortic SMCs were incubated in the calcification medium containing 3 mM phosphate and 10% fetal bovine serum. Calcification media were supplemented with either vehicle, lithium chloride (15 mM), or SB216763 (10 μM); the latter two are known as GSK-3 inhibitors. After 14 days of incubation, calcification of human aortic SMCs was assessed by von Kossa staining and calorimetric quantification of calcium (Ca) content after elution with 0.6N hydrochloride. The expressions of Wnt/β-catenin signaling pathway and apoptosis-related proteins were analyzed by western blotting.

Results: Calcification medium increased the Ca content in the human aortic SMCs in parallel with an increased expression of cleaved caspase-3. Both GSK-3 inhibitors decreased Ca deposition and reduced phosphorylated-β-catenin to total-β-catenin ratio, suggesting the activation of Wnt/β-catenin signaling pathway. The increased expression of cleaved caspase-3 was suppressed by the treatment with both GSK-3 inhibitors.

Conclusions: GSK-3 inhibitors attenuated Pi-induced calcification via suppression of apoptosis in human aortic SMCs.

FR-PO1025

High Phosphorus Leads to Aortic Calcification via β-Catenin in Chronic Kidney Disease Li Yao, Tianhua Xu, Chuang Ren, Xing Fan, Jiangmin Feng, Jianfei Ma, Lining Wang. *Nephrology, The First Hospital of China Medical Univ, ShenYang, LiaoNing, China.*

Background: Vascular calcification is a risk factor for cardiovascular events and has high prevalence with occurrence of chronic kidney disease (CKD). However, the molecular mechanism underlying this pathogenic process is still obscure.

Methods: Vascular smooth muscle cells (VSMCs) were induced by high concentration of phosphorus (Pi) at 2.5 mM and subjected to cell calcification analyzes. The effect of high Pi on Wnt/β-Catenin pathway was measured by TOP/FOP-Flash reporter assay. The transcriptional regulatory of β-Catenin on Pit-1 was confirmed by promoter reporter and ChIP assays. 5/6 nephrectomized (Nx) rat were used asin vivo model and divided into four different groups. Serum levels of phosphate, calcium, creatinine and blood urea nitrogen were measured. Abdominal aortic calcification was examined.

Results: High Pi induced VSMCs calcification, down-regulated expression levels of VSMC markers and up-regulated levels of osteogenic markers. High Pi activated Wnt/β-Catenin pathway and β-Catenin activity. And β-Catenin was involved in the process of high Pi induced VSMC calcification. Further investigation revealed that β-Catenin transcriptionally regulated Pit-1, a necessary player in VSMC osteogenic phenotype change and calcification. The in vivo study showed that β-Catenin was involved in rat abdominal aortic calcification induced by high Pi. When knocking down expression of β-Catenin in rat, the occurrence of aortic calcification was reduced.

Conclusions: These results suggest that β-Catenin is an important player in the process of high phosphorus induced aortic calcification in CKD.

FR-PO1026

Hydrogen Sulfide (H2S) Attenuates CPP-Induced Calcification of Vascular Smooth Muscle Cells via Activation of the KEAP1/NRF2/NQO1 Signaling Pathway Parisa Aghagolzadeh,[1] Ramin Radpour,[1] Matthias Bachtler,[1] Harry Van Goor,[2] Edward R. Smith,[3] Alex Odermatt,[4] Willi Jahnen-Dechent,[5] Andreas Pasch.[1] *[1]Univ Hospital Bern, Bern, Switzerland; [2]Univ Medical Center Groningen, Netherlands; [3]Royal Melbourne Hospital, Australia; [4]Univ of Basel, Switzerland; [5]RWTH Univ of Aachen, Germany.*

Background: Vascular calcification is associated with increased morbidity and mortality in chronic kidney disease (CKD). Secondary calciprotein particles (CPP) and oxidative stress induce calcification of Vascular Smooth Muscle Cells (VSMC) in vitro. Hydrogen sulfide (H_2S) is a signaling molecule with antioxidant properties. Here we investigated the anticalcific properties of H_2S in a CPP-induced *in vitro* model of VSMC mineralisation.

Methods: We used next-generation sequencing to investigate differential transcriptomic changes in NaHS- (H_2S-donor) treated versus non-treated calcifying VSMC. The potential role of regulatory pathways in calcification-prevention identified using this approach were investigated using RT-PCR, Western-blotting and silencing with small interfering RNA (siRNA).

Results: Secondary CPP induced calcification of VSMC. Transcriptomic analysis revealed the dysregulation of 423 genes in VSMC upon exposure to secondary CPP. H_2S-treatment prevented calcification and exerted anti-oxidant activity in VSMC. The specific anti-calcification activity of H_2S was mediated via NAD(P)H dehydrogenase [quinone] 1 (NQO1). Corroborating this finding, silencing of the Kelch-like ECH-associated protein 1 (KEAP1) (84% silencing) enhanced NQO1 expression, while silencing of Nuclear factor (erythroid-derived 2)-like 2 (NRF2) (85% silencing) reduced the expression of NQO1 and the calcification-suppressing activity of H_2S.

Conclusions: H_2S attenuates CPP-induced calcification of VSMCs *in vitro* via activation of the *NQO1* and KEAP1-NRF2 antioxidant defense system.

FR-PO1027

The Protective Effects of Caloric Restriction on P-Induced Calcification via the Up-Regulation of SIRT1 in Human Vascular Smooth Muscle Cells Masanori Tokumoto,[1] Shunsuke Yamada,[2] Kazuhiko Tsuruya,[3] Takanari Kitazono,[2] Hiroaki Ooboshi.[1] *[1]Dept of Internal Medicine, Fukuoka Dental College, Fukuoka, Japan; [2]Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; [3]Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.*

Background: It is well-known that caloric restriction is effective for the prevention of premature aging via the up-regulation of sirtuin. However, the effect of caloric restriction on vascular calcification remains unknown. Thus, we examined how caloric restriction affects P-induced calcification in human vascular smooth muscle cells (VSMCs).

Methods: Human VSMCs were cultured in the culture media (DMEM) with low or high glucose (100 or 450 mg/dl) for a week, followed by either low or high glucose DMEM with the additional P load of 0, 1.0, 1.5, or 2.0mM for another week. The degree of calcification, the content of calciprotein particles (CPP) in the media, and the expression of SIRT1, intrinsic calcification inhibitors and osteogenic differentiation markers were examined at Day 8 and 14. The degree of calcification was expressed as the Ca content precipitated on the human VSMCs, and the CPP content was expressed as the Ca content in the precipitation centrifuged by 16,000g for 2 hours at room temperature.

Results: Regardless of P load amount, the degree of both calcification and CPP formation and the expression of bone morphogenetic protein 2 (BMP2), an osteoblastic differentiation marker, at Day 14 were the lowest in human VSMCs with the alternation of DMEM from high to low glucose (caloric restriction). At Day 8, the expression of SIRT1 and osteoprotegerin (OPG), a calcification inhibitor, was up-regulated by caloric restriction. The content of calcification at Day 14 correlated with CPP content and BMP2 expression at Day 14, and inversely with SIRT1 and OPG expression at Day 8. The OPG expression at Day 8 correlated with SIRT1 expression at Day 8, and inversely with BMP2 expression at Day 14.

Conclusions: In conclusion, caloric restriction maintained the phenotype of VSMCs and inhibited P-induced calcification via the up-regulation of SIRT1 expression in human VSMCs.

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FR-PO1028

Heparin Induces Sclerostin Release in Humans Jacek Borawski, Justyna Zoltko, Barbara Labij-Reduta, Beata Naumnik. *Ist Dept of Nephrology, Medical Univ, Bialystok, Poland.*

Background: Sclerostin (Scl) - an inhibitor of bone formation is also involved in cardiovascular calcification that is highly prevalent in maintenance HD patients. Recently, intriguing heparin-binding features of Scl molecule were discovered. We conducted a pilot study to challenge for the first time the hypothesis that iv enoxaparin (ENX) releases Scl into the blood.

Methods: In 16 males (46.7±11.3 yrs, 85.5±8.62 kg, BMI 26.7±3.11 kg/m^2) fasted venous blood samples (T_0) were obtained and an iv bolus of ENX was injected (82.5±6.83 mg, 0.97±0.06 mg/kg, 3.12±0.32 mg *per* kg/m^2). The consecutive samples were drawn after 10 min (T_{10}), 2 h (T_{2h}), 6 h (T_{6h}) and 24 h (T_{24h}).

Results: Plasma immunoreactive Scl levels changed following iv ENX administration (χ^2 ANOVA=50.7, P<0.0001). They increased consistently by a mean of 184% (min 51% - max 461%): from 0.56±0.17 ng/mL at T_0 to a median of 1.36 (1.08–1.97) ng/mL at T_{10} (Wilcoxon P=0.0004). At T_{2h} Scl levels were 0.71±0.19 ng/mL, lower than those at T_{10} (P=0.004) and elevated by a median of 21% vs baseline (P=0.0005). At T_{6h} Scl levels were 0.61±0.16 ng/mL and still higher by a median of 8.7 % vs baseline (P=0.017). At T_{24h} they normalized (0.56±0.16 ng/mL).The percentage of increase in plasma Scl (ΔScl) at T_{10} tended to be directly associated with the dose of ENX *per* kg (Spearman *rho*=0.430, P=0.096) and was significantly and directly correlated with ENX dose *per* kg/m^2 of BMI (*rho*=0.587, P=0.017). Notably, the ΔScl at T_{10} strongly and inversely correlated with the baseline levels of Scl (*rho*= -0.747, P=0.0008). The above relation was also inverse but not significant for ΔScl at T_{2h} and T_{6h} (both P>0.138). A strong negative association between the ΔScl increment at T_{10} vs baseline and the ΔScl fall at T_{2h} vs T_{10} was also observed (*rho*= - 0.835, P<0.0001).

Conclusions: The rapid, extensive and dose-dependent increase in plasma Scl constitutes a novel pharmacological effect of iv ENX. Plausible hypotheses to prove and of importance to nephrologists are: 1) the rise in Scl results from its liberation from vascular stores; 2) the effect leads to depletion of the inhibitor; 3) the use of ENX for HD anticoagulation (~75.000 mg a year!) promotes/propagates vascular calcification in HD patients.

Funding: Government Support - Non-U.S.

FR-PO1029

MicroRNA-34b/c Inhibits Uremia Related Vascular Smooth Muscle Cells Calcification via a SATB2/Runx2 Pathway Jianbing Hao, Lirong Hao. *The Second Nephropathy and Hemodialysis Center, The First Affiliated Hospital of Harbin Medical Univ, Hrbin, Heilongjiang, China.*

Background: Vascular (vascular smooth muscle cell, VSMC) calcification is a common complication of end stage renal disease (ESRD). Increasing evidence shows that aldosterone and specific microRNAs play an important role in VSMC calcification. In this study, we aimed to explore the mechanistic links between miR-34b/c and aldosterone in VSMC calcification *in vitro* and *in vivo*.

Methods: First, the levels of aldosterone, miR-34b/c, and special AT-rich sequence-binding protein 2 (SATB2) were measured. Then, miR-34b/c mimics or inhibitors were transfected into VSMCs to evaluate the function of miR-34b/c. Luciferase reporter assays were used to demonstrate whether SATB2 was a direct target of miR-34b/c.

Results: Aldosterone and SATB2 were found to be markedly upregulated during VSMC calcification, whereas miR-34b/c expression was downregulated. Treatment with the mineralocorticoid receptor (MR) antagonist eplerenone inhibited VSMC calcification. In aldosterone-induced VSMC calcification, miR-34b/c levels were downregulated and SATB2 protein was upregulated. Furthermore, miR-34b/c overexpression alleviated aldosterone-induced VSMC calcification as well as inhibiting the expression of SATB2 protein, whereas miR-34b/c inhibition markedly enhanced VSMC calcification and upregulated SATB2 protein. In addition, luciferase reporter assays showed that SATB2 is a direct target of miR-34b/c in VSMCs. Overexpression of SATB2 induced Runx2 overproduction and VSMC calcification.

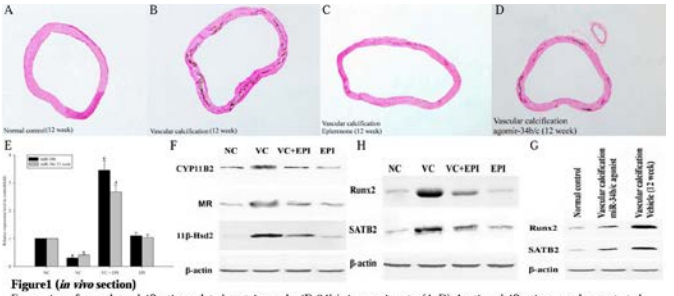

Figure1 (*in vivo* section)
Expression of vascular calcification-related proteins and miR-34b/c in uremia rats. (A-D) Aortic calcification was demonstrated by Von Kossa staining (10×4). (E) Expression of miR-34b/c in aortic tissue as detected by qPCR. (F) The levels of aldosterone and aldosterone function-related protein (MR, 11β-Hsd2, and CYP11B2) were increased in the calcified aortas of uremic rats. (G-H) Levels of SATB2 and Runx2 protein in aortic tissue as detected by western blot analysis (n = 8, mean ± SD, *P < 0.001 versus normal control group, #P < 0.001 versus vascular calcification).
NC: normal control; **VC:** vascular calcification; **VC+EPI:** vascular calcification+ eplerenone; **EPI:** eplerenone

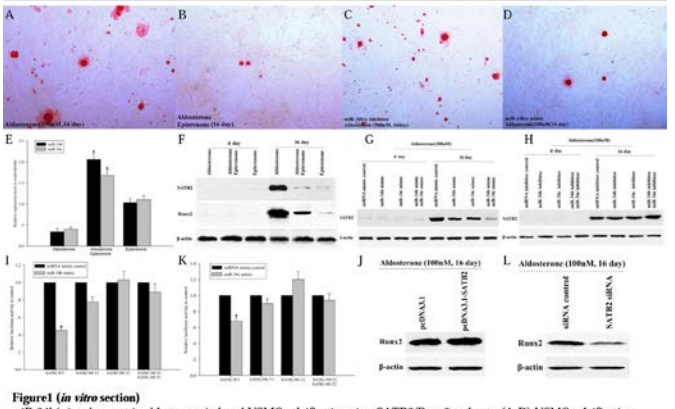

Figure1 (*in vitro* section)
miR-34b/c involvement in aldosterone-induced VSMC calcification via a SATB2/Runx2 pathway. (A-D) VSMC calcification was evaluated by Alizarin Red S staining (10×20). (E) Expression of miR-34b/c in calcified VSMCs as evaluated by qPCR. (F-H) The SATB2 and Runx2 levels in calcified VSMCs were detected by western blot analysis (n=3, mean ± SD, *P < 0.001 versus day 0). (I-K) miR-34b/c targets the 3'-UTR of the SATB2 gene in VSMCs. (n=3, mean ± SD, *P < 0.01 versus the miRNA mimic control). (J-L) SATB2 regulates VSMC calcification via a Runx2-dependent pathway. (n=3, mean ± SD, *P < 0.01 versus the siRNA control).

Conclusions: miR-34b/c participates in aldosterone-induced VSMCs calcification through a SATB2/Runx2 pathway in uremic rat. miR-34b/c might be a negative regulator and potential therapeutic target of VSMC calcification.

Funding: Government Support - Non-U.S.

FR-PO1030

β-Glucans Counteract Phosphate-Induced Vascular Calcification by Reducing miR-145-Driven Osteogenic Differentiation of Vascular Smooth Muscle Cells

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Background: In CKD, high phosphorus (P)-induced inflammatory signals and osteogenic vascular smooth muscle cell (VSMC) differentiation contribute to vascular calcification. Because anti-inflammatory dietary barley ß-glucans reduce aortic calcification in uremic rats fed high P, this study characterized ß-glucans anti-calcifying properties.

Methods: Aortic calcium, miR-145 content, mRNA levels of inflammatory (TNFa, ADAM17) and/or osteogenic differentiation (a-actin, Runx2, Osterix) markers were measured in: a) Aortas from 5/6 nephrectomized rats fed high P, with or without 40mg of barley ß-glucans daily, for 4 weeks; b) Aortic rings from normal rats or c) A7r5 cells (rat VSMC) exposed to calcifying media (2mM Ca; 3mM P), with or without synthetic barley ß-glucans (100 ug/ml) for 4 days.

Results: In uremic rats, dietary ß-glucans reduced aortic calcium content by 50%, which paralleled 80% decreases in TNFa and ADAM17 mRNA expression, an inflammatory loop that down-regulates miR-145, critical to maintain VSMC phenotype. Importantly, in these uremic rats, aortic miR-145 reductions correlated with increased calcification ($r=0.83$; $p<0.05$). Overexpression and silencing of miR-145 in A7r5 cells corroborated this novel role for miR-145 reductions in the osteogenic differentiation and calcium deposition induced by a calcifying medium. Significantly, in aortic rings and A7r5 cells exposed to calcifying media, ß-glucans reduced calcium deposition by 68% and attenuated both miR-145 reductions (35%) and osteoblastic VSMC differentiation (a-actin reductions (53%); Runx2 (54%) and osterix (57%) increments).

Conclusions: ß-glucans protect against high P-induced calcification, at least in part, by an unprecedented action: The maintenance of miR-145 levels and the phenotype of VSMC.

Funding: Pharmaceutical Company Support - Unrestricted grants from Shire, Amgen and VIFOR/Fresenius, Government Support - Non-U.S.

FR-PO1031

Matrix Vesicles Induce Cell-Cell Communication That Facilitates Vascular Calcification

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Background: In patients with CKD and ESRD, the major risk factor for progression of arterial calcification is the presence of existing (baseline) calcification. We have shown that VSMC from CKD rats produce matrix vesicles (MV) that are similar to exosomes. We hypothesized that calcification of arteries is propagated/extended by MV induced cell-cell communication from calcifying VSMC to normal VSMC.

Methods: We isolated MV from VSMC from Cy/+ rats with advanced CKD incubated with high phosphorus media. MVs were co-cultured with VSMC from normal littermates and endocytosis examined by confocal microscopy. MV mediated alteration of intracellular calcium ($[Ca]_i$), MAP kinase signaling, and gene expression in recipient VSMC were assessed using calcium Rhod-3 Calcium Imagingt, Western blot, and qPCR, respectively.

Results: The addition of MV from VSMC from CKD rats enhanced the calcification of recipient VSMC. Confocal imaging confirmed that MV can be endocytosed by recipient VSMC. The addition of MV to normal VSMC increase $[Ca^{2+}]_i$. In contrast, the addition of MV similarly isolated from NIH-3T3 fibroblasts to VSMC had no effect on $[Ca^{2+}]_i$despite evidence that both MV can be endocytosed. MV-induced increased in $[Ca^{2+}]_i$ in recipient VSMC is partially mediated by 1,4,5-trisphosphate (IP3)-induced $[Ca^{2+}]_i$release as treatment with an IP3 inhibitor reduced MV-induced increase in $[Ca^{2+}]_i$ In contrast, blocking L-type calcium channel with verapamil had no effect. The addition of MV also increased the activity of phospho-p44/42 MAPK and phospho-MEK1 in recipient VSMC. The inhibitor of MAP kinase, U0126, also decreased MV-induced increase in $[Ca^{2+}]_i$ in VSMC. Finally, the addition of MV altered gene expression involved in VSMC phenotype (SM22α), osteoblastic differentiation (BMP-2) and oxidative stress [NOX1 and angiotensin II type I receptor (AT1R)] in recipient VSMC.

Conclusions: MV isolated from VSMC from rats with CKD are endocytosed by recipient VSMC from normal rats, increase $[Ca^{2+}]_i$ and MAPK cell signaling, modify gene expression and increase calcification of the normal recipient VSMC. This cell-cell communication may lead to propagation of arterial calcification in CKD.

Funding: Other NIH Support - NIH/NIAMS, VA Support

FR-PO1032

Vitamin K2 Supplementation and Arterial Stiffness in the Renal Transplant Population – A Single-Arm, Single-Center Clinical Trial

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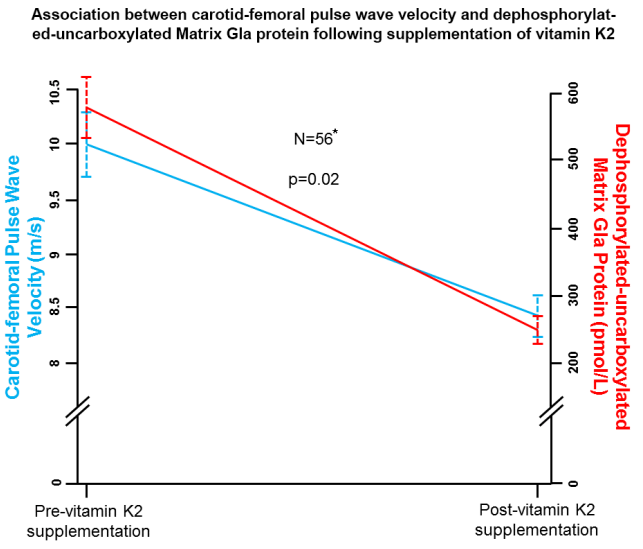
Background: Functional vitamin K2 deficiency is highly prevalent among renal transplant recipients and is associated with an increased risk of cardiovascular (CV) disease. The association between vitamin K2 supplementation and improvement in arterial stiffness, a surrogate of early CV disease, has not been investigated.

Methods: The KING trial is a single-arm pilot study that evaluated the association between the change in measures of functional vitamin K2 status and arterial stiffness following 8 weeks of vitamin K2 supplementation (360 µg qd) among 60 renal transplant recipients with stable graft function. Functional vitamin K2 deficiency was defined as serum dephosphorylated-uncarboxylated Matrix Gla Protein (dp-ucMGP) > 500 pmol/L. Arterial stiffness was evaluated by carotid-femoral pulse wave velocity (CFPWV).

Results: At baseline, the prevalence of functional vitamin K2 deficiency was 53.3%. After supplementation, mean dp-ucMGP concentration was significantly reduced by 55.1%, and the prevalence of functional vitamin K deficiency decreased to 13.3% ($p=0.001$). Vitamin K2 supplementation was associated with a 14.2% reduction in mean CFPWV at 8 weeks (mean pre-CFPWV=10.0±2.4 m/s vs. mean post-CFPWV=8.4±1.5 m/s; $p<0.001$). When controlled for age, duration of hemodialysis and transplant, and change in mean arterial pressure from baseline to 8 weeks, the improvement in arterial stiffness remained independently associated with the improvement in dp-ucMGP ($p=0.02$).

Conclusions: Among renal transplant recipients, vitamin K2 supplementation for 8 weeks is associated with improvement in functional vitamin K2 status and arterial stiffness.



Funding: Pharmaceutical Company Support - Omicron Pharmaceuticals

FR-PO1033

Apabetalone Reduces Levels of Key Markers Involved in Vascular Calcification Ewelina Kulikowski,[1] Dean Gilham,[1] Laura Tsujikawa,[1] Sylwia Wasiak,[1] Kamyar Kalantar-Zadeh,[2] Christopher Halliday,[1] Jan O. Johansson,[1] Michael Sweeney,[1] Norman C.W. Wong.[1] *[1]Resverlogix, Calgary, AB, Canada; [2]Univ of California, Irvine, Orange, CA.*

Background: Apabetalone (RVX-208) treatment lowered alkaline phosphatase (ALP) in CVD patients in phase II studies. Apabetalone inhibits the interaction of BET (bromodomain extra terminal) proteins & acetyl-lysine marks on histone tails. BET proteins control recruitment of transcriptional machinery to coordinate gene transcription of sensitive genes, including factors that contribute to vascular calcification. Vascular calcification is an underlying process in CKD pathogenesis. We examined the effect of apabetalone on markers known to contribute to vascular calcification in vitro & in the clinic.

Methods: Microarrays of human whole blood (WB) & primary human hepatocytes (PHH) treated with apabetalone were analyzed. Expression of vascular calcification markers was evaluated using real-time PCR in PHH & U937 macrophages. Proteomic analysis of plasma samples (n=47 apabetalone; n=47 placebo) from phase II CVD trials was performed using SOMAscan™. SOMAscan™ uses aptamers which are highly specific for their cognate protein, to assess levels of ~1300 proteins.

Results: In WB treated with apabetalone, microarrays showed suppression of a variety of vascular inflammation & calcification factors. Expression of osteopontin (SPP1), a proinflammatory molecule, is reduced in LPS stimulated U937 macrophages (-94%) as well as in PHH (-82%). Expression of additional calcification related genes was also reduced in PHH including ALP, RANKL, CCL2, IL8, OPG & BMP2. In the 26 week ASSURE trial, circulating levels of OPG (associated with higher incidence of arterial calcification) & IBSP (major component of bone matrix) were reduced by 14% & 18% ($p<0.05$) versus placebo.

Conclusions: BET inhibition by apabetalone decreases expression & circulating levels of markers known to contribute to vascular calcification, which may decrease pathology & mortality in CKD. The potential of apabetalone to treat high-risk diabetes & CKD patients is being explored in the phase III BETonMACE trial. Further, a PK study in severe renal impaired patients is underway.

FR-PO1034

Hemodialysis versus Peritoneal Dialysis: A Five Years, Two International Centers, Retrospective, Observational Study Renhua Lu,[1,2,3] Leonardo Claudino Ribeiro,[3] Claudio Ronco.[3] *[1]Dept of Nephrology, Kashgar Prefecture Second People's Hospital, Kashgar, Sinkiang, China; [2]Dept of Nephrology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong Univ, Shanghai, China; [3]Nephrology, Dialysis and Transplantation, San Bortolo Hospital, the International Renal Research Inst of Vicenza, Vicenza, Veneto, Italy.*

Background: It is well known that the incidence of ESRD become increasingly higher all over the world. Given that it is difficult to randomize ESRD patients to either HD or PD, differences between these two renal replacement therapy are of major interest and still controversial.

Methods: All data of maintenance dialysis patients including HD and PD during 2009 to 2013 in Ren Ji Hospital, china and San Bortolo Hospital, Italy were selected by Network. Patients who changed the therapy from HD to PD or PD to HD during this study were excluded.

Results: 919 maintenance dialysis patients were included in this study (HD=509,PD=410). Baseline laboratory test data were comparable. After five years follow-up, to compare with PD, MAP and weight were higher in HD patients. The level of HCO_3^- was significantly better in PD patients than that in HD patients. Regarding the infection markers such as WBC and CRP were significantly higher in PD patients than HD patients. Hemoglobin was significantly higher in PD patients than HD patients. Total albumin and phosphate were higher in HD patients than PD patients. The top three causes of death in HD patients ranged as cerebral vascular disease, infection and cardio vascular disease. In PD, infection was the main cause of death, followed as cerebral vascular disease and cardio vascular disease. The Kaplan-Meier patient survival was similar between HD and PD patients.

Conclusions: Based on 5 years data of two international dialysis centers, we demonstrated that lipid metabolism and nutrition were better in HD patients. However, BP control, acid-base balance, P control and the concentration of Hb and iron were better in PD patients. PD patients might have more chance of infection. The main cause of death in HD and PD is cerebral vascular disease and infection respectively. Considering to dialysis vintage, the 5-year survival rate for HD and PD patients is similar.

FR-PO1035

Outcomes of Pediatric Peritoneal Dialysis Patients: Experiences from a Single Center in Khartoum, Sudan Alice Topping,[1] Rasha Hassan Hussein,[2] Jochen G. Raimann,[1] Peter Kotanko,[1,3] Hasan Abu-Aisha.[4] *[1]Renal Research Inst, New York, NY; [2]Soba Univ Hospital, Khartoum, Sudan; [3]Icahn School of Medicine at Mount Sinai, New York, NY; [4]Sudan PD Program.*

Background: Peritoneal dialysis (PD) is the most common modality for pediatric patients (pts) with end stage renal disease (ESRD) (Warady, et al 2012) and is particularly advantageous in developing countries due to less resource requirements. The Soba University Hospital (SUH) in Khartoum, Sudan, began its PD program in 2005. It aims to encourage PD use, particularly in children, and train health professionals on PD. This descriptive analysis aims to characterize the population and their outcomes at the hospital.

Methods: Retrospective study of all pediatric PD pts treated at SUH from 06/2005 to 06/2015. Descriptive statistics of pt demographics, causes of ESRD and clinical outcomes including episodes of peritonitis. Factors associated with mortality are analyzed by development of a Cox Proportional Hazards (PH) model.

Results: One hundred twenty pts who received treatment during the study period were included in this analysis (44% male, median age 10 yrs [1-17 yrs], median length of PD 350 days). Forty pts traveled >200km to the center for treatment. The most common causes of ESRD were glomerulopathy (38%) and congenital urological malformation (24%). Fifty-two cases of peritonitis were recorded, 46 first episodes (eps) and 6 secondary eps. The rate of first peritonitis ep was one ep/2.85 years of follow-up. The rate of second peritonitis ep was one ep/6.39 years of follow up. During the study period, 24% of pts died, 32.5% switched to HD and 17.5% received transplants. The mortality rate was 16.6 deaths/100 patient years at risk. The Cox PH model shows 3 times higher hazard of death in winter compared to summer [HR 3.0 (95% CI 1.67-5.39)] and a 2.5 higher hazard in autumn (95% CI 1.43- 4.54). Age was also associated with risk of death (HR 1.07 [95% CI 1.01-1.13]).

Conclusions: PD is a common and appropriate method of renal replacement therapy for pediatric ESRD pts. These results provide a view into the potential of PD in pediatric pts in developing countries. Funding for PD programs such as at SUH can help provide essential services to children with ESRD.

Funding: Pharmaceutical Company Support - Fresenius Medical Care

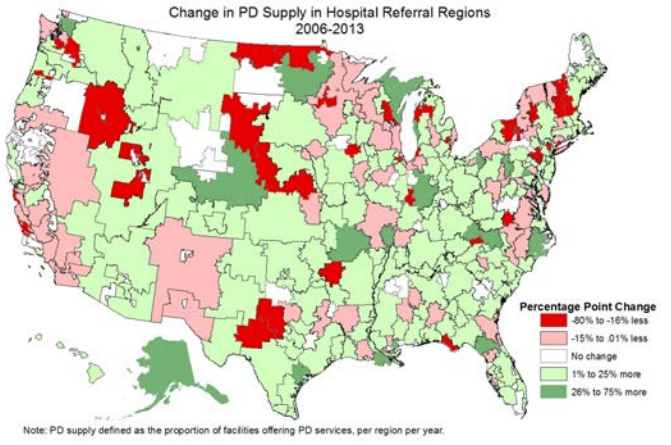
FR-PO1036

Changes in Regional Dialysis Facility Provision of Peritoneal Dialysis after Medicare Payment Reform Virginia Wang,[1,2] Cynthia Coffman,[1,2] Linda L. Sanders,[1] R. Hirth,[3] Shoou-Yih Daniel Lee,[4] Matthew L. Maciejewski.[1,2] *[1]Duke Univ, Durham, NC; [2]HSRD, Durham VA Med Ctr, Durham, NC; [3]Univ of Mich, Ann Arbor, MI; [4]UNC-CH, Chapel Hill, NC.*

Background: Much attention has been paid to patient use of peritoneal dialysis (PD), with little consideration of the supply-side PD provision by dialysis facilities. Medicare implemented an ESRD bundled payment that is expected to encourage greater PD provision among providers.

Methods: We used data from the USRDS on dialysis facilities in 2006-2013. Choropleth maps illustrated change in the regional distribution of facilities offering PD services before and after bundled payment in 2011. A random effects model examined the impact of payment reform on the change in the proportion of facilities offering PD in regions, adjusting for facility and patient demographics.

Results: Growth in the number of facilities offering PD outpaced growth in total US dialysis facilities, but there was significant regional variation in PD supply. Between 2006 and 2013, the unadjusted mean (± SD) percentage of regional US facilities offering PD increased from 41% (± 20%) to 43% (±20%). The majority of regions experienced growth in PD service offerings, most notably in rural portions of the South, Midwest, and West.



In adjusted analysis, the mean percentage of regional facilities offering PD increased 2.8% [95% CI 1.6%, 4.1%] before and after the bundled payment (2011-13). Regional PD prevalence, white ESRD patients, concentrated dialysis markets (versus more competitive markets), and per capita income were associated with increases PD supply; employed ESRD patients was associated with diminished PD supply (all $p< 0.0001$).

Conclusions: Results suggest the success of bundled payment to align patient preferences as demonstrated by increasing availability of PD. Future research should explore the extent to which modality choice is available and accessible to various subgroups of patients with ESRD.

Funding: NIDDK Support

FR-PO1037

Effect of Distance and Time to a Home Dialysis Unit on Home Dialysis Utilization Rajat Maheshwari,[1] Ninad S. Chaudhary,[2] Russell Griffin,[2] Eric L. Wallace.[1] *[1]Nephrology, Univ of Alabama at Birmingham, Birmingham, AL; [2]Dept of Epidemiology, Univ of Alabama at Birmingham, Birmingham, AL.*

Background: Distance to a home dialysis unit (HDU) may pose a barrier to home dialysis uptake and impact outcomes. Studies have shown that with increasing distance to an HDU, home dialysis utilization increases, however its impact on outcomes has received less attention.

Methods: This is a retrospective cohort analysis of incident dialysis patients in 2010 using USRDS data. Patients and dialysis units were geocoded to the population center of each zip code using from which the travel distance and time to their closest HDU was calculated. Driving distance was further categorized as: 0-10 miles, 10-30 miles, >30 miles, and the travel time was categorized as: 0-30, 30-60, >60 mins. We assessed the first dialysis modalities in-center hemodialysis (ICHD), and home dialysis which included PD and home hemodialysis (HHD). Bivariate associations were reported using one-way ANOVA and chi-square tests were deemed appropriate. Logistic regression analyses adjusted for demographics, and medical conditions were used to determine the effect of distance and time to the closest HDU on utilization of home dialysis compared to ICHD.

Results: We analysed 84202 incident dialysis patients. Overall, 91% utilized ICHD, 8.3% PD, and 0.7% HHD. Dialysis patients living >30 miles from a HDU were more likely to utilize PD (OR=1.40; 95%CI 1.28-1.53) but less likely to use HHD (OR=0.66; 95%CI 0.47-0.93) than those living <10 miles. Patients living >30 miles from their closest HDU on home dialysis trended towards higher technique failure rates than those <10 miles (OR=1.17 95%CI 0.77-1.77) but this did not reach statistical significance. Patients >30 miles from an HDU whose primary modality was ICHD trended towards an increased likelihood of switching to home dialysis (OR=1.13, 95%CI 0.96-1.32). Similar significant effects were observed when stratifying by time to a HDU.

Conclusions: Patients living remotely from their closest HDU are more likely to use PD but less likely to use HHD. Larger studies are needed to determine if the effect of distance from a HDU truly impacts outcomes such as technique failure rates.

Funding: Pharmaceutical Company Support - Baxter Healthcare

FR-PO1038

Does Dialysis Modality Impact Employment? A Cross Sectional Study R. Ram,[1] Boju Sangeetha Lakshmi,[1] Anil Kumar Cheni Venkata,[1] Hari Krishna Reddy Mogili,[1] V. Siva Kumar,[1] Abhilash Koratala.[2] *[1]Sri Venkateswara Inst of Medical Sciences, India; [2]Univ of Florida.*

Background: Long-term dialysis therapy for End stage renal disease (ESRD) takes a heavy toll on quality of life the patient. Dialysis creates a whole range of obstacles to employment which includes, health related barriers, economic barriers and attitudinal barriers. This study was designed to gain insights into the employment rates in maintenance dialysis patients which no Indian study has reported so far to the best of our knowledge.

Methods: A cross-sectional study of employment of patients on hemodialysis (HD) and peritoneal dialysis (PD) in a state government run tertiary institute in South India was performed between June 2015 and December 2015. Only patients who completed 3 months of regular dialysis were included. The data was collected using a de-identified, self-administered patient survey after obtaining a formal written consent.

Results: The number of patients on HD was 157 and on PD was 69.The employment status before initiation of dialysis was 60% (93 out of 155) and 63.7% (44 out of 69) in HD and PD groups respectively. After initiation, loss of employment was observed in 44% (41 out of 93) in HD and 51.2% (26 out of 44) in PD group (p= 0.2604). Even though there was fall in absolute number of job holders in both the blue and white collar jobs, the proportion of job holders in the white collar jobs improved. On univariate analysis, the factors that are associated with the loss of employment were male sex, age between 50 and 60 years,number of comorbidities > 2, illiteracy and blue collar versus white collar job before the initiation of dialysis. The majority of patients had the scores above 80 on Karnofsky Performance Scale and the majority belonged upper and middle strata than lower strata on Modified Kuppuswamy's socioeconomic status scale.

Conclusions: Our study shows that there was no difference between HD and PD in the loss of employment of our patients which is in contrast to the impression that the PD offers freedom from treatment schedules and possibility for out-of-work-hours dialysis, making it a suitable option for employed patients.

FR-PO1039

Factors Associated with Eventual Renal Replacement Therapy Decisions after Evaluation of Patients Initially Planned for Peritoneal Dialysis Benjamin Zhi En Khoo,[1] Hankun Wang,[2] Adrian Liew.[1] *[1]Renal Medicine, Tan Tock Seng Hospital, Singapore; [2]National Univ of Singapore.*

Background: Ideal outcomes in patients on peritoneal dialysis (PD) are dependent on multiple medical and social factors. Patients with end-stage renal disease are often started on PD without in-depth assessment for these influences. Since 2011, our centre mandated that all patients being planned for PD are to be evaluated by a multidisciplinary PD team. This study aims to evaluate the factors that determined the eventual therapy outcome after pre-PD assessment (PDA).

Methods: We conducted a case-controlled study of 252 patients who were initially planned for PD, undergoing PDA from 2011-2015. Outcomes after the PDA included continuation with PD [n=171,67.8%], switch to hemodialysis (HD) [n=64,25.4%] or acceptance of palliative treatment (PALL) [n=17,6.8%]. Demographics, medical and social variables were obtained from medical records.

Results: 252 patients (mean age 63.2±14.1 years, 52% female, 75.8% Chinese and 75.2% diabetics) were evaluated during PDA. Older patients (PALL:79.5±7.6 vs PD:62.4±14.3 vs HD:61.1±12.0,p<0.0001) with a higher Charlson Comorbidity Index (PALL:9.35±1.80 vs PD:7.02±2.72 vs HD:7.07±2.46,p=0.0022), requiring ADL (PALL:47.1% vs PD&HD:11.5%,p=0.002) and mobility assistance (PALL:82.4% vs PD&HD:43.8%,p=0.006) were likely to accept PALL after PDA. For patients who eventually started dialysis, those who continued with the decision for PD were more likely not to have received interim HD (68.4% vs 42.2%,p<0.001), and had higher serum albumin (30.7±5.5 vs 28.6±6.0,p=0.0096). Factors which were traditionally thought to have a poorer impact on the choice of PD were not significantly different between the dialysis groups, including BMI, DM, HbA1c, prior abdominal surgery, ADPKD, respiratory diseases, small housing size or having pets.

Conclusions: Engagement on the option of palliative treatment could be considered for older patients with poorer functional status. Exposure to prior hemodialysis is likely to waive the initial decision for PD. With improved PD technology and effective mitigation of social factors, traditional issues that were previously unattractive are no longer obstacles to PD.

FR-PO1040

Routine Use of Decision Making Tools Increases Peritoneal Dialysis Choice and Take on in an International Setting Belen Marron,[1] Janusz Ostrowski,[2] Delia Timofte,[3] Marietta Török,[4] Michael Roesch,[5] Claudia Martin,[6] Pawel Kochman,[2] Orosz Attila,[7] Jose C. Divino-Filho,[8] Jorgen B.A. Hegbrant.[9] *[1]Diaverum Home Therapies. Medical Office, Munich, Germany; [2]Wloklawek Diaverum Clinic, Wloclawek, Poland; [3]Sema Diaverum Clinic, Bucharest, Romania; [4]Rokus Diaverum Clinic, Budapest, Hungary; [5]Schlankreye Diaverum Clinic, Hamburg, Germany; [6]Barracas Diaverum Clinic, Buenos Aires, Argentina; [7]Bajcsy Diaverum Clinic, Budapest, Hungary; [8]Karolinska Inst., Stockholm, Sweden; [9]Diaverum Medical Office, Lund, Sweden.*

Background: Lack of patient choice or inability to offer high quality modality information programs remain as causes for low PD use.

Objectives:To analyze the impact of a structured modality information program with the use of decision making tools (DMTs) on type of modality choice and start.

Methods: Observational, prospective and international registry. All patients under ESRD 4-5 and/or after an unplanned dialysis start (if non-informed before) were recruited to undergo a DMTs process for RRT choice. Process included: personal values evaluation, RRT information with different tools, deliberation support and patient´s modality election.

Results: 1141 patient-aimed modality information between Aug. 2014-Dec. 2015 in 45 clinics (Poland, Romania, Hungary, Germany and Argentina). Staff considered PD as contraindicated in 32%. 800 patients (mean 59,5 y.) were considered optimal for HD/PD (48% were prone for a home therapy). Written information was largely used for 69-95% of patients; DVD in 14-30% and in centre HD/PD touring visits in 10-76%. Relatives' participation in the process was 82%. PD choice (39%) varied among countries: 16% (RO, 12 clinics), 38% (PL, 19 cl.) 41% (HU, 10 cl.), 84% (GE, 3 cl.) and 93% (AR,1 cl.). For patients who started dialysis (n= 612), PD as chronic RRT reached 31% (10% with an unplanned HD start); 13% (RO), 30% (PL), 36% (HU), 75% (GE), 93% (AR).

Conclusions: Use of DMTs at the time of RRT modality choice complies with patient empowerment. A remarkable increase in PD take-on occurred in our clinic network after DMTs process introduction. Therefore, modality information should always be delivered through a structured information process based on decision sharing.

FR-PO1041

Peritoneal Dialysis Annual Dropout in a Large International Setting Belen Marron,[1] Gustavo Lorenzo Moretta,[2] Michael Roesch,[3] Janusz Ostrowski,[4] Marietta Török,[5] Daniel Eduardo Perez,[6] Delia Timofte,[7] Carlos Zuniga,[8] Paul Stroumza,[9] Elisabeth Fabricius,[10] Jorgen B.A. Hegbrant.[11] *[1]Diaverum Home Therapies. Medical Office, Munich, Germany; [2]Diaverum LA Medical Office, Buenos Aires, Argentina; [3]Schlankreye Clinic, Hamburg, Germany; [4]Wloklawek Clinic, Wloclawek, Poland; [5]Rokus Diaverum Clinic, Budapest, Hungary; [6]SEINE Clinic, Montevideo, Uruguay; [7]Sema Clinic, Bucharest, Romania; [8]Colina Clinic, Concepción, Chile; [9]Marseille Clinic, Marseille, France; [10]Visby Clinic, Visby, Sweden; [11]Diaverum Medical Office, Lund, Sweden.*

Background: Peritoneal dialysis (PD) growth is limited by a high annual drop out (DO) (40-75%) which is often not routinely measured.

Objectives: To analyze the introduction of a new tool based on the monitoring of accumulated annual PD DO and the underlying DO causes.

Methods: Observational, prospective registry in 6 European (EU) countries (FR, GE, HU, PL, RO, SWE) and 3 Latin American (LA) countries (AR, CH, UR). LA provided results as a one single region. During Jan 1-Dec 31 2015, all prevalent and incident PD patients were tracked on a monthly basis for DO due to: transplantation (TX), residual renal function (RRF) recovery, transfer to HD (due to peritonitis, exit site issues, catheter problems, ultrafiltration failure, low adequacy, burn out or others), transferred to other centers or death. Total DO, controllable DO (transfer to HD and to other centers) and underlying causes are provided as result/patients at risk.

Results: 1011 pt. (667 prevalent and 344 incident) in 61 clinics were tracked. PD withdrawal: 312 pt. Total DO and controllable DO varied among regions: 49% and 19% in EU vs. 42 and 18% in LA. TX accounted for 8% (higher in PL and lower in LA, GE and RO), RRF recovery 0.3%, transfer to other centers 4%, death 18% (lower in LA and PL). Half of deaths were attributed to cardiac events and 6% to peritonitis. Transfer to HD: 15% (peritonitis 6.5%, catheter issues 2%, low adequacy 1.3%, UF failure 0.4%, burn out 1.2%, others 3.5%).

Conclusions: Annual accumulated DO monitoring increase quality in PD. This tool allows homogeneous comparisons across countries and provides assessment of DO causes that if promptly and efficiently resolved may improve technique and patient survival.

FR-PO1042

Offering Patients Therapy Options in Unplanned Start (OPTiONS) Anna Machowska,[1] Mark Dominik Alscher,[2] Satyanarayana Reddy Vanga,[3] Michael Koch,[4] Michael Aarup,[5] Abdul Rashid Tony Qureshi,[1] Bengt Lindholm,[1] Peter Rutherford.[6] *[1]Renal Medicine & Baxter Novum and Renal Medicine, CLINTEC, Karolinska Inst, Huddinge, Sweden; [2]Robert-Bosch- Krankenhaus, Stuttgart, Germany; [3]Univ Hospital of North Staffs, Stoke, United Kingdom; [4]Nephrologisches Zentrum, Mettmann, Germany; [5]Odense Univ Hospital, Odense, Denmark; [6]Quintiles, Reading, United Kingdom.*

Background: Patients (pts) with unplanned dialysis start (UPS) have worse clinical outcomes than non-UPS pts, and receive peritoneal dialysis (PD) less frequently. In the OPTiONS study an educational programme (UPS-EP) aiming at improving care of UPS patients and enabling informed choice of dialysis modality was implemented. We report impact of UPS-EP on modality choice and clinical outcomes in UPS pts.

Methods: This non-interventional, prospective, multi-centre, observational study included 270 UPS pts from 26 centres in 6 European countries (Austria, Germany, Denmark, France, United Kingdom and Sweden) presented acutely, or followed by nephrologist but required urgent dialysis start. Effects of UPS-EP on choice and final decision of dialysis and outcomes in 12 months follow up were analyzed.

Results: Among 270 pts, 214 received and 203 completed UPS-EP while 56 pts - who were older ($p=0.01$) and had higher Charlson comorbidity index (CCI; $p<0.01$) - did not receive UPS-EP. Among 177 pts who chose dialysis modality, 103 (58%) chose PD (but only 81% of them received PD) and 74 (42%) chose HD (95% received HD). Logistic regression analysis showed that diabetes, OR=2.62 (CI, 1.38 – 4.97) and receiving UPS-EP, OR=3.80 (CI, 1.63 – 8.89) predicted receipt of PD. Patients choosing PD had higher CCI ($p=0.01$), higher prevalence of congestive heart failure ($p<0.01$) and myocardial infarction ($p=0.02$), and were more likely in-patients ($p=0.02$) or referred from primary care ($p=0.02$). One year survival did not differ significantly between PD and HD pts. Peritonitis and septicaemia rates were better than international guideline standards.

Conclusions: UPS-EP predicted patient use of PD but 19% of those choosing PD after UPS-EP did not receive the modality they preferred. Patient survival in patients choosing and/or receiving PD was similar to HD despite age and comorbidity disadvantages of the PD groups.

Funding: Pharmaceutical Company Support - Baxter Healthcare, Government Support - Non-U.S.

FR-PO1043

Practical Experience with Automated Peritoneal Dialysis (APD) for Urgent Start Peritoneal Dialysis Yang Li, Haiyun Wang, Ying Wang, Zijuan Zhou, Bingyan Liu, Wei Yang, Ying Cui, Xuemei Li, Limeng Chen. *Dept of Nephrology, Peking Union Medical College Hospital, Beijing, China.*

Background: Recently APD has become an option for urgent start PD in new end-stage renal disease (ESDR) patients. However, there were limited knowledge about urgent start APD in China. This study aims to analysis the survival outcomes of APD in urgent start PD compared to non-APD.

Methods: Retrospective data of 625 peritoneal dialysis (PD) patients in our center from 1996-03 to 2015-12 were analyzed. Urgent-start dialysis were defined as starting unplanned dialysis within 14 days after catheter insertion due to late referral or unexpected deterioration of residual renal function among known patients. Kaplan-Meier analysis were used to evaluate the survival and technique survival. The survival outcome was analyzed by the Cox's regression model.

Results: About 190 patients receiving urgent start PD (30.4%). The survival rate at 3 months, 1 year for urgent and non-urgent start PD group were 95.2%, 83.3% vs. 97.4% ,90.7% respectively ($P=0.025$). And there is no significant difference of the technical survival rate and peritonitis frequency between urgent and non-urgent start PD patients. For urgent start PD patients, 25 patients (13.2%) received APD (30.4% women, 62.1±19.1 years old), and 48.0% of them were diabetic nephropathy. Both APD group and non-APD group had no significant difference of age, gender, Kt/V, CCr and nPCR at baseline. The median survival time of APD and non-APD group was similar (42m vs 49m, $P=0.227$). The survival rate and the technical survival rate at 3 months and 1 year of were also similar. The peritonitis frequency of APD and non-APD was 1 episode/ 82.71 months and 1 episode/ 81.18 months. After adjusted by gender and PD modality, age (1 years, HR=1.051, 95%CI 1.029-1.074, $P=0.000$) and diabetic nephropathy ($P=0.002$) independently predicted the mortality in urgent start PD patients.

Conclusions: Urgent start PD has a lower 1-year survival rate than non urgent start PD patients. However, there is no difference of the 3-month and 1-year survival and technical survival rate between APD and non-APD in urgent start PD.

FR-PO1044

Designer Dialysis: Designing a Peritoneal Dialysis Prescription That Fits a Patient's Lifestyle Nicholas B. Helmstetter, Mihran V. Naljayan, Simone Fertel. *Internal Medicine, LSUHSC - New Orleans, New Orleans, LA.*

Background: Peritoneal dialysis (PD) is a renal replacement therapy for patients with end-stage renal disease, and is typically done daily via 4 manual exchanges, or a cycler overnight. Clearance is measured using Kt/V which accounts for PD and residual renal function (RFF). We hypothesize that patients with some RRF can perform less PD and still achieve adequate removal of toxins and volume. By maximizing use of RRF, we can reduce the numbers of daily exchanges, cycler time, or even the number of days of dialysis each week. We hypothesize that this will preserve RRF for a longer time, limit peritoneal membrane exposure to glucose leading to longer membrane life, and improve patient quality of life.

Methods: We recruited 10 patients with RRF Kt/V above 1 and total Kt/V above 1.7. Patients were counselled for reducing their PD regimen to a new prescription calculated to preserve adequacy levels. Adequacy checks were performed after one month and every three months following to ensure adequate levels of total Kt/V, and residual renal Kt/V are preserved. Monthly 24 hour urine collections were performed to assess for volume and creatinine clearance. All patients were maintained on Furosemide 160 mg twice daily.

Results: After six months of modified PD, all but one patient were above adequate levels for total Kt/V. A t-test of the 1st and 6th month data indicated a significant reduction in PD (0.775, $p=0.0105$) and total Kt/V (2.183, $p=0.0071$), but did not indicate a significant change in RRF Kt/V (1.411, $p=0.0892$). Six patients were enrolled in the study for 9 months, and this data shows a similar trend of lowered PD Kt/V and preserved RRF and total Kt/V. A t-test of the 9th and 6th month data indicated that Kt/V changes for PD (0.775, $p=0.3981$), RRF (1.318, $p=0.1130$), and total Kt/V (2.093, $p=0.0691$) were not significant.

Conclusions: Our study has shown that after reducing the PD prescription, RRF and total Kt/V can be preserved at or above adequate values. By reducing the frequency of exchanges, patient quality of life can be significantly improved in regards to reducing the likelihood of burnout, decreasing glucose exposure, and potentially reducing other complications.

FR-PO1045

A Mobile Medical App May Help Peritoneal Dialysis Patients to Share Relevant Clinical Information with Their Doctors Francesco Iannuzzella, Mattia Corradini, Sonia Pasquali. *Dept of Internal Medicine, Nephrology and Dialysis Unit, IRCCS Arcispedale Santa Maria Nuova, Reggio Emilia, Italy.*

Background: Using only free online resources, we developed an intuitive medical app to empower peritoneal dialysis (PD) patients to take an active role in their health. The app allows PD patients to record all the information needed for their monthly visits, including ultrafiltration, weight, blood pressure and the presence or absence of specific symptoms. This information is then automatically transmitted to the PD clinic in either a table format or graphs.

Methods: We screened all patients who attended our PD clinic between January 2015 and May 2016. From a total of 73 PD patients, 53 patients were excluded because they did not have access to the internet. Seven patients were excluded as they refused to give informed consent. Consequently, 13 (8 M/5 F) patients, aged between 24 and 74 years

(median 51 years) formed the final study cohort. This remote monitoring group answered daily symptom question and took daily weight, ultrafiltration, and blood pressure readings for a mean follow-up of 94+/- 13 days. The self-administered KDQOL-SF Instrument was used to assess quality of life. Continuous variables were reported as mean +/- SD, categorical data as frequencies per 100 patient-days or percentages. Student's t-test was used for normal distribution variables and Wilcoxon test for not normally distributed variables.

Results: Enrolled patients were significantly younger than other screened patients and showed a better socioeconomic status and a higher degree of instruction. Seven of 13 patients used a mobile phone, whereas the remainder used both mobile phones and other devices. Missing readings throughout the study showed a frequency of 0.6 per 100 patient-days. On a total of 851 recordings, data were reported erroneously in 2.3% of cases. There was no significant difference in QoL during the study period, but significant changes were reported for the items of emotional well-being and patient satisfaction.

Conclusions: A mobile app was successfully adopted as a telemonitoring system for a group of PD patients, showing an impressive compliance and an acceptable percentage of errors in data collection.

FR-PO1046

Shared Medical Appointment for Peritoneal Dialysis Patients Sana Waheed, Roy A. Jhagroo. *Div of Nephrology, Univ of Wisconsin School of Medicine and Public Health, Madison, WI.*

Background: Improving access to care by allowing providers with demanding clinical schedules to see patients with the same chronic condition in a group setting is the main driving force behind shared medical appointments (SMAs). Despite potential advantages of improved efficiency and better patient satisfaction with this model, it has not been implemented for dialysis patients. In this abstract, we describe our single center experience of SMAs with our peritoneal dialysis (PD) patients.

Methods: Our SMA comprises of 4-5 patients, a dietitian, a social worker, patient's primary nurse and a nephrologist. We spend an hour discussing their laboratory data, dietary changes and social issues. We collected laboratory data on patients who take part in the SMAs (n=9) and compared the quality metrics of these patients to the ones who do not (n=32).

Results: Majority of patients in both groups were Caucasian males. There were no significant differences in terms of outcomes between the two groups.

	SMA [Mean(SD)]	Non-SMA [Mean (SD)]
White (%)	89	69
Male (%)	55.6	59
Albumin (g/dL)	3.6 (0.3)	3.5 (0.5)
Hemoglobin (mg/dL)	11.1 (1.4)	11 (1.5)
Calcium (mg/dL)	9.5 (0.5)	9.3 (0.5)
Phosphorus (mg/dL)	4.6 (0.9)	5.4 (1.2)
Magnesium (mg/dL)	2.0 (0.2)	2.3 (0.4)

Conclusions: Our results emphasize that despite requiring less provider time, patients attending SMAs have similar medical outcomes as patients who are seen individually. In our program, SMAs for PD patients were started in an effort to expand our home dialysis population despite provider time constraints. Since giving patients the option of attending SMAs, our home program census has increased from 35 to 50, which accounts for 19% of our total dialysis population-a number much higher than the national average. Moreover, these meetings provide a support system for home dialysis patients as the can discuss their struggles with others who are undergoing similar experiences. In conclusion, SMAs provide an efficient system for providing care to PD patients and are an attractive alternative to the conventional clinic visits for PD patients.

FR-PO1047

Patient-Centric User-Interface in Automated Peritoneal Dialysis: Impact on Training and Outcomes at a Single Center Shuchita Sharma,[1] Mary Grace Gonzales,[1] James A. Sloand,[2] Jaime Uribarri.[1] *[1]Nephrology/Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; [2]Renal Div, Baxter Healthcare Corporation.*

Background: Automated peritoneal dialysis (APD) is a preferred method to do peritoneal dialysis (PD) by many patients. It gives the patients the comfort of performing multiple overnight exchanges using a cycler. A new, recently approved APD cycler (AMIA 2.0) has additional features of animated graphics, voice guidance and a touchscreen control panel. These patient-centric features could hypothetically increase the efficiency of training and administration of therapy. The cycler also has a remote web-based connectivity platform which allows health care providers to have access to the patient's treatment data remotely. We sought to assess whether these new technologies had any benefits over using the legacy cycler (Home-choice, HC). We report our single-center experience comparing outcomes in our first 14 patients on AMIA with historic controls on HC.

Methods: We conducted a retrospective chart review of 28 patients (14 in each group, respectively). Data collection included age and demographics for the patients, their training and treatment characteristics, and relevant clinical outcomes and laboratory data, over 60 days after initiating treatment on the cycler.

Results: We found a significant difference in number of training days for the two cyclers (AMIA vs HC): 3.07 +/- 0.83 vs 4.36 +/- 1.6, p-value: 0.015. The age and demographics were similar in the two groups. There was no difference in drop-out rate (0/14 vs 1/14), rate of peritonitis (0/14 in each group), exit site infections (0/14 vs 1/14), or hospitalizations (1/14 vs 2/14) at 60 days. We also did not find any significant difference in dialysis adequacy, serum phosphate, calcium- phosphate product, and anemia parameters when compared at the initiation and again at 60 days of cycler therapy.

Conclusions: New patient-centric features for APD cycler were found to provide more efficient training for patients. No impact was seen on 60-day dropout or other clinical parameters with this limited number of patients; a longer term follow-up and a larger N will be required to confirm these outcomes.

FR-PO1048

Assisted Peritoneal Dialysis in British Columbia: Results of a 12 Month Pilot Project Micheli U. Bevilacqua,[1,2] Rajinder S. Singh,[1] Helen Chiu,[2] Adeera Levin,[1,2] Michael A. Copland,[1] Paul Andrew Taylor.[1] *[1]Nephrology, Univ of British Columbia, Vancouver, BC, Canada; [2]British Columbia Provincial Renal Agency, Vancouver, BC, Canada.*

Background: PD is challenging to patients with compromised strength, dexterity, vision and/or cognitive deficits who have high attrition from the therapy; assisted PD (PDA) has been used in other jurisdictions to maintain patients on PD instead of transferring to HD. A 12 month pilot spanning multiple health authorities in BC was conducted to examine the effect of PDA on PD technique survival, clinical outcomes and cost.

Methods: Eligible CCPD patients for PDA service were identified by standardized criteria at 4 pilot sites. Participating patients received daily assistance with cycler dismantle and setup provided by a contracted caregiver. Patients remained responsible for other aspects of PD including connections and choice of dialysate. Outcomes for the PDA cohort were compared against: the general CCPD cohort and patients who met criteria for PDA but did not utilize the service (PDA eligible) in BC.

Results: The 53 PDA patients had an 88% (95% CI: 78-97%) 1-year death and transplant censored technique survival on PD, which was similar to the general CCPD cohort (84% [95% CI: 81-87%]) and PDA eligible cohort (86% [95% CI: 77-96%]). PDA cohort had lower peritonitis rates (0.18 episodes per patient-year vs 0.22 and 0.36), but higher hospitalization (55% vs. 34% and 35%). Qualitative feedback from patients and PD clinicians was overwhelmingly positive for PDA. The cost of PDA was approx. $15,000/year in addition to existing PD costs. PD with PDA costs $29,000/year less than HD or $23,500 less than long term care.

Conclusions: PDA was an effective way to support independent CCPD patients who were identified as at risk of PD technique failure and yielded acceptable clinical outcomes for this at risk group. The annual PDA cost is less than transfer to HD or placement in long term care, which represents a cost-minimization for a failing self-care PD patient. The strengths of our study include recruiting multiple health authorities and using a very similar comparator (PD eligible) in addition to the general CCPD population comparator.

FR-PO1049

Pilot Use of Assisted Peritoneal Dialysis for Temporary Interruptions in Self-Care Peritoneal Dialysis Micheli U. Bevilacqua,[1,2] Rajinder S. Singh,[1] Helen Chiu,[2] Adeera Levin,[1,2] Michael A. Copland,[1] Paul Andrew Taylor.[1] *[1]Nephrology, Univ of British Columbia, Vancouver, BC, Canada; [2]British Columbia Provincial Renal Agency, Vancouver, BC, Canada.*

Background: Acute illness, injury or caregiver absence can render PD patients temporarily unable to perform dialysis independently. These patients remain in hospitals, care facilities or are transferred to HD. We evaluated Respite PDA (assisted PD) for: reasons for use, duration of service, cost and impact on self-care PD retention.

Methods: This was one part of a 12-month pilot of PDA. Patients with acute interruptions in self-care CCPD were offered Respite PDA. Patients received daily assistance with cycler setup/dismantle provided by an contracted caregiver. Patients were responsible for other aspects of PD including connections and dialysate choice.

Results: 11 patients received Respite PDA. The most common reasons for use were primary caregiver absence and MSK injury. 8/11(73%) patients returned to self-care PD, 1 transferred to HD, 1 transferred to long term PDA and 1 deceased with PDA facilitating palliation. Median use of respite PDA was 29 days (range:1 to 213 days). Excluding existing PD costs, PDA cost $43/visit or approx. $1,250 for the median PDA respite usage. Estimated cost of hospital admission or transfer to HD is $7000-$10000 for the same duration.

Reason for Respite PD	Frequency	Duration of Respite PD (Days)	Disposition after Respite PDA
Primary caregiver away	2 pts*2 uses 2 pts*1 use	13, 16,2,2 3,32	All returned to self-care PD
Fall: wrist fracture	1 pt	40	Self-care PD
Hand injury	1 pt	14	Self-care PD
Fall: tibia fracture	1 pt	91	Self-care PD
Arm fracture	1 ptt	70	Self-care PD
Neurologic: allow assessment for long term care	1 pt	1	Transferred to HD
Palliative support prior to hospice placement	1 pt	12	Hospice
Surveillance for general weakness	1 pt	213	Convert to long term PDA, then long term care

Conclusions: Respite PDA is an effective way to support patients with temporary interruption in self-care PD. Majority of patients returned to independent PD. Respite PDA is cost-effective compared to hospital admission or transfer to HD.

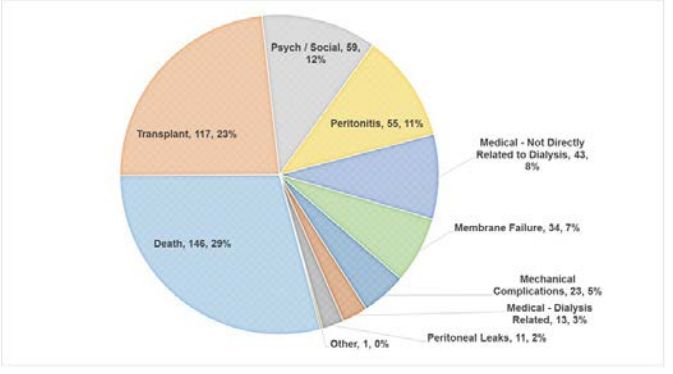
FR-PO1050

Peritoneal Dialysis Dropout - Experience from an Integrated Healthcare System with High PD Prevalence Leonid Pravoverov, Chitra R. Reddy, Neelam M. Bhalla, Joanna Mroz, Maribeth Ann Alcaraz, Sijie Zheng. *Nephrology, The Permanente Medical Group, CA.*

Background: Peritoneal Dialysis (PD) is an excellent option for renal replacement therapy (RRT). Kaiser Permanente Northern California (KPNC) is an integrated health care system with approximately 4 million members and 4700 patients on dialysis. KPNC has a higher PD prevalence (24%) compared with the national average (10%). We retrospectively analyzed the reasons patients discontinue PD.

Methods: Retrospective analysis of all patients on PD from 10/1/2013 to 12/21/2014 was conducted. Patients were followed through 3/31/2015. Patients who stopped PD for at least 60-days were identified and analyzed further. We excluded patients who lost KP membership while active on PD and included patients who stopped PD due to a kidney / SPK transplant.

Results: 502 PD patients were identified in the study period. Death (29%) and Transplantation (23%) were the two main reasons for discontinuing PD. Other reasons included: 1. Psychosocial (12%); 2. Peritonitis (11%); 3. Non-PD related medical issues (8%); 4. Peritoneal membrane failure (7%); 5. Mechanical complications (5%); 6. Medical – Dialysis related (3%); 7. Peritoneal Catheter Leaks (2%); 8. Other (<1%). The average time on PD was 2.01 years (Median was 1.36 years; with a range from 0.02 to 17.59 years).



Conclusions: Besides death and transplantation, psychosocial issues and peritonitis were the top potentially preventable reasons for patients to discontinue PD in our study. Further analysis is required to identify primary cause of death; strategies to prevent peritonitis, and steps to provide psychosocial support for patients to remain on PD.

FR-PO1051

Technique Survival and Rates of Short Term Dropout in Peritoneal Dialysis Miguel Goncalves,[1,2] Vanda Guardado,[2] Maria Joao Carvalho,[2] Jorge Malheiro,[2] Andreia Campos,[2] Ana Castro,[2] António Cabrita,[2] Anabela Rodrigues.[2] *[1]Nephrology, Hospital Central do Funchal, Funchal, Portugal; [2]Nephrology, Centro Hospitalar do Porto, Porto, Portugal.*

Background: Peritoneal dialysis (PD) and hemodialysis (HD) are equivalent modalities for CKD stage 5d treatment. PD is underused, and this may be due to the high drop-out. Objective: evaluate the specific causes of technical failure according to treatment time.

Methods: Analysis of longitudinal registry data of incidents patients admitted since 1985. Technique survival analysis considered competitive risks. Risk factors for drop-out were explored (age, sex, diabetes, type of technique and first modality for renal replacement therapy). Poison test used to compare drop-out rates according to tertile of time of follow-up.

Results: Studied population: 525 patients, 211 (40,2%) male, a mean age of 48±15,7yr, a median follow up of 23 months (IQR 9-41,5). The reasons for drop-out were: transfer to HD (n=186, 35,4%); kidney transplantation (27,6%) and death (21,7%). Transfer probability for HD was 19,2% at 2yr and 34.2% at 5yr. Transfer rates to HD by specific reasons in early and late follow-up are expressed in table.

Tertile at time of follow-up (Months)	No. patients	**Drop-out causes** (Episodes / 100 patient-months)			
		Infection related to access	Hypervolaemia/ inadequate UF/ sub-optimal dialysis	Nonadherence / inability to perform the technique	Surgical causes/ mechanical catheter complications
0,5-13	72	6.9	2.4	3.5	5.1
14-33	48	1.8	0.9	0.5	0.6
34-173	66	0.8	0.5	0.1	0.2
ρ		0.000003	0.019	0.0003	0.00002

No predictors for early failure were identified.

Conclusions: The spectrum of causes changed with time of follow-up. The critical period is the initial phase of PD threatened by complications in postoperative management of catheter (infections or mechanical/surgical), as well as non adherence/inability to technique. Early drop-out occurred unexpectedly due to hypervolaemia/inadequate UF, probably reflecting lack of compliance to fluid restrictions since baseline UFF is rare. Drop-out rates decrease with time. Investment in surgical team and infection prophylaxis, and better selection/coaching of incident patient can minimize premature failure.

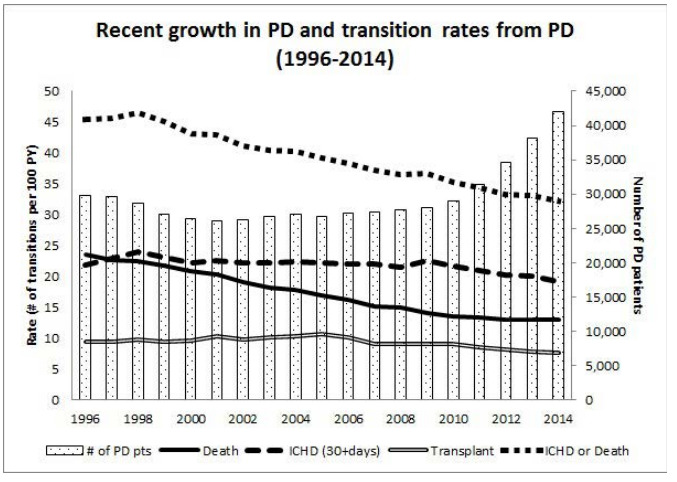
FR-PO1052

Transitions from Peritoneal Dialysis to Other Renal Replacement Therapies: Trends in the United States Renal Data System from 1996-2014 Nidhi Sukul,[1] Purna Mukhopadhyay,[2] Jeffrey Pearson,[2] Douglas E. Schaubel,[1] Marc Turenne,[2] Rajiv Saran,[1] Bruce M. Robinson,[2] Ronald L. Pisoni.[2] *[1]Univ of Michigan, Ann Arbor, MI; [2]Arbor Research Collaborative for Health, Ann Arbor, MI.*

Background: Transitioning from peritoneal dialysis (PD) to in-center hemodialysis (ICHD) is highly disruptive to patients (pts) and has been associated with higher mortality and hospitalization rates. To understand how transitions from PD to other renal replacement therapies have changed over time, we examined trends in the United States Renal Data System.

Methods: Annual cohorts of pts on PD for at least 30 consecutive days as of Jan 1st were tracked over one year for transition to ICHD (defined as ICHD for 30+ days), transplant, or death. Time at risk (expressed per 100 patient-years [PY]) was calculated as days from Jan 1st until date of transplant, death, 30 days after switching to ICHD, recovery of renal function, loss to follow-up, discontinuation of dialysis, or year end.

Results: From 1996 to 2014, the size of the annual PD cohort increased by 41%, from 29,749 to 42,035 pts. Trends in transition rates per 100 PY from 1996 to 2014 were: 23.5 to 13.1 for death, 21.8 to 19.1 for ICHD, 45.4 to 32.2 for ICHD or death, and 9.5 to 7.6 for transplant. The percent of PD pts with no transition over one year increased from 58% to 67%.



Conclusions: From 1996 to 2014, mortality rates declined sharply among prevalent PD pts, and with recent increases in new PD starts, the prevalent counts of PD pts will likely continue to rise. In contrast, the rate of transition to ICHD declined only modestly, underscoring the need for further efforts to avoid or delay transition to ICHD. Future research is needed to better understand patient-level and center-level predictors of transition; the effects of transition on medical complications and the patient experience; and rates and determinants of transition among incident PD pts.

Funding: NIDDK Support

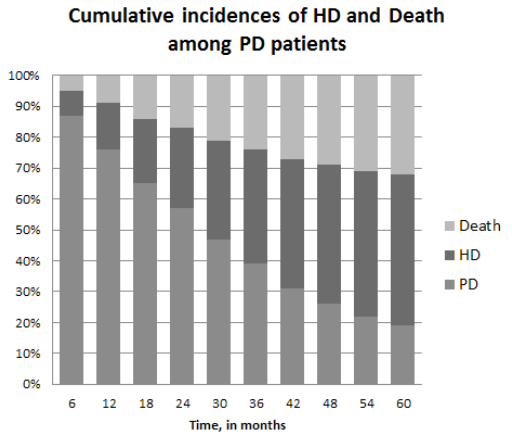
FR-PO1053

Hemodialysis Vascular Access Needs among Peritoneal Dialysis Patients Rita L. McGill, Eduardo K. Lacson, Robin Ruthazer, Klemens B. Meyer, D. Miskulin, Daniel E. Weiner. *Nephrology, Tufts Medical Center, Boston, MA.*

Background: When peritoneal dialysis (PD) patients transfer to hemodialysis (HD), >90% initiate with HD catheters. HD access is sought later in the natural history of kidney failure, reducing the likelihood of AV fistulas or grafts. Obtaining pre-emptive HD access in all PD patients may subject some patients to unnecessary surgery. Accordingly, we examined subsequent vascular access needs of patients who initiate therapy with PD.

Methods: A cohort of all incident adult PD patients in USRDS 2005-2007 were followed until a non-PD outcome occurred. Death was analyzed as a competing risk; successful kidney transplant, recovery, and loss to follow-up were censored. Cumulative incidence was calculated over five years. Competing risk regression (CRR) was used to model the impact of multiple clinical covariates on the cause-specific hazards of transfer to HD in a subset with 2 years of pre-PD Medicare.

Results: Among 16,506 incident PD patients followed over a mean of 2.3 (range 0-8.6) years, 42% transferred to HD, 28% died, and 20% received kidney transplants. HD was a more common outcome than death at all time points. Cumulative PD technique survival was less than 50% by 2½ years, by which time 32% of patients were receiving HD. Cumulative PD technique survival was < 20% at 5 years.



In the multivariable CRR model (subset n=4,687), Black race and BMI>25 were associated with more HD and less death; older age, arrythmia, and lower creatinine were associated with more death and less HD; diabetes as the cause of kidney failure was associated with increases in both HD and death (p<0.001 for all).

Conclusions: More than 40% of PD patients eventually transfer to HD, despite the competing risk of death. Vein protection and a vascular access plan are needed for any PD patients expected to survive more than 2-3 years without access to early kidney transplantation.

FR-PO1054

Dialysis Modality Change and Complications in PD Patients following CABG or Laparoscopic Surgery Lu Y. Huber,[1,2] Matt Day,[1] Sandra Tadros,[1] Jennifer L. Waller,[3] Mufaddal F. Kheda,[1] Jake Everett Turrentine,[4] Rhonda E. Colombo,[1] N. Stanley Nahman.[1,2] *[1]Medicine, Augusta Univ, Augusta, GA; [2]Medicine, Charlie Norwood VA Medical Center, Augusta, GA; [3]Biostatistics and Epidemiology, Augusta Univ, Augusta, GA; [4]Dermatology, Augusta Univ, Augusta, GA.*

Background: There is an increasing effort to avoid interruption of PD when PD patients undergo surgery. We queried the USRDS to investigate patterns of dialysis modality change and post-op complications in PD patients undergoing CABG and laparoscopic surgeries.

Methods: Incident PD patients in 2004-2011 who underwent CABG or laparoscopic surgeries were queried. Groups with no interruption of PD (group P), planned temporary (PHP) or permanent switch to HD (PHH), urgent temporary (UHP) or permanent switch (UHH) were identified. Demographics and comorbidities were assessed. The relative risk (RR) for complications within 3 months post-op was estimated.

Results: 8743 incident PD patients with CABG (1445), laparoscopic (7298) or both (332). 57% female, 19% black. Age 55±18yrs. Average time on PD 18±19mos. Post-op outcomes Table 1. Risk factors for complications in Table 2.

Variable	PHP	PHH	UHT	UHH	T
	2508 (28.7)	1600 (18)	322 (3.7)	304 (3.5)	4009 (46)
Hospitalizations	1.5 +/- 1.3	0.8 +/- 0.9	1.8 +/- 1.2	1.2 +/- 1.0	0.7 +/- 0.9
Peritonitis	84 +/- 3.4	15 +/- 0.9	29 (9.0)	11 (3.6)	79 (2.0)
Bacteremia	328 +/- 13.1	69 +/- 3.7	49 (15.2)	42 (10.5)	120 (3.0)
Wound Infection	76 +/- 3.0	20 +/- 1.3	2 (6.8)	15 (4.9)	40 (1.0)
Variable	Peritonitis	Bacteremia	Wound Infection		
PHD vs. P	1.66 (1.2-2.2)	4.38 (3.52-5.45)	2.31 (1.56-3.42)		
PHH vs. P	0.45 (0.26-0.78)				
UHP vs. P	4.95 (3.17-7.73)	5.30 (3.70-7.58)	5.94 (3.46-10.21)		
UHH vs. P	1.93 (1.01-3.68)	3.47 (2.29-5.26)	3.54 (1.91-6.55)		

Conclusions: Continuing PD during CABG or laparoscopic surgery appears safe. Need for urgent HD (UHP) is uncommon but associated with a higher risk of post-op complications. Future studies may focus on risk stratification to identify these patients prior to surgery.

FR-PO1055

Longer Peritoneal Dialysis Is Associated with Better Survival in Peritoneal Dialysis Patients Hironori Nakamura, Yasushi Makino, Anayama Mariko, Masaki Nagasawa. *Dept of Nephrology, Shinonoi General Hospital, Nagano, Japan.*

Background: The Japanese Society for Dialysis Therapy reported 5- and 10-year survival rates of 60.5% and 36.2% for hemodialysis (HD) patients. However, the survival rate of peritoneal dialysis (PD) patients after the therapy is switched to HD remains unknown in Japan and worldwide.

Methods: One hundred and thirty-five patients who underwent PD were retrospectively analyzed. We investigated the long-term survival rate of patients, including those who switched from PD to HD, and evaluated the correlation between survival time and clinical features at PD initiation. Death was considered a final event, and patients who were transferred to another hospital, who underwent transplantation, or the end of the study period (April 2016) were censored. Age, gender, body mass index (BMI), diabetes, serum albumin (Alb), creatinine (Cr), PD duration, dialysate to plasma creatinine ratio (D/PCr), peritoneal protein excretion (PPE) amount, and urine volume were included and analyzed by the Cox proportional hazard model and Kaplan–Meier tests.

Results: 1) The following patient characteristics were observed: mean age, 63.8 ± 15.1 years; BMI, 23.8 ± 4.6 kg/m^2; diabetes, 35.2%; Alb, 3.3 ± 0.5 g/dL; Cr, 8.6 ± 4.1 mg/dL; D/PCr, 0.67 ± 0.16; urine volume, 716 ± 522 mL; and PPE, 5644 ± 2723 mg. Mean PD duration was 44.8 ± 35.8 months, and survival was 66.5 ± 57.8 months. 2) Univariate analysis revealed significant effects of age, PD duration, Alb, PPE, and urine volume on survival. Cox proportional hazard analysis revealed that survival was significantly affected by age [hazard ratio (HR), 1.07; 95% confidence interval (95% CI), 1.03–1.11; $p < 0.001$] and PD duration (HR, 0.96; 95% CI, 0.94–0.98; $p < 0.001$). 3) Survival analysis between the two groups revealed an estimated survival of 47.2 ± 7.0 months in the short-duration PD group and 141.7 ± 10.3 months in the long-duration PD group (log rank, $p < 0.001$). Cumulative patient survival rates were: 58.3% (5 years) and 39.3% (10 years).

Conclusions: Longer PD duration was significantly associated with better survival of PD patients. The long-term survival of PD patients was similar to that of HD patients, although these were non-comparable situations.

FR-PO1056

Incidence, Hospital Charges, Length of Stay, and Mortality for Peritonitis in Children Undergoing Chronic Peritoneal Dialysis in the U.S.A. Neha Dhingra, Brian Becknell, Rose M. Ayoob. *Pediatric Nephrology, Nationwide Childrens Hospital, Columbus, OH.*

Background: Peritoneal dialysis (PD) is the most common modality utilized for children with End Stage Renal Disease (ESRD) worldwide. Peritoneal dialysis catheter-related infections cause significant morbidity and mortality in children. The frequency of peritonitis in children is increased compared to adults. The Pediatric Health Information System (PHIS) is a comprehensive pediatric database which includes clinical, administrative, and financial details for more than six million patients in participating US children's hospitals.

Methods: Data was collected for patients hospitalized with the principal diagnosis of PD catheter-related infection and ESRD (ICD-9 codes 996.68 and 585.6) from 2007 to 2015 using the PHIS database.

Results: From 2007 to 2015, the total number of hospitalizations with the diagnosis of PD catheter-related infections was 944, of which 62% were male. The total number of patients age 0-18 years was 881, with 30% of patients in the 1-4 year age group. Individuals <1 year of age accounted for 10% of total hospitalizations, but had the longest mean length of stay (69.9 days), highest mean charges ($317,093), and the highest aggregate charges (over $28 million dollars). Furthermore, in the patients in the < 1 year of age group, there were more reported deaths. More than 50% of patient hospitalizations occurred in the south region of the United States.

Conclusions: PD catheter-related infections remain a significant cause of morbidity and mortality in children with ESRD. Patients <1 year of age account for only 10% of total discharges but have longer LOS, mean charges and aggregate charges as well as higher number of deaths. The PHIS database can be a useful tool to follow trends specifically related to mortality and hospital charges in pediatric-related disease, in which there are often smaller number of patients.

FR-PO1057

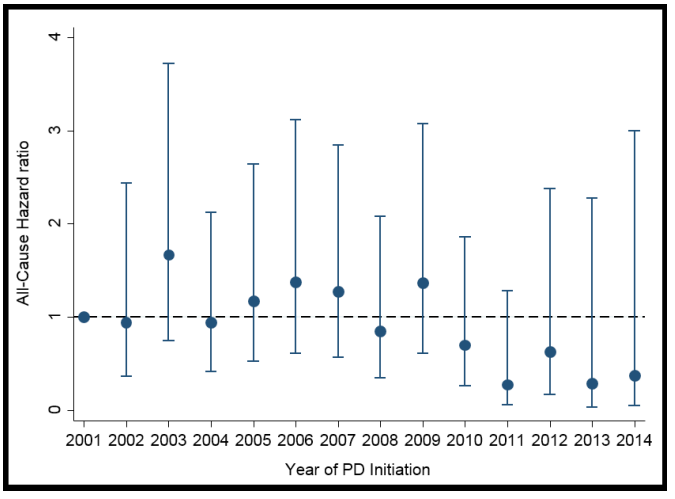
Death Risks over Time from 2001 to 2015 in Incident Peritoneal Dialysis Patients: A Retrospective Cohort Study with 15-Year Follow-Up Byeongwoo Kim,[1] Sunwoo Kang,[1] Yeong Hoon Kim,[1] Miyeon Kim,[2] Hyun Woo Kim,[2] Tae Hee Kim.[1] *[1]Internal Medicine, Inje Univ, Busan, Republic of Korea; [2]Internal Medicine, Jeju National Univ, Jeju, Republic of Korea.*

Background: Even though previous study has shown that there was no difference for survival between hemodialysis and peritoneal dialysis (PD) since 2002, the incident rate to initiate PD in patients with end-stage renal disease has decreased in developed countries. Hence, we investigated the change in trends and death risk in incident PD patients followed over up to 15 years.

Methods: In a 15-year (1/2001-12/2015) cohort of 592 incident peritoneal dialysis patients in our dialysis center, we examined death risk across the year of PD initiation from 2001 to 2014 using Cox proportional hazard models. To account for the competing

risk of transplantation across the year of PD initiation, we conducted the competing risk regression to estimate sub—hazard ratios of death risk. Models were adjusted for age, female, and diabetes.

Results: Patients were 50±13 years old, 45% female, and 50% diabetic. A total of 178 (30%) all-deaths were reported. 133 (23%) among 592 patients received kidney transplantation. Median follow up period was 2.8 years (IQR 1.4, 4.8 years) Compared with the patients who started PD in 2001, death risk tends to decrease with each subsequent year of PD initiation since 2010, but there was no significant difference across the year of PD initiation.



These trends were very similar in competing risk regression as well.

Conclusions: The survival rates in PD patients did not change until 2009 and then tended to improve since 2010. However, it has not shown significant association with the year of PD initiation over up to 15-year follow-up period. Further studies to understand the conditions influencing these death risks are needed.

FR-PO1058

Body Mass Index Trends in Patients Undergoing Peritoneal Dialysis for Decades and Their Effect on Patient Survival: Analysis of Data from an End-Stage Renal Disease Registry (1985_2014) in Korea Seon Deok Hwang,[1] Moon-Jae Kim,[2] Seoung Woo Lee.[3] *[1]Inha Univ College of Medicine; [2]Inha Univ College of Medicine; [3]Inha Univ College of Medicine.*

Background: Significant increases in the prevalence of obesity have been observed among patients with incident end-stage renal disease (ESRD). However, the changes in body mass index (BMI) status in prevalent Korean patients undergoing peritoneal dialysis (PD) over the recent decades and their impact on patient survival remain unknown.

Methods: Among 80,674 patients from the ESRD registry of the Korean Society of Nephrology since 1985, 6075 patients who were undergoing PD were included in the study. According to BMI, registered year, and serum albumin (SA) concentration the first-registered year, the patients were classified as follows: underweight (UW; <18 kg/m^2), normal weight (NL; 18–22.9), overweight (OW; 23–24.9), and obese (OB; ³25); low (<2.5 g/dL) and high (>2.5), respectively. The patients' BMIs were compared with those of 4986 subjects in the general population who participated in the sixth Korea National Health and Nutrition Examination Survey (KNHANES), 2014.

Results: The mortality risks of the OW and OB groups were respectively 1.149 and 1.188 times higher than that of the NL group after adjustments. When the patients in the NL and high SA groups were considered as reference groups, the mortality risks of the patients in the UW + low SA group and UW + high SA groups were respectively 2.73 and 1.72 times higher than that of the reference groups, even after adjustment for age, sex, diabetes, hemoglobin level, and blood pressure. We found that the mortality risk of the patients with OB and high albumin levels was 1.165 times higher than that of the reference patients. When the analysis was restricted to patients who were undergoing PD for 1 year, the mortality risks were similar to those of all the patient groups.

Conclusions: In the Korean PD patients, no significant increase in the number of UW patients was observed over the recent decades, but the proportion of OB patients tended to increase, similar to that of the general population. Both the UW and OB patients showed increased mortality risk.

FR-PO1059

Relationship between Future BMI and Baseline Nutritional Markers in Incident Peritoneal Dialysis Patients Emma H. Elphick, Mark Lambie, Simon J. Davies. *Keele Univ.*

Background: A higher body mass index (BMI) is known to relate to better survival in haemodialysis, but this remains uncertain in peritoneal dialysis (PD). BMI is frequently used as an epidemiological marker of nutritional status in the PD population however it is not known what biological determinants are involved in this assessment.

Methods: We used incident PD patients from the Global Fluid Study to test for associations between nutritional markers with baseline BMI and change in BMI after 2 years on PD. These included plasma and dialysate interleukin 6 (IL6), serum albumin, creatinine generation rate, urine volume, urine urea, ultrafiltration, dialysate glucose exposure, icodextrin use, age, gender, ethnicity and comorbidity score. A multivariate linear regression analysis was used.

Results: 297 patients had BMI measurements taken before 6 months and after 2 years on PD. Of these 214 were used. At baseline there was a significant positive association between BMI and creatinine generation rate (coeff 2.10 95% CI 0.6-3.6 p=0.006), glucose exposure (coeff 0.02 95% CI 0.007=0.030 p=0.001), urine urea (Wald 3.57 p=0.03) and urine volume (coeff 0.001 95% CI 0.0002-0.002 p=0.015). There was a negative association with male gender (coeff -1.2 95% CI -2.5 to -0.02 p=0.045) and Korean ethnicity (vs Caucasian) (coeff -2.5 95% CI -4.0 to -1.0 p=0.001). Change in BMI over 2 years had a significant positive association with age (coeff 0.03 95% CI 0.006 – 0.05 p=0.012), comorbidity score (Wald 2.49 p=0.044), Korean ethnicity (coeff 1.0 95% CI 0.3 – 1.8 p=0.009) and a negative association with creatinine generation rate (coeff -9.8 95% CI -17 to -2.4 p=0.009).

Conclusions: An increase in muscle mass is associated with an increase in BMI at baseline but a larger reduction in BMI over time. Korean centres had a lower initial BMI but less of a reduction in BMI over time. Fluid balance is positively associated with BMI at baseline but did not influence change in BMI. Albumin and inflammation did not have a significant effect.

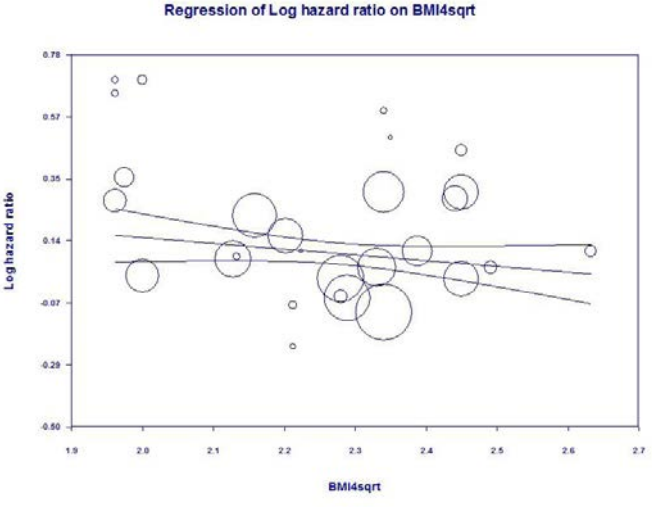
FR-PO1060

The Association between Body Mass Index and Mortality in Peritoneal Dialysis Patients Jin Ho Hwang,[1] Chae Rim Kim,[1] Geun Joo Choi,[2] Hyun Kang.[2] *[1]Internal Medicine, Chung-Ang Univ Hospital, Seoul, Republic of Korea; [2]Anesthesiology and Pain Mecidine, Chung-Ang Univ Hospital, Seoul, Republic of Korea.*

Background: Unlike the general population, a higher body mass index (BMI) was consistently found to be a strong predictor of decreased mortality in patients with end-stage renal disease who receive maintenance hemodialysis (HD). This phenomenon has been referred to as the "Obesity paradox" or "reverse epidemiology". Similar tendency has been observed in several studies with peritoneal dialysis (PD) patients, but the studies have reported conflicting results. We conducted this study to evaluate the association between BMI and all-cause mortality in PD patients.

Methods: A systematic search was conducted for published studies in Medline, EMBASE, and the Cochrane library databases from 1970 to April 2015. We identified the studies evaluating the impact of BMI on mortality among PD patients. Data of hazard ratios and 95% confidence intervals (CIs) were obtained for respective BMI groups provided by each study. We performed meta-regression analysis using unrestricted maximum likelihood model.

Results: The Medline, EMBASE, and the Cochrane library search provided a total of 3,047 articles. After screening of all titles, 513 abstracts were selected. Finally, 9 cohort studies with 33,090 patients were included in the final analysis. Log hazard ratio for all-cause mortality showed a trend negatively associated with increasing four square root of BMI (slope coefficient: -0.1976, 95% CI -0.4110 to 0.0158, p= 0.0695).



Conclusions: In PD patients, BMI was inversely associated with mortality as in HD patients. Other outcomes such as cardiovascular death, peritonitis incidence, and technical failure will be additionally evaluated.

FR-PO1061

Impact of Metabolic Syndrome in Incipient Peritoneal Dialysis Patients Silvia Ros. *Nephrology, Regional Malaga Hospital, Malaga, Spain.*

Background: Metabolic syndrome (MS) is a clustering of risk factors among which are included diabetes mellitus (DM) and cardiovascular disease (CVD). It is associated with a high morbidity and mortality in general population. Its prognostic implication among patients undergoing peritoneal dialysis (PD) is not clearly defined. We studied MS and its individual components effect on both patient and technique survival.

Methods: Incident PD patients from the period of 1 January 1992 to 31 december 2014 were included. Demographic and biochemical variables were analyzed including blood, urine and peritoneal effluent. Modified National Cholesterol Education Program (Adult Treatment Panel III) criteria was used to define MS. We used t-student and chi-square to compare the results and the survival was expressed by Kaplan- Meier curves. P < 0.005 was considered significant.

Results: Two hundred and sixty-two patients were included, among them 139 (53%) fulfilled the NCEP criteria with an average age of 60 ± 14,8 years (55% men). Sixty-six per cent patients were in automated peritoneal dialysis. The patient follow-up was 22,1 ± 13,4 months. Patients with MS showed higher incidence of DM (42% vs 2,6%, p=0.0001), CVD (34,5% vs 17%, p=0.005) and body mass index (30 ± 5,3 vs 25 ± 3,7, p=0.0001); lower normalized protein catabolic rate (1,04 ± 0,3 vs 1,13 ± 0,3 g/kg/day, p=0.012) and were older (63 ± 12,5 vs 58 ± 16,6 years, p=0.009) compared with patients without MS. Patient and technique survival did not differ between patients with and without SM irrespective of the diabetic status (log-rank test, p=0.937; log-rank test, p=0.941, respectively).

Conclusions: The presence of MS at the begining of PD was not associated with a lower patient and technique survival despite the higher morbidity. Further studies are needed to establish new prognostic factors for risk stratification of patients undergoing PD.

Funding: Other NIH Support - Health public service

FR-PO1062

Increased Serum Lactate in Peritoneal Dialysis Patients Presenting with Intercurrent Illness Emilie Trinh, Nalinee Saiprasertkit, Joanne M. Bargman. *Univ Health Network, Toronto, ON, Canada.*

Background: Lactate is the most commonly used buffer in peritoneal dialysis (PD) solutions. It rapidly diffuses from the PD fluid to the blood and is metabolized via the Krebs cycle or gluconeogenesis. While prior studies have shown that lactate blood values are normal in stable PD patients, the purpose of our study was to evaluate if abnormal lactate values are more common in PD patients presenting to the emergency department (ED) and have the same significance as in the general population.

Methods: This observational cohort study assessed the prevalence of elevated lactate blood values among PD patients presenting to the emergency and evaluated clinical factors associated with an abnormal lactate value.

Results: We studied 172 patient visits in 89 PD patients to the ED at a major academic center between January 1, 2015 and December 31, 2015. An initial venous blood lactate value was performed in 91 visits (53%) and was found to be elevated (>2 mmol/L) in 26 cases (29%). While an abnormal lactate was associated with signs of hemodynamic compromise such as ICU admission (26.9% vs. 10.8%, p=0.05) and tachycardia (46.2% vs. 9.2%, p<0.01), in 46% of the cases with elevated lactate, there was no evidence of hemodynamic instability at initial presentation. Moreover, an abnormal lactate value was also associated with a greater likelihood of undergoing an abdominal CT scan (46.2% vs. 18.5%, p<0.01), but bowel ischemia was present in only one case.

Conclusions: An abnormal lactate value is often seen in PD patients presenting in the ED, even in the absence of signs of hemodynamic instability, and very rarely indicates bowel ischemia. We postulate that in the setting of an acute intercurrent illness, there is a transient disruption in the metabolism of the PD fluid lactate. This novel observation suggests that elevated serum lactate in the sick PD patient does not necessarily indicate tissue hypoperfusion or gut ischemia and may obviate unnecessary investigations.

FR-PO1063

Impact of Anemia on Loss of Residual Kidney Function in Patients on Peritoneal Dialysis Kazuhiko Tsuruya,[1] Hisako Yoshida,[1] Takanari Kitazono.[2] *[1]Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; [2]Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.*

Background: Anemia control has been considered to be important for the reduction of mortality in end-stage kidney disease patients on peritoneal dialysis (PD) as well as those on hemodialysis. Recent studies have demonstrated the importance of RKF in the survival of chronic dialysis patients, and also stressed the importance of RKF in anemia management. However, it remains elucidated whether anemia impacts on RKF.

Methods: In the present study, we investigated the effect of anemia on loss of RKF in 106 PD patients treated at our hospital. The primary outcome was loss of RKF defined as urine output <100 mL. The subjects were divided into four groups based on their hemoglobin (Hb) levels; <9, 9.0–9.9, 10–10.9, and ≥11 g/dL. The time-dependent Cox hazard model was used to determine the impact of Hb levels on loss of RKF.

Results: During median (range) follow-up period of 42 (6–102) months, 31 subjects developed RKF loss. The univariable and multivariable-adjusted incidence rate of RKF loss increased significantly with lower Hb levels (*P* for trend = 0.03). Compared with those with Hb of ≥11.0 g/dL, the multivariable-adjusted hazard ratios for the development of RKF loss were 0.55 (95% confidence intervals, 0.15–2.04), 1.71 (0.53–5.55), and 4.65 (1.27–16.94) in subjects with Hb of 10–11 g/dL, 9–10 g/dL, and <9 g/dL, respectively, after adjustment for age, sex, origin of kidney disease (diabetic nephropathy or not), renal Kt/V, systolic blood pressure, serum albumin, logarithmic serum brain natriuretic peptide, PD modality (automated PD or not), and use of icodextrin solution, 2.5% glucose solution, diuretics, and renin-angiotensin receptor antagonists.

Conclusions: This result suggests that severe anemia as indicated by an Hb level <9 g/dL is a significant risk factor for loss of RRF, thus indicating the importance of anemia management. To the best of our knowledge, no reports have described the effect of anemia on RKF, which makes the findings of the present study particularly noteworthy.

FR-PO1064

Ferric Carboxymaltose Intravenous Administration to Control Anemia in Patients with Peritoneal Dialysis Jose Luis Merino, Vicente Paraiso, Sara Castrillo, Esther Garcia, Blanca Bueno, Patricia Dominguez, Beatriz Espejo, Alicia Gomez. *Nephrology, Hospital Univ del Henares, Coslada, Madrid, Spain.*

Background: A single dosage of ferric carboxymaltose(FCM) has proven effective to control iron-deficiency anemia in hemodialysis patients as well as in situations of end-stage renal disease. Its application in patients on peritoneal dialysis(PD) is less known. We show the observation of FCM administration in PD patients.

Methods: Patients on PD treatment were included in this study. The criteria for the administration of the iv iron therapy were: hemoglobin <12 g/dL, serum ferritin levels<200,TSI<30, oral iron therapy and/or the erythropoietic stimulating factors(ESF) treatment. Patients with a previous reaction to other iv iron formulations were excluded. The dosage was 1,000 mgivFCM, and not to exceed 15mg of iron per Kg. of body weight.

Results: Sixteen PD patients were administered the iv FCM. At the time of the study, two had received a kidney transplant only 6 months prior and three still have not followed up after the 6 month check-up. Finally eleven patients have completed at least 6 months of the treatment after the administration of FCM. The average age was 53±16 years. The etiology of kidney disease was glomerulonephritis in 6 cases, 5 diabetes cases, 2 interstitial nephritis, unknown in 2 cases and 1 patient, polycystosis. The results are reflected in the table. Five patients received oral iron therapy at the beginning, and all but one received ESF.

Conclusions: The FCM is an easy alternative to manage and has few side effects. It also maintains recommended levels of ferritin up to at least six months after administration. The requirements of ESF and oral dosage of iron could be reduced.

(1) P<0.001 (2) P<0.05	basal	2 meses	4 meses	6 meses
Hemoglobine (g/dL)	11+/-1	11.2+/-0.9	11.4+/-1	11.5+/-1
Hematocrit (%)	33+/-3	34+/-2	35+/-3	34+/-4
Ferritin (ng/mL)	202+/-105	439+/-145 (1)	467+/-237 (1)	485+/-279 (2)
TSI (%)	18+/-5	31+/-11 (1)	33+/-20	27+/-6
Darbepoetin (mcg/week)	14+/-16	15+/-15	12+/-8	13+/-10
Seric Calcium (mg/dL)	8.8+/-0.6	8.6+/-0.5	8.9+/-0.7	9+/-0.5
Seric Phosphorous (mg/dL)	4.9+/-1	4.8+/-1	4.8+/-1	4.8+/-0.6

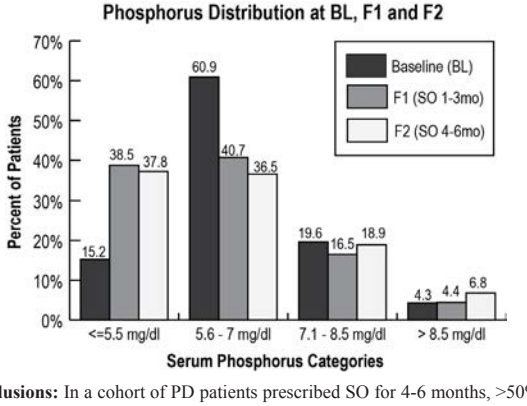
FR-PO1065

Serum Phosphorus and Phosphate Binder Pills per Day in Peritoneal Dialysis Patients Switched to Sucroferric Oxyhydroxide as Part of Routine Care Vidhya Parameswaran, Linda H. Ficociello, Carly R. Van Zandt, Norma J. Ofsthun, Claudy Mullon, Franklin W. Maddux, Robert J. Kossmann. *Fresenius Medical Care North America, Waltham, MA.*

Background: The majority of dialysis patients require phosphate binders (PB) to control serum phosphorus (sP) levels. However, poor adherence to PB prescription is common and may be related to high pill burden. This retrospective analysis assesses changes in sP control and PB pills/day in peritoneal dialysis (PD) patients who switched to sucroferric oxyhydroxide (SO) as part of routine clinical care.

Methods: PD patients (n=92) prescribed SO through a renal pharmacy service for 4-6 months were analyzed. Patients were required to be on PB monotherapy. Changes in percent of patients achieving sP ≤ 5.5 mg/dl and PB pills/day were compared during baseline (BL; 3 months prior to SO switch), F1 (1-3 months of SO) and F2 (4-6 months of SO).

Results: At BL, 84.8% of patients had hyperphosphatemia (sP > 5.5 mg/dl), and were being prescribed, on average, 9.9 PB pills/day. After SO prescription, a 58% and 54% reduction (p<0.0001) in pill burden was observed at F1 (4.2 pills/day) and F2 (4.6 pills/day), respectively. Significant improvement (all comparisons, p<0.001) in percent of patients achieving sP ≤ 5.5 mg/dl was observed comparing BL to F1 (153% increase) and BL to F2 (149% increase). Additionally, percent of patients with sP between 5.6 – 7 mg/dl decreased by 33% and 40% between BL and F1 (60.9% to 40.7%, p=0.002) and BL and F2 (60.9% to 36.5%, p<0.0001).



Conclusions: In a cohort of PD patients prescribed SO for 4-6 months, >50% fewer PB pills/day (mean decrease of >5 pills/day) were prescribed and patients with sP ≤ 5.5 mg/dl more than doubled.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

FR-PO1066

Time of Therapy with Paricalcitol Is Related with Peritoneal Protein Loss in Peritoneal Dialysis - A Double-Center Study Teresa M. Jeronimo,[1] Gloria Del Peso,[2] Anabela M. Guedes,[1] Lucia Rodriguez-Gayo,[2] Ana Paula Silva,[1] Pedro Neves,[1] Rafael Selgas,[2] Maria A. Bajo.[2] *[1]CHAlgarve; [2]Hospital La Paz.*

Background: Peritoneal protein losses (PPL) are a good marker for endothelial dysfunction and an independent predictor for mortality in Peritoneal Dialysis (PD). Little is known about the effect of paricalcitol on PPL in PD, namely after the identification of Vitamin D Receptor on the peritoneal membrane.

Methods: In a cross-sectional study we included patients stable on PD for a minimum period of three months. The patients were divided into two groups: Group 1 (G1), treated with paricalcitol at least for three months, and group 2 (G2), without paricalcitol. Clinical and laboratory data were collected from all patients at the time of PPL analysis. In statistical analysis Student's t-test, Chi-square test and Linear Regression Model were used.

Results: Eighty-two patients (G1=41; G2=41) were included: 53 male, age 55±17 years, time on PD 23.5±20.1 months, Charlson Comorbidity Index 5±3, 22% with diabetes, 61% in automated PD (APD), 62.2% medicated with angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs) during 9.5±11.1 months. The mean residual renal function (RRF) was 5.4±3.1 mL/min, reactive C protein (RCP) 8.3±14.5 mg/L, creatinine dialysate-to-plasma ratio (D/P creatinine) 0.67±0.11 and the majority of patients were high-average (52.4%) or low-average (22.0%) transporters, without differences between the two groups. The mean time of paricalcitol therapy was 5.1±8.5 months. We found higher PPL in G2 (6.34±2.07 vs. 5.01±1.87 g/24h, p=0.003). Patients in CAPD and with higher transport status (D/P creatinine>0.68) had higher PPL than patients in APD (6.35±2.28 vs. 5.30±1.85 g/24h, p=0.026) and lower transport status (6.43±2.11 g/24h vs. 4.97±1.80 g/24h, p=0.002). We found that time of therapy with paricalcitol (r=-0.283; p=0.021) was related with PPL, adjusted for diabetes, PD modality, RCP, D/P creatinine and time of therapy with ACEIs/ARBs.

Conclusions: In this study, time of therapy with paricalcitol was related with lower PPL. Prospective controlled studies, with greater number of patients comparing paricalcitol with placebo are needed to confirm the effect of paricalcitol on PPL.

FR-PO1067

Predictors of Outcome in Patients Commenced on Peritoneal Dialysis for Chronic Cardiorenal Syndrome Nalinee Saiprasertkit, Rory F. McQuillan, Emilie Trinh, Joanne M. Bargman. *Div of Nephrology, Univ of Toronto, Toronto, ON, Canada.*

Background: Studies have demonstrated that PD is a safe and efficient therapeutic modality in patients with cardiorenal syndrome (CRS), leading to decreased hospitalization rates, and improved functional status and quality of life. We have observed that some of these patients thrive on PD, while others continue to deteriorate. However, the predictors of outcome of PD in this group of patients have not yet been identified.

Methods: In this retrospective cohort study, we assessed the 6-month technique survival and hospitalization rates of all incident PD patients with CRS at a major academic center. Subsequently, clinical and laboratory parameters predicting 6-month PD (patient and technique) survival were examined.

Results: Of 185 patients who initiated PD between January 1, 2013 and February 29, 2016, 39 patients with CRS were identified. Median survival on PD was 252 days (4-1079 days).The 180-day PD survival rate was 62.2%, with a mortality rate of 35.1% and technique failure of just 2.7%. Hospitalization rates for congestive heart failure 6 months after initiation of PD were significantly lower compared to the 6 months prior to the start of dialysis (7.1% after vs. 85.7% before). Moreover, a baseline serum sodium less than 135 mEq/L was found to be a significant predictor of shorter PD survival (OR12.1[95%CI2.1-70.2], p= 0.005). Age, gender, etiology of heart failure, baseline ejection fraction, diabetic status, and hemoglobin levels were not predictive of survival on PD.

Conclusions: While patients with cardiorenal syndrome on PD have an overall poor prognosis, the initiation of PD in these patients significantly decreased hospitalization rates. Interestingly, as in the general population, hyponatremia is a major prognostic factor for reduced PD survival in this cohort.

FR-PO1068

Peritoneal Dialysis in Orthotopic Liver Transplantation Recipients: One Center's Experience Nalinee Saiprasertkit,[1] Camila Hitomi Nihei,[2] Joanne M. Bargman.[1] *[1]Div of Nephrology, Univ of Toronto, Toronto, ON, Canada; [2]Div of Nephrology, Univ de Sao Paulo, Sao Paulo, Brazil.*

Background: Despite the lack of evidence, many programs are reluctant to initiate Peritoneal Dialysis (PD) in liver transplant patients needing renal replacement therapy. This retrospective study reviews the outcome of PD in liver transplant patients at a major transplantation and dialysis center.

Methods: We performed a retrospective cohort study in patients who underwent liver transplant followed by chronic PD between the years of 1991 and 2016. Patient demographics, laboratory parameters and adverse events were collected from our electronic database.

Results: Between 1991-2016, 15 patients underwent liver transplant and subsequently received PD. Mean age was 58.7 ± 8.1 years; 40% women; mean time from transplant to peritoneal dialysis initiation was 9.0 ± 4.2 years; follow up in PD was 31.2 ± 25.6 months. Hepatitis C was the main cause of liver failure (7 patients). Calcineurin nephropathy was the lead cause of End Stage Kidney Disease (12 patients), biopsy-proven in four. Eight patients underwent liver biopsies during their time on PD without complication. The overall peritonitis rate was one episode every 43.8 months (0.27 episodes per year at risk). There was one case of relapsing peritonitis, and one patient had severe infection and died. Mean survival time was 58.9 ± 11.2 months, 5 patients died, 3 received a kidney transplant, one patient was transitioned to hemodialysis due to poor ultrafiltration, two patients were transferred to other programs, two remain on PD and two patients recovered renal function. Peritonitis and mortality rates were no different from other solid organ recipients, or even from our general PD population.

Conclusions: There appears to be no specific concern related to liver transplant patients undertaking PD. Peritonitis and mortality rates were no different from other solid organ recipients or even from the general PD population. The hepatic graft was never threatened, even during peritonitis. Therefore, these patients should not be denied the option for peritoneal dialysis.

FR-PO1069

Peritoneal Dialysis for Patients with Refractory Heart Failure and Chronic Kidney Disease Nageswara Pamidi,[3] Aruna Mangipudi,[1] Hari Krishna Reddy Mogili,[1] Anil Kumar Cheni Venkata,[1] Boju Sangeetha Lakshmi,[1] R. Ram,[1] V. Siva Kumar,[1] Abhilash Koratala.[2] *[1]Sri Venkateswara Inst of Medical Sciences, India; [2]Univ of Florida; [3]Care Hospitals, Hyderabad, India.*

Background: Heart failure (HF) is a major public health problem in India and the proportion of patients presenting with both HF and chronic kidney disease (CKD) is large and steadily increasing. Currently available therapies for decongestion mainly rely on diuretics which have their shortcomings. Peritoneal dialysis (PD) is a relatively simple choice for chronic, gentle fluid removal, and appears to be an useful option for the management of patients with HF with difficult to manage volume status. Our objective is to study the impact of PD on CKD patients with refractory HF for which, there is limited data in Indian patients.

Methods: In this 3-year prospective study conducted at a tertiary health center in South India, we initiated PD in patients with refractory HF (NYHA class IV) with varying degrees of CKD. We excluded patients with end stage renal disease. We recorded the pertinent data before and after initiation of PD.

Results: During the study period, we treated 7 patients with HF & CKD with PD. Mean age of the patients was 56.8 years and 6 out of 7 were males. The mean duration of follow up was 11.4 ± 9.8 months. Results are as follows:

Parameter (Mean ± SD)	Before PD	After PD
Serum Creatinine (mg/dL)	3.2± 0.6	1.8± 0.4
eGFR (ml/min)	36 ± 9.1	32 ± 3
Ejection fraction	28.2± 3.3	36.2 ± 3*
Urine output (cc)	950± 135	1450 ± 205*
No. of exchanges per day	-	1
Ultrafiltration per session (cc)	-	650± 80
No. of days of hospitalization per month	12 ± 3	1±1*
BNP (pg/mL)	1702± 1177	882.2 ± 757.2*

The asterisk (*) symbol indicates significant P value. 2 episodes of non-refractory peritonitis were observed.

Conclusions: We conclude that PD is a beneficial treatment strategy for optimizing fluid status in patients with refractory HF with CKD. It improves laboratory parameters including ejection fraction, diuretic resistance and decreases the hospital stay of these patients. Larger controlled trials are needed to explore the potential impact of PD on the mortality of patients with HF.

FR-PO1070

Peritoneal Dialysis in Adult Polycystic Kidney Disease Ying Ma, Haiyun Wang, Zijuan Zhou, Bingyan Liu, Xuemei Li, Limeng Chen. *Nephrology Dept, Peking Union Medical College Hospital, Beijing, China.*

Background: Adult Polycystic kidney disease (APKD) is the most common hereditary cause of renal failure. PKD renal failure has been traditionally considered a relative contraindication for peritoneal dialysis (PD) because of overexposing to technique failure and peritonitis. This study was to compare the outcomes and dialysis efficacy in PKD renal failure patients treated with PD, in comparison with hemodialysis (HD) and non-PKD subjects.

Methods: From1993 to 2015, total 47 ESRD patients with PKD in Peking Union Medical College Hospital were recruited. Dialysis adequacy, PD-related complications, PD-technique failure, clinical outcomes and survival rate were compared among patients with PKD-HD group (n=33), PKD-PD group (n=14) and non PKD-PD group (n=43, random sampling from 622 cases PD patients).

Results: The average age of PKD-PD patients was 56±14years old, of which 57.1% were women. One patients received APD treatment and others were CAPD. When compared with PKD-HD group and non PKD-PD group respectively, no significant difference of age, gender, comorbidities and biochemical index were observed in PKD-PD patients at baseline. The Kt/V, Ccr of PKD-PD patients were similar to non PKD-PD group at 3 months, 1 year, 3 years and 5years. The average time on dialysis of PKD-PD was 36.2±33.1months, which was similar to non PKD-PD group (33.6±28.9, *P*=0.551) and PKD-HD group (45.4±39.5, *P*=0.760). There were no significant difference of the peritonitis rate and technical survival rate between the PKD-PD group and non PKD-PD group. The survival rate at 1 year, 3 years, and 5 years for PKD-PD group was similar to non PKD-PD group and PKD-HD group respectively.Three PKD-PD patients convert to HD because of peritonitis and 3 received kidney transplantation. Multivariate Cox regression analysis showed that neither PKD nor PD independently predicted the mortality.

Conclusions: PD could be an option for ESRD patients with APKD.
Funding: Government Support - Non-U.S.

FR-PO1071

A Multicenter, Randomized, Controlled Trial Comparing Cefepime Monotherapy versus Combination of Cefazolin plus Ceftazidime for Empirical Treatment of CAPD-Associated Peritonitis
Thidarat Kitrungphaiboon,[1] Piyatida Chuengsaman,[2] Guttiga Halue,[3] Monchai Siribamrungwong,[4] Saraporn Matayart,[5] Kamonrat Chongthanakorn,[6] Ussanee Poonvivatchaikarn,[7] Chanchana Boonyakrai,[8] Wanida Somboonsilp,[9] Pisut Katavetin,[1] Talerngsak Kanjanabuch.[1] *[1]Chulalongkorn Univ, Bangkok, Thailand; [2]Banphaeo Hospital, Bangkok, Thailand; [3]Phayao Hospital, Phayao, Thailand; [4]Lerdsin Hospital, Bangkok, Thailand; [5]Buddhasothorn Hospital, Chachoengsao, Thailand; [6]Charoenkrung Pracharak Hospital, Bangkok, Thailand; [7]Nakhonpathom Hospital, Nakhonpathom, Thailand; [8]Chaophraya Yommarat Hospital, Suphanburi, Thailand.*

Background: To avoid laboring and contamination risk of combination antibiotics for empirical treatment of continuous ambulatory peritoneal dialysis (CAPD)-associated peritonitis, single broad-spectrum antibiotic should be proposed instead.

Methods: In a multicenter, open-label, noninferiority trial, we randomly assigned patients who diagnosed CAPD-associated peritonitis to receive intraperitoneal cefepime 1 g loading then 250 mg all exchanges (dose increased by 25% in patients with residual renal function) or combination of cefazolin and ceftazidime with the same regimen for 14 to 21 days. Patients were followed for 28 days after treatment completion. A primary outcome was primary response (at day 10) rate, with a noninferiority limit of 10 percentage points.

Results: 146 patients were randomized (72 in the monotherapy group and 74 in combination group). Patient characteristics of both groups were comparable. Cefepime monotherapy was noninferior to cefazolin plus ceftazidime as the primary response rate was 81.9% in monotherapy group and 81.1% in combination group (difference points = 0.8, 95% confidence interval (CI) -9.7 – 21.4). Initial response (at day 5) and end treatment response rates were 66.67% and 87.5% in monotherapy group versus 60.81% and 89.2% in combination groups [(difference points = 5.86, 95% CI -9.7 – 21.4), (difference points = -1.7, 95% CI -12.1 – 8.7)], respectively. No serious adverse event of cefepime were reported.

Conclusions: Intraperitoneal administration of cefepime monotherapy is noninferior to combination of cefazolin and ceftazidime. Cefepime monotherapy should be considered as an alternative empirical antibiotic for CAPD-associated peritonitis.

Funding: Pharmaceutical Company Support - Siam Pharmaceutical Co., Ltd, Government Support - Non-U.S.

FR-PO1072

Identifying Peritoneal Fluid Microbiome in Patients Receiving Maintenance Peritoneal Dialysis
Esho Georges, Holly J. Kramer, Vinod K. Bansal, Julia Schneider, Michael Zilliox, Kavitha Vellanki. *Dept of Nephrology and Hypertension, Loyola Univ Medical Center, Maywood, IL.*

Background: Peritoneal fluid is considered to be sterile in patients receiving peritoneal dialysis (PD) in the absence of peritonitis. No data exists on the microbiome of peritoneal fluid in stable PD patients. The aim of this single site pilot study is to identify peritoneal fluid microbiome characteristics in PD patients without clinical peritonitis.

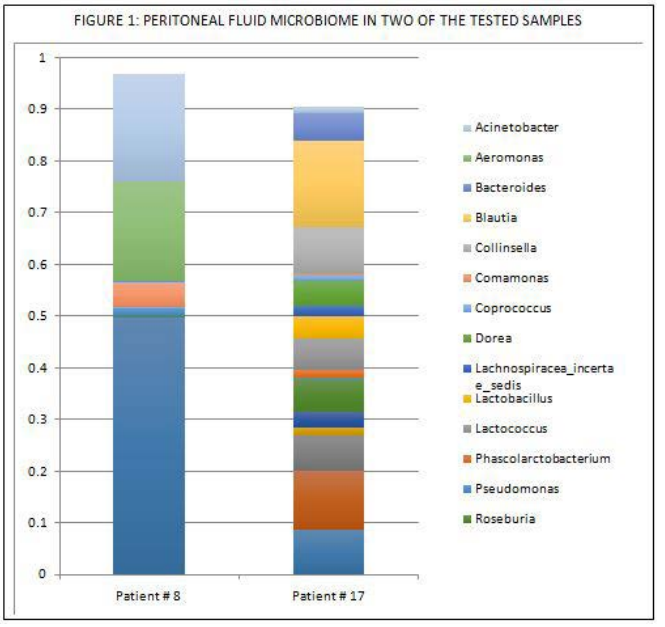
Methods: Patients who are 18 years and older, receiving maintenance PD with no symptoms of peritonitis were included. We collected 10 cc of PD output from each patient participant using routine sterile techniques and 16S rRNA gene sequencing was used to identify bacteria not routinely cultivated by clinical microbiology laboratories. The bacterial types for each specimen were identified.

Results: Of the 25 patients receiving PD at our site, 20 were included in the study. Baseline characteristics are shown in table 1.

Table 1: Baseline Characteristics of Study Population (n=20)

Mean age in years	57.5 years
Sex (M:F)	1:1.2 (9:11)
Race	AA: 35 % (7) Hispanic: 25 % (5) Others: 40 % (8)
Diabetes	45 % (9)
History of peritonitis (over last year)	15 % (3)
History of abdominal surgery	85 % (17)
Type of transporter	High Average: 55 % (11) Low Average: 20 % (4) High: 15 % (3) Low: 0 % (0) Undetermined: 10 % (2)
Native urine output	45 % (9)
Mean dialysis vintage time in years	2.65 years

Two patients tested positive for bacteria above the cut off threshold (> 2000 reads).



Both patients with positive reads are females with no history of peritonitis and are high average transporters.

Conclusions: Peritoneal microbiome may not be sterile in some PD patients without clinical peritonitis. Further research is needed to delineate its role in the success/failure of long term PD.

FR-PO1073

Impact of Hypokalemia on Peritonitis in Peritoneal Dialysis Patients: A Systematic Review
Kentaro Nakai,[1,2] Kei Saitoh,[1,2] Shinichi Nishi.[1,2] *[1]Div of Nephrology and Kidney Center, Kobe Univ Graduate School of Medicine, Kobe, Japan; [2]Dept of Nephrology and Kidney Center, Kakogawa East City Hospital, Kakogawa, Japan.*

Background: Hypokalemia is a common electrolyte disorders in peritoneal dialysis patients. Some studies showed the association of serum potassium levels with all-cause and cardiovascular mortality and infection, and hypokalemia can cause muscle weakness, paralytic ileus and peritonitis. This review aims to clarify the relationship of hypokalemia and peritonitis in peritoneal dialysis.

Methods: The MEDLINE and Cochrane Library databases were searched for articles published from 1990 to May 2016. The following search terms were used: hypokal(a)emia, potassium, peritoneal dialysis, peritonitis, infection. Additional studies were identified by hand searching through references and using the MEDLINE related articles option.

Results: A total of 159 abstracts were identified, and 6 trials were included in the systematic review (n=3613). One prospective study and three retrospective studies indicated that hypokalemia increases the risk of peritonitis, whether a prospective observational study and a case-control study indicated otherwise.

Conclusions: Convincing clinical trial data are unavailable to show the association of hypokalemia with peritonitis in peritoneal dialysis patients, and we need to clarify whether the therapeutic intervention to normalize serum potassium levels, such as KCl, spironolactone, adjustment of food or dialysate, decreases the risk of peritonitis and infection-related mortality in peritoneal dialysis patients.

FR-PO1074

Risk Factors and Outcomes of Vancomycin-Resistant Enterococcus Colonization in Patients on Peritoneal Dialysis
Jason Yeung, John Yiu Han Chan, Wai-Leung Chak. *Medicine, Queen Elizabeth Hospital, Hong Kong.*

Background: Vancomycin-resistant Enterococcus (VRE) colonization is common among patients with chronic renal diseases, including those undergoing peritoneal dialysis (PD). The aim of this study is to evaluate the risk factors and various clinical outcomes for VRE colonization among PD patients within a tertiary dialysis centre in Hong Kong.

Methods: This is a single-centered retrospective cohort study of 166 hospitalized patients who used PD as mode of renal replacement therapy from 1 st August 2013 to 31 st July 2014. All patients were screened for VRE colonization status via rectal swabs or stool specimen during hospitalization. They were categorized into two groups: VRE-positive group and VRE-negative group. Baseline characteristics and other potential risk factors were analyzed in both groups. Clinical outcomes including all-cause mortality, infection with VRE, peritonitis-free survival, length of hospitalization, VRE spontaneous clearance rate and VRE relapse rate were also analyzed.

Results: Among the 166 PD patients, 28 (16.9%) were VRE-positive. Multivariate analysis showed that previous contact history with VRE-positive patients (OR: 417.86; 95% CI: 17.21-10147.26, p<0.01), previous use of vancomycin in 3 months (OR: 130.32; 95% CI: 5.35-3176.30, p<0.01) and age (OR: 1.13; 95% CI: 1.02-1.24, p=0.02) were the

three independent risk factors for VRE colonization. Patients in VRE-positive group had significantly longer length of hospitalization stay but there was no significant difference in all-cause mortality and peritonitis-free survival.

Conclusions: VRE-colonization is an important issue among hospitalized PD patients. Cautious use of antibiotics and infectious control measures may be necessary to prevent spreading of VRE especially in those higher risk patients.

FR-PO1075

Electron Microscopy in the Evaluation of Renal Transplant Biopsies: Global Practices and Trends Indicate the Need for Standardization

Harsharan Kaur Singh,[1] Volker Nickeleit,[1] Candice A. Roufosse.[1] *[1]Dept of Pathology, The Univ of North Carolina, Chapel Hill, NC; [2]Dept of Cellular Pathology, Hammersmith Hospital, Imperial College, London, United Kingdom.*

Background: Electron microscopy (EM) is universally accepted in workup of native renal biopsies with established criteria in use worldwide. However, use of EM in the transplant setting outside of the workup for recurrent / de novo glomerular diseases is not well standardized. Glomerular basement membrane (GBM) duplications / remodeling, including changes seen by EM only, presence of peritubular capillary basement membrane [PTC] multi-laminations (PTCL) and endothelial cell activation are considered adjunct EM features of rejection induced injury. In 2015, a Banff-EM-Working Group was created to define and validate EM criteria for diagnosing rejection related changes. A survey was conducted to evaluate current EM practices and results are reported here.

Methods: Members of the European Society for Pathology- Nephropathology Working Group and The Banff Society were surveyed (SurveyMonkey).

Results: 135 members responded [79% United States-Europe; 10% Asia; 5% Latin America; 2% Middle East; 1% each-Russia, Africa, Australia]. 75% were specialized renal pathologists with >10 year experience, access to EM facilities, and evaluation of >100 transplant biopsies annually. EM was performed in only 38% of indication biopsies worldwide after 3 months post-transplantation. Presence of proteinuria (69%) or suspicion of recurrent disease (86%) were the most common triggers for EM evaluation. The approach to find and study lesions varied greatly [<50% agreement] including: #glomeruli/glomerular loops examined, scope magnification and #PTC optimal for PTCL assessment, criteria to record results and to approach diagnostic decision-making [geographic location showed no significant differences].

Conclusions: The current survey shows that ultrastructural changes in rejecting renal allografts are incompletely defined and diagnostic criteria lack standardization. The Banff-EM-Working Group will next develop criteria to standardize detection and recording of EM changes followed by evaluation of diagnostic cut-off levels for GBM and PTCL lesions.

FR-PO1076

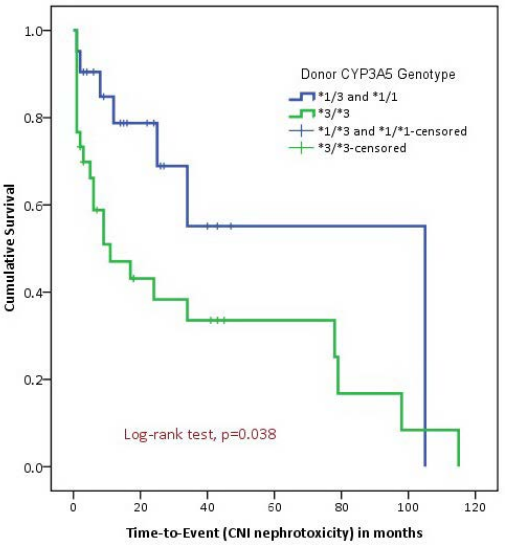
Association of Donor CYP3A5 Genotype and Tacrolimus Nephrotoxicity in Kidney Transplantation

Suwasin Udomkarnjananun,[1] Pajaree Chariyavilaskul,[2] Kroonpong Iampenkhae,[3] Yingyos Avihingsanon,[1] Kearkiat Praditpornsilpa,[1] Natavudh Townamchai.[1] *[1]Nephrology, Chulalongkorn Univ, Thailand; [2]Pharmacology, Chulalongkorn Univ; [3]Pathology, Chulalongkorn Univ.*

Background: The CYP3A5,which is mainly expressed in liver,is also expressed in kidney tissue and might contribute to local drug clearance.This study aim to evaluate the association between the kidney allograft CYP3A5 (donor genotype) and transplant outcomes in Asian population which has variety of CYP3A5 expression.

Methods: Genotyping for donor *CYP3A5* expression were carried out by RT-PCR of the available specimens,blood samples from living donor and extraction from kidney biopsy paraffin tissue in deceased donor.CNI nephrotoxicity was documented by renal pathologist from surveillance biopsy,blindly to CYP3A5 genotype.The primary outcome is time-to-CNI nephrotoxicity in the expressor genotype compare to the non-expressor genotype.

Results: The total of 51 patients were enrolled,21 donors were the expressor genotype (*1/*1 and *1/*3) and 30 donors were the non-expressor genotype (*3/*3).Baseline characteristic showed no difference in donor age, follow-up time, and tacrolimus dosage(C0/mg) between groups.The incidence of CNI nephrotoxicity was significantly higher in non-expressor compared to expressor(73% vs 33%, p<0.05).Median time to event was 11 months in non-expressor group and 105 months in expressor groups(p<0.05).



Cox regression analysis showed hazard ratio of 0.306 (p<0.05) for the donor expressor genotype compare to non-expressor genotype.

Covariates	Hazard ratio	p-value
Donor CYP3A5(expressor vs non-expressor)	0.306	0.028
Delayed graft function(Yes vs NO)	0.825	0.687
Donor age	1.005	0.821
Recipient age	1.037	0.069
TAC C0/mg	0.435	0.019

Conclusions: Donor CYP3A5 non-expressor genotype (*3/*3) is an independent risk for CNI nephrotoxicity, probably due to poor local allograft tissue drug clearance.

FR-PO1077

Impact of Tacrolimus Formulation Switching on Trough Variability

Edward Lee,[2] Ashley R. Perry,[1] David Facklam,[1] Jason J. Schwartz,[2] Billy Franks,[2] Gary Thal,[2] James R. Spalding,[2] Maria E. Vassilakis,[2] William Irish.[1] *[1]CTI Clinical Trial and Consulting, Cincinnati, OH; [2]Astellas Pharma Global Development, Inc., Northbrook, IL.*

Background: For a narrow therapeutic index drug like tacrolimus (TAC), variations in exposure could result in reduced immunosuppression or toxicity.

Methods: This retrospective cohort study examined differences in trough variability between fixed regimen (FR) and variable regimen (VR) patients (pts). US National Drug Codes (NDC) for TAC, 3–15 months (mos) post-transplant (tx), were used to allocate pts to FR or VR groups. VR was defined as a change in NDC within a specific strength or a dose adjustment that resulted in an NDC change for any continuing dose strength. Adult kidney tx pts, between 09/2009 through 12/2012, with stable renal function (SCr<1.5mg/dL), and no acute rejection at 3 mos post-tx, were eligible. A total sample size of 816 pts was expected.

Results: Data on 305 of the proposed 816 pts were collected from 4 sites: 261 pts (86%) in the FR group and 44 (14%) in the VR group. Thirty-five (80%) VR pts came from a single site. VR pts tended to be non-white (70% v 36%), on dialysis longer (57 vs 39 mos), had government insurance (84% vs 65%), and had received an ECD kidney (30% vs 4%). Key results were summarized:

Month 3–15 Post-Tx	Fixed (n=261)	Variable (n=44)	P-value
Mean no. of dose adjustments	2.40	2.77	0.237
Mean cumulative mg dose change	3.40	3.72	0.506
Mean trough to dose (T/D) ratio	2.02	2.22	<0.001
Mean no. of trough measurements	22.6	29.2	<0.001
TAC levels above 120% or below 80% of a pt's overall mean were examined. Excursions outside this range were significantly higher for the VR group 3–15 mos post-tx (13.8 vs 10.5, P<0.001).			

Conclusions: Preliminary findings show that VR pts in this study were more vulnerable and were associated with greater TAC trough level excursions and a difference in T/D ratio, and may explain why more TAC trough measurements were observed in VR pts. This may be relevant given recent evidence linking several outcome measures with increases in TAC variability. However, small sample size and potential for selection bias in VR pts needs to be considered when interpreting results.

Funding: Pharmaceutical Company Support - Astellas pharma

FR-PO1078

Variation in Tacrolimus Level Is Associated with Pediatric De Novo DSA and Renal Allograft Rejection Hilda E. Fernandez,[1] Sandra Amaral,[1] Susan L. Furth.[1] *[1]Columbia Univ Medical Center; [2]Children's Hospital of Philadelphia.*

Background: De novo donor specific anti-HLA antibodies (dnDSA) following kidney transplant (txplt) have been demonstrated to increase risk of rejection (rjxn) in renal allografts. Variation in tacrolimus (CV TAC) immunosuppression has been associated with non-adherence to medical therapy and increased risk of rjxn. This study assessed CV TAC in relation to appearance of dnDSA and allograft rejection in pediatric (ped) kidney transplant.

Methods: Retrospective study of ped renal txplt patients (pts) at CHOP from 2008 to 2011 with routine monitoring of DSA post-txplt.

Results: From 9/2008 - 12/2011, 47 pts were transplanted and had serially monitored DSA post-transplant. Induction was primarily antithymocyte globulin (85%), 57% were male, 21% had living kidney txplt, 62% were Caucasian, with 43% having CAKUT as cause of ESRD. 25% had a prior allograft txplt, and 83% had >2 HLA mismatch. During a median follow-up time of 4.3 yrs, 23 pts developed dnDSA in a median 0.77 yrs following txplt. No sig diff in sex, ethnicity, living donor, HLA MM seen between pts w/and w/o dnDSA. Pts w/ dnDSA had higher allograft rejection (15 v 1) and allograft loss (7 v 1) than pts w/ out dnDSA ($p < 0.01$). Pts w/ dnDSA had significantly higher CV TAC following KT than pts w/out dnDSA up to 18 months post-txplt ($p = 0.04$). Also, pts w/ dnDSA had a faster rate of decline of creatinine over the period of follow-up than pts w/o dnDSA ($p = 0.03$).

Conclusions: Pts with dnDSA had higher CV TAC, more allograft rejection and loss, and greater decline in creatinine than pts without dnDSA. As CV TAC has been associated with allograft rejection, this suggests that higher variation in tacrolimus levels are reflected in the development of dnDSA.

Funding: NIDDK Support

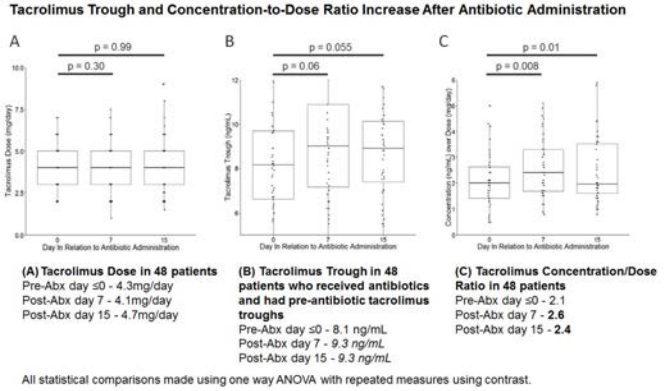
FR-PO1079

Antibiotics and Tacrolimus Trough Variability in Kidney Transplant Recipients Yuanpu Zheng, Anjali Masand, Michael P. Wagner, Thangamani Muthukumar, Darshana Dadhania, Manikkam Suthanthiran, John R. Lee. *Nephrology and Transplantation Medicine, Weill Cornell Medical Center, New York, NY.*

Background: Based on our recent finding suggesting that the gut microbial community structure is associated with tacrolimus dose requirements, we tested the hypothesis that antibiotics, documented to alter the gut microbiota, increase tacrolimus trough variability.

Methods: We conducted a retrospective study of 229 kidney recipients transplanted 2012 to 2013 at New York Presbyterian Hospital - Weill Cornell. Patients receiving antibiotic therapy during post-operative day (POD) 0-30 were assigned to the Antibiotic group (ABX, n= 60) and those who did not receive antibiotics were assigned to the No Antibiotic group (No ABX, n=169). We analyzed pre- and post-antibiotic tacrolimus trough and dose changes in the ABX group. We also compared tacrolimus trough variability using intra-patient Standard Deviation (SD) and Coefficient of Variation (CV) between both groups.

Results: In the ABX Group, the mean tacrolimus dose did not change from pre-antibiotic to post-antibiotic day 7 and 15 ($p=0.30$ and $p=0.99$, Panel A), but tacrolimus trough levels increased ($p=0.06$ and $p=0.055$, Panel B) and the ratio of tacrolimus trough to dose increased ($p=0.008$ and $p=0.01$, Panel C) from pre-antibiotic to post-antibiotic day 7 and 15. The ABX subgroup that received penicillin class antibiotics had an increased ratio of trough to dose ($p=0.03$) after antibiotics.



Intra-patient SD and CV of tacrolimus troughs taken during POD 31-45 were significantly higher in the ABX group than the No ABX group (SD: median 2.6 ng/mL vs. 1.4 ng/mL, p=0.008, Wilcoxon; CV: median 0.29 vs. 0.17, p=0.004, Wilcoxon).

Conclusions: We have identified that antibiotic use impacts tacrolimus trough level variability and recommend closer monitoring of tacrolimus trough concentrations after antibiotic treatment.

Funding: Other NIH Support - KL2 TR000458 (John Lee) and by the award K23 AI 124464 (John Lee)

FR-PO1080

Pharmacokinetics of Once-Daily Envarsus XR in Diabetic versus Non-Diabetic Kidney Transplant Recipients: A Pooled Subgroup Analysis Daniel C. Brennan,[1] Patricia West-Thielke,[2] Daniel R. Stevens.[3] *[1]Washington Univ, St. Louis; [2]Univ of Illinois, Chicago; [3]Veloxis Pharmaceuticals.*

Background: Tacrolimus (tac) has a narrow therapeutic range. In transplant recipients, too low exposure risks graft rejection while too high risks toxicity. The pharmacokinetics (PK) of tac may be unfavorably affected by diabetes. In particular, gastroparesis is common in individuals with diabetes and may impact drug absorption and ultimately, drug exposure. In clinical studies, the MeltDose® formulation of once-daily extended release tac (Envarsus® XR; LCPT) showed improved bioavailability with quicker attainment of therapeutic trough levels, lower peak-to-trough fluctuation, and a lower dose requirement vs. twice-daily immediate release tac (Prograf®; IR-Tac). With LCPT the release of tac occurs over a larger portion of the GI tract and over an extended period of time vs. IR-Tac. We sought to assess LCPT PK in patients with diabetes, a high proportion of whom may have gastroparesis.

Methods: This pooled analysis of data from two phase III and one phase II randomized trials examined tac PK in 123 stable kidney transplant patients with (n=50; 72% male; mean age: 52.9±9.9) and without diabetes (n=73; 58% male; mean age: 45.5±11.3) who were converted from IR-Tac to LCPT at doses 67-80% of the pre-conversion total daily tac dose.

Results: The PK parameters associated with LCPT (lower C_{max} and lower peak-to-trough fluctuation while maintaining a therapeutic trough) were evident regardless of diabetes status [Table1]. All PK comparisons for LCPT were not statistically significant.

Conclusions: Results show that the improved PK previously documented with LCPT is maintained in kidney transplant patients with diabetes.

	LCPT		IR-Tac	
Day 7 PK Parameter	No Diabetes (N=73)	Diabetes (N=50)	No Diabetes (N=73)	Diabetes (N=50)
T_{max}[1]	5.9 (3.0-7.9)	5.9 (4.0-6.0)	1.5 (1.0-2.0)	1.5 (1.0-2.9)
AUC[2]	246.7 (97.6)	221.4 (74.0)	216.7 (66.9)	212.8 (74.5)
C_{max} (ng/mL)[2]	16.1 (7.0)	14.6 (6.1)	20.2 (8.4)	20.4 (11.4)
C_{min} (ng/mL)[2]	7.6 (3.1)	6.8 (2.4)	6.7 (1.9)	6.7 (2.1)
% fluctuation[1]	77.7 (47.6-104.9)	73.1 (51.9-109.7)	131.9 (106.7-179.7)	133.8 (87.7-193.9)
[1]median (IQR); [2]mean (SD)				

Funding: Pharmaceutical Company Support - Veloxis Pharmaceuticals

FR-PO1081

Evaluation of Flexible Tacrolimus Drug Level Monitoring Approach in Patients Receiving Extended-Release Envarsus XR® Benjamin Philosophe,[1] Nicolae Leca,[2] Patricia West-Thielke,[3] Timothy A. Horwedel,[4] Daniel R. Stevens.[5] *[1]Johns Hopkins Univ; [2]Univ of Washington Medical Center; [3]Univ of Illinois; [4]Barnes Jewish Hospital; [5]Veloxis Pharmaceuticals.*

Background: Tacrolimus is a drug with a narrow therapeutic range. To ensure adequate exposure in transplant patients, 12-hour post-dose monitoring is required for twice-daily tacrolimus capsules. Due to timing of every 12-hour administration of twice daily tacrolimus, most patients will need phlebotomies at similar times which creates clinic backlogs and logistical challenges. Once daily tacrolimus tablets (Envarsus XR®) are made with proprietary MeltDose technology which results in a tacrolimus formulation with 50% increased bioavailability vs. twice-daily immediate-release tacrolimus capsules (Prograf®) and similar efficacy and safety, at a 30% reduced dose.

Methods: This analysis examined whether the trough measurement window could be extended for Envarsus XR due to its flatter kinetic curve. Extending the window for trough level measurement would allow greater flexibility in timing of blood draws for tacrolimus levels, potentially reducing early morning patient overload in clinics. PK data from 30 Envarsus XR-treated kidney transplant patients participating in an open label cross-over study were used. Primary results were previously reported; here, the 21-27 slow-tail analysis is reported.

Results: Results for Envarsus XR showed that AUC_{0-24} and C_{21}, C_{24}, C_{27}, are highly correlated (Pearson's correlation coefficient >0.9168; $p<0.0001$) with corresponding levels of (mean ±SE) 7.204 ng/mL±0.538; 6.801±0.521; 6.296±0.506 respectively. The elimination rate was -1.90% per hour between C21 and C24 and -2.61% per hour between C24 and C27; The results show that therapeutic drug monitoring window of +/- 3 hours for LCPT tacrolimus levels in clinics can be performed with confidence and without any/minimal adjustment for the differences in time points. This offers an alternate solution with greater flexibility for clinicians and patients.

Conclusions: Extending "trough measurement window" provides the opportunity for potentially improving the provider and out-patient experience.

Funding: Pharmaceutical Company Support - Veloxis Pharmaceuticals

FR-PO1082

Long-Term Results of a Prospective Randomized Study of Efficacy and Safety of Early Tacrolimus Conversion to Sirolimus after Kidney Transplantation Amgad E. El Agroudy. *Medicine, Arabian Gulf Univ, Manama, Bahrain.*

Background: We report a prospective, open-label, randomized study to evaluate the safety and efficacy of converting patients with stable renal function from Tacrolimus (Tac)-based regimen to a Sirolimus (SRL)-based regimen after kidney transplantation.

Methods: Fifty eight low risk renal allograft recipients who were eligible to the study, 6 months posttransplant and receiving Tac, were randomly assigned to continue Tac (n=29) or convert to SRL (n=29). We evaluated the 3-year outcomes including patient and graft survival, graft function and safety profile.

Results: 3-year patient and graft survival in SRL and Tac groups was 93.1% vs. 100% (P=0.32), and 89.7% vs. 100% (P=0.11), respectively. However, the SRL group had significantly better renal function, from the second year post-transplant until the last follow-up. Four (13.8%) patients in the SRL group and 3 (10.3%) in the Tac group (P=0.5) developed biopsy proven acute rejection. Mean urinary protein excretion increased significantly after SRL conversion. Diastolic blood pressure was significantly lower at the end of the study in patients who eliminated tacrolimus (80.4 vs. 75.6 mmHg in Tac and SRL group, respectively) (P = 0.03). Mean hemoglobin concentrations decreased after SRL conversion and remained significantly lower from 12 months to 36 months (P=0.01). The mean serum cholesterol (6.1±0.5 mmol/l) and triglyceride (2±0.3 mmol/l) levels increased significantly in the SRL group, compared to TAC group (5.5±0.7 mmol/l) (P=0.03) and 1.6±0.3 mmol/l) (P= 0.04).

Conclusions: our experience demonstrates that conversion to sirolimus from calcinuerin inhibitors (CNI)-based therapy may result in better renal function and blood pressure control.

FR-PO1083

Inadequate Mycophenolic Mofetil Exposure Is Associated with More Ejection and Graft Loss in Kidney Transplant Patients Amgad E. El Agroudy. *Medicine, Arabian Gulf Univ, Manama, Bahrain.*

Background: Although MMF is generally well tolerated, optimal therapy may be limited by adverse effects, in particular gastrointestinal toxicity. MMF dose changes resulting from these adverse events may lead to sub-therapeutic dosing and impaired clinical outcomes. Aim of our study is to investigate the impact MMF dose reduction on the incidence of acute rejection and graft survival.

Methods: In this study, a cohort of 150 kidney transplant recipients who received immunosuppression using MMF in conjunction with cyclosporine and prednisone was evaluated. We classified patients into 3 groups according to MMF dose per day in gm; group I with 2 gm/day, group II 1.5 gm/day and group III 1 gm or less per day. Clinical outcomes were compared and contrasted between patients with and without MMF dose changes post-transplantation. The study followed the Declaration of Istanbul (DOI) ethics' statement. The study was undertaken in accordance with the Declaration of Helsinki, and all subsequent amendments, and was approved by the local ethics committees.

Results: The majority of patients (52.7%) had at least one dose change within the first post-transplant year. Compared with the 79 patients who did not have a dose change, these patients had a significantly higher incidence of acute rejection within the first post-transplant year (36% vs. 10%, p <0.01). This resulted in a significantly decreased 5-yr death-censored graft survival (77% vs. 68% and 57% in the groups I, II and III, respectively, p = 0.04). The incidence of acute rejection for patients who had a dose change was highest if the dose change occurred within the first post-transplant 6 months (38%). The duration to the first acute rejection was dose related (2.3±1.1 and 4.6±1.4 months in group II and III, respectively, p<0.05). Regarding other complications, there was no significant differences in terms of incidence of infections and malignancy within five year of follow-up.

Conclusion: Altering the dose of MMF within the first post-transplant year correlated with a significantly worse clinical outcome in renal transplant recipients. These data suggest that avoidance of MMF dose changes would result in improved graft survival.

FR-PO1084

Outcome of Conversion from Calcineurin Inhibitors or mTOR Inhibitors to Belatacept in Renal Transplant Patients Sahil Bawa,[1] Marat Abdullin,[2] Michael J. Germain.[2] *[1]Nephrology, RTANE, Springfield, MA; [2]Nephrology, Baystate Medical Center, Springfield, MA.*

Background: Calcineurin Inhibitors(CNI's) are used in over 90% of RTP in the United States.The efficacy of mTOR inhibitors for primary maintenance immunosuppressive therapy in RTP is well documented.The use of Belatacept(BELA) is a reasonable alternative.

Methods: Patients(Pt's) who were switched to belatacept from CNI or mTOR inhibitors were studied.Laboratory data including hemoglobin(Hb),serum creatinine(SCr),triglyceride s(Tg),serum glucose(SG),urinary protein/creatinine ratio(PCR) before and after conversion were compared. We used 3 measurements for SCR, Hb and BS, and 2 measurements for Tg and PCR before and after transition.

Results: 66 Pt's(14 male and 10 female) were switched from CNI group(11 Pt's) and mTOR group(13 Pt's) based regimens to BELA.Pt's average age was 45.3(17-74) years old. Average allograft age was 8(1.5-20) years. Average follow up on BELA therapy was 13.2(4-28) month.Indications for conversion were various side effects of conventional immunosuppression,including proteinuria,pulmonary toxicity,uncontrolled diabetes,CNI toxicity,etc.SCr decreased in Pt's converted from CNI and remained unchanged in mTOR group.There was insignificant increase in Hb in both groups.Tg and fasting hyperglycemia improved in both groups.PCR decreased in both groups.No significant side effects with BELA were reported.Blood Pressure is still being evaluated and be reported later.14 Pt's responded to questionnaire. On a three point Lickert scale 10 out 14 Pt's reported feeling better after conversion,none of them felt worse.10 out of 14 Pt's felt that side effects they had with conventional immunosuppression either resolved or improved. None of the Pt's we asked wanted to go back to the old immunosuppressive regimen.

Conclusions: Clinical experience of conversion to BELA from CNI and mTOR inhibitor demonstrated that this is a safe alternative which is well-tolerated by Pt's and associated with improved renal function in Pt's transitioned from CNI and stable renal function in Pt's transitioned from mTOR inhibitor. It was also associated with improved metabolic parameters and decrease proteinuria.

FR-PO1085

Effectiveness and Safety Profile Comparison of Sirolimus and Everolimus in Renal Transplantation Priscilla P. How,[1,4] Li Fang Goh,[2] Puay Hoon Lee,[2] Petrina Fan,[2] Terence Kee Yi Shern.[3] *[1]Dept of Pharmacy, National Univ of Singapore; [2]Dept of Pharmacy, Singapore General Hospital; [3]Dept of Renal Medicine, Singapore General Hospital; [4]Dept of Medicine (Nephrology), National Univ Hospital.*

Background: Mammalian target of rapamycin inhibitors (MTOR-I), such as sirolimus (SRL) and everolimus (ERL) are used as alternative immunosuppressive agents in renal transplant patients who develop calcineurin-inhibitor intolerance. However, no head-to-head trials comparing ERL and SRL have been reported. This study aimed to compare the effectiveness and safety outcomes between patients receiving ERL and SRL over a 12-month period.

Methods: A retrospective cohort study was conducted on kidney transplant patients in the Singapore General Hospital who were started on ERL or SRL as part of their immunosuppressive regimen, regardless of period of MTOR-I initiation post-transplant. The patients were followed for 12 months or until MTOR-I was discontinued. The primary endpoint was the incidence of biopsy-proven acute rejection (BPAR) and calculated creatinine clearance (CCT). Secondary endpoints included patient's urinary protein-to-creatinine ratio (UPCR), hemoglobin, as well as incidences of dyslipidemia, hypertriglyceridemia, diabetes, and hospitalization for infections and pneumonitis.

Results: Ninety-one patients were included (ERL n=47, SRL n=44). At 12 months, 8 and 12 patients in the ERL and SRL groups, respectively, developed BPAR (p=0.24). Mean CCT in the ERL and SRL groups were similar among patients who were initiated on MTOR-I early post-transplant (ERL vs SRL: 53.7 vs 40.1ml/min, p=0.12) and among late MTOR-I initiators (43.4 vs 36.3ml/min, p=0.07) at 12 months. Although no significant between-group differences in post-baseline secondary endpoints were observed, trends towards smaller increase in proteinuria and lesser impact on lipid profile were seen in patients on SRL.

Conclusions: No significant differences in the effectiveness and safety endpoints between ERL and SRL were noted. However, SRL may be preferred in patients with severe proteinuria and uncontrolled lipid profile at baseline.

FR-PO1086

Long-Term Outcomes with Everolimus (EVR) and Other Regimens in Kidney Transplantation in the United States Diane Cibrik,[1] William Irish,[2] Kevin M. Mccague,[3] Dharmesh Patel,[3] Helio Tedesco Silva.[4] *[1]Univ of Michigan, MI; [2]CTI Consulting, NC; [3]Novartis, NJ; [4]Hospital do Rim UNIFESP, Brazil.*

Background: Using the United Network for Organ Sharing database, we compared long-term clinical outcomes of regimens used in kidney transplant (KTx) recipients.

Methods: First time kidney only transplant recipients, ≥ 18 years old, transplanted between January 1, 1998 and December 31, 2014, and receiving EVR or sirolimus (SIR) or mycophenolic acid (MPA) + calcineurin inhibitor (CNI) ± steroids at time of discharge were included in the analysis. KTx recipients were excluded if their allograft failed prior to hospital discharge, they had received a donor organ with cold ischemia time >40 hours or transplantation occurred in 2001 or 2008-2009 (when EVR was not used). Treatment selection bias was addressed using risk-adjusted methods in the design and analysis. Cohorts were matched based on the propensity score for EVR using a greedy matching algorithm within donor type (living vs. deceased donor). Two mutually exclusive transplant periods were defined (ERA1: 1998-2007 and ERA2: 2010-2014; EVR was approved in the US in 2010). Kaplan-Meier and stratified Cox hazard models were used to estimate and compare outcomes between cohorts.

Results: Median follow-up was 8 years. Propensity score matching created clinically well-matched cohorts. Results (rate ± standard error) are below. Risk of graft failure was comparable between the EVR vs SIR and EVR vs MPA cohorts. The relative effect of EVR vs SIR and EVR vs MPA was comparable when the analysis was restricted to tacrolimus-based regimens.

Donor Type	Cohort comparison	Adjusted Graft survival at 5 years (%)
Living	EVR (n=369) vs SIR (n=1,173)[1]	85.8 ± 1.1 vs 84.4 ± 1.0
	EVR (n=432) vs MPA (n=2,034)[2]	87.3 ± 0.9 vs 86.3 ± 0.9
Deceased	EVR (n=352) vs SIR (n=1,203)[1]	74.3 ± 1.3 vs 72.0 ± 1.3
	EVR (n=403) vs MPA (n=1,936)[2]	75.1 ± 1.4 vs 73.3 ± 1.4

[1] Rates adjusted for ERA, antibody induction & donation after cardiac death [2] Rates adjusted for ERA and tacrolimus maintenance immunosuppression at time of discharge.

Conclusions: Long term graft survival outcomes were similar for EVR vs SIR and EVR vs MPA regimens in KTx regardless of donor status and CNI.

Funding: Pharmaceutical Company Support - Novartis Pharmaceuticals Corporation

FR-PO1087

Everolimus-Facilitated Cyclosporine A Sparing Immunosuppression Might Improve Glycemic Control in Kidney Transplant Recipients – A Retrospective Analysis Florian Kälble,[1] Jörg Seckinger,[2] Matthias Schaier,[1] Christian Morath,[1] Martin G. Zeier,[1] Claudia Sommerer.[1] *[1]Nephrology, Medical Univ Hospital, Heidelberg, Germany; [2]Internal Medicin, Div Nephrology, Zug Cantonal Hospital, Baar, Switzerland.*

Background: Mammalian target of rapamycin inhibitors (mTORi) allow calcineurin inhibitor (CNI) sparing therapy in renal transplant recipients with possible beneficial effects on the long-term allograft function and cardiovascular risk profile. While the adverse effects of CNI on glucose metabolism have been documented, the influence of mTORi is still under discussion.

Methods: In a retrospective analysis, renal allograft recipients switched from a cyclosporine A (CsA) to an everolimus (EVR) based immunosuppression in the first year after transplantation were compared with patients on continued CsA treatment. Clinical and biochemical data were collected at 6-month intervals. The prevalence of impaired fasting glucose (IFG) and new onset of diabetes after transplantation (NODAT) was documented.

Results: A total of 146 renal transplant recipients were included in the present study. The cumulative prevalence of IFG and NODAT 30 months post transplantation was significantly lower in patients switched to a primary immunosuppression with EVR compared to patients on continued CsA treatment (10% versus 22%, p=0.049). Patients switched to EVR revealed a mean HOMA-IR (homeostasis model assessment insulin resistance) <2 while the index in patients on continued full-dose CsA was 4 (1.7±1.3 versus 3.9±1.1, p<0.05), suggestive of insulin resistance. Patients switched to a CsA-sparing regimen showed a higher incidence of acute cellular rejection episodes in the first 12 months (23% versus 12%, p=0.048).

Conclusions: The switch to an EVR-based immunosuppression was associated with an improvement in glycemic control. However, due to higher rates of acute cellular rejections, patients switched to EVR should be carefully selected and closely monitored.

FR-PO1088

Effect of Everolimus on the Cardiac Function in Kidney Transplant Recipients Kazuma Tsujimura. *Surgery, Tomishiro Central Hospital, Tomishiro-shi, Okinawa, Japan.*

Background: In this study, we evaluated the effect of everolimus (EVR), one of the mammalian targets of rapamycin on cardiac function in kidney transplant recipients.

Methods: We retrospectively studied 76 participants who underwent kidney transplantation (KTx) between March 2009 and May 2017. All participants received tacrolimus or cyclosporine, mycophenolate mofetil, and methylprednisolone for maintenance immunosuppression after KTx. To standardize EVR administration at our institution, the following criteria were used: (1) The recipient did not have donor-specific antigen before KTx. (2) The recipient did not have proteinuria and uncontrollable hyperlipidemia after KTx. (3) Acute rejection was not observed on protocol biopsy 3 months after KTx. According to these criteria, we included EVR administration for maintenance immunosuppression after KTx. We compared the cardiac function of the group receiving treatment with EVR (n=30) and the non-treatment group (n=46). All participants underwent echocardiography before KTx and every year after KTx.

Results:

Table 1 Patient Characteristics (Mean±SD)

	Treatment group (n=30)	Non-treatment groip (n=46)	p-value
Male, n (%)	22 (73.3%)	29 (63.0%)	0.351
Age (years)	48.7 ± 14.2	49.2 ± 12.9	0.867
Scr before KTx (mg/dL)	10.8 ± 3.5	11.5 ± 3.9	0.452
EF before KTx (%)	65.6 ± 8.1	65.4 ± 8.9	0.931
FS before KTx (%)	36.4 ± 5.8	36.3 ± 6.4	0.948
E/A ratio before KTx	1.00 ± 0.38	0.95 ± 0.33	0.494

Scr, serum creatinine; EF, ejection fraction; FS, fractional shortening; E/A ratio, E-wave/A-wave

The characteristics of the 2 groups did not differ significantly (Table 1.). The mean observation period of the treatment and non-treatment group was 41.3 ± 12.6 and 43.9 ± 19.8 months, respectively (p=0.573). The mean ejection fraction (EF), fractional shortening (FS), and E-wave/A-wave (E/A) ratio of the treatment and non-treatment groups after KTx was 66.5 ± 7.9 % vs. 69.6 ± 5.5 % (p=0.024), 37.1 ± 6.2 % vs. 39.3 ± 4.7 % (p=0.045), and 1.07 ± 0.44 % vs. 0.94 ± 0.31 % (p=0.494), respectively.

Conclusions: Supplementary administration of EVR after KTx may not affect cardiac diastolic function, but may reduce cardiac systolic function.

FR-PO1089

Utility of Cystatin C–Based Equation for GFR Estimation in a Living Kidney Donor Takayuki Adachi,[3] Kazuma Tsujimura.[1,2] *[1]Surgery, Tomishiro Central Hospital, Tomishiro-shi, Okinawa, Japan; [2]Urology, Tokyo Women's Medical Univ, Shinjuku-ku, Tokyo, Japan; [3]Nephrology, Tomishiro Central Hospital, Tomishiro-shi, Okinawa, Japan.*

Background: To evaluate the utility of the cystatin C–based equation for determining the estimated glomerular filtration rate (eGFR) in a live kidney donor.

Methods: Between March 2010 and March 2016, 83 donors were evaluated at our institution; they provided written informed consent. The study population included 27 men and 56 women, with a mean age of 52.9 ± 11.9 years (range, 24–76 years). Based on the guidelines of the Japanese Society of Nephrology, eGFR was estimated using the creatinine-based equation (eGFRcre) and the cystatin C–based equation (eGFRcys). The eGFRcre and eGFRcys values were calculated as:

$eGFRcre = 194 \times Scr^{-1.094} \times Age^{-0.287}$ (× 0.739 for females)

$eGFRcys\ (male) = (104 \times Cys\text{-}C^{-1.019} \times 0.996^{age}) - 8$

$eGFRcys\ (female) = (104 \times Cys\text{-}C^{-1.019} \times 0.996^{age} \times 0.929) - 8$

The creatinine clearance rate (CCr) was measured using a 24-hour urine collection test. We compared eGFRcre and eGFRcys values with the CCr in living kidney donor.

Results: The mean serum creatinine level was 0.67 ± 0.13 mg/dL (range, 0.45–1.02 mg/dL), and the mean serum cystatin C level was 0.82 ± 0.11 mg/dL (range, 0.60–1.09 mg/dL). The mean CCr, eGFRcre, eGFRcys were 108.4 ± 21.6 mL/min/1.73 m^2 (range, 63.7–168.7 mL/min/1.73 m^2), 81.5 ± 14.2 mL/min/1.73 m^2 (range, 55.4–117.5 mL/min/1.73 m^2), 91.4 ± 16.3 mL/min/1.73 m^2 (range, 59.9–128.9 mL/min/1.73 m^2), respectively. The eGFRcre was significantly lower than the Ccr ($p < 0.001$). The correlation coefficient for the relationship between the eGFRcre and Ccr values was 0.445, and the mean difference between the two values was -26.9 (24.8%), with a root mean square error of 19.5. The eGFRcys was significantly lower than the Ccr ($p < 0.001$). The correlation coefficient for the relationship between the eGFRcys and Ccr values was 0.466, and the mean difference between the two values was -17.0 (15.7%), with a root mean square error of 19.2. Bland-Altman plots showed that eGFRcre and eGFRcys underestimated GFR values compared with Ccr in 79 and 65 of 83 cases, respectively.

Conclusions: Although eGFRcys was more useful than eGFRcre, it still did not accurately estimate GFR in Japanese living kidney donors.

FR-PO1090

Late Conversion to Belatacept in Biopsy Proven Tacrolimus Toxicity Shruti Gupta, David Wojciechowski. *Nephrology, Massachusetts General Hospital.*

Background: The calcineurin inhibitor tacrolimus is excellent at preventing acute rejection in renal transplantation. However, it is associated with chronic nephrotoxicity, manifested as interstitial fibrosis/tubular atrophy (IF/TA) and arteriolar hyalinosis on biopsy. Once toxicity develops, a tacrolimus minimization strategy is often used but ongoing allograft injury can still occur even with reduced tacrolimus exposure. Conversion from tacrolimus to belatacept may be a potential strategy to preserve renal function.

Methods: We evaluated a cohort of 7 patients biopsied for a rising creatinine. These patients were found to have chronic tacrolimus toxicity with at least 1+ IF/TA and 1+ arteriolar hyalinosis by Banff, and were thereafter converted to belatacept. We conducted a retrospective analysis of these patients 1) comparing changes in eGFR at conversion to the eGFR at 6 and 12 months post conversion, and 2) assessing allograft and patient survival at 1 year post conversion. We also assessed the incidence of infection and rejection post-conversion.

Results: The mean age at conversion was 52.3. Four of 7 patients were male. Causes of ESRD were IgA nephropathy, lithium toxicity, obstructive uropathy, FSGS, dysplastic kidney disease, and nephrocalcinosis. Patients were converted to belatacept 7.7 to 18.3 years post-transplant. The eGFR (mL/min/1.73m^2) at conversion and post-conversion is listed in the table.

Patient	1	2	3	4	5	6	7
GFR at conversion	14	38	38	46	35	41	32
Month 3	15	40	46	43	37	37	31
Month 6	11	40	50	38	32	37	31
Month 12	11	50	50	34	31	34	34

Three of 7 patients had no infections post conversion, while 1 patient had a citrobacter urinary tract infection, 1 had gastroenteritis, and 2 patients had bacteremia. All grafts survived except for patient 1, whose graft dysfunction led to retransplantation 13 months after conversion.

Conclusions: In patients with late allograft dysfunction due to chronic tacrolimus toxicity, conversion to belatacept stabilized the eGFR in 4 out of 7 patients and resulted in an increased eGFR in 2 of 7 patients. This strategy should be evaluated in a larger cohort of patients to better assess the efficacy of this approach.

Funding: Clinical Revenue Support

FR-PO1091

One Year Outcome of Preemptive Low Dose Rituximab in Flow Cytometery Crossmatch Positive Kidney Transplant Recipients Sagar Gupta, Thin Thin Maw, Daniel C. Brennan. *Nephrology, Washington Univ in Saint Louis, St. Louis, MO.*

Background: Significance of positive flow cytometry crossmatch(+ve FCC) in kidney transplantation remains unclear,though such patients tend to have poorer outcomes.The role of B cells in the pathogenesis of acute rejection and late allograft dysfunction continues to be increasingly recognized.Anti-B cell therapy can impair antigen-presenting function of B cells,suppress antibody production and other mechanisms of immune mediated injury.

Methods: Retrospective chart review for patients transplanted at our center between May2009 and October2014 with +ve T or B cell FCC was performed. 28 out of 155 transplant recipients received one dose of rituximab(200 mg) preemptively before discharge. Incidence of acute rejection, DSA development, renal function and graft survival over 12 months were recorded.

Results: Among 28 patients who received rituximab, 8 had pre-formed DSA and 10 developed de novo DSA. However, 50% (14/28) had a prior transplant in this group. They

tend to be younger with a mean age of 43 years. The mean serum creatinine (Sr Cr) trended to be lower in rituximab group at all points during the 12-month follow up period, though this was not statistically significant. Acute cellular rejection (ACR), antibody mediated rejection (AMR) and graft loss at 1 year were lower in rituximab group, not reaching statistical significance given low sample size and incidence numbers.

	Rituximab(n=28)	No Rituximab(n=127)	p-value
Mean age (yrs)	43	50	0.013
Prior transplant	14(50%)	32(25%)	0.090
T cell flow (MCS)	79	49	0.047
B cell flow (MCS)	125	127	0.900
Preformed DSA	8(28.6%)	2(1.6%)	<0.001
Denovo DSA	10(35.7%)	21(16.5%)	<0.026
Sr Cr mg/dl(mean)			
1 mo	1.4	1.55	0.36
3 mo	1.2	1.41	0.32
6 mo	1.29	1.34	0.53
9 mo	1.33	1.44	0.48
12 mo	1.3	1.47	0.30
ACR	1(3.6%)	7 (5.5%)	0.1
AMR	1(3.6%)	6 (4.7%)	1
ACR+AMR	1(3.6%)	12 (9.4%)	0.46
Graft loss 1 yr	0	5 (3.9%)	0.586

Conclusions: Although there is no statistically significant difference in Sr Cr, acute rejection rate and graft loss at 1 year between rituximab group and no rituximab group,there was a trend towards lower acute rejection rate and graft loss in rituximab group.

FR-PO1092

Effects of Basiliximab on Lymphocyte Subsets in Living-Related Kidney Transplantation

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Background: To observe the effects of basiliximab on peripheral lymphocyte subsets in early time of living-related kidney transplantation (LRKT).

Methods: 28 LRKT recipients were enrolled in the study. 12 accepted the induction therapy of basiliximab (induction group), and 16 were not given induction therapy (control group). The maintenance immunosuppressive regimen consisted of tacrolimus, mycophenolate mofetil and steroids. The peripheral lymphocyte subsets were monitored before and one week after the operation by using flow cytometry. The renal allograft function, infection and acute rejection were observed by month six after transplantation.

Results: One week after the operation, the percentages of Th lymphocyte, Ts lymphocyte and B lymphocyte in the induction group were 44.1%±6.4%, 28.1%±7.0% and 23.8%±5.6%, whereas the percentages in the control group were 39.9%±8.6%, 28.2%±8.0% and 21.9%±6.4% respectively. (p=0.1, p=1.0, p=0.4, respectively).

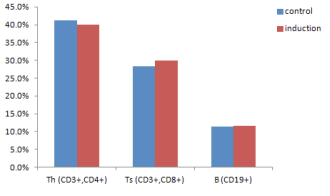

Fig 1: lymphocyte subsets before transplantation

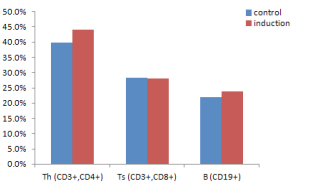

Fig 2: lymphocyte subsets after transplantation

The serum creatinine concentrations by month six in the induction and control group were 120.8±48.9μmol/L and 119.6±29.2μmol/L (p=0.9). The estimated glomerular filtration rate (eGFR-EPI) by month six after transplantation in the induction and control group were 66.9±16.5ml/min and 70.8±18.2ml/min (p=0.6). During the first six months, there was 1 case of infection (1/12, 8.3%) needed hospitalization in the induction group, and 3 cases (3/18, 18.8%) in the control group, the difference was not significant (p=0.4). In both groups, there was 1 case of acute rejection (1/12, 9.3% vs 1/18, 6.3%, p=0.7) by month six after transplantation.

Conclusions: Basiliximab would not influence the lymphocytes subsets of LRKT recipients in the early time after transplantation, and would not influence the renal allograft function, occurrence of infection and acute rejection either.

FR-PO1093

Safety of Percutaneous Pancreas Allograft Biopsy in Enteric Drained Pancreas Transplant: A Single Center Experience in the New Millennium

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Background: Pancreas allograft biopsy (Bx) is the gold standard in diagnosing allograft rejection. The safety of this procedure has been controversial, thus limiting its widespread use. The largest safety data was published 15 years ago describing the rate of complications with ultrasound (US) guided percutaneous Bx in both enteric and bladder drained pancreas transplants (Tx). Since then, pancreas Tx surgical techniques have evolved, including mostly enteric rather than bladder drained Tx. We hereby review the safety of US and computed tomography (CT) guided percutaneous pancreas allograft Bx in 109 consecutive Bx of enteric drained pancreas allografts.

Methods: We reviewed 271 cases of pancreas Tx performed at our institution between 2001 and 2014. 68 patients (30 simultaneous pancreas kidney, 19 pancreas after kidney, and 19 pancreas Tx alone) underwent one or more percutaneous allograft Bx. Biopsies were performed with an 18-gauge needle, under direct US or CT guidance.

Results: A total of 109 Bx were performed. 30 Bx were in patients with enteric exocrine venous portal drainage (PD) and 79 in patients with systemic drainage (SD). 25 Bx were performed under CT guidance and 84 under US guidance. 84% of the Bx in the CT group and 86.6% of the Bx in the US group were adequate (p=0.74). There were a total of 4 Bx related complications (3.67%), all occurring in the US guided group. Those included 2 inadvertent small bowel punctures that were clinically silent and 2 intra abdominal bleeds that were managed conservatively. The small bowel punctures occurred in patients with PD as opposed to the bleeds that occurred in those with SD. No complications occurred in the CT guided group. There were no graft losses and no complications requiring surgical intervention.

Conclusions: Percutaneous pancreas allograft Bx has a low incidence of complications in the most recent era of enteric drained pancreas Tx, and appears to be as safe as renal allograft Bx. The more recent widespread use of CT guided Bx, rather than US guided Bx, seems to be promising in decreasing the incidence of Bx related complications, but larger studies are needed to corroborate this hypothesis.

FR-PO1094

Antiproteinuric Effect of Spironolactone in Kidney Transplant Recipients: Results of a Brazilian Reference Center

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Background: Proteinuria is a marker of kidney damage and increases cardiovascular risk. Onset of proteinuria in transplantation is associated with impaired allograft function and mortality. Aldosterone is involved in progression of chronic transplant dysfunction. Spironolactone appears to be protective in kidney allograft, reducing proteinuria.

Methods: Retrospective cohort in kidney transplant recipients with persistent proteinuria treated with spironolactone. Exclusion criteria: hyperkalemia, medication hypersensivity, graft dysfunction (serum creatinine >3 mg/dL) and hard-to-control hypertension (MAP>120 mmHg). Discontinuity criteria: refractory hyperkalemia, drug intolerance. Demographic, clinical and laboratorial data were obtained at beggining and at 1st, 3rd, 6th, 9th and 12th months. Data were analyzed using EpiInfo7; categorical data were compared with Bartletts test and numerical data with T-student test.

Results: 144 individuals, mean age: 49±13.2 years, 75% male. Average time post transplant: 90+136.5 months. Most cases (78%) were from deceased donor, 18.7% expanded donor, with cold ischaemia time of 20.4+6 hours. 96.1% of recipients were previosly hypertensive and 15.7% diabetic. None of the subjects were discontinued of the study due to hyperkalemia or drug intolerance. Individuals were divided into 3 groups according to initial proteinuria and results are shown in Table 1, * indicates p<0.05.

	A(<1g,n=31)	B(1-3g,n=82)	C (>3g,n=27
Time post transplantation*	58.4±60.5	85.6±96.3	74.5±59.5
Initial proteinuria	0.6±0.2	1.6±0.5	5.9±2.2
Initial GFR*	43.5±22	44.6±18.2	36.4±11.1
Proteinuria 6m	0.6±0.6	1.1±1	3.3±2.8
Proteinuria 12m	0.6±0.4	1±0.8	2.8±2.2

In B and C groups, a significant reduction in proteinuria was observed at 6th month and 1st year follow-up. Half of group B and a third of group C decreased their proteinuria to less than 1g after one year.

Conclusions: Spironolactone seems to be an alternative to control and reduce proteinuria in this population, particularly in proteinuria over 1g, and it is a safe drug for this population.

FR-PO1095

Double-Negative T Cells Are Reduced in Transplanted Patients Treated with mTOR-Inhibitor

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Background: CD4-CD8-double-negative T cells (DNTs) are CD3+ T lymphocytes which lack CD4, CD8 and CD56. They are specifically involved in immune regulation and tolerance and constitute about the 1-5% of lymphocytes in healthy human donors. DNTs express either aß or γΔT-cell receptors (TCR) and can act both as regulatory T cells (Tregs) or as cytotoxic T cells. The aim of this study was to assess the frequency and the phenotype of circulating DNTs in transplanted patients (pts) treated with mTOR-inhibitor compared with pts treated with CNI (without mTOR-inhibitor) and healthy donors as controls.

Methods: Peripheral blood (PB) samples of 15 transplanted pts (6/24 months from Tx) treated with mTOR inhibitors (Everolimus or Rapamycin) and 15 pts with CNI (Cyclosporine or Tacrolimus) were selected. As control PB samples of 10 healthy donors were collected. Circulating DNT subsets (TCRαβ+ and TCRγΔ+) were characterized for their ontogeny, tolerogenic or cytotoxic attitude by staining with the following antibodies:

CD3,CD4,CD8,CD56,CD45,TCRαβ,CD45Ra,CD45Ro,CCR7,CD27and CD28. Tregs were also characterized with CD3,CD4,CD25 and CD127. Isotype-matched MAbs were used as staining controls. Data were acquired using an 8-colour flow cytometer and analyzed using Kaluza software. Data were compared among the groups using the Mann-Whitney non-parametric test.

Results: As expected, mTOR inhibitors significantly increased Tregs compared with CNI population (p=0.005). Interestingly, the αβDNTs significantly decreased in mTOR inhibitor treated-pts as compared with CNI (p=0.04) and were comparable with healthy controls. Furthermore, αβDNTs showed a tolerogenic phenotype, associated with a decrease of terminally differentiated effector memory (DNT-EMRA; $CD45RA^+CCR7^-CD27^-CD28^-$) known to be DNT cells expressing high levels cytotoxic molecules.

Conclusions: DNTs are increased in kidney-transplanted pts with CNI treatment and significantly decreased by mTOR inhibitors treatment. Additional investigations will be necessary to determine their exact role and association with kidney graft dysfunction.

FR-PO1096

Inconsistency between KDIGO Draft and Japanese Living Kidney Donors Guidelines in Kidney Function Evaluation

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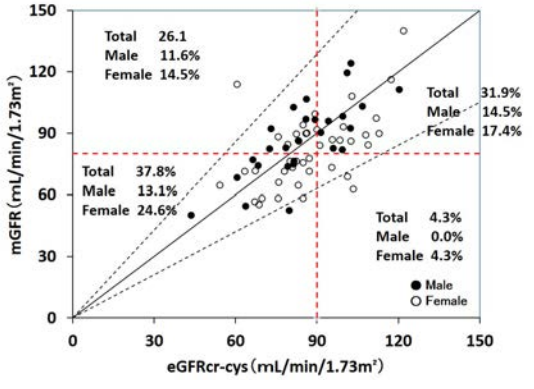
Background: KDIGO Living Kidney Donors draft guideline (GL) recommends that measured GFR (mGFR)≥90 mL/min/1.73m² as an acceptable level of kidney function, and that eGFR based on serum cystatin C (Cys) or the combination of serum creatinine (Cr) and Cys is acceptable if mGFR is not available. And Japanese GL recommends mGFR≥80 for kidney donation. Inconsistency between 2 GLs was analyzed in this study.

Methods: The study subjects were 69 (42 female) kidney transplant donor candidates whose GFR were measured by inulin clearance in Nagoya University Hospital. IDMS-traceable Cr values were measured by enzymatic method and standardized Cys values were measured by colloidal gold immunoassay. Estimated GFR was calculated by Japanese and CKD-Epi equations based on Cr, Cys and combination, and inconsistency rate was analyzed.

Results: Baseline characteristics (mean±SD) of study subjects in male and female were 58.4±6.9 and 61.1±8.0 years old, 168.5±4.1 and 154.0±4.9 cm, 68.5±6.2 and 54.2±9.0 kg, Cr: 0.79±0.15 and 0.56±0.09 mg/dL and Cys: 0.90±0.20 and 0.81±0.14 g/L. 30% accuracy and RMSE in eGFRcr, eGFRcys, eGFRcr-cys, EPIcr, EPIcys and EPIcr-cys were 0.855, 0.812, 0.928, 0.700, 0.797, 0.607 and 17.30, 16.35, 15.20, 21.02, 18.76, 21.32, respectively. Inconsistency between mGFR≥80 and eGFR≥90 was demonstrated in 31.9 (male: 17.4, female14.5), 20.3 (male: 7.2, female: 13.1) and 26.1 (male:11.6, female: 14.5)% underestimation and in 4.3 (male: 0.0, female: 4.3), 3.7 (male: 0.0, female: 8.7) and 4.3 (male: 0.0, female: 4.9) % overestimation by eGFRcr, eGFRcys and eGFRcr-cys, respectively.



Conclusions: Japanese GFR equations were superior to EPI equations, and eGFRcr-cys was the most accurate among Japanese kidney transplant donor candidates, however GFR should be measured because of considerable under- and overestimation rate, especially in female.

Funding: Government Support - Non-U.S.

FR-PO1097

Consequences of Using Estimated GFR in Living Kidney Donors: The Nephrologist in the Mist

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Background: An accurate assessment of GFR before donation is crucial to reduce the risk of renal impairment after donation and to provide acceptable renal mass to the donor. Formulas that estimate GFR (eGFR) have a wide error in reflecting real GFR. This may have consequences in the evaluation of living kidney donors.

Methods: 54 consecutive donors with eGFR >80 ml/min (cut-off level for donation) based on MDRD and/or two 24-h creatinine clearances (CCL) underwent the plasma clearance of iohexol to measure GFR (mGFR). Subjects with mGFR <80 ml/min who had eGFR >80 ml/min were analyzed. The agreement between mGFR and eGFR assessed by 52 creatinine and/or cystatin-based formulas was evaluated with the Concordance correlation coefficient (CCC), total deviation index (TDI) and coverage probability (cp).

Results: In 5 subjects of 54 (9%) mGFR was <80 ml/min (~70 ml/min) while MDRD and/or CCR were >90 ml/min. All were women, with reduced weight, height, BMI and Body Surface Area (BSA) compared with those in whom MDRD, CCR and mGFR were >80 ml/min.

	mGFR < 80 ml/min eGFR/CCL > 80 ml/min	mGFR >80 ml/min eGFR/CCL < 80 ml/min
N	5	49
Age (yr)	45 ± 11	46 ± 11
Gender (female)	5 (100%)	28 (57%)
Weight (kg)	57 ± 7	72 ± 11*
Height (cm)	156 ± 10	166 ± 7*
BSA (m^2)	156 ± 18	180 ± 11*
BMI (kg/m^2)	23.5 ± 4	26 ± 3*
24h CCL	90 ± 9	106 ± 29
aMDRD	87 [70-93]	82 [76-93]
S creatinine (mg/dL)	0.78 ± 0.18	0.86 ± 0.16
mGFR	72.1 ± 1.6	96.6 ± 15.2

These cases were excluded for donation. All formulas showed poor agreement with mGFR: CCC–0.50; TDI:from 47.3% to 26.1% (~37%), indicating that 90% of eGFR had an error of ±37%. No formula included 90% of the estimations within a cp of ±10%.*$p<0.05$.

Conclusions: Formulas and CCL are not appropriate to evaluate living donors since they may overestimate real renal function, particularly in women with reduced BSA. Measured GFR is an important tool in the evaluation of living donors.

Funding: Government Support - Non-U.S.

FR-PO1098

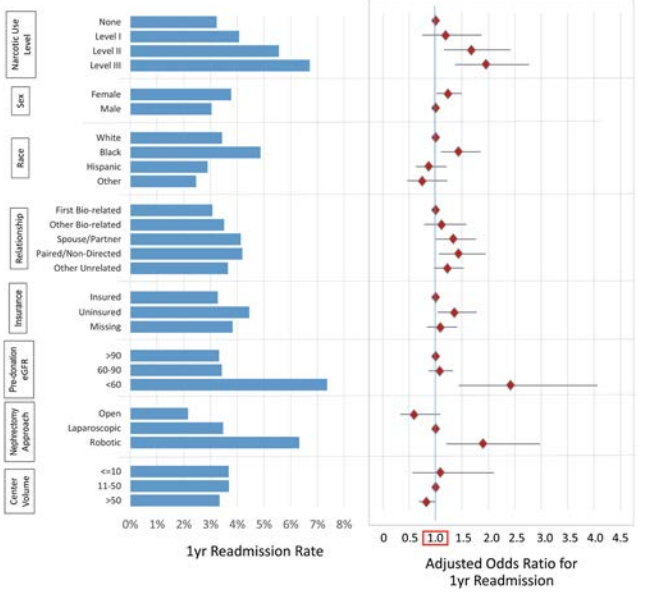
Pre-Donation Prescription Narcotic Use: A Novel Risk Factor for Readmission after Living Kidney Donation

Krista L. Lentine,[1] Ngan Lam,[2] Mark Schnitzler,[1] Gregory P. Hess,[3] Bertram L. Kasiske,[4] David A. Axelrod,[5] Amit X. Garg,[6] Jesse D. Schold,[7] Daniel C. Brennan,[8] Dorry L. Segev.[9] *[1]Saint Louis Univ; [2]Univ Alberta; [3]Symphony Health; [4]Hennepin County Med Center; [5]Brody School of Med; [6]Western Univ; [7]Cleveland Clinic; [8]Washington Univ; [9]Johns Hopkins.*

Background: Implications of narcotic use in living kidney donors for key outcomes, including readmission rates after nephrectomy, are unknown.

Methods: We integrated 1) national Scientific Registry of Transplant Recipients data with 2) pharmacy fill records from a nationwide pharmacy claims clearinghouse, and 3) administrative records from an academic hospital consortium (98 centers, 2008-2012). Narcotic fills in the yr before donation were assessed and normalized to morphine equivalents. Associations of predonation narcotic use (adjusted odds ratio, aOR) and other baseline clinical, procedural, and center factors with readmission within 1 yr postdonation were examined using multivariate logistic regression.

Results: Among 14,959 living donors, 11.3% filled ≥1 narcotic prescription in the year before donation. Pre-donation narcotic use level bore graded associations with 1-yr readmission; donors with the highest pre-donation narcotic use were twice as likely to be readmitted as non-users (6.7% vs. 3.2%; aOR 1.95, 95% CI 1.38-2.77). Adjusted readmission risk was also significantly (p<0.05) higher for women (aOR=1.23), African Americans (aOR=1.43), exchange participants (aOR=1.44), uninsured donors (aOR=1.36), donors with pre-donation estimated glomerular filtration rate <60 mL/min/1.73 m² (aOR=2.42), and after robotic nephrectomy (aOR=1.90). Donors at high-volume centers (>50 per yr) had lower readmission rates (aOR=0.83).



Conclusions: Pre-donation narcotic use is independently associated with readmission after donor nephrectomy. Future research should examine underlying mechanisms and approaches to reducing risks of post-donation complications.

Funding: NIDDK Support

FR-PO1099

Identifying Donors at Risk for Developing Chronic Kidney Disease Using Non-Invasive Ultrasound-Based Measurement of Glomerular Diameter

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Background: There is a non-insignificant risk for developing chronic kidney disease (CKD) or end stage renal disease (ESRD) in the donor. The lifelong risk of ESRD in living kidney donors is as high as 11 folds that of control group. One important risk factor which is neglected, mainly due to inability to access, is nephron endowment in the donor. Donors how have low nephron endowment are at risk for developing hyperfiltration injury. The persistent hyperfiltration injury leads to chronic kidney disease and ultimately ESRD.

Methods: Technique was validated using pig kidney. Cohort: Single center prospective study. All living donors at Froedtert kidney transplant program who are willing to participate were included in the study. **Clinical Data and Biochemical analysis:** Standard of care data. **Sonographic data collection:** Raw radiofrequency data were collected of kidneys before donation, 9 days post donation, 6 month, and 1 year after donation. **Data Analysis by blinded observer:** Glomeruli are delineated and measured using acoustic scatter and integrated backscatter.

Results: The technique is valid and provide accurate measurement of glomerular diameter. Moreover, we encountered donors with glomerular diameters which are significantly larger than the median. Donors with expected low nephron endowment (prematurity and/or low birth weight) have larger glomeruli predonation or have significant glomerular enlargement over time. Those donors failed to recover renal function 6 month after donation.

Conclusions: Pre-donation Glomerulomegally or significant increase in glomerular diameter after donation could indicate low nephron endowment. These subjects are at higher risk for post-donation CKD. Measuring glomerular diameter using ultrasound could prove to be very useful tool in assessing live kidney donor risk for CKD post donation. Failure to identify kidney donors who have reduced nephron endowment will put them at risk for developing CKD and possibly ESRD in their life time. The renal disease progression in these subjects is usually driven by hyperfiltration injury from surgical reduction in nephron number below a threshold that meets the metabolic demand.

FR-PO1100

Utilizing Renal Efficiency to Determine Graft Quality in Live Kidney Donors

Alejandro Diez, Garrett P. Diltz, Rima Kang. *Div of Nephrology, The Ohio State Univ, Columbus, OH.*

Background: Donor age and renal function along with mass and volume donated kidney graft are factors that have been associated with subsequent living donor kidney transplant outcomes. Measurements of renal volume (size) and function (measured or estimated GFR and Creatinine Clearances) are routinely performed prior to donation. Currently, there is no term which describes the quality of the donated tissue. We coined the term: "Renal Efficiency" (RE) to describe this concept. We defined RE as the creatinine clearance that is produced per milliliter (ml) kidney tissue.

Methods: Under IRB approval, we designed a single center retrospective study of all consecutive living kidney donors who donated between January 1, 2008 and December 31, 2013; abstracting demographic and clinical data. Renal function was determined using the CKD-EPI equation and 24hr timed creatinine clearance measurements (mCrCl). 24 hour urine collections were included when the observed urine creatinine excretion rate was within 25% of the expected production (derived from Cockcroft-Gault). All CT-V were calculated using semi-automated region of interest [ROI] volumetry.

Results: 312 cases were reviewed. The average total CT-V (combined right and left kidneys) was 349.91 ml (sd 65.96). The mean mCrCl was 123.21 ml/min (sd 27.34) whereas the mean GFR (CKD-EPI) was 98.87 ml/min sd (15.39). We found a strong correlation between mCrCl and total CT-V (Pearson Correlation: 0.65, $p<0.001$). This was not replicated when utilizing CKD-EPI (Pearson Correlation: 0.122, $p<0.05$). Utilizing mCrCl, we determined the average RE was 0.35 ml/min (clearance) per ml (renal tissue) [Std Error: 0.003, 95% CI: 0.343 – 0.357]. Both univariable (unadjusted) and multivariable (adjusted) linear regression modeling showed significant correlations with patient age and race; for every ten year increase in age we noted a renal efficiency decreases of 4% ($p < 0.001$). Whereas non-white as compared to white race increased efficiency by 10% ($p = 0.001$).

Conclusions: We hope to incorporate RE in further studies to show that combined measurements of renal efficiency and renal volume may be a surrogate for "renal dosing" to predict renal function in kidney transplant recipients.

FR-PO1101

Correlation between Renal Volume and Function in Living Kidney Donors

Alejandro Diez, Rima Kang, Garrett P. Diltz. *Div of Nephrology and Comprehensive Transplant Center, The Ohio State Univ, Columbus, OH.*

Background: CT imaging utilized in pre-donation testing allows for the evaluation of renal anatomy and vasculature. Recent data suggest that renal morphology (kidney volume) may correlate with renal function. Surprisingly, previous work has failed to show a statistically meaningful correlation between renal function as defined by 24 hr timed creatinine clearance measurements (mCrCl) and renal volume as determined by 3D reconstructions of CT angiograms (CT-V). We set forth to determine if a strong correlation exists in a large cohort utilizing strict data validation and enhanced imaging techniques.

Methods: Under IRB approval, we designed a single center retrospective study of all consecutive living kidney donors who donated between January 1, 2008 and December 31, 2013; abstracting demographic and clinical data, pre-donation mCrCl, and CT-V. 24 hour urine collections were included when the observed urine creatinine excretion rate was within 25% of the expected production (derived from Cockcroft-Gault). All CT-V were calculated using semi-automated region of interest [ROI] volumetry.

Results: 322 cases met inclusion criteria; (Male vs Female 102:220 (32%:68%); White vs Non-White = 284:38 (88%:12%); Ave Age: 43y/o (sd 11.64). The average total CT-V (combined right and left kidneys) was 349.91 ml (sd 65.96). The average mCrCl was 123.21 ml/min (sd 27.34) Univariable linear regression modeling showed male sex, weight, height, and BSA to be associated with both increasing renal volume and function (all $p<0.001$). Increased age was inversely associated with mCrCl ($p<0.001$). Multivariable linear regression modeling (adjusted) showed that BSA remained associated with both increasing renal volume and function ($p<0.001$). Increased age remained inversely associated with mCrCl ($p<0.001$). Pearson correlation between CT-V and mCrCl was 0.65 ($P < 0.001$).

Conclusions: Our analysis of a large cohort using strict data validation methodology and improved imaging reconstruction shows the strong linear relationship that exists between renal size and function.

FR-PO1102

Living Renal Donation – Gender Effects on Quality of Life

Claudia Sommerer, Sarah Estelmann, Matthias Schaier, Christian Morath, Martin G. Zeier. *Nephrology, Medical Univ Hospital, Heidelberg, Germany.*

Background: A careful donor selection is important as well as a consistent donor follow-up. Gender specific effects might be detected concerning quality of life.

Methods: Living renal donors at the Transplant Center Heidelberg, University Hospital, were evaluated using the standardized 36-item short form health survey [SF-36] questionnaire).

Results: Altogether 211 living renal donors were evaluated (131 female, 62.1%). The SF-36 physical component summary score was comparable in female and male donors (51.8±10.1 versus 53.9±7.9; ns). The SF-36 mental component summary score was significantly lower in female donors compared to male donors (47.6±13.0 vs. 51.7±11.0, $p=0.012$). In all sub-scale male donors presented higher scores compared to female donors. Male donors had the highest scores in social functioning, female donors in physical functioning. In most of the SF-36 scales, female donors showed comparable or even better results compared to a German general population. However, in the scales social functioning, emotional role functioning and mental health female donors had lower scores compared to an age- and gender-matched general population. Male donors presented higher scores in all SF-36 sub-scales compared to an age- and gender-matched general population (significant scales: vitality, physical component summary score).

Conclusions: Quality of life assessed by the SF-36 questionnaires shows several gender specific differences in living renal donors. Especially, female donors are on increased risk concerning mental and emotional health after donation. Careful evaluation of these female donors is mandatory.

FR-PO1103

5 Year Follow-Up Results of the HERAKLES Study: Superior Renal Function after Early Conversion to an Everolimus-Based Calcineurin Inhibitor Free Regimen

Claudia Sommerer,[1] Wolfgang Arns,[1] Ingeborg A. Hauser,[1] Volker Kliem,[1] Petra Reinke,[1] Rolf A. Stahl,[1] Bruno Vogt,[2] Martina Porstner,[3] Thomas Rath,[1] Frank Lehner,[1] Oliver Witzke,[1] Klemens Budde.[1] *[1]Herakles Study Group, Germany; [2]Herakles Study Group, Switzerland; [3]Novartis Pharma GmbH, Germany.*

Background: To follow up on renal function (GFR) 5 years after kidney transplantation (KTx) in patients (pts) on immunosuppressive regimen with different everolimus (EVR) and calcineurin inhibitor (CNI) exposures.

Methods: 1 year, prospective, open-label, randomized, controlled multi-center study with observational follow-up (FU) to Mo 60 post Tx. After induction therapy all pts received cyclosporine A (CsA), enteric-coated mycophenolate sodium (EC-MPS) and steroids. 3 Mo post Tx, 499 pts were randomized 1:1:1 to either a) continue standard CsA (100-180ng/ml) + EC-MPS (n=166) (STD) or convert b) to a calcineurin inhibitor (CNI)-free regimen with EVR (5-10ng/ml) + EC-MPS (n=171) or c) to a CNI-reduced regimen with EVR (3-8ng/ml) + reduced CsA (50-75ng/ml; n=162). All pts continued on steroids according to centers practice. In total 81% of pts completed the FU period.

Results: GFR (Nankivell, ITT) was similar at randomization 3 Mo post Tx and had significantly improved at Mo12 by +5.6mL/min ($p<0.001$) and remained significantly improved by +6.7mL/min in favor of the CNI-free regimen after 5 years ($p<0.001$; Fig1). There was no significant difference between the CNI-reduced and STD groups (p=ns). Benefit on GFR was highest for non-switcher pts: CNI-free Mo60 GFR was 78.33mL/min vs. 64.33mL/min for CNI-reduced and 61.68mL/min for STD pts ($p<0.0001$). Mean CsA C0-levels at Mo60 were 80ng/mL in CNI-reduced and 109ng/mL in STD group (ITT).

eGFR (Nankivell) [mL/min/1.73m2] ITT FU pop. to Mo60	CNI-free	CNI-reduced	Standard CNI	Difference: CNI-free vs standard CNI (95% CI) P value*	Difference: CNI-reduced vs standard CNI (95% CI) P value*	Difference: CNI-free vs CNI-reduced (95% CI) P value*
Nankivell formula (ITT population)						
Unadjusted eGFR, mL/min/1.73m², mean(±SD)	68.94 (21.31)	58.27 (19.27)	59.20 (19.92)	-	-	-
Adjusted (ANCOVA) eGFR, mL/min/1.73m², LS mean (95%CI)*	66.98 (63.78-70.17)	58.74 (55.58-61.90)	60.24 (57.11-63.38)	6.73 (3.22-10.24) 0.0002	-1.50 (-5.01-2.01) 0.4008	8.23 (4.73-11.73) <0.0001
Nankivell formula (non-switcher)						
Unadjusted eGFR, mL/min/1.73m², mean(±SD)	78.33 (13.02)	64.33 (19.78)	61.68 (18.58)	-	-	-
Adjusted (ANCOVA) eGFR, mL/min/1.73m², LS mean (95%CI)*	74.69 (69.61-79.77)	64.61 (58.51-70.71)	60.32 (56.04-64.59)	14.37 (9.14-19.59) <0.0001	4.29 (-2.29-10.87) 0.1996	10.08 (3.04-17.12) 0.0053
(*) ANCOVA model with treatment, center, donor type as factors and GFR value at V4/M3/BL2 as covariate Replacement of missing values: LOCF = last observation (>Randomization) carried forward						

Conclusions: CNI-free EVR regimen was associated with significant higher eGFR maintained for 5 years after Tx. The results of this large trial confirm previous reports of improved GFR after CsA withdrawal with EVR-based regimen.

FR-PO1104

Living Renal Donation – Association between Gender and Mental Stress after Living Donation Claudia Sommerer, Sarah Estelmann, Matthias Schaier, Christian Morath, Martin G. Zeier. *Nephrology, Medical Univ Hospital, Heidelberg, Germany.*

Background: In living renal donation, careful donor selection is as important as consequent donor follow-up. This includes both, physical and mental health. There might be some gender specific differences. The question to be answered by this evaluation was: Are there any associations between gender and signs of mental stress or impairment?

Methods: Living renal donors at the Renal Transplant Center Heidelberg were evaluated using standardized questionnaires (Hamilton Anxiety Depression Scale, HADS-D; Perceived Stress Scale (PSS)).

Results: Altogether, 211 of 261 (80.8%) questionnaires could be analyzed. Mean age at time of donation was 51.7±9.9 years (131 female), and mean time after donation was 9.7±5.2 years. Results on the HADS-D depression scale (4.0±3.71 vs. 3.68±3.58) and as the anxiety scale (5.09±3.54 vs. 4.4±3.56) were comparable in female and male donors. Female and male living donors aged >60 years had better results compared to a German general population. Female and male living donors aged 40 to 59 years showed comparable results to a German general population. Mental stress was evaluated using the PSS. Female donors presented significantly increased mental stress compared to male donors (p=0.003).

Conclusions: Generally, there is no increased mental stress after living donation compared to a general population. However, there are distinct gender- and age-specific differences. Female donors should be evaluated carefully concerning mental health.

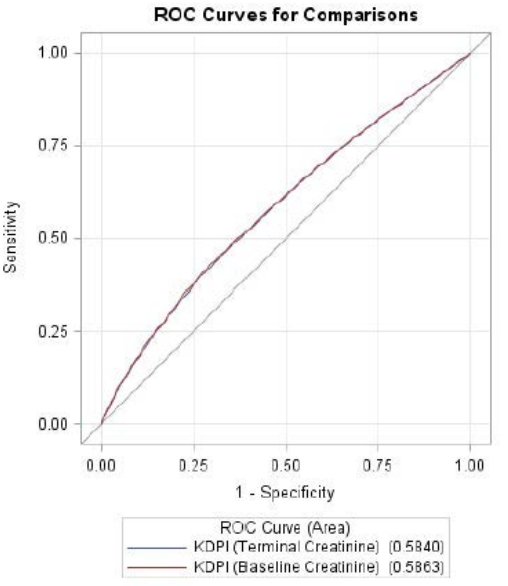
FR-PO1105

Using the Baseline Creatinine Instead of the Terminal Creatinine to Calculate the Kidney Donor Risk Index Mariana C. Chiles,[1] Dustin Carpenter,[1] Rachel E. Patzer,[3] Stephen O. Pastan,[3] Bekir Tanriover,[2] Jae Hyung Chang,[1] David J. Cohen,[1] Sumit Mohan.[1] *[1]Columbia Univ Medical Center, New York, NY; [2]Univ of Texas Southwestern Medical Center, Dallas, TX; [3]Emory Univ School of Medicine, Atlanta, GA.*

Background: The Kidney Donor Risk Index (KDRI) is a numerical expression of deceased donor organ quality and is currently used as part of the New Kidney Allocation System in the US. The KDRI includes the terminal creatinine (Cr_{ter}) even though the baseline creatinine (Cr_{base}) may be a more appropriate, particularly for kidneys with AKI that are already at increased risk of discard.

Methods: Our analysis included 112,809 deceased donor kidneys from 62,370 donors with data provided by the Organ Procurement Transplant Network (OPTN) procured for transplanted from 2002-2015 with $Cr_{base} < Cr_{ter}$ and excluded donors with $Cr_{base} < Cr_{ter} \geq 8$mg/dL. ROC curves were constructed to illustrate the diagnostic performance of the KDRI when calculated with baseline ($KDRI_{base}$) and terminal ($KDRI_{ter}$) creatinine on predicting death-censored graft failure.

Results: In the cohort, 50.4% of kidneys had evidence of AKI ($Cr_{ter} > 0.3$mg/dL above Cr_{base}) and were 1.96 times more likely to be discarded. Transplanted kidneys were obtained from donors who were 62% male, 17.2% black with a mean age of 38.7±15.9 years, the median Cr_{ter} was 2.5mg/dL (IQR = 3.6), the median Cr_{base} was 1.20mg/dL (IQR = 0.7), the median delta creatinine was 0.26mg/dL (IQR = 0.4) and the median delta KDRI was 0.05 (IQR =0.08) The ROC curve depicting the power of $KDRI_{ter}$ had an AUC of 0.5840 while the $KDRI_{base}$ had an AUC of 0.5863 (p<.0001).



Conclusions: Our results suggest that while the overall classification benefit of using Cr_{base} over Cr_{ter} is limited, using the lower $KDRI_{base}$ in individual instances is more reflective of the true quality of the kidney and may help to lower the discard of kidneys with AKI.

FR-PO1106

Comparison of Estimated and Measured Glomerular Filtration Rate in Longitudinal Follow-Up after Living Kidney Donation Marco van Londen, Jan-Stephan Sanders, Jannieta J. De Vries, Margriet Fleur Charlotte de Jong, Robert Pol, Stefan P. Berger, Gerjan Navis, Martin H. De Borst. *UMCG, Groningen, Netherlands.*

Background: Donor safety requires reliable long term follow-up of renal function after donation. We tested the longitudinal performance of estimated Glomerular Filtration Rate (eGFR) to detect renal function loss after donation.

Methods: We compared the slopes of MDRD, Cockcroft-Gault (CG) and CKD-EPI equations with mGFR (^{125}I-iothalamate) to assess renal function loss from 3 months after donation until 5 or 10 years after donation. We tested eGFR slopes for bias by tertiles of mGFR slopes.

Results: At donation, donors (age 51(10) years, 53% male) had a median [IQR] mGFR of 103 [92-115] mL/min. After donation, mGFR was 65 [59-72], 66 [57-75] and 69 [61-77] mL/min at 3 months, 5 and 10 years, respectively. In donors with decreasing mGFR, the slope was underestimated by all eGFR equations (table 1) (P<0.001).

	Tertiles of mGFR slopes		
	Low	Intermediate	High
5 years (N=146)			
mGFR slope	-0.5 [-1.3;0.0]**	1.1 [0.8;1.6)]**	3.5 [2.8;4.2]
CKD-EPI slope	1.6 [0.4;2.8]*	1.6 [0.7;2.7]	2.6 [1.2;4.2]
bias	-2.4 [-3.8;-1.1]**	-0.5 [-1.4;0.4]*	0.7 [-1.0;1.9]
MDRD slope	1.7 [0.5;2.9]	1.7 [0.9;2.7]	2.4 [1.4;3.9]
bias	-2.6 [-3.7;-1.2]**	-0.6 [-1.4;0.2]*	0.7 [-1.0;2.0]
CG/BSA slope	0.5 [-0.2;1.3]*	0.4 [-0.8;0.9]	1.6 [0.5;2.0]
bias	-0.6 [-2.2;-0.3]*	0.6 [-0.1;2.1]	1.6 [1.3;3.4]
10 years (N=59)			
mGFR slope	-0.2 [-0.9;0.0]**	0.5 [0.3;0.6]**	1.6 [1.1-2.0]
CKD-EPI slope	0.5 [-0.0;0.9]	1.0 [0.2;1.3]	1.0 [0.4;1.7]
bias	-0.7[-1.8;-0.3]**	-0.6 [-0.8;-0.1]*	0.6 [-0.1;1.2]
MDRD slope	0.6 [0.1;1.0]	1.1 [0.4;1.5]	1.1 [0.5;1.8]
bias	-0.8 [-1.9;-0.5]**	-0.6 [-0.9;-0.1]*	0.5 [-0.2;1.1]
CG/BSA slope	0.2[-0.2;0.3]*	0.6 [0.2;0.9]	0.5 [0.3;1.6]
bias	-0.3 [-1.1;-0.1]**	-0.2 [-0.4;0.2]*	0.8 [0.4;1.6]
* P<0.05, ** P<0.001 vs. highest mGFR slope tertile Slopes are in mL/min/1.73m²/yr			

In donors with an mGFR decline of >1 mL/min/yr, all equations underestimated the decline vs. donors with less or no decline (p<0.001).

Conclusions: eGFR equations underestimate the slope of renal function in living donors with pronounced mGFR loss, underlining the value of mGFR in long term follow-up.

FR-PO1107

Overweight Young Female Donors Have a Lower Post-Donation Reserve Capacity - Implications for Preeclampsia Marco van Londen,[1] Anouk Wma Schaeffers,[1] Gerjan Navis,[1] Martin H. De Borst,[1] Titia Lely.[2] *[1]Univ Medical Center Groningen, Groningen, Netherlands; [2]Univ Medical Center Utrecht, Utrecht, Netherlands.*

Background: Young female kidney donors are at increased risk of gestational hypertension or preeclampsia. Absence of pregnancy-induced renal vasodilation is a hallmark of preeclampsia and might reflect low renal reserve capacity (RC). We previously observed that higher donor BMI is associated with a lower RC after donation. Therefore, we now studied the relationship between BMI and renal RC before and after donation in female donors of childbearing age.

Methods: RC, defined as rise in glomerular filtration rate (GFR, 125I-Iothalamate clearance) during dopamine, was measured in female donors of childbearing age (<45 years) at 4 months prior and 2 months after kidney donation. Difference between overweight (BMI>25) and non-overweight donors was tested by t-test; the association between BMI and renal hemodynamics was tested with linear regression analysis.

Results: We included 105 female donors who were 41 [36-43] (median[IQR]) years old at donation with a BMI of 25 [22-27] kg/m2. Pre-donation GFR was 118 (17) ml/min (mean(SD)) rising to 128 (19) ml/min during dopamine; mean RC was 10 (10) ml/min. BMI was positively associated with GFR (st. beta 0.31, p=0.001) but not with pre-donation RC (st. beta -0.04, p=0.70). Post-donation GFR was 76 (13) ml/min, rising to 80 (12) during stimulation; RC was 3 (6) ml/min (p<0.001 vs. predonation). Loss of RC was more prominent in overweight donors (-7 vs. -4 ml/min, p=0.05), and higher BMI was associated with lower RC after donation, independent of GFR, age, and use of antihypertensives or contraceptives (st. beta -0.37, p=0.02).

Conclusions: BMI is inversely associated with post-donation RC in female donors of childbearing age. Reduced renal RC might be involved in the increased risk of preeclampsia and gestational hypertension in overweight female kidney donors. Overweight female kidney donors with the desire to have children should be counselled to reach a normal BMI.

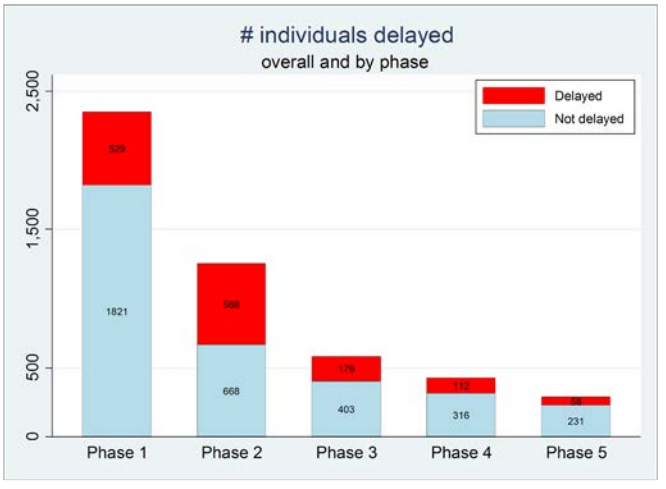
FR-PO1108

Clearance and Delays in the Live Kidney Donor Evaluation Process Joseph Leanza, Dorry L. Segev. *Surgery, Johns Hopkins Univ, Baltimore, MD.*

Background: The live kidney donor evaluation process is a poorly understood barrier to live donation. We quantified clearance time for each evaluation phase and identified factors associated with spending excessive time in each phase, i.e. getting "delayed."

Methods: Eligible potential donors (PDs), who initiated evaluation at Johns Hopkins between 1/1/2011 and 12/31/2014, were followed through five evaluation phases: 1, questionnaire; 2, blood and tissue typing; 3, routine screening and physical exam; 4, evaluation and clearance; 5, recipient clearance, scheduling and donation. Delay was defined for each phase as ≥ 90th percentile of time spent by PDs who cleared that phase (respectively 41, 159, 149, 106, and 328 days).

Results: Of 2,738 PDs, 90.3% completed phase 1, 27.4% phase 2, 18.8% phase 3, 13.0% phase 4, and 9.6% donated. There were 1,466 total delays.



On multivariate logistic regression, African American donors had lower odds of ultimately donating (p<0.01) and of clearing phases 1 (p<0.01), 3 (p=0.03), and 5 (p<0.001). African Americans had higher odds of delay in phase 3 (p=0.03) and phase 5 (p=0.03).

Conclusions: Nearly 50% of PDs were delayed at some point, particularly those of African American race. Efforts to improve LKD rates in this subgroup may benefit from nephrologist involvement at early phases or optimizing the evaluation process.

Funding: NIDDK Support, Private Foundation Support

FR-PO1109

Clinical Outcome of Elderly Living Kidney Donors Kohei Unagami, Masayoshi Okumi, Kazunari Tanabe, Hideki Ishida. *Urology, Tokyo Women's Medical Univ, Tokyo, Japan.*

Background: Previous studies and current guidelines have suggested that elderly persons can be living kidney donors; however, reports on elderly donors >70 years old are limited. In order to clarify the donor safety and feasibility, we investigate the clinical outcomes of living kidney donors > 70 years old after nephrectomy.

Methods: We conducted a case-series study of living kidney donations involving 48 donors aged >70 years at the time of transplantation. The kidney donations occurred between 2001 and 2014 at our institution. The primary outcomes were survival or end-stage renal disease (ESRD)-free rate and all crude event-free rates, including cardiovascular-, infection-, ESRD-, or death-free rate. The secondary outcome was serum creatinine level at the end of the follow-up period.

Results: The 48 cases were followed up for a median of 4 years. The survival rate among the donors was 100% until the fifth year, and only two donors died during follow-up. The ESRD-free rate was 100% during the follow-up period. The overall event-free rate was 100% at 1 year, 85.7% at 3 years, and 75.0% at 5 years. The mean serum creatinine level was 1.18 ± 0.24 mg/dL at the time of hospital discharge and did not increase (1.18 mg/dL) at the end of follow-up.

Conclusions: Living kidney donation from elderly donors >70 years old appears to be a safe and acceptable option for patients requiring renal-replacement therapy.

FR-PO1110

Opinions of the Medical Community at the University of Iowa Regarding Disincentives and Incentives in Living Kidney Donation Based on Age Maria T. Story,[1] Sarat C. Kuppachi.[1,2] *[1]Internal Medicine, Univ of Iowa Hospitals and Clinics, Iowa City, IA; [2]Organ Transplant Center, Univ of Iowa Hospitals and Clinics, Iowa City, IA.*

Background: As the kidney transplant waiting list continues to increase annually, transplant societies have been debating options of incentives to increase organ donation. We surveyed healthcare employees at our institution regarding removal of disincentives and providing incentives to living kidney donors to determine if differences in opinions exist based on age.

Methods: The opinions of employees in Internal Medicine, General Surgery, Nursing, and medical students were collected via a web-based survey of 18 questions. IRB approval was obtained. Responses were analyzed using the chi-square test for independence.

Results: Out of 624 who completed the survey, 120 were <25 years old. 58.7% thought it acceptable to reimburse expenses, while 25.7% advocated for additional incentives. 38.3% believed it was unethical to offer financial incentives for exchange of an organ, while 22.8% believed it was ethical. 82.5 % were concerned about exploitation if financial incentives were offered. There were no differences in these opinions based on age < or >25. Respondents aged <25 were significantly more likely (p=0.0002) to accept money for a kidney than those >25.

Perspective on incentivizing living kidney donation P= 0.3514		
	Age<25 N=120	Age>25 N= 504
Donation is altruistic; no incentives	8	45
Acceptable to reimburse expenses (remove disincentives)	74	296
Acceptable to provide incentives	33	130
I don't have an opinion	2	25

Conclusions: Individuals < 25 were more likely to accept financial incentives for kidney donation than those >25. As transplant societies contemplate incentives in organ donation, we believe awareness of the increased interest from the younger community is important given that long-term outcomes of living kidney donation at a young age are not well understood. Further studies will be necessary to better understand factors for the differences in opinion.

FR-PO1111

Abstract Withdrawn

FR-PO1112

Nationwide Strategy for Kidney Transplantation with Controlled Cardiac Death Donor (cDCD) Has Improved Global Results. Spanish Multicentre SENTRA-GEODAS Group Jose M. Portoles,[1,2] Maria Jose Perez Saez,[1,2] Anna Manonelles,[1,2] María Marques Vidas,[1,2] Naroa Maruri,[1] Anton Fernandez Garcia,[1] Auxiliadora Mazuecos,[1] Rosalia Valero,[1] Alberto Rodriguez-Benot,[1] Julio Pascual,[1,2] Maria Jose Perez Saez. *[1]Nephrology, Hospital Puerta de Hierro SENTRA / GEODAS, Majadahonda, Spain; [2]Public Health Research Net RedinRen16/009/009 RETYC ISCIII.*

Background: Controlled donation after cardiac death (cDCD) programs are running in US for years and some European countries has recently started on it. National transplant organization (ONT) has developed a nationwide program in Spain from jan-2012 and 45 Centers had joined by Dec2015 (370 cDCD donors on 2012-15). Eighteen centres have entered our study group. We present here the main clinical outcomes.

Methods: Observational prospective multicentre study. Systematic inclusion of every kidney transplant-KTx from cDCD at joined units. Local center surgical procedures and IS protocols.

Results: We included 215 cDCD, donors aged 56,9 year who have died mainly due to CV events (74%). Effective harvest rate was 93% higher than reported for uncontrolled DCD by ONT (66%) 13 kidneys were discharged for several reasons; his pairs were successfully implanted. 28 transferred and implanted in centers out of our group. We include 389 ESRD recipients: 56.3y, 69.1% males, for 75,6%of them were the first KTx .Immunosuppression regimen included 98,8% induction (Thymoglobulin 67,3%/ Basiliximab 31,5%) plus prednisone-MMF-Tacrolimus (83,1%) or mTOR (6,9%). Median Cold ischemia time (CIT) was 12,5h and warm IT 24min. Median HLA-mismatch was 4 [0-5]. **Clinical outcomes:** Primary graft failure (PGF) rate was 3% mainly associated to vascular problems no single hyperacute rejection case. Delayed graft function (DGF) was defined as dialysis use on 1st week after KTx. In spite of DGF rate of 49,7% the death censored graft survival was 97,9% at 1 yr and92,2% at 2 yr.13 patient died with functional graft and patient survival was 95,3% (Kaplan-Meier).

Conclusions: Harvested graft rate for cDCD are higher than reported for uncontrolled DCD. KTx with cDCD present higher DGF than historic reference for brain death donor but similar PGF rate and patient or graft survival rates. Our results aim us to promote this cDCD all over the country.

FR-PO1113

Neighborhood Poverty and Gender Disparities in Live Donor Kidney Transplant Outcomes in the United States Tanjala S. Purnell, Xun Luo, Deidra C. Crews, Lisa A. Cooper, Dorry L. Segev. *Johns Hopkins Univ.*

Background: Little is known about the association of neighborhood poverty with gender differences in live donor kidney transplant (LDKT) outcomes in the United States.

Methods: Using data from the Scientific Registry of Transplant Recipients and the US Census, we tested whether neighborhood poverty modifies gender disparities in death-censored graft loss and patient death after LDKT. We performed Cox regression models to compare 5-year outcomes among 27,978 men and 17,263 women who received a first LDKT in 2005-2013. We adjusted all models for recipient, donor, and center factors, and we categorized neighborhoods as poor (≥20% poverty), middle-income (5-19% poverty), or wealthy (<5% poverty).

Results: Women living in poor (aHR: 1.34, 95% CI: 1.16-1.55) and middle-income (aHR: 1.26, 95% CI: 1.13-1.40) neighborhoods had higher risk of graft loss than men, but there were no gender differences in graft loss among recipients in wealthy neighborhoods (aHR: 0.98, 95% CI: 0.80-1.21) (p for gender/poverty interaction = 0.029). **(Figure 1A)** In subsequent models, women living in wealthy (aHR: 0.74, 95% CI: 0.61-0.92) and middle-income (aHR: 0.84, 95% CI: 0.76-0.94) neighborhoods had lower risk of mortality than men, but women living in poor areas did not experience a statistically significant survival advantage over men (aHR: 0.90, 95% CI: 0.75-1.07). **(Figure 1B)**

Figure 1A. Gender Differences in Graft Loss after LDKT by Neighborhood Poverty

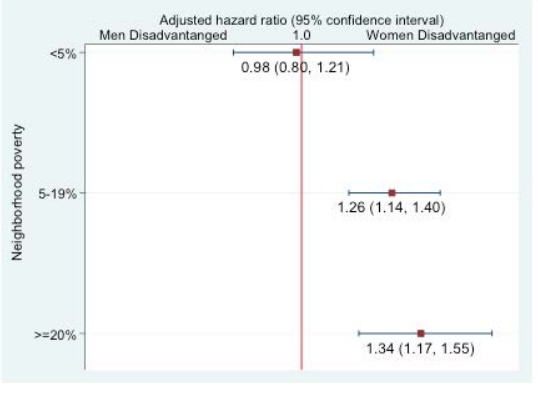
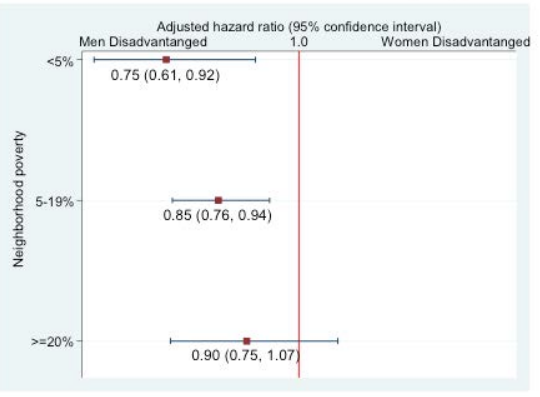


Figure 1B. Gender Differences in Patient Death after LDKT by Neighborhood Poverty



Conclusions: Women living in poor neighborhoods were at highest risk of graft loss after LDKT. Targeted efforts to address barriers among women living in poor areas may help to mitigate gender disparities in LDKT outcomes.

Funding: NIDDK Support, Other NIH Support - NHLBI

FR-PO1114

Diabetes Mellitus in Living Pancreas Donors: Use of Integrated National Registry and Pharmacy Claims Data to Characterize Donation-Related Health Outcomes Ngan Lam,[1] Mark Schnitzler,[2] Dorry L. Segev,[3] Gregory P. Hess,[4] Bertram L. Kasiske,[5] David A. Axelrod,[6] Amit X. Garg,[7] Daniel C. Brennan,[8] Krista L. Lentine.[2] *[1]Univ of Alberta, Edmonton, AB; [2]Saint Louis Univ, St. Louis, MO; [3]Johns Hopkins School of Medicine, Baltimore, MD; [4]Univ of Pennsylvania, Philadelphia, PA; [5]Univ of Minnesota, Minneapolis, MN; [6]Dartmouth Hitchcock Medical Center, Hanover, NH; [7]Western Univ, London, ON; [8]Washington Univ School of Medicine, St. Louis, MO.*

Background: Living donor pancreas transplant is a potential treatment for diabetic patients with end-organ complications. While early surgical risks of donation have been reported, long-term medical outcomes in living pancreas donors are not known.

Methods: We integrated national Scientific Registry of Transplant Recipients data (1987-2015) with records from a nationwide pharmacy claims warehouse (2005-2015) to examine prescriptions for diabetic medications and supplies as a measure of post-donation diabetes mellitus. To compare outcomes in controls with baseline good health, we matched living pancreas donors to living kidney donors (1:3) by demographic traits and year of donation.

Results: Among 73 pancreas donors in the study period, 45 were identified in the pharmacy database: 62% women, 84% white, and 80% relatives of the recipient. Over a mean post-donation follow-up period of 16.3 years, 26.7% of pancreas donors filled prescriptions for diabetes treatments, compared with 5.9% of kidney donors (odds ratio [OR] 4.13, 95% confidence interval [CI] 1.91-8.93; $P = 0.0003$). Use of insulin (11.1% vs. 0%) and oral agents (20.0% vs. 5.9%; OR 4.50, 95% CI 2.09-9.68; $P = 0.0001$) was also higher in pancreas donors.

Conclusions: Diabetes is more common after living pancreas donation than after living kidney donation, supporting clinical consequences from reduced endocrine reserve.

Funding: NIDDK Support

FR-PO1115

The Impact of Donor Cannabinoid Intoxication on Outcomes of Kidney Transplantation Blaithin A. McMahon, Khushleen Jaggi, Edward S. Kraus, Tessa Kimberly Novick, Steven Menez, Niraj Desai, Sami Alasfar. *Johns Hopkins Univ School of Medicine, Johns Hopkins Univ, Baltimore, MD.*

Background: Most transplant centers now accept kidney grafts from victims who have acute drug intoxications. Despite the widely acceptance of many of these donors the effect of the acute intoxication on graft outcome is poorly understood.

Methods: This is a single center retrospective cohort analysis of patients undergoing deceased donor kidney transplantation (DDKT). Donor and recipient characteristics and post transplantation outcomes were obtained from the institutional transplant database. Urine toxicology agents tested from donor urine was alcohol, heroin, cocaine, opioids/methadone, cannabinoids, benzodiazepines, ecstasy, methamphetamine and LSD. Delayed graft function (DGF) was defined as the need for dialysis within 1 week of kidney transplantation (KT). Graft failure was defined as the need to return to dialysis. Multiple logistical regression (MLR) analysis was used to assess the odds of DGF and graft failure and was adjusted for donor age, donor race, donor terminal creatinine, cold ischemic time and baseline urinary flow rate.

Results: Of 300 random KTs performed at our institution between January 2012 and October 2015, 200 were from deceased donors. 92 deceased donors (46%) were current drug users. The main toxins detectable in donor urine were alcohol (n=45, 23%), heroin (n=29, 15%), opioid/methadone (n=17, 9%), cocaine (n=16, 8%), cannabinoids (n=38, 19%), benzodiazepines (n=5, 3%), ecstasy (n=1, 0.5%), methamphetamine (n=6, 3%), LSD (n=1, 0.5%). Alcohol, heroin, cocaine, opioids/methadone, benzodiazepines, ecstasy, methamphetamine and LSD were drugs of abuse that had no significant effect on KT

outcomes (DGF and graft failure). However, cannabinoid use in donors had significantly higher odds of DGF (odd ratio 2.9 +/- 1.4, P< 0.05) but no effect on graft loss or death (median follow up of 1.69 years). 42 donors (n=18) who used cannabinoids had concomitant use of alcohol but there was no interaction seen.

Conclusions: Cannabinoid use is known to cause acute kidney injury. Our data suggest that cannabinoid use in kidney donors may increase the risk of DGF.

FR-PO1116

Why Kidney Transplants from Uncontrolled Donation after Cardiac Death Donors (UDCDD) Don't Reach a Good Renal Function? Maria Molina, Eduardo Gutierrez-Martinez, Enrique Morales, Manuel Praga, Amado Andres. *Nephrology, Hospital Univ 12 de Octubre, Madrid, Spain.*

Background: Kidneys grafts from UDCDD have higher ischemia injury. It develops in higher primary non function, lower graft survival and worst renal function compared to ideal donors. The aim was to describe risk factors associated with poor renal function (PRF) in a group of renal transplants (RT) from UDCDD.

Methods: We review all RT from UDCDD performed in our center with functioning graft at 1 year. We classified grafts into two groups: Group I grafts with serum creatinine (SCr) ≥ 2 mg/dL at 1 year from kidney transplantation and Group II with SCr < 2 mg/dl. We compared characteristics in both groups.

Results: Our center have performed 207 RT from UDCDD. We excluded 14 (7%) primary non-function and 9 (4%) grafts lost in the first year. 184 (89%) grafts were functioning at 1 year of transplantation. 13 (7%) patients were into Group I and 171 (93%) patients were into Group II. Characteristic of two groups are showed in Table.

	Group I: SCr > 2 mg/dL (13 patients)	Group II: SCr < 2 mg/dL (171 patients)	p
Donor gender (male)	92% (12)	88% (150)	ns
Donor age (years)	51 (47-54)	41 (35-50)	< 0.01
Donor SCr (mg/dL)	1.4 (1.2-1.6)	1.3 (0.9-1.5)	ns
Cold ischemia time (hours)	14 (9-15)	11 (9-14)	ns
Recipient age (years)	48 (41-58)	47 (39-56)	ns
Recipient weigh (kg)	78 (74-91)	70 (60-82)	0.01
Delayed graft function	69% (9)	76% (130)	ns
Contralateral functioning kidney at one year	62% (8)	85% (146)	0.04
LDH serum	1776 (1160-2280)	1463 (822-2520)	ns
SCr at 6 month	2.3 (2.1-2.8)	1.4 (1.1-1.7)	0.01
Graft survival at the end of follow-up	69% (9)	99% (169)	<0.01

Conclusions: The prevalence of PRF at 1 year in RT from UDCDD is low in our center although confers a bad renal graft prognosis. PRF is associated to donor age, non-function of contralateral kidney graft, recipient weigh and gender and acute rejection. A better screening of potencial UDCDD, more adecuate allocation of these kidneys and a lower acute rejection rate could improve the outcome of renal transplantation from UDCDD.

FR-PO1117

Donation after Cardiac Death, Not Extended Criteria Donor Maria Molina, Enrique Morales, Eduardo Gutierrez-Martinez, Manuel Praga, Amado Andres. *Nephrology, Hospital Univ 12 de Octubre, Madrid, Spain.*

Background: There are few experiences published about long term follow-up of renal transplant (RT) from Donation after Cardiac Death Donors (DCDD) from category II of Maastricht classification (Uncontroled DCDD) (people presenting a irreversible cardiac arrest at home or on the street and dead despite appropriate resuscitation maneuvers). Outcomes from grafts from Uncontrolled DCDD are classically lower than organs from the Donation after Brain Death Donors (DBDD) .

Methods: We reviewed all characteristics from RT from Uncontrolled DCDD performed between July 2005-December 2012 in our hospital. We compared with a paired RT from DBDD, no hyperimmunized, first renal transplants with similar donor age performed in our hospital during the same period of time.

Results: We included 207 RT in Uncontrolled DCDD group and 207 RT in DBDD group. Results are shown on the table.

	DCDD group N=207	DBDD group N=207	P
Donor age (years)	43±10	41±11	ns
Recipient age (years)	48±11	45±11	0.01
Donor serum creatinine (mg/dl)	1.2±0.4	0.8±0.3	0.01
Delayed onset of Tacrolimus with Thymoglobulin induction (%)	187 (90%)	0 (0%)	0.01
Primary non-function (%)	14 (7%)	7 (3%)	ns
Delayed graft function (%)	162 (78%)	110 (53%)	0.01
1-year incidence of biopsy-proven acute rejection (%)	22 (11%)	27 (14%)	0.01
Graft survival (%)* / **	178 (86%)* / 182 (88%)**	176 (85%)* / 184 (89%)**	ns*/**
Patient survival (%)*	202 (98%)	200 (97%)	ns
Final serum creatinine (mg/dl)	1.5±0.8	1.4±0.7	ns

*at the end of the follow-up, **death censored

The high incidence of delayed graft function in uncontroled DCDD group, probably due to the high ischemic strees suffering these donors, has no negative impact on graft outcome.

Conclusions: Uncontroled DCDD is an adequate kidney donors. The expansion of this kind of donors can significantly increase the number of organ recovered and improve results in kidney transplant programs, particularly for median age recipients.

FR-PO1118

Assessing Deceased Donor Quality Using the Kidney Donor Risk Index: Performance in a Canadian Setting Ann Young,[1] Eric McArthur,[2] Stephanie Dixon,[2] Greg A. Knoll,[2,3] Amit X. Garg,[2,4] Charmaine E. Lok,[1,2] Ngan Lam,[5] Joseph Kim.[1,2] *[1]Dept of Medicine, Univ of Toronto, ON, Canada; [2]Inst for Clinical Evaluative Sciences, ON, Canada; [3]Div of Nephrology, Univ of Ottawa, ON, Canada; [4]Div of Nephrology, Western Univ, ON, Canada; [5]Div of Nephrology, Univ of Alberta, Edmonton, AB, Canada.*

Background: Deceased donor kidney allocation in the United States is guided by the Kidney Donor Risk Index (KDRI). The applicability of this newer allocation system in a Canadian setting is unknown.

Methods: This population-based cohort study followed deceased donor kidney transplant recipients in Ontario, Canada from Jan 2005 to Mar 2011. Subjects were identified from Ontario's Trillium Gift of Life Network and linked to other provincial healthcare databases. Ten donor factors were used to calculate the KDRI. Multivariable Cox proportional hazards models were used to assess the association of KDRI with graft loss or death. The role of KDRI in predicting long-term recipient outcomes, when compared to only using donor age, was explored using the likelihood-ratio test.

Results: A total of 1,299 deceased donor kidney transplants were divided into KDRI quintiles. Median follow-up time was 5.5 years. Mean donor age increased across KDRI quintiles from 27 to 64 years. A log-linear association between KDRI and total graft loss (i.e., death, return to chronic dialysis, or preemptive re-transplant) was observed. Total graft loss increased across KDRI quintiles from 39.6 to 90.2 events per 1,000 patient years. The adjusted hazard ratios (95% CI) from Q2 to Q5 (referent = Q1) were 1.27 (0.89, 1.80), 1.58 (1.13, 2.22), 1.43 (1.01, 2.02), and 2.15 (1.54, 2.99), respectively. Increased hazard ratios across KDRI quintiles were also observed for death-censored graft loss, but not for death. In this cohort, the KDRI significantly improved the assessment of donor quality compared to models using donor age alone (p=0.009).

Conclusions: The KDRI can be used in Canadian patients to identify kidneys at increased risk for graft loss, and can potentially inform risk assessment beyond using donor age alone. Whether the KDRI can be further refined in this population, and effectively applied in other Canadian jurisdictions, requires further study.

Funding: Government Support - Non-U.S.

FR-PO1119

Risk Stratification for Optimized Utilization of Deceased Donor Kidneys with Acute Kidney Injury by KDIGO criteria Mi-Yeon Yu, Yong Chul Kim, Jung Pyo Lee, Yon Su Kim, Hajeong Lee. *Internal Medicine, Seoul National Univ Hospital, Seoul, Republic of Korea.*

Background: Deceased donor kidneys with acute kidney injury (AKI) raise fear of poor graft outcomes to clinicians and consequently are often discarded. However, the growing evidence has suggested that they may be a good solution to overcome organ shortage. Although previous studies have focused on fair outcome of donor AKI, there is a limited data regarding the factors affecting long-term graft and recipient outcomes in patients received deceased donor kidneys with AKI.

Methods: We included all patients who received decreased donor kidney transplant from 2005 to 2011. We defined AKI by KDIGO criteria. Primary outcome was graft survival beyond 10 years by donor AKI stage. Secondary outcomes were 6 month, 1, 3, 5 years graft function, and 5-year recipient survival.

Results: Among a total of 413 patients, 156 received kidneys from donors with AKI including 84 stage 1, 38 stage 2, and 34 stage 3. Other 257 were received kidneys from donors without AKI (no AKI group). AKI developed more in ECD and hypotensive donors. There was no significant difference in delayed graft function, overall graft and recipient survival among AKI and no AKI groups. Interestingly however, when we followed up annual graft function, patients who received stage 3 AKI donor kidneys showed significantly lower 5-year graft function (median eGFR 45 [23–67] mL/min/1.73m^2), compared with no AKI (median eGFR 65 [40–90]), stage I AKI (median eGFR 59 [39–79]), and stage 2 AKI (59 [34–84]), respectively (P=0.019). Risk factor analysis for graft survival demonstrated worsening renal function just before transplantation elevated risk of both graft failure (adjusted HR 7.65, 95% CI 1.63–35.89) and patient survival (adjusted HR 20.67, 95% CI 1.33–321.99).

Conclusions: Although deceased donor AKI was not associated with overall graft and recipient survival, stage 3 AKI had an influence on lower graft function. Moreover, worsening renal function just before transplantation was an independent risk factor for both graft and patient survival.

FR-PO1120

Differential Intragraft Gene Expression Profile of Kidney Transplant Patients on Angiotensin Converting Enzyme Inhibitor (ACEI) or Angiotenin Receptor Blocker (ARB) Christian Suarez-Fuentes, Yi Bao, Enver Akalin. *Montefiore Einstein Transplant Center, Bronx, NY.*

Background: Treatment with ACEI/ARB has been shown to have anti-inflammatory effects in animal models but this effect has not been investigated in kidney transplant recipients. We aimed to study the effect of ACEI/ARB treatment on intragraft gene expression profiles of transplant kidney biopsies using microarrays.

Methods: We identified near normal biopsies with chronic sum allograft injury score (ct+ci+cv) ≤ 3 for gene expression profiling. Biopsies with a diagnosis of acute or chronic rejection, glomerular disease, or polyoma nephropathy were excluded. The gene expression profiles were studied by Affymetrix HuGene 1.0 ST expression arrays. We compared 2 groups; Group 1 (n=16), patients with no exposure of ACEI/ARB treatment and Group 2 patients (n=13) with exposure to ACEI/ARB at least 6 months prior to kidney biopsy.

Results: Both groups had similar demographics characteristics in terms of age, race, sex, type of transplant, previous history of transplantation or acute rejection, panel reactive antibody levels and immunosuppressive treatment. There were no differences in acute and chronic Banff allograft injury scores between the 2 Groups. Intragraft gene expression profiles of ACEI/ARB treated Group 2 biopsies showed decreased gene transcripts of interferon-gamma and rejection-associated transcripts (GRIT) and constitutive macrophage-associated transcripts (CMAT) compared to Group 1 biopsies. There were no statistically significant differences in expression of cytotoxic T cell (CAT), regulatory T cell (TREG), B-cell (BAT), natural killer cell (NKAT), and endothelial cell-associated transcripts (ENDAT) between the 2 Groups.

Pathogenesis Based Transcripts	G2 VS G1 (DOWNREGULATED)
GRIT	0.048
CAT	0.18
TREG	0.07
BAT	0.42
NKAT	0.35
CMAT	0.048
ENDAT	0.52

Conclusions: We have shown that exposure to ACEI/ARB was associated with down-regulation of GRIT and CMAT. This anti-inflammatory effect could be an additional benefit in kidney transplant recipients.

Funding: Other NIH Support - T-32 Research Grant

SA-PO001

Epitope Sharing Causing Crossmatch Positivity in a Kidney Transplant Candidate with Very Low Pre-Transplantion Anti-Human Leukocyte Antigen Antibody Titer: A Case Report Iris C. De Castro,[1] Paul Warner,[2] Christopher D. Blosser.[1] *[1]Nephrology, Univ of Washington, Seattle, WA; [2]Bloodworks Northwest, Seattle, WA.*

Introduction: Human leukocyte antigen (HLA) have multiple epitopes. An epitope or *antigenic determinant* is a part of an antigen that is capable of stimulating an immune response. Epitopes can be shared by different HLA's. HLA antibodies usually react to epitopes rather than antigens. We present a patient who, despite having very low titer HLA antibodies, repeatedly tested positive on B cell flow crossmatch (FXM) with 6 potential donors making her not suitable to receive the kidney offer.

Case Description: 62yo ABO A+, Caucasian female with 3 pregnancies, no blood transfusions and ESRD from chronic glomerulosclerosis on peritoneal dialysis. Despite cPRA 0% and single antigen bead (SAB) test showing HLA Class I and II under 1,000MFI (positive cutoff is >2500MFI), she tested FXM positive with 6 potential donors. On review, all HLA-DR beads except HLA-DR7 were clustered with MFI between 300 and 950. She was found to have an antibody to a shared epitope by all HLA-DR antigens except HLA-DR7. As it was a single antibody, it only showed low level MFI on SAB making each, individually, insignificant. But, when crossmatched against non-DR7 lymphocytes, this was sufficient to yield a positive result. This was confirmed by FXM against numerous surrogate donors with different HLA-DR antigens. She had positive FXM with cells carrying any DR antigen other than DR7 and negative FXM to all HLA-DR7 homozygous donors.

Discussion: HLA antibodies that recognize broadly expressed epitopes can produce seemingly normal, low-level MFI SAB results, but FXM positive when exposed to only one of the antigens carrying the target epitope. Previous literature have reported that pre-transplantation low-level donor specific antibodies can induce severe acute antibody mediated rejection early after transplantation as a result of shared epitopes. Since the patient had persistent positive FXM against non-DR7 cells, all other DR antigens were added as unacceptable, resulting in a cPRA 99%. This case illustrates the importance of recognizing epitope sharing and its implications on kidney transplant allocation.

SA-PO002

Hyperkalemia during Voriconazole Treatment in Three Kidney Transplant Patients Mohammed Nazmul, Scott G. Westphal, Clifford D. Miles. *Nephrology, Univ of Nebraska Medical Center, Omaha, NE.*

Introduction: Voriconazole (VOR) is a commonly used antifungal agent in renal transplant recipients who develop fungal infection. Here we present a previously unreported observation of moderate to severe hyperkalemia occurring in three patients started on VOR. In each case, the hyperkalemia developed despite adjustment in tacrolimus (TAC) dose to maintain therapeutic, low serum levels.

Case Description: We identified three kidney transplant recipients who were started on VOR for the treatment of histoplasmosis, and developed hyperkalemia following its initiation. Each patient was maintained on a TAC-based immunosuppression regimen. Hyperkalemia was not present in any of the three patients prior to starting VOR, and TAC dose was decreased to keep trough levels at 3-6 ng/ml. All patients were instructed to follow a low potassium diet and additional medications known to cause hyperkalemia were avoided. Patient #1 had several episodes of severe hyperkalemia with a peak potassium level 8.5 mmol/L occurring 40 days after starting voriconazole. At that time, his TAC level was 4.1 ng/ml and creatinine was 2.3 mg/dl. He ultimately was converted from TAC to everolimus, and the hyperkalemia resolved. Patient #2 had persistent hyperkalemia following initiation of VOR. His peak serum potassium reached 6.5 mmol/L occurring 75 days after starting VOR. His TAC level was 4.0 ng/dl and creatinine was 1.8 mg/dl at that time. Patient #3 had intermittent moderate hyperkalemia after starting VOR. His peak potassium level was 5.7 mmol/L which occurred 54 days after starting VOR. At the time of his peak potassium, his TAC level was 2.1 ng/ml and creatinine was 2.9 mg/dl.

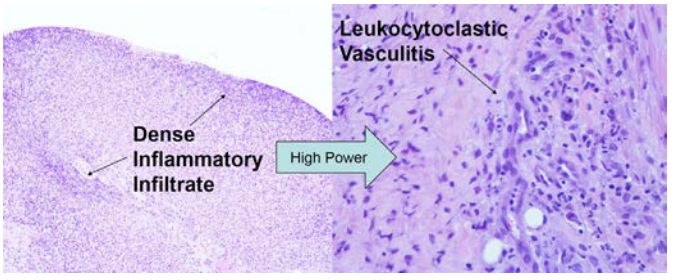
Discussion: While interactions between azoles and calcineurin inhibitors are widely recognized, this is the first report describing new onset hyperkalemia following initiation of VOR in kidney transplant patients receiving TAC. In each patient, the hyperkalemia developed despite maintaining low level, therapeutic TAC levels. The mechanism behind this observation remains unclear, but may warrant further investigation. Clinicians should be vigilant for hyperkalemia when TAC and VOR are used concurrently.

SA-PO003

Autoimmunity following Kidney Transplantation: A Case of De Novo Behcet's Disease Isabel Remedios,[1] Isa Ashoor.[2] *[1]Pediatrics, Louisiana State Univ Health Sciences Center, New Orleans, LA; [2]Nephrology, Children's Hospital, New Orleans, LA.*

Introduction: Autoimmune disease is a rare occurrence following kidney transplant (KT). Its development may be a marker of inadequate immunosuppression secondary to altered drug pharmacokinetics or non-adherence. We present a case of Behcet's disease (BD), a rare mucocutaneous ulcerative autoimmune condition in a non-adherent sexually active young adult KT recipient that was initially mistaken for Herpes Simplex Virus (HSV) infection.

Case Description: A 19 year-old African American female with a history of bilateral Wilms tumors, and prior failed KT due to chronic rejection presented 4 years following her second deceased donor KT with acute fever, non-bloody diarrhea, and ulcerations of the mouth, vulva, and perianal region. Her transplant course was notable for multiple rejection episodes and several sexually transmitted infections. The ulcers appeared herpetiform and aphthous in nature. Given her chronic immunosuppression with tacrolimus, mycophenolate, and prednisone, and and recent sexual encounter, disseminated HSV was suspected. She was empirically treated with IV acyclovir. After 1 week of therapy, fever and diarrhea resolved, but ulcers remained unchanged. All infectious studies returned negative. Lupus serologies and Crohn's disease screening tests were negative. Vulvar punch biopsy showed a neutrophilic/leukocytoclastic vasculitis consistent with BD.



Symptomatic treatment with analgesia, wound care, and sitz baths led to complete resolution within 3 weeks.

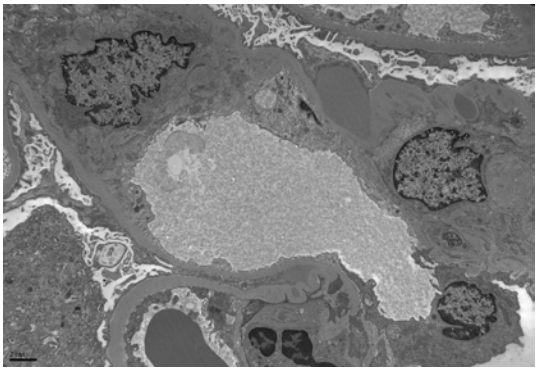
Discussion: Although rare, BD is an important cause of non-infectious orogenital ulcers. We describe the only KT patient in the literature with biopsy confirmed de novo BD independent of pre-existing glomerulonephritides. A high index of suspicion is required to diagnose BD in this population to limit prolonged exposure to nephrotoxic medications.

SA-PO004

De Novo Post-Streptococcal Glomerulonephritis as the Cause of Transplant Acute Kidney Injury Alexander Bullen, Mita M. Shah. *Div of Nephrology-Hypertension, Univ of California San Diego, San Diego, CA.*

Introduction: Acute kidney injury (AKI) is common in kidney transplant recipients (KTR) and is a risk factor for graft failure and death. We present a rare cause of AKI in a KTR, acute post-streptococcal glomerulonephritis (APSGN).

Case Description: A 45-year-old male with history of ESRD secondary to unknown etiology status post living donor kidney transplant two years prior, with baseline serum Cr of 1.5 mg/dL, presented to kidney transplant clinic. He was recovering from a "cold" the week prior. His immunosuppressive regimen consisted of tacrolimus 3 mg BID, mycophenolate mofetil 750 mg BID and prednisone 10 mg QD; he had inadvertently been taking 1 mg BID of tacrolimus for several weeks. On clinical exam he was normotensive and afebrile, without graft tenderness or bruit; 3-4 mm pitting edema was noted in the lower extremities. Laboratory data showed a Cr of 2.2 mg/dL increased from 1.6 mg/dL a month prior, tacrolimus trough of 4.9, UA moderate blood, > 50 RBCs, 3+ protein and urine protein/creatinine ratio of 8.2. UA a month prior did not reveal blood or proteinuria. Anti-streptolysin O antibody was elevated at 603 (0-330 IU/mL), C3 was low and C4 was normal. Biopsy revealed submembranous electron dense deposits in mainly paramesangial areas and large subepithelial electron dense deposits, consistent with APSGN and no evidence of cell or antibody mediated rejection.



A month later, Cr had decreased to 1.9 mg/dL. In three months, it had returned to baseline and proteinuria and hematuria had resolved.

Discussion: APSGN is caused by nephritogenic strains of group A beta-hemolytic streptococcus. The clinical spectrum ranges from asymptomatic disease to acute nephritic syndrome as in our patient. This case reveals the importance of a prompt and thorough evaluation of AKI in KTRs having a low threshold to perform a renal biopsy to assess for other entities such as APSGN.

SA-PO005

Haunted by Ghosts: An Unlikely Explanation of Hematuria in a Renal Transplant Patient Ruchita Jariwala,[1] Dia Rose Waguespack,[1] William F. Glass,[2] Angelina Edwards.[1] *[1]Div of Renal Diseases and Hypertension, The Univ of Texas Health Science Center at Houston, Houston, TX; [2]Div of Pathology and Laboratory Medicine, The Univ of Texas Health Science Center at Houston.*

Introduction: Anticoagulant use for the prevention and treatment of thrombosis is indicated in variety of clinical settings. Anticoagulant nephropathy is a clinical entity of great importance as more anticoagulants are developed and used in broader clinical settings. We report a case of anticoagulant nephropathy in a renal transplant recipient after the initiation of warfarin for lower extremity deep vein thrombosis.

Case Description: A 62-year-old man underwent a living related donor kidney transplant for end stage renal disease secondary to Hypertension and Diabetes. He had a complicated postoperative course requiring surgical correction of ureteral leak with stent placement, repair of the transplant renal artery and anticoagulation initiation with warfarin for lower extremity DVT. Despite his international normalized ratio (INR) remaining less than 3, he had persistent microscopic hematuria with intermittent episodes of gross hematuria. Upon completion of anticoagulation, a renal transplant biopsy was performed for evaluation of elevated creatinine and persistent microscopic hematuria. Biopsy was negative for rejection but showed acute tubuloepithelial injury with red blood cell (RBC) casts and RBC ghosts suggestive of prior glomerular hemorrhage and anticoagulant related nephropathy. His hematuria resolved at follow up and his creatinine gradually improved with cessation of anticoagulation.

Discussion: Anticoagulant related nephropathy is a cause of acute kidney injury (AKI) that is frequently underdiagnosed and underappreciated. Although most cases occur with supratherapeutic INR, anticoagulant related nephropathy can occur even with modest elevations. In this case, the pathologic findings of RBC ghost casts suggest lysis and degeneration of RBCs from prior bleeding episode. Thus, anticoagulant related nephropathy can be clinically relevant even after discontinuation of anticoagulation. Our case serves to broaden the differential of AKI and hematuria in a kidney transplant patient previously on anticoagulation.

SA-PO006

An Unusual Case of Acute Myeloid Leukemia Cell Infiltration of the Renal Allograft Sandhya Manohar,[1] Insara Jaffer Sathick,[1] Joseph P. Grande,[2] Ziad El-Zoghby,[1] Nelson Leung.[1] *[1]Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [2]Pathology, Mayo Clinic, Rochester, MN.*

Introduction: Native kidney involvement of hematological malignancies is common and can often be the presenting feature. Renal involvement is seen in about 34% of patients by autopsy studies. To our knowledge, there has been no reported case of acute myeloid leukemia (AML) infiltration in the kidney allograft and here we present such a case in a kidney transplant patient.

Case Description: A 59-year-old male presented to us for management of his recently diagnosed AML. He had a history of end stage renal disease from diabetic nephropathy and underwent deceased donor kidney transplant at an outside facility. He was maintained on a prednisone and cyclosporine regimen with a unremarkable course for 14 years. A year prior to presentation, his platelet count was 50 X 10^9cells/L with a concurrent rise in creatinine. A bone marrow biopsy showed increased myeloid precursors with increased blasts (29%) consistent with the diagnosis of AML and he was sent to us for further management. Upon presentation to us, his creatinine was 2.7 mg/dl. His urinalysis revealed mild hematuria with 24 hour urine protein of 953 mg/g of creatinine. He underwent a kidney allograft biopsy which revealed multifocal myeloid infiltrates compatible with renal involvement of AML. He was started on chemotherapy but he progressively deteriorated and passed away.

Discussion: It is well known that transplant patients are at a higher risk of developing cancers with dermatological cancers and lymphomas being the bulk of these but AML is less common. The Cincinnati Transplant Tumor registry of 1991 noted 2.7% of the cancers to be due to leukemia, of which 43% were AML. A study of autopsy cases of patients with hematological cancers had shown renal involvement in 34% of the cases. It was most common in patients with acute lymphoid leukemia (83%) but interestingly patients with AML had the most dense infiltration with involvement of almost the entire kidney. But to our knowledge there are no reported cases of such malignancies involving the renal allograft and should be a consideration in transplant patients presenting with elevated creatinine.

SA-PO007

A Case Report - Phenytoin Overdose Treated with Hemodialysis Using a High Cutoff Filter Joelle Mardini,[1] Monique Cormier,[1] Simon Desmeules,[2] Marc Ghannoum.[1] *[1]Nephrology, Hopital de Verdun, Montreal, QC, Canada; [2]Nephrology, Centre Hospitalier Univ de Québec, Quebec, QC, Canada.*

Introduction: The role of hemodialysis (HD) to enhance phenytoin clearance in overdose cases is uncertain. Because of phenytoin's high protein binding (90%), it is hypothesized that dialysis using more porous filters may accentuate clearance of phenytoin. This report is the first description of phenytoin removal using a Theralite™ filter, a high cut-off filter that allows the removal of molecules with a molecular mass of up to 45 kDa.

Case Description: A 54-year-old man who ingested an unknown amount of phenytoin had a phenytoin level of 51.2 mg/L (therapeutic range 10-20mg/L) and coma, both of which remained relatively constant for 12 days. HD was prescribed to enhance elimination of phenytoin. Blood and dialysate flow were prescribed at 350 and 750 ml/min, respectively. Phenytoin and albumin sampling were simultaneously drawn from the arterial (entering) line of the dialyzer and the effluent line every 60 minutes from the start of HD. Phenytoin concentration decreased by 28.6% during the 8-hour HD treatment, and a total of 1.1 g of phenytoin was removed. During HD, measured apparent half-life was 18.5 hours, compared to 1109.8 hours before HD and 56.3 hours after HD [Figure 1]. Instantaneous phenytoin clearance remained constant during HD and averaged 80.1 mL/min, whereas a steady decline in albumin clearance was observed during the 8-hour session. Albumin removal from the Theralite filter was most important at the beginning of HD, which suggests adsorption (and saturation) of albumin on the filter.

Discussion: The high clearance of phenytoin obtained with this filter was due to its high surface area rather than its capacity to remove the albumin-phenytoin complex. This case confirms current data and recommendations that HD should be considered in phenytoin poisoning[1].

1. Anseeuw, K., et al. (2016). "Extracorporeal Treatment in Phenytoin Poisoning: Systematic Review and Recommendations from the EXTRIP (Extracorporeal Treatments in Poisoning) Workgroup." Am J Kidney Dis 67(2): 187-197.

SA-PO008

Renal Auto-Transplantation: An Emerging Approach to Revascularization in Takayasu Arteritis-Induced Renal Artery Stenosis (TARAS) Joelle Mardini, Catherine L. Weber. *Nephrology, McGill Univ Health Center, Montreal, QC, Canada.*

Introduction: Takayasu arteritis (TA) can lead to stenosis, occlusion or aneurysmal transformation of the aorta and its primary branches. Renal artery involvement is common leading to renovascular hypertension and its complications. Renal revascularization in this setting has been shown to control blood pressure and enhance long-term renal and cardiac function as well as survival.We describe a case of successful renal revascularization via renal auto-transplantation (RAT).

Case Description: A 38 year-old hypertensive female was diagnosed with TA in 2014 when CT imaging revealed diffuse wall thickening of pulmonary arteries, abdominal aorta and bilateral renal artery stenosis: 100% on the right with an atrophic kidney and 80% on the left proximal to the first bifurcation with normal size kidney. Her immunosuppression included Prednisone and MMF as well as 4 anti-hypertensives to control her blood pressure. She experienced recurrent disease flares requiring high dose Prednisone as well as several episodes of acute kidney injury (worst Cr 6.4mg/dL). In April 2016, when disease activity was at its minimal, a RAT was performed to prevent loss of renal function in her remaining kidney. Her left kidney was removed and cold-perfused while the left saphenous vein was harvested and anastomosed to the renal artery above the first major bifurcation. The left kidney was then auto-transplanted onto the right external iliac vessels. Pre-op Cr was 1.0mg/dL; peaked post-op day 1 at 2.1mg/dL and returned to baseline on post op day 3. Today, she remains on 4 anti-hypertensive medications, Cr is 1.0mg/dL and renal function is stable.

Discussion: Optimal management of TARAS is not well established. While percutaneous angioplasty techniques are accessible and safe, their results seem less durable than bypass grafts. RAT has been described as the procedure of choice in patients for whom angioplasty and bypass graft are deemed too technically challenging due to advanced tissue inflammation. Although more studies are needed, it appears RAT should be favored in complex TARAS cases for blood pressure control and long-term renal function preservation.

SA-PO009

Preserved Renal Allograft Function While Using the PD-1 Pathway Inhibitor Nivolumab Valerie Suzanne Barta, Madhu C. Bhaskaran, Kenar D. Jhaveri, Nicole M. Ali, Viren G. Amin, Richard L. Barnett. *Nephrology, Northwell Hofstra School of Medicine, Great Neck, NY.*

Introduction: Treatment of malignancies in renal transplant (RT) recipients has largely consisted of targeting the cancer and reducing the immunosuppression. Newer therapies using programmed cell death protein 1 (PD-1) pathway inhibitors such as Nivolumab (N) have been associated with transplant rejection usually within 6-8 weeks of initiation. We report a living related donor (LRRT) where a pre-emptive steroid and sirolimus(S) regimen prevented the immune response of N on the kidney transplant.

Case Description: 70 year old Caucasian male, ESRD consequent to bilateral nephrectomy in 2000 and 2007 for renal cell cancer underwent LRRT in 2010. In early 2015 he developed adenocarcinoma of the duodenum metastatic to liver treated in the past year with intestinal stenting and with minimal response to multiple rounds of chemotherapy. Further disease progression led to initiation of N in 3/2016. 40mg/d prednisone was instituted and prograf was replaced by S. Serum Cr was 1.33mg/dl and dipstick protein negative. S was adjusted for trough levels 4-6 ng/ml. The following month upper intestinal obstruction was addressed with feeding J tube and venting G tube. In 5/2016 he was successfully treated for a port related Klebsiella bacteremia. Since N therapy his body weight has been maintained at 90kg, serum albumin 3.0g/dl, Cr DECLINED to 0.7 and urine protein/Cr was 0.3. 6/2016 donor specific antibodies were negative and CT scan revealed no disease progression.

Discussion: Checkpoint inhibitors of PD-1 class (N) and CTLA-4 antagonists have demonstrated benefit by restoring T cell mediated tumor suppression. Their use has been associated in the four prior RT case reports with rapid cell and antibody mediated rejection. In these patients lower dose steroids with calcineurin inhibitors were employed. We present a novel strategy to prevent rejection in the RT patients receiving PD-1 inhibitors using pre-emptive steroids and sirolimus.

SA-PO010

Babesiosis: An Unusual Cause of Sepsis in a Kidney Transplant Recipient
Negiin Pourafshar, Imtiaz M. Ather, Denise Schain, Asmita A. Gupte, Michael J. Casey. *Univ of Florida, Gainesville, FL.*

Introduction: Infections are a common cause of morbidity and mortality in solid organ transplant recipients due to the use of chronic immunosuppressive therapy necessary to prevent rejection. There is a dearth of literature regarding parasitic infections in organ transplant patients, with no randomized studies. We report a unique case of babesiosis presenting as sepsis in a renal transplant recipient.

Case Description: This case reports a 70-year-old female with a history of deceased-donor kidney transplant who presented with a recent history of severe fatigue and intermittent fevers. Vital signs and laboratory values met criteria for sepsis with 3 of 4 systemic inflammatory response syndrome (SIRS) criteria, along with a suspected source of infection. She was also noted to have acute kidney injury (AKI) and hemolytic anemia. A thorough workup did not reveal any specific hematologic etiology, and blood and urine cultures were negative for bacterial infection. Ultimately serology was positive for Babesia species, confirmed by PCR. The patient was successfully treated with a course of atovaquone and azithromycin and had a full recovery.

Discussion: Our case highlights the inherent difficulty in early recognition of babesiosis in the transplant patient population, in whom pancytopenia is a common finding with a broad differential diagnosis. Another interesting aspect of our case was the fact that our patient clinically presented with sepsis with a suspected source of infection. Parasites are usually an uncommon cause of sepsis, although it has been seen in severe malarial infections. In conclusion, our case represents the fifth reported case of babesiosis in a solid organ transplant recipient, as well as the first case of babesiosis presenting as sepsis which was successfully treated. As the solid organ transplant population has a high susceptibility to infection as well as numerous potential etiologies for the development of hemolytic anemia, it is essential for the clinician to be aware of babesiosis and consider it in the differential diagnosis in this setting.

SA-PO011

A Rare Case of Severe Emphysematous Pyelonephritis of the Transplant Kidney Successfully Treated with Percutaneous Drainage and Antibiotics
Abdul Hameed Zaid, Anup Patel. *Internal Medicine, Saint Barnabas Medical Center, Livingston, NJ.*

Introduction: EPN is usually categorized into four prognostic classes based upon CT scan findings. Current evidence[1] suggests that most cases of EPN, especially those with extensive emphysematous changes (Class 3 and 4) in the presence of renal insufficiency, do not respond to percutaneous drainage (PCD) and antibiotics alone and require an allograft nephrectomy. We present a rare case of Class 3A emphysematous pyelonephritis of the transplant kidney in a diabetic successfully treated with PCD and antibiotics.

Case Description: A 41 year old lady with a history of ESRD from diabetes with a deceased donor renal transplant two years ago was transferred to our hospital after being treated for a urinary tract infection at an outside facility. She had sepsis and ongoing acute oliguric renal insufficiency and was started on intravenous antibiotics and fluids. Although her prednisone and tacrolimus were continued, mycophenolate was held due to the infection. An ultrasonogram revealed hyperechoic foci within renal transplant corresponding to regions of air with subcapsular and perinephric fluid collections with a CT scan confirming the same. A CT guided aspiration of the biggest fluid containing areas was performed the following day and purulent fluid drained. Over the next several days, her renal failure resolved and creatinine returned to baseline. She was discharged on oral antibiotics to complete a total of two weeks of antimicrobial therapy. A CT scan obtained 3 weeks later showed resolution of emphysematous changes with only trace perinephric stranding remaining.

Discussion: The case described above is a rare instance of severe EPN where an allograft nephrectomy was avoided and PCD with antibiotic therapy proved successful. Although available evidence[1] suggest that severe EPN has not been shown to respond to conservative management, early intravenous antimicrobial therapy and percutaneous drainage of identifiable pockets of gas and fluid may help salvage the allograft and give a new lease of life to it. 1. Emphysematous pyelonephritis. Clinicoradiological classification, management, prognosis and pathogenesis. Huang et al. *Arch Intern Med.* 2000;160(6):797-805.

SA-PO012

Furosemide Desensitization for Sulfonamide Hypersensitivity
Musab S. Hommos,[1] Jay Jin,[2] Gerald W. Volcheck,[2] Suzanne M. Norby.[1] *[1]Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [2]Div of Allergic Diseases, Mayo Clinic, Rochester, MN.*

Introduction: Thiazide and loop diuretics with the exception of ethacrynic acid contain a sulfonamide moiety that can cause hypersensitivity reactions. While sulfonamide sensitive patients can take ethacrynic acid safely, volume management becomes challenging when ethacrynic acid is not tolerated.

Case Description: A 58-year-old male with systolic heart failure and chronic kidney disease stage IIIb developed a maculopapular skin rash and pruritus while taking furosemide. Skin biopsy showed subacute dermatitis with eosinophils compatible with drug reaction. A trial off his medications revealed furosemide as the probable cause of the rash. With two attempts at using ethacrynic acid, severe diarrhea occurred. Trials of sulfonamide-containing bumetanide, torsemide, hydrochlorothiazide and metolazone all resulted in rash. Ten days after stopping all diuretics, he was hospitalized for decompensated heart failure and underwent ultrafiltration. Repeat skin biopsy ruled out vasculitis, lichenoid tissue reaction and immunobullous disorders. During the next week, rash, pruritus and dyspnea resolved. Furosemide desensitization procedure was performed as outlined below without recurrence of skin rash. He was dismissed from hospital on furosemide 40 mg BID.

Discussion: Sulfonamide hypersensitivity is a clinical diagnosis with a variety of presentations, from limited skin reactions to life threatening anaphylaxis. Providers need to be aware of the possibility of cross reactivity due to the sulfonamide moiety present in many diuretics. Although desensitization is usually done for immediate type hypersensitivity, it is also reported to be successful in cases of delayed type hypersensitivity. Desensitization is a potential option when treating patients with diuretic intolerance due to sulfonamide hypersensitivity.

Oral Furosemide Desensitization (15 minutes between each dose)
Using furosemide 0.1 mg/ml:
Dose 1: 0.05 ml = 0.005 mg
Dose 2: 0.1 ml = 0.01 mg
Dose 3: 0.3 ml = 0.03 mg
Dose 4: 1 ml = 0.1 mg
Using furosemide 1 mg/ml:
Dose 5: 0.1 ml = 0.1 mg
Dose 6: 0.3 ml = 0.3 mg
Dose 7: 1 ml = 1 mg
Using furosemide 10 mg/ml:
Dose 8: 0.1 ml = 1 mg
Dose 9: 0.3 ml = 3 mg
Dose 10: 1 ml = 10 mg
Dose 11: 2 ml = 20 mg
Dose 12: 4 ml = 40 mg

SA-PO013

Infection in the Transplanted Kidney: TB or Not TB?
Megha Salani, Manish Anand, Mark Lusco, Beatrice P. Concepcion, Paul Persad. *Vanderbilt Univ Medical Center.*

Introduction: Solid organ recipients with latent tuberculosis infection (LTBI) are at increased risk for TB reactivation. These patients can have variable presentations, commonly with pulmonary, lymph node, and/or genitourinary tract involvement. We present a unique case of TB reactivation limited to the renal allograft.

Case Description: A 38 year old Indonesian female with ESRD due to IgA nephropathy underwent a deceased donor kidney transplant in 1/2015. Immediately post-transplant, she was found to have an LTBI and was treated with 9 months of isoniazid (INH). In 11/15, she presented with fever, allograft pain, and headaches. These symptoms persisted despite the use of broad-spectrum antibiotics. Initial blood and urine cultures were negative. Creatinine increased over the hospital course. The patient eventually underwent evaluation with a PET scan, which demonstrated hypermetabolic activity in the renal allograft. Kidney biopsy was performed and revealed diffuse multi-focal necrotizing granulomatous interstitial nephritis with a diffuse pleomorphic interstitial infiltrate. Bacterial, fungal, and mycobacterial stains, PCR, and cultures from the biopsy were negative. Adenovirus was detected but the pattern of granulomas was not consistent with adenovirus. Due to a high suspicion of TB based on histopathology, the patient was started on empiric INH, rifabutin, ethambutol, pyrazinamide, and moxifloxacin. After one week of therapy, her fevers resolved and her creatinine returned to baseline. She has completed 6 months of treatment and is currently without evidence of disease.

Discussion: Solid organ transplant recipients more commonly have extrapulmonary and disseminated TB than the general population. Our patient had a unique presentation limited to her renal allograft but was ultimately diagnosed with TB reactivation based on her history, histopathology on biopsy, and response to therapy. Given the low sensitivites of mycobacterial assays, a high index of suspicion for TB is warranted in patients with risk factors despite negative cultures or PCR. Particularly, the finding of necrotizing granulomas in a patient with prior TB exposure should prompt consideration of empiric TB treatment.

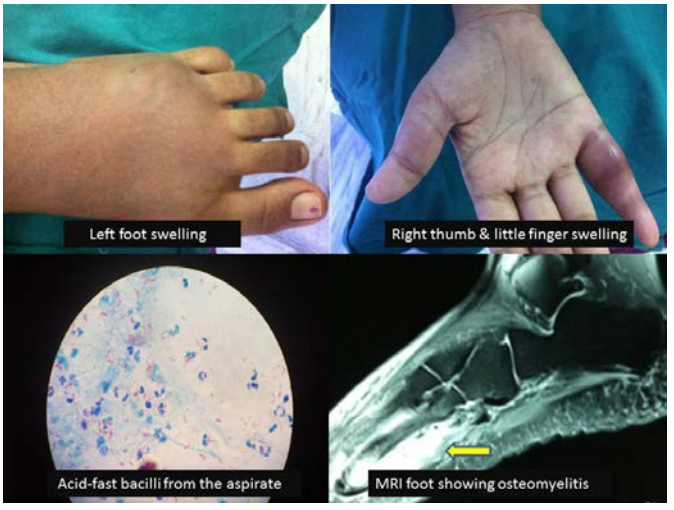
SA-PO014

Multi-Focal Tuberculous Osteomyelitis in a Renal Transplant Recipient
Hari Krishna Reddy Mogili,[1] Boju Sangeetha Lakshmi,[1] Anil Kumar Cheni Venkata,[1] R. Ram,[1] V. Siva Kumar,[1] Abhilash Koratala.[2] *[1]Sri Venkateswara Inst of Medical Sciences, India; [2]Univ of Florida.*

Introduction: Tubercular osteomyelitis, an uncommon form of extra-pulmonary tuberculosis (EPT), accounts for 1- 2% of all cases of tuberculosis (TB) and 10% cases of EPT. Spine is the most common location of skeletal TB accounting for ~50% cases. Multifocal tuberculous osteomyelitis with involvement of metatarsals and phalanges is extremely rare. Herein, we report a case of metatarsal and pharyngeal tubercular osteomyelitis in a kidney transplant recipient.

Case Description: A 26 year old Asian-Indian female presented to our institution for painful swelling in the left foot for ~10 days. She has history of End stage renal disease secondary to Lupus Nephritis and underwent deceased donor renal transplantation 3 months prior to presentation. At the time of transplant, she got Basiliximab induction and currently maintained on Tacrolimus 0.75mg bid, Mycophenolate mofetil 1000mg bid and Prednisone

17.5 mg/day. MRI of the foot showed osteomyelitis of second metatarsal with overlying abscess. Needle aspiration of the abscess revealed numerous acid-fast bacilli (AFB) with positive Mycobacterium TB polymerase chain reaction. 3 days later, she developed painful swelling of the right thumb and little finger and aspiration showed AFB. We started her on rifampicin-free anti-TB therapy and she responded well with clinical improvement over next two weeks.Pertinent findings are shown in the figure.



Discussion: Patients with skeletal TB usually present insidiously without systemic signs such as fever, night sweats, toxicity or extreme weakness. This condition may mimic malignancy, both clinically and radiographically. It's prudent for clinicians to consider this differential in immunocompromised patients presenting with long-term musculoskeletal pain especially those travelling from or transplanted in TB-Endemic countries.

SA-PO015

Emphysematous Cystitis in a Renal Transplant Recipient Don Henry Esprit, Abhilash Koratala, Michael Casey, Alfonso Santos, Shehzad Rehman, Karl L. Womer. *Nephrology, Hypertension and Renal Transplantation, Univ of Florida.*

Introduction: Emphysematous cystitis (EC) is a rare, but severe manifestation of urinary tract infection (UTI) characterized by spontaneous gas formation in the bladder lumen and bladder wall. Diabetes is the most common predisposing factor followed by neurogenic bladder and chronic bladder outlet obstruction. We report a case of EC in a kidney-pancreas transplant recipient on immunosuppressive therapy (IS) who is currently not a diabetic.

Case Description: 57 year old male with Diabetes mellitus type I, hypertension and ESRD status post combined Kidney-pancreas transplant 10 years ago presented with suprapubic pain, dysuria, and hematuria for 3 days. His maintenance IS included tacrolimus 6 mg bid, mycophenolate 750 mg bid and prednisone 10 mg daily. No fever. Labs showed hemoglobin 11.5 g/dL, WBC 9200 cells/cmm with 72.2% neutrophils. Serum creatinine was 1.2 mg/dl.Urinalysis showed hematuria and pyuria, urine culture revealed > 100,000 CFU/mL of Klebsiella pneumoniae. CT scan showed distended urinary bladder with abnormal urothelial enhancement and multiple foci of air in the bladder wall, suggestive of EC. Renal allograft was unremarkable and native kidneys were atrophic. Cystoscopy showed diffuse submucosal emphysematous lesions. He was treated with intravenous antibiotics and made a full recovery.

Discussion: EC is caused by gas-forming bacteria and fungi with the most common organism being E.coli. Patients usually present with symptoms of bladder irritation. Pneumaturia, if present, is highly suggestive of EC. CT scan is a better test to delineate the extent of the disease and patients usually respond to antibiotic therapy.EC should be considered in immunosuppressed patients and those with other predisposing conditions presenting with lower UTI symptoms to avoid delayed diagnosis which may put them at risk for life threatening infections and bladder rupture.

SA-PO016

Cerebral Lymphomatoid Granulomatosis (LYG) Treated Effectively with Rituximab in a Simultaneous Pancreas-Kidney (SPK) Transplant Patient Faisal Khaled Alhomayani, Muhammad A. Bukhari, David C. Holland, M. Khaled Shamseddin. *Nephrology Div, Queen's Univ, Kingston, ON, Canada.*

Introduction: Lymphomatoid granulomatosis (LYG) is a rare multisystem angiocentric B-lineage lymphoproliferative disease with significant malignant potential and mortality, affecting primarily immunocompromised patients . A 51 year-old female presented with a two-day history of headache, and vomiting. She had a history of type I diabetes, end stage renal disease, and SPK transplantation in 2004 (CMV: Donor negative/Recipient negative; EBV: Donor negative/Recipient positive), with normal function of both grafts. She had been induced with basiliximab then maintained on mycophenolate mofetil and tacrolimus. Post transplant course was uneventful, without any complication. Physical examination was unremarkable. investigations: CBC, electrolytes, creatinine, urea,LFT, INR, PTT were unremarkable. An enhanced MRI head showed seven ring-enhancing brain lesions. CT chest, abdomen and pelvis were unremarkable. The mycophenolate was tapered off, tacrolimus was reduced and prednisone introduced. The patient was diagnosed with LYG based on cerebral biopsy. With switching tacrolimus to sirolimus combined with 4 weekly doses of IV rituximab, complete resolution of 5/7 lesions occurred while the other lesions decreased significantly in size on MRI one-month post rituximab. She is clinically well with stable both graft functions. Her Epstein-Barr virus (EBV) viral load fell from 14,990 copies/ml to 0 at the cessation of rituximab. Post-transplant lymphoproliferative disease (PTLD) is the worst complication of solid organ transplantation occurring in 0.5-1.9% of patients . LYG is rarer than PTLD in transplant patients: both diseases may be triggered by EBV. Literature review identified seven cases of LYG in renal transplant patients. To our knowledge, this is the second report of successfully rituximab-treated cerebral LYG; the other being a renal transplant recipient with a durable (>4 years) complete remission of LYG.

Funding: Clinical Revenue Support

SA-PO017

Acute Posttransplant aHUS due to a Homozygous Deletion of CFHR1/CFHR3 with CFH-Autoantibodies Managed by a CNI-Free Regimen with Belatacept and Eculizumab Johannes Muench, Anette Bachmann, Christof Mayer, Tom H. Lindner, Jan Halbritter. *Internal Medicine, Div of Nephrology, Univ of Leipzig, Leipzig, Germany.*

Introduction: Acute renal graft failure may clinically present as atypical hemolytic uremic syndrome (aHUS), resulting from excessive activation of the complement cascade. Mutations of the complement coding genes predispose for development of aHUS. "Second hits" (e.g. drugs, pregnancy) commonly trigger the full-blown clinical picture. As calcineurin inhibitors (CNI) are considered as one of these potential triggers, CNI-free regimens would be favorable for avoidance of aHUS manifestation and long-term toxicity. However, there is little experience regarding management of posttransplant aHUS and adequate long-term immunosuppression in these patients.

Case Description: A 58-year old Caucasian female (ESRD of unknown origin) developed acute renal graft failure within days after transplantation, which clinically presented as aHUS (hemolytic anemia, thrombocytopenia, glomerular thrombotic microangiopathy). While complement anaylsis revealed autoantibodies against complement factor H (CFH), genetic testing yielded a concomitant homozygous deletion of *CFH-related 1* (*CFHR1*) and *CFHR3*. Therapy consisted of plasmapheresis, eculizumab (C5-inhibitor), and belatacept (blocker of T-cell co-stimulation) instead of CNI. Subsequently, renal graft function partially recovered (eGFR of 32 ml/min) and hematologic remission (absence of hemolysis) was observed for 18-month of follow up under continued administration of belatacept, eculizumab, mycophenolate mofetil (MMF) and low dose prednisolone.

Discussion: This case describes successful management of posttransplant aHUS using an individualized CNI-free immunosuppressive regimen based on eculizumab and belatacept. Especially in patients with ESRD of unknown origin, (preemptive) recognition of predisposing risk factors, such as complement abnormalities, are crucial for initiation of tailored immunosuppressive regimens and better long-term renal graft survival.

SA-PO018

Fever in a Transplant Patient: Is It Always Infection? Abhilash Koratala, Volodymyr Chornyy, Alfonso Santos. *Univ of Florida.*

Introduction: Immune reconstitution inflammatory syndrome (IRIS), first recognized in HIV patients during HAART is an intense inflammatory response from recovery of the immune system leading to deterioration in clinical status. We report a unique case of IRIS in a non-HIV, immunocompromised renal transplant recipient due to interaction between rifampin and tacrolimus (FK).

Case Description: 74 year old Asian male with history of orthotopic liver transplant 4 years ago for Hep C cirrhosis, ESRD due to calcineurin inhibitor toxicity and status post deceased donor kidney transplant a year ago was transferred to our institution for management of disseminated TB. He was on RIPE (rifampin, isoniazid, pyrazinamide, ethambutol) therapy initiated at the originating hospital. Due to abdominal pain, his pyrazinamide was switched to levofloxacin with improvement of the symptom. Serum FK level at presentation was undetectable likely due to its accelerated metabolism from interaction with rifampin. He later developed fever (Tmax 104.4F), tachycardia, tachypnea and mild hypotension. There were no localizing findings or imaging evidence suggestive of infectious source. C reactive protein (CRP) was markedly elevated. He was started on broad spectrum antibiotics after obtaining cultures. Blood and urine cultures, serology for CMV, Histoplasma, Cryptococcus were negative. He was diagnosed with IRIS, antibiotics

were discontinued, treated with iv methylprednisolone and FK dose adjusted to achieve goal levels. He responded well and symptoms resolved. CRP trended down rapidly. His IRIS was probably due to immune system reactivation in the setting of improving infection and low FK levels.

Discussion: With the increasing use immunosuppressive and immunomodulatory agents with potent effects on the immune system in transplant patients, it is important for physicians of various specialties caring for these patients to be familiar with these drugs and their potential interactions. Rifampin is an inducer of CYP3A4 and P-glycoprotein in the liver and small bowel leading to increased metabolism of FK which may predispose to IRIS in patients with resolving TB. Timely recognition and appropriate treatment of IRIS is critical for prevention of severe complications including graft loss.

SA-PO019

A Novel Form of Retroviral Associated Proliferative Glomerulonephritis? Sumoyee Basu, Sanjana Gupta, Paul Bass, Ian Proctor, Sally Hamour, Alan D. Salama. *UCL Centre for Nephrology, Royal Free Campus, London, United Kingdom.*

Introduction: Numerous HIV-1 associated nephropathies have been described including HIVAN, HIVICK and diffuse infiltrative lymphocytosis syndrome (DILS) characterised by CD8+ interstitial deposits. Our case does not fall into any of these categories.

Case Description: A 41 year old Brazilian man presented with fever, diarrhoea, vomiting and visible haematuria. Past medical history included treated syphilis and schistosomiasis. He was newly diagnosed with HIV-1 with a viral load of $0.65x10^6$ copies/ml and CD4 count of $0.32x10^9$/L. Creatinine was 340 mcmol/l without a previous baseline rising rapidly to 852. He had proteinuria of 117 mg/mmol without leucocyturia. No other infectious agents were identified including Zika, Chikungunya, Nipah & BK viruses. Virology revealed successful hepatitis B immunisation, previous hepatitis A and hepatitis C negative. Renal biopsy showed a diffuse proliferative glomerulonephritis with neutrophils and sparse microthrombi. Alongside high anti-streptolysin titre, this prompted amoxicillin and prednisolone which had no effect on renal function.

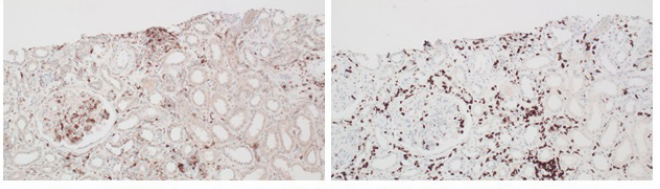


Figure 1: CD4+ glomerular and patchy tubular infiltrate (left) vs CD8+ stain (right)

Further review revealed hypercellular glomeruli with tuft inflammatory cells and no evidence of collapsing glomerulopathy. The glomerular and patchy tubular infiltrate was of predominantly CD3+ CD4+ but not CD8+ lymphocytes. There were no definite immune complexes on immunohistochemistry. Electron microscopy revealed tubuloreticular inclusions but no electron dense deposits. p24 antigen stain was negative. Commencement of high active retroviral therapy elicited viral load <40 copies/ml and a concomitant fall in creatinine and urine protein excretion.

Discussion: We believe this represents a novel form of HIV-1 associated nephropathy characterised by predominantly glomerular infiltration with CD4+ cells without immune complex deposition. We term this a 'diffuse glomerular lymphocytosis syndrome'.

SA-PO020

Rethinking Peritubular Capillary Basement Membrane Multilayering in Renal Transplant Histopathology: A Case Report Diana Maria Lopategui,[3] Elena N. Levtchenko,[1] Evelyne Lerut,[2] Noel Knops.[1] *[1]Pediatric Nephrology and Solid Organ Transplantation, UZ Leuven, Leuven, Belgium; [2]Morphology and Molecular Pathology, UZ Leuven, Leuven, Belgium; [3]Univ of Barcelona, Barcelona, Spain.*

Introduction: Severe multilayering of the peritubular capillary basement membranes (ML) in kidney allografts is considered an ultra-structural hallmark of chronic antibody mediated rejection (CAMR).We describe the findings in a young man with underlying focal segmental glomerulosclerosis who underwent a living-related donor transplant procedure, questioning the specificity of this phenomenon.

Case Description: The patient received a kidney from his mother, whose donor screening was unremarkable. He developed nephrotic-range proteinuria shortly after the procedure. The post-transplant biopsies performed within the first 6 months demonstrated ML (5-6 layers), suggestive for the onset of CAMR. Since there were no other criteria for CAMR, electron microscopy was performed on the baseline biopsy, and also demonstrated ML. Seven years later the donor still has no signs of kidney disease.

A review of the literature suggest this case to be the first description of ML in a person without apparent features of kidney disease. ML is believed to result from repeated endothelial injury and is also described in native kidney disease (lupus nephritis and thrombotic microangiopathy). The severity of ML is linked to the type and duration of endothelial distress. The presence of high-grade ML (≥7) in an allograft is considered highly suggestive for CAMR; the number of layers appears to increase with time after transplantation. In contrast, more than 5 layers are uncommon in native kidney disease. Additional clinical and genetic testing (including genes expressed in the glomerular and tubular basement membrane) could not reveal underlying kidney disease in the donor.

Discussion: We conclude that ML in the setting of renal transplantation is not specific for CAMR, can exist in several kidney diseases and even in asymptomatic donors. Further research is needed to determine the prevalence of ML in allograft biopsies at baseline and in non-allograft renal biopsies, which will enable us to better determine its value for renal histopathology.

SA-PO021

Prolonged Delayed Graft Function for Nine Months due to Renal Transplant Venous Hypertension Irfan Ahmed Moinuddin, Gaurav Gupta, Dhiren Kumar. *Nephrology, VCU Medical Center, Richmond, VA.*

Introduction: Delayed graft function (DGF) is defined as the need for dialysis within the first week of kidney transplantation (KTxp). The longest reported duration of DGF in literature is 4 months (Schulz et al, Am J Case Rep. 2016). Renal transplant venous hypertension has been reported in one case (McArthur et al, J Ultrasound Med. 2011) as the etiology of impaired allograft function although DGF has not been reported.

Case Description: We report the case of a highly sensitized (PRA=83%) thirty-nine year old female who was on anti-coagulation due to a history of access clots. She received a flow crossmatch positive second deceased donor KTxp in November 2013. She had a right thigh arterio-venous fistula (AVF) distal to the KTxp anastomosis. She had initial DGF for which a transplant biopsy was performed at 12 days post-txp. This biopsy showed antibody-mediated rejection. She was treated with plasmapheresis, rituximab, bortezomib and eculizumab. Her serologic and histologic evaluation six weeks later demonstrated absence of donor-specific antibodies and complete resolution of rejection. Despite this she remained hemodialysis dependent. Two additional biopsies over the next 2 months remained unrevealing. Molecular profile of her biopsy (MMDx, Alberta, Canada) demonstrated acute kidney injury but no rejection or fibrosis. Serial ultrasound imaging demonstrated increasing venous collaterization around the ktxp. A subsequent procedure to declot her thigh AVF revealed a thrombosed inferior vena cava. This was partially recanalized. Overtime her urine output started improving. It was felt that her DGF was related to renal venous hypertension due to IVC thrombosis as well as arterialization of the renal vein due to high venous return from her AVF. AVF ligation was considered but her renal function improved spontaneously and dialysis was discontinued at nine months post-transplant. Her most recent creatinine 30 months post-transplant is 1.7mg/dL.

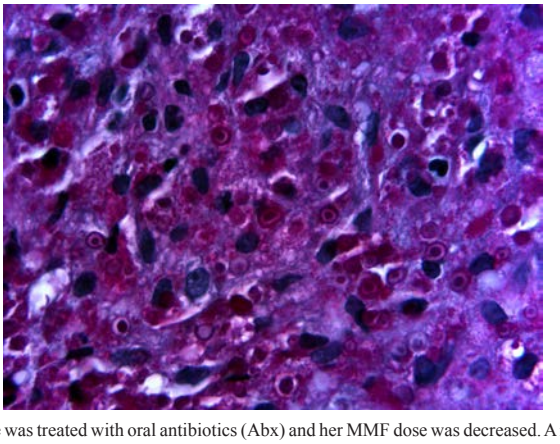
Discussion: Renal transplant venous hypertension should be considered in the rare case when other etiologies have been ruled out. The presence of a thigh graft on the side of kidney transplant or IVC thrombosis should particularly raise this concern.

SA-PO022

Renal Parenchymal Malacoplakia in an Asymptomatic Kidney Transplant Recipient Yvonne El Kassis,[1] Richard A. Fatica,[1] Leal C. Herlitz,[2] Andres G. Chiesa-Vottero,[2] Ziad S. Zaky.[1] *[1]Nephrology and Hypertension, Cleveland Clinic Foundation, Cleveland, OH; [2]Anatomic Pathology, Cleveland Clinic Foundation.*

Introduction: Malacoplakia (MCP) is a rare granulomatous inflammation thought to be secondary to impaired phagocytic activity of macrophages, leading to incomplete bacterial elimination. We report a case of MCP found incidentally on the 6-month protocol biopsy (PBx) of an asymptomatic kidney transplant recipient (KTR).

Case Description: The patient is a 55 year-old female with bipolar disorder and ESRD secondary to lithium toxicity, who underwent a cadaveric kidney transplant. She received Thymoglobulin for induction and Tacrolimus, Mycophenolate Mofetil (MMF) and prednisone for maintenance immunosuppression (IS). Her post-transplant course was notable for recurrent asymptomatic E.coli urinary tract infections (UTIs). A 6-month PBx revealed focal granulomatous inflammation with foamy macrophages and abundant cytoplasmic inclusions consistent with Michaelis-Gutmann bodies, characteristic of MCP.



She was treated with oral antibiotics (Abx) and her MMF dose was decreased. A repeat 1-year PBx showed no evidence of ongoing MCP but did have inflammation consistent with BANFF borderline changes. Her urine cultures (UCx) remained positive, prompting a new prolonged course of intravenous Abx.

Discussion: MCP has been described in states of IS, including organ transplantation. It has been most commonly associated with E.coli UTIs and presents with obstructive uropathy or lower urinary tract masses mimicking malignancy. Untreated infections can lead to graft

loss and salt wasting nephropathy. Treatment focuses on reduction of IS and prolonged Abx therapy. To our knowledge, this is the first case of MCP incidentally discovered in PBx, highlighting a unique presentation of this rare disease. While her repeat Bx was negative for MCP this may represent failure to sample a patchy process, as her UCx remains positive.

SA-PO023

Cloud-Based Connectivity Platform Allows for Remote Management of Automated Peritoneal Dialysis and Early Recognition of Catheter Dysfunction: First Swiss Experience Valérie Jotterand Drepper,[1] Pierre-Yves F. Martin,[1] James A. Sloand.[2] *[1]Nephrology, Geneva Univ Hospital, Geneva, Switzerland; [2]Renal Div, Baxter Healthcare Corporation, Deerfield, IL.*

Introduction: Incident peritoneal dialysis (PD) patients tend to encounter more technical problems in weeks following training. Remote patient management (RPM) has the potential to detect early issues, allowing intervention prior to development of more significant problems that might lead to emergency visits, hospitalization or technique failure.

Case Description: A 23-year-old ESRD patient required hospitalization for urgent start of renal replacement therapy. Because of prior non-adherence, a newly available automated peritoneal dialysis (APD) RPM system (Sharesource) with cloud-based connectivity was implemented. Post-APD training and on return home, the patient's treatment was both remotely observed and altered regularly. Pre-defined RPM threshold parameters were set to identify clinically relevant issues, including PD catheter drain times.

On initial home discharge, the RPM system revealed no dashboard flag alerts and normal PD cycle volume profiles (Fig1a). However, in ensuing days, red flag dashboard alerts heralded prolonged drain times (Fig1b) leading to an early diagnosis of and surgical repositioning for catheter displacement.

Post-PD catheter repositioning, drain times were again normal as indicated by disappearance of flag alerts and cycle volume profiles. Non-adherence with clinic visits recurred, however, the RPM platform confirmed patient compliance with daily PD treatment.

Discussion: RPM of APD patients with a two-way cloud-based connectivity platform allows for monitoring and adjustment of therapy, as well as early recognition and timely management of adverse clinical issues. Larger scale observational studies will determine the impact of RPM in APD technique survival and resource utilization.

SA-PO024

Refusal of Dialysis in End Stage Renal Disease Patients Residing in Skilled Nursing Facilities Farida Migally, William Luke Whittier, Sheri Korbet. *Nephrology, Rush Univ Medical Center, Chicago, IL.*

Introduction: The number of ESRD pts in skilled nursing facilities (SNF) continues to grow. These pts have more co-morbidities and higher mortality when compared to those not living in SNFs. SNF ESRD pts on hemodialysis (HD) undergo either conventional three times weekly (CHD)(on site or in-center) or shorter more frequent HD (DHD). DHD is utilized to allow pts to adhere to rehabilitation which may translate to improvement in functional status. When pts on HD enter a SNF that performs DHD, they are often switching from CHD to DHD. Our hypothesis is that when ESRD pts who are naïve to DHD enter into a SNF that offers DHD, adherence to the more frequent sessions is low due to refusals. This may result in inadequate HD over time and could adversely affect outcomes.

Case Description: Data from nine SNFs with on-site HD programs were retrospectively compared from May-Dec 2015. Five programs delivered CHD, defined as conventional 3xs weekly HD using Fresenius equipment targeting a KT/V of 1.2. Four programs delivered DHD, defined as four or five times weekly HD using the NxStage System One, targeting a weekly KT/V of 2.0. Pts were excluded if they had been on DHD prior to entering the SNF. Missed treatments due to refusals were defined as a pt missing the entire HD session (without it being rescheduled) while residing in the SNF. Statistical analysis was performed using Fischer exact test for categorical data and Mann–Whitney for continuous data. Data was reported as mean±standard deviation.

There were a total of 335 pts who underwent 11,043 HD treatments. 171 underwent DHD with 6,398 treatments and 164 underwent CHD with 5,005 treatments (p=0.074). Both groups had similar ages (DHD 70±11 yrs vs. CHD 71±12 yrs, p=0.426). Missed treatments due to refusals were higher in DHD compared to CHD (DHD, 40.6±42% vs. CHD, 11.4±28%, p<0.0001).

Discussion: In our experience with HD in the SNF, there was a significant increase in percentage of missed treatments due to patient refusals in DHD. This lack of adherence to the dialysis prescription could adversely affect outcomes.

SA-PO025

Care of Kidney Transplant Recipients in Syrian War Zones Kamel Hatahet,[1] Nada Alachkar,[2] Crystal A. Gadegbeku,[1] Sami Alasfar.[2] *[1]Temple Univ Hospital, Philadelphia, PA; [2]The John Hopkins Univ, Baltimore, MD.*

Introduction: Care of kidney transplant recipients is complex and requires an organized infrastructure.The current Syrian conflict has led to deterioration in medical care for these patients. The information on management and outcome of such patients in Syrian war zones is lacking.

Case Description: prospective obervational study of 138 kidney transplant recipients in the Syrian northwestern providences, which are greatly affected by the war. Data on the patients are collected during the patients' clinic visits to two physicians involved in their care.

Mean follow up is 1.5 years. Patients are seen every month if their transplant is within 6 months and every 2 months if their transplant >6 months old. Routine labs checked includes CBC, BMP, UA, and drug levels.

Clinical parameters	N=138
Mean age at transplantation (yr)	40 +/- 10.9
Gender (M)	77%
Cause of original kidney disease Diabetes Hypertension Glomerulonephritis Other/Unknown	 7% 21% 24% 48%
Donor's type Living related Living unrelated	 60% 40%
Immunosuppression Tacrolimus Cyclosporine	 51% 49%
Mean most recent Creatinine	1.35 ± 0.67
Mean most recent CSA level	254 ± 215
Mean most recent FK level	5.8 ± 1.9
Mean distance from clinic (KM)	36 ± 21
Mean time from clinic (Min)	49 ± 28
Rejection (n)	4
Graft loss (n)	0

Complicated cases are referred to one nephrologist in the area or discussed through social media means with nephrologists in the US. Major Barriers to care identified as following: 1-availability of the immunosuppressions; 2-Cost of drug monitoring, 3- Lack of security during transportation. 4- Fear of targeting doctors. 5- Limited medical staff and ancillary studies. 6-Time needed to obtain results of lab and imaging studies.

Discussion: Despite many barriers and poor infrastructure, teamwork between physicians in Syrian war zones, Syrian American Nephrologists, and humanitarian organizations has translated into a life saving support to the Syrian renal transplant patients. More sustained effort and financial aid is needed for optimal management of these patients.

SA-PO026

Extracorporeal Treatments to Enhance Dapsone Elimination: A Case Report Amelie Bernier-Jean,[1] Marc Ghannoum,[2] Monique Cormier,[2] Dave Brindamour,[1] Clement Deziel,[1] Josee Bouchard.[1] *[1]Hôpital du Sacré-Coeur de Montréal, Canada; [2]Hôpital Verdun, Canada.*

Introduction: Intentional dapsone intoxication can be life-threatening. There is very limited data on the effect of extracorporeal treatments (ECTRs) on dapsone elimination. We describe a case of severe dapsone toxicity and report clearance, quantification and half-life of dapsone and its metabolites with different ECTRs.

Case Description: A 23 year-old woman was admitted 2.5 hours after ingesting 2.2 g of dapsone. On admission, the patient complained of headache, and the physical exam was remarkable for cyanosis. She developed severe methemoglobinemia (39.9%) and showed signs of toxicity (hemodynamic instability and slow processing) despite multiple-activated charcoal, methylene blue, vasopressors, and endotracheal intubation. Continuous venovenous hemofiltration (CVVH) was then initiated for 5 hours, followed by intermittent hemodialysis with hemoperfusion (IHD-HP) for 4 hours, and CVVH for another 48 hours. The platelet count dropped three hours after IHD-HP (nadir was 32 X 10^9/L). The elimination half-life of dapsone was 2.0 hours during IHD-HP, and 14.2 hours during CVVH. Mean dapsone clearance with IHD was 62 ml/min and with CVVH, 22 ml/min. Renal clearance was 6ml/min. IHD removed 95.3 mg, and CVVH removed 67.8 mg over 3.8 hours. The sieving coefficient of dapsone was 0.24-0.30. No rebound occurred following ECTR cessation. The toxicokinetics of dapsone metabolites were also accelerated during ECTR. The patient was extubated after 3.5 days and discharged without sequelae after 7 days.

Discussion: Contrary to previous reports and despite its high protein binding, dapsone appears to be dialyzable due to improvements in dialysis filters and catheters. In addition, ECTRs can accelerate dapsone elimination compared to multiple-dose activated charcoal alone. Although we obtained a shorter elimination half-life by combining IHD and HP, it remains unclear if this benefit is worth the costs and the risk of severe thrombocytopenia compared to IHD alone. We suggest that IHD with or without HP be considered following massive dapsone ingestion with life-threatening manifestations and high methemoglobinemia levels.

SA-PO027

Recurrent Acute Hypotension with Initiation of Dialysis and Ventricular Interdependence Sumeet Munjal,[2] Asma Mursleen,[2] Alberto Morales.[1] *[1]Div of Cardiology, Univ of South Florida; [2]Div of Nephrology, Univ at Buffalo, NY.*

Introduction: Ventricular interdependence is the mechanism whereby right heart failure (RHF) can cause left heart dysfunction. The primer bolus used before initiating dialysis can lead to an acute right ventricular volume overload. We report a case where primer bolus lead to acute RHF causing mobilization of interventricular septum towards the left, reducing cardiac output and lead to recurrent severe hypotension and syncope.

Case Description: 44 yo AAF with history of ESRD, DM, Non-ischemic cardiomyopathy (EF 15%) s/p AICD, presented after an episode of syncope while on dialysis. Patient had similar episode 2 weeks back and was started on midodrine before dialysis. Work up showed gram negative bacteremia due to infected catheter and was treated for septic shock with fluids, pressors and antibiotics. Patient recovered from sepsis but became volume overload requiring daily dialysis. However with each dialysis, she would become acutely unresponsive and apneic within 4-6 minutes after initiating dialysis causing early termination of sessions. Various interventions including albumin, lowering dialysate temperature and step sodium profiling was used to avoid hypotension, without any success. EEG negative for any seizure. Patient underwent TEE during dialysis which revealed worsening righ ventricular dilatation, severe hypokinesis and septal bouncing within minutes after starting dialysis. This was accompanied with drop in SBP from 128 to 78mm Hg. The septum shifted to the left consistent with right ventricle volume overload, ventricular interdependence accompanied with severe hypotensive. Hemodialysis was stopped and patient was given neosynephrine with improvement in BP. We concluded that primer bolus was sufficient to cause ventricular interdependence leading to severe hypotension. Dialysis was reinitiated but primer bolus was purged, patient successfully completed dialysis without any hypotension or syncope.

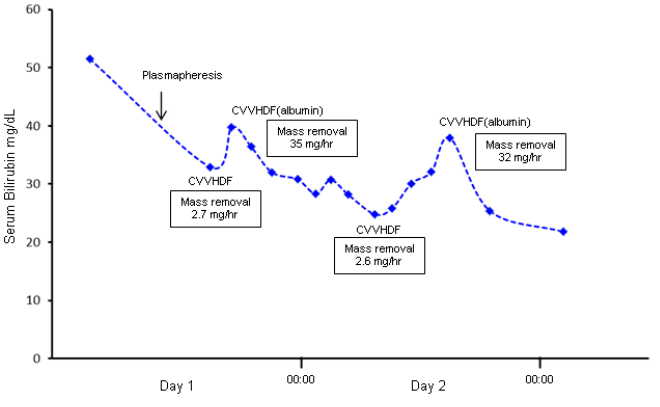
Discussion: Our case illustrates that 300cc of primer bolus is enough to cause acute RHF with subsequent LHF, causing recurrent severe hypotension and syncope. Simple purging of primer bolus allowed the patient to undergo dialysis repeatedly without any complications.

SA-PO028

Single-Pass Albumin Dialysis during Continuous Renal Replacement Therapy for Severe Hyperbilirubinemia Nathan T. Beins,[1] Marita Thompson,[2] Darcy K. Weidemann,[1] Rebecca M. Greene,[2] Uttam Garg,[3] Vimal Chadha.[1] *[1]Nephrology, Children's Mercy Hospital and Clinics, Kansas City, MO; [2]Critical Care Medicine, Children's Mercy Hospital and Clinics, Kansas City, MO; [3]Pathology and Laboratory Medicine, Children's Mercy Hospital and Clinics, Kansas City, MO.*

Introduction: Severe hyperbilirubinemia (SHB) is uncommon in critically ill children with multi-organ dysfunction syndrome (MODS). SHB can be a surrogate marker of hepatic failure and is associated with increased mortality. Furthermore, SHB can interfere with laboratory assays and near-infrared spectroscopic (NIRS) monitoring. While CRRT is commonly utilized for the management of acute kidney injury and fluid/electrolyte issues in children, it does not clear serum bilirubin. Molecular adsorbent recirculating system (MARS) has been successfully used for the management of hepatic failure, but is not FDA approved for SHB, and is unavailable in most centers. There are few case reports of single-pass albumin dialysis (SPAD) enhancing bilirubin clearance in children.

Case Description: A 7 month old male infant presented with MODS (underlying disease - autoimmune hemolytic anemia and hemophagocytic histiolymphocytosis) who developed SHB (peak total serum bilirubin 51.5 mg/dL). While he received CRRT and intermittent plasmapheresis, the serum bilirubin levels continued to remain significantly elevated. We performed SPAD (1.85% albumin in dialysate bag) for two consecutive days. Serum and dialysate bilirubin concentrations were monitored and are shown below:



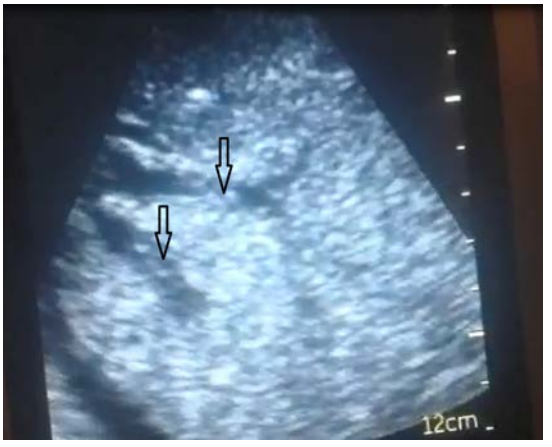
Discussion: Our experience shows >10-fold increase in bilirubin clearance with SPAD during CRRT. While SPAD is effective in decreasing serum bilirubin and possibly other protein-bound toxins, its impact on removal of nutrients and medications is unknown and needs to be carefully explored. Large scale studies are needed to see if SPAD can improve patient outcomes.

SA-PO029

Using Ultrasound to Detect Non-Occlusive Mesenteric Ischemia in a Hemodialysis Patient Sean Verma,[1] Alfredo M. Peguero,[2] Jorge A. Lamarche,[2] Craig S. Courville,[2] Marina Antar-Shultz,[2] Mohamed M. Taha.[2] *[1]Internal Medicine, Univ of South Florida; [2]Nephrology, James A. Haley Veterans' Hospital.*

Introduction: Non-occlusive mesenteric ischemia (NOMI) is a rare disorder seen in the hemodialysis (HD) population that carries a high mortality rate. The risk for NOMI in HD patients is estimated to be 44 times the risk of the average population. Ultrasound (US) is an adjunct diagnostic tool to diagnose NOMI in an HD patient.

Case Description: A 62-year-old woman with ESRD, malnourishment, and hypertension was admitted for failure to thrive. Vitals showed tachycardia and blood pressure 116/70 mmHg. Physical exam revealed cachexia and anasarca. Labs showed albumin 1.2 g/dL. She had prolonged intra and post dialytic hypotension associated with abdominal pain. A bedside US showed a collapsed inferior vena cava and gas (arrows) in the portal vein.



Also, extraluminal fluid accumulation, thinning of the bowel wall, and ileus were seen on US. Labs showed leukocytosis 10.99 10^9/L, lactic acid 3.5 mg/dL, and anion gap metabolic acidosis. CT scan showed portal venous gas and pneumatosis of the gastric fundus with patency of the mesenteric arteries suggestive of NOMI. She was not felt to be a surgical candidate due to her comorbidities. She was treated with albumin, fluids, and empiric antibiotics but expired 4 days later.

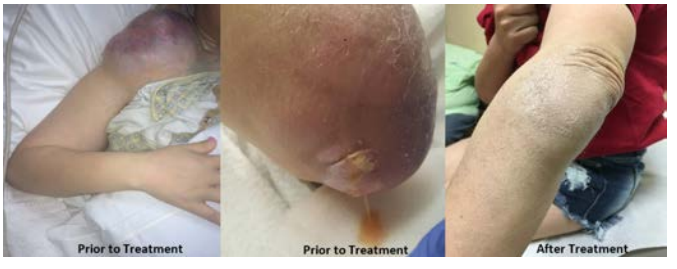
Discussion: Common NOMI findings include abdominal pain, fever, metabolic acidosis, and leukocytosis following intradialytic hypotension. Portal vein gas and/or mesenteric gas are ominous but late signs that are most consistent with mesenteric ischemia. US hasn't conventionally been used to detect NOMI and evaluate for portomesenteric gas, as CT scan has been the imaging of choice. However, bedside US is quicker and comparable in sensitivity. US with clinical suspicion for NOMI in ESRD patients may allow for a more prompt diagnosis via earlier CT scan ordering, and earlier initiation of treatment.

SA-PO030

An Extreme Case of Tumoral Calcinosis in End Stage Renal Disease Sean Verma,[1] Tambi Jarmi.[2] *[1]Internal Medicine, Univ of South Florida, Tampa, FL; [2]Nephrology, Univ of South Florida, Tampa, FL.*

Introduction: Tumoral Calcinosis is a rare and severe sequela of end stage renal disease (ESRD) patients on hemodialysis (HD) in which calcium salt deposits occur in periarticular soft tissue, typically around large joints such as the shoulder, elbow, and wrist.

Case Description: A 19-year-old woman with ESRD due to hemolytic uremic syndrome on HD presented for right shoulder and left elbow masses. She had a living related donor transplant at age fourteen with rejection two years later. Physical exam revealed right shoulder mass with overlying telangiectasias and left elbow mass with seropurulent, gritty drainage. Labs were notable for calcium 10.5 mg/dL, phosphorus 6.3 mg/dL, and intact parathyroid hormone 955 pg/mL. Right shoulder MRI revealed a periarticular heterogeneous mass with cystic and calcific components, consistent with tumoral calcinosis. Given the extent of her disease, the patient underwent parathyroidectomy for tumoral calcinosis due to tertiary hyperparathyroidism. In addition, she was treated with HD with low-calcium dialysate for five days per week. Upon two month follow up her calcium masses had decreased significantly in size.



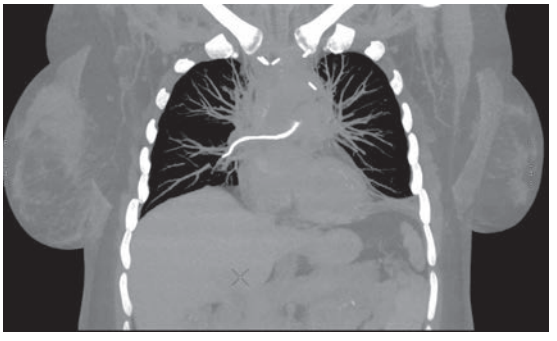
Discussion: Tumoral calcinosis tends to occur more frequently in patients with high calcium-phosphate product, secondary/tertiary hyperparathyroidism, or hypervitaminosis D. Treatment involves intensification of HD with low-calcium dialysate, non-calcium containing phosphate binders, parathyroidectomy for secondary or tertiary hyperparathyroidism, and possible surgical removal of the calcium depositions. Surgical excision of the masses has often shown to be ineffective long term as they are prone to recur, unless biochemical correction of calcium-phosphate product can be achieved. Tumoral calcinosis is difficult to treat but has been shown to resolve after successful kidney transplantation.

SA-PO031

Apparent Picture of Dialysis Catheter in Chest CT Mariusz Kusztal, Tomasz Golebiowski, Krzysztof Letachowicz, Magdalena Krajewska, Marian Klinger. *Nephrology and Transplantation Medicine, Wroclaw Medical Univ, Wroclaw, Poland.*

Introduction: Unintentionally leaving dialysis catheter in the central vein is almost impossible. Here we present the case of a female patient with a history of dialysis catheter placement when chest CT scans strongly suggested migrated portion of central venous catheter (CVC).

Case Description: 44yo female with a 15 y history of SLE with poststeroidal osteoporosis who underwent plasmapheresis due to paresis. A week later the patient was admitted to the neurosurgery clinic for spinal fusion with vertebroplasty (polymethylmethacrylate cement injection) for osteoporotic fractures (L3). Subsequently, she became pyrexial and started cough. After admission to the pulmonology clinic, chest CT revealed a small lung abscess and a "portion of dialysis catheter".



After a failed endovascular attempt to retrieve the catheter, the patient was prepared for thoracotomy. Because the nephrologist was sure of the complete catheter removal initially, an alternative explanation of the findings was proposed. Thorough differentials and scrutiny in anamnesis (i.e. review of various chest CT scans from patients with implanted CVC) revealed that the catheter-like picture was in fact cement embolism in the right pulmonary artery – a complication of vertebroplasty occuring in 10-60% of such cases. Features distinguishing CVC from cement on CT scans are as follows: hollow and equal outline of CVC (usual diameter range of CVC 3.8-6mm). Based on measurements taken from 10 other patients with CVC in the chest, mean Hounsfield units were 1309 (range 1000-1585). Cement embolism in this case had an unequal outline (3.8-4.5 mm in diameter) and 1880 (1670-2020) Hounsfield units.

Discussion: This case is notable because two independent radiologist suggested catheter left in the chest as its implantation was reported in medical files, however cement embolism with high glare was the case.

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SA-PO032

Encapsulating Peritoneal Sclerosis in Peritoneal Dialysis with Kidney Transplant Arun Kottarathara,[1] Matthew Abramson,[2] Yezina T. Nigatu,[1] Nand K. Wadhwa.[1] *[1]Dept of Nephrology, Stony Brook Univ Medical Center; [2]Dept of Medicine, Stony Brook Univ Medical Center.*

Introduction: Encapsulating peritoneal sclerosis (EPS) is a complication of long term chronic peritoneal dialysis (PD) following discontinuation of PD. We present two cases of EPS occurring following kidney allograft receiving steroid free immunosuppressive protocol.

Case Description: Case 1: A 41 year-old woman with End Stage Renal Disease (ESRD) secondary to hypertensive nephrosclerosis, on PD for 10 years, received a living related kidney allograft. 10 days post transplant (PT) S Cr was 1.3 mg/dl. PD catheter was removed 1 week PT. She developed nausea, vomiting and diffuse abdominal pain, and physical examination unremarkable. CT abdomen showed dilated small bowels and treated conservatively. S Cr was 0.8 mg/dl. 3 days later, she was readmitted with nausea, vomiting and abdominal pain. CT abdomen revealed dilated small bowels. GI follow through showed atonic small bowels. 23 days PT, she underwent exploratory laparotomy which revealed extensive brownish yellow peritoneum encapsulating entire bowel. She received IV prednisolone followed by oral prednisone in addition to tacrolimus and mycophenolic acid with complete resolution of symptoms in 4 weeks. She is prednisone 5 mg daily since and has been symptom free for 8 years. **Case 2:** A 48 year-old woman with ESRD of unknown etiology, on PD for 6 years received a deceased kidney allograft. 3 days PT, her S Cr was 3.0 mg/dl. 11 days PT, she had recurrent nausea, vomiting and diarrhea. CT abdomen revealed distended small bowels encased in fibrotic inflammatory membrane suggestive of abdominal cocoon**.** She needed nasogastric decompression and IV prednisolone, transitioned to oral prednisone. Prednisone 5 mg was continued with mycophenolic acid and tacrolimus. She has been symptom free for 13 months.

Discussion: Both patients had excellent outcomes with bowel rest and steroids. Our institution's transplant protocol involves alemtuzumab induction and steroid withdrawal within 3 days post-transplant. We suggest that PD patients undergoing renal transplant remain on immunosuppressive regimen including steroids to prevent EPS.

SA-PO033

Calciphylaxis after Acute Kidney Injury: A Mysterious Case of Painful Skin Necrosis Elizabeth Upton, Vimal K. Derebail. *UNC Kidney Center, Univ of North Carolina, Chapel Hill, NC.*

Introduction: We describe a case of calciphylaxis in an individual without end-stage renal disease (ESRD) who had recovered from an episode of acute kidney injury (AKI).

Case Description: A 43-year old female with history of prior Roux-en-Y gastric bypass surgery, non-alcoholic steatohepatitis, and former alcohol abuse presented with 8 weeks of skin necrosis on her abdomen, buttocks, and thighs. Three months prior to evaluation, she was admitted for sepsis complicated by liver and kidney failure not requiring dialysis. Admission labs included creatinine of 0.6 mg/dL, AST 15 U/L, ALT 25 U/L, PTH 44 pg/mL, and calcium phosphate product of 57. Skin biopsy demonstrated calcium deposition in the subcutaneous tissue and vessels, dermal and subcutaneous fat necrosis, and neutrophil and lymphocyte infiltration, consistent with calciphylaxis. Hypercoagulable, autoimmune, and infectious workups were negative. After therapy with intravenous sodium thiosulfate 25 g thrice weekly, oral sevelamer, and topical silver sulfadiazine, she had dramatic improvement over 6 months.

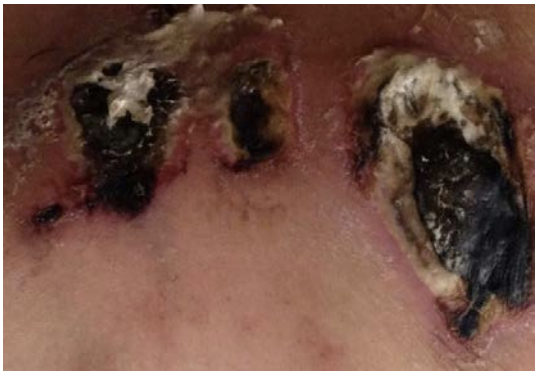


Figure 1: Necrotic skin lesion secondary to calciphylaxis.

Discussion: Calciphylaxis occurs rarely in patients without ESRD with other risk factors including female sex, obesity, primary hyperparathyroidism, malignancy, alcoholic liver disease, corticosteroid use, protein C/S deficiency, or a history of a Roux-en-Y surgery. Defects in vascular calcification pathways such as fetuin-A and matrix Gla protein and increased serum levels of matrix metalloproteinases contribute to calciphylaxis. Patients with underlying liver disease with AKI may be especially susceptible. Prognosis remains poor with mortality approaching 50%. Further studies are needed to elucidate the pathogenesis of all forms of calciphylaxis to develop specific treatments.

SA-PO034

Atypical Mycobacterial Peritoneal Dialysis Catheter Related Infections in Pediatric End-Stage Renal Disease Patients: A Case Series Jackson Londeree,[3] Donald K. Murphey,[2] David H. Simon,[1] Kartik Pillutla.[1] *[1]Pediatric Nephrology, Dell Children's Medical Center of Central Texas, Austin, TX; [2]Pediatric Infectious Diseases, Dell Children's Medical Center of Central Texas, Austin, TX; [3]Univ of Texas at Austin Dell Medical School, Austin, TX.*

Introduction: Atypical Mycobacterium peritoneal dialysis catheter related infections are rare and serious infectious complications. We report three cases of catheter related infections over eight months in our center.

Case Description: Case #1: A 10 month-old male with ESRD secondary to bilateral renal agenesis on peritoneal dialysis presented with an exit site and tunnel infection. His culture grew Mycobacterium fortuitum. **Case #2:** A 12 month-old with ESRD secondary to urethral agenesis on peritoneal dialysis presented with an exit site infection. His culture grew Mycobacterium fortuitum. **Case #3:** An 18 month-old with ESRD secondary to obstructive uropathy on peritoneal dialysis presented with peritonitis. His peritoneal culture grew Mycobacterium abscessus.

Discussion: All three patients were treated with antimicrobial therapy and catheter removal.

	Organism	Infection Type	Treatment	Exit site care	Outcome
Patient #1	M. fortuitum	Tunnel	Amikacin, TMP-SMX, Ciprofloxacin	Anti-bacterial soap and tap water	Catheter removal, conversion to hemodialysis
Patient #2	M. fortuitum	Exit site, Peritonitis	Amikacin, TMP-SMX, Ciprofloxacin	Anti-bacterial soap and tap water	Catheter removal, conversion to hemodialysis
Patient #3	M. abscessus	Peritonitis	Amikacin, Linezolid, Clarithromycin	Anti-bacterial soap and tap water	Catheter removal, conversion to hemodialysis

Infection control was consulted. Patients were non-ambulatory, began peritoneal dialysis in infancy and had gastrostomy tubes. Catheters were well healed and caregivers demonstrated appropriate technique. Exit site care consisted of washing site with soap and tap water followed by topical gentamicin daily. As atypical mycobacterium are found in the natural environment tap water contamination was suspected. Our policy was changed to clean the exit site with chlorhexidine gluconate in place of tap water for non-ambulatory patients.

SA-PO035

Longest Survival on Hemodialysis: 47 Continuous Years and Counting Laura Pilozzi-Edmonds, Murray L. Vasilevsky. *Nephrology, McGill Univ Health Centre, Montreal, QC, Canada.*

Introduction: We report a case of uninterrupted hemodialysis for 47 years and counting, which is the longest recorded in the published literature. This case illustrates the advances of hemodialysis over the years in technique, vascular access, treatment of bone disease and anemia. In the era of multi-modality renal replacement therapies, it also highlights a case of successful single modality hemodialysis for an exceptionally long period of time.

Case Description: The patient is a 57 year old man who developed end-stage renal disease at the age of 10 months secondary to congenital bladder neck obstruction. He was started on home hemodialysis in 1969 at age 11 and was the first pediatric patient to be dialyzed in Canada. His initial access was an ankle AV shunt. He had an AV fistula created in 1983 which lasted 23 years and undoubtedly contributed to his longevity on hemodialysis. He started dialysis with a Kiil dialyzer which required long treatments and sterilization. The introduction of hollow-fiber dialyzers improved dialysis efficiency and his quality of life by shortening his required dialysis time. Over time, he developed fractures due to osteitis fibrosa cystica and fluorosis from fluorinated city water. He was treated with subtotal parathyroidectomy and addition of a deionizer to his water treatment system. He was later found to have significant aluminum on bone biopsy from exposure to aluminum-based phosphate binders. He was transfusion dependent until the development of ESAs in 1989. The patient was never a candidate for renal transplantation or peritoneal dialysis and despite being on hemodialysis for most of his life he completed his education, studied architecture at a technical college and participated in the workforce for 28 years. He continues on center dialysis three times per week via a tunneled catheter.

Discussion: This case parallels the history of advances in hemodialysis from innovations in vascular access, dialyzers and water treatment to the development of non-aluminum phosphate binders and erythropoietin stimulating agents. It illustrates that single modality hemodialysis can be associated with excellent outcomes, including exceptional longevity and quality of life, in some patients.

SA-PO036

Hemodialysis Associated Thrombocytopenia Corrected with Changing Membrane Sterilization Method Sharica Brookins, Juan Pablo Arroyo, Ed Gould. *Nephrology, Vanderbilt Univ Medical Center, Nashville, TN.*

Introduction: Hemodialysis (HD) associated thrombocytopenia (TCP) is a rare, but serious complication which needs to be identified quickly to prevent further morbidity and mortality in HD dependent patients. While a variety of membrane and sterilization techniques have been associated with the development of TCP, we present the first case of HD associated TCP which resolved after switching from electron beam sterilization to steam membrane sterilization.

Case Description: A 40 year-old Caucasian female with Polycystic Kidney Disease was admitted for initiation of dialysis in advance of bilateral nephrectomy to prepare for renal transplantation. Her platelet count was 226 $x10^3/\mu L$ one month prior to admission. Platelet count decreased to 114 $x10^3/\mu L$, 60 $x10^3/\mu L$, and then 14 $x10^3/\mu L$, after each consecutive dialysis session with the electron beam sterilized polysulfone HD membrane. A work-up for causes of TCP, including heparin induced thrombocytopenia, bleeding, and auto-immune disorders returned negative. Following platelet recovery, re-challenge with the same membrane once again led to decline in platelet count to 76 $x10^3/\mu L$. The HD membrane was changed to a steam sterilized dialysis membrane. With that change, pre (118 $x10^3/\mu L$) and post (110 $x10^3/\mu L$) HD platelet counts remained stable. Surgery was postponed, and her platelets recovered to 232 $x10^3/\mu L$ while receiving ongoing HD.

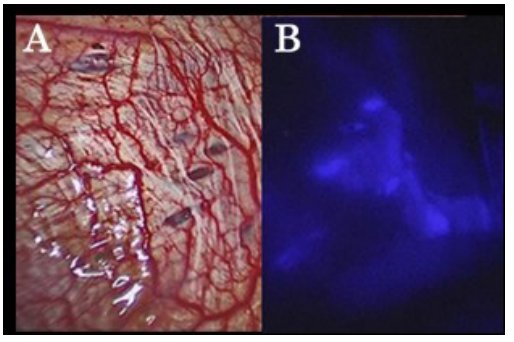
Discussion: Platelet half-life can be directly impacted by the dialysis membrane. HD membrane sterilization techniques, e.g., ethylene oxide, gamma-ray or electron-beam, and steam, are varied and may alter their biocompatibility. In our patient the switch from electron-beam sterilization to steam sterilization corrected the TCP. Previous case reports switched to either electron-beam or gamma-ray sterilization, we present the first reported case of platelet recovery after switching from electron beam to steam sterilization. This has only been previously reported to improve HD associated leukopenia and not TCP. It is important to note that although changes in biocompatibility are rare, early identification and management are essential to improving the care of the HD dependent patient.

SA-PO037

A Successful Case of Peritoneal Dialysis-Related Pleuroperitoneal Communication Diagnosed by Contrast-Enhanced Ultrasonography and Treated by Thoracoscopic Surgery Mimiko Matsumura, Takaaki Higashihara, Rie Uni, Hideki Takano. *Dept of Nephrology, Tokyo Teishin Hospital, Tokyo, Japan.*

Introduction: Pleuroperitoneal communication is a famous complication of peritoneal dialysis (PD). It is difficult to diagnose and treat because there may be no way to identify the pleural holes certainly. Here, we present a successful case of pleuroperitoneal communication.

Case Description: A 66-year-old woman with ESRD due to chronic glomerulonephritis was admitted to our hospital to start PD. After the PD catheter was inserted successfully, right-sided hydrothorax occurred caused by pleuroperitoneal communication. Immediately after injecting of Perflubutane into abdominal cavity through PD catheter, we could detect high echoic area around the pleural holes by contrast-enhanced ultrasonography. To prevent fluid reaccumulation, video-assisted thoracic surgery (VATS) was performed. Under an infrared light thoracoscope, the flow through holes in the diaphragm was clearly confirmed with the fluorescence color of indocyanine green (ICG) contained in the PD solution (figure 1). The holes in the diaphragm were removed with surgical stapling devices. She subsequently resumed automatic PD without recurrence for 6 months before undergoing kidney transplantation from a living donor.



A thoracoscopic view showing holes of the diaphragm (A), and an infrared light thoracoscopic view showing the inflow of indocyanine green (B).

Discussion: Contrast-enhanced ultrasonography using Perflubutane is a safe way for detection of the leakage and VATS is a feasible method for treating pleuroperitoneal communication.

SA-PO038

Case Report of Hypophosphatemia Occurring with the Use of Filgastrim in a Patient on Hemodialysis Sarath G. Nath, Vadim Abramov, Moro O. Salifu, Mary C. Mallappallil. *Medicine, SUNY Downstate Medical Center, Brooklyn, NY.*

Introduction: Hypophosphatemia is an electrolyte disturbance in which there is abnormally low level of phosphate in the blood. Hypophosphatemia most commonly seen in malnourished patients. Hypophosphatemia is rare in patients with end stage renal disease (ESRD) who are on hemodialysis (HD). Filgastrim is a granulocyte colony-stimulating factor analog used to stimulate the proliferation and differentiation of granulocytes that can result in hypophosphatemia. We report a rare case of severe hypophosphatemia 0.9 mg/dl after use of filgastrim in a HD patient being treated for neutropenia that was caused by use of carbamazepine.

Case Description: A 69 year old man with hypertension, seizure disorder, ESRD on HD, presented to the emergency room with a temperature of 101 Fahrenheit from his dialysis center. Admission laboratory were significant for white cell count (WBC) of of 0.81 10^9/l, phosphate 2.7 mg/dl. On the second day of admission he was started on filgastrim. He received 5 doses of filsgasrim before it was stopped as laboratory was noted for WBC count of 29.97 10^9/l, and phosphate of 0.9 mg/dl. Chemistry was repeated to show the value to be real. He was supplemented with phosphate while he continued to receive dialysis as scheduled. He had rapid resolution of his fever and quickly resumed his usual diet. He was not on phosphate binders and not on any medications which could cause hypophosphatemia. His serum calcium levels were 8.3mg/dL and his intact parathyroid hormone level was 208pg/mL.

Date	Serum Phosphate	WBC	Dialysis day
11/25/15	2.3	0.9	Yes
11/26/15	1.7	5.13	No
11/27/15	0.9 (pre dialysis early morning value)	29	Yes
11/28/15	2.4	33	No
11/29/15	1.4	52	No

He was never on Valproic acid (which has been noted to cause hypophosphatemia via Fanconi's syndrome).

Discussion: Hypophosphatemia is a possible outcome with figastrim use in a dialysis patient. Possible mechanism includes the combination of dialysis and consumption of phosphate in the process of rapid cell turnover of white cells. We report a case of severe hypophosphatemia that was cased with filstagtrim use in a patient on HD.

SA-PO039

Chyloperitoneum in a Neonate with ESRD on Peritoneal Dialysis: A Case Report Xiaoyan Wu, Molly R.W. Vega, Sarah J. Swartz, Mini Michael. *Pediatrics, Texas Children's Hospital.*

Introduction: Chyloperitoneum (CP) is a rare complication of peritoneal dialysis (PD). CP is diagnosed when triglyceride (TG) level (>110 mg/dL) in the PD effluent is elevated. Treatment is by changing to medium chain triglyceride (MCT) based diet as MCTs are absorbed by the intestine & transported by the portal system bypassing lymphatics, allowing the chylous fistula to heal naturally. We report a case of CP in an neonate on PD successfully managed with diet change alone.

Case Description: A 5 wk old male infant with ESRD due to bilateral cystic renal dysplasia initiated on manual PD at low exchange volume (EV) (10 ml/kg) at 12 days old, wt 3.5 kg & sCr 6.69 mg/dL. EV slowly increased by 10 ml every 5-7 days. Milky PD effluent (Fig1) developed without any other signs of infection 3 weeks after initiation of PD. PD effluent TG 184 mg/dL. Diet at diagnosis was expressed breast milk (EBM) supplemented with Similac PM 60/40, Duocal & Beneproteine. It was changed to skimmed EBM (sEBM) with MCT oil 1 ml/kg/day while waiting for MCT based formula. PD was continued. Within 12 hrs of formula change, milky appearance cleared & by 24 hrs, TG level of PD effluent returned to normal (< 10 mg/dL). Commerical formula with high % MCT (Enfaport) supplemented with Solcarb and Beneprotein added to sEBM & MCT oil once available. Regular EBM slowly reintroduced after 10 days. He tolerated transition to full feeds with EBM over 1 wk without recurrence of CP. PD EV advanced to full prescription (35 ml/kg) over the next 3 months without recurrence of CP. He was discharged home at 5 months on CCPD, on EBM + Similac PM 60/40 with Beneprotein without further problems.

Fig1: Milky PD effluent.

Discussion: CP is a rare complication of PD. Prompt diagnosis is important as it can be easily managed with change of diet to MCT based formula without cessation of PD. Regular formula can be slowly reintroduced after 1 wk.

SA-PO040

Successful Treatment of Severe Hyperkalemia and Hyponatremia Using Continuous Venovenous Hemodialysis Melissa L. Swee, Doreen Ventura. *Dept of Nephrology, Univ of Iowa Hospitals and Clinics, Iowa City, IA.*

Introduction: Renal replacement therapy has long been utilized as a potent means of correcting severe electrolyte disturbances, but does incur the risk of altering levels of other electrolytes, leading to unforeseen consequences. In particular, use of conventional fluids for RRT may treat hyperkalemia but also lead to unpredictable rises in [Na+], leading to osmotic demyelination. We present a case in which D5 and sodium bicarbonate in D5W were utilized to improve hyperkalemia while avoiding rapid shifts in serum sodium concentration.

Case Description: A 59-year old male with recently diagnosed CLL presented with acute respiratory failure due to H1N1 influenza. Vital signs were notable for tachycardia (114 bpm) and hypotension (96/52mmHg) on norepinephrine and vasopressin. Other vital signs were within normal limits (Temp 36.3*F, RR 16 bpm, SatO2: 98% on 40% FiO2). Laboratory data revealed serum creatinine 1.4 mg/dL, BUN 29 mg/dL, and [Na+] 118 mEq/L. Whole blood [K+] was persistently >14 mEq/L. He underwent leukopheresis and was started on CVVHD (dialysate rate: 5L/hr and blood flow rate: 250cc/min). The pre-filter replacement fluid was 150mEq of sodium bicarbonate/L D5, while the post-filter fluid was D5W. He was also started on an insulin infusion. [Na+] improved to 124mEq/L on day 2 and 130mEq/L on day 3. He continued to be hyperkalemic and both the pre- and post-filter were changed to normal saline (0.9%) for continued potassium clearance. [K+] normalized after day 4 (4.7mEq/L) while [Na+] remained between 136 and 140mEq/dL until day 14. The patient was discharged 2 weeks post induction of chemotherapy.

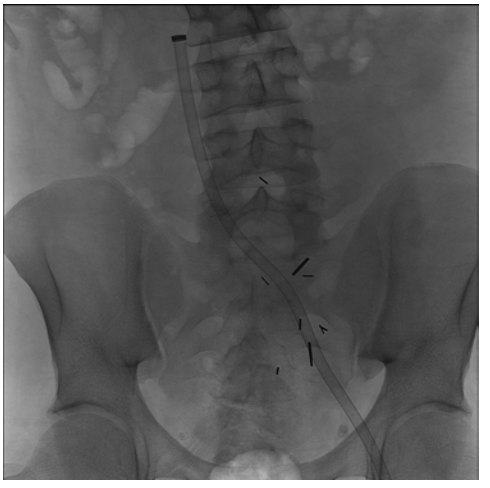
Discussion: Hyperkalemia is a life-threatening electrolyte disturbance that may be addressed promptly with RRT; at the time, rapid correction of concommitant hyponatremia, which may occur when using conventional forms of dialysate, may lead to other unforeseen consequences. This case illustrates that CVVHD using low [Na+] replacement fluids is a viable option for treating severe hyperkalemia without incurring osmotic demyelination. To our knowledge, this is the first instance of such a strategy being used to correct hyperkalemia while avoiding rapid shifts in [Na+].

SA-PO041

Thigh HeRO Catheter: The "Last Resort" Dialysis Vascular Access Alian Albalas,[1] Ahmed Kamel Abdel Aal,[2] Ammar Almehmi.[3] *[1]Nephrology, UAB, Birmingham, AL; [2]Radiology, UAB, Birmingham, AL; [3]Nephology and Radiology, UAB, Birmingham, AL.*

Introduction: Thigh vascular access is commonly employed in dialysis patients with upper extremity central venous system occlusive disease. On the other hand, Hemodialysis Reliable Outflow (HeRO) catheters have been used in tunneled catheter-dependent patients who have exhausted other access options. However, thigh HeRO catheter is rarely utilized as a possible vascular access option in those patients.

Case Description: This is a 34-year-old African American male with known history of end-stage renal disease due to hypertension, protein C deficiency who was started on hemodialysis via neck tunneled catheter 12 years ago. Multiple graft and fistula accesses on both upper extremities failed due to recurrent stenotic lesions and thromboses. In 2004, he underwent deceased kidney transplant that remained functional for 7 years. In 2011, he presented with acute kidney injury due to graft rejection (due to non-compliant with immunosuppressive medications), volume overload and respiratory failure that required renal replacement therapy via left femoral vein catheter. Due to the limited available vascular estate in this patient, the decision was to proceed with left thigh HeRO catheter placement.



He started using the HeRO catheter within 3 weeks after placement. Despite few thrombotic episodes, the HeRO catheter remains functional and provides a reasonable hemodialysis access in this patient for the last 5 years. It is worth mentioning that this patient is non-compliant with warfarin therapy used to treat protein C deficiency, which could explain the recurrent thromboses of the dialysis access.

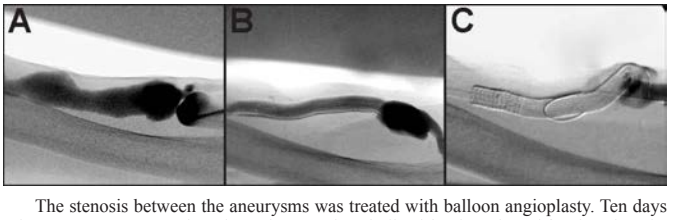
Discussion: The Hemodialysis Reliable Outflow (HeRO) catheter of lower extremities is a plausible "last resort" option and can be utilized in the subset of patients in whom the other vascular access options are exhausted.

SA-PO042

Using Stent Grafts for Fistula Aneurysms Exclusion: Case for Caution Alian Albalas,[1] Ahmed Kamel Abdel Aal,[2] Ammar Almehmi.[3] *[1]Nephrology, UAB; [2]Radiology, UAB; [3]Nephology and Radiology, UAB.*

Introduction: Dialysis fistula aneurysms are commonly encountered in clinical practice. Most of the fistula aneurysms do not require direct intervention other than making sure that the draining veins are adequate and the fistulae are not pressurized. Direct surgical interventions, are warranted only when there are associated clinical issues, such as active bleeding, skin defect/erosion, mural thrombosis, infection, and significant cosmetic issues.

Case Description: This is a 70-year-old hemodialysis patient with a left brachiocephalic arteriovenous fistula presented with low fistula flow and difficult cannulation. Six months prior to the current presentation, a fistulogram revealed multiple aneurysmal formations of the fistula vein



The stenosis between the aneurysms was treated with balloon angioplasty. Ten days prior to current presentation, the patient was hospitalized for thrombosed fistula, where he underwent thrombectomy as well as a stent graft placement in the fistula vein.

On current presentation, the physical examination disclosed diffuse infiltration over the fistula body and weak thrill. Additionally, large aneurysmal formations of the fistula body were noted. Angiographic exam revealed a long stent graft in the fistula vein. When viewed from a different angle, the distal end of the stent graft was kinked within the aneurysm and the lateral wall of the distal stent graft was blocking fistula blood flow.

Further endovascular intervention was unsuccessful due to the kinked stent graft and the fistula flow was not sufficient for dialysis. Consequently, the patient necessitated tunneled dialysis catheter insertion in order to continue his dialysis therapy.

Discussion: A high degree of caution is needed for the "off-label" use of stent grafts to manage fistula aneurysms and their associated complications, as stent grafts may create more problems than they are intended to solve.

SA-PO043

Development of Pancreatitis in an ESRD Patient with Preceding Sodium Thiosulfate Usage Sean Kumar. *Internal Medicine, Univ at Buffalo School of Medicine, Buffalo, NY.*

Introduction: Sodium thiosulfate is a drug with few known medical indications including cyanide poisoning, calciphylaxis and extravasation management in some chemotherapeutic regimens. Herein we present a case of acute pancreatitis in an ESRD patient with recent sodium thiosulfate usage with calciphylaxis. Sodium thiosulfate is a drug used frequently in calciphylaxis management in ESRD patients, but has not been previously documented to be associated with pancreatitis.

Case Description: A 58 year old Female with past history significant for ESRD on HD, presented to the hospital with 1 week history of nausea, vomiting, and epigastric pain. She was started on IV sodium thiosulfate with HD for calciphylaxis ten days prior to the admission. Full workup for typical etiologies of pancreatitis including alcohol use and cholelithiasis was negative. Labs were significant for a lipase of 1160 on admission. Triglyceride level was 152. Calcium level was 9.0. Abdominal CT study demonstrated changes consistent with acute pancreatitis. Patient underwent MRCP to evaluate pancreatic ducts with no pathology found. Patient was treated conservatively and Sodium thiosulfate was discontinued due to potential for drug-induced pancreatitis (no other medications of concern identified). No subsequent episodes of pancreatitis reported after discontinuation.

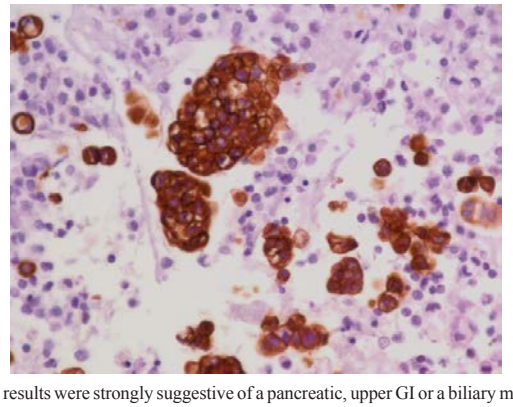
Discussion: Various etiologies have been identified in acute pancreatitis, with heavy alcohol consumption and gallstones being top culprits. Drug induced pancreatitis reflects a smaller portion of the total cases, estimated at 0.3 to 1.4%. The temporal relationship between initiation of a drug and development of pancreatitis is unclear, as some drugs demonstrate more immediate effects and others after weeks. There have not been any major studies involving sodium thiosulfate and its effects on the human pancreas to date. Based upon extensive review, sodium thiosulfate was believed to contribute to our patient's presentation. Withholding the suspected drug and conservative measures were all that was required for management. As the prevalence of ESRD continues to rise, consideration of sodium thiosulfate as a contributor to acute pancreatitis may become a prudent differential diagnosis.

SA-PO044

Use of Tenckoff Catheters in Diagnosing Abdominal Malignancies Sarthak Virmani,[1] Ari B. Geller.[2] *[1]Dept of Medicine, Univ of Connecticut School of Medicine, Farmington, CT; [2]Div of Nephrology, St. Francis Hospital, Hartford, CT.*

Introduction: Tenckoff catheters have been used for peritoneal dialysis since 1968. Peritonitis, traumatic chylous effusions, exit site infections, migration of the catheter and omental obstructions are common complications.

Case Description: We present a case of an 82-year-old male with a history of long standing uncontrolled hypertension leading to progressive chronic kidney disease (CKD). A clinical decision was made to initiate renal replacement therapy based on progressive fatigue and a reported 15 lbs weight loss. Despite his advanced age, the patient preferred peritoneal dialysis because of his active life style. A week after the insertion of the Tenckoff catheter, straw colored, hazy effluent was noted during his initial catheter drain. He did not complaint of pain and on physical exam, the abdomen was non-tender with no palpable masses. Peritoneal fluid analysis demonstrated a nucleated cell count of 247 and no bacteria. The total protein level was less than 3 gm/dl with albumin being 1200 mg/dl. Fluid triglycerides level was 69 mg/dl, glucose 661 mg/dl and LDH 70 U/L. Cytological analysis of the fluid revealed cells that were consistent with metastatic adenocarcinoma. Immunohistochemical staining showed positivity to BerEp4, CK7, EpiCAM, CEA and CA19.



These results were strongly suggestive of a pancreatic, upper GI or a biliary malignancy. Further diagnostic workup revealed elevated serum CA 19-9 levels (1393 U/ml). A subsequent PET-CT scan showing a hyper metabolic mass in the pancreatic body, confirming the diagnosis of pancreatic adenocarcinoma.

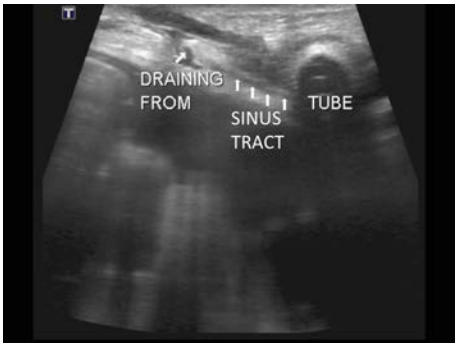
Discussion: This case demonstrates the diagnostic potential of cytologic analysis of peritoneal fluid. It also exemplifies the need for a broad differential when evaluating abnormal dialysis effluent in a newly placed peritoneal dialysis catheter.

SA-PO045

Two Tunnels for One Peritoneal Dialysis Catheter! A Rare Delayed Surgical Complication Volodymyr Chornyy, S. Irfan Qadri, Amir Kazory. *Nephrology, Hypertension and Renal Transplantation, Univ of Florida, Gainesville.*

Introduction: Catheter tunnel infection (CTI) is a known cause of adverse outcomes in peritoneal dialysis (PD)-related peritonitis. Extension of exit site infection is the most common reported reason for CTI. We report a case of PD-related peritonitis due to a delayed surgical complication.

Case Description: A 54 year old man with a history of end stage renal disease due to polycystic kidney disease (PCKD) was treated with continuous cycling PD for the past 5 years. He presented with fever, abdominal pain, and cloudy PD effluent. His abdomen was diffusely tender. Except for extruded external cuff, the PD catheter exit site was unremarkable. Serous drainage was noted one inch from the exit site where the trocar was inserted for laparoscopic PD catheter placement. The patient reported increasing drainage for 4 weeks prior to presentation. Laboratory studies were consistent with PD-related peritonitis. Broad spectrum antibiotics were initiated. Abdominal ultrasound confirmed a 1.5 inch sinus tract connecting the surgical trocar insertion site to the inner segment of the catheter tunnel.



The patient deteriorated rapidly but removal of the PD catheter resulted in progressive improvement in his clinical status.

Discussion: In addition to its rarity, this case is notable for a number of teaching points. Patients with PCKD are at risk for early PD fluid leak due to increased intra-abdominal pressure. Although uncommon, such complications can appear later and create a diagnostic dilemma. Moreover, this case shows importance of ultrasound imaging in evaluation of unexplained PD-related peritonitis even without overt symptoms of exit site infection. If technically feasible, it is prudent to insert the surgical trocar as far as possible from the exit site and the catheter tunnel. Finally, sinus formation should be considered when a previously healed scar develops abundant drainage.

SA-PO046

Diffuse Dermal Angiomatosis; an Unusual Cause for Painful Ulcerative Lesions in Patients with End Stage Renal Disease Hassan Alhalabi,[1] Meral K. El Ramahi,[1] Anna Marie Burgner,[1] Adriana Hung.[1,2] *[1]Vanderbilt Univ, TN; [2]TVHS, TN.*

Introduction: Diffuse Dermal Angiomatosis (DDA) is a benign vascular condition associated with peripheral vascular disease (PVD) and calciphylaxis in End Stage Renal Disease (ESRD) patients and presents as painful, ulcerative skin lesions. We describe two patients with ESRD who presented with painful ulcers and found to have DDA by skin biopsy. Given that DDA is hypothesized to be secondary to underlying hypoxia and ischemia, we treated each patient with topical Nitroglycerin and witnessed improvement in wound healing.

Case Description: Case 1: A 51 year old African American female with a history of end stage renal disease on hemodialysis and pulmonary embolism on Coumadin; was admitted with recurrent painful sacral and right breast wounds; which were previously felt to be due to calciphylaxis. Patient had a sub-total parathyroidectomy earlier with no improvement in her skin lesions. Later a skin biopsy showed Diffuse Dermal Angiomatosis. The patient was subsequently treated with topical Nitroglycerin with significant clinical improvement. Case 2: A 36 year old African American female with a history of poorly controlled diabetes mellitus, hypertension and end stage renal disease on peritoneal dialysis; who presented with gastroparesis related symptoms and a large very tender ulcerative abdominal wound, which developed from a small non healing laparoscopic surgical wound. Wound cultures showed a usual skin flora; diffuse dermal angiomatosis was shown on the skin biopsy. The patient was started on topical Nitroglycerin with significant clinical improvement.

Discussion: DDA is a rare, benign, acquired disease. It is characterized clinically by very painful erythematous to violaceous patches with central ulceration and histologically by diffuse vascular endothelial cell proliferation within the dermis. It has been thought to be caused by local hypoxia and described in association with PVD. Revascularization is very effective and treatment with steroids and isotretinoin had been successful occasionally. In our two patients; we used topical Nitroglycerin with good wound healing. The proposed mechanism of action for nitroglycerin is improvement of local perfusion.

SA-PO047

Shunt Nephritis and Pyogenic Spondylitis with a Positive PR3-ANCA Associated with Chronically Infected Ventriculo-Arterial Shunt Hiroyuki Ono, Seiji Kishi, Taizo Inagaki, Masanori Tamaki, Taichi Murakami, Kojiro Nagai, Hideharu Abe, Toshio Doi. *Nephrology, Tokushima Univ Hospital, Tokushima, Japan.*

Introduction: Shunt nephritis is a rare complication mostly described in the setting of chronic infection of venticulo-atrial (VA)-shunts. Although shunt nephritis is a well-recognized entity, diagnosis can be challenging and may be overlooked.

Case Description: A 56-year-old Japanese man presented with a persistent low grade fever for 4 months, hematuria and proteinuria and progressive kidney dysfunction. He had a history of secondary hydrocephalus associated with non-HIV cryptococcal meningitis at the age of 50, which was treated by ventriculo-peritoneal (VP) shunt, followed by replacement with VA shunt because of intraabdominal abscess. On admission, physical examination was unremarkable except for mild lower back tenderness. Laboratories revealed renal insufficiency (serum creatinine 2.35 mg/dl, baseline 0.86 mg/dl), hypocomplementemia (CH50 28 U/mL), elevated C-reactive protein(CRP) (4.33 mg/dl), positive PR3-ANCA (67.4U/ml), proteinuria (1.63 g/gCr) and hematuria (>100 erythrocytes/HPF). Blood culture and CSF culture were both returned positive for Staphylococcus captis. Transthoracic echo showed no vegetation. Lumbar-spine magnetic resonance imaging demonstrated findings consistent with pyogenic spondylitis. There was increased uptake in both kidneys on gallium scintigraphy. VA shunt was removed and antimicrobial therapy was immediately started. He had resolution of proteinuria and hematuria, improvement of renal function and hypocomplementemia, and normalization of CRP. He didn't show symptoms related to hydrocephalus again without a VA shunt and signs or symptoms of Wegener's granulomatosis. We didn't perform renal biopsy because urinalysis and renal function began to improve after treatment.

Discussion: We successfully treated a patient with shunt nephritis with antibiotic treatment and hematuria, proteinuria and progressive kidney dysfunction all improved. Physicians should be aware of the risks of infection-related GN in patients with VA shunts as early diagnosis and treatment initiation with antibiotics and shunt removal is a key to the successful management.

SA-PO048

Babesiosis Mimicking Hemolytic Uremic Syndrome as Cause of Hemolytic Anemia in an End Stage Renal Disease Patient Avantika Chenna, Pradeep Reddy Thodima, Mauricio Alexander Pedroza, Rasib Raja, Imara Dissanayake. *Nephrology, Albert Einstein, Philadelphia, PA.*

Introduction: Babesiosis is a tick borne disease and is seen in patients with recent history of travel to endemic areas. Since the advent of erythropoetic agents in ESRD patients, the number of cases of transfusion related babesiosis cases have diminished. We present a case of severe hemolytic anemia from babesiosis in ESRD patient from blood transfusion being misdiagnosed as HUS. There have been cases of babesiosis reported in HIV, splenectomy and renal transplant recipients. This is the first case described in ESRD patient to the best of our knowledge.

Case Description: 52 year old male with h/o ESRD recently started on hemodialysis, HTN , CHF with EF< 15% was admitted with low Hemoglobin (Hb) of 6.5gm/dl (baseline about 8-9g/dl).During previous admission for gastrointestinal bleeing,he received 1 unit of PRBC before discharge. During the current admission, physical exam was significant for - Jaundice, ejection systolic murmur, pedal edema and splenomegaly. Vital signs were normal. Labs showed – Hb-6.5 g/dL WBC-8.7 and Plt count of 52x10^3 /mcL. Na134,K 3.7, Cl 97, HCO3 22 mmol/L, BUN 78 and Cr 5.9 mg/dL. Coombs test was negative. LDH 724 IU/L with Haptoglobulin low at 8 mg/dL. Peripheral Blood smear was positive for occasional schistocytes . He was thus started on plasmapheresis and steroids for presumed HUS/TTP per hematology. ADAMTS 13 was pending. After receiving 3 sessions of plasmapheresis , due to persistent anemia and thrombocytopenia ,hematology repeated peripheral blood smear. It showed intra and extra erythrocytic ring forms concerning for parasitic infection. Plasmapheresis was thus discontinued. Patient was started on atovaquone and azithromycin per infectious disease . Babesia PCR was sent out. There was improvement in LDH, Hb and thrombocytopenia following the treatment.

Discussion: It is very rare to see hemolytic anemia from babesiosis in ESRD patients. Babesiosis and other arthropod born illnesses should be considered in ESRD patients even in the absence of localizing symptoms if patients are not improving with the standard treatment.

SA-PO049

Actinomyces Peritonitis: A Novel Therapy and Case Review Aaron P. Coulon, Rahul V. Kamat, Ashwin P. Jaikishen, Mihran V. Naljayan. *Dept of Medicine, Section of Nephrology and Hypertension, LSUHSC School of Medicine, New Orleans, LA.*

Introduction: Peritonitis is a leading complication of peritoneal dialysis (PD). Actinomyces is a very rare cause of PD peritonitis, and each of the previously reported cases employed a different management plan. We chose a unique, simplified approach using ceftriaxone without catheter removal.

Case Description: The patient is a 40-year-old female with end stage renal disease on PD for 2 months. She was on apixiban for a deep venous thrombosis and presented to the dialysis unit with a three-day history of pink effluent. Cell count, gram stain, and cultures were obtained, and she was empirically given vancomycin 1 gram intraperitoneal (IP). Initial cell count showed WBC 771 and RBC <10,000. She was admitted to the hospital and found to have leukopenia (4.1 x10^9/L) and anemia (hemoglobin 6.6 g/dL) with a normal abdominal exam. Repeat peritoneal fluid analysis showed WBC 266 and RBC 730, which decreased to 0 and 2, respectively, on hospital day three. A repeat culture grew gram positive rods (Diphtherioids), and the initial culture grew Actinomyces. We decreased apixiban and started ceftriaxone 1 gram IP daily for three weeks with a six-hour dwell and fluconazole 200 mg every other day. All follow up cultures were negative and effluent was clear.

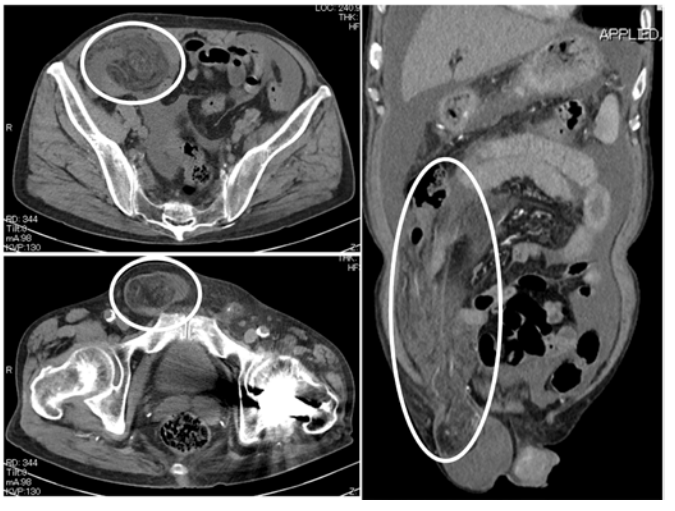
Discussion: Actinomyces can cause abdominal and pelvic infections, but peritonitis is rare. Infection classically follows mucosal compromise and causes fibrosis, abscesses, and fistulas. Penicillins are the cornerstone of therapy. The four previous PD peritonitis cases that used antibiotics chose penicillin, amoxicillin, or clindamycin either as primary treatment or to prevent relapse. Ceftriaxone has been successfully used in cases involving various organ systems, but no one had used IP ceftriaxone for peritonitis. We had success with three weeks of ceftriaxone IP and fluconazole for fungal prophylaxis. In this case, removal of the PD catheter and penicillin were not necessary. This case is one of a rare disease, actinomyces PD peritonitis, treated in a novel way. It is the first report of treatment with ceftriaxone alone, and it provides another example of successful treatment with catheter preservation.

SA-PO050

A Case of Tuberculous Peritonitis Diagnosed at the Onset of Omental Torsion after Six Years of the Cessation of Peritoneal Dialysis Daisuke Nakashima, Yukio Maruyama, Naoki Sugano, Ai Katsuma, Izumi Yamamoto, Nanae Matsuo, Yudo Tanno, Ichiro Ohkido, Keitaro Yokoyama, Takashi Yokoo. *Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan.*

Introduction: It is well-known that the incidence and prevalence of tuberculosis in patients with chronic kidney disease, especially dialyzed patients, is extremely higher than those of non-renal patients. Furthermore, dialyzed patients had a high percentage of extrapulmonary tuberculosis and it makes the diagnosis difficult for a nephrologist.

A 67-year-old man was admitted with complaints of pyrexia, abdominal pain, and acute inflammatory reaction. He initiated peritoneal dialysis for end-stage renal disease due to nephrosclerosis ten years ago, and transferred to hemodialysis because of underdialysis six years ago. He had no history of peritonitis as well as encapsulating peritoneal sclerosis. Subsequent abdominal computerized tomography (CT) showed right inguinal hernia, and it contained omentum majus.



We performed an emergency hernia operation. We diagnosed as omental torsion and remove damaged omentum. Then patient became asymptomatic. We suspected tuberculous peritonitis as the cause of omental torsion, because epithelioid granuloma was found in the specimen from resected omentum and ascites concentration of adenosin deaminase (ADA) was high. We initiated antituberculous agents without diagnostic confirmation from bacteriological examination. Tuberculosis bacterium was detected from the peritoneum six weeks later, and we confirmed the diagnosis.

Discussion: Dialyzed patients are susceptible to tuberculosis, especially extrapulmonary tuberculosis. Although tuberculous peritonitis is difficult to diagnose because of low detection rate of tuberculosis bacterium from ascites, this should be considered in the management of acute abdominal condition in dialized patients.

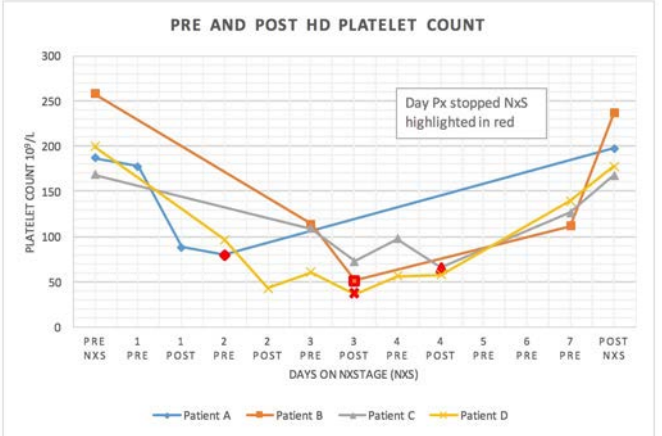
SA-PO051

Thrombocytopenia during NxStage Home Hemodialysis (HHD) Orla Marie Dunne, Catherine Brumby, Yangmin Zeng, Rajinder S. Singh, Michael A. Copland. *British Columbia Provincial Renal Agency and Univ of British Columbia, Vancouver, BC, Canada.*

Introduction: The NxStage HHD machine was specifically designed for the home and offers simplified technology compared with traditional HHD machines. A key benefit of the streamlined NxStage setup is a drop-in cartridge which houses dialyzer tubing with a pre-attached dialyzer. The pre-attached dialyzer is composed of a gamma-ray sterilized polyethersulfone-PVP membrane. Our program has encountered four patients who have developed severe thrombocytopenia suspected to be directly related to the cartridge system.

Case Description: Four of twenty-six patients that have been exposed to NxStage dialysis in British Columbia developed platelet counts of <100 x10^9/L within the first week following transition from conventional HD as outlined in figure below. They did not experience any symptoms suggesting hypersensitivity or any clinical events related to thrombocytopenia. No changes, other than exposure to a new dialysis system, were made during these periods. HIT was unlikely as these patients were able to tolerate heparin during conventional HD treatments. Their platelets dropped incrementally with each NxStage dialysis session but rebounded back to baseline when switched back to conventional hemodialysis.

Discussion: The mechanism by which this dialysis-related thrombocytopenia developed is not understood, but the timing and pattern suggest that it is related either to the pre-attached dialyzer or dialysis tubing. Dialyzer-related thrombocytopenia has previously been linked to the composition of the dialyzer membrane and/or method of dialyzer sterilization. Although an alternate cartridge allows manual replacement of the dialyzer, this negates much of the advantage of the cartridge system. HHD programs using NxStage should monitor for thrombocytopenia and consider the platelet threshold at which patients require a dialyzer or machine change.



Platelet Count x10^9/L	Patient A	Patient B	Patient C	Patient D
Pre HD prior to NxS	187	258	169	200
Pre HD on NxS (nadir)	80	114	98	61
Post HD on NxS (nadir)	89	52	66	37
Pre HD after NxS (Day 7)		112	127	140
Pre HD on conventional HD	198	237	168	178

SA-PO052

Survival among Patients with End Stage Renal Disease in Low versus High Serum FLC Levels Yoonkyung Song, Jieun Kim, Gang Jee Ko, Young-Joo Kwon. *Div of Nephrology, Korea Univ, Seoul, Republic of Korea.*

Introduction: Approximately 500 mg/day polyclonal free light chain (FLC) is released into the blood in chronic inflammatory disease. Serum polyclonal FLC levels may reflect the activity of the adaptive immune system and is cleared by the kidney and reticular system. Moreover, some recent studies reported an association between polyclonal FLC level and mortality rate in CKD patients. This study was designed to determine whether polyclonal FLC level correlated with mortality rate in end-stage renal disease (ESRD) patients undergoing dialysis.

Case Description: Initially, 432 ESRD patients who started hemodialysis or peritoneal dialysis after 2005 were enrolled. The levels of serum total FLC, FLC kappa, FLC lambda were determined at the start of dialysis. Of the 432 patients, only 300 patients whose status, whether alive or dead, was available in the data from Korean Society of Nephrology were included in this study.

Of the 300 patients, 75 were dead and 225 were alive at the start of this study. Patient's survival status had no significant influence on the mean FLC levels. Furthermore, the levels of FLC as well as other serum parameters, including hemoglobin, phosphate, calcium, albumin, cholesterol, and PTH, showed no correlation with survival rate. For subgroup analysis, the patients were assigned to one of two groups based on age: ≤60 years and above 60 years. In the ≤60 years group, significant difference was observed in the mean FLC levels of surviving and non-surviving patients. In cox regression analysis, elevated total FLC levels were significantly correlated with overall mortality when stratified according to the five-fold upper limit of reference values (P = 0.015, exp(B) 3.7). FLC lambda showed significant positive correlation with mortality in the ≤60 years group when stratified according to the mean value, (P = 0.009, exp(B) 2.874). FLC kappa levels showed no significant association with adjustment of compounding factors.

Discussion: FLC levels were positively correlated with mortality in young patients (<60 years old). This finding highlights the importance of FLC level measurement for dialysis patients.

Funding: Pharmaceutical Company Support - Dowbiomedica company, Republic of Korea

SA-PO053

Gentamicin-Resistant Gram Negative Exit Site Infection in a Peritoneal Dialysis Patient Salma Elbehary,[1] Anupkumar Shetty.[2] *[1]Nephrology, Baylor Univ Medical Center, Dallas, TX; [2]Nephrology, Dallas Nephrology Associates, Dallas, TX.*

Introduction: Infection is the most common complication of peritoneal dialysis (PD). Prevention of exit site infection (ESI) is an important component of care of patients on PD. Bernardini *et al*. showed that topical prophylaxis at the exit site with gentamicin results in reduction of ESI with Gram-positive and Gram-negative organisms including *Pseudomonas*. Since publication of this paper, most dialysis centers have been using gentamicin 1% cream instead of mupirocin to prevent ESI.

Case Description: A 52 year old non diabetic African American male with end-stage renal disease was started on PD in November 2012 and he was using topical gentamicin cream to the exit site with each dressing change to prevent ESI. In April 2014, he was treated for gentamicin sensitive coagulase- negative *Staphylococcus* epidermidis exit-site infection with antibiotics. After completing treatment, we continued prophylactic gentamicin cream with dressing changes. He was doing well until April 2015, when he developed ESI. Culture grew pseudomonas aeruginosa resistant to gentamicin. He received oral Levaquin. Patient had unusually large amount of crust with underlying proud flesh that needed frequent cauterization with silver nitrate. More recently exit site swab in March 2016 grew gram positive bacilli. He continues to have large amount of crust and proud flesh. We switched to topical mupirocin cream along with topical sodium hypochlorite.

Discussion: There is a potential risk of developing gentamicin resistance which would limit antibiotic options for the treatment of ESI. Use of gentamicin cream alternating with mupirocin cream for prevention of PD related ESI needs to be investigated.

SA-PO054

Potential Role of Plasmapheresis in Severe CMV Infection with Ongoing Immune-Mediated Hemolysis and Low Complement Levels Yougandhar Akula,[1] Swetha Rani Kanduri,[1] Arnaldo F. Lopez-Ruiz,[1] Tibor Fulop.[2] *[1]Div of Nephrology, Univ of Mississippi Medical center, Jackson, MS; [2]Div of Transplantation, Univ of Debrecen, Jackson, MS.*

Introduction: Symptomatic CMV infection in patient with no previous history of immunosuppressive therapy is rare and it has only been reported after long hospitalization. We report the atypical case of young woman with ESRD who has developed a CMV infection resulting in liver damage and multiple systemic complications.

Case Description: A 33 year old woman with htn, type 2 diabetes chronic anemia and end-stage renal disease was admitted for acute diarrhea, elevated liver enzymes, and vaginal candidiasis. She was on hemodialysis for four months prior to admission. She had unexplained lower extremity weakness for same duration. C. diff testing by polymerase chain reaction was negative on three consecutive occasions. stool and blood cultures for bacteria, fungi and parasites were negative. Serology for HIV, acute hepatitis, autoimmune hepatitis or SLE were also negative. However, she was found to have low C3 and CH50 and low IgM and total IgG. Hemolytic work-up revealed ongoing hemolysis with low haptoglobin level and direct Coombs positivity. In the context of chronic unexplained wasting, persistently low albumin, chronic diarrhea and elevated liver enzymes, CMV serum PCR was obtained, revealing massive elevation at 9 million copies/mm^3. While CMV IgG titer was positive, IgM titer was negative repeatedly. CSF analysis was unremarkable including negative CMV PCR. Bone marrow biopsy was normal. Given Pt was unstable and has elevated viral load, pt had plasmapheresis for three sessions, CMV immune globulin and I.V. ganciclovir. After 2 weeks of therapy with ganciclovir, CMV decreased to 2600 viral copies/cm^3. But she developed unilateral blindness and right hemiparesis.

Discussion: This case was very unusual for the profound viremia without neutropenia and presence of CMV-mediated hemolysis with low complement level and negative IgM antibody during the illness and broadens our horizon of potential CMV-associated illnesses. Timely initiation of PLEX and CMV immune globulin infusion may contributed to recovery in our case.

SA-PO055

Basement Membrane Nephropathy Like Phenotype in a Family with an ARHGAP24 Mutation Known to Cause Familial FSGS Elizabeth Kotzen,[1] Gentzon Hall,[1] Megan Chryst-Ladd,[1] Guanghong Wu,[1] Brandon M. Lane,[1] Shashi K. Nagaraj,[1] John W. Foreman,[1] Michael J. Randles,[2] Rachel Lennon,[2] David Howell,[2] Rasheed A. Gbadegesin.[1] *[1]Pediatrics, Duke Univ Medical Center; [2]Pediatrics, Univ of Manchester, United Kingdom.*

Introduction: Alport Syndrome (AS), other glomerular basement membrane (GBM) disorders, and focal segmental glomerulosclerosis (FSGS) are major causes of glomerular disease worldwide. The pathogenesis and phenotypic spectrum of these conditions is not completely known, however recent genomic discoveries have demonstrated significant phenotypic overlap. In this study, we report a family with a mutation in the FSGS gene *ARHGAP24* and predominant GBM defects on renal biopsy.

Case Description: We identified a 3-year-old Hispanic female with persistent microscopic hematuria and proteinuria. Renal biopsy was performed. Light microscopy showed unremarkable glomeruli with no sclerosis or significant GBM thickening or duplication. Immunofluorescence staining showed patchy, discontinuous staining for alpha-3 and -5 chains of type IV collagen and electron microscopy revealed areas of thinning and thickening suggesting an AS phenotype. Audiologic and ophthalmologic evaluation were normal. Targeted sequencing of the *COL4A3, COL4A4, COL4A5, and MYH9* genes was

normal. Whole exome sequencing (WES) revealed the Q158R mutation in *ARHGAP24*. Q158R was previously reported as a cause of hereditary FSGS in a Hispanic kindred. We did not find a mutation in any of the known >50 FSGS genes, nor in *COL4A* genes. Direct sequencing of the family showed that the father, who had 1+ proteinuria, also carried the same mutation. *In-silico* analyses showed that *ARHGAP24* interacts with *TIAM1*, known to play a role in cell-matrix interactions.

Discussion: Rare variants in *ARHGAP24* may mimic GBM disorders such as AS. *In-silico* analysis of the *ARHGAP24* interactome suggests that the mutation may disrupt podocyte-matrix interactions at the GBM. Alternatively the disease in this family may represent a digenic inheritance of *ARHGAP24* and an unidentified functional deep intronic sequence variant in a *COL4A* gene. These findings emphasize the need for a multifaceted approach to glomerular disease classification that integrates clinical, morphologic, and genomic data.

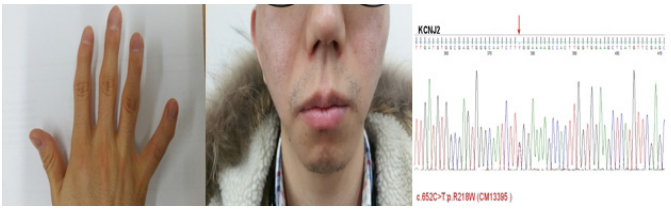
SA-PO056

Andersen Tawil Syndrome Presented with Hypokalemic Periodic Paralysis

Jong-Hwan Jung, Seon-Ho Ahn. *1 Div of Nephrology, Dept of Internal Medicine, Wonkwang Univ College of Medicine, Iksan, Jeonlabukdo, Korea.*

Introduction: Hypokalemic periodic paralysis is often developed in clinical settings, such as thyrotoxicosis, renal tubular dysfunction, and channelopathies related with potassium. The channelopathy of inward rectifier K^+ channel, I_{K1} is a disorder associated with mutations in an ion channel gene. Andersen Tawil syndrome associated with the channelopahty is characterized by dysmorphic features, ventricular arrhythmia, and hypokalemic periodic paralysis.

Case Description: A 25-year-old male visited our hospital due to lower legs paralysis. He took a medicine to control fever by acute pharyngotonsilitis for recent three days. He has no chronic disease. However, he has been on a bisoprolol daily for ventricular tachycardia during several years. His vital signs were stable on arrival. Electrocardiography showed normal sinus rhythm. His serum sodium and potassium were 145 mEq/L and 2.5 mEq/L. Arterial blood gas analysis showed normal. Hormonal assay also was within normal range. We were also not able to find out any evidence of renal potassium loss on urinalysis. But, he showed dysmorphic features, including clinodactyly and micrognathia [figure1]. We considered a genetic channelopathy such as Andersen Tawil syndrome. We did DNA sequencing for *KCNJ2* gene, encoding potassium channels.



We could confirm Andersen Tawil syndrome. His symptoms were completely improved after only supplement of potassium.

Discussion: Nephrologists will usually consider inherited renal tubular dysfunction related with hypokalemia or use of diuretics in situation of hypokalemic periodic paralysis without thyroid dysfunction. However, if the patients have distinctive features and arrhythmias, nephrologists also need to consider channelophathies. This effort can often reduce misdiagnosis in hypokalemic settings, especially.

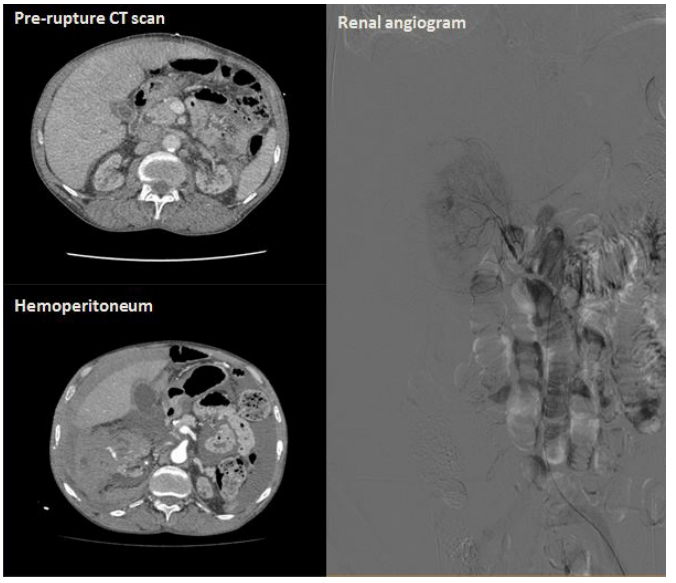
SA-PO057

A Fatal Complication (Hemoperitoneum) of Acquired Cystic Kidney Disease

Vikrampal Bhatti, Abhilash Koratala, Ashutosh M. Shukla. *Nephrology, Hypertension and Renal transplantation, Univ of Florida.*

Introduction: Acquired Cystic Kidney Disease (ACKD) in patients with advanced chronic kidney disease (CKD) and end stage renal disease (ESRD), unlike other forms of cystic renal diseases, is largely considered a benign pathology with no clear recommendations for follow up care.We present a unique complication due to ACKD resulting in death of a patient.

Case Description: A 48 year old man with ESRD on hemodialysis (HD) for 14 years developed acute abdominal pain during his outpatient HD session and was sent to the ER. He was found to be hypotensive requiring fluid resuscitation and vasopressors and acute anemia with hemoglobin of 8.5 g/dL. Abdominal CT revealed large Hemoperitoneum with a right perinephric sentinel clot, bilateral multiple renal cysts, and features suspicious of bleeding originating from the upper anterior pole of right kidney.Renal angiogram showed active ongoing extravasation from multiple branches of the right renal artery.



Selective right renal artery embolization was unsuccessful. An emergent laparotomy revealed a torn right renal capsule with subcapsular hemorrhage and a 1.4 cm ragged defect in the inferior portion of the kidney. He underwent right nephrectomy and pathology was negative for malignancy. Because of religious reasons, patient refused blood transfusion and unfortunately died of hemorrhagic shock after the surgery.

Discussion: Our case shows a fatal and potentially preventable complication due to ACKD. Without clear guidelines for follow up and majority of the studies on cystic renal diseases excluding patients with ACKD, the true incidence of complications in these patients is not known. We believe an observational cohort study on the lines of Bosniak classification, in patients with advanced CKD/ESRD should be considered such that natural history of this condition, including potential complications e.g. malignancy/bleeding can be better predicted.

SA-PO058

Improvement of Kidney Function by Everolimus in a Patient with Kidney Angiomyolipoma due to Tuberous Sclerosis Complex

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Introduction: Tuberous sclerosis complex (TSC) is a multisystem genetic disorder characterized by growth of hamartomas in various organs throughout the body, including the brain, kidney, and skin. In the kidney, angiomyolipomas occur in most patients with TSC and can lead to kidney failure. Recently, clinical trials with mTOR inhibitors have demonstrated promising results for several indications, such as renal angiomyolipoma, subependymal giant cell astrocytoma. Here we report for the first time a case of kidney angiomyolipoma due to TSC in which kidney function improved after administration of an mTOR inhibitor, everolimus.

Case Description: The patient was a 39-year-old man who had been diagnosed as having TSC associated with facial angiofibromas, brain subependymal nodules and angiomyolipoma in the kidney and liver. He also had neurological symptoms including intellectual disability and seizures. Both kidneys were fully filled with angiomyolipomas, and kidney function had decreased gradually to eGFR 13.7 mL/min/1.73 m^2. Because of his intellectual disability, it had been expected that initiation of dialysis would present many difficulties for him and his family. Therefore, we administered everolimus to preserve the patient's kidney function and to delay the initiation of renal replacement therapy. Although the rate of eGFR decline had been -4.6 mL/min per year before everolimus treatment, the eGFR recovered to 20.2 mL/min/1.73 m^2 (+4.7 mL/min per year) after four months of everolimus administration.

Discussion: Although everolimus has been approved as a new treatment option for TSC patients with kidney angiomyolipoma and is effective for reduction of tumor size, no previous report has indicated that it can improve kidney function. Although this is only a single case report based on short-term observation, everolimus therapy may be a promising new option for TSC patients with kidney insufficiency.

SA-PO059

Gastroparesis in a Patient with ADPKD

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Introduction: ADPKD is associated with cystic enlargement of the kidneys and has rarely been reported to cause mechanical bowel obstruction. Here, we document the first case of a kidney cyst causing gastroparesis in a patient with ADPKD.

Case Description: A 60 yo female with a history of ADPKD was referred with one year of intractable nausea and vomiting with oral intake, chronic right sided abdominal and flank pain, 25lb weight loss and malnutrition. The inability to tolerate any oral nutrition led to repeated hospitalizations for volume depletion. Exam revealed a chronically ill woman, enlarged kidneys, and tenderness to palpation in the right upper quadrant and right flank. Laboratory studies revealed a BUN 8mg/dL, Cr 0.7mg/dL, K 3.5mEq/L, Mg 1.4mg/dL, PO4 1.8mg/dL and albumin 2.9g/dL. CT scan revealed a 9.3cm x 6.5cm cyst in the upper pole of the right kidney directly abutting, but not obstructing, the gastric outlet. Upper endoscopy and endoscopic ultrasound were negative for anatomic lesion or luminal obstruction. A gastric emptying study was performed after withdrawal of anti-emetic, anxiolytic, and opioid medications which revealed a prolonged half-emptying time of 34.5 minutes (normal <19). TPN was initiated after GI consultation. Given the close proximity to the gastric outlet, the decision was made to pursue laparoscopic decortication of the large cyst. Within weeks after the procedure, she was tolerating oral nutrition, without symptoms. TPN was discontinued. Three months post-operatively, she was tolerating an unrestricted diet without need for anti-emetic or analgesic medication. Four months post-procedure a gastric emptying study and gastric motility were entirely normal.

Discussion: Large renal cysts have previously been reported to cause mechanical bowel obstruction, but this report is the first case of a cyst causing delayed gastric emptying without imaging or endoscopic evidence of luminal obstruction. We hypothesize the large renal cyst was an irritant to the nerve plexus responsible for gastric motility in the distal stomach. Decortication of the cyst has provided permanent relief of her abdominal pain, nausea, and vomiting.

SA-PO060

A Mutation of the Gene KLHL3 as a Cause of Gordon Syndrome Olufemi B. Aina, Nobuyuki (Bill) Miyawaki, Joseph Mattana, James Drakakis. *Medicine, Winthrop Univ Hospital, Mineola, NY.*

Introduction: Hyperkalemic hypertension (Gordon Sydrome or pseudohypoaldosteronism type 2) can be defined as a disorder of abnormal regulation of the thiazide sensitive NaCl co-transporter (NCC). There have been several gene mutations implicated, including a gain of function in WNK1 (With No lysine 1) or a loss of function in WNK4. Other genes such as KLHL3 (kelch-like family member 3) and CUL3 (cullin 3) are also involved through interactions with WNK kinases, leading to increased sodium chloride reabsorption. Here, we report a case of adult hypertension and hyperkalemia, ultimately found to have a dominant mutation in the gene KLHL3.

Case Description: A 54 year old male with past medical history of uncontrolled hypertension and long standing hyperkalemia- thought to have caused two cardiac arrests, presented for evaluation. Serum K^+ was consistently 5.8-5.9 mmol/l. Medication list was without offending agent. Family history was significant for hypertension but without obvious inheritance pattern. Laboratory tests showed serum Na^+ 143 mmol/l, Cl^- 103 mmol/l, bicarbonate 21 mmol/l, BUN 18 mg/dl, creatinine 1.32 mg/dl. Plasma renin was suppressed at 0.24 ng/ml and aldosterone was 7.8. Transtubular potassium gradient was 2.3, consistent with failure to appropriately excrete potassium. Given this constellation, a presumptive diagnosis of Gordon syndrome was made and he was started on hydrochlorothiazide 12.5 mg 3x per week and sodium restriction. This led to improved blood pressure and serum K^+ values. During this course, results of genetic testing done several months prior revealed a dominant mutation in the KLHL3 gene.

Discussion: Gordon syndrome involves abnormalities in WNK kinases, proteins that affect the thiazide sensitive NCC. Mutations involving WNK1 and WNK4, or the proteins affecting their degradation can lead to unregulated chloride reabsorption in the distal tubule. Without luminal electronegativity, the driving force for aldosterone mediated potassium and hydrogen secretion is lost. Here, we report a case with high clinical suspicion of Gordon syndrome, confirmed with a discovered mutation in KLHL3, one such protein known to impair degradation of WNK kinases, leading to cellular accumulation.

SA-PO061

A Rare Genetic Cause of Profound Hypomagnesemia in a Patient with a History of an Eating Disorder Vinod Raman, Robert A. Cohen. *Div of Nephrology, Beth Israel Deaconess Medical Center, Boston, MA.*

Introduction: Determining the precise etiology of hypomagnesemia in a patient with an eating disorder history is challenging. We report a case of renal magnesium wasting in such a patient that remained unsolved for over a decade.

Case Description: A 39 year-old female is referred for chronic hypomagnesemia. Complaints: myalgias and palpitations. Past history: major depressive disorder; anorexia nervosa with laxative and diuretic abuse. No family history of renal disease, electrolyte disorders or diabetes. Medications: oral magnesium oxide (4800mg/day with variable compliance); twice weekly intravenous magnesium sulfate. She denies laxative or diuretic use, anorexia or bulimia in recent years. Hypomagnesemia has rarely been associated with hypokalemia. Exam: positive Chvostek sign. Labs: Mg 1.0mg/dL; Na 136mEq/L; K 4.3mEq/L; Cl 98mEq/L; HCO3 31mEq/L; BUN 11mg/dL; Cre 1.1mg/dL; Ca 9.1mg/dL; Phos 3.5mg/dL; Albumin 4.1g/dL, PTH 31pg/mL. Spot urine: Cre 109mg/dL, Na 45mEq/L, K 57mEq/L, Cl 66mEq/L, Mg 7.4mg/dL (serum Mg 1.2mg/dL). FEMg: 8.8%. Urine diuretic screens: negative three times. 24hr urine: 700ml; Cre 629mg; Mg 50mg; Ca 59mg; K 19.5mg. Renal ultrasonography: 8.3cm right kidney; 8.5cm left kidney, with1.2cm upper pole cyst. 24hr cardiac monitoring: frequent PVCs. Differential included occult diuretic use or Gitelman's. Genetic analysis: heterozygous whole gene deletion of the hepatocyte nuclear factor-1-beta (HNF1B) gene.

Discussion: HNF1B variants, which present with hypomagnesemia due to renal magnesium wasting, are most commonly associated with maturity-onset diabetes of the young with renal cysts (MODY5). Variants have also been associated with abnormal renal development or multiple simple renal cysts. Our case phenotypically resembles Gitelman's. It is a rare presentation of an HNF1B mutation given the absence of significant structural abnormalities or diabetes. Hypomagnesemia was previously mistakenly attributed to laxative or diuretic abuse. This case underscores the importance of maintaining a broad differential diagnosis and avoiding premature closure, particularly in a patient with a confounding history.

SA-PO062

2,8-Dihydroxyadenine Crystalline Nephropathy: A Forgotten Cause of Renal Allograft Dysfunction Mohammed Alzubaidi, Raghavesh Pullalarevu, Evelyn Bruner, Sally Self, Maria Aurora C. Posadas. *Medical Univ of South Carolina, Charleston, SC.*

Introduction: We describe a case of 2,8-dihydroxyadenine crystalline nephropathy (DHACN) in renal allograft leading to graft dysfunction. This disease is under-recognized and frequently missed. Complications in renal allograft can be prevented by prophylaxis with allopurinol prior to kidney transplant (txp).

Case Description: 39/F with ESRD due to presumed HTN received a deceased donor kidney. A month after transplant, pt developed AKI with Cr of 5 mg/dL. Renal txp US showed moderate hydronephrosis, not relieved by foley catheter. Kidney biopsy showed no evidence of acute rejection but brown, polarizable, crystalline material within tubular epithelium and lumina consistent with 2,8-DHA crystals. No crystals were identified on urine sediment. Urinary stone risk panel showed elevated oxalate and decreased citrate. Pt was started on allopurinol and sodium citrate. She required anterograde ureteral stent removal as stent broke during cystoscopy. Cr leveled off at 2.4 mg/dL at 4 months. Pt never had personal or familial history of kidney stones and was not on triamterene. Pt was found to have adenine phosphoribosyltransferase (APRT) deficiency by enzymatic activity testing.

Discussion: APRT deficiency is a rare AR disorder of purine metabolism. In the absence of APRT, adenine is oxidized by xanthine dehydrogenase to 2,8-DHA, which is poorly soluble and forms crystals at physiologic urine pH resulting in 2,8-DHA nephrolithiasis and crystalline nephropathy. APRT deficiency is frequently missed, owing to the absence of specific manifestations and lack of awareness of the disease among physicians. In kidney txp pts who are not on prophylactic treatment, 2,8-DHACN can recur in the kidney txp leading to allograft loss in more than 25% of cases. To date, only a few cases of recurrent 2,8-DHACN in kidney txp have been reported. In a series of 9 pts with 2,8-DHACN, diagnosis was missed in all cases prior to txp. 2,8-DHACN after kidney txp can manifest as delayed graft function or primary graft non-function. Management of APRT deficiency includes allopurinol which reduces the generation of 2,8-DHA, fluid intake, and avoidance of purine-rich diet.

SA-PO063

A COL3A1 Gene Mutation in a Young Male with Rupture of a Dissected Renal Artery Aneurysm: A Case Report Rio Noto,[1] Hideki Yokoi,[2] Tomoki Saito,[3] Hiroko Morisaki,[4] Akihiro Yoshimoto,[1] Motoko Yanagita.[2] *[1]Dept of Clinical Nephrology, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan; [2]Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; [3]Dept of Thoracic Surgery, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan; [4]Dept of Medival Genetics, Sakakibara Heart Inst, Hucyu, Tokyo, Japan.*

Introduction: We presented the case at the ASN Kidney Week two years ago, however, we couldn't show the definite diagnosis of a rupture of renal artery aneurysm (RAA) with dissection in a young healthy male. The following genetic testing of specimen demonstrated the disease he actually suffered.

Case Description: A 26 year old male with a history of recurrent pneumothorax presented with progressive left flank pain. A computed tomography angiography (CTA) demonstrated a typical "string of beads" appearance with dissections of bilateral renal arteries and infarctions of bilateral kidneys. On day 8, he suddenly felt severe, left-sided abdominal pain. His hemoglobin decreased from 15.9 g/dl to 11.0 g/dl, and serum creatinine increased from 0.69 mg/dl to 1.52 mg/dl. He received blood transfusion and CTA, showing large retroperitoneal hemorrhage from ruptured left RAA. He was treated with a coil embolization of left renal artery, and then right RAA was embolized two days later with endovascular stent emplacement in right renal artery dissection. His renal function has luckily recovered. Two years later, he underwent video-assisted thoracoscopic bullectomy for recurrent pneumothorax. The DNA sequencing of the lung specimen and whole blood revealed a missense base mutation in the COL3A1 gene (c.3193G>A(p.Gly1065Arg)), which controls the production and assembly of type III collagen.

Discussion: Ehlers-Donlos syndrome (EDS) is a connective tissue disorder composed of several subtypes with distinct genetic and clinical features. The vascular type, EDS IV, represents the most severe form of the disease associated with the COL3A1 gene. Patients frequently experience rupture of arteries and intestine. He is fortunately spared from the next rupture but the same thing can happen anytime. Careful observation is necessary in order to avoid his sudden death.

SA-PO064

New Mutation Identified for Fabry Disease Fernanda Paula Feres Rios Da Costa, Alicia Imada, Luiz Fernando Christiani, Maria Izabel Neves de Holanda. *Nephology, Hospital Federal de Bonsucesso, Rio de Janeiro, Brazil.*

Introduction: Fabry disease affects about 1/40 000 live births X-linked, caused by partial or complete deficiency ofthe enzyme alpha-galactosidase A (alpha-GAL A). The absence of this enzyme leads to the progressive accumulation of neutral glycosphingolipids

with α-galactosyl terminal residue in the plasma and in the lysosomes of endothelial cells of several organs, mainly skin, kidney, cardiovascular system, eye, and brain, which results in functional loss. Clinical manifestations include angiokeratomas, acroparesthesia, anhidrosis, corneal/lens opacification, cardiovascular disease, cerebrovascular and kidney failure. Due to high morbidity and mortality of this disease it is important to recognize and treat it early.

Case Description: We report a case of a patient with a new mutation, never described before that presents severe manifestations.

M.M.C, male patient, 36 years old, presented acroparesthesiarelated to temperature changes since the age of 8y/o, fatigue,arthralgias, headache, tinnitus, extremity edema and reduced cognitive understanding. He was admitted in the emergency room and chronic renal failure was evident in the laboratory exams. He started hemodialysis and was evaluate for several diferential diagnoses. Fabry disease was thinking and the determination of alpha enzyme activity GAL A was collected. The result demonstrate avticity of 0.00 umol / L. The genotype of alpha gene GAL A showed pathological mutation in Exon 3 p.K168Q. This is a new mutation not described before in the literature, but potentially pathogenic. The treatment with enzyme replacement was started and he hadimprovement of symptoms, but didn't recovery renal function. The patient's brother was also screened, and the enzyme activity showed a very low activity and the same mutationwas identified He was diagnosed with Chronic kidney diseaseneeding hemodialysis.

Discussion: This mutation showed how aggressive this disease can be, since this patient had severe symptons and was underdiagnoses. We need to report this new mutations, so we can increase our knowledge about it. The diagnosis and its possible mutations enables early treatment and may prevents disease progression and complications.

SA-PO065

Rare Association of Autosomal Dominant Polycystic Kidney Disease (ADPKD) with Chromophobe Cell Carcinoma in a Young Patient Elena Beznea,[1] Andreea Andronesi,[1] Raluca Bobeica,[1] Bogdan Constantin Haineala,[2] Monica Gratiela Hortopan,[3] Emi Marinela Preda.[3] *[1]Nephrology, Fundeni Clinical Inst, Bucharest, Romania; [2]Urology, Fundeni Clinical Inst, Bucharest, Romania; [3]Pathology, Fundeni Clinical Inst, Bucharest, Romania.*

Introduction: ADPKD is one of the most common genetic disease caused by the mutation of PKD1 and PKD2 genes. There are very few cases described of ADPKD-chromophobe cell carcinoma association.

Case Description: A female patient, aged 32, without significant medical history, is admitted for pain in the lumbar left spine and pollakiuria. A CT-scan was done before in another medical facility which revealed ADPKD and a tumor 35 mm in diameter in the right kidney (RK), incompletely characterized by CT (angiomyolipoma? oncocytoma?). On admission the patient was afebrile, with normal blood pressure, positive Giordano sign on the left side, normal diuresis. The kidney ultrasound confirmed the diagnosis of ADPKD and the presence in the upper pole of the RK of a solid mass with a 38 mm diameter with significant deformation of the capsule, difficult to assess if it was an angiomyolipoma or a calcified cyst. Serum creatinine and urinalysis were normal. There were no inflammation, anemia, or changes in the clotting factors. Immunological assessment and tumor markers were negative kidney MRI was done confirming the polycystic kidneys with cortical cysts type Bosniak I, II and II F, and a RK medio-renal solid mass, possible an oncocytoma or a renal carcinoma with chromophobe cells. A total RK nephrectomy was done in the Urology department. The histiological exam established the positive diagnosis of chromophobe cell kidney carcinoma (the clear and eosinophilic variant).

Discussion: We present the case of a special association between a genetic kidney disease with a very rare histological type of kidney malignancy in the absence of hypertension, hematuria**,** or familly history of kidney cancer.

SA-PO066

Polycythemia and Peritubular Capillary Rarefaction in Two Adolescents Born Prematurely with Extremely Low Birth Weight Nariaki Asada,[1] Takanori Tsukahara,[3] Daisuke Matsuoka,[3] Megumi Furuhata,[6] Shunsuke Noda,[5] Kuniaki Naganuma,[4] Akinori Hashiguchi,[2] Midori Awazu.[1] *[1]Dept of Pediatrics, Keio Univ School of Medicine, Tokyo, Japan; [2]Dept of Pathology, Keio Univ School of Medicine, Tokyo, Japan; [3]Dept of Pediatrics, Shinshu Univ, Nagano, Japan; [4]Dept of Pediatrics, Iida Municipal Hospital, Nagano, Japan; [5]Dept of Pediatrics, Nagano Red Cross Hospital, Nagano, Japan; [6]Dept of Pediatrics, Saku Central Hospital, Nagano, Japan.*

Introduction: Low birth weight (LBW) infants have reduced number of nephrons and are at risk of chronic kidney disease (CKD). While CKD causes capillary rarefaction, LBW and/or prematurity may affect peritubular capillary development.

Case Description: Patient 1 and 2, born at 25 weeks of gestation with birth weight of 466 g and 728 g, showed mild proteinuria at age 6 and 8 years, respectively. In association with increasing proteinuria and blood pressure (BP), polycythemia developed at adolescence. Patient 1 and 2 underwent renal biopsy at age 15 and 18 years, when their BP was 143/59 and 137/82 mmHg, eGFR 90 and 114 ml/min/m^2, hemoglobin 18.7 and 19.0 g/dL, erythropoietin (EPO) 24.5 and 17.8 U/L, respectively. Polycythemia was considered to be due to increased EPO. Light microscopy showed glomerular hypertrophy, focal segmental glomerulosclerosis without severe interstitial fibrosis. Immunohistochemically, CD31- or CD34-positive endothelial cells were reduced showing peritubular capillary rarefaction, which probably resulted in renal hypoxia and elevated EPO. Since kidney function was almost normal and fibrosis was not severe, we considered that the capillary rarefaction was largely attributable to LBW and/or preterm birth. Varsartan was started after the biopsy, and hemoglobin, urinary protein, and BP normalized.

Discussion: Premature decrease of tubular VEGF causes peritubular capillary rarefaction leading to elevated EPO-induced polycythemia (Dimke, J Am Soc Nephrol 2015). VEGF expression becomes reduced with exposure to extrauterine relative hyperoxia after premature birth. Placental insufficiency also suppresses VEGF in the embryonic kidney. We therefore considered that the capillary rarefaction seen in our patients was caused by premature delivery and/or LBW.

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SA-PO067

A Case of Epstein Syndrome with Slower Development of Kidney Impairment Miki Yarita, Naoki Sugano, Maiko Furuya, Nobuo Tsuboi, Yoichi Miyazaki, Makoto Ogura, Gorou Tokudome, Takashi Yokoo. *Nephrology and Hypertention, The Jikei Univ School of Medicine, Minato-ku, Tokyo, Japan.*

Introduction: It is estimated that there are about 200 patients suffered from Epstein syndrome (ES) around the world. This is an autosomal dominant hereditary disease characterized by sensorineural hearing loss, macrothrombocytopenia, and nephritis. ES is also known as myosin heavy chain 9-related disorder. Generally, renal biopsy cannot be undergone because of severe thrombocytopenia, however in this case, he was received Eltrombopag, which raise platelet count, therefore he could be received renal biopsy.

Case Description: The patient is 29 years old male with progression of proteinuria. In X-24, thrombocytopenia was identified, and he was diagnosed as Idiopatic thrombocytopenic purpura . Although steroid therapy was administered, platelet count was about 10,000. In X-11, he visited the department of Hematology of our hospital, and was suspected to be ES, due to macrothrombocytopenia, bilateral sensorineural hearing loss and deterioration in renal function. In X-8, he was referred to our department of outpatient. Since the proteinuria increased, Lisinopril was administered under routine monitoring. Because of thrombocytepenia, renal biopsy was not possible to perform ever, however, since he was received Eltrombopag, the drug which raise platelet count, and in X-1, platelet count was increased to 80,000, therefore he was able to receive renal biopsy.His histological change is focal segmental glomerulosclerosis, typical finding of ES. However, usual clinical course of ES presents end stage of renal disease by age 20 in most cases, however his clinical course was not be similar to typical course. Genetic examination was conducted, and it was revealed that the gene variation of him is MYH9 R702 mutation. Consequently, he was duly diagnosed as ES and was confirmed to be administered Lisinopril continuously.

Discussion: Taking into account the slower development of kidney impairment, renal protective effect was foreseen by a long term administration of Lisinopril. Further investigation is expected to review the effectiveness of inhibition of RAS for the patients suffered from kidney impairment caused by gene variation in MYH9.

SA-PO068

Everolimus Can Induce Regression of Inferior Vena Cava and Renal Vein Tumour Thrombus in Invasive Renal Angiomyolipoma Emily J. See,[1] Simon T. Wood,[2] Nicole Isbel.[1] *[1]Dept of Nephrology, Princess Alexandra Hospital, Brisbane, Australia; [2]Dept of Urology, Princess Alexandra Hospital, Brisbane, Australia.*

Introduction: Tuberous sclerosis complex (TSC) is a genetic disorder characterised by multi-organ hamartomatous lesions, which frequently involve the kidney. The most common renal manifestation is angiomyolipoma (AML). Tumour thrombus invasion into the renal vein and inferior vena cava (IVC) is a rare complication and usually necessitates nephrectomy with tumour thrombectomy. Everolimus, an inhibitor of Mammalian target of rapamycin (mTORi), has been shown to have efficacy in reducing the size of uncomplicated renal AMLs, however its use in complicated disease has not been described.

Case Description: We report the case of a 19-year-old female with TSC manifesting as bilateral renal AMLs with normal biochemical function; cortical tubers with frequent seizures and neuropsychiatric deficits; myocardial involvement without outflow tract obstruction; and facial angiofibromas. She had previously experienced a life threatening retroperitoneal haemorrhage which required embolisation. On surveillance imaging, she was found to have extension of her right renal AML into the renal vein and IVC. There were no features to suggest renal cell carcinoma. To avoid the risks associated with extensive surgery, she was commenced on everolimus 10mg daily. Within 3 months, she experienced improvement in seizure frequency, neurocognitive function and cutaneous disease. The dose was increased to 15mg daily in split dosing to achieve trough levels of 5-10. At 6 months, partial regression of the IVC tumour was demonstrated on MRI. By 12 months, there was complete resolution of the IVC and renal vein tumour and reduction in the size of the intra-renal AMLs. Drug toxicity included mouth ulcers and intermittent mild neutropenia.

Discussion: This is the first reported case of tumour thrombus regression with everolimus in complicated renal AML. Traditionally, vascular invasion has been managed surgically due to the risk of cardiac or pulmonary tumour embolus, however operative intervention of this nature involves significant morbidity. Treatment with mTORi in patients with aggressive disease including tumour thrombus warrants consideration.

SA-PO069

Rothia Mucilaginosa Peritonitis Khurram Mehtabdin, Mala Sachdeva. *Div of Nephrology and Hypertension, Northwell Health, Great Neck, NY.*

Introduction: Peritonitis is a known complication in patients who are on peritoneal dialysis (PD) and is usually caused by *Staphylococcus* species, *Escherichia Coli*, and *Pseudomonas Aeruginosa.* Physicians should be aware of uncommon causes of bacterial peritonitis. We report a rare case of *R.mucilanginosa* peritonitis requiring catheter removal. To date, there have been only 5 reported cases of *Rothia mucilaginosa* peritonitis*, formerly known as Stomatococcus mucilaginosus* associated with PD.

Case Description: We report an 80 year old male on PD for eight years, with a history of *Bacillus* peritonitis four years prior who presented with nausea, vomiting, abdominal pain, and cloudy effluent. The patient had a history of poor dentition with numerous dental procedures in the years prior including tooth extractions and a jaw fracture with subsequent oral surgery. Initial cell count revealed 1856 total nucleated cells, and 97% polys. Final culture grew *Stomatococcus mucilaginosus*. The patient was started on intraperitoneal vancomycin. Day 5 cell counts showed 708 total nucleated cells and 90% polys, with the culture being negative. The patient continued to report malaise, weakness, and lack of appetite. Day 8 counts showed total nucleated cell count of 43, 85% polys; however the culture was again positive. Due to refractory peritonitis, his PD catheter was removed and he began hemodialysis.

Discussion: *R. mucilagnosa* is an encapsulated gram-positive, coagulase negative organism found in pairs, clusters and tetrads. It is considered to be part of the normal flora of the mouth or respiratory tract. Risk factors for this organism include dental work as this species has also been found in dental caries and plaques, indwelling catheters, leukemia, valvular disease, intravenous drug use, severe neutropenia or immunocompromised state. Prior cases have demonstrated this organism to be susceptible to penicillins. Despite treatment, the patient presented had refractory peritonitis, requiring removal of the PD catheter. Our case illustrates the importance of quick diagnosis and timely treatment in patients with rare organisms causing peritonitis.

SA-PO070

IVC Filter Migration Associated with Bilateral Renal Vein Thrombosis Treated with Thrombolytic therapy Arouna Senthilkumar, Benjamin Ling, Julia Schneider. *Nephrology and Hypertension, Hines VA Hospital, Hines, IL.*

Introduction: Little is known about the migration of IVC filters. Here we present a case of dislodged IVC filter, bilateral renal vein thrombosis with acute renal failure successfully treated with *tissue plasminogen activator (tPA).*

Case Description: 87 year old man with history of PE twice and a lower extremity DVT in 2014 treated with Warfarin but complicated by GI bleeding. VenaTech IVC filter was placed and Warfarin was stopped. He presented to the ED 10 days later with bilateral lower extremity edema, gross hematuria and acute oliguric renal failure. His baseline creatinine was 0.9mg/dl but on presentation was 3.4 mg/dl. Creatinine continued to rise by 1mg/dl per day. He was not volume depleted, not septic. There were no new medications. A non-contrast CT scan showed that the IVC filter migrated above the renal veins. There was also an ill-defined high density in the IVC suspicious for thrombus. A venogram demonstrated an IVC thrombus at the level of pre-existing filter, bilateral renal ostia and a suprarenal IVC. A venous duplex did not demonstrate new DVT in the lower extremities. The filter could not be retrieved. He underwent catheter guided thrombolysiswith 4 mg of *tPA* in each renal vein and 8mg in the inferior vena cava. Next, fogarty balloon was used for a pullback thrombectomy in the bilateral renal veins. Slow local tPA infusion (a total of 8mg overnight) was started. The next day, surveillance venogram showed significant improvement in clot burden. The renal function started to improve in 48 hours. Creatinine stabilized at 2mg/dl by discharge. He did not require dialysis during this admission.

Discussion: We report a second case of renal failure due to bilateral renal vein thrombosis associated with IVC filter migration. This was successfully treated with low dose tPA without having to retrieve IVC filter. At about two months after presentation creatinine had returned to normal. This report highlights that renal vein thrombosis is a rare but serious complication of IVC filter movement and that it could be treated non-surgically.

SA-PO071

A Case Report of Erdheim-Chester Disease Involving the Kidney and Retroperitoneum Vinay Srinivasa. *Medicine, Gold Coast Univ Hospital, Gold Coast, Queensland, Australia.*

Introduction: Erdheim-Chester Disease (ECD) is a rare non langerhans cell histiocytosis neoplasm, that has multi organ involvement The renal and retroperitoneum can be the primary sites of involvement and account for 30% of cases. We present an interesting case report of a gentleman who presented with multiple episodes of obstructive oliguric acute kidney injury with hydronephrosis who required repeat ureteric stenting. CT with non contrast revealed soft tissue thickening surrounding the left kidney. Open biopsy of this tissue showed features of ECD. Interestingly our case had a right nephrectomy for Renal cell Carcinoma in 2002. Retrospective review of biopsy showed features of ECD.

Case Description: Our patient initially presented to the nephrology outpatient clinic with deteriorating renal functions that were previously normal. He had multiple episodes of acute kidney injury with associated hydronephrosis on renal ultrasound. Ureteric stents were placed and his renal functions improved. CTKUB scan revealed a 15 mm soft tissue thickening around the left kidney which was not present in his initial CT scan. Open biopsy of the perinephric tissue showed features of ECD marked by histiocytes within the perinephric tissue. The biopsy was tested for the BRAF V600 mutation and was positive. He was commenced on Dabrafenib, an oral BRAF inhibitor.

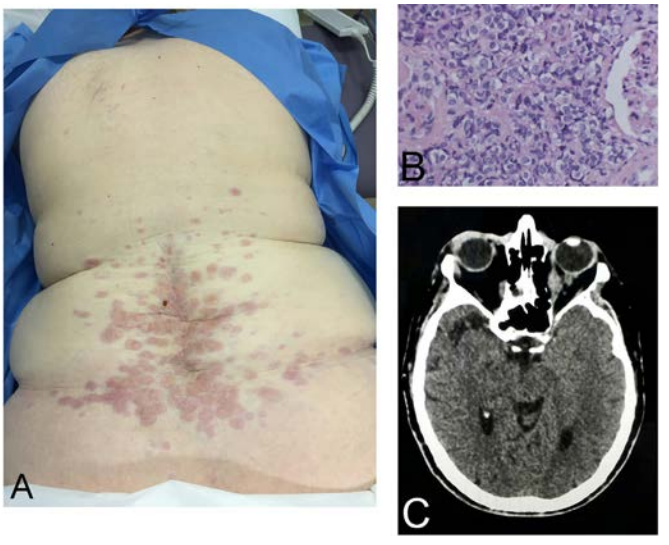
Discussion: Since its first description in 1930, over 500 cases of ECD have been reported. Common clinical manifestations include bone pain, diabetes insipidus and neurological complaints. Hydronephrosis, abdominal pain and dysuria are chief renal complaints. Retroperitoneal fibrosis illustrates retroperitoneal involvement. CTKUB reveals perinephric and peri-ureteric thickening giving the hairy kidney sign. Biopsy reveals xanthogranulomatous inflammation that may be BRAF mutation positive. BRAF mutation positive status has important implications; it is a tumour responsive mutation. Good response rates have been achieved using oral BRAF inhibitors. It is a potent therapeutic agent that can improve survival to a disease that was previously fatal.

SA-PO072

Breast Adenocarcinoma Infiltrates the Kidney and Skin Dearbhla Kelly,[1] Gasim Ahmed,[1] Anthony M. Dorman,[2] Liam F. Casserly.[1] *[1]Dept of Nephrology, Univ Hospital Limerick, Limerick, Ireland; [2]Dept of Pathology, Beaumont Hospital, Dublin, Ireland.*

Introduction: Kidney disease frequently complicates malignancy or its treatment. Renal failure in this setting is often multi-factorial. It includes pre-renal causes such as volume depletion, intrinsic renal disease such as membranous nephropathy or amyloidosis, and obstructive disease due to lymphadenopathy or retroperitoneal fibrosis.

Case Description: A 68-year-old woman presented with lower limb swelling and a nodular skin rash *(Figure 1A).* She had a non-oliguric acute kidney injury (AKI) (peak serum creatinine 360 µmol/L). Her urinalysis showed trace blood and 1+ protein. Renal ultrasound showed normal sized kidneys without hydronephrosis. Kidney biopsy *(Figure 1B)* showed diffuse parenchymal infiltration by malignant cells. The tumour cells were large with little cytoplasm, hyperchromatic nuclei and prominent nucleoli. They showed vacuolization with PAS-positive material. The features were most suggestive of high-grade breast adenocarcinoma. Breast examination revealed a hard mass in her left upper outer quadrant. The breast needle core biopsy confirmed invasive ductal carcinoma. Computerized tomography scans detected metastatic disease affecting her left orbit (*Figure 1C)*, peritoneum, vertebral bodies and pelvis. A punch skin biopsy from the left inframammary region was also consistent with infiltrative carcinoma.



Discussion: Although renal parenchymal invasion by solid and hematologic cancers is not uncommon, AKI in this context is unusual. Lymphomas and leukaemias are the most common culprits with metastatic extrarenal solid tumors causing AKI being especially rare. Those cases severe enough to cause acute renal failure are typically associated with widespread parenchymal replacement in both kidneys as in this case. Large kidneys in the absence of hydronephrosis are suggestive of tumor infiltration.

SA-PO073

Squamous Cell Carcinoma of the Renal Pelvis Associated with Nephrolithiasis Bryan Tucker, Anushree C. Shirali. *Section of Nephrology, Yale Univ School of Medicine, New Haven, CT.*

Introduction: Primary squamous cell carcinoma (SCC) is uncommon among kidney tumors, comprising less than 1% of renal cancers. We report a case of rapidly metastatic SCC of the renal pelvis associated with nephrolithiasis.

Case Description: A 55 y.o. female was admitted with bilateral hydronephrosis and acute kidney injury (AKI). Her history included stage 4 chronic kidney disease from bilateral staghorn calculi. CT imaging demonstrated cortical thinning on the right kidney and bilateral hydronephrosis (figure 1). To salvage residual renal function, she underwent a left percutaneous nephrolithotomy. This was complicated by a bleed requiring a left nephrostomy tube (NT). Her AKI progressed rapidly to ESRD requiring hemodialysis. At outpatient follow-up, she had pain around the NT site with a non-erythematous, tender bulge at her left flank, which CT scan reported as a 6.5cm soft tissue collection. She was re-admitted with a fever and growing flank mass. Repeat CT scan (Figure 2) revealed serial extension of the mass along the tract of the NT site. Differential diagnoses included abscess, hematoma or malignancy. Biopsy established the diagnosis of metastatic squamous cell carcinoma of the renal pelvis urothelium. The patient refused chemotherapy and one month later she died of malignancy related complications.

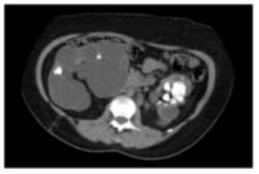


Figure 1. CT scan demonstrating severe hydronephrosis in both kidneys with staghorn calculi. Right kidney also shows cortical thinning.

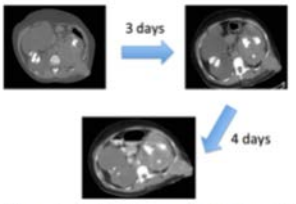


Figure 2. Serial CT scans displaying rapid extension of the left flank mass. Top arrow (from left to right) shows progression of the mass in 3 days, while the downward arrow shows progression over the next 4 days.

Discussion: Though rare, the incidence of kidney SCC is increased with nephrolithiasis, particularly with staghorn calculi. Other risk factors include horseshoe kidney, tobacco use, recurrent pyelonephritis, and use of phenacetin-containing analgesics. Early diagnosis is critical but kidney SCC is asymptomatic till later stages. As illustrated by our case, metastatic disease can be aggressive and has poor outcomes. At this stage, prognosis is poor even with radical nephroureterectomy with bladder cuff removal and chemotherapy, with overall 1-year survival at 52% and 5-year survival at 10%.

SA-PO074

Renal Manifestations of Leptospirosis Josef Bautista, Andrew Rogers, Jie Tang. *Section of Hypertension and Nephrology, Dept of Medicine, Rhode Island Hospital - Brown Univ, Providene, RI.*

Introduction: In the setting of infection, acute kidney injury is usually secondary to renal hypoperfusion and cytokine-induced inflammation, but not the infectious organism itself. Rarely, however, the infectious organism can directly injure the glomeruli and renal tubules. The net results are decreased glomerular filtration and electrolyte or acid-base disorders. In this case we present a patient with severe leptospirosis who developed acute kidney injury (AKI), hypokalemia, glucosuria, and non-anion gap acidosis. We also review the existing literature regarding the effects of leptospirosis on the renal tubules.

Case Description: A 55-year-old male with no significant past medical history presented with jaundice, myalgia and malaise. He had non-oliguric acute kidney injury with a creatinine of 10 md/dl, thrombocytopenia, transaminitis, hyperbilirubinemia and rhabdomyolysis. Physical examination revealed normotension, icterus, pulmonary crackles and no rash. Notable laboratory findings included serum potassium of 3.1 mg/dl, bicarbonate of 11 meq/L with anion gap of 10, and a urinalysis showing glucosuria with normal serum glucose. Urine microscopy showed muddy brown casts and renal tubular epithelial cells. He was treated with ceftriaxone for presumed leptospirosis, which was later confirmed by urine PCR. He became anuric within 24 hours, coincident with worsening pulmonary status. He was intubated and started on renal replacement therapy until his renal function recovered. On follow-up his hypokalemia and glucosuria resolved.

Discussion: This case highlights the several renal manifestations of leptospirosis, i.e. hypokalemia, proximal tubular dysfunction and acute tubular necrosis. While it is well established that Leptospira sp can directly injure the renal tubule and interstitium, more recent evidence also showed that Leptosiral infection could lead to altered expressions of sodium-hydrogen antiporter 3 and Na-KCl cotrasporter channels. Taken together, we can better appreciate the pathophysiologic mechanisms of the classic electrolyte and acid-base disorders associated with Leptospirosis infection.

SA-PO075

Atypical Presentation of Primary Renal Lymphoma Syed Rizwan A. Bokhari,[1] Abeera Mansur,[1] Maria Rizwan Bokhari.[2] *[1]Nephrology, Doctors Hospital and Medical Center, Lahore, Pakistan; [2]Radiology, Jinnah Hospital, Lahore, Pakistan.*

Introduction: Primary renal lymphoma (PRL) is a very rare disease, accounting for less than 1 % of extra nodal lymphomas. Usually renal tissue is devoid of lymphoid tissue, but it can be involved in cases of disseminated disease. We present a case of a young patient with bilaterally enlarged kidneys.

Case Description: 21-year-old male medical student presented with a 4-month history of left shoulder pain, continuous fever (100-101^0) and weight loss (13 lbs in 4 months) down to 53kg. He developed dull, generalized abdominal pain a week before presentation. There was no previous history of diabetes, hypertension, cardiovascular, hepatic, pulmonary or kidney disease. Patient received multiple courses of antipyretics, antibiotics, steroids and NSAIDS from local practitioners with no improvement. Personal and family history were insignificant. Examination no significant positive physical findings.

Laboratory data showed complete blood count within normal limits, chemistry panel indicated renal dysfunction with baseline creatinine of 1.3 that had increased to 2.1 over the last 2 months, no electrolyte or liver function tests abnormality was noted. Urine complete exam and culture sensitivity were unremarkable. Autoimmune profile, complement levels, thyroid function tests, lipid, coagulation and Infectious profile were all within normal limits. X rays of chest and left shoulder were normal. Ultrasound abdomen showed bilateral enlarged kidneys with grade I echogenicity, size had increased compared to a prior scan. Percutaneous renal biopsy revealed B cell CD 20, Ki-67, CD3 and Tdt positive lymphoblastic Non Hodgkin Lymphoma (NHL). CT scan of chest, abdomen and pelvis revealed bilateral diffuse enlargement of kidneys with heterogenous enhancement. No mediastinal or abdominopelvic lymphadenopathy was noted. Patient was referred to oncologist for NHL chemotherapeutic treatment. Patient is on regular follow up after chemotherapy with creatinine of 1.2.

Discussion: Although PRL is quite uncommon, it should be distinguished from other causes of renal enlargement, mainly renal cancer and infectious etiology apart from metastatic involvement. Prompt diagnosis and timely management can help as promising outcome.

SA-PO076

An Odd Thyroid Nodule Adel S. Haque,[1] Charles Thomas Tucker,[2] Matthew J. Diamond.[1] *[1]Div of Nephrology, Medical College of Georgia at Augusta Univ, Augusta, GA; [2]Coastal Nephrology Associates, Brunswick, GA.*

Introduction: The greatest risk of recurrence of Renal Cell Carcinoma (RCC) is within five years after nephrectomy. Current guidelines suggest active surveillance for recurrence of RCC for five years after removal. Rarely, RCC can recur ten years or more after nephrectomy, mostly in the contralateral kidney or a pulmonary lesion. We present a case of RCC recurrence solely as a solitary thyroid nodule twenty years after treatment of primary RCC with radiation and nephrectomy.

Case Description: A 76-year-old female was recently started on hemodialysis (HD) via a tunneled catheter in her right internal jugular vein. She has a history of RCC managed with a total right nephrectomy and radiation therapy twenty years before starting HD. Shortly after starting HD, she complained of dysphagia, as well as a new neck mass. Examination revealed a rapidly-enlarging thyroid nodule. All lab results, including thyroid function studies, were unremarkable. Ultrasound (US) guided fine needle aspiration of the nodule yielded non-discrete results leading to surgical excision. The patient underwent total thyroidectomy; subsequent pathology identified a 3.5x4.5x7.5cm hypervascular mass in the right lobe of the thyroid. Sectioning and staining of the mass confirms the recurrence of RCC, which was positive for CD10 and PAX-2, along with having a classic chicken-wire vascular appearance and clear cells on histologic analysis. US of the remaining kidney and whole-body PET/CT scan did not delineate further areas of malignancy, suggesting the recurrence of RCC was confined to the thyroid.

Discussion: While the bulk of RCC recur within five years of curative nephrectomy, long-term recurrence has been reported after a decade. Our patient is unique, as she presented with a thyroid nodule that was the discreet recurrence of her RCC excised two decades prior. Although RCC has been shown to metastasize to the thyroid, recurrence of RCC solely in the thyroid has not been reported in English literature. The findings of the case support the notion that any new mass in a patient treated for RCC should be considered a potential recurrence of the disease, even beyond the five-year active surveillance window.

SA-PO077

Bence Jones Cast Nephropathy in Two Patients with Lymphoma Amanda DeMauro Renaghan,[1] M. Lia Palomba,[2] Carol S. Portlock,[2] Steven Salvatore,[3] Surya V. Seshan,[3] Ilya Glezerman.[4] *[1]Nephrology, NY-Presbyterian Hospital/Cornell, NY; [2]Oncology, Memorial Sloan Kettering Cancer Center, NY; [3]Pathology, NY-Presbyterian Hospital/Cornell, NY; [4]Nephrology, Memorial Sloan Kettering Cancer Center, NY.*

Introduction: Monoclonal immunoglobulins may lead to renal damage through multiple pathogenetic mechanisms, so called monoclonal gammopathies of renal significance (MGRS). Most patients with cast nephropathy have multiple myeloma, while this pattern of injury is rarely seen in lymphoma. We present two cases of MGRS due to light chain (LC) cast nephropathy in patients with indolent lymphoma.

Case Description: 55 year old man with indolent marginal zone lymphoma (MZL) who was managed expectantly until he developed fever and night sweats. Exam: Notable for lymphadenopathy, splenomegaly. Labs: Cr 2.5 mg/dL, WBC 15.0 K/mcL, hemoglobin 10.0 g/dL, 2.91 g/dL M-spike (IgG lambda), free lambda LC 140 mg/dL. Urine studies: Trace protein, 2 RBCs and 2 WBCs per HPF, no casts on urinalysis (UA); 2.8 g protein on 24 hr urine collection; 33.9 mg/dL M-spike on UPEP. Kidney biopsy revealed abnormal tubular casts staining positive for monoclonal lambda LC consistent with cast nephropathy, as well as diffuse interstitial atypical lymphoid infiltrates consistent with extranodal MZL. Cr improved with steroids and hydration. Chemotherapy was administered several weeks later. 51 year old man with Stage IV lymphoplasmacytic lymphoma and normal baseline Cr who was monitored expectantly. Routine labs: Cr 6.4 mg/dL, WBC 5.7 K/mcL, hemoglobin 7.8 g/dL, 0.33 g/dL M-spike (IgM kappa), free kappa LC 236 mg/dL. Urine studies: 30 mg/dL protein, 2 RBCs and 2 WBCs per HPF on UA; spot urine protein/Cr 2; 87.0 mg/dL M-spike on UPEP. Kidney biopsy revealed extranodal low-grade B-cell neoplasm involving the renal tubulointerstitium and atypical tubular casts staining for kappa LC consistent with cast nephropathy. The patient was treated with chemotherapy. Most recent Cr was 2.8 mg/dL.

Discussion: We present two unique cases of MGRS presenting as cast nephropathy in patients with lymphoma. They highlight the relationship between the presence of LC and the development of renal damage, and underscore the role for therapies aimed at reducing the malignant clone and decreasing LC production.

SA-PO078

IgG4-Related Kidney Disease in a Patient with Plasma Cell Dyscrasia Chandrashekar Kashyap,[1] Anees Quyyumi,[1] Alton Brad Farris,[2] Kyle Bradley.[2] *[1]Dept of Nephrology, Emory Univ, Atlanta, GA; [2]Dept of Pathology, Emory Univ, Atlanta, GA.*

Introduction: IgG4-related disease (IgG4-RD) is an immune-mediated disease with manifestations in various organs. IgG4-RD has been increasingly recognized in nephrology for its role in causing acute or chronic renal failure. We report a case of a 80 year old male with plasma cell dyscrasia who presented with progressive renal failure. Kidney biopsy showed IgG4 related tubulointerstitial nephritis.

Case Description: An 80 year old Black male was referred to the Renal Clinic for evaluation of worsening renal function. Past medical history included plasma cell dyscrasia (diagnosed 2013) with stable plasma cells on bone marrow biopsy, hypothyroidism, hypertension, chronic pancreatitis and lymphadenopathy. He was asymptomatic with normal physical exam and blood pressure of 140/78. Lab Results: Baseline SCr was 0.89mg/dL in Aug 2014. SCr ranged from 3.1 to 3.7mg/dL from Oct 2015 to Jan 2016. SCr was 3.97 in Feb 2016. Complements were low; Autoimmune screen, hepatitis panel and HIV were negative; Serum IgG level was high at 4220mg/dL; Kappa/Lambda Ratio 1.86. Serum protein electrophoresis revealed IgG kappa paraprotein and urine electrophoresis spotted a faint IgG paraprotein band. Urine dipstick positive for 1+ protein. Proteinuria of 652mg/24hr was noted on 24 hr urine study. Kidneys showed normal size and echogenicity with no hydronephrosis on Renal ultrasound. A 3.5 x 3.4 x 3.2 cm cyst was seen in the interpolar right kidney. Kidney biopsy in Mar 2016 confirmed IgG4 related tubulointerstitial nephritis. Key biopsy findings were: Lymphoplasmacytic inflammation with dense IgG4+ plasma cell infiltrate, eosinophils and storiform fibrosis. Immunohistochemistry showed 50-100 IgG4+ plasma cells/high power field. IgG4/IgG ratio > 40%. Patient was started on prednisone at 40mg/day.

Discussion: IgG4-RD can masquerade many infectious, malignant and inflammatory conditions. This case illustrates the need to consider IgG4-related kidney disease as a potential differential in the workup of CKD and AKI. Thorough history and physical exam is vital as it can affect multiple organs. Early identification is necessary as it is a potentially treatable disorder.

SA-PO079

Diffuse Large B-Cell Lymphoma Localized in Peritubular Capillaries Diagnosed by Percutaneous Kidney Biopsy Kenji Harada,[1] Kosuke Masutani,[2] Kazuhiko Tsuruya,[2] Hidetoshi Kanai.[1] *[1]Div of Nephrology, Kokura Memorial Hospital, Kitakyusyu, Fukuoka, Japan; [2]Dept of Medicine and Clinical Science, Kyushu Univ, Fukuoka, Japan.*

Introduction: Diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype of non-Hodgkin's lymphoma, and gastrointestinal DLBCL is a frequent form of extranodal lymphoma. We hereby report a rare case of DLBCL showing various neurological symptoms and diagnosed by kidney and bone marrow biopsy.

Case Description: A 38-year-old Japanese male developed disturbance in gait, general fatigue, and nausea. He also developed urinary disturbance, and saw a neurologist. Physical examination revealed patellar tendon hyperreflexia, and paresthesia in both legs. Blood test showed increased alkaline phosphatase, lactate dehydrogenase, C reactive protein and soluble interlueukin-2 receptor levels. Thoracolumbar MRI revealed high intensity area in Th11, and brain MRI revealed multiple white matter lesions, suggesting malignant lymphoma (ML). The patient was transferred to our hospital for further examination. Random skin biopsy, and cytology of cerebrospinal fluid failed to diagnose ML. But we found abnormal uptake in bone marrow and bilateral kidneys on positron emission computerized-tomography (PET). Although urinary abnormalities and renal dysfunction were not evident, we performed percutaneous kidney biopsy as well as bone marrow biopsy. Kidney biopsy sample included six glomeruli in which one showed global sclerosis, and five non-sclerotic glomeruli did not show any abnormal findings. Moderate lymphoplasmacytic interstitial infiltration and minimal interstitial fibrosis/tubular atrophy were noted. The most striking finding on kidney biopsy was atypical cells localized in peritubular capillaries. We also found atypical cells in bone marrow, and the diagnosis of DLBCL was made. The patinet was treated with systemic chemotherapy and up-front auto peripheral blood stem cell transplantation (PBSCT), finally complete remission was achieved.

Discussion: This case serves as a reminder of the differential diagnosis of ML, and the usefulness of kidney biopsy to confirm diagnosis when a patient presents abnormal uptake in the kidney on PET.

SA-PO080

Post Transplant Mucormycosis: A Case Series of Four Patients with Pulmonary and Rhino-Orbital Involvement Louisette Soussan, Christopher Richard Kern, Gregory Malat, Dong Heun Lee, Alden Michael Doyle, Karthik M. Ranganna, Sandeep Aggarwal. *Transplant Nephrology, Drexel Univ College of Medicine.*

Introduction: Mucormycosis is a rare but fatal fungal infection that occurs in immunocompromised patients. Risk factors include DM, malignancies, radiation, cirrhosis, AKI, immunosuppression, neutropenia, burns/trauma, transplants and malnutrition. Here, we report 4 cases of Mucormycosis infection in kidney transplant recipients.

Case Description: All patients received Thymoglobulin (6mg/kg) as induction therapy. For maintenance immunosuppression, all received Tacrolimus (goal 6-8) and Prednisone 5 mg and either Mycophenolate mofetil (3 patients) or Azathioprine (1 patient). All patients were on standard immunoprophylaxis. Mean creatinine was 1.28±0.47 mg/dL. Mean HbA1C during the post-transplant period was 6.43±1.02. Median time from transplant to infection was 470 days (IQR 193, 853). All patients were treated with liposomal Amphotericin B; in addition, two received Isavuconazonium. Demographics/Individual patient data in table 1.

Age (years)	Sex	Ethnicity	Etiology of ESRD	Site of Infection	Specific Risk Factors	Comments
63	F	Black	DM	Rhino-orbital	Chronic mastoiditis /Cholesteatoma	ocular enucleation
65	M	Black	HTN	Disseminated Pulmonary	COPD/inhaled steroids	h/o RCC
74	F	Indian	DM	Rhino-orbital	Thyroid radiation/ epidural steroid injections	h/o BK viremia
65	M	White	DM	Localized Pulmonary	COPD/inhaled steroids	Had episode of AHR & received PLEX/ IVIG & Rituximab

Cell cycle inhibitors were stopped. Tacrolimus dose was reduced with levels maintained around 2-5 ng/mL. Both patients with pulmonary Mucormycosis died. One of the two patients with rhino-orbital disease survived requiring enucleation of the eye with resolution of infection and a functioning allograft.

Discussion: Mucormycosis, though a rare fungal infection, can result in a fatal outcome in kidney transplant recipients. In patients with risk factors, high clinical suspicion is essential for early diagnosis . Prompt use of adequate antifungal therapy along with surgical debridement/resection is critical for better outcomes.

SA-PO081

Development of a Functional Glomerulus at the Organ Level on a Chip to Mimic Hypertensive Nephropathy Mengying Zhou. *Dept of Nephrology, The First Affiliated Hospital of Dalian Medical Univ, Dalian, Liaoning, China.*

Introduction: To develop a microfluidic rapid evaluating of multi-inductors device to reproduce the structure and function of glomeruli. And studying the effect of glomerular hemodynamic on glometular filtration function under hypertension by microfluidic devise.

Case Description: This device consists of PDMS and polycarbonate membrane. Glomerular endothelial cell (MGEC) and podocyte (MPC-5) were co-cultured on the chip. MGEC cells and MPC-5 cells of each culiture unit were incubated under flow rate of 5μl/min, 10μl/min, 15μl/min medium. After 0h, 6h, 12h and 24h, the function of GFB were detected by liuorescence microplate, the expression of F-actin, CD-31, vWF of MGEC cells and F-actin, synaptopodin, nephrin, podocin of MPC-5 cells weredetected by immunofluorescent staining.The cell apoptosis was assessed by DAPI staining.

Compared with traditional cell-culture, MGEC cells and MPC-5 cells grew well and morphological features showed no significant change cell apoptosis.When MGEC cells and MPC-5 cells were treated with medium under 20μl/min, the function of GFB was promoted and the distribution of F-actin was changed. When MGEC cells and MPC-5 cells were treated with medium under flow rate of 10μl/min and 15μl/min.The function of GFB was impaired and the distribution of F-actin was changed obviously. CD-31 decreased and vWF increased progressively over flow rate increasing and time extend. Nephrin and podocin, markers of MPC-5 cells, deceased progressively over flow rate increasing and time($P<0.05$). The cell apoptosis increased under 15μl/min for 24h ($P<0.05$).

Discussion: This work provides an reappearance of the hypertransfusion, high filtration and high transmembrane pressure in glomerular capillary when hypertension leads to renal blood flow decompensation by adjusting the fluid infusion speed on glomerular microfluidic device which confirmed directly that the abnormal hemodynamic factors can degrade GFB function by injuring the skelemin of endothelial cells and podocytes and ligandin between cells.

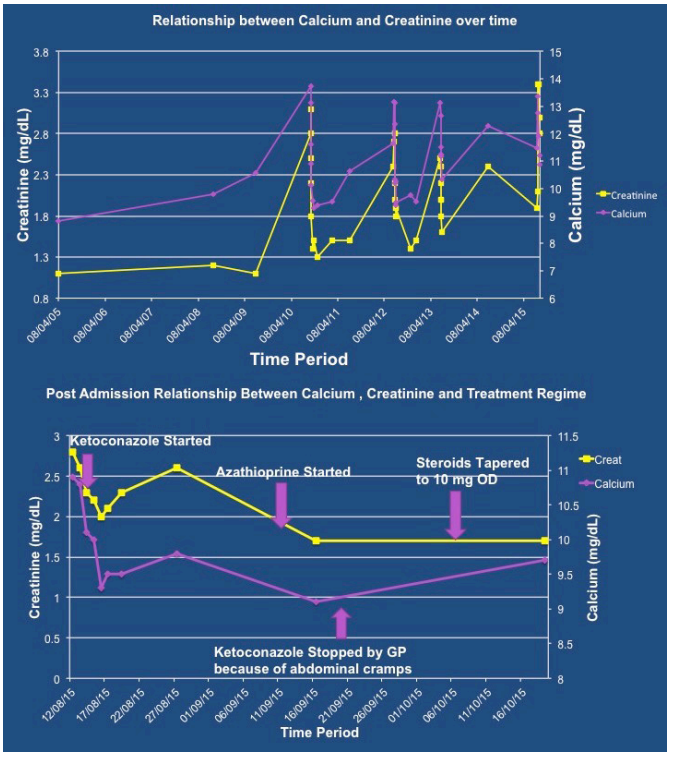
Funding: Government Support - Non-U.S.

SA-PO082

Treatment in the Absence of Guidelines: Ketoconazole Sucessfully Resolves Hypercalcemia-Associated Acute Kidney Injury in Steroid-Resistant Sarcoidosis: A Case Report Muhammad Umair Sharif,[1,2] Mohamed Elsayed,[1,2] Ahmed Alghali,[1,2] Maurice O'Farrell,[2] Austin G. Stack.[1,2,3] *[1]Graduate Entry Medical School (GEMS), Univ of Limerick, Limerick, Ireland; [2]Dept of Nephrology, Univ Hospital Limerick, Limerick, Ireland; [3]Health Research Inst (HRI), Univ of Limerick, Limerick, Ireland.*

Introduction: Sarcoidosis is a multisystem granulomatous disease of unknown etiology characterized by the presence of non-caseating granulomas. Hypercalcaemia associated with sarcoidosis exhibits seasonal variability with peak incidence during summer months associated with elevated production of 1, 25 $(OH)_2$ Vitamin D. The impact of this on short-term and long-term kidney function and the extent to which it can be managed with corticosteroid treatment is poorly understood.

Case Description: Herein, we report on the case of a 64year male who presented to our unit with acute kidney injury (AKI) (peak creatinine 3.38 mg/dL) and moderate hypercalcemia (peak calcium 13.2 mg/dL) on a background of sarcoidosis, chronic kidney disease (CKD) and type II diabetes. Serum calcium levels failed to normalize despite two-weeks of high dose oral corticosteroid therapy and high volume normal saline infusion. Treatment with oral ketoconazole (200mg once daily) resulted in an immediate and sustained reduction in serum calcium levels with subsequent resolution of his AKI. A careful review of the patient's previous ten-year medical history revealed a seasonal pattern to his hypercalcemic episodes, corresponding with maximum daylight hours and triggering severe AKI.



Discussion: This report demonstrates the need for 1) vigilant monitoring of serum calcium levels among patients with sarcoidosis especially during summer months, 2) normalization of hypercalcaemia to prevent AKI, 3) the efficacy of ketoconazole in steroid-resistant hypercalcaemia, and the need for 4) frequent longitudinal surveillance of kidney function in sarcoidosis.

SA-PO083

Phospholipase C γ 2 Is Required for the Renal Adaptation to Alkalosis
Nicolas Picard,[1] Igor E. Deyev,[2] Pascal Houillier,[1] Alexander Petrenko.[2] *[1]Centre de Recherche des Cordeliers, INSERM/CNRS, Paris, France; [2]Laboratory of Receptor Cell Biology, Inst of Bioorganic Chemistry, Moscow, Russian Federation.*

Background: Renal intercalated cells contribute to renal acid and base handling by modulating proton or bicarbonate secretion in the distal nephron. Bicarbonate loading stimulates bicarbonate secretion by β-intercalated cells (β-IC). To better understand the regulation of such processes, transcriptomic analysis of mouse connecting tubule (CNT) and collecting duct (CD) was performed to identify novel CNT/CD-enriched gene products. It identified the phospholipase C gamma 2 (PLCG2) as a protein expressed in the CNT/CCD. PLCG2 is part of the transduction pathways activated by membrane receptors such as tyrosine kinase receptors. PLCG2 is usually phosphorylated and its activity parallels its phosphorylation level. This study aims at understanding the role of this enzyme in the distal nephron.

Results: Colocalisation experiments with a specific β-IC marker (Pendrin) indicated that PLCG2 was expressed only in β-IC cells in human and mouse kidney. $NaHCO_3$ loading in the mouse increased renal PLCG2 phosphorylation whereas acid loading decreased it. To assess the role of PLCG2 in bicarbonate handling, PLCG2 null mice ($PLCG2^{-/-}$) were treated by NaHCO3 (0.28M in drinking water) for 14 days. After 3 days of the $NaHCO_3$ load, blood HCO_3^- was higher in $PLCG2^{-/-}$ mice than in $PLCG2^{+/+}$ ($PLCG2^{+/+}$ 27.6 ± 2.1 mM vs $PLCG2^{-/-}$ 33.6 ± 1.7 mM $p<0.05$). Blood HCO_3^- difference persisted after 14 days of $NaHCO_3$ treatment ($PLCG2^{+/+}$ 27.4 ± 0.8 mM vs $PLCG2^{-/-}$ 32.0 ± 1.5 mM $p<0.05$). Insulin receptor-related receptor (IRR) is a receptor tyrosine kinase activated by alkaline pH and is specifically expressed in β-IC where it increases distal bicarbonate secretion. Overexpression of both IRR and PLCG2 in HEK293 cells stimulated PLCG2 phosphorylation upon exposure to an alkaline medium. IRR inhibition by linsitinib blunted the effect of the alkaline medium on PLCG2 phosphorylation.

Conclusions: Overall, we propose that PLCG2 is important for the renal adaptation to alkaline load and may be part of the signaling pathway downstream to IRR in renal intercalated cells.

SA-PO084

Monophosphoryl Lipid A Prevents Inhibition of Bicarbonate Absorption by LPS in Medullary Thick Ascending Limb (MTAL) Through a TLR4-PI3K-Akt Pathway
Bruns A. Watts,[1] Thampi George,[1] Edward R. Sherwood,[2] David W. Good.[1] *[1]Univ TX Medical Branch; [2]Vanderbilt Univ Medical Center.*

Background: Monophosphoryl lipid A (MPLA) is a detoxified derivative of LPS that is used as a vaccine adjuvant in humans due to its immunomodulatory properties. MPLA functions as a TLR4 agonist to augment the innate host response to infection and pretreatment with MPLA reduces inflammation and increases survival in models of sepsis and endotoxemia. Whether MPLA may protect against sepsis- or LPS-induced kidney dysfunction is not known. Previously we demonstrated that LPS inhibits HCO_3^- absorption in the MTAL through a basolateral TLR4-ERK signaling pathway. Here we examined whether pretreatment of MTALs with MPLA would attenuate the effect of LPS to inhibit HCO_3^- absorption and the mechanisms involved.

Results: MTALs from rats were perfused in vitro with MPLA (1 µg/ml) in bath and lumen or bath alone for 2 hr, then LPS was added to (and MPLA removed from) the bath solution. Pretreatment with MPLA eliminated the effect of LPS to inhibit HCO_3^- absorption. In contrast, in MTALs pretreated with MPLA plus a phosphatidylinositol 3-kinase (PI3K) or Akt inhibitor, LPS decreased HCO_3^- absorption by 26%. Treatment with MPLA increased Akt phosphorylation 1.4-fold in dissected MTALs. The activation of Akt by MPLA was eliminated by a PI3K inhibitor and in MTALs from TLR4-deficient mice. Pretreatment of MTALs with MPLA prevented LPS-induced ERK activation; this effect of MPLA was eliminated by a PI3K inhibitor. Thus, blocking activation of PI3K or Akt by MPLA restored the ability of LPS to activate ERK and inhibit HCO_3^- absorption in MPLA-treated MTALs. MPLA alone had no effect on HCO_3^- absorption, indicating an ability of MPLA to convey resistance to LPS without inherent toxicity.

Conclusions: We conclude that pretreatment with MPLA prevents the effect of LPS to inhibit HCO_3^- absorption in the MTAL. This effect is mediated through MPLA stimulation of a TLR4-PI3K-Akt pathway, which prevents LPS-induced ERK activation. These studies show that MPLA induces protection against LPS in MTAL cells and identify TLR4-based immunomodulators as potential novel therapeutic agents to prevent or treat sepsis-induced renal tubule dysfunction.

Funding: NIDDK Support

SA-PO085

The NH3-H+ Transport Stoichiometry of Human SLC4A11
Xuesi Max Shao,[2] Liyo Kao,[1] Ira Kurtz.[1] *[1]David Geffen School of Medicine, UCLA, Los Angeles, CA; [2]Dept of Neurobiology, UCLA, Los Angeles, CA.*

Background: SLC4A11 was reported to be capable of functioning as a NH_3-H^+ co-transporter (Zhang et al. 2015) with a transport stoichiometry of 1 NH_3:2 H^+, and a suggested role in renal ammonia handling. The use of conventional reversal potential (E_{rev}) methods without a specific inhibitor to estimate the transport stoichiometry can be inaccurate due to currents mediated by other plasma membrane endogenous channels/electrogenic transporters.

Methods: HEK-293 cells expressing SLC4A11 were whole-cell voltage clamped, and steady state currents were measured at various voltages to obtain the I-V relationships. We first analyzed the I-V relationship using the delta current method (Shao et al. 2014). The NH_4Cl concentration in the patch pipette ($[NH_4Cl]_i$) was 1 mM, and the bath NH_4Cl concentration ($[NH_4Cl]_o$) was switched from 1 mM to 3 mM. The NH_3-H^+ transport stoichiometry was also estimated by recording the I-V relationship of HEK-293 cells expressing SLC4A11 and the I-V relationship of mock-transfected cells, with 1 mM $[NH_4Cl]_i$ and 3 mM $[NH_4Cl]_o$. The SLC4A11-specific IV curve was obtained by subtracting the mean I-V curve of mock-transfected cells from the mean I-V curve of SLC4A11-expressing cells.

Results: Using the delta current method, the NH_3-H^+ transport stoichiometry calculated according to: $2RT/(FV_2)\ln(\Delta I_{V2}/\Delta I_{V1=0})$, was 1 NH_3:2.94 H^+ (n = 14) or ~ 1:3, where ΔI_{V2} is the delta current at V2 = -10 mV, and $\Delta I_{V1=0}$ is the delta current at V1 = 0 mV. In the second series of experiments, the E_{rev} of the SLC4A11-specific I-V curve (SLC4A11-expressing cells, n = 14; mock-transfected cells, n= 8) was -8.6 mV which approximates the expected E_{rev} value of -9.3 mV for a 1 NH_3:3 H^+ stoichiometry calculated according to: $RT/(F(Z_p p+Z_q q))\ln(([NH_3]_i/[NH_3]_o)^p([H^+]_i/[H^+]_o)^q)$ when p = 1 and q = 3; where p is the stoichiometry of NH_3, q is the stoichiometry of H^+, Z_p is the valence of NH_3 (Z_p = 0), and Z_q is the valence of H^+ (Z_q = 1).

Conclusions: We used two independent methods to determine the NH_3-H^+ transport stoichiometry of SLC4A11 that correct for bias due to endogenous channel/transporter currents. Our results consistently demonstrate that the SLC4A11 transport stoichiometry is 1 NH_3:3 H^+.

SA-PO086

Normal Intrinsic Na/HCO3 Cotransport Activity but Altered Plasma Membrane Abundance of Phosphomimetic NBCe1-A Mutants
Evan J. Myers, Aniko Marshall, Mark Parker. *Physiology and Biophysics, SUNY at Buffalo, Buffalo, NY.*

Background: Renal phosphoproteomic studies by others have revealed two in-vivo phosphorylation sites (Ser982 and Ser985) on the cytosolic C-terminus of the renal Na/HCO_3 cotransport NBCe1-A that can exhibit a phosphorylated state either individually (pS982 or pS985) or in tandem (pS982/pS985). Others have suggested that dephosphorylation of Ser982 can change the Na:HCO_3 stoichiometry from 1:2 (as observed in most heterologous expression systems) to 1:3 (as predicted, but rarely observed, in kidney cells).

Methods: In order to probe the phosphorylation status of the NBCe1-A C-terminus in our experiments, we generatednovel phosphospecific antibodies designed to detect the singly phosphorylated state pS982/S985 or the doubly phosphorylated state pS982/pS985. We also created a series of EGFP-tagged phosphomimetic mutants D982/A985, D982/D985, A982/D985, and A982/A985. To investigate the consequence of phosphorylation, we performed western blotting on cell extracts, two-electrode voltage clamp on *Xenopus* oocytes heterologously expressing NBCe1-A, and immunofluorescence on MDCK-II cells.

Results: We detected both phosphorylation states of NBCe1-A in mouse kidney and *Xenopus* oocytes. Our electrophysiological studies reveal that all phosphomimetic mutants exhibit a similar per-molecule HCO_3-dependent cotransport activity and a reversal potential consistent with a 1:2 stoichiometry. However, biotinylation assays and fluorescence microscopy on oocytes reveal significant differences in plasma membrane abundance among the mutants, notably A982/D985 was least abundant (75% less abundant than D982/D985). In polarized MDCK-II cells all mutants except A982/D985 consistently localized to the basolateral membrane; 3 of 6 cells transfected with A982/D985 exhibited evidence of intracellular NBCe1-A retention.

Conclusions: Our data confirm that Ser982 and Ser985 are phosphorylated in vivo and suggests that the phosphorylation status of Ser982 influences plasma membrane abundance but not activity. Our antibodies will allow us to probe changes in the phosphorylation state of these two residues in response to physiological and pathological cues.

SA-PO087

Proximal Tubule Glutamine Synthetase Expression Is Necessary for the Normal Response to Dietary Protein Restriction Hyun-Wook Lee,[1] Gunars Osis,[1] Mary E. Handlogten,[1] Chao Chen,[1] Jill W. Verlander,[1] I. David Weiner.[1,2] *[1]Nephrology, Univ of Florida College of Medicine, Gainesville, FL; [2]Nephrology and Hypertension Section, NF/SGVHS, Gainesville, FL.*

Background: Dietary protein restriction has multiple benefits in kidney disease. Because protein intake is a major determinant of endogenous acid production, it is important that net acid excretion decreases during protein restriction. Glutamine synthetase (GS) catalyzes the reaction of NH_4^+ and glutamate, which regenerates the essential amino acid, glutamine, and can decrease net ammoniagenesis. GS is highly expressed in the proximal tubule, and its expression increases during dietary protein restriction. This suggests ammonia recycling via GS during protein restriction could decrease net ammoniagenesis and decrease ammonia excretion. The current study's purpose was to determine proximal tubule GS's role in the renal response to protein restriction.

Methods: We generated mice with proximal tubule-specific GS deletion (PT-GS-KO) using Cre-loxP techniques. Cre-negative control (C) and PT-GS-KO mice in metabolic cages were fed 20% protein diet for 2 days and were then changed to low protein (6%) diet for the next 7 days. Additional PT-GS-KO mice were maintained on 20% protein diet.

Results: Dietary protein restriction caused a rapid decrease in urinary ammonia in both genotypes, but the decrease was significantly less in PT-GS-KO mice. There were no significant genotype-dependent differences in urinary pH or volume, or in ABG parameters. Immunoblot analyses of cortical and medullary homogenates from mice fed 6% protein showed no differences between C and PT-GS-KO mice in expression of other proteins involved in renal ammonia handling, including NHE3, PDG, PEPCK, NKCC2 and Rhbg. In PT-GS-KO mice fed either 20% or 6% protein diet, mice fed 6% protein had decreased discrete apical H-ATPase a4 subunit, apical Rhcg and basolateral Rhbg immunolabel in medullary collecting duct intercalated cells compared to 20% protein fed mice, consistent with decreased H^+ and NH_3 transport mediated ammonia secretion.

Conclusions: Proximal tubule glutamine synthetase is necessary for the expected decrease in ammonia excretion during dietary protein restriction.

Funding: NIDDK Support, VA Support

SA-PO088

Expression of Sodium-Dependent Dicarboxylate Transporter 1 (NaDC1/SLC13A2) in Normal and Neoplastic Human Kidney Hyun-Wook Lee,[1] Gunars Osis,[1] Mary E. Handlogten,[1] William L. Clapp,[2] Dara N. Wakefield,[2] Jill W. Verlander,[1] I. David Weiner.[1,3] *[1]Nephrology, Univ of Florida College of Medicine, Gainesville, FL; [2]Pathology, Univ of Florida College of Medicine, Gainesville, FL; [3]Nephrology and Hypertension Section, NF/SGVHS, Gainesville, FL.*

Background: Regulated citrate excretion is critical to acid-base homeostasis and to prevention of calcium nephrolithiasis. Luminal citrate reabsorption via NaDC1 is believed to be the primary mechanism regulating renal citrate excretion. However, the cellular distribution of NaDC1 expression in human kidneys has not been reported previously. The purpose of the present study was to determine the expression of NaDC1 in normal and neoplastic human kidneys.

Methods: We used commercially available human kidney protein lysates for immunoblot analysis and used kidneys removed for routine clinical treatment that were no longer needed for diagnostic purposes for immunohistochemical analyses. We used previously described anti-NaDC1 antibodies validated for specificity using NaDC1 knockout mice.

Results: Immunoblot analysis of human whole kidney and cortical protein isolates demonstrated expression of a protein of ~58 kDa. Immunohistochemistry showed apical NaDC1 immunolabel in the proximal tubule of normal human kidney tissue; well-preserved proximal tubule brush border was clearly labeled. We confirmed proximal tubule localization by double-immunolabel with antibodies to NBCe1. No NaDC1 immunolabel was detected in other renal cells. NaDC1 immunolabel was not detected in renal tumors of presumed proximal tubule origin, clear cell and papillary renal cell carcinoma.

Conclusions: In summary: 1) this is the first study reporting the cellular expression of NaDC1 in the human kidney; 2) in human kidney, NaDC1 is present in the apical region of the proximal tubule including the brush border, which is identical to NaDC1 distribution in mouse and rat kidney; and, 3) detectable NaDC1 immunolabel is not present in renal cell carcinoma derived from proximal tubule cells, likely indicating cellular dedifferentiation. These studies support a similar role for NaDC1 in the human kidney as identified in experimental rodent studies.

Funding: NIDDK Support, VA Support

SA-PO089

In Silico and In Vitro Characterization of Low pH-Induced Genes in Intercalated Cells of the Collecting Ducts Yuichiro Izumi,[1] Koji Eguchi,[1] Naomi Matsuo,[1] Yushi Nakayama,[1] Hideki Inoue,[1] Hiroshi Nonoguchi,[2] Yutaka Kakizoe,[1] Takashige Kuwabara,[1] Masashi Mukoyama.[1] *[1]Dept of Nephrology, Kumamoto Univ, Kumamoto, Japan; [2]Dept of Internal Medicine, Kitasato Univ Medical Center, Saitama, Japan.*

Background: Recent studies have suggested that metabolic acidosis exacerbates chronic kidney disease. Dietary acid intake accumulates acids in interstitium of the kidney. The effect of low pH on renal tubular cells is unclear. We have presented transcriptional start site-sequencing (TSS-Seq) of low pH-induced gene transcripts in the intercalated cells of the collecting ducts at Kidney Week 2015. In the present study, we further performed comprehensive analyses to characterize the global effect of low pH on intercalated cells and molecular biology experiments to support the findings obtained from the analyses.

Methods: We performed Gene Ontology (GO) and motif analyses for low pH-induced gene transcripts obtained from TSS-Seq using a rat intercalated cell line (IN-IC cells) that are incubated either in pH 7.4 or 7.0 for 24h. To evaluate ubiquitin-proteasome pathway, cells were incubated either in pH 7.4 or 7.0 for 12h, then further incubated in the presence of MG132, a proteasome inhibitor, for 8h. Western blotting was examined using anti-ubiquitin antibody. Quantitative PCR was examined to measure the expressions of specific mRNAs after cells were incubated either in pH 7.4 or 7.0.

Results: GO analysis showed the enrichment of genes that are classified into "programmed cell death": Fgf2, Jak2, Tgm2, and Gclc. Those genes are known to be involved in renal fibrosis. We found many ubiquitin-proteasome system (UPS)-related genes up-regulated by low pH: six ubiquitin protein ligases, five ubiquitin conjugating enzymes, two deubiquitinating enzymes, and four other genes involved in UPS. Western blot showed that low pH induced global ubiquitination of protein. Motif analysis predicted motif sequences associated with low pH-induced transcription that possibly interact with specific transcription factors such as EGR1, SP1, and KLF5. We found that the expression of EGR1 mRNA was immediately increased by low pH in 2h.

Conclusions: The results implied various possible mechanisms that are involved in acidosis-induced renal injury.

Funding: Government Support - Non-U.S.

SA-PO090

Why Does SLC26A7 Not Compensate the Loss of kAE1 in Distal Renal Tubular Acidosis? A.K.M. Shahid Ullah,[1] Rawad Lashhab,[1] Jennifer C. King,[3] Valentina Peleh,[2] Johannes M. Herrmann,[2] R. Todd Alexander,[1] Emmanuelle Cordat.[1] *[1]Dept of Physiology, Univ of Alberta, Edmonton, AB, Canada; [2]Cellular Biology, Univ of Kaiserslautern, Kaiserslautern, Germany; [3]Univ of Calgary, Calgary, AB, Canada.*

Background: SLC26A7 and kidney anion exchanger 1 (kAE1) proteins are Cl^-/HCO_3^- exchangers that are both expressed at the basolateral membrane of the α-intercalated cells in the medullary collecting duct of the kidney. Mutations in the kAE1 gene or knockout of the SLC26A7 gene can cause distal renal tubular acidosis (dRTA) in humans and mice, respectively. This study aimed to clarify the role of the SLC26A7 protein in renal epithelial cells under physiological or pathological conditions. We hypothesized that the SLC26A7 activity is compromised in dRTA patients due to the loss of kAE1.

Methods: MDCK cells expressing SLC26A7 were grown in either normal, hypertonic or acidic growth conditions to mimic the medulla and dRTA environment, respectively, and the protein were examined by immunoblot. kAE1 or SLC26A7 functions were examined using the pH-sensitive fluorescent probe BCECF-AM.

Results: Comparison of SLC26A7 or kAE1 abundance when expressed in Madin-Darby Canine Kidney (MDCK) cells grown in normal or hypertonic conditions showed that, in contrast with kAE1, SLC26A7 is upregulated by hyperosmotic conditions. Functional assays showed an increase in the SLC26A7 anion exchange activity after incubation in hypertonic conditions. However, growing MDCK cells under acidic conditions, as occurs in dRTA patients, resulted in decreased abundance of SLC26A7 suggesting that in dRTA patients, SLC26A7 is downregulated and unable to compensate for the loss of kAE1 protein. Furthermore, total anion transport was reduced in cells co-expressing both SLC26A7 and kAE1 R901X dRTA mutant compared to cells expressing individual proteins, suggesting an inhibitory effect of one protein on the other when co-expressed.

Conclusions: This study provides insight into the physiological role of SLC26A7 in kidney epithelial cells under various hyperosmotic or low extracellular pH conditions and thus an explanation for the lack of a compensatory effect of SLC26A7 in dRTA patients.

Funding: Government Support - Non-U.S.

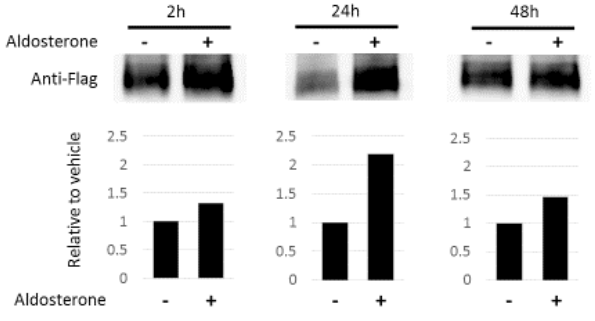
SA-PO091

Involvement of Aldosterone and the Ubiquitin-Proteasome System in the Regulation of Expression of an Ammonia Transporter, Rhesus Blood Group C Glycoprotein, in the Intercalated Cells Koji Eguchi, Yuichiro Izumi, Yushi Nakayama, Hideki Inoue, Yutaka Kakizoe, Takashige Kuwabara, Naomi Matsuo, Terumasa Nakagawa, Masashi Mukoyama. *Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan.*

Background: Acid-base balance is regulated by aldosterone which stimulates acid secretion in the intercalated cells of the collecting ducts of the kidney. Rhesus blood group C glycoprotein (Rhcg) is an ammonia transporter which cooperates with H^+-ATPase to secrete H^+ from the intercalated cells. We presented in Kidney Week 2015 that aldosterone induces the expression of Rhcg in membrane fraction *in vivo* and *in vitro*. In the present study, we further investigated the regulation mechanism of Rhcg.

Methods: We established a cell population of IN-IC cells (a rat intercalated cell line) stably expressing mouse Flag-tagged Rhcg (Rhcg-Flag). Cells were treated with aldosterone (10^{-6} M) for 2, 24, and 48 h, and then membrane fraction was extracted. To see whether the ubiquitin-proteasome system (UPS) is involved in the regulation of Rhcg, cells were treated with MG132, a proteasome inhibitor, and whole cell lysates were extracted. Immunoprecipitation using anti-Flag antibody was performed to examine coimmunoprecipitation with ubiquitin. Western blotting was applied with anti-Flag and anti-ubiquitin antibodies.

Results: Treatment with aldosterone increased the expression of Rhcg-Flag in membrane fraction by 30, 120, and 50 % at 2, 24, and 48 h, respectively.



Treatment with MG132 (5 to 50 uM) increased the expression of Rhcg-Flag protein in whole cell lysates in a dose dependent manner. Immunoprecipitation showed that Rhcg-Flag was coimmunoprecipitated with ubiquitin.

Conclusions: These results indicate that aldosterone and UPS should regulate the expression of Rhcg protein, suggesting a crosstalk between aldosterone and UPS in the intercalated cells.

SA-PO092

The Stimulation of Ammoniagenesis Plays an Important Role in the Development of Renal Hypertrophy in Diabetes Mellitus Hassane Amlal, Sihame Amlal, Sulaiman Sheriff. *Internal Medicine, Univ of Cincinnati, Cincinnati, OH.*

Background: Studies have shown that total ammonia ($NH_4^+ + NH_3$) causes renal cell hypertrophy *in vitro* and that diabetes mellitus (DM) is associated with an early increase in kidney mass. However, whether hyperglycemia-induced ammoniagenesis plays a role in the development of early renal hypertrophy in DM remains elusive.

Methods: Rats treated with streptozotocin (STZ) and Akita mice and their wild-type (Type I DM); *ob/ob* mice and their lean controls (Type II DM) and adenine-treated rats (model of renal failure) and their controls were housed in metabolic cages for food and water balance studies. Urinary NH_4^+ excretion was analyzed and correlated with changes in kidney mass (kidney weight/BW).

Results: STZ-treated rats exhibited a significant increase in Kidney mass, which correlated with a 4-fold increase in urinary NH_4^+ excretion as early as 6 days of hyperglycemia. The stimulation of ammoniagenesis is corrected by insulin treatment. Hyperglycemic Akita mice showed a 4-fold increase in NH_4^+ excretion at 4 weeks and kidney mass doubled at 9 weeks of age vs. wild-type mice. Similarly, *ob/ob* mice exhibited a sharp hyperglycemia which correlated with a 7-fold increase in NH_4^+ excretion with significant increase in kidney mass at 9 weeks of age vs. lean mice. Lastly, normoglycemic adenine-treated rats exhibited a sharp increase in ammoniagenesis with 32% increase in kidney mass after 1 week of treatment vs. controls.

Conclusions: The development of renal hypertrophy correlates with early hyperglycemia-induced ammoniagenesis in both type I and type II DM models. The stimulation of ammoniagenesis also correlated with early renal hypertrophy in the adenine fed rat model known to progress to renal failure. Hence, ammoniagenesis likely contributes to the development of early renal hypertrophy, which subsequent progresses to kidney disease in diabetes mellitus and in the adenine-fed animals.

Funding: NIDDK Support, Clinical Revenue Support

SA-PO093

Interaction of the Renal NH3/NH4+ Transporters Rh Glycoproteins with Cellular Proteins Involved in Acid-Base Homeostasis Nazih L. Nakhoul,[1,2] L. Lee Hamm,[1] Karen Brown,[1] Solange Abdulnour-Nakhoul.[1,2] *[1]Medicine, Tulane Medical School, New Orleans, LA; [2]SLVHCS.*

Background: Renal excretion of NH_4^+ accounts for at least two-thirds of net acid excretion and increases significantly during acid loads. In the collecting duct, two Rh glycoproteins, Rhbg and Rhcg, expressed in the intercalated cells are involved in trans-cellular NH_3 and NH_4^+ transport. Our earlier studies showed that Rhbg transported NH_4^+ and NH_3, whereas Rhcg predominantly transported NH_3. Little is known about regulation of these transporters. Recent data indicate that Rh proteins may interact with other cellular proteins. In this study, we examined whether Rhbg and Rhcg associate with specific membrane proteins known to affect acid-base transport.

Methods: We determined the association of Rhcg with pendrin (both at the apical membrane) and Rhbg and Rhcg with carbonic anhydrases (CA IV & CA II). We used immunohistochemistry to co-localize Rhbg, CA IV, CA II and pendrin in mouse kidney sections. We then used co-immunoprecipitation of kidney lysates from either medulla or cortex to investigate the association of the specific proteins with Rh transporters.

Results: We used Rhbg antibody (Rhbg-ab) bound to activated magnetic beads to pull down CA IV and Rhcg-ab to pull down pendrin. The reverse configuration and appropriate controls were also used. The eluates were examined by Western analysis. The blots showed positive staining for Rhbg in the eluates when Rhbg or CA IV antibodies were coupled to the beads, and positive staining for CA IV when CA IV or Rhbg antibodies were on the beads. Similar results were obtained with pendrin and Rhcg. Immuno-precipitating Rhcg with H-ATPase was negative. To confirm the co-IP results we demonstrated that pulled-down Rhbg band was glycosylated (at 50 KD) and that it can be de-glycosylated (to 37 KD) similar to the native Rhbg in kidney lysates. Lastly, using pH measurements by microelectrodes we showed that co-expressing Rhbg with CA IV in frog oocytes attenuated NH_3/NH_4^+ transport by Rhbg.

Conclusions: These data are consistent with association of Rhbg with CA IV and Rhcg with Pendrin. It is likely that this interaction may affect expression, trafficking or regulation of NH_3/NH_4^+ by the Rh proteins.

Funding: VA Support

SA-PO094

Insulin Stimulates Renal Proximal Tubule Sodium Transport via Akt2/mTORC2 Pathway Motonobu Nakamura,[1] Masashi Suzuki,[1] Nobuhiko Satoh,[1] George Seki,[2] Atsushi Suzuki,[1] Yusuke Sato,[3] Yukio Homma,[3] Shoko Horita,[1] Masaomi Nangaku.[1] *[1]Dept of Internal Medicine, The Univ of Tokyo Hospital; [2]Yaizu City Hospital; [3]Dept of Urology, The Univ of Tokyo Hospital.*

Background: We found that the IRS2/PI3K-dependent stimulation of renal proximal tubule (PT) sodium transport by insulin is preserved even in insulin resistance or overt diabetic nephropathy (JASN 16, 2005, Kidney Int 87, 2015, BBRC 461, 2015), indicating that hyperinsulinemia, by facilitating sodium retention, may contribute to hypertension associated with these pathological conditions. The roles of Akt isoforms or mammalian target of rapamycin complex (mTORC1/2) have been well established in insulin-stimulated glucose uptake into adipocytes. However, the roles of these protein kinases in insulin-mediated PT sodium transport regulation remain unknown.

Methods: By monitoring cell pH decrease in response to bath HCO_3 reduction with a pH-sensitive dye BCECF, we measured Na-HCO_3 cotransporter (NBCe1) activity in freshly-isolated rat PTs or human PTs obtained during surgery for renal cell carcinoma. For rat PTs, we also measured NBCe1 activity after 24-hr incubation with siRNA against Akt1, Akt2, Raptor (an mTORC1 component), or Rictor (an mTORC2 component).

Results: In freshly-isolated rat and human PTs 10^{-8} M insulin induced 50-80% increase in NBCe1 activity above baseline, and this stimulation was completely suppressed by Akt1/2 inhibitor VIII. Furthermore, incubation with siRNA against Akt2, but not Akt1, completely suppressed the stimulatory effect of insulin in rat PTs. While an mTORC1/2 inhibitor PP242 completely suppressed the insulin-mediated NBCe1 stimulation in rat and human PTs, an mTORC1-specific inhibitor rapamycin failed to affect the insulin effect. Moreover, siRNA against Rictor, but not Raptor, completely suppressed the insulin-mediated NBCe1 stimulation in rat PTs. Consistent with the essential roles of Akt2 and mTORC2, Akt1/2 inhibitor VIII and PP242, but not rapamycin, strongly suppressed the insulin-induced Akt Ser^{473} phosphorylation in renal cortex of rats and humans.

Conclusions: Stimulation of PT sodium transport by insulin is mediated via Akt2/mTORC2 pathway, which may be a therapeutic target for hypertension in metabolic syndrome.

Funding: Government Support - Non-U.S.

SA-PO095

Gprc5c - A Renal GPR Involved in Systemic pH Homeostasis Premraj Rajkumar,[1] Boyoung Cha,[2] Mark Donowitz,[2] Jennifer L. Pluznick.[1] *[1]Physiology, Johns Hopkins SOM, Baltimore; [2]Medicine & Physiology, Johns Hopkins SOM, Baltimore; [3]Molecular Membrane Neuroscience, RIKEN Brain Science Inst, Japan.*

Background: Recent studies have identified orphan G-protein coupled receptors (GPRs) as sensors of physiological metabolites. Our goal is to elucidate the functional role of an understudied renal GPR, Gprc5c, which we previously found to be highly expressed in the kidney (Rajkumar et al., 2014).

Methods: Immunofluorescence (IF) was performed on mouse kidney sections. Ligand-induced GPCR internalization assays were performed in HEK293T cells. Blood pH and electrolytes were measured using iSTAT (CG4+ & CHEM8+) and blood pressure by tail cuff. Ratiometric fluorescence was measured in BCECF-AM loaded HEK293T cells using a PTI spectrofluorometer.

Results: We find that Gprc5c localizes to the apical renal proximal tubules (PTs) in wild-type (WT) mice by IF, where it colocalizes with two PT markers - LTA & megalin. Staining was absent in Gprc5c knockout (KO) mice. In an *in vitro* assay, alkaline pH (but not other chemicals tested) triggered Gprc5c internalization (an index of activation), with maximal internalization seen above pH 7.4 (pH 8.0>pH 7.4>pH 6.5). Other GPCRs tested as controls showed no changes in internalization over the pH range tested. *In vivo*, Gprc5c KO were not different from WT with respect to blood pressure, kidney/body weight, blood levels of Na^+, Cl^- & glucose, and urine levels of creatinine & glucose. However, Gprc5c KO had higher urine pH (WT: 5.48±0.01, n=6; KO: 5.81±0.06, n=6; p<0.05). In addition, the blood pH of Gprc5c KO mice trends acidic compared to WT in unanaesthetized mice (WT: 7.44±0.04, n=4; KO: 7.34±0.02, n=4; p=0.07), or in mice under isofluorane (WT: 7.22±0.03, n=5; KO: 7.03±0.04, n=5; p<0.05). Furthermore, in an *in vitro* assay Gprc5c increases sodium proton exchange under alkaline conditions (pH8) by 1.6 fold compared to empty vector controls (p<0.05); this increase is Tenapanor-sensitive, implying that it is mediated via NHE3 (a transporter which localizes apically in the renal PT).

Conclusions: Gprc5c localizes to the renal PTs apically where it contributes to systemic pH homeostasis via modulation of NHE3 function.

Funding: Private Foundation Support

SA-PO096

Decreased Renal Threshold for Urinary Excretion of Ammonia Underlies Proximal Renal Tubular Acidosis in TASK2 K Channel-Deficient Mice

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Background: TASK2 (TWIK-related acid-sensitive K^+ channel)-deficient ($task2^{-/-}$) mice showed metabolic acidosis (Warth et al, 2004) and may be a good model for proximal renal tubular acidosis (pRTA). However, the pathophysiological mechanism by which this metabolic acidosis occurs has yet to be elucidated.

Methods: In $task2^{+/+}$ (WT) and $task2^{-/-}$ (KO) mice, we investigated the effects of acid/alkali-containing diet on blood and urine data to evaluate the maximum capacity of the renal acid/base transport system. We also investigated the acid/alkali-load-induced changes on immunostainings of carbonic anhydrase type II (CAII) and phosphoenolpyruvate carboxykinase (PEPCK) in the kidney.

Results: We confirmed that KO mice fed normal diets showed hyperchloremic metabolic acidosis (pH 7.24 (KO) vs. pH 7.37 (WT), n=6 each, $P < 0.005$) with negligible urinary excretion of both HCO_3^- (1.1 +/- 0.3 µmol/d) and NH_3/NH_4^+ (1.0 +/- 0.2 mg/mgCre). Interestingly, when WT and KO mice were treated with $NaHCO_3$ for 6 days, plasma pH returned to normal (7.43 +/- 0.01 (WT), 7.38 +/- 0.02 (KO), n=3 each) in association with increased urinary loss of HCO_3^- (60.1 +/- 32.7 (WT) and 136.4 +/- 24.9 µmol/d (KO), $P > 0.05$). On the other hand, when treated with HCl-containing diet for 6 days, the urinary NH_3/NH_4^+ excretion significantly ($P < 0.005$) increased to 15.0 +/- 1.1 (WT) and 15.8 +/- 1.9 mg/mgCre (KO) (n=5 each, vs. Day 0). Most importantly, the renal threshold for urinary NH_3/NH_4^+ excretion significantly decreased by ~0.1 pH unit (plasma) in the KO mice. Moreover, immunostaining of CAII (PT, CCD, OMCD) and PEPCK (PT), faint in normal diet, increased similarly and markedly upon acid-load (6 d).

Conclusions: We conclude that the decreased threshold is caused by inappropriately suppressed ammoniagenesis which is the result of putative intracellular alkalinization in the proximal tubule.

SA-PO097

Targeted Deletion of the NCOA7 Gene Results in Incomplete Distal Renal Tubular Acidosis in Mice

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Background: Primary distal renal tubular acidosis (dRTA) is a rare disease with various levels of severity from growth retardation in its complete form to almost asymptomatic when it is incomplete. Three genes, SLC4A1, ATP6V1B1 and ATP6V0A4, are known to cause this disease in humans. However in some dRTA cases no mutations in any of them have been found, suggesting that other genes are involved. By generating a renal V-ATPase interactome, we recently discovered that several novel proteins (including NCOA7, nuclear receptor coactivator-7 of unknown function) interact with ATP6V1B1 and may regulate V-ATPase function.

Methods: To study if deletion of the NCOA7 gene can cause dRTA, blood pH and bicarbonate (HCO3) levels, and urine pH were compared in wild type (WT) mice and NCOA7 knockout (KO) mice fed a standard rodent diet and after acid loading with ammonium chloride (NH4Cl) for 3 days. Kidney intercalated cells were examined by immunofluorescence microscopy with anti-V-ATPase antibodies.

Results: On the standard diet, there was no significant difference between WT and KO mice in blood pH (7.26±0.07 vs 7.26±0.06) and HCO3 level (20.31±2.79 vs 20.43±2.79 mM), but urine pH was significantly higher in KO than in WT (6.98±0.56 vs 6.15±0.39). At the microscopic level, intercalated cells in the inner stripe of outer medulla were larger and formed continuous rows in NCOA7 KO compared to WT mice, a phenotype previously associated with acidosis. When WT and KO mice were challenged with NH4Cl, their blood pH was slightly reduced to a similar degree (7.23±0.08 and 7.22±0.10 respectively). HCO3 levels were reduced in WT but even more in KO mice (17.58±3.31 and 14.71±3.70 mM). pCO2 levels were also lower in NCOA7 KO (36.46±6.14 vs 43.43±6.04 mmHg). Urine pH was reduced after NH4Cl treatment in both WT and KO mice, but was still higher in KO mice (5.88±0.10 vs 5.60±0.15).

Conclusions: NCOA7 KO mice do not maximally acidify their urine and demonstrate incomplete dRTA. This suggests that the NCOA7 gene may play a role in regulating V-ATPase induced urinary acidification.

Funding: NIDDK Support

SA-PO098

Maternal Acidosis Directs Intercalated Cell Subtype Distribution in Young Progeny

Jeffrey M. Purkerson, Alexandra N. Marasco, George J. Schwartz. *Pediatrics, Univ of Rochester Medical Center, Rochester, NY.*

Background: In the cortical collecting duct (CCD), modulations of acid-base balance are mediated by α and β intercalated cells; α-intercalated cells (IC) secrete protons via a basolateral AE1 and apical B1-VATPase, whereas β-IC secrete bicarbonate via apical pendrin and basolateral H^+-ATPase. A previous study in rats suggested that maternal acid-base status during pregnancy influences intercalated cell differentiation (Narbaitz et al. AJP 264:F415, 1993).

Methods: To confirm and extend this study maternal acidosis was induced in pregnant rabbit does via administration of ammonium chloride in water and food during the 3rd-4th week of gestation, and its effect on intercalated cell differentiation in rabbit progeny at one to three weeks was studied. The numbers of $AE1^+$(α-IC), PND^+(β-IC) and $B1^+$(total IC) per unit length (i.e.100 µm) of CCD were determined in images of immunofluorescent stained kidney sections.

Results: The normal IC subtype distribution in the adult rabbit CCD is α:β, 23%:77%, and this distribution is relatively stable during normal rabbit maturation (1 week old kits: 26%:74%; 3 week old kits: 22%:78%). In contrast, maternal acidosis (5 days) reduced the number of β-IC from 7.4±0.5 in normal control kits to 5.2±0.5/100µm at 1 week and from 9.0±1.0 to 5.9±0.2 in 3 week old kits (p<0.05 Normal®Maternal acidosis. In normal kits and adults there are 2.6±0.1 α-IC/100µm, whereas maternal acidosis increased this number to 3.0±0.3 and 3.1±0.1 in one and three old kits (p<0.05 Normal®Maternal acidosis) such that the IC subtype distribution was 37%:63% and 34%:66%, respectively.

Conclusions: The influence of maternal acidosis on IC subtype differentiation persists for at least several weeks. Whether postnatal acid-base status overrides developmental programming and promotes differentiation of β- over α-subtypes to compensate for the alkaline-rich diet is currently under investigation.

Funding: NIDDK Support

SA-PO099

The Pseudohypoaldosteronism Type II-Causing Mutant Cul3 Protein Forms Dimer with KLHL3 and Inhibits the Degradation of WNK4 with a Dominant-Negative Effect

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Background: Pseudohypoaldosteronism type II (PHAII) is a hereditary hypertensive disease caused by mutations in four different genes: WNK1 and 4, KLHL3, and cullin 3 (Cul3). Cul3 and KLHL3 form an E3 ligase complex that ubiquitinates and reduces WNK4 protein. PHAII causing mutation in cullin 3 gene results in the production of Cul3 protein with a 57-amino acid deletion ($Cul3^{\Delta 403\text{-}459}$). However, precise mechanism how $Cul3^{\Delta 403\text{-}459}$ causes PHAII is unclear. And it is controversial whether $Cul3^{\Delta 403\text{-}459}$ is a gain-of-function mutation or loss-of-function mutation.

Methods: We generated and studied the mice which express $Cul3^{\Delta 403\text{-}459}$ by the induction of Cre-loxP recombination. $Cul3^{WT}$ and $Cul3^{\Delta 403\text{-}459}$ constructs carrying the mutation K712R, in which Cul3 neddylation site was mutated, were expressed in HEK293T cell. Co-immunoprecipitation assays were used to assay interaction of $Cul3^{WT}$, $Cul3^{\Delta 403\text{-}459}$, and KLHL3.

Results: We successfully generated $Cul3^{WT/\Delta 403\text{-}459}$ mice. These mice had the phenotype similar to PHAII; hyperkalemia, metabolic acidosis and hypertension. $Cul3^{WT/\Delta 403\text{-}459}$ mice revealed that $Cul3^{\Delta 403\text{-}459}$ were highly neddylated and the expression level of $Cul3^{WT}$ was suppressed than wild type mice. Co-IP assays revealed that $Cul3^{\Delta 403\text{-}459}$ formed a dimer with $Cul3^{WT}$ and KLHL3. While neddylation is generally required for efficient ubiquitylation, $Cul3^{\Delta 403\text{-}459\ K712R}$ mutant also interfered the degradation of WNK4 by $Cul3^{WT}$-KLHL3 complex, though $Cul3^{WT\ K712R}$ did not.

Conclusions: Expression level of $Cul3^{WT}$ was reduced in mutant Cul3 PHAII model mice. Our studies showed that the inactive Cul3 mutant composed complex with $Cul3^{WT}$ and KLHL3 and interfered the degradation of WNK4 with a dominant-negative effect. This dominant-negative inhibition was not dependent on neddylation of Cul3. This may explain why $Cul3^{\Delta 403\text{-}459}$ causes a more severe phenotype than other mutations.

Funding: Government Support - Non-U.S.

SA-PO100

The Corticosteroid-Repressible Protein DCNL4 Promotes WNK Kinase Degradation via the KLHL3/CUL3 Complex Ankita Roy, Lubika J. Nkashama, Cary R. Boyd-Shiwarski, Michael Butterworth, Arohan R. Subramanya. *Univ of Pittsburgh.*

Background: WNK kinases regulate NaCl and K transport in the distal nephron. Abundance of these kinases is controlled by the KLHL3/CUL3 complex, a cullin-RING E3 ligase (CRL) that ubiquitylates the WNKs, marking them for degradation. Little is known about the mechanisms that physiologically regulate KLHL3/CUL3 activity. Mammalian DCN-like (DCNL) proteins are a family of 5 CRL co-activators that promote cullin activity through neddylation. Of these proteins, DCNL4 was identified as a candidate stimulator of KLHL3/CUL3 activity and WNK substrate turnover, as a kidney RNAseq database noted DCNL4 expression in the distal tubule, and 4 independent prediction algorithms identified DCNL4 as a target of miR-27, a corticosteroid-induced microRNA whose activity is linked to cardiovascular disease. Thus, we hypothesized that corticosteroid-mediated repression of DCNL4 might downregulate KLHL3/CUL3 activity, increasing WNK expression and activity in the distal nephron.

Methods: We evaluated DCNL4 expression in the mouse kidney by RT-PCR, IF, and Western. DCNL4 was transiently coexpressed with KLHL3/CUL3 and WNKs in 293 cells to assess CUL3 neddylation and WNK turnover by CHX chase. mCCD cells were treated with aldo (50nM) or a miR27 mimic and DCNL4 mRNA was quantified by qRT-PCR.

Results: Renal DCNL4 was detectable by RT-PCR & immunoblot. Under standard diet, DCNL4 antibodies recognized a strong proximal and distal tubule-specific signal. In 293 cells, DCNL4 enhanced CUL3 neddylation. Compared to KLHL3/CUL3, KLHL3/CUL3/DCNL4 coexpression decreased WNK4 abundance by 80%, via enhanced proteasomal degradation. Consistent with KLHL3/CUL3 dependency, DCNL4 did not reduce WNK4 abundance when it was coexpressed with FHHt-associated KLHL3 mutants that disconnect WNK4 from CUL3. In mCCD cells, aldo and miR27 mimics reduced DCNL4 mRNA by 50%.

Conclusions: These data support a model in which DCN-like proteins trigger the degradation of WNK kinases by potentiating KLHL3/CUL3 complex activity through neddylation. MicroRNA-mediated downregulation of active KLHL3/CUL3/DCNL4 complexes might represent a novel mechanism by which corticosteroid hormones can augment WNK signaling in the distal nephron.

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SA-PO101

RFxV Motif Analysis in WNK4: Mechanistic Insights into the WNK4-SPAK Pathway Alejandro Rodriguez-Gama, Adrian R. Murillo-de-Ozores, Silvana Bazua-Valenti, Gerardo Gamba, Maria Castañeda-Bueno. *Molecular Physiology Unit, INCMNSZ-IIB-UNAM, Mexico City, Mexico.*

Background: WNK kinases modulate activity of SPAK/OSR1 kinases which in turn regulate SLC12 Cation-Chloride Cotransporters (CCCs). PF2 domains in SPAK/OSR1 can mediate interactions with RFxV motifs present in WNKs and CCCs. WNK kinases present one RFxV motif within the kinase domain (KD) and one or more in the C-terminal region. Elimination of the KD motif of WNK1 or WNK3 impairs their ability to activate SPAK-NCC without affecting kinase activity. The functional consequence of the absence of C-terminal RFxV motifs in full-length WNK1 and WNK4 has not been tested. Here we addressed the role of each of the two RFxV motifs present in WNK4. We also investigated the role of the WNK4's PF2-like domains which may have the potential to interact with RFxV motifs.

Methods: HEK293 cells were used to express WNK4 and SPAK wild-type and mutant constructs. SPAK-S373 and WNK4-T-loop phosphorylation was measured by Western Blot. Protein-protein interactions were assessed by coimmunoprecipitation and colocalization assays.

Results: Both RFxV motifs in WNK4 were required for SPAK-S373 phosphorylation, but only motif #2 (in the C-terminus) was necessary for co-immunoprecipitation. The lack of SPAK activation by WNK4-RFxV motif #1 (KD) mutant was not due to loss of catalytic activity since the mutant displayed autophosphorylation. SPAK-independent WNK4-NKCC1 interaction was observed. WNK1, WNK2 and WNK3 present an RFxV motif in the KD in a different position to that observed in WNK4. Introduction of an RFxV motif in this position in WNK4 could not restore function of WNK4-motif #1 mutant. Confocal microscopy showed a vesicular localization for WNK4. This pattern was replicated by SPAK, but not in the presence of WNK4-motif #2 mutant. The PF2-like domains in WNK4 were required to fully activate SPAK, but were not essential for SPAK and NKCC1 interaction.

Conclusions: WNK4´s RFxV motif #1 is required for SPAK activation and motif #2 is critical for SPAK interaction. Integrity of PF2-like domains in WNK4 is crucial for full kinase activity.

Funding: Government Support - Non-U.S.

SA-PO102

A Novel Regulatory Mechanism of WNK4 Activity Involving Canonical Angiotensin II-PKC or PKA Mediated Phosphorylation Maria Castañeda-Bueno,[1,3] Juan Pablo Arroyo,[1] Junhui Zhang,[1] Jeremy Puthumana,[1] Shigeru Shibata,[1] Orlando Yarborough,[1] Lorena Leonor Rojas,[3] Gerardo Gamba,[3] Jesse Rinehart,[2] Richard P. Lifton.[1] *[1]Dept of Genetics, Yale Univ School of Medicine and Howard Hughes Medical Inst.; [2]Dept of Cell and Molec. Physiology and Systems Biol. Inst., Yale Univ School of Medicine, USA; [3]UNAM and INCMNSZ, Mexico City, Mexico.*

Background: The With-No-lysine kinase 4 (WNK4) regulates activity of the thiazide-sensitive Na^+:Cl^- cotransporter (NCC) by phosphorylating the kinases SPAK (Ste20-related Proline Alanine rich Kinase) and OSR1 (Oxidative Stress Responsive kinase), which in turn phosphorylate and activate NCC. WNK4 levels are regulated by binding in to KLHL3, which targets WNK4 for ubiquitylation and degradation. This activity is regulated by phosphorylation of KLHL3 via protein kinase C (PKC), downstream of Angiotensin II (AngII) or via PKA, likely downstream of vasopressin.

Methods: We tested whether these signaling pathways also have effects on phosphorylation and activity of WNK4 using mass spectrometry, pharmacological inhibitors, site-specific phosphoantibodies, *in vitro* kinase assays and mouse studies.

Results: By tandem mass spectrometry we identified several WNK4 phosphorylation sites, five of which are phosphorylated by PKC *in vitro* and in mammalian cells, downstream of AngII (S47, S64, S1169, S1180, S1196). They are also target for phosphorylation by PKA. Elimination of these phosphorylation sites prevents WNK4-mediated activation of SPAK in HEK293, which is attributable to loss of phosphorylation at S64 and S1196 in WNK4. Loss of phosphorylation at these sites markedly reduces activation of WNK4 kinase via phosphorylation of the kinase T-loop at S322. Thus, AngII signaling leads to phosphorylation of WNK4, which stimulates kinase's activation, inducing downstream signaling. We further show that phosphorylation occurs *in vivo* in mouse with AngII stimulation, primarily in the distal convoluted tubule, where phosphorylated WNK4 co-localizes with SPAK.

Conclusions: AngII activates WNK4 through direct phosphorylation of key sites in WNK4 C- and N-terminal domains. Activated WNK4 then orchestrates activation of SPAK/OSR1-NCC, resulting in increased Na^+ and Cl^- reabsorption.

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SA-PO103

Distal Convoluted Tubule Aggrephagy Involving WNK Kinases Is a Response to Metabolic Stress Causing NCC Activation Tim Michael Bewarder,[1] Aljona Borschewski,[1] Katharina Ilse Blankenstein,[1] Alejandro Federico Cornejo Mueller,[1] Carsten Dittmayer,[1] Andrew Terker,[2] David H. Ellison,[2] Kerim Mutig,[1] Sebastian Bachmann.[1] *[1]Inst für Vegetative Anatomie, Charité, Berlin, Germany; [2]Div of Nephrology & Hypertension, Oregon Health & Science Univ, Portland, OR; [3]VA Portland Health Care System, Portland, OR.*

Background: Sodium chloride reabsorption by the distal convoluted tubule maintains K^+ homeostasis during periods of metabolic stress, through WNK kinases and enhanced thiazide-sensitive NaCl cotransporter (NCC). Early work, using cultured cells, suggested that osmotic stress leads to the accumulation of WNK kinases in vesicular structures representing the trans-Golgi network. in vivo, hypokalemia induced by OSR1 knockout or low K^+ diet, also leads to SPAK/WNK4 puncta. Here, we tested whether stress generates unique cellular structures.

Methods: Mice received high salt/low K^+ (HS/LK) or control diets for 10 days. Rats received furosemide or vehicle via osmotic minipump for 7 days. WNK1-transfected HEK293 cells were exposed to vehicle or hyperosmotic stress (0.2 M NaCl). Immunostaining for WNK1, WNK4, SPAK, S383-phospho-SPAK, and autophagy markers was performed.

Results: Both HS/LK and furosemide led to accumulation of WNKs and SPAK in perinuclear puncta within DCT cells. These puncta were undetectable in mice on high NaCl or control diets. The autophagy marker ATG5 colocalized in the puncta, whereas standard lysosomal markers did not. Electron microscopy revealed abundant aggresome-like structures adjacent to autophagosomes in kidneys from HS/LK or furosemide-treated animals, but not in controls. In transfected cells, hyperosmotic stress-induced formation of similar, WNK1/ATG5-positive puncta, with markers suggesting that they too are autophagosomes. In control cells, WNK1 and ATG5 did not co-localize and were, instead, diffusely expressed in the cytoplasm.

Conclusions: Activation of the DCT induces formation of perinuclear, autophagosome-like structures containing WNK pathway proteins involved in the phosphoregulation of renal distal transporters. Our data suggest that the autophagy pathway is permissively involved in the regulation of salt reabsorption along the distal nephron.

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SA-PO104

WNK4 Regulates Adipocyte Differentiation in 3T3-L1 Cells Daiei Takahashi, Takayasu Mori, Eisei Sohara, Motoko Chiga, Yuichi Inoue, Naohiro Nomura, Moko Zeniya, Tatemitsu Rai, Shinichi Uchida. *Dept of Nephrology, Tokyo Medical and Dental Univ, Bunkyo-ku, Tokyo, Japan.*

Background: The with-no-lysine (WNK) 1 and WNK4 genes are responsible for pseudohypoaldosteronism type II (PHAII), a hereditary hypertensive disease. We previously demonstrated the importance of the WNK4–OSR1/SPAK–NCC signaling cascade in the kidney for blood pressure regulation. WNKs are widely expressed in the body, and recent studies have suggested that, other than this cascade, WNKs also regulate cell growth,

differentiation, and development. However, neither their metabolic functions nor their extrarenal roles are clear, especially in case of WNK4. In the present study, we report a novel role of WNK4 as a regulator of adipogenesis in 3T3-L1 cells.

Methods: We stimulated 3T3-L1 fibroblasts and induced adipogenesis with differentiation medium, containing insulin, dexamethasone, and 3-isobutyl-1-methylxantine. The potential function of WNK4 in the 3T3-L1 cells was examined by knockdown experiments using siRNA specific to WNK4 (si-WNK4). The effect of WNK4 inhibition on 3T3-L1 adipocytes was examined by Oil-red O staining, qRT-PCR, and immunoblotting.

Results: The expression level of WNK4 mRNA in the undifferentiated 3T3-L1 cells was low. However, when adipogenesis was induced, WNK4 expression was markedly increased to 44 fold in the very early phase of adipocyte differentiation, preceding the expression of key transcriptional factors PPARγ and C/EBPα. When the differentiated cells were transfected with siWNK4, they exhibited impaired lipid accumulation and PPARγ expression, and the results were supported by immunoblot analysis. It was also indicated that involvement of WNK4 with adipocyte differentiation was independent of WNK1 or the known downstream effector, OSR1/SPAK-NKCC1 signaling cascade.

Conclusions: We found a novel role of WNK4 as a regulator of adipocyte differentiation in 3T3-L1 cells and have offered novel insights into the relationship between WNKs and adipogenesis. Our results also indicate that WNK4 inhibition might be beneficial in the management of both hypertension and obesity.

Funding: Government Support - Non-U.S.

SA-PO105

Phosphorylation of KLHL3 at Serine 433 Impairs Its Interaction with the Acidic Motif of WNK4: A Molecular Dynamics Study Lingyun Wang, Ji-Bin Peng. *Div of Nephrology, Dept of Medicine, Nephrology Research and Training Center, Univ of Alabama at Birmingham, Birmingham, AL.*

Background: Interaction between the acidic motif (AM) of protein kinase WNK4 and the Kelch domain of KLHL3 are involved in the pathogenesis of pseudohypoaldosteronism type II, a hereditary form of hypertension. This interaction is disrupted by some disease-causing mutations in either WNK4 or KLHL3, or by angiotensin II- and insulin-induced phosphorylation of KLHL3 at serine 433, which is also a site frequently mutated in patients. However, the mechanism by which this phosphorylation disrupts the interaction is unclear.

Methods: In this study, we approached this problem using molecular dynamics simulation with structural, dynamical and energetic analyses.

Results: Results from independent simulations indicate that when S433 was phosphorylated, the electrostatic potential became more negative in the AM binding site of KLHL3 and therefore was unfavorable for binding with the negatively charged AM. In addition, the intermolecular hydrogen bond network that kept the AM stable in the binding site of KLHL3 was disrupted, and the forces for the hydrophobic interactions between the AM of WNK4 and KLHL3 were also reduced. As a result, the weakened interactions were no longer capable of holding the AM of WNK4 at its binding site in KLHL3.

Conclusions: In conclusion, phosphorylation of KLHL3 at S433 disrupts the hydrogen bonds, hydrophobic and electrostatic interactions between the Kelch domain of KLHL3 and the AM of WNK4. This study provides a key molecular understanding of the KLHL3-mediated regulation of WNK4, which is an integrative regulator of electrolyte homeostasis and blood pressure regulation in the kidney.

Funding: NIDDK Support

SA-PO106

Molecular Dynamics Simulation Unveils Impaired Interactions between the Acidic Motif of WNK4 and KLHL3 Carrying Disease-Causing Mutations on the Surface of the Kelch Domain Lingyun Wang, Ji-Bin Peng. *Div of Nephrology, Dept of Medicine, Nephrology Research and Training Center, Univ of Alabama at Birmingham, Birmingham, AL.*

Background: Mutations in Kelch-like 3 (KLHL3) and with-no-lysine [K] kinase 4 (WNK4) are found in patients with pseudohypoaldosteronism type II, a hereditary form of hypertension. At least ten disease-causing mutations are localized in the Kelch domain of KLHL3, which is involved in the interaction with WNK4, an important step for WNK4 ubiquitination and degradation. However, the mechanisms by which these mutations disrupt the interaction between KLHL3 and WNK4 are not well understood.

Methods: To approach this problem, molecular dynamics simulations with structural, dynamical and energetic analyses were performed based on the crystal structure of the Kelch domain of KLHL3 in complex with the acidic motif of WNK4.

Results: Significant increases in the distance between the acidic motif and the Kelch domain were observed for mutations on the surface of the Kelch domain, including Q309R, S432N, S433N, R528H,and N529K. These mutations also altered the electrostatic potential in the binding site for the acidic motif and disrupted the hydrogen bonds and hydrophobic interactions between the Kelch domain and the acidic motif. In addition, S432, S433, and R528 of KLHL3 form hydrogen bonds with residues in the acid motif of WNK4; and these bonds were directly disrupted by the S432N, S433N and R528H mutations. For the mutations not on the surface of Kelch domain, including A340V, R384Q, L387P, S410L and A494T, no significant changes were observed in the distance, hydrogen bond and hydrophobic interaction between the Kelch domain and the acidic motif.

Conclusions: In conclusion, molecular dynamics simulation well detected the disruption of interaction between the acidic motif of WNK4 and the Kelch domain of KLHL3 by the mutations on the surface of the Kelch domain. Further studies are needed to determine the impairments caused by the mutations buried inside the Kelch domain.

Funding: NIDDK Support

SA-PO107

Single-Cell RNA Sequencing Reveals Transcriptomes of Four Cell Types Isolated from the Mouse Renal Collecting Duct Lihe Chen, Chung-Lin Chou, Mark A. Knepper. *National Heart Lung and Blood Inst.*

Background: The renal collecting duct contains principal cells (PCs) and at least two types of intercalated cells (ICs). These cell types bear different molecular signatures and mediate different physiological functions. The development of next generation DNA sequencing techniques offers the ability to carry out RNA sequencing (RNA-Seq) in single cells. Here, we use this technology to profile transcriptomic profiles of all cell types in the renal collecting duct.

Methods: We isolated cells from mouse kidney cell suspensions using reagents that recognize two collecting duct cell surface markers to enrich collecting duct cells, viz. c-kit for ICs and *Dolichos biflorus* agglutinin (DBA) for PCs. The resulting cells were used for single cell RNA-Seq using a microfluidic single-cell isolation device (Fluidigm) followed by reverse transcription, initial amplification, and library preparation with bar coding, prior to sequencing on an Illumina HiSeq2500 platform.

Results: We profiled transcriptomes in 66 individual cells with an average of 10.9M reads, and 95% of mapped reads and 78% uniquely mapped reads per cell. The average transcriptome depth was 3386 genes (RPM>1). We classified each of the 66 cells, based on canonical markers for each cell type, as follows: 21 PCs, 13 β-ICs, 3 α-ICs, 14 "hybrid" ICs, 4 fibroblasts, one distal convoluted tubule cell, and 10 unclassified cells. The "hybrid" ICs are of particular interest. These cells expressed IC-specific H-ATPase subunits plus a combination of α and β IC markers. Interestingly, seven of the 30 cells classified as ICs also expressed aquaporin-2 at low, but readily detectable levels, suggesting that aquaporin-2 expression is not an exclusive characteristic of PCs or connecting tubule cells.

Conclusions: In conclusion, single cell RNA-Seq in mouse renal collecting duct cells showed the presence of intermediate cell types that are not clearly identifiable as PCs, α-ICs, or β-ICs based on standard markers. The single cell RNA-Seq method, more broadly applied, has the potential of identification of the mechanisms of cell-type specific gene expression and physiological regulation in the collecting duct.

Funding: Other NIH Support - NHLBI

SA-PO108

Empagliflozin Lowers Blood Pressure and Inhibits NHE3 Activity in Hypertensive Rats Adriana C.C. Girardi,[1] Corina De Albuquerque Silva,[1] Regiane Cardoso Castelo Branco,[3] Renato Crajoinas,[1] Gerhard Malnic,[3] Weverton M. Luchi.[2] *[1]Heart Inst, Univ of Sao Paulo Medical School, Sao Paulo, Brazil; [2]Hospital Univ Cassiano Antonio de Moraes, Federal Univ of Espirito Santo, Sao Paulo, Brazil; [3]Physiology and Biophysics, Univ of Sao Paulo, Sao Paulo, Brazil.*

Background: SGLT2 inhibitors have clinically significant antihypertensive effects in patients with type 2 diabetes. In the proximal tubule, SGLT2 co-localizes with the major apical sodium transporter NHE3.The aim of this study was to test the hypothesis that inhibition of SGLT2 by empagliflozin reduces blood pressure and inhibits proximal tubule NHE3 activity in an experimental model of hypertension not associated with hyperglycemia.

Methods: Fourteen-week-old male spontaneously hypertensive rats (SHR) were treated with empagliflozin (10 mg/kg/day) or vehicle (control) for two weeks. Blood pressure and renal function were measured before (baseline) and after treatment (post-treatment). Post-treatment proximal tubule NHE3 activity and expression were determined by stationary in vivo microperfusion and immunoblotting, respectively.

Results: Blood pressure decreased in empagliflozin-treated SHRs (188 ± 4 vs. 177 ± 5 mm Hg, $p < 0.05$) and increased in vehicle-treated SHRs (187 ± 4 vs. 200 ± 6 mm Hg, $p < 0.05$, post-treatment vs. baseline). Urinary flow, sodium and glucose excretion were similar between the two groups of rats at baseline, increased significantly after treatment with empagliflozin and remained similar with baseline in vehicle-treated rats. Proximal tubule NHE3-mediated bicarbonate reabsorption was remarkably lower in empagliflozin-treated SHRs compared to control (0.67 ± 0.09 vs. 1.18 ± 0.09 nmol/cm^2.s, $p < 0.001$). No differences were observed on renal cortical NHE3 protein expression between the two groups of rats.

Conclusions: Collectively, these results indicate that inhibition of SGLT2 reduces blood pressure in euglycemic hypertensive rats. Inhibition of NHE3 activity by empagliflozin may contribute to the antihypertensive effect of empagliflozin in SHRs.

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SA-PO109

Claudins along the Cortico-Medullary Axis of the Thick Ascending Limb of Henle's Loop Nina Himmerkus,[1] Vera C. Wulfmeyer,[1] Hoora Drewell,[2] Kerim Mutig,[2] Tilman Breiderhoff,[3] Jianghui Hou,[4] Markus Bleich,[1] Dorothee Günzel,[3] Susanne Milatz.[1] *[1]Inst of Physiology, Christian-Albrechts-Univ, Kiel, Germany; [2]Dept of Anatomy, Charité – Universitätsmedizin, Berlin, Germany; [3]Inst of Clinical Physiology, Charité – Universitätsmedizin, Berlin, Germany; [4]Dept of Internal Medicine – Renal Div, Washington Univ School of Medicine, St. Louis, MO, Germany.*

Background: The thick ascending limb of the loop of Henle (TAL) fulfills distinct physiological tasks in the kidney: (a) Being water tight but actively transporting NaCl it is considered to be the motor which drives the counter current mechanism and the concentration ability of the kidney. (b) Providing a lumen-positive transepithelial potential

it is one of the main sites of divalent cation reabsorption through the tight junction (TJ). The TJ is composed of different claudins which interact within the same plasma membrane (*cis*-interaction) and between neighboring plasma membranes (*trans*-interaction) resulting in the formation of a complex TJ strand meshwork.

Methods: Electrophysiological measurements of transcellular and paracellular transport were performed on freshly isolated cortical and medullary TAL in combination with claudin expression analyses by subsequent immunostaining and confocal laser-scanning microscopy. *Cis*- and *trans*-interaction of the relevant TAL claudins was examined by means of live cell imaging and Förster/fluorescence resonance energy transfer (FRET) in an overexpression system.

Results: Cortical and medullary TAL differed regarding their paracellular permeability properties and their equipment with claudins 3, 10, 11, 16, and 19. A clear correlation between dominance of specific claudins within the TJ and ion selectivity was observed. Not all claudins were expressed in the same TJ in native TAL and some of them failed to interact with each other in *cis*- or in *trans*-configuration in the overexpression system.

Conclusions: We reveal a specific claudin expression pattern in the TAL which can be explained by the particular interaction capabilities of different claudins. On that basis, we suggest the existence of at least two spatially distinct types of paracellular pores with different preferences for Na^+, Ca^{2+} and Mg^{2+} in the TAL.

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SA-PO110

Technical Advance to Identify Novel Associated Proteins with CLC-5 Chloride Channel by Integrated Analysis of Immunoprecipitation Assays with a Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) Hisato Sakamoto, Miyuki Ogawa, Makoto Itakura. *Nephrology, Graduate School of Medical Sciences, Univ of Kitasato, Sagamihara, Kanagawa, Japan.*

Background: CLC-5 plays an important physiological role in regulation of receptor-mediated endocytosis and trafficking of megalin and cubilin. However, little is known about the functional molecular regulation of this channel. Previous study only demonstrated the interaction between CLC-5 and kinesin family member 3B (KIF3B) using yeast two-hybrid strategy (*Am J Physiol* 298: F365–F380, 2010). In this work we aimed to identify novel associated proteins with CLC-5 more effectively rather than yeast two-hybrid screening.

Methods: We generated specific anti-peptide antibodies (Ab) against a synthetic peptide corresponding to the C- or N-terminal of ClC-5. Following to immunoisolation of ClC-5-bearing vesicles using the magnetic beads, we performed the analysis by LC-MS/MS and immunoprecipitation assays to identify specific binding partners. Furthermore CLC-5 and co-localization with associated proteins were imaged using confocal microscopy.

Results: In the direct analysis of highly complex protein mixtures with CLC-5 after proteolysis by LC-MS/MS, the 75-100-kDa band contained CLC-5 (H^+/Cl^- exchange transporter 5), H^+-ATPase accessory subunit a4, Kinesin-like protein KIF2**C**, meprin, and GABA receptor-associated proteins (GABARAP). Among these identified proteins, we focused on the GABARAP, which was thought to be important for the protein trafficking. Actually co-immunoprecipitation studies revealed that the CLC-5 interacted directly with GABARAP, and also immunocytochemistry showed significant co-labeling of ClC-5 and GABARAP in brush-border membrane and subapical intracellular vesicles of the proximal tubule.

Conclusions: The integration of immunoprecipitation assays with analysis by LC-MS/MS might be advanced approach to elucidate a novel regulation of channel trafficking. Enhanced understanding about the associated proteins that control CLC-5 expression may ultimately inform therapeutic strategies to correct or repair the disorder of tubular endocytosis of low molecular weight proteins.

Funding: Private Foundation Support

SA-PO111

Identification and Functional Characterization of CLCNKB Mutations in Patients with Classic Bartter's Syndrome Shih-Hua P. Lin, Jen-Chi Chen, Yi-Fen Lo, Chih-Jen Cheng. *Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan.*

Background: Classic Bartter's syndrome (cBS) is caused by mutations in *CLCNKB* gene encoding voltage-gated chloride ClC-Kb channel. More than 50 *CLCNKB* mutations have been identified in patients with cBS, but less than half of these mutations have been functionally validated, partly due to poor ClC-Kb expression in mammalian cells.

Methods: In this study, we thoroughly investigated the functional consequences of 22 uncharacterized *CLCNKB* mutations including 2 novel missense mutations (L335P, G470E) in our patients.

Results: The wild type human *CLCNKB* construct was poorly expressed in HEK-293 cells. In-frame green fluorescent protein (GFP) insertion, either in N- or C-terminal cytoplasmic domain, greatly boosted the protein expression of ClC-Kb channel, probably by improving protein stability. Co-transfection of barttin further enhanced the protein level of ClC-Kb channel. Most cBS pathogenic mutations, especially those in transmembrane domains and linkers, significantly disrupted the protein expression of ClC-Kb channel and reduced ClC-Kb-barttin current by 30~100%. Besides the nonsense mutations in transmembrane domains, mutations in dimer interface (P216L, A242E) and in selectivity filter (G437C) resulted in most severe functional loss. Of note, mutations in C-terminal cytoplasmic domain, including three cystathionine-β-synthase (CBS) motif truncated mutations (Q513X, W610X and C667X), did not affect protein expression, membrane trafficking or current. Analysis of the potential correlation between patients' genotype and phenotype showed a significant association between the severity of current reduction by mutation and the patient's age at diagnosis ($p = 0.0125$).

Conclusions: In conclusion, in-frame GFP motif and co-expression of barttin enhances ClC-Kb protein expression. Most *CLCNKB* mutations reduced the protein expression to various degrees except the mutations in C-terminal cytoplasmic domain, indicating that two CBS motifs may modulate other intracellular regulations for ClC-Kb channel. With the extensive functional studies of nearly all *CLCNKB* mutations, we identified a significant genotype-phenotype association in cBS patients.

Funding: Government Support - Non-U.S.

SA-PO112

Phosphorylation of Na-Cl Cotransporter Regulates Its Interaction with AP3 Sung-Sen Yang, Chih-Jen Cheng, Chih-Chien Sung, Shih-Hua P. Lin. *Div of Nephrology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan.*

Background: Reduced σ subunit of adaptor protein 3 (AP3), a lysosomal sorting-related protein, was observed in hypertensive patients and Na-Cl cotransporter (NCC) was reported to interact with AP3.To uncover the physiological role of AP3 on the regulation of NCC *in vitro* and *in vivo*.

Methods: The interaction between AP3 and phosphor-mimic or phosphor- defective NCC was tested *in vitro*. We also generated and analyzed both the kidney tubule-specific cadherin gene promoter driven flag-tagged mouse AP3S1 (KSP-Flag-mAP3S1) transgenic (Tg) and AP3S1 heterozygous (He) knockout mice. The phenotype and expression of NCC and other interested targets were evaluated at age of 10-12 weeks fed with normal rodent chaw.

Results: In AP3S1 Tg mice, normal serum electrolytes but an enhanced urine K+ and Ca2+ excretion as well as an attenuation of total and phosphor-NCC expression were observed. While, hyperkalemia with lower urine K+ and Ca2+ excretion as well as an enhanced total and phosphor-NCC were found in AP3S1 He knockout mice. SPAK/OSR1 and WNK1/4 abundance was not significantly changed in both AP3S1 Tg and He knockout mice. We also observed that the phosphorylation status of NCC T60 residue, which locates in one of the putative canonical YXXθ ($YNT_{60}I$) binding motifs of the μ subunit of AP complexes, could affect its binding ability with AP3. Leupeptin (a lysosome inhibitor) could enhance the membrane expression of phosphor-defective T60M-NCC in MDCK cells and NCC T58M knock-in mice.

Conclusions: AP3 could regulate NCC abundance and phosphorylation of NCC T60 residue, the most important phosphor acceptor site of SPAK/OSR1 kinase, might play a role on affecting AP3-realted lysosomal degradation of NCC.

Funding: Government Support - Non-U.S.

SA-PO113

14-3-3 γ Modulates NCC Through ERK1/2-NEDD4-2 Signaling Pathway Independent of SPAK/OSR1 Signaling Xiuyan Feng,[1,2] Shan Chen,[1,3] Hui Cai.[1,2] *[1]Medicine/Renal Div, Emory Univ School of Medicine, Atlanta, GA; [2]Nephrology, Atlanta VA Medical Center, Decatur, GA; [3]Nephrology, Union Hospital, Tongji Medical College, Huazhong Univ of Science and Technology, Wuhan, Hubei, China.*

Background: 14-3-3 γ belongs to a family of multifunction regulatory proteins that mainly bind to phosphorylated Ser/Thr residues in the target proteins. Our previous data also suggested that 1433 γ decreased NCC expression via increasing its ubiquitination. The purpose of this study is to investigate whether SPAK/ORS1, ERK1/2 or NEDD4-2 is involved in NCC ubiquitination induced by 1433 γ.

Methods: Cell culture, transfection, Western Blot analysis, Immunostaining and immunoprecipitation, WT C57/B6 mice aldosterone osmotic mini-pump manipulation were used in this study.

Results: We first did co-immunoprecipitation (Co-IP) which showed 14-3-3γ binding to NCC N-terminus. To investigate whether SPAK/OSR1 signaling involves the 14-3-3 γ-mediated NCC modulation, we mutated the SPSK/OSR1 phosphorylation sites on NCC (T46A, T50A, T55A, T60A, S73A and S91A). Co-IP showed that 14-3-3 γ binds to all of these hNCC mutants. We then knocked down the 14-3-3γ by siRNA in Cos-7 cells and transfected cells with same amount hNCC WT and all hNCC mutants. We found that NCC expressions were increased in hNCC WT and all mutants groups while the 14-3-3 γ was knocked down. We also analyzed the phosphorylation of SPAK, ERK1/2 and NEDD4-2 expression and found that SPAK/OSR1 did not change while the NCC expression increased in 14-3-3γ siRNA group compared to these in the control group, whereas both ERK1/2 phosphorylation and total NEDD4-2 expression increased in the 14-3-3γ siRNA group. To further test the effect of 14-3-3γ on ERK1/2 phosphorylation and NEDD4-2, we overexpressed 14-3-3 γ in Cos7 cells and found that ERK1/2 phosphorylation increased in a dose- dependent manner. While knocking down 14-3-3γ we found that NEDD4-2 expression decreased. Moreover, when we knocked down the ERK1/2 expression, the NEDD4-2 expression decrease as well, whereas the 14-3-3γ expression did not change.

Conclusions: 1433 γ modulates NCC through ERK1/2-NEDD4-2 signaling pathway independent of SPAK/OSR1 Signaling.

Funding: VA Support

SA-PO114

Site Specific Ubiquitylation of the Thiazide Sensitive Sodium Chloride Cotransporter NCC Is Important for Plasma Membrane Abundance and Function Lena Lindtoft Rosenbæk,[1] Federica Rizzo,[3] Olivier Staub,[3] Robert A. Fenton.[2] *[1]Dept of Neuroscience and Pharmacology, Univ of Copenhagen, Denmark; [2]Dept of Biomedicine, Univ of Aarhus, Denmark; [3]Dept of Pharmacology and Toxicology, Univ of Lausanne, Switzerland.*

Background: A critical role for phosphorylation to modulate NCC function is well established, but recent findings indicate that NCC is ubiquitylated on at least 11 conserved lysine residues. Although the role of each of these sites is not established, we have recently demonstrated that an inverse relationship between NCC phosphorylation and ubiquitylation corresponds with the levels of NCC in the apical cell membrane. The aim of this study was to systematically assess the role of various ubiquitylated lysines in NCC for modulation of NCC function.

Methods: Novel tetracycline inducible MDCKI cell lines stably expressing human wt NCC and various K-R mutants were generated and characterized using immunoprecipitation coupled to biotin-based membrane abundance assays and phospho-specific antibodies. A Na^{22} uptake assay was developed to measure NCC activity in these polarized cell lines.

Results: Relative to wt NCC, 4 mutants (K706R, K828R, K885R, and K909R) had significantly higher abundance in the apical plasma membrane under basal conditions. Low chloride stimulation significantly increased membrane abundance of these and additional K128R and K706R mutants, to similar or greater levels than wt NCC. Under basal conditions K828R, K909R, and K948R mutants had detectably lower ubiquitylated NCC in the plasma membrane, and all mutants displayed reduced NCC ubiquitylation following low chloride stimulation. Thiazide-sensitive Na^{22} uptake assays verified elevated transport activity in the K706R, K828R, and K909R mutants.

Conclusions: Several specific ubiquitylation sites in NCC are important for modulation of NCC function.

Funding: Government Support - Non-U.S.

SA-PO115

A New Ubiquitylation Site Plays a Role in the Regulation of the Sodium/Chloride Cotransporter NCC Federica Rizzo,[1] Lena Lindtoft Rosenbæk,[2] Robert A. Fenton,[3] Olivier Staub.[1] *[1]Univ of Lausanne, Switzerland; [2]Univ of Copenaghen, Denmark; [3]Univ of Aarhus, Denmark.*

Background: The Na-Cl Cotransporter (NCC) is expressed in cells of the Distal Convoluted Tubule (DCT), where it plays an important role in NaCl reabsorption and maintenance of blood pressure. NCC is intricately regulated by a variety of post-translational modifications such as glycosylation, phosphorylation and ubiquitylation. In this study we aimed to address the role of ubiquitylation in the modulation of NCC function.

Methods: A UbiScan assay on mouse kidney lysates and analysis of human/rat urinary exosomes identified several ubiquitylated lysines (K) in NCC. These individual sites in NCC were mutated to arginine (R), and the WT NCC and various mutants expressed in HEK293 and MDCK cells to examine NCC localization and activity.

Results: Biotinylation assays determined that four NCC K-R mutants were of greater abundance in the plasma membrane compared to WT NCC when transiently expressed in HEK293 cells. In particular K828R NCC was increased about 50% in the membrane compared to NCC WT. This result was confirmed in tetracycline-inducible NCC expressing MDCKI cell lines. In these cells the quantity of K828R NCC in the apical membrane in normal chloride conditions is comparable to the amount of NCC WT in the apical membrane after low chloride stimulation, which has been previously demonstrated to dramatically increase function and membrane expression of the cotransporter. Furthermore the increase of the mutant in the apical membrane is coupled with a reduction in the basolateral one suggesting an involvement of the ubiquitylation in lysine 828 in the trafficking of NCC. Na^{22} uptake demonstrated increased NCC activity in the K828R mutant relative to WT NCC, which correlates well with its increased membrane expression.

Conclusions: Our data indicate that at least one ubiquitylated lysine in NCC has an important role in the trafficking, membrane expression and activity of the cotransporter. To our knowledge, this is the first identification of an ubiquitylation site directly involved in the regulation of the cotransporter.

SA-PO116

Synergistic and Profound Diuretic Effect of Hydrochlorothiazide/Probenecid Combination Sharon L. Barone,[1,2] Jie Xu,[1] Marybeth Brooks,[1,2] Kamyar A. Zahedi,[1,2] Manoocher Soleimani.[1,2] *[1]Dept of Medicine, Univ of Cincinnati, Cincinnati, OH; [2]Research Services, Veterans Affairs Medical Center, Cincinnati, OH.*

Background: Concomitant deficiency of Na-Cl co-transporter (NCC) and pendrin leads to significant salt wasting and diuresis. Probenecid is an inhibitor of the organic anion transporter, OAT3, in the kidney proximal tubule and a uricosuric agent. Probenecid is also an inhibitor of pendrin in mammary cells. The diuretic effect of HCTZ, which is a specific inhibitor of NCC, is significantly blunted due to compensatory salt absorption by pendrin. We hypothesized that pre-treatment with probenecid will downregulate pendrin, therefore enhancing the diuretic effect of HCTZ.

Methods: The effect of probenecid treatment on pendrin-transfected HEK-293 cells and male Sprague Dawley rats (200-225 g) was examined.

Results: Probenecid (0.5 mM) significantly inhibited pendrin-mediated Cl^-/HCO_3^-exchange in transfected HEK293 cells as measured by the pH sensitive dye, BCECF. Daily treatment of rats with probenecid (250mg/kg) for 6 days significantly reduced pendrin expression in B-intercalated cells without affecting diuresis; while treatment of rats with HCTZ (40mg/kg) alone caused a very mild diuresis (12.5 to 14 ml/24 hrs after 4 days of HCTZ, $p>0.05$). However, co-administration of HCTZ and probenecid to rats that were pre-treated with probencid for 6 days caused a significant increase in urine output (15.3 ml/day in rats treated with probenecid for 10 days vs 35 ml/day in rats treated with probenecid for 6 days and then with HCTZ plus probenecid for 4 additional days). Compared to either probenecid or HCTZ treatment animals, rats pre-treated with probenecid for 6 days and then given probenecid plus HCTZ for 4 days exhibited enhanced kidney renin expression and volume depletion. While probenecid partially interfered with HCTZ secretion into the urine, the higher HCTZ blood levels were unlikely to be responsible for the profound diuresis.

Conclusions: Despite being considered a mild agent, we propose that HCTZ could be a potent diuretic when administered in individuals pre-treated with probenecid.

Funding: VA Support

SA-PO117

Reverse Feeding with High Salt Impairs Diurnal Variation of Sodium Excretion Joshua S. Speed, Kaehler J. Roth, Dingguo Zhang, Chunhua Jin, Karen L. Gamble, David M. Pollock. *Medicine and Psychiatry, Univ of Alabama at Birmingham, Birmingham, AL.*

Background: Night shift work increases risk of cardiovascular disease associated with an altered time of day feeding behavior. Elevating this risk is the overall increase in salt intake observed in the typical Western diet. Our lab has shown that high salt intake alters renal circadian rhythms that has been shown to affect Na^+ handling. Normally, renal Na^+ excretion has a distinct diurnal pattern, independent of time of intake, yet the interaction between the time of intake and the amount of salt ingested has yet to be determined. The hypothesis of the current study is that reversed feeding (RF, food restricted to inactive period) in addition to high salt feeding will disrupt the diurnal rhythm of renal Na^+ excretion.

Methods: Male Sprague Dawley rats were placed on either normal (NS 0.49% NaCl) or high (HS, 4% NaCl) salt diet. Rats were housed in metabolic cages and allowed food ad libitum or subject to RF. Urine was collected every 12 hours. Data is expressed as mean ± SEM of the inactive to active ratio (I/A).

Results: As expected, rats fed NS and allowed food *ad libitum* had a diurnal rhythm in Na^+ excretion (0.37±0.08 I/A). Interestingly, the rhythm in Na^+ excretion was not significantly different after 5 days of RF compared to *ad libitum* rats (0.42±0.12 I/A). In response to HS, the diurnal rhythm in Na^+ excretion (0.26±0.07 I/A) was similar to NS fed rats, but was abolished after 5 days of reverse feeding (1.5±0.4 I/A). In addition, RF significantly reduced the diurnal variation in urinary aldosterone excretion in both NS (0.33±0.05 vs. 0.85±0.19, *ad libitum* vs. RF) and HS (0.36±0.06 vs. 1.21±0.30, *ad libitum* vs. RF) fed rats. There was no difference in 12 hour mean arterial pressure as measured by telemetry.

Conclusions: These data support the hypothesis that high salt intake impairs circadian mechanisms associated with renal Na^+ excretion. Finally, these data suggest that consuming food during one's typical inactive phase impairs diurnal variation in aldosterone production and provide a possible mechanism for increased cardiovascular risk in night shift workers.

Funding: Other NIH Support - NHLBI

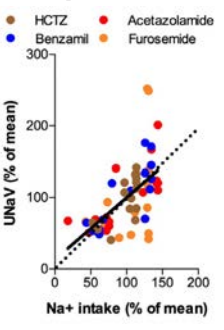
SA-PO118

Sodium Intake Affects Excretion over Short Time Periods in Steady-State C57Bl/6J Mice Jonathan Nizar,[1] Lise Bankir,[2] Vivek Bhalla.[1] *[1]Nephrology, Stanford Univ, Palo Alto, CA; [2]Centre de Recherche des Cordeliers, INSERM, Paris, France.*

Background: Homeostatic balance of sodium is a criterion for the study of channel/transporter-specific tubular transport or any physiological process that regulates sodium excretion. Traditionally, animals are thought to balance sodium over 12 to 24 hours, with relatively little effect of sodium intake during shorter time periods. We tested the hypothesis that in mice with tight control of sodium intake over days, small amounts of sodium intake over 2 - 4 hours would not influence sodium excretion.

Methods: To accomplish this, adult C57BL/6J mice were fed a high sodium diet as gel food over two weeks. In metabolic cages, mice consumed 2.6 +/- 0.05 mmoles Na^+ / day for at least three days before undergoing intraperitoneal injection with saline or one of several diuretics and urine collection over 4 hours.

Results: After each diuretic and saline injection, sodium excretion varied predictably with the diuretic or vehicle treatment and significantly varied with the amount of ingested sodium during the collection period ($p<0.001$, linear regression compared to slope = 0), despite nearly identical intake over the prior 24 hours.



Solid line indicates linear regression of all drugs in aggregate.

Conclusions: These results highlight the technical challenges of balance experiments in mice and warrant the need to adjust excretion data for intake, even during short collection intervals.

Funding: NIDDK Support

SA-PO119

Dietary Salt Impacts Active Sodium Transport and Metabolic Sensing along the Kidney Tubule Khalil Udwan,[1] Ahmed Abed,[1] Carla Bettoni,[2] Isabelle Roth,[1] Carsten A. Wagner,[2] Eric Feraille.[1] *[1]PHYME, Univ of Geneva, Geneva, Switzerland; [2]Inst of Physiology, Univ of Zurich, Zurich, Switzerland.*

Background: Variations of dietary sodium intake induce adaptive changes in renal sodium handling in order to maintain sodium balance. Both glomerular filtration rate and tubular reabsorption process are modulated in response to dietary sodium load. The physiological changes in active sodium reabsorption by tubular cells are associated with changes in ATP and oxygen consumption. These changes may modulate the activity of metabolic sensors such as HIF and AMPK promoting anaerobic glycolysis.

Methods: We used micro-dissected kidney tubules to identify segment-specific effect of salt intake on ion transport systems and metabolic sensor pathways such as HIF and AMPK. Control mice were placed on low (LSD 0.06%), normal (NSD 0.18%) or high (HSD 1.26%) sodium diet for 7 days.

Results: HSD increased the GFR but paradoxically decreased the total expression levels of most Na^+ transporters in both kidney cortex and medulla. However, analysis of the expression levels and activity of Na,K-ATPase as well as the activation levels of metabolic sensors such as HIF and AMPK, revealed that Na^+ transport is actually increased all along the kidney tubule except in distal convoluted tubule. On the other hand, LSD slightly decreased GFR and significantly increased the expression of apical Na^+ transporters NCC and ENaC in DCT and collecting duct, respectively. This effect was associated with increased Na,K-ATPase activity in CD but decreased HIF and AMPK activities. These results indicate that the driving force for Na^+ reabsorption in CD was increased but that actual Na^+ transport was decreased in relation with low Na^+ delivery.

Conclusions: From our experiments, we conclude that the actual Na^+ transport in different segments of the nephron is better reflected by the expression level of Na,K-ATPase and the activation level of metabolic sensors, rather than the expression levels of apical Na^+ transporters alone. Our results show that under physiological conditions, ATP and oxygen supplies are limited enough to trigger both HIF and AMPK signaling pathways.

Funding: Government Support - Non-U.S.

SA-PO120

Role of β_1Pix in the Regulation of ENaC by AMPK Pei-Yin Ho,[1] Hui Li,[1] Tengis S. Pavlov,[2] Lei Cheng,[3] Robert A. Fenton,[3] Alexander Staruschenko,[2] Kenneth R. Hallows.[1] *[1]Medicine, USC Keck School of Medicine, Los Angeles, CA; [2]Physiology, Medical College of Wisconsin, Milwaukee, WI; [3]Biomedicine, Aarhus Univ, Aarhus, Denmark.*

Background: AMP-activated protein kinase (AMPK) inhibits the epithelial Na^+ channel (ENaC) by increasing binding of Nedd4-2 to ENaC. The Rho-GEF protein β_1Pix promotes Nedd4-2 targeting of ENaC by impairing the 14-3-3/Nedd4-2 association. We hypothesized that AMPK may enhance ENaC degradation by regulation of β_1Pix and the Nedd4-2/14-3-3 association.

Methods: Mass spectrometry (MS) and in vitro phosphorylation assays were used to detect AMPK phosphorylation sites in β_1Pix. Wild-type and mutant β_1Pix were overexpressed in lentivirally transduced collecting duct mpkCCD$_{c14}$ cells. Co-immunoprecipitation (co-IP) assays were used to examine modulation of β_1Pix/14-3-3/Nedd4-2 interactions by AMPK in renal epithelial cells. Patch-clamp and epithelial volt-ohmmeter (EVOM) studies were performed in CHO and mpkCCD$_{c14}$ cells co-expressing ENaC and various β_1Pix and AMPK constructs.

Results: AMPK directly phosphorylates β_1Pix in vitro, and at least two potential AMPK phosphorylation sites were detected by MS. AMPK stimulation by metformin inhibited the binding of Nedd4-2 to 14-3-3 proteins but did not modulate 14-3-3-β_1Pix interaction in MDCK cells. Whole-cell ENaC currents were decreased by the AMPK activator AICAR or by β_1Pix over-expression in CHO cells, but these effects were not additive. Co-expressing a β_1Pix mutant unable to bind 14-3-3 protein (Δ602-611) abolished the ENaC current inhibition by AICAR or overexpression of a constitutively active AMPK mutant. Finally, over-expression of β_1Pix Δ602-611 increased, whereas wild-type β_1Pix decreased ENaC short-circuit currents in mpkCCD$_{c14}$ cells, supporting the results found in CHO cells.

Conclusions: The regulation of ENaC by AMPK requires both functional Nedd4-2 and β_1Pix. AMPK reciprocally stimulates Nedd4-2-ENaC binding and inhibits Nedd4-2-14-3-3 binding, thereby promoting ENaC degradation. β_1Pix participates in this regulation, but the mechanisms involved are currently unclear. The potential role of AMPK phosphorylation of β_1Pix in the regulation of ENaC will be assessed through additional mutagenesis studies.

Funding: NIDDK Support

SA-PO121

Regulation of the Epithelial Sodium Channel by Paraoxonase-2 Shujie Shi, Carol L. Kinlough, Allison L. Marciszyn, Rebecca P. Hughey, Thomas R. Kleyman. *Renal-Electrolyte Div, Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.*

Background: Paraoxonase-2 (PON-2) is a membrane-bound lactonase with unique anti-oxidative property. PON-2 shares key structural elements with *C. elegans* MEC-6, an endoplasmic reticulum-residingchaperone that is indispensable for the worm's gentle touch response. MEC-6 is required for proper folding and assembly of MEC-4, a pore-forming subunit of the mechanosensitive ion channel in *C. elegans* touch receptor neurons. MEC-4 belongs to the same family as the epithelial Na^+ channel (ENaC), a key mediator of Na^+ uptake in the aldosterone-sensitive distal nephron. As the overall structures are highly conserved between MEC-4 and ENaC subunits, we hypothesized that mechanisms by which these ion channels are regulated are also evolutionally conserved and that PON-2, like MEC-6 by analogy, regulates ENaC activity.

Methods: We therefore examined PON-2 expression in mouse kidney, and its interaction with ENaC subunits in HEK293 cells. The function of PON-2 on ENaC activity was assessed in *Xenopus* oocytes.

Results: We found tubular-specific expression of PON-2 in mouse kidney, including principle cells and intercalated cells of distal nephron segments. When co-expressed with ENaC in *Xenopus* oocytes, PON-2 reduced amiloride-sensitive whole cell Na^+ currents, but not K^+ currents mediated by ROMK, the renal outer medullar potassium channel. As ENaC activity is tightly regulated by a variety of endogenous or external factors that affect channel biogenesis or gating, the inhibitory effect of PON-2 could reflect a reduction in channel P_O or the number of channels on cell surface. We found that PON-2 did not alter ENaC gating in response to extracellular Na^+, flow-mediated shear stress, or α-chymotrypsin, suggesting that channel P_O was not altered by PON-2. In contrast, surface expression of ENaC was reduced by PON-2 co-expression Additionally, we found that PON-2 interacted with ENaC subunits in HEK293 cells and PON-2 inhibited ENaC activity in a dose-dependent manner.

Conclusions: In summary, our results suggest that PON-2 functions as a chaperone to regulates the surface expression of ENaC.

Funding: NIDDK Support

SA-PO122

Effect of ENaC Inhibition on Na+ Reabsorption Is Partially Compensated by a Reduction in Paracellular Secretion: A Modeling Study Anita T. Layton,[1] Aurelie Edwards,[2] Volker Vallon.[3] *[1]Dept of Mathematics, Duke Univ, Durham, NC; [2]Centre National de la Recherche Scientifique, Centre de Recherche des Cordeliers, Paris, France; [3]Dept of Medicine and Pharmacology, Univ of California San Diego, San Diego, CA.*

Background: The amiloride-sensitive Na^+ channel (ENaC) is expressed on the apical membrane of the principal cells in the distal nephron. Together with the basolateral Na^+-K^+-ATPase, ENaC regulates Na^+ reabsorption and plays a major role in total body salt and water homeostasis and blood pressure control. We aimed to investigate the extent to which ENaC inhibition alters urinary solute excretion and Na^+ transport (T_{Na}) efficiency.

Methods: We developed a multi-nephron computational model that represents detailed transcellular and paracellular transport processes along the nephron of a rat kidney. Using that model, we simulated the inhibition of ENaC.

Results: Under baseline conditions, ENaC was predicted to mediate ~7% of renal T_{Na}, more than commonly thought. ENaC-mediated Na^+ reabsorption was accompanied by substantial paracellular Na^+ secretion. Consequently, ENaC-mediated T_{Na} exceeded total Na^+ reabsorption along the distal nephron segments. ENaC inhibition was predicted to significantly impact connecting tubule T_{Na}. However, the fractional reduction in active T_{Na} was substantially lower than the fractional inhibition of ENaC. That discrepancy can be attributed to the elevated luminal [Na^+], which increased the driving force for transmembrane Na^+ reabsorption and attenuated paracellular Na^+ secretion. Connecting tubule T_{Na} efficiency, given by the number of moles of Na^+ reabsorbed per moles of O_2 consumed, decreased from 4.5 (baseline) to -1.6 (full ENaC inhibition). Additionally, ENaC inhibition lowered K^+ secretion, most notably into the connecting tubules, since Na^+ reabsorption generates the transmembrane potential difference that drives K^+ secretion. When ENaC was fully inhibited, urinary Na^+ and K^+ excretion was predicted to increase by ~3.5 folds and to decrease by ~80%, respectively.

Conclusions: ENaC inhibition has a major impact on both transcellular and paracellular T_{Na} along the distal nephron, and on K^+ secretion and excretion.

Funding: NIDDK Support, VA Support

SA-PO123

Exaggerated Urine Sodium Excretion by Mineralocorticoid Receptor (MR) Antagonists in Rats when Tested against Fludrocortisone Rather Than Aldosterone Krister Bamberg, Lena William-Olsson, Ulrika Johansson, Caroline Wingolf, Rasmus Jansson-Lofmark, Judith Hartleib-Geschwindner. *CVMD iMed, AstraZeneca R&D, Molndal, Sweden.*

Background: Electrolyte effects of MR antagonists in man are typically assessed by analysing urinary sodium secretion after single doses in presence of the orally administered mineralocorticoid fludrocortisone (fludro). In preclinical settings, effect of single dose MR antagonists on urinary sodium secretion is typically assessed in presence of subcutaneously administered aldosterone (aldo) or after a three day low salt diet to elevate endogenous aldo. AZD9977 is a novel MR modulator which in preclinical testing dissociates organ protective

effects from effects on urine electrolytes. To bridge preclinical data on electrolyte effects generated with aldo to clinical data generated with fludro, anti-mineralocorticoid effects of AZD9977 and eplerenone were compared using aldo or fludro as mineralocorticoid.

Methods: Aldo or fludro was administered repeatedly to healthy rats to achieve equivalent drug exposures. 2h after initiation a single dose AZD9977 or eplerenone was administered and amount sodium (mmol) secreted in urine over 6h was assessed.

Results: At AZD9977 and eplerenone doses yielding maximal effects, aldo mediated sodium retention (0.04±0.01 vs 0.22±0.05 for vehicle) was reversed by eplerenone (0.21±0.03), while AZD9977 had only a minimal effect (0.07±0.02). Fludro mediated sodium retention (0.06±0.01 vs 0.15±0.03 for vehicle) was reversed by AZD9977 (0.12±0.02), while eplerenone not only reversed sodium retention but also stimulated a natriuresis in excess of vehicle treated animals (0.43±0.11). At low doses that restore fludro induced sodium retention to vehicle levels, AZD9977 and eplerenone display similar effects on urine sodium, thus the differentiation between AZD9977 and eplerenone on urine electrolytes observed in presence of aldo is only apparent at saturating antagonist doses when tested against fludro.

Conclusions: The exaggerated effect on urine sodium excretion in rats seen by MR antagonists when tested against fludro rather than aldo indicates differences in the mode of action of fludro vs aldo. It remains to be established whether this is true also in man.

Funding: Pharmaceutical Company Support - AstraZeneca R&D

SA-PO124

Electrolyte Homeostasis in AQP-2-Principal-Cell-Targeted Insulin Receptor (IR) and Mammalian-Target-of-Rapamycin (mTOR) Knockout (KO) Mice under Low- and Normal-Sodium Diets

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Background: Insulin has been shown to increase the reabsorption of sodium in the renal collecting duct (CD), but less is known about its effects on potassium or chloride handling at this site. Dysregulation of these key electrolytes can affect acid-base homeostasis and blood volume. Previous studies have demonstrated that mTOR may play a role in activation of ENaC by insulin in the collecting duct.

Methods: We assessed the impact of low-sodium (Na+) diet (0.05%, LSD) on blood chemistry and urine excretion in male AQP2-principal-cell-targeted insulin receptor and mTOR knockout (IRKO and mTORKO) mice, as compared to their respective WT littermates. Urine (24-hr) was collected on days 1-3 and 7 of LSD. Volume and electrolyte excretion was measured. In a separate experiment, mice were randomized to receive the LSD or control diet (0.5% Na+, n = 5-7/group) for one week, mice were euthanized, and blood was analyzed by iSTAT (EG8 cartridge) for chemistry profile.

Results: No obvious differences in urine Na+ excretion were found between genotypes; however, hematocrit was significantly ($p < 0.05$) higher (4-6%) in the IRKO and mTORKO versus their WT littermates under LSD. Plasma K+ levels tended to be lower in the KO (both types) on either control or LSD, while plasma Cl- was significantly reduced by LSD in the KO, but not WT. Furthermore, mTORKO had mild alkalosis as determined by significantly elevated blood pH, HCO_3, base excess, and reduced pCO_2, relative to WT, independent of diet. These differences were absent in the IRKO mice.

Conclusions: Overall, these results support a role for CD IR and mTOR in electrolyte homeostasis and blood volume control. Increased hematocrit in both KO lines suggested mild volume contraction under LSD, absent in WT mice. Similarities between the phenotypes with regard to plasma electrolyte profile suggests that IR may indeed be working through mTOR to regulate these electrolytes; however, differences in acid/base status suggest additional roles for CD mTOR independent of IR.

SA-PO125

A Mathematical Model of the Rat Kidney: K-Induced Natriuresis

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Background: Increased K^+ intake is associated with natriuresis, but the renal locus of this effect is uncertain.

Methods: A model of the rat nephron (Am. J. Physiol. 308:F1098, 2015) has been extended with the addition of medullary vasculature. Within outer medulla (OM), the model specifies 20000 short descending vasa recta (DVR) and 4000 long DVR; within inner medulla (IM), long DVR coalesce, halving their number with each mm of medullary depth; cortical medullary rays (MR) are supplied by 7200 DVR. In all regions, ascending vasa recta (AVR) are twice the number of DVR, which provides for slower AVR flows, and secures equilibration of AVR and interstitial concentrations. Blood vessels contain all 15 solutes from the nephron model (Na^+, K^+, Cl^-, HCO_3^-, H_2CO_3, CO_2, urea, phosphate, ammonia, formate, and glucose), plus 14 additional species from the model of Atherton et al. (Am. J. Physiol. 247:F61, 1984), which represent hemoglobin buffering. For this kidney model, the global unknowns are initial proximal tubule pressures and flows (plus connecting tubule pressure) from the nephron model, plus medullary interstitial pressures and solute concentrations. With partitioning of OM into 2 sections, of IM into 5 sections, and a single MR section, there are 128 interstitial variables, yielding a total of 141 unknowns for the full kidney model.

Results: Solution of the model under antidiuretic conditions predicts OM interstitial gradients for Na^+, K^+, CO_2, and NH_4^+, such that at OM-IM junction, the respective concentrations relative to plasma are 1.2, 3.0, 2.9, and 8.0; within IM, there is high urea and low HCO_3^-, with concentration ratios of 11 and 0.5 near the papillary tip. When plasma K^+ is increased from 5.0 to 5.5 mM, Na^+ and K^+ excretion are predicted to increase 2.5- and 1.3-fold. The natriuresis derives from a 4% decrease in proximal Na^+ reabsorption, and occurs despite delivery-driven increases in Na^+ reabsorption in all distal segments; the kaliuresis derives from a 30% increase in connecting tubule Na^+ delivery.

Conclusions: Thus, in the absence of other regulation, this model favors the importance of proximal over distal events in K^+-induced diuresis.

Funding: NIDDK Support

SA-PO126

The Distal Convoluted Tubule Requires Kir4.1 to Sense Plasma Potassium and Regulate Potassium Homeostasis Properly

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Background: Urinary potassium excretion is mediated by secretion along the connecting tubule and collecting duct, but a key role for the upstream segment, the distal convoluted tubule has been recognized recently. The potassium channel, Kir4.1, which appears to be the dominant potassium conductive pathway in these cells, appears to play a key role. We recently developed a mouse model in which Kir4.1 can be deleted along the nephron in adult mice. The mice exhibit hypokalemia and decreased thiazide-sensitive NaCl cotransporter (NCC) abundance.

Methods: To test whether Kir4.1 is essential for the physiological response to a dietary K^+ challenge, kidney-specific Kir4.1 knockout (KS-Kir4.1 KO) mice were fed with diets deficient in K^+ (0% K^+,LK), rich in K^+ (5% K^+, HK) and with normal K^+ (0.8% K^+, NK) for 4 days each.

Results: On NK, KS-Kir4.1 KO mice were hypokalemic and alkalemic ([K+]: 2.5±0.1; [CO_2]: 25±2.4). When exposed to LK, the mice exhibited dramatic hypokalemia (1.0±0.1 mmol/l) along with even more marked metabolic alkalosis (35 ±0.8 CO_2 mmol/l), accompanied by continued urinary K^+ wasting. Even HK failed to normalize plasma [K+] in KS-Kir4.1 KO mice (3.2±0.1,mmol/L). The mechanism for K^+ wasting in the KS-Kir4.1 KO mice was revealed by analysis of NCC abundance. In contrast to wild type mice in which NCC abundance correlates inversely with dietary K^+ intake, NCC abundance was nearly undetectable in KS-Kir4.1 KO mice and unaffected by diet.

Conclusions: Together, these data show that Kir4.1 is required for the kidney to sense plasma [K^+] and that NCC activity is required to maintain K^+ balance, even under usual diet conditions.

Funding: NIDDK Support, VA Support

SA-PO127

Disturbed Renal K Handling in Carriers of the Gly40Ser Mutation of the Glucagon Receptor Suggests a Role for Glucagon in K Homeostasis

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Background: Clearance studies in rats showed that iv glucagon (Gluc) infusion increases urinary K excretion dose-dependently and reversibly [Ahloulay, *AJP* 269:F225,1995]. The present study investigates K handling in humans, taking advantage of the Gly40Ser mutation of the Gluc receptor that has been shown to induce a partial loss of function (lesser cAMP release by rat hepatocytes in vitro; lesser rise in plasma glucose after Gluc infusion in humans).

Methods: In the Olivetti cohort (male workers), 25 subjects who carried this mutation were matched 1:4 to 100 non-carriers for age (mean 57y) and weight (mean BMI 27-28 kg/m^2). Estimated osmolarity (Osm) of plasma and 24h urine was calculated as [(Na+K)*2+glucose+urea]. Transtubular K gradient (TTKG) reflecting the intensity of K secretion in distal nephron was calculated as [(urine K/serum K)/(urine Osm/serum Osm)].

Results: There was no significant difference in blood pressure, serum insulin, serum or urine urea and Na excretion. Urine volume was slightly higher and Osm slighly lower in carriers than non-carriers (but NS).

Means (interquartile range)	Non-Carriers (n=100)	Carriers (n=25)	p
Creat.Clear (ml/min/1.73m^2)	86 (82-90)	88 (81-95)	NS
Serum K (mmol/L)	4.5 (4.4-4.6)	4.5 (4.3-4.6)	NS
Urine K (mmol/L)	47 (43-51)	38 (34-43)	**p=0.030**
K excretion (mmol/d)	68 (64-73)	66 (57-74)	NS
TTKG	5.0 (4.7-5.2)	4.2 (3.9-4.6)	**p=0.015**

The difference in urine K and TTKG remained statistically significant after adjustments for serum insulin and 24h K and Na excretion.

Conclusions: These results in humans, along with previous observations in rats, strongly suggest that Gluc stimulates K secretion in the distal nephron. Infusion of K has been shown to stimulate both insulin and Gluc secretion in conscious dogs [Santeusanio, *JLabClinMed* 81:809, 1973]. Thus, besides insulin (that favors K entry into muscle cells), glucagon most likely also participates in K homeostasis by promoting renal K excretion, as hypothetized recently [Bankir, *AJP-Renal* Art.in press].

Funding: Government Support - Non-U.S.

SA-PO128

Role of Cilia in Ca2+-Dependent Flow-Induced K Secretion (FIKS) in Rabbit Cortical Collecting Duct (CCD) Rolando Carrisoza-Gaytan,[1] Carlos Schreck,[1] Thomas R. Kleyman,[2] Lisa M. Satlin.[1] *[1]Pediatrics, Icahn SOM at Mount Sinai, New York, NY; [2]Medicine, Univ of Pittsburgh SOM, Pittsburgh, PA.*

Background: BK channels, present in both CCD principal (PC) and intercalated (IC) cells, mediate Ca^{2+}-dependent FIKS. PCs possess an apical cilium which responds to manipulation with an increase in cell Ca^{2+} concentration $[Ca^{2+}]i$, and are considered to mediate transepithelial Na absorption and K secretion. Immunoperfusion of rabbit CCDs with anti-BKα Ab revealed robust immunodetectable protein in PC cilia (MS in preparation).

Methods: (see Results)

Results: To test whether cilia BK channels mediate FIKS, net transepithelial transport (Jx) of Na and K was measured in microperfused control or deciliated (by luminal perfusion with 1 mM dibucaine, 30 min) CCDs isolated from NZW rabbits. Flow-stimulated JNa (70.4±4.5 and 53.2±7.8 pmol/min.mm; p=0.12) and FIKS (-21.2±1.6 and -19.0±3.6 pmol/min.mm; p=0.63) were similar in control and deciliated CCDs (n=4 and 5, respectively). The detection of FIKS in deciliated CCDs suggested that a flow-induced increase in $[Ca^{2+}]i$ must be preserved in absence of cilia. To test this, flow-induced $[Ca^{2+}]i$ transients, inferred from fluorescence intensity ratios (FIRs), were measured in control, deciliated or suramin (100 μM; nonspecific P2 receptor antagonist) pretreated CCDs loaded with fura-2. In control CCDs, a rapid increase in tubular fluid flow rate led to a typical high amplitude peak increase in FIR in both PC and IC, presumably reflecting release of Ca^{2+} from internal stores and influx of Ca^{2+} from the extracellular space, followed by gradual decay to a plateau value, considered to be mediated by luminal Ca^{2+} entry. Deciliation led to loss of the flow-induced Ca^{2+} peak, but the plateau elevation in FIR above baseline was retained during a period of sustained high flow. Suramin-treated CCDs subject to acute increase in flow exhibited a slow increase in $[Ca^{2+}]i$ to a sustained plateau, but no early peak response.

Conclusions: We conclude that cilia BK channels do not mediate FIKS in the CCD, and speculate that apical BK channels in CCDs that mediate FIKS are activated by elevations in $[Ca^{2+}]i$ elicited by mechanoactivated cilium- and P2 receptor-independent signaling.

Funding: NIDDK Support

SA-PO129

14-3-3 γ Modulates BK Function Through Altering ERK1/2 Signaling Pathway Shan Chen,[1] Xiuyan Feng,[1,3] Douglas C. Eaton,[2] Hui Cai.[1,2,3] *[1]Renal/Medicine, Emory Univ School of Medicine, Atlanta, GA; [2]Physiology, Emory Univ School of Medicine, Atlanta, GA; [3]Nephrology, Atlanta VA Medical Center, Decatur, GA.*

Background: 14-3-3 γ belongs to a family of multifunction regulatory proteins that mainly bind to phosphorylated Ser/Thr residues in the target proteins. 14-3-3 has been shown to play an important role in the regulation of many potassium channels. Previous studies have shown that Big K (BK) channel has many associated proteins including 14-3-3. Sequence analysis of BK shows a 14-3-3 binding site (R*XX*S/T) between amino acid 1091-1164. Thus, we hypothesized that 14-3-3 modulates BK function.

Methods: Cell culture, transfection, electrophysiology study, western blot analysis and immunoprecipitation were used in this study.

Results: To determine whether 14-3-3 interacts with BK channel, we first did co-immunoprecipitation (Co-IP) experiments. We found that 14-3-3 β and γ interact with BK protein. To further investigate whether 14-3-3 γ affects BK activity, we did electrophysiology experiments in HEK 293 stably expressing BK cells transfected with or without 14-3-3 γ. We found that 14-3-3 γ significantly decreased the channel activity (NPo), channel numbers per patch and channel open probability (Po) of BK channel compared to the control group (n=11 for 14-3-3 γ group and n=9 for the control group, $p < 0.05$) in HEK 293 stably expressing BK cells using single channel recording. We further investigated whether 14-3-3 γ affects BK protein expression in Cos-7 cells transfected with both BK plasmid and an increasing doses of 14-3-3 γ. We found that 14-3-3 γ decreased BK protein expression in a dose-dependent manner while increasing ERK 1/2 phosphorylation.

Conclusions: These data suggested that 14-3-3 γ inhibits BK channel activity and its protein expression through altering ERK1/2 signaling pathway.

Funding: VA Support

SA-PO130

Kidney CD4-CD8- Double Negative T Cell Development Is MHC Dependent Mohanraj Sadasivam, Sanjeev Noel, Sul A. Lee, Abdel Hamad, Hamid Rabb. *Dept of Medicine, Johns Hopkins Univ School of Medicine, Baltimore, MD.*

Background: Prior studies have established important roles of $CD4^+$ T cells, natural killer T cells, and $CD4^+CD25^+FoxP3^+$ Tregs in acute kidney injury (AKI) pathogenesis. Recently, $CD4^-CD8^-$ (double-negative; DN) T cells have been found in mouse and human kidney, and directly influence the course of experimental AKI (*J Am Soc Neph* 2015). However, little is known about the immunobiology of these cells and mechanism of action in AKI. We hypothesized that MHC restricts the quantity and function of kidney DN T cells.

Methods: C57BL6-β2m MHC class-I , MHC class-II knockout (KO) and WT control mice were used to determine the MHC restriction kidney DN T cells (n=3-4). The lymphocytes from the kidneys, lymph node (LN) and thymus were analyzed by flow cytometry. Microarray analysis of kidney DN T cells compared to $CD4^+$ & $CD8^+$ was performed.

Results: Kidneys from both class I and class II MHC KO mice have reduced total numbers of DN T cells compared to WT controls (WT, 3,355±1,077 vs. MHC I KO, 1,016±471 vs. MHC II KO, 1,538±639; P<0.01). DN T cell numbers in LN were 16,546± 1,740 in WT, 9,383± 372 in MHC I KO and 21,988±7,157 in MHC II KO. (P<0.01) in thymus were 19,735±7,681 in WT, 7,610±3,215 in MHC I KO and 26,390±6150 in MHC II KO. (P<0.05) We also evaluated percentage of DN T percentage in comparison to $CD4^+$ & $CD8^+$ cells in kidney, LN and thymus (Table). Microarray analysis also revealed major differences between kidney cell types.

Table. Percentage of T cells

Mouse groups	DN T cells	$CD4^+$ T cells	$CD8^+$ T cells
Kidney			
WT	18.6 ± 3	54 ± 4	26± 4
MHC class-I KO	13 ± 3*	83 ± 4	2 ± 1*
MHC class-II KO	31 ± 1	14 ± 4*	50 ± 4
LN			
WT	4 ± 2	63 ± 6	33 ±3
MHC class-I KO	2 ± 1*	98 ± 1	1± 0.1*
MHC class-II KO	7 ± 2	4 ± 1*	85 ± 4
Thymus			
	2± 1	75 ± 2	15 ± 1
MHC class-I KO	1 ± 1*	90 ± 2	1 ± 1*
MHC class-II KO	5 ± 1	17 ± 2*	43 ± 1
* P value < 0.01			

Conclusions: These data demonstrate that DN T cells in the kidney have similarities but also unique MHC restriction compared to other lymphoid organs. Microarray analysis demonstrated further insightful differences. Further dissection of kidney DN T cell biology will help us understand the pathogenesis of AKI and other immune mediated kidney diseases.

Funding: NIDDK Support

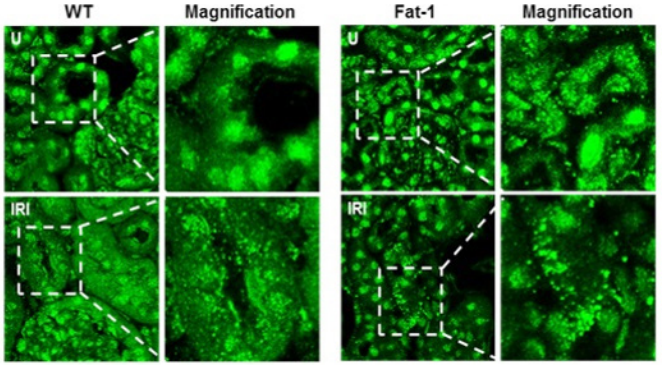
SA-PO131

Transgenic Mice with High Endogenous Omega-3 Fatty Acids Are Protected from Ischemia-Reperfusion-Induced Acute Kidney Injury via Basal Autophagy Activation Won Min Hwang, Se-Hee Yoon, Sung-Ro Yun. *Dept of Nephrology, College of Medicine, Konyang Univ, Daejeon, Republic of Korea.*

Background: Several studies found that omega(ω)-3 fatty acid diet reduces kidney dysfunction followed by ischemic injury. However, oral appliance of ω-3 PUFA to experimental animals, in fact, can cause much variability arisen from diet procedure. fat-1 transgenic mouse produce abundant ω-3 PUFA, resulting in balanced ω-6 : ω-3 ratio than wild type mouse. We investigated to see whether ω-3 PUFA has advantages in ischemia/reperfusion(IR)-induced AKI using fat-1 transgenic mice. In addition, we investigated the involvement of autophagy process as a possible underlying mechanism of these protection.

Methods: Bilateral kidneys of experimental animals (fat-1 and C57BL/6 mice) were subjected to 30 min of warm ischemia. After 24hrs and 72hrs of reperfusion, animals were sacrificed. The effects of ω-3 PUFA on IR-induced AKI were evaluated in terms of serological marker for kidney function, kidney injury marker, morphology, and inflammatory cell infiltration. Finally, autophagy status in renal tubular cells with or without IR-induction was assessed by confocal microscopic observation.

Results: After I/R-induced AKI, fat-1 mice showed the reduced level of serum BUN and creatinine compared with control. Furthermore, Kim-1 levels and morphological damage of renal tubule were reduced. Neutrophil infiltration into renal cortex were minimized in fat-1 mice compared with control. Interestingly, immunohistochemical detection of autophagosomes revealed that autophagy were activated in fat-1 mice kidney at basal status. After IR-induced AKI challenges, autophagy levels were unchanged in fat-1 mice. Activated autophagy in basal status might contributed to tubular protection against AKI.



Conclusions: Long-term and high dose of omega-3 supplement may protect renal function and structures against AKI via basal autophagy activation.

SA-PO132

Interaction between miR-21 and Hypoxia Induced Factors (1α and 2α) in Ischemia /Reperfusion Induced Acute Kidney Injury

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Background: Accumulating evidence suggests that miR-21 is importantly involved in pathophysiological processes of ischemia/reperfusion (I/R) injury. It was reported that overexpression of miR-21 and hypoxia-inducible factor (HIF) induced by hypoxia preconditioning protected against kidney I/R injury. However, it is little known whether miR-21 and HIF interact with each other in the progress of kidney I/R injury.

Methods: In this protocol, we applied in vitro [hypoxia ($1\%O_{2\ \text{for 6 hours}}$)/ reoxygenation($21\%O_{2\ \text{for 1 hour}}$), H/R] and in vivo [ischemia (bilateral renal pedicles were clamped for 35 min)/reperfusion (24hours), I/R] experimental models to investigate the feedback loop between miR-21 and HIF.

Results: The results revealed that expression of miR-21, HIF1α and HIF2α were increased by H/R in vitro and I/R in vivo . Interference expression of HIF1α and 2α by siRNA modulated elevated expression of miR-21 induced by hypoxia and inhibition of hydrolysis of HIF by L-mimosine (500μM) or $CoCl_2$ (200μM) increased expression of miR-21. Activation of AKT/mTOR pathway was stimulated by H/R, in vitro. Silence of miR-21 repressed phosphorylation of AKT and mTOR and reduced expression of HIF1α, HIF2α induced by H/R. Inhibiting AKT/mTOR pathway by LY294002 (20μM) and rapamycin (10nM) attenuated up-regulation of HIF1α and HIF2α induced by H/R. Additionally, Silence of miR-21, HIF1α and HIF2α increased necrosis of HK-2 cells caused by H/R. And Silence of miR-21 in vivo aggravated renal injury, however, administration of L-mimosine or $CoCl_2$ reduced kidney I/R injury.

Conclusions: In summary, our finding indicated that HIFα regulated expression of miR-21 and miR-21 interacted with HIFα by AKT/mTOR pathway in turn. The feedback loop between miR-21 and HIFα suppressed kidney I/R injury and may be a potential therapeutic target for I/R induced acute kidney injury. Additionally, the up-regulation of miR-21, HIFα during acute kidney injury may imply a self-protection mechanism of the kidney.

Funding: Government Support - Non-U.S.

SA-PO133

Transcriptional Profile in Kidneys Subjected to Ischemia Reperfusion Injury Modified by CHBP and Caspase-3 siRNA

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Background: Ischemia reperfusion (IR) injury is a major cause of acute kidney injury (AKI) without effective treatment. Identifying the etiology and mechanism of AKI could facilitate individualised intervention timely. Here, transcriptional profiles were investigated in mouse IR injury kidneys, with or without erythropoietin derived cyclic helix B surface peptide (CHBP) or caspase-3 small interfering RNA (C3siRNA).

Methods: Genomic profiling along with other injury parameters was detected in mouse kidneys subjected to 30-min bilateral renal occlusion followed by 48-h reperfusion. Comparisons were performed in 4 groups: IR, IR+24 nmol/kg CHBP, IR+CHBP+0.03 mg/kg C3siRNA, and IR+CHBP+NCsiRNA.

Results: CHBP altered 97 genes expression in the IR kidneys, while differentially expressed genes between C3siRNA and NCsiRNA in the IR+CHBP kidneys increased to 228, with only 5 genes in common such as PDK4 (1.5-fold, $p<0.05$). These genes broadly involved in multi tissue injury and repair processes and 28 genes have been reported closely related to renal-related injury. 8 genes such as CALCA and CYP3A13 positively and MYO5A and FGF1 negatively associated with tubulointerstitial damage (TID), with CALCA also positively related to serum creatinine (SCr) and apoptosis; and additional 7 genes related to apoptosis and caspase-3 activation, which were all reduced by CHBP. On the other hand, due to additional C3siRNA, PDK4, GREM1 and TMEM100 negatively related to TID; additional 13 genes, APLN and TM7SF21 positively associated with SCr, rest 11 genes such as GREM1, TMEM100 and CFHR2 negatively related to SCr and apoptosis. Most interestingly, attributed to C3siRNA+CHBP treatment, TMEM100 and COL11A1 positively related to all SCr, apoptosis, TID and caspase-3 activation.

Conclusions: IR injury might be closely related to genes involving in vascular integrity and renal cell survival, which was improved by CHBP and further enhanced by C3siRNA. Candidate genes such as PDK4, CALCA, TMEM100 and COL11A1, as potential biomarkers and therapeutic targets, need to be further validated.

Funding: Government Support - Non-U.S.

SA-PO134

The Endothelial Hypoxia-Inducible Factor -1 and -2 Mediate Protection from Acute Kidney Injury in the Context of Endothelial Prolyl Hydroxylase Domain 2 Deficiency

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Background: Prolyl-hydroxylases (PHDs) have emerged as safeguards of cellular metabolism through their oxygen sensing function, which enables them to regulate the activity of hypoxia-inducible factors (HIF). We have previously reported that loss of endothelial PHD2 protected from renal ischemia reperfusion injury (IRI) but the molecular mechanisms remain undefined. Here, we investigated the contribution of HIF in renoprotection induced by endothelial PHD2 loss and examined the impact of HIF-activation in endothelial cell (EC) metabolism.

Methods: EC-specific HIF activation was achieved by crossing Vecadherin (Cdh5)-Cre transgenics to Phd2 floxed mice, while the contribution of each HIF isoform was assessed by generating double mutants lacking both PHD2 and HIF1 (PHD2HIF1) or PHD2 and HIF2 (PHD2HIF2). IRI was induced by unilateral renal artery clamping. Metabolic profiling was conducted by LC/MS and GC/MS while bioenergetic analysis was performed using a Seahorse Extracellular Flux Analyzer.

Results: Deletion of either endothelial HIF1 or HIF2 in endothelial PHD2 deficient background reversed the renoprotection conferred by endothelial PHD2 loss as indicated by histological injury scores and *Kim1* mRNA levels in kidney homogenates (Day 3 post IRI, n=8 mice/group). Metabolomic analysis of ECs exposed to PHD inhibitor revealed significant increase in glycolytic metabolites with simultaneous reduction in TCA cycle metabolites suggesting that HIF activation led to glycolytic shift and suppression of mitochondrial metabolism (n=5), also indicated by reduction in oxygen consumption rate on bioenergetic analysis. In contrast, preconditioning of ECs with PHD inhibitor abolished the significant defects in mitochondrial metabolism triggered by hypoxia-reoxygenation (H/R).

Conclusions: Our data establish that both HIF-1 and HIF-2 are required in endothelial PHD2 mediated renoprotection. Furthermore, we show that the PHD/HIF axis leads to alterations in EC metabolism with critical consequences in response to H/R. Therefore, endothelial HIF may promote resistance to kidney injury by reprogramming EC metabolism.

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SA-PO135

Similar Serum Creatinine, but Non-Overlapping Gene Expressions

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Background: Acute kidney injury (AKI) is currently diagnosed by the rise in serum creatinine (sCr) or a decrease in urine output without emphasis on its potential etiologies or on its clinical heterogeneity. While any etiology of AKI worsens patient outcomes, it remains unknown how hemodynamic or volume-responsive (vAKI) is related to intrinsic AKI with tubular damage (iAKI).

Methods: To clarify their relationship, we performed renal transcriptional profiling in mouse models of vAKI and iAKI with matched sCr levels.

Results: We found thousands of genes responding specifically to vAKI or to iAKI with limited overlap. These gene sets activated different signaling pathways, were functionally unrelated, and were expressed in different regions of the kidney. Moreover some of these proteins encoded by these genes demonstrated distinctive patterns in human urine. A cytokeratin was expressed in human iAKI urine but not in vAKI urine, while a placental-associated protein that may play a role in salt-sensitive volume stress, was expressed in human vAKI urine, but was absent in iAKI due to its proteolysis, demonstrating the potential loss of a protective mechanism. This distinct patterning of vAKI and iAKI in human urine has a number of clinical applications including the possible utility of a new class of biomarkers responsive to reversible volume stresses.

Conclusions: Consequently, despite similar sCr levels, vAKI and iAKI in our models were biologically distinct, implying that tests for these genes could refine and enhance current definitions of acute injury of the kidney.

Funding: NIDDK Support

SA-PO136

Regulation of IL-17 mRNA Expression by Elevated Sodium and Ang II in AKI Primed CD4+ T Cells Is Dependent on Cytosolic Ca+2 Signaling

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Background: Th17 cells have been implicated in the pathogenesis of immune-mediated diseases and in acute kidney Injury (AKI). We have shown that during the AKI-chronic kidney diease (CKD) transition, the number of Th17 cells increased 2-4 fold. In addition, post ischemic rats on high salt diet when treated with angiotensin receptor (AT1) blocker, losartan significantly reduced IL-17+ cell infiltration as compared to vehicle control. To investigate IL-17 responses in post ischemic rats, CD4+T cells isolated from injured rats were treated with both Ang II (10^{-7}M) and elevated Na^+ (170 mM) in vitro. IL-17 mRNA expression significantly increased 5 fold when treated with both elevated Na^+ and Ang II as compared to either elevated Na^+ and Ang II alone. Interestingly, no IL-17 response was measured in CD4+ T cells isolated from sham-operated rats. The IL-17 response was significantly reduced by 2-aminoethoxydiphenyl borate (2-ABP) (93%; $p<0.05$) an inhibitor of store-operated Ca^{+2} channel and the L-type Ca^{+2} channel inhibitor, Nifedipine (1μM) (85%; $p<0.05$). In contrast there was no induction of IL-17 expression when osmolality was raised to the same degree by mannitol or choline chloride, suggesting the response was specific to extracellular Na^+. Multiple studies suggest that T cell receptor stimulation and Ang II independently increase intracellular free Ca^{+2} concentration, which induces proliferation and cytokine secretion. We hypothesize that elevated Na^+ and Ang II may enhances a Ca^{+2} influx in T cells leading increased IL-17 secretion.

Methods: Fura-2 was used to measure Ca^{2+} in renal CD4+T cells isolated from post-ischemic or sham operated rats 7 days post-surgery.

Results: Interestingly, elevated Na^+ and Ang II induced a sustained elevation of calcium influx, measured at the single cell level. The increase in Ca^{2+} response in post ischemic rats was present in 50% of the cells, whereas <1% of the sham-operated cells showed any effect.

Conclusions: Taken together, these data suggest that IL-17 gene regulation in AKI-primed T cells is dependent on on increased cytosolic Ca^{2+} via Ca^{2+} influx.

Funding: NIDDK Support

SA-PO137

Protective Role of Endothelin B Receptor against the Development of Tunicamycin-Induced Renal Apoptosis Carmen De Miguel,[1] Janet Hobbs,[1] Pamela K. Carmines,[2] David M. Pollock,[1] Jennifer S. Pollock.[1] *[1]Medicine/ Nephrology, Univ of Alabama at Birmingham, Birmingham, AL; [2]Cellular and Integrative Physiology, Univ of Nebraska Medical Center, Omaha, NE.*

Background: Renal injury is normally preceded by renal tubular apoptosis and loss of nephrons. The vasoactive peptide endothelin-1 (ET-1) is upregulated in cardiovascular and renal disease; however, the exact mechanisms by which ET-1 leads to renal injury are unclear. These studies were designed to determine the role of ET-1 receptors in the development of renal apoptosis in response to the acute kidney injury inducer tunicamycin (TM; 2 mg/g body weight i.p.).

Methods: ET_B deficient (ET_B def) or transgenic (TG) control rats were pre-treated with the ET_A antagonist ABT-627 (5mg/kg/day, drinking water) or vehicle for 1 week prior to TM injection. 24 hours after TM administration kidneys were collected and renal apoptosis assessed by TUNEL assay. TUNEL+ cells were evident in cortex and, to a greater extent, in medulla of TG control and ET_B def rats 24 hours after TM administration.

Results: Pre-treatment of TG control rats with ABT-627 almost completely obliterated TM-induced apoptosis in renal cortex (decreasing from 13.5±1.6 to 1.3±0.4 TUNEL+ cells/field; n=5-6/group; $p<0.05$) and medulla (decreasing from 30.2±2.7 to 1.6±0.4 TUNEL+ cells/field; n=5-6/group; $p<0.05$), indicating that ET_A receptor activation is critical for the development of renal apoptosis. In contrast, ABT-627 failed to prevent TM-induced cortical and medullary apoptosis in ET_B def rats (cortex: 17.6 ± 2.0 TUNEL+ cells/field; medulla: 39.0± 4.4 TUNEL+ cells/field), highlighting the important protective role of the ET_B receptor against development of renal apoptosis. Examination at high magnification revealed that the TUNEL+ cells in renal tissue are interstitial cells located between tubules and/or near vasa recta.

Conclusions: Taken together, these results underscore the involvement of the ET_A receptor in the development of TM-renal apoptosis and highlight the ET system as a possible therapeutic target against acute kidney injury. Funded by NIH T32 DK007545 to CDM and P01 HL95499 and P01 HL69999 to DMP and JSP.

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SA-PO138

Macrophages Regulate the Expression of Stromal Cell-Derived Factor 1 via Indoleamine 2,3-Dioxygenase after the Renal Acute Ischemia--Reperfusion Injury Xin Wan, Changchun Cao. *Dept of Nephrology, Nanjing First Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: To observe the expression of indoleamine 2,3-dioxygenase(IDO) and stromal cell-derived factor 1(SDF-1) in the kidney after ischemic reperfusion injury(IRI), and explore the relationship between IDO, SDF-1 and macrophage by depleting macrophages before the IRI.

Methods: A total of 32 healthy C57BL/6 male mice were used to establish renal IRI model by clamping unilateral renal pedicle for 60 minutes followed by reperfusion. Kidney tissue samples were collected at indicated time points. Renal histological changes were estimated. The expression of SDF-1 and IDO were determined by immunohistochemistry, ELISA and real-time PCR. In LC group, after the liposomal clodronate was injected intraperitoneally, the location of CD68 was observed by immunofluorescence. In 1-MT group, IDO was evaluated by immunofluorescence after injecting intraperitoneally with 1-methyl-tryptophan. Renalhistology and protein expression of SDF-1 and IDO were also detected.

Results: Compared with sham-operated group, classical tubular damage was found in IRI group, accompanied by a lot of inflammatory cells infiltrate. The expression of total renal SDF-1 and IDO peaked on day 1 and decreased to normal levels after two weeks. IDO doesn't express in healthy kidneys, while SDF-1 in healthy kidney was localized at cortex and expand to the other area of the kidney during IRI. Compared with IRI groups, elimination of macrophageby injection of liposomal clodronate alleviated renal IRI and down-regulated the expressions of CD68 while up-regulating SDF-1. In 1-MT group, which IDO was depleted by using 1-MT, the expression of CD68 was normal while SDF-1 was up-regulated.

Conclusions: SDF-1 expression is up-regulated in IRI kidney and is associated with macrophages express with IDO. SDF-1 may play a role in the early phase of acute kidney injury and IDO inhibiter can be a new medicine in therapy of AKI.

Funding: Government Support - Non-U.S.

SA-PO139

Inhibiting PERK Phosphorylation Prevents Expression of the Pro-Apoptotic Protein CHOP Rachel Carlisle,[1,2] Jeffrey G. Dickhout.[1,2] *[1]Medical Sciences, McMaster Univ, Hamilton, ON, Canada; [2]Nephrology, St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada.*

Background: Acute kidney injury (AKI) is a major cause of morbidity and mortality in North America, and is regularly associated with endoplasmic reticulum (ER) stress. Tunicamycin, a nucleoside antibiotic, is often used as a mouse model of ER stress-induced AKI. Tunicamycin treatment results in vacuolization of the tubular epithelium, denudation and loss of cellular nuclei, apoptosis, and increased expression of ER stress markers, including GRP78 and CHOP. Interestingly, transgenic knock out of the pro-apoptotic protein CHOP prevented tunicamycin-mediated renal damage, implicating CHOP in the pathogenesis of AKI. GSK2606414 inhibits the phosphorylation of PERK, which is upstream of CHOP. We hypothesized that inhibiting PERK phosphorylation with GSK2606414 would prevent tunicamycin-induced CHOP expression and AKI.

Methods: Immortalized human proximal tubular cells were treated with vehicle, tunicamycin (1 μl/ml), tunicamycin and GSK2606414 (1 μM), or GSK2606414 alone, for 4 or 24 hrs. RT-PCR was performed for CHOP and Western blotting for CHOP and GRP78. Male wild type C57BL/6 mice were treated with a single dose of tunicamycin (0.5 mg/kg I.P.) or co-treated with tunicamycin and daily GSK2606414 (50 mg/kg) oral gavage. Mice were sacrificed after 3 days, and kidneys were subsequently stained for CHOP.

Results: Results demonstrate that tunicamcyin significantly increased CHOP mRNA and protein expression in proximal tubular cells; inhibiting PERK phosphorylation with GSK2606414 prevented this increase. Mice treated with tunicamycin exhibited an increase in nuclear CHOP staining. Mouse kidneys were protected from increased CHOP expression by co-treatment with GSK2606414.

Conclusions: These results suggest that CHOP plays a significant role in ER stress-induced renal damage, and attenuating its expression may provide new therapeutic strategies to protect against certain forms of AKI. Funding - Dr Dickhout is a Krescent New Investigator.

SA-PO140

Niclosamide Relieves Renal Ischemia-Reperfusion Injury by Promoting Fatty Acid Oxidation in Tubular Epithelial Cells Jining Wu, Junwei Yang. *Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Acute kidney injury (AKI) induced by ischemia/reperfusion (I/R) injury is one of the major clinical challenges with increasing of morbidity and mortality. Defective fatty acid oxidation (FAO) is evident after I/R, which is fatal to tubular epithelial cells. It was recently reported that niclosamide, a mitochondrial uncoupling agent, could promote FAO in liver cells. However, whether niclosamide could reduce I/R injury via improving FAO is largely unknown.

Methods: Male C57BL/6J mice were subjected to renal I/R. Niclosamide was given orally from 1 day before the surgery till the end of the study. Renal function, kidney histological abnormalities and FAO disorders were examined.

Results: Compared to vehicle control, niclosamide treatment marked relieved renal dysfunction at day 1 after I/R as demonstrated by reduced the increase of blood urea nitrogen. Histological examination showed the relief of tubular injury in cortex and outer medulla by niclosamide. I/R-induced fatty acid deposition in tubular epithelium was almost diminished in niclosamide-treated mice. The reduced expressions of enzyme and transcription factor that mediates and regulates FAO (CPT1 and PPAR-α) after I/R were largely restored by niclosamide.

Conclusions: In this study, it was demonstrated that niclosamide protects IR-induced AKI by promoting FAO. Our results raised the possibility that correcting the defective FAO may be useful for preventing and treating acute kidney injury.

Funding: Government Support - Non-U.S.

SA-PO141

NAD+ Degradation in the Injured and PGC1α-Deficient Kidney Mei T. Tran, Samir M. Parikh. *Div of Nephrology, Beth Israel Deaconess Medical Center, Boston, MA.*

Background: NAD+ is a key regulator of cellular energy metabolism. The kidney expends large amounts of energy in its main functions of reabsorption and secretion. Recent work showed that total NAD+ is markedly reduced in the kidney following ischemia reperfusion injury. Genetic induction of PGC1α activated de novo biosynthesis of NAD+, resulting in faster recovery from ischemic injury. Whether biosynthesis, reduced consumption from NAD-dependent enzymes, or a critical balance of both confers this NAD-related protection requires further investigation.

Methods: Genetic mice null (KO) or overexpressing PGC1α in the kidney (iNephPGC1α) underwent 20 min of bilateral renal ischemia, then 24h of reperfusion. Organs were harvested at 24h post-injury. Wildtype C57BL6 mice were injected with niacinamide (Nam, IP 400 mg/kg). Total NAD and Sirt1 activity were measured by colorimetric and fluorimetric assays. Gene expression was measured by qPCR.

Results: Enzymes involved in NAD+ biosynthesis were upregulated in iNephPGC1α mice at baseline, and remained elevated compared to control animals post-IRI. KO mice had lower basal expressions of these enzymes, which were further depleted in IRI. The rise and fall of these enzymes coincided with total NAD. To address if NAD+ fluctuations were due to increased NAD+ consumption, rather than reduced NAD+ biosynthesis, sirtuin expression and activity levels were measured in Nam-treated wildtype mice. Total NAD+ was elevated in Nam-treated mice, with no change in Sirt1 activity. Following IRI, NAD+ levels and Sirt1 activity decreased across all conditions. Relative to injured controls, total NAD+ was still greater in injured Nam-treated mice, and unexpectedly, Sirt1 activity was similarly elevated.

Conclusions: Results suggest that depletion of NAD+ in the injured or PGC1α-deficient kidney may not be due to greater NAD+ consumption, but as recent work proposes, inability to synthesize NAD+. Furthermore, though Nam is known to inhibit Sirt1, these studies show that basal Sirt1 activity was unchanged with systemic Nam administration. Even more surprising is that Sirt1 activity is higher in the injured Nam-treated mice, suggesting that sirtuin activity reflects overall kidney health.

Funding: NIDDK Support

SA-PO142

Pannexin1 Deletion Protects Kidneys from Ischemia-Reperfusion Injury in Mice Jakub Jankowski,[1] Heather M. Perry,[1] Liping Huang,[1] Hong Ye,[1] Brant Isakson,[2] Kodi S. Ravichandran,[3] Mark D. Okusa.[1] *[1]Div of Nephrology; Center for Immunity, Inflammation and Regenerative Medicine, Univ of VA; [2]Dept of Molecular and Cellular Physiology, Univ of VA; [3]Dept of Microbiology, Immunology, and Cancer Biology, Univ of Virginia, Charlottesville, VA.*

Background: Extracellular ATP can contribute to inflammation following cell damage or death through its action as a danger molecule on P2X and P2Y receptors. The cellular mechanism of ATP release and its impact on kidney ischemia-reperfusion injury (IRI) are largely unknown. Pannexin1 (PANX1), a transmembrane channel, can be activated to release ATP yet its impact on kidney IRI is not known. We hypothesize that deletion of PANX1 and reduction of ATP release is protective in kidney IRI. We also predict this effect may be mediated by PANX1 in proximal tubules (PT), as they are a rich source of ATP and highly susceptible to IRI.

Methods: Global PANX1 (*Panx1*$^{-/-}$, n=10) and PT-specific PANX1 (*PepckCrePanx1*$^{f/f}$, n=4) KO mice and appropriate controls (n=9 and 3 respectively) were subjected to 26' bilateral kidney IRI or sham operation and 24h of reperfusion. Kidney function was assessed by plasma creatinine (PCr) and kidney injury by stereological quantification of acute tubular necrosis (% of outer medulla area) of H&E stained kidney sections. Proinflammatory markers were quantified by real-time PCR of whole kidney lysates. Apoptosis was assessed by detection of cleaved caspase3 by immunohistochemistry.

Results: Increased PCr (mg/dL) in WT mice after IRI was blunted in *Panx1*$^{-/-}$ mice (1.4 vs. 0.21; p<0.0001). Consistent with better kidney function, *Panx1*$^{-/-}$ kidneys had less necrosis (%) (19.65 vs 81.01, p<0.0001) and fewer cleaved-caspase 3 positive tubule cells. The increase in kidney mRNA of proinflammatory cytokines (*Tnfa, Il6, Csf1*), chemokines (*Cxcl1, Cxcl2*) and leukocyte adhesion molecules (*Icam1, Sele, Selp*) in WT mice after IRI was attenuated in *Panx1*$^{-/-}$ mice. Lastly, the increase in PCr in controls after IRI was markedly reduced in *PepckCrePanx1*$^{f/f}$ mice (1.84 vs 0.16 respectively).

Conclusions: These results show that both global and PT loss of PANX1 protect mouse kidneys from IRI and suggest that PANX1 may serve as a therapeutic target in AKI.

SA-PO143

Drp1-Dependent Mitophagy Protects against Cisplatin-Induced Apoptosis of Renal Tubular Epithelial Cells by Improving Mitochondrial Function Yanggang Yuan, Ningning Wang, Huijuan Mao, Chang Ying Xing. *Dept of Nephrology, The First Affiliated Hospital of Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Mitochondrial dysfunction plays an important role in cisplatin induced nephrotoxicity. Degradation of damaged mitochondria is carried out by mitophagy. Little is known of the precise role of mitophagy and its molecular mechanisms during cisplatin induced nephrotoxicity. Also, evidence that activation of mitophagy improved mitochondrial function is lacking. Furthermore, several evidences have shown that mitochondrial fission coordinates with mitophagy. The aim of this study was to investigate whether activation of mitophay protects against mitochondrial dysfunction and renal tubular cells injury during cisplatin treatment. The effect of mitochondrial fission on mitophagy was also investigated.

Methods: Autophagy was evaluated by autophagy markers and mRFP-GFP-LC3 adenovirus. Mitophagy was determined the co-localization of mitochondria with lysosomome. ROS levels were determined by DCFDA and MitoSOX. Mitochondrial membrane potential was assessed by JC-1. ATP concentration was quantitatively determined using an ATP determination kit. Cell viability and cell apoptosis were accessed by CCK-8 assay and AnnexinV-FITC–PI double staining assay respectively. Mitochondrial morphology was visualized by using MitoTracker Red. siRNAs were used to knock down mitochondrial fission main regulator dynamin-related protein-1 (Drp1) expression and subsequent changes were observed.

Results: In cultured human renal proximal tubular cells, we observed that 3-methyladenine, a pharmacological inhibitor of autophagy, blocked mitophagy and exacerbated cisplatin-induced mitochondrial dysfunction and cells injury. In contrast, autophagy activator rapamycin enhanced mitophagy and protected against the damage effects of cisplatin on mitochondrial function and cells viability. Knockdown of Drp1 decreased cisplatin-induced mitophagy. Meanwhile, Drp1 suppression protected against cisplatin-induced cells injury by inhibiting mitochondrial dysfunction.

Conclusions: Our results provide evidence that Drp1-depedent mitophagy has potential as renoprotective targets for the treatment of cisplatin-induced AKI.

SA-PO144

Thioredoxin-Interacting Protein (TXNIP) Regulates Mitochondrial Function of Renal Tubular Cells and Prognosis of Ischemia/Reperfusion-Induced Acute Kidney Injury Shigeru Nojima, Tatsuki Matsumoto, Koh Takahashi, Hirofumi Nishikawa, Yoshiko Shimamura, Kosuke Inoue, Yoshinori Taniguchi, Taro Horino, Shimpei Fujimoto, Yoshio Terada. *Dept of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi Univ, Nankoku, Kochi, Japan.*

Background: Thioredoxin-interacting protein (TXNIP) has been found to regulate the cellular reduction-oxidation (redox) state by binding to and inhibiting thioredoxin in a redox-dependent fashion. However, little is known about the role of TXNIP in mitochondrial function and acute kidney injury (AKI) pathogenesis.

Methods: We evaluated the role of TXNIP in renal function in bilateral renal ischemia (27 min)/reperfusion injury (IRI) model using TXNIP knock-out (KO) and wild type (WT) mice. We evaluated mitochondrial enzymes, morphology, ATP production, and membrane potentials of mitochondria from KO and WT mice. We also evaluate mitochondrial enzymes, inflammasomes by transfection of siRNA for TXNIP in cultured renal tubular cells (NRK-52E cells).

Results: TXNIP KO mice had significantly higher SCr (0.78+0.28 versus 0.45 + 0.17 mg/dl) and significantly higher BUN (152.5+32.5 versus 75.3+17.2 mg/dl) at 24h post ischemia compared to WT mice. Immunohistological examination showed severer tubular injury in cortex and outer medulla in TXNIP KO mice compared to WT mice. The number of TUNEL positive tubular cells was increased in TXNIP KO mice compared to WT mice. Dysmorphic mitochondria were observed in proximal tubules of TXNIP KO mice compared to WT mice. The protein expressions of mitochondrial enzymes (ATP5a, PGC1α and complex IV), ATP production, and membrane potentials were decreased in TXNIP KO mice at 24h post ischemia. In vitro experiments, protein levels of ATP5a, complex IV, PGC-1α were significantly decreased, and inflammasomes were activated by H_2O_2, and siRNA for TXNIP reduced changes of these enzymes in NRK-52E cells.

Conclusions: These data demonstrate that deficiency of TXNIP exaggerates IRI induced tubular injury. TXNIP changes mitochondrial function of renal tubular cells in oxidative conditions. These results indicate that TXNIP plays a key role in mitochondrial function and the pathophysiology of AKI.

Funding: Government Support - Non-U.S.

SA-PO145

UCP2 Protects Tubular Epithelial Cells against Acute Ischemia/Reperfusion Injury by Regulating Fatty Acid Oxidation Yang Zhou, Junwei Yang. *Center for Kidney Disease, Second Affiliatted Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Tubular epithelium reclaims more than 100l/d from glomerular filtrate. Reabsorption of so many sodium and solutes is an energy consumption process. Kidney is only second to heart in mitochondrial content—the energy producing plant. Tubular epithelial cells are especially rich in mitochondria. Moreover, tubular epithelial cells apply fatty acid oxidation (FAO) in mitochondria as its major energy resource, which is the most efficient way to generate ATP. Ischemia/reperfusion (I/R)-induced acute kidney injury (AKI) demonstrates both widespread mitochondrial injury and defective FAO. Uncoupling protein 2 (UCP2) is a mitochondrial anion carrier protein located in the inner membrane, which regulates the ratio of FAO vs. glucose metabolism during cell proliferation. Nevertheless, the role of UCP2 in FAO and AKI remains largely unknown.

Methods: Expression levels of UCP2 in kidneys were firstly examined after acute I/R injury. Proximal tubular cell specific UCP2 knockout mice were generated by cre-LoxP recombinant enzyme system. Mice were fed standard diets with conjugated linoleic acid (CLA) to upregulate UCP2. Both of them were applied to investigate the role of UCP2 in I/R-induced AKI.

Results: We examined the I/R injured kidneys and identified remarkable upregulation of UCP2 in the diseased kidneys. The proximal tubule specific UCP2 knockout mice were born and growth normal without kidney histological abnormalities or renal dysfunctions. As compared with littermates (wild-type), deletion of UCP2 exacerbated I/R-induced AKI as demonstrated by developing more severe renal dysfunction and worse morphologic abnormalities. In particular, we found that knockout mice had more significant declined expression of key enzymes and regulators of FAO and increased intracellular lipid deposition compared to wild-type mice. In contrast, upregulation of UCP2 by feeding CLA protected mice from I/R-induced AKI and mitigated FAO disorders. In vitro experiments indicated that UCP2 promoted FAO in primarily cultured tubular epithelial cells.

Conclusions: Our results raise the possibility that mitochondrial UCP2 may be useful for protecting tubular epithelium and treating AKI.

Funding: Government Support - Non-U.S.

SA-PO146

Effect of Hypertonic Saline Solution and Pentoxifylline on Lipid Peroxidation and Apoptosis of Acute Kidney Injury Induced by Obstruction and Intestinal Ischemia in Rats Miguel A. Goes,[1,2] Roberto Rasslan,[3] Edna Frasson de Souza Montero,[3] Edivaldo Massazo Utiyama,[3] Samir Rasslan,[3] Gustavo Scapini.[2,3] *[1]Neprhology, Federal Univ of Sao Paulo, Sao Paulo, SP, Brazil; [2]Nephrology, Hospital Israelita Albert Einstein, Sao Paulo, SP, Brazil; [3]Surgery, Sao Paulo Univ, Sao Paulo, SP, Brazil.*

Background: Sepsis after intestinal obstruction and ischemia is associated to acute kidney injury (AKI). Apoptosis and oxidative stress are hallmarks of sepsis-induced AKI. Fluid resuscitation decrease sepsis-induced AKI. Objective: To evaluate the effects of hypertonic saline and pentoxifylline on oxidative stress and renal apoptosis in sepsis.

Methods: 48 male Wistar rats were underwent laparotomy to an obstruction and intestinal ischemia. They were treated randomly with different resuscitation solutions: Sham (n=8); Ringer Lactate (RL; n=16); Hypertonic Saline Solution 7.5% - (HSS; n=8); Pentoxifylline (PTX; n=8) and HSS associated with PTX (HSSPTX; n=8). They were infused over a 5 min period. The animals were sacrificed after 3 hours. Histopathological and immunohistochemical analyzes were performed with BcL-2 (ng/mg of protein), Bax (ng/mg) and TUNEL (ng/mg). Peroxynitrite (μM/mg of kidney tissue) by spectrophotometry and malondialdehyde (MDA- nmol/mg of protein) with the TBARS method dosages were performed.

Results: We observed a positive correlation between the levels of Bax and BcL-2 (r = 0.55; p <0.001), Bax and TUNEL (r = 0.48; p = 0.001), Bax and peroxynitrite (r = 0.32; p=0.03), Bax/BcL-2 and peroxynitrite (r=0.48; p=0.01). We found higher Bax

levels in PTX (5.75+0.71) than the RL (3.75+1.77; p<0.001). HSSPTX (1.38+0.74) had lower Bax levels than the RL (3.75+1.77) and PTX groups (5.75+0.71; p<0.001). BCL-2 immunohistochemical levels were higher in Sham group (5.50+1.69) than in the other groups (p<0.001). The Bax/BcL-2 ratio was higher in PTX (3.25+0.89) than HSSPTX group (2.38+0.92; p=0.009). TUNEL immunohistochemical levels were lower in HSS (18.5+6.93) and HSSPTX (10.7+2.77) groups than in the other groups (p<0.001). We did not observe difference in the concentration of MDA between the groups (p=0.62).

Conclusions: HSSPTX attenuated oxidative stress and decreased the immunohistochemical markers of apoptosis in sepsis-induced AKI.

SA-PO147

Preconditioning with a Pharmacologic Activator of Adenine Monophosphate-Activated Kinase Reduces Apoptosis of Proximal Tubular Cells Exposed to Metabolic Stress: Role of Akt and Glycogen Synthase Kinase

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Background: We have reported that preconditioning proximal tubular cells (PTCs) with A-769662, an activator of adenine monophosphate-activated kinase (AMPK), ameliorates stress-induced apoptosis by preserving cell ATP stores (AJP: In Press). We now examine the role of Akt, a pro-survival kinase, and of glycogen synthase kinase-3b (GSK-3b) a pro-apoptotic kinase, in mediating the pro-survival effects of A-769662.

Methods: After preconditioning, PTCs were subjected to metabolic stress induced by antimycin without dextrose. Apoptosis was evaluated by FACS, the activity of Akt, GSK-3b, BAD and BAX by immunoblotting and cell survival using the MTT assay.

Results: Preconditioning with A-760662 reduced stress-induced apoptosis, increased the activation of Akt (by phosphorylating Thr-308 and Ser-437) and inhibited the activation of GSK-3b (by phosphorylating Ser-9). Preconditioning with A-760662 also inhibited the activation of BAD by phosphorylating Ser-136 (an effect mediated by Akt), and inhibited the allosteric activation of BAX, (an effect mediated by inhibition of GSK-3b). Knocking down AMPK activity reduced all these effects of A-769662 suggesting that they are mediated by AMPK activation. The increase in stress-induced cell survival induced by preconditioning with A-769662 alone, was reduced by preconditioning with A-769662 + MK-22-2 (an Akt inhibitor). Post-stress cell survival after preconditioning with MK-2202 alone, was lower than cell survival after preconditioning without A-769662 or MK-2202. The increased stress-induced survival of cells induced by preconditioning with A-769662 alone, or with A-769662 + TZDZ-8 (an inhibitor of GSK-3b) was comparable, while the post-stress cell survival after preconditioning with TZD alone was lower than after preconditioning with A-769662 + TZDZ-8, but higher than that after preconditioning without A-769662 or TZDZ-8.

Conclusions: The pro-survival effects of preconditioning PTCs with A-769662 before exposing them to stress is mediated, in part, by the activation of Akt and the inhibition of GSK-3b.

Funding: VA Support

SA-PO148

Vascular Adhesion Protein-1 Promotes Neutrophil Infiltration via Hydrogen Peroxide Generation in Renal Ischemia-Reperfusion Injury

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Background: Vascular adhesion protein-1 (VAP-1) acts as an adhesion molecule as well as an ectoenzyme catalyzing oxidative deamination of primary amines to generate hydrogen peroxide in extracellular space. While VAP-1 is implicated in leukocyte trafficking in various inflammatory diseases, its role in acute kidney injury is incompletely characterized. Thus, we examined the effect of VAP-1 inhibition in a rat model of renal ischemia-reperfusion (IR) injury.

Methods: Rats were subjected to left renal ischemia for 45 min after right nephrectomy, followed by reperfusion for 48 h. A specific VAP-1 inhibitor, Compound A (R-Tech Ueno, Tokyo, Japan; 40 mg/kg/day; in feed), or vehicle was administered to rats from 7 days before IR surgery.

Results: Immunofluorescence analysis suggested that VAP-1 was predominantly expressed in pericytes of rat kidneys. Primary mouse kidney pericytes expressed and released enzymatically active VAP-1. In vivo, Compound A administration significantly suppressed VAP-1 enzyme activity in the whole kidneys (7.0±1.3 vs 0.9±0.1 pmol/mg protein/min), which was accompanied by better renal function (BUN: 139±15 vs 69±6 mg/dL, Cr: 2.5±0.2 vs 1.4±0.1 mg/dL; p<0.01) and ameliorated histological tubular injury in the drug group. The number of neutrophils in the corticomedullary junction was significantly decreased in the drug group. There were no differences between groups in the numbers of macrophages/T lymphocytes or in the expression of other adhesion molecules. The protective effect of VAP-1 inhibition was absent in neutrophil-depleted rats. Moreover, in the under-agarose migration assay with purified human neutrophils, recombinant human VAP-1 significantly induced neutrophil migration, which was inhibited by Compound A or catalase.

Conclusions: These data suggest that VAP-1 plays an important role in the pathophysiology of renal IR injury by generating a local hydrogen peroxide gradient to enhance neutrophil infiltration, offering a promising view that VAP-1 inhibition can be a novel therapeutic target in ischemic acute kidney injury.

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

SA-PO149

Methionine Sulfoxide Reductase A (MsrA)-Gene Deletion Aggravates Cisplatin-Induced Nephrotoxicity in Mice

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Background: Methionine sulfoxide reductase A (MsrA) catalyzes stereospecifically the reduction of methionine-*S*-sulfoxide, and plays an antioxidant enzyme that scavenges reactive oxygen species (ROS). Cisplatin is the most widely used for the treatment of solid tumors. However, its side effects including nephrotoxicity limit use. In the present study, we investigated the role of MsrA in cisplatin-induced nephrotoxicity using MsrA gene-deleted ($MsrA^{-/-}$) and wild-type ($MsrA^{+/+}$) mice.

Methods: Mice were administrated with vehicle or cisplatin (10 mg/kg, i.p.) for 5 days.

Results: Cisplatin-induced renal functional and morphological impairments were greater in the $MsrA^{-/-}$ than in $MsrA^{+/+}$ kidneys. Cisplatin increased superoxide anion formation, hydrogen peroxide (H_2O_2) production, lipid peroxidation, and the ratio of oxidized glutathione (GSSG) to total glutathione (GSH) in the kidneys. These increases were much higher in $MsrA^{-/-}$ than in $MsrA^{+/+}$ kidneys. Cisplatin reduced the expression and activity of MsrA and MsrBs in the kidneys. Cisplatin reduced the expression of cystathionine-β-synthase (CBS) and cystathionine-γ-lyase (CSE), both of which are H_2S-producing enzymes, in the kidneys. Cisplatin exacerbated mitochondria dysfunction, reducing the levels of mitochondria fission 1 (Fis1), promoter of mitochondrial fission. Cisplatin also enhanced the pro-apoptotic response and increased the number of apoptotic cells. MsrA deficiency increased the cisplatin-induced mitochondrial dysfunction and apoptosis in the kidneys.

Conclusions: Taken together, these results demonstrate for the first time that cisplatin reduces MsrA activity and MsrA gene deletion exacerbates cisplatin-induced nephrotoxicity via increased oxidative stress, mitochondrial dysfunction, and apoptosis. It suggests that MsrA plays a crucial role in the pathogenesis of cisplatin-induced acute kidney injury (AKI) and may be a useful target protein to prevent cisplatin-induced nephrotoxicity.

SA-PO150

Mitochondrial Function during Injury and Recovery from AKI

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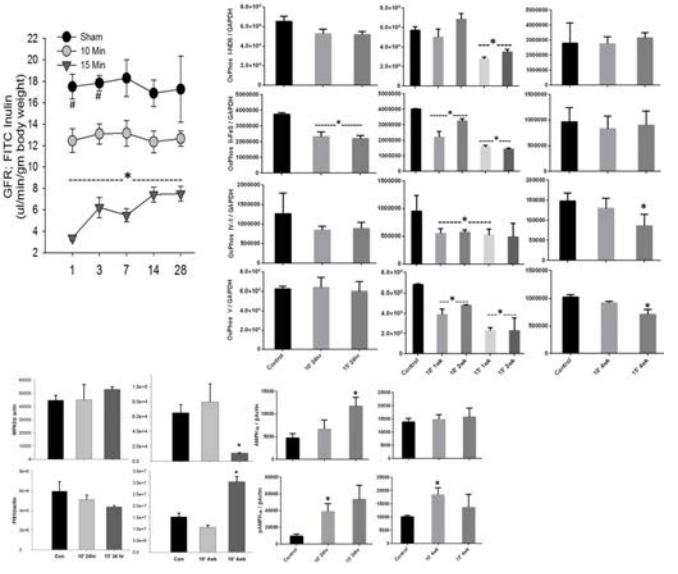
Background: Renal tissue hypoxia is a common link between AKI and CKD. The kidney has high mitochondrial oxidative metabolism, and is exquisitely sensitive to hypoxic injury. Mitochondria play a central role in cell injury and their dysfunction has been implicated in various forms of AKI, but information on mitochondrial function during recovery from AKI is limited.

Methods: We performed 10-min and 15-min of bilateral renal artery clamping (IR) in mice and then serial GFR measurement by FITC inulin kinetics at days 1, 3, 7, 14 and 28 after ischemia and protein expression of mitochondrial oxidative phosphorylation complexes (Ox phos), fission, fusion and AMPK at the same time points.

Results:



Serial GFRs: In the 10-min group, GFR was significantly lower at days 1 and 3 but improved after that to levels similar in shams. In the 15-min group, GFR was dramatically reduced with partial recovery over 4 weeks. **Ox Phos expression:** Significant reduction in expression for both 10 and 15 min IR at 1-2 weeks for most complexes, with recovery in expression at 4 weeks for 10-min, but persistent reduction for 15-min IR. **Mitochondrial Proteins**-at 4weeks, 15-min IR showed significant reduction in Mfn2 and increase in Fis1 expression. Total **AMPK** expression was increased at day1, but no increase in pAMPK was seen in the 15-min IR kidney. In 10-min IR, pAMPK was increased at 24 hrs and persisted at 4 weeks.

Conclusions: Our findings show duration of IR corresponding with severity of injury and impaired recovery in GFR, and mitochondrial dysfunction with decreased Ox phos proteins and altered dynamics with impaired AMPK activation in IR kidneys, corresponding to severity of injury, but in some instances despite functional recovery. These may be important in transition of AKI to CKD. Additional studies to compare these two models when manipulated with maneuvers to worsen or improve recovery from IR are ongoing.

Funding: NIDDK Support, VA Support

SA-PO151

Antrum Mucosal Protein-18 Prevents Cisplatin-Induced Acute Kidney Injury in Mice Patrick Cunningham, Bradley K. Hack, Peili Chen, F. Gary Toback. *Section of Nephrology, Univ of Chicago, Chicago, IL.*

Background: Cisplatin induced nephrotoxicity is a frequent complication which limits the use of platinum based chemotherapy and increases morbidity in cancer patients. Antrum mucosal protein-18 (AMP-18) is a protein produced in the stomach which has mitogenic and protective effects on epithelium, mediated in part by strengthening intercellular tight junctions, previously demonstrated in cell culture and models of intestinal injury. We hypothesized that AMP-18 peptide would protect against cisplatin-induced nephrotoxicity in mice, which causes severe injury to the tubular epithelium (acute tubular necrosis, or ATN).

Methods: C57BL6 mice were given daily injections of AMP-18 peptide (25 mg/kg) starting two days before cisplatin administration. At day zero, mice were given cisplatin (30 mg/kg i.p.). AMP-18 injections were continued until sacrifice at 72 h after cisplatin (n = 6 per group). Serum was analyzed for BUN, and kidneys were collected for light microscopic staining and analysis of protein and mRNA.

Results: Mice in the cisplatin alone group had significant renal failure, but AMP-18 injected mice were profoundly protected (BUN 113.6 +/- 21.8 mg/dl in cisplatin + vehicle group, versus 39.8 +/- 5.2 mg/dl in cisplatin + AMP-18, $p < 0.01$). Mice injected with AMP-18 also had significantly less tubular necrosis on light microscopy (injury score 5.1 +/- 1.0 v. 1.0 +/- 0.2, $p = 0.003$), which correlated tightly with BUN readings. AMP-18 injected mice also had significantly less albuminuria after cisplatin (941 +/- 185 v. 444 +/- 105 mcg/mg creatinine, $p < 0.01$), as well as fewer apoptotic nuclei as seen by TUNEL staining. Immunofluorescence showed relatively preserved tight junctions in the tubular epithelium in AMP-18 treated mice.

Conclusions: In summary, AMP-18 peptide showed a strong protective effect in preventing cisplatin-induced nephrotoxicity. This finding may ultimately lead to therapies which could prevent cisplatin nephrotoxicity in patients.

Funding: NIDDK Support

SA-PO152

Renoprotection of CHBP against Ischemia Reperfusion-Related Renal Injury Associated with Inhibiting Endoplasmic Reticulum Stress Qian Wang,[1] Yufang Zhang,[2] Aifen Liu,[2] Yuanyuan Wu,[4] Feng Liu,[1] Hui Wang,[1] Bin Yang.[1,2,5] *[1]Nephrology, Affiliated Hospital of Nantong Univ, China; [2]Basic Medical Research Centre, Nantong Univ, China; [3]Shanghai Key Laboratory of Organ Transplantation, Fudan Univ, China; [4]Pathology, Nantong Univ, China; [5]Infection, Immunity and Inflammation, Univ of Leicester, United Kingdom.*

Background: Ischemia reperfusion (IR) injury plays a key role in transplant and native kidneys alike. Our previous study revealed the renoprotection of cyclic helix-B surface peptide (CHBP) derived from erythropietin in IR injury, but its mechanism has not been fully defined. Endoplasmic reticulum stress (ERS) affects apoptosis and inflammation, involving in the pathogenesis of many diseases. This study aimed to explore the effects of CHBP on ERS in IR-related renal injury.

Methods: IR-related injury was established in mouse tubular epithelial cells via H_2O_2 stimulation and in mouse kidneys subjected to 30 min bilateral ischemia and followed by 2 & 8-wek reperfusion, with or without CHBP treatment. CHOP, an ERS hallmark, and its upstream regulatory PERK, and apoptosis and/or inflammation-related genes JNK and HMGB1 at mRNA and protein level were measured. In addition, apoptosis, cell viability and tubulointerstitial damage was also evaluated. Finally, the correlations between CHOP and assessed parameters were analyzed.

Results: The mRNA and protein of CHOP, PERK, JNK and HMGB1 were significantly increased in the TCMK1 cells stimulated by H_2O_2, while apoptosis was aggravated and cell viability was reduced. However, these effects were reversed by CHBP. In addition, CHOP protein was also significantly enhanced in the IR kidneys, but reduced by CHBP. Further more, CHOP mRNA was correlated with PERK mRNA and JNK protein ($r=0.955$ & 0.765, both $p<0.01$), while CHOP mRNA, PERK mRNA or JNK protein was respectively correlated with apoptosis positively ($r=0.647$ & 0.722, both $p<0.01$; $r=0.416$, $p<0.05$) and cell viability negatively ($r=-0.519$, -0.481 & -0.438, all $p<0.05$) *in vitro*. In addition, the level of CHOP protein was correlated with TID ($r=0.955$, $P < 0.01$) *in vivo*.

Conclusions: The renoprotection of CHBP in TCMK1 cells and kidneys subjected to IR-related injury might be associated with inhibiting ERS.

Funding: Government Support - Non-U.S.

SA-PO153

Renal Cold Storage plus Transplantation Alters Mitochondrial Dynamics: Involvement of Oxidants? Lee Ann MacMillan-Crow, Nirmala Parajuli, Stephen Shrum. *Pharmacology/Toxicology, Univ of Arkansas for Medical Sciences, Little Rock, AR.*

Background: A major hurdle in the field of renal transplantation is the shortage of suitable donor kidneys. Renal transplantation using living-donor organs perform better when compared to deceased donor kidneys that were exposed to cold storage (CS) prior to transplantation (Tx). We recently reported that 4 hr CS compared to auto transplantation resulted in more severe mitochondrial and renal damage (J. Kidney, 2: 114, 2016). The purpose of the current study was to evaluate whether mitochondrial dynamics (fusion/fission pathways) were altered during CS/Tx and to dissect the molecular pathways involved.

Methods: Male rodent (Lewis) kidneys were isolated and cold stored for 0 or 18 hr and then transplanted in a naïve Lewis rat followed by right nephrectomy. Mitochondrial function was assessed via high resolution respirometry and ATP measurement. Mitochondrial dynamics were monitored using western blotting and electron microscopy (EM).

Results: EM data revealed marked mitochondrial fragmentation following CS+Tx Likewise, mitochondrial function was inhibited at complexes I, II, and III. Interestingly, CS alone led to impaired mitochondrial fusion (loss of long form of Opa1, which is critical for inner membrane fusion). CS+Tx also showed impaired Opa1 processing and decreased mitofusion expression (critical for outer membrane fusion). The mitochondrial protease, Oma1, has been shown to be activated by stress (and oxidants) which can lead to increased Opa1 processing and impaired mitochondrial fusion. Early studies show altered Oma1 activity during CS+Tx.

Conclusions: In summary, these studies suggest that renal CS initiates a defect in mitochondrial dynamics that likely involves increased oxidant-induced Oma1 protease function which then impairs mitochondrial fusion. Further studies designed to blunt Oma1 activity may protect donor kidneys from CS-mediated damage prior to transplantation.

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SA-PO154

Proximal Tubule-Specific Deletion of Cyclophilin D Prevents Cisplatin Nephrotoxicity Hee-Seong Jang,[1] Babu J. Padanilam.[1,2] *[1]Cellular and Integrative Physiology, Univ of Nebraska Medical Center, Omaha, NE; [2]Internal Medicine, Section of Nephrology, Univ of Nebraska Medical Center, Omaha, NE.*

Background: Damage of proximal tubule cell by chemotherapeutic agent cisplatin causes kidney injury and dysfunction. However, the underlying mechanism of cisplatin-induced tubular injury remains to be elucidated.

Methods: Since cyclophilin D (CypD) plays a critical role in necrotic cell death, we investigated whether proximal tubule-targeted deletion of CypD prevents cisplatin-induced kidney injury.

Results: Loss of proximal tubule CypD preserved mitochondrial morphology and function and prevented downregulation of mitochondrial biogenesis and expression of mitochondrial metabolism-related genes. Fatty acid metabolism was impaired in wild type mice, but was preserved in mice with proximal tubule deletion of CypD after cisplatin treatment. Consistent with mitochondrial damage, proximal tubule-targeted deletion of CypD suppressed cisplatin-induced tubular necrosis, apoptosis, inflammation, and kidney dysfunction. Pharmacological inhibition of CypD using Sanglifeherin A also prevented cisplatin-induced kidney injury. However, inhibition of ferroptosis by ferrostatin-1 did not protect, rather worsened, cisplatin-induced kidney injury, suggesting a dispensable role of ferroptosis in cisplatin nephrotoxicity.

Conclusions: Collectively, targeting CypD prevents cisplatin nephrotoxicity through preservation of mitochondrial metabolism, and may be developed asa potential therapeutic strategy for cisplatin nephrotoxicity.

Funding: NIDDK Support, Private Foundation Support

SA-PO155

Effect of Mitochondrial NADP+-Dependent Isocitrate Dehydrogenase (IDH2) on Cisplatin-Induced Nephrotoxicity Min Jung Kong,[1] Sang Jun Han,[1] Jee In Kim,[2] Kwon Moo Park.[1] *[1]Dept of Anatomy and BK21 Plus, Kyungpook National Univ School of Medicine, Daegu, Korea; [2]Dept of Molecular Medicine and MRC, Keimyung Univ School of Medicine, Daegu, Korea.*

Background: Mitochondrial $NADP^+$-dependent isocitrate dehydrogenase (IDH2) is a major producer of NADPH producer which is critical for maintenance of glutathione (GSH) redox balance in the mitochondria. Cisplatin is one of the most common anticancer drugs. However, its nephrotoxicity due to a reduction of intracellular levels of glutathione by formation of cisplatin-GSH complex limits to use. Here, we investigated the role of IDH2 in cisplatin-induced nephrotoxicity using IDH2 gene-deleted ($IDH2^{-/-}$) and wild type ($IDH2^{+/+}$) mice.

Methods: Mice were administrated intraperitoneally cisplatin (20 mg/kg body weight). Some mice were treated Mito-Tempo, a mitochondria-specific antioxidant, before cisplatin injection.

Results: IDH2 deficiency aggravated cisplatin-induced renal functional and morphological impairments. MT reduced those cisplatin-induced renal functional and morphological impairments both $IDH2^{-/-}$ and $IDH2^{+/+}$ mouse kidneys. Cisplatin reduced NADPH levels in the kidney. This cisplatin-induced reduction of NADPH levels were greater in the $IDH2^{-/-}$ mouse kidneys than $IDH2^{+/+}$ mouse kidneys. Cisplatin increased hydrogen peroxide, lipid peroxidation and GSSG/total GSH ratio. These increases were

greater in the IDH2$^{-/-}$ mouse kidneys than IDH2$^{+/+}$ mouse kidneys. MT reduced those cisplatin-induced reduction of NADPH, and increases hydrogen peroxide, lipid peroxidation and GSSG/total GSH ratio both IDH2$^{-/-}$ and IDH2$^{+/+}$ mouse kidneys. Mitochondrial damage and renal cell death after cisplatin injection were greater in the IDH2$^{-/-}$ than IDH2$^{+/+}$ mouse kidneys. MT reduced those cisplatin-induced mitochondrial damage and cell death both IDH2$^{-/-}$ and IDH2$^{+/+}$ mouse kidneys. Above effects of MT were greater in IDH2$^{-/-}$ mouse kidneys when compared with IDH2$^{+/+}$ mouse kidneys.

Conclusions: These results indicate IDH2 deficiency aggravates cisplatin-induced nephrotoxicity by increasing mitochondrial oxidative damage, suggesting that IDH2 plays a crucial role in the pathogenesis of cisplatin-induced acute kidney injury (AKI).

SA-PO156

Deletion of Sirtuin 7 Ameliorates Cisplatin-Induced Acute Kidney Injury Through Regulation of Inflammatory Response Yoshikazu Miyasato,[1,2] Tatsuya Yoshizawa,[1] Terumasa Nakagawa,[2] Yutaka Kakizoe,[2] Yuichiro Izumi,[2] Takashige Kuwabara,[2] Masataka Adachi,[2] Eva Bober,[3] Masashi Mukoyama,[2] Kazuya Yamagata.[1] *[1]Medical Biochemistry, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan; [2]Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan; [3]Cardiac Development and Remodeling, Max-Planck-Inst for Heart and Lung Research, Bad Nauheim, Germany.*

Background: Sirtuin 7 (SIRT7) is an NAD$^+$-dependent deacetylase. It is reported that SIRT7 has significant roles in disease conditions such as hepatic steatosis, cardiac dysfunction and cancer. However, very little is known about the functional roles of SIRT7 in kidney diseases. Therefore, we investigated the role of SIRT7 in acute kidney injury.

Methods: Acute kidney injury was induced by intra-peritoneal cisplatin administration (20mg/kg body weight) in SIRT7 deficient (SIRT7-/-) and wild-type (WT) mice. Mice were sacrificed at day 3 after cisplatin administration. Knockdown of SIRT7 in NRK52E, a rat renal proximal tubular cell line, was induced by short hairpin RNA (shRNA).

Results: SIRT7-/- mice showed significantly lower serum creatinine levels compared with WT mice (0.50±0.25 vs 0.85±0.38 mg/dL, $p<0.05$). Histological analysis revealed lower kidney injury score and macrophage accumulation in SIRT7-/- mice. The number of TUNEL positive cells was also significantly low. The survival rate of SIRT7-/- mice was significantly higher than WT mice at day 7 after cisplatin administration (Log-rank test, $p<0.01$). There were significant decreases in inflammation-related gene expression (TNF-α, IL-1β, IL-6, MCP-1) and oxidative stress-related gene expression (NOX2, p47 phox) in the kidney of SIRT7-/- mice compared with WT mice. In NRK52E, knockdown of SIRT7 ameliorated cell viability in WST-1 assay under cisplatin-exposed condition. In addition, the expression of inflammation-related genes also tended to lower in SIRT7 knockdown cells, but that of oxidative stress-related genes showed no change.

Conclusions: Our data demonstrated that the deletion of SIRT7 ameliorated cisplatin-induced acute kidney injury in mice, suggesting a possibility of novel pathogenic roles for SIRT7 in acute kidney injury through promoting inflammatory responses.

SA-PO157

Silencing Numb Exacerbates Cisplatin-Induced Acute Kidney Injury by Promoting Mitochondrial Fragmentation Ze Liu, Jing Nie. *The Key Laboratory of Organ Failure Research, Nanfang Hospital, Southern Medical Univ, Guangzhou, China.*

Background: Numb is a multifunctional protein involved in diverse cellular processes. We previous study showed that Numb is expressed in proximal tubules. Depletion Numb from proximal tubular cells attenuated interstitial fibrosis. The aim of the present study is to investigate the role of Numb in acute renal injury.

Methods: Scramble siRNA or Numb siRNA was injected into male BALB/C mice (18-20g) through tail vein. Cisplatin was administrated 24 h after siRNA injection and mice were sacrificed at day 3 after cisplatin injection. Renal function was evaluated by the level of serum creatinine. Renal morphology was examined by Hematoxylin and eosin staining. The apoptosis of tubules was tested by TUNEL assay, flow cytometry and western blotting. The mitochondrial morphology was assessed by electronic microscopy (EM) and immunofluorescence staining. The mitochondrial damage was evaluated by the release of cytochrome C.

Results: The expression of Numb was significantly upregulated after cisplatin administration both *in vivo* and *in vitro*. Silencing Numb exacerbated cisplatin-induced renal injury shown as increased Scr (2.0±0.4mg/dl vs 1.0±0.3mg/dl, $P<0.05$) and more severe morphological damage. TUNEL assay and flow cytometric analysis demonstrated that Numb deficiency dramatically increased cisplatin-induced apoptosis both *in vivo* and *in vitro*. EM showed that there was more mitochondrial fragmentation in Numb siRNA injected mice after cisplatin treatment. Similarly,compared with scramble siRNA transfected cells, mitochondrial fragmentation and cytochrome C release were more severe in Numb siRNA transfected NRK-52E cells after cisplatin treatment. Western blot analysis revealed that silencing Numb increased the protein level of Drp1, a key mitochondrial fission protein, after cisplatin stimulation both *in vitro* and *in vivo*. Pretreatment with mdivi-1, a pharmacological inhibitor of Drp1, attenuated cisplatin-induced mitochondrial fragmentation and apoptosis in Numb siRNA trasfected NRK-52E cells.

Conclusions: our data suggest that Numb plays a protective role in cisplatin-induced acute kidney injury by suppressing mitochondrial fragmentation, and the subsequent tubular cell apoptosis.

SA-PO158

Loss of Neutral Ceramidase in Mice Protects from Cisplatin-Induced Acute Kidney Injury Deanna L. Siow,[1] Tess Dupre,[1] Mark A. Doll,[1] Cierra Sharp,[1] Kumar Saurabh,[2] Judit Megyesi,[4] Ashley J. Snider,[5] Lina M. Obeid,[5] Yusuf A. Hannun,[6] Levi J. Beverly,[1,2,3] Leah J. Siskind.[1,3] *[1]Pharmacology and Toxicology, Univ of Louisville, Louisville, KY; [2]Medicine, Univ of Louisville, Louisville, KY; [3]JG Brown Cancer Ctr, Univ of Louisville, Louisville, KY; [4]Internal Medicine, Univ of Arkansas for Medical Sciences/Central Arkansas and Veterans Healthcare Sys, Little Rock, AR; [5]Medicine, Stony Brook Cancer Center, Stony Brook Univ, Northport Veterans Affairs Medical Center, Stony Brook, NY; [6]Medicine, Stony Brook Cancer Center, Stony Brook Univ, Stony Brook, NY.*

Background: Acute kidney injury (AKI) resulting from the use of the chemotherapeutic agent, cisplatin, remains a dose- and treatment-limiting obstacle for many patients. Sphingolipids, especially ceramide, play a central role in regulating the toxic effects of cisplatin on the kidney. Neutral ceramidase (nCDase) is a central enzyme in sphingolipid metabolism and loss of this enzyme has proven to be protective in traumatic injuries of both the brain and heart. We hypothesized that loss of nCDase would offer protection for cisplatin-induced AKI.

Methods: In this study we utilized a transgenic mouse whereby expression of nCDase has been depleted (nCDase$^{-/-}$) in combination with an established murine model of cisplatin-induced AKI. Nine week old nCDase$^{-/-}$ and wild-type (WT) C57BL/6 mice were used for this study.

Results: Our data indicate that loss of nCDase protects the kidney from cisplatin injury as evidenced by improved markers of kidney function (BUN, Serum Creatinine), reduced markers of kidney injury (NGAL), and improved kidney pathology. Expression levels of pro-inflammatory chemokines and cytokines (TNF-α, IL-1β, IL-6,MCP-1, and CXCL-1) and the numbers of inflammatory infiltrates were reduced in nCDase$^{-/-}$ mice as compared to that of the WT. Additionally, western blot analysis revealed that nCDase$^{-/-}$ mice exhibited reduced markers of ER stress (pERK, pJNK, IRE1α, CHOP, cleaved caspase 12).

Conclusions: Data presented indicate that loss of nCDase protects the kidney from the nephrotoxic effects of cisplatin treatment and thus inhibiting this enzyme is a potential renal protective strategy during cisplatin chemotherapy.

Funding: NIDDK Support

SA-PO159

Renoprotective Effect of Prothymosin α-Derived Hexapeptide against Cisplatin-Induced Acute Kidney Injury Kenta Torigoe,[1] Yoko Obata,[1] Miki Sawa,[1] Satoru Oka,[1] Takehiko Koji,[2] Hiroshi Ueda,[3] Tomoya Nishino.[1] *[1]Dept of Nephrology, Nagasaki Univ Hospital, Nagasaki, Japan; [2]Dept of Histology and Cell Biology, Nagasaki Univ Graduate School of Biomedical Sciences, Nagasaki, Japan; [3]Dept of Pharmacology and Therapeutic Innovation, Nagasaki Univ Graduate School of Biomedical Sciences, Nagasaki, Japan.*

Background: Prothymosin alpha (ProTa) is reported to exert neuroprotective actions by inhibition of ischemia-induced necrosis and apoptosis in the brain and retina. Recently, the 6-amino acid peptide/P_6Q (NEVDQE), modified active core 6-amino acid peptide (a.a.51-56) in ProTa, also showed protective effect against retinal ischemia. Acute kidney injury (AKI) is caused by insults such as ischemia, hypoxia and nephrotoxicity, and is a common clinical event leading to high mortality and development of chronic kidney disease. However, to date, no effective treatment for AKI have been established. In this study we investigated the renoprotective effect of P_6Q against cisplatin-induced AKI.

Methods: 8 week old male Wistar rats were divided into 3 groups: vehicle-treated group, cisplatin (8mg/kg)-treated group, cisplatin-treated group with P_6Q (30mg/kg) injection. Cisplatin and P_6Q were administered intravenously, and P_6Q was injected 30 minutes before cisplatin treatment. Renal function was assessed at 1, 3, 5, 7, 9 days after cisplatin treatment by measuring serum creatinine. Renal histological change was assessed by PAS staining, and apoptosis of renal tubular cell was assessed by TUNEL staining.

Results: Serum creatinine level peaked at 5 days after cisplatin treatment. Histologic examination revealed extensive tubular damage such as tubular epithelial cell swelling, vacuolar degeneration, and desquamation in cisplatin-treated rats. Cisplatin treatment also increased the number of TUNEL-positive apoptotic cells at day 5. P_6Q injection significantly suppressed cisplatin-induced AKI and apoptosis of tubular cells.

Conclusions: We showed the renoprotective effect of ProTa-derived hexapeptide against cisplatin-induced AKI via suppression of apoptosis. Our results suggest that ProTa-derived hexapeptide may become a preventive drug for cisplatin-induced AKI.

SA-PO160

Irf8 Regulated by DNA Methylation Contributes to Cisplatin-Induced Acute Kidney Injury Chunyuan Guo,[1,2] Xiao Xiao,[1] Qingqing Wei,[1,2] Huidong Shi,[3] Zheng Dong.[1,2] *[1]Dept of Cellular Biology and Anatomy, Augusta Univ, Augusta, GA; [2]Charlie Norwood VA Medical Center, Augusta, GA; [3]Dept of Biochemistry and Molecular Biology, Augusta Univ, Augusta, GA.*

Background: Acute kidney injury (AKI) is a major side effect of cisplatin chemotherapy in cancer patients. The pathogenesis of cisplatin-induced AKI remains largely unclear. This study was designed to determine the role of DNA methylation in cisplatin-induced AKI and identify the specific genes regulated by DNA methylation.

Methods: Reduced representation bisulfite sequencing (RRBS) was performed to determine the genome-wide DNA methylation changes in cisplatin-induced AKI. We also examined the effects of the DNA methylation inhibitor--5-aza-2'-deoxycytidine

(5-aza) on cisplatin-induced AKI in vitro. Furthermore, we determined the involvement of specific genes, such as Irf8, with methylation changes in cell culture model of kidney tubular cell injury.

Results: The genome-wide DNA methylation analysis showed aberrant DNA methylation alterations in cisplatin-induced AKI. DNA methylation inhibitor 5-aza sensitized RPTC cells to cisplatin-induced apoptosis. To identify the key genes regulated by DNA methylation which are involved in cisplatin-induced AKI, we analyzed the genome-wide DNA methylation data and found Irf8 showed hypomethylation at 5' UTR. This hypomethylation was associated with a marked increase of Irf8 expression in both mRNA and protein levels in cisplatin-induced AKI. Moreover, in RPTC cells, inhibition of DNA methylation by 5-aza upregulated Irf8 expression with or without cisplatin. And silencing Irf8 in RPTC cells inhibited cisplatin-induced apoptosis.

Conclusions: These results suggest that DNA methylation plays an important role in cisplatin-induced AKI by regulating specific genes, such as Irf8.

Funding: NIDDK Support, VA Support

SA-PO161

Mechanisms of Decreased Acute Kidney Injury (AKI) and Decreased Tumor Growth by Mitogen-Activated Extracellular Signal-Regulated Kinase (MEK) Inhibition

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Background: The pathogenesis of cisplatin (Cis) AKI involves the MEK/ERK pathway. The MEK inhibitor U0126 blocks ERK activation. The effect of U0126 on AKI and tumor growth was determined in a 4 wk model of cisplatin AKI in tumor bearing mice.

Methods: Mice were injected with lung cancer cells. 10 days later, Cis (10 mg/kg/wk) and U0126 (5 mg/kg 2X/wk) were given for 4 wks. RIP3, a marker of necroptosis, cleaved caspase-3 (CC-3), a marker of apoptosis, PD-L1, an immune system suppressor, p-JNK and p-ERK (MAPK signaling) were measured by immunoblot. MAPK signaling RT² Profiler™ PCR Array was used to profile genes in the kidney.

Results: U0126 resulted in a significant decrease in BUN, SCr in mice with or without tumor. In kidney, U0126 protected against AKI despite increasing RIP3. ERK regulated cell cycle genes specifically cyclins, cyclin-dependent kinases (Cdk) and Cdk inhibitors were up to 78-fold increased by Cis and reduced by U0126. U0126 decreased tumor weight, potentiated the effect of cisplatin, increased CC-3, decreased p-ERK and p-JNK, had no effect on PDL1 in tumors.

	Vehicle	Veh+U0126	Cis	Cis+U0126
No cancer BUN	29	23	53 *	34 **
No cancer SCr	.14	.12	.25 *	.15 **
Cancer BUN	27	27	59 *	40 **
Cancer SCr	.1	.1	.3 *	.18 **
Kidney RIP3	+	++	+++	++
Tumor wt (g)	1.8	1.0	0.9 *	0.5 *
Tumor CC-3	+	+++	+	+++
Tumor PD-L1	+	+	+	+
Tumor p-JNK	+	+	+++	+
Tumor p-ERK	+	+	+++	+
Kidney gene	Fold increase by Cis	Fold decrease by U0126		
Cyclin A1	78	2.3		
Cyclin A2	58	11		
Cyclin B2	26	9		
Cyclin D1	22	2		
Cdk 4	9	.25		
Cdk inhibitor 1A (P21)	26	2.5		
Cdk inhibitor 1C (P57)	12	3		
Cdk inhibitor 2C	14	4		
	*P<0.05 vs. Vehicle, **P<0.05 vs. Cis			

Conclusions: The effect of U0126 to decrease AKI and tumor growth is independent of the presence of tumor. In kidney, U0126 increased RIP3 and the large increase in gene expression of cell cycle proteins regulated by ERK was decreased by U0126. Cell cycle proteins regulated by ERK signaling in AKI and cancer merits further study.

Funding: VA Support

SA-PO162

Doxycycline Ameliorates Cisplatin-Induced Nephrotoxicity in Mice Through Directly Acting on Proximal Tubular Cells and Promoting Cell Viability

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Background: Cisplatin (CDDP) is a widely used anticancer agent but its use is sometimes limited by nephrotoxicity. We reported in Kidney Week 2015 that doxycycline (Dox) suppressed CDDP-induced acute kidney injury in mice through its anti-inflammatory, anti-oxidative and enzyme-inhibiting effects. In this study, in order to further explore the mechanism, we investigated the effect of Dox on the accumulation of CDDP in kidney tissue. Furthermore, we studied whether Dox attenuates cell injury caused by CDDP using cultured renal tubular cells.

Methods: C57BL/6J mice were divided into following three groups: 1) Control, 2) CDDP (20mg/kg, intraperitoneally) and 3) CDDP+Dox (2mg/ml in drinking water). After 7-day pretreatment of Dox, CDDP was administrated, and animals were sacrificed 24 hr later. The amount of platinum in the kidney tissue was measured by ICP-MS. Next, after cultured proximal tubular cells (NRK52E) were treated with CDDP and Dox, cell viability (WST-1) and mRNA expressions of cell injury markers were assessed.

Results: Renal accumulation of CDDP was not inhibited by treatment with Dox (CDDP 23.1±6.1 vs CDDP+Dox 21.5±8.2 pg/mg tissue), indicating that Dox may not affect pharmacokinetics of CDDP but exert protective effects by inhibiting detrimental reactions caused by CDDP within tubular cells. In NRK52E cells, CDDP reduced cell viability and induced mRNA expressions of IL-6, MCP-1, p67phox and Fas. These changes were mitigated significantly by treatment with Dox.

Conclusions: Dox suppressed CDDP-induced nephrotoxicity not through inhibiting CDDP accumulation but through directly attenuating detrimental reactions within tubular cells, suggesting that Dox could become a potential therapeutic strategy against CDDP-induced nephrotoxicity.

SA-PO163

Exacerbated Cisplatin-Induced Renal Injury in NHERF1 KO Mice Is Associated with NF-E2 Regulation

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Background: Cisplatin, an effective chemotherapeutic drug, is highly nephrotoxic, limiting its use. Cisplatin toxicity is associated with acrolein accumulation in the cytosol of damaged renal tubules, yet the precise mechanisms underlying these events are unknown. Acrolein is known to modulate sodium-phosphate co-transport in renal cells, of which sodium-hydrogen exchange regulatory factor 1 (NHERF1) is a key mediator. Preliminary studies demonstrate renal regulation of Nuclear Factor Erythroid-derived 2 (NF-E2) by acrolein. Therefore, we hypothesized that mice treated with cisplatin induces kidney damage and fibrosis by modulating NF-E2 expression in a NHERF1-dependent manner.

Methods: Wild-type (WT) and NHERF1 knockout (NHERF1 KO) mice were treated with saline or cisplatin [20 mg/kg body weight] and sacrificed after 72 hours. Kidney homogenates and plasma samples were immunoblotted with appropriate antibodies. Kidney tissue sections were subjected to H&E staining and NF-E2 immunohistochemistry.

Results: Renal NF-E2 expression decreased in NHERF1 KO mice, compared to WT mice, which decreased further after cisplatin treatment, while cleaved-Cas-3 and Connective Tissue Growth Factor (CTGF) expression increased further. Cisplatin treatment resulted in loss of NF-E2 expression from the renal brush-border membrane in WT mice kidneys which was decreased further in cisplatin treated NHERF1 KO mice. Interestingly, NF-E2 was detected in the plasma of NHERF1 KO mice which was enhanced further after cisplatin treatment. Furthermore, NHERF1 KO mice were sensitized to more renal damage after cisplatin treatment compared to WT mice.

Conclusions: NHERF1 expression regulates intracellular and extracellular NF-E2 expression. Thus, NF-E2 could serve as a biomarker of AKI alleviating need for biopsies. NHERF1 could serve as a therapeutic target to modulate NF-E2 expression and treat AKI halting its progression to ESRD, in addition to potentially blocking cisplatin's nephrotoxic effects.

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SA-PO164

MAP3K14 Promotes Acute Kidney Injury Maria D. Sanchez-Niño,[1] Lara Valiño Rivas,[1] Laura Gonzalez-Lafuente,[1] Ana Belen Sanz,[1] Sergio A. Mezzano,[3] Harald Mischak,[4] Holger Husi,[2] Antonia Vlahou,[5] Alberto Ortiz.[1] *[1]Nephrology, IIS-Fundacion Jimenez Diaz, Madrid, Spain; [2]Inst of Cardiovascular and Medical Sciences, Univ of Glasgow, United Kingdom; [3]Nephrology, Inst de Medicina, Univ Austral de Chile, Valdivia, Chile; [4]Mosaiques Diagnostics GmbH, Hannover, Germany; [5]Biomedical Research Foundation Academy of Athens, Greece.*

Background: The incidence of acute kidney injury (AKI) is increasing. There is currently no therapy that reliably prevents the progression to AKI or accelerates recovery of renal function. An improved understanding of pathogenic pathways may identify novel acute kidney injury therapeutic approaches.

Methods: Unbiased LC-MS/MS protein expression profiling combined with focused data mining identified MAP3K14 and non-canonical NFkB activation at the crossroads of the enriched pathways MAPK, chemokines, NFkB and apoptosis in the kidney cortex of experimental toxic AKI. Immunohistochemistry localized MAP3K14 expression to tubular cells. Validation of non-canonical NFkB pathway activation in experimental acute kidney injury (cisplatin, folic acid, bone marrow transplantation). siRNA targeting to study MAP3K14 in tubular cells.

Results: In AKI, the upstream kinase MAP3K14, the NFkB DNA binding heterodimer RelB/NFkB2, and proteins involved in NFkB2 p100 ubiquitination and proteasomal processing to p52, were up-regulated. Immunohistochemistry localized MAP3K14 expression to tubular cells in experimental and human AKI. In vivo evidence of MAP3K14 activation in experimental AKI consisted of NFkB2 p100 processing to p52, nuclear location and DNA binding of RelB and NFkB2. MAP3K14 activity-deficient aly/aly mice were protected from kidney dysfunction, inflammation and apoptosis in AKI. MAP3K14 siRNA targeting in cultured tubular cells decreased inflammation and cell death. Bone marrow transplantation experiments where consistent with a protective effect of renal cell MAP3K14 targeting. Cell culture and in vivo studies identified chemokines as MAP3K14 targets in tubular cells, thus identifying potential mediators of the deleterious effect of MAP3K14 in kidney injury.

Conclusions: In conclusion, MAP3K14 promotes kidney injury through promotion of inflammation and cell death and is a promising novel therapeutic target.

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SA-PO165

Apolipoprotein A-I Protects against Post-Myocardium Infarct Radiocontrast-Induced Acute Kidney Injury Roberto De Souza Moreira,[1,2] Jose Manuel Condor Capcha,[1] Talita R. Sanches,[1] Maria C. Irigoyen,[1] Lucia Andrade.[1] *[1]Univ of Sao Paulo School of Medicine, Sao Paulo; [2]Federal Univ of Goias, Goias, Brazil.*

Background: Radiocontrast (RC)-induced AKI develops in many patients after cineangiography and is associated with mortality and adverse outcomes. Hypercholesterolemia decreases nitric oxide availability, aggravating myocardial infarct (MI) and RC-induced AKI. ApoA-1 mimetic peptide 4F (4F) improves vascular function, reducing LDL oxidation.

Methods: Rats fed a high-cholesterol diet were sham-operated (n=6) or induced to MI by left anterior descending coronary artery ligation, treated or not 6h later: MI (n=15), MI+RC (intrafemoral iopamidol 2.9g/kgBW iodine, n=15), MI+4F (10 mg/kgBW i.p. 4F, n=8) and MI+RC+4F (n=8). At 24h, we analyzed echocardiograms; creatinine clearance (Ccr); serum total cholesterol, HDL and LDL; renal CD68 and TUNEL; and renal/cardiac eNOS. Data are mean±SEM.

Results:

	Sham	MI	MI+RC	MI+4F	MI+RC+4F
C_{cr} (ml/min/100gBW)	0.85±0.07	0.37±0.08[a,b,c]	0.17±0.04[a,b,c,d]	0.78±0.23	0.83±0.12
Cardiac output (ml/min)	75.2±3.8	23.1±2.0[a,b,c]	28.6±2.7[a,b,c]	44.7±4.7[a]	42.6±3.8[a]
LV ejection fraction (%)	83.7±2.1	34.1±3.4[a,b,c]	25.4±6.0[a,b,c]	62.8±6.1[a]	55.8±7.2[a]
Infarct % (apex)		48.6±1.0[b,c]	50.8±3.6[b,c]	35.6±2.8	37.4±3.7
Infarct % (papilla)		41.7±3.5[b,c]	43.5±3.4[b,c]	30.2±1.5	31.7±1.3
Cholesterol (mg/dl)	91.7±7.0	167.5±24[a,b,c]	175.7±22[a,b,c]	93.8±11.4	100.1±14
HDL (mg/dl)	74.3±5.3	44.2±14.0[a,b,c]	42.3±10.0[a,b,c]	80.3±4.1	72.6±4.1
LDL (mg/dl)	35.5±4.2	116.3±3.3[a,b,c]	106.3±13.5[a,b,c]	26.2±8.9	40.6±6.3
Renal eNOS (%)	100±8.0	74.4±7.5[a,b,c]	39.4±2.5[a,b,c,d]	104±2.3	101±2.0
Cardiac eNOS (%)	100±6.6	73±7.3[a,b,c]	59.4±6.0[a,b,c]	101±5.0	95±5.0
TUNEL (cells/mm²)	9.6±4.6	33.4±7.3[a,b,c]	60.1±14[a,b,c,d]	13.4±2.4	13.6±4.2

[a]*P*<0.05 vs. sham; [b]*P*<0.05 vs. MI+4F; [c]*P*<0.05 vs. MI+RC+4F; [d]*P*<0.05 vs. MI

MI and MI+RC group mortality was 40% and 50%, respectively. CD68+ cell counts were significantly higher in MI and MI+RC rats than in other rats.

Conclusions: 4F inhibits inflammation and apoptosis, strengthening endothelia and providing nitric oxide-dependent cardio- and reno-protection. (Supported by FAPESP).

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Resveratrol Rescues Renal Function following Contrast-Induced Acute Kidney Injury in 5/6 Nephrectomy Rats Cassiane Dezoti da Fonseca, Daniel Malisani Martins, Mirian Watanabe, Sheila Marques Fernandes, Maria De Fatima Vattimo. *School of Nursing, Univ of Sao Paulo, Sao Paulo, Brazil.*

Background: Contrast-Induced acute kidney injury (CI-AKI) is a common adverse effect in patients with chronic kidney disease. CI-AKI promotes renal vasoconstriction, hypoxia, activation of inflammatory cascade, oxidative cell damage and impaired renal function,This study evaluated the renoprotection of resveratrol (RSV), a polyphenol with vasodilating and anti-inflammatory properties in nephrectomized rats treated with iodinated contrast (IC).

Methods: Wistar, adult, male rats were randomized in four groups; Sham; Nx: 5/6 nefrectomy; Nx+IC: Nx rats that received iodinated contrast (6mg/kg); Nx+IC+resveratrol: Nx rats that received iodinated contrast (6 ml/kg, intraperitoneal, i.p.) and resveratrol (25 mg/Kg, i.p., 30 minutos before IC);. Renal function and hemodynamics were evaluated.

Results:

Groups (n)	Blood Pressure (mmHg)	Renal Blood Flow (mL/min)	Renal Vascular Resistance (mmHg/mL/min)	Inulin Clearance (mL/min)	NGAL (mg/dL)
SHAM (5)	87±6	9.5±1.6	9.4±2.4	0.66±0.10	47.9±19.1
Nx (5)	132±13*	8.7±2.3	16.1±4.8*	0.28±0.04*	76.7±31.3
Nx+IC (5)	122±6*	3.2±1.3*#	37.9±15.0*#	0.10±0.03*#	153.5±70,0*#
Nx+IC+RSV (5)	114±8*#	6.4±0.4°	18.0±2.2*°	0.24±0.04*°	57.5±22.1°

*p<0.05 vs SHAM; # p<0.05 vs Nx; ° p<0.05 vs Nx+IC Nx rats presented a decrease in inulin clearance and increase in NGAL levels. Renal hemodynamics showed an increase in renal vascular resistance, while IC enhanced this damage. Resveratrol maintained inulin clearance and NGAL levels and decreased renal vascular resistance in rats treated with IC.

Conclusions: Association between chronic kidney disease with CI-AKI predisposes to severe kidney injury. Resveratrol ameliorates renal function in CI-AKI by modulationg renal hemodynamics in Nx rats.

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SA-PO167

Indole Analog MA-5 Protect against Contrast-Induced Renal Injury Takehiro Suzuki, Ryunosuke Numakura, Tetsuro Matsuhashi, Koichi Kikuchi, Hisato Shima, Eikan Mishima, Chitose Suzuki, Sadayoshi Ito, Takaaki Abe. *Tohoku Univ.*

Background: Contrast-induced nephropathy (CIN) is the most common cause of the iatrogenic and drug-induced kidney injury, but the therapeutic procedures have not been established. The renal hypoxia and the direct toxic effects of contrast media on renal tubular cells are postulated as the pathophysiologic mechanisms of CIN. Recently we reported mitochondria-targeted indole-derivative mitochonic acid-5 (MA-5) increased intracellular ATP, decreased mitochondrial ROS and improved cell survivals of fibroblasts form mitochondrial disease patients. MA-5 also improved the renal function and tubular cell injuries in murine renal ischemia reperfusion and cisplatin induced nephropathy models. The aim of this study is to examine the protective effects of MA-5 on CIN (Suzuki T. JASN 2015).

Methods: Immortalized human proximal tubular cell line HK-2 cells were cultured to 80% confluent and MA-5 at 10uM final concentration for 24hr without serum and then added radiocontrasts sodium ditrizoate, Iopamidol and iohexol at 75mg iodine /ml for another 1hr. Cell viability and cytotoxicity were accessed by WST-8 assay and LDH assay respectively. Male CD-1 mice, Body weight 30-35g were left-nephrectomized (Nx) and MA-5 was administrated, at 50mg/kg body weight by gavage, to mice 2hr before they injected with an inhibitor of prostaglandin synthesis (indomethacin, 10 mg/kg) intraperitoneally before iohexol (300 mg iodine/ml, 2 g iodine/kg) intravenously injection. 24hr after iohexol injection, mice were sacrificed, serum creatinine (Cr), urinary Neutrophil gelatinase-associated lipocalin (NGAL) and renal pathology were examined.

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

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

SA-PO168

UII Receptor Knockout Prevents Mice from Acute Contrast-Induced Nephropathy Li Jie Zhang, Ai Hua Zhang. *Dept of Nephrology, Peking Univ Third Hospital, Beijing, China.*

Background: UII is a vasoactive, somatostatin-like cyclic peptide of 11 amino acids initially isolated from the urophysis of the goby fish. UII is generally agreed to be the most potent endogenous vasoconstrictor discovered to date. The present study explores whether UII can aggravate CIN and its pathogenesis in CIN by wild type C57Bl/6 mice with CIN and UIIreceptor gene knockout mice with CIN.

Methods: Plasma and urinary UII were measured by RIA, neutrophil gelatinase-associated lipocalin (NAGL) and retinol-binding protein 4 (RBP4) were measured by ELISA, immunohistochemistry and western blot were conducted on the kidney tissues of CIN with UII receptor gene knock-out mice (KO-CIN) , CIN with wild type mice (WT-CIN), and wild type control mice. Apoptosis of renal cells were detected by TUNE methods. Markers for autophagy (LC3-II and p62) were analyzed.

Results: Plasma creatinine was significantly increased in WT-CIN group and KO-CIN group in comparison to control group; however, plasma creatinine was significantly lower in KO-CIN group than in WT-CIN. Renal UII expression , urinary UII, NGAL and RBP4 significantly increased in WT-CIN group and KO-CIN group in comparison to normal control, whereas NGAL and RBP4 levels were significantly decreased in KO-CIN than those of WT-CIN. Apoptosis is increased in renal tubular epithelial cell in WT-CIN mice than that of normal control; however, apoptosis is inhibited in KO-CIN in comparison to WT-CIN mice. Expression of LC3-II is increased and P62 is reduced in comparison to that of the normal control, while expression LC3II is decreased and P62 is increased in KO-CIN mice in comparison to WT-CIN.

Conclusions: UII plays important roles in CIN and it can aggravate renal tubular epithelial cell injury. It can alleviate renal tubular epithelial cell injury in CIN if we interfere in UII action. The mechanisms involve inhibiting apoptosis and inhibiting overactive autophagy of renal tubular epithelial cells.

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Thymoquinone Prevents Contrast-Induced Nephropathy
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Background: Thymoquinone (TQ), the main constituent of the volatile oil from Nigella sativa seeds, is reported to possess strong anti-oxidant and anti-inflammatory properties. Pathophysiology of contrast induced nephropath (CIN) associates multipl factors including renal vasoconstruction, oxidative stress and increased inflammation. We hypothesized that TQ can attenuate renal injury in the rat experimental contrast induced nephropathy (CIN) model.

Methods: CIN was induced by injection of the radiocontrast medium diatrizoate in adddition to inhibition of prostoglandin and nitric oxide (NO) synthesis after 2 days of water deprivation.Rats were divided into 7 groups: control (C), L-NAME+INDO (NG-nitro-L-arginine+ indomethacin), contrast media (CM), TQ1 (TQ 1 mg/kg day), TQ 1.75 (TQ 1.75 mg/kg day), TQ1+CM, TQ 1.75+CM. TQ was given at two different doses (1 or 1.75 mg/kg day) for 4 days intraperitoneally before the contrast injection.

Results: Administration of 1 mg dose of TQ significantly attenuated the resulting renal dysfunction and inflammatory process **(table 1)** and histologic renal injury in the light microscopy.

	C	L-Name +Indo	CM	TQ1	TQ1.75	TQ1 +CM	TQ1.75 +CM	p
Creatinine (mg/dl)	0.3 ±0.03	0.56 ±0.27	2.03 ±1.28	0.29 ±0.01	0.28 ±0.02	0.41 ±0.06	2.23 ±0.8	CM vs TQ1+CM:0.004
BUN (mg/dL)	20.7 ±1.4	67.5 ±64.7	197.7 ±98	17.6 ±1.9	16.2 ±1.8	21.9 ±9.4	210 ±62	CM vs TQ1+CM:<0.001
NF-KB expression	%100	%79	%112	%102	%104	%72	%104	CM vs TQ1+CM:0.044
iNOS expression	%100	%109	%109	%93	%94	%45	%142	CM vs TQ1+CM:<0.001

Serum malondialdehyde and superoxide dismutase levels did not show any significant difference between the groups.

Conclusions: This study suggests that administration of thymoquinone may have potential as a new therapeutic approach to prevent CIN.

SA-PO170

Megalin Blockade with Cilastatin Suppresses Drug-Induced Nephrotoxicity
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Background: Nephrotoxicity induced by anti-microorganism or anti-cancer drugs is a serious clinical problem. Megalin, an endocytic receptor expressed at the apical membranes of proximal tubules, mediates the nephrotoxicity of aminoglycosides (AGs) and colistin (CLT), which are key antimicrobials for multidrug-resistant organisms. The mechanisms underlying the nephrotoxicity induced by vancomycin (VCM), an antimicrobial for methicillin-resistant *Staphylococcus aureus*, and cisplatin (CDDP), an important anti-cancer drug, are unknown, but the nephrotoxicity of these drugs and of gentamicin (GM), an AG, is known to be suppressed experimentally with cilastatin (CS), which was developed originally as an inhibitor of renal dehydropeptidase-I. Here, we studied the mechanism underlying CS-mediated suppression of such drug-induced nephrotoxicity and the role of megalin.

Methods: Using quartz-crystal microbalance (QCM) analysis, we examined the binding of these drugs to megalin in the presence or absence of CS.Kidney-specific mosaic megalin knockout mice were used to investigate megalin-mediated nephrotoxicity with CLT, VCM, and CDDP. C57BL/6J mice were used to analyze the suppression of CLT-induced nephrotoxicity by CS. We performed agar disk diffusion analysis to assess whether CS affects the anti-bacterial activity of GM, CLT, and VCM.

Results: QCM analysis revealed that megalin is also bound by VCM and CDDP, and that the binding of GM, CLT, VCM, and CDDP to megalin is competed with CS. In addition, the nephrotoxicity induced by CLT, VCM, and CDDP was found to depend on megalin expression in the proximal tubules. CLT-induced nephrotoxicity in C57BL/6J mice was suppressed by concomitant CS administration. CS did not inhibit the anti-bacterial activity of GM, CLT, and VCM *in vitro*, just as CS was previously found not to affect the anti-cancer activity of CDDP.

Conclusions: Megalin blockade with CS efficiently suppressed the nephrotoxicity induced by GM, CLT, VCM, and CDDP.

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SA-PO171

Reduced Glomerular Number in a Juvenile Rabbit Model of AKI Detected by MRI
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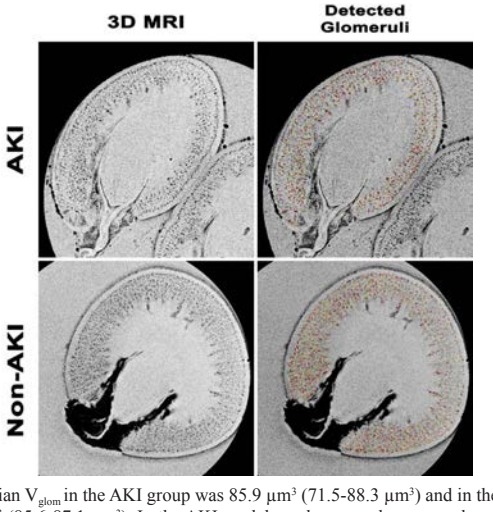
Background: There is a strong association between low nephron endowment and CKD. MRI techniques have made it possible to measure whole-kidney glomerular endowment (N_{glom}) and volume (V_{glom}) in the intact kidney, revealing pathology not detected by traditional biomarkers. Here we applied cationic ferritin enhanced-MRI (CFE-MRI) to investigate nephron loss from acute kidney injury (AKI) in a juvenile rabbit model.

Methods: New Zealand rabbits received 4 days of indomethacin (5 mg/kg) and gentamicin (100 mg/kg) during nephrogenesis at 1 wk of life. At 6 wks the AKI and controls received horse CF (1.92 mg/100 g BW, n=3/grp). Ninety minutes after the injection, the animals were euthanized. Images of intact kidneys were acquired with a 7T ClinScan (gradient echo: TE/TR: 80/20, 3 averages, resolution: 59x59x200 microns, slice thickness: 170 μm). N_{glom} and V_{glom} were determined using custom software.

Results: The AKI group weighed less than controls (diff: 655 g, p=0.004) and there was no difference the serum creatinine between the groups at 6 wks. Median N_{glom} by CFE-MRI in the AKI group was 100,932.5 (75,726-127,783) and in the controls median N_{glom} was 191,652 (138,417-251,180).



The median V_{glom} in the AKI group was 85.9 μm³ (71.5-88.3 μm³) and in the controls was 86.7 μm³ (85.6-87.1 μm³). In the AKI model, nephron number was reduced by 49% and histologic changes in AKI are consistent with a circumferential lesion of smaller, immature glomeruli.

Conclusions: CFE-MRI was used to detect glomerular morphology in the intact juvenile kidney. Induced AKI in neonatal rabbits causes a significant decrease in N_{glom} but no observed change in V_{glom} by 6 weeks of age, possibly due to the short duration from injury to evaluation. AKI in rabbits, induced by common medications and monitored through noninvasive MRI, provides an important model to study the impact of AKI on renal development later in life.

SA-PO172

Ferroptosis, but Not Necroptosis, Plays an Important Role in Nephrotoxic Folic Acid Induced Acute Kidney Injury
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Background: Acute kidney injury is characterized by necrotic cell-death and inflammation. Diverse pathways of regulated necrosis have been reported to contribute to AKI but there is no agreement on the molecular regulators involved. We explored the contribution of ferroptosis and necroptosis to folic acid (FA) AKI in mice. FA-AKI in mice is associated with lipid peroxidation and downregulation of glutathione metabolism proteins, features that are typical of ferroptotic cell death.

Methods: We induced AKI with an overdose of folic acid in wild type, RIP3K-KO and MLKL-KO mice. Renal function was measured by plasma creatinine and BUN levels. Protein studies were assessed by western blot and immunohistochemistry, mRNA analyzing were tested by real-PCR. For cell death detection we use TUNEL.

Results: We demonstrate that ferrostatin-1 (Fer-1), an inhibitor of ferroptosis, preserved renal function and decreased histological injury, oxidative stress and tubular cell death in this model. With respect to the immunogenicity, we demonstrate that Fer-1 prevented the upregulation of IL-33, an alarmin that has been linked to necroptosis, and other chemokines and cytokines, as well as macrophage infiltration, suggesting that Fer-1 prevents renal inflammation by inhibition of ferroptosis. By contrast, the pan-caspase inhibitor zVAD-fmk was not protective. Additionally, although FA-AKI resulted in increased protein expression of the necroptosis mediators RIPK3 and MLKL, targeting necroptosis with the RIKP1 inhibitor necrostatin-1, or genetic deficiency of RIPK3 or MLKL did not preserve renal function. MLKL KO mice displayed more severe AKI. By contrast, inflammation was milder in RIPK3 KO mice.

Conclusions: These data suggest that ferroptosis is the primary cause of FA-AKI, and that immunogenicity secondary to ferroptosis may further worsen the damage, while necroptosis related proteins may play additional roles in AKI.

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SA-PO173

Vitamin D Deficiency Induces Acute Kidney Injury in Rats Treated with Lipid Formulation of Amphotericin B

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Background: Lipid emulsion of Amphotericin B (AmB/LE) attenuates AmB-related nephrotoxicity and represents a lower cost alternative formulation with similar antifungal activity. In view of the high worldwide incidence of vitamin D deficiency (VDD), the aim of this study was to investigate whether VDD may induce AmB/LE-related nephrotoxicity.

Methods: Male Wistar rats were fed 25(OH)D-free or normal diets for 30 days. We studied four groups: control (C, n=8), VDD (n=6), AmB/LE (n=7, receiving 5mg/kg/day of AmB/LE intraperitoneally [IP] for 4 days) and VDD+AmB/LE IP for 4 days (n=9). We measured serum 25-hydroxyvitamin D (25(OH)D, ng/mL); inulin clearance (GFR, mL/min/100g); arterial blood pressure (BP, mmHg); urinary volume (UV, mL/24h) and osmolality (U_{Osm}, mOsm/kgH_2O); and urinary magnesium excretion ($U_{Mg}V$, mg/day). Immunoblotting for protein expression of aquaporin-2 (AQP2, %) was performed in kidney tissue. Morphological kidney damage was scored from 0 to 4. Data are expressed as mean ± SEM.

	C	VDD	AmB/LE	VDD+AmB/LE
25(OH)D	44.3±2.4	4.3±0.4[c]	45.4±5.2[f]	4.4±0.7[cg]
GFR	0.97±0.04	0.79±0.02[a]	0.99±0.06[d]	0.55±0.04[ce]
BP	130±3	129±4	131±5	148±5[a]
UV	20±1	26±1	21±1	32±2[cdg]
U_{Osm}	1028±89	656±64[c]	635±32[c]	367±21[cfg]
$U_{Mg}V$	1.91±0.16	1.81±0.10	2.03±0.15	3.21±0.31[cfg]
AQP2	100±3	75±15[a]	43±2[cd]	46±6[cd]
Kidney Damage	0.13±0.02	0.31±0.04	0.25±0.05	0.40±0.08[a]

[a]p<0.05,[b]p<0.01,[c]p<0.001 vs. C; [d]p<0.05,[e]p<0.01,[f]p<0.001 vs. VDD; [g]p<0.001 vs. AmB/LE

Results: Body weight was not different among the 4 groups. Association of AmB/LE and VDD resulted in reduced GFR, hypertension. These alterations were associated witn an increased urinary volume, lower U_{Osm} and more elevated $U_{Mg}V$.

Conclusions: VDD induces impaired renal function and tubular damage in AmB/LE treated rats. Therefore, the assessment of vitamin D in patients is essential independently of the modified formulations of AmB prescribed. Fapesp 2015/05513-1, CNPq 306148/2013-7.

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SA-PO174

Modeling Polymyxin B-Induced Renal Injury Using a Human Kidney Proximal Tubule Microphysiological System

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Background: Our lab has developed a platform culturing proximal tubule epithelial cells (PTECs) in a microphysiological system (MPS) that recapitulates the physiology of the proximal tubule. A key application of our system is the response to nephrotoxicant exposure, as shown by induction of injury markers. We are using this MPS to determine the mechanism(s) of polymyxin-induced nephrotoxicity. Polymyxin antibiotics are one solution to the increasing frequency of drug-resistant microbes, despite clinical observations of severe renal injury. To mitigate these adverse effects, a polymyxin structural variant, which retains therapeutic efficacy, yet decreased *in vitro* toxicity, is currently being evaluated in our kidney MPS.

Methods: PTECs were cultured for 1 week (to reach confluency) and treated with 0 uM or 50 uM polymyxin B, or 50 uM polymyxin-analog, for 48 hours. Effluent was collected in 24 hour intervals and analyzed for kidney injury molecule-1 (KIM-1). Cell-associated injury was measured via induction of heme-oxygenase-1 (HO-1). Additionally, transcriptional response to drug will be analyzed via RNA-seq.

Results: In three separate donors, polymyxin B-induced toxicity was observed via induction of cell-associated HO-1 as well as a significant increase in KIM-1 biomarker in the effluent. Furthermore, the polymyxin-analog demonstrated a greater than 10-fold higher level of safety in comparison to polymyxin B when tested in standard 2D monolayer PTEC cultures.

Conclusions: We have demonstrated that our MPS can model polymyxin-induced injury and capable of screening novel analogs for an assessment of improved safety. Understanding the transcriptional response to polymyxin B and structural variants will allow identification of pathways involved in injury. Furthermore, we will define the transporter-mediated uptake mechanisms resulting in tubular accumulation and toxicity of this class of antibiotics using our MPS. This research was supported by an unrestricted gift from the Northwest Kidney Centers to the Kidney Research Institute.

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SA-PO175

Cilastatin Attenuates Vancomycin-Induced Nephrotoxicity via P-Glycoprotein

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Background: Oxidative stress is one of the main pathogenic mechanisms in vancomycin-induced nephrotoxicity(VIN). In addition, animal studies suggest proximal renal tubular cell necrosis by vancomycin accumulation. Previous studies demonstrated that cilastatin has protective effects against drug-induced nephrotoxicity. P-glycoprotein (P-gp) is a strong membrane efflux pump extruding a variety of chemicals outside the cell. We investigated whether the P-gp regulation of cilastation prevent VIN in *in vitro* and *in vivo* models.

Methods: We tested in vitro study using immortalized proximal tubule epithelial cell line from HK-2, and in vivo study using Male C57BL/6J mice.

Results: Vancomycin showed toxicity at dose and time dependent pattern in HK2 and cilastatin attenuated VIN. Vancomycin provoked ROS at dose dependent pattern on DCF-DA. Caspase 3/7 activity increased in dose dependent pattern. Apoptosis was confirmed by Tunnel assay at 24 hr (Vancomcyin 2 mM). Cilastatin attenuated vancomycin indcued ROS production and apoptosis. Vancomycin suppressed p-gp function using Calcein AM test. Cilastatin attenuated vancomycin induced p-gp suppression. In vivo, vancomycin (400mg/kg, 600 mg/kg IP, 7day) induced acute kidney injury. Also histological examination indicated greater tubular damage in VIN.The number of TUNEL-positive cells was greater in mice kidney with VIN, and cilastatin attenuated these findings. Bax levels were significantly increased in VIN. The cilastatin treatment significantly ameliorated this pro-apoptotic marker in vancomycin injury Cilastatin treatment significantly decreased the vancomycin concentration of blood and kidney. When either cilastatin or vancomycin was administered, the P-gp expression on cellular membrane was increased in the regions of proximal tubular cells, and their cotreatment further enhanced the membrane expression of P-gp.

Conclusions: Our study showed that vancomycin induced nephrotoxicity might be involved suppression of P-gp function in kidney. Also cilastatin attenuated the VIN.

SA-PO176

The Role of TLR4 Signaling in the Nephrotoxicity of Heme and Heme Proteins

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Background: In experimental AKI, renal and plasma levels of heme are increased. In endothelial cells heme is known to be proinflammatory by activating the TLR4 receptor. This study examined the role of TLR4 signaling in renal responses to heme in vitro and in vivo.

Methods: Studies in vitro examined the proinflammatory effects of heme in tubular epithelial cells (TECs) and the effect of inhibiting TLR4 signaling with TAK-242. The role of TLR4 in mediating heme and heme protein-induced nephrotoxicity was assessed in vivo by the use of the TLR4 inhibitor, TAK-242, and $TLR4^{-/-}$ mice.

Results: TECs exposed to 5 μM heme exhibited NF-KB activation, upregulation of MCP-1 mRNA, and increased MCP-1 protein production; TAK-242 markedly reduced these proinflammatory effects. Acute administration of heme in vivo decreased renal blood flow (RBF), and pretreatment with TAK-242 led to greater preservation of RBF at 30 min: 0.24 ± 0.06 vs 0.71 ± 0.07 ml/min. As heme contributes to heme protein-mediated AKI in the glycerol model, we examined whether TAK-242 pretreatment is protective in this model. TAK-242 compared to vehicle did not significantly alter either BUN at day 1 (163 ± 4 vs 155 ± 8 mg/dl) and day 2 (219 ± 12 vs 212 ± 15 mg/dl), or serum creatinine at day 1 (1.7 ± 0.1 vs 1.7 ± 0.1 mg/dl) and day 2 (1.9 ± 0.3 vs 2.1 ± 0.4 mg/dl). We also tested the role of TLR4 in this model using $TLR4^{+/+}$ and $TLR4^{-/-}$ mice; there were no significant differences in filtration markers in $TLR4^{+/+}$ and $TLR4^{-/-}$ mice at day 1 and 2 after glycerol-induced AKI.

Conclusions: We conclude that: 1) "free" heme is proinflammatory and vasoconstrictive, and that these effects involve TLR4-dependent mechanisms; and 2) the in vivo nephrotoxicity of heme proteins does not involve TLR4-dependent pathways. We speculate that the contribution of heme to heme protein-induced AKI reflects the effects of intracellular heme, with little meaningful contribution by extracellular heme engaging membrane-based TLR4 receptors.

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SA-PO177

The Renoprotective Effect of 5-Aminolevulinic Acid in Murine Rhabdomyolysis-Induced Acute Kidney Injury Is Independent of Heme Oxygenase-1 Activation Atsushi Uchida, Minoru Satoh, Tamaki Sasaki, Naoki Kashihara. *Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Okayama, Japan.*

Background: Rhabdomyolysis often occurs after severe skeletal muscle injury, and high morbidity and mortality have been reported for the acute kidney injury (AKI). 5-aminolevulinic acid (ALA) is the naturally occurring metabolic precursor of heme and serves as a protein material related to energy production. A previous study showed that ALA has the potential to prevent cisplatin-induced AKI via induction of heme oxygenase (HO)-1. To evaluate the renoprotective effect of ALA in another AKI model, we examined the efficacy of ALA and the role of HO-1 in a mouse model of rhabdomyolysis-induced AKI.

Methods: Male C57BL/6 mice were used. Mice were subdivided into 4 groups: (1) control group, (2) Rhabdomyolysis group, (3) Rhabdomyolysis+ ALA group, and (4) Rhabdomyolysis+ ALA+ ZnPPIX (HO-1 inhibitor) group. Rhabdomyolysis-induced AKI was caused by intramuscular injection of glycerol. ALA and ZnPPIX were administered each day at 48 h before glycerol administration. These mice were euthanized 72 h after glycerol injection, and the blood and renal tissues were collected.

Results: Serum creatinine, blood urea nitrogen, and urine neutrophil gelatinase-associated lipocalin excretion increased in the Rhabdomyolysis group compared to that in the control group. ALA significantly attenuated these changes. ALA also ameliorated glycerol-induced morphological tubular damage. Excretion of urinary 8-hydroxy-2'-deoxyguanosine, an oxidative stress marker, was suppressed by ALA. ALA significantly attenuated macrophagic infiltration and expression of proinflammatory cytokines. Notably, these changes did not disappear in the Rhabdomyolysis+ ALA+ ZnPPIX group.

Conclusions: ALA has a renoprotective effect and prevents tubular injury in rhabdomyolysis-induced AKI. It is already used for tumor diagnosis and fluorescence-guided resections in humans. Therefore, the safety of this drug has been proven in clinical practice. ALA treatment may be a new therapeutic target in rhabdomyolysis-induced AKI, but the mechanism is independent of HO-1. The renoprotective mechanisms of ALA in AKI should be elucidated.

SA-PO178

Quantitative Phosphoproteomic Analysis of Rat Renal Cortical Tubules in Response to Phospholipase A2 from Russell's Viper Venom Kavee Limbutara,[1,2] Poorichaya Somparn,[2] Narumol Pakmanee,[3] Lawan Chanhome,[3] Orawan Khow,[3] Narongsak Chaiyabutr,[3] Visith Sitprija,[3] Kearkiat Praditpornsilpa,[1] Trairak Pisitkun.[2] *[1]Div of Nephrology, Faculty of Medicine, Chulalongkorn Univ, Thailand; [2]Systems Biology Center, Faculty of Medicine, Chulalongkorn Univ, Thailand; [3]Queen Saovabha Memorial Inst, The Thai Red Cross Society, Thailand.*

Background: Russell's viper is a medically important snake causing multiple effects including impairment of renal sodium reabsorption. Phospholipase A2 (PLA2) is a major component in the Russell's viper venom (RVV) and possibly mediates the nephrotoxicity. This study was designed to uncover the direct effects of PLA2 and RVV to renal tubules.

Methods: PLA2 was purified from crude RVV by HPLC. Renal cortical tubules were isolated from Sprague Dawley rats by enzymatic digestion and centrifugation. Tubules were incubated with either 10 μg/mL of PLA2 or RVV for 10 minutes and vehicle as control. Samples were digested with trypsin and dimethyl-labelled. Phosphopeptide enrichment was performed using titanium dioxide columns and were analysed by LC-MS/MS. Data analysis was done using MaxQuant and Perseus.

Results: We identified a total of 1,957 phosphorylation sites from all samples combined. PLA2 treatment significantly induced up-regulation in 13 sites and down-regulation in 4 sites whereas RVV treatment significantly activated 10 up-regulated sites without down-regulated sites. Six phosphoproteins, including SMIM24, CANX, EEF1D, SGPP1, NHERF1, and OSTF1 were consistently up-regulated by both PLA2 and RVV. NHERF1 (Na+/H+ exchange regulatory cofactor 1) is predominantly expressed in renal proximal tubule where most of sodium reabsorption occurs. This regulatory protein has been shown to control expression and activity of sodium transporters. Conservation analysis of this site in NHERF1 (S287) also demonstrated perfect identity among mammalian species, indicating potentially functional importance.

Conclusions: PLA2 and RVV induced changes in phosphorylation of many proteins in rat renal cortical tubules. Phosphorylation of NHERF1 at S287 by the venom is potentially a key mediator of inhibitory effect on sodium reabsorption. This finding should be confirmed with functional study of sodium transport.

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SA-PO179

The Cat as a Model of Renal Interstitial Fibrosis: Characterisation of Primary Cultures of Feline Tubular Epithelial Cells Jack S. Lawson, Harriet M. Syme, Robert Purcell, Caroline Pd Wheeler-Jones, Jonathan Elliott. *Royal Veterinary College, London, United Kingdom.*

Background: Chronic kidney disease (CKD) is common in aged domestic cats, and the most prevalent pathology in these animals is chronic tubulointerstitial inflammation and fibrosis. These cases are a naturally occurring model for the study of tubulointerstitial fibrosis, offering some advantages over the murine unilateral ureteral obstruction model. Currently, little is known regarding the mechanisms involved in the progression of tubulointerstitial fibrosis in the cat. Epidemiological risk factors for progression include proteinuria, hyperphosphataemia and anaemia. The aim of this study was to isolate and characterise feline proximal tubular epithelial cells (fPTEC) and assess their response to TGF-β1 in comparison to the human proximal tubular cell line HK-2.

Methods: Cells were isolated from the kidneys of cats euthanized for welfare reasons with owner informed consent. Cells were characterised using immunofluorescence for intermediate filament proteins, enzyme histochemistry for gamma-glutamyl transamidase (GGT) and alkaline phosphatase (ALP), and RT-qPCR for gene expression analysis (normalised to GAPDH/RPS7). The fPTEC and HK-2 cells were exposed to 0-10ng/ml human recombinant TGF-β1 for 24-72hrs.

Results: Feline PTECs were successfully isolated from both normal and diseased feline kidneys. The fPTECs co-expressed the epithelial marker cytokeratin alongside vimentin, demonstrated ALP and GGT activity similar to HK-2 cells and expressed both N-Cadherin and E-Cadherin mRNA. Both fPTECs and HK-2 cells demonstrated a concentration-dependent induction of Col1a1, CTGF and TGF-β1 mRNA expression after TGF-β1 stimulation. Additionally, the fPTECs and HK-2 underwent morphological changes suggestive of epithelial-to-mesenchymal transition which was accompanied by a trend for decreased E-Cadherin and increased N-Cadherin mRNA expression.

Conclusions: In summary, it is feasible to obtain PTECs from feline kidneys. These are phenotypically similar to human proximal tubular cells and respond similarly to TGF-β1 stimulation. These data support the use of the cat as a model of tubulointerstitial fibrosis.

Funding: Pharmaceutical Company Support - Elanco Animal Health

SA-PO180

In Vivo Evidence of mTORC1-S6 Kinase Pathway Involvement in the Development of Glomerulosclerosis in Human IgA Nephropathy Kojiro Nagai, Tatsuya Tominaga, Taichi Murakami, Eriko Shibata, Seiji Kishi, Motokazu Matsuura, Hideharu Abe, Toshio Doi. *Nephrology, Inst of Biomedical Sciences, Tokushima Univ Graduate School, Tokushima, Japan.*

Background: Human IgA nephropathy is the most common glomerulonephritis. The disease results from abnormal IgA deposits in mesangial area. To clarify the mechanism of IgA nephropathy progression, mesangial function should be evaluated *in vivo,* but mice Cre-loxP system to knock out a target molecule in mesangial cells has not been established yet. Besides, mTOR complex 1 (mTORC1) -S6 kinase pathway plays an important role in cell proliferation and hypertrophy.

Methods: The aim of this study is to clarify mTORC1-S6 kinase pathway involvement in the development of glomerulosclerosis in human IgA nephropathy. First, 12 human IgA nephropathy cases derived from three men and nine women aged 15 to 63 years (mean ± SD, 32.8 ± 16.8years) were analyzed. Immunohistochemistry of phosphorylated ribosomal protein S6 (phospho-rpS6) (a surrogate marker of mTORC1-S6 kinase pathway) was performed. Next, mesangium-specific mTORC1 activation was induced by ablation of an upstream negative regulator, Tuberous sclerosis complex 1 (TSC1), using tammoxifen-induced Foxd1-Cre mice to clarify the role of mTORC1-S6 kinase pathway in the development of glomerulosclerosis.

Results: Phospho-rpS6 was detected in mesangial area of human IgA nephropathy. Mesangium-specific TSC1 ablation in mice (MsKOTSC1) caused rpS6 phosphorylation in mesangial area confirmed by immunohistochemistry and westernblot analysis. MsKOTSC1 showed IgA nephropathy features, including the increase of collagen IV accumulation at 12 weeks of age and collagen I and alpha smooth muscle actin upregulation at 1 year of age in glomeruli. However, MsKOTSC1 did not exhibit significant albuminuria. Furthermore, rapamycin treatment of MsKOTSC1 could suppress the increase of collagen IV expression.

Conclusions: Mesangium-specific mTORC1-S6 kinase pathway activation could develop glomerulosclerosis in mesangial area, which mimics human IgA nephropathy. However, the activation of mTORC1-S6 kinase pathway was not enough to cause albuminuria. Mesangium-specific Cre-loxP system is useful to clarify the mechanism of human IgA nephropathy.

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SA-PO181

Vitamin D Receptor Contributes to Disparate Effects during the Initiation and Progression of HIV-Associated Nephropathy (HIVAN) Xiqian Lan,[1] Waqaar Khawar,[1] Manoj K. Tembhre,[1] Judith Eng,[1] Seyedeh Shadafarin Marashi Shoshtari,[1] Hanan K. Tawadrous,[2] Anil K. Mongia,[2] Ashwani Malhotra,[1] Pravin C. Singhal.[1] *[1]Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY; [2]Pediatrics, Down State Medical Center, Brooklyn, NY.*

Background: Renin angiotensin system plays a role in the progression of HIV-associated nephropathy (HIVAN). Since angiotensinogen (Agt) is a substrate for renin, we hypothesized that mice with enhanced expression of Agt would display accelerated progression of HIVAN. We evaluated the effect of different copies of Agt in the initiation and progression of renal lesions in genetically engineered HIVAN mice (Tg26).

Methods: Control and Tg26 mice with 2 (Tg26/Agt-2) and 4 (Tg26/Agt-4) copies of Agt were evaluated for severity of renal lesions, arteriosclerosis and hypertension at 8 weeks and 16 weeks. Renal cortical sections were stained with sirus red and PAS. RNA was extracted from renal tissues and probed for AT1, AT2, PAI-1, VDR, and molecules involved in Tert and epithelial mesenchymal transition (EMT) pathways.

Results: Tg26/Agt-4/8wks showed lower blood pressure ($P<0.01$) vs. Tg26/Agt-2/8 wks. While Tg26/Agt-4/16wks displayed higher blood pressure vs. Tg26/Agt-2/16wks. Tg26/Agt-4/8wks displayed attenuated expression of PAI-1 vs. Tg26/Agt-2/8wks; however, Tg26/Agt-4/16wks showed 3-fold greater PAI-1 expression than to Tg26/Agt-2/16wks.

Tg26/Agt-2/8wks displayed attenuated expression VDR and enhanced production of Ang II vs. Tg26/Agt-4/8wks, however this pattern reversed at 16 wks. Tg26/Agt-4/8wks displayed attenuated expression of AT1 and AT2 and down regulation of Tert, TGF-β, Snail, and vimentin when compared to Tg26/Agt-2/8wks. However, all these markers were comparable between these groups at 16 wks of age. Tg26/Agt-2/8wks developed renal lesions which were more advanced than Tg26/Agt-4/8wks. Conversely, Tg26/Agt-4/16wks displayed more advanced renal lesions vs. Tg26/Agt-2/16wks.

Conclusions: VDR dynamics determined the initiation and acceleration of renal lesions in Tg26/Agt-4 and Tg26/Agt-2 mice both at early and later time periods.

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SA-PO182

VDR Agonist Preserves Podocyte Molecular Phenotype Through Reversal of Epigenetic Alterations in HIV Milieu Nirupama Chandel, Kamesh R. Ayasolla, Vinod Sharma, Abheepsa Mishra, Ashwani Malhotra, Pravin C. Singhal. *Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY.*

Background: Epigenetic alterations play a role in the development of HIV-associated Nephropathy. We recently reported that HIV stimulated podocyte SNAIL expression. We now hypothesize that HIV-induced podocyte SNAIL expression would compromise podocyte molecular phenotype (nephrin and p-cadherin) through epigenetic mechanisms and a vitamin D receptor (VDR) agonist (VDA) would be able to preserve it through reversal of epigenetic alterations.

Methods: Renal tissues of 6 week old control, HIVAN (Tg26), and VDR agonist (VDA) treated Tg26 (2 weeks) mice and vector (V/HP) or HIV (NL4-3)-transduced (HIV/HPs) human podocytes were evaluated for expression SNAIL, VDR, nephrin, and p-cadherin. ChIP assays were carried to confirm binding of SNAIL at nephrin promoter. Immunoprecipitation studies were carried out to analyze composition of SNAIL repressor complexes. Genomic DNA was isolated and CpG island methylation was measured in V/HPs and HIV/HPs.

Results: Protein blots of renal tissues from HIVAN mice and HIV/HPs displayed enhanced expression of SNAIL but down regulation of nephrin, p-cadherin, and VDR. VDA partially preserved expression of nephrin in renal tissues of Tg26 mice as well as in HIV/HPs. Genomic DNA methylation studies confirmed hypermethyalated CpG islands at *Nephrin* promoter in HIV/HPs.ChIP assay suggested that enhanced SNAIL expression by HIV/HPs was the consequence of histone 3 methylation at lysine (K) 4 residues (H3K4me3) on *SNAIL* promoter, whereas, down regulation of nephrin seems to be the consequence histone 3 methylation at lysine 27 residues (H3K27me3). Co-immunoprecipitation studies in lysates of HIV/HPs revealed the association of histone deacetylase (HDAC) 4, DNMT3b and DNMT1, mSin3A and EZH2 with SNAIL; conversely, VDA treatment of HIV/HPs decreased the expression of HDAC4, DNMT3B, DNMT1, mSin3A, and EZH2 (disruption of SNAIL complex).

Conclusions: VDA preserves podocyte nephrin expression through down regulation of SNAIL transcription, disruption of SNAIL repressor complex and attenuation of methylation at H3K27 residue at nephrin promoter.

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SA-PO183

Autophagy Activity and Expression Pattern of Autophagy-Related Markers in the Podocytes of Patients with Lupus Nephritis: Association with Pathological Classification Juan Jin, Yiqiao Li. *Dept of Nephrology, Zhejiang Provincial People's Hospital.*

Background: To identify the significance of autophagy in lupus nephritis (LN), we counted the number of autophagosomes in podocytes and evaluated the expression of multiple molecular markers associated with autophagy in LN specimens.

Methods: Autophagosomes in podocytes were counted using transmission electron microscopy. Beclin-1, microtubule-associated protein light chain 3 (LC3), autophagy-related gene 7 (Atg7), and UNC-51-like kinase 1 (ULK1) expression levels were measured using immunohistochemistry in renal biopsy specimens from 90 patients with LN and 15 healthy controls.

Results: The number of autophagosomes in patients with LN types III, IV, and combined V-IV type were significantly higher than in controls ($p<0.0001$; $p<0.0001$; $p=0.009$, respectively). However, autophagosomes numbers in patients with II and V types LN were significantly lower than controls (both $p<0.0001$). Various levels of marker expression were identified, and correlated significantly with LN pathology classifications. The percentage of marker expression in LN types III, IV and V-IV were significantly higher than controls ($p<0.05$), while marker expression in types II and V were lower than controls, although the differences for LC3 and ULK1 were not statistically significant.

Conclusions: Autophagy activity and expression pattern of autophagy-related markers in podocytes were significantly positively correlated with LN types III, IV and V-IV, but negatively correlated with II and V types. Autophagy could therefore be a useful predictor of LN pathology type, and could be informative for the development of treatment strategies in a clinical setting.

SA-PO184

Ubiquitin C-Terminal Hydrolase L1 (UCH-L1) Is Required for Regulated Protein Degradation Through the Ubiquitin Proteasome System in Murine Kidneys in Health and Immune-Complex Nephritis Jan Hendrik Knop, Anna Reinicke, Ulrich O. Wenzel, Rolf A. Stahl, Catherine Meyer-Schwesinger. *Internal Medicine, Univ Medical Center Hamburg-Eppendorf.*

Background: UCH-L1 is a major deubiquitinating enzyme of the nervous system. In the human kidney, UCH-L1 is expressed in tubular and parietal epithelial cells and in the setting of glomerulonephritis UCH-L1 is upregulated in the tubular compartment and de novo expressed in podocytes. Biochemically, UCH-L1 is thought to regulate the intracellular pool of monoubiquitin, required for ubiquitination procedures. Nothing is known about the significance of UCH-L1 in the kidney in health and disease.

Methods: We generated constitutive UCH-L1-deficienct mice which were phenotypically characterized by histological and biochemical assays. Anti-podocyte-nephritis (APN), an immune-complex glomerulonephritis, was induced by injection of anti-podocyte antibodies and clinical and morphological disease development was monitored.

Results: Naïve UCH-L1-deficient mice developed systemic hypotension and urine retention in the bladder due to over-all neurodegeneration. The renal and glomerular pool of polyubiquitinated and of oxidative-modified proteins was increased. Simultaneously, proteasomal activity was decreased and the balance between the 26S and the i26S proteasomal content was altered in both whole kidney and in isolated glomeruli. Interestingly, UCH-L1-deficient mice developed proteinuria and podocytes showed signs of stress despite an inconspicuous overall glomerular morphology. Induction of APN in wild-type mice demonstrated that similarly to human glomerulonephritis, UCH-L1 is up-regulated in tubular cells and in glomerular cells such as podocytes and endothelial cells. UCH-L1-deficient mice exhibited an exacerbated course of disease with increased tubulointerstitial and glomerular damage and nephrotic syndrome. UCH-L1-deficient mice failed to upregulate the proteolytic effective i26S proteasome resulting in decreased proteasomal activity and accumulation of oxidative-modified and of K48-polyubiquitinated proteins in whole kidney and glomeruli.

Conclusions: UCH-L1 is required for regulated protein degradation in murine kidneys in health and disease.

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SA-PO185

Evaluation of DLK1 Absence in Unilateral Ureteral Obstruction Model Laura Marquez-Exposito,[1] Carolina Lavoz,[3] Eva Blanco,[2] Sandra Rayego-Mateos,[1] Raquel Rodrigues-Diez,[1] Sergio A. Mezzano,[3] Marta Fierro-Fernández,[2] Santiago Lamas,[2] Marta Ruiz-Ortega.[1] *[1]Univ Autónoma Madrid; [2]Centro de Biologia Molecular, Madrid, Spain; [3]Univ Austral, Chile.*

Background: The Notch signaling molecular pathway is involved in kidney embrionary development. Notch expression is virtually absent in adult human kidneys, whereas overexpression of ligands and receptors have been described in many human chronic renal diseases. There are several non-canonical Notch ligands that can activate or inhibit Notch signaling. The non-canonical ligand DLK1 (Delta-like homologue 1) has been suggested as a Notch inhibitor in Drosophila and mammal cells *in vitro*, regulating several processes, including adipogenesis, differentiation and angiogenesis. However, its role in renal injury is unknown.

Methods: The role of DLK1 in renal damage was evaluated using a Dlk1-null mice in the model of unilateral ureteral obstruction (UUO).

Results: In obstructed kidneys, activation of the canonical Notch/Jagged-1 pathway was found at 2 days, determined by nuclear translocation of active Notch-1, production of Jagged-1 and increased gene expression of the effector Hes-1, as previously described. Interestingly, upregulation of the non-canonical ligands Dlk1 and Dlk2 gene expression was observed after 5 days, later than Notch/Jagged-1 activation. In several tissues and pathological conditions, Dlk1 deletion was associated to over-activation of the Notch pathway. However, neither control nor obstructed kidneys of Dlk1-null mice presented further renal Notch/Jagged-1 activation than wild-type mice. Only hey-1 and Dlk2 gene levels were significantly elevated in Dlk1 null mice compared to wild-type. In obstructed kidneys of Dlk1-null mice a marked gene expression of renal injury biomarkers was found, but there were no significant differences compared to wild-type mice, at any time evaluated until 14 days. Moreover, there were no significant changes in inflammatory parameters or renal fibrosis between wild-type and Dlk1-null mice.

Conclusions: Our data suggest that DLK1 is not acting as an endogenous Notch inhibitor, at least in the experimental model of unilateral ureteral obstruction.

Funding: Government Support - Non-U.S.

SA-PO186

Rapamycin Attenuates Parietal Epithelial Cell Proliferation in a Model of Collapsing Focal Segmental Glomerulosclerosis Bart Smeets,[1] Shagun Sharma,[2] Jack F. Wetzels,[2] Brigith Willemsen,[1] Marinka Bakker-van Bebber,[2] Marcus J. Moeller,[3] Henry Dijkman,[2] Johan Van der Vlag.[2] *[1]Pathology, Radboud Univ Medical Center, Netherlands; [2]Nephrology, Radboud Univ Medical Center, Netherlands; [3]Nephrology and Clinical Immunology, RWTH Univ of Aachen, Germany.*

Background: Thy-1.1 transgenic mice develop glomerular lesions that mimic human collapsing FSGS. We questioned whether the mTOR inhibitor rapamycin (sirolimus) could prevent the development of these lesions and if protection is related to glomerular epithelial cell proliferation.

Methods: Anti-Thy-1.1 injected mice (day 0) were treated with sirolimus (oral gavage, 4mg/kg/day) during the development of the glomerular lesions (early treatments from day -3 to days 4, 7, and 21). In addition, we treated mice after development of the collapsing FSGS lesions (late treatment from day 11 to day 31). We compared kidney function, the development of glomerular lesions and kidney cell proliferation, between sirolimus- and vehicle-treated mice. In addition, the direct effects of rapamycin on cell activity (MTT assay) and growth of mouse primary parietal epithelial cells were examined.

Results: Early treatment with sirolimus from day -3 to days 4, 7 and 21 attenuated the development of glomerular lesions, whereas, late treatment from day 11 did not. The reduced number of glomerular lesions was associated with a significantly less activation (CD44 expression) and proliferation (Ki-67) of parietal epithelial cells, at day 4 and 7 after anti-Thy-1.1 injection. Interestingly, at these time points sirolimus treatment did not have an effect on albuminuria, blood urea nitrogen and podocyte injury reflected by the expression of desmin. In cell culture, we observed dose dependent reduction of the activity and growth of mouse primary parietal epithelial cells.

Conclusions: Inhibition of mTOR, attenuates the development of experimental collapsing FSGS. We propose that the effects are related to the ability of rapamycin to reduce parietal cell activation and proliferation.

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SA-PO187

Knocking Down Thymosin β4 in Endothelial Cells Impairs Recovery after Acute Tubular Injury, wth Decreased Peritubular Capillary Number and Function Jianyong Zhong,[1,2] Haichun Yang,[1,2] Agnes B. Fogo.[1,2] *[1]Pathology, Microbiology and Immunology, Vanderbilt Univ Medical Center, Nashville, TN; [2]Pediatric Nephrology, Vanderbilt Univ Medical Center, Nashville, TN.*

Background: Thymosin ß4 (Tß4) is a G-actin sequestering protein expressed ubiquitously, which affects cell proliferation, migration and angiogenesis. We previously found that exogenous Tß4 ameliorated matrix accumulation at day 14 after unilateral ureteral obstruction. In this study, we investigated the effect of Tß4 on endothelial cells and subsequent renal injury.

Methods: We generated inducible endothelial cell Tß4 knockdown mice (Tß4 KD) by mating Tß4 shRNA loxp mice with inducible SCL Cre mice, all on C57/BL6 background. SCL Cre negative mice were used as control (Cont). Folic acid (240ng/kg BW, i.p) was injected in male mice, age 12 weeks. Tamoxifen (5 times, i.p, qod) was administrated starting two weeks after folic acid to induce Tß4 knockdown. Mice were sacrificed at 6 weeks after folic acid injection.

Results: Tß4 expression in endothelial cells was significantly reduced in Tß4 KD compared to Cont. Peritubular capillary density, assessed by CD31 staining, was significantly decreased in Tß4 KD mice (Tß4 KD 1.00±0.12 *vs.* Cont 1.84±0.20%, P<0.01). Dextran was infused i.v., with more dextran leakage to interstitial areas in Tß4 KD than Cont mice. Tß4 KD mice had significantly higher collagen I (Tß4 KD 2.48±0.40 *vs.* Cont 1.09±0.12, P<0.05) and TGFß mRNA expression vs. Cont (Tß4 KD 1.11±0.12 *vs.* Cont 0.71±0.07, P<0.05), but Col I protein, assessed by IHC, was not different between the groups. Urinary NGAL, a marker of tubular injury, was also higher in Tß4 KD vs Cont (Tß4 KD 1872.47±373.52 *vs.* Cont 413.26±118.47 P<0.01).

Conclusions: We conclude that knockdown of thymosin ß4 in endothelial cells results in decreased endothelial cell number and impaired function, which decreases recovery of tubular injury.

Funding: NIDDK Support

SA-PO188

Potassium Chloride in Hypoelectrolytic Isoosmotic Solution for Infusion Prevents an Artifact of Electron Microscopic Morphology for Fresh Renal Biopsy Specimen Takashi Takaki, Yasuhiro Nakamura, Naomi Sato, Kensuke Joh. *Tohoku Univ Graduate School of Medicine, Dept of Pathology, Sendai, Miyagi, Japan.*

Background: Wrapping fresh kidney biopsy specimens in saline-soaked gauze in order to avoid the drying of the specimens could be the major factor of artifacts.Hypoelectrolytic isoosmotic solution for infusion (SOLDEM 3A) instead of saline for soaking gauze prevents artifacts in electron micrograph(Pathol Int 2015 Nakamura et al).Concerning an underlying mechanism,high glucose concentration for maintaining osmolality or potassium chloride lacking in the saline were suspected as factors contributing a maintenance of morphology. Therefore,the purpose was to provide an evidence for finding a mechanism of preventing an artifact.

Methods: Before fixation with 2.5% GA in PB,fresh small cubes of the tissue from male SD rat were macerated either in group A(SOLDEM 1:Na^+90mEq/L,Cl^-70mEq/L,L-Lactate20mEq/L,Osmotic pressure ratio 1) or in group B(SOLDEM 3A:Na^+35 mEq/L,K^+20mEq/L,Cl^-35mEq/L,L-Lactate20mEq/L,Osmotic pressure ratio 1) for 10 min or 30 min.Thereafter,the samples were processed by 1% OsO_4 and embedded for observation. Each group was composed of five pieces of kidney tissue, respectively. In control group, the tissues were dropped directly into the fixative.

Results: In group A(SOLDEM 1 lacking potassium chloride),swollen endothelium and podocyte showing a dilatation of endoplasmic reticulum, mesangium showing a swollen capillary protuberance in the glomeruli as well as swollen mitochondria and swollen bush border of the tubules were seen after 10 min.maceration.These findings became prominent after 30 min.maceration.Foot processes were relatively preserved.In group B(SOLDEM 3A with potassium chloride),no abnormal findings,which were identical with those of control group,were seen after 10 min. and 30 min.maceration.

Conclusions: Since ATP driven sodium potassium pump links the export of sodium and import of potassium ions from the cell against their respective electrochemical chemical gradients,we suspect that a buffer containing potassium can help the maintenance of morphological architecture of the specimens,even after a cessation of the ion pump due to a removal of the tissue from the body.

SA-PO189

Hyaluronidase Treatment Blocks the Glomerular Homing of Memory T Cells and Improves Proteinuria and Survival Rate in the NZM Mouse Model of Lupus Nephritis Hiroyuki Kadoya,[1] Chaim O. Jacob,[2] Janos Peti-Peterdi.[1] *[1]Physiology and Biophysics, Univ of Southern California, Los Angeles, CA; [2]Medicine/Rheumatology, Univ of Southern California, Los Angeles, CA.*

Background: Lupus Nephritis (LN) is a major cause of morbidity and mortality in patients with systemic lupus. The exact pathomechanism of LN has been elusive, and therefore current non-specific therapies are limited to general immunosuppression. The present study aimed to test the hypothesis that an interplay between cellular components of the immune system (activated memory T cells) and local kidney tissue factors (the CD44 ligand hyaluronic acid (HA) in the glomerular endothelial glycocalyx) is critically important in the glomerular homing of T cells, and therefore in the development and potential therapy of LN.

Methods: Intravital imaging with serial multiphoton microscopy (MPM) was used to track the fate of exogenous FACS sorted splenic activated memory T cells (1×10^6 cells) injected iv, or endogenous T cells labeled with anti-CD3 and anti-CD44 antibodies in vivo in New Zealand mixed (NZM) mice.

Results: Glomerular size, sclerosis and albuminuria were significantly increased at 4 weeks old NZM mice compared with control healthy mice. Activated memory T cells (the vast majority of all immune cells found in LN kidney) homed into affected glomeruli in LN mice and in a model of endothelial dysfunction (two weeks after L-NAME treatment and on high salt diet), but not into healthy kidneys. On average, we observed 30-40 $CD3^+CD44^+$ T cells per glomerulus sticking to endothelial cells within glomerular capillaries of LN mice, but not in control healthy mice. In a robust effect, a single iv injection of hyaluronidase (200 Unit) significantly reduced (by ~40%) the number of homed $CD44^+$ cells in glomeruli already within 1 hour after injection, and improved albuminuria and survival rate of NZM mice with high proteinuria.

Conclusions: Our results support the major importance of HA in the endothelial glycocalyx in the glomerular homing of memory T cells in the development and pathobiology of LN. Hyaluronidase treatment is a promising new therapeutic approach for LN.

SA-PO190

Transmembrane Protein 14A Is Differently Expressed in Human Proteinuric Renal Diseases Josephine Bonnemaijer, Ramzi Khalil, Jan A. Bruijn, Hans J. Baelde. *Pathology, Leiden Univ Medical Center.*

Background: Identifying individual components of the glomerular filtration barrier that are involved in the development of proteinuria can help to find new potential therapeutic targets for CKD. We previously showed that transmembrane protein 14A (TMEM14A) is involved in the development of proteinuria. In this study, we aim to assess its localization in the glomerulus and whether it is differentially expressed in human proteinuric renal diseases and in spontaneously proteinuric rats.

Methods: TMEM14A protein expression was assessed by immunohistochemistry in glomeruli of patients with IgA nephropathy, lupus nephritis, minimal change disease, and healthy controls. Renal tissue of spontaneously proteinuric Dahl rats and non-proteinuric SHR rats were also stained for TMEM14A protein. Furthermore, QPCR was performed to investigate TMEM14A mRNA expression in podocytes, HEK, and Huvec and compared to renal tissue.

Results: TMEM14A was primarily localized in podocytes, as shown by immunohistochemistry and *in vitro*. Expression was significantly higher ($p<0.05$, chi-square test) in glomeruli of proteinuric patients compared to controls. In Dahl rats, TMEM14A expression was significantly diminished ($p<0.05$, mann-whitney u-test) in Dahl rats aged 2 and 4 weeks of age compared to SHR rats, before onset of proteinuria.

Conclusions: Here, we show that TMEM14A is primarily expressed by podocytes and is differentially expressed under proteinuric circumstances. Interestingly, TMEM14A protein expression in Dahl rats is decreased before onset of proteinuria, similar to our previous findings in mRNA expression. In contrast with the findings in our rat model, we found that TMEM14A protein expression was significantly higher in glomeruli of patients with various proteinuric renal diseases. Based on the results of this study, we hypothesize that TMEM14A is part of a regulatory system that is involved in the development of proteinuria.

SA-PO191

Role of Non-Adrenergic α(2A)-Adrenoceptors in Renal Fibrosis
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Background: Increased sympathetic tone leads to progression of chronic kidney disease (CKD). α2A-adrenoceptors (α2A-AR) in adrenergic neurons are known for regulating sympathetic tone by a negative feedback mechanism. Not much is known about their function on non-adrenergic cells. Here, we investigate the impact of α2A-AR the development of renal fibrosis.

Methods: Unilateral ureteral obstruction (UUO) was performed in α2A-AR knockout (KO) and wild-type (WT) mice on a FVB background. Immunohistochemistry and gene expression analysis were performed 7 days after UUO.

Results: Despite increased renal sympathetic neurotransmission release, fibrosis, assessed by sirius red/fast green collagen staining ($p<0.05$) and collagen-1 expression ($p<0.001$), was attenuated in kidneys of KO compared to WT mice 7 days after UUO. Moreover, expression of the pro-inflammatory and pro-fibrotic cytokines and chemocines TNF-α, TGF-β, CCL2 and CCL5 ($p<0.05$) were reduced in KO compared to WT mice. In order to dissect between adrenergic and non-adrenergic effects, we also generate α2A-AR-KO mice in which α2A-ARs are restored in adrenergic cells under the control of the human dopamine beta-hydroxylase (DbH-KO). In DbH-KO, renal sympathetic neurotransmission was significantly reduced compared to KO but similar to WT mice suggesting functional presynaptic α2A-ARs in DbH-KO mice. Beside fibrosis, macrophage infiltration was significantly reduced in obstructed kidneys of DbH-KO compared to WT but similar to total KO suggesting a crucial role of non-adrenergic α2A-AR on immune cells in renal fibrosis. Indeed, stimulation of isolated macrophages from WT mice with the α2-AR-agonist UK14.304 (0.1μM) increased TNF-α expression of TNF-α ($p<0.05$).

Conclusions: Although adrenergic α2A-ARs are considered as a negative regulator of sympathetic tone, they also seem to promote inflammation and fibrosis in response to kidney injury. These effects seem to be mediated by non-adrenergic α2A-AR which might be a good candidate for reducing the progression of CKD.

SA-PO192

The Role of Resistance Training (Exe), before and after Nephrectomy (5/6Nx) Reduce Mortality and Prevent the Increase of Proteinuria in Rats with Chronic Kidney Desease
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Background: The aim of this study was to evaluate the EXE effects on renal function and mortality rate in rats with 5/6Nx.

Methods: Adult Wistar rats were divided in two groups (n=8): Previous Exercise + Nx 5/6 + exercise (EXE-EXE), Previous exercise + Nx 5/6 (EXE-SED). The protocol was employed in 5/6Nx rats after 7 days from the surgical procedures, 6 to 12 climbs/day, 5 days/week, 40 a 60% of maximal loading, 8 weeks total (4 weeks before surgery Nx56 and 4 weeks after) for the group EXE-EXE and 4 weeks for EXE-SED (only 4 weeks after surgery). It was evaluated mean arterial pressure (MAP), creatinine clearance (CrCl), proteinuria (uProt), blood urea nitrogen (BUN) as well mortality rate.

Results: EXE did not modify the increment in MAP but prevent the increase in proteinuria rate (43,2±2,9 vs.82,1±2,5mg/24h, $p<0.0001$) and mean BUN in EXE+SED was higher compared with EXE+EXE, (114,2±8,4 vs 76,9±2,0mg/dl ,$p<0.0019$). A higher mortality rate was observed in EXE-SED (50%) vs EXE-EXE (0%).

	EXE-SED	EXE-EXE
MAP (mmHg)	215±7	213±8
Weight (g)	381±4	365±17
CrCL (ml/min/BW)	1,00±0,15	1,28±0,11
uProt (mg/24h)	82,1±2,5	43,2±2,9*
Mortality Rate (%)	50	0
BUN (mg/dl)	114,2±8,4	76,9±2,0*

* vs. EXE-SED.

Conclusions: Results suggested that the EXE minimize the impact of 5/6Nx, with much lower increase in BUN (28%), proteinuria (48%) and lower mortality in EXE+EXE vs EXE+SED. Minor impact of 5/6Nx on CrCl indicate that exercise could have a protective effect, especially under this experimental protocol. Thus, it is reasonable to suggest that EXE could be an additional strategy to be employed in CKD.

SA-PO193

Meprin Expression/Activity Impacts Metabolite Profiles in Kidney Tissue of Mice with STZ Induced Type 1 Diabetes
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Background: Meprin metalloproteinases are the most abundantly expressed proteins in the brush border membranes of proximal kidney tubules. Meprins have been shown to play a role in the pathophysiology of diabetic nephropathy (DN) in humans and mice. In vitro and in vivo studies have identified several meprin targets in the kidney which include cytoskeletal proteins, tight junction proteins, extracellular matrix proteins, and cell signaling molecules. It's not known how proteolytic processing of these and other targets by meprins impacts metabolic pathways in the kidney. This knowledge is important in delineating the mechanism(s) by which meprins modulate the progression of DN.

Methods: Low dose streptozotocin (STZ) was used to induce type 1 diabetes in 8 week old male wild-type (WT) and meprin ß knockout (ßKO) mice. The mice were sacrificed at 8 weeks post-STZ injection and kidney tissue harvested for metabolomics analysis. Biochemical assessment of kidney injury utilized ELISAs for creatinine, neutrophil gelatinase associated lipocalin (NGAL), and kidney injury molecule-1 (KIM-1). Lyophilized kidney proteins were reconstituted in 95:5 acetonitrile and loaded onto a UPLC-QTOF system for separation by HILIC chromatography and detection in MS^E mode.

Results: Metabolomics analysis found more than 200 compounds associated with diabetes in both WT and meprin βKO mice, including two annotated as the osmolytes glycerophosphocholine and betaine. One of the metabolites STZ only affected in WT mice, is N-Methyl-pyridone-carboxamide. It's isomers, 4-PY and 2-PY, are markers of peroxisome proliferation and inflammation and correlate with creatinine clearance as well as glucose concentrations in oral glucose tolerance tests. Importantly, the anti-diabetic drug, vildagliptin, lowers the concentrations of both isomers in urine.

Conclusions: The meprin ß-associated changed metabolites (e.g N-methyl-4-pyridone-3-carboxamide) have been implicated in kidney injury suggesting that meprins impact metabolic pathways that influence the progression of DN.

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SA-PO194

Changes in Malondialdehyde Levels with Age in the Nucleus, Cytosol and Mitochondria from Rat Kidney Cortex and Medulla
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Background: Oxidative stress caused by free radicals generated in aerobic metabolism contributes to cell injury and dysfunction seen with age. Malondialdehyde (MDA) is a product of lipid peroxidation of cell and organelle membranes by free radicals, and is used as an indicator of oxidative stress. The present study was undertaken to investigate the effect of age on changes in MDA levels in the nucleus, cytosol and mitochondria from rat kidney cortex and medulla.

Methods: Young (3 months of age) and Old (22 months of age) female Lewis rats were used. The kidneys were harvested from anesthetized rats after being perfused with isotonic saline via a catheter in the abdominal aorta. The kidneys were separated into cortical and medullary sections and homogenized in isotonic saline. Differential centrifugation was used to isolate the nuclear, cytosolic and mitochondrial fractions. MDA levels were measured in the fractions using a spectrophotometric assay and expressed as nmol/g kidney wet weight. Differences were evaluated using a Student's t Test.

Results: There was a significant increase in MDA levels with age in the nucleus, cytosol and mitochondria from rat kidney cortex. There was not a significant increase in MDA levels with age in the nucleus, cytosol and mitochondria from rat kidney medulla. MDA levels of nuclei and mitochondria from kidney medulla were higher than MDA levels from kidney cortex in both Young and Old rats.

	Young (n = 6)	Young (n = 6)	Old (n = 6)	Old (n = 6)
	Cortex	**Medulla**	**Cortex**	**Medulla**
MDA - nmol/g kid wet wt				
Nucleus	5.56 ± 0.54	10.57 ± 0 .95[a]	7.38 ± 0.51*	9.20 ± 0.82[a]
Cytosol	14.81 ± 0.68	20.74 ± 1.30[a]	21.48 ± 2.50*	20.68 ± 3.70
Mitochondria	2.63 ± 0.24	7.04 ± 0.45[a]	4.06 ± 0.38*	6.65 ± 0.39[a]

All data expressed as X ± SEM; * significantly different from Young Cortex; [a] significantly different from age-matched Cortex.

Conclusions: The findings suggest that there is increased oxidative stress in the nucleus, cytosol and mitochondria from rat kidney cortex but not rat kidney medulla with age.

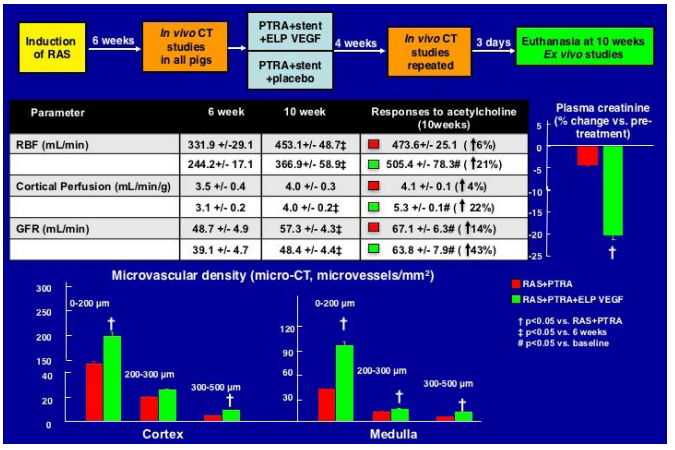
SA-PO195

Angioplasty Combined with Intra-Renal Administration of a Biopolymer-Delivered VEGF Construct to Improve Renal Recovery: A New Therapeutic Strategy
Alejandro R. Chade, Erika Guise, Luke J. Vincent, Gene L. Bidwell. *Univ of Mississippi Medical Center.*

Background: Renal angioplasty and stenting (PTRAS) can resolve renal artery stenosis (RAS) but not always improve renal function, possibly due to persistent parenchymal damage. We recently designed a novel bioengineered fusion of a drug delivery vector (elastin-like polypeptides, ELP) with VEGF, and showed that ELP-VEGF therapy improved stenotic-kidney function and damage. We aim to increase the therapeutic efficacy of PTRAS and hypothesize that co-adjuvant ELP-VEGF therapy following PTRAS will enhance renal recovery compared to PTRAS alone.

Methods: Unilateral RAS was induced in 10 pigs. Six weeks later, basal and stimulated stenotic-kidney blood flow (RBF), cortical perfusion, and filtration (GFR) were quantified *in vivo* using multi-detector CT, and then pigs were randomly divided in RAS+PTRAS or RAS+PTRAS followed by a single intra-renal infusion of ELP-VEGF (n=5 each). Pigs were observed for 4 additional weeks, *in vivo* CT studies repeated, and then euthanized for micro-CT quantification of the renal microvasculature and plasma creatinine.

Results: Pre-PTRA renal hemodynamics was reduced in all pigs. PTRAS similarly resolved RAS and improved basal GFR. However, RBF, cortical perfusion, responses to endothelium-dependent challenge (acetylcholine, intra-renal infusion), and creatinine showed greater improvements in RAS+PTRAS+ELP-VEGF compared to PTRAS alone, accompanied by marked recovery in renal microvascular density.



Conclusions: Our study determined the effectiveness of a novel co-adjuvant intervention for PTRAS. A single intra-renal administration of ELP-VEGF improved stenotic kidney outcomes after PTRAS by protecting the renal microvascular architecture and function, supporting the potential of a new strategy to enhance renal recovery in RAS.

Funding: Other NIH Support - NHLBI, Private Foundation Support

SA-PO196

Renal Tubular-Specific Jagged1 Deletion Ameliorates Kidney Fibrosis

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Background: Fibrosis is the histological manifestation of chronic kidney disease (CKD). Recent studies highlighted the reemergence of developmental pathways in fibrosis including Notch, Wnt, and Hedgehog. Notch is a basic cell-cell communication pathway where expression of the ligand, Jagged1,2 or Delta1,3,4 on signal-sending cells induces an intramembrane proteolysis of the receptor, Notch1-4 on the signal-receiving cell. Our group previously established that tubular epithelial cell (TEC) Notch signaling plays a key role in fibrosis by using models with global Notch deletion. However, the precise ligand and receptor pairs that contributes to kidney fibrosis still remains unknown. Here we performed a systematic analysis to define the specific ligand of Notch-induced fibrosis development.

Methods: Genome wide gene expression analysis of microdissected human kidney tubule samples (59 control and 36 CKD) was performed using Affymetrix microarrays. For *in vivo* study, Jagged1 flox/flox mice were crossed to transgenic mice expressing Cre recombinase under the cadherin 16 to generate animals with TEC deletion of Jagged1 (Ksp^{cre}/$Jagged1^{flox/flox}$). Kidney injury was induced by administering folic acid intraperitoneally. Histological and gene expression changes were analyzed in mouse kidneys. *In vitro* studies were performed using a co-culture system of rat fibroblasts and mouse stromal cells that expressed Jagged1.

Results: In human tissue samples, Jagged1 showed the best correlation with the degree of interstitial fibrosis (p=0.005). Ksp^{cre}/$Jagged1^{flox/flox}$ mice showed no kidney specific alterations. On the other hand, following folic acid injection kidney histology was markedly protected in the ksp^{cre}/$Jagged1^{flox/flox}$ mice. There was marked reduction in inflammatory and profibrotic gene expression in the Jagged1 knock-out mice when compared to littermate controls. *In vitro* co-culture studies indicated that Jagged1 expression induces proliferation and myofibroblastic transdifferentiation of resting fibroblasts.

Conclusions: Excessive Jagged1 activation in tubular epithelial cells stimulates myofibroblast proliferation and activation and leads to kidney fibrosis.

Funding: NIDDK Support

SA-PO197

Pericyte C1q and Complement Activation in Tubulointerstitial Fibrosis

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Background: Increased complement expression and activation occurs in kidney cells during acute kidney injury but little is known about its potential pathogenic role during progressive kidney disease.

Methods: We performed real time-PCR, immunoblots, immunohistochemistry, in situ hybridization and flow analysis in kidney tissue from WT, C1qA and C3 knockout mice subjected to unilateral ureteral obstruction and folic acid injury.

Results: We show that pericytes/myofibroblasts (PDGFβR+ cells) cultured from UUO or mice treated with folic acid secrete C1q without increased C1r/C1s, with increased cytokine and extracellular matrix production and Wnt signaling that are hallmarks of myofibroblast activation. Increased expression of C1q protein in tubulointerstitium space and mRNA expression of C1r/C1s in PDGFβR- cells were observed. Alternative pathway components C3b and C5 were also increased. Flow studies localized C1q to pericytes/myofibroblasts as well as CD11bhi F4/80hi cells and C3b to CD45+ cells in UUO mice. Global deletion of C1qa prevented C1qa secretion, but did not reduce fibrosis or prevent increased expression of C1r/C1s or C3b in whole kidney tissue. In contrast, global deletion of C3 reduced expression of C1r/C1s, resulting in reduced fibrosis. Clodronate-mediated depletion of CD11bhi F4/80hi macrophages in UUO mice resulted in reduced expression of C1r/C1s, C3, C5 and reduced fibrosis.

Conclusions: Our studies highlight the pathogenic role and complexity of complement activation in tubulointerstitial fibrosis. The undesirable activation of classical and alternative complement pathways in specific cell types represents novel therapeutic targets to ameliorate progression of chronic kidney disease.

Funding: NIDDK Support, VA Support

SA-PO198

Redirecting TGF-β Signaling via β-Catenin/Foxo to Prevent Kidney Fibrosis

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Background: Conflicting effects of TGF-β (profibroticversus anti-inflammatory) have caused a challenge in treatment of kidney fibrosis. We propose that inhibition of β-catenin/TCF, the key of factor inTGF-β profibrotic pathways, will increase β-catenin/Foxo and thereby increase TGF-β's anti-inflammatoryeffects via regulatory T cells (iTreg).

Methods: iTregs were examined by flow cytometry analysis of Foxp3 expression, and by T cell fate mapping using Foxp3gfp Ly5.1 & Ly 5.2 mice.ICG-001 was used to inhibit β-catenin/TCF binding. The role of β-catenin/Foxo was investigated in vitro and in mouse unilateral ureteral obstruction (UUO).

Results: Inhibition of β-catenin/TCFincreasedβ-catenin/Foxo and Foxp3 expression, as shown by β-catenin/Foxo binding to Foxp3 promoter in EL-4 cells, and by cell fate mapping in rhTGF-β1-treated Foxp3gfpLy5.2 mice transfused with GFP(-)CD4(+)Ly5.1 T cells[16.92±2.13 *vs.* 13.36±2.56 GFP(+) cells %]. Co-administration of rhTGF-β1 with ICG-001 reduced UUO-induced kidney inflammation, with less infiltration (rhTGF-β1+ICG001 treated group vs. UUO group) of $CD45^+$ cells ($18.61\pm3.90\times10^4$ *vs.* $35.30\pm7.65\times10^4$), CD3 (18.32±4.79 *vs.* 48.96±8.36 cell/HPF) and F4/80 cells (4.20±1.02 *vs.* 14.69±3.65 area %), and in HE staining of infiltrating cells [29.07±6.98 *vs.* 104.89±24.21 cells/10 HP). Kidney fibrosis was also significantly reduced (Gomori trichrome:11.27±2.76 *vs.* 24.64±4.87 area %); Sirius red: (2.34±0.46 *vs.* 4.61±1.07 area %). Fibrosis caused by rhTGF-β1 in distant organs (Liver, Lung) was also prevented.

Conclusions: Targeting β-catenin/Foxo dissociates TGF-β's profibrotic effects from its anti-inflammatory effects, therebyallowing TGF-β to reduce both inflammation and fibrosis.

SA-PO199

The Proteasome Inhibitor Bortezomib Attenuates Renal Fibrosis in Mice

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Background: Renal fibrosis is a common pathologic consequence of various chronic kidney diseases (CKD) with uncertain mechanisms.Recently, a number of studies have shown that the proteasome inhibitor bortezomib attenuated renal impairment in patients with multiple myeloma (MM). We have already reported a case study of a MM patient with severe acute kidney injury, who received long-term bortezomib therapy resulting in a continuous recovery in renal function. This case indicated the possibility that bortezomib might be effective in directly preventing renal interstitial fibrosis. In this study, we investigated the effects of bortezomib to renal injury in a mouse model.

Methods: We investigated the renal effects of bortezomib in aristolochic acid nephropathy (AAN) mice as a renal fibrosis model. Mice were administered aristolochic acid-I with or without bortezomib twice a week for 10 weeks. After the treatment periods, we examined renal functions, expression of renal injury marker proteins, and pathological changes in the kidneys.

Results: In the AAN model, renal fibrosis accompanied with renal dysfunction occurred after the 10-week administration period. Treatment with bortezomib significantly attenuated AAN-induced renal dysfunction (sCre 0.428mg/dl to 0.275mg/dl), albuminurea, and reduced protein expression of renal fibrosis and kidney injury markers such as aSMA, Kim1 and Ngal. Furthermore, bortezomib prevented renal fibrosis pathologically assessed by Masson's trichrome stain. TGF-β1 mRNA expression in the kidney was also reduced in the bortezomib-treatment group.

Conclusions: Bortezomib may have great potential as a drug directly inhibiting renal fibrosis in CKD possibly via reducing TGF-β1 expression.

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SA-PO200

Critical Role of Histone Deacetylase 3 in the Regulation of Inflammation and Renal Fibrosis Yuguo Wang,[1] Yanlin Wang.[1,2] *[1]Medicine, Baylor College of Medicine, Houston, TX; [2]Center for Translational Research on Inflammation Diseases, Michael E. DeBakey VA Medical Center, Houston, TX.*

Background: Inflammation and fibrosis are common features of chronic kidney disease. However, the mechanisms underlying the development of inflammation and fibrosis are not fully understood. In this study, we examined the role of histone deacetylase 3 (HDAC3) in the regulation of inflammation and fibrosis.

Methods: To examine the role of HDAC3 in vivo, we generated mice with inducible deletion of HDAC3 using Cre-LoxP strategy, and we treated wild-type mice with RGFP966, a selective HDAC3 inhibitor. Unilateral ureteral obstruction (UUO) and ischemia-reperfusion injury (IRI) models were used to induce renal fibrosis. Cultured cells were used to examine the role of HDAC3 in the regulation of inflammation and fibroblast activation in vitro.

Results: HDAC3 expression was increased in the kidneys during the development of renal fibrosis. RGFP966 reduced the number of myofibroblasts and total collagen deposition in the kidney and inhibited production of extracellular matrix (ECM) proteins following UUO. Mice with tamoxifen-inducible deletion of HDAC3 (CAG-Cre, floxed HDAC3) were born normal and had no obvious morphological abnormality in the kidney. Compared with Cre negative, floxed HDAC3 mice, mice with tamoxifen-induced deletion of HDAC3 exhibited fewer myofibroblasts and expressed less α-SMA protein in the kidneys following UUO or IRI. Furthermore, inducible deletion of HDAC3 significantly reduced total collagen deposition and ECM protein production in the kidneys in response to UUO or IRI. Real-time RT-PCR showed that pro-inflammatory cytokines were significantly increased after UUO or IRI, which were significantly diminished in HDAC3 deficient mice. In cultured macrophages, HDAC3 deficiency reduced pro-inflammatory cytokine expression after stimulation with LPS or TNF-α. In cultured fibroblasts, deletion of HDAC3 or treatment with RGFP966 attenuated α-SMA and ECM protein expression in response to TGF-β1.

Conclusions: Our study identifies HDAC3 as a critical regulator ofinflammation and fibrosis. Therefore, HDAC3 may represent a novel therapeutic target for chronic kidney disease.

Funding: NIDDK Support, VA Support

SA-PO201

Uromodulin Deficiency Modifies Tubular and Interstitial Cell Responses to Chronic Kidney Injury while Fibrosis Severity Is Not Altered Allison A. Eddy,[1] Olena Maydan,[1] Paul G. McDade,[1] Yan Liu,[2] Xue-Ru Wu.[2] *[1]Pediatrics, Univ of British Columbia; [2]Urology, New York Univ.*

Background: Human GWAS and Mendelian genetic studies have linked polymorphic variants and mutations in the human uromodulin gene (*UMOD*) with chronic kidney disease. The primary function of this unique kidney-specific and secreted protein remains elusive. This study investigated whether the response to unilateral ureteral obstruction (UUO)-induced kidney injury was altered by genetic UMOD deficiency.

Methods: Kidneys harvested from groups of 129SvEv male wild-type (WT) and knockout (KO)mice (n=7-10 each) were studied 7, 14 and 21 days after UUO.

Results: Compared to sham kidneys, UMOD kidney protein levels increased* 9-13x after UUO in the WT mice and were associated with increased urinary UMOD levels. TUBULAR RESPONSES:KIM-1 protein levels were higher* in the KO group at all time-points (4-13x), while NGAL protein levels were increased to similar levels on days 7 and 14, but were 66% lower* on day 21 in the KO group. Ksp-cadherin protein levels were 40-57% lower* in the KO groups. ROMK2, NKCC2 and AQ2 mRNA levels decreased* while TRPV5 mRNA levels were markedly increased* after UUO; only TRPV5 levels differed by UMOD genotype (1.5-7.0x higher* in the WT group). Levels of pro-apoptotic genes (TNFα, FasL) and the epithelial cell apoptotic protein marker M30 (cleaved cytokeratin 18) (day 14 only) were significantly lower in the KO groups. INFLAMMATION. MCP-1 and RANTES mRNA levels and macrophage F4/80 protein levels were all lower* in the KO groups. FIBROSIS. Kidney αSMA levels showed biphasic differences between the genotypes: higher* on day 7, similar on day 14 and lower* on day 21 in the KO groups. Total kidney collagen levels were similar on days 7 (1.4x and 1.6x sham kidney levels), 14 (3.0x and 2.6x) and 21 (3.4x and 3.8x); WT vs KO. * $P<0.05$.

Conclusions: UMOD protein accumulates in the kidney with marked intraluminal precipitation after UUO. In the absence of UMOD, tubular apoptosis and interstitial inflammation are attenuated, yet overall kidney fibrosis severity is unchanged. Elevated KIM-1 levels in the KO mice after UUO were remarkable nd merit further investigation.

Funding: Government Support - Non-U.S.

SA-PO202

Activation of Fibroblast β-Catenin Signaling Contributes to Kidney Fibrosis by Promoting Tubular EMT and Cell Cycle Arrest Dong Zhou, Haiyan Fu, Youhua Liu. *Dept of Pathology, Univ of Pittsburgh School of Medicine, Pittsburgh, PA.*

Background: Activation of Wnt/β-catenin signaling plays a critical role in the pathogenesis and progression of a variety of chronic kidney diseases (CKD). As the principal mediator of canonical Wnt signaling, β-catenin controls the expression of a host of fibrosis-related genes. However, tubule-specific knockout of β-catenin does not affect kidney fibrosis after unilateral ureteral obstruction (UUO), suggesting β-catenin signaling in other cell types may play a predominant role. In this study, we examined the potential role of β-catenin signaling in interstitial fibroblasts in the pathogenesis of kidney fibrosis.

Methods: Mice with fibroblast-specific deletion of β-catenin were generated by mating Gli1-Cre transgenic mice and β-catenin-floxed mice. Mouse models of kidney fibrosis were established by UUO or ischemia/reperfusion injury (IRI). Kidneys were analyzed by Masson's trichrome staining, immunostaining, Western blotting.

Results: Fibroblast-specific ablation of β-catenin markedly reduced renal fibrosis, which was accompanied by reduced epithelial-mesenchymal transition (EMT), characterized by an increased E-cadherin and decreased vimentin, fibroblast specific protein 1 (FSP-1), Snail 1 and α-Smooth muscle actin. In addition, fibroblast-specific deletion of β-catenin in mice inhibited tubular epithelial cell cycle arrest at G2/M with reduced phospho-Histone H3, compared to the controls. Furthermore, less renal infiltration of inflammatory cells such as CD3 positive T cells and F4/80 positive macrophages was found in conditional knockout mice, comparing to controls. We found an increased hepatocyte growth factor (HGF) expression in mice with fibroblast-specific deletion of β-catenin. Similar results were observed in the kidney at 10 days after IRI. In vitro, Wnt ligands inhibited HGF expression in cultured normal rat kidney interstitial fibroblasts (NRK-49F).

Conclusions: These results demonstrate that loss of fibroblast β-catenin attenuates renal fibrosis by inhibiting partial EMT and tubular cell cycle arrest at G2/M, which is likely to be mediated by an increased HGF expression and secretion by interstitial fibroblasts.

Funding: NIDDK Support

SA-PO203

NMDA Receptors-Mediated CaMKII/Erk Pathway Activation Contributes to Renal Fibrosis Jia Shen, Pengpeng Yan, Jingyi Zhou, Rending Wang, Xuelin He, Jianghua Chen. *Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China.*

Background: Renal fibrosis (RF) occurs virtually as a common end point in almost every type of chronic kidney disease. NMDARs, known as key ionotropic glutamate receptors, are widely expressed in the brain and peripheral tissues, and also in kidney. NMDARs are stimulated in acute injured and diabetic kidney, while it is unknown whether NMDARs expression change and participate in the development of the structural and functional degradation in RF.

Methods: Unilateral ureteral obstruction (UUO) model was used to induce RF in male C57BL/6 mice. Lentiviral vector-mediated shRNA interference the functional subunit NR1 expression via retrograde ureteral delivery, and KN93 were used to inhibit CAMKII activation. Fibrosis and the expressions of NMDAR subunit NR1, α-SMA, fibronectin, and S100A4 were evaluated in the obstructed kidneys.

Results: UUO caused up-regulated expressions of NR1, α-SMA, fibronectin, and S100A4. The fibrotic morphology and the expressions of α-SMA, fibronectin, S100A4, CaMKII, and Erk, as well as the activations of CaMKII and Erk were reduced by NR1 knockdown. KN93 significantly suppressed RF as well as the expression and activation of Erk, but not decreased the expression of NR1. KN93 only or combined with NR1 knockdown showed no significant difference on fibrosis severity and Erk activation.

Conclusions: NMDARs participate in the pathogenesis of RF at least partly through CaMKII activated Erk in UUO mice, which could be a potential therapeutic target for Renal fibrosis.

Funding: Government Support - Non-U.S.

SA-PO204

Endoglin Expressed by Myofibroblasts in Patients with Diabetic Nephropathy Correlates with Interstitial Fibrosis and Reduced Renal Function Tessa Gerrits, Malu Zandbergen, Ingeborg M. Bajema, Jan A. Bruijn, Marion Scharpfenecker. *Pathology, Leiden Univ Medical Center, Leiden, Netherlands.*

Background: Diabetic nephropathy (DN) is the leading cause of end stage renal disease (ESRD). Thus far there is no treatment to stop the progression towards ESRD. A common histological change in DN is interstitial fibrosis, which contributes to the development of ESRD and the decline of kidney function. We observed an upregulation of endoglin in the interstitium of patients with DN suggesting that endoglin may be an important regulator of fibrosis. Upregulation of endoglin has also been described in other human fibrotic tissues such as liver, heart and intestine. Therefore, we correlated endoglin expression in the interstitium to other histologic and clinical parameters of diabetic patients. We also characterized the endoglin-expressing cell type in the interstitium.

Methods: Kidney autopsy material of 123 diabetic patients was collected. Sections were stained for endoglin and scored semi-quantitatively. A fibrotic index was determined on Sirius Red stained sections. Immunofluorescent double stainings for endoglin and a-SMA, vimentin, CD31 and CD68 were performed on biopsy material from a patient with and without DN.

Results: A significant correlation was found between the amount of interstitial endoglin expression and kidney fibrosis ($p<0.001$). In addition, endoglin expressed in the interstitium correlated with increased creatinine($p=0.004$), presence of proteinuria ($p=0.009$) and reduced GFR in diabetic patients ($p=0.001$). Immunofluorescence showed co-expression of endoglin with the myofibroblast marker a-SMA, whereas no co-localization with fibroblast (vimentin) or macrophage (CD68) markers was observed.

Conclusions: Endoglin plays a role in the development of fibrosis and progression towards ESRD in DN. Endoglin producing interstitial cells were identified as myofibroblasts. Ongoing studies aim at identifying the role of endoglin in differentiation and ECM production in these cells. Our research shows that Endoglin could be a future therapeutic target for patients with DN.

SA-PO205

MAD2B Promotes Tubular Epithelial-to-Mesenchymal Transition and Renal Tubulointerstitial Fibrosis via Skp2 Chen Ye, Hui Tang, Hua Su, Chun Zhang. *Nephrology, Union Hospital, Tongji Medical College, Huazhong Univ of Science and Technology, Wuhan, Hubei, China.*

Background: The mitotic arrest deficient protein MAD2B is a well-defined anaphase-promoting complex/cyclosome (APC/C) inhibitor and a small subunit of DNA polymerase zeta. It is critical for mitotic control and DNA repair. However, the pathological role of MAD2B in renal fibrosis has not been fully elucidated.

Methods: The objects of this study included patients with renal tubulointerstitial fibrosis (TIF) (secondary glomerulonephritis and interstitial nephritis were excluded), unilateral ureteral obstruction (UUO) mice and in vitro cultured rat proximal tubular epithelial cell line (NRK-52E). In vivo gene silence of MAD2B was carried out by intrarenal lentiviral gene delivery.

Results: By immunofluorescence and immunohistochemistry, we found an obvious MAD2B enhancement in tubular area of TIF patients and UUO mice. In vitro, transforming growth factor-β1 (TGF-β1) induced a time-dependent MAD2B accumulation prior to tubular epithelial-to-mesenchymal transition (EMT) in NRK-52E. Knocking down MAD2B with siRNA dramatically inhibited TGF-β1-induced tubular EMT process and subsequent extracellular matrix (ECM) production. We also found that the expression of Skp2, an APC/C-CDH1 substrate and E-cadherin destroyer, was increased in TGF-β1-treated NRK-52E, which could be suppressed by MAD2B depletion. Consistently, Skp2 expression was increased in renal tubular area of UUO mice. Locally knocking down MAD2B in renal cortex by using lentiviral transfection inhibited Skp2 expression, tubular EMT and subsequent ECM accumulation.

Conclusions: Our data suggests a pro-fibrotic role of MAD2B in the pathogenesis of tubular EMT and TIF by inducing Skp2 expression. MAD2B-Skp2 axis might be a promising target for renal TIF interventions.

Funding: Government Support - Non-U.S.

SA-PO206

The Role of Galectin-3 in the Renal Tubular Epithelial-Mesenchymal Transition Yuchen He, Linlin Qiu, Wenbin Tang, Hui Li, Ping Xiao, Qiaoling Zhou. *Dept of Nephrology, Kidney Inst, Changsha, Hunan, China.*

Background: Galectin-3 is a pleiotropic lectin that plays an important role in cell proliferation, apoptosis, adhesion and inflammatory responses. Recent evidence suggest that Galectin-3 may play a key role in the development of fibrosis, but the pathogenesis is still unclear. The Objective of this study is to observe the role of Galectin-3 in the renal tubular epithelial-mesenchymal transition and renal fibrosis.

Methods: In vivo, the model of renal fibrosis was induced by unilateral ureteral obstructive in Sprague Dawley rats. HE and Masson staining was used to evaluate the level of renal tissue fibrosis. The location and expression of Galectin-3, E-cadherin and α-SMA in renal tissue were tested by immunohistochemistry. In vitro, NRK-52E cells were treated with Ang-II or high glucose for different time. Furthermore, Galectin-3 was inhibited by modified citrus pectin(MCP) .The expressions of Galectin-3, E-cadherin, α-SMA were detected by Realtime-PCR and Western blot.

Results: In vivo, compared with the sham group rats, more severe tubular dilation, interstitial fibrosis and inflammatory cells infiltration were noted in UUO model rats. E-cadherin was downregulated and α-SMA was upregulated significantly especially in renal tubular cells. Meanwhile, the expression of Galectin-3 was upregulated in UUO model rats. In vitro, expressions of Galectin-3 and α-SMA increased remarkably in NRK-52E cells induced by angiotesin II or high glucose in a time-dependent manner compare with the control, however expression of E-cadherin reduced remarkably. The expression of Galectin-3 was negatively correlated with E-cadherin, but positively correlated with α-SMA. When Galectin-3 inhibitor MCP were used in NRK-52E cell stimulated by high glucose, α-SMA expression was significantly increased, E-cadherin expression was significantly reduced.

Conclusions: Galectin-3 was upregulated during the process of renal tubular EMT. Galectin-3 inhibitor MCP can promote EMT in renal tubular epithelial cells induced by high glucose. In view of these findings it is conceivable that Galectin-3 may serve as a potential novel target in pre-EMT states for the amelioration renal fibrosis seen in CKD.

Funding: Government Support - Non-U.S.

SA-PO207

Apoptosis Signal-Regulating Kinase 1 (ASK1) Inhibitor GS-4997 Decreases Tubulointerstitial Fibrosis in a Rat Model of Ureteral Obstruction John T. Liles, Saili Yi, Swetha Vandana Pendem, David G. Breckenridge. *Gilead Sciences, Inc., Foster City.*

Background: GS-4997 is a potent and selective ASK1 inhibitor that is currently in clinical development for the treatment of Diabetic Kidney Disease (DKD). ASK1 is a critical signaling node through which oxidative stress promotes inflammation, apoptosis, and fibrosis via downstream activation of the MAPK kinases p38 and c-Jun N terminal kinase (JNK). This study evaluated the pharmacodynamics and efficacy of GS-4997 in a rodent model of renal tubulointerstitial fibrosis, which is a final common pathway for progressive kidney diseases such as DKD.

Methods: Male Sprague-Dawley rats were subjected to unilateral ureteral obstruction (UUO) surgery(n=10/group) or sham surgery (n=6) and were orally administered GS-4997 (1, 3, 10 or30 mg/kg, BID) or vehicle for 7 days. Fibrosis was assessed by immunohistochemistry for collagen IV and alpha-smooth muscle actin (a-SMA) quantified using ImageScope software (Aperio).Collagen IV protein was also quantified in kidney cortex lysates by ELISA. ASK1 pathway activation was assessed by western blot and/or ELISA for phosphorylated ASK1 (p-ASK1), p-38 (p-p38) and JNK (p-JNK).

Results: ASK1 pathway activation was significantly increased in UUO kidneys compared to sham (15 ± 4 vs 1 ± 0.06, p-ASK1/IP90; 6 ± 2 vs 1 ± 0.01, p-p38/IP90; and 2 ± 0.2 vs 1 ± 0.02 p-JNK/IP90; $p<0.01$ for all groups), and was decreased by GS-4997 in a dose-dependent manner back to sham control levels. Increased immunostaining for interstitial collagen IV and αSMA positive myofibroblasts detected in UUO kidneys was reduced by GS-4997. In addition, collagen IV protein levels in kidney lysates was increased in UUO compared to sham (2.68 ± 0.2 vs 0.9 ± 0.1 mg/mg, $p<0.05$), and treatment with the ASK1 inhibitor GS-4997significantly decreased renal collagen IV protein levels (2 ± 0.3, 1.4 ± 0.07, and 1.6 ± 0.09 g/mg for the 3, 10, 30 mg/kg doses, respectively, $p<0.05$ for all groups).

Conclusions: GS-4997 inhibits ASK1 pathway activation and ameliorates renal fibrosis in the obstructed kidney. These data support the investigation of GS-4997 as a therapyto reduce renal fibrosis and halt progression in kidney diseases such as DKD.

Funding: Pharmaceutical Company Support - Gilead Sciences, Inc.

SA-PO208

Tight Junction Dysfunction in Proximal Tubular Cells Is Prohibited by Activation of the HSP72-Klotho Axis Jen Xu,[1] Frank Xu,[1] Li-Lun Ho,[1] Huixia Cao,[1] Kenneth Lim,[2] Tianqing Kong,[1] Tzongshi Lu.[1] *[1]Renal Div, Brigham and Women's Hospital, Boston, MA; [2]Nephrology Div, Massachusetts General Hospital, Boston, MA.*

Background: Tight junctions (TJ) are specialized membrane domains that play multiple functions in kidney epithelial cells, including the maintenance of cellular polarity and work as a primary regulatory barrier. Studies indicate emerging links between TJ dysfunction and the development of kidney disease, particularly in autosomal dominant polycystic kidney disease (ADPKD) and ischemic acute renal failure. Klotho is a transmembrane protein that has been shown to exert anti-aging properties and its deficiency is involved in the development of renal failure. Heat shock proteins (HSPs) are universally expressed and their induction by a variety of stressors in organisms and cultured cells has been shown to be involved in the maintenance of cellular integrity and normal physiological functions. In this study, we describe a HSP72-Klotho axis and its role in preventing renal fibrosis and cystogenesis in ADPKD, through the regulation of TJs.

Methods: Madin-Darby canine kidney (MDCK) Tet-off inducible Gα12 and Gα12QL cell lines, HK2 cells were used to generate a ADPKD and fibrosis *in vitro* model, respectively. Sprague Dawley rats were used in an ischemia-reperfusion animal model. Heat shock proteins were induced by heat shock treatment (HST) at 43 °C for 30 minutes.

Results: Klotho expression was decreased in ADPKD and HK2 cells, however was preserved by HST. This was associated with the preservation of TJ proteins Occludin and Claudin-5. We also found that matrix metalloproteinase-2 (MMP2) and A Disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) were significantly increased in ADPKD cells and fibrotic kidney tissues. This was associated with significantly decreased Klotho expression. However, HSP72 was induced by HST and this resulted in partial reversal of ADAM10 and MMP2 changes with an increase in Klotho expression and forms a HSP72-Klotho complex.

Conclusions: Our data describes a potential HSP72-Klotho axis in the stabilization of TJ proteins. Further investigation into the molecular mechanisms and clinical application are needed.

Funding: Private Foundation Support

SA-PO209

Trimethylamine-N-Oxyde (TMAO) Plasma Accumulates in Uremic Mice and Promotes the Progression of Kidney Fibrosis Caroline C. Pelletier,[1,2] Maud Rabeyrin,[1] Mikael Croyal,[3] Michel Krempf,[3] Laurent Juillard,[1,2] Christophe O. Soulage.[2] *[1]Nephrology, Hospices Civils de Lyon, France; [2]Univ Lyon, INSA-Lyon, INSERM U1060, CarMeN Lab, France; [3]INRA, UMR 1280, CRNH, Mass Spectrometry Area, Nantes, France.*

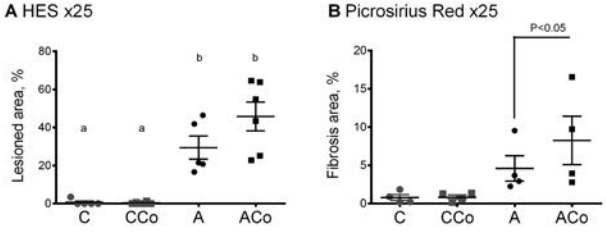
Background: TMAO was recently associated with poor cardiovascular outcomes in the general population and was described to accumulate in patients with chronic kidney disease (CKD). Some recent studies have suggested that the accumulation of TMAO could contribute to renal function.

Methods: TMAO was assayed in 18 control and 18 CKD mice, induced by 3 weeks of an adenin rich diet (0.25%w/w). In each group, half of the mice were then fed for 3 additional weeks with a 1% (w/w) choline-enriched diet to promote the production of TMAO.

Results: TMAO level is significantly increased in control mice after a choline supplementation, to the TMAO level of the CKD mice. TMAO concentration is 10-folds higher in CKD mice fed with choline-enriched diet.

Characteristics of control and CKD mice, with or without enriched choline food					
	Control		CKD		P-value
	Standard food	Enriched Choline food	Standard food	Enriched Choline food	
	C	CCo	A	ACo	
Kidneys, mg	298±28	300±42	150±11	125±10	****
24h-Diuresis, ml	0.74±0.18	0.11±0.06	2.84±1.91	2.48±0.39	****
Plasma urea, mg/dL	57.6±6.6	57.5±11.2	163.3±14.4	145.3±25.5	****
Proteinuria, mg/24h	-	0.08±0.03	1.71±1.45	0.79±0.48	**
TMAO µM	5.8±1.1	39.1±12.1	31.8±5.6	424.8±71.0	****
Means were compared with ANOVA test and sgnificant p was <0.05					

Supplementation decreased the survival of CKD mice (-33%, P<0.05) and promotes renal fibrosis assessed by 2 different histopathology techniques (HES and picro sirius red satinings).



Conclusions: Plasma TMAO accumulates in CKD mice. Higher plasma TMAO level in mices triggers an expansion of renal parenchyma fibrosis.

Funding: Clinical Revenue Support

SA-PO210

The Role of Flavin Monooxygenase 3 in Renal Fibrosis Jing Xu, Lei Jiang, Junwei Yang. *Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Renal proximal tubular cells (PTCs) have been recognized as one of the important contributors to renal fibrosis. Prior studies reported that trimethylamine-N-oxide (TMAO) is elevated in subjects with impaired renal function, and it contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. Since flavin monooxygenase (FMO) family members, especially FMO3 exhibit the highest activity in TMAO metabolism, deciphering the role and mechanisms for FMO3 in renal fibrosis are very necessary.

Methods: In this study, we employed mice with unilateral ureter obstruction (UUO) and TGFβ1-treated NRK-52E cells/primary PTCs as two model systems. FMO3 plasmid was injected one day before UUO surgery. Cells were transfected with FMO3 plasmid or siRNA to downregulate FMO3 expression and FMO3 activity was decreased by using methimazole.

Results: Here, western blot analysis and immunofluorescence staining confirmed that FMO3 expression was decreased in kidney from UUO and folic acid induced renal fibrosis mouse model. Then, we observed that both NRK-52E and primary proximal tubular cells transfected with plasmid or siRNA exhibit higher expression of fibronectin (FN), α-smooth muscle actin (α-SMA), Type1 collagen (COL I) compared with control. In line with this, cells treated with FMO3 activity inhibitor methimazole revealed similar results. Furthermore, 6-8 weeks old mice were injected with FMO3 plasmia via tail vein one day before UUO surgery. We found both gene and protein assay showed that the levels of FMO3 was downregulated in mouse kidneys with plasmia injection and mice that downregulated of FMO3 developed more serious kidney fibrosis in terms of higher expression of FN, α-SMA, COL I. Similar results were found in mice intragastric administration of methimazole. In addition, the mechanisms of FMO3 affect the development of renal fibrosis may through apoptotic pathway.

Conclusions: These results demonstrated that decreased activity or expression of FMO3 is critical for the development of renal fibrosis. Drugs that could specifically target FMO3 may attenuate renal fibrosis and need further research.

Funding: Government Support - Non-U.S.

SA-PO211

The MRTF/TAZ Pathway Is a Critical Inducer of the Profibrotic Epithelial Phenotype Andras Kapus,[1] Maria Zena Miranda,[1] Janne Folke Bialik,[1,2] Pamela Speight,[1] Qinghong Dan,[1] Stine Falsig Pedersen,[2] Katalin Szaszi.[1] *[1]Keenan Research Centre, St. Michael Hospital, Toronto, ON, Canada; [2]Cell Biology, Univ of Copengagen, Copenhagen, ON, Canada.*

Background: The Hippo effector TAZ and the Rho/actin-regulated myocardin-related transcription factor (MRTF) are TGFβ- and mechanosensitive transcriptional coactivators with key roles in the pathogenesis of organ fibrosis. We have shown that MRTF and TAZ exhibit crosstalk and both are critical for epithelial-myofibroblast (MF) transition (EMyT). Although *in vivo* the epithelium is a minor source of MFs, it is a key driver of fibrosis via a profibrotic epithelial phenotype (PEP) shift, hallmarked by the secretion of fibrogenic cytokines. We thus hypothesized that TAZ and MRTF mediate not only EMyT but also PEP and fibroblast-MF transition. Further, our recent data suggest that TAZ is regulated also at the level of its expression. Thus, we aimed to 1) characterize the effect of fibrogenic stimuli on TAZ expression and define the underlying mechanisms and 2) assess the role of MRTF and TAZ in PEP.

Methods: For in vitro studies 10T1/2 fibroblasts or LLC-PK1 proximal tubular cells were exposed to fibrogenic stimuli (TGFβ or cyclic stretch) with/without interfering with MRTF or TAZ. To detect PEP in vivo, renal fibrosis was induced in mice by unilateral ureteral obstruction (UUO), the tubular compartment was isolated by laser capture microdissection and analyzed.

Results: TGFβ induced a rapid and robust increase in TAZ mRNA and protein both in fibroblasts and tubular cells via a Smad3-indpendent, p38- and Akt-mediated process. These pathways converged on MRTF. Pharmacologic (CCG1423) or siRNA-mediated MRTF inhibition prevented the TGFβ-induced rise in TAZ, while MRTF overexpression induced TAZ expression and promoter activation. UUO concomitantly increased *tubular* TAZ mRNA and tubular TGFβ, PDGF, CTGF and Indian Hedgehog (IHH) mRNA levels. Stretch increased mRNAs for TGFβ, CTGF, IHH, and PDGF in LLC-PK1 cells, and these effects were suppressed by pharmacological (verteporfin for TAZ, CCG1423 for MRTF) or siRNA-mediated inhibition of TAZ or MRTF.

Conclusions: MRTF controls TAZ expression both in fibroblasts and epithelial cells, and both MRTF and TAZ are essential mediators of PEP.

Funding: Government Support - Non-U.S.

SA-PO212

PP242 Inhibits Fibroblast Activation and Kidney Fibrosis in Mice with Unilateral Ureter Obstructive Nephropathy Jianzhong Li, Chunsun Dai. *Nanjing Medical Univ.*

Background: PP242, an mTOR kinase inhibitor, caninhibit both mTORC1 and mTORC2 signaling pathways in many types of cell. Regarding the profibrotic role for mTORC1 and mTORC2 in kidney diseases, it is highly possible that blockade of mTOR signaling with PP242 may diminish fibroblast activation and kidney fibrosis.

Methods: In this study, NRK-49F cells, a rat kidney interstitial fibroblast cell line, were stimulated with TGFβ1. Unilateral ureter obstruction (UUO) was used to induce kidney fibrosis in mice.

Results: In cultured NRK-49F cells, TGFβ1 treatment could activate both mTORC1 and mTORC2 signaling in cultured NRK-49F cells at a time dependent manner, while administration of PP242 could dose dependently inhibit TGFβ1-induced mTORC1 and mTORC2 signaling activation. Additionally, PP242 could also dose dependently reduce TGFβ1-induced α-SMA and fibronectin expression in NRK-49F cells. In mice with UUO nephropathy, PP242 administration could markedly diminish total collagen deposition, fibronectin and α-SMA expression in the fibrotic kidneys with UUO nephropathy compared to those treated with vehicle.

Conclusions: In summary, these results suggest that PP242 may act as a new therapeutic reagent for fibrotic kidneys through inhibiting both mTORC1 and mTORC2 signaling pathways.

Funding: Government Support - Non-U.S.

SA-PO213

Wnts Promote Fibroblast Activation and Kidney Fibrosis Involving Smad Signaling Lei Jiang, Qi Sun. *Nanjing Medical Univ.*

Background: Wnts are divided into canonical and non-canonical subgroups relying on whether it can activate b-catenin or not.

Results: In this study, we found that several Wnt family members including Wnt3a, Wnt5a and Wnt5b but not Wnt4, Wnt9b or Wnt11 could markedly induce smad3 phosphorylation in many types of kidney cell including podocyte, NRK-49F cell and HKC. In addition, Wnt3a, Wnt5a and Wnt5b but not Wnt4, Wnt9b or Wnt11 could stimulate a-SMA and fibronectin expression in NRK-49F cells. Blockade of smad3 signaling with smad3 siRNA or SIS3 could largely abolish Wnt3a, Wnt5a and Wnt5b induced a-SMA expression, suggesting an indispensible role for smad3 signaling activation in such Wnts-induced fibroblast activation. Co-immunoprecipitation as well as co-immunostaining analysis demonstrated the co-localization of Wnt3a and type I receptor of TGFb1 in NRK-49F cells. Blockade of type I receptor of TGFb1 with siRNA or SB43152 could almost completely abolish Wnts-induced a-SMA and fibronectin expression. In mouse model with kidney fibrosis after UUO or IRI, Wnt5b expression was induced in kidney tissue and ectopic expression of exogenous Wnt5b could induce smad3 phosphorylation and mild kidney interstitial fibrosis in mice.

Conclusions: Together, this study indicates that smad3 phosphorylation mediates Wnt3a, Wnt5a and Wnt5b stimulated extracellular matrix production in kidney cells, which may be a novel mechanism for Wnts in promoting kidney fibrosis.

Funding: Government Support - Non-U.S.

SA-PO214

Omega-3 Polyunsaturated Fatty Acids Ameliorate Fibroblast Activation and Kidney Fibrosis Involving Suppression of mTOR Signaling Pathway Zhifeng Zeng, Chunsun Dai. *Nanjing Medical Univ, Nanjing.*

Background: Epidemiologic studies have shown the correlation between the deficiency in omega-3 polyunsaturated fatty acids (PUFAs) and the progression of chronic kidney diseases (CKD), however, the role for omega-3 PUFAs in protecting against kidney fibrosis in CKD and the underlying mechanisms remains obscure.

Results: Here, NRK-49F cells, a rat kidney interstitial fibroblast cell line, were stimulated with TGFb1. DHA, one member of omega-3 PUFAs family, couldremarkably suppress TGFb1-induced fibroblast activation at a dose dependent manner. In addition, DHA could markedly reduce TGFb1 up-regulated p-Akt (Ser473), p-Akt (Thr308) but not p-S6 or p-smad3 abundance in NRK-49F cells. To further decipher the role for omega-3 PUFAs in protecting against kidney fibrosis, we deployed transgenic mouse model capable of endogenously producing omega-3 PUFAs while reducing omega-6 PUFAs owing to the expression of a Caenorhabditis elegans fat-1 gene encoding an omega-3 fatty acid desaturase. The mice were operated with unilateral ureter obstruction (UUO) to induce kidney fibrosis. Compared to the wild type mice, fat-1 transgenics developed much less kidney fibrosis and inflammatory cell accumulation accompanied by less p-Akt (Ser473), p-Akt (Thr308), p-S6 or p-smad3 in kidney tissue at day 7 after UUO.

Conclusions: Thus, omega-3 PUFAs strongly attenuate fibroblast activation and kidney fibrosis and may provide a therapeutic strategy for retarding the progression of chronic kidney diseases.

Funding: Government Support - Non-U.S.

SA-PO215

Dznep Ameliorates Tubulointerstitial Fibrosis via Reduction of TIMP2

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Background: Tubulointerstitial fibrosis has been recently reported to be caused by the collapse of epigenetic regulations for kidney diseases. We examined whether one of inhibitors for histone modifications is effective against renal fibrosis. Dznep (3-deazaneplanocin A) is originally developed as an anti-cancer drug to delete repressive histone mark, H3K27me3. We found that Dznep contributes to the reduction of tubulointerstitial fibrosis. The aim of our study is clarifying the epigenetic mechanisms of ameliorating renal fibrosis using genome-wide analysis of mRNA and microRNA.

Methods: Although ischemia reperfusion injury model is well known to cause acute kidney injury, we have found that the unilateral ischemia reperfusion model also leads to chronic tubulointerstitial fibrosis after two months. We administered Dznep to these model mice for 8 weeks intravenously. Because epigenetic regulation is specific to the cell species, we need to focus only on the tubular cells. Therefore we picked up only tubular cells from *in vivo* samples using laser captured microdissection. We examined the level of mRNA and microRNA in tubular cells using high throughput sequencers (RNA-seq) to identify novel epigenetic factors associated with renal fibrosis. We also performed RNA-seq using *in vitro* samples of renal proximal tubular cell lines with the stimuli of hypoxia and Dznep.

Results: We analysed the results of RNA-seq and found that TIMP2 (tissue inhibitor of metalloproteinase 2) is suppressed with Dznep both *in vivo* and *in vitro* samples. TIMP2 is reported to be associated with promoting fibrosis. In addition, we identified the novel microRNAs which target TIMP2. The novel microRNAs have possibility of inhibiting the gene expression of TIMP2, leading to reducing renal fibrosis.

Conclusions: We found the novel epigenetic molecular mechanisms showing the inhibition of TIMP2 via microRNAs might contribute to reducing renal fibrosis.

Funding: Government Support - Non-U.S.

SA-PO216

Angiopoietin-1 Deficiency Increases Tubulointerstitial Fibrosis

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Background: Renal tubulointerstitial fibrosis is predictive of progressive decline in kidney function, independent of underlying disease. It is characterized by an increase in aSMA+ fibroblasts, myofibroblasts, that produce collagen. Identification of factors that regulate the fibrotic response are excellent candidate targets for treatment of kidney diseases. We previously showed that loss of Angiopoietin-1 (Angpt1) in adult mice predisposes to fibrosis in wound healing and diabetic nephropathy. Angpt1 acts through the Tie2 tyrosine-kinase receptor expressed on endothelial cells. Here, we test the hypothesis that loss of Angpt1-Tie2 signaling results in an increased fibrotic response in kidney fibrosis.

Methods: We first performed lineage tagging experiments using Tie2-Cre to better understand if cells using Angpt1-Tie2 signaling could contribute to the myofibroblast population in kidney fibrosis. FACS was used to isolate the tagged cells and to study gene regulation of myofibroblast markers. To study the role of Angpt1 in renal fibrosis we utilized Angpt1 conditional knockout mice in the unilateral ureter obstruction (UUO) model of kidney fibrosis.

Results: The Tie2-lineage contributed to almost 20% of myofibroblasts 10 days after UUO. I addition, there was a significant ($p<0.001$) upregulation of Tgfb and Fibronectin-1 gene expression in FACS sorted lineage tagged cells after UUO, suggesting that part of this population have become myofibroblasts. Angpt1 deficient mice showed a significant ($p<0.05$) increase in SMA+ area 3 days after UUO as well as an increase in the expression of Fibronectin-1 ($p<0.01$), Tgfb ($p=0.023$) and Kim-1 ($p=0.06$).

Conclusions: Our results suggest that loss of Angpt1-Tie2 signaling increases tubulointerstitial fibrosis as seen by the increased expression of fibrosis markers in Angpt1 deficient mice. Ongoing work is designed to use other models of fibrosis and to elucidate the mechanism(s).

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SA-PO217

MicroRNA Fine-Tuning of Endothelial Dysfunction and Prevention of Fibrosis by miR127-Complementary Locked Nucleic Acid Oligonucleotides

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Background: Endothelial cells (EC), especially SIRT1-deficient, subjected to TGFβ develop premature senescence. It has been demonstrated previously that microRNAs (miR) are causally involved in induction of cell senescence and dysfunction, which in turn generates pro-fibrogenic secretome.

Methods: For this reason we performed profiling miRs in EC isolated from control and SIRT1-/- mice renal microvasculature. The samples were labeled using the miRCURY LNA™ microRNA Hi-Power Labeling Kit, Hy3™/Hy5™ and hybridized on the miRCURY LNA™ microRNA Array (7th Gen, Exiqon), following a dual-color experimental design. The microRNA profiling performed on the miRCURY™ LNA array identified microRNAs that have a log fold change > than 1. We have contrasted miR profile of wild-type and endothelial SIRT1-/- EC under basal and TGFβ-stimulated conditions.

Results: Notably, the known TGFβ-induced miRs -145a, -379 and -143 were present in both screens of EC, a proof of technical validity. Among differentially displayed (at least a log-difference) signatures of control and endothelial SIRT1-/- EC stimulated by TGFβ, miR-127 3p increased by 1.6 log FC. miR-410 3p, also identified as a downstream target of p16(INK4a) pathway (induced in cell senescence) and shown to reduce the expression of VEGF, was also upregulated. To gain insight into the in vivo role of elevated miR-127 and miR-410, complementary locked nucleic acid (LNA) oligonucleotides and respective scrambled controls were synthesized. Experiments were performed in 10-12 week-old α-SMA-GFP mice subjected to UUO. We treated UUO mice with LNA complementary to miR-127 3p and miR-410 3p. We observed no deleterious effects of LNA in FVBmice. The degree of fibrosis of UUO kidneys was significantly reduced in mice that received complementary LNA to miR-127 compared to scrambled LNA-treated mice. Mice receiving LNA to miR-410 showed a moderate reduction in fibrosis.

Conclusions: These studies demonstrate that complementary 127 3p LNA-induced amelioration of endothelial dysfunction leads to the concomitant reduction of renal fibrosis, thus establishing it as a valid therapeutic target.

Funding: NIDDK Support

SA-PO218

Galunisertib Is a Promising Drug Candidate for the Treatment of Renal Fibrosis in Ex Vivo Tissue Slice Cultures

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Background: Galunisertib (Galu) is an inhibitor of the TGFβR1 kinase and is currently tested in clinical trials as an anticancer drug. Galu could be a potential candidate for the treatment of fibrosis. Our objective was to investigate the effects of Galu on the early and end stages of fibrosis using precision-cut mouse and human kidney slices (PCKS).

Methods: PCKS were prepared from healthy and diseased mouse and human kidneys and incubated for 48 hours in the presence of 10 μM Galu, a non-toxic concentration. Unilateral ureteral obstruction (UUO) for 7 days was used to induce renal fibrosis in mice. Gene expression of key fibrosis markers, such as procollagen α1(I) (*Col1α1*), α-smooth muscle actin (*αSMA*), heat shock protein 47 (*Hsp47*) and fibronectin (*Fn*), was determined by qPCR.

Results: Incubation of healthy PCKS resulted in the early onset of fibrosis, as demonstrated by an up-regulation of the fibrosis markers in mouse (*Col1α1* 8.6 fold; *HSP47* 5.0 fold; *Fn* 176.7 fold) and human (*Col1α1* 2.8 fold). The fibrosis markers were even further increased in fibrotic PCTS prepared from UUO vs control mice (*Col1α1* 1.4 fold, *HSP47* 1.5 fold and *Fn* 4.7 fold). Galu inhibited gene expression of fibrosis markers in healthy mouse PCKS (*Col1α1* by 97%; *αSMA* by 89%; *HSP47* by 51%; *Fn* by 99%) and in PCKS prepared from UUO mice (*Col1α1* by 87%; *αSMA* by 63%; *HSP47* by 48%; *Fn* by 83%). In healthy human PCKS Galu inhibited gene expression of *Col1α1* (by 70%) and *Fn* (62%). The pilot experiment with fibrotic human PCKS indicated a similar trend (*Col1α1* was inhibited by 90%; *HSP47* by 58%; *Fn* by 76%).

Conclusions: Galu exhibits strong antifibrotic activity in the early and the end stage of fibrosis in mouse and human PCKS. The PCKS technique is a promising model to test antifibrotic agents both in rodent and human tissues, considering the latter as a bridge to clinical studies.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim, Government Support - Non-U.S.

SA-PO219

The DNA Damage Response Protein, Breast Cancer Factor 1 (BRCA1) Induces Interstitial Fibrosis Through Cell Cycle Arrest following Tubular Injury Akinwande A. Akinfolarin, Venkata Sabbisetti, Amrendra Kumar Ajay, Sarah J. Hill, Joseph V. Bonventre. *Nephrology, Brigham and Woman's Hospital, Boston, MA.*

Background: Repetitive tubular injury leads to chronic fibrotic kidney disease. Chemical, ischemic and obstructive kidney injuries lead to double strand DNA breaks (DSB), triggering the DNA damage response. *BRCA1* is a breast tumor suppressor gene with a role in homologous recombination (HR) and maintenance of genome integrity by DNA repair. Here we deplete BRCA1 in the adult mouse proximal tubule (PT) to examine its effect on development of interstitial fibrosis.

Methods: SLC34A1 Cre mice were crossed to mice with a floxed *BRCA1* allele yielding models of PT *BRCA1* gene deletion. After Tamoxifen-induced Cre induction, we subjected mice to bilateral ischemia/reperfusion (I/R), unilateral ureteric obstruction (UUO), or aristolochic acid (AA)-induced injury. Kidney extracts were evaluated by western blot, real time PCR and Masson's trichrome (MT) and Pico Sirius Red (PS) staining of kidney tissue for markers of interstitial fibrosis. Markers of DNA damage, cell cycle arrest and senescence were examined by immunofluorescence. PT cells were isolated from mice and treated with AA to explore the relationship between injury and cell cycle stage, apoptosis and senescence.

Results: Heterozygosity was associated with a reduction in PT *BRCA1* mRNA by in situ hybridization. There was reduced kidney interstitial fibrosis in mice heterozygous for PT *BRCA1* deletion compared to WT littermate controls by MT and PS staining after I/R and AA. PCR analysis of whole kidney cortex revealed reduction in fibrogenic factors such as CTGF, COL4A1, fibronectin and ACTA2. There was also a reduction in markers of G2 cell cycle arrest and senescence although markers of apoptosis were increased in heterozygous mice compared to WT. These murine data are supported by in vitro experiments with AA after depleting BRCA1 in PT cells which secreted fewer fibrogenic factors.

Conclusions: BRCA1 facilitates interstitial fibrosis following kidney tubular injury in mice through its role in DNA damage response.

Funding: NIDDK Support

SA-PO220

Metanephric Mesenchymal Cells Can Inhibit and Partially Reverse Epithelial to Mesenchymal Transition of Renal Tubular Epithelial Cells Yuansheng Xie,[1] Pengfei He,[1,2] Kai Wei,[1,2] Bo Fu,[1] Shaoyuan Cui,[1] Xiang-Mei Chen.[1] *[1]Dept of Nephrology, Chinese PLA General Hospital, Chinese PLA Inst of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing, China; [2]Medical College, NanKai Univ, Tianjin, China.*

Background: The epithelial-to-mesenchymal transition (EMT) of renal tubules is one of the main pathogenesis of renal interstitial fibrosis. In this study, we investigated the effects of metanephric mesenchymal cells (MMCs) on the EMT of renal tubular epithelial cells in order to provide new therapeutic strategies for renal interstitial fibrosis.

Methods: MMCs were extracted from the renal cortex of fetal pig 70 days after pregnancy. Transforming growth factor-β1 (TGF-β1) was used to induce EMT of a pig proximal tubular epithelial cell line (LLC-PK1). Transwell chambers were applied to co-culture MMCs with LLC-PK1. Light microscope,immunofluorescence confocal microscopy and western blotting were used to identify the MMCs and detect the phenotypic changes of LLC-PK1.

Results: The primary MMCs were spindle-shaped, positive for six2 and vimentin, and negative for cytokeratin-18 and e-cadherin. 10ng/ml TGF-β1 could induce the EMT of LLC-PK1 manifested as a change of pebble shaped epithelial cells into spindle-shaped fibroblast-like cells, down-regulation of e-cadherin and up-regulation of vimentin and α-SMA. Co-cultured MMCs with LLC-PK1 when administrated with TGF-β1 significantly inhibited EMT of LLC-PK1. Co-cultured MMCs with LLC-PK1 after incubation of TGF-β1 for 48h obviously ameliorated the extent of EMT, but this effect disappeared when the incubation time extended to 72h. Furthermore, MMCs could also inhibit TGF-β1 induced activation of β-catenin/ZEB1 signaling pathway, which indicated that this signaling pathway might involve in the inhibition and reverse of EMT.

Conclusions: Pig MMCs can inhibit and partially reverse TGF-β1 induced EMT of renal tubular epithelial cells, and β-catenin/ZEB1 signaling pathway may involve in the above processes. Our results may provide a new idea for the early intervention of renal interstitial fibrosis.

Funding: Government Support - Non-U.S.

SA-PO221

Inhibition of BET Family Proteins as a Potential Epigenetics-Based Therapy for Renal Fibrosis Chongxiang Xiong, Monica V. Masucci, Xiaoxu Zhou, Shougang Zhuang. *Dept of Medicine, Rhode Island Hospital, Brown Univ, Providence, RI.*

Background: Bromodomain and extra-terminal (BET) protein inhibitors have been shown to effectively inhibit tumorgenesis by directly targeting bromodomain proteins that bind acetylated chromatin markers. However, its role in renal fibrogenesis remains to be explored.

Methods: In this study, we studied the role of BET in the activation of cultured renal interstitial fibroblasts and development of renal fibrosis in a murine model of unilateral ureteral obstruction as well as mechanisms involved.

Results: Our results show that in cultured renal interstitial fibroblasts, exposure of cells to I-BET151, or silencing of bromodomain-containing protein 4 (Brd4), a key BET protein isoform, significantly reduced their activation as indicated by decreased expression ofa-smooth muscle actin, collagen 1 and fibronectin. In a murine model of renal fibrosis induced by unilateral ureteral obstruction (UUO), administration of I-BET151 suppressed renal fibroblast activation, fibrotic fibril deposition, and macrophage infiltration. Mechanistically, I-BET151 treatment abrogated UUO-induced phosphorylation of epidermal growth factor receptor and platelet derived growth factor receptor. It also inhibited the activation of Smad-3, STAT3 and NF-κB pathways, as well as the expression of c-Myc and P53 transcriptional factors in the kidney. Moreover, BET inhibition resulted in reduction of renal epithelial cells arrested at G2/M phase of cell cycle after UUO injury. Finally, injury to the kidney increased Brd4 expression and Brd4 was also highly expressed in human fibrotic kidneys.

Conclusions: These data indicate that BET proteins are implicated in the regulation of molecular and cellular machinery associated with renal fibrogenesis, and suggest that targeting BET proteins could be a potential epigenetics-based therapy for renal fibrosis.

Funding: NIDDK Support

SA-PO222

Nintedanib, a Triple Tyrosine Kinase Inhibitor, Inhibits Fibroblast Activation and Ameliorates Renal Fibrosis in Chronic Kidney Disease Feng Liu, Li Wang, Yi Wang, Shougang Zhuang. *Dept of Nephrology, Shanghai East Hospital Tongji Univ, Shanghai, China.*

Background: Nintedanib (BIBF1120) is a triple kinase inhibitor of platelet derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR) and vascular endothelial growth factor receptor (VEGFR) that has recently been approved by FDA to treat idiopathic pulmonary fibrosis. However, its efficacy in renal fibrosis remains unknown.

Methods: In this study, we evaluated the anti-fibrotic effect of nintedanib in a murine model of renal fibrosis induced by unilateral ureteral obstruction (UUO).

Results: Administration of nintedanib immediately or 3 days after UUO injury attenuated renal fibrosis and inhibited activation of renal interstitial fibroblasts and expression of two extracellular matrix proteins, fibronectin and type I collagen. Delayed administration of nintedanib also partially reversed established renal fibrosis. Injury to the kidney induced phosphorylation of PDGFRb, FGFR1 and VEGFR2 as well as activation of several intracellular signaling molecules associated with renal fibrosis, including signal transducer and activator of transcription-3, nuclear factor-κB and Smad-3 in the kidney. Treatment with nintedanib blocked all these responses. In cultured renal interstitial fibroblasts, nintedanib abrogated transforming growth factor β1-induced activation of renal fibroblasts and phosphorylation of Smad3.

Conclusions: These data indicate that nintedanib is a potent anti-fibrotic agent in the kidney and may hold therapeutic potential as a treatment of chronic fibrotic kidney disease.

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SA-PO223

Jak-Stat Pathway Inhibition Attenuates UUO-Induced Renal Fibrosis in Rats Damian C. Matera, Glenn Gibson, Mark Mchugh, R. Paul Fracasso, James W. Tanner, Hu Sheng Qian, Glenn A. Reinhart, Steven M. Weldon. *CardioMetabolic Diseases Research, Boehringer Ingelheim, Ridgefield, CT.*

Background: The Janus kinase (Jak)-Signal transducer and activator of transcription (Stat) signaling pathway is implicated as an important regulator of inflammatory diseases and currently under clinical evaluation in rheumatoid arthritis. Understanding of Jak-Stat involvement in chronic kidney disease (CKD) is limited but attractive as a potential therapeutic target based on recent data demonstrating Stat3 involvement in the development of tubulointerstitial fibrosis (TIF) induced by unilateral ureteral obstruction (UUO). Our study was designed to understand the role of Jak-Stat activation and related inflammatory mediators in UUO-induced TIF in the rat.

Methods: Male rats were treated with EX76545 (Jak1/2 inhibitor; 1, 3, 10mg/kg, p.o.) or the anti-inflammatory agent EX76166 (10mg/kg, p.o.) that initiated concurrently with UUO surgery and continued daily for 7 days post-UUO. Blood was collected on days 4 and 7; kidneys collected on day 7 post-UUO. Kidneys were evaluated for TIF via Sirius Red morphometry (SRM) and pathway components (Jak1, Jak2, Stat3, and Socs3) via qPCR and ELISA.

Results: Following UUO, kidney mRNA transcripts for Jak1, 2 and Stat3 increased (2-2.5X) while Socs3 increased 25X compared to sham (RNAseq). UUO induced significant TIF in the vehicle group (SRM score=9.71±0.66*($p<0.05$), vs. sham (4.93±0.62). EX76545 reduced TIF by 52%* and 40%* for the 3 and 10 mg/kg doses, respectively, and was comparable to EX76166 (48%*). UUO-induced TIF was accompanied by increases in inflammatory (MCP-1, CSF-1, Txnip) and profibrotic (TGFβ, Fn, Acta2) genes that were attenuated by EX76545 demonstrating direct impact of Jak signaling on these pathways. EX76545 reduced protein expression of phos-Stat3 by 67%*, 99%*, and 112%* (1, 3, 10mg/kg, respectively) compared to vehicle control or EX76166 that were without effect, demonstrating target engagement and Jak-Stat pathway inhibition.

Conclusions: These results demonstrate for the first time that Jak1/2 inhibition reduces TIF and related pro-fibrotic and inflammatory genes generated by UUO highlighting inflammatory modulation as a potential therapeutic area for CKD.

Funding: Pharmaceutical Company Support - Boehringer Ingelheim

SA-PO224

Post Translational Modifications to H3K9 during Renal Myofibroblast Differentiation Timothy D. Hewitson,[1] Chrishan S. Samuel,[2] Stephen G. Holt,[1] Edward R. Smith.[1] *[1]Nephrology, Royal Melbourne Hospital, Melbourne, VIC, Australia; [2]Pharmacology, Monash Univ, Melbourne, VIC, Australia.*

Background: Epigenetic regulation of fibroblasts is a key determinant of progression in renal disease. Although DNA methylation and miRNA regulation of fibroblasts are reported, the pattern of post-translational histone modifications (marks) and their significance are largely unknown. Lysine 9 on Histone 3 (H3K9) is of particular interest as it can be both methylated and acetylated. In this study we examined the distribution and acquisition of H3K9 modifications in fibrogenesis.

Methods: Confocal microscopy with histone mark specific antisera was used to examine global H3K9 acetylation (H3K9Ac) and tri-methylation (H3K9Me3) after 3 and 10 days of unilateral ureteric obstruction (UUO). Cell culture studies using confocal/ super-resolution microscopy and flow cytometry examined the effect of TGF-β1 on structural arrangement of these marks, and their relationship with kinetics and differentiation.

Results: Staining for H3K9Ac was diffuse and did not change after UUO, while H3K9Me3 was more intense in both proximal tubules (LTL lectin-positive cells) and myofibroblasts (α smooth muscle actin-positive cells). Sub-nuclear localisation in cultured primary rat renal fibroblasts and a proximal tubule cell line (NRK52e) showed that H3K9Ac was co-localised with phosphorylated-Ser2 RNA polymerase II (pRNAPol II), while H3K9Me3 was not, consistent with permissive and repressive effects on gene expression, respectively. H3K9Ac was diffusely distributed throughout the nucleus while H3K9Me3 was tethered to the nuclear membrane. Exogenous TGF-β1 had no effect on co-localisation with pRNAPol II, but resulted in a redistribution of H3K9Me3 within the fibroblast nucleus. This was unrelated to any change in mitogenesis. Flow cytometry showed that H3K9Me3 but not H3K9Ac was acquired in myofibroblast differentiation.

Conclusions: Myofibroblast differentiation is accompanied by changes in both histone mark arrangement and the acquisition of the repressive H3K9Me3 mark. Future studies will need to identify the genes involved and their ramifications.

Funding: Government Support - Non-U.S.

SA-PO225

Fibrosis and Altered Wnt10b Expression Occurs with Aging in the Kidney Priyantha Sumudhu Kulatilake, Helen Williams, Gavin Iain Welsh, Sarah J. George. *School of Clinical Sciences, Univ of Bristol, Bristol, England, United Kingdom.*

Background: Kidney fibrosis occurs with ageing, however little is known about the involvement of Wnt/β-catenin signalling in this process. Here we examined whether Wnt10b was altered with ageing and coincided with age-related renal fibrosis.

Methods: C57/Bl6 mice were aged to 18 months (old) and compared to mice aged 8 weeks (young). We excised the kidneys and processed them for RNA, protein and histological analysis.

Results: Initially, western blotting showed increased β-galactosidase protein in the old ($n=3$ $p<0.05$) mice and picrosirius staining of histology sections demonstrated increased fibrosis ($n=15$ $p<0.05$), confirming ageing and fibrosis, respectively. We observed a significant decrease in Wnt10b ($n=5$ $p<0.05$) protein with age and active β-catenin protein ($n=7$ $p<0.05$). Interestingly, the mRNA levels of Wnt10b however increased with age ($n=11$ $p<0.05$), suggesting suppressed mRNA translation of this protein. We scanned online databases for potential microRNAs (miRs) that could target Wnt10b mRNA. Predicted miRs that target Wnt10b included miR-22 and miR-29a, which we found to be increased with age, ($n=7$ $p<0.01$ and $n=7$ $p<0.05$, respectively). As miR-22 and miR-29a are not validated targets of Wnt10b our next step is to validate them as targets against Wnt10b with a luciferase assay.

Conclusions: These results suggest that decreased Wnt10b protein and resultant β-catenin activity may occur in the kidney due to an increase in interfering microRNA preventing Wnt10b translation into protein and this may be associated with kidney fibrosis.

SA-PO226

Shikonin and 2-Deoxyglucose Attenuate Renal Fibrosis via Inhibiting Aerobic Glycolysis in Renal Interstitial Fibroblast Hao Ding, Junwei Yang. *Center for Kidney Disease, Second Affiliatted Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Almost all chronic kidney diseases lead to renal fibrosis, however, the mechanism that governs renal fibrosis remains unclear. Recently energy metabolism became as particularly interesting topic in kidney disease research, the questions whether aerobic glycolysis is required for renal myofibroblast activation and whether modulation of renal fibroblast aerobic glycolysis can affect the occurrence and progression of renal fibrosis still remain to be addressed.

Methods: In this study, we employed mice with unilateral ureter obstruction (UUO) and TGFβ1-treated kidney interstitial fibroblast cells as two model systems. We profiled the gene expression involved in glucose metabolism by using RT2 Profiler PCR arrays. In addition, we examined pyruvate kinase type M2 (PKM2) levels in 20 renal biopsy samples from individuals with different degrees of renal fibrosis.

Results: Here we demonstrated that a switch of metabolism from oxidative phosphorylation to aerobic glycolysis in renal fibroblasts was the primary feature of fibroblast activation during renal fibrosis, and that suppressing renal fibroblast aerobic glycolysis could significantly reduce renal fibrosis. Both gene profiling and protein assay showed that the expression of glycolysis enzymes was upregulated in mouse kidneys with UUO surgery or TGFβ1-treated renal interstitial fibroblasts. Aerobic glycolysis flux, indicated by glucose uptake and lactate production, was increased in mouse kidney with UUO or TGFβ1-treated renal interstitial fibroblasts and positively correlated with fibrosis process. In line with this, aerobic glycolysis inhibitors shikonin and 2-deoxyglucose (2-DG) attenuate UUO-induced renal fibrosis and TGFβ1-stimulated myofibroblast activation. Furthermore, mechanistic study indicated that shikonin inhibits renal aerobic glycolysis via reducing phosphorylation of PKM2, a rate-limiting glycolytic enzyme associated with cell reliance on aerobic glycolysis.

Conclusions: In conclusion, our findings demonstrate the critical role of aerobic glycolysis in renal fibrosis and provide the treatment of aerobic glycolysis inhibitors shikonin and 2-DG as a potential anti-fibrotic strategy.

Funding: Government Support - Non-U.S.

SA-PO227

Evolutionary Conserved Transcriptional Changes in Kidney Fibrosis Jihwan Park, Chengxiang Qiu, Shizheng Huang, Szu-Yuan Li, Yi-An Ko, Katalin Susztak. *Renal Electrolyte and Hypertension Div, Univ of Pennsylvania, Philadelphia, PA.*

Background: Kidney fibrosis is the histological manifestation of chronic kidney disease (CKD) and observed in all forms of progressive kidney disease. In patients fibrosis is associated with global gene expression changes, some of them might be causally related to disease development, while others change as a consequence of disease. Mouse models can provide platform for understanding fibrosis and pathways that are recapitulated in a different species could have a higher likelihood to be causal, but individual mouse model do not fully recapitulate the complexity of the human disease.

Methods: We performed expression profiling for a large cohort (n=95) of human microdissected normal and CKD tubule samples. Using an adjusted linear regression model we identified genes those expression significantly associated with phenotypic changes including GFR and tubulointerstitial fibrosis. By using RNA sequencing we have examined gene expression changes in four mouse fibrosis models; folate induced fibrosis (FA), unilateral uretheral obstruction (UUO), tubule specific Notch transgenic and podocyte specific APOL1 transgenic mice.

Results: The expression of large number of genes correlated with fibrosis severity in human patient samples. To narrow target genes we identified 761 conserved expression changes between mouse and human and examined their correlation with fibrosis development. Genes differentially expressed in mouse models allowed proper clustering of control and diseased human kidney samples. Genes involved in immune response showed positive correlation with fibrosis development while genes with metabolism and oxidative reduction showed negative correlation both in mouse and human samples. Some of the known therapeutic target genes such as Il1a, Aoc3 and Itgb6 showed distinct patterns between mouse models. We are performing functional studies to identify key transcriptional regulators of fibrosis development.

Conclusions: Comparative analysis of human and mouse kidney fibrosis have identified conserved genes and pathways in kidney fibrosis. These genes can serve as potential new biomarkers or therapeutic targets for kidney disease development.

Funding: NIDDK Support

SA-PO228

PBI-4425, a Novel Anti-Inflammatory/Fibrotic Compound, Improves Kidney Function in 5/6-Nephrectomized Rats Brigitte Grouix, Lilianne Geerts, Kathy Hince, François Sarra-Bournet, Liette Gervais, Alexandra Felton, Alexandre Laverdure, William Gagnon, Martin Leduc, Pierre Laurin, Lyne Gagnon. *ProMetic BioSciences Inc., Laval, QC, Canada.*

Background: Chronic kidney disease (CKD) represents an important health problem worldwide, and affects approximately one-seventh of adults in the US. PBI-4425, a novel first-in-class treatment for fibrotic diseases, possesses a pleiotropic mechanism of action with anti-inflammatory, antioxidant and anti-fibrotic properties. The aim of this study was to investigate the protective effect of PBI-4425 on kidney function and structure in the 5/6-nephrectomized (NX) rat model of CKD.

Methods: Sprague-Dawley rats were partially nephrectomized (2/3 of the left kidney) on day 0. On day 7 the right kidney was removed. Oral treatment with PBI-4425 (100 mg/kg, once a day) or vehicle was initiated at day 21, following randomization based on glomerular filtration rate (GFR) results. GFR was measured at day 21 and assessed every 3 weeks up to day 128 at which time the animals were sacrificed.

Results: Treatment with PBI-4425 resulted in a significant improvement in GFR as well as a significant reduction of urinary albumin to creatinine ratio (ACR). Histological kidney lesion scores were also significantly ($p<0.05$) decreased in PBI-4425-treated rats (2.51 ± 0.9) compared to control (4.47 ± 0.9), as determined by HPE, PAS and Masson's trichrome staining. PBI-4425 reduced the overexpression of inflammatory and fibrotic markers such as IL-6, MCP-1, TGF-β1, CTGF, collagen I, α-SMA, PAI-1, and MMP2 in kidney. Furthermore, a significant reduction of urinary MCP-1 and Beta-2 microglobulin levels was observed in PBI-4425-treated 5/6 nephrectomized rats.

Conclusions: Taken together, these results suggest that PBI-4425 offers the potential as a novel therapy for chronic kidney disease by reduction of fibrosis and can potentially improve residual kidney function in patients with end stage renal failure.

SA-PO229

Gremlin 1 Neutralization Does Not Attenuate Markers of Fibrosis in the Unilateral Ureteral Obstruction Model Philippe Costet,[1] Yanqing Kan,[1] Liyang Wang,[2] Sheena Mumick,[3] Kashmira Shah,[3] Tian-Quan Cai,[2] Michael Judo,[2] Brian E. Hawes,[3] Xiaoda Niu,[3] Kenny K. Wong,[2] Masahisa Handa,[4] Mohammad Tabrizifard,[5] Shirly Pinto.[1] *[1]Cardiometabolic Diseases, Merck, Kenilworth, NJ; [2]Discovery Bioanalytic, Merck, Palo Alto, CA; [3]Pharmacology, Merck, Kenilworth, NJ; [4]Pharmacology, Merck, Palo Alto, CA; [5]Discovery Operations, Merck, Palo Alto, CA.*

Background: Gremlin 1 (Grem1) is a secreted antagonist of the anti-proliferative bone morphogenic protein (BMP) signaling pathway, present in the extracellular space in rodents and in plasma in humans. Grem1 also promotes pro-fibrotic TGFb signaling. Grem1 expression is increased in fibrotic organs in patients with idiopathic pulmonary fibrosis, diabetic nephropathy. In mice, grem1 overexpression worsens kidney fibrosis in the unilateral ureteral obstruction (UUO) model. Grem1-/+ mice rendered diabetic with streptozotocin have improved kidney function compared with STZ WT mice. Our goal was to verify whether an antibody raised against gremlin 1 can attenuate fibrosis in the kidney.

Methods: We synthesized two antibodies raised against gremlin 1 and characterized their binding affinities for human and mouse gremlin using biacore, and their activity toward BMPs using functional assays.Next we evaluated their effect of in a preventive fashion in the unilateral ureteral obstruction model.

Results: We determined the EC50 for mAb1 and mAb2 to be 1 and 5 nM by measuring BMP4-stimulated psmad1/5/9 accumulation in mouse 3T3 cells. UUO mice exhibited increased expression of gremlin 1 mRNA, decreased BMP signaling and increased TGFb signaling compared to sham-operated mice. In an experiment with a total duration of 10 days post-surgery, Grem1 antibodies decreased TGFb activity marker psmad2 protein but there was only a trend in the increase of BMP target engagement marker psmad1/5/8. Some markers of fibrosis were improved, in particular col4A1 and PAI-1 mRNAs (-33% and -46% respectively, P<0.01)) and aSMA protein (-44%, P<0.05)). These findings were not reproduced in an experiment with an extended duration of 14 days despite similar level of exposure.

Conclusions: Gremlin 1 neutralization did not confer robust protection against kidney fibrosis in the UUO model.

Funding: Pharmaceutical Company Support - Merck

SA-PO230

Treatment Efficacy of PBI-4050, an Orally Active Anti-Fibrotic Agent, Can Be Monitored by Measuring Urinary Biomarkers in 5/6-Nephrectomized Rats Lyne Gagnon, François Sarra-Bournet, Martin Leduc, Alexandre Laverdure, Lilianne Geerts, Brigitte Grouix, Jean-Simon Duceppe, Boulos Zacharie, Pierre Laurin. *ProMetic BioSciences Inc., Laval, QC, Canada.*

Background: PBI-4050, a novel first-in-class orally active compound which is currently in clinical phase Ib/II in chronic kidney disease (CKD) patients, displays anti-fibrotic activities via a novel mechanism of action. In the present study, we examined the anti-fibrotic effect of PBI-4050 by evaluating urine biomarkers in 5/6 nephrectomized (NX) rats.

Methods: Sprague-Dawley rats were partially nephrectomized (2/3 of the left kidney) on day 0. On day 7 the right kidney was removed. Oral treatment with PBI-4050 (200 mg/kg, once a day) or vehicle was initiated at day 21, following randomization based on their glomerular filtration rate (GFR) results. GFR was measured at day 21 and assessed every 3 weeks up to day 190. Urinary protein biomarker levels were determined by Multiplex analysis.

Results: Treatment with PBI-4050 resulted in a significant improvement (up to three fold relative to control) in GFR and also significantly reduced proteinuria. Histological kidney lesion scores were also significantly (p<0.05) decreased in PBI-4050-treated rats (2.7 ± 1.5) compared to control (3.9 ± 1.4), as determined by HPE, PAS and Masson's trichrome staining. In correlation with improved kidney function, a significant reduction of urine protein biomarker (β-2 microglobulin, calbindin, cystatic C, NGAL, clusterin, Kim-1 and MCP-1) levels was observed in PBI-4050-treated 5/6-nephrectomized rats.

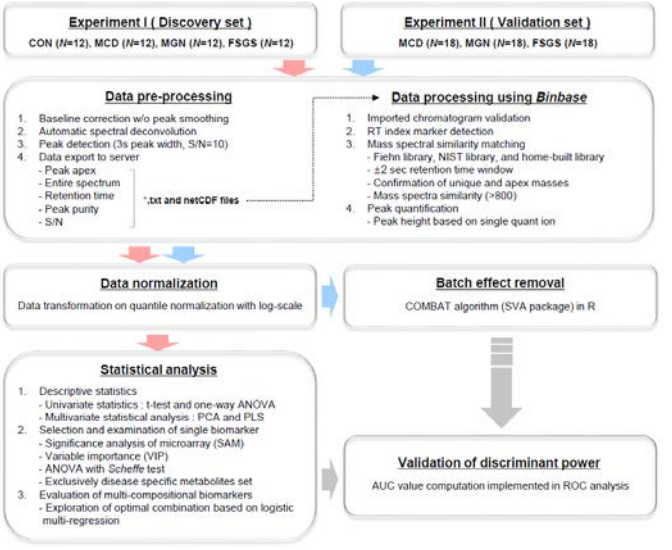
Conclusions: These results suggest that PBI-4050 offers the potential as a novel therapy for chronic kidney disease by reduction of fibrosis and treatment efficacy can be monitored with urinary biomarkers.

SA-PO231

Systematic Biomarker Discovery and Coordinative Validation for Different Primary Nephrotic Syndromes Using Gas Chromatography-Mass Spectrometry Sang-Ho Lee,[1] Yu Ho Lee,[1] Jung-Eun Lee,[2] Yang Gyun Kim,[1] Kyung-Hwan Jeong,[1] Tae Won Lee,[1] Chun-Gyoo Ihm,[1] So-Young Lee,[3] Dong Ho Yang,[3] Do Yup Lee.[2] *[1]Div of Nephrology, Dept of Internal Medicine, Kyung Hee Univ, Seoul, Korea; [2]The Dept of Bio and Fermentation Convergence Technology, Kookmin Univ, Seoul, Korea; [3]Div of Nephrology, Dept of Internal Medicine, Bundang CHA Univ Hospital, Seongnam, Korea.*

Background: Since urine metabolites may mirror disease-specific functional perturbations in kidney injury, we examined urine samples for distinctive metabolic changes to identify biomarkers for clinical applications. The goal of this study is to identifysystematic biomarker panelfor primary nephrotic syndromes from urine samples by applying a non-target metabolite profiling.

Methods: Measurements Urine samples from discovery sets (MCD, FSGS, MGN and control, respectively, n=12) were analyzed using mass spectrometry-based metabolite profiling. After multiple corrections, we created disease-specific panels based on the different metabolic alterations to discriminate three different causes of NS and applied these panels to validation sets (MCD, FSGS and MGN, respectively, n=18).



Results: Thirty-three urine metabolites were significantly altered compared with controls, particularly, branch-chained amino acids. We developed three models using the combination of altered metabolites: one of the model including citric acid, pyruvic acid, fructose, ethanolamine, and cysteine effectively discriminated FSGS from the others (area under the curve [AUC]: 0.812 against MCD and 0.802 against MGN), but not MCD from MGN. Thus, we developed an additional metabolite panel, including methionine, cysteine, citrulline, and pyruvic acid, which could discriminate between MCD and MGN (AUC 0.843).

Conclusions: We identified a disease-specific panel from common urine metabolites that mayhelp identify NS and guide therapeutic plans.

Funding: Private Foundation Support

SA-PO232

The Assessment of CD80 Expression and Urinary CD80 Excretion in Childhood Nephrotic Syndrome Rezan Topaloglu,[1] Fehime Kara Eroglu,[1] Mihriban Inozu,[1] Ali Duzova,[1] Fatih Ozaltin,[1] Diclehan Orhan.[2] *[1]Pediatric Nephrology, Hacettepe Univ Faculty of Medicine, Ankara, Turkey; [2]Pediatric Pathology, Hacettepe Univ Faculty of Medicine, Ankara, Turkey.*

Background: Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are the most common causes idiopathic nephrotic syndrome (INS) in children and pathogenesis is still unknown. Persistent CD80 expression was attributed in pathogenesis which may be caused by failure of regulatory T cells (Treg). But recent studies, which included mostly adult patients, questioned the reliability of immunohistochemistry (IHC) assays. Here we aimed to investigate CD80 podocyte expression and urinary CD80 excretion in a large cohort of pediatric patients and delineate the possible role of Tregs in pathogenesis.

Methods: IHC analyses of CD80, FOXP3 and CD4 were performed to 67 archival biopsies from 59 INS patients. CD80 expression was repeated with a different primary antibody by immunofluorescence (IF). Urine CD80 excretion was also measured by ELISA.

Results: All but four biopsies showed negative expression for CD80 with IHC staining. But 23 (%57) biopsies were stained positive for CD80 in IF staining. CD80 expression was significantly higher in steroid responsive patients (p=0,041) but did not differ significantly between MCD and FSGS (p=0,169) nor presence of proteinuria at the time of biopsy (p=0,153). Urine CD80 level was significantly higher in MCD patients with relapse compared to controls (p=0,001) and MCD patients in remission (p=0,014) but showed no significant difference with FSGS patients (p=0,402). FOXP3+ CD4 T cells were observed in 20 (%36) samples(18 FSGS, 2 MCD). FSGS had significantly high interstitial FOXP3+ cells/mm2 than MCD and controls (p <0,001 and 0,001). MCD had similar FOXP3+ cells compared to controls (p=0,843).

Conclusions: Although we cannot exclude that CD80 expression may vary in different stages of disease, it seems not a solid marker of disease activity in terms of proteinuria and for differentiating MCD and FSGS. FOXP3 positive Treg cells seem to play role in MCD not in a paracrine manner but increased infiltration seem to correlate with inflammation and chronicity in FSGS.

SA-PO233

Urinary Metabolomics in Clinical Hypertensive Nephrosclerosis – Is It a Real Disease or Normal Age-Related Kidney Function Decline with High Blood Pressure? Marius Altern Øvrehus,[1,2] Manjula Darshi,[3] Per Bruheim,[4] Kumar Sharma,[3] Stein I. Hallan.[1,2] *[1]Inst of Cancer Research and Molecular Medicine, Norwegian Univ of Science and Technology, Trondheim, Norway; [2]Dept of Nephrology, St. Olavs Hospital Trondheim Univ Hospital, Trondheim, Norway; [3]Inst of Metabolomic Medicine, Univ of California San Diego, San Diego, CA; [4]Dept of Biotechnology, Norwegian Univ of Science and Technology, Trondheim, Norway.*

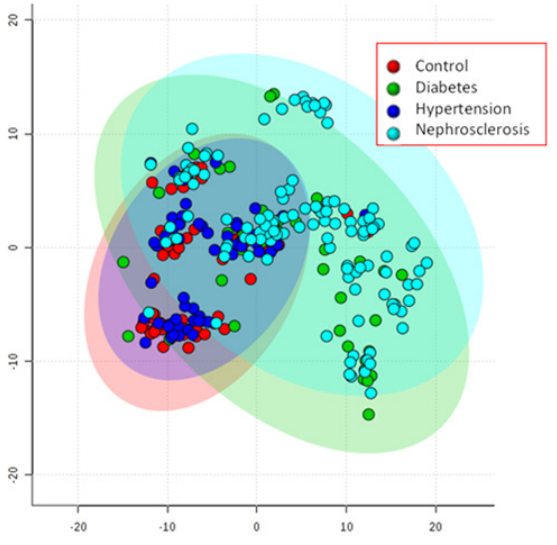
Background: The clinical diagnosis of hypertensive nephrosclerosis (HN) is debated and not well studied. Some argue that these patients only reflect normal aging. We therefore compared metabolic characteristics in HN cases to age- and sex-matched relevant groups.

Methods: Urine samples from HN (n=126), diabetic nephropathy (DN, n=41), hypertension (HTN, n=60) and healthy controls (CTR, n=60) from the HUNT 3 study (2006-08, Norway) were analyzed. Nephrosclerosis was defined as eGFR <60mL/min/1.73m^2 with ≥10 years of hypertension, and no diabetes, hematuria or proteinuria. Samples were analyzed with gas chromatography coupled to tandem mass spectrometry (GC-MS/MS).

Results: Of 75 organic acids, 31 displayed significant differences between groups. Principal component analysis (PCA) components 1, 2 and 3 explained 68% of the total variance. PLS-DA analysis showed that HTN and CTR overlapped strongly. HN and DN had substantial overlap and a large proportion of these patients were outside the 95% CI of CTR. Random forest analysis selected phenyllactic, butyric, and methylcitric acids as most important for classification. The top-25 list also included several medium-chain fatty acids, TCA-cycle metabolites, and gut microbial end products.

Conclusions: Hypertensive nephrosclerosis patients have metabolic disturbances which make them cluster together with diabetes nephropathy rather than with hypertensive patients or healthy controls.

Figure 1. Discriminant analysis (PLS-DA) analysis showing separation of diagnoses based on measured metabolites.



Funding: Government Support - Non-U.S.

SA-PO234

The Urinary Metabolomic Fingerprint of Hypertensive Nephropathy Marius Altern Øvrehus,[1,2] Manjula Darshi,[3] Per Bruheim,[4] Kumar Sharma,[3] Stein I. Hallan.[1,2] *[1]Inst of Cancer Research and Molecular Medicine, Norwegian Univ of Science and Technology, Trondheim, Norway; [2]Dept of Nephrology, St. Olavs Hospital Trondheim Univ Hospital, Trondheim, Norway; [3]Inst of Metabolomic Medicine, Univ of California San Diego, San Diego, CA; [4]Dept of Biotechnology, Norwegian Univ of Science and Technology, Trondheim, Norway.*

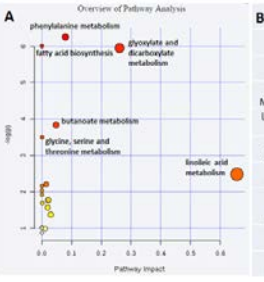
Background: Hypertensive nephropathy (HN) is a common cause of end-stage renal disease. In contrast to diabetic nephropathy, it has been the focus of only a few -omics based studies.

Methods: Urine samples from 126 HN patients and 60 age- and sex-matched healthy controls (mean age 71.8 vs 70.0 years, mean eGFR 50.5 vs 87.7 mL/min/1.73m^2) from the HUNT 3 Study (2006-08, Norway) were analyzed. Nephrosclerosis was defined as eGFR <60mL/min/1.73m^2 with at least 10 years of hypertension, and no diabetes, hematuria or proteinuria. Samples were derivatized and organic acids were quantified by targeted analysis with gas chromatography coupled to tandem mass spectrometry (GC-MS/MS).

Results: Out of 75 organic acids quantified 27 were significantly different between patients and controls, among which 17 remained significant after correction for multiple testing. Principal component analysis (PCA) components 1, 2 and 3 explained 63% of the variance. Cross validation showed acceptable model fit (R^2 0.6). The most significant metabolites were butyric acid, methylcitric, phenyllactic, octanoic, linoleic, glyceric, stearic and palmitic acids. Pathway analysis showed involvement of phenylalanine, glyoxylate/dicarboxylate, fatty acid, butanoate, and linoleic acid metabolism.

Conclusions: Urine metabolomic analysis identified global metabolite differences in hypertensive nephropathy patients compared with controls. Involved pathways covered phenylalanine, fatty acid, and glyoxylate/dicarboxylate acid metabolism.

Figure 1. A: Pathway plot. Impact on x-axis, -log(p) on y-axis. B: List of metabolite concentrations with largest difference between groups, with respective pathways.



B

Concentration

Compound	Controls	Cases	p	FDR	Pathway
Butyric acid	6.0	2.3	3.63E-10	2.6499E-8	Fatty acid metabolism
Methylcitric acid	0.02	6.0	9.3543E-9	3.4143E-7	Tricarboxylic acid metabolism
L-3-Phenyllactic acid	0.3	0.2	2.5164E-7	6.1232E-6	Phenylalanine metabolism
Octanoic acid	0.8	1.2	1.6059E-5	2.9308E-4	Fatty acid biosynthesis
Linoleic acid	0.4	0.3	2.0708E-5	3.0103E-4	Linoleic acid metabolism
Glyceric acid	6.0	8.0	2.4742E-5	3.0103E-4	Glyoxylate/dicarboxylate metabolism
Stearic acid	5.0	3.0	4.8938E-5	5.1036E-4	Fatty acid biosynthesis
Palmitic acid	8.0	5.0	1.0816E-4	8.8993E-4	Fatty acid biosynthesis

Funding: Government Support - Non-U.S.

SA-PO235

Urine Epidermal Growth Factor, Monocyte Chemoattractant Protein-1 or Their Ratio as Biomarkers for Interstitial Fibrosis and Tubular Atrophy in Primary Glomerulonephritis Supanat Worawitchawong,[1] Chagriya Kitiyakara,[1] Suchin Worawichawong.[2] *[1]Dept of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol Univ, Bangkok, Thailand; [2]Dept of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol Univ, Bangkok, Thailand.*

Background: The degree of tubular atrophy and interstitial fibrosis (IFTA) is an important prognostic factor in glomerulonephritis. Imbalance between pro-inflammatory cytokines such as monocyte chemoattractant protein-1 (MCP-1) and protective cytokines such as epidermal growth factor (EGF) likely determines IFTA severity. In separate studies, elevated MCP-1 and decreased EGF have been associated with IFTA severity, but the value of the combining of the two biomarkersin primary glomerulonephritis (GN) are unknown. In this study, we aim to evaluate the predictive value of urinary EGF/MCP-1 ratio compared to each biomarker individually for IFTA in primary GN.

Methods: Urine samples were collected from healthy controls (n=18) and primary GN (n=58) at biopsy. MCP-1 and EGF were analyzed by enzyme-linked immunosorbent assay.

Results: GN included IgA nephropathy, FSGS , minimal change disease, and membranous nephropathy. Compared to healthy controls, MCP-1 was higher (p<0.001), EGF levels were similar, and the EGF/MCP-1 ratio was lower in GN (p<0.001). In GN, MCP-1 correlated with GFR, and inversely with proteinuria. EGF correlated strongly with GFR (R=0.83), but not proteinuria. EGF/MCP-1 ratio correlated with eGFR and inversely with proteinuria. EGF, MCP-1 and EGF/MCP-1 ratio all correlated with IFTA. Univariate analysis showed that GFR, EGF, and EGF/MCP-1 ratio were associated with moderate to severe IFTA. By multivariate analysis, only EGF/MCP-1 ratio was independently associated with IFTA [OR: 0.92, p=0.008]. EGF/MCP-1 ratio of 17.7 ng/ng had a sensitivity of 88% and specificity of 74 % for IFTA. By ROC curve analysis, EGF/MCP-1 had good discrimination for moderate to severe IFTA (AUC=0.85), but the improvement over EGF alone was not significant.

Conclusions: EGF/MCP-1 ratio is independently associated IFTA severity in primary glomerulonephritis, but the ability of EGF/MCP-1 ratio to discriminate moderate to severe IFTA may not be much better than EGF alone.

Funding: Other NIH Support - Mahidol University

SA-PO236

Urinary Periostin Excretion Predicts Renal Outcome in IgA Nephropathy: A Prospective, Cohort Study Jin Ho Hwang,[1] Chae Rim Kim,[1] Jung Pyo Lee,[2] Seung Hee Yang,[3] Jung Nam An,[2] Hajeong Lee,[4] Yun Kyu Oh,[2] Kwon Wook Joo,[4] Dong Ki Kim,[4] Yon Su Kim,[4] Chun Soo Lim.[2] *[1]Internal Medicine, Chung-Ang Univ Hospital, Seoul, Republic of Korea; [2]Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul; [3]Kidney Research Inst, Seoul National Univ Hospital, Seoul, Republic of Korea; [4]Internal Medicine, Seoul National Univ Hospital, Seoul, Republic of Korea.*

Background: Periostin is a matricellular protein and plays a vital role tissue regeneration, fibrosis, and wound healing. However, data on its significance in nephrology are limited. We investigated the correlation between urinary periostin excretion and its clinical significance including renal histologic findings and prognosis in IgA nephropathy (IgAN).

Methods: Of 399 patients from a glomerulonephritis cohort recruited between Jan. 2009 and Dec. 2014, 314 were enrolled. Serum and urine POSTN were measured using ELISA. We divided the patients into 3 groups by urine periostin/creatinine (uPOSTN/Cr): group 1 (undetectable), group 2 (lower than the median), and group 3 (higher than the median). The occurrence of ESRD was the primary outcome of this study.

Results: The uPOSTN level was correlated with pathologic classifications and both initial and final IDMS-MDRD eGFRs (both *P*<0.001). Histologically, group 3 patients

were correlated with severe interstitial fibrosis/tubular atrophy (P=0.004), interstitial inflammation (P=0.007), hyaline arteriolosclerosis (P=0.001), and glomerular sclerosis (P<0.001). A higher initial uPOSTN/Cr level was associated with a greater decline in eGFR during follow-up (P=0.043 when initial eGFR≥60; P=0.025 when eGFR<60 mL/min/1.73 m^2), and the renal outcomes with ESRD (P=0.003), ESRD and/or eGFR decrease of >30% (P=0.033), and ESRD and/or eGFR decrease of >50% (P=0.046) occurred significantly more in group 3. In multivariate analysis, uPOSTN group 3 (HR, 2.839 vs. group 1+2; CI, 1.013-7.957; P=0.047) was independently associated with ESRD in IgAN patients.

Conclusions: Urine POSTN/Cr value at initial diagnosis correlated with renal fibrosis and predicted the renal outcomes in patients with IgAN. It could be a promising urinary biomarker for renal fibrosis.

Funding: Pharmaceutical Company Support - This study was supported by research grant from Pfizer Inc., NY, USA

SA-PO237

Urine Exosomal Ceruloplasmin - A Potential Early Marker of Kidney Damage That Precedes Proteinuria Krishnamurthy P. Gudehithlu,[1] Peter D. Hart,[1,2,3] Amit J. Joshi,[1,3] George Dunea,[1,2] Jose A.L. Arruda,[3,1,4] Ashok K. Singh.[1,2,4] *[1]Div of Nephrology, John H.Stroger, Jr. Hospital of Cook County, Chicago, IL; [2]The Hektoen Inst of Medicine, Chicago, IL; [3]Internal Medicine and Pathology, Rush Medical College, Chicago, IL; [4]Section of Nephrology, Univ of Illinois at Chicago, Chicago, IL.*

Background: Pilot studies showed increased ceruloplasmin (CP) in urine exosomes of membranous nephropathy (n=9), lupus nephritis (n=8), FSGS (n=8), and IgA nephropathy (n=7) patients, suggesting that it could be a general marker of kidney damage. In this study we tested whether urine exosomal CP could serve as an early biomarker of kidney damage preceding proteinuria.

Methods: Experiments were performed in the rat model of passive Heymann nephritis (PHN), which mimics human membranous nephropathy. PHN induced by injecting rats with anti-gp600 antibodies. At times 0, week 1, 2 and 3, urine exosomes were isolated by differential centrifugation. Exosomal pellets were extracted for measurement of CP by ELISA and protein by Bio-Rad method. PHN was confirmed by histology (trichrome staining) and glomerular IgG deposits using immunofluorescence. Histochemical staining for CP was performed to validate the ELISA results. Control rats were injected with saline instead of antibody.

Results: Rats injected with antibody showed typical intramembranous IgG deposits by week 1, and loss of brush border suggestive of proteinuria by week 2. Accordingly, PHN rats were non-proteinuric (<20 mg/day) at week 1, but presented with proteinuria (>400 mg/day) at weeks 2 and 3 (n = 6). Urine exosomal CP levels (ng/mg of exosomal protein) at times 0 was 64.5±15, which increased by 3.5 fold at week 1 (228 ±39) and 6 fold by week 2 (409 ±17) and 3 (399 ±36) after the induction of PHN, suggesting that exosomal CP increased significantly even before proteinuria. These results were confirmed by enhanced immunofluorescent staining for CP observed in the interstitial area of proximal tubules of PHN rats compared to controls.

Conclusions: In conclusion, increase in urine exosomal CP could serve as a potential early biomarker of kidney damage that precedes the onset of proteinuria.

Funding: Private Foundation Support

SA-PO238

Dysmorphic Urinary Red Blood Cells: Clinical Utility in Glomerular Disease Abdurrahman M. Hamadah, Kamel A. Gharaibeh, Samar M. Said, Samih H. Nasr, Nelson Leung. *Mayo Clinic.*

Background: Dysmorphic red blood cells (dRBCs) assessment on urine microscopy has been used to differentiate glomerular vs. non-glomerular disease. However, large studies to establish its usefulness are lacking. In this study, we assess the prevalence of dRBCs in a large group of biopsy proven kidney disease, and evaluate dRBCs ability to differentiate glomerular from non-glomerular kidney disease.

Methods: This is a retrospective study of adult patients with biopsy-proven diagnoses and concurrent urine microscopy between 2012 and 2015 at our institution. The prevalence of dRBCs in glomerular vs. non-glomerular disease was assessed. dRBCs cutoff values of < 25% and ≥ 25% were compared using sensitivity, specificity, positive and negative predictive values (PPV and NPV). Variables potentially associated with glomerulonephritis (GN) (proteinuria, level of hematuria, dRBCs≥ 25%, creatinine, and serum albumin) were assessed using univariable and multivariable logistic regression.

Results: We identified 482 patients who had native kidney biopsy with concurrent urinalysis. Mean age was 55 years, 47.7 % were female, and 87.3% were white. Based on kidney biopsy findings, 372 (77.2 %) had glomerular disease (GD) (GN 46% and non-GN 54%), and 110 (22.8%) had non-glomerular disease. Significant dRBCs (≥ 25%) was seen in 28% of GN, in 12.4% of non-GN glomerular disease, and in 3.6% of non-GD. Dysmorphic RBCs level ≥ 25% showed a sensitivity of 28.5%, specificity 90.6%, PPV 63.5%, and NPV 68.7% for the diagnosis of GN. The logistic regression model showed that both dRBCs ≥ 25% (p<0.001) and urine RBC level (11-50 vs < 11 (p= 0.003) or > 50 vs < 11 (p=0.01) RBCs/hpf) were associated with presence of GN on univariable analysis, however, only urine RBC level (11-50 vs < 11 (OR 6.9, 95% CI (3.8-12.7), p= 0.003) or > 50 vs < 11 (OR 6.6, 95% CI (2.9-15.4), p= 0.03)) RBCs/hpf) was predictive of GN in multivariable analysis.

Conclusions: Based on a large group of biopsy-proven diverse renal disease entities, the finding of ≥ 25% dRBCs on urine microscopy, despite being specific for GN, did not add to the ability of hematuria (> 10 RBCs/hpf) to predict presence of GN on kidney biopsy, and may not have a significant diagnostic yield in this setting.

SA-PO239

The Association of Cardio-Metabolic Index with Microalbumiuria in General Population Joon-Sung Park,[1] Jong Wook Choi.[3] *[1]Internal Medicine, Hanyang Univ College of Medicine, Seoul, Korea; [2]Internal Medicine, Hanyang Univ College of Medicine, Seoul, Korea; [3]Internal Medicine, Hanyang Univ College of Medicine, Seoul, Korea.*

Background: Cardio-metabolic index (CMI) is novel indicator of metabolic disturbance and it can discriminate diabetes and predict risk atherosclerosis progression. Here, we investigate whether CMI is related with development of microalbuminuria in general population.

Methods: We analyzed anthropometric and biochemical data from a nation-wide, population-based, case-control study (the Korean National Health and Nutritional Examination Surveys KNHANES VI). Eligibles as cases were all native Korean who were aged 20 years or more and had no any medical illness.

Results: A total of 5398 participants were divided into five CMI quintiles. Participants in highest CMI quintile were more hypertensive and had greater glycemic exposure, increased urine protein/creatinine ratio (UACR) and decreased kidney function as compared with other quintiles.Our Cochran-Armitage test showed that CMI had dose-response relationship with prehypertension, prediabetes, microalbuminuria, and early impaired kidney function.Adjusted multiple logistic regression analysis revealed that increased CMI was independently associated with prehypertension (adjusted OR = 1.161, 95% *CI* = 1.092-1.234), prediabetes (adjusted OR = 1.081, 95% *CI* = 1.021-1.142), and microalbuminuria (adjusted OR = 1.075, 95% *CI* = 1.001-1.154) although early impaired kidney function was not.

Conclusions: In this study, we demonstrated that mild increase of CMI is associated with slightly elevated blood pressure, mild hyperglycemia, and increased urinary excretion of albumin in the healthy population and may be a reliable predictor of with harmful effect of metabolic disturbance on kidney before appearance hypertension and diabetes mellitus. To confirm these findings, large population-based prospective clinical should be needed.

SA-PO240

Tubular Subsegmental Omics and Quantitative 3D Imaging of Human Kidney Biopsies Reveal Signatures Underlying Progression of Renal Disease Tarek M. El-Achkar,[1,4] Michael T. Eadon,[1] Ken Dunn,[1] Seth Winfree,[1] Timothy A. Sutton,[1] Katherine J. Kelly,[1] Takashi Hato,[1] Bruce A. Molitoris,[1,4] Matthew D. Breyer,[3] Brad H. Rovin,[2] Samir Parikh,[2] Pierre C. Dagher.[1,4] *[1]Medicine, Indiana Univ, Indianapolis, IN; [2]Internal Medicine, The Ohio State Univ, columbus, OH; [3]Lilly Research Laboratories, Indianapolis, IN; [4]Medicine, Roudebush VA Medical Center, Indianapolis, IN.*

Background: Tubulointerstitial fibrosis is a determinant of outcome in all renal pathologies. Remarkably, patients with apparently identical biopsy readings exhibit variable rates of progression to terminal fibrosis. To date, investigation of the glomerular lesions and tubulointerstitium has failed to account for this unpredictable rate of progression. We now propose that the rate and extent of tubulointerstitial fibrosis, regardless of the initiating lesion, are determined by molecular signatures specific to individual tubular subsegments and the immune make-up of the interstitium.

Methods: We interrogated routine human kidney biopsies with broad "omics" readouts conducted on tubular subsegments obtained by laser microdissection. We also developed a novel 3D microscopy quantitative approach to quantify the immune cell make-up in the same biopsies.

Results: We show that tubular subsegmental transcriptomics and proteomics can be reliably obtained from a routine human kidney biopsy. The same biopsy can also be analyzed quantitatively with 3D fluorescence microscopy to reveal the type and distribution of immune cells in relation to renal tubular segments. Using this approach we examined biopsies from diabetic nephropathy patients who exhibited different rates of progression despite similar traditional biopsy readings. Our studies revealed unique signatures specific to each patient that correlated well with disease progression.

Conclusions: Our studies support the hypothesis that, at a subsegmental level, a unique molecular and cellular signature exists which determines the progression of most kidney diseases. This signature will guide our ability to determine best therapy and prognosis for individual patients, validate animal models and identify novel therapeutic targets.

Funding: NIDDK Support, VA Support, Private Foundation Support

SA-PO241

Proteomics of Diabetic Nephropathy Glomerulus for Understanding Pathophysiology Tadashi Yamamoto,[1] Keiko Yamamoto,[1] Hidehiko Fujinaka,[2] Shigeru Miyazaki.[3] *[1]Biofluid Biomarker Center (BBC), Niigata Univ, Niigata, Japan; [2]Pediatrics, Niigata National Hospital, Kashiwazaki, Niigata, Japan; [3]Internal Medicine, Shinrakuen Hospital, Niigata, Japan.*

Background: Diabetic nephropathy (DN) is a crucial complication of diabetes mellitus, progressing to the end-stage of chronic kidney disease (CKD). However, molecular mechanisms of the progression or pathophysiology have not clarified yet. We aimed to understand the molecular mechanisms by analyzing glomerular proteomes of DN by mass spectrometric proteomics and bioinformatics since glomeruli are initially injured in DN.

Methods: Formalin-fixed paraffin-embedded kidneys from autopsy cases of DN patients were sectioned for laser microdissection of glomerular sections. Glomerular lesions of DN were classified into three categories, early (minor abnormalities or diffuse lesion), intermediate and advanced (marked increase of mesangial matrix or nodular lesion) (n=5

each) by histological examination. The glomerular sections were directly digested with trypsin and tryptic peptides were collected by using C18 column for liquid chromatography (LC)-MS. Proteins were identified by Mascot search engine and semi-quantified by the normalized spectrum index. The glomerular proteomes were compared between the three DN lesions and non-disease kidneys. The glomerular proteins, which increased or decreased more than 2-fold, were selected for IPA pathway analysis.

Results: Approximately more than one thousand proteins (by gene names) were identified in each glomerular sample semi-quantitatively by MS. Cellar localization was predicted for the proteins of more than 2-fold change in DN glomeruli at plasma membrane (10~15%) and cytoplasm (50~60%). Pathways related to Cell Death & Survival, Cell Mobility, Immunity & Inflammation and others were enhanced in the DN glomeruli and also upstream proteins, such as TGFb1 were depicted.

Conclusions: Proteomic analysis of DN glomeruli successfully demonstrated acceleration of several molecular pathways in the sites, providing knowledge of the pathophysiology and making possible to select crucial molecules for drug discovery.

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

SA-PO242

KidneySeq™: A Comprehensive Inherited Kidney Disease Panel M. Adela Mansilla,[1] Ramakrishna Sompallae,[1] Sara Mason,[1] Carla Nishimura,[1] Anne E. Kwitek,[1] Colleen Ann Campbell,[1,2] Christie P. Thomas,[2] Richard J. Smith.[1,2] *[1]Inst of Human Genetics, Univ of Iowa, Iowa City, IA; [2]Internal Medicine, Univ of Iowa, Iowa City, IA.*

Background: KidneySeq™ is a comprehensive inherited kidney disease panel using next generation sequencing developed by the Iowa Institute of Human Genetics (IIHG) and the Division of Nephrology at the University of Iowa.

Methods: This clinical genetic test simultaneously interrogates 179 renal genes implicated in 75 renal diseases, facilitating the diagnosis of genetic renal diseases as well as aiding living kidney donor selection. Sequence data are processed through a custom bioinformatics workflow that includes detection of a wide range of genetic variation (single nucleotide polymorphisms, insertions, deletions and copy number variations). A parallel work flow for *PKD1* is included based on the complexity of unambiguous *PKD1* variant detection caused by pseudogene sequences. Each final variant list is reviewed by a multidisciplinary team of physicians, genetics counselors, bioinformaticians and researchers in the context of the patient's clinical data to determine whether a plausible genetic cause for the observed phenotype has been identified.

Results: Since launching KidneySeq™ 6 months ago, we have tested 21 clinical samples that include disorders of tubular ion transport, glomerulopathies, congenital anomalies of kidney and urinary tract (CAKUT) and ciliopathies. A genetic diagnosis was identified in 10 cases (48%). By disease type, the solve rate was: disorders of tubular ion transport, 33 % (3 of 9 cases); glomerulopathies, 50 % (3 of 6 cases); CAKUT, 67 % (2 of 3 cases); and ciliopathies, 67 % (2 of 3 cases).

Conclusions: In 7 cases, the genetic diagnosis differed from the clinically suspected diagnosis, emphasizing the overlapping phenotypic spectrum that characterizes several renal diseases and highlighting the value of comprehensive genetic testing. KidneySeq™ provides a rapid, cost-effective method to improve the care of patients with renal disease.

Funding: Private Foundation Support

SA-PO243

Assessment of the IRIDICA Technique for Rapid Detection of Acute Infection in Renal Patients Recently Treated with Antimicrobials Anamika Adwaney,[1] Sevda Hassan,[1] Arikana Massiah,[2] Mark Wilks,[2] Raj Thuraisingham.[1] *[1]Renal, Bartshealth Trust, London, United Kingdom; [2]Microbiology, Bartshealth Trust, London, United Kingdom.*

Background: The IRIDICA bacterial bloodstream (BAC BSI) assay is a semi-quantitative diagnostic test that uses polymerase chain reaction (PCR) and electrospray ionized-mass spectrometry (ESI-MS) to detect and identify bacterial, viral and fungal nucleic acids from a blood sample within 6 hours. Prompt management of sepsis is essential. Detection of pathogens with the current gold standard blood culture is challenging in the context of recent antimicrobial therapy. We compared the IRIDICA assay against blood culture technique in pyrexial renal patients.

Methods: We included renal patients who presented with a fever of >38ºC from January 2015 to April 2016. This included immunosuppressed transplant recipients and dialysis patients. A 5ml EDTA sample was taken with blood culture for retrospective IRIDICA analysis. The IRIDICA technician was blinded. We used our renal database to establish if patients had received antimicrobial therapy in the preceding 30 days. We excluded the patients who did not have a blood culture analysis at the time of fever.

Results: We analysed 182 samples from January 2015 – April 2016. Mean age of patients was 57.6 years. This included patients who had more than one presentation during this period. Compared to blood culture the IRIDICA assay demonstrated a sensitivity and specificity of 70%. The positive predictive value was 26% and the negative predictive value was 94%. 39 (21%) samples were positive for IRIDICA but negative for blood culture. Of these 72% had received antimicrobials in the preceding 30 days. 14 samples had both positive blood culture and IRIDICA samples. None of these patients had antimicrobial therapy in the preceding 30 days.

Conclusions: The IRIDICA assay is superior to blood cultures when detecting a pathogen in a renal patient who has been treated with antimicrobials in the preceding 30 days. IRIDICA is also effective in excluding infection. Without preceding antibiotic use, blood cultures are just as effective as the IRIDICA assay. However, the IRIDICA assay allows faster identification of pathogens compared blood culture, which can take 5 days.

SA-PO244

Decreased Expression of the Gut-Homing CCR9 Chemokine Receptor on Memory B-Cell Subsets in IgA Nephropathy Marten Segelmark,[1] Camilla Skoglund,[1] Daniel Söderberg,[1] Per Eriksson.[2] *[1]Medical and Health Sciences, Linköping Univ, Linköping, Östergötland, Sweden; [2]Clinical and Experimental Medicin, Linköping Univ, Linköping, Östergötland, Sweden.*

Background: IgA nephropathy and IgA vasculitis are characterized by the deposition of polymeric undergatactosylated IgA1 (GdIgA1) in the renal mesangium. GdIgA1 should normally be secreted into the respiratory and gastrointestinal tract, but is in IgAN often elevated in the systemic circulation. Defective homing of lymphocytes could contribute to ectopic production of GdIgA1.

Methods: The putative human counterparts to the three B-cells lineages defined in mice: B1-, B2- and MZ-B-cells were characterized by multi-channel flow cytometry and the percentage of each subset expressing IgA as wells as the chemokine receptor CCR9 was determined. 25 patients with IgAN/IgAV were compared with 20 healthy age matched controls.

Results: There were no differences between IgAN and IgAV patients. IgAN/V patients tended to have more lymphocytes and a larger percentage of B-lymphocytes, but differences were not significant. There were no differences in the proportion of naïve, B1-, MZ- and B2-like populations between patients and controls. Similarly the proportion of IgA+ cells was similar in all subsets. However, patients exhibited a significantly lower proportion of CCR9+ B1-like cells. When comparing the CCR9+ on IgA positive cells, the proportion was lower in patients for all types of memory B-cells, the most pronounced difference was found among the MZ-like cells.

	B1-like cells (CD43+,CD27+)		MZ-like cells (CD27+, IgM++,CD45RB++)		Memory B2- cells (CD27+, IgM-/int)	
	Pat/Con	p	Pat/Con	p	Pat/Con	p
I. % of B-cells	5.7/5.7	ns	12.6/10.7	ns	22.8/19.3	ns
II. % IgA+ of I	36.2/39.9	ns	11.8/9.5	ns	28.5/30.3	ns
III % CCR9+ of I	10.6/15.6	0.007	9.8/10.8	ns	9.6/11.5	ns
IV % CCR9+ of II	10.1/17.5	0.03	14.5/24.6	0.003	9.8/13.1	0.02

Conclusions: IgA bearing memory B-cells of three different subsets, but not naïve B-cells, from patients with IgAN and IgAV exhibit a lower percentage of CCR9 expressing cells. As CCR9 directs B-cells to the small intestine this could possible facilitate extra-mucosal production of GdIgA1.

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

SA-PO245

Identification of CD146 as a Novel Biomarker to Evaluate the Disease Progression and Prognosis in Early Diabetic Nephropathy Yang Fei,[1] Ying Fan,[1] Li Zheng,[2] Jiemin Wang,[2] Jiejun Wen,[1] Zhenzhen Jiang,[1] Li He,[1] John C. He,[3] Niansong Wang.[1] *[1]Nephrology, Shanghai Jiao Tong Univ Affiliated Sixth People's Hospital, Shanghai, China; [2]Project and Portfolio Management Team, Asia & Emerging Market iMED, AstraZeneca R&D, Shanghai, China; [3]Medicine, Icahn School of Medicine at Mount Sinai, New York.*

Background: Glomerular endothelial cell injury plays a crucial role in the development and progression of diabetic nephropathy (DN). CD146, an endothelial marker, was reported to increase in chronic renal failure reflecting endothelial dysfunction. However, the role of CD146 in DN remains largely unknown.

Methods: 159 non-dialysis type 2 DN patients from 2008 to 2015 were enrolled to measure the serum concentration of soluble CD146 (sCD146). 94 pure diabetes mellitus type 2 and 100 healthy participants were taken as controls. The subjects were categorized by their CKD stages and CKD1-3 was defined as early eGFR loss. Another independent cohort of 49 patients with definite diagnosis of DN by kidney biopsy were eligible for the immunohistochemistry study of CD146.

Results: Our data showed that serum concentration of sCD146 was upregulated in patients with DN (648.2±292.6 ng/mL) as compared to DM(434.68±150.01ng/ml) and healthy control (358.3±121.4 ng/ml,$P<0.01$) . Elevated serum sCD146 was inversely associated with renal function ($p<0.01$) and proved to be a more optimal marker(AUC=0.803) than urine albumin creatinine ratio (UACR) (AUC=0.574, $p<0.01$) to evaluate disease progression of DN at early GFR loss. In kidney tissues, CD146 was co-localized with endothelial marker CD31 and increased in DN when compared with MCD and normal controls. The intensity of CD146 in kidney was associated with disease progression and with severity of pathological findings in DN patients at early GFR loss. The univariate Cox regression suggested that both serum concentration of sCD146 and kidney *in situ* expression of CD146 were associated with the renal outcomes.

Conclusions: Our findings demonstrate that CD146 could be a practical biomarker to evaluate disease progression and predict renal outcomes in patients with early to moderate stages of DN. The aberrant expression of CD146 may reflect endothelial dysfunction and vascular angiogenesis in DN.

SA-PO246

Isolated Segmental Sclerosis (Without Significant Proteinuria) in the Early Post-Transplant Period Rarely Leads to Focal Segmental Glomerulosclerosis Vighnesh Walavalkar, Zoltan G. Laszik, Kuang-Yu Jen. *UCSF Medical Center, San Francisco, CA.*

Background: The aim is to study isolated segmental sclerosis (IS) seen in transplant (Tx) biopsies (Bx) from patients (pt) who do not have proteinuria.

Methods: TxBx from 01/2000-12/2015 were included. IS was defined as segmental sclerosis seen within 12 months of Tx from a pt without significant proteinuria (<750 mg/day) at time of Bx. Histology data, pt demographics and follow-up (FU) data ranging from 6-72 months were analyzed.

Results: IS was seen in 21/6366 (0.33%) of all Bx in the study period. 7/21 (33%) resulted in eventual graft loss, 1/21 (4.7%) of which progressed to focal segmental glomerulosclerosis (FSGS) with nephrotic range proteinuria (NRP). 14/21 (67%) had stable creatinine levels and no proteinuria in the 72 month FU period. 20/21 (95%) had FSGS-like histology. 5/21 (24%) had concurrent acute cellular rejection. Electron microscopy in 12 Bx showed: 5 with intact podocytes; 7 with focal effacement; and 0 with diffuse effacement.

Conclusions: IS in the early post-Tx period is rare. 1 case (4.7%) progressed to NRP, consistent with FSGS. Our study did not reveal sex, age or race predilection for IS. IS had no correlation with acute rejection. Histology could not predict which IS lesions would progress to FSGS. Awareness of IS and avoidance of usage of the term "FSGS" may help to prevent unnecessary treatment. Further studies are needed.

	Hyalinosis	Visceral epithelial cell hyperplasia	Intracapillary foam cells	Adhesions	Podocyte protein resorption droplets
1	X		X	X	X
2	X	X		X	X
3		X	X		X
4	X		X	X	
5		X			X
6	X	X		X	
7		X		X	
8		X		X	X
9			X	X	
10	X		X	X	
11					
12		X		X	X
13	X	X			
14	X	X	X		
15	X	X		X	
16	X	X		X	
17	X	X		X	
18	X			X	
19	X	X			X
20		X		X	
21	X		X	X	

SA-PO247

Validation of Whole Slide Digital Imaging in the Renal Biopsy Service at a Large Academic Medical Center Vighnesh Walavalkar, Kuang-Yu Jen, Zoltan G. Laszik. *UCSF Medical Center, San Francisco, CA.*

Background: The aim of the study was to validate the use of whole slide digital imaging (WSDI) in the renal biopsy (RBx) service at our institution. Patient care, efficiency, education and quality control (QC) were emphasized.

Methods: From 11/1/2015 to 4/30/2016 three slides (2H&E and 1 PAS) from all consecutive 'rush' transplant and native RBx (n=160) were scanned in on Philips UFS scanners at 40x and the WSDI were prospectively interpreted for a preliminary diagnosis (pDx). Review of the glass slides served as the "gold standard" for interpretation. A prospectively designed workflow was used to validate the process. WSDI were evaluated for QC in three areas: histotechnological deficiencies (HD), scanning errors (SE), and interpretative errors (IE). IE (due to either HD or SE) were further subdivided into minor IE, defined as those which did not affect making a pDx; and major IE, defined as those which precluded making a pDx by WSDI and required review of glass slides.

Results: Using WSDI, an efficient workflow was established to convey a pDx to the nephrologist. An average turnaround time (TAT) from the time of biopsy to pDx was established at 5.5 hours which included IF stain interpretation. HD caused minor IE in 9 cases (6%) and a major IE in 1 case (0.6%). SE caused minor IE in 11 cases (7%) and no major IE (0%). Drawbacks reported were hand fatigue (among some trainees); difficulty in appreciating fibrin thrombi [2 cases (1.2%)] and difficulty in appreciating arteriolar hyalinosis [5 cases (3.1%)]. A virtual environment was developed and used for trainee teaching, daily clinical conferences and remote RBx review with nephrologists at other sites. Both trainees and nephrologists had a favorable outlook to using WSDI for future RBx review.

Conclusions: Standardized histology and scanning operational protocols were crucial for validating the use of WSDI for RBx interpretation. There were no major IE attributed to WSDI and the TAT decreased significantly for a pDx. WSDI also contributed to improved education and allowed for remote on-line RBx review with nephrologists at other sites. Overall use of WSDI was met with great enthusiasm by technologists, trainees and referring nephrologists.

SA-PO248

Glomerulonephritis Associated with Allogeneic Bone Marrow Transplantation Yu Tateishi,[1,2] Eiji Ishimura,[1] Mari Sakura,[1,2] Mitsuru Ichii,[1] Yoshiteru Ohno,[1] Shinya Nakatani,[1] Akihiro Tsuda,[1] Masayuki Hino,[1] Masaaki Inaba.[1] *[1]Osaka City Univ Graduate School of Medicine, Japan; [2]Ishikiri Seiki Hospital, Japan.*

Background: Clinicopathological characteristics of glomerulonephritis (GN) associated with allogeneic bone marrow transplantation (BMT) are still insufficient. Previous reports on these cases have mainly referred to glomerular immunological changes; while tubulointerstitial and vascular lesions are known to be major findings of graft rejection in cases with renal transplantation.

Methods: Out of 129 BMT cases in Osaka City University Hospital from 2008 to 2011, nephrotic syndrome (NS) was seen in 4 patients (50.8 ± 9.3 year-old, 3 males and 1 female) after BMT. Their primary hematologic diseases consisted of 2 cases with acute lymphocytic leukemia, 1 with adult T-cell leukemia, and 1 with aplastic anemia. We analyzed these 4 cases with BMT associated GN clinicopathologically.

Results: Mean duration (± SD) between BMT and the onset of NS was 29.5 (± 9.8) months. One case received immunesuppressive therapy (cyclosporine (CsA) 10mg/day) at the onset. Urinary protein level was 7.4 ± 4.2 g/day. Renal histological diagnosis of membranous GN (MGN) and proliferative GN (PGN) was made in 3 cases and in 1 case, respectively. Moderate to severe interstitial infiltration of mononuclear cells accompanied by tubulitis, approximately 20-50% of parenchyma, was observed in 2 cases with MGN. In a case with PGN, several glomerular segmental double contours with segmental endocapillary proliferations were seen in light microscopy. The lesions were not accompanied with epithelial cell increase nor mesangial proliferation, suggesting the presence of acute endothelial cell injury. Mild interstitial infiltration of mononuclear cells was also observed in this case. All 4 cases were treated with prednisolone 40-50 mg/day and/or CsA 40-100 mg/day. Complete or partial remission was achieved after the treatment (urinary protein levels: 1.1 ± 0.9 g/day) within 3 months.

Conclusions: This study indicates that MGN is main lesion and acute tubulointerstitial and vascular lesions accompany BMT-associated GN, which may not be so rare complication of BMT. Clinically, favorable response to immunosuppressive therapy can be expected.

SA-PO249

Improvement of Clinical Outcome in Kidney Diseases via Online Thai Glomerular Disease Registry: The First Year Report Ratana Chawanasuntorapoj. *Thai Glomerular Disease Collaborative Network, Bangkok.*

Background: End stage renal disease (ESRD) cause the high morbidity, mortality, and cost in health care system. The prevention of ESRD is the early recognition and appropriate treatment. Glomerulonephritis is the third most common cause of ESRD in Thailand comparable to the Western country. In 2013, Thailand Renal Replacement Therapy (TRT) reported Lupus nephritis (LN) was the most common cause of ESRD followed by IgA nephropathy (IgAN), and focal segmental glomerulosclerosis (FSGS). The quality registry and network can provide the prompt management in these patients.

Methods: Thai Glomerular Disease Collaborative Network (TGDCN) originally consists of 9 tertiary care centers, We developed the Web-based Online registry to collect the data from GN patients with aged>18 years. We recorded the demographic data including gender, age, education, native habitat, the laboratory tests, and the pathological findings.

Results: We recruited666 patients performed native kidney biopsy during Jul 1, 2014 to Jun 30, 2015. The female to male ratio was 2.16:1. The mean age, creatinine, albumin, and cholesterol were 42 (18-82) years, 1.4 (0.4-13) mg/dL, 2.9+0.8 g/dL, and 296+118 mg/dL in respectively. The median proteinuria was 3.2 (0-22) g/day. The patients presented with 34% of nephrotic syndrome, 22% of nephritis, 21.7% of nephrotic nephritis, 52% of renal impairment (creatinine>1.2 mg/dL), and 54.4% of new or aggravated hypertension. The renal pathological findings showed 38% of LN, 17.6% of IgAN, and 9% of FSGS. The mean age of LN, IgAN, and FSGS were 34, 38, and 46 years. The average creatinine at biopsy of LN, IgAN, and FSGS were 1.9, 2.4, and 2.4 mg/dL.

Conclusions: Our study described the first three common renal pathological findings including LN, IgAN, and FSGS with the initial renal impairment at kidney biopsy. This might be the severity of the disease or the delay in performing biopsy due to facility of kidney biopsy and referring system. All three diseases were the most common GN causing the ESRD in Thailand. The development of qualified registry and GN network may improve the health care service and support the further study in both clinical and translational research.

Funding: Private Foundation Support

SA-PO250

Serum Cholesterol in Predicting Nephrotic Syndrome Diseases
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Background: Hypercholesterolemia is one of the criteria for nephrotic syndrome. However, the cut-off level of serum cholesterol for nephrotic syndrome has been not well defined.

Methods: The pathologic reports of native kidney biopsies of patients >18 years of age with proteinuria ≥3 g/day performed at Mayo Clinic, Rochester, MN between 1/2000 and 8/2014 were reviewed. Patients who had liver disease, malnutrition, urinary dysmorphic RBC or RBC cast, paraproteinuria with urine albumin < 3 g/day, inconclusive diagnosis, no electron microscopy report or received immunosuppression within 6 months prior to renal biopsy were excluded. Patients were divided into group 1: nephrotic syndrome diseases (MCD, primary FSGS, membranous nephropathy and amyloidosis) and group 2: other diseases presented with nephrotic range proteinuria (secondary FSGS, diabetic nephropathy, glomerulonephritis, TMA, advanced kidney disease and other diseases). Receiver operating characteristic (ROC) curve was used to determine sensitivity and specificity of serum cholesterol for prediction of nephrotic syndrome diseases.

Results: From total of 6,707 native renal biopsy reports, 251 patients fulfilled the above criteria and were included in the study. 137 patients were classified into group 1 and 114 were in group 2. The average serum cholesterol was significantly higher in group 1 (303±105 vs 206±68 mg/dL, P<0.0001). The ROC area under the curve for serum cholesterol to predict nephrotic syndrome diseases was 0.79 (P<0.001). Serum cholesterol 300 and 350 mg/dL were highly specific to nephrotic syndrome diseases (specificity 89% and 99%, respectively).

Serum Cholesterol (mg/dL)	Sensitivity	Specificity
≥200	85%	56%
≥250	65%	76%
≥300	55%	89%
≥350	29%	99%

Conclusions: Total cholesterol ≥ 300 mg/dL is highly specific to nephrotic syndrome diseases and may help differentiate with other diseases that also contribute to nephrotic-range proteinuria. Renal biopsy should be considered in patients with nephrotic-range proteinuria and serum cholesterol more than 300 mg/dL.

SA-PO251

Bedside Real-Time Ultrasound-Guided Kidney Biopsy Service Fully Run by Nephrology: Safety and Specimen Adequacy
Mohammed Alzubaidi, Jalal E. Hakmei, Na'Da Abouhassan, Juan Carlos Q. Velez. *Internal Medicine, Div of Nephrology, Medical Univ of South Carolina, Charleston, SC.*

Background: Percutaneous kidney biopsy (PKB) is routinely performed by a nephrologist with ultrasound (US) guidance from a radiologist, or solely by interventional radiology (IR). There is paucity of data regarding safety and feasibility of PKBs performed by a nephrology (NEPH) team without participation of a radiologist. We hypothesized that PKBs independently performed by a NEPH team are as safe and optimal in yield of kidney tissue as those performed by IR.

Methods: We established a NEPH clinical service to independently perform bedside real-time US-guided PKBs. Records were reviewed to compare complication rate [minor: hematoma, gross hematuria; major: blood transfusion (ordered at the discretion of the hospitalist) invasive procedure, intensive care or death] and biopsy adequacy (successful retrieval of glomeruli-containing tissue fully available for light, immunofluorescence and electron microscopy) of PKBs performed by the NEPH team vs. those performed by IR under computer tomography (CT) guidance.

Results: We identified 109 PKBs performed by NEPH (16g needle) and 103 by IR (68% 16g, 32% 18g) over the last 3 years. Groups were comparable regarding age (46.0 vs. 50.2 yrs) and baseline hemoglobin (10.6 vs. 10.2 g/dL) and platelet count (229 vs. 232 x10^3/mm^3), whereas mean body mass index (BMI) (28.5 vs. 31.8 kg/m^2; p=0.012) and estimated glomerular filtration rate (eGFR) (57.1 ± 47 vs. 32.3 ± 37 ml/min/1.73m^2; p<0.008) were different for NEPH and IR, respectively. Complication rates were similar between groups (major: 6.4% vs. 4.9%; minor: 2.7% vs. 6.8%, for NEPH and IR, respectively), even among those with BMI > 30 kg/m^2 or eGFR < 45 ml/min. Two IR cases but no NEPH cases required arterial embolization. One death occurred with IR, none with NEPH. Adequate tissue specimens were obtained in 104 cases (95.4%) of the NEPH cohort vs. 84 (81.6%) of the IR cohort (p=0.002).

Conclusions: Real-time US-guided PKBs performed by a NEPH service are as safe as CT-guided PKBs performed by IR in a high risk population at an academic medical center, and may provide superior tissue retrieval.

SA-PO252

The Characteristics of Class II MHC+ Mononuclear Cells within Native Kidney Are Distinct from Peripheral Blood and Transplant Kidney
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Background: Mononuclear phagocytes (MPh) are a heterogeneous population of cells that resides in the kidney. Little is known of their phenotype in normal human kidney and of their contribution to injury compared to influx of circulating monocytes from blood.

Methods: Healthy kidney from 12 human nephrectomies and 3 transplant biopsy cores was enzymatically digested and compared to paired peripheral blood leukocytes using 7 color-flow cytometry. Nephrectomies were from subjects with normal renal function. Transplant biopsies were performed for worsening renal function. Lymphocytes, B and NK cells were excluding by negatively gating $CD3^+$, $CD56^+$ and $CD20^+$. The surface expression of $CD45^+$Class II MHC (HLA-DR), CD11b, CD11c, CD14 and, in a subset, CX3CR1, CD33, CD40 and CD86 was analyzed.

Results: The proportion of $CD45^+$ mononuclear cells positive for HLA-DR and their HLA-DR surface expression levels were higher for native kidneys compared to blood leukocytes and transplants. Three populations of HLA-DR^+ cells were identified in kidney. Their expression of the monocyte marker CD14 was compared among native kidney, transplant and matching blood leukocytes (table 1). Autofluorescent cells were increased in transplant and native kidneys experiencing ischemia during removal. CXC3R1, CD33, CD40, CD86 were found to be most highly expressed by $CD11b^{++}$/$CD11c^+$ MPh of native kidneys.

HLA-DR^+ Sub-population (%CD14)	Native Kidney	Blood (Native)	Transplant	Blood (Transplant)	P value
$CD11b^{++}$/$CD11c^+$	86.2 ±3.6*	83.9 ±4.9	46.4 ±26.9*	97.2 ±1.6	0.02*
$CD11b^+$/$CD11c^+$	33.6 ±8.8	18.2 ±4.8	88.8 ±11.1**	14.9 ±8.2**	0.005**
$CD11b^+$/$CD11c^-$	60.9 ±9.2^	10.8 ±8.2^	44.2 ±25.9	1.2 ±1.2	0.0006^
*Native Kidney vs. Transplant, **Transplant vs. Blood (Transplant), ^Native kidney vs. Blood (native)					

Conclusions: Class II MHC^+ MPh subpopulations from healthy human kidney, have higher HLA-DR expression than their counterparts in blood. Renal MPh subpopulations variably express the monocyte marker CD14. $CD14^+$ MPh were less frequent in transplant compared to native kidney.

Funding: Private Foundation Support

SA-PO253

The Clinicopathological Characteristics in Renal Insufficiency Patients with Different Renal Parenchymal Thicknesses
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Background: The normal value of renal parenchymal thickness (RPT) by ultrasound is about 1.5cm (1.28 to 2.08cm) in the adults, usually. The reduced renal parenchymal thickness is associated with renal impairment in patients with kidney disease. The aim of this study was to explore the pathological features in renal insufficiency patients with different renal parenchymal thickness.

Methods: The patients with kidney disease from our hospital from December 2014 through to December 2015 were screened. The inclusion criteria: 1) age ≥18 years old; 2) serum creatinine ≥115μmol/L (the reference value is 20~115μmol/L) or eGFR<60ml/mim/m^2 and 3) undergoing renal biopsy. The exclusion criteria:1) patients with renal biopsy specimen less than 10 glomerulus. 2) Patients with prerenal and postrenal kidney dysfunction. The clinical data, kidney dimensions at sonography and renal histopathologic data were collected. And the patients were divided into two groups according to the RPT value of 1.5cm, the normal RPT group and the reduced RPT group. SPSS 22.0 software was used for all analyses.

Results: 187 patients (aged 18-84 years) were enrolled. Compared to the normal RPT group (69 cases), the patients in the reduced RPT group (118 cases) showed less eGFR (28.0 (15.9, 40.9) vs. 36.8(17.4, 48.2) ml/(min*1.73 m^2) and lower total urine protein ((2.8 (1.2, 4.9) vs. 3.7(1.5, 8.1) g/day), higher albumin (33.7(27.6, 39.2) vs. 28.7(18.8, 36.0) g/L), respectively. And there is no significant difference in age, blood pressure, hemoglobin, serum creatinine and lipids. In the reduced RPT group, the ratio of total glomerular sclerosis >50% (40.7% vs. 15.9%, p<0.05),renal tubular atrophy (83.1% vs. 60.9%, p<0.05), interstitial inflammatory cell infiltration with fibrosis (80.5% vs. 60.9%, p<0.05), and small artery vitreous degeneration(53.4% vs. 36.2%, p<0.05), are higher than the normal RPT group, respectively.

Conclusions: The patients with the reduced RPT showed more glomerular sclerosis and interstitial fibrosis.

Funding: Government Support - Non-U.S.

SA-PO254

Endogenous Measures of Tubular Secretion in Spot versus Timed Urine Specimens
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Background: Tubular secretion is an important kidney function essential for drugs excretion. Recent studies using 24 hour urine samples have identified endogenous compounds that are highly secreted and are associated with mortality and progressive kidney disease. We aimed to evaluate the utility of spot urine specimens for assessing tubular secretion.

Methods: Three healthy adult male volunteers provided two spot serum samples and urine samples at 4 hourly intervals over 24 hours. Liquid chromatography tandem mass spectrometry was used to quantify serum and urine concentrations of solutes and the fractional excretion (FE, %) of each was calculated as (Metabolite urine × Creatinine serum)/(Metabolite serum × Creatinine urine)×100. We measured FE of 15 metabolites including 5 that in prior studies have shown to be secreted (FE > 100% relative to creatinine) and 10 others with unknown kidney handling. Among those metabolites found to be secreted, we evaluated the mean variability over 24 hours.

Results: The mean age was 38 years and the mean creatinine clearance using 24 hour urine collection was 138 ml/min. Overall 6 of 15 markers had FE > 100 (range 218 –1019%), 5 of which had been reported in prior studies using 24 hour urine samples. The FE of these 6 candidate secretion markers was relatively stable, with diurnal variation in secretion described as maximum to minimum FE ratios as high as 3.2:1 for cinnamoylglycine to a low of 1.9:1 for phenylacetylglutamine.

Fractional Excretion (%) of Candidate Secretion Markers over 24 hours

	4PM	8PM	12AM	4AM	8AM	12PM	4PM	Mean	SD	Maximum/ Minimum Ratio
Tigaglycine	766	737	1490	1313	1036	1162	627	1019	323	2.4
Isovalerylglycine	989	692	1012	857	1024	1444	608	947	273	2.4
Hippuric acid	826	682	1029	703	715	776	488	746	164	2.1
Phenylacetylglutamine	567	565	817	600	680	589	366	598	136	1.9
Suberic acid	194	204	337	214	186	235	171	220	55	2.0
Cinnamoylglycine	159	209	361	155	318	213	114	218	90	3.2

Abbreviations: SD- intra-individual standard deviation

Conclusions: Several endogenous markers of tubular secretion are relatively stable over the day, making spot urine specimens feasible for assessing tubular secretion. Studies evaluating these markers in older persons and across a wide range of eGFR are needed.

SA-PO255

Stretching and Exposure to Protein Synergistically Activate Innate Immunity and Inflammation in Proximal Tubular Cells Simone C.A. Arias,[1] Viviane D. Faustino,[1] Luciene dos Reis,[1] Flavia G. Machado,[2] Niels O.S. Camara,[1] Clarice K. Fujihara,[1] Roberto Zatz.[1] *[1]Univ of Sao Paulo; [2]Washington Univ.*

Background: Cell cyclic stretching (ST) stimulates inflammation in glomerular cells, but it is unclear whether tubular cells respond to ST in the same manner. Moreover, a conceivable effect of ST on innate immunity activity has not been examined. In addition, the effect of ST has been studied in the absence of protein, a condition not seen in vivo. We investigated whether: 1) ST alone activates innate immunity in proximal tubular cells (PTC); 2) Simultaneous PTC exposure to ST and protein results in more intense inflammation and innate immunity activation than ST alone.

Methods: Rat PTC (NRK52E) were cultured and subjected to ST (20% maximum elongation) (ST, N=4) or ST plus bovine serum albumin (BSA), 1 mg/mL (ST+BSA, N=4). Control cultures (C, N=4) were exposed to no ST or BSA. After 24 h, MCP-1 (pg/mL), IL-6 (pg/mg) and IL-1β (pg/mg) were evaluated by ELISA, while TGF-β, Collagen-1 (COLL-1), TLR4 and Caspase-1 contents were assessed by WB (x C).

Results:

	C	ST	ST+BSA
MCP-1	45±10	120±34	1112±204[ab]
TGF-β	1.0±0.2	1.8±0.1[a]	1.9±0.2[a]
COLL-1	1.0±0.2	2.0±0.5	3.4±0.9[a]
Caspase-1	1.0±0.1	2.3±0.4	4.2±1.1[ab]
TLR4	1.0±0.2	0.9±0.1	2.1±0.2[ab]
IL-1β	1.9±0.5	6.5±1.5	10.0±5.4
IL-6	1.2±0.4	1.0±2.8	11.1±6.8

Mean±EP, [a]p<0.05 vs C, [b]p<0.05 vs ST

Exposure of PTC to ST or ST+BSA resulted in no limitation of cell viability or proliferative capacity (not shown). ST alone significantly increased TGF-β. Exposure to both ST+BSA increased MCP1, IL-6 and COLL1 protein expression. In addition, ST+BSA activated innate immunity, as indicated by increased expression of TLR4, caspase-1 and IL-1β.

Conclusions: ST and BSA synergistically cooperate to activate innate immunity and enhance inflammation and COLL production. Since both abnormalities can be present in chronic kidney disease, this double insult can be an important factor leading to progressive tubulointerstitial fibrosis in this setting. FAPESP/CNPq.

SA-PO256

The Low Albuminuria in the Face of Overt Proteinuria Reported in the African American Study of Kidney Disease and Hypertension (AASK) Patients Is an Artifact Caused by Acetic Acid Used as a Preservative Salem Almaani, Daniel J. Birmingham, Brad H. Rovin, Lee A. Hebert. *Div of Nephrology, Ohio State Univ, Columbus, OH.*

Background: The pathogenesis of AASK nephropathy (AASK-N) is unclear. As previously reported, progression occurred at low levels of proteinuria, most of which was non-album proteinuria (NAP). We attempted to determine whether the NAP of AASK-N consisted of low molecular weight proteins characteristic of a tubulopathy.

Methods: We obtained 298 AASK 24-hour urine samples from the NIDDK biorepository. From this, we selected 37 samples based on protein-to-creatinine ratios (PCR) of 0.2-1.0. Levels of albumin (Alb), cystatin C (Cys), beta-2 microglobulin (B2M), epithelial growth factor (EGF), neutrophil-gelatinase-associated lipocalin (NGAL), osteopontin (OPN), and uromodulin were measured. For comparison, levels were also obtained from 24-hour urine samples of 20 lupus nephritis (LN) patients with similar PCRs and storage conditions, and from 15 African American controls. Urine samples were also assessed by SDS-PAGE for overall protein quality.

Results: The AASK-N urines showed lower concentrations of Alb, B2M, Cys, EGF, and OPN compared to LN samples or to controls (all P < 0.01). In fact Alb, B2M, Cys, and OPN were undetectable in the majority of AASK-N samples. SDS-PAGE revealed near-absence of the intact 68kD albumin band in most AASK-N samples, but two prominent bands of <10 kD, documenting protein degradation. By comparison, the LN urines showed intact albumin and no bands <10 kD. A second NIDDK batch of the AASK-N urines as well as urines from these patients collected at different study visits revealed similar results. Attempts to replicate degradation in LN samples by storage up to 5 days at 37^0 C or after 8 freeze-thaw cycles were unsuccessful. However, treatment of these LN urine samples with acetic acid at the same concentration used for urine collections in the AASK protocol (0.5%) did replicate the protein degradation pattern seen in the AASK-N urines.

Conclusions: The low urine albumin and high NAP reported in AASK-N likely is an artifact related to the use of acetic acid as a preservative.

Funding: Private Foundation Support

SA-PO257

Risk of Percutaneous Renal Biopsy of Native Kidneys in the Evaluation of Acute Renal Failure Stephen M. Korbet, William Luke Whittier. *Internal Medicine, Rush Univ Medical Center, Chicago, IL.*

Background: The purpose of this study is to assess the risk of bleeding complications in pts undergoing percutaneous renal biopsy (PRB) of native kidneys for the evaluation of acute renal failure (ARF).

Methods: PRB of native kidneys was performed in 958 adult pts from 1991 through 2015 at Rush Medical Center with real-time ultrasound and an automated biopsy needle. Baseline demographic, clinical and laboratory information was collected along with the indication for PRB and pts were followed prospectively for complications. PRB for evaluation of ARF was performed in 160 pts (17%). The remaining 798 pts were biopsied for hematuria, and/or proteinuria, and/or chronic kidney disease. Complication rates were compared between these 2 groups. A complication was defined by the need for an intervention (transfusion of packed red blood cells, an interventional radiologic (IR) or surgical procedure) or the need for re-admission or death. Statistical analysis was performed using Fischer exact test for categorical data and Mann-Whitney test for continuous data. Results are reported as means ± standard deviation and a p-value of <0.05 was considered significant.

Results: Pts biopsied for ARF were older (58±17 vs. 44±16 yrs, P <0.01), had a higher level of serum creatinine (SCr) (4.5±2.7 vs. 1.8±1.6 mg/dl, P <0.01 and >1.5 mg/dl in 94% vs. 37%,P <0.01), a lower hemoglobin (10.4±1.7 vs. 12.1±2.1, P <0.01 and <10.0 g/dl in 43% vs. 17%, P <0.01), and a greater proportion with an abnormal bleeding time (>9 min: 13% vs. 7% (P <0.05) and/or an abnormal PTT (>33 seconds: 15% vs. 5%, P <0.01), all risk factors for complications. The diagnostic adequacy of the biopsy was similar in both groups (ARF-98% vs. 99%). Complications post-PRB were significantly greater in pts biopsied for ARF (11.3% vs. 6.6%, P <0.05; OR 1.78) with pts biopsied for ARF requiring more transfusions (10% vs. 5.1%, P = 0.03) and twice as many IR procedures (1.9% vs. 1.0%, P = 0.4). There were no deaths in pts biopsied for ARF.

Conclusions: We conclude that pts biopsied for evaluation of ARF have increased risk factors for a complication and a greater rate of complication requiring intervention post-PRB compared to pts biopsied for other reasons.

SA-PO258

Proteomic Analysis of Micro-Dissected Nephron Segments and Urine Selected PLA2R1 and GGT5 as New Urinary Biomarker Candidates for Chronic Kidney Disease Hidehiko Fujinaka,[1,4] Shigeru Miyazaki,[2] Chizuko Kitabayashi,[3] Yoshio Konishi,[3] Tadashi Yamamoto.[4] *[1]Inst for Clinical Research, Niigata National Hospital, Kashiwzaki, Niigata, Japan; [2]Shinrakuen Hospital, Niigata, Japan; [3]Osaka City General Hospital, Osaka, Japan; [4]COI-s Biofluid Biomarker Center, Inst of Research Collaboration and Promotion, Niigata Univ, Niigata, Japan.*

Background: New biomarkers have been searched for the early diagnosis of chronic kidney disease (CKD), mostly in patients urine with overt proteinuria. The trials have not been so successful since most of the urinary proteins are derived from plasma in the patients.

Methods: We have changed the strategy for urinary biomarkers discovery: 2 proteome datasets of each nephron segment and of urine were analyzed. Each of the kidney nephron segment without apparent diseases was collected by laser micro-dissection and directly digested by trypsin. Urine proteins were purified from healthy volunteers and subjected to in-solution digestion with trypsin. Both of these obtained peptides were analyzed by mass spectrometry followed by semi-quantitative analysis. By comparing these proteome datasets, nephron-segment-unique urinary proteins were selected as urinary biomarker candidates. The site-uniqueness in the kidney was confirmed by IHC using specific antibodies. Amounts of the selected proteins in urine were measured by Surface Plasmon Resonance System in IgA nephropathy (IgAN) patients and healthy volunteers.

Results: Nephron-segment-unique urinary proteins were selected: glomerulus; 89, proximal tubule; 68, distal tubule; 8, collecting duct; 5, and others. Amongst them, PLA2R1 expression was confirmed in glomerular podocytes, and GGT5 in the interstitial matrix by IHC. PLA2R1 urinary excretion was significantly higher in IgAN rather than in normal (p<0.01), and the excretion in CKD stage 1 IgAN tended to be higher than that in normal (p=0.07). GGT5 urinary excretion was significantly higher in IgAN rather than in normal (p<0.01).

Conclusions: Proteomic analysis of the micro-dissected nephron segments and urine with antibody-based validation revealed that podocyte-derived PLA2R1 and interstitial-matrix derived GGT5 are proposed as new urinary biomarkers for glomerular injury and interstitial events.

SA-PO259

The Clinicopathological Characteristics of Central Fibrosis Nodule in Glomerular Vascular Pole Satoshi Hara,[1] Yutaka Yamaguchi,[2] Mitsuhiro Kawano.[1] *[1]Internal Medicine, Kanazawa Univ Graduate School of Medicine, Kanazawa, Ishikawa, Japan; [2]Yamaguchi's Pathology Laboratory, Chiba, Japan.*

Background: Central fibrous nodule in glomerular vascular pole (CFN) is histologically characterized by periodic acid Schiff-negative small nodular lesion located in glomerular vascular pole. Although this pathological finding is observed in various disease entity, the clinicopathological characteristic remains fully undetermined. The present study was conducted to clarify the epidemiology and clinicopathological characteristics of CFN.

Methods: 103 kidney needle biopsy specimens diagnosed in Kanazawa University Hospital during 2015 were used. First, the components of CFN were analyzed by immunostaining and electron microscopy. Second, patients were divided into 2 groups [CFN (+) or CFN (-) group], according to the presence of CFN. Clinical and histological features were compared between 2 groups.

Results: CFN was observed in 57 of 103 cases (55.3%). Immunostaining revealed that CFN consisted of fibrillar collagens (collagens I and III) in addition to collagen IV. Congo red staining was negative in all cases. Electron microscopy confirmed fibril-rich lesions of CFN. Clinically, CFN (+) group were older age (62.3±2.0 vs. 49.8±3.0 years; $p<0.01$) and had significant increase of hypertension (69.6 vs. 41.3%; $p<0.01$) and hyperlipidemia (58.9 vs. 34.9%; $p<0.05$) compared with CFN (-) group. Histologically, elastofibrosis of interlobular artery (72.5 vs. 44.2%; $p<0.01$) and arteriolar hyalinosis (66.7 vs. 41.3%; $p=0.01$) were significantly evident in CFN (+) group compared with CFN (-) group. There were no significance in regard to gender, body mass index, diabetes mellitus, hyperuricemia, proteinuria, hematuria, kidney dysfunction, and background kidney disease.

Conclusions: CFN is a fibril-rich nodule and the formation is associated with aging, hypertension and hyperlipidemia clinically. CFN is also associated with arteriolosclerosis and arteriolar hyalinosis histologically, suggesting that the pathophysiology of CFN resembles that of atherosclerosis in the kidney.

SA-PO260

A Novel Transgenic Mouse Model to Study Renal Tumorigenesis Anna Julie Peired,[1] Alessandro Sisti,[2] Giulia Antonelli,[1] Paola Romagnani.[1,2] *[1]Excellence Centre DENOTHE, Univ of Florence, Florence, Italy; [2]Nephrology Unit, Meyer Children's Univ Hospital, Florence, Italy.*

Background: Kidney cancer accounts for about 2% of all cancers, with about 190,000 new cases per year worldwide, with a higher incidence in developed countries. Recent studies suggest that chronic kidney disease (CKD) is a crucial risk factor for the development of kidney cancer. As other studies hint that the Notch pathway may be critical for CKD progression to end stage kidney disease, we created a transgenic mouse model that chronically express Notch1 in the tubular compartment, in order to study the mechanisms of kidney regeneration.

Methods: To this aim, we developed Pax8-rtTA/tetO-Cre/Rosa26-Confetti/Rosa26-Notch1 mice, in which the constitutive expression of cleaved Notch1 is limited to Pax8+ tubular cells, and is controlled by the inducible Tet-On system, allowing us to activate Notch1 expression only in adult animals. The Confetti reporter activated together with Notch1 led to the stochastic expression of one out of four fluorescent proteins, allowing us to verify the eventual presence of clonal cell proliferation.

Results: Analysis of kidneys showed numerous, multicentric and progressive pretumoral and tumoral lesions. Indeed, persistent Notch1 expression in tubular cells led to the formation of a broad spectrum of lesions of proliferative and non-proliferative nature. Monitoring over 9 months post induction allowed the determination of the evolutionary nature of the various types of lesions: glomerular cysts, simple tubular cysts, simple and atypical tubule hyperplasia. In addition, lineage tracing studies showed their evolution into papillary adenomas and even adenocarcinomas, characteristic of an increasingly aggressive phenotype. We could also observe the progressive loss of renal function. The Confetti reporter showed that most of the lesions were mono- or biclonal, demonstrating for the first time the clonal nature of pretumoral and tumoral renal lesions.

Conclusions: This mouse model represents a useful new tool for the study of tumor development mechanisms in the kidney and provides the first experimental demonstration of the link between CKD and the development of renal pre-neoplastic and neoplastic lesions up to cancer.

Funding: Government Support - Non-U.S.

SA-PO261

Influence of Physical Preconditioning in Renal Damage Induced by Adriamycin in Rats and Its Relationship with Endothelial Lesions and Angiogenesis in the Renal Cortex Camila M. Faleiros, Heloisa Della Coletta Francescato, Cleonice Silva, Terezila Machado Coimbra. *Univ of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil.*

Background: A single dose of adriamycin (ADR) in rats induces a progressive and irreversible proteinuria that progresses to focal segmental glomerulosclerosis and tubulointerstitial lesions. Regular physical activity can be a preventive and therapeutic intervention in clinical and experimental conditions. Physical training has beneficial effects on endothelial function. This study evaluated the influence of physical preconditioning in renal damage induced by ADR in rats and its relationship with endothelial lesions and angiogenesis.

Methods: Male Wistar rats were submitted or not to treadmill running for 4 weeks and injected (i.v.) with ADR (2.5 mg/kg) or saline. The animals were divided in: sedentary+saline (SED+SAL), physical training+saline (PhT+SAL), sedentary+adriamycin (SED+ADR), physical training+adriamycin (PhT+ADR) groups. Twenty-four-hour urine samples were collected 7, 30, and 60 days after injections to quantify albuminuria. The kidneys were removed 60 days after treatment for morphometric and immunohistochemical analysis.

Results: SED+ADR group presented progressive increase in albuminuria from the 7th to 60th days, which were less intense in PhT+ADR group. Those animals also presented higher desmin expression (marker of podocyte lesion) at the glomerular edge (1.31±0.15), enlargement of tubular interstitial area (33.7±2.12%), as well as higher macrophage numbers in the renal cortex (10.56±1.17) compared to control. These alterations were smaller in PhT+ADR group (0.65±0.09, 21.23±1.71, 6.37±0.58, respectively). The SED+ADR group also presented reduction in vascular endothelial growth factor (0.95±0.1), endothelial cells (0.74±0.15) and endothelial nitric oxide synthase (3.41±0.36) expressions in the renal cortex, which were attenuated in the PhT+ADR group (1.2±0.06, 1.07±0.08, 5.61±0.48, respectively).

Conclusions: Physical training prior to ADR injection reduced the renal damage induced by this drug. This effect was related to angiogenesis, reduction in the endothelial lesions and inflammatory process in the renal cortex of these animals. Grants: CAPES, FAPESP (12/50180-2).

Funding: Government Support - Non-U.S.

SA-PO262

Primary Endothelial Lesions in Mouse Kidneys Induce a Platelet Mediated Inflammatory Response Sophie Lengning, Jan Sradnick, Anika Luedemann, Bernd Hohenstein, Christian Hugo. *Div of Nephrology, Dept of Internal Medicine III, Univ Hospital CGC, Dresden, Germany.*

Background: We have recently shown that platelets (PLT) directly mediate endothelial lesions in a murine model of site-selective endothelial cell (EC) injury. With respect to indirect, pro-inflammatory effects, PLT's status remains unclear. To further investigate their potential role for the inflammatory response we here induced EC lesions and depleted PLT 24 hours later.

Methods: The induction of EC injury was performed by renal-arterial perfusion of Concanavalin (ConA)/ anti-conA in 51 C57Bl/6 mice. On day 1, PLT were depleted using anti-GPIb alpha antibodies (n= 13), mice perfused with NaCl solution (n= 23) or polyclonal non-immune rat IgG (n= 15) served as controls (CTRL). Mice were sacrificed on days 2 and 5. FACS analysis was used to verify PLT depletion (morphological and $CD41^+$), and recruitment of neutrophils ($CD11b^+GR1^+$), macrophages ($F4/80^+CD11b^+CD11c^+GR1^-$), B-cells ($IgM^+B220^+CD19^+$) and T-cells ($CD4^+$ or $CD8^+$). Harvested kidneys were also partly fixed for immunohistochemical staining with MAC2, F4/80 and CD31 antibodies.

Results: Platelet depletion was successfully established (CD41+ CTRL: 92.99% vs. PLT depleted: 2.42%). FACS analysis detected a significant reduction of T-Cells, $CD4^+$ (day 2: 2.02% vs. 1.01% and day 5: 1.96% vs 1.14% in CTRL vs. PLT depleted mice), as well as $CD8^+$ (day 2: 2.64% vs. 1.08%, day 5: 3.77% vs. 1.87%). B-Cells were not different. Monocytes and their subpopulation of macrophages were reduced in PLT depleted mice (day 2: 0.29%, day 5: 0.48%) compared to CTRL (day 2: 0.53%, day 5: 0.84%). This finding was approved by periglomerular cell count of F4/80 positive cells and glomerular cell count of MAC2 positive cells. Systemic measurements did not reveal differences in cell counts.

Conclusions: The present study emphasizes the relevance of activated platelets after EC injury. It directly links the presence of platelets with the recruitment of various inflammatory cells in injured kidneys, representing an additional therapeutic aspect of platelet inhibition.

SA-PO263

Compound K Inhibits NF-κβ/NLRP3 Inflammasome Activation and Ameliorates Renal Inflammation in Unilateral Ureteral Obstruction Mice Shuk-Man Ka,[1] Ann Chen.[2] *[1]Graduate Inst of Aerospace and Undersea Medicine, National Defense Medical Center, Taipei, Taiwan; [2]Dept of Pathology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan.*

Background: Compound K (CK), a major absorbable intestinal bacterial metabolite of ginsenosides, has been shown to be anti-inflammatory, but its effect on renal inflammation and fibrosis remains largely unknown.

Methods: In the present study, we verified both the renoprotective and therapeutic effects on renal inflammation and fibrosis in a mouse unilateral ureteral obstruction (UUO) model and investigated the mechanisms of action, including the use of urine samples retained in the dilated pelvic cavity of the diseased kidney, renal draining lymph nodes, renal tubular epithelial cells (TECs) under mechanical-induced pressure, and macrophages.

Results: The results show that administration of CK decreased: [1] parenchymal loss, inflammation and fibrosis; [2] infiltration of macrophages and T cells; and [3] production of proinflammatory cytokines (renal tissues and in urine samples, the latter of which was collected from dilated pelvic cavity), in the kidney of the treated UUO mice. Notably, while given three days after the induction of UUO, CK clearly improved the tubulointerstitial lesions in the UUO mice. These beneficial effects from CK treatment correlated well with the inhibition of [1]NF-κB/NLRP3 inflammasome in the kidney; [2] NLRP3 inflammasome in cultured renal TECs under a mechanical-induced pressure; [3] NF-κB/NLRP3 inflammasome and mitochondrial damage in cultured macrophages; and [4] CD4 T cells activation in renal draining lymph nodes. These mechanistic investigations were also partly confirmed by a quantitative proteomics analysis.

Conclusions: We concluded that CK conferred its favorable effects on the renal tubulointerstitial lesions of UUO mice mainly by negatively regulating the NF-κB/NLRP3 inflammasome-mediated inflammatory pathway in the kidney.

Funding: Government Support - Non-U.S.

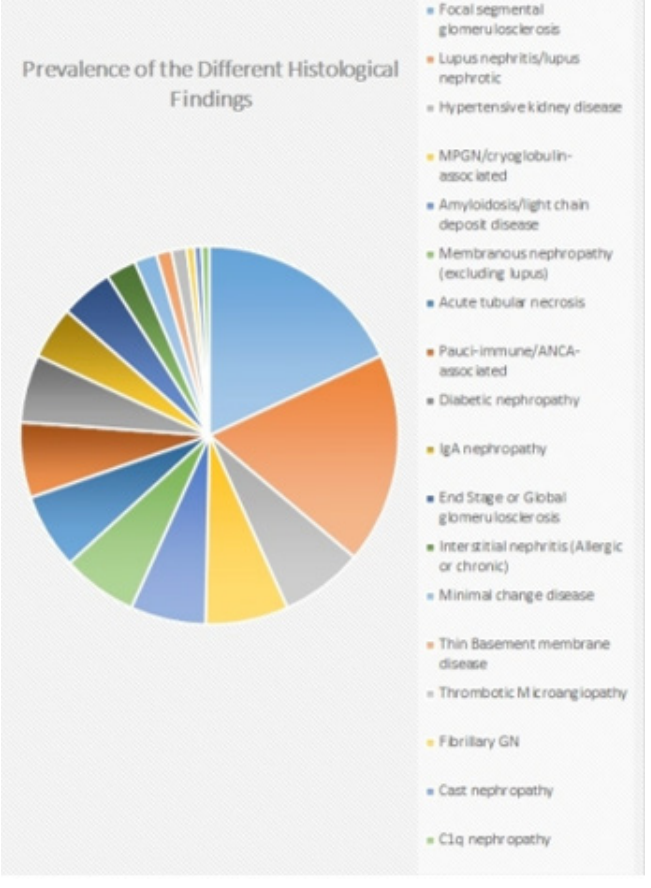
SA-PO264

Retrospective Review of a Kidney Biopsy Series in an Urban Teaching Hospital among a Predominantly African-American Cohort Ravi K. Thimmisetty, Nashat Burhan Imran, Muhammad Omar Azam, Yahya M. Osman Malik. *Internal Medicine Dept/Nephrology Div, Wayne State Univ, Detroit, MI.*

Background: Kidney biopsy can aid in confirming a diagnosis, anticipating disease recurrence, and prognostication. It may alter the pre-biopsy proposed management. Indications include nephrotic/nephritic syndrome, and unexplained acute kidney injury.

Methods: Epidemiological retrospective analysis, single-center, urban hospital with a predominant demographic of African Americans. All kidney biopsies from February, 1st 2011 till June, 6th 2016. All biopsies were done using ultrasound guidance by either the nephrology service or interventional radiology.

Results: There were total of 561 biopsies in this time period. All pediatric, transplant, and surgical biopsies were excluded. The final 143 biopsies were analyzed with the following results: average age was 43.6 years (18-86), 49% male, 76.2% African Americans, average proteinuria 4.8 g/g, hypertension 76.2%. Unexplained acute kidney injury was the most common indication for biopsy (34%) followed by nephrotic syndrome (31%). Pre-biopsy clinical diagnosis was accurate in only 49% of the time. Focal segmental glomerulosclerosis (FSGS) and lupus nephritis classes were the two most common diagnoses (28% each).



Among African Americans, FSGS diagnosis was incorrectly presumed in 53% of the cases and was not suspected in 65% of patients with histological diagnosis of FSGS. There was a weak correlation between extent of fibrosis and creatinine values (Pearson coefficient r=0.358).

Conclusions: Percutaneous native kidney biopsy in an urban center showed FSGS and lupus nephritis as the most common diagnosis. Presumption that African American patient would have FSGS was incorrect in more than half of the time and was not suspected in 65% of the cases. There was a weak correlation between creatinine values and different extents of fibrosis.

SA-PO265

Plasma Soluble Coagulation Receptor Levels Are Not Associated with Venous Thromboembolism in Systemic Vasculitis Sarah Margaret Moran,[1] Alice M. Coughlan,[1] Eóin O'Brien,[1] Yvelynne P. Kelly,[1] Roger Preston,[2] Mark Alan Little.[1] *[1]Trinity Health Kidney Centre, Trinity College Dublin, Dublin, Ireland; [2]Haemostasi Research Group, Trinity College Dublin, Dublin, Ireland.*

Background: ANCA associated vasculitis patients have a significantly elevated incidence of venous thromboembolism (VTE) compared to the general population, however, the molecular mechanisms underlying this increased risk remain elusive. We hypothesised that increased secretion of anticoagulant receptors from the vessel wall may predispose to VTE, or conversely, that increased soluble tissue factor may induce inappropriate clot formation.

Methods: Patients with vasculitis were identified within a longitudinal cohort. Clinical information was available for 346 patients. Soluble tissue factor (sTF), thrombomodulin (sTM) and endothelial protein C receptor (sEPCR) were measured by ELISA in a subset of 80-160 patients with available plasma samples.

Results: 9.5% of patients suffered a VTE, with an event rate of 6.95 per 100 patient years (64% PE, 18% DVT, 18% other VTE). sTF levels were moderately increased in active vasculitis (20.8 pg/ml, SD 31.3 pg/ml) compared to remission (14.0 pg/ml, SD 23.5 pg/ml, p value 0.019).There was no difference in sTF levels when stratified on VTE history (20.5 v 17.3pg/ml). sTM levels were unchanged between VTE history (mean level of 2952pg/ml in both VTE positive and negative), disease activity (active 2812pg/ml, remission 3044pg/ml) or disease severity (as defined by BVAS). sEPCR levels were below the level of detection of the assay.

Conclusions: sTF, sTM and sEPCR levels are not associated with increased VTE risk in our population.

Funding: Government Support - Non-U.S.

SA-PO266

Serum (pro)Renin Receptor Is Associated with the Index of Glomerular Lesion in Mesangioproliferative Glomerulonephritis Kaori Narumi, Emiko Sato, Takuo Hirose, Tae Yamamoto, Takashi Nakamichi, Mariko Miyazaki, Hiroshi Sato, Sadayoshi Ito. *Tohoku Univ Hospital, Sendai, Miyagi, Japan.*

Background: (Pro)renin receptor [(P)RR] is initially identified as a member of renin angiotensin system. (P)RR also functions as intracellular acidification as a part of V-ATPase, cell proliferation through Wnt signaling and inflammatory reaction via ERK1/2 pathway. We reported that (P)RR was present on infiltrating inflammatory cells around glomeruli with a crescent in anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (GN). Our finding suggests that (P)RR could contribute to the pathophysiology of GN. Soluble (P)RR [s(P)RR] is secreted into the extracellular space and is presented in plasma, implying that s(P)RR could become a biomarker for renal injury. Therefore, we examined association s(P)RR with various pathological indexes for renal injury in the patients with GN.

Methods: We measured serum s(P)RR and indoxyl sulfate (IS), one of a uremic toxin, in the mesangioproliferative GN patients diagnosed by renal biopsy at our hospital for past four years (n = 69). We evaluated the index of glomerular lesion (IGL), infiltration area of inflammatory cells and interstitial fibrosis area as pathological index. IGL is used for evaluation of chronic phase in mesangioproliferative GN and is converted into numerical values by the degree of mesangial proliferation or glomerulosclerosis. We investigated the association between serum s(P)RR and the pathological indexes or IS. Mouse mesangial cells, SV40 MES13, were used to evaluate the expression of (P)RR under IS stimulation.

Results: The serum s(P)RR was significantly associated with IGL after adjusted with confounding factors. Especially in IgA nephropathy patients, s(P)RR was significantly correlated with IGL and IS. In SV40 MES13, (P)RR expression was significantly increased depending on IS concentration and time.

Conclusions: The serum s(P)RR could reflect the degree of glomerulosclerosis. (P)RR could be involved in the mechanism of mesangial proliferation or glomerulosclerosis.

Funding: Government Support - Non-U.S.

SA-PO267

Vancomycin-Associated Nanospheres Cast Nephropathy Yosu Luque,[1,2] Kevin Louis,[1] Chantal Jouanneau,[2] Placier Sandrine,[2] Emmanuel Esteve,[2] Perrine Frere,[2] Eric Rondeau,[1,2,4] David Buob,[2,4,5] Emmanuel Letavernier,[2,4,6] Alice Mathilde Wolfromm,[7] Laurent Mesnard.[1,2,4] *[1]APHP, Hôpital Tenon, Urgences Néphrologiques et Transplantation Rénale, Paris, France; [2]Inserm UMR S 1155, Paris, France; [3]Laboratoire de Physique des Solides, Univ Paris Sud, France; [4]Sorbonne Univs, UPMC Univ Paris 06; [5]APHP, Hôpital Tenon, Anatomie et Cytologie Pathologiques, Paris, France; [6]APHP, Hôpital Tenon, Explorations Fonctionnelles Multidisciplinaires, Paris, France; [7]APHP, Hôpital Avicenne, Hématologie Clinique, Paris, France.*

Background: Vancomycin is a widely prescribed drug but some debate remains on its nephrotoxicity and the pathophysiological mechanism involved.

Methods: Here we initially described the case of a 56-year-old woman with normal renal function who developed unexplained very acute renal failure after administration of vancomycin.

Results: The renal biopsy, despite performed 2 weeks after vancomycin withdrawal, showed acute tubular necrosis with atypical granular tubular casts formation. These casts were surrounded by macrophagic infiltration and exhibited the infrared spectroscopy vancomycin signature. The location of vancomycin deposits was also confirmed by immunohistochemistry that we developed in-house. Scanning electron microscopy showed that the vancomycin-associated casts were made of non-crystal vancomycin nanospheres. To confirm these findings, we retrospectively analyzed from 1999 to 2016 seven additional cases of unexplained ATN associated with high vancomycin trough levels. We found similar tubular vancomycin deposits in these patients. Genuine control (that is ATN with concomitant vancomycin injection at time of the renal biopsy) did not express the staining of vancomycin. Finally, similar vancomycin nephrotoxicity mechanism was replicated experimentally in mice following vancomycin infusion. Intravital microscopy using fluorescent-tagged vancomycin dye showed vancomycin deposits formation in tubular lumens, starting 40 minutes after drug injection.

Conclusions: Taken together, these data confirm the yet unsuspected mechanism of acute tubular injury associated with vancomycin toxicity and the deleterious effect of nanospheric non-crystal vancomycin intra-tubular deposits.

SA-PO268

Autoantigen Determinants of Complement Activation by Goodpasture and Anti-PLA2R Autoantibodies Dorin-Bogdan Borza,[1] Tanu Rana,[1] Joshua M. Thurman,[2] Stephen Tomlinson,[3] Paul E. Brenchley,[4] Rachel Lennon.[5] *[1]Dept of Microbiology, Meharry Medical College, Nashville, TN; [2]Univ of Colorado School of Medicine, Denver, CO; [3]Medical Univ of South Carolina, Charleston, SC; [4]Manchester Royal Infirmary, Manchester, United Kingdom; [5]Univ of Manchester, Manchester, United Kingdom.*

Background: Complement activation is a prominent effector mechanisms of IgG autoantibodies (autoAbs) binding to glomerular autoantigens. Major epitopes targeted by Goodpasture (GP) autoAbs in anti-GBM disease and anti-PLA2R autoAbs in membranous nephropathy (MN) have been identified, but their role in complement activation is not known.

Methods: We assayed in vitro complement activation by GP autoAbs bound to a3(IV) collagen NC1 domain (a3NC1) or MN autoAbs bound to PLA2R. Recombinant autoantigen fragments containing select epitopes as well as competing mouse IgG mAbs were used to modulate the subsets of autoAbs forming immune complexes.

Results: GP sera containing predominantly IgG1 autoAbs activated complement, requiring a functional classical pathway, while the alternative pathway (AP) further amplifying C3 but not C4 deposition. GP autoAbs bind to two major epitopes (EA and EB) within a3NC1; inhibiting autoAb binding to either epitope significantly reduced deposition of C3 and C5b9, suggesting that both GP epitopes synergistically activate complement. Moreover, mAbs targeting these a3NC1 epitopes competitively inhibited complement activation by human GP autoAbs. For MN autoAbs, complement activation (C3 deposition) was inhibited by the PLA2R N-C3 domain or a peptide from the CysR domain, encompassing a major epitope, and also by mAbs raised against the N-C3 domain.

Conclusions: These results provide proof of concept that complement activation by autoAbs mediating glomerular disease can be inhibited in antigen-specific manner. Thus, detailed knowledge of the pathogenic epitopes may translate into disease-specific therapies.

Funding: Other NIH Support - NIMHD, Private Foundation Support

SA-PO269

Proteomic Analysis of Complement Expression in Kidneys of Patients with Membranous Nephropathy Isabelle Ayoub,[1] Michael Merchant,[3] John P. Shapiro,[1] Daniel J. Birmingham,[1] Sergey V. Brodsky,[2] Jon B. Klein,[3] Tibor Nadasdy,[2] Brad H. Rovin.[1] *[1]Medicine, The Ohio State Univ, Columbus, OH; [2]Pathology, The Ohio State Univ, Columbus, OH; [3]Medicine, The Univ of Louisville, Louisville, KY.*

Background: Membranous nephropathy (MN) is a common cause of adult nephrotic syndrome. It is an autoimmune disease characterized by glomerular sub-epithelial deposits containing IgG. In experimental MN these deposits activate complement and cause kidney damage. The role of complement in human MN is less clearly defined. To further our understanding of this role, we performed a proteomic study of kidney biopsy tissue of MN, and focused the analysis on complement proteins.

Methods: Samples of normal kidney (n=5) were compared to 3 types of MN defined as: PLA2R+ (by glomerular staining or serum anti-PLA2R levels, n=3); PLA2R- (n=5), PLA2R- with electron dense spherules in the GBM (EDS, n=4). Glomeruli were isolated by laser capture microdissection, and analyzed by mass spectrometry. The levels of each complement protein among the four groups were analyzed by ANOVA or by Kuskal-Wallis for non-parametric data, and those showing significant differences were further analyzed by appropriate post-hoc tests. The alpha level for significance was set at 0.05.

Results: Seven complement activation proteins (C3, C4, C5, C6, C7, C8, C9) and two complement regulators (complement receptor type 1 (CR1), and FH-related protein 2 (FHR2)) were differentially present. Of the activation proteins, compared to normal controls, C3 and C4 levels were higher in all three MN groups, while C5, C6, C7, C8, and C9 were significantly higher only in MN with EDS. Of the regulators, compared to normal controls, CR1 levels were lower in EDS and PLA2R-, and FHR2 levels were greater in EDS.

Conclusions: Elevated levels of C3 and C4 in all MN groups, and decreased CR1 levels in at least two MN groups, support the involvement of complement activation in the pathogenesis of MN. Finding components of the membrane attack complex (C5-C9) only in EDS MN suggests complement's effect may be more severe, and direct, in this type of MN. These data raise the possibility that anti-complement therapies may be effective in some forms of MN.

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SA-PO270

Synthesis of Complement Protein C3 in Podocytes Is an Important Mediator of Renal Injury in Glomerular Diseases Xuejuan Li, Jie Ding, Fangrui Ding. *Peking Univ First Hospital, Beijing, China.*

Background: We previously study demonstrated complement C3 was increased after podocyte injury by puromycin in vivo and in vitro. Podocytes are one of the major intrinsic glomerular cells, the foot processes of the neighboring podocytes form slit diaphragm, which is considered to be one of the most important structures for the glomerular filtration barrier, plays an important role in preventing the initiation and development of proteinuria. However, whether the increased podocyte-derived C3 is involved in glomerular podocyte injury are important questions that remain unclear. Therefore, the role of podocyte-derived C3 involving podocyte injury, as well as in proteinuric kidney diseases, further investigation is needed.

Methods: We generated transenic mice that overexpress C3 in podocytes using the podocin promoter. The genotyping of these transgenic mice were performed by conventional PCR. The gene and protein expression of C3 was detected by Real-time PCR and confocal in isolated transgenic mice glomerular. C3 transgenic mice were treated with PAN or saline solution. Excretion of albumin was expressed as the albumin-to-creatinine ratio. Transmission electron microscopy was used to evaluate the ultrastructural changes of glomerular. The confocal and western blot were used to detecte the podocyte injury marker proteins expression changes.

Results: We successfully constructed the podocyte specific overexpression C3 transgeninc mice. The albumin-to-creatinine ratio and podocytes damage in PAN induced wild type mice were aggravated in the Podocyte specific overexpression of C3 (Podo-C3) transgenic mice. Moreover, the expression of podocyte injury marker protein nephrin, synaptopodin, podocin decreased in PAN induced Podo-C3 transgenic mice. Moreover, the expression and distribution of the activated C3 cleavage fragment C3a and the C3aR were significantly increased in Podo-C3 PAN nephropathy model.

Conclusions: We demonstrated for first time that the podocyte-derived C3 aggravated podocyte damage in PAN nephropathy model. The possible mechanism might be through up-regulation of complement C3aR.

SA-PO271

Complement Activation in Diabetic Nephropathy Pascal Bus, Jamie S. Chua, Celine Klessens, Malu Zandbergen, Jan A. Bruijn, Ingeborg M. Bajema, Hans J. Baelde. *Pathology, LUMC, Leiden, Zuid-Holland, Netherlands.*

Background: Complement activation plays a role in various renal diseases. Experimental models suggest a role for complement activation in diabetic nephropathy. Therefore, the aim of this study was to investigate the prevalence and significance of complement deposits in a large cohort of renal tissue from patients with diabetes and diabetic nephropathy.

Methods: We investigated the presence of glomerular C4d, C1q, MBL, C5b-9 depositions on 163 renal autopsies with both type 1 and type 2 diabetes mellitus. Diabetic patients were divided into 2 groups: patients with and without histologically proven diabetic nephropathy; confirmed by light- and electron microscopy. Autopsies were re-evaluated histologically. Complement deposition patterns were scored blinded to the clinical and histological data.

Results: Diabetic nephropathy was present in 63% of patients. Complement activation marker C4d was significantly more prevalent in patients with DN (45%), compared to patients without DN (26%) ($p<0.05$). Glomerular C4d was associated with the presence of C1q ($p<0.01$) and C5b9 ($p<0.01$). MBL was infrequently observed (6% of all diabetic patients). C4d and C5b-9 deposits were significantly more prevalent in patients with interstitial fibrosis and tubular atrophy, than patients without these deposits ($p<0.05$). Patients with C4d also had more arteriosclerosis, and glomerular and arteriolar hyalinosis, than patients without C4d. No difference was seen between patients with type 1 DM and type 2 DM.

Conclusions: Complement activation is present in a selected number of patients with diabetic nephropathy, and seems to be associated with chronic lesions. Classic pathway complement activation was the route most frequently found. In our study, there were no differences between complement deposits in type 1 and type 2 diabetes.

SA-PO272

Clinically Available Janus Kinase (JAK) Inhibitors May Offer Treatment for Recurrent Focal Segmental Glomerulosclerosis (rFSGS) Virginia J. Savin,[1,2] Mukut Sharma,[1,2] Ellen T. McCarthy,[3] Tarak Srivastava,[5] Ram Sharma,[1] Jean-Francois Gauchat,[4] Jianping Zhou.[1] *[1]Nephrology, KC VA Medical Center, Kansas City, MO; [2]Research, MBRF, KC VA Medical Center, Kansas City, MO; [3]Kidney Inst, KU Medical Center, Kansas City, KS; [4]Pharmacology, Univ of Montreal, Montreal, QC, Canada; [5]Nephrology, Children's Mercy Hospital, Kansas City, MO.*

Background: Plasma of patients with rFSGS alters glomerular barrier function. We have identified CLCF1 in rFSGS plasma and proposed that its signaling via the JAK/STAT pathway is essential to injury induced by rFSGS plasma. Podocytes express primarily JAK2 and STAT3 and specific JAK2 or STAT3 inhibition prevents the effects of CLCF1 or of rFSGS plasma. We studied 3 clinically available JAK inhibitors Ruxolitinib, Incyte (Rux), Baricitinib, Lilly (Bari) and Tofacitinib, Pfizer (Tofa) to determine ability to block effects of CLCF1 on immortalized podocytes.

Methods: FDA approved JAK inhibitors Rux (1-15 nM) and Tofa (6-36nM), as well as Bari, (6-36nM), which is under FDA review, and BMS911543, a JAK2-specific inhibitor not used in clinical trials (1-5 nM), were studied at concentrations proximate to their respective IC_{50} for STAT3. CLCF1 (100nM) was included in some groups; this concentration increases both pSTAT3 and P_{alb}. pSTAT3 (Tyr^{705}) in immortalized mouse podocytes was analyzed using Western blotting at 5-60min.

Results: The JAK2-specific inhibitor BMS911543 prevented increases in pSTAT3 and glomerular P_{alb} caused by rFSGS serum or CLCF1 ($p<0.001$) (Transl Res 2015, 166:384-98). Rux, Tofa and Bari each decreased basal podocyte pSTAT3 in a dose- and time-dependent manner. At 60 min, Rux (3nM), Tofa (6nM) or Bari (5nM) prevented CLCF1-induced increase in pSTAT3 ($P<0.001$).

Conclusions: JAK2 inhibition is sufficient to prevent STAT3 and P_{alb} responses to CLCF1; JAK1 and JAK3 inhibition do not appear to be required. Repurposing available JAK inhibitor(s) may offer effective and specific treatment of rFSGS. Since Rux and Bari have relative specificity for JAK1 and JAK2 they may provide favorable toxicity profiles compared to Tofa. A clinical trial based on JAK2 inhibition in rFSGS may be warranted.

Funding: VA Support

SA-PO273

An Endothelin Receptor Antagonist as a Promising Drug for Minimal Change Nephrotic Syndrome: Its Anti-Proteinuric Effect in Puromycin Aminonucleoside-Induced Nephrosis in Rats Jiro Kino, Shoji Tsuji, Sohsaku Yamanouchi, Chikushi Suruda, Takahisa Kimata, Kazunari Kaneko. *Pediatrics, Kanasai Medical Univ, 2-5-1 Shin-machi, Hirakata-shi, Osaka, Japan.*

Background: In recent years, the abnormal expression of podocyte-related molecules has been attracting attention with respect to the pathogenesis of minimal change nephrotic syndrome (MCNS). The endothelin (ET) receptor expressed on podocytes has been reported to be responsible for proteinuria and structural changes in podocytes. Therefore, we investigated, using a rat model, whether an endothelin A (ETA) antagonist could be used as a therapeutic agent for MCNS.

Methods: MCNS was induced by a single intravenous injection of puromycin aminonucleoside (PAN) in female Wistar rats. Two groups of 10 rats each were treated, either with the ETA antagonist ambrisentan or with 0.5% methylcellulose (control), orally. Treatment was administered once daily, starting 2 days before PAN injection lasting up to Day 9. Rats were euthanized at Day 12, and blood and tissue samples were collected for histological evaluation. Statistical significance between groups was evaluated by the Mann-Whitney U test. Significance was defined as $p < 0.05$.

Results: Proteinuria in the treatment group was significantly lower than in the control group (Day 9: antagonist group: 272.6 mg/kg/day, controls: 747.7 mg/kg/day, $p<0.05$). Same-day urine volume and serum creatinine values were not significantly different between the two groups (urine volume of Day 9: $p=0.82$, serum creatinine values of Day 9: $p=0.47$). Electron microscopy showed characteristic foot process fusion of podocytes in the control group, but not in the treatment group.

Conclusions: The results suggest that the ETA antagonist ambrisentan, an approved drug for pulmonary hypertension, acts directly on podocytes to exhibit an anti-proteinuric effect that is independent of renal vasoconstriction, and could potentially be used as a therapeutic agent for MCNS.

SA-PO274

B-Cell Signature in FSGS Rituximab Responders Chang-Yien Chan, Isaac Liu, Kar Hui Ng, Wee Song Yeo, Hui Kim Yap. *Paediatrics, National Univ of Singapore, Singapore.*

Background: We recently reported a subgroup of FSGS patients bearing an immunological signature of T-cell hyporesponsiveness who responded to rituximab treatment, suggesting a possible role of B-T cell interactions in modulating podocyte injury. This study aimed to investigate the cytokine-producing "regulatory" and "effector" B-cell subsets in FSGS patients in order to elucidate the role of B-cells in FSGS rituximab responders.

Methods: 22 FSGS patients (median age 14.4 years) were recruited prospectively to receive rituximab. Median duration of follow-up was 26.7 months. At baseline, B-cells were isolated using CD19 microbeads and cultured for 4 hours with and without lipopolysaccharide (LPS). Cytokine levels in culture supernatant were quantified using multiplex suspension bead array system, and compared with 16 healthy controls using Mann-Whitney U test.

Results: 12 patients (54.5%) responded to rituximab therapy, defined as complete resolution of proteinuria with cessation of prednisone and calcineurin inhibitors within 3 months. Baseline B-cell production of IL-4, IL-13, Eotaxin and MCP-1 in FSGS rituximab responders were significantly higher than non-responders and controls. Following stimulation, IL-4, IL-13, MCP-1 and IL-10 levels were also significantly higher in responders. No difference was seen in IFNγ, IL-12 and TNFα.

Cytokines	Unstimulated			LPS-stimulated		
	Responders	Non-responders	Control	Responders	Non-responders	Control
IL-4	2.8±0.4[a,b]	1.7±0.3	1.6±0.3	5.1±0.6[a,b]	2.9±0.3	2.9±0.3
IL-13	0.9±0.2[a,b]	0.3±0.1	0.3±0.1	1.4±0.2[a,b]	0.5±0.2	0.7±0.2
Eotaxin	19.5±2.0[a,b]	12.6±1.8	13.2±1.9	19.5±2.8[a,b]	20.3±2.1	20.1±1.6
MCP-1	12.1±3.5[a,b]	2.9±0.6	3.6±1.1	55.5±36.6[a,b]	3.7±0.7	3.2±0.9
IL-10	3.5±1.0	2.0±0.4	3.2±1.2	6.4±1.8[a,b]	2.3±0.3	3.7±1.2

[a]$P<0.05$, comparing responders and non-responders; [b]$P<0.05$, comparing responders and healthy controls

Conclusions: FSGS rituximab responders demonstrated higher baseline levels of IL-4, IL-13 and MCP-1 producing Be-2 cells and IL-10 producing regulatory B-cells, possibly explaining the T-cell hyporesponsiveness.

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SA-PO275

Cytokine Profiling of Pediatric Minimal Change Nephrotic Patients Wee Song Yeo, Chang-Yien Chan, Isaac Liu, Kar Hui Ng, Hui Kim Yap. *Pediatrics, National Univ of Singapore, NUHS, Singapore.*

Background: Studies examining the etiology of minimal change nephrotic syndrome (MCNS) have suggested a role for cytokine(s) in its pathogenesis. The results of these studies have been mixed. This study aimed to reconcile the cytokine profile in MCNS patients using high throughput multiplexed Luminex® assay.

Methods: Forty MCNS patients (median age 12 years, range 3-25 years), of whom 12 had paired samples in relapse and remission, were analyzed. Paired blood samples were obtained from these patients when they were: i) Not on any treatment during blood sampling, or ii) On prednisolone only during relapse and remission for steroid-dependent patients. Forty aged-matched controls and seven pediatric focal segmental glomerulosclerotic (FSGS) patient controls were included in the analysis. Plasma cytokine profiling was performed using multiplexed Luminex® Cytokine Human 27-Plex assay. Statistical analysis was performed using Wilcoxon signed-rank test and Mann-Whitney U with a p-value of less than 0.05 considered as statistically significant.

Results: Of the 27 cytokines analyzed, there was no significant difference in each measured plasma cytokine level between controls and MCNS patients in remission. There were significantly higher plasma levels of IL-1b, IL-1RA, TNF-α, IL-6, IL-2, IL-5, IL-9, IL-13, IL-10, PDGF-BB, IL-8 and a significantly lower plasma level of RANTES in MCNS patients in relapse compared to controls ($p<0.05$). FSGS patients in relapse had significantly higher plasma levels of IL-1RA, IL-10 and PDGF-BB compared to controls ($p<0.05$). In the paired analysis, there were significantly higher plasma levels of IL-6, IL-15, IL-4, IL-5, IL-13, IL-17, IL-10, and VEGF in MCNS patients in relapse compared to remission ($p<0.05$). Common cytokines that were consistently significantly different between MCNS patients in relapse and remission/controls in both paired and unpaired analyses were IL-5, IL-6, IL-10, and IL-13, majority of which were Th2-related cytokines.

Conclusions: Cytokine profiling of pediatric MCNS patients in relapse demonstrated a Th2-cytokine bias, distinctly different from FSGS patients. Further mechanistic studies are required to ascertain the roles of these cytokines in the pathogenesis of MCNS.

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SA-PO276

Altered B Cell Homeostasis in Nephrotic Syndrome Pediatric Patients Marina Vivarelli, Manuela Colucci, Giorgia Corpetti, Francesco Emma. *Nephrology, Bambino Gesù Pediatric Hospital - IRCCS, Rome, Italy.*

Background: A pathogenic role of B cells in non-genetic nephrotic syndrome (NS) has been suggested by the efficacy of rituximab, a B cell–depleting antibody, in inducing a prolonged remission. However, little or no information is available on B cell homeostasis in NS patients.

Methods: We retrospectively evaluated by flow cytometry levels of B cell subsets in 19 healthy age-matched children (HCs) and in 66 NS pediatric patients in different states of disease (37 in active disease and 29 in remission) and treated with differently combined immunosuppressive agents. 20 patients were at disease onset (active disease before any treatment), 17 were at relapse (12 treated with prednisone (PDN), 1 with cyclosporine (CSA), and 2 with PDN+CSA), and among the patients in remission, 7 were treated with PDN+mycophenolate mofetil (MMF), 13 with PDN+CSA/tacrolimus, and 9 with PDN+MMF+CSA/tacrolimus (triple immunosuppression).

Results: At onset, patients presented comparable levels of $CD19^+$, transitional, and total memory B cells respect to HCs, whereas mature B cells were reduced ($p<0.01$) and switched memory B cells were increased ($p<0.05$). Levels of B cell subsets did not significantly differ between patients at onset and in relapse, despite PDN and CSA treatment. Prednisone alone did not seem to have any effect on B cell subpopulations. $CD19^+$ levels were significantly reduced only in patients undergoing triple immunosuppression when

compared to HCs, patients at onset and patients in relapse ($p< 0.01$). Association of PDN with one or two IS drugs mainly affected transitional B cells ($p<0.001$ for all treatments compared with HCs and patients at onset), and mature B cells were mainly reduced in patients treated with PDN+MMF (with or without CSA/tacrolimus treatment; $p<0.02$ vs patients at onset). Immunosuppressive treatment excluding rituximab did not significantly modify memory B cell levels.

Conclusions: At onset, prior to all immunosuppressive treatment, patients with nephrotic syndrome seem to have reduced mature and increased switched memory B cells. Prednisone, non-steroidal and non–antiCD20 immunosuppressive treatment seems unable to modify these B cell subset alterations.

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SA-PO277

Enhanced Monocyte Responses to Toll-Like Receptor (TLR) and Inflammasome Stimuli in Chronic Kidney Disease Serika D. Naicker,[1] Susan Logue,[1] Grace A. O'Malley,[1] Matthew D. Griffin.[1,2] *[1]School of Medicine, Regenerative Medicine Inst (REMEDI), National Univ of Ireland, Galway, Ireland; [2]Nephrology Services, Galway Univ Hospital, Saolta Univ Health Group, Galway, Ireland.*

Background: CKD is associated with systemic inflammation but the stimuli and pathways responsible remain poorly understood. We compared the profiles and responses of blood monocytes to TLR ligands ± the inflammasome activator extracellular (e)ATP in healthy adults and subjects with CKD.

Methods: Peripheral blood mononuclear cells (PBMCs) from healthy adults (Ctrl, n=23) and adults with CKD stages 2-5 (n=90) were analyzed by 8-colour flow cytometry to quantify monocyte subsets and their expression of TLRs and the ATP-binding receptor P2X7R. PBMCs were stimulated with TLR4 (LPS, 0.5ng/ml) or TLR7/8 (R848, 50ng/ml) ligands for 2hrs followed by eATP(5mM) for 45mins ± P2X7R blocker. Additionally, healthy adult PBMCs were cultured with 5% Crtl or CKD serum during activation. Cytokines were quantified by ELISA. Assay results were correlated with clinical and laboratory indices. Statistical analyses were performed using GraphPad Prism© software.

Results: Surface P2X7R (but not TLR2,4,7,8) was increased on classical($CD14^{++}CD16^{-}$) monocytes of CKD compared to Ctrl and correlated with serum uric acid and total cholesterol. Monocyte release of IL-1β following TLR4 or TLR7/8 + eATP was greater for CKD3/4 compared to Ctrl and was partially suppressed by P2X7R blockade. LPS/eATP-triggered IL-1β release correlated with classical monocyte count and with eGFR. R848/eATP-triggered IL-1β release correlated with intermediate($CD14^{++}CD16^{+}$) and non-classical($CD14^{-}CD16^{++}$) monocyte count, serum creatinine and with eGFR. LPS and R848-triggered release of TNFα and IL-6 was greater for CKD3/4 compared to Ctrl irrespective of eATP presence. Culture of healthy PBMCs with serum from CKD compared to Ctrl resulted in greater TNFα (but not IL-1β or IL-6) release following LPS+eATP.

Conclusions: Our results indicate that CKD is associated with altered inflammatory response profiles of classical and intermediate monocytes involving multiple TLR pathways and the inflammasome. The mechanism underlying monocyte inflammatory profiles in CKD is likely to be multi-factorial.

Funding: Government Support - Non-U.S.

SA-PO278

Increased Neutrophil Extracellular Trap (NET) Formation Is Associated with Chronic Inflammation and Coronary Artery Disease in Uremic Patients Jwa-Kyung Kim,[1] Sun Ryoung Choi,[2] Jae-Won Lee,[3] Sung Gyun Kim.[1] *[1]Internal Medicine, Kidney Research Inst, Hallym Univ Sacred Heart Hospital, Anyang, Korea; [2]Internal Medicine, Sahmyook Medical Center, Seoul, Korea; [3]Internal Medicine, G sam Hospital, Anyang, Korea.*

Background: Neutrophils are involved in the pathogenesis of atherosclerosis by neutrophil extracellular traps (NETs) formation. End-stage renal disease (ESRD) patients have extremely higher mortality rate because of uremic toxins-associated inflammation and advanced ahterosclerosis, We hypothesized that the NETs formation of neutrophils might be changed in ESRD patients, leading to the higher prevalence of cardiovascular diseases.

Methods: A cross-sectional study was performed in 60 maintenance hemodialysis (MHD) patients, 30 age- and sex-matched healthy individuals (HV, negative control), and 30 patients with acute infection (positive control). Neutrophil activation and function was measured with reactive oxygen species (ROS) activity, degranulation, and NET formation. Also, changes of neutrophil phenotypes were assessed.

Results: Compared with HV patients, neutrophils extracted from MHD individuals displayed significantly higher levels of basal NET formation as well as ROS production, indicating that they were activated spontaneously. The median levels of NET fluorescence were 5187.3, 7767.6, and 9784.2 in the HV, MHD, and positive control groups, respectively. And neutrophils from HV patients were normal $CD16^{bright}/CD62L^{bright}$ cells; however, neutrophils from MHD patients were $CD16^{bright}/CD62L^{dim}$, similar to those from patients with acute infections. Baseline NET formation was positively correlated with the prevalent coronary artery disease (CAD), peripheral neutrophil count, and inflammatory markers such as neutrophil/lymphocyte ratio, and hs-CRP levels. Multivariate analyses identified the prevalent CAD and neutrophil counts as independent predictors of baseline NET formation ($\beta=0.323, p=0.016$ and $\beta=0.369, p=0.006$, respectively).

Conclusions: In ESRD, NET formation is significantly increased at basal state, and it has a close relationship with *in vivo* inflammatory conditions and prevalent CAD. Baseline neutrophil activation may be a sign of the presence of atherosclerotic vascular complications.

SA-PO279

Increased Tubulointerstitial Recruitment of Human Natural Killer Cells in Renal Fibrosis and Chronic Kidney Disease Helen G. Healy,[1,2] Becker Meng-Po Lo,[1,2,3] Xiangju Wang,[1,2] Andrew J. Kassianos,[1,2,3,4] Ray Wilkinson.[1,2,3,4] *[1]Conjoint Kidney Laboratory, Pathology Queensland, Brisbane, Queensland, Australia; [2]Kidney Health Service, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia; [3]Faculty of Health, Queensland Univ of Technology, Brisbane, Queensland, Australia; [4]School of Medicine, Univ of Queensland, Brisbane, Queensland, Australia.*

Background: Natural killer (NK) cells are innate lymphoid cells that play a significant role in immune surveillance of stressed autologous cells. Mouse studies suggest a pathological role for NK cells in immune-mediated models of kidney disease. This study evaluates the NK cell profile in human fibrotic chronic kidney disease (CKD).

Methods: We extracted NK cells from healthy kidney tissue and diseased biopsies with and without fibrosis. NK cell subsets were identified, enumerated and phenotyped by twelve-colour flow cytometry. Localisation of NK cell subsets was examined by multi-colour immunofluorescent microscopy.

Results: We detected significantly elevated numbers of total NK cells ($CD3^{-}CD56^{+}$) in diseased biopsies with interstitial fibrosis compared with diseased biopsies without fibrosis and healthy kidney tissue. Numbers of both the $CD56^{dim}$ NK cell subset and, in particular, the $CD56^{bright}$ NK cell subset, were also significantly elevated in fibrotic kidney tissue. The increased numbers of $CD56^{bright}$ NK cells correlated significantly with loss of kidney function (eGFR). Furthermore, expression of the activation molecule CD69 on $CD56^{bright}$ NK cells was significantly increased in fibrotic biopsies compared with non-fibrotic kidney tissue, indicative of a pathogenic phenotype. Chemokine receptor analysis showed CXCR3 and CX3CR1 expression on $CD56^{bright}$ NK cells. Immunofluorescent staining of fibrotic kidney tissue localised the accumulation of NK cells within the tubulointerstitial compartment.

Conclusions: The correlation of activated $CD56^{bright}$ NK cells with functionally more severe CKD suggests a pathological role. Further functional dissection of this NK cell subset is necessary for the development of therapeutics capable of blocking this previously untargeted immune cell population.

Funding: Government Support - Non-U.S.

SA-PO280

Leukemia Inhibitory Factor Attenuates Tubulointerstitial Fibrosis by Suppression of Pro-Inflammatory Cytokines Sebastian Alexander Potthoff, Fabian Srugies, Lars C. Rump, Ivo Quack. *Nephrology, Medical Faculty - Heinrich-Heine Univ, Duesseldorf, Germany.*

Background: Tubulointerstitial fibrosis is common in chronic kidney disease which is often sustained by chronic inflammation. CD4+ T-cells play an important role in immune response in kidney disease. Leukemia inhibitory factor (LIF), a member of the Interleukin 6 family, and Interleukin 6 (IL-6) play a crucial role in regulating the balance between Th17- and regulatory T-cells (Treg): LIF augments expression of forkhead-box-P3 (Foxp3) leading to Treg, IL-6 induces RAR-related orphan receptor gamma (RORyt) driving Th17 lineage development. Dysregulation or overproduction of Th17 cells result in sustained inflammation. Here, we showed that LIF influences inflammatory response in a UUO model.

Methods: 6-week old male C57BL/6 mice were treated intraperitoneally daily either with LIF (10µg/kgBW; n=6 day 3;n=7 day 10) or PBS (control;n=8 day 3;n=8 day10). 3 and 10 days after UUO, kidneys, spleen and paraaortal lymphnodes were extracted.

Results: LIF treatment significantly reduced tubulointerstitial fibrosis in obstructed kidneys. qPCR from tissue lysates of obstructed kidneys day 3 (OB) revealed that IL-1b, MCP-1, RANTES, IL-6, TNF-α, Col1a1, TGFß and PAI-1 were upregulated in LIF treated mice. In contrast, qPCR from tissue lysates of obstructed kidneys day 10 (OB) revealed that NFκB and RANTES as well as collagen1 and TGF-β were significantly downregulated in LIF treated mice. There was no significant difference between IL17a, IL-1b, MCP1, IL-6, TNFα, PAI1 and PDGFR1. Accordingly, expression of MCP1, NFκB, RANTES and TNFα in paraaortal lymphnodes were reduced by LIF. IL-1b and IL-6 expression were reduced by LIF but failed to reach statistical significance. CD3+cells accumulated in obstructed kidneys. LIF significantly reduced CD3+cells at day 10 (OBvs.OB+LIF: 144±6vs.115±8; $p<0.01$) but not day 3. LIF treatment lead to a significant increase of the anti-inflammatory cytokine IL-10 ($p<0.001$) and downregulated pro-inflammatory IL-6, RANTES or G-CSF in plasma.

Conclusions: These data confirm the critical role of inflammation in UUO. LIF treatment suppresses a prolonged inflammatory response after UUO and therefore protects against tissue injury and fibrosis.

Funding: Clinical Revenue Support

SA-PO281

T-Cell Depletion Improves Diastolic Dysfunction in Mice with Uremic Cardiomyopathy Pamela D. Winterberg,[1] Mandy L. Ford.[2] *[1]Pediatric Nephrology, Emory Univ; [2]Dept of Surgery, Emory Univ, Atlanta, GA.*

Background: Uremic cardiomyopathy, characterized by left ventricular hypertrophy (LVH) and diastolic dysfunction, is a significant cause of morbidity and mortality among patients with chronic kidney disease (CKD), but the underlying mechanisms are incompletely understood. We aimed to determine whether T cells are involved in cardiac remodeling during CKD.

Methods: CKD was established in male 129X1/SvJ mice via two-stage partial nephrectomy with sham-operated mice serving as controls. CKD mice were further randomized to receive isotype antibody (Ab) or anti-CD3 Ab to deplete T cells. LVH

and diastolic dysfunction were assessed via echo at 6 weeks of CKD. Flow cytometry was performed to verify depletion of T cell populations in spleen, blood, and mediastinal lymph nodes and to characterize memory (CD44) and activation (PD-1) status of T cells. Blood pressures were measured using the tail-cuff method. Kidney function was assessed via measurement of plasma urea and cystatin C concentrations.

Results: Mice with CKD developed LVH and diastolic dysfunction as previously described, and displayed enlarged mediastinal lymph nodes (mLN) and accumulation of T cells bearing markers of activation (PD-1) and memory differentiation ($CD44^{hi}$) in spleen and mLN. Anti-CD3 Ab resulted in 100-fold reduction of T cell counts in blood and 50-75% reduction in splenic T cell counts compared to sham controls. Measures of diastolic function including isovolumic relaxation time (IVRT: isotype 22.3 ± 2.28 vs anti-CD3 16.9 ± 2.25 ms; $p<0.01$), myocardial performance index (0.63 ± 0.05 vs 0.48 ± 0.08; $p<0.001$) and trans-mitral flow index (E/A ratio: 0.9 ± 0.14 vs 1.2 ± 0.23; $p<0.01$) improved in CKD mice receiving T cell depletion, however, LVH, systolic blood pressure and measures of renal function were unaltered.

Conclusions: Mice with uremic cardiomyopathy have profound alterations in T cell differentiation and activation status including mediastinal lymphadenopathy. Depletion of T cells improved diastolic function in mice with CKD independent of blood pressure and kidney dysfunction. We are pursuing further work into the mechanisms by which T cells mediate diastolic dysfunction during uremic cardiomyopathy.

SA-PO282

Sulfatide-Selective NKT Cells Mediate M2 to M1 Polarization Resulting in Amelioration of Kidney Fibrosis Sunhwa Lee,[1] Seung Hee Yang,[1] Yong Chul Kim,[2] Mi-Yeon Yu,[2] Seung Seok Han,[1] Hajeong Lee,[2] Jung Pyo Lee,[3] Ran-Hui Cha,[4] Dong Ki Kim,[2] Yon Su Kim.[2] *[1]Biomedical Research Inst, Seoul National Univ; [2]Seoul National Univ Hospital; [3]Seoul National Univ Boramae Medical Center; [4]National Medical Center.*

Background: Kidney fibrosis is the major pathological features of chronic kidney disease, and currently efficient treatment for kidney fibrosis is absent. Macrophage subtype polarization has been suggested as a key player related to kidney fibrosis. However, the immunomodulatory role of natural killer T (NKT) cell in macrophage transdifferentiation has not been elucidated.

Methods: Sulfatide-selective NKT II cells from unilateral ureteral obstruction (UUO) B6.Jα281$^{-/-}$ mice lacking the invariant type I NKTs were used to elucidate its impact on phenotypic switch of bone marrow derived M1/M2 macrophages and interstitial fibrosis. A co-culture system, primary cultured proximal epithelial cells with sulfatide-selective type II NKT cells, was designed. In addition, macrophages stimulated by Sulfatide-selective NKT cells were adoptively transferred to the kidney capsule of WT and B6.Jα281$^{-/-}$ on the 7th day of UUO, followed by isolation of total cellular RNAs from minced kidney tissue for microarray.

Results: Severity of renal fibrosis of B6.Jα281$^{-/-}$ was attenuated comparing to WT. Subsequently added Sulfatide-selective NKT cells stimulated transdifferentiation from M2 to M1 accompanying by increased iNOS, STAT1, SOCS3 and decreased arginase, STAT3, followed by reducing fibrosis in proximal tubular epithelial cells. Profibrotic transcripts, fibronectin and TGFβ, decreased by adding sulfatide-selective NKT induced M1 of B6.Jα281$^{-/-}$ to macrophage-depleted B6.Jα281$^{-/-}$. Moreover, the expression level of NGAL and IL-1β, a marker of kidney damage and inflammation, was attenuated. At the same time, diminution of immunologic transcripts such as CD44, CCL5, CCL9, and macrophage mannose receptor 1 was also observed.

Conclusions: Sulfatide-selective NKT cell mediates transdifferentiation from M2 to M1 macrophage via switching on STAT1 resulting in ameliorating renal fibrosis. Inducing the polarization of macrophages by modulation of NKT cells can be suggested as therapeutic target for curbing fibrosis.

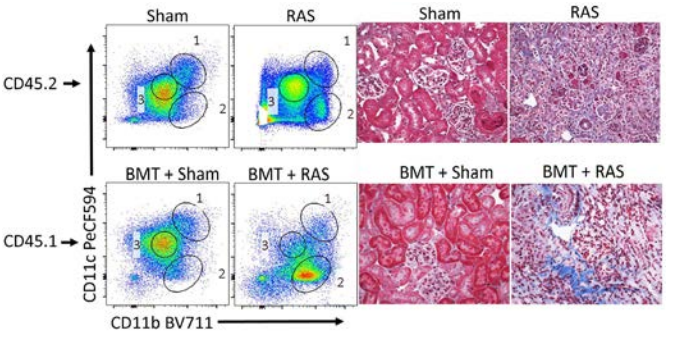
SA-PO283

Reparative Renal Macrophages Contribute to Curtailing Fibrosis in the Stenotic Murine Kidney Amrutesh Puranik,[1] John R. Woollard,[1] Luke Barron,[3] Kyra L. Jordan,[1] Hui Tang,[1] Stephen C. Textor,[1] Jeremy Stuart Duffield,[3] Lilach O. Lerman.[1] *[1]Divs of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [2]Biogen, Cambridge, MA.*

Background: We have previously demonstrated that chronic renal artery stenosis (RAS) induces increase in $CD64^{+}F4/80^{high}CD11b^{int}CD11c^{int}$ macrophages (MΦ3s) and that these protect against renal fibrosis in RAS. This study tested the hypothesis that renal MΦ3s are partly derived from bone marrow (BM), but the replenished MΦ3s might not abolish fibrosis effectively.

Methods: Wild type C57 CD45.2 mice underwent whole-body irradiation. Within 6 hours, BM cells obtained from donor CD45.1 mice were transplanted (BMT) retro-orbitally. After a reconstitution period of 60 days, unilateral RAS was induced and stenotic kidneys harvested 28 days later to study MΦ3s populations (polychromatic flow cytometry) and assess fibrosis (trichrome). Wild type mice 28 days after RAS or Sham served as controls. We also examined the ability of MΦ3s in vitro to inhibit TGFb-induced induction of pro-fibrotic genes (qPCR) and protein (FlowSight, Millipore) in murine embryonic fibroblast (MEF) obtained from Cola1-gfp mice.

Results: Flow cytometry data showed that in BMT+Sham MΦ3s repopulate from donor-derived (CD45.1) BM (Figure). However, upon induction of RAS in BMT mice, the donor-derived MΦ3s decreased significantly in RAS+BMT compared to untreated RAS and Sham kidneys, and mice with BM-derived MΦ3 experienced enhanced fibrosis.



In vitro, MΦ3s blunted expression of TGFb-induced profibrotic genes in MEF.

Conclusions: BM can regenerate MΦ3s in healthy kidneys following radioablation, but are incapable of sustaining their MΦ3 phenotype and anti-fibrotic properties in response to kidney injury. Hence, endogenous renal MΦ3s protect the stenotic kidney against injury more effectively than BM-derived MΦ.

Funding: NIDDK Support

SA-PO284

The Immunoglobulin Heavy Chain Locus Enhances Susceptibility to Renal Injury in Hypertensive Rats Isha Dhande,[1] Stacy M. Cranford,[1] Yaming Zhu,[1] Manuel Leonardo Gonzalez-Garay,[1] Scott E. Wenderfer,[2] Michael C. Braun,[2] Peter A. Doris.[1] *[1]Inst of Molecular Medicine, Univ of Texas Health Science Center at Houston, Houston, TX; [2]Dept of Pediatrics, Baylor College of Medicine, Houston, TX.*

Background: Hypertensive renal injury involves an immune component, though the specific molecular pathways are incompletely understood. We have demonstrated that high levels of genetic divergence exist in the immunoglobulin heavy chain (IgH) locus across the renal injury-prone spontaneously hypertensive rat SHR-A3 strain and the closely related SHR-B2 strain that resists renal injury. This divergence affects the complement of VDJ genes and creates functional variation in Fc encoding genes in the IgH locus. Additionally, serum IgG levels are genetically determined by sequence variation in the IgH locus across these two lines. We hypothesized that congenic substitution of the IgH locus from SHR-B2 into the SHR-A3 genetic background to create SHR-A3(chr6-IgH-SHR-B2) will reduce renal injury without affecting BP in this model.

Methods: We generated a congenic rat line in which the SHR-B2 IgH locus was transferred by backcrossing onto the SHR-A3 genetic background. The congenic status of the line was confirmed by genome-wide SNP genotyping and by examining serum IgG levels. BP was measured in conscious, unrestrained rats by telemetry for 7 weeks starting at age 18 weeks of age, when renal injury begins to emerge in SHR-A3 rats. Urine and kidneys were collected at 40 weeks of age to assess albuminuria and renal injury.

Results: Measurements of BP by telemetry indicated no difference between SHR-A3 and the congenic line both before and during the emergence of renal damage and proteinuria. Glomerular and tubulointerstitial injury, but not albuminuria, were significantly reduced in the congenic line compared to SHR-A3 rats at 40 weeks of age.

Conclusions: Our findings provide evidence that genetic variation in the IgH locus contributes to susceptibility to glomerular and tubular injury, independently of hypertension in SHR-A3 rats. However, factors distinct from the IgH variation possibly contribute to the complex phenotype of urinary albumin excretion.

Funding: NIDDK Support, Private Foundation Support

SA-PO285

Hemoglobin Levels Increased by ESA Suppress the Progression of Renal Injury in Chronic Glomerulonephritis Rats Ryohei Kawasaki, Yoshihito Tashiro, Ken Aizawa, Yasushi Shimonaka, Michinori Hirata. *Product Research, Chugai Pharmaceutical Co., Ltd., Kamakura, Kanagawa, Japan.*

Background: It has been reported that erythropoiesis stimulating agents (ESAs) confer renoprotection in several kidney disease models. We previously reported that a single injection of epoetin beta pegol (continuous erythropoietin receptor activator; C.E.R.A.) conferred more effective renoprotection than a single injection of epoetin beta (EPO) in chronic glomerulonephritis (cGN) rats. At that time, hemoglobin levels were higher in the C.E.R.A-treated group than in the EPO-treated group in the early phase of the disease. Therefore, we evaluated whether hemoglobin levels increased by ESA affect the amelioration of renal injury in cGN rats.

Methods: To increase hemoglobin levels, EPO (1,000 IU/kg) was intravenously injected into rats (F344, 6 wks old, male) once on Days 0 (EPO first injection), 2 and 4. cGN was induced by injection of anti-Thy1.1-antibody (OX-7, 0.6 mg/kg, i.v.) to uninephrectomized rats (7 wks old) 5 days after the last EPO injection (Day 9) in order for EPO not to affect the amelioration of renal injury directly. To evaluate renal function, 24-hr urinary total protein (uTP) and 24-hr liver-fatty acid-binding protein (L-FABP) levels were measured at Day 67. Hemoglobin levels and EPO levels in blood were measured at cGN induction (Day 9).

Results: Hemoglobin levels were significantly higher in the EPO-treated group than in the vehicle-treated group (15.5 ± 0.1 vs. 12.9 ± 0.1 g/dL, mean ± SEM, n=15, $p<0.05$) at the cGN induction (Day 9). At that time, plasma EPO was not detected in either group. In the vehicle-treated cGN group, uTP levels (212.1 ± 16.6 mg/day, n=10) and L-FABP

levels (287.7 ± 28.6 ng/day, n=10) were high at Day 67. In the EPO-treated cGN group, uTP levels (93.8 ± 14.4 mg/day, n=10, p<0.05) and L-FABP levels (141.3 ± 18.1 ng/day, n=10, p<0.05) were significantly lower than those in the vehicle-treated cGN group at Day 67.

Conclusions: This study suggested that hemoglobin levels themselves increased by ESA could suppress the progression of renal injury in cGN rats.

Funding: Pharmaceutical Company Support - Chugai Pharmaceutical Co., Ltd.

SA-PO287

NaCl - Hypertonicity Inhibits the Cross-Priming Capacity of Dendritic Cells Zoran Popovic, Federica Chessa, Mahnaz Bonrouhi, Viola Nordström, Hermann-Josef Groene. *Dept of Cellular and Molecular Pathology, German Cancer Research Center, Heidelberg, Germany.*

Background: Biophysical microenvironmental signals may modulate gene expression pattern and functional signature of infiltrating and resident mononuclear phagocytes. Tissue hyperosmolarity may be associated to physiologic and pathologic conditions, including both inflammation and neoplasia. Cross-priming is crucial for initiation of a specific cytotoxic immune response.

Methods: Here, we examined how a hyperosmotic microenvironment (340 mOsm – 450 mOsm) affects cross-priming capacity of dendritic cells. We applied ex vivo antigen uptake, processing, presentation and cross-priming assays involving murine bone marrow-derived dendritic cells; and stimulated emission depletion (STED) imaging as well as proximity ligation assay to analyze surface receptor cluster formation.

Results: Exposure of dendritic cells to hyperosmotic micromilieu inhibited the cross-priming in a NFAT5-independent manner. A significant inhibition of cross-priming has been achieved by application of nonionic osmolyte mannitol as well. We have observed TRIF as a key mediator of this phenomenon. Moreover, we have identified a hypertonicity-triggered, TRIF-dependent clustering of MHC class I – SIINFEKL complexes, but not of single MHCI molecules, associated with reduced dendritic cell – T cell contact. Our in vivo data using a renal allotransplantation approach has shown a similar distribution of T lymphocytes across kidney compartments of normotonic cortex and hyperosmolar medulla upon transplantation to TRIF-deficient recipients.

Conclusions: Collectively, this study provides evidence that high salt reduces cross-priming and suggests a novel mechanism of antigen-specific immune response inhibition in hyperosmolar microenvironments.

SA-PO288

Renal Sodium Gradient Orchestrates a Dynamic Antibacterial Defence Zone Miriam Berry, Rebeccah J. Mathews, Chenzhi Jing, Menna R. Clatworthy. *Dept of Medicine, Univ of Cambridge, United Kingdom.*

Background: Urinary tract infections are one of the commonest bacterial infections in humans yet infection of the renal parenchyma (pyelonephritis) is relatively rare. This protection is often attributed to the anterograde flow of urine which limits the ascent of bladder microbes. The medulla is the region of the kidney most vulnerable to infection, and also presents a novel environmental challenge to bacteria and resident immune cells due to the regional hypersalinity generated in order to concentrate urine. Little is known about mechanisms of innate immunity that protect the human kidney from infection, nor the modulating role played by the specialised micro-environment.

Methods: We characterised human kidney macrophages and DCs (mononuclear phagocytes, MNPs) using entire human kidneys, and evaluated the effect of the renal micro-environment on their role in defence against infection.

Results: We show that to counter the threat of bacterial infection, the mammalian immune system uses the renal sodium gradient to position functionally specialised MNPs in the region of the kidney most susceptible to infection. In human renal medulla, we identified an enrichment of MHC II+ CD11c+ CD14+ MNPs that avidly phagocytosed UPEC and promoted neutrophil recruitment and activation via the production of interleukin (IL)8, IL6, and tumour necrosis factor (TNF) αlpha. The high sodium environment in the medulla orchestrated CD14+ MNP position by stimulating TonEBP-dependent production of chemokines (MCP1 and CX3CL1) by renal tubular epithelial cells. Upon bacterial challenge, MNPs secrete the epidermal growth factor-like molecule amphiregulin to enhance epithelial survival and chemokine production, further amplifying local immunity. Increased extracellular sodium also optimised the antibacterial functions of MNPs, such that developmental, pharmacological or pathological disruption of the intrarenal sodium gradient in mice and humans resulted in aberrant MNP localisation and susceptibility to pyelonephritis and sepsis.

Conclusions: We show that urinary concentrating mechanisms essential for homeostasis in terrestrial mammals also act as a cue to optimise local immune defence in the kidney.

SA-PO289

Clinical Factors Associated with the Gene Expression of Angiotensin II Type 1 Receptor-Associated Protein on Human Leukocytes Kotaro Haruhara,[1,2] Kouichi Tamura,[1] Hiromichi Wakui,[1] Masato Ohsawa,[1] Kengo Azushima,[1] Kazushi Uneda,[1] Sona Haku,[1] Ryu Kobayashi,[1] Kohji Ohki,[1] Sho Kinguchi,[1] Nobuo Tsuboi,[2] Takashi Yokoo.[2] *[1]Dept of Medical Science and Cardiorenal Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Japan; [2]Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan.*

Background: Previous studies have shown that the leukocyte gene expression of the renin-angiotensin system, particularly type1 angiotensin II receptor (AT1R), is involved in the pathogenesis of non-communicated diseases and target organ diseases. We found that AT1R-associated protein (ATRAP) is a novel molecule that specifically binds to AT1R and promotes internalization of AT1R along with the suppression of activated AT1R signal in animal models of non-communicated diseases. The aim of this study is to determine the factors that may regulate the gene expression of ATRAP on human leukocytes.

Methods: Blood samples were obtained from outpatients. The exclusion criteria were patients i) diagnosed with a hematological disease, ii) with a history of corticosteroid or immunosuppressive therapy within three months, and iii) undergoing renal replacement therapy. We examined the relationships between ATRAP mRNA on leukocytes and clinical variables.

Results: We obtained blood samples from 86 patients (mean age 63 years, hypertension in 95%, dyslipidemia in 76%, CKD in 63%). The ATRAP mRNA was positively correlated with the age, leukocyte count, neutrophil count, monocyte count, and serum CRP, and negatively correlated with the estimated urinary sodium chloride excretion and serum triglyceride levels. These associations remained significant after adjustment for age, sex, estimated glomerular filtration rate, and urinary albumin excretion. Furthermore, the ATRAP mRNA was positively correlated with the interleukin-1β and toll-like receptor 4 mRNA on leukocytes. In contrast, blood pressure, diabetes status, and the indices of arterial stiffness were not significantly associated with the ATRAP mRNA in these patients.

Conclusions: These results suggest that aging, inflammation, and dietary contents are involved in the regulation of the gene expression of ATRAP on human leukocytes.

SA-PO290

Knockdown of UGCG Induces Renal Tertiary Lymphoid Organ Formation Tess Dupre,[1] Kumar Saurabh,[2] Deanna L. Siow,[1] Cierra Sharp,[1] Levi J. Beverly,[2] Leah J. Siskind.[1] *[1]Pharmacology/Toxicology, Univ of Louisville; [2]Medicine, Univ of Louisville.*

Background: Glycosphingolipids (GSLs) are thought to play a role in a number of kidney pathologies including aging-related declines in kidney function, lupus nephritis, diabetic nephropathy, and transplant rejection.

Methods: To study the role of GSLs in kidney biology and pathology, we generated mice containing a doxycyline inducible shRNA that targets expression of UGCG (Tet-O-shUgCg); UGCG is the gene that encodes for glucosylceramide synthase, the enzyme that catalyzes synthesis of glucosylceramide from ceramide. Tet-O-shUgCg mice were bred with $CAG^{+/-}$rtTA3 mice (CAG-rtTA3/Tet-O-shUgCg) for universal expression of the shRNA.

Results: Following UGCG knockdown (KD), organized accumulations of CD19+ B cells and CD3e+ T cells associated with PNAd+ lymphatic vessels formed in the kidneys, which are defining features of tertiary lymphoid organs (TLOs). TLOs are are ectopic accumulations of lymphoid cells that can arise in areas of chronic inflammation via lymphoid neogenesis. In addition, cytokines and chemokines associated with both inflammation and TLO formation were increased following doxycycline administration to CAG-rtTA3/Tet-O-shUgCg mice but not control mice. To elucidate whether TLO formation in the kidneys was due to UGCG KD in the hematopoietic system or in the kidney (or both), bone marrow chimera experiments were performed. Data indicate that UGCG KD in either the bone marrow or the kidney was sufficient to induce TLO formation, as both control mice receiving CAG-rtTA3/Tet-O-shUgCg bone marrow and CAG-rtTA3/Tet-O-shUgCg mice receiving control bone marrow showed evidence of TLO formation. Data also indicate that TLO formation was not specific to the kidney as it was observed in the lungs and liver following UGCG KD.

Conclusions: Understanding the mechanism by which KD of UGCG expression leads to TLO formation and identifying the specific lipids responsible for this phenotype will improve our understanding of the role for GSLs in chronic inflammation and lymphoid neogenesis in a variety of disease states.

Funding: NIDDK Support

SA-PO291

Acute Interstitial Nephritis Secondary to Programmed Death-1 Blockade: Role for Loss of PD-L1 Inhibition of T-Cell:MHC Class II Interaction on Renal Microvascular Endothelium Bairbre A. McNicholas, Jonas M. Kwiatkowski, Mark Joseph Manalang Torres, Susan K. Anderson, Kimberly A. Muczynski. *Div of Nephrology, Univ of Washington, Seattle, WA.*

Background: Human renal microvascular endothelial cells (RMEC) normally express high levels of MHC class II. Role for the high level of MHC Class II on RMEC without associated inflammation remains unexplained but may be a mechanism for peripheral immune tolerance. We have previously shown that isolated RMEC activate T cells in a class II-peptide dependent manner leading to T cell proliferation and cytokine secretion. This

effect is blocked by antibodies to CD40, CD58 and HLA-DR and enhanced by antibodies to PD-L1 (B7-H1,CD274). We hypothesized that RMEC express PD-L1 in vivo to prevent or limit T cell activation to HLA class II presented peptides.

Methods: Normal human kidney from nephrectomies was reduced to single cell suspension for flow-cytometry. Surface expression of stimulatory and inhibitory second signaling components on RMEC ($CD34^{+,}$ $HLA\text{-}DR^{+}$, $CD45^{-}$) and renal-T cells ($CD45^{+}$, $CD3^{+}$) were assessed using 7 color-flow cytometry. Patients who developed AKI following PD-1 blockade with nivolumab were evaluated.

Results: RMEC express CD58, CD275 (ICOS L), CD274 (PD-L1), CD273 (PD-L2), B7-H3 and B7-H4. They lack CD80 and CD86. Renal T cells express CD2, CD28, CD274 (PD-L1) and CD279 (PD1), the receptor for CD274 and CD273. New PD-1 blocking monoclonal antibodies, such as nivolumab, are being used to treat advanced cancers by selectively blocking PD-1 interactions with ligands PD-L1 (CD274, B7H1) and PD-L2 (CD273, B7H2) present on tumor cells. We identified four cases of AKI in patients receiving PD-1 pathway blockade. Biopsies revealed an intense non-eosinophilic interstitial nephritis in the area of the class II expressing RMEC. No other causes of interstitial nephritis were identified from clinical history.

Conclusions: RMEC are poised to present peptide from circulating antigen to T-cells as an immune surveillance system, with the PD1 pathway functioning to restrain T cell activation. Acute interstitial nephritis following use of PD-1 monoclonal antibody may be due to loss of PD1 mediated immune checkpoint blockade.

Funding: Private Foundation Support

SA-PO292

Accumulation of Dysregulated Renal Mononuclear Phagocytes (rMoPh) and Th1 Cells in the Kidney of CD11c-Specific SHP-1 Knockout Mice

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Background: Renal mononuclear phagocytes (rMoPh) have attracted increasing attention because of their immunoregulatory roles in healthy and diseased kidneys (JASN 23:194, 2012). rMoPh simultaneously express traditional markers for either macrophages (such as F4/80) or dendritic cells (CD11c). We have previously reported that CD11c-specific ablation of protein tyrosine phosphatase, SHP-1, a negative regulator of hematopoietic cell signaling, spontaneously developed autoimmune nephritis in mice (J Immunol 2012, ASN 2015). To further explore mechanisms of renal injury of SHP-1 conditional knockout (SHP-1 CKO) mice, we characterized immune cells in the kidney.

Methods: Flow cytometry analysis were performed to characterize immune cells in the kidney of SHP-1 CKO and its control mice at 40 weeks.

Results: SHP-1 CKOdeveloped proliferative glomerulonephritis and tubulointerstitial nephritis. Immunohistochemical staining showed marked accumulation of $CD11c^{+}$ cells in both glomeruli and tubulointerstitial area and of $F4/80^{+}$ and $CD4^{+}$ cells in tubulointerstitial area of SHP-1 CKO. Flow cytometric analysis revealed that most $CD11c^{+}$ cells simultaneously expressed F4/80, suggesting that they are rMoPh. These cells showed lower expression of MHC class II, and higher expressions of CD11b, CX3CR1, and CCR5. In addition, rMoPh of SHP-1 CKO were more frequently positive for Ki67, a marker for proliferation, and produced more pro-inflammatory cytokines, TNFα and IL-6, than control mice. Flow cytometry also showed increased $CD4^{+}$ cells, predominantly producing IFNγ. The majority of $CD4^{+}$ cells had memory-phenotype ($CD62L^{low}CD44^{high}$), and the activated T cell marker, CD69.

Conclusions: CD11c-specific ablation of SHP-1 causes autoimmune nephritis characterized by the marked accumulation of dysregulated rMoph and Th1 cells.

Funding: Government Support - Non-U.S.

SA-PO293

IL-33-Mediated Expansion of Type 2 Innate Lymphoid Cells Ameliorates Progressive Glomerulosclerosis

Martina Becker,[1] Jan-Hendrik Riedel,[1] Mathis Duester,[1] Catherine Meyer-Schwesinger,[1] Rolf A. Stahl,[1] Ulf Panzer,[1] Jan-Eric Turner.[1] *[1]III.Medizinische Klinik, Univ Medical Center Hamburg, Hamburg, Germany; [2]Mill Hill Laboratory, T.*

Background: Over the last years, innate lymphoid cells (ILC) have been shown to play an important role in the immune systems response to different forms of infectious and non-infectious pathologies. Especially, IL-5- and IL-13-producing type 2 ILCs (ILC2s) have been implicated in repair mechanisms that are aimed at restoring tissue integrity after injury. Therefore, we characterized ILC populations in the human and murine kidney and addressed their role in a mouse model of CKD.

Methods: ILC populations in the human and murine kidney were analysed by flow cytometry. ILC2s were expanded in mice by treatment with recombinant IL-33. The effect of IL-33-mediated ILC2 expansion was tested in a mouse model of progressive glomerulosclerosis that is induced in BALB/c mice by injection of Adriamycin.

Results: In the present study, we show that ILC populations are present in in the human and murine kidney. A detailed characterization of kidney-residing ILC populations revealed that $IL\text{-}33R^{+}$ ILC2s are a major ILC subtype in the kidney of human and mice. Short-term IL-33 treatment in mice lead to sustained expansion of $IL\text{-}33R^{+}$ kidney ILC2s and ameliorated progressive chronic kidney disease induced by Adriamycin-injection in BALB/c mice. The IL-33 effect was independent of T and B cells but depended on the presence of ILCs for protection from progressive CKD. The tissue-protective mechanisms employed by IL-5- and IL-13-producing ILC2s included enhanced activation of alternatively activated macrophages, recruitment of eosinophils and limitation of neutrophil influx by downregulation of neutrophil-attracting chemokines.

Conclusions: In summary, we show that kidney-residing ILC2s can be effectively expanded by IL-33 in the mouse kidney and are central regulators of renal repair mechanisms. The presence of ILCs in the human kidney tissue, identifies ILCs as attractive therapeutic targets for chronic kidney disease in humans.

Funding: Government Support - Non-U.S.

SA-PO294

Renal Insufficiency and Impaired T-Cell Differentiation

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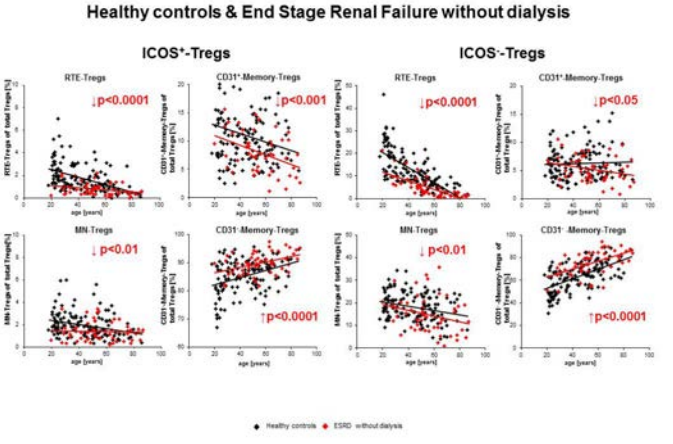
Background: Regulatory T cells (Tregs) play a key role in maintaining immune homeostasis. The influence of renal insufficiency on Treg differentiation has not been elucidated. However patients with end-stage renal disease (ESRD) often present with an impairment of their immune system functions. The underlying mechanisms are not yet understood. Moreover the influence of a renal replacement therapy on a possible recovery of T-cell function needs further investigation.

Methods: Six-color flow cytometric analysis was used to determine the percentages of different subsets of naïve and memory T-cells within total $ICOS^{+}$- and $ICOS^{-}$-Tregs. Hence, the differentiation of both $ICOS^{+}$- and $ICOS^{-}$-RTE-Tregs in healthy patients (N=131), in patients with ESRD (N=49) and dialysis treatment (N=61) and in patients after kidney transplantation (N=190) could be analyzed.

Results: Patients with ESRD show significantly reduced amounts of naïve Tregs compared to healthy control patients, possibly induced by uremia toxins. Hence the share of highly differentiated CD31- memory Treg cells is increased reducing the adaptability of immune systems function.



However, after initiation of a hemodialysis treatment Treg cell function recovers as the percentage of naïve Tregs increased compared to ESRD patients without renal replacement therapy having started. This effect is even clearer after kidney transplantation.

Conclusions: Present data eludicate for the first time possible mechanisms underlying an impaired immune system of ESRD patients. The share of naïve Treg cells is significantly reduces compared to healthy control patients. Moreover evidence is given for a remarkable improvement after initiation of a renal replacement therapy.

SA-PO295

NET-Inducing Capacity Is a Potential Biomarker in MPA and GPA Independent of ANCA Antibodies

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Background: Neutrophil extracellular traps (NETs) play an important role in the pathogenesis of ANCA-associated vasculitis (AAV). Sera of MPO-ANCA or PR3-ANCA positive patients can induce NETs in vitro. This study investigates whether NET induction could serve as a biomarker in MPO- and PR3-positive AAV patients.

Methods: Healthy neutrophils were stimulated with 10% serum from 62 GPA patients, 37 MPA patients and 18 healthy subjects. NETs were imaged by automated 3D confocal microscopy. NET-inducing capacity was defined as fold increase of quantified NETs relative to healthy controls. To investigate NET induction by ANCA autoantibodies, IgG was isolated using protein G agarose beads. IgG depletion in the flow through was confirmed with ELISA.

Results: Both GPA and MPA samples showed significantly higher NET-inducing capacity (fold change mean±SEM for GPA 40±7.4, $p<0.0001$ and for MPA 153.2±44.9, $p<0.01$). MPA sera had a significantly higher NET-inducing capacity than GPA ($p<0.0001$).

In 14 AAV patients who had seroconverted, we observed that the NET-inducing capacity was similar to levels of healthy controls (1.40±0.42, p=0.37). However, we found no correlation of NET-inducing capacity with titers of MPO and PR3 antibodies (r=0.17, p=0.35 for MPO and r=-0.04, p=0.79 for PR3). To further determine whether NET release was mediated by ANCA autoantibodies, we isolated MPO-ANCA IgG and PR3-ANCA IgG from 5 sera. The purified IgG antibodies did not show NET-inducing capacity (1.40±0.33, p=0.45). In contrast, corresponding IgG-depleted sera had a similar NET-inducing capacity as whole sera (12.91±4.5 for IgG-depleted sera and 18.88±7.26 for whole sera, p=0.51).

Conclusions: These data show that NET release in AAV patients is independent of MPO- or PR3-ANCA. In addition, these data indicate that NET release might be a novel biomarker in AAV, independent of ANCA autoantibodies. Our data supports the hypothesis that NETs are a source of autoantigens for the production of ANCA.

SA-PO296

A Mouse Model of THSD7A-Associated Membranous Nephropathy

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Background: Thrombospondin type-1 domain-containing 7A (THSD7A) and phospholipase A2 receptor 1 (PLA2R1) are podocyte membrane proteins that have been identified as target antigens for autoimmunity in membranous nephropathy (MN). The investigation of the pathogenicity of the involved autoantibodies has been hampered by the fact that PLA2R1 is not expressed on rodent podocytes. On the other hand, THSD7A is expressed on mouse podocytes and shares over 90% of sequence homology with the human protein. We have recently demonstrated that anti-THSD7A antibodies isolated from a patient with THSD7A-associated MN can cause morphological and clinical MN in mice, allowing further investigations of disease pathogenesis. However, THSD7A-associated MN is a rare entity, incapacitating patient antibodies for larger experimental procedures.

Methods: Polyclonal rabbit antibodies against human and mouse THSD7A were generated using cDNA immunization. Purified IgG from these rabbits recognized, like patient autoantibodies, (a) conformation-dependent epitope(s) present in both native human and mouse THSD7A *in vitro*.

Results: Two hours after intravenous injection into mice, rabbit IgG was bound along the glomerular filtration barrier. Two days later, mice developed proteinuria that rapidly increased and reached around 10 g/g after 5 days and 200-300 g/g albumin-to-creatinine after 14 days with some mice developing a severe nephrotic syndrome with ascites and hyperlipidemia. In immunofluorescent analysis, granular rabbit IgG was found subepithelially along the glomerular filtration barrier after 14 days and immunohistochemistry for rabbit IgG showed the classic picture of human MN. Mice injected with purified IgG from rabbit serum that was taken before THSD7A-immunization failed to develop any of these changes.

Conclusions: Our study introduces a heterologous mouse model that allows further mechanistic investigations of the molecular events leading to membranous nephropathy.

SA-PO297

Glomerular and Tubulointerstitial Gene Expression Correlate with Anti-PLA2R Titer in Membranous Nephropathy

Laurence H. Beck,[1] Laura H. Mariani,[2] Sean Eddy,[2] Huateng Huang,[2] C. Avila-Casado,[3] Rivka Ayalon,[1] Peter X.K. Song,[4] David J. Salant,[1] Matthias Kretzler.[2] *[1]Boston Univ Medical Center; [2]Univ of Michigan School of Medicine; [3]Univ of Toronto; [4]Univ of Michigan School of Public Health.*

Background: NEPTUNE is a multicenter prospective cohort study of children and adults with proteinuric renal diseases enrolled at the time of renal biopsy. The NEPTUNE membranous nephropathy (MN) cohort provides a unique opportunity to examine glomerular and tubulointerstitial gene expression and assess correlation with novel parameters such as anti-PLA_2R titer.

Methods: Anti-PLA_2R was assayed by Western blot and ELISA using baseline sera. For those with a negative/equivocal anti-PLA_2R result, a corresponding kidney biopsy slide was immunostained for the presence of PLA_2R within immune deposits. On the basis of these assays, the cohort was grouped into PLA_2R-associated and non-PLA_2R-associated MN (Table). Gene expression was assessed using the Affymetrix 2.1 ST microarray from the glomerular and tubulointerstitial compartments of protocol renal biopsy cores. Genes significantly correlated with anti-PLA_2R titer (fdr <0.1) were analyzed for enrichment of canonical pathways and upstream regulators using the Ingenuity Pathway Analysis Software Suite.

Results:

	Entire MN cohort (n= 78)	PLA_2R assoc MN (n= 67)	Non-PLA_2R assoc MN (n= 11)
Age, yr (SD)	50 (15)	49 (14)	50 (15)
Female, n (%)	30 (38%)	25 (37%)	5 (45%)
Black Race, n (%)	16 (21%)	14 (21%)	2 (18%)
Baseline eGFR, mL/min/1.73m^2, mean (SD)	81 (28)	81 (28)	86 (31)
Baseline UPCR, mg/mg, median (IQR)	3.9 (2.4, 7.1)	3.6 (2.3, 6.5)	6.8 (4.8, 9.4)

The top predicted upstream regulators associated with the glomerular gene set (88 anti-PLA_2R correlated genes) implicate innate immunity pathways (e.g. LPS, IFNG, TNF). In contrast, there was a relative enrichment of adaptive immunity upstream regulators (e.g. TCR, BCR) in the tubulointerstitial gene set (109 correlated genes).

Conclusions: The titer of circulating anti-PLA_2R correlated with the expression level of a number of glomerular and tubulointerstitial genes. Such an approach offers a means by which to explore novel pathogenetic mechanisms in human MN.

Funding: NIDDK Support, Other NIH Support - Office of Rare Diseases Research / National Center for Advancing Translational Sciences

SA-PO298

Identification of Components of the Canonical Wnt Signalling Pathway in the Developing Kidney

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Background: The Wnt-signalling pathway has been shown to be essential for kidney development and exhibits a very specific and tightly regulated expression pattern, however, the specific signal transduction components have yet to be identified. Wnt specificity is determined by a co-receptor complex, consisting of one Frizzled (Fzd) and one Lipoprotein related receptor protein (Lrp). More recently, R-spondin1 (Rspo1), expressed in the developing kidney, has been shown to associate with this complex and also act as a Wnt agonist, increasing the signal transduction capacity of the signalling complex.

Methods: We investigated the role of a specific Wnt receptor complex responsible for potentiating response to Wnt9b exposure in M15 cells, a cell model representative of an early renal progenitor cell (RPC). To measure activation of the canonical Wnt pathway, we transfected our cells with reporter plasmid 8X TOPFlash and measured luciferase activity. RT-qPCR was also performed to determine mRNA expression levels.

Results: We took a systematic approach to test the effect of the addition of Fzds, Lrps and Rspo1 on Wnt response to determine the components involved in priming a RPC to complete a normal differentiation program. Exposure to exogenous Wnt9b resulted in no luciferase activity suggesting a signalling component is absent in our cell line. Signal activation was only observed in Wnt9b+Rspo1 conditions, indicating Rspo1 is a potent activator of Wnt signalling in our cells. Next, knockdown of Lrp6 using siRNA resulted in a 60% reduction in luciferase and mRNA levels. Lastly, we tested the effect of ectopic Fzds (Fzd1-10). A significant increase in luciferase activity was only observed in the Fzd5 condition in addition to Wnt9b and Rspo1 suggesting it is involved in potentiating a Wnt9b signal.

Conclusions: These data suggest that early RPCs require a specific receptor complex consisting of Fzd5, Lrp6 and Rspo1 to become responsive to a Wnt9b stimulus and to activate canonical Wnt-signalling during kidney development.

Funding: Government Support - Non-U.S.

SA-PO299

Development of Multipotent Adult Kidney Stem Cells

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Background: Nephrons are formed prenatally, and loss of nephrons leads to chronic kidney disease (CKD). In the past few years, it has been possible to use adult tissues to "reprogram" cells into adult stem cells that can be used to make variety of cell types, though the kidney remains a major challenge because of its complexity both in structure and function. To date, no one has been able to regenerate or model functional mammalian nephrons from normal or diseased kidneys. Recently, we identified a member of the ARID transcription factor family that regulates plasticity in renal cells. When knocked out, *ARID3a* allowed the generation of developmentally plastic cell lines from adult kidney that exhibited increased expression of multiple pluripotency-associated genes.

Methods: In this study, we explored the utility of an adult mouse *ARID3a*-knockout kidney cell line (KKPS5) for generating nephron structures in both *in vitro* and *in vivo* model systems. Furthermore, we determined the effect of ARID3a knockdown at the adult stage of kidneys using both mice and medaka.

Results: We showed that an adult mouse *ARID3a*-knockout kidney cell line (KKPS5) contains adult renal progenitors, and that these cells spontaneously developed into different kidney cell types in 3D matrigel cultures. Importantly, ARID3a elimination increased the number of renal adult stem cells in mice and in medaka kidneys. We are unaware of the existence of this unique multipotent property.

Conclusions: These data implicate KKPS5 cells provide a unique advantage for exploring kidney development. Moreover, we predict that further studies based on our findings will provide renal tissue available for transplantation for CKD treatment.

Funding: Private Foundation Support

SA-PO300

Lineage Tracing Identifies c-Kit as a Marker of a Progenitor Cell Population with Regenerative Potential in Adult Kidney Erika B. Rangel,[1,2] Samirah A. Gomes,[1,3] Janaina Paulini Aguiar,[1] Matheus Van Schaik,[1] Garrett Goss,[4] Bradley J. Goldstein,[4] Barbara Seidler,[5] Dieter Saur,[5] Joshua M. Hare,[4] Erika B. Rangel.[1,2] *[1]Albert Einstein Hospital, Sao Paulo, SP, Brazil; [2]Federal Univ of Sao Paulo, Sao Paulo, SP, Brazil; [3]Univ of Sao Paulo, Sao Paulo, São Paulo, Brazil; [4]Interdisciplinary Stem Cells Inst, Univ of Miami, Miami, FL; [5]Medizinische Klinik, Technische Univ München, Munich, Germany.*

Background: We recently reported that c-Kit cells isolated from developing kidneys exhibit progenitor cell properties. We hypothesize therefore that c-Kit cells represent a tissue-specific progenitor population that is involved in kidney development, is maintained during adult life, and contributes to kidney regeneration.

Methods: We crossed the inducible c-Kit Cre reporter mice with IRG, mT;mG, LacZ, and multicolored Confetti mice. By varying the timing of tamoxifen treatment, c-Kit+ cells and their descendants were specifically labelled with enhanced green fluorescent protein (EGFP), LacZ or multicolor fluorescence, and their spatiotemporal distribution was followed during kidney development and acute kidney injury (ischemia-reperfusion and rhabdomyolysis).

Results: c-Kit expression was more abundant in early postnatal (P) period (7.91 in P0.5-3.5; 10.6 in P7-14 vs 3.13 in embryonic [E]17.5-18.5, P<0.0001), and was maintained in adult life, although at lower levels (5.7 in P30 and 2.2 in P90-180). When tamoxifen was administered during E7.5-9.5, a few EGFP/LacZ+ cells were observed in tubular segments from cortex to medulla, and at E10.5-12.5, when metanephros development initiates, ribbons of c-KitEGFP/LacZ+ cells expanded to form tubular structures and were detected in structures resembling the S-shaped bodies. In postnatal period, the number of c-Kit-EGFP/LacZ/clonal multicolored cells increased in the cortex, medulla, and papilla. In adult mice, c-Kit-EGFP/LacZ/clonal multicolored cells were found in distinct renal segments (macula densa, distal tubules and collecting ducts). After acute kidney injury, the number of c-Kit clones increased from 10±3 to 36.5±8 (P<0.0001) in the outer medulla.

Conclusions: c-Kit marks a kidney progenitor population that is maintained in adult life and may have therapeutic application.

Funding: Government Support - Non-U.S.

SA-PO301

A Novel Method to Differentiate Human ES Cells into Renal Tubule-Like Cells by a Combination of Transcription Factors Administration Ken Hiratsuka,[1] Toshiaki Monkawa,[1] Shintaro Yamaguchi,[1] Ryuji Morizane,[1] Shigeru B.H. Ko,[2] Hiroshi Itoh,[1] Minoru S.H. Ko.[2] *[1]Dept of Internal Medicine, Keio Univ School of Medicine, Shinjuku-ku, Tokyo, Japan; [2]Dept of Systems Medicine, Keio Univ School of Medicine, Shinjuku-ku, Tokyo, Japan.*

Background: Various protocols to differentiate human pluripotent stem cells (hPSCs) into kidney organoids have been developed recently. In a previous study, we have reported a method to differentiate human Embryonic Stem Cells (hESCs) to the cells which are positive for proximal tubule markers in kidney by an administration of single transcription factor (TF) with synthetic mRNAs. Here, we report successful differentiation of renal tubule-like cells of multi-segments from hESCs by a combinatorial administration of defined TF mRNAs.

Methods: To identify TFs which promote differentiation towards a renal lineage, we utilized the comprehensive date set, and represents correlation of gene expression response to the induction of human TFs (~350 genes) under doxycycline (Dox) control in hESCs with tissue-specific gene expression. Modified mRNAs for TFs were synthesized by in vitro transcription. hESCs were transfected with several combinations of synthetic mRNAs for TFs by lipofection and cultured for up to 9days. Morphological changes of these cells were microscopically observed. Marker gene expression were examined by qPCR analysis and protein expression by immunohistochemistry.

Results: By analyzing the data in silico, three candidate TFs which show highest correlation scores to the gene expression profiles of human kidney at 48 hours after Dox induction of each human TF were identified. Two days after the transfection of 3 TFs together into hESCs, intermediate mesoderm cell populations ($PAX2^+$, $LHX1^+$) were induced. On day 9, differentiated, epithelial cell-like morphological changes were clearly observed. mRNA expressions of proximal tubule cell markers such as AQP1, KSP or MEGALIN and distal tubule cell marker SLC12A3 were detected.

Conclusions: We have identified a set of specific TFs for the differentiation of hESCs toward renal lineage via intermediate mesoderm, and generated renal tubule-like cells from hESCs by a novel differentiation method using synthetic mRNAs.

SA-PO302

Functional Role of Epigenetic Memory Genes in Human Kidney Derived iPS Cells Osamu Takase, Taro Tsujimura, Masaomi Nangaku, Keiichi Hishikawa. *Dept of Advanced Nephrology and Regenerative Medicine, Graduate School of Medicine, the Univ of Tokyo, Tokyo, Japan.*

Background: Kidney specific differentiation induction method using iPS cells is not still established. Last year, we reported 73 epigenetic memory genes for advantage of kidney specific induction by genome-wide methylation analysis between fibroblast-derived iPS cells (F-iPS) and kidney epithelial-derived iPS cells (K-iPS).

Methods: We have analyzed the exhaustive 60,000 genes, OSR1 and T (brachyury) as the kidney development key gene by DNA microarray. As two kinds of induction methods using F-iPS and K-iPS cells, one is an intermediate mesoderm cell lines system (induction 1) (Nature Commu.), another is body axis stem cell lines system (induction 2) (Cell Stem Cells).

Results: In microarray cluster analysis, the whole gene expression of kidney induction using K-iPS cells was consistent with the renal epithelial cells, moreover was stronger expressed the kidney development gene than F-iPS cells. Also we confirmed the expression change (iPS cells/origin cells) in 73 epigenetic memory genes. In high methylation 56 genes, some gene expressions were downregulated in F-iPS cells as compared with K-iPS cells, such as GPR137B (F-iPS/K-iPS=0.39), HSPB1(0.49), and MAP3K5 (0.35). In low methylation 17 genes, some gene expressions were upregulated in F-iPS cells, such as GRB10 (2.27) and SOX8 (5.41). Further the expression of OSR1 (0.16) and T (0.45) was downregulation in F-iPS cells. Especially by kidney induction, the expression of OSR1 did not show strong expression, but T showed markedly strong expression by kidney induction 2 using K-IPS cells.

Conclusions: Interestingly, the expression of HSPB1 and SOX8 which regulates cell development and differentiation, showed high expression with kidney induction using K-IPS cells as compared with F-IPS cells. Transcription factor T which regulates mesoderm formation and notochord differentiation, may be newly involved in HSPB1 and SOX8. Our results demonstrate the functional role of epigenetic memory genes in human kidney derived iPS cells, and the mechanical role of these genes, including OSR1 and T, in kidney lineage specific induction will be discussed.

SA-PO303

Should I Stay or Should I Go? Influence of Cell Cycle on Self-Renewal and Differentiation in Human Nephrogenic Progenitors Stefano Da Sacco, Matthew Edward Thornton, Astgik Petrosyan, Ursula Kreuser, Sinem Kargin, Brendan Grubbs, Roger E. De Filippo, Laura Perin. *Children's Hospital Los Angeles.*

Background: Nephron progenitors (NP), co-expressing SIX2 and CITED1, control nephron endowment through proliferation and differentiation. The mechanisms involved in maintaining this balance are still poorly understood. Recent studies have linked lineage commitment and cell cycle progression; self-renewing cells present a short cell cycle and spend most of their time in replicative phase. In this work, we have investigated the relationship between cell cycle and renal differentiation in NP isolated from human fetal kidneys (hFK).

Methods: NP were isolated using RNA Smartflare probes. Nephrogenic characteristics were confirmed by RNA-seq and nephrogenic potential by in vitro differentiation and dissociation/reaggregation assays. Expression of cell cycle markers was confirmed by RNA-seq and by immunofluorescence on hFK. Cell cycle was studied using FUCCI (Fluorescent Ubiquitination-based Cell Cycle Indicator) in isolated NP under self-renewing or differentiating conditions.

Results: RNA-seq confirmed elevated expression of renal developmental genes including SIX2, SIX1, CITED1, WT1, EYA1 within NP and they differentiated into functional podocytes and tubules. RNA-seq analysis also revealed high levels of CDK1/cyclin B, CDK1/cyclin A, E2F2/E2F1 and low levels of retinoblastoma protein and cyclin E possibly suggesting that NP are in M or S phase. Immunofluorescence analysis on hFK confirmed expression of CDK4 and cyclin B in NP but lack of terminally differentiated cell markers like p21 or p27. We also found that increased G1 phase length leads to higher rates of NP differentiation, suggesting a key role of G1 in determining cell fate in NP.

Conclusions: We successfully isolated and characterized for the first time human NP based on SIX2 and CITED1 expression, confirming their nephrogenic identity. Our preliminary data indicate a strong link between cell cycle progression and induction. Since renal diseases correlate with nephron endowment deficit, identifying factors affecting nephron number like self-renewal/differentiation balance can potentially advance our understanding of renal disease initiation and progression.

Funding: Private Foundation Support

SA-PO304

Hemodialysis Patients-Derived Induced Pluripotent Stem Cells Can Be Powerful Tool for Kidney Regeneration Susumu Tajiri,[1,2] Toshinari Fujimoto,[1,2] Shuichiro Yamanaka,[1] Kei Matsumoto,[1] Makoto Ogura,[1] Takashi Yokoo.[1] *[1]Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan; [2]Div of Regenerative Medicine, The Jikei Univ School of Medicine, Tokyo, Japan.*

Background: We could generate neokidnies using human-derived mesenchymal stem cells (hMSCs). However, we previously reported that hemodialysis (HD) patients derived- hMSC might not be appropriate for kidney regeneration due to their long-term uremic condition. Therefore, we hypothesized that induced pluripotent stem cells (iPSc) generated from HD patients could reset the uremic condition and could be useful cell source for kidney regeneration.

Methods: Three patients with end stage renal disease attending our institution for HD were enrolled. Of the three, one had diabetes mellitus and the other 2 had chronic glomerulonephritis. We generated and characterized iPSc from all patients and differentiated iPSc into nephron progenitor cells (NPC) following published protocol. Gene expression markers were compared between healthy control-derived NPC (HC-NPC) and HD patients-derived NPC (HD-NPC) using quantitative RT-PCR. To investigate whether NPC could undergo mesenchymal-to-epithelial transition (MET), we co-cultured them with spinal cords and conducted a histological analysis and gene expression of the structures.

Results: Established iPSc lines showed typical human embryonic stem cell -like morphology and expressed pluripotency markers. Moreover, they exhibited the ability to give rise to teratomas that contained derivatives of all three germ layers and a G-band analysis confirmed normal karyotype. We could differentiate them into HD-NPC that expressed several markers including WT1, PAX2 and SIX2 at the same level as HC-NPC. In addition, HD-NPC exhibited the ability to undergo MET and exhibited robust tubulogenesis. Moreover, clustered podocytes were formed and they expressed podocyte specific markers, such as nephrin and podocin.

Conclusions: To the best of our knowledge, this is the first instance of generating NPC, which were derived from HD patients and then differentiated them into renal tubules and podocyte. Our study demonstrated that HD patient-derived iPSc can be useful cell source for kidney regeneration.

SA-PO305

Identification of a microRNA Signature in Renal Cancer Stem Cells: A New Regulatory Mechanism Grazia Serino,[1,2] Fabio Sallustio,[2] Vanessa Galleggiante,[2] Monica Rutigliano,[2] Claudia Curci,[2] G. Lucarelli,[2] P. Ditonno,[2] M. Battaglia,[2] Francesco Paolo Schena.[2] *[1]IRCCS, Castellana Grotte, Ba, Italy; [2]Univ of Bari, Bari, Italy.*

Background: Clear cell renal cell carcinoma (ccRCC) is the most common form of kidney cancer in adults. Recent evidences show that in several human cancers a small subset of tumor cells called cancer stem cells (CSCs) is present. These cells can be responsible for tumor initiation, growth, metastasis, drug resistance and recurrence. CSCs have been found and characterized also in ccRCC tissue. To date, the role of microRNAs (miRNAs) in ccRCC have been extensively studied, but their function in renal CSCs has not yet been reported.

Methods: We isolated $CD133^{+}/CD24^{+}$ cells from healthy and tumor renal tissue of 28 patients who underwent nephrectomy for ccRCC. Cells were characterized for their mesenchymal phenotype and stemness proteomic profile. The global miRNA profile was identified using small RNA-Seq (llumina). Target gene prediction was performed using bioinformatic analysis. Results were confirmed by qRT-PCR.

Results: We identified 120 miRNAs differentially expressed in renal CSCs compared to healthy counterpart, of which 12 were downregulated and 108 were upregulated. Then, we studied the genomic distribution of the differentially expressed miRNAs. Interestingly, we found that 48 upregulated miRNAs were codified all together in a cluster on chr14:101341370-101533138, near the region 14q LOH that is associated with tumor progression of ccRCC. Moreover, some of these miRNAs putatively regulated the VHL gene that is involved in the ccRCC pathogenesis. Pathways analysis showed that all deregulated miRNAs were implicated in several pathways typical of cancer and renal cell carcinoma, as TGF-β signaling, PI3K-AKT signaling, WNT signaling. The real-time PCR on miR-205-5p, miR-543, miR-127-3p, miR-136-3p, miR-654-3p, miR-1246 and miR-889-3p confirmed results obtained from sequencing.

Conclusions: Our data support a new role of miRNAs in renal CSCs and these new molecules could provide a potential pharmacological target for new therapeutic approaches in ccRCC.

Funding: Government Support - Non-U.S.

SA-PO306

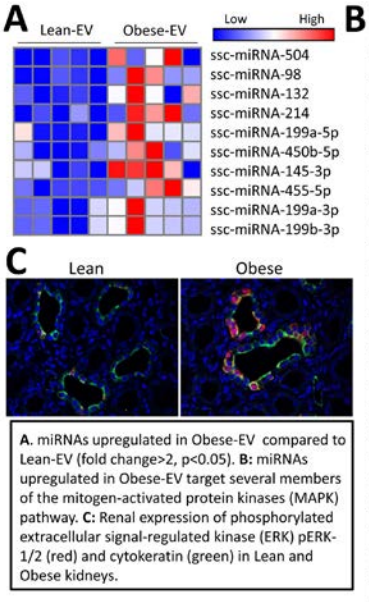
Obesity Modulates the miRNA Cargo Packed within Mesenchymal Stem/Stromal Cell-Derived Paracrine Extracellular Vesicles Alfonso Eirin, Xiang-Yang Zhu, Sreela Jonnada, Kyra L. Jordan, Amir Lerman, Andre J. Van Wijnen, Lilach O. Lerman. *Mayo Clinic.*

Background: Mesenchymal stem/stromal cells (MSC) are prevalent in many organs, and their kidney counterparts act as a reservoir of undifferentiated cells to address the repair needs of the kidney. MSC release extracellular vesicles (EV) that shuttle miRNA to damaged parenchymal cells, activating an endogenous repair program. Obesity is an important cardiovascular risk factor that may coexist with kidney disease. Our studies focus on the key question whether there are changes in the miRNA cargo of MSC-derived EV that could affect the endogenous repair system.

Methods: Autologous MSC were collected from abdominal fat of domestic pigs after 16 weeks of normal (Lean) or high cholesterol/carbohydrate (Obese) diet (n=5 each). EV were subsequently collected by ultracentrifugation. Next-generation sequencing (RNAseq) was performed to identify sequences differentially expressed between Lean- and Obese-EV. Functional annotation clustering analysis was used to identify cellular pathways regulated by miRNA altered in Obese-EV.

Results: RNAseq generated reads for over 400 miRNA, of which 10 were upregulated in Obese-EV compared to Lean-EV (fold change>2, $p<0.05$). These miRNA preferentially target mitogen-activated protein kinases (MAPK), a signaling pathway that acts as a defense mechanism via upregulation of pro-survival, anti-inflammatory, and anti-apoptotic factors. Notably, the expression of the MAPK member ERK1/2 was upregulated in vivo in renal tubular cells from obese pigs.

Conclusions: MSC-derived EV obtained from obese pigs have a distinct RNA content compared to their lean counterparts and are enriched for miRNA that selectively modulate renal expression of several members of the MAPK pathway. Modulation of MAPK signaling may be an important mechanism by which MSC exert their tissue effects and identifies this pathway as a novel therapeutic target.



B

miRNA	Target Score	MAPK genes
miR132	90	MAPK1
	75	MAPK8
	66	MAPKBP1
	60	MAP3K3
	59	GAREM
	57	MAPKAP1
miR-98	96	MAPK6
	93	MAP4K3
	73	MAPK8
	65	MAP3K1
	59	MAP4K4
miR-455-5p	57	MAPK13
miR214	90	MAP3K4
	70	MAPK1IP1L
	52	MAPK1
miR-199a-5p	93	MAP3K11
	69	MAP4K3
	63	TAB3
miR-450b-5p	80	GAREM
	69	MAP3K13
	60	MAP3K2
	57	MAPK6
miR-145-3p	69	MAPK14
miR-199a-3p	98	MAP3K4
	89	MAP3K5
	67	MAP3K1
	52	MAP3K2
miR-199b-3p	98	MAP3K4
	89	MAP3K5
	67	MAP3K1
	52	MAP3K2

Funding: NIDDK Support

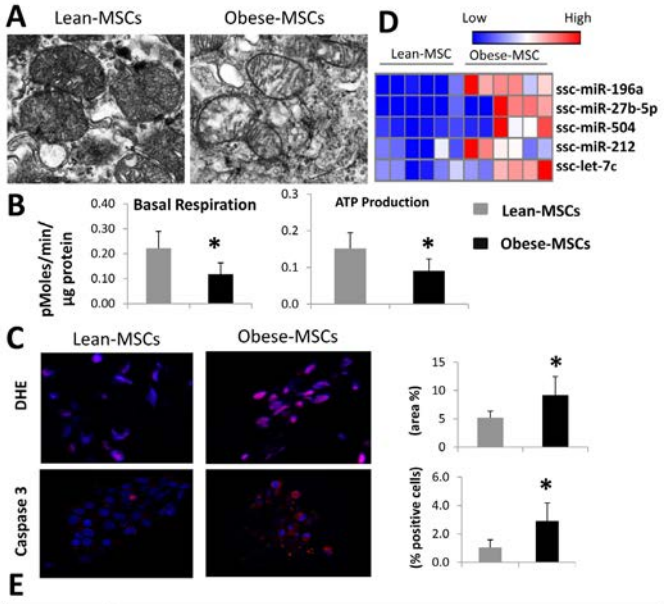
SA-PO307

Obesity-Induced Mitochondrial Dysfunction in Porcine Adipose Tissue-Derived Mesenchymal Stem Cells Yu Meng, Alfonso Eirin, Xiang-Yang Zhu, Hui Tang, Amir Lerman, Andre J. Van Wijnen, Lilach O. Lerman. *Mayo Clinic.*

Background: Transplantation of autologous mesenchymal stem cells (MSC) may be a viable option for treatment of chronic kidney disease (CKD). MSC efficacy depends on their mitochondrial function, which might be impaired in a noxious milieu. We hypothesized that obesity compromises mitochondrial structure and function, possibly via microRNA (miRNA)-based mechanisms.

Methods: MSCs were collected from swine abdominal adipose tissue after 16 weeks of Lean or Obese diet (n=6 each). Mitochondrial structure was assessed by electron microscopy, their respiration and ATP production by Seahorse Analyzer, oxidative stress by dihydroethidium, and apoptosis by caspase-3 staining. Next-generation sequencing (RNA-seq) of miRNAs was performed to identify miRNAs upregulated in Obese-MSCs, and predicted mitochondrial target genes were then identified (MitoCarta).

Results: Compared to Lean-MSCs, mitochondria from Obese-MSCs were swollen and showed cristae remodeling, fragmentation, and loss (Figure). Basal respiration and ATP production were decreased in Obese-MSCs, associated with increased oxidative stress and apoptosis. RNA-seq generated reads for 413 miRNAs, of which 5 miRNAs were upregulated in Obese-MSCs (fold change >2, $p<0.05$) and found to target 43 specific mitochondrial genes (Figure).



E

	Targeted specific mitochondrial genes
ssc-miR-196a	HEMK1,DNAJC15,METTL8,MRS2,PANK2,MRPS25,MRPL35,ALDH1L2,PDK1,SLC30A6,ACP6,ACSL6,PDE12,XPNPEP3,PPTC7,MRPL42,SYNJ2BP,AMACR
ssc-miR-27b-5p	MRPL42,HEMK1,SLC16A7,SDHC,MAVS,ATP5S,C15orf40,METTL8,DNAJC15,ACP6
ssc-miR-504	MAVS,HEMK1,SLC16A7,SDHC,PDK1,C15orf40,PDE12,MRPL42
ssc-miR-212	NDUFS1,MAVS,SPTLC2,HEMK1,SLC16A7,DNAJC15.PDK1,C15orf40,PDE12,XPNPEP3
ssc-let-7c	NDUFS1,MAVS,SPTLC2,HEMK1,SLC16A7,ATP5S,ALDH1L2,ACP6,PDE12,MRPL42,SYNJ2BP,AMACR

A. Transmission electron microscopy showing that Obesity impairs MSC mitochondrial structure. **B:** Basal respiration and ATP production were decreased in Obese-MSC. **C:** Dihydroethidium (pink) and Caspase-3 (red) were increased in Obese-MSC. **D:** miRNAs upregulated in Obese-MSCs compared to Lean-MSCs . **E:** List of mitochondrial genes targeted by miRNAs upregulated in Obese-MSCs. *p<0.05 vs. Lean-MSC.

Conclusions: Obesity impairs MSC mitochondrial structure and function, possibly mediated partly through miRNA-induced mitochondrial gene regulation, leading to increased MSC apoptosis and oxidative stress. Importantly, these alterations may limit the use of autologous MSCs in subjects with CKD and obesity.

Funding: NIDDK Support

SA-PO308

Generation and Characterization of a Pkd1 Mutant Kidney MSC Line In Vitro Pamela Kairath Oliva,[1,2,3] Joan Li,[3] Melissa H. Little.[1,2,3] *[1]Murdoch Research Inst, Melbourne, Victoria, Australia; [2]Dept of Pediatrics, The Univ of Melbourne, Melbourne, Victoria, Australia; [3]Inst for Molecular Bioscience, Brisbane, Queensland, Australia.*

Background: The existence of an adult mesenchymal stem cell population resident within kidney (k-MSCs) was recently reported by our laboratory, providing the exciting prospect of a powerful treatment to repair acutely damaged organs. Microinjection of EGFP+ k-MSCs into the renal parenchyma of CD1 mice has shown that they home to and integrate into collecting duct structures, persisting for at least 15 days post-delivery.

Methods: Here we report the Long-term evaluation of kidney MSCs into the renal parenchyma of CD1 mice and the generation and evaluation of a new mutant kidney MSCs cell line isolated from a Pkd1 (flox/flox) mice.

Results: We found persistence of EGFP+ k-MSCs within the collecting duct even after 10 weeks post-delivery, with an average integration of 7.6 %. In order to test the true functional integration capacity of the k-MSC into the collecting duct, a Pkd1 mutant k-MSCs cell line was generated by isolation of bulk kidney k-MSC from a Pkd1 (flox/flox) mice. Derived k-MSCs then underwent *in vitro* CRE excision and clonal cell derivation to isolate a clone in which a homozygous recombination event had occurred. In order to prepare for further *in vivo* evaluation, a second Pkd1 mutant kMSC line was derived by crossing Pkd1 flox/flox mice with a tdTomato reporter line to enable to tracing of these cells post injection. Characterization of MSCs properties of the Pkd1 mutant k-MSC line compared to the previously described wildtype k-MSC line showed equivalent adherence to plastic and expression of key MSC surface markers CD44, CD81 and Sca1. In addition, genetic modification of the Pkd1 gene did not affect the migration capacity of these cells.

Conclusions: Taken together, we can conclude that Pkd1 gene inactivation did not alter the properties of kidney-derived mesenchymal stem cells, supporting the feasibility of microinjections of Pkd1 mutant k-MSCs into kidney compartments.

Funding: Government Support - Non-U.S.

SA-PO309

Urine of Cystinosis Patients as Source of Undifferentiated Renal Cells for Disease Modelling and Therapy Fanny Oliveira Arcolino, Koenraad Veys, Mohamed A. Elmonem, Lambertus P.W.J. Van den Heuvel, Elena N. Levtchenko. *Dept of Development and Regeneration, KU Leuven, Leuven, Belgium.*

Background: Cystinosis is characterized by the pathological accumulation and crystallization of cystine in the lysosomes. If not treated, end stage renal disease invariably develops within the first decade of life. We have shown that cystinosis patients void excessive number of podocytes and proximal tubular cells in urine and here we hypothesized that in compensation for cell loss, ongoing regeneration might happen, and it could be reflected by the presence of undifferentiated cells in urine of patients.

Methods: We estimated the total number of cells and the number of kidney-undifferentiated cells in urine using pre-amplified cDNA from fresh urine samples of healthy donors (n = 10, range 4-12 years old) and cystinosis patients (n = 8, range 4-15 years old). None of cystinosis patients had kidney graft. The expression of vimentin was correlated to calibration curves derived from known numbers of adult kidney progenitor cells and normalized to volume of urine. We have cultured urinary cystinosis undifferentiated cells and characterized them at genetic and protein levels. Later we differentiated progenitor cells into functional podocytes or proximal tubular cells.

Results: We demonstrate a significant increased loss of kidney-undifferentiated cells in cystinosis patients' urine, while in controls these cells were not found. Cultured cells from patients expressed mesenchymal stromal cell proteins as CD73, CD44, CD105, CD29, did not express hematopoietic cell markers and were positive for the kidney proteins CD24 and CD133. The cells were positive for nephron progenitor genes, such as Vimentin, *PAX2* and *CITED1* and were able to differentiate into functional podocytes or proximal tubular cells.

Conclusions: Our data demonstrate the presence of kidney-undifferentiated cells in urine of cystinotic patients, which might indicate a fast turnover of cells and the attempt of tissue regeneration to compensate epithelial cell loss. Urinary undifferentiated cystinotic cells might have a therapeutic application in regenerative medicine once the correction of the genetic defect and consequent correction of the phenotype are successful.

SA-PO310

Direct Reprogramming of Fibroblasts into Renal Tubular Epithelial Cells by Defined Factors Michael Kaminski,[1] Jelena Tosic,[2] Catena Kresbach,[1] Roman Pichler,[1] Florian Grahammer,[1] Tobias B. Huber,[1] Gerd Walz,[1] Sebastian Arnold,[2] Soeren S. Lienkamp.[1,3] *[1]Dept of Medicine, Renal Div, Univ of Freiburg Medical Center, Freiburg, Germany; [2]Dept of Clinical Pharmacology, Inst of Experimental and Clinical Pharmacology, Freiburg, Germany; [3]Center for Biological Signaling Studies (BIOSS), Univ of Freiburg, Freiburg, Germany.*

Background: Over-expression of transcription factors can convert one cell type into another. This process, referred to as direct reprogramming, is fast and bypasses pluripotency. However, conversion of fibroblasts towards renal cell types has not been achieved yet.

Methods: Based on in-silico analysis and whole-mount in-situ screens we identified candidate renal reprogramming factors. These transcription factors were tested for their potential to convert cells towards a renal fate using fibroblasts from tubule specific reporter mice. Induced cells were analyzed for their transcrpitomic profile, renal marker expression and function.

Results: We identified four transcription factors whose combined expression induced cells with high similarity to native renal tubular epithelial cells. They displayed typical epithelial characteristics, a global expression profile resembling their native counterparts, functional properties of renal tubular epithelial cells and sensitivity to nephrotoxic drugs. Further, they formed tubules along the extracellular matrix of decellularized kidneys and integrated into renal organoids.

Conclusions: Candidate reprogramming factors can be predicted based on their expression characteristics. Directly reprogrammed renal tubular epithelial cells could facilitate nephrotoxicity and drug testing, serve as a platform for disease modeling and may pave the way for regenerative approaches.

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SA-PO311

Differentiation of Human iPSC into Functional Renal Proximal Tubular Cells and Functional Podocytes with the Application for Drug Toxicity Screening Anja Wilmes, Caroline Rauch, Georg Kern, Elisabeth Feifel, Gerhard Gstraunthaler, Paul Jennings. *Medical Univ of Innsbruck, Dept Physiology and Medical Physics, Physiology, Innsbruck, Tirol, Austria.*

Background: Prevalence of chronic kidney disease (CKD) is estimated to be around 10% worldwide. While CKD is mainly a disease of age, it can be accelerated by certain risk factors including exposure to pharmaceuticals, chemicals and environmental pollutants. Furthermore, it is estimated that there is considerable individual variability in the sensitivity to toxins due to altered expression in xenobiotic uptake, extrusion and metabolizing proteins. Within the nephron, proximal tubular cells (PT) and podocytes are the most frequently affected cell types by drug induced kidney injury. The aim of our research is to develop methods to differentiate human induced pluripotent stem cells (iPSC) into monocultures of PTs or podocytes that can be used for drug toxicity testing and individual susceptibility.

Methods: Within the StemBANCC consortium, somatic cells from more than 300 patients have been reprogrammed with Sendai virus to generate iPSC. iPSC are cultured on Matrigel and then differentiated into either podocyte-like cells or proximal tubular-like cells with a combination of small molecules and growth factors.

Results: Toxicity studies require relatively pure cultures of single cell types. Both, podocyte-like cells and PT-like cells are derived in a relative pure culture after 10 and 16 days, respectively. Characterization of these cells show expression of specific podocyte marker, including synaptopodin and podocin, as well as specific PT markers including, claudin 2, AQP1, megalin and CD13. Functional analysis showed secretion of VEGF by podocytes-like cells and uptake of albumin and fluorescent labeled cations by PT-like cells. Preliminary toxicity experiments have been carried out with Doxorubin (aka Adriamycin), a gold standard compound for glomerular toxicity, and with Bardoxolone methyl (aka CDDO) an activator of the Nrf2 oxidative stress response pathway.

Conclusions: While we have made some gains in the development of renal target cells, more efforts need to be invested to increase the differentiation status, purity and stability of the derived cells.

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SA-PO312

Urinary Renal Progenitors as a Novel Predictor of Graft Outcome Anna Manonelles,[1] Roser Guiteras,[3] Oriol Bestard,[1,3] Paola Romagnani,[2] Josep M. Cruzado.[1,3] *[1]Nephrology and Transplant Unit, Hospital Univ de Bellvitge, Barcelona, Catalunya, Spain; [2]Nephrology, Meyer's Children Hospital, Florence, Italy; [3]Nephrology and Transplant Unit, IDIBELL, L'Hospitalet de Llobregat, Spain.*

Background: Long-term improvement of kidney allograft (KA) survival remains as unmet need. Most studies focus on environmental mechanisms of graft injury, whereas kidney reparative mechanisms were neglected. Isolation of Renal Progenitors from urine (uRP) may be a potential tool to evaluate the intrinsic regenerative capacity of the graft.

Methods: We include 66 recipients at the time of 6 month protocol biopsy. After cell culture, uRP were FACs cell-sorted (CD24/CD133). Cells were differentiated into podocytes and tubular cells. Clinical (demographic parameters, type of KA, treatment), analytical (GFR, proteinuria) and immunological data (donor specific antibodies, ELISPOT, urinary biomarkers) were assessed. Kidney biopsy was evaluated according to Banff classification and CD133/CD44 staining performed. We followed this cohort for 2 yrs.

Results: uRPs were isolated in 62.1% patients at the time of 6-m protocol biopsy. Therefore we divided patients in two groups: Group A having uRP and Group B without uRP. Study groups were comparable regarding baseline characteristic, immunosuppression, DGF, acute rejection, GFR and proteinuria. Protocol biopsy evaluation was similar between groups, without differences for particular Banff items. Glomerular CD44 staining was higher in patients without uRP. T-cell IFN-γ ELISPOT assay and donor specific antibody determination was comparable. We determined the variation of GFR between month 6 and months 12 and 24. Interestingly, patients with uRP at 6m showed a significant increase of GFR at 12m in comparison with stabilization of renal function in patients without uRP (+10±2 vs -3±1%; P=0.003), finding maintained at 2 years.

Conclusions: Despite showing similar effector mechanisms of damage, renal function and 6-month graft histology to patients without uRP, the presence of renal progenitors on urine of kidney recipients at 6 months identifies a subgroup of patients with significant improvement of GFR at 1 year. This finding raises new prospects as novel predictors of better graft outcomes.

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SA-PO313

Dedifferentiation-Reprogrammed Mesenchymal Stem Cells with Improved Therapeutic Potential in Diabetic Nephropathy Yang Liu, Alice Zou, Wai Han Yiu, Dickson W.L. Wong, Kam Wa Chan, Loretta Y.Y. Chan, Joseph C.K. Leung, Kar Neng Lai, Sydney C.W. Tang. *Dept of Medicine, The Univ of Hong Kong, Queen Mary Hospital, Hong Kong.*

Background: Podocyte loss is a hallmark of diabetic nephropathy (DN). Stem cell therapy has shown rescue effects on podocytes in animal models of DN, but low efficiency and poor survival of transplanted cells still are the major obstacles. We previously reported that dedifferentiation-reprogrammed mesenchymal stem cells (De-MSCs) derived from bone marrow mesenchymal stem cells (BM-MSCs) had therapeutic advantages compared to unmanipulated BM-MSCs in a brain hypoxic-ischemic animal model (Liu Y, et al. Stem Cells 2011). Here, we explored the therapeutic potential of renal lineage reprogrammed De-MSCs in DN.

Methods: De-MSCs were generated by inducing human BM-MSCs to go through renal differentiation, followed by dedifferentiation. De-MSCs were characterized by cell surface markers, multilineage differentiation, gene array profile and survival ability under H_2O_2 challenge. Immortalized human podocytes were exposed to glycated human serum albumin (AGEs) and co-cultured with De-MSCs or BM-MSCs. BTBR ob/ob mice, an animal model of type 2 DN, were transplanted with De-MSCs, BM-MSCs or PBS.

Results: Compared to BM-MSCs, De-MSCs retained stem cell properties with similar morphology but enhanced survival ability under normal condition or H_2O_2 stress. Co-culture with De-MSCs significantly prevented apoptosis in podocytes exposed to AGEs via rescuing expression of Bcl-2 and survivin, and cytoskeleton related genes synaptopodin, CD2AP and tight junction protein ZO-1. Compared with PBS- and BM-MSCs-treated groups, BTBR ob/ob mice injected with De-MSCs had significantly lower urinary albumin-to-creatinine ratio and BUN. Mechanistically, De-MSC treatment in animals remarkably restored podocin expression and reduced renal cortical HIF1 and p44/42 phosphorylation.

Conclusions: De-MSCs achieved improved therapeutic potential in DN both *in vitro* and *in vivo* over their BM-MSC counterpart, and deserve further investigation as a potentially important source of stem cell-based therapy for DN.

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SA-PO314

Pharmacological Proof-of-Concept of Extracorporeal Mesenchymal Stromal Cell Immunotherapy in Large Animals Biju Parekkadan. *Surgery (Bioengineering), Harvard Medical School, Boston, MA.*

Background: Human mesenchymal stromal cells (MSCs) metabolize and secrete molecular mediators that can globally shift a wound healing response. Controlled exposure to this cell therapy has been challenging with intravenous infusion of MSCs due to limits in tolerable cell dose and the rapid clearance of MSCs by the body. We have developed an extracorporeal MSC technology that maintains MSC viability and enables the continuous, controlled delivery of MSC molecules into the blood stream in a clinical setting. A human scale prototype of the technology will be presented showing sustained cell viability and function throughout cGMP manufacturing.

Methods: MSCs were integrated into hollow-fiber bioreactor devices whereby the cells, separated by a permeable membrane, can directly and dynamically provide systemic immunotherapy without entering the body. Pharmacological analysis of this bioreactor technology in a large animal toxicology and efficacy study in acute kidney injury (AKI) allowed for an unprecedented look at MSC therapy during product use.

Results: The study verified a pharmacokinetic and pharmacodynamic response to extracorporeal MSCs that is consistent with a potent immunomodulatory mechanism of action in large animals. The presentation will also report encouraging *in vivo* survival results of extracorporeal MSCs in a canine model of ischemic AKI.

Conclusions: We expect that a combined approach to optimize MSC therapy that employs pharmacology principles and cell delivery strategies will be essential to translating this stem cell product to AKI in humans and many other clinical applications of immunotherapy.

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SA-PO315

Late Stage Therapy of Chronic Kidney Disease with Multiple-Doses of Mesenchymal Stem Cells Improves Renal Function in a Rat Model Jon D. Ahlstrom,[1] Huihui Shi,[1] Jorge Isaac,[2] Anna Gooch,[1] Christof Westenfelder.[1,3] *[1]Dept of Medicine, Div of Nephrology, Univ of Utah and Salt Lake City VA Medical Center, Salt Lake City, UT; [2]Pathology, UPSI & Intermountain Healthcare, Murray, UT; [3]Dept of Physiology, Univ of Utah, Salt Lake City, UT.*

Background: Advanced stages of Chronic Kidney Disease (CKD) are difficult to treat and eventually require dialysis or a kidney transplant. We developed and clinically tested a Mesenchymal Stem Cell (MSC)-based therapy for cardiac surgery patients at high risk for post-operative AKI (NCT00733876). This intervention was shown to be safe and it prevented post-operative AKI, mortality and development of CKD long term. These observations prompted us to test in the present preclinical studies whether MSC therapy might also be of benefit to patients at later stages of CKD.

Methods: MSCs were derived from Sprague-Dawley (SD) rat bone marrow and used for therapy at passage 3 (~10 population doublings). After late-phase CKD was established in male SD rats as indicated by reduced renal function, elevated albuminuria and blood pressure (10-16 weeks post 5/6th nephrectomy), MSC therapy was given i.v. (2 million cells/kg b.wt.) 1 x per week for 4 weeks. MSC therapy was then halted and the progression of CKD was further monitored for 10 additional weeks.

Results: Our CKD model of 5/6th nephrectomy led to a progressive decline in renal function, elevated systolic blood pressures and albuminuria. MSC therapy given at this late-phase CKD significantly improved renal function (reduced SCr and BUN, increased GFR) and reduced albuminuria and blood pressures compared to vehicle controls. Improvements in albuminuria and hypertension from MSC therapy were sustained for 10 weeks after cessation of MSC therapy, while renal function again began to decline.

Conclusions: These data suggest that MSC therapy for CKD may be clinically feasible, even at later stages of CKD, a time when most pharmacological interventions become less or are no longer effective in the prevention of progression to end stage renal disease. Optimal long-term treatment protocols and investigation of the underlying mediator mechanisms of administered MSCs are in progress.

Funding: VA Support

SA-PO316

SGLT2 Inhibitor Attenuates Ischemia Reperfusion Renal Injury via HIF1 Activation Jin Young Jeong,[1,2] Hyunsu Choi,[3] Yoon-Kyung Chang,[4,5] Hong Jin Bae,[1] Young Rok Ham,[1] Dae Eun Choi,[1] Ki Ryang Na,[1] Kang Wook Lee.[1] *[1]Nephrology, Chungnam National Univ, Daejeon, Korea; [2]Medical Science, Chungnam National Univ, Daejeon, Korea; [3]Clinical Research Inst, Daejeon Saint Mary Hospital, Daejeon, Korea; [4]Nephrology, Catholic Univ, Seoul, Korea; [5]Nephrology, Daejeon Saint Mary Hospital, Daejeon, Korea.*

Background: SGLT2 inhibitor, dapagliflozin were developed for diabetes control. it wastes the glucose to urine. Some studies showed SGLT2 inhibition have renal protection(reduction of hyperfiltration and tubular oxidative stress) in Type1 DM. We evaluate whether SGLT2 inhibitor reduces the renal damage via ischemia reperfusion (IR). Also, we investigate the associating molecular pathway.

Methods: n vitro, hypoxia was simulated by mineral oil in HK-2 cells. Cell survival, apoptosis signal pathway, reactive oxygen species (ROS) generation, HIF1, ERK, and AMPK were evaluated in control and hypoxic HK-2 cell with or without SGLT2 inhibitor.

In vivo 10 weeks C57BL/6 mice were divided into 4 groups; vehicle (n=5) and dapagliflozin (10mg/kg) treated sham group (n=5), vehicle (n=7) and dapagliflozin (n=7) with ischemia reperfusion renal injury. Kidneys and blood were harvested 24hr after IR injury. We performed real time RT-PCR, western blot and immunohistochemistry for molecular study and H&E stain and PAS stain for histologic examination.

Results: Dapagliflozin treatment significantly increase survival of hypoxic HK-2 cells. Dapagliflozin treatment increase the level of HIF1 in hypoxic HK-2 cells. Also it decrease the Bax/Bcl2 ratio and 8-OH deoxyguanosine generation. in vivo, Dapagliflozin treatment significantly reduced the levels of BUN and serum creatinine in IR mice (p <0.05). In microscopy, dapagliflozin significantly reduced renal tubular epithelial cell necrosis and detachment in IR mice kidney. Dapagliflozin significantly increased the expression of HIF1 in IR kidney. Dapagliflozin significantly reduced the level of Bax/Bcl-2 ratio and cleaved caspase-E, 8-OH deoxyguanosine positive and TUNEL positive cells in IR kidney.

Conclusions: dapagliflozin significantly increases HIF1 in IR injured kidney. Also it attenuates ischemia reperfusion renal injury.

SA-PO317

Extra Domain A Fibronectin Is an Acute Marker in AKI and a Novel Therapeutic Target in a Murine Model of Aristolochic Acid Nephropathy

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Background: In models of tissue injury in animals and in vitro in human cells, production of Extra Domain A fibronectin (EDA + FN) is preferentially directed by alternative splicing. We explored the potential of EDA + FN as a target for RNAse H Independent antisense oligonucleotide(ASO) therapy with a view to attenuating fibrosis in a murine model of acute kidney injury induced by aristolochic acid (AA). We have previously shown effective knockdown of EDA + FN in human proximal tubule cells.

Methods: We compared expression of EDA + FN in 2 murine models. CD1 mice were injected with Intraperitoneal AA at 3.5mg/kg at D1 and 5, RNA from whole kidney lysate was extracted at D0, 12, 20 and 100 and qPCR performed using primers targeted to EDA + FN, EDA - FN and CTGF. Folic acid model (FA) model involved IV injection of Folic acid at D0 and D21 at 125mg/kg and whole kidney lysate retrieval at D0 and D84.

Results: In the AA model of kidney injury at D0 there was negligible detection of EDA + FN RNA by qPCR, at D12 there was a >2500 fold increase in its expression compared to its normal saline control (p<0.005), at D20 there was >900 fold (p<0.005) which was reduced to 13 fold (p<0.05) at D100 compared to control. EDA - FN RNA expression was also increased at D12, 20 and 100 (p<0.005) but to a lesser degree (40-70 fold increase) compared to normal saline control. CTGF expression followed a similar pattern with peak at D12 and subsequent fall. By comparison in FA model there was a 15 fold (p<0.005) increase in EDA + FN RNA expression at D84.

Conclusions: EDA+FN expression is significantly increased in the acute phase of kidney injury by AA. This isoform appears to be preferentially expressed by alternative splicing in response to insult. RNAse H independent ASOs can modulate splicing to prevent formation of EDA + FN and attenuate fibrosis and this will be the next step towards a therapeutic option for AKI and CKD following AKI.

SA-PO318

Ameliorating Effect of Gemigliptin on Renal Injury in Murine Adriamycin-Induced Nephropathy

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Background: Previous studies demonstrated anti-apoptotic and anti-inflammatory potential of DPP-IV in experimental models of renal injury. We assumed that renoprotective effect of gemigliptin in adriamycin-induced nephropathy might be mediated by suppression of apoptosis, inflammation and oxidative stress.

Methods: The mice were randomly separated into four groups and received a single tail-vein injection of normal saline(control), gemigliptin(GM), adriamycin(ADR) and adriamycin combined with gemigliptin(ADR+GM). Body weight change, urine albumin creatinine ratio(UACR) and serum glucose level between four groups were compared. Apoptosis, inflammation and oxidative stress-related molecules were analyzed by western blotting and real-time PCR. Glomerulosclerotic index(GSI) and tubulointerstitial index(TII) were examined using light microscope. WT-1 and nephrin were evaluated by immunofluorescence microscopy.

Results: In ADR+GM group, UACR significantly decreased compared with ADR group on day 15(ADR: 402.20±138.23 mg/g vs. ADR+GM: 133.70±60.57 mg/g, p=0.049). Serum DPP-IV activity was decreased and active GLP-1 level was increased in ADR+GM group compared with ADR group. GSI and TII in mice of adriamycin-induced nephropathy was decreased with treatment of gemigliptin([GSI] ADR: 62.79% vs. ADR+GM: 21.93%, p<0.01, [TII] ADR: 16.29% vs. ADR+GM: 3.74%, p=0.012). Mice of adriamycin-induced nephropathy expressed higher levels of apoptosis markers(Bax/Bcl-2 ratio, TGF-B1), oxidative stress-related molecules(Nitrotyrosin, iNOS, NOX4) and inflammatory cytokines(MCP-1, PAI-1, TNF-a) than control mice. Upregulation of these molecules was significantly reduced by treatment with gemigliptin. In ADR group nuclear WT-1 and nephrin were reduced but, these changes were inhibited in ADR+GM group([WT-1] ADR: 15.60 vs. ADR+GM: 8.27, p<0.01, [Nephrin score] ADR: 3.54 vs. ADR+GM: 2.09, p=0.04).

Conclusions: We demonstrated that gemigliptin ameliorated renal injury in adriamycin-induced nephropathy. These effect may be attributable to decreased inflammation, apoptosis and oxidative stress.

SA-PO319

Estrogen-Related Receptor (ERR)-γ Protects against Puromycin Aminonucleoside-Induced Podocyte Apoptosis by Targeting PI3K/Akt Signaling

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Background: Accumulating evidence has shown that podocyte apoptosis is of vital importance for the development of glomerulosclerosis and progressive loss of renal function. However, the molecular mechanisms leading to podocyte apoptosis are still elusive. In this study, we investigated the role of estrogen-related receptor (ERR)-γ in modulating podocyte apoptosis, as well as the underlying mechanisms.

Methods: Puromycin Aminonucleoside (PAN) was administered to the cultured podocytes or rats to induce podocyte injury. ERRγ siRNA and PI3K inhibitor were used to determine their roles in this experimental setting.

Results: Application of PAN caused a dose- and time-dependent podocyte apoptosis in line with a significant reduction of ERRγ by about 50%. Interestingly, the occurrence of ERRγ downregulation appeared earlier than the onset of cell apoptosis, suggesting a potential that ERRγ reduction triggers apoptotic response in podocyte. To test this hypothesis, ERRγ siRNA was subjected to the podocytes. Strikingly, ERRγ silencing resulted in a significant cell apoptosis accompanied with increased injury markers of B7-1 and cathepsin L and decreased podocyte protein nephrin. In contrast, overexpression of ERRγ remarkably attenuated PAN-induced cell apoptosis. More importantly, ERRγ overexpression stimulated PI3K/Akt signaling pathway evidenced by increased expression of PI3K subunits p85α (+1.2 folds) and p110α (+88%) and phosphorylated Akt (+12.7 folds). Application of LY294002, a specific PI3K inhibitor, entirely reversed the anti-apoptotic effect of ERRγ following PAN treatment. Finally, we observed a remarkable reduction of ERRγ (66%) in PAN-treated rat kidneys in line with an apoptotic response, suggesting that this cell model could replicate the in vivo condition.

Conclusions: These data highly suggested that ERRγ played a novel role in regulating apoptotic process in podocytes by targeting PI3K/Akt signaling pathway.

SA-PO320

Relaxin Attenuates the Aristolochic Acid Induced Human Tubular Epithelial Cell Apoptosis In Vitro by Activation of PI3K/Akt Signaling Pathway

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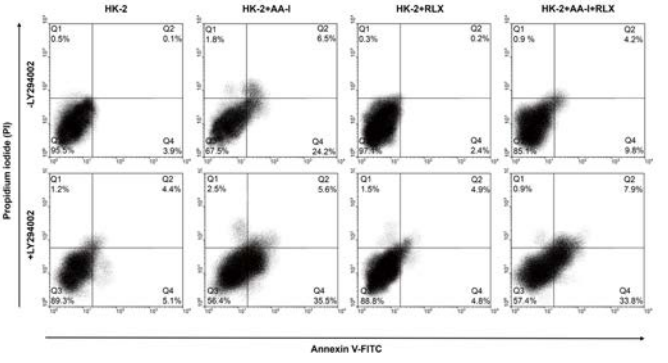
Background: Aristolochic acid nephropathy (AAN) has long been known as a rapidly progressive renal fibrosis associated with the intake of Chinese herbs containing aristolochic acids (AAs). The treatment strategies remain limited. Emerging evidence has shown that H2 relaxin possesses powerful antifibrosis and anti-apoptotic properties, therefore, we aimed to investigate whether H2 relaxin can be employed to reduce AA-induced cell apoptosis.

Methods: Human proximal tubular epithelial (HK-2) cells exposed to AA-I were treated with or without H2 relaxin. Cell viability was examined using the WST-1 assay. Apoptotic morphologic alterations were observed using Hoechst 33342 stating method. Apoptosis was detected using flow cytometry. The expression of Caspase3, Bax, Bcl-2, and Akt proteins were determined by Western blot.

Results: Increased apoptosis was observed in AA-I treated group, which was reversed by relaxin co-treatment.



Immunoblotting showed the expression of phosphorylated Akt (p-Akt) decreased in AA-I treated cells, which was restored by relaxin. Increased Bax/Bcl-2 ratio and cleaved form of caspase-3 were found in AA-I treated cells, both of which were counteracted by relaxin co-treatment. Whereas, this anti-apoptotic effect of relaxin was attenuated by co-administration of Akt inhibitor LY294002, indicating the anti-apoptocic effect of H2 relaxin was mediated via PI3K/Akt dependent manner.

Conclusions: The present study demonstrated H2 relaxin can decrease AA-I induced increases of apoptosis through activation of PI3K/Akt signaling pathway, suggesting H2 relaxin might play a beneficial role in delaying the progression of AAN.

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SA-PO321

The Role of BMP4 Signal Pathway on the Podocyte Injury in Diabetic Early Stage Yui Fujita, Tatsuya Tominaga, Taichi Murakami, Seiji Kishi, Kojiro Nagai, Hideharu Abe, Toshio Doi. *Nephrology, Biomedical Sciences, Tokushima Univ Graduate School, Tokushima, Japan.*

Background: The glomerulosclerosis induced by podocyte injury is most evident in the pathological change mechanisms. However, loss and apoptosis of podocyte in human renal biopsy is a rare case, podocyte injury mechanism has not been definitively elucidated. BMP4 is an important cytokine that cause mesangial expansion, we examined the mechanism of podocyte injury by BMP4-TAK1 pathway in this study.

Methods: We focused on the BMP4-TAK1 signaling and BMP4-Smad1 signaling in the development of podocyte injury. In cultured podocyte cells, apoptosis-related molecules (caspase3, p38) and tight junction molecule (nephrin, connexin 43) were analyzed under BMP4 stimulation. As inhibition experiments were analyzed using Smad1 suppression molecule (Dorsomorphin) and p38 suppression molecule (SB203580) for the analysis of apoptosis induction. The podocyte specificity induction Bmp4 transgenic mice were generated by CAG-CAT-Bmp4 (Bmp4 Tg) mice and Podocin Cre (PodCre) mice. These mice were induced diabetes by streptozotocin infusion. From these experiments, we clarified the detailed mechanism of the BMP4 signal, which induce podocyte apoptosis.

Results: The expression of pSmad1, pTAK1, pp38 and cleaved caspase3 was increased by BMP4 stimulation in the cultured podocyte cells. The expression of nephrin and connexin 43 was decreased by BMP4 treatment. The activated of pp38 and cleaved caspase3 was inhibited by SB203580 under BMP4 treatment. Dorsomorphin inhibited the phosphorylation of Smad1, but did not affect the activation of p38 and caspase 3. Bmp4 Tg x PodCre mice increased the expression of BMP4 in the kidney as age advances. Diabetic Bmp4 Tg x PodCre mice showed significantly expansion of mesangial matrix as compared to the control group in early stage.

Conclusions: We made clear that podocyte apoptosis was induced by BMP4-TAK1-p38 signal pathway. Bmp4 Tg x PodCre was shown to accelerate the development of glomerulosclerosis. These results suggested that BMP4 acted on the podocyte apoptosis in the early stage of diabetes and induces glomerulosclerosis.

Funding: Government Support - Non-U.S.

SA-PO322

Protective Effect of Epigallocatechin-3-Gallate (EGCG) against Oxalate-Induced Epithelial-Mesenchymal Transition (EMT) of Renal Tubular Cells Visith Thongboonkerd, Rattiyaporn Kanlaya. *Medical Proteomics Unit, Office for R&D, Siriraj Hospital, Mahidol Univ, Bangkok, Thailand.*

Background: Oxalate can induce oxidative stress, cellular injury, calcium oxalate kidney stone formation, and chronic kidney disease (CKD). However, the underlying mechanisms of oxalate-induced CKD remained largely unknown. Our present study evaluated effects of oxalate on epithelial-mesenchymal transition (EMT), one of the priming phenomena preceding CKD. Moreover, epigallocatechin-3-gallate (EGCG), the most abundant polyphenol found in *Camellia Sinensis* (green tea), was also assessed for its potential anti-fibrotic property.

Methods: MDCK renal tubular cells were incubated with 0.5 mM sodium oxalate for 24-h with/without 1-h pretreatment with 25 μM EGCG. The cells were then subjected to morphological analysis, immunofluorescence staining and Western blot analyses of mesenchymal and epithelial markers, flow cytometric analysis of intracellular reactive oxygen species (ROS) production using dichlorofluoresceindiacetate (DCFH-DA) assay, immunofluorescence staining of Nrf2, and Western blot analysis of an anti-oxidant, catalase.

Results: Microscopic examination, immunoblotting and immunofluorescence staining revealed that oxalate-treated cells gained mesenchymal phenotypes by fibroblast-like morphological change and increasing expression of vimentin and fibronectin, while levels of epithelial markers (E-cadherin, occludin, cytokeratin and ZO-1) were decreased. EGCG pretreatment could prevent all these changes and molecular mechanisms underlying the prevention by EGCG were most likely due to reduced production of intracellular ROS through activation of Nrf2 signaling and increased catalase anti-oxidant enzyme.

Conclusions: Taken together, our data indicate that oxalate turned on EMT of renal tubular cells that could be prevented by EGCG. These findings also shed light onto development of novel therapeutics or preventive strategies of renal fibrosis in the future.

Funding: Government Support - Non-U.S.

SA-PO323

HIV Promotes SNAIL Expression and Proliferative Molecular Phenotype in Glomerular Epithelial Cells via Down Regulation of Micro-RNA193a Abheepsa Mishra, Vinod Sharma, Manoj K. Tembhre, Waqaar Khawar, Seyedeh Shadafarin Marashi Shoshtari, Judith Eng, Ashwani Malhotra, Pravin C. Singhal. *Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY.*

Background: Micro-RNA (miR) 193a has been considered to be a tumor suppressor and its down regulation has been reported to stimulate epithelial mesenchymal transition (EMT). EMT has been reported to play a role in proliferation of parietal epithelial cells (PECs)/podocytes (PDs) in HIV-associated nephropathy. We hypothesized that HIV might be stimulating PEC/PD proliferation via down regulation of miR193a and this effect of HIV could be abrogated by using rapamycin.

Methods: Renal tissues of 4 week old control and HIVAN (Tg26) mice (n=4) were assayed for microRNA profile. In another set of experiments, 4 week old Tg26 mice (n=4) were administered either normal saline or rapamycin (2.5 mg/kg, twice a week) for 4 weeks. Renal tissues were assayed for microRNA profile, severity of renal lesions and expression of epithelial mesenchymal transition markers such as SNAIL, α-SMA, PCNA, vimentin, and FSP-1 (immunoblotting of renal tissues and immunohistochemical studies of renal cortical sections). PECs and PDs were transduced with either vector or HIV (NL4-3) and evaluated for miR193a and SNAIL expression. Control and experimental cells were pretreated with rapamycin (100 ng/ml) for 24 hours followed by assay for miR193a and SNAIL expression.

Results: Renal tissues of Tg26 mice displayed a 4 fold decrease in miR193a expression; however, renal tissues of HIVAN mice receiving rapamycin displayed mir193a expression comparable to control mice. Renal tissue/renal cortical sections of Tg26 mice revealed enhanced expression of α-SMA, PCNA, and SNAIL; however, rapamycin attenuated this effect of HIV in Tg26 mice. In *in vitro* studies HIV down regulated miR193a expression but upregulated SNAIL expression both in PECs and PDs. Nonetheless, rapamycin inhibited down regulation of miR193a and prevented enhanced SNAIL expression in HIV-transduced PECs/PDs.

Conclusions: HIV-induced SNAIL expression and proliferative phenotype in glomerular epithelial cells may be mediated via down regulation of miR193a.

SA-PO324

IL-β Contributes to Parietal Epithelial Cell Proliferative Phenotype in HIV-Associated Nephropathy Vinod Sharma,[1] Nirupama Chandel,[1] Manoj K. Tembhre,[1] Abheepsa Mishra,[1] Catherine Meyer-Schwesinger,[2] Ashwani Malhotra,[1] Pravin C. Singhal.[1] *[1]Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY; [2]Medicine, Univ Medical Center Hamburg-Eppendorf, Hamburg, Germany.*

Background: Proliferating glomerular cells in HIVAN have been considered to be of parietal epithelial cell (PECs) lineage. However, the involved mechanism of PECs's proliferation is not clear. Since HIV promotes pyroptosis in podocytes (Am J Pathol, 2016), we hypothesize that IL-1 β production by HIV-infected podocytes leads to PEC proliferation in HIVAN.

Methods: Vector- transduced and HIV (NL4-3)-transduced podocytes were incubated in media for 48 hours. Incubation media (conditioned media, C. media) of vector –transduced podocytes (Control C. media) and HIV-transduced podocytes (HIV C. media) were collected (stored at -80°C). Equal numbers of PECs were plated in Petri dishes. PECs were serum starved for 24 hours, followed by incubation in serum-free media containing vector conditioned media (Control C. media , 10%), HIV conditioned media (HIV C. media, 10%), HIV conditioned media + IL-1β neutralizing antibody (HIV C. media + IL-1βab, 20 μg/ml), IL-1β antibody alone or human IgG (20 μg/ml) for 48 hours at 33°C (n=4). To determine the dose response effect of IL-1β, equal number of PECs were plated in Petri dishes and serum starved for 24 hours, followed by incubation in serum-free media containing variable concentrations of IL-1β (0, 100, 200, 400 ng/ml) for 48 hours at 33°C (n=4). At the end of experimental periods, the cells were counted. Renal tissue and serum levels of IL-1 β in control and HIVAN (Tg 26) mice were measured (n=6).

Results: HIV conditioned media enhanced proliferation of PECs ($P<0.05$) and this effect of HIV conditioned media was inhibited by IL-1β neutralizing antibodies. IL-1β enhanced PEC proliferation in a dose dependent manner (IL-1β 0 vs 100 ngml, $P<0.01$; IL-1β 200 and 400 ng/ml vs 100 ng/ml, $P<0.05$). Renal tissues as well as serum levels IL-1 β in HIVAN mice were several fold higher ($P<0.01$) than in control mice.

Conclusions: HIV infection of podocytes may be contributing to parietal cell proliferation in HIVAN via generation of IL-1β.

Funding: NIDDK Support

SA-PO325

The Role of Chemerin/ChemR23 in the Regulation of Inflammation and Endothelial-Mesenchymal Transition of Glomerular Endothelial Cells in Diabetic Kidney Disease Luyao Wang,[1,2] Jia Guo,[1,2] Yanna Dou,[1,2] Zhanzheng Zhao.[1,2] *[1]The Nephrology Center, The First Affiliated Hospital of Zhengzhou Univ, Zhengzhou, Henan, China; [2]Inst of Nephrology, Zhengzhou Univ, Zhengzhou, Henan, China.*

Background: DKD has become the leading cause of end-stage kidney disease, there is no effective treatments so far. Chemerin, a novel adipocyte-derived factor, plays multiple roles by combining with its main ligand chemR23. Chemerin and its ligand chemR23 are closely associated with inflammation and Endothelial-to-mesenchymal transition (EndMT) of glomerular endothelial cells (GEnCs) which play important roles in the process of DKD. GEnCs injury could lead to an increased filtration of albumin in DKD . However, the role of Chemerin / ChemR23 in the pathogenesis of DKD is still not clear.

Methods: GEnCs were incubated with normal condition, 35mmol/L glucose (high glucose) or osmotic control for pre-set time course.And then GEnCs were incubated with normal condition, 10ng/ml Chemerin, 50ng/ml Chemerin, 100ng/ml Chemerin, 200ng/ml Chemerin respectively for 24 hours. Cell morphology was studied by light microscopy. The protein expressions of Chemerin, ChemR23, CD31, α-SMA, TGF-β1, AKT, phosphorylated AKT (p-AKT) were measured by Western Blot. The protein expressions of IL-6, TNF-α were measured by ELISA. The cells co-expression of α-SMA and CD31 were determined by immunofluorescence double labeling.

Results: 1.The expressions of Chemerin, IL-6, TNF-α, TGF-β1, α-SMA, AKT, p-AKT were significant increased and the expression of CD31 was decreased in GEnCs treated with high glucose for 48h($P<0.05$). Additionally, adjacent cells did not attach to each other as closely as control cells. The initially cobble-stone-like cells also adopted a spindle-like morphology. 2.The protein expressions of ChemR23, IL-6, TNF-α were significantly increased and the expression of CD31 was decreased after 200ng/ml Chemrin treatment

for 24hours($P<0.05$). Similarly, the protein expressions of α-SMA, TGF-β1, AKT, p-AKT were increased after 50ng/ml for 24hours with a Chemerin concentrations dependent manner($P<0.05$).

Conclusions: The inflammation and EndMT of GEnCs could be induced by high-glucose. Chemrerin played an important role in inflammation and EndMT of GEnCs.

Funding: Other NIH Support - Provincial Department of Science and Technology

SA-PO326

The Phosphodiesterase 5 Inhibitor Can Alleviate the Epithelial Mescenchymal Transition in Kidney via Klotho Modulation Independent of Nitric Oxide System Jae Won Yang,[1] Jae Seok Kim,[1] Min Keun Kim,[1] Minseob Eom,[2] Byoung Geun Han,[1] Seung-Ok Choi.[1] *[1]Internal Medicine, Yonsei Univ Wonju College of Medicine, Wonju, Republic of Korea; [2]Pathology, Yonsei Univ Wonju College of Medicine, Wonju, Republic of Korea.*

Background: The phosphodiesterase-5 inhibitor can vasodilate through blocking of cyclic GMP degradation. However, there are many controversies in whether it has another action in case of blocked nitric oxide system.The renal klotho level decreased in animals treated with L-NAME, suggesting that decreased NO result in down-regulation of klotho gene, but the inter-relationship between these two proteins is still obscure. We investigated PDE-5i can preserve epithelial mesenchymal transition and whether relationship existed between the NO pathway and the klotho expression in kidney.

Methods: The 10th weeks male SD rats were divided four groups. We supplied low salt diet to the control group (N=6), L-NAME 1 mg/mL in drinking water to the L-NAME group (N=6), udenafil 5mg/kg SQ to Udenafil group, and L-NAME and udenafil to the L-NAME and udenafil group (N=6) for 4 weeks. After the collection of blood and urine on day 28,serum creatinine was measured andurine nitrate/nitrite,NGAL, and cGMP were measured by ELISA, and kidney tissues were investigated by IHC stains or western blot of PCNA, α-SMA, E-cadherin, and klotho expression.

Results: The urine cGMP level showed 2.59±0.88, 1.79±0.99, 1.20±0.22, 0.69±0.59 nmol /μl ($p<0.05$, control vs Udenafil and L-NAME with udenafil). The klotho protein expression was increased in L-NAME with udenafil group compared with L-NAME group. The urine NGAL showed 279.8±126.8, 651.0±195.3, 473.7±114.9, 326.5±279.4 ng/ml ($p<0.05$ control vs LNAME and LNAME with udenafil), and PCNA expression showed 0.11±0.06, 0.31±0.14, 0.17±0.02, 0.19±0.08 cells ($p<0.05$, control vs L-NAME, and L-NAME vs L-NAME with udenafil). α-SMA showed increased density in L-NAME group compared with L-NAME with udenafil group ($p<0.05$) and E-cadherin protein density was decreased in L-NAME group compared with other groups ($p<0.05$).

Conclusions: The phosphodiesterase 5 inhibitor can alleviate the epithelial mescenchymal transition in kidney via klotho modulation independent of nitric oxide system.

SA-PO327

PGC1α Regulates NAD+ Biosynthesis, Mitochondrial Function, and Injury-Related Cellular Metabolism Kenneth M. Ralto, Vinod Raman, Samir M. Parikh. *Div of Nephrology, Beth Israel Deaconess Medical Center, Boston, MA.*

Background: PPAR-γ coactivator 1 alpha (PGC1α) is transcriptional coactivator which regulates mitochondrial biogenesis. This protein has been shown to be protective against neurodegenerative diseases, ischemia-reperfusion injury, and toxicant exposure. NAD^+ is a coenzyme involved in cellular redox reactions and is a transporter of electrons for use in oxidative phosphorylation. Both PGC1α and NAD^+ play key roles in cells with high energy requirements, such as those found in the renal tubular epithelium.

Methods: A stable PGC1α-overexpressing mIMCD3 cell line was created with lentiviral transduction. A PGC1α knockout mIMCD3 cell line was developed using the CRISPR-Cas9 system. RNA isolation was performed, followed by quantitative PCR to measure expression of NAD^+ biosynthesis enzymes and electron transport chain (ETC) proteins in the transgenic cell lines. ATP and XTT cell proliferation assays were used to characterize metabolic response in the transgenic cell lines after exposure to cisplatin.

Results: PGC1α overexpressing mIMCD3 cells showed higher expression of NAD^+ biosynthetic enzymes (30-96% increase) and ETC proteins (41-66% increase). The PGC1α knockout cells showed reduction in most NAD^+ biosynthetic enzymes (48-70% reduction) and ETC proteins (38-60% reduction). PGC1α knockout cells showed 78.5% reduction in cell proliferation after cisplatin treatment ($p=0.001$) compared to only a 32.9% reduction in cell proliferation in PGC1α overexpressing cells ($p<0.0001$). Cisplatin exposure resulted in 30.6% higher ATP content in the PGC1α overexpressing cells compared to control ($p=0.0029$). In the PGC1α knockout cells, cisplatin exposure resulted in a 69.7% reduction in ATP content compared to control ($p<0.0001$).

Conclusions: PGC1α regulates the expression of several enzymes involved both in the biosynthesis of NAD^+ and in cell energy metabolism. PGC1α overexpressing and knockout transgenic cell lines will allow for research to further elucidate the role of PGC1α in mitochondrial function and energy metabolism.

Funding: NIDDK Support

SA-PO328

High-Throughput Microfluidic Platform for Culture of 3D-Kidney Tissue Models Marianne K. Vormann, Remko Van Vught, Sebastiaan Trietsch, Jos Joore, Paul Vulto, Henriëtte Lanz. *Mimetas, Leiden, Zuid Holland, Netherlands.*

Background: Drug toxicity remains a major issue in drug discovery and stresses the need for better predictive models. Here, we describe the development of a perfused renal proximal tubule cell (RPTC) model in Mimetas' OrganoPlates®[1] to predict kidney toxicity. The OrganoPlate® is a microfluidic platform, which enables high-throughput culture of boundary tissues in miniaturized organ models. In OrganoPlates®, extracellular matrix (ECM) gels can be freely patterned in microchambers through the use of PhaseGuide technology. PhaseGuides (capillary pressure barriers) define channels within microchambers that can be used for ECM deposition or medium perfusion. The microfluidic channel dimensions not only allow solid tissue and barrier formation, but also perfused tubular epithelial vessel structures can be grown. The goal of developing a perfused RPTC model is to reconstruct viable and leak-tight boundaries for cytotoxicity, as well as transport and efficacy studies.

Methods: Human RPTC (SA7K clone, Sigma) were grown against an ECM in a 3channel OrganoPlate®, yielding access to both the apical and basal side.

Results: Confocal imaging revealed that the cells formed a tubular structure. Staining showed tight junction formation (ZO-1), cilia pointing into the lumen (acetylated tubulin) and correct polarization with microvilli on the apical side of the tubule (ezrin). Tightness of the boundary over several days was shown by diffusion of a dextran dye added to the lumen of the tubule. Addition of toxic compounds resulted in disruption of the barrier which could be monitored in time. The time point of loss of integrity corresponds with the concentration and the toxic effect of the compound. Furthermore, fluorescent transport assays showed functional transport activity of in- and efflux transporters.

Conclusions: The 3D proximal tubules cultured in the OrganoPlate® are suitable for high-throughput toxicity screening, trans-epithelial transport studies, and complex co-culture models to recreate an in vivo-like microenvironment. [1] Trietsch, S. J., Israëls, G. D., Joore, J., Hankemeier, T. & Vulto, P. Microfluidic titer plate for stratified 3D cell culture. Lab Chip 13, 3548–54 (2013).

Funding: Private Foundation Support

SA-PO329

A Podocyte High Throughput Screen Identifies a B-RAF Inhibitor as a Therapeutic Strategy for Kidney Disease Jonas Sieber,[1,2] Peter Mundel,[5] Andreas Werner Jehle,[4] Anna Greka.[1,2,3] *[1]Medicine, Brigham and Women's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Broad Inst of Harvard and MIT, Cambridge, MA; [4]Biomedicine, Univ Hospital Basel, Basel, Switzerland; [5]Medicine, Massachusetts General Hospital, Boston, MA.*

Background: Urgently needed therapies for kidney disease have been lacking for several decades. Recent discoveries revealed that damage and loss of podocytes contribute to progressive kidney diseases and ultimately kidney failure. Strategies protecting podocytes from cell death are now at the center of new efforts in kidney therapeutics. The objective of this study is to establish and validate a high throughput screen assay to identify small molecules preventing podocytes from ER stress –dependent and –independent death, which may lead to new potential therapeutic strategies.

Methods: Conditionally immortalized podocytes were differentiated for at least 11 days. Cell death was assessed by quantifying relative ATP-levels (high throughput screens) and annexin V positivity. shRNA-based gene silencing was performed by using a lentiviral system. mRNA and protein expression, and protein localization were analyzed by qPCR, Western blotting and IF staining, respectively.

Results: We developed and validated an ATP–based high throughput podocyte viability assay to screen small molecule libraries and to identify podocyte death–preventing compounds. A proof of concept screen of a library of clinically used and preclinical bioactive molecules identified the B-RAF inhibitor GDC-0879 and forskolin, an adenylate cyclase agonist, as inhibitors of podocyte death. We show that the effect of forskolin is mediated by cyclic AMP, but in a PKA– and Epac–independent fashion. Surprisingly, GDC-0879 and forskolin interfere at the level of cell death execution, which intriguingly points to a common and potentially druggable final pathway to podocyte death.

Conclusions: This study reports the development and successful implementation of a high throughput assay to identify podocyte protective compounds, and reveals downstream effects of the B-RAF inhibitor GDC-0879 and forskolin as podocyte-protective strategies.

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

SA-PO330

Assessment of Telomere Length and Mitochondrial DNA Damage in Male Patients with Chronic Kidney Disease Prasanta Debnath,[1] Om Prakash Kalra,[1] Ashish Goel,[1] Rajarshi Kar,[2] Mohit Mehndiratta.[2] *[1]Internal Medicine, Univ College of Medical Sciences, New Delhi, Delhi, India; [2]Biochemistry, Univ College of Medical Sciences, New Delhi, Delhi, India.*

Background: Patients with CKD have accelerated aging process which may be reflected by reduced telomere length and increased mitochondrial DNA damage. The present study was intended to evaluate telomere length and mitochondrial DNA damage in male CKD patients and compare the same with age matched healthy controls and elderly healthy controls in the age group 61-70 years.

Methods: A case-control study which included 35 male patients with CKD between ages 31-40 years as the cases, an equal number of age matched healthy male controls and an equal number of elderly healthy male controls in age group 61-70 years, was conducted. Telomere length was measured by Real Time PCR (RT-PCR) for which telomere specific primer was used. Number of copies of mtDNA was estimated by RT-PCR using specific primers.

Results: The median (Inter-quartile range) values of relative telomere length in CKD patients was found to be 15 (6.25-27); whereas in elderly healthy controls it was 19 (10-35) and in age matched healthy controls it was 103 (70-202). On comparing CKD patients with age matched healthy controls, there was significant difference in telomere length ($p < 0.001$) while on comparing CKD patients with elderly healthy controls there was no significant difference. The median (Inter-quartile range) values of mitochondrial DNA copy number in CKD patients was found to be 123 (73.75-282.25), and that in elderly healthy controls to be 139 (76-185) and that in age matched healthy controls it was found to be 289 (214-541). There was significant difference in number of copies of mtDNA between CKD and age matched healthy controls but comparable results between CKD group and elderly healthy control group.

Conclusions: In our study it was found that telomere length and number of copies of mitochondrial DNA, a marker of mtDNA damage, were markedly reduced in CKD patients when compared with healthy controls of same age group but were comparable with that of elderly healthy controls.

SA-PO331

Increased Cellular Senescence in the Murine Stenotic Kidney: Effect of Mesenchymal Stem Cells

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Background: Cellular senescence is a proliferation arrest evoked in response to stress and damage, and is irreversible without experimental intervention. Renal artery stenosis (RAS) may induce stenotic kidney (STK) ischemia and injury, but it is unclear whether these are associated with cellular senescence. Furthermore, while mesenchymal stem cells (MSC) decrease some forms of STK injury, it remains unknown if they can reverse cellular senescence in RAS. We hypothesized that murine RAS evokes STK cellular senescence, which would be ameliorated by MSC.

Methods: Three groups (n=6 each) of 129-mice were studied after 4 weeks of RAS, RAS treated with a tail-vein injection of MSC (5×10^5 cells) 2 weeks after induction, or sham. β-galactosidase activity (fluorometric) and H_2AX (western blot), P16, P21, P53, Activin-A and HIF-1α gene expression were used to assess senescence in STK, CLK, or sham homogenates.

Results: After 4 weeks of RAS, the STK was smaller than the sham and contralateral kidney (CLK) (both $P \leq 0.033$), and blood pressure was higher than sham ($P=0.049$). MSC had no effect on either kidney weight ($P=0.59$ vs. RAS) or blood pressure ($p=0.83$ vs. RAS). β-galactosidase activity was significantly increased in RAS ($P=0.009$ vs. sham) and normalized in MSC treated mice ($P=0.009$ vs. RAS). Renal P16, P21, P53, Activin-A and HIF-1α gene expression was markedly (up to 1,000-fold) elevated in the STK compared to sham and CLK (all $p \leq 0.007$), but showed no change after MSC delivery ($p \geq 0.4$ for all vs. RAS).

Conclusions: This study shows that murine RAS triggers cellular senescence, implicating this process in STK injury. MSC therapy only partly mitigates renal senescence activity, supporting exploration of a targeted senolytic therapy in RAS.

Funding: Private Foundation Support

SA-PO332

Oligomerization of Fn14-TRAIL by Endogenous TWEAK Leads to Robust, TRAIL-Mediated, Apoptosis of Renal Cell Carcinoma

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Background: Renal Cell Carcinoma(RCC), the most abundant kidney tumor has no current treatments available for disseminated disease. TNF-Related Apoptosis-Inducing Ligand (TRAIL) was reported to induce selective apoptosis of malignant cells and spare normal ones. TNF-Related Weak Inducer of Apoptosis (TWEAK) with its receptor, Fn14, was shown to contribute to tumor growth and metastasis. Treatments designed to activate TRAIL signaling or block TWEAK were not effective enough in clinical trials and ways to potentiated TRAIL activity specifically at tumor microenvironment are needed. The novel dual signaling fusion protein Fn14-TRAIL (FT) is comprised of Fn14 domain that can bind and block endogenous TWEAK and of TRAIL domain that can direct apoptotic signals to TRAIL receptor bearing cells.

Methods: Potency of FT as apoptosis inducing agent of RCC was tested in-vitro (by flow-cytometry, MTS and WB), and in a xenograft model.

Results: 1) FT induces apoptosis in different RCC cell lines, while sparing non-malignant renal cells; 2) FT is more effective than sTRAIL, Fn14-Fc or their combination; 3) TRAIL decoy receptors expression was negatively correlated with sensitivity to FT 4) FT's activity can be blocked by anti-TRAIL or Fn14 Abs; 5) TWEAK KO cells lost sensitivity to FT effect and this could be reversed by TWEAK addition. 6) Interestingly, adding TWEAK to FT results in the formation of large Fn14-TRAIL-TWEAK complex with robust apoptotic activity specifically in RCC cells and not in non-malignant renal cells, and 7) FT effectively inhibits the growth of RCC tumors in a xenograft model.

Conclusions: These findings suggest that FT specifically in TWEAK's presence becomes super-active inducer of apoptosis of malignant cells, probably because of the larger complex presenting TRAIL to the target cells in a cluster form that is known to trigger the TRAIL receptors better than the trimer form. Taken together, these results propose Fn14-TRAIL as a potential treatment for TWEAK expressing RCC.

Funding: Pharmaceutical Company Support - KAHR Medical LTD

SA-PO333

Interleukin-15-Receptor-α Contributes to Podocyte Anti-Apoptotic Signaling Through Activation of the PI-3K/AKT and JAK/STAT3 Pathways

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Background: We recently identified a rare heterozygous missense variant (K47R) in the Interleukin-15 Receptor-α (IL-15Rα) as a contributor to autosomal dominant FSGS in an African American kindred. The K47R variant occurs within the high-affinity "sushi" ligand binding domain of IL-15Rα and exerts a loss-of-function effect on the receptor, which impairs podocyte anti-apoptotic signaling. To further characterize the role of IL-15Rα in podocyte anti-apoptotic signaling, we examined the effects of IL-15Rα overexpression and gene knockdown (KD) on its two known downstream effector pathways, PI-3K/AKT and JAK/STAT.

Methods: We used immunoblotting and immunofluorescence imaging to evaluate PI3K/AKT and JAK/STAT signaling in IL-15Rα knockdown, IL-15Rα*WT* -overexpressing, and IL-15$R\alpha_{K47R}$-overexpressing podocytes.

Results: In response to IL-15 stimulation, podocytes overexpressing IL-15$R\alpha_{K47R}$ exhibited reduced AKT and STAT3 activation relative to IL-15$R\alpha_{WT}$ -overexpressing podocytes. Nuclear localization of activated STAT3 was also reduced in IL-15$R\alpha_{K47R}$ -overexpressing podocytes stimulated with IL-15. In *IL-15Rα* KD podocytes, AKT and STAT3 activation were decreased with concomitant reductions in BAD phosphorylation at the AKT target site Ser136 and STAT3-mediated Bcl-2 and Bcl-xL expression. Cleaved Caspase 3 was also upregulated in *IL-15Rα* KD podocytes consistent with the initiation of apoptosis.

Conclusions: IL-15Rα is a key component of the podocyte anti-apoptotic signaling repertoire and the PI-3K/AKT and JAK/STAT3 pathways are important mediators of IL-15/IL-15Rα-induced anti-apoptotic signaling.

Funding: NIDDK Support, Private Foundation Support

SA-PO334

mTORC1 Regulates TCA Cycle in Renal Cyst Formation and Transformation

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Background: In many syndromes the kidney is affected by cyst formation, benign lesions of renal tubules. These lesions can evolve into cystadenomas and then renal cell carcinomas (RCC). Molecular causes of these manifestations are largely unknown.The mTOR pathway has been widely implicated in RCC.

Methods: To investigate the role of selective upregulation of mTORC1 in the kidney, we developed a mouse model carrying kidney-specific inactivation of the *Tsc1* gene. These mice develop renal cysts due to downregulation of PC-1, the product of the PKD1 gene mutated in Autosomal Dominant Polycystic Kidney Disease (*Pema et al, NatComm 2016*). In *Tsc1* mutants cortical lesions progressively transform with complete penetrance within a short window of time (3 months). Biochemical analysis performed on kidneys displaying cysts (P20), cystadenomas (P50) and carcinomas (P80) show the expected upregulation of mTORC1.

Results: We performed metabolomic profiling by NMR and LCMS on kidneys from *Tsc1* mutants and control mice. The analysis revealed unexpected increased levels of TCA cycle metabolites in the mutants. Fumarate was virtually exclusively detected in the mutant kidneys. qRT-PCR analysis revealed significantly reduced expression of the *Fh1* (*Fumarate Hydratase*) enzyme, deputed to convert fumarate into malate. Moreover, *Tsc1*$^{-/-}$, *Tsc2*$^{-/-}$ MEFs and mIMCD cells *knocked-down* for *Tsc1* show an accumulation of fumarate and a downregulation of *Fh1*, effects reverted by rapamycin treatment (72hrs). Finally, analysis of direct effectors of fumarate storage either by mass-spectrometry or by IHC showed a correlation between disease progression and fumarate increase in the *Tsc1* mutant kidneys.

Conclusions: To our knowledge this is the first animal model recapitulating a progressive RCC in kidney cortex. Our data suggest a previously unreported link between mTORC1 upregulation and TCA cycle alterations. Most importantly we show that mTORC1 can directly regulate the storage of fumarate in this mouse model, likely leading to progressive transformation.

SA-PO335

Intrinsic APOL1 Toxicity Requires Acidification along the Secretory Pathway Joseph Giovinazzo, Russell P. Thomson, Anibelky Almanzar, Simranjit Singh, Jayne Raper. *Biological Sciences, Hunter College, New York, NY.*

Background: Apolipoprotein L-1 (APOL1) is an innate immunity protein that forms pores in trypanosomes. Variants in APOL1 have been linked to kidney disease, yet the mechanism responsible remains controversial. Here we tested the hypothesis that APOL1 toxicity is cell intrinsic and dependent upon secretion via the Golgi, and thereby acidification followed by neutralization upon delivery to the plasma membrane, whereupon the cation selective pore initiates plasma membrane wound repair.

Methods: HEK293 cells were transfected with APOL1 and its variants, including deletion of the signal peptide. After 48h, cell cytotoxicity and viability were measured. Treatment with ammonium chloride was performed 2h prior to transfection to screen for prerequisite acidification. Recombinant APOL1 was purified from E. coli and reconstituted in planar lipid bilayers, where ion channel conductivity and selectivity were measured. 24 and 48h after transfection with APOL1, lysosomal enzyme activity of acid sphingomyelinase (ASM) and β-hexosaminidase were assayed in the supernatant, to probe for plasma membrane repair.

Results: Toxicity of APOL1 required the signal peptide, with complete ablation of toxicity across all variants. Pre-treatment of cells with ammonium chloride prior to transfection reduced the toxicity of all APOL1 variants. In planar lipid bilayers, rAPOL1 allowed the passage of Ca^{2+}. Influx of Ca^{2+} activates the cell wound repair pathway by causing lysosomal migration and fusion with the plasma membrane, releasing lysosome contents to initialize repair. Expression of APOL1 indeed activates the cell wound healing process, assayed by an increase in ASM and β-hexosaminidase activity in the supernatant. Continued delivery of pores to the membrane ultimately causes cell lysis.

Conclusions: These results support a model of APOL1 cell death, which mirrors that in trypanosomes. Herein, endogenous APOL1 inserts into membranes due to acidification along the secretory pathway, and forms pores upon neutralization at the plasma membrane. Prior to cell lysis, the lysosomal contents are released into the supernatant in an attempt to repair the APOL1-mediated damage at the cell surface.

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SA-PO336

Comparison of Gene Expression Profiles in Podocyte Caused by APOL1 Wild Type and Risk Variants Guolan Xing,[1] Xiqian Lan,[1,2] Judith Eng,[2] Karl Leon Skorecki,[3] Ashwani Malhotra,[2] Pravin C. Singhal.[2] *[1]Dept of Nephrology, First Affiliated Hospital of Zhengzhou Univ, Zhengzhou Univ Inst of Nephrology, Henan, China; [2]Medicine, Feinstein Inst for Medical Research, Hofstra North Shore LIJ Medical School, Great Neck, NY; [3]Medicine, Rambam Health Care Campus, Haifa, Israel.*

Background: Increasing evidences have demonstrated that African Americans develop chronic kidney diseases at higher ratios than European Americans, and this disparity has been attributed to two coding sequence variants (G1 and G2) in *APOL1* gene. However, the underlying mechanisms are poorly understood. Previous studies from our group as well as other groups showed that the variants G1 and G2 are more toxic than G0 to kidney cells. To further reveal the molecular mechanisms involved in APOL1-associated nephropathy, We have evaluated their gene expression profiles in podocytes expressing G0, G1, and G2.

Methods: We have generated human podocyte cell lines steadily expressing APOL1 wild type (G0), G1, or G2 proteins. To compare the expression profiles among these cells, podocytes expressing APOL1G0, G1 and G2 underwent RNA-seq, real time-PCR, and Western blot analysis.

Results: Podocytes APOL1 risk variants (G1 and G2) displayed multiples genes related to cellular endoplasmic reticulum (ER) stress, necrosis, and proliferation; RNA-seq results further revealed that the eIF2 signaling pathway was down regulated by G1 and G2.

Conclusions: Our study demonstrated the different gene expression profiles caused by APOL1 wild type and its variants, and will help to reveal the underlying molecular mechanisms of APOL1 variants caused kidney injury, which may highlight novel therapeutic targets for the prevention and treatment of APOL1-associated nephropathy.

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SA-PO337

Expression of APOL1 Risk Allele in Drosophila Nephrocytes Induces Hypertrophy and Leads to an Accelerated Cell Death Zhe Han, Yulong Fu, Jun-Yi Zhu, Adam Richman, Patricio E. Ray. *Children's National Health Systems, Washington, DC.*

Background: Apolipoprotein-1 (APOL1) risk alleles are strongly associated with an increased risk of developing renal diseases among persons of African ancestry. However, the mechanisms underlying APOL1 associated renal diseases are unknown. Because the *APOL1* gene is unique to humans and some primates, new experimental models are needed to understand the function of the *APOL1* risk alleles *in vivo*.

Methods: We generated transgenic *Drosophila* lines expressing the human *APOL1* wild type (G0) and the predominant *APOL1* risk allele (G1) in different tissues, including the nephrocytes, which share striking similarities to human podocytes. Various functional and structural assays were formed to access the role APOL1-RA effects in different tissues with focus on the nephrocytes.

Results: Ubiquitous expression of either G0 or G1 ApoL1 in *Drosophila* induced lethal phenotypes, with G1 being more toxic than G0. When G0 and G1 were expressed specifically in *Drosophila* nephrocytes, the structurally and functionally homologous of mammalian podocytes, these cells showed first an upregulated endocytic activity and increased accumulation of hemolymph proteins, dextran particles, and silver nitrate, leading to increase nephrocyte size and function. As these flies aged, the function of nephrocytes declined, and showed a reduced endocytic activity associated with progressive cell swelling, and cell death, mimicking the changes seen in cultured podocytes overexpressing APOL1. Furthermore, G0 and G1 impaired the acidification of organelles in nephrocytes.

Conclusions: We conclude that overexpression of APOL1 G0/G1 in fly nephrocytes, first increases the function of nephrocytes, causing hypertrophy rather than direct cell death. This new *Drosophila* model suggest a novel mechanism through which overexpression of APOL1 could precipitate renal diseases in humans, and may enable the identification of APOL1 interacting molecules that could serve as new targets for treatments against APOL1-associated renal diseases.

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SA-PO338

Scaffolding Protein JLP Modulates Kidney Fibrosis Induced by Unilateral Ureteral Obstruction via Mediation of Autophagy Activation Qi Yan, Huiming Wang, Ming Shi, Guohua Ding. *Dept of Nephrology, Renmin Hospital of Wuhan Univ.*

Background: Scaffolding protein JNK-associated leucine (JLP) plays a crucial role in signal transduction and molecular trafficking. Our previous study found that JLP deficiency deteriorated kidney fibrosis in mice model of unilateral ureteral obstruction (UUO), but the precise contribution of JLP in kidney fibrosis remains unknown. In the present study, we investigate the effect of JLP on the activation of autophagy in kidney fibrosis of UUO model.

Methods: *jlp* Wild type ($jlp^{+/+}$) and *jlp* deficient ($jlp^{-/-}$) mice were divided into six groups: $jlp^{+/+}$- and $jlp^{-/-}$-sham-operated groups, $jlp^{+/+}$- and $jlp^{-/-}$-unilateral ureteral obstruction (UUO)-operated groups ($jlp^{-/-}$- UUO group and $jlp^{+/+}$- UUO group), $jlp^{+/+}$- and $jlp^{-/-}$-unilateral ureteral obstruction (UUO)-operated plus Rapamycin groups ($jlp^{-/-}$- UUO + Rapa group and $jlp^{+/+}$- UUO + Rapa group). Mice were sacrificed at the days of 7 to evaluate the fibrosis by Masson and H&E staining. The expression of α-smooth muscle actin (α-SMA) were assayed by immunohistochemistry staining. The activity of autophagy was measured by expression of LC3 and p62.

Results: 1) One week after the surgery, more collagen deposition and expression of α-SMA was observed in the renal interstitial area in $jlp^{-/-}$- UUO group compared with $jlp^{+/+}$- UUO group. Moreover, the collagen deposition and α-SMA expression was also increased in $jlp^{-/-}$- UUO + Rapa group rather than in $jlp^{+/+}$- UUO + Rapa group. 2) Expression of LC3 were significantly increased in $jlp^{-/-}$- UUO-operated groups compared with $jlp^{+/+}$- UUO group, whereas expression of p62 show opposite trend. 3) Expression of LC3 was also significantly higher in $jlp^{-/-}$- UUO-operated + Rapa group than in $jlp^{+/+}$- UUO + Rapa group, whereas expression of p62 were decreased in $jlp^{-/-}$- UUO-operated + Rapa group compared with $jlp^{+/+}$- UUO + Rapa group.

Conclusions: Scaffolding protein JLP deficiency activates autophagy, which aggravates kidney fibrosis in UUO model.

Funding: Government Support - Non-U.S.

SA-PO339

Human Point Mutation in Umod Causes Progressive Interstitial Kidney Disease and Organ Failure in Mice Bryce Gordon Johnson, Lan Dang, Allie M. Roach, Jeremy Stuart Duffield. *R&D, Biogen, Cambridge, MA.*

Background: An estimated 10% of adults in the U.S. (~20 million individuals) are living with Chronic Kidney Disease (CKD), and kidney failure is a leading cause of death. UAKD accounts for <1% of CKD cases. The hallmarks of UAKD are hyperuricemia, polyuria, cortico-medullary cysts, and progressive tubulo-interstitial fibrosis leading to kidney failure by 30-70y. UAKD is caused by mutations in the *UMOD* gene that result in misfolding of the protein, and accumulation in the ER. This aggregation of misfolded protein sets off cascades of ER stress response.

Methods: We designed and generated the *Umod* $^{C147W/+}$ point mutation knock-in mouse model with Crispr/Cas9 technology. Whole kidney tissue preps and individual cell populations were isolated from mutant mice and analyzed compared to wild type littermates. Immortalized human UMOD+ cell lines were generated harboring both WT and C147W mutant alleles.

Results: Heterozygous mice develop spontaneous and progressive kidney disease with organ failure, highly similar to humans, over 24 wks.There is activation of the PERK/ATF4 and IRE1a/XBP1 ER stress pathways in the cells expressing misfolded protein. Surprisingly, autophagy is inhibited in this setting, potentially by putative inhibitors of ATF4/CHOP. The mTOR pathway, which antagonizes autophagy, is highly active in the kidneys of diseased animals. Diseased cells express increased amounts of pro-apoptotic factors, and are more susceptible to TNFa and Trail induced apoptosis in vitro.

Conclusions: We conclude that this new mouse model provides an excellent means for studying progressive human renal disease, as well as other human disease characterized by insult to proteostasis by mutant protein accumulation, leading to organ failure.

Funding: Pharmaceutical Company Support - Biogen

SA-PO340

D-Serine, a Novel Emerging Uremic Toxin Candidate, Induces Cell Cycle Arrest and Apoptosis Through Up-Regulation of ER Stress and Oxidative Stress in Proximal Tubular Cells Akira Okada,[1] Tzu-Ming Jao,[2] Hiroshi Maekawa,[1] Yu Ishimoto,[1] Masaomi Nangaku,[1] Reiko Inagi.[2] *[1]Div of Nephrology and Endocrinology, The Univ of Tokyo Graduate School of Medicine, Tokyo, Japan; [2]Div of CKD Pathophysiology, The Univ of Tokyo Graduate School of Medicine, Tokyo, Japan.*

Background: Elevated D-serine concentration in plasma has been reported to be a poor prognosis marker of patients with chronic kidney disease (CKD), indicating the pathophysiological significance of D-serine in the kidney. However, the molecular mechanisms underlying D-serine induced toxicity in the kidney remain largely unknown. In the present study, we aimed to explore D-serine-mediated signaling pathways in the proximal tubular cells.

Methods: Human proximal tubular cell line, HK-2, was treated with D- or L-serine for 48 hr and evaluated the cell damages by cell proliferation (MTS assay and cell count), cell cycle status (PI staining, p53), apoptosis (Annexin V staining and caspase 3/7 activity). To find out the molecular mechanism of the cell damage by D-serine, we assessed the status of endoplasmic reticulum (ER) stress (real time RT-PCR and Western blotting for GRP78 and CHOP), oxidative stress (NADPH oxidase activity, mitochondrial ROS), pro-inflammatory cytokine expression (IL-1β, and IL-6) known as senescence-associated secretory phenotype (SASP). CHOP siRNA was also used.

Results: D-serine, but not L-serine, induced ER stress signal and oxidative stress associated with increased intracellular ROS, and thereby caused G2/M cell cycle arrest. Importantly, the cell arrest by D-serine was associated with the upregulation of p53 and SASP-related pro-inflammatory cytokines in HK-2. D-serine also induced apoptosis mediated by CHOP, namely apoptotic ER stress axis. It was supported by the results showing that CHOP siRNA ameliorated the apoptosis.

Conclusions: D-serine causes tubular cell damage via both premature senescence and apoptotic signals, both of which are mediated by ER stress or oxidative stress, suggesting a novel renal pathogenesis of D-serine as a potential uremic toxin in CKD patients. Our study sheds a new light on CKD pathophysiology from the point of view of vicious cycle of tubular damage by uremic toxins including D-serine.

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SA-PO341

Effect of Cyanate on the p-AMP Kinase, Isocitrate Dehydrogenase, and Apoptosis in Huh7 Cells Yaerim Kim,[1,2] Sang Mok Yeo,[1,2] Seong Sik Kang,[1,2] Woo Yeong Park,[1,2] Kyubok Jin,[1,2] Sung Bae Park,[1,2] Kyo Chul Mun,[2,3] Seungyeup Han.[1,2] *[1]Dept of Internal Medicine, Keimyung Univ School of Medicine, Daegu, Republic of Korea; [2]Keimyung Univ Kidney Inst, Daegu, Republic of Korea; [3]Dept of Biochemistry, Keimyung Univ School of Medicine, Daegu, Republic of Korea.*

Background: Urea is a major factor of uremic syndrome which is accumulated by decreased kidney function. It can be degraded by ammonia and cyanate. We studied alteration of major enzyme for energy metabolism and effectiveness of apoptosis to confirm the impact of cyanate on energy metabolism in a patient of chronic kidney disease.

Methods: We checked pAMP kinase and isocitrate dehydrogenase which are major enzymes of energy metabolism. It was performed by using Huh7, liver cell carcinoma cell strain which is key cell in creation of energy. After cyanate processing to Huh7, we analyzed a viability of cell, performed western blot analysis about pAMP kinase and apoptotic factors like PARP, p53, cytochrome C, cIAP, and xIAP. And we checked activity of isocitrate dehydrogenase and took reverse transcriptional polymerase chain reaction.

Results: The viability of Huh7 cell was decreased in proportion to the concentration and exposure time to cyanate. According to the western blot analysis about cell apoptotic factors, protein of PARP was cleaved in accordance with the exposure time, and p53 was strongly expressed after cyanate processing. Free cytochrome C and xIAP was decreased in proportion to time of cyanate processing, cIAP was increased after cyanate processing. After cyanate processing to Huh7 cell, p-AMP kinase which mainly works in energy metabolism was decreased as time passes in Western blot analysis. Although isocitrate dehydrogenase activity was increased compared with control, expression of mRNA of isocitrate dehydrogenase was decreased after cyanate processing.

Conclusions: In our study,cyanate as uremic toxin induced apoptosis in Huh7 cells, activated TCA cycle, and inhibited energy metabolism. As a result, it leads to decline of energy generation, which makes CKD patients meet with fatigue, musculoskeletal problem and hypothermia.

SA-PO342

a-Lipoic Acid Attenuates p-Cresol Sulfate-Induced Renal Tubular Injury Through Suppression of Apoptosis and Autophagy in Human Proximal Tubular HK-2 Cells Jung Sun Park, Hoon In Choi, Eun Hui Bae, Seong Kwon Ma, Jong Un Lee, Soo Wan Kim. *Internal Medicine and Physiology, Chonnam National Univ Medical School, Kwang Ju, Korea.*

Background: The protein bound solute p-cresol sulfate accumulates in chronic kidney disease, and may play significant roles in the progression of renal injury. a-lipoic acid (ALA) is known to acts as antioxidants in cell injury protection. Here, we investigated the effects of a-lipoic acid treatment on p-cresol sulfate-induced renal tubular injury.

Methods: The effects ofa-lipoic acid by p-cresol sulfate-induced cell death were determined using human proximal tubular (HK-2) cells. A apoptosis was determined by flowcytometry using annexin-V-FITC/PI assay and levels of lactate dehydrogenase (LDH). The protein expression of apoptosis- and autophagy-related proteins (Bax, Bcl-2, cytochrome C, and LC3B, Beclin-1) was determined by semiquantitative immunoblotting. Mitochondria membrane potential (MMP/DY_m) was evaluated using fluorescence microscopy and flow cytometry analysis with Rho123 as the fluorescent probe.

Results: p-Cresol sulfate treatment significantly increased levels of lactate dehydrogenase (LDH) and induced time-, dose-dependent cell death in HK-2 cells. p-Cresol sulfate increased the expression of apoptosis-related protein Bax/Bcl-2, cytochrome C, as well as autophagy-related protein Beclin-1 and LC3B in HK-2 cells. In contrast, a-lipoic acid significantly reduced p-cresol sulfate-induced the expression of Bax/Bcl-2, cytochrome C, and loss of mitochondria membrane potential. Apoptosis of p-cresol sulfate-induced HK-2 cells was significantly reduced by specific autophagy inhibitor 3-methyladenine. Additionally, in the presence of the specific apoptosis inhibitor Z-VAD-FMK, p-cresol sulfate-induced autophagy was significantly reduced.

Conclusions: a-lipoic acid attenuated p-cresol sulfate-induced cell death through suppression of apoptosis and autophagy in HK-2 cells.

Funding: Government Support - Non-U.S.

SA-PO343

R428 as a Novel Therapeutic Agent for the Treatment of Experimental Immune-Mediated Nephritis Wenhai Shao. *Medicine, Temple Univ, Lewis Katz School of Medicine, Philadelphia, PA.*

Background: Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease. Glomerulonephritis is a major cause of morbidity in SLE. Nephrotoxic serum-mediated anti-glomerular basement membrane (anti-GBM) disease is a well-studied mouse model of immune-mediated glomerulonephritis. Glomerular proliferation is essential for the pathogenesis and progression of glomerular diseases. Axl receptor tyrosine kinase mediates glomerular cell survival signaling, resulting in proliferative responses. R428 is a recently described selective small molecule inhibitor of Axl.

Methods: R428 was administered through oral gavage two day before nephrotoxic serum injection and continued for 12 days. Control mice were administered with the vehicle buffer. Blood samples were collected. Kidney samples were prepared for RNA and Western analysis.

Results: Our results show R428 effectively prevents disease progression and exacerbation with significantly reduced blood urea nitrogen levels and enhance survival rates as compared to the vehicle-treated nephritic mice. Mechanistic studies revealed that R428 suppresses the expression of pro-inflammatory cytokines and reduces Akt phosphorylation in the kidney.

Conclusions: In summary, these results indicate that R428, currently under clinical trial in cancer patients, may have clinical therapeutic application in lupus nephritis patients.

Funding: NIDDK Support

SA-PO344

Nicotine Induces Podocyte Apoptosis Through Increasing Oxidative Stress Xiqian Lan, Judith Eng, Seyedeh Shadafarin Marashi Shoshtari, Ashwani Malhotra, Pravin C. Singhal. *Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY.*

Background: Cigarette smoking plays an important roles in the progression of chronic kidney disease (CKD). Nicotine, one of the major components of cigarette smoking, has been demonstrated to increase proliferation of renal proximal tubular and mesangial cells. In this study, we examined the effect of nicotine on podocyte injury.

Methods: To determine the expression of nicotine receptors (nAChR subunits) in both cultured human podocytes and mouse kidney, protein blots and cDNAs of renal tissues and cellular lysates were probed for nAChR. We studied the effect of nicotine on podocyte ROS generation (DCFDA loading followed by fluorometric analysis), cell proliferation, and cell apoptosis (morphologic assays). We evaluated the effect of nicotine on podocyte downstream signaling (phosphorylation of AKT, ERK1/2, JNK, and p38) and established causal relationships by using specific inhibitors.

Results: Human podocytes displayed robust mRNA and protein expression of nAChR. Immunofluorescence studies in renal cortical sections of mice revealed co-localization of nAChR along with synaptopodin. Nicotine stimulated podocyte ROS generation; however, antioxidants such as N-acetyl cysteine and TEMPOL (superoxide dismutase mimetic agent) inhibited this effect of nicotine. Nicotine did not modulate proliferation but promoted apoptosis in podocytes. Nicotine enhanced podocyte phosphorylation of AKT, ERK1/2, JNK, and p38 and their respective inhibitors attenuated nicotine-induced apoptosis.

Conclusions: Nicotine induces podocyte apoptosis through ROS generation and associated downstream signaling. The present study provides insight into molecular mechanisms involved in smoking associated progression of chronic kidney disease.

Funding: NIDDK Support

SA-PO345

Podocyte Damage Is Mitigated by Normal High Density Lipoprotein (HDL) Yohei Tsuchida,[1] Jianyong Zhong,[1] Talat Alp Ikizler,[3] Agnes B. Fogo,[2] Haichun Yang,[2] Valentina Kon.[1] *[1]Pediatrics, Vanderbilt Univ Medical Center, Nashville, TN; [2]Pathology, Vanderbilt Univ Medical Center, Nashville, TN; [3]Medicine, Vanderbilt Univ Medical Center, Nashville, TN.*

Background: HDL is beneficial to many different cells types. We showed that CKD makes HDL dysfunctiona. Although the glomerular filtration barrier limits direct contact and influence of HDL on podocytes, disruption in the filtration barrier permits greater interaction. We investigated the effects of normal HDL and its major apolipoprotein, ApoA1, on injured podocytes and compared these effects to HDL isolated from subjects with CKD.

Methods: Primary mouse podocytes were exposed to puromycin and injury compared to that seen with added HDL isolated from controls with normal kidney function, individuals with CKD or ESRD, or normal ApoA1 (EMD Millipore Company). We assessed podocyte viability by XTT Cell Viability, proliferation by Cell Titer96® Aqueous One Solution Cell Proliferation Assay, and cellular production of superoxide by HPLC. The membrane lipid raft component, phosphorylated caveolin-1 (Cav-1), was measured by western blot.

Results: PAN significantly reduced cell viability, proliferation, and increased ROS production.

	Cell viability	Cell proliferation	ROS production (pmol/mg)
PAN (-)	0.47±0.02	0.48±0.05	0.98±0.05
PAN (+)	0.37±0.03*	0.34±0.02*	1.84±0.05*
PAN (+)/ApoAI	0.41±0.02†	0.44±0.04†	1.30±0.03†
PAN (+)/HDL^{Cont}	0.41±0.03†	0.43±0.07†	1.29±0.05†
PAN (+)/HDL^{CKD}	0.40±0.06	0.41±0.06	1.48±0.04†#

Each of these effects was significantly quelled by exposing podocytes to ApoA1 or HDL^{Cont} and more variable nonsignificant results with HDL^{CKD}. Significant increase in PAN-induced Cav-1 phosphorylation was returned to baseline level by HDL^{Cont} 0.65±0.04vs 0.81±0.05 vs 0.70±0.09, respectively).

Conclusions: We conclude that podocyte damage can be mitigated by normal HDL or its main lipoprotein ApoA1, findings that parallel beneficial biological function of HDL/ApoA1 in other cell types. Restoration of normal HDL or exposure to normal HDL may mitigate podocyte injury and promote podocyte resilience.

Funding: Other NIH Support - NHBLI

SA-PO346

COX-2/mPGES-1/PGE2 Cascade Mediates Uric Acid-Induced Mesangial Cell Proliferation Shuzhen Li,[2] Wei Gong,[2] Jing Yu,[2] Yue Zhang,[1] Guixia Ding,[1] Songming Huang,[1] Aihua Zhang,[1] Zhanjun Jia.[2] *[1]Dept of Nephrology, Nanjing Children's Hospital affiliated to Nanjing Medical Univ, Nanjing, China; [2]Nanjing Key Lab of Pediatrics, Nanjing, China.*

Background: Hyperuricemia is not only the main feature of gout but also a cause of gout -related organ-injuries including glomerular hypertrophy and sclerosis. Uric acid (UA) has been proven to directly cause mesangial cell (MC) proliferation, however, the mechanism is still elusive. Here we examined the role of inflammatory cascade of COX-2/mPGES-1/PGE_2 in UA-induced MC proliferation.

Methods: UA was administered to the mesangial cells to induce cell proliferation. Specific COX-2 inhibitor and mPGES-1 siRNA were used to determine their roles in this pathological process.

Results: By performing dose- and time-dependent experiments in MCs, UA increased cell proliferation as shown by increased number of cells in S and G2 phases by about 2 folds in parallel with the upregulation of cyclin A2 and cyclin D1 at both mRNA (1.5 and 2 folds, respectively) and protein levels (0.5 and 2.5 folds, respectively). Interestingly, UA-induced cell proliferation was accompanied by selectively induced COX-2 (not COX-1) and mPGES-1(not mPGES-2 and cPGES) protein and mRNA expressions by around 2 to 3 folds. Similarly, PGE2 production in medium was also elevated by 7 folds. Importantly, inhibition of COX-2 via specific COX-2 inhibitor NS398 markedly blocked UA-induced MC proliferation in parallel with an abolished PGE2 production. Furthermore, inhibiting specific PGE2 synthase mPGES-1 by a siRNA approach in MCs also ameliorated UA-induced MC proliferation by detecting the number of cells in the S and G2 phases and expressions of cyclin A2 and cyclin D1.

Conclusions: Our findings indicated that COX-2/mPGES-1/PGE_2 cascade mediated UA-induced MC proliferation. The study offered potential targets for the treatment and prevention of hyperuricemia-related glomerular hypertrophy and sclerosis.

SA-PO347

Proliferation and Migration Ability of Renal Carcinoma Cells Is Enhanced by Autocrine MCP-1/CCR2 Signaling Christoph Kueper,[1] Franz Xaver Beck,[1] Wolfgang Neuhofer.[2] *[1]Cellular Physiology, Univ of Munich, Munich, Germany; [2]Nephrology, Clinic Traunstein, Traunstein, Germany.*

Background: The chemokine MCP-1 is an important mediator of monocyte recruitment during inflammatory processes via binding to CCR2. High expression levels of MCP-1 have been observed in various cancers, among them renal cell carcinoma (RCC), and are often associated with infiltration of proinflammatory monocytes, which promote tumor progression and metastasis. Besides paracrine effects, also autocrine MCP-1/CCR2 signaling has been described in cancer cells. The aim of the present study was to evaluate the function and the regulation of MCP-1 in RCC.

Methods: RCC cell lines and peripheral blood monocytes (PBM) were grown under standard conditions. MCP-1 and NFAT5 expression was determined by qRT-PCR, ELISA, and immunoblot. Migration and proliferation of RCC and PBM was determined by Boyden chamber, scratch assay and MTT assay in the presence or absensce of CCR2 inhibitor, MCP-1 neutralizing antibody, or recombinant MCP-1. NFAT-5 knockdown in RCC was achieved by specific siRNA.

Results: Experiments were performed in the RCC cell lines CaKi-1 (VHL-positive) and 786-O (VHL-negative). In both cell lines, expression of MCP-1 was significantly enhanced compared with non-cancerous control cells. As expected, secretion of MCP-1 facilitated the recruitment of PBM via the CCR2 receptor. Administration of an MCP-1 neutralizing antibody or of a CCR2 antagonist significantly decreased proliferation and migration ability of RCC cells; additionally, recombinant human MCP-1 stimulated cell migration, compared with untreated control cells. In CaKi-1 cells, expression of MCP-1 is largely mediated by the transcription factor NFAT5, while in 786-O cells deletion of the tumor suppressor gene VHL is probably responsible for MCP-1 upregulation.

Conclusions: Taken together, our results indicate that expression of MCP-1 in RCC cells promotes tumor progression and metastasis not only by paracrine, but also by autocrine MCP-1/CCR2 signaling events, which enhances cell proliferation and migration ability. These findings therefore suggest the MCP-1/CCR2 axis as a potential target for future therapeutic strategies in the treatment of metastatic RCC.

SA-PO348

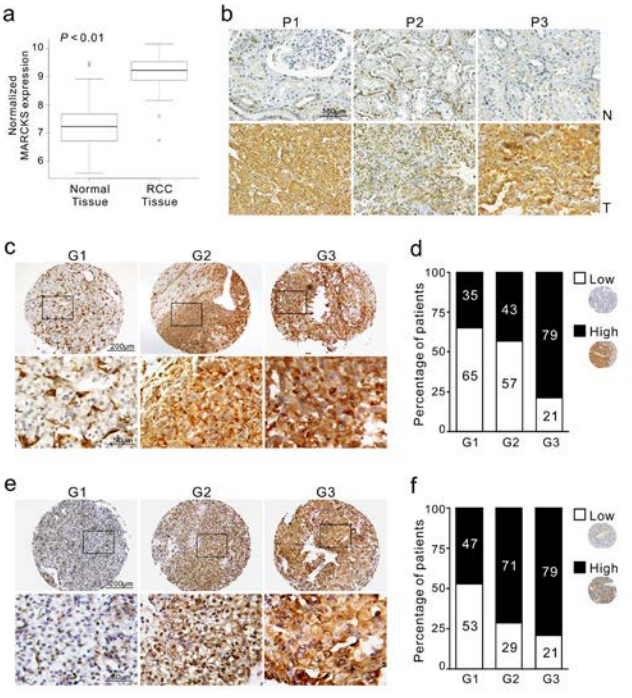
Up-Regulation of MARCKS in Kidney Cancer and Its Potential as Therapeutic Target Ching-Hsien Chen,[1] Eric Yu,[1] Muhammad S. Arif,[1] Robert H. Weiss.[1,2] *[1]Div of Nephrology, Dept of Internal Medicine, Univ of California, Davis, Davis, CA; [2]Cancer Center, Univ of California, Davis, Sacramento, CA.*

Background: Targeted therapeutics such as targeting hypoxia inducible factor (HIF)/VEGF signaling are initially effective against kidney cancer (or renal cell carcinoma, RCC); unfortunately, drug resistance occurs by activation of bypass pathways. Through genome-scale integrated analysis of the HIF-α network, we identified the major protein kinase C substrate MARCKS as a potential target molecule in kidney cancer. In this study, we aimed to determine if MARCKS can serve as a therapeutic target.

Methods: The clinical relevance of MARCKS and its phosphorylation was first confirmed. Next, we used genetic and pharmacologic approaches to verify the functionality and molecular mechanisms of MARCKS in RCC.

Results: In a screen of 56 patients with RCC, we found that MARCKS expression and its phosphorylation are increased in RCC specimens and positively correlated with tumor grade. Genetic and pharmacologic suppression of MARCKS in high grade RCC cells led to a decrease in cell proliferation and migration. We further demonstrated that higher MARCKS expression promotes xenograft tumor growth and angiogenesis. Mechanistically, MARCKS acted upstream of the AKT/mTOR pathway and thereby activated HIF-target genes, especially VEGF-A. Following knockdown of MARCKS, the inhibitory concentration 50% of a multi-kinase inhibitor regorafenib was reduced in RCC cells. Consistently, MARCKS inhibition using the MPS peptide synergistically interacted with regorafenib treatment and decreased survival of kidney cancer cells through inactivating AKT and mTOR.

Conclusions: Our data suggest the major contribution of MARCKS to kidney cancer growth and also provide an alternative therapeutic strategy by improving the efficacy of multi-kinase inhibitors.



Funding: Other U.S. Government Support

SA-PO349

Genetic Variation at the 8q24.21 Renal Cancer Susceptibility Locus Affects HIF-Binding to an Enhancer of Oncogenic MYC and PVT1 Expression Steffen Grampp,[1] James L. Platt,[2] Victoria Lauer,[1] Rafik Salama,[2] Kai-Uwe Eckardt,[1] Peter J. Ratcliffe,[2] David Robert Mole,[2] Johannes Schödel.[1] *[1]Dept of Medicine 4 Nephrology and Hypertension, Univ Erlangen-Nürnberg, Erlangen, Germany; [2]Henry Wellcome Building for Molecular Physiology, Univ Oxford, Oxford, United Kingdom.*

Background: Clear cell renal cell carcinoma (ccRCC) origin from tubular cells. ccRCC is characterized by loss of von Hippel-Lindau protein (VHL) and uncontrolled expression of hypoxia inducible transcription factors (HIF). A genome-wide association study (GWAS) identified single nucleotide polymorphisms (SNP) on chromosome 8q24.21 interposed between *MYC* and *PVT1*. The SNPs are associated with increased susceptibility for ccRCC. MYC is upregulated in ccRCC, but compared to other tumors amplification of the MYC locus is rare. Hence, dysregulation of MYC in ccRCC must be caused by other mechanisms.

Methods: Using RNA analysis, chromatin immunoprecipitation (ChIP), analysis of open Chromatin, allele specific assays and genome editing (CRISPR/Cas9) we have investigated the 8q24.21 locus in primary human tubular cells and RCC cell lines.

Results: Hypoxia led to induction of MYC and PVT1 in primary tubular cells and VHL re-expressing ccRCC cell lines in a HIF-dependent manner. Strikingly, HIF-ChIP-seq experiments identified HIF-binding events in a distal regulatory DNA element which encompasses the ccRCC associated SNPs identified in GWAS. Hypoxic regulation of MYC and PVT1 RNA, HIF-binding and open chromatin at the 8q24.21 locus are highly cell type specific and restricted to cells of renal tubular origin. Physical and functional interaction of the distal enhancer with the MYC promotor was verified by capture-c-assay and genome editing. In cell lines heterozygous for the SNP, allele specific assays showed an increased activity of chromatin and HIF-binding for the risk haplotype.

Conclusions: In cells of tubular origin HIF are capable of regulating MYC and PVT1 expression through binding to a distal enhancer. Therefore, in VHL-defective ccRCC unrestrained expression of HIF leads to overexpression of the oncogenes MYC and PVT1. We conclude that the ccRCC associated SNP on 8q24.21 promotes these effects by modifying accessibility and activity of this site.

SA-PO350

Erythrocyte Sodium Sensitivity: Distribution in Hemodialysis Patients and Correlation with Eryptosis Anna Meyring-Wosten,[1] Viktoriya Kuntsevich,[2] Israel Campos,[1] Jie Ma,[1] Samir D. Patel,[1] Schantel Williams,[1] Stephan Thijssen,[1] Peter Kotanko.[1,2] *[1]Renal Research Inst, New York, NY; [2]Mount Sinai Beth Israel, New York, NY.*

Background: The glycocalyx of the vascular endothelium and erythrocytes selectively buffers sodium. Hence, damage of the glycocalyx leads to increased erythrocyte sodium sensitivity (ESS), which can be quantified by the 'salt blood test' (SBT) [Oberleithner and Wilhelmi, Pflugers Arch 2013].Eryptosis, suicidal death of red blood cells (RBCs), is accelerated in hemodialysis (HD) patients and is characterized by phosphatidylserine (PS) exposure on the RBC surface. While both ESS and eryptosis relate to RBC surface properties, their relationship has not yet been explored. Also, the acute impact of HD on eryptosis and ESS warrants investigation.

Methods: We enrolled 20 chronic HD patients. Blood samples were collected pre- and post-dialysis. SBT was performed in triplicates. PS exposure, a measure of eryptosis, was determined in duplicates from Annexin-V-FLUOS (ROCHE, Germany) binding by BD FACSCalibur™ System.

Results: The age of the subjects ranged from 28 to 75 years, 55% were white, 45% male, and 50% diabetic. ESS ranged from 2.4 to 8.0 with median at 3.4 before HD and from 1.9 to 7.7 with median at 3.5 after HD. The ESS dropped on average by 0.2 (95% confidence interval,-0.5 to 0.1; p=0.64). PS exposure decreased from 0.60±0.42% to 0.34±0.13% (p=0.02) during HD. There was no correlation between ESS and % eryptotic RBCs (R^2=0.005).

Conclusions: Glycocalyx integrity estimated by ESS did not correlate with suicidal death of erythrocytes. Kliche et al. [Cell Physiol Biochem 2015] observed a decrease of the ESS after dialysis in patients with high ESS. This could not be confirmed in our population, possibly due to a different dialysis modality (hemodialysis vs. postdilutional hemodiafiltration). The decrease of eryptosis after the hemodialysis treatment is contrary to findings by Abed et al. [J Mol Med, 2014] which might be the result of using ultrapure dialysate, a different type of erythropoiesis-stimulating agent used or uremic toxin removal.

Funding: Pharmaceutical Company Support - Renal Research Institute

SA-PO351

Lipophagy Maintains Energy Homeostasis during Prolonged Starvation in the Kidney Proximal Tubule Satoshi Minami,[1] Takeshi Yamamoto,[1] Yoshitsugu Takabatake,[1] Atsushi Takahashi,[1] Tomoko Namba,[1] Jun Matsuda,[1] Taiji Matsusaka,[2] Fumio Niimura,[3] Yoshitaka Isaka.[1] *[1]Dept of Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; [2]Inst of Medical Science and Dept of Molecular Life Science, Tokai Univ School of Medicine, Isehara, Kanagawa, Japan; [3]Dept of Pediatrics, Tokai Univ School of Medicine, Isehara, Kanagawa, Japan.*

Background: Autophagy is a self-degradation process and combats starvation. Lipids are main energy source in the kidney proximal tubular cells (PTCs). Under starvation, PTCs increase fatty acids (FAs) uptake, form intracellular lipid droplets (LDs), and hydrolyze them for use. The involvement of autophagy in lipid metabolism in the kidney remains largely unknown.

Methods: We investigated the autophagy-mediated regulation of renal lipid metabolism under prolonged starvation using PTC-specific Atg5-deficient (*Atg5$^{F/F}$*;KAP) mice and *in vitro* serum starvation model.

Results: Twenty-four hours of starvation comparably induced LDs formation in the PTCs of control and *Atg5$^{F/F}$*;KAP mice; however, additional 24 hours of starvation lead to the reduction of the number of LDs in control mice, whereas they rather increased in *Atg5$^{F/F}$*;KAP mice. Autophagic degradation of LDs (lipophagy) in the PTCs was demonstrated by electron microscopic observation and biochemical analysis. *In vitro* pulse-chase assay elucidated that lipophagy mobilizes FAs from LDs to mitochondria during starvation, whereas impaired LDs degradation in autophagy-deficient PTCs lead to decreased ATP production and subsequent cell death. In contrast to the *in vitro* assay, despite impairment of LDs degradation, ATP content was preserved in 48 hour starved *Atg5$^{F/F}$*;KAP mice probably due to increased utilization of ketone bodies. This compensatory mechanism was accompanied by higher plasma fibroblast growth factor (FGF) 21 level and its expression in the PTCs; however, which is not essential for production of ketone bodies in the liver under prolonged starvation.

Conclusions: Autophagy combats prolonged starvation by promoting lipophagy in the PTCs to avoid cellular energy depletion.

SA-PO352

Endothelial Autophagy Is Essential for the Integrity of Glomerular Capillaries Jun Matsuda,[1] Tomoko Namba,[1] Yoshitsugu Takabatake,[1] Atsushi Takahashi,[1] Takeshi Yamamoto,[1] Satoshi Minami,[1] Tomonori Kimura,[1] Jun-Ya Kaimori,[2] Isao Matsui,[1] Yoshitaka Isaka.[1] *[1]Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; [2]Advanced Technology for Transplantation, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan.*

Background: Autophagy is a lysosomal degradation system by which cytosolic materials and damaged organelles are broken down into basic components. Although some previous studies have suggested endothelial autophagy contributes to maintaining vascular homeostasis, the physiological role of glomerular endothelial autophagy remains poorly understood.

Methods: We generated endothelial cell-specific Atg5-deficient mice (Tie2-Cre *Atg5* flox/flox mice: KO mice). As Tie2 is expressed in some hematopoietic lineages as well as the endothelial cells, KO mice are dead by 3 months of age due to pancytopenia. Therefore, we subjected 1-month-old KO mice and controls to irradiation followed by bone marrow transplantation from Tie2-Cre negative littermates (WT®Δ*Atg5* and WT®WT mice, respectively).

Results: Although 1-month-old KO mice had no obvious changes except for splenomegaly, their glomeruli exhibited slightly distended capillary loops. Furthermore, electron microscopic analysis revealed segmental loss of glomerular endothelial fenestra accompanied with foot process effacement of podocytes adjacent to the transformed endothelial cells. The accumulation of reactive oxygen species and the number of apoptotic endothelial cells were increased in the glomerular capillaries of KO mice. Glomeruli of 2-month-old KO mice demonstrated lobular pattern with thickening of capillary loops and mesangial matrix expansion. WT®Δ*Atg5* mice exhibited similar glomerular phenotypes of KO mice, while no obvious histological changes were detected in other organs. In addition, mesangiolysis and glomerulosclerosis were observed in 12-month-old WT®Δ*Atg5* mice, and they developed significant increase in serum urea nitrogen and albuminuria compared with WT®WT mice.

Conclusions: These data suggest that endothelial autophagy protects glomeruli from oxidative stress and maintains the integrity of glomerular capillaries. Enhancing endothelial autophagy may provide a novel therapeutic approach to minimize glomerular diseases.

SA-PO353

Autophagy in Primary Renal Tubular Epithelial Cells Mediates Cellular Senescence Arpita Baisantry,[1,2] Sagar Bhayana,[2] Christoph Wrede,[3] Jan Hegermann,[3] Hermann G. Haller,[2] Anette Melk,[1] Roland Schmitt.[2] *[1]Kidney, Liver and Metabolic Diseases, Children's Hospital, Hannover Medical School (MHH), Hannover, Germany; [2]Nephrology, MHH, Hannover, Germany; [3]Functional and Applied Anatomy, MHH, Hannover, Germany.*

Background: Autophagy and senescence are two discrete pathways triggered during acute kidney injury and during renal repair especially in tubular epithelial cells. Although autophagy is considered renoprotective, it's a proven mediator of oncogene induced senescence and its specific role in promoting or exacerbating senescence is still debatable.

We have shown that genetic ablation of autophagy in a subset of kidney tubular cells abrogates *in vivo* senescence. Hence, to further investigate the potential link between autophagy and renal senescence we isolated primary tubular epithelial cells (PTEC) and tested the impact of autophagy modulation on senescence development.

Methods: PTEC isolated from C57BL/6J mice were driven towards accelerated senescence using γ-irradiation and retroviral overexpression of constitutively active mutant H-Ras oncogene (H-RasV12). Additionally, PTEC were allowed to undergo replicative senescence in culture by passaging. Autophagy induction by rapamycin and inhibition by chloroquine and Atg5 siRNA was validated by established autophagy markers and electron microscopy. Cellular senescence was evaluated by BrdU uptake, $p16^{INK4a}$ expression and quantification of $\gamma\text{-H2AX}^{+}/\text{Ki67}^{-}$ cells.

Results: Our results indicate that ex vivo PTEC culturing is associated with development of senescence and is preceded by a strong induction of baseline autophagy. Specific inhibition of this autophagic activity by Atg5 silencing counteracted senescence development under baseline and stress conditions and preserved the epithelial phenotype. Interestingly, while autophagy inhibition by chloroquine mildly enhanced senescence induction, rapamycin treatment bypassed senescence in PTEC.

Conclusions: Our results highlight a complex interaction between cell culture induced stress, autophagy and renal senescence. While chemical modifiers of autophagy such as chloroquine and rapamycin might have off-target effects, specifically silencing Atg5 attenuates the pro-senescent pathway of stress induced autophagy in vitro.

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SA-PO354

Autophagy in Kidney Allografts of Rapamycin Treated Patients Arpita Baisantry,[1,2] Sagar Bhayana,[2] Thomas D. Kraemer,[2] Christoph Wrede,[3] Clemens L. Bockmeyer,[4] Jan U. Becker,[5] Jan Hegermann,[3] Wilfried Gwinner,[2] Hermann G. Haller,[2] Anette Melk,[1] Roland Schmitt.[2] *[1]Kidney, Liver and Metabolic Diseases, Children's Hospital, Hannover Medical School (MHH), Hannover, Germany; [2]Nephrology, MHH, Hannover, Germany; [3]Functional and Applied Anatomy, MHH, Hannover, Germany; [4]Pathology, Uniklink Erlangen, Erlangen, Germany; [5]Pathology, Unikinik Köln, Köln, Germany.*

Background: Autophagy is a cellular mechanism critical to many biological processes and diseases. Mammalian target of rapamycin (mTOR) inhibitors are used as autophagy inducers in experimental studies, but despite their growing use as immunosuppressants for solid organ transplantation, autophagy induction in renal allografts has never been investigated and constituted the aim of this proof-of-principle study.

Methods: Transplant biopsies of 15 patients receiving rapamycin along with calcineurin inhibitors and MMF were compared to biopsies of 20 patients treated with cyclosporine and MMF alone. An additional control group included 6 patients treated with belatacept and MMF. Autophagosomal volume fractions (AVF) were stereologically quantified using electron microscopy (EM). To prevent cell type bias and allow intersample comparability, the analysis was restricted to podocytes. Expression of autophagy related genes was evaluated in laser microdissected glomeruli using qPCR and by semiquantitative analysis in immunohistochemistry.

Results: EM quantification showed a significant >50% increase in AVF in Rapamycin treated patients. Transcriptional profiling of autophagy genes in laser microdissected glomeruli from the same patients showed no differences. Immunohistochemically, a significant increase in podocytic LC3 was observed, but autophagy degradation product p62 remained unchanged. No differences were found between biopsies of patients treated with CNI or belatacept.

Conclusions: Our results indicate an association of rapamycin treatment and autophagosome formation in renal transplants. Our biochemical findings indicate an autophagosomal buildup rather than increased autophagic flux. Hence, further investigation is needed to determine the functional consequences of the complex interaction between mTOR inhibitors and autophagy and its effect on short- and long-term outcome in transplant patients.

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SA-PO355

JAK2 Regulates Transcription Factor EB Expression and Autophagy Completion in Podocytes Tamadher A. Alghamdi,[1] Syamantak Majumder,[1] Sri Nagarjun Batchu,[1] Kathryn E. White,[2] Youan Liu,[1] Angela S. Brijmohan,[1] Suzanne L. Advani,[1] Minna Woo,[3] Andrew Advani.[1] *[1]St. Michael's Hospital, Toronto, ON, Canada; [2]Newcastle Univ, Newcastle upon Tyne, United Kingdom; [3]Univ Health Network, Toronto, ON, Canada.*

Background: The cytosolic kinase JAK2 has garnered attention as a promising therapeutic target for the treatment of chronic kidney disease. However, being ubiquitously expressed in the adult it is likely also to be important for normal organ function. Here, we examined the consequences of JAK2 depletion from glomerular podocytes.

Methods: Experiments were performed in conditional knockout mice and in cultured podocytes.

Results: Mice in which JAK2 had been conditionally deleted from podocytes exhibited an elevation in urine albumin excretion that was accompanied by increased podocyte autophagosome and lysosome fractional volume and p62 aggregation indicative of impaired completion of autophagy. In cultured podocytes, knockdown of JAK2 similarly impaired autophagy, which was accompanied by downregulation of the expression of a number of lysosomal genes and a reduction in cathepsin D activity, suggesting that the impairment in autophagy completion was due to lysosomal dysfunction. Because transcription factor EB (TFEB) has recently emerged as a master regulator of autophagosome-lysosome function, controlling the expression of several of the genes downregulated by JAK2 knockdown, we questioned whether the transcription factor itself is regulated by JAK2. We found that the downstream mediator of JAK2 signaling, STAT1 binds to the TFEB promoter and that JAK2 knockdown decreases TFEB promoter activity and gene expression. Finally, overexpression of TFEB was able to reverse lysosomal dysfunction in JAK2 deficient podocytes and to restore albumin permselectivity.

Conclusions: Collectively, these observations highlight the homeostatic actions of JAK2 in podocytes and the importance of TFEB to autophagosome-lysosome function in these cells. They also raise the possibility that therapeutically modulating TFEB activity may improve podocyte health in glomerular disease.

SA-PO356

Role of TGF-β1 in the Aberrant Autophagy of Podocyte Induced by Mesangial Cell Proliferation Xing Mao,[1] Xialian Xu,[2,3] Zhigang Zhang,[1,2] Huijuan Wu.[1,2] *[1]Dept of Pathology, Fudan Uni., Shanghai, China; [2]Shanghai Inst for Kidneys and Dialysis, Shanghai, China; [3]Dept of Nephrology, Zhongshan Hospital, Fudan Uni., Shanghai, China.*

Background: Proteinuria is a common clinical manifestation of IgAN and an indicator of a damaged filtration membrane of which podocyte is an indispensable component. Under physiological condition, autophagy plays a pivotal role in podocyte homeostasis. During mesangial cells (MCs) proliferation, the activated MCs release various cytokines which influence other glomerular cells. Among those cytokines, it remains unknown whether and how TGF-β1 excreted by MCs interfered the autophagy of podocytes and what role decorin (DCN), a natural inhibitor of TGF-β1, acted.

Methods: In IgAN and rat anti-Thy1.1 nephritis, proteinuria was examined by gel electrophoresis, and podocyte autophagy was observed by electron microscope and LC3 staining;serum TGF-β1 and DCN were quantified by ELISA and TGF-β1/Smad/mTORC1 signaling was examined by western blot. Then *in vitro*, we firstly examined autophagy and TGF-β1/Smad/mTORC1 signaling in the cultured podocytes treated by TGF-β1 with/without Chloroquine. We next quantified TGF-β1 in the supernatant of MCs treated by TNF-α or PDGF-BB using ELISA and western blot. Furthermore, in the podocytes treated by TGF-β1 with/without SB431542 and TGF-β1 with/without soluble DCN, autophagy and TGF-β1/Smad/mTOR signaling were detected by western blot and IF.

Results: In IgAN and anti-Thy1.1 nephritis, we observed a presence of proteinuria, accompanied by aberrant autophagosome and decreased LC3; serum TGF-β1 was eminently elevated and DCN declined. In the glomeruli of anti-Thy1.1 nephritis and the cultured podocytes treated by TGF-β1, TGF-β1/Smad/mTORC1 signaling was activated with LC3II/LC3I ratio declined. When activated, the cultured MCs excreted a bulk of TGF-β1. Inhibition of autophagy by TGF-β1 could be reversed by SB431542 or DCN.

Conclusions: Activated MC excreted excessive TGF-β1 which mediated the abortion of macroautophagy in podocyte by activating mTORC1 in a TGF-β/smad2-dependent way. The deficiency of DCN in serum failed to neutralize TGF-β1 activity, making DCN and TGF-β1 potential clinical indicators of IgAN.

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SA-PO357

High Fat Diet-Induced Lysosomal Dysfunction and Impaired Autophagic Flux Contribute to the Lipotoxicity in the Kidney Takeshi Yamamoto,[1] Yoshitsugu Takabatake,[1] Atsushi Takahashi,[1] Tomoko Namba,[1] Jun Matsuda,[1] Satoshi Minami,[1] Tomonori Kimura,[1] Taiji Matsusaka,[2] Fumio Niimura,[3] Yoshitaka Isaka.[1] *[1]Dept of Nephrology, Osaka Univ Graduate School of Medicine, Suita, Osaka, Japan; [2]Inst of Medical Science and Dept of Molecular Life Science, Tokai Univ School of Medicine, Isehara, Kanagawa, Japan; [3]Dept of Pediatrics, Tokai Univ School of Medicine, Isehara, Kanagawa, Japan.*

Background: Excessive fat intake contributes to the progression of metabolic diseases via cellular injury and inflammation (termed lipotoxicity).

Methods: We investigated 1) the pathophysiology of lipotoxicity in the kidney proximal tubular cells (PTCs) with a focus on lysosomes and mitochondria, 2) lipid overload-mediated alterations in autophagic activity *in vivo* and *in vitro*, and 3) the effects of autophagy-deficiency on kidney morphology and function during lipid overload.

Results: High fat diet (HFD) first induced autophagy in the PTCs, which in itself mobilized phospholipids from cellular membranes to lysosomes, resulting in an accumulation of phospholipids in the enlarged lysosomes. Autophagic degradation activity progressively stagnated due to the impaired lysosomal acidification and consequent excessive lipid accumulation. Autophagy also suppressed HFD-induced mitochondrial dysfunction and inflammasome activation. However, HFD-fed mice had no capacity to further augment autophagic activity upon another pathological stress; this HFD-mediated autophagic numbness resulted in severer injury on ischemia-reperfusion. Pharmacological correction of phospholipid accumulation by eicosapentaenoic acid successfully restored autophagic flux. Finally, phospholipid accumulation in the enlarged lysosomes and impaired autophagic flux were recapitulated in the kidneys of obese patients.

Conclusions: Lysosomal dysfunction and impaired autophagic flux play the key role in the pathogenesis of lipotoxicity in the kidney. The findings provide key insights on the pathophysiology of lipotoxicity and clues to a novel treatment for obesity-related diseases.

Funding: Government Support - Non-U.S.

SA-PO358

Fatty Acids Suppress Autophagy in Renal Proximal Tubule Epithelial Cells Aala Jaberi, Ryan M. Mulhern, Angela Nolin, Steven C. Borkan, John H. Schwartz, Andrea Havasi. *Renal Section, Boston Univ Medical Center, Boston, MA.*

Background: Fatty acids are an important source of energy in renal tubular cells and have a key role in cellular signaling. However, under pathological conditions excess fatty acids promote lipotoxicity. In proteinuric states, large amounts of fatty acids carried by albumin enter proximal tubular epithelial cells by crossing both the basolateral and apical membranes. We hypothesize that fatty acid endocytosis with albumin results in tubular cell damage and suppresses macroautophagy including mitophagy, a process that maintains healthy organelles.

Methods: Autophagosomes, lysosomes, albumin and fatty acids were visualized in live cells using specific fluorescent markers. The effect of fatty acids on primary tubular cell autophagy was assessed by measuring autophagic flux, LC3-II and p62 levels. Mitochondrial morphology was visualized using confocal microscopy. Mitochondrial fusion and fission proteins were assessed by Western blot. Mitophagy was assessed by confocal imaging of mCherry-GFP-LC3 transfected tubular cells.

Results: Exposure of primary proximal tubular epithelial cells to albumin-bound fatty acids caused rapid endocytosis of these compounds and transport to both lysosomes and autophagosomes as well as decreased autophagic flux and mitophagy. Fatty acid treatment also altered mitochondrial morphology evidenced by increased mitochondrial fission and greater phosphorylation of dynamin-1 like protein (DRP-1), a mitochondrial fission protein.

Conclusions: Albumin-bound fatty acid endocytosis suppresses mitophagy in proximal tubular cells leading to decreased clearance and accumulation of fizzed, potentially toxic mitochondria. Mitochondrial dysfunction might contribute to tubular damage in proteinuric states.

SA-PO359

Synchronized Regulation of mTOR and Autophagy in Podocytes Tillmann Bork,[1] Wei Liang,[1] Kosuke Yamahara,[1] Pierre-Louis Tharaux,[2] Tobias B. Huber.[1] *[1]Dept of Nephrology, Univ Hospital Freiburg, Freiburg, Germany; [2]PARCC Paris Cardiovascular Centre, INSERM, Paris, France.*

Background: Autophagy emerged as a key mechanism to eliminate unwanted cytoplasmic materials, thereby preventing cellular damage and stress to safeguard long-lived podocytes. The atypical serine/threonine kinase mTOR (mammalian target of rapamycin) is a central regulator of cell growth and metabolism. Active mTOR signaling is a strong suppressor of autophagy in many tissues and cell lines. Podocytes however show highly activated mTOR-signaling in parallel with active autophagy. Aim of our experiments was to further elucidate the interplay of mTOR signaling and autophagy in podocytes.

Methods: Autophagy levels were monitored *in vivo* by crossing GPF-LC3 reporter mice to models of mTOR hyperactivation (Tsc1 PcKO) and mTOR loss of function (Raptor PcKO). In addition, podocyte-specific Raptor and Tsc1 KO mice were crossed to a Tomato/eGFP reporter line to efficiently isolate podocytes for primary cell culture studies. Treatment studies were performed to assess autophagic flux and dynamic changes in autophagy regulation *in vivo* and *in vitro*.

Results: Strikingly, podocytes did exhibit high basal autophagy rates independently of the mTOR activation status. There was no difference in LC3 conversion *in vivo* and no difference of the GFP-LC3 signal between Raptor and Tsc1 PcKO mice. Pharmacologic mTOR inhibition with Rapamycin increased autophagy, whereas long-term treatment showed no effect. *In vitro* and *in vivo* experiments revealed AMPK as an alternative regulator of autophagy bypassing the mTOR signaling cascade.

Conclusions: mTOR and autophagy are key regulators of podocyte function and maintenance. Our data highlight now a podocyte-specific AMPK-autophagy regulatory cascade, which allows to operate mTOR activity and high basal autophagy rates simultaneously in podocytes.

Funding: Government Support - Non-U.S.

SA-PO360

Murine Double Minute-2 Prevents Tubular Atrophy by Inhibiting p53 Overactivation-Dependent Cell Death (Podoptosis) in Tubular Cells Dana Thomasova,[1] Martrez Ebrahim,[1] Kristina Fleckinger,[1] Moying Li,[1] Helen Liapis,[2] Hans J. Anders.[1] *[1]Renal Div, Medizinische Klinik und Poliklinik IV, Klinikum der Univ München, Munich, Germany; [2]Dept of Pathology & Immunology, Washington Univ School of Medicine, St. Louis, MO.*

Background: The E3-ubiquitin ligase MDM2 is a non-redundant element of NF-κB signaling and the master negative regulator of tumor suppressor gene p53. We recently showed that MDM2 blockade can suppress renal damage in the early post-ischemic injury phase via NFkB modulation but MDM2 inhibition impairs subsequent tubular regeneration by p53-mediated cell cycle arrest. However, the role of the robust constitutive MDM2 expression in non-damaged tubular cells is unknown.

Methods: We generated and characterized doxycycline-inducible tubular-specific MDM2-knockout mice (Pax8-rtTACre/MDM2flox). In vitro we knocked-down MDM2 and p53 by siRNA.

Results: MDM2 depletion in a tubular cell line or in primary tubular cells caused tubular cell death, which could be rescued by co-deletion of p53. The analysis of Pax8-rtTACre/MDM2flox mice showed significant MDM2 decrease and p53 increase compared to controls by day 8 of doxy treatment. The tubular damage markers such as NGAL, TIMP2 or KIM-1 were also highly up-regulated. The histological analysis of tubular-MDM2 KO mice revealed progressive tubular cells swelling, their loss, tubular atrophy and granular casts. The proximal tubules were affected the most. Ultrastructural tubular changes such as vacuolation and cytoplasmic and mitochondrial swelling were prominent. The immunostaining showed massive upregulation of p53 in the tubular compartment. The tubular damage was associated with oliguria and increase of BUN and plasma creatinine from day 6 on. The tubular cell loss in this model was not sensitive to the pan-caspase inhibitor ZVAD-FMK treatment, excluding apoptosis and pyroptosis as modes of the tubular cell death due to the p53-overactivation (podoptosis). The pathology was rescued by co-deletion of MDM2 and p53 genes, confirming the p53-dependency.

Conclusions: In contrast to the pathogenic role of MDM2 in early phase of tubular injury in postischemic kidney, tubular cells need MDM2 during homeostasis to prevent podoptosis.

SA-PO361

Heme Oxygenase-1 Protects Proximal Tubule Epithelial Cells from Ferroptosis Oreoluwa O. Adedoyin,[1] Ravindra Boddu,[1] Amie Traylor,[1] Jeremie M. Lever,[1] James George,[2] Anupam Agarwal.[1,3] *[1]Div of Nephrology, Dept of Medicine, Univ of Alabama at Birmingham, Birmingham, AL; [2]Div of Cardiothoracic Surgery, Dept of Medicine, Univ of Alabama at Birmingham, Birmingham, AL; [3]Birmingham VA Medical Center, Birmingham, AL.*

Background: Ferroptosis is an iron-dependent form of programmed cell death that occurs in models of acute kidney injury (AKI) in vitro and in vivo. A potential source of iron for this process is HO-1, a cytoprotective enzyme that is robustly induced in renal proximal tubules in AKI where it generates CO, biliverdin, and iron. Therefore, we tested the hypothesis that HO-1 plays a role in regulation of ferroptotic cell death in renal proximal tubular epithelial cells (PTECs).

Methods: Immortalized PTECs obtained from HO-1$^{+/+}$ and HO-1$^{-/-}$ mice were treated with erastin (ferroptosis inducer), and analyzed for morphological changes and cellular metabolic activity. Induction of HO-1 in response to erastin treatment, and following co-treatment with anti-oxidants, iron, or an iron chelator were determined using qPCR and western blotting.

Results: Treatment of HO-1$^{+/+}$ PTECs with erastin resulted in a dose-dependent increase in HO-1 expression, as well as significant inhibition of cellular metabolic activity compared to vehicle-treated controls (mean ± SEM, control: 100±1.8; erastin 0.1μM: 91.6±2.5; erastin 1μM: 58.3±0.9, and erastin 10μM: 62.5±1.8%, $p<0.0001$, n=3/group). Iron supplementation using ferric ammonium citrate in cells treated with 1μM erastin further reduced cell viability from 54.7±1.5% to 38.4±1.5% ($p=0.0012$). Interestingly, co-treatment with 1μM hemin (HO-1 inducer), 0.1mM deferoxamine (iron chelator), or 0.1M N-acetyl-L-cysteine (glutathione replenisher) significantly increased cell viability. To test if ferroptosis is dependent on HO-1, HO-1$^{-/-}$ PTECs were treated with erastin. This resulted in increased sensitivity to ferroptosis (mean ± SEM, control: 100±3.1; erastin 0.1μM: 68.7±2.2; 1μM: 44.0±0.7, and 10μM: 53.8±1.9 %, $p<0.0001$, n=3/group).

Conclusions: HO-1 induction appears to attenuate erastin-induced ferroptotic cell death in renal epithelial cells; therefore, it may serve as a viable therapeutic target for intervention in AKI.

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SA-PO362

Wnt9a Accelerates Renal Fibrosis Through Induction of Tubular Senescence Lili Zhou, Congwei Luo. *Dept of Nephrology, Nanfang Hospital, Southern Medical Univ, Guangzhou, Guangdong, China.*

Background: As a key factor, Wnt is involved in pathogenesis of kidney diseases. However, the underlying mechanism is unknown. In this study, we detected the potential role of Wnt9a in tubular cell senescence and renal fibrosis.

Methods: Wnt9a was tested in mouse models of ADR nephropathy, UUO, and ischemia-reperfusion. The co-localization of Wnt9a and a biomarker for senescence, p16, was checked in sequential sections. In unilateral ischemic/reperfusion injury, ectopic overexpression or knockdown of Wnt9a was respectively induced.Fibrosis and tubular senescence were detected. To further confirm the effect of Wnt9a in senescence, 2 and 24-month-old mice were performed the surgery of UIRI, and a vector encoding the secreted form of Klotho was administrated to inhibit Wnt9a. In cultured tubular epithelial cells (HK-2), cell cycle and senescence-related gene were determined by overexpression of Wnt9a. In some cells, siRNA to Wnt9a was used in aristolochic acid (AA)-induced senescence. The cell-cell communication between fibroblasts and tubular cells was also examined.

Results: Wnt9a was upregulated in UUO and ADR nephropathy, and mainly located in tubules. Wnt9a overexpression was correlated with tubular senescence and renal fibrosis, as detecting by $p16^{Ink4A}$, Kim-1, Klotho and fibronectin. The exogenous expression of Wnt9a dramatically promoted renal fibrosis, deteriorated renal function, and induced tubular senescence. To the contrary, knockdown of Wnt9a protected renal fibrosis and tubular senescence. Compared to young mice, Wnt9a was remarkably upregulated in aging mice. Using cultured cell line HK-2, we found Wnt9a induced cell cycle arrest and upregulation of senescence-related gene $p16^{Ink4A}$, ARF and p21. However, siRNA to Wnt9a significantly inhibited AA-induced S-phase arrest and senescence-related gene expression. Wnt9a also directly induced fibroblasts proliferation, or indirectly induced secretion of matrix protein through conditioned-medium from cultured tubular cells. On the other hand, Wnt9a conditioned-medium from fibroblasts promoted senescence in tubular cells.

Conclusions: These results suggest that Wnt9a accelerates renal fibrosis through induction of tubular senescence.

Funding: Government Support - Non-U.S.

SA-PO363

The Effects of Periostin on the Aging Process Sehoon Park,[1] Jung Nam An,[2,3] Eun Nim Kim,[4] Sunhwa Lee,[1] Jinhyuk Kim,[2] Seung Hee Yang,[1] Dong Ki Kim,[1] Yun Kyu Oh,[2] Chun Soo Lim,[2] Yon Su Kim,[1] Jung Pyo Lee.[2] *[1]Dept of Internal Medicine, Seoul National Univ Hospital, Seoul, Korea; [2]Dept of Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Korea; [3]Dept of Critical Care Medicine, Seoul National Univ Boramae Medical Center, Seoul, Korea; [4]Dept of Internal Medicine, The Catholic Univ of Korea, Seoul, Korea.*

Background: Periostin, a matricellular protein, has been reported in diverse processes and pathologies in tissue remodeling through the promotion of adhesion, cell survival, cellular dedifferentiation, and fibrogenesis. However, its role in aging process is unknown.

Methods: We investigated expressions of periostin in normal human kidney tissues classified by age (20, 40, and 60 years) and in mice kidney tissues of wild type (WT) C57BL/6 mice or *Postn null* (*Postn*$^{-/-}$) mice aged 24 months. In addition, chemistry data including serum creatinine and histopathology findings of WT mice or *Postn null* mice classified by age (young vs. aged; 2-months old vs. 24-months old) were examined.

Results: Periostin expressions in normal human kidney tissues were significantly different according to the age. Intrarenal periostin expressions were prominent in the patients aged 60 years compared to those aged 20 years. *In vivo*, the gross appearance and the kidneys of aged WT mice were bigger and heavier than young WT mice. Serum creatinine levels were also higher in the aged WT mice compared to those in the young WT mice. However, all these changes were diminished in the aged *Postn null* mice; serum creatinine levels were considerably lower in aged *Postn null* mice than in aged WT mice. Apparent tubular atrophic changes, interstitial fibrosis, and collagen fiber deposition which were prominent in the aged WT mice than in the young WT mice, were remarkably alleviated in aged *Postn null* mice. Furthermore, the expressions of periostin were also attenuated in aged *Postn null* mice compared to in aged WT mice.

Conclusions: Aging resulted in morphologic/physiologic changes and increased expressions of periostin. Periostin ablation could have protective effects in aging process.

SA-PO364

Cost-Effectiveness of Eculizumab Treatment after Kidney Transplantation in Atypical Hemolytic Uremic Syndrome Jan A.J.G. van den Brand, Jacobien Verhave, Eddy M. Adang, Jack F. Wetzels. *Radboud Univ Medical Center, Nijmegen, Netherlands.*

Background: Kidney transplantation in patients with atypical hemolytic uremic syndrome (aHUS) is frequently complicated by recurrence of aHUS, often resulting in graft loss. Eculizumab prophylaxis prevents recurrence, improving graft survival. An alternative treatment strategy has been proposed where eculizumab is administered upon recurrence. We combined available evidence and performed a cost-effectiveness analysis of these competing strategies.

Methods: We created a decision tree with treatment strategies for aHUS patients with end stage renal disease (ESRD): *dialysis treatment*; *kidney transplantation*; kidney transplantation with *eculizumab upon recurrence* of aHUS; and kidney transplantation with *lifelong eculizumab* prophylaxis. We assumed that transplantation was performed with a kidney from a living donor. We performed a Markov analysis to compare cost-effectiveness of the strategies.

Results: The predicted probability of recurrence in the *kidney transplantation* and *eculizumab upon recurrence* strategies was 23% and 37% after 3 and 12 months. *Kidney transplantation* was the least costly alternative. By comparison, *dialysis* was more costly and resulted in fewer Quality Adjusted Life Years (QALYs) gained, and was therefore considered inferior to *kidney transplantation*. *Eculizumab upon recurrence* was more costly than *kidney transplantation* without eculizumab, but resulted in more QALYs gained. The incremental cost effectiveness ratio (ICER) was $42,961 per QALY. *Lifelong eculizumab* was even more costly, and gave an ICER of $63.1 million compared to *eculizumab upon recurrence*.

Strategy	Costs ($)	QALYs gained	ICER (Δ$/ΔQALY)
Kidney transplantation	425,032	6.52	
Dialysis	447,296	2.57	dominated
Eculizumab upon recurrence	559,499	9.65	42,961
Lifelong eculizumab	6,126,944	9.74	63,107,200

Conclusions: *Kidney transplantation* was more cost-effective than *dialysis* to treat ESRD due to aHUS. However, *Eculizumab upon recurrence* was more cost-effective than *kidney transplantation*. Gain in QALYs in the *lifelong eculizumab* strategy was offset by extremely high costs. Therefore, *eculizumab upon recurrence* of aHUS was more acceptable.

SA-PO365

Kidney Transpalnt in Atypical HUS: A Single Center Experience Gianluigi Ardissino,[1] Donata Cresseri,[1] Antenore Giussani,[1] Stefania Salardi,[1] Francesca Tel,[1] Sara Testa,[1] Michela Perrone,[1] Fabio Paglialonga,[1] Mirco Belingheri,[1] Martina Sgarbanti,[1] Lucrezia Furian,[2] Angela Nocco,[1] Silvana Tedeschi,[1] Piergiorgio Messa.[1] *[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; [2]Univ Hospital, Padova , Italy.*

Background: For decades, atypical hemolityc uremic syndrome (aHUS) has been considered a controindication to kidney transplant (KTx) for the very high risk of disease recurrence. The availability of Eculizumab (ECU) has made it possible to safely address patients (pts) with aHUS to KTx but the best approach to treatment (Rx) as to timing of 1st dosing, schedule, possibility of Rx discontinuation and pts' monitoring, is not well established.

Methods: During the past decade, a total 20 pts (6 children) with aHUS were followed for KTx at our Center (in 3 KTx had been performed elsewhere). Five pts had a previous KTx. The median time on RRT prior to KTx was 8.5 years. One pt has received the graft from a living-related donor. CFH-related disease (n:13) was the most common etiology followed by mutations on CFI (n:4), C3 (n:1), MCP (n:1) and Idiopathic (n:1). Based on the strategy used to prevent disease relapse before and after KTx, 3 groups can be identified (some pts were exposed to multiple preventive strategies): A: no prophylaxis (n:7); B: plasmaexchange/plasmainfusion (n:5); C: ECU (n:14).

Results:

	Group A	Group B	Group C
Etiology (CFH-related/other)	3/4	5/0	12/2
Cumulative observation period on KTx (yrs)	47	7	44
Relapse rate (event/patient/10 yrs)	0.4	1.4	0
Graft loss due to relapse	1	0	0
Graft loss for other causes	1	1	1

Pts in group B were switched to ECU once available. One pt discontinued ECU as soon as AntiCFHAb were no longer detectable. Based on complement activity targeted to <30%, out of the 12 pts currently on ECU, 4 are regularly receiving the infusion every 3 weeks and 8 every 4 weeks.

Conclusions: Our experience favours the prophylactic use of ECU in pts undergoing KTx with a history of aHUS. We recommend complete characterization (as to disease etiology) pre-KTx and that maintenance Rx is continued lifelong.

SA-PO366

Kidney Transplant Discussion Timing and Subsequent Wait Listing in a National Cohort Nancy G. Kutner,[1] Yijian Huang,[2] Rebecca H. Zhang.[2] *[1]Rehabilitation Medicine, Emory Univ, Atlanta, GA; [2]Biostatistics, Emory Univ, Atlanta, GA.*

Background: Patient awareness and understanding of kidney transplantation (KT) are widely shared goals, but variables associated with timing and outcomes of KT discussion merit ongoing study.

Methods: The USRDS CDS survey of 1634 incident dialysis patients (18+, median vintage 4 mos) from 296 randomly selected clinics asked "Was kidney transplantation discussed with you before you started your regular treatment for kidney failure?" and, later in the interview, "Has kidney transplantation been discussed with you since your started dialysis?" Patient characteristics, early nephrology care, whether "informed of KT options," and wait-listing (WL) events were identified in USRDS files. Excluding 60 patients with pre-dialysis WL, the adjusted association of KT discussion timing with WL (333 events, median 21.7 mos follow-up) was examined in Cox models.

Results: KT discussion was reported (a) Pre- and post-dialysis by 37.3% (b) Post-dialysis only by 25.4% (c) Pre-dialysis only by 12.5% (d) Not at all by 24.8%. Compared with no discussion, discussion post-dialysis only was associated with greater likelihood of WL (HR 3.78 [95% CI 2.28-6.25]), but patients with both pre- and post-dialysis discussion had even greater WL likelihood (HR 4.20 [95% CI 2.58-6.84]). Pre-ESRD nephrology care was highest (82.2%) in the duel exposure group. Patients with only pre-dialysis discussion had no increased likelihood of WL. Overall, 75% of patients reported exposure to KT discussion *at one or both* time points, similar to the proportion reported by providers on CMS Form-2728 as informed of KT options (72%).

Conclusions: Consistent with other research, perceived KT discussion after dialysis start was associated with greater likelihood of subsequent WL, but pre-dialysis plus post-dialysis exposure was associated with even greater likelihood. Patient/provider discrepancy in reported KT information exposure was minimal when patient-reported exposure included pre- and post-dialysis experience. The content as well as timing of reported "KT discussion" and "informed of KT options" are important variables in ongoing efforts to advance the understanding of effective KT education.

Funding: NIDDK Support

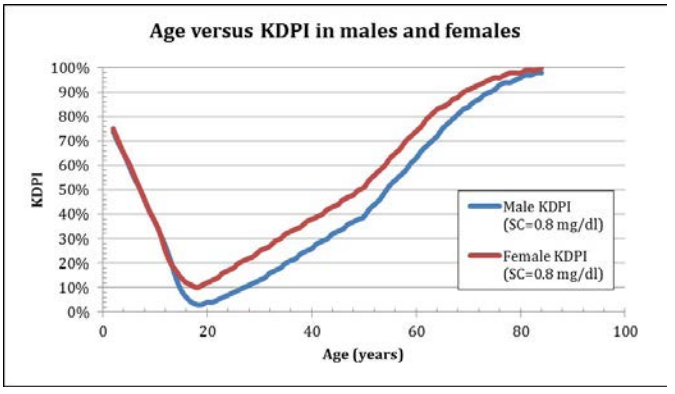
SA-PO367

New KAS May Inappropriately Limit Access of Pediatric Donor Kidneys to Pediatric Recipients Based on KDPI Allison Peng,[1] Daniel Elchediak,[1] Meera Gupta,[1] Sandra Amaral,[2] Susanna Matsen Nazarian,[1] Matthew H. Levine.[1] *[1]Surgery, Univ of Pennsylvania/Children's Hospital of Philadelphia, Philadelphia, PA; [2]Nephrology, Children's Hospital of Philadelphia, Philadelphia, PA.*

Background: The 2014 OPTN Kidney Allocation System (KAS) prioritizes allografts with Kidney Donor Profile Index (KDPI) ≤ 35 to pediatric recipients. Most donors < age 12 have KDPI over 35 even with ideal function. We sought to determine if transplants using such grafts differed in outcomes compared to ideal KDPI ≤ 35 grafts.

Methods: UNOS data from first deceased donor renal transplants 2000-2010 with follow-up to 3/31/2014 were used to compare graft survival among donors and recipients across age groups, using Kaplan Meier. Public Health Service (PHS) high risk comparisons used Pearson's chi-square. Donor height and weight median from US growth charts for age with no additional risk parameters were used to calculate KDPI.

Results: Pediatric recipients (listed age 0-17) had equivalent 1,3, 5, and 10 year graft survival when transplanted with grafts from donors with donors age 3-11 years with KDPI > 35 compared to older KDPI ≤ 35 donors (p=0.97). Young adult recipients (age 18-40) also had no different graft survival with these age 3-11 grafts vs. ideal grafts with KDPI ≤ 35 (p=0.51). Grafts from donors aged > 46 years with KDPI > 35 had diminished 5 and 10 year graft survival in both pediatric and young adult recipients vs. other donor groups. Donors age 12-46 years with KDPI ≤ 35 were more likely to be PHS high risk than donors age 3-11 (11% vs 1.5%, p < 0.001).



Conclusions: There is no evidence of excess graft loss for donors age 3-11 compared to those with KDPI ≤ 35 and these donors convey less PHS high risk exposure. These kidneys are not prioritized for allocation to children based on KDPI in the new KAS, thereby potentially limiting high quality kidney graft access for children with ESRD.

Funding: NIDDK Support

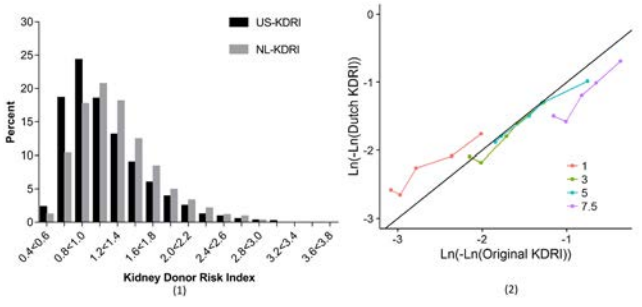
SA-PO368

Validation, Calibration and Model Revision of the Kidney Donor Risk Index Scoring System of a Deceased Donor Kidney for Transplantation in the Netherlands Hessel Peters-Sengers,[1] Martin B.A. Heemskerk,[2] Jaap Homan Van Der Heide,[1] Stefan P. Berger,[3] Frederike J. Bemelman.[1] *[1]AMC, Amsterdam, Netherlands; [2]Dutch Transplant Foundation, Leiden, Netherlands; [3]UMCG, Groningen, Netherlands.*

Background: The prognostic Kidney Donor Risk Index (KDRI)—developed and validated (c-statistic 0.62) in the US—is a widely used tool to predict transplant outcome of a deceased donor kidney at time of organ offer.

Methods: We aimed to externally validate the KDRI as proposed by Rao et al. (2009), containing 10 donor and 4 transplant factors. We used the Dutch Organ Transplantation Registry to include recipients (≥18y), transplanted from 2002 to 2012 with a first brain-death or circulatory-death donor kidney (≥18y). Outcome of graft survival was defined as time from transplantation to graft failure or death.

Results: Among 2554 transplanted kidneys, the median of the KDRI was higher compared with the US (1.05 *vs*. 1.21, see figure 1). Kidneys in the highest KDRI quintile (1.45+) had an adjusted 5-year graft survival of 68.9%, whereas the lowest KDRI quintile (<0.79) showed 84.7% survival. At year 1, the time-dependent (t) ROC of the KDRI showed 0.65 discriminative ability. At year 3, year 5, and year 7.5, the tROC was maintained (0.63;0.65;0.67, respectively). There was need to recalibrate the baseline hazard (see figure 2): graft failure in the first year was higher in the Dutch cohort, but lower after 7.5 years compared with the US. The calibration slope was 1.24 and higher than 1 (p=.012), indicating improved discrimination in the Dutch cohort. The revised tROC was improved at year 1 (0.67), and year 3 (0.67).



Conclusions: The NL-KDRI distinguished donors with low and high KDRI scores (<1 *vs.* >1.45) better than middle-ranged scores. We corrected the baseline risk and re-calibrated donor factors from the KDRI into the NL-KDRI. The discriminative ability of the NL-KDRI performs at least as well as in the US, and is useful for decision-making regarding the acceptance of a kidney organ offer.

SA-PO369

Impact of the New Kidney Allocation System on the Transplant Rate of HLA Sensitized Patients. A Single Center Experience Maria Ajaimy, Adriana Colovai, Enver Akalin. *Montefiore Transplant Center, Albert-Einstein College of Medicine.*

Background: Increasing access to transplantation of difficult-to-match patients was a key goal of the new kidney allocation system (KAS) implemented on Dec 4, 2014. In this study, we evaluated the impact of the new KAS on the transplantation rate of HLA sensitized candidates at our center.

Methods: During Jan 1 - Dec 4, 2014 (pre-KAS interval) and Jan 1 - Dec 4, 2015 (post-KAS interval), immunologic risk was assessed prior to transplantation using the same approach. Unacceptable HLA antigens were defined using the following cutoffs: 5000 MFI for HLA-A, -B and -DR, and 10,000 MFI for HLA-C and -DQ antigens. Deceased donor cross-matches (XMs) were performed by flow cytometry and complement dependent cytotoxicity (CDC). Patients were transplanted based on a negative flow and/or negative CDC XM.

Results: A 65% increase in total number of deceased donor cross matches performed during post-KAS (1188) and pre-KAS (715) intervals was observed, respectively. The percentage of XMs performed for sensitized patients (cPRA>0%) increased from 19% pre-KAS to 26% post-KAS (p<0.0001). A significant increase in the rate of transplantation of sensitized patients was observed. Out of 115 patients who received deceased donor kidney transplantation pre-KAS, only 16 (14%) patients had cPRA>0%. Post-KAS, out of 129 transplanted patients, there were 34 (25%) with cPRA>0% (p<0.0001). The percent of sensitized patients who received transplantation increased from 5% to 8% in the cPRA 50-79% subgroup, from 4% to 5% in the 80-98% subgroup, and, remarkably, from 0% to 8% for patients with cPRA>98%. This increase was balanced by a decrease in the percent of non-sensitized recipients (from 86% to 75%, pre- and post-KAS, respectively) and recipients with cPRA 0-49% (from 4% to 3%, respectively). At a median 8 months follow-up, the patient (94% vs. 94%) and graft (91% vs. 91%) survival and acute rejection rate (4% vs. 6%) were similar in patients with 0% cPRA compared to patients with cPRA>0%, respectively, in the post-KAS era.

Conclusions: The new KAS facilitated a marked increase in the transplant rate of sensitized candidates at our center.

SA-PO370

Employment and Transplant Status among End-Stage Renal Disease Patients Receiving Dialysis Deborah S. Evans,[1] Duane V. Dunn,[1] Shelley Murphy,[1] Kristine Robinson,[1] Rich Mutell,[2] Paul J. Broughton,[2] Deborah A. Benner.[1] *[1]DaVita Inc, Denver, CO; [2]Apex Health Innovations, Simi Valley, CA.*

Background: For patients with end-stage renal disease receiving dialysis, receipt of a transplant offers the best possible long-term treatment option. However, qualification for placement on the active transplant list requires a high level of patient motivation and engagement. Here, we sought to characterize transplant status among employed versus unemployed patients of a large dialysis organization (LDO).

Methods: Data on patient employment and transplant status were derived from LDO electronic health records. Employment and transplant status information is collected by LDO social workers during the course of routine care. Employment status categories considered were: employed (regular full-time, regular part-time, or per diem), unemployed, retired, and other. Transplant status categories considered were: active, delisted, denied, in work-up, inactive, no longer interested, on hold, and pending patient follow-up.

Results: As of May 2016, there were 91,231 active patients with available transplant and employment status information in the LDO database. Of these, 17,816 (19.5%) were employed, 28,185 (30.9%) were unemployed, and 24,352 (26.7%) were retired. Compared to unemployed patients, employed patients were more likely to have transplant status listed as active (34% vs 19%) and less likely to have transplant status listed as denied or pending patient follow-up (11% vs 20% and 20% vs 25%, respectively). Stratification of patients on the basis of age revealed that trends were conserved across age groups.

Conclusions: Among LDO patients who had expressed interest in transplant, those who were employed were more likely to progress through the qualification steps to active transplant status than those who were unemployed. Many of the factors identified by dialysis patients as barriers to working (eg, transportation issues, depression/lack of motivation), may also impede a patient's ability to successfully navigate the transplant qualification process. Conversely, positive outcomes of employment, such as improved financial status, may facilitate process completion.

Funding: Pharmaceutical Company Support - DaVita Inc.

SA-PO371

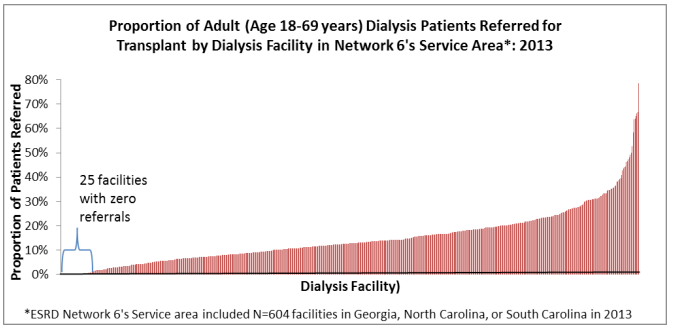
Variation in Dialysis Facility Referral for Kidney Transplantation in the Southeastern United States Rachel E. Patzer,[1] Jennifer C. Gander,[1] Laura Plantinga,[1] Amber M. Reeves-Daniel,[2] Matthew Jay Ellis,[3] Stephen O. Pastan.[1] *[1]Emory Transplant Center, Atlanta, GA; [2]Wake Forest Baptist Medical Center, Winston-Salem, NC; [3]Duke Univ, Durham, NC.*

Background: While variability in dialysis facility kidney transplant (KTx) referral between dialysis units has been studied in one state (Georgia), regional, facility-level data for KTx referral has not been examined.

Methods: We analyzed ESRD Network 6 data on KTx referrals from dialysis facilities in 2013, collected from 8 transplant centers in Georgia, North Carolina, and South Carolina. We linked with the 2012 Dialysis Facility Report data to obtain dialysis facility

characteristics. Multivariable-adjusted linear regression models were used to identify characteristics associated with low KTx referral (=% of prevalent dialysis patients aged 18-69 years referred in 2013).

Results: Among 604 dialysis facilities, the median facility-level percentage of adult prevalent dialysis patients referred for transplant in 2013 was 12.7% (IQR: 7.2%-19.6%; range: 0% to 78.6%); 25 facilities (4.1%) referred no dialysis patients.



In multivariable models, factors associated with lower facility referral included higher facility-level percentage of patients not being informed of transplant as a treatment option and higher percentages of patients who were smokers, had congestive heart failure, and had longer times on dialysis (all $p<0.05$). Facility profit status, number of staff, and the percentages of patients who were black or had employer insurance were not associated with facility–level referral.

Conclusions: The observed facility variability in transplant referral suggests the need to use transplant referral as a quality measure for dialysis facilities that could be tracked nationally.

Funding: Other NIH Support - National Institutes on Minority Health and Health Disparities

SA-PO372

Willingness of Canadian ESRD Patients to Consider Transplant Tourism

Gurleen Gill, Caren L. Rose, John S. Gill, Adeera Levin, Jagbir Gill. *Medicine-Nephrology, Univ of British Columbia, Vancouver.*

Background: Transplant tourism refers to travel for transplantation that involves organ trafficking and/or transplant commercialism, and is associated with poor outcomes after transplantation. While characteristics of transplant tourists have been described, there are no data on end-stage renal disease (ESRD) patients who may be at high risk for engaging in this practice.

Methods: We surveyed Stage V chronic kidney disease (CKD) and dialysis patients in British Columbia, Canada to determine their willingness to travel outside of Canada and purchase a kidney.

Results: Of 592 patients surveyed, 342 (58%) were willing to travel for transplantation, with 149 (25%) strongly willing to travel. Figure 1 shows the willingness of patients to travel for transplantation under different circumstances. N=354 (60%) were willing to travel if they had a related living donor in another country or could be placed on an official transplant list in another country, while 143 (24%) were willing to pay for the kidney on top of paying the medical costs of the transplant. Thirty-three percent were willing to travel even if they knew the donor was an executed prisoner, but only 4% admitted that they were willing to break the law to obtain the transplant.

Patients that were willing to travel and purchase a kidney included a higher proportion of patients that were younger, male, of Asian ethnicity, had higher median household income, had initiated dialysis within the last year, and were less knowledgeable about the risks and legality of transplant tourism.

Conclusions: Nearly one quarter of ESRD patients surveyed were willing to purchase a kidney outside of Canada, and may be at high risk to engage in transplant tourism. Educating at- risk patients (particularly those who recently started dialysis) about the legal and medical risks of transplant tourism may help to deter this practice.

Funding: Government Support - Non-U.S.

SA-PO373

Histo-Molecular Assessment of Pre-Implantation Biopsies Demonstrates That Many Discarded Kidneys Are Similar to Successfully Transplanted Kidneys in Other Center

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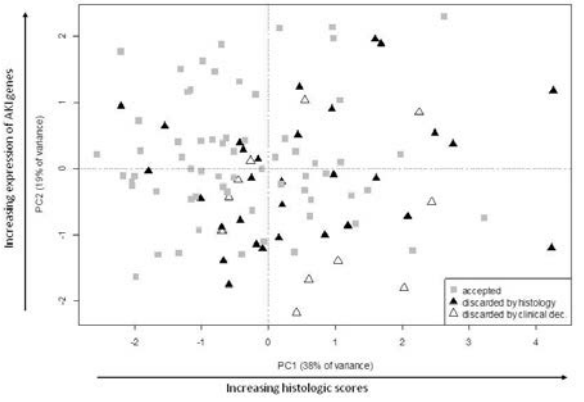
Background: Increasing numbers of kidneys from older brain dead donors (DBD) are considered for transplantation. Many of these kidneys are discarded based on conventional (clinical or histologic) features. We previously observed that 50% of DBD kidneys discarded by conventional features had similarly low expression of Acute Kidney Injury (AKI) associated genes as those that were transplanted. Here, we are asking whether the combined histology and expression of AKI genes, that also are associated with transplant fibrosis, can demonstrate that kidneys discarded by conventional features are indeed similar to kidneys accepted for transplantation, using discarded and accepted kidneys from different centers.

Methods: We compared 43 discarded kidneys in one USA center to 64 accepted kidneys transplanted in one European center, all from older DBD, using Principal Component Analysis. All 64 functioned and 63 were surviving at 3 months post transplant. Following variables were used: summarized expression of AKI genes and histologic lesion scores: glomerulosclerosis, fibrous intimal thickening, fibrosis/atrophy and arterial hyalinosis.

Results: The Principal Component 1 (PC1) was associated with histologic lesions, while PC2 component (PC2) represented the summarized expression of AKI genes. Both PC1 and PC2 component scores did not show clear separation of discarded kidneys from the accepted kidneys (figure 1), also confirmed by the density plot analysis of PC1 and 2 scores.

Figure 1. Principal Component Analysis of discarded and accepted kidneys using histo-molecular assessment.



Conclusions: Combined histo-molecular features were not able to separate discarded kidneys in one center from the kidneys accepted and functioning in another center. We conclude that the current criteria for discarding kidneys based on conventional features, particularly histology, need to be reassessed.

SA-PO374

Requiring Demonstration of Persistently Low Renal Function Meaningfully Changes Timing of Kidney Transplant Waitlist Qualification

Benjamin J. Lee,[1] Charles E. McCulloch,[2] Barbara A. Grimes,[2] Sindhu Chandran,[1] Cynthia Delgado,[1] Chi-Yuan Hsu.[1] *[1]Medicine, Div of Nephrology, UCSF, San Francisco, CA; [2]Epidemiology and Biostatistics, UCSF, San Francisco, CA.*

Background: According to U.S. Organ Procurement and Transplantation Network policies, "measured ... creatinine clearance level or calculated glomerular filtration rate (Cockcroft-Gault or other reliable formula) less than or equal to 20 mL/min" triggers start of time-accrual on the kidney transplant waitlist. Since only a single CrCl or eGFR ≤20 is needed, the policy implicitly assumes that decline in renal function is monotonic (Mitch et al, Lancet 1976), but recent studies demonstrate that this is often not the case (Li et al, AJKD 2012).

Methods: To assess whether requiring patients to demonstrate renal function "persistently ≤20" would change waitlist qualification, we compared time to qualification as defined by 2 different rules: 1) at first eGFR ≤20, regardless of subsequent measurements (current paradigm) and 2) at second eGFR ≤20 given a prior eGFR ≤20 at least 3 months before (akin to the definition of CKD). We applied the CKD-EPI equation to serial creatinine measurements from 3 patient cohorts: 1 of waitlisted patients at a major U.S. academic center and 2 national, multicenter cohorts of CKD patients (the NIH-sponsored AASK and MDRD studies). Kaplan-Meier curves for the two rules were constructed for each cohort and used to estimate median times to qualification.

Results: Requiring patients to demonstrate eGFR ≤20 on two occurrences at least 3 months apart delays median time to qualification on the order of 0.5 to 2 years.

		Median Times to Waitlist Qualification (Days)	Difference between Rule 1 and Rule 2 (Years)
UCSF Cohort	1st eGFR ≤20	379	2.1
	2nd eGFR ≤20	1149	
AASK Cohort	1st eGFR ≤20	449	1.5
	2nd eGFR ≤20	988	
MDRD Cohort	1st eGFR ≤20	122	0.6
	2nd eGFR ≤20	356	

Conclusions: Requiring a single CrCl or eGFR ≤20 for waitlist qualification among non-dialysis-dependent patients may be insufficient. Demonstration of persistently low renal function may more appropriately identify when patients should qualify for the waitlist and meaningfully change time to waitlist qualification.

Funding: Other NIH Support - K24

SA-PO375

Health Disparities Impact Transplant Referral Antonia Harford,[1] S. Paine,[2] R. Schrader,[2] D. Miskulin,[3] Ambreen Gul,[2] Philip Zager.[1,2] *[1]Nephrology, UNM, Albuquerque, NM; [2]DCI, Albuquerque, NM; [3]Tufts, Boston, MA.*

Background: Kidney transplantation (TXP) offers longer life expectancy and better quality of life than any dialysis modality and is the treatment of choice for ESRD patients. We postulated that racial/ethnic and demographic factors may be associated with transplant related health disparities, which significantly impact referral, refusal, wait-listing and ultimately TXP rates.

Methods: To explore this hypothesis we studied 11,950 dialysis patients under age 70, treated in 230 facilities in 2015 operated by DCI, a large not-for-profit provider. We used DCI's MIS to abstract demographic data and TXP status. We constructed a random intercept, multinomial logistic regression model using Proc Glimmix in SAS with adjustment for clustering within facilities.

Results: Overall, 34.5% were referred but not yet listed, 19.3% refused referral, 23.8% were not referred, 18.7% were waitlisted (WL) and 3.7% received a transplant. The odds ratios for each step in the process leading to TXP by patient characteristics are shown. Females were more likely than males to refuse evaluation but if referred they were just as likely to progress to being WL or TXP. African Americans were more likely than whites to be referred but were less likely to progress to WL/TXP. Asians were less likely than whites to refuse. Extremes of BMI (<22 or ≥37), in-center dialysis, and age ≥63 years were associated with less likely to be referred and more likely to refuse referral.

Effect	Not Referred	Refused	Waitlisted/TXP
Females vs. Males	1.11	1.22*	1.05
African Americans vs. Whites	0.84*	0.89	0.86*
Asians vs. Whites	0.61*	0.47*	1.54*
Native Americans vs. Whites	0.98	0.88	0.61*
Age ≥ 63 vs. 50-62	1.41*	1.61*	0.89
BMI < 22 vs. 22-36	1.31*	1.20*	0.68*
BMI ≥ 37 vs. 22-36	1.56*	1.17*	0.48*
Place In-center vs. Home	2.02*	1.54*	0.57*
* P < 0.05			

Conclusions: Racial/ethnic and demographic factors are associated with significant TXP related health disparities leading to decreased referral. Dialysis facilities should have increasing roles in educating patients about TXP, referring patients and facilitating completion of evaluation and listing.

SA-PO376

Risk Factors for Preterm Birth in Kidney Transplant Recipients Swati Rao,[1] Fengzheng Zhu,[2] Dawn Armenti,[3] Lisa Coscia,[3] Mythili Ghanta,[1] Iris J. Lee,[1] Avrum Gillespie,[1] Serban Constantinescu,[1,3] Michael J. Moritz.[3,4] *[1]Nephrology, Temple Univ; [2]Fox School of Business, Temple Univ; [3]Gift of Life Inst; [4]Lehigh Valley Health Network.*

Background: The rate of preterm birth (<37 wks) in kidney transplant (KT) recipients is 5 times higher than general population (10%), but the risk factors have not been well quantified.

Methods: We analyzed 1374 pregnancies which resulted in live birth in 948 KT recipients from the National Transplantation Pregnancy Registry using logistic regression.

Results: The mean conception age was 29.7 yrs, gestational age was 36 wks, and birth weight was 2567g. The preterm birth rate was 49%. Recipients with HTN, DM, pre-eclampsia, acute rejection during pregnancy, higher serum creatinine pre-conception and during pregnancy had significantly increased risk of prematurity. Longer interval from transplant to conception was associated with higher odds for full term birth.

	Preterm Birth (< 37 weeks)				
	No n=701	Yes n=673	P value	Odds Ratio	P value
Pre-conception characteristics					
Age at conception, yrs, median	29.9	29.6	NS		
HTN, %	38.0	51.4	<0.001	1.72	<0.001
DM, %	2.8	6.5	0.001	2.41	0.002
Interval from transplant to conception, yrs %			<0.001		
<2	19.6	24.1		1	
2-5	32.8	38.5		0.95	0.751
5-10	32.2	24.9		0.62	0.003
>10	15.4	12.5		0.65	0.025
Pre-conception serum creatinine, mg/dl, median (range)	1.17 (0.50-4.00)	1.34 (0.58-4.40)	<0.001	2.99	<0.001
Deceased donor, %	35.74	43.75	0.002	1.39	0.003
Pregnancy characteristics					
HTN, %	41.8	60.4	<0.001	2.12	<0.001
DM, %	5.2	11.5	<0.001	2.37	<0.001
Preeclampsia, %	19.6	40.5	<0.001	2.80	<0.001
Serum creatinine, mg/dl, median (range)	1.17 (0.50-4.90)	1.56 (0.60-10.90)	<0.001	3.10	<0.001
Acute rejection, %	0.3	1.8	0.007	6.16	0.018

Conclusions: Graft function and co-morbid conditions significantly influence the risk of preterm birth, and should guide management of female KT recipients contemplating pregnancy.

SA-PO377

Association of Body Composition with Changes in Frailty after Kidney Transplantation Natalia Cortez, Daniel Velez, Eugenia Xiao, Sumit Mohan, Tom Nickolas. *Dept of Medicine, Columbia Univ, NY, NY.*

Background: Frailty is emerging as a risk factor for poor clinical outcomes in kidney transplantation (KT). Preoperative frailty is associated with increased risk for early hospital readmission, delayed graft function and mortality after KT independent of age. Weight loss is a component of frailty that can occur after KT, but changes in weight and body mass index (BMI) do not fully account for changes in lean and fat mass, which have opposing associations with frailty. We hypothesized that lower lean and higher fat mass at KT would be associated with greater degree of frailty 1-month after KT.

Methods: Whole body composition was obtained by dual-energy X-ray absorptiometry (DXA) within 3-weeks of KT. The Fried Frailty Assessment was completed both pre- and 1-month after KT. Each frailty component was scored 0 or 1 (absent or present) and the aggregate frailty score was calculated. Increases in frailty after KT were defined as an increase of ≥1 in the frailty score. Associations between percent lean and fat mass with frailty and change in frailty were determined by logistic regression and expressed as the odds ratio (95% CI).

Results: Forty-seven participants were enrolled (64% men) with a mean age of 51±14 years and BMI of 28.7±5.7; mean percent lean mass was 67.6±8.6% and fat mass was 32.4±8.6%. At baseline 56% were frail and at 1-month after KT 47% had an increase in frailty. Higher degree of frailty after KT was associated with older age (OR 1.10; 1.03-1.17), higher BMI (OR 1.13; 1.01-1.28) and fat mass (OR 1.12; 1.02-1.22), and lower lean mass (OR 0.90; 0.82-0.98) at baseline. An increase in frailty at 1-month after KT was associated with lower frailty (OR 0.09;0.02-0.43) before KT and decreases in BMI (OR 0.89; 0.79-0.99) after KT.

Conclusions: Frailty early after KT is associated with higher fat and lower lean mass at the time of KT, while increases in frailty after KT are associated with lesser frailty pre-KT and decreases in BMI after KT. Assessment of body composition before KT may predict frailty status early after KT. Future work will investigate how changes in body composition 12-months after KT affect frailty status and clinical outcomes.

Funding: Private Foundation Support

SA-PO378

Calcium Scores in Pre-Transplant Myocardial Perfusion Scans Are Increased by Beta-Blockers Rosa M. Montero, Fiyyaz Ahmed-Jushuf, Azhar Ali, Roshni Patel, Mona Wahba. *Epsom & St. Helier Univ Hospitals, Renal & Transplantation, United Kingdom.*

Background: End stage kidney disease(ESKD) is a risk factor for cardiovascular mortality. The prognostic value of myocardial perfusion scan(MPS) is reported to be 90% in renal transplants.Previous reports show a person with high calcium scores reflect coronary artery calcification and increased narrowing of the coronary arteries compared with a low calcium score. It is unclear if traditional cardiac risk factors or medications in particular beta-blockers affect the calcium score in patients with ESKD.

Methods: All pre-renal transplant patients in a single centre were identified. Clinical data, including;medications, cardiology investigations results were recorded in patients who underwent MPS as part of their transplant workup between 2011-2014. Cardiac risk factors including; hypertension, previous cardiovascular incident, cardiac family history, hypercholesterolaemia, diabetes mellitus(DM), body mass index(BMI) and smoking were recorded. Calcium scores of >100 reflected moderate atherosclerotic disease with high risk of coronary artery disease and significant vessel narrowing. Logistic regression was used for statistical analysis.

Results: 172 patients had a MPS with analysis performed on 154 who had no coronary stents. 62%M:56%F. 56% had DM. 95 patients on RRT. Median age was 60yrs(20-83). There was strong evidence that the odds of having Calcium scores >100 were 5.5x higher in patients on beta-blockers than those without(OR 6.07, 95%CI 2.62-14.1, p<0.001) and increased with 9.3% for each year of age(OR 1.093, 95%CI 1.04-1.14, p<0.001), independent of other factors. Weaker evidence that patients from black ethnicity had 83% lower odds(OR 0.17, 95%CI 0.042-0.69, p=0.013), while patients withT2DM had 3.2 fold higher odds of having calcium score>100(OR 3.17, 95%CI 1.25-8.03, p=0.015), adjusted for beta-blocker intake and age. Calcium scores were unaffected by calcium antagonists, ACE inhibitors/angiotensin receptor blockers, vitamin D, other traditional cardiac risk factors or dialysis.

Conclusions: We show beta-blockers are associated with a raised calcium score that is independent of age. The beta-blocker effect on calcium scores requires further investigation.

SA-PO379

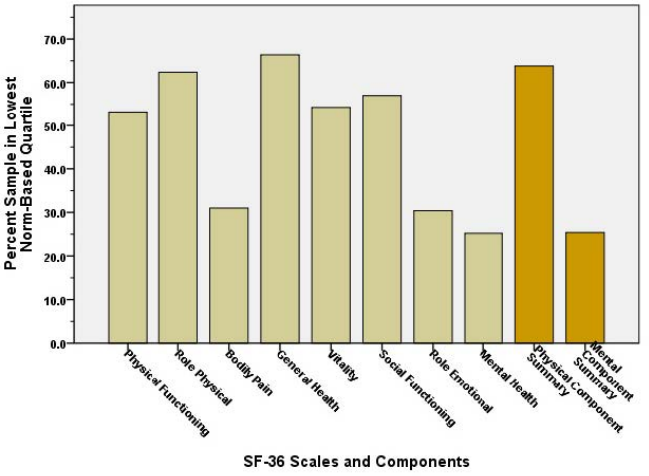
Pre-Transplant Health Related Quality of Life Is Not Associated with Short-Term Outcomes after Kidney Transplantation Beatrice P. Concepcion, Hassan Alhalabi, Rachel C. Forbes, Irene D. Feurer. *Vanderbilt Univ Medical Center.*

Background: Novel measures, such as frailty and physical functioning, which forecast post transplant outcomes are increasingly being recognized as potentially useful tools in risk stratifying kidney transplant candidates. We investigated whether pre-transplant patient-reported health-related quality of life (HRQOL) is associated with short-term adverse events after kidney transplantation.

Methods: Pre-transplant HRQOL was measured using the 8 scales and physical and mental component summary scores of the Short Form 36 Health Survey. Continuous scores were stratified based on scale- and component-specific general population norm quartiles. Binary outcomes (present/absent) were: delayed graft function (DGF), readmission within 90 and 365 days of transplant, any acute rejection episode(s). Data were analyzed using multivariable logistic regression models that adjusted for age, donor type and cardiovascular disease.

Results: The sample included 230 adults who were referred to our center for kidney transplantation and were subsequently transplanted. Patients were 59% male, 50% had a living donor, 49±14 years of age, 24% with CV comorbidity. Time pre-transplant at HRQOL was 13±9 months and follow-up time 52±35 months. Figure 1 shows the proportion of patients that were in the lowest norm-based quartile for each pre-transplant measure.

Figure 1



Post-transplant, 6% had DGF, 30% and 48% were readmitted within 90 and 365 days, respectively, and 12% had acute rejection. Multivariable models demonstrated that compared to patients in the upper quartiles, patients at the lowest quartile for each HRQOL measure did not have an increased risk for DGF, readmission within 90 or 365 days, or acute rejection (all p>0.5).

Conclusions: Pre-transplant HRQOL is not a useful metric for risk stratification of kidney transplant candidates for short-term adverse events after transplantation.

SA-PO380

Effect of Pre-Transplant Dialysis Modality and Duration on Recipient's Outcome: A National Population-Based Cohort Study between 2005 and 2008 in Korea Hyunjeong Cho,[3] Jung Nam An,[1,2] Yunmi Kim,[3] Eunjeong Kang,[3] Dong-Ryeol Ryu,[4] Kyoung Hoon Kim,[5] Yun Kyu Oh,[2] Chun Soo Lim,[2] Yon Su Kim,[3] Jung Pyo Lee.[2] *[1]Critical Care Medicine, Seoul National Univ Boramae Medical Center, Seoul, Korea; [2]Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul; [3]Internal Medicine, Seoul National Univ College of Medicine, Seoul, Korea; [4]Internal Medicine, Ewha Womans Univ, Seoul, Korea; [5]Public Health, Graduate School, Korea Univ, Seoul, Korea.*

Background: So far the effects of pre-transplant dialysis modality or duration on clinical outcomes after kidney transplantation (KT) have not been investigated.

Methods: We analyzed the clinical outcomes of 1,563 KT recipients among the 35,422 adult patients who were started hemodialysis and peritoneal dialysis from 2005 to 2008, using the Korean Health Insurance Review & Assessment Service database.

Results: During the median 6.9 years follow-up after KT, 106 (6.8%) patients were died and 28 (1.8%) patients had experienced major adverse cardiovascular events (MACE). In the multivariable-adjusted Cox proportional hazard model, pre-transplant dialysis modality was not associated with an increased risk of mortality and the development of MACE. Pre-transplant dialysis duration was not associated with the occurrence of MACE; however, the HR for mortality (comparing the group greater than 10.8 months with the group lower than 10.6 months regarding the duration of dialysis before KT) was 1.66 (95% CI 1.11-2.47) in total populations. In each group of hemodialysis and peritoneal dialysis, the duration of pre-transplant dialysis was also an independent risk factor for mortality.

Conclusions: The duration of dialysis before KT was independently associated with mortality, regardless of the dialysis modality in this national population-based cohort study. Pre-transplant dialysis duration could be useful marker in predicting mortality in KT recipients.

SA-PO381

Perception of Kidney Transplant Candidates of Deceased Donor Waiting List Outcomes Allyson Hart,[1,2] Marilyn J. Bruin,[3] Ajay K. Israni.[1,2] *[1]Nephrology, Hennepin County Medical Center, Minneapolis, MN; [2]Medicine, Univ of Minnesota, Minneapolis, MN; [3]College of Design, Univ of Minnesota, Minneapolis, MN; [4]Medicine, Minneapolis Veterans Affairs Medical Center, Minneapolis, MN.*

Background: Despite steady growth of the waitlist, living donor kidney transplant rates have fallen over the past decade. We sought to understand what transplant candidates understand about likely waitlist outcomes.

Methods: Adult (aged ≥ 18 years) kidney transplant candidates were recruited for in-depth interviews from 2 centers in Minnesota between March and June 2016 during their transplant evaluation. Systematic inductive and deductive analyses of the interviews were performed. Text was axial coded for expected answers, then open coded for new concepts within and across questions.

Results: 8 in-depth interviews were conducted. Mean age of the participants was 49.9 ± 12.6 yrs; 6 (75.0%) participants were male, 4 (50.0%) Caucasian and 4 (50.0%) African American. All had at least some college education; household income ranged from < $15,000 to > $75,000. Analyses revealed several themes, including a limited understanding of likely outcomes on the waiting list, the importance of friends and family in medical decision-making, and fear of the unknown. Several participants expressed dissatisfaction with generalizations and a desire to be given individualized descriptions of the outcomes. A conceptual model of how these factors may impact clinical decision making is shown in figure 1.

Conclusions: Kidney transplant candidates have a limited understanding of likely outcomes on the waiting list even after undergoing pre-transplant education and despite a high level of education. These findings suggest a need to provide candidate-specific, comprehensible information, and suggest a role for including friends and family in the education process.

Funding: Other NIH Support - National Center for Advancing Translational Sciences in the National Institutes of Health Award Number UL1TR000114

SA-PO382

Internet Use Impact on Health-Related Quality of Life (HRQOL) in Renal Transplant Recipient (RTR) in France Yosra Mouelhi,[1] Valerie Moal,[2] Bertrand Dussol,[2] Stephanie Gentile.[1] *[1]Sante Publique et Evaluation Medicale, CHU Marseille, Marseille, France; [2]nephrology Unit, CHU Marseille, Marseille, France.*

Background: The Internet may provide new opportunities for communication that can help RTR to improve their quality of life (QOL). The aim of this study is to evaluate the impact of Internet access and social networks connections on HRQOL of RTR during long term renal transplantation.

Methods: This study analyzed psychosocial data (Internet access and social networks connections) and HRQOL measures by the generic scale (SF36) and a disease specific questionnaire validated in French language: the ReTransQol (RTQ). Self-administered questionnaires were completed by patients in a 2-year longitudinal and multicenter study of 1,424 RTR. We performed univariate analysis in order to determine the relationships between internet access and social networks connection and HRQOL scores.

Results: Nearly 80% of RTR had access to the internet. Among them, 80% regularly connected to a social network. Internet access was significantly associated with a better HRQOL for all dimensions of SF-36, and only for physical and for mental health of RTQ. Social networks connections played a significant role in the improvement of HRQOL for physical dimensions for both questionnaires.

Conclusions: This study showed significant association between internet access and a better HRQOL in our population. Providing internet access and encouraging social networks connections may be feasible to improve consistency of information to RTR ant their physical and psychosocial well-being.

SA-PO383

Factors Associated with Health-Related Quality of Life (HRQOL) in Renal Transplant Recipient (RTR) in France Yosra Mouelhi,[1] Valerie Moal,[2] Bertrand Dussol,[2] Stephanie Gentile.[1] *[1]Sante Publique et Evaluation Medicale, CHU Marseille, Marseille, France; [2]Nephrology Unit, CHU Marseille, Marseille, France.*

Background: The factors associated with HRQOL are not well defined in renal transplantation studies using extensive observations in large cohorts. A cohort of RTR was conducted in 5 university hospitals in France in order (a) to improve a disease specific questionnaire, the ReTransQol (RTQ) validated in french language for RTR (b) to identify factors associated with HRQOL in this population.

Methods: A 2-year longitudinal study was conducted in a representative sample of RTR. Measures included a patient questionnaire (socio-demographic characteristics), a medical questionnaire including kidney disease, health status, comorbidities, treatments and their side effects, and biological data. The RTQ and the generic scale (SF36) were used. Multiple linear regressions analysis were performed for RTQ and SF36.

Results: A total of 1,424 adults RTR were included. Patient's mean age was 56 ± 13 years and 61.4% were male. 38% had college education level, 39% had full time job, 35% were recipients of disability, and 68% lived with a partner. Clinical data were : 13% had a preemtive transplantation, 15% suffered from at least one rejection episode, 31% had a chronic transplant dysfunction (serum creatinine > 16mg/l). 18% had diabetes mellitus, 82% hypertension, and 15% obesity. In both questionnaires, we identified that older age, female gender, diasibility, to receive any social support, a chronic transplant dysfunction, and a high Charlson Comorbidity index were associated with a low HRQOL scores. HRQOL increased with higher monthly incomes, employment status and high Karnofsky performance scale (≥70%). Home internet connection increased significantly HRQOL for mental health dimensions.

Conclusions: We evidenced several variables related to HRQOL in RTR. A better understanding of the psychosocial factors' roles is essential for the development of psychosocial interventions to improve HRQOL in the context of long-term transplantation.

SA-PO384

Utility of Pre-Implanatation Deceased Donor Kidney Biopsy and Scoring System in Predicting Early Graft Outcome Based on Kidney Donor Profile Index and Estimated Post-Transplant Surival Shirley Shwu-Shiow Chang, Mareena Susan Zachariah. *Internal Medicine, Univ of Buffalo, Buffalo, NY.*

Background: Demand for kidney (K) grafts excces supply of avilable organs. There is increasing interests in evaluating the intrinsic donor organ quality by performing pre-transplant (tx) k biopsies (bx), especially in the older donors, is improtant for post-tx histologic evolution & long-term graft survival. Kidney Donor Profile Index (KDPI) characterizes deceased donors based on 10 factors, ranges from 1% to 100%. Estimated Post Transplant Survival (EPTS), assigned to tx candidates on the waiting list, is based on 4 factors (age, time on diaysis, diabetes status, and prior solid organ tx). We are interested in assessing pre-tx donor k bx, KDPI, EPTS affecting early graft outcome.

Methods: This is a single center retrospecitve study from University of Buffalo Transplant Center from January 2012 to Sept 2015. 183 deceased kidney tx recipients who had time zero donor kidney biopsies were inclueded. Induction immunosuppression was with Thymoglobulin 3 mg/kg, maintenance therapy was with prednisone, tacrolimus, MMF. All pre-implantation bx performed were scored based on modifed chronic Banff criteria (interstital fibrosis, tubular atrophy, glomerular mesangial matrix, vascular narriowing, and hyalinosis). glomerulosclerosis, inflammation, ATN. Each of above histologic features were graded from scales from 0 to 3, except for ATN (present or absent). Clinical data such as serum Cr, estimated GFR, was collected at 1 week, 1 month, 3 months, 6 months, 1 year, 2 years post-tx. The follow-up period was up to 4 years. Mutivariate mixed modeling was used.

Results: Increasing KDPI, modified Banff chronic score, cold ischemic time (CIT) were found highly signifcant for decreasing eGFR at baseline (all p values <0.001). Overtime, chronic Banff, EPTS, CIT had significant effects on eGFR ($p<0.03$, $p<0.04$, $P<0.02$, respectively).

Conclusions: While KDPI was meant to rank order the quality of donor k as defined by an aggregate population relative risk, a well graded time zero donor k bx could add to the ability along with composite clinical parameters as predictore of k allograft outcome.

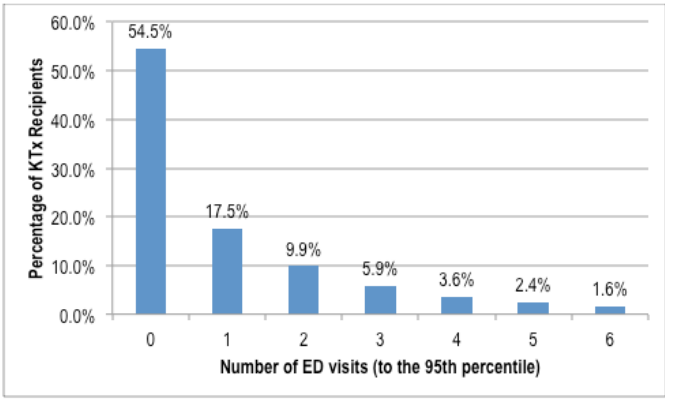
SA-PO385

Emergency Department Utilization among Kidney Transplant Recipients in the United States Brendan P. Lovasik, Rebecca H. Zhang, Justin D. Schrager, Stephen O. Pastan, Rachel E. Patzer. *Emory Univ, Atlanta, GA.*

Background: Single center studies suggest that kidney transplant recipients have a high rate of emergency department (ED) utilization, with 1.48 ED visits/patient-year, and ED visits are associated with graft failure and patient mortality. However, ED utilization among national renal transplant recipients has not been examined.

Methods: We examined a cohort of 103,155 incident adult kidney transplant patients in the United States Renal Data System from 2005-2011. ED utilization, hospital admission, and diagnoses were obtained from the USRDS and Medicare Physician/Supplier and Inpatient databases for Medicare Part A/B claims. Multivariable Poisson regression was conducted to assess the association of patient variables with ED utilization.

Results: In the first post-transplant year, nearly half (45.5%) of all kidney transplant recipients utilized the ED, with an average of 1.63 ED visits/patient-year; 22% visited the ED in the first 30 days. The national range was 0 to 216 ED visits, with 95th percentile 6 visits. Nearly 40% of ED visits resulted in hospital admission; graft complications, sepsis, and urinary tract infections were the most common diagnoses. Both patient death and graft failure were highly correlated with ED visits ($p<0.001$). Older age and male sex were associated with higher ED utilization; private insurance, preemptive transplant, and living donor transplant were associated with lower ED utilization (all $p<0.0001$).



Conclusions: This study is the first to our knowledge to describe ED utilization in a national sample of kidney transplant patients. Compared to the national average, transplant patients have higher ED utilization (1.63 vs. 0.4) and hospital admission rates (40% vs. 12%). A comprehensive understanding of factors associated with ED utilization can improve population health management by targeting interventions to high-risk patients.

SA-PO386

Early Renal Hemodynamic Changes with Doppler Ultrasound after Renal Transplantation Amir Shabaka, Estefania Yerovi, Victor Burguera, Maite Rivera, Fernando Liano. *Nephrology, Hospital Univ Ramón y Cajal, Madrid, Spain.*

Background: Doppler Ultrasound facilitates the global evaluation of intrarenal vasculature, making it a valuable noninvasive tool for early diagnosis of complications in renal transplants. The aim of this study was to explore the evolution of renal graft hemodynamics in the immediate postoperative and early periods.

Methods: A retrospective study in which all Doppler Ultrasound studies done within the first month of transplantation were reviewed in patients who received a renal graft at our centre from January 2013 to May 2015. We excluded patients with primary graft failure, delayed graft function, acute rejection, surgical complications (severe hemorrhage or urinary fistulae), significant hydronephrosis, or hemodinamically significant arteriovenous fistulae. We recorded receptor/donor characteristics, renal morphology, a subjective classification of renal vasculature by Color Doppler and hemodynamic measurements by Pulsed Doppler (intrarenal resistive index (RI), Systolic Acceleration Index (AI), Intrarenal Acceleration Time (AT), Peak systolic velocity at the arterial anastomosis (PSV), and wave morphology in the intraparenchymatous, renal and iliac arteries.

Results: Out of the 179 patients with renal transplantation, 71 patients met the inclusion/exclusion criteria; 74.6% males, mean age 53.6±13.6 years, 85.9% received their first graft, 39.4% were preemptive renal transplants, 32.4% were previously on hemodialysis and 28.2% on peritoneal dialysis, 91.5% received grafts from donors after brain death and 8.5% from live donors. Immunosuppression induction was done with basiliximab in 73.2%, ATG in 7.5% and 18.3% went without induction. 37.3% presented an AI <300 cm/s^2 in the first two days post-transplantation, decreasing to 16.7% between the third and tenth day($p=0.008$) and 0% in the last ten days of the first month($p<0.001$). There were no statistically significant differences in the evolution of RI, AT, PSV or wave morphology.

Conclusions: In uncomplicated renal transplants, the Systolic Acceleration Index by Doppler Ultrasound may be abnormal in the first two postoperative days, with gradual normalization within the first month of transplantation.

SA-PO387

Predictors of Survival in Deceased Kidney Transplant Using Data Mining Methods Ammar Almehmi,[1] Kazim Topuz,[3] Ferhat Zengul,[2] Mehmet Yildirim.[3] *[1]Nephrology and Radiology, Univ of Alabama in Birmingham, Birmingham, AL; [2]UAB-Dept of Health Administration, Birmingham, AL; [3]Wichita State Univ, Wichita, KS.*

Background: Prediction of graft survival after kidney transplantation is the most important factor in the donor-patient matching process. Several conventional statistical methods are employed to assess the effect of certain candidate variables on graft survival. However, the role of data mining using a large pool of variables in predicting survival is unknown. The objective of this study was to define predictors of renal graft survival by analyzing a large set of variables using data analytical approaches.

Methods: In this study, we used UNOS database of deceased kidney transplantation between. A comprehensive variable selection methodology was employed using medical literature search, conventional statistics and data analytic approaches. The analytical approaches included Elastic Net regression and structured data analytic based information fusion technique. The selected variables obtained from the medical literature and analytical methods were incorporated in the Bayesian Belief Network (BBN) to create a multi-class prediction survival model and to identify the interactions between these variables.

Results: A total of 31,207 deceased kidney transplants were included in this study between July 1, 2004 and March 31, 2015. We found that UNOS database contained more than 450 variables. Further, a total of 56 variables were found in the medical literature as predictors of kidney transplant survival. Another 28 variables were selected using data analytic methods. The interactions and relationships among the different selected variables were calculated using multi-class Bayesian risk level prediction as depicted in Figure 1. We found that the recipient's functional status (RFS) at listing was the most interacted variable in this model. Moreover, this variable was the strongest predictor of renal graft survival.

Conclusions: In this large cohort of deceased kidney transplant, we found that the RFS was the most prominent predictor of renal graft survival. Further, data mining approach was a powerful tool in exploring the complex relationships between multiple variables.

SA-PO388

Time Varying Proteinuria Is a Strong Predictor of Mortality and Graft Loss in Patients after Kidney Transplantation Benaya Rozen-Zvi,[1,2] Shelly Lichtenberg,[1,2] Hefziba Green,[1,2] Ruth Rahamimov.[1,2] *[1]Nephrology and Hypertension, Rabin Medical Center, Petach-Tikva, Israel; [2]Sackler School of Medicine, Tel Aviv Univ, Tel Aviv, Israel.*

Background: proteinuria is known to be associated with decreased graft and patient survival after kidney transplantation. Nevertheless, most of the data comes from cross sectional and cohort studies and the effect time varying proteinuria was not adequately evaluated.

Methods: we used the routine dipstick urine protein evaluation performed every three to six month for all patients at our post transplantation follow-up clinic. Urine protein concentration was allocated into ordinal scale (no proteinuria, trace, 25 ng/dl, 75 mg/dl, 150 mg/dl and 500mg/dl). The follow-up time was divided into 6 months intervals and proteinuria was evaluated by using all available protein measurements during each interval. The primary outcome was graft loss defined as the combination of death from any cause and graft dysfunction requiring chronic dialysis or retransplantation. Time dependent Cox proportional hazard model was used using univariate and multivariate adjusted analysis.

Results: One thousand two hundred and twenty patients transplanted between 1/1/2000 and 31/12/2013 had 153 events (91 graft loss and 62 death events) during median follow-up of 4 years (range 0.5 to 12.9 years). Time varying proteinuria was strongly associated with increased graft loss Hazard Ratio (HR) 1.78 per stage, 95% Confidence Interval (CI) 1.62-1.95,p<0.001), the association was not changed after adjusting for age, gender, time on dialysis, recipient heart disease, diabetes, donor type (living or deceased), donor age, HLA mismatch, panel reactive antibodies, delayed graft function, duration of hospital stay following transplantation ,creatinine at six month and urine protein level at 6 months (HR 1.78, 95% CI 1.61-1.96,p<0.001). Death censored graft survival was also associated with time varying proteinuria at univariate and multivariate analysis (HR 2.1, 95% CI 1.86-2.36,p<0.001) and (HR 2.16, 95% CI 1.87-2.49,p<0.001) respectively.

Conclusions: Time varying proteinuria is strongly associated with poor graft survival even after adjustment for baseline proteinuria and renal function.

SA-PO389

Do Phosphate-Binders Affect the Calcium Score in Pre-Renal Transplant Myocardial Perfusion Scans? Fiyyaz Ahmed-Jushuf, Roshni Patel, Azhar Ali, Rosa M. Montero, Mona Wahba. *Epsom & St. Helier Univ Hospitals, Renal & Transplantation, London, United Kingdom.*

Background: Myocardial perfusion scans(MPS) is used in pre-transplant workup as a minimally invasive tool to determine coronary artery disease in the potential recipient. The prognostic value of using this test has been reported with sensitivity 90%, specificity 85%. Vascular calcification is common with many renal patients taking calcium-based phosphate binders/vitamin D analogues to help regulate bone metabolism and reduce renal bone disease. It is unclear whether using calcium-based phosphate binders(CBPB) adds to vascular calcification. This retrospective study looked at whether calcium-based phosphate binders caused a high Calcium score predicting underlying coronary artery disease and high cardiovascular risk.

Methods: All patients undergoing a MPS as part of their pre-renal transplantation work-up were identified in a single centre from 2011-14. Clinical data, cardiac work-up investigations and serum calcium, phosphate and parathyroid hormone(PTH) levels were collected from notes of these patients. Logistic regression was used for analysis.

Results: 172 patients underwent MPS as part of their renal transplantation workup. 147 had no previous coronary artery stents. 14 went onto renal transplantation. 10 died from non-cardiac events; 61%M; 79 White, 24 Black, 44 Asian. 67 patients were on CBPB and 85 had PTH available for analysis. The mean corrected calcium levels were 2.33nmol/l(1.38-2.86), phosphate levels of 1.49nmol/l(0.7-3.11) and median PTH of 35pmol/l(3.3-209).52 patients(35%) had Calcium score >100. There was no association between Calcium score and serum calcium levels or Calcium score and CBPB. No effect was seen of phosphate binders on MPS outcome or cardiac investigations.

Conclusions: In this small cohort, phosphate binders did not affect Calcium scores in patients pre-renal transplant workup, irrespective of:age, gender, serum calcium or PTH levels. There were no coronary complications in those who went onto to have renal transplants. Further larger studies are required to confirm these findings and elucidate the mechanisms behind coronary artery vascular calcification in renal patients thereby providing novel therapeutic targets.

SA-PO390

A Single Center Experience of Kidney Transplant Recipients due to Scleroderma Kidney Disease Nishkarsh Saxena, Arjang Djamali, Brad C. Astor, Didier A. Mandelbrot, Maha A. Mohamed, Sandesh Parajuli. *Nephrology, Univ of Wisconsin School of Medicine and Public Health, Madison, WI.*

Background: There is limited information on renal transplant recipients with end stage renal disease (ESRD) due to scleroderma.

Methods: This was an observational study that included patients with ESRD due to scleroderma kidney disease who received renal transplant between 01/1994 and 06/2013.

Results: There were ten kidney transplant recipients during the study period. They were all caucasian females. Mean post-transplant follow up was 76.75 ± 56.18 months. Mean age at time of transplant was 56.6 ± 11.99 years. Seven of them were living kidney transplant recipients. Mean dialysis vintage was 46.4 ± 80.35 months, ranging from 8 to 272 months. Mean serum creatinine (SCr) at 3, 6 and 12 months were 1.31 ± 0.47 mg/dL, 1.35 ± 0.51 mg/dL and 1.34 ± 0.49 mg/dL respectively. There were five graft failures with median graft survival of 101 months.Causes of graft failure were chronic transplant glomerulopathy in three patients, thrombotic microangiopathy and antibody mediated rejection in the other two patients. In those without graft failure, mean SCr at last follow up was 0.96 ± 0.39 mg/dL. Six patients were on angiotensin converting enzyme inhibitors (ACE-I) after transplant. One patient had developed new onset diabetes after transplant. In univariate analysis, none of the factors including, age at time of transplant (HR 1.10, 95% CI 0.89 to 1.36, p= 0.35), dialysis vintage (HR 1.01, 95% CI 0.99 to 1.02, p= 0.16), use of ACE-I (HR 0.57, 95% CI 0.09 to 3.54, p= 0.55), living transplant (HR 3.8, 95% CI 0.38 to 38.38, p= 0.25), CMV infection (HR 1.89, 95% CI 0.31 to 11.43, p= 0.49) and SCr at 1 year (HR 1.49, 95% CI 0.26 to 8.64, p= 0.66), were predictive of graft survival.

Conclusions: In this observational study we found a wide variation in outcomes after kidney transplantation in patients with scleroderma kidney disease. More studies are needed to assess the factors that may influence graft survival in this rare disease.

SA-PO391

Pre-Transplant Cardiovascular Risk Factors Affect Kidney Allograft Survival: A Multi-Center Study in Korea Jung Nam An,[1] Eunjin Bae,[4] Eunjeong Kang,[2] Yun Kyu Oh,[1] Chun Soo Lim,[1] Yon Su Kim,[2] Young Hoon Kim,[3] Jung Pyo Lee.[1] *[1]Dept of Internal Medicine, Seoul National Univ Boramae Medical Center, Seoul, Korea; [2]Dept of Internal Medicine, Seoul National Univ Hospital, Seoul, Korea; [3]Dept of Surgery, Asan Medical Center, Seoul, Korea; [4]Dept of Internal Medicine, Gyeongsang National Univ Changwon Hospital, Korea.*

Background: Pre-transplant cardiovascular (CV) risk factors affect the development of CV events even after successful kidney transplantation (KT). However, the impact of pre-transplant CV risk factors on allograft failure (GF) has not been reported.

Methods: We analyzed the graft outcomes of 2,902 KT recipients who were enrolled in a multi-center cohort from 1997 to 2012. We calculated the pre-transplant CV risk scores based on the Framingham risk model using age, gender, total cholesterol level, smoking status, and history of hypertension.

Results: Vascular disease (a composite of ischemic heart disease, peripheral vascular disease, and cerebrovascular disease) was noted in 6.5% of the patients. During the median 6.4 years follow-up, 286 (9.9%) patients had developed GF. In the multivariable-adjusted Cox proportional hazard model, pre-transplant vascular disease was associated with an increased risk of GF (HR 2.51; 95% CI 1.66-3.80). The HR for GF (comparing the highest with the lowest tertile regarding the pre-transplant CV risk scores) was 1.65 (95% CI 1.22-2.23). In the competing risk model, both pre-transplant vascular disease and CV risk score were independent risk factors for GF. Moreover, the addition of the CV risk score, the pretransplant vascular disease, or both had a better predictability for GF compared to the traditional GF risk factors.

Conclusions: In conclusion, both vascular disease and pre-transplant CV risk score were independently associated with GF in this multi-center study. Pre-transplant CV risk assessments could be useful in predicting GF in KT recipients.

SA-PO392

Sustained Improvement in Depression after Renal Transplantation Aditi Gupta, David K. Johnson, Jeffrey M. Burns. *Univ of Kansas Medical Center.*

Background: Depression is a common problem in patients with end stage renal disease (ESRD). Whether renal transplantation improves depression is unexplored.

Methods: We followed patients with ESRD prospectively till one year after their renal transplantation. We assessed depressive symptoms by administering Beck Depression Inventory (BDI) at baseline (pre-transplant), 12 weeks and one year post-transplant. We used paired t tests for analyzing the change in depression scale from baseline to 12 weeks after transplant, baseline to one year after transplant and 12 weeks after transplant to one year after transplant.

Results: The participants were 56.5 ± 10.7 years old, 11 men and 2 women, 10 Caucasian and one African American. All 11 patients had successful transplantation with a mean serum creatinine of 1.6 ± 0.6 mg/dl with an estimated glomerular filtration rate (eGFR) of 45.2 ± 11.2 ml/min at 12 weeks after transplantation. The mean BDI score of depressive symptoms at baseline was 11.09 ± 8.14, at 12 weeks after transplant was 4.55 ± 2.98 and at one year after transplant was 5.73 ± 6.28. Compared to baseline scores there

was a significant improvement in depression score 12 weeks after transplantation (p = 0.02), which persisted at one year after transplantation (p=0.003). There was no significant difference in score at 12 weeks and at one year after transplantation (p=0.48). After 12 weeks of transplantation, only one patient had mild depression with a BDI score of >11 compared to five patients (45%) who had a BDI score of >11. There was no association of these scores with the eGFR.

Conclusions: Renal transplantation is associated with a significant improvement in depressive symptoms, which is sustained at one year after transplantation.

SA-PO393

Machine Learning Approach for Prediction of Graft Survival in Kidney Transplant Using a Multicenter Cohort Kyung Don Yoo,[1] Junhyug Noh,[2] Hajeong Lee,[3] Dong Ki Kim,[3] Chun Soo Lim,[3] Young Hoon Kim,[4] Yon Su Kim,[3] Gunhee Kim,[2] Jung Pyo Lee.[3] *[1]Dongguk Univ Medical Center, Gyeongju; [2]College of Engineering, Seoul National Univ; [3]Seoul National Univ College of Medicine; [4]General Surgery, Asan Medical Center.*

Background: Accurate prediction of graft survival has important implications for clarifying the benefits of kidney transplantation(KT). However, the complexity and heterogeneity of risk factors on allograft survival were remained.

Methods: This multicenter cohort study included adult KT recipients admitted to two experienced tertiary hospitals in Korea between 1997 and 2014. A total of 3,117 recipients were enrolled. Graft survival of these recipients was investigated by the individual learning algorithms such as survival decision tree, survival ridge/lasso/Cox regression, and ensemble learning algorithms such as survival bagging and random forest.

Results: We analyzed 3,117 recipients' records. Among them, we chose 33 independent attributes which could affect graft survival for building our models. Among various conventional decision tree (DT) models, serum creatinine at 3month from KT was found to be a first decision node and the most important risk factor for graft failure (Concordance index 0.711, predicted 10 year GF rate 77.1%). Survival tree algorithm had presented the most accurate prediction model, and it outperforms a conventional DT (Concordance index 0.808 vs. 0.711, respectively). In the survival decision tree model using graft survival duration, acute rejection episode within first year was found to be the most important prognostic factor. In the case of having rejection episode in the first year, risk of graft failure was predicted in 4.27 times compared to overall recipients. Serum creatinine at three months after KT, and also recipients' age showed significant association with graft survival. In recipients without rejection episode, creatinine cut-off value over 1.65 mg/dl showed high probability of graft failure (HR 3.001).

Conclusions: In this study, reducing acute rejection episode at the first year following the transplant might had been the most important factor for allograft survival. Machine learning modeling could present an accurate and versatile tool for forecasting graft survival.

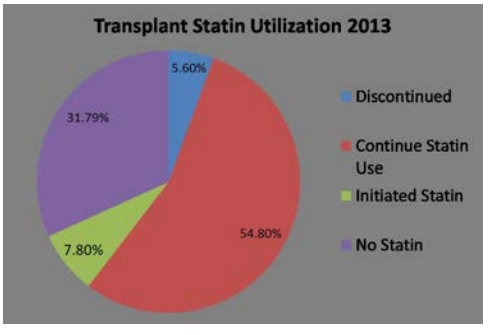
SA-PO394

Utilization of Statin Medications in U.S. Veterans with Post-Transplant Chronic Kidney Disease Arouna Senthilkumar, Talar Markossian, Kevin Stroupe, Nicholas Burge, Vinod K. Bansal, David J. Leehey, Julia Schneider, Holly J. Kramer, Benjamin Ling. *Hines VA Hospital, Hines, IL.*

Background: KDIGO and KDOQI guidelines recommend statin medications for kidney transplant recipients due to demonstrated cardiovascular benefits of statins with graded evidence of 2A. Results from few empirical studies suggest that statins are underutilized in transplant patients.

Methods: Retrospective analysis of U.S. Department of Veterans Affairs Healthcare System (VA) national databases to determine statin use in post-transplant patients with CKD. Medications acquired within the VA system were obtained from the Managerial Cost Accounting National Data Extracts. Medications acquired outside the VA were obtained from the Corporate Data Warehouse (CDW). Statin medication utilization was ascertained from pharmacy dispensing records in 2012 and 2013.

Results: A total of 626 veterans with CKD and history of kidney transplantation were identified. The majority of patients (97.3%) were male, 74.4% were aged ≥50 years and <2% were aged ≥75 years; 52.4% were white and 37.4% were African-American. Coronary artery disease, peripheral vascular disease and diabetes were present in 26.8%, 6.4% and 54.4% respectively. In 2012, 60.4% were using statins but only 54.8% were using statins during years 2012 and 2013 with 5.6% discontinued statins in 2013 while 7.8% initiated statins in 2013.



Conclusions: Despite KDIGO and KDOQI guidelines recommending statin use in transplant recipients, statin use is suboptimal in patients with post-transplant CKD receiving care in the VA health system. Interventions are needed to increase knowledge among treating physicians regarding the clinical importance of statin use in adults with post-transplant.CKD

Funding: VA Support

SA-PO395

Outcomes after Open Heart Surgery in Kidney Transplant Recipients and Matched Controls Bartlomiej J. Witczak,[1] Jan L. Svennevig,[3] Anders Hartmann,[2] Anders Aasberg.[2] *[1]Dept of Nephrology, Akershus Univ Hospital, Norway; [2]Dept of Transplant Medicine, OUS, Rikshospitalet, Norway; [3]Dept of Thoracic and Cardiovascular Surgery, OUS, Rikshospitalet, Norway.*

Background: Cardiovascular disease is common in kidney transplant recipients. We evaluated results of open heart surgery in these recipients at our center 1989-2015.

Methods: Ninety-five kidney transplant recipients underwent open heart surgery (48 coronary artery bypass operations, 27 valve replacements and 20 combined procedures) in the period. Controls (n=95) were matched for age, sex, diabetes and type and year of surgery. Mean follow-up time was 5.6 (4.9) years. Cox regression analyses were performed in the transplant group.

Results: Included were 76 men and 19 women with mean age 60.3 (11.1) years. Demographic and comorbidity data were similar, except a lower eGFR, more hypertension and less pulmonary hypertension in transplant recipients (p<0.001). Intraoperative data did not differ between groups, except that transplant recipients had higher hemorrhage volume (p=0.009). Postoperative data were also similar, although, transplant recipients received more red cell transfusions (p=0.04). Thirty-day mortality was similar in transplant patients and controls, but long-term survival was significantly lower in the former (p<0.001). Median survival in transplants was 6.3 years and in controls 13.3 years. Univariate Cox-regression analyses revealed only age, pulmonary hypertension and dialysis as risk factors for long term mortality. In a multivariate Cox-regression model, the same risk factors were significant: age (HR 1.07 per year, p<0.001), chronic dialysis (HR 4.29, p<0.001) and pulmonary hypertension (HR 2.53, p=0.02). Excluding transplant patients on chronic dialysis at time of surgery (n=13) showed similar results.

Conclusions: Kidney transplant recipients experienced more bleeding postoperatively. Intraoperative data and other postoperative complications, including short-term survival, were similar in kidney transplant patients compared with controls. Long-term survival was significantly lower in transplant recipients. Independent preoperative risk factors for long-term mortality were age, pulmonary hypertension and chronic dialysis.

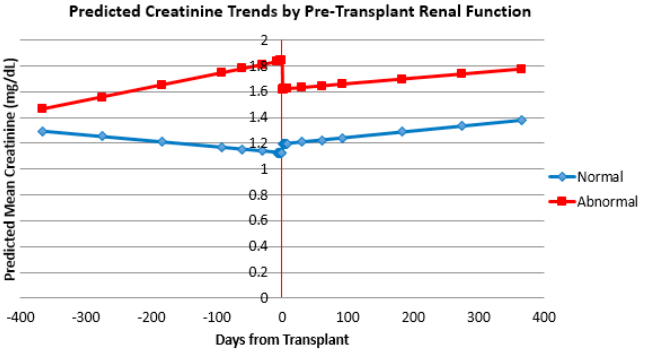
SA-PO396

Trajectory of Renal Function following Heart Transplant: Single Center, Retrospective Cohort Study Adetokunbo A. Taiwo, Margaret R. Stedman, Kiran K. Khush, Jane C. Tan. *Nephrology, Stanford Univ, Palo Alto, CA.*

Background: Heart transplant recipients with pre-transplant renal impairment have higher rates of mortality in the years following transplantation. Identifying appropriate candidates for combined heart-kidney transplantation relies on our ability to estimate the trajectory of renal function following heart transplantation. This study assessed longitudinal creatinine trends in heart transplant recipients stratified by pre-transplant renal function.

Methods: Using the Stanford Translational Research Integrated Database Environment, we identified all adult heart transplant recipients between May 1, 2008 and December 31, 2014. A mixed model analysis was used to assess pre- and post-transplant creatinine trends in those with normal versus abnormal pre-transplant renal function (defined as creatinine ≥ 1.5 mg/dL in the week prior to transplant).

Results: Twenty-two of the 115 identified heart transplant recipients had abnormal pre-transplant renal function. Baseline demographics and co-morbidities were similar in both groups. Renal function declined in both groups over time, but the group with abnormal pre-transplant renal function demonstrated initial improvement in renal function immediately following transplant (see figure 1). For patients with normal pre-transplant renal function, creatinine values continued to climb after transplant, however, on average, these values did not exceed 1.5 mg/dL 1-year post transplant. The likelihood of having a creatinine below 1.5mg/dL at 1-year post-transplant was 74% and 21% in the normal and abnormal renal function groups respectively.



Conclusions: Many patients with pre-transplant renal dysfunction experience initial improvement in renal function following heart transplantation, however, renal function in this group gradually worsens with time at a rate that is similar to those with normal pre-transplant renal function.

Funding: Other NIH Support - T32 Grant, Diversity Supplement

SA-PO397

Can Be Relied on Estimated GFR Decline in Renal Transplantation? The Nephrologist in the Mist Sergio Luis Lima,[1] Domingo Marrero,[1] Ana González Rinne,[1] Armando Torres,[1] Natalia Negrín,[1] Federico J. Gonzalez-Rinne,[1] Esteban Porrini.[2] *[1]Hospital Univ de Canarias, Spain; [2]Univ de La Laguna, Spain.*

Background: Renal transplant patients have a high rate of graft loss (4% per year). Thus, a reliable evaluation of graft function is crucial. Estimated GFR (eGFR) is neither accurate nor precise in the prediction of real GFR. Whether this error masks renal function loss in this population is not clear.

Methods: We measured GFR in 67 patients with the clearance of iohexol annually during 3 years. eGFR was evaluated by 52 creatinine and/or cystatin-c formulas. The agreement between mGFR- and eGFR-based decline was analyzed with the Concordance Correlation Coefficient (CCC).

Results:

	Accuracy	Precision	CCC
Creatinine-based			
aMDRD	0.94 (0.82)	0.44 (0.26)	0.42 (0.24)
CKD_EPI	0.91 (0.79)	0.43 (0.25)	0.39 (0.22)
Effersoe	0.95 (0.83)	0.45 (0.28)	0.43 (0.26)
Rule-MC	0.87 (0.74)	0.39 (0.20)	0.33 (0.17)
Cystatin-c-based			
Hoek	0.85 (0.71)	0.32 (0.12)	0.27 (0.10)
RuleCisc	0.84 (0.70)	0.31 (0.11)	0.26 (0.09)
CKD_EPI_ciscc	0.84 (0.70)	0.29 (0.09)	0.24 (0.07)
Creatinine + cystatin-c			
Stevens	0.96 (0.87)	0.49 (0.32)	0.47 (0.31)
Mac	0.98 (0.87)	0.48 (0.31)	0.47 (0.31)
CKD_EPI_creciscc	0.97 (0.86)	0.41 (0.2)	0.39 (0.22)

Table 1 shows the results of mGFR and eGFR decline for a representative group of 10 formulas (similar results were observed for the remaining equations). Mean GFR decline (mGFR) was 0.89±5.89 ml/min/year; 21 (31%) patients showed fast (< -3 ml/min/y), 28 (42%) slow or stable renal decline (-3 ml/min/y to 3 ml/min/y) and 18 (27%) increased mGFR decline (>3ml/min/yr). The agreement analysis showed poor accuracy and precision combined, which lead to a low concordance: CCC ranged from 26.08 to 47.84 (average~37.3%) between real and estimated GFR decline. Accordingly, formulas showed either over or underestimation of real GFR decline.

Conclusions: Renal function decline cannot be evaluated by estimation formulas in renal transplant patients. This can have important consequences in clinical trials and in day-to-day clinical practise.

Funding: Government Support - Non-U.S.

SA-PO398

Cystatin C-Based Equation for the Prediction of Glomerular Filtration Rate in Kidney Transplant Recipients Inryang Hwang, Youngae Yang, Kyu Yeun Kim, Min Jung Kim, Wonseok Do, Taehoon Yim, Sukyung Lee, Hee-Yeon Jung, Ji-Young Choi, Sun-Hee Park, Yong-Lim Kim, Chan-Duck Kim, Jang-Hee Cho. *Dept of Internal Medicine, Kyungpook National Univ Hospital, Daegu, Korea.*

Background: Precise monitoring of glomerular filtration rate (GFR) is necessary for an optimal estimation of allograft function in kidney transplant recipients (KTRs). GFR is widely estimated by the formula based on serum cystatin C (SCys) as well as serum creatinine (SCr). We aimed to compare the efficacy of SCys-based equation with SCr-based equation to predict allograft function in KTRs.

Methods: We calculated the Modification of Diet in Renal Disease (eGFRMDRD), Chronic Kidney Disease Epidemiology Collaboration (eGFRCKD-EPI), CKD-EPI creatinine-cystatin C ($eGFR_{CKD\text{-}EPI\ Cr/Cys}$), and CKD-EPI cystatin C (eGFRCKD-EPI-Cys) equations in 66 KTRs. The measured GFR (mGFR) was defined as the GFR estimated by technetium-diethylen-etriaminepentaacetic acid (^{99m}Tc-DTPA) clearance. The accuracy and precision of the equations were compared to mGFR. The performance characteristics of a SCr and SCys were analyzed using receiver operating characteristic curves to ascertain the sensitivity and specificity at the cut off value lower than 45 ml/min/1.73m^2 DTPA.

Results: In overall patients, eGFRMDRD and eGFRCKD-EPI-Cys did not show significant differences from mGFR (P=0.760 and P =0.093 respectively) whereas eGFRCKD-EPI and $eGFR_{CKD\text{-}EPI\ Cr/Cys}$ significantly underestimated mGFR (P<0.001 and P= 0.008 respectively). In subgroup of mGFR lower than 45 ml/min/1.73m^2, eGFRCKD-EPI-Cys showed little bias (P=0.111), however, eGFRMDRD significantly underestimated mGFR (P=0.025). The area under curve for predicting mGFR less than <45 ml/min/1.73m^2 was 0.784 for SCys which was better than that for SCr of 0.745.

Conclusions: Cystatin C-based equations showed a better predictive performance of allograft function than creatinine-based equations especially for the KTRs with lower GFR. Cystatin C might be a good alternative method to monitor allograft function after kidney transplantation.

SA-PO399

Association of Gender and Age with Delayed Graft Function after Deceased Donor Kidney Transplantation Xun Luo, Allan Massie, Dorry L. Segev. *Johns Hopkins.*

Background: Previous studies demonstrated that better tolerance of ischemia-reperfusion injury, and hence lower delayed graft function (DGF) rate among females were mediated by higher estrogen level. Given the decreased estrogen level among older females, we hypothesized that the protective association between female sex and DGF might be attenuated among older recipients.

Methods: We identified adult kidney-only deceased donor recipients between 2000-2013 from SRTR data. DGF was defined as dialysis needed within the first week post-transplant. Recipients with primary non-functioning graft were excluded. We modeled DGF using logistic regression, adjusting for recipient, donor and transplant characteristics, and incorporating an interaction term of age (categorized as <40y, 40-59y, and 60+y) and female sex.

Results: Out Of 120,533 recipients, 47,603 (39.5%) were female. The rate of DGF was 19.4% among females and 26.1% among males. After adjustment, female sex was associated with 32% lower odds of DGF ($aOR=_{0.66}0.68_{0.71}$, p<0.001). The aOR was attenuated with greater age. Among recipient age <40, 40-59, and 60+, female sex was associated with 39% ($aOR=_{0.57}0.61_{0.65}$, p<0.001), 32% ($aOR=_{0.65}0.68_{0.71}$, p<0.001), and 26% ($aOR=_{0.71}0.74_{0.78}$, p<0.001) lower risk of DGF, respectively. Older age was associated with higher DGF rate only among female recipients (Table 1).

Table 1. The association of recipient age and DGF by recipient gender

	Adjusted odds ratio of DGF			
Age	Female	p value	Male	p value
<40	$_{0.82}\mathbf{0.88}_{0.94}$	**<0.001**	$_{0.93}0.98_{1.03}$	0.4
40-59	Reference	Reference	Reference	Reference
60+	$_{1.01}\mathbf{1.06}_{1.12}$	**0.03**	$_{0.93}0.97_{1.01}$	0.2

Conclusions: Female recipients had lower risk of DGF than male recipients. This association was attenuated among older recipients. Older age conferred higher DGF among female recipients but not male recipients. Clinical caution is warranted for older female recipients.

SA-PO400

30 Years of Kidney Transplantation in Infants (Age < 2 Years): A Single Center Experience Blanche M. Chavers,[1] Michelle N. Rheault,[1] Scott Jackson,[2] Arthur J. Matas,[3] Marie E. Cook,[3] Srinath Chinnakotla.[3] *[1]Pediatrics, Univ of Minnesota, Minneapolis, MN; [2]Transplant Information Services, Univ of Minnesota, Minneapolis, MN; [3]Surgery, Univ of Minnesota, Minneapolis, MN.*

Background: Infants (age < 2 years) with end stage renal disease (ESRD) have increased morbidity and mortality on dialysis compared to older age groups. Yet, because of technical and management issues, there are still concerns about transplanting infants. We evaluated our long-term experience with kidney transplants (KTx) in infants.

Methods: Between 1984-2014, 136 infants (mean age 1.3 ± 0.4 years) underwent KTx (116 living donor) with cyclosporine, prednisone, azathioprine maintenance immunosuppression. We examined trends in survival rates and complications by era (1984-1993 [era 1, n=59], 1994-2003 [era 2, n=42], 2004-2014 [era 3, n=35]).

Results: Patients were 92.6% Caucasian, 70.6% male, and 61.8% with ESRD due to congenital renal anomalies. Mean follow up was 15.7 ± 7.9 years. PostTx initial length of hospital stay declined 37% over the 30-year period (24 d era 1 vs 15 d era 3, p <0.01). Five-year patient survival improved from 95% in eras 1 and 2 to 100% era 3 (not statistically significant). Ten-year death censored graft survival improved from 60% era 1 to 80% era 2 (p=0.04). The incidence of acute rejection, renal artery thrombosis, cytomegalovirus, and urine leaks did not significantly change across eras. Epstein Barr virus (EBV) infection (era 2 vs 3, p < 0.01) frequency increased. PostTx lymphoproliferative disorder (PTLD) incidence was increased in era 2 versus eras 1 and 3 (p=0.03). Hypertension, post Tx diabetes mellitus, and avascular necrosis frequency did not significantly change across eras. Urine leaks (p=0.01) and EBV infection (p=0.02) but not PTLD were higher in infants compared to Tx patients > 2 years of age.

Conclusions: This is the largest series on complications of KTx in infants. Length of initial hospital stay, patient and graft survival rates after KTx have improved in infants since 1984. Urine leaks and EBV infection remain significant postTx complications in infants.

Funding: NIDDK Support

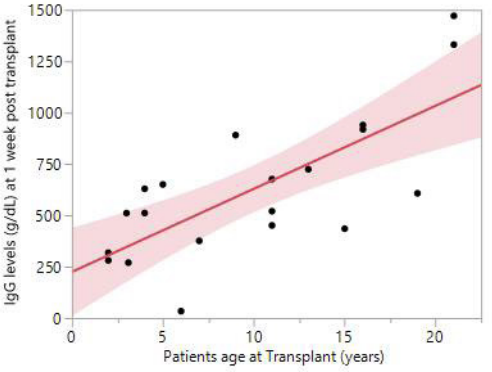
SA-PO401

Immunological Profiling after Pediatric Kidney Transplantation Mariselis Rosa-Sanchez,[1] Marissa J. Defreitas,[1] Chryso P. Katsoufis,[1] Carolyn L. Abitbol,[1] Wacharee Seeherunvong,[1] Yonique P. Petgrave,[1] George William Burke,[2] Aura Jeannette Arenas Morales,[1] Jayanthi Chandar.[1] *[1]Pediatric Nephrology, Jackson Memorial/Holtz Children's Hospital, Miami, FL; [2]Miami Transplant Inst, Univ of Miami, Miami, FL.*

Background: Induction immunosuppressive therapy with anti-thymocyte globulin (rATG) is used by 22% of centers in the US after pediatric kidney transplantation (KT). We assessed the evolution of lymphocyte subsets and Immunoglobulin G (IgG) in the first year after KT in children with our center protocol.

Methods: Data was collected by retrospective analysis of pediatric KT recipients from January 2012 to June 2015 and included demographics, lymphocyte subsets and IgG in children <21 years of age at baseline, 1 week, 1, 6 and 12 months. Induction therapy consisted of rATG (cumulative dose of 3 to 5mg/kg), 2 doses of basiliximab and high dose methylprednisolone for 5-7 days with maintenance therapy of tacrolimus and mycophenolic acid.

Results: Among 52 patients, racial distribution was predominantly Hispanic and African American and 63% were male. Mean age was 10 ±6years. There was a significant drop from baseline in CD4 (55%), CD8 (63.5%), CD25 (13.4%) and NK cells (55%) at week one and a rise at 1 month with a gradual increase to baseline levels between 6 months to 1 year and a significant decline in IgG in younger children at 1 week (see figure; $p<0.0002$;$R^2$0.55) post transplant which improved with time. One child developed bacteremia following treatment of rejection and another had BK virus nephropathy. 1 year graft and patient survival were 98% and 100% respectively.



Conclusions: Triple induction therapy facilitated a steroid sparing protocol with good 1 year graft survival. However, younger patients were prone to hypogammaglobulinemia. Therefore, it is important to exercise vigilance and avoid excessive immunosuppression in the vulnerable younger patients.

SA-PO402

Donor Specific Antibodies and Graft Function in Pediatric Kidney Transplant Recipients Gilad Hamdani,[1] Jens W. Goebel,[2] Paul Brailey,[3] Elizabeth Portwood,[3] David K. Hooper,[1] Alin L. Girnita.[3,4] *[1]Div of Nephrology & Hypertension, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [2]Nephrology Div, Children's Hospital Colorado, Aurora, CO; [3]Hoxworth Blood Center, Univ of Cincinnati Academic Health Center, Cincinnati, OH; [4]Dept of Surgery, Univ of Cincinnati Medical Center, Cincinnati, OH.*

Background: Anti-HLA donor specific antibodies (DSAs) are associated with antibody mediated rejection (AMR) and graft loss in kidney transplant recipients. We aimed to find an association between specific DSA IgG subclasses and graft outcomes in pediatric and young adult kidney transplant recipients (KTRs).

Methods: We performed a single center retrospective chart review of pediatric KTRs with positive anti-HLA DSAs. Data regarding number, HLA classes, MFI, and IgG subclasses of the first positive DSAs was collected. Outcomes studied included AMR (based on the 2013 Banff criteria), clinical AMR (AMR with 15% eGFR reduction), and significant graft dysfunction (graft loss/50% decrease in eGFR).

Results: 35 patients (median age 15.6y, 66% white, 68% male) with DSAs detected 8 days-14 years post transplantation were included and were followed for a median time of 2.8y. Rates of IgG subclass detection were 89%, 31%, 57%, and 26% for IgG1, IgG2, IgG3, and IgG4, respectively. 76% of patients had AMR following DSA detection, 58% had clinical AMR, and 29% experienced significant graft dysfunction during follow up. No association between any IgG subclass and AMR was found. However, 91% of patients with significant graft dysfunction during follow up, all with clinical AMR, had positive IgG3 DSAs compared with 42% with more stable graft function (p=0.01). This association remained significant in a multivariable analysis (table).

Logistic Regression Analysis of Factors Associated with Significant Graft Dysfunction			
Parameter	**Estimate**	**95% CI**	***P* value**
IgG3 DSA	72.91	2.50->1,000	0.013
Time Post Transplantation (y)	1.34	1.03-1.74	0.029

Conclusions: Presence of IgG3 donor specific antibodies is independently associated with significant graft dysfunction in pediatric and young adult kidney transplant recipients.

Funding: Private Foundation Support

SA-PO403

Longitudinal Renal Function after Liver Transplantation in Pediatric Patients Mai Sato,[1] Koichi Kamei,[1] Mureo Kasahara,[2] Kenji Ishikura.[1] *[1]Div of Nephrology and Rheumatology, National Center for Child Health and Development, Tokyo, Japan; [2]Transplantation Center, National Center for Child Health and Development, Tokyo, Japan.*

Background: Adult liver transplant (LT) recipients commonly develop advanced kidney disease; however, the burden of chronic kidney disease (CKD) in children is not well described. The objective of this study was to determine the incidence of CKD after pediatric LT.

Methods: We retrospectively analyzed the data of patients aged < 20 years who underwent LT between November 2005 and March 2015 in our institute. The following potential risk factors for renal dysfunction were analyzed: sex, age, primary liver disease, pre-existing kidney disease, rejection, and immunosuppressive agents.

Results: The cohort included 314 pediatric LT recipients (135 males). The median age at LT was 3.3 years (IQR 4.5) and the median follow-up duration was 3.9 years (IQR 4.5). Thirty-one patients died after LT. We divided the patients to three groups according to the primary disease: BA (biliary atresia), non-BA (other liver disease without primary renal complication), and KD (patients with pre-existing kidney disease). There were 143 patients (47 males) in the BA group, 139 (70 males) in the non-BA group, and 32 (18 males) in the KD group. The KD group comprised autosomal recessive polycystic disease (13 cases), methylmalonic acidemia (13 cases), primary hyper-oxaluria (5 cases) and nephronophthisis (1 case). Five-year renal survival, which endpoint was CKD stage 3, was 0.97 in BA group, 0.91 in non-BA group and 0.61 in KD group. We performed Cox regression survival analysis to adjust renal survival for confounding risk factors. There was no independent predictor by multivariate analyses, sex, age, rejection, but male and adolescent patients were likely to develop CKD.

Conclusions: In non-pre-existing kidney disease patients, 1.9% of patients developed over CKD 3 and 0.35% developed ESKD. These rates were lower than those in previous reports. Immunosuppressant strategy, additional mycophanolate mofetil and lower calcineurin inhibitor level may be effective to prevent progressive kidney damage.

SA-PO404

Sex and Age Differences in Medication Adherence in Adolescent and Young Adult Kidney Transplant Recipients Julie Boucquemont,[1,2] Bethany J. Foster,[1,2] The TAKE-IT Investigators.[3] *[1]Research Inst. of the McGill Univ Health Centre, Montreal, QC, Canada; [2]Dept of Epidemiology, Biostatistics and Occupational Health, McGill Univ, Montreal, QC, Canada; [3]The TAKE-IT Investigators.*

Background: Immunosuppressive medication adherence is poorer in adolescents than younger children, but it is unknown whether adherence differs between males and females, or by age, among adolescent and young adult kidney transplant recipients. We aimed to determine whether adherence differs by sex and age in this population.

Methods: We examined data from the 3-month run-in period (no intervention) of the randomized TAKE-IT trial. Adherence was monitored using a multidose electronic pillbox in 124 patients (11-24 y, ≥3 mo. post-transplant, followed in 8 transplant centers in Canada and USA), and classified as perfect (all doses taken; all doses on time) or not for each day of observation for each patient. We used logistic regression, with a random effect to account for correlation between adherence measurements within patients, to estimate the association between sex and adherence. We adjusted for race and time since transplant, and included an age by sex interaction.

Results: Among 124 patients, 61% were male; 65% were white. Median age at baseline was 16.2y [IQR 13.6-17.5]; median time since transplant was 2.7y [IQR 0.8-7.0]. There was a significant interaction between age and sex (p=0.009). Males ≥17y had a significantly lower likelihood of perfect adherence than younger males (OR=0.26, 95% CI [0.14-0.48]). There was no significant difference by age for females. Adherence did not differ by sex among patients <17y. Among those ≥17y, females had a significantly higher likelihood of perfect adherence than males (OR=3.82, 95% CI [1.09-13.40]).

Conclusions: Male kidney transplant recipients ≥17y have poorer adherence than younger adolescent males, whereas adherence does not differ by age among females. Adherence does not differ by sex in those <17 y, but among those ≥17y, adherence may be poorer in males than females.

Funding: NIDDK Support

SA-PO405

Risk Factors for Decline in eGFR Below 60 mL/min/1.73 m² after Kidney Transplantation in Japanese Children Kiyonobu Ishizuka, Ken-Ichiro Miura, Keiichi Takizawa, Yuji Tomii, Yohei Sasada, Naoto Kaneko, Tomoo Yabuuchi, Yasuyuki Sato, Hiroko Chikamoto, Yuko Akioka, Motoshi Hattori. *Dept of Pediatric Nephrology, Tokyo Women's Medical Univ, Tokyo, Japan.*

Background: Maintenance of eGFR above 60 ml/min/1.73m² is necessary for optimal growth in children after kidney transplantation (KTx). The objective of this study was to investigate serial change in eGFR after KTx in children and identify risk factors for decline in eGFR below 60 ml/min/1.73m².

Methods: This study was approved by the Institutional Review Board at Tokyo Women's Medical University. Fifty-eight children aged < 20 years with congenital anomalies of kidney and urinary tract who underwent living donor KTx from 2003 to 2013 and were followed up for at least 1 year were included in this analysis. Immunosuppressive agents used were calcineurin inhibitors (CNI), mycophenolate mofetil, methylprednisolone, and basiliximab. eGFR values were calculated using formula developed for Japanese children (Clin Exp Nephrol 2013). Cox proportional hazard models were used to determine risk factors affecting the decline in eGFR below 60 ml/min/1.73m^2. The covariates included donor's age, recipient's age, body weight and height at KTx, graft weight, CNI (tacrolimus or cyclosporine), CNI toxicity, T cell-mediated rejection, antibody-mediated rejection, CMV infection, EB virus infection, BK virus infection. The median follow-up duration was 5.0 years (interquartile range, 3.0 to 5.0 years).

Results: The median eGFR values after RTx were 78.6 [68.5 to 88.3], 67.4[56.0 to 74.9], 65.2 [54.7 to 73.2], and 60.1 [54.2 to 67.2] ml/min/1.73m^2 at 1 month, 6 months, 1 year, and 5 years, respectively. The proportion of patients with eGFR above 60 ml/min/1.73m^2 was 65.9% and 52.1% at 1 year and 5 years, respectively. On multivariate analysis, independent risk factors for decline in eGFR below 60 ml/min/1.73m^2 were donor's age (hazard ratio [HR] 1.1, 95% confidential interval [CI] 1.0 to 1.1) and antibody-mediated rejection (HR 4.2, 95%CI 1.4 to 12.5).

Conclusions: Our study demonstrated that posttransplant eGFR values were unsatisfactory in a substantial proportion of children. Donor's age and antibody-mediated rejection were independent risk factors for decline in eGFR after KTx.

SA-PO406

Outcomes of Kidney Transplantation in Children and Young Adults with Cystinosis in the United States Sarah J. Kizilbash,[1] Jon J. Snyder,[2] Hassan N. Ibrahim,[3] Blanche M. Chavers.[1] *[1]Pediatric Nephrology, Univ of Minnesota, Minneapolis, MN; [2]Minneapolis Medical Research Foundation, Minneapolis, MN; [3]Nephrology, Univ of Minnesota, Minneapolis, MN.*

Background: Cystinosis is the cause of end-stage renal disease in 2% of kidney transplant recipients in the United States (US). Cysteamine has improved the prognosis of cystinosis; however, its impact on long-term kidney transplant outcomes is unknown.

Methods: All kidney transplant recipients (≤ 21 years of age) with data in the Scientific Registry of Transplant Recipients, transplanted before 12/31/2015, were included. We arbitrarily divided the study period into 3 eras: era1 (< 1995), era2 (1/1/1995-12/31/2005) and era3 (1/1/2006-12/31/2015). Survival rates were estimated using Kaplan-Meier methods. Hazard ratios were adjusted for era, age at transplant, race, gender, donor type and pre-transplant dialysis using cox proportional hazard models.

Results: We identified 317 patients with cystinosis and 26,554 without cystinosis who met our inclusion criteria. The median age at transplant for cystinosis did not change significantly over time (era1=12.5, era2=13.7, era3=13.6; p 0.4). The patient and graft survival are given in table 1. Delayed graft function was significantly lower in patients with cystinosis after adjusting for covariates (adjusted hazard ratio (aHR): 0.40 (0.19 – 0.85); p 0.018). The 5-year graft survival rates for cystinosis were 71.3%, 84.3% and 71.7% for era1, era2 and era3, respectively. After adjusting for covariates, patients transplanted in era2 had a 75% lower hazard of graft loss at 5 years compared to era1 (aHR: 0.25 (0.08 – 0.77); p 0.02), however, the 5-year graft survival was not significantly different between era1 and era3 (p 0.23).

Conclusions: The median age at transplant for cystinosis in the US has not changed from 1995-2015. Patients with cystinosis have superior 1 and 5-year graft survival compared to non-cystinosis patients. Alarmingly, the 5-year graft survival for US cystinosis patients has deteriorated over the last decade.

	Cystinosis (n = 317)	Non-cystinosis (n = 26,554)	P value
Patient survival (%)			
1-year	98.9	98.2	0.29
5-year	94.9	95.24	0.88
10-year	89.5	91.7	0.73
Graft survival (%)			
1-year	95.4	90.9	0.007
5-year	77.5	71.3	0.012
10-year	53.1	51.4	0.15

Funding: NIDDK Support

SA-PO407

Infectious Complications in Pediatric Kidney Transplant Recipients Treated with Rituximab: A Single-Center Study Naoto Kaneko, Ken-Ichiro Miura, Yuji Tomii, Keiichi Takizawa, Yohei Sasada, Tomoo Yabuuchi, Yasuyuki Sato, Kiyonobu Ishizuka, Yuko Akioka, Motoshi Hattori. *Pediatric Nephrology, Tokyo Women's Medical Univ.*

Background: To date, few reports have assessed safety of rituximab (RIT) use in pediatric kidney transplantation. The aim of this study was to evaluate infectious complications of RIT which occurred during the first year after transplantation.

Methods: This study was approved by the Institutional Review Board at Tokyo Women's Medical University. A total of 90 patients aged < 20 years underwent living donor kidney transplantation at our center between January 2005 and March 2016 and were divided into two groups; RIT group (21 patients) and non-RIT group (69 patients). Medical records were reviewed for clinical information. Immunosuppressive regimen consisted of calcineurin inhibitors, mycophenolate mofetil, methylprednisolone, and basiliximab in all patients. Indication of preoperative RIT use included primary focal segmental glomerulosclerosis, ABO incompatible transplantation, and HLA sensitized transplant. RIT group received a single dose of RIT (145 mg/m^2 [124 to 166 mg/m^2]) before transplantation. Antimicrobial prophylaxis was administered to all patients. We compared incidence of serious infections and late-onset neutropenia during one year after transplantation in two groups. Serious infection was defined by any bacterial, viral, and fungal infection requiring admission or prolongation of hospitalization. Late-onset neutropenia was defined by neutrophil count < 1000 /μL which occurred after 4 weeks of transplantation.

Results: The overall incidence of serious infection in two groups was comparable (23.8% in RIT group and 36.2% in non-RIT group, respectively, P=0.30). There were no significant differences in the occurrence of bacterial infection (9.5% versus 14.5%, P=0.72), viral infection (14.3% versus 13.0%, P=1.0), and late-onset neutropenia (9.5% versus 2.9%, P=0.23) between RIT and non-RIT groups. There were no fungal infections. CMV disease occurred only in non-RIT group (5.8%, P=0.57).

Conclusions: Our preliminary study indicates that RIT use does not increase infection risk during one year after kidney transplantation in pediatric population.

SA-PO408

Extremely High Risk of Cancer after Solid Organ Transplant in Childhood Abhijat Kitchlu,[1] Stephanie Dixon,[2] Jade S. Hayward,[3] Rahul Chanchlani,[1] Jovanka Vasilevska-Ristovska,[3] Karlota Borges,[3] Paul Nathan,[3] Vicky Ng,[3] Diane Hebert,[1,3] Joseph Kim,[1] Rulan S. Parekh.[1,3] *[1]Div of Nephrology, U of Toronto; [2]Inst for Clinical Evaluative Sciences; [3]Hosp for Sick Children.*

Background: Long-term immunosuppression after solid organ transplantation has been shown to increase the risk for subsequent neoplasm in adults. There is a paucity of data regarding cancer outcomes in pediatric solid organ transplant recipients.

Methods: We conducted a population-based retrospective cohort study in Ontario, Canada. We assessed recipients of pediatric solid organ transplants at the Hospital for Sick Children in Toronto between 1991-2014. We compared cancer outcomes to a non-transplanted population of Ontario residents (<18 years old) using provincial administrative data. The primary outcome was overall incidence of cancer. Secondary outcomes included survival and incidence of solid/non-solid cancers.

Results: A total of 951 childhood transplant recipients (kidney n=400, liver n=283, heart n=218, lung n=36, multiorgan n=14) were compared to over 5 million children from the general population of similar ages. Median age was 8 years old; 50% were male. Over a median follow-up of 10 years (range 0 - 24), the cumulative incidence of cancer was 20% in transplant recipients and 1.2% in the general population. Incidence of cancer, cancer-free and all-cause mortality are shown in Table 1. The incidence rate ratio of cancer in transplanted vs. non-transplanted was 33.

Conclusions: Recipients of solid organ transplants in childhood have a 30 times higher incidence of cancer compared to the general population up to 24 years after transplantation. Our data suggest that early surveillance may be warranted in this high-risk population.

Table 1: Incidence of Cancer and Mortality

	Event rate/1000 patient-years(95%CI)		Incidence rate ratio
	Non-transplant	Transplant	
	N=5,276,621	N=951	
All Cancers	0.32 (0.31-0.33)	10.6 (8.53-13.1)	32.9
Non-solid Cancers (incl PTLD)	0.08 (0.07-0.08)	6.28 (4.77-8.28)	81.3
Solid Cancers	0.24 (0.24-0.25)	4.27 (3.06-5.98)	17.6
Cancer-free Mortality	0.26 (0.26-0.27)	18.5 (15.7-21.7)	70.0
All-cause Mortality	0.29 (0.29-0.30)	21.2 (18.3-24.6)	73.1

SA-PO409

Impact of Obesity and Metabolic Syndrome on Myocardial Function and Strain in Children after Kidney Transplant Kl Sgambat, S. Clauss, M. Lasota, Asha Moudgil. *Children's National.*

Background: In light of the major impact of cardiovascular (CV) morbidity on outcomes in children with End Stage Renal Disease (ESRD), a prospective controlled longitudinal study was conducted to investigate myocardial function and strain in children before and after kidney transplant (Tx). Impact of obesity and metabolic syndrome (MS) on CV morbidity was investigated.

Methods: Kidney Tx recipients (3-20 yrs) had standard echo and myocardial strain by speckle tracking measured at 12 months pre-Tx, and 1, 18, and 30 months post-Tx. More negative strain signifies better cardiac contractility. Tx with MS met ≥3 criteria: glucose intolerance (HbA1c>5.6%or glucose>100), BP>95th%ile,central obesity(WC>95th%),HDL<5th%ile, TG>95th%ile. Controls were healthy, non-obese children. Statistical analysis by Student's t-test used for comparison between groups(pre-,post-Tx, and controls) and multivariate longitudinal GEE regression for association of variables.

Results: 39 Tx recipients(23 lean, 16 obese) were compared to 24 healthy children (age 12.7±0.3 vs. 11±0.1 yrs, p=0.2). LVM/Ht$^{2.7}$ was worse pre-Tx compared with controls (39.1±3.5 vs. 29.1±3.7),p=0.04, and did not improve within the first 30 months post-Tx (35.8±1.4). Ejection Fraction(EF) pre-Tx (61.4±0.9)was worse vs. controls (64.1±0.4%,p=0.01) but improved to 64.6±0.3% post-Tx, p=0.0003. There were no differences in LVM/Ht$^{2.7}$ or EF between lean and obese children, pre or post-Tx. Speckle tracking analysis revealed worse myocardial strain in obese vs. lean children post-Tx(-18.6±0.4 vs.-20.1±0.4, p=0.03). Overall strain improved from -17.8±0.7 pre-Tx to

-19.5±0.3 post-Tx (p=0.02), but remained worse vs controls (-23.1±0.4), p=0.02. GEE regression showed only obesity was significantly associated with impaired strain (β=1.32, p=0.006); MS and its individual components were non-significant.

Conclusions: Children with ESRD demonstrate improved EF after Tx, but continue to exhibit impaired myocardial strain, indicating ongoing subtle LV dysfunction detected by speckle tracking echo. Myocardial function after Tx is negatively impacted by obesity, which was also detectable only by speckle tracking echo. Efforts to prevent obesity may help to improve CV outcomes in this high risk population.

SA-PO410

Acute Rejection Is the Primary Determinant of Worse Kidney Allograft Outcomes in Patients with De Novo Donor-Specific Antibodies Scott Davis,[1] Jane Gralla,[2] Alexander C. Wiseman,[1] James E. Cooper.[1] *[1]Medicine, Univ of Colorado, Aurora, CO; [2]Pediatrics, Univ of Colorado, Aurora, CO.*

Background: Although many patients develop de novo donor-specific antibodies (dnDSA), only a portion will experience associated graft impairment or loss. Clinical acute rejection (cAR) may lead to or result from the development of dnDSA and may be the primary determinant of worse graft survival among these patients. The purpose of this study was to delineate the impact of cAR and dnDSA on graft outcomes.

Methods: From 2007 to 2013, 593 consecutive kidney recipients without pre-existing DSA were screened for dnDSA at months 1, 6, 12, yearly and when indicated. Acute rejection was diagnosed by clinical suspicion and was biopsy-proven in 89% of cases. Graft survival was assessed by KM analysis and time-dependent Cox modeling with median (IQR) follow-up time of 49 (31-69) months.

Results: 204 (34.4%) patients developed dnDSA (median onset 8.3 months). 5-year death-censored graft survival was lower in patients with dnDSA (Figure 1). cAR was more common in dnDSA(+) vs. dnDSA(-) patients (27% vs. 5%, p<0.001) and its timing relative to dnDSA detection did not effect graft outcomes. When stratifying patients by cAR and dnDSA status, patients had worse eGFR (p<0.001), more proteinuria (p<0.001), and lower 5-year graft survival (p<0.001) only when combined with cAR, regardless of dnDSA status (Figure 2). In a multivariable analysis accounting for both cAR and dnDSA, cAR had a stronger association with graft loss (HR 9.1, 95% CI 4.3-19.0, p<0.001) compared to dnDSA alone (HR 2.2, 95% CI 1.1-4.5, p=0.026).

Figure 1:
Death Censored Graft Survival by dnDSA(+) vs. dnDSA(-)

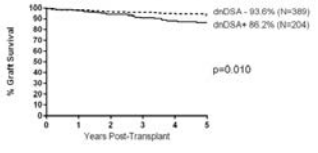
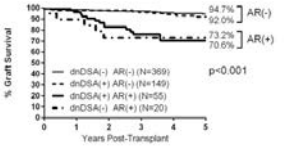


Figure 2:
Death Censored Graft Survival by dnDSA and Acute Rejection



Conclusions: In this large retrospective analysis of a prospective dnDSA screening protocol, both dnDSA and cAR were associated with inferior intermediate term graft outcomes. Importantly, the deleterious impact of dnDSA on eGFR, proteinuria, and graft loss was only seen when combined with cAR.

SA-PO411

Indoleamine 2,3-Dioxygenase Is a Biomarker of Rejection in Experimental Kidney Transplantation Youli Wang,[2] Randi Lassiter,[1] Chak-Sum Ho,[4] Daniel Kleven,[3] Ryan P. Jajosky,[3] Eslam Mohamed,[2] Matthew Winn,[1] N. Stanley Nahman,[2] Todd D. Merchen.[1] *[1]Surgery, Medical College of Georgia at Augusta Univ, Augusta, GA; [2]Medicine, Medical College of Georgia at Augusta Univ, Augusta, GA; [3]Pathology, Medical College of Georgia at Augusta Univ, Augusta, GA; [4]Gift of LIfe Michigan, Ann Arbor, MI.*

Background: Indoleamine 2,3-dioxygenase (IDO) degradation of tryptophan promotes the induction of regulatory T cells (Treg), implying a role for IDO in mitigating allograft rejection. However, the effects of renal ischemia (RI) and allo transplantation on kidney IDO expression remain undefined. To address this question, we conducted auto and allo kidney transplants (Tx) in pigs.

Methods: Pigs underwent orthotopic allogeneic kidney Tx (Allo) (n=9) or autoTx (Auto) (n=10). For Allo, pairs of mismatched Yorkshire piglets were operated simultaneously with left kidneys exchanged. Allo and Auto had ~30 minutes of RI. All pigs had right nephrectomy (Nx) prior to closure and left Nx at sacrifice at 72hrs. No immunosuppression was used. IDO activity in kidney homogenates was assessed using HPLC. IDO mRNA was quantitated by PCR. Tissue IDO expression was assessed using IHC with IDO antibody. Activation of Tregs, dendritic cells (DC) and macrophages (MP) were identified using IHC with specific antibodies.

Results: All pigs experienced increased postop creatinine with significantly higher levels in Allo vs Auto (8.12±1.50 vs 2.83±0.60 mg/dL respectively, P=0.006). Auto had mild tubular injury without significant changes in IDO mRNA nor IDO activity when compared to right Nx controls (n=16). In contrast, Allo demonstrated acute rejection, increased IDO mRNA, and a 19.5 fold increase in IDO activity vs Auto. IDO expression (IHC) came from infiltrated cells and sloughed tubular cells. Both Auto and Allo had a notable infiltration of MP. There was a substantial accumulation of Tregs and DC observed in Allo kidneys vs Autos.

Conclusions: IDO does not increase as a consequence of RI. A dramatic increase of IDO mRNA, protein, and activity occurs in rejecting renal allografts. These data suggest that IDO may act as a biomarker of rejection in experimental renal transplantation.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO412

The Clinical Significance of Severe Ischemia-Reperfusion Injury (IRI) in Triggering Rejection Ibrahim Batal,[1] Glen S. Markowitz,[1] Vivette D. D'Agati,[1] Demetra Tsapepas,[1] Russell J. Crew,[1] Vanesa Bijol,[2] Mark A. Hardy,[1] Sumit Mohan,[1] Anil K. Chandraker.[2] *[1]Columbia Univ, New York, NY; [2]Brigham & Women's Hospital/Harvard Medical School, Boston, MA.*

Background: In non-immunosuppressed animals, IRI enhances allograft immunity and triggers rejection. In the era of potent immunosuppression, the effects of severe IRI on allograft function and alloimmunity in kidney transplant recipients need to be systematically assessed.

Methods: Acute tubular injury in post-reperfusion biopsies is a morphologic reflection of the severity of IRI. All post-reperfusion biopsies from patients who underwent deceased donor kidney transplantation at Columbia University Medical Center from 2006 through 2009 (n=382) were assessed for the presence of diffuse acute tubular injury (ATN) as a reflection of severe IRI. The samples were classified as "ATN" (n=134) and "no ATN" (n=248).

Results: Compared to patients without ATN, patients with ATN had a trend toward worse allograft survival (P=0.08) and a higher incidence of primary non-function [10/134 (8%) vs. 7/248 (3%), P=0.07]. However, even when primary non-function were excluded, patients with ATN had a mean lower eGFR at 1-year (P=0.04), 2-years (P=0.003), and 3-years (P=0.001) post-transplantation and showed increased number of rejection episodes during 1st year after transplantation [44/124 (35%) vs. 61/241 (25%), P=0.05], and higher frequency of rejection episodes/year [0.46 +/-0.99 vs. 0.30 +/-0.85, P=0.03] compared with patients without ATN. To provide a better understanding of the potential role of graft dendritic cells (DCs) in triggering rejection, DCs were assessed in a pilot cohort of post-reperfusion biopsies with (n=15) or without (n=12) subsequent rejection using the BDCA-1 marker. Patients who developed subsequent rejection had lower DC density compared to these without rejection (0.4 +/- 0.5 vs. 0.8 +/- 0.6 cells/high power field, P=0.007).

Conclusions: ATN in post-reperfusion biopsies is associated with subsequent inferior allograft function and increased rejection episodes in later biopsies. Low DC density in post-reperfusion biopsies may be associated with increased allograft immunogenicity.

Funding: Clinical Revenue Support

SA-PO413

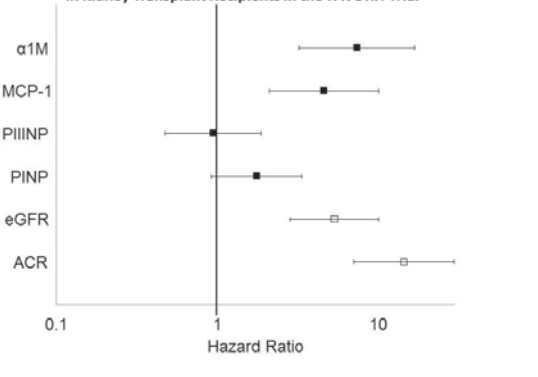
Urine Fibrosis Markers and Risk of Kidney Allograft Failure: The FAVORIT Trial Joachim H. Ix,[1] Ronit Katz,[2] Nisha Bansal,[2] Meredith C. Foster,[3] Daniel E. Weiner,[3] Vasantha Jotwani,[4] Jan M. Hughes-Austin,[1] Dianne B. McKay,[1] Francis B. Gabbai,[1] Chi-Yuan Hsu,[4] Andrew Bostom,[5] Andrew S. Levey,[3] Michael Shlipak.[4] *[1]UCSD; [2]UW; [3]Tufts; [4]UCSF; [5]Rhode Island.*

Background: Tubulo-interstitial fibrosis marks risk of allograft failure in kidney transplant recipients (KTRs) but is poorly captured by eGFR or urine ACR. Urine alpha 1 macroglobulin (α1M), monocyte chemoattractant protein-a (MCP1), procollagen type III (PIIINP) and type 1 (PINP) N-terminal propeptide are correlated with tubulo-interstitial fibrosis on biopsy. Whether these markers can noninvasively identify risk of allograft failure independent of eGFR and ACR is unknown.

Methods: In this case-cohort study in KTRs participating in the FAVORIT trial, we measured urine α1M, MCP1, PIIINP, and PINP in random sub-cohort of 491 participants and 257 allograft failure cases. We used weighted Cox models adjusted for demographics, CKD risk factors, eGFR, ACR, and urine creatinine (to account for tonicity). Each biomarker was evaluated on the log2 scale ("per doubling") and by quartiles.

Results: In the random sub-cohort, mean age was 51± 9 years, median graft vintage was 3.7 years, 42% had live donors, and mean baseline eGFR was 46±18 ml/min/1.73m^2. During 3.5 years mean follow-up, there were 257 kidney allograft failure events. Higher α1M (HR per doubling 1.73 [1.43, 2.08]) and MCP1 (HR 1.60 [0.32, 1.93]) were associated with allograft failure, independent of eGFR, ACR and other risk factors. Evaluating high vs. low quartiles, associations were similar in strength to extreme eGFR and ACR quartiles, despite adjusting for eGFR and ACR. Urine PIIINP and PINP were not independently associated with allograft failure.

Adjusted Association of High Quartile of Each Marker with Risk of Allograft Failure in Kidney Transplant Recipients in the FAVORIT Trial



Adjusted for urine creatinine, age, sex, race, country, FAVORIT randomization group, diabetes, SBP, CVD, smoking, graft vintage, living donor status, eGFR, and urine ACR.

Conclusions: Measurement of α1M and MCP1 in urine of KTRs may serve as a non-invasive marker of tubulo-interstitial fibrosis severity and risk of allograft failure independent of eGFR and ACR.

Funding: NIDDK Support, Private Foundation Support

SA-PO414

Outcomes of Severe Tubulitis Are as Poor as Vascular Rejections Shefali Patel, Hilda E. Fernandez, Ibrahim Batal, Russell J. Crew. *Columbia Univ, NY.*

Background: The continuum of renal transplant acute cellular rejection(ACR) progresses in severity from borderline changes to tubulitis to vasculitis. Optimal treatment of severe tubulitis (grade 1B) is poorly defined w/ some centers given steroids and others immediately using lymphocyte depletion.

Methods: We identified transplant rejections and collected the following: demographics, induction therapy, rejection grade, other pathology findings, treatment, therapy response and infectious complications. Rejectors were compared to a control group without rejection.

Results: From 1/2012-12/2014, we transplanted 681 pts using lymphocyte depletion (antithymocyte globulin[ATG] or campath 1H), tacrolimus, mycophenolate, and rapid steroid withdrawal. 169 patients had ACR: 91 Borderline, 42 ACR1A, 39 ACR1B, 14 ACR2A and 1 ACR2B. There were no differences in age, sex, race, induction, or donor type between pts w/ ACR1B or ACR2. Creat at time of rejection was similar (2.83 vs 2.77, p-NS) as was time to rejection. ATG was used in 64.1% of ACR1B and 78.5% of ACR2. Creat remained higher in the ACR1B group during follow up (2.55 vs 1.73, approaching statistical significance ($p = 0.064$)), despite no initial difference in the distribution of chronic pathologic findings. Persistent (59%) and recurrent (7.9%) rejections were common in ACR1B group, but similar to ACR2 group (33% and 20%). Allograft failure occurred in 5 ACR1B vs 1 ACR2. There were no differences in creat, persistent or recurrent rejections among ACR1B pts who received ATG vs steroids alone. Viremic complications after treatment were similar between groups (1B rejectors= 3 BK, 5 CMV, 1 EBV; grade 2= 3BK). IFTA > 25% on initial ACR1B biopsy was associated with a higher creat at last follow-up 2.8 mg/dL vs 1.69 mg/dL ($p = 0.019$) but not failure or recurrent rejections. A control group of 40 pts w/out rejection had a median serum Cr 1.38 mg/dl at last follow-up ($p < 0.0001$) w/ 100% graft survival ($p = 0.029$).

Conclusions: Even in an era with more potent immunosuppression, ACR continues to impact allograft survival. In particular, pts w/ more severe tubulitis and vasculitis tend to have repeated rejections episodes despite antibody depleting therapy with increased infectious complications.

SA-PO415

The Effect of Histological CD20 Positive B Cell Infiltration in Acute Cellular Rejection on Kidney Transplant Allograft Survival Rending Wang, Jingyi Zhou, Jia Shen, Jianghua Chen. *The Kidney Disease Center, The First Affiliated Hospital of Zhejiang Univ, Hangzhou, Zhejiang, China.*

Background: Acute rejection, especially the irreversible episodes, has definite impact on renal allograft. However, it is controversial whether lymphocytes infiltration exhibited in biopsy specimens is important for transplant outcomes. This study focused on the effect of CD20+ B cell infiltration in the biopsy specimens from the allografts with acute cellular rejection in Chinese population.

Methods: Totally 217 cases of biopsy-proved acute cellular rejection were documented in our renal transplantation system from Sep. 2001 to Dec. 2014. There was only 1 case lost-to-follow. According to the presence of CD20+ B cell infiltration and its degree, all 216 cases included were divided into CD20-group (n=83), mild CD20+ group (n=76), moderate CD20+ group (n=36), and severe CD20+ group (n=21). Baseline information, serum creatine and GFR before and after treatment, steroid resistance, reversal rate, graft loss and survival were analyzed.

Results: There was no significant difference between groups in baseline information. Steroid and antibodies combination treatment in CD20+ group (39.1%, 52/133) and CD20- group (59.0%, 49/83) didn't show significant difference (p=0.004). CD20+ group showed better serum creatine and GFR before treatment. After treatment, however, groups showed similar graft function. CD20+group had fewer graft loss (18.8% vs. 32.5%, p=0.022) and better survival rate. Further exploration in infiltration degree suggested that it was positively related with graft survival with no statistical significance.

Conclusions: Acute cellular rejection with CD20+ B cell infiltration showed better outcomes after treatment. The presence of CD20+ B cells is protective for renal allografts.

Funding: Government Support - Non-U.S.

SA-PO416

The Effect of Histological Isolated Endarteritis Combined with CD20 Positive B Infiltration in Acute Cellular Rejection on Kidney Allograft Survival Rending Wang, Jingyi Zhou, Jia Shen, Jianghua Chen. *The Kidney Disease Center, The First Affiliated Hospital of Zhejiang Univ, Hangzhou, Zhejiang, China.*

Background: Endarteritis post renal transplantation is regarded as T-cell mediated acute rejection (AR) by Banff classification. Results from DNA microarrays suggested that endovasculitis did not represent T-cell mediated AR exactly and its effect on allograft outcomes was unclear.

Methods: Totally 217 cases of biopsy-proved AR rejection were documented in our renal transplantation system from Sep 2001 to Dec 2014. There was only 1 case lost- to-follow. After 24 cases excluded because of tubulointerstitial rejection, 192 cases were included with 95 Class IA,16 Class IB, 79 Class IIA,and 2 Class IIB. According to the presence of endarteritis and CD20+B cell infiltration, all 192 cases were divided into CD20-endarteritis-group (n=33), CD20+endarteritis-group (n=78),CD20-endarteritis+ group (n=46), and CD20+endarteritis+group (n=35). Baseline information, serum creatine and GFR before and after treatment, steroid resistance, reversal rate, graft loss and survival were analyzed.

Results: There was no significant difference between groups in baseline information. Average time to rejection was separately 182 days, 374 days, 493 days and 729 days. The percentage of steroid and antibodies combination treatment was separately 42.8%, 63.0%, 54.5% and 35.9% (p=0.022). Graft loss was separately 8.6% (3/35), 23.9% (11/46), 42.4% (14/33) and 23.1% (18/78) (p=0.013). Endarteritis + group showed earlier rejection (291 days vs. 659 days) but higher reversal rate (77.5% (86/111) vs. 90.1% (73/81), p=0.022). GFR in endarteritis - group was significantly higher before and at rejection but signigicantly lower 3-60 months after biopsy. Endarteritis + group had a much lower graft loss rate (17.3% (14/81) vs. 28.8% (32/111), p=0.064). Although general survivals were similar, survival rate after rejection in endarteritis + group was higher. The best survival was observed in CD20+ endarteritis + group.

Conclusions: Acute cellular rejection with endarteritis showed better outcomes after treatment. Endarteritis with CD20+B cell infiltration implies lower graft loss and better graft survival.

Funding: Government Support - Non-U.S.

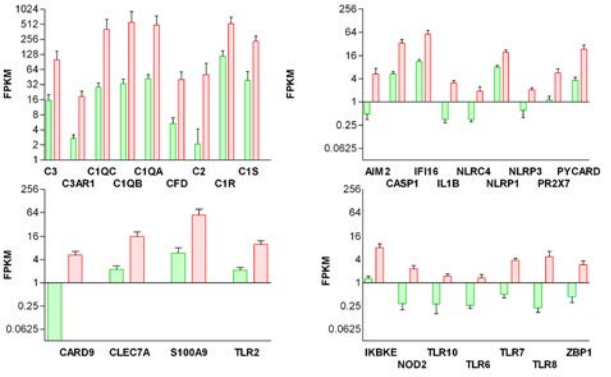
SA-PO417

Innate Immunity Is a Strong Feature of Acute Cellular Rejection in Human Kidney Allografts Franco B. Mueller, Hua Yang, Carol Y. Li, Karan Jatwani, Catherine Snopkowski, Liana S. Perry, Matthew Magruder, John R. Lee, Steven Salvatore, Darshana Dadhania, Surya V. Seshan, Manikkam Suthanthiran, Thangamani Muthukumar. *Weill Cornell Medicine.*

Background: Immunity is traditionally dichotomized as innate immunity and adaptive immunity. We and others have reported intragraft expression of mRNA encoding T and B cell proteins, cytokines and chemokines central to adaptive immunity. We now report that innate immunity is a strong feature of human allograft rejection following RNA-sequencing (RNA-Seq) of human kidney allograft biopsies.

Methods: We did RNA-Seq of of 5 clinically indicated acute cellular rejection (ACR) biopsies from 5 patients and 5 surveillance normal biopsies from 5 patients. Total RNA isolated from the biopsies were sequenced using the Illumina HiSeq platform. Differential gene expression analysis was done using edgeR. We used KEGG and NCBI databases for molecular gene grouping, gene family or gene pathway.

Results: As predicted, there was overexpression of adaptive immunity related transcripts in ACR biopsies. In addition, innate immunity related transcripts were overexpressed in ACR biopsies. In the ACR biopsies, 9 complement genes, 9 inflammasome-related genes, 5 damage associated molecular pattern (DAMP) genes and 11 pathogen associated molecular pattern (PAMP) genes were significantly differentially expressed. In the figure, genes belonging to overlapping categories are shown once only.



Kidney intragraft expression of **Complement genes** (top left), **Inflammasome genes** (top right), **DAMP genes** (bottom left) and **PAMP genes** (bottom right)
Bar graph depicts mean±SE
Red: For-cause biopsies showing acute cellular rejection (N=5); Green: Surveillancebiopsies reported as normal
FPKM- Fragments Per Kilobase of transcript per Million mapped reads

Conclusions: RNA-Seq of human kidney allograft biopsies provides a panoramic view of participants in acute cellular rejection in human kidney allografts. Very surprisingly, genes integral to innate immunity were a striking feature of acute cellular rejection, a process long considered to be the exclusive province adaptive immunity. Our novel findings invite consideration of other anti-inflammatory drugs such as IL-1 receptor antagonist, TNF-antagonist or alpha-1-antitrypsin as anti-rejection agents.

Funding: NIDDK Support

SA-PO418

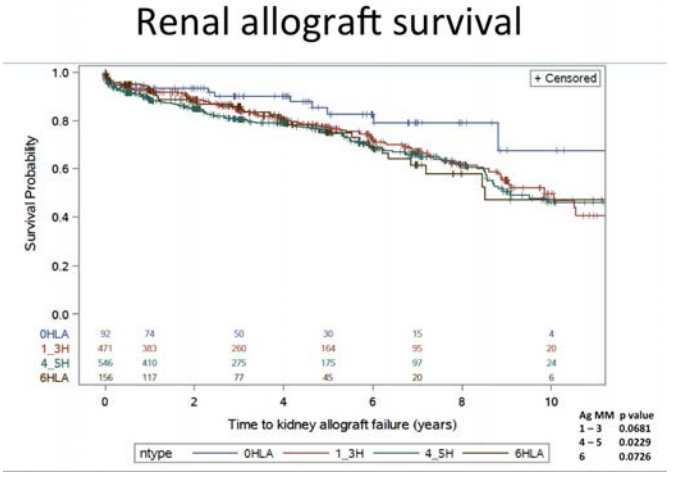
Impact of HLA Mismatch on the Renal Allograft Survival among ABO Incompatible Renal Transplant Karthikeyan Venkatachalam, Tarek Alhamad, Bilal A. Kanawati, Daniel C. Brennan. *Div of Nephrology, Washington Univ in Saint Louis, Saint Louis, MO.*

Background: Given the advances in immunosuppressive regimens and medical care, ABO incompatible kidney transplantation has become an acceptable option for highly sensitized patients. Data on the influence of HLA matching among ABO incompatible renal transplant outcomes are sparse.

Methods: We performed a retrospective analysis of ABO incompatible transplant recipients over 18 years of age at the time of transplantation from the Organ Procurement and Transplantation Network (OPTN) Database between 2000 and 2013. Patients were categorized into 4 groups according to the level of HLA mismatch; 0, 1-3, 4-5 and 6 HLA mismatches (HLA MM). Associations between HLA MM and post-transplant graft failure and patient death were examined by Cox regression.

Results: There were 1266 ABO incompatible living transplant recipients. Out of these, 7.3% had 0 HLA MM, 37.2% had 1-3 HLA MM, 43.2% had 4-5 HLA MM, and 12.32% had 6 HLA MM.

0 Antigen MM as control	Hazard ratio
1 - 3 Ag MM	1.705
4 - 5 Ag MM	1.932
6 Ag MM	1.792



Conclusions: 0 antigen mismatched ABO incompatible transplants had a better kidney allograft survival compared to other HLA mismatches. No significant differences existed between 1-6 antigens mismatched ABO incompatible recipients.

SA-PO419

The Effect of Regulatory T Cells on the Interaction of T Follicular Helper Cells and Memory B Cells during Plasmablast Formation Paul Fadakar, Kevin Hadi, Camila Macedo, Diana Metes. *Starzl Transplantation Inst, UPMC, Pittsburgh, PA.*

Background: Donor-specific antibodies (DSA) are an important biomarker for acute rejection, transplant glomerulopathy and late allograft failure in kidney transplantation. However, few studies have looked at the immunologic events that occur prior to DSA formation. T follicular helper (Tfh) cells provide B cells with critical cognate help necessary for differentiation into plasmablasts that secrete antibodies in response to antigen stimulation. Our previous results obtained in a cohort of KTx recipients receiving Thymoglobulin induction showed an imbalance between circulating Tfh cells and regulatory T cells (Tregs), which correlated with development of DSA. Here, we inquired whether Tregs can temper Tfh cell function to interfere with B cell responses, or if they directly modulate B cells' ability to differentiate into plasmablasts (PBs).

Methods: We isolated peripheral blood mononuclear cells from 5 healthy controls and FACS-sorted Tfh cells (CD4+CD45RO+CXCR5+), memory B (mB) cells (CD19+CD27+) and Tregs (CD4+CD25+CD127-). We co-cultured Tfh cells with mB cells at a 1:1 ratio for 6 days in the presence or absence of SEB to mimic antigen-specific interactions, with or without Tregs. In parallel, CD3/CD28-stimulated CFSE-labeled Tfh cells or mB cells exposed to a cytokine cocktail mimicking T cell help were incubated with or without Tregs at decreasing ratios for 6 days *in vitro*. Inhibition of Tfh cell proliferation measured by CFSE dilution and PB formation (CD19+CD27+CD38+) were measured to assess Treg function.

Results: Co-culture of mB cells with Tfh cells induced 30-80% of mB cells to differentiate into PBs. Addition of Tregs suppressed PB formation in a dose-dependent manner with 50-70% suppression at 1:1 ratio. Tregs inhibited proliferation of Tfh cells with 50% inhibition at 1:1 ratio, 30% at 1:2, 12% at 1:4 and 2% at 1:8.

Conclusions: Tregs suppress PB formation via direct effect on mB cells and indirectly by tempering Tfh cell function. These results provide valuable mechanistic understanding of the role of Tfh cells and Tregs during antibody responses with implications for monitoring for early detection of patients at risk for DSA generation.

Funding: NIDDK Support

SA-PO420

Protective Effect of 1α,25-Dihydroxyvitamin D3 on Effector CD4+ T Cell Induced Injury in Human Renal Proximal Tubular Epithelial Cells Ji-Yeun Chang,[1,2] Kyoung Chan Doh,[2] Byung Ha Chung,[1,2] Chul Woo Yang.[1,2] *[1]Div of Nephrology, Dept of Internal Medicine, Seoul St. Mary's Hospital, The Catholic Univ of Korea, Seoul, Korea; [2]Transplant Research Center, Seoul St. Mary's Hospital, The Catholic Univ of Korea, Seoul, Korea.*

Background: The aim of this study was to investigate the effects of Vitamin D pretreatment on inflammatory response in human proximal renal tubular epithelial cells (HRPTEpiCs) induced by effector T cells or inflammatory cytokines.

Methods: First, we investigated the effect of 1α,25-dihydroxyvitamin D3 [1,25$(OH)_2$D3] on CD4+ T cell proliferation by FACs analysis and ELISA. Second, we investigated the effect of 1,25$(OH)_2$D3 on IL-6, IL-8, KIM-1 and fibronectin 1 expression in HRPTEpiCs, co-cultured with/without activated CD4+T cells using ELISA and real-time PCR and we analyzed mTOR/STAT3 signaling. Lastly, we divided 90 kidney transplant recipients (KTR) according to serum 25-hydroxyvitamin D [25(OH)D] level (<20 ng/mL or not) and compared the level of urine IL-6, IL-8, and KIM-1 between the groups.

Results: Pre-incubation with 1,25$(OH)_2$D3 significantly reduced the percentage of Th1 and Th17 cells compared to Th0 condition ($P<0.05$ for each). In contrast, 1,25$(OH)_2$D3 increased the proportion of Th2 and Treg cells in a dose dependent manner ($P<0.05$ for each). To evaluate the direct protective effect of vitamin D on the target organ, we investigated whether vitamin D protects HRPTEpiCs against inflammatory cytokine or effector T cell-induced inflammation. Our results showed that inflammatory cytokines (TNF-a, IL-17 and TGF-β) induced IL-6, IL-8 or KIM-1 production from HRPTEpiCs in a dose-dependent manner.Treatment with 1,25$(OH)_2$D3 significantly reduced the level of these cytokines ($P<0.05$ for all). In western blot analysis, mTOR/STAT3 pathway was down-regulated by 1,25$(OH)_2$D3 in HRPTEpiCs. Lastly,the concentration of urine IL-6/creatinine(Cr) ($p < 0.05$) and Kim-1/Cr ($p < 0.05$) was higher in low 25(OH)D group (n=41)) than in normal 25(OH)D group (n=49) in KTRs.

Conclusions: In conclusion, we suggest that treatment with 1 α, 25-dihydroxyvitamin D3 could be a new therapeutic strategy to reduce allograft tubule cell injury by effector T cells in kidney transplantation.

Funding: Government Support - Non-U.S.

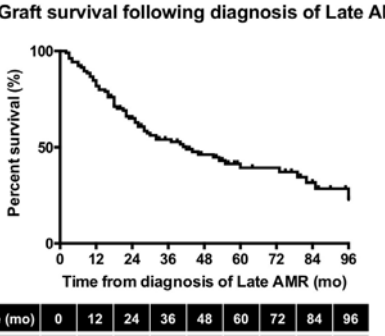
SA-PO421

Late Antibody Mediated Rejection in Renal Transplant: Retrospective Review of Outcomes and Prognostic Indicators Irene Ruderman,[1] Matthew Sypek,[1] Moira J. Finlay,[2] Rosemary Masterson,[1] Peter D. Hughes.[1] *[1]Dept of Nephrology, Royal Melbourne Hospital, Melbourne, Victoria, Australia; [2]Dept of Anatomical Pathology, Royal Melbourne Hospital, Melbourne, Victoria, Australia.*

Background: Late antibody mediated rejection (AMR) is recognised as a major contributing cause to late allograft failure. Our aim was to identify predictors of renal allograft outcomes in late AMR in the context of a previously normal three-month protocol biopsy in a single centre transplant population.

Methods: We conducted a retrospective review and identified 106 transplant patients with late AMR. We went on to analyse the impact of histological, antibody and clinical factors on graft survival and compared the characteristics of this cohort with 968 patients without late AMR transplanted during the same period.

Results: Median time to diagnosis of rejection was 58 months post-transplant (range 26-97months). Thirty three percent of the cohort with late AMR was ABO incompatible (ABOi). Compared with the control group the late AMR group were younger ($p<0.001$) and had higher rates of ABOi. Late AMR was associated with a 2.8 times increased risk of graft loss compared to non-AMR controls. In the late AMR group, high chronicity scores on diagnostic biopsy and high serum creatinine at the time of diagnosis but not the degree of micro-vascular inflammation, C4d positivity or dsDNA were associated with worse graft outcomes. Graft survival was poor in the late AMR group with 50% graft loss 29 months post late AMR diagnosis.



Time (mo)	0	12	24	36	48	60	72	84	96
Total	106	85	56	40	21	18	15	4	1

Conclusions: Late AMR is associated with high rates of graft loss despite current treatments. Chronicity score on biopsy and lower kidney function are markers of poor graft survival.

SA-PO422

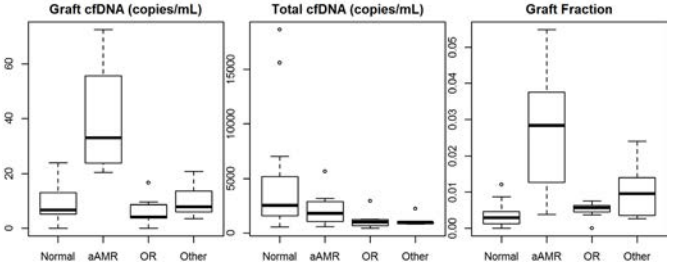
Absolute Measurements of Plasma Graft-Derived Cell-Free DNA Are Higher in Kidney Transplant Antibody Mediated Rejection

John B. Whitlam,[1] Ling Ling,[2] Francesco L. Ierino,[1] Damien Luis Bruno,[2] Howard Slater,[2] David A. Power.[1] *[1]Nephrology Dept, Austin Health, Heidelberg, Australia; [2]Murdoch Childrens Research Inst, Royal Children's Hospital, Parkville, Australia.*

Background: Cell-free DNA is an emerging biomarker of graft injury. We have developed a novel strategic approach that exploits ubiquitous copy number variation (specifically deletion), to create a "negative background" against which multiple independent informative markers can be used to measure absolute graft-derived cfDNA (gdcfDNA) using digital droplet PCR without prior donor or recipient genotyping.

Methods: A panel of 31 copy number variation assays was run on cfDNA extracted from plasma of 38 adult kidney transplant recipients undergoing biopsy for acute graft dysfunction. GdcfDNA and total cfDNA (tcfDNA) concentrations were measured and graft fraction (GF) calculated. The results were correlated with diagnostic biopsy histopathology.

Results: Biopsy results included 18 normal, 8 acute antibody mediated rejection (aAMR), 7 other rejection (OR) and 5 other non-rejection pathologies ("Other"). GdcfDNA was significantly elevated in aAMR compared with all other groups ($p<0.01$)(Figure 1, left panel). GF was higher in aAMR ($p<=0.01$) compared to all groups except "Other" ($p=0.1$)(Figure 1, right panel). For aAMR diagnosis, there is an indication that gdcfDNA is a better measure than GF.



Conclusions: Unlike other methods which rely upon GF, this novel approach permits absolute quantification of both gdcfDNA and tcfDNA. Both gdcfDNA and GF appear to be higher primarily in aAMR. Further study is warranted to confirm this pattern and establish whether dependence on GF by other approaches is subject to confounding by coincident rises in tcfDNA.

Funding: Private Foundation Support

SA-PO423

Urinary 1-Methylhistidine and 3-Methylhistidine Excretion as Biomarkers for Meat Intake and Long-Term Outcomes in Renal Transplant Recipients

Mohammad Yusof Said,[1] Joëlle Catharina Schutten,[1,2] Lyanne M. Kieneker,[1,2] Else van den Berg,[1] Gerjan Navis,[1,2] M. Rebecca Heiner-Fokkema,[1] Stephan J.L. Bakker.[1,2] *[1]Univ Medical Center Groningen; [2]Kidney Center, Groningen, Netherlands.*

Background: Mild protein restriction is recommended for chronic kidney disease (CKD) patients. It is unknown whether this also holds true for renal transplant recipients (RTR). Studies in CKD subjects did not take variation in nutritional value into account. Questionnaire-derived information may be biased, while information derived from biomarkers is more objective. We therefore aimed to study the associations of 24h urinary 1-methylhistidine and 3-methylhistidine excretion (U1ME and U3ME respectively) with meat intake and with the risk of mortality and graft failure (retransplantation or return to dialysis) in RTR.

Methods: We used food frequency questionnaires to assess total and specific protein intake, such as fish and processed meat intake. We measured 24h urinary amino acid excretion by the colorimetric ninhydrin method. Linear and Cox regression analyses were applied to analyse associations with outcome.

Results: We included 342 RTR, with mean age 53±13 years, 188(55%) males and mean eGFR 45±19 ml/min. Median U1ME and U3ME were 343 µmol/24h [IQR: 162-716] and 199 µmol/24h [IQR: 151-264], respectively. U1ME was associated with intake of white meat (R^2=0.072, St. β=0.181, P0.002) and U3ME with intake of processed red meat (R^2=0.137, St. β=0.131, P=0.02), both independent of adjustment for age, sex, and eGFR. During median follow-up of 3.9 years [IQR: 3.5-4.1], 52 RTR died and 24 developed graft failure. U1ME was neither associated with mortality nor graft failure. U3ME was associated with decreased risk of mortality, independent of adjustment for age, sex, eGFR, and urinary albumin excretion (HR 0.38, 95%CI 0.20-0.70). In a similar model, U3ME was independently associated with increased risk for graft failure (HR 3.68, 95%CI 1.29-10.49).

Conclusions: Our data suggest that high intake of red meat protein, as represented by U3ME, protects against premature mortality, while it increases the risk of graft failure. Optimal protein intake from the perspective of mortality may therefore be offset with increased risk of graft failure and vice versa.

SA-PO424

Evaluation of Soluble Urokinase Receptor as a Biomarker in Plasmapheresis Managed Focal Segmental Glomerulosclerosis

David Changli Wei,[1] Jing Li,[1] Jochen Reiser,[1] Nada Alachkar.[2] *[1]Dept of Medicine, Rush Univ Medical Center, Chicago, IL; [2]Dept of Medicine, Johns Hopkins Univ School of Medicine, Baltimore, MD.*

Background: Plasmapheresis is the standard therapy in the management of recurrent focal segmental glomerulosclerosis (FSGS) post kidney transplantation. However, an effective biomarker justifying its application is still lacking. Elevated soluble urokinase receptor (suPAR) level was found independently associated with chronic kidney disease incidence and could contribute to the development of FSGS. In this study, we evaluated the applicability of suPAR as a biomarker in plasmapheresis managed post-transplant FSGS.

Methods: A retrospective cohort of post-transplant FSGS (n=19) managed at Johns Hopkins Hospital was analyzed for serum suPAR levels pre and post-transplantation, post-transplant FSGS diagnosis, before and after plasmapheresis. suPAR was then correlated with the clinical course. A prospective cohort of recurrent FSGS (n=14) was used for validation. suPAR downstream effector β3 integrin activity was indicated by podocyte AP5 immunofluorescence intensity.

Results: In the retrospective cohort, post-transplant suPAR was significantly lower than that at pre-transplant, but not distinct from that at the diagnosis of post-transplant FSGS. Plasmapheresis therapy alone or with Rituximab effectively reduced serum uPAR. The decrease in suPAR after treatment was correlated with the decrease in proteinuria ($r=0.59$, $p<0.05$). In the prospective cohort of recurrent FSGS, single course of plasmapheresis lowered serum suPAR by (37.0 ± 2.8)%. The combined treatment significantly decreased serum suPAR and proteinuria in 7 out of 11 patients. For the patients resistant to therapy, a high podocyte AP5 activity was persisted after treatment; 2 of 3 had increased in serum suPAR as well. When the two cohorts analyzed together, the results remained unchanged in that the combined therapy lowered suPAR and proteinuria significantly in 16 out of 26 patients, and that the changes of the both were significantly correlated.

Conclusions: In this study of post-transplant FSGS, our data suggests that serum suPAR is an effective biomarker in the monitoring of plamsapheresis therapy.

Funding: Pharmaceutical Company Support - Terumo BCT

SA-PO425

Diffuse Extent of Peritubular Capillaritis in Late Antibody Mediated Rejection - Association with Transplant Glomerulopathy and More Severe Chronic Allograft Damage

Zeljko Kikic,[1] Farsad Alexander Eskandary,[1] Harald Herkner,[2] Georg Bohmig,[1] Nicolas Kozakowski.[3] *[1]Nephrology and Dialysis, Medical Univ Vienna; [2]Emergency Medicine, Medical Univ Vienna; [3]Inst of Clinical Pathology, Medical Univ Vienna.*

Background: Peritubular capillaritis (ptc) is a diagnostic criterion of antibody-mediated rejection (ABMR). Recently diffuse ptc extent (> 50% of the cortical renal tissue) has been identified as an independent risk factor for inferior outcomes.

Methods: This study assesses the clinical relevance of ptc subcharacterization (ptc score, extent and leukocytic subpopulation) in recipients with donor-specific antibody (DSA) and is a secondary analysis of a large prospective trial (BORTEJECT,-NCT01873157). It included 85 out of 741 stable transplant recipients subjected to cross-sectional antibody screening (≥6 months post transplantation). Based on DSA detection [mean fluorescence intensity (MFI) threshold >1,000], patients underwent protocol biopsy (scoring according Banff 2013 scheme). Outcomes were the presence of transplant glomerulopathy (TG) and the chronic lesion score (CLS), scoring was performed by one pathologist blinded for the outcome.

Results: Ptc (n=42) scores 1, 2, and 3 were present in 36%, 55% and 9 % while focal and diffuse ptc were found in 36% vs. 64%. Monocytes were the most prevalent leukocytic subpopulation (76%). Recipients with diffuse ptc were more frequently pre-sensitized, and presented with significantly higher post transplant DSA MFI sum (5172 (IQR: 3007-13783) vs. 2444 (IQR: 1355-7873), p=0.019). TG and CLS scores were significantly higher in recipients with diffuse ptc extent (1.1±1.1, p=0.002 and 6.8±2.2, p=0.01, respectively) vs. no ptc (0.3±0.6 and 5.2±3.3). Ptc score 2 was only associated to TG (1.2±1.0, $p<0.001$) but not to CLS. In cox regression analysis diffuse ptc remained an independent risk factor for TG (OR: 4.22 (95%CI: 1.47-12.14,p=0.007). and higher CLS (regression coefficient: 1.63 (95%CI 0.19-3.07) p=0.03) while ptc score 2 lost its significant association.

Conclusions: Our results suggest diagnostic and prognostic relevance of reporting diffuse ptc extent and further emphasize its role as a risk factor for chronic damage in kidney allografts.

SA-PO426

Circulating and Renal Expression of HLA-G Prevented Renal Allograft Dysfunction in Japanese Recipients

Yuki Okushi, Kazuaki Okino, Kiyotaka Mukai, Yuki Matsui, Norifumi Hayashi, Hiroki Adachi, Hideki Yamaya, Hitoshi Yokoyama. *Nephrology, Kanazawa Medical Univ, Uchinada, Ishikawa, Japan.*

Background: Although the risk for morbidity and mortality is studied in subjects with renal transplantation, there are limited data to access the long-term renal survival effects of non-classical HLA class I (HLA-G) in Japanese.

Methods: We investigated the alteration of estimated glomerular filtration rate (eGFR) based on the 3-variable GFR-estimating equation for Japanese (194 x serum creatinine $(SCr)^{-1.094}$ x $age^{-0.287}$ x 0.739, if female), and factors affecting the eGFR in 156 adult

Japanese subjects (97 males, 59 females; 125 living donors, 31 cadaveric donors) with at least 3 years of allograft survival in our hospital. Clinical backgrounds, gender, HLA matching, ischemic times, ABO incompatibility, immunosuppressive therapy, and serum soluble (s) HLA-G5 levels were examined. In addition, 22 renal biopsied specimens (9 males, 13 females; 19 living donors, 3 cadaveric donors) at before, 2-4 weeks and one year after transplantation were also evaluated for HLA-G1 expression using monoclonal anti-HLA-G antibody (clone 87G).

Results: During follow-up period, the rates of change per year of eGFR (ΔeGFR) and sHLA-G5 were -1.65 ml/min/1.73 m^2 and 11.6 ng/ml in median levels, respectively. ΔeGFR and sHLA-G5 showed positive correlation (r = 0.18, p=0.02). On multiple regression analysis, sHLA-G5, HLA matching and immunosuppressive therapy and were significant improving factors on ΔeGFR (beta 0.36535, p= 0.0210; beta -1.4956, p=0.0134; beta 0.56654, p= 0.0034 respectively). On histological examinations for HLA-G1 expression, 10 specimens showed perinuclear positive pattern on renal tubular epithelial cells after renal transplantation 2-4 weeks later. On the other hand, 12 specimens were negative for HLA-G1 staining except for interstitial infiltrating cells.

Conclusions: sHLA-G5 levels, HLA matching and immunosuppressive therapy were independent improving factors for renal allograft function judged by ΔeGFR in Japanese allograft recipients. HLA-G1 was also expressed on renal tubular epithelial cells 2-4 weeks after renal transplantation in some allograft recipients.

SA-PO427

A Paired Analysis of the Outcome after Kidney Transplantation in Peritoneal and Hemodialysis Patients Alicja Debska-Slizien,[1] Agnieszka Bobkowska-Macuk,[1] Beata Bzoma,[1] Grazyna Moszkowska,[2] Anna Milecka,[3] Dariusz Zadrozny,[3] Wojciech Wolyniec,[4] Andrzej Chamienia,[5,6] Monika Lichodziejewska,[1] Ewa Krol,[1] Zbigniew Sledzinski,[3] Boleslaw Rutkowski.[1] *[1]Nephrology, Transplantology and Internal Medicine, Medical Univ, Gdansk, Poland; [2]Dept of Clinical Immunology and Transplantology, Medical Univ, Gdansk, Poland; [3]Dept of General, Endocrine, and Transplant Surgery, Medical Univ, Gdansk, Poland; [4]Dept of Occupational, Metabolic and Internal Medicine, Medical Univ, Gdynia, Poland; [5]Kidney Transplant Regional Waiting List, Medical Univ, Gdansk, Poland; [6]Dept of General Nursing, Faculty of Medical Sciences, Medical Univ, Gdansk, Poland.*

Background: The impact of dialysis modality before transplantation on outcomes is not clear.

Methods: We analyzed the influence of dialysis modality on transplantation outcome. To minimize the donor bias, a paired kidney analysis was applied. 132 pairs of peritoneal dialysis PD and hemodialysis HD patients transplanted in our center between 1994 and 2015 who received kidneys from the same donor were included. There were no difference in the age of patients (44.9 vs 48.1 years), also Charlson Comorbidity Index was similar (3,13 vs 3,27) in both groups. The groups did not differ with respect to immunosuppressive protocols and number of mismatches.

Results: One-year patient (97 vs 98%) and graft (92 vs 95%) survival was similar, the Kaplan-Meier curves of patients and graft survival did not differ significantly. DGF and AR occurred more often in HD recipients (p>0.05). Graft vessel thrombosis resulting in graft loss occurred in 9 PD (7%) and in 4 HD (3%) patients (p>0.05). Creatinine serum and eGFR (MDRD) one-year and at last visit did not differ. On univariable analysis factors associated with graft lost were: age, DGF, eGFR and tacrolimus usage, the independent predictors upon multivariate analysis were age and eGFR. On univariable analysis the age and NOTAD were associated with death, but only age was the independent predictor.

Conclusions: Long-term outcome of renal transplantation is similar in PD or HD patients. PD patients experience significantly less DGF and AR. In both groups age was an independent predictor of the death of the patient and graft lost.

SA-PO428

The Closure of Arteriovenous Fistula Is Associated with a Significant Acceleration of eGFR Decline in Kidney Transplant Recipients Francois Jouret,[1] Pierre Delanaye,[1] Pauline Vanderweckene,[1] Hans Pottel,[2] Laurent E. Weekers.[1] *[1]Univ of Liège; [2]Kulak.*

Background: The creation of arteriovenous fistula (AVF) may retard CKD progression in the general population. Conversely, there is limited literature regarding the impact of AVF closure on renal function in kidney transplant recipients (KTR).

Methods: All KTR were retrospectively identified from 01/2007 to 12/2013, and grouped into: (0) no AVF; (1) closed AVF; and (2) left open AVF. GFR was estimated (eGFR) upon MDRD equations. Linear mixed models calculated the slope and intercept of eGFR decline *versus* time, starting at 3 months post transplantation (Tx).

	(0) No AVF	(1) Closed AVF	(2) Open AVF	p	
				ANOVA	(1) vs (2)
n	90	114	81		
Recipient					
Age (year)	48.5 ± 16.0	48.8 ±13.0	54.2 ± 13.7	<0.05	<0.05
Gender (F/M)	50/40	40/74	28/53	NS	
Donor					
Age (year)	42.5 ± 14.6	42.5 ± 14.8	48.1 ± 14.0	<0.05	<0.05
Gender (%M)	55	57	56	NS	
Transplant					
CIT (min)	653 ± 332	705 ±340	743 ± 325	NS	
DGF (%)	13	16	26	NS	
eGFR at 3 months post Tx (ml/min)	69 ± 29	64 ± 20	55 ± 21	<0.05	<0.05
eGFR slope (ml/min/month)	-0.204 ± 0.039	-0.102 ± 0.035	-0.186 ± 0.042	NS	

Comparative analyses of eGFR slopes were performed among groups, as well as before *vs* after AVF closure in group 1. For the latter, time was balanced before *vs* after AVF closure, with at least 10 observations per patient.

Results: The cohort included 285 KTR, with a median follow-up of 1750 days. Focusing on group 1, AVF closure occurred after a mean time of 653 ± 441 days post Tx. Balanced study periods before *vs* after AVF closure lasted 15.7 and 14.9 months, respectively. No difference was found between corresponding intercepts (p, 0.11) but eGFR slopes were significantly different before (0.043 ml/min/month) *versus* after (-0.176 ml/min/month) AVF closure (*p, 0.0115, n=95*).

Conclusions: A significant acceleration of eGFR decline is observed over the 15 months following the closure of functioning AVF in KTR.

SA-PO429

Machine Learning Approach for Prediction of Patient Survival in Deceased Donor Kidney Transplant Using a Nationwide Cohort from the Korean Network for Organ Sharing Database Kyung Don Yoo,[1] Junhyug Noh,[2] Hajeong Lee,[3] Dong Ki Kim,[3] Chun Soo Lim,[3] Young Hoon Kim,[4] Yon Su Kim,[3] Gunhee Kim,[2] Jung Pyo Lee.[3] *[1]Dongguk Univ Medical Center; [2]College of Engineering, Seoul National Univ; [3]Seoul National Univ College of Medicine; [4]Asan Medical Center.*

Background: The Korean Network for Organ Sharing was founded in 2000 for organ allocation in Korea. We propose a novel prediction approach of recipient survival based on machine learning techniques using KONOS data.

Methods: Our dataset is collected from 2000 to 2014 by the KONOS. Patients' survival of these recipients was investigated by the individual learners such as survival decision tree, survival ridge/lasso regression, and ensemble learners such as bagging and random forest.

Results: We analyze records of 5,430 deceased donor kidney transplants (DDKT) with more than 31 attributes, among which we choose 15 independent attributes to learn our models. Survival lasso algorithm had created the most accurate prediction model, and it outperforms a conventional method such as Cox regression (Concordance index 0.709 vs. 0.660, respectively). Among various survival decision tree models, the tree using patient's survival duration and age was found to be the best performed model for test dataset (Concordance index 0.690). In recipients under 51.5 years, survival hazard ratio (HR) was predicted as 0.58 compared to overall recipients. Duration from KT date showed significant association with mortality. If more than 51.5-years-old patient with longer duration from KT(>8.5years), predicted survival HR was 3.14. Even above the 51.5 years of recipients' age, if the age is not more than 61.5 years of age at the time of KT and shorter duration from KT(<8.5years), survival HR is only 0.97. Consequently, patients with over 61.5 years and longer duration from KT(>8.5years) were depend on donor's body weight for survival HR. In heavy donor (over 75kg) for old recipients, survival HR was increased up to 4.20.

Conclusions: We propose machine learning based models with estimated-death risks for presenting more accurate than conventional models. In our final model, recipient's age, duration from KT and body weight of donor were chosen as notable risk factors for mortality in KT recipients.

SA-PO430

Characterizing Glomerular Injury of Pediatric Kidneys Transplanted to Adult Recipients Steven Salvatore, Surya V. Seshan, Meredith J. Aull, Thangamani Muthukumar. *Weill Cornell Medical College.*

Background: Pediatric deceased donor kidneys are used effectively in transplantation to standard weight adult recipients. Due to postulated hyperfiltration-induced glomerular injury, the recipients may manifest proteinuria in the post-transplant period with pathology revealing "pediatric donor glomerulopathy" (PDG). We aim to characterize the spectrum of podocyte and glomerular injury.

Methods: From 2006-2016, 54 kidney transplant biopsies from 33 patients (of 86 total pediatric kidney recipients) were evaluated. Immunohistochemical (IHC) stains for podocin, WT1, CK AE1/AE3, and Ki67 were performed on 29 biopsies. Clinicopathologic parameters and follow-up were analyzed.

Results: 33 patients were studied, mean 373 days from transplant (range 11-1820d) for elevated creatinine, 0.7-21 mg/dL (M 4.0). 68% had proteinuria, 0-10g/24hr (M 2g).

The donor ages were 2 mo- 6 yrs with weights 6.5-20kg. Donor:recipient weight ratio was 8.3-37%, 3 patients had en bloc transplants. Biopsies showed PDG in 15/33, alone in 12 or with superimposed disease, 3. Other transplant related diagnoses included rejection in 10 (4 ACR, 5 AMR, 1 mixed), acute tubular injury 4, CNI toxicity 3, BKV 1, TMA 1, recurrent MGN 1, and 1 protocol. Among PDG cases, 53% had fetal glomeruli, 4 with collapsing glomerulopathy. Variable podocyte injury was seen by IHC in 45% and by EM in 68%. Ten (37%) had GBM lamellation, 13 (48%) endothelial injury. Follow-up was available on all cases for a mean 3.07 years (212 d to 7.9 yrs). Nine of 33 (27%) failed within mean 659 days (0-1193 d) , 23 had functioning grafts with Cr 0.95-5.2 and proteinuria 0-1.35 g at last follow-up, and 1 patient died with a functioning graft. Graft failures were from rejection (4/9), BKV (1), TMA (1), and only 3 had PDG. Overall, 13/23 pts had proteinuria and 12/23 had hematuria at last follow-up, 89% of patients had improvement in proteinuria.

Conclusions: Deceased donor pediatric kidneys are a viable option for increasing transplant demands. While PDG associated podocyte and glomerular basement membrane injury may lead to proteinuria and hematuria in the post-transplant setting, long term graft survival is preserved. Recognition of this form of glomerular injury may be amendable for therapy.

SA-PO431

Are Repeat Mismatches Associated with Decreased Kidney Graft Survival in Kidney Transplant Recipients Who Have Previously Been Transplanted with a Non-Renal Solid Organ? Jean Maxime Cote,[1] Mourad Dahhou,[2] Xun Zhang,[2] Edith A. Renoult,[1] Bethany J. Foster,[2] Heloise Cardinal.[1] *[1]Medicine, Univ de Montreal, Montreal, QC, Canada; [2]Medicine, McGill Univ, Montreal, QC, Canada.*

Background: Previous exposure to mismatched HLA antigens through a first transplant can lead to sensitization and increase the immunological risk of kidney transplantations (KT) performed after non-renal solid organ transplantation (SOT). We asked whether repeated mismatches were associated with lower kidney graft survival in patients who received a KT after a non-renal SOT.

Methods: Using the Scientific Registry of Transplant Recipients, we conducted a retrospective cohort study of patients who received a KT after one or more previous non-renal SOT between January 1st 1990 and August 15th, 2014. A repeated mismatch was coded if at least one HLA mismatch between the donor and the recipient at the time of KT had also occurred with a previous non-renal organ donor. We used a Cox regression model to assess the association between repeated HLA mismatches, overall and death-censored kidney graft survival.

Results: The full cohort comprised 4924 KT, of which 830 failed on follow-up. We observed no relationship between repeated mismatches and overall graft survival (hazard ratio (HR): 1.02, 95% confidence interval (CI) 0.87-1.19 for class 1 and HR: 0.88, 95%CI 0.72-1.08 for class 2). Donor age (HR: 1.23 per 10-year increase, 95%CI 1.17-1.29), African American donor (HR: 1.58, 95%CI 1.26-1.99), recipient race (HR: 1.32, 95%CI 1.05-1.67) and number of mismatches with the kidney donor (HR: 1.35 for 2-3, 95%CI 1.06-1.71 and HR: 1.52 for 4-6 versus 0-1, 95%CI 1.22-1.91) were associated with an increased risk of graft failure. Living donation (HR: 0.64, 95%CI 0.54-0.76) and older recipient age at transplantation (HR: 0.94 per 10-year increase, 95%CI 0.89-0.99) were associated with a decreased risk of graft failure. Similar results were observed for death-censored graft failure.

Conclusions: Repeated HLA mismatches with previous donors had no negative impact on overall or death-censored graft survival in KT performed after previous non-renal SOT. Hence, repeated mismatches should not be used as a criterion to refuse a kidney donor.

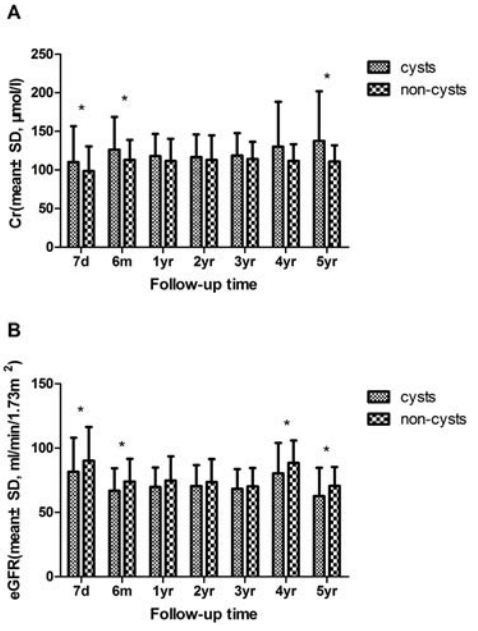
SA-PO432

Graft Bearing Cysts Contribute to Accelerated Decline of Kidney Allograft Function Wenxian Qiu, Wenhan Peng, Jianghua Chen. *Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China.*

Background: Simple renal cysts are the most common structural abnormality observed in adult kidneys. We investigated whether graft bearing sporadic cysts is associated with the accelerated decline of kidney allograft function in living donor kidney transplantation.

Methods: We retrospectively reviewed donors and recipients records of 716 living donor kidney transplants performed between April 2007 and April 2015 in our hospital. 64 recipients of grafts with cysts were noted. We compared this cohort to 128 non-cysts controls matched for the donors and recipients' gender, donor age, donor/recipient body surface area ratio, recipient age and donor baseline serum creatinine in turn.

Results: The mean serum creatinine of recipients in the two groups were 110.3±46.52 vs 98.86±31.88, 126.28±42.32 vs 113.24±25.65, 137.64±64.29 vs 111.16±20.99μmol/l on postoperative day 7, month 6, year 5 respectively($P<0.05$). Estimating glomerular filtration rate levels were 81.74±26.30 vs 90.19±26.36, 66.97±17.47 vs 74.02±17.68, 80.38±23.74 vs 88.45±17.55, 62.85±21.94 vs 70.63±14.64ml/(min·1.73m^2) on day 7, month 6, year 4, year 5 after surgery separately($P<0.05$).



However, the two groups did not significantly differ in terms of the other characteristics.

Conclusions: The donating kidney with cysts can influence the early and long-term allograft function. In living donor kidney transplantation, kidney presenting cystic diseases should be considered to be the next choice for transplantation.

SA-PO433

Interleukin-6 Production by Monocytes Is Associated with Graft Function Decline in Patients with Borderline Changes Suspicious for Acute T Cell-Mediated Rejection Sacha A. De Serres,[1] Olivier Desy,[1] Stephanie Beland,[1] Patrice Vallin,[1] Julie Riopel,[2] Eva Latulippe,[2] Anil K. Chandraker,[4] Ibrahim Batal.[3] *[1]Renal Div, Univ Health Center of Quebec, Laval Univ, Québec, QC, Canada; [2]Dept of Pathology, Univ Health Center of Quebec, Laval Univ, Québec, QC, Canada; [3]Dept of Pathology, Brigham and Woman's Hospital, Boston, MA; [4]Renal Div, Brigham and Woman's Hospital, Boston, MA.*

Background: The borderline changes suspicious for acute T-cell-mediated rejection (BL) is a diagnostic category questioned for its relevance. The undetermined clinical significance of this diagnosis leads to heterogeneous therapeutic management. Based on previous observations, we hypothesized that measuring IL-6 secretion by peripheral blood mononuclear cells (PBMCs) in patients with BL identifies those with ongoing graft damage.

Methods: From a cohort of 105 patients with concurrent biopsy and PBMC collection, we studied 28 patients with BL, in the absence of ABMR. The primary outcome was the change in eGFR at 6 months. We measured IL-6 levels secretion in PBMC culture supernatants. We characterized patients IL-6 secreting cells by flow cytometry, followed by characterization of mouse dendritic cells (DCs).

Results: The primary outcome was strongly associated with IL-6 levels (5.0±1.5 mL/min for each increase in log10 IL-6; $p=0.004$). These results were consistent after adjustment for baseline eGFR and antirejection treatment ($p=0.003$). 3mo samples were available in 19 patients and demonstrated that the secretion of IL-6 was stable over time. The main source of IL-6 was $CD14^+CD16^-CCR2^+HLADR^+CD86^+CD11c^+$ monocytes. In an independent cohort, we found a significant correlation between IL-6 secretion and interstitial DC density in the biopsy. In mice, we observed that kidney DCs share features with macrophages and function as effector cells secreting IL-6. Kidney DCs showed a lower capacity for proliferation of CFSE-labeled T cells and a lower production of IL-2 in MLR supernatants, compared with splenic DCs.

Conclusions: These data suggest that IL-6 is a potential marker of active rejection in patients with BL, is produced by monocytes in the blood, and correlates with DCs in the allograft.

SA-PO434

Urinary Tissue Inhibitor Metalloproteinase-2(TIMP-2) X IGF-Binding Protein-7(IGFBP7) Predict Delayed Graft Function after Kidney Transplantation Jihyun Yang, Sung Yoon Lim, Young Ju Na, Myung-Gyu Kim, Sang-Kyung Jo, Won-Yong Cho. *Dept of Internal Medicine, Div of Nephrology, Korea Univ Medical College, Seoul, Republic of Korea.*

Background: Recently, urinary TIMP-2 and IGFBP-7, markers for G1 cell cycle arrest, have been identified and validated in predicting the development of AKI in critically ill patients. It is unknown, however, whether these two biomarkers could predict the development of delayed graft function (DGF) after kidney transplantation.

Methods: This is a single center, prospective observational study. We enrolled 56 patients who underwent KT (living donor: 8, deceased donor: 48) between August 2013

and December 2015. Urine sample were collected right after the operation. The primary outcome was development of DGF as defined by need for dialysis of more than 1 session within 7 days of KT.

Results: Sixtenn patients (28%) were diagnosed as DGF. In univariate analysis, kidneys from expanded criteria donors, donor serum creatinine, donor estimated glomerular filtration rate (eGFR), urinary IGFBP-7 and TIMP-2 were significantly different between early graft function (EGF) and DGF. However, in multivariate analysis adjusting for effects of donor eGFR only IGFBP7 x TIMP-2 at 0 hour post transplantation could predict the development of DGF. The receiver operating characteristic curve for prediction of DGF showed an area under the curve of 0.77 (sensitivity 0.77, specificity 0.81) for a cut off value of 1.76.

Conclusions: Our results indicate that urine IGFBP7 x TIMP-2 immediately after transplantation could be an early, predictive biomarker of DGF in kidney transplantation.

Funding: Private Foundation Support

SA-PO435

HLA-DR Expression in Tubular Epithelial Cells and the Subsequent Development of Antibody-Meditated Rejection in Transplant Kidneys

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Background: The mechanism of antibody-mediated rejection (ABMR), a prominent cause of kidney allograft loss, is associated with donor-specific antibody (DSA). It has been speculated that T-cell mediated rejection (TCMR) enhances *de novo* DSA and ABMR. High HLA-DR expression in tubular epithelial cells is correlated with TCMR. However, the clinical significance of HLA-DR expression in tubular epithelial cells and TCMR as a cause of ABMR is not clear. This study evaluated whether the early expression of HLA-DR in tubular epithelial cells is associated with ABMR of kidney allografts.

Methods: This retrospective cohort study enrolled consecutive renal allograft recipients transplanted at the Department of Urology, Tokyo Women's Medical University, from January 2005 to December 2009. We assessed biopsy samples obtained from 212 kidney allograft recipients at early phase. The HLA-DR expression in tubular epithelial cells was evaluated using immunofluorescence. The cases were classified into four groups according to HLA-DR expression and the progression of TCMR: the DR+TCMR+ (n=28), DR+TCMR– (n=70), DR–TCMR+ (n=15), and DR–TCMR– (n=99) groups. The incidence of ABMR and graft survival were analyzed using the Kaplan–Meier method and log-rank test.

Results: Overall, the kidney allograft survival was worse in the DR+TCMR+ group than in the DR–TCMR– group (p=0.0081). ABMR was more frequent in the DR+TCMR+ group than in the DR–TCMR– group (p=0.0284). Of note, in the DR+TCMR+ group, 21 of 28 (75%) cases simultaneously expressed HLA-DR and showed TCMR, and another 25% (7 of 28) of cases developed TCMR within 1 year. Of these, 15 recipients (7.1%) developed ABMR a median of 35 (range 0–116) months after HLA-DR expression.

Conclusions: These results suggest that HLA-DR expression in tubular epithelial cells and the subsequent development of TCMR are associated with ABMR and allograft survival.

SA-PO436

Short Term Modulation of Glomerular Filtration Rate and Funcional Renal Reserve by Protein Restriction in Healthy Living Kidney Donors

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Background: Dietary protein is an important modulator of glomerular filtration rate (GFR). Renal Reserve (RR) (> 20% increase in GFR after a protein load) is used to assess kidney function in living kidney donors. In some donors, RR is negative, particularly in those whose GFR is high. Because dietary protein content is usually high in Argentina, we decided to further standardize RR through protein restriction 48-hours prior as to avoid the effect of variation in dietary protein content on RR.

Methods: A 24-hour creatinine clearance (CrCl) without protein restriction was used to measure GFR prior (7-60 days) to RR. Two days before RR, patients received 1600 mg/d of cimetidine to inhibit Cr secretion and dietary protein was restricted by avoiding meat, eggs and dairy products. RR was then assessed as described previously: a baseline GFR was obtained by averaging 3 consecutive 30-40 min urine and collections and 1 blood sample for urinary and serum Cr. Immediately after, patients consumed a 1.5 g/kg dairy protein meal, and 4 more blood/urine collections were obtained. The RR was calculated as the percentage increase in GFR after the protein meal (highest post-protein meal GFR – pre-protein GFR/pre-protein GFR * 100%).

The 24-hour CrCl (no dietary restrictions) was compared to the RR baseline GFR (protein restricted). Results are expressed as mean ± SE. GFR differences were compared by a paired T-test.

Results: 61 patients were included (36 females, 25 males, age range: 24-73 years-old)). GFR after protein restriction + cimetidine was lower than the unrestricted 24-hour CrCl (102.2 ± 3.1 ml/min/1.73m² vs 130.3 ± 4.4 ml/min/1.73m², p < 0.00001). The increase in GFR after the dairy protein meal was 54.2 ± 4.8 ml/min/1.73m² (102.2 ± 3.1 ml/min/1.73m² pre-meal vs 156.4 ± 5.7 ml/min/1.73m² post-meal, p < 0.00001) and RR was 55.8 ± 4.8 %.

Conclusions: Protein restriction before RR is a useful method to standardize conditions for the test. It also allows to assess the ability to negatively modulate GFR.

SA-PO437

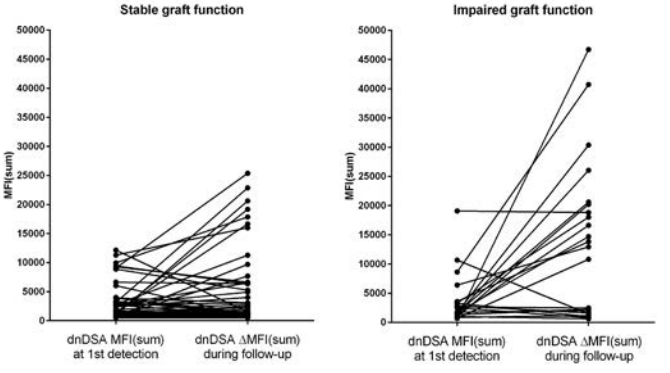
Change in De Novo Donor-Specific Antibody Intensity Predicts Allograft Dysfunction

Scott Davis,[1] Jane Gralla,[2] Alexander C. Wiseman,[1] James E. Cooper.[1] *[1]Medicine, Univ of Colorado, Aurora, CO; [2]Pediatrics, Univ of Colorado, Aurora, CO.*

Background: Although de novo donor-specific antibodies (dnDSA) are associated with decreased graft survival in multiple studies, it is not clear which patients with dnDSA will ultimately experience graft dysfunction or loss. Monitoring change in antibody mean fluorescence intensity (MFI) over time may identify patients at risk for antibody-mediated graft complications yet studies are lacking. The purpose of this analysis was to determine whether an increase in antibody intensity was associated with worse graft function in what represents the largest study of its kind.

Methods: Seventy-four kidney and kidney-pancreas recipients with stable renal function (eGFR ≥ 40 ml/min/1.73 m²) at the time of first detection of dnDSA were prospectively followed for 2 years with serial antibody testing. The sum MFI (MFIsum) of all dnDSA detected at a given time point was calculated and change in MFIsum (ΔMFIsum ≥50% and ΔMFIsum ≥100%) was compared between patients with stable graft function after dnDSA detection (ΔeGFR ≤25%) and patients who had evolving graft impairment (ΔeGFR >25%).

Results: Fifty-two patients had stable graft function and 22 patients had graft impairment after dnDSA detection. The graft impairment group experienced more acute rejection (50% vs. 13%) and death-censored graft loss (41% vs. 4%, p<0.001). A change in MFIsum greater than 50% (n=29) and greater than 100% (n=25) was significantly associated with graft impairment (p=0.036 and p=0.018, respectively). Actual change in MFI is shown in Figure 1.



Conclusions: An increase in dnDSA intensity over time is associated with allograft dysfunction. Serial monitoring of dnDSA intensity after detection to identify patients at risk for complications may be warranted.

SA-PO438

Prompt Follow-Up Biopsies Define Outcomes after Treatment of Antibody Mediated Rejections

Sandesh Parajuli, Maha A. Mohamed, Brenda L. Muth, Brad C. Astor, Robert R. Redfield, Weixiong Zhong, Didier A. Mandelbrot, Arjang Djamali. *Univ of Wisconsin- Madison.*

Background: There is limited information on the role of follow-up biopsies after the treatment of antibody medicated rejection(AMR) in kidney transplantation (KTx).

Methods: This observational study included patients diagnosed with AMR based on Banff 2013 between 03/2013 and 12/2015. Additional inclusion criteria were (a) follow-up biopsy within 3-12 weeks and (b) AMR treatment with steroids/IVIG ± rituximab (ritux). In cases with multiple episodes of AMR, only the first episode was included.

Results: Forty-eight of the 221 patients with AMR satisfied our selection criteria. Mean time from KTx to AMR was 76.8±72.05 months. Mean time between the two biopsies was 45±15.32 days. Mean follow-up after the diagnosis of AMR was 10.1±8.01 months. 26 patients received ritux (R+ group) and 22 did not (R- group). Aside from a younger age at KTx (37.3±16.37 vs. 49.9±16.37 years, p=0.01) there were no significant clinical, pathological or immunological differences between R+ and R- groups prior to the treatment. Immunopathological changes at the time of the follow-up biopsy demonstrated a significant decline in DSA class I (MFI_{sum} 7,418 ± 9,328 to 4,110 ± 5,147; p=0.002), DSA class II (MFI_{sum} 18,498± 15,853to 14,608±14,490; p<0.001), ptc+g score (2.56± 1.01to 1.56±1.23; p<0.001), and c4d score (1.5±1.32 to 0.95±1.24; p=0.001) after treatment. In the absence of ritux, the decline in ptc+g score and DSA class II reached statistical significance, but the decline in C4d score and DSA class I did not. Ritux was associated with a statistically significant decline in all four parameters. There were no significant differences in graft loss, last serum creatinine (Scr), or proteinuria between the R+ and R- groups. The immunopathological changes observed on follow up biopsies were not predictive of short term graft loss or poor kidney function (Scr > 2.5 mg/dl) using univariate or multivariate regression analyses.

Conclusions: In this short-term follow-up study, treatment of AMR with ritux was associated with improved class I and II DSA, microcirculation inflammation and C4d.Long-term studies are needed to determine whether follow-up biopsies after AMR are helpful.

SA-PO439

Molecular Crosstalk in Chronic Dysfunction of Renal Allografts: An Integrative Approach Sai Vineela Bontha, Daniel Maluf, Valeria Mas. *Surgery, Univ of Virginia.*

Background: Chronic renal allograft dysfunction (CRAD) with interstitial fibrosis and tubular atrophy (IFTA) in kidney transplant recipients (KTRs) is a major cause of graft loss. Considering the complexity associated with CRAD, its underlying molecular interactions need to be explored through an integrative approach to gain mechanistic insights. Thereby, the current study was done to get a holistic view of the molecular changes & interactions at epigenetic (miRNA, DNA methylation (DNAm)) and gene expression levels.

Methods: A total of 70 graft biopsies were evaluated. DNAm, gene expression and miRNA arrays were done from each of the kidney biopsies from KTRs with IFTA (n=10) and normal functioning allograft (n=11). Additional methylation arrays (n = 40) were performed in donor pre-implantation biopsies to evaluate if the methylation changes were IFTA specific and *denovo*.*Minfi*, *oligo & limma* Bioconductor packages in R were used for analysis of the arrays and the data was integrated. Differentially expressed miRNA and their gene targets thus obtained were further validated by qPCR in training (n=10) and independent sets (n=10).

Results: Integration analysis resulted in 3 miRNA that were hypomethylated in promoter regions and upregulated in IFTA biopsies. The gene targets of these 3 miRNA were further integrated using gene expression arrays from the same biopsies. Biological analysis of the integrated gene expression data showed that the genes repressed by these miRNA had kidney tissue specific metabolic functions, especially in the tubular epithelial cells (*BHMT2, CLCN5, G6PC, NTRK2, CLCNKB, PPM1H, AHCYL1*). Also, among them were inhibitors of TGF beta signaling pathway (*PPM1H, TGFB3*). Top disease functions associated with these genes in IPA analysis show dysgenesis, cell death, growth failure and hypoplasia (z-score > 2.621).

Conclusions: The results suggest that DNAm changes in graft biopsies are *denovo*. DNAm could be a consistent upstream regulatory mechanism through which the miRNA and thereby their gene targets are dysregulated and contribute to renal tubule dysfunction and may be partly responsible for tubular atrophy and tubulo-interstitial fibrosis.

SA-PO440

Surveillance Renal Transplant Biopsies: Useful or Irrelevant? William M. Bennett, Erica Simonich, Alison M. Garre, Shaban Demirel, Margaret E. Marksthaler, Thomas D. Batiuk. *Legacy Transplant Services, Legacy Transplant Services, Portland, OR.*

Background: Performance of surveillance biopsies in kidney transplantation remains somewhat controversial. There are many centers that biopsy patients based only on rises in serum creatinine or symptoms.

Methods: Since 2011 we have performed surveillance biopsies at 2 months and 6 months post-transplant with follow up at 1 year for any abnormal results. Immunosuppression was Thymoglobulin induction (3 mg/kg) followed by Tacrolimus, mycophenolate and Prednisone.

Results: In 422 surveillance biopsies 54 (12.7%) had subclinical acute cellular rejection or borderline changes, 0.6% showed other abnormalities. In 241 biopsies "for cause" 35.7% were normal while 54.7% had acute cellular rejection or borderline changes. There were additional 5.4% of samples with abnormalities. Six (3.6%) patients had acute antibody mediated rejection. In 624 cases where C4d was available 78 (12.5%) were positive with 31 occurring in the surveillance biopsies. Thus there were many C4d positive patients without concurrent histologic evidence of antibody mediated rejection. There were no bleeding complications requiring transfusion or loss of function of the transplanted kidney.

Conclusions: Surveillance biopsies are safe and provide information valuable to patient management. C4d positivity was common in surveillance biopsy samples. Long term outcomes will ultimately determine the utility of our surveillance protocol.

SA-PO441

Early Loss of Peritubular Capillaries after Kidney Transplantation Is Associated with Later Renal Function Decline: A Validation Study in 121 Patients Anke Keijbeck,[1] Floortje Steegh,[1] Marielle Gelens,[2] Ernest Van Heurn,[3] Maarten H.L. Christiaans,[2] Carine Peutz-Kootstra.[1] *[1]Pathology, MUMC, Maastricht, Netherlands; [2]Internal Medicine, MUMC, Maastricht, Netherlands; [3]Surgery, AMC, Amsterdam, Netherlands.*

Background: Chronic transplant dysfunction is a major cause of renal graft loss and is preceded by interstitial fibrosis/tubular atrophy (IF/TA) in protocol biopsies. Previously we showed in a pilot study of 48 patients that IF/TA development is preceded by peritubular capillary (PTC) loss in the first 3 months after transplantation (Steegh *et al.* JASN 2011). The aim of this study is to validate these findings in a separate cohort.

Methods: The validation cohort consisted of 121 new patients, who received a kidney transplantation between August 2003 and December 2009 at the Maastricht University Medical Centre and of whom representative protocol biopsies were taken at transplantation, and 3 and 12 months posttransplant. IF/TA, PTC number and eGFR (MDRD) were studied as described in the pilot study.

Results: A significant loss of PTCs in the first three months after transplantation was found in post-mortal donor kidneys only (P<0.01). In univariate analyses, this PTC loss was associated with longer first warm and cold ischemia time, delayed graft function (DGF), (sub)clinical rejection, and with higher PTC density and IF/TA in the pre-implantation biopsy. This early PTC loss is associated with higher IF/TA score (ρ-0.372, P<0.01) after 1 year. Additionally, early PTC loss is correlated with lower eGFR at year 1 (ρ0.219, P=0.021) and 2 (ρ0.202, P=0.037) posttransplant. Although demographic and pre-transplant clinical variables were similar, PTC loss was less severe in the validation than in the pilot cohort, which may be related to lower incidence of DGF and shorter first warm ischemia time in deceased after cardiac death (DCD) donors.

Conclusions: This study confirms that PTC loss occurs mainly in postmortal donor kidneys, in the first three months after transplantation and is associated with higher IF/TA scores and a decreased eGFR at year 1 and 2. Preserving microvascular integrity may aid in prevention of chronic transplant dysfunction.

SA-PO442

Intratubular Calcification of Renal Allografts Detected by Protocol Biopsies: A New Classification - The Purple Study Ana Coloma,[1] Noa Diaz,[1] Manel Sole,[2] Jose-Vicente Torregrosa.[1] *[1]Nephrology, Hospital Clinic, Barcelona, Spain; [2]Pathology, Hospital Clinic, Barcelona, Spain.*

Background: Intratubular calcification has been described in renal allograft though its clinical relevance remains to be established. The aim of this observational study was to investigate mineral bone metabolism and graft function association to calcification of serial protocol biopsies done at 3 and 12 months after kidney transplantation.

Methods: We studied 515 biopsies from 271 kidney recipients in our center. Histological grouping was established according to intraluminal calcification findings: grade 0 had none or one (P0), grade 1 had two (P1) and grade 2 had more than two (P2). Demographic and transplant data was collected and laboratory data was evaluated at the moment of transplantation, 3, 6, 12, 24 and 36 months after.

Results: We observed more than one calcification in 112 recipients (41.3%). Calcification was not related neither to patient age and gender, dialysis mode, nor immunosuppressive drugs. Non-hearth-beating donor calcification grade (71.8%) was higher than both brain-dead (35.1%) and living ABO-compatible donor (30.5%) p<0.001. ABO-incompatible grafts revealed higher calcification grade when compared to ABO-compatible (65% and 30.5%; p<0.001). Patients on P1 and P2 groups had significantly delayed renal graft function (DGF) (66.2%; p<0.001). Histology of grafts at 3 months with moderate interstitial fibrosis and tubular atrophy had more calcifications than mild grade (Banff) p<0.05. In the first year of transplantation, patients with more calcifications had significantly higher serum parathormone (p<0.05) and alkaline phosphate, remaining the later higher during the 3 years of follow-up. Renal graft function was not related to calcification grade during the entire study period.

Conclusions: Non-hearth-beating donor, living ABO-incompatible donor and recipients with DGF had higher intratubular calcification grade in protocol biopsies. Mineral bone metabolism data and biopsy calcifications association could help to consider an earlier treatment. We propose to include calcification grade in protocol biopsies since it could provide information about type of donor and initial renal graft function.

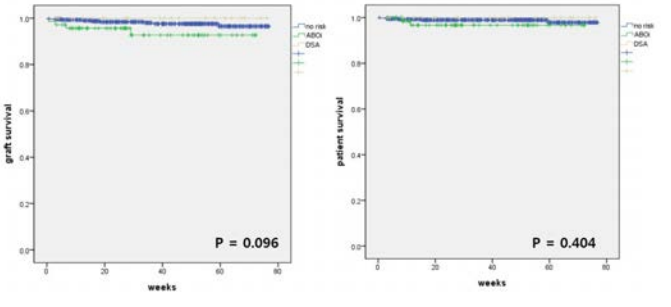
SA-PO443

Long Term Outcome in Donor Specific Antibody Positive and ABO-Incompatible Living Donor Kidney Transplant Patients after Desensitization: A Single Center Experience Yong Chul Kim, Mi-Yeon Yu, Dong Ki Kim, Kook-Hwan Oh, Kwon Wook Joo, Yon Su Kim, Hajeong Lee. *Internal Medicine, Seoul National Univ Hospital, Republic of Korea.*

Background: The kidney organ shortage and increasing number of waiting kidney transplantation (KT) is a global issue. One of the solution is KT in ABO incompatible (ABOi) and Donor specific antibody (DSA) positive patients after desensitization.

Methods: We retrospectively analyzed 510 living donor KT patients from January 2010 to February 2016 at Seoul National University Hospital including 71 ABOi KT and 21 DSA positive KT patients who underwent desensitization with anti-CD20 Ab, plasmapheresis and intravenous immunoglobulin. Four hundred seventeen patients without anti-HLA antibodies (no risk) served as control group.

Results: Mean follow-up duration was 38.8 ± 21.5 weeks and mean age was 40.5 ± 16.5 years. There were no difference in 1-year and 3-year graft survival rate in these three groups (no risk vs ABOi vs DSA positive group) respectively (graft survival 1yr: 99.3% vs 95.7%, 100.0%, 3yr: 98.0% vs 92.7% vs 100.0%). One-year and 3-year patient survival were also similar (patient survival 1yr: 99.3% vs 96.7% vs 100.0%, 3yr: 99.0% vs 96.7% vs 100.0%).



There were more acute antibody-mediated rejection in ABOi KT and DSA positive KT than No risk group (ABOi : 17 (23.7%) vs DSA : 6 (28.5%) vs no risk : 23 (5.5%), p<0.001).

Conclusions: Despite there seems to be more acute antibody-mediated rejection, ABO-incompatible and DSA positive kidney transplantation after desensitization has a favorable graft and patient outcome.

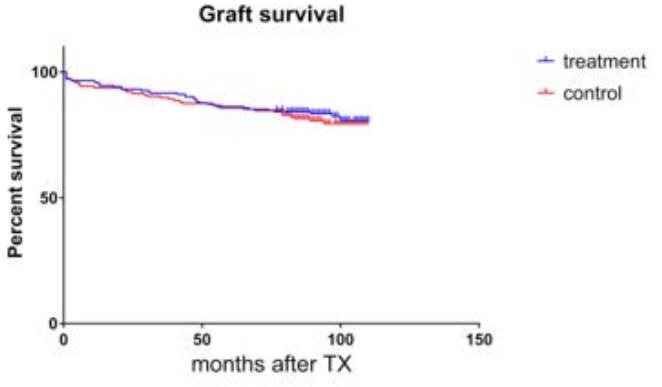
SA-PO444

Long Term Outcome of Steroid Pretreatment of Organ Donors – A Randomized, Controlled Trial Roman Reindl-Schwaighofer, Rainer Oberbauer, Alexander Kainz, Julia Wilflingseder. *Nephrology and Dialysis, Medical Univ of Vienna, Vienna, Austria.*

Background: Organs from deceased donors show a reduced graft survival compared to organs from living donors. A major difference between the two groups is the rate of delayed graft function (DGF) that occurs in roughly 25% of recipients of organs from a deceased donor compared to below 5% following kidney transplantation from a living donor. Gene expression analysis in donor kidney biopsies revealed that organs with DGF showed an up-regulation of genes associated with inflammation, complement activation and apoptosis induction.

Methods: To determine whether systemic anti-inflammatory treatment of kidney donors following brain death reduces the incidence of DGF and improves long-term graft survival we performed a randomized placebo-controlled trial and enrolled 306 donors and 455 renal transplant recipients between February 2006 and November 2008. Donors either received 1000 mg of methylprednisolone or placebo.

Results: Incidence and duration of DGF at 1-week post translpant could not be reduced by corticosteroid treatment of the donors (Kainz et al. 2010). At the 5-year follow-up death censored graft survival as well as patient survival did not differ between the two groups. This is visualized by a KM plot (Figure 1). To assess influence on graft function we calculated the slope of eGFR. Again, no statistically significant difference between the two groups was observed.



Conclusions: Steroid treatment of donors prior to organ harvesting did not improve long term graft survival and function.

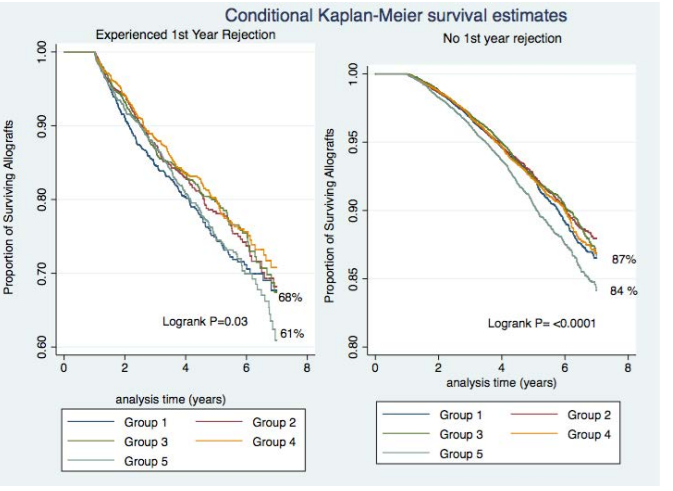
SA-PO445

Impact of Inadequate Donor Nephron Mass on First Year Rejection Risk Abhijit S. Naik, Roger C. Wiggins, Diane Cibrik. *Dept of Internal Medicine, Univ of Michigan, Ann Arbor, MI.*

Background: Inadequate donor nephron mass is associated with hyper-filtration injury and reduced graft survival. Injury and the accompanying inflammation could stimulate an alloimmune response.However, whether inadequate nephron mass is associated with an increased risk of acute rejection remains unclear.

Methods: Study data were drawn from national transplant registry (OPTN data as of December 2015)) data for adult kidney-only recipients in 2008 to 2013. Inadequate donor nephron mass was defined as the recipient and donor body surface area mismatch (RDM) ratio, and categorized according to RDM quintiles as: Group 1, <0.87; Group 2, >0.87 to <=0.97; Group 3, > 0.97 to <= 1.07; Group 4, >1.07 to <=1.20; and Group 5, >1.20. A multivariate logistic regression model was used to determine associations between RDM and first-year acute rejection, adjusted for transplant, recipient and donor factors. Kaplan Meier Survival curves (conditional to allografts surviving first year) were constructed to assess long term (7 year) allograft outcomes.

Results: Among 73,624 recipients, the overall rejection rate was 9.15 % and ranged from 10.5 % in Group 5 to 8.4 % in Group 1. After covariate adjustment, compared to Group 3, Group 1 (OR=0.80 95% CI: 0.72-0.89) and Group 2 (OR= 0.85, 95% CI: 0.78-0.93) were associated with a lower rejection risk, while Group 4 (OR=1.10, 95 % CI 1.01-1.19) and Group 5 (OR=1.31, 95% CI: 1.19-1.44) were associated with increased risk. Recipient body mass index (BMI)> 30 (OR=1.12, p<0.05) and donor BMI (OR=1.01 per kg/m2, p<0.0001) were also independently associated with rejection. Long-term allograft outcomes across RDM groups were notable for worse outcomes in Group 5 (vs Group 1) both with and without rejection (P<0.05 for both).



Conclusions: Inadequate donor nephron mass is independently associated with increased risk of first year rejection and this effect is independent of both recipient and donor BMI. Efforts to minimize RDM may help mitigate this risk.

SA-PO446

Predicting Post-Transplant Mortality: A Single Center Comparison of Comorbidity Indices Ronald Brian Vigo, Wadi N. Suki, Duc T.M. Nguyen, Edward Graviss, Ahmed Osama Gaber. *Nephrology, Houston Methodist Hospital, Houston, TX.*

Background: Patients listed for renal transplantation can have multiple comorbidities leading to early mortality post-transplant. Multiple models have been developed to objectively measure the burden of these comorbid illnesses and some have been used successfully to predict mortality post-transplant. Our goal was to evaluate the utility of three of these tools as objective measures to predict negative outcomes in renal transplant recipients at our center.

Methods: We evaluated medical records from kidney recipients transplanted at our institution between 5/30/2008 and 5/31/2015. Patients who died within the first year post-transplant were included. Patients who survived beyond the first year were matched by age, sex and race in a 2:1 ratio and selected as controls. Data was analyzed using a Cox regression model. A base model which included outcome variables was developed with the intent of adding statistical power to the results. Variable selection for the multivariate model was based on Hosmer and Lemeshow's methodology. Bayesian information criterion (BIC) and likelihood ratio testing were used to assess the performance of the full and simplified predictive models.

Results: 23 patients with 46 matched controls were included in our study. Increased comorbidity was associated with reduced patient survival. Of the models examined, the Charlson Comorbidity Index(CCI) and its different versions yielded statistically significant results in patients aged <65.A CCI model adjusted for age and albumin offered the best results (p=0.001). None of the models yielded significant results for recipients ≥65. The CCI adjusted for base model yielded significant results in all patients and patients <65, but not in patients ≥65.

Conclusions: The CCI is a suitable tool for the objective measurement of comorbidity in renal transplant recipients aged <65. CCI adjusted for age and serum albumin increases the effectiveness of the CCI in predicting post-transplant mortality. CCI and age-adjusted CCI models when adjusted for with the base model significantly predicted post-transplant mortality in all patients.

SA-PO447

Predictors of Mortality in Renal Transplantation Recipients Marcos A. Meniconi,[1] Krissia K.S. Wallbach,[1,3] Luiza Pego Silva,[1] Jose Medina-Pestana,[1,3] Miguel A. Goes.[1,2,3] *[1]Nephrology, Federal Univ of Sao Paulo, Sao Paulo, SP, Brazil; [2]Nephrology, Hospital Israelita Albert Einstein, Sao Paulo, SP, Brazil; [3]Nephrology, Hospital do Rim e Hipertensão, Sao Paulo, SP, Brazil.*

Background: Graft and patient survival after kidney transplantation have improved over the past decade. In that context, death with a functioning graft has increased during this time. Our objective is to assess the mortality predictors after renal transplantation.

Methods: 688 patients were prospectively analyzed for 72 months post-renal transplantation. Follow-up started 90 days after renal transplantation and mortality was the primary outcome. Demographic data, pre-transplantation time on dialysis, delayed graft function (DGF), EPI-CKD, Hb concentration at baseline, type of kidney donor and medication used during follow-up were reported. We used t test to compare differences between groups (mortality versus non-mortality groups) and X^2 to analyze categorical variables. Binary logistic regression was used to determine independent predictors of mortality when p<0.1.

Results: Mean time on dialysis was 46+21 months. The main causes of ESRD were diabetes (35%) and hypertension (18%), followed by chronic glomerulonephritis (10%);

Kidney donation was 43% from deceased donors, 48% related living donors and 9% unrelated living donors; 67% used FK-506, 24% cyclosporine and 8% rapamycin as immunosuppressive drugs; EPI-CKD 69+27 mL/min and Hb 11.7+2.5g/dL at baseline. 68 patients died during follow-up (Mortality group). We observed that this group was older (49+12, 39+15 yo;p<0.001), had a longer time on dialysis (4+3,2+1 yr;p<0.001), higher cold ischemia time (20+12h,14+5h;p<0.001), used higher rHuEPO doses (5389+3560,3824+1616 IU;p=0.006), had lower Hb (10.6+3.1,12.7+2.5) and CKD-EPI (45+23,55+27; p=0.007) at baseline and also higher DGF (p<0.001). After binary logistic regression, age (b=1.063 95%CI 1.034-1.091;p<0.001), Hb (b=0.715 95%CI 0.634-0.808;p<0.001) and cold ischemia time (b=1.001 95% CI 1.000-1.001;p=0.009) were determined independent predictors of mortality.

Conclusions: This study shows that patient age, Hb concentration and cold ischemia time were independent predictors of mortality in renal transplant recipients.

SA-PO448

Long-Term Changes in Cardiovascular Structure and Function after Kidney Transplantation Nikita P. Punjabi, Azhar Ali, Sabiha Gati, Kristel E. Medina-Rodríguez, Juan Carlos Kaski, Debasish Banerjee. *Renal Dept, St. George's, Univ of London, London, United Kingdom.*

Background: Cardiovascular events rates are high in chronic kidney disease patients, which improve with kidney transplantation. However, the long-term cardiovascular structural and functional changes with kidney transplantation are poorly understood. This study prospectively investigates these changes in live-donor kidney transplant recipients.

Methods: 24 non-diabetic, live-donor kidney transplant patients (20 dialysis and 4 pre-dialysis, mean age 45±13 years, 75% male, 75% Caucasian) completed baseline (1-7 days before transplant) measurements. Patients underwent a detailed echocardiogram and a vascular endothelial function investigation using brachial artery flow-mediated dilatation (FMD). These were conducted together with routine blood and clinical examinations. Patients were followed up with the same investigations in the short term (9 patients, 8±0.5 months) and long-term (17 patients, 28±6 months).

Results: Left ventricular mass (LVM) regressed (208±82g to 178±63g) and ejection fraction (EF) improved (59±9% to 69.5±9%) over time, significantly in the long-term after transplantation. No significant changes were observed in FMD; however, a significant improvement was observed in nitroglycerin-mediated dilatation (NMD) (10±6% to 15±5.5%, p=0.022). Higher NMD values at baseline were correlated with greater improvement in LVM Index at follow up (p=0.009).

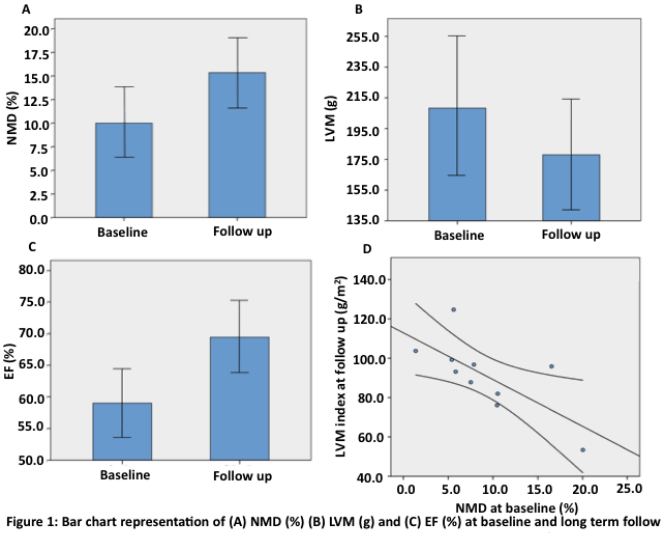


Figure 1: Bar chart representation of (A) NMD (%) (B) LVM (g) and (C) EF (%) at baseline and long term follow up. (D) Correlation between NMD at baseline (%) and LVM index at long term follow up (g/m2)

Conclusions: Cardiac structure and function significantly improved in the long term after kidney transplantation. The regression in LV hypertrophy, may be related to improvement in vascular distensibility.

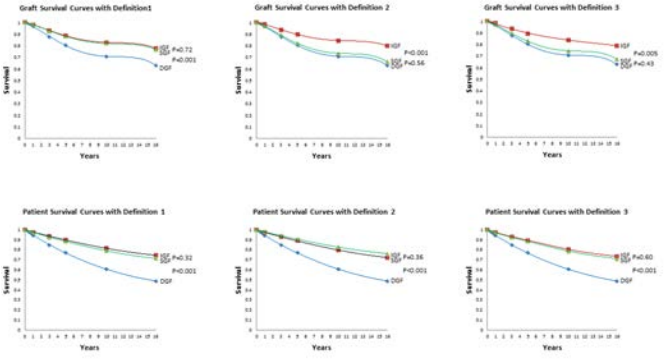
SA-PO449

Three Competing Definitions of Graft Function: Associations with Outcomes in Kidney Transplantation Ahmad M. Tuffaha,[1] Milind A. Phadnis,[3] Jonathan D. Mahnken,[3] James B. Wetmore,[2] Connie J. Wang.[2] *[1]Div of Nephrology, Univ of Kansas, Kansas City, KS; [2]Div of Nephrology, Hennepin County Medical Center, Minneapolis, MN; [3]Dept of Biostatistics, Univ of Kansas, Kansas City, KS.*

Background: We investigated how three competing definitions of post-kidney transplant (KT) graft function were associated with graft and patient survival.

Methods: A total of 1221 KT recipients were studied. In all three definitions (Def), delayed graft function (DGF) was defined as need for dialysis by postoperative (POD) 7. In Def 1, immediate graft function (IGF) was defined as a creatinine (Cr) reduction ratio between POD 1 and 2 ($CrRR_{1\text{-}2}$) of ≥30%, while slow graft function (SGF) was defined as $CrRR_{1\text{-}2}$ <30%. In Def 2, IGF was defined as Cr <3mg/dL by POD 5, and SGF as Cr ≥3mg/dL by POD 5. In Def 3, IGF was defined as Cr ≥1.5 or $CrRR_{1\text{-}3}$≥20% by POD 3, while SGF was Cr >1.5 and $CrRR_{1\text{-}3}$<20%. Association of each definition with time to graft failure and, separately, time to death was examined using a multi-regression model.

Results: For graft survival, there was a distinct difference between DGF and both IGF (p<0.001) and SGF (p=0.001), but no difference between IGF and SGF (p=0.72) for Def 1.



However, for both Def 2 and Def 3, there was no difference between DGF and SGF, while IGF was distinct from SGF and DGF (p<0.001 and p=0.005, respectively). In contrast, for patient survival, there was a distinct difference between DGF and both IGF (p<0.001 for all three definitions) and SGF (p<0.001 for all definitions), but no difference between IGF and SGF (p≥0.33 for all definitions).

Conclusions: Def 1 offers no value beyond the traditional dichotomy of requiring dialysis by POD 7. However, Def 2 and Def 3 utilize a useful construct, namely SGF, which categorizes patients as at risk for graft failure (like those with DGF) but not mortality (like those with IGF).

SA-PO450

Multi-Stakeholder Perspectives on the Relative Importance of Outcomes for Trials in Kidney Transplantation: An International Best Worse Scaling Survey Martin Howell,[1,2] Germaine Wong,[1,2,3] Benedicte Sautenet,[1] Nicole Evangelidis,[1,2] Jonathan C. Craig,[1,2] Allison Tong,[1,2] Kirsten Howard.[2] *[1]Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, NSW, Australia; [2]School of Public Health, Univ of Sydney, Sydney, NSW, Australia; [3]Centre for Transplant and Renal Research, Westmead Hospital, Westmead, NSW, Australia.*

Background: To optimize the benefits of kidney transplantation, recipients and clinicians should have an agreed, shared management plan. This relies on prioritizing the same outcomes but patient experiences of transplantation and dialysis are likely to result in quite different preferences. As a sub study of the SONG-Transplant core outcome for clinical trials initiative, the aim was to evaluate the relative importance of outcomes in kidney transplantation.

Methods: Participants completed a best-worst scaling survey to elicit preferences for 16 critical outcomes identified by stakeholder consensus. Each participant was randomly assigned to five lists, each containing six of the outcomes and identified the most and the least important outcome from each list. Relative importance scores were calculated for each outcome and normalized to the range 0 (least important) to 1 (most important).

Results: In total, 334 (175 patients/caregivers, 149 health professionals) from 46 countries participated. Death was most important for health professionals (importance score 1.0 95% confidence intervals 0.92 to 1.07) compared to patients/caregivers where death (0.71:0.63 to 0.79) was ranked below graft function (0.94:0.87 to 1.00) and graft loss (0.82:0.75 to 0.88). In addition patients/caregivers placed greater importance on chronic and acute graft rejection, skin cancer, surgical complications and blood pressure, and less importance on hospitalization.

Conclusions: Patients consider graft function, graft loss, and chronic and acute rejection to be as important as death, or more important, compared to health professionals. This focus on graft-centric outcomes may reflect a strong aversion to returning to dialysis and equating graft dysfunction with graft loss.

Funding: Government Support - Non-U.S.

SA-PO451

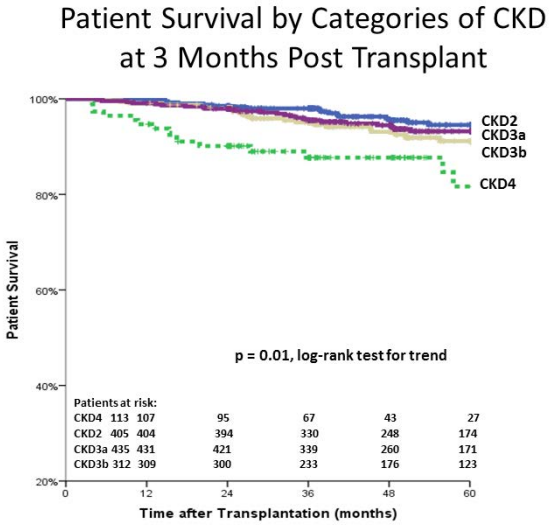
Impact of Early Graft Function on Patient Survival Post Kidney Transplantation Muna Alnimri, Angelo M. De Mattos. *Internal Medicine Section of Transplant Nephrology, UC Davis Medical Center, Sacramento, CA.*

Background: Early kidney allograft function affects pts survival post transplant.

Methods: single center historic cohort study. Adult recipients of kidney transplants between 1/2005 and 6/2013 were included. Pts with failed graft within 3 months or not followed for at least 2 years were excluded. MDRD formula was used to estimate GFR at 3 months. Categories of CKD were created according the NKF guidelines.

Results: 1,265 pts included.386(31%) had living and 879(69%)deceased donor(DD). 113 pts (8.9%) had CKD4, 312(25%) CKD3b, 435(34%) CKD3a, 405(32%) CKD2,at 3 months. Pts with CKD4 (57±12.3y) and 3b (55±12.9 y) were older than pts with CKD3a (52±13.6y) and 2 (50±14.1y)and received older kidneys (47±13.9 and 46±14y vs. 41±15.2 and 35±15y)p<0.001. CKD4 and 3b pts had higher proportion of DD(88% and 73%)vs CKD3a and 2 pts (61%,70%) p<.001. Years on dialysis, gender, diabetes, CAD were not

different among gps. At 2 years 32 pts (2.5%)expired (sepsis 11, cardiac/cva 11, cancers 6,other 4). CKD4 pts had higher mortality than pts with CKD3 or higher at 3 months (9.7% vs.1.8%; p<.001). Recipients of DD (2.8%, p=.001), and age (HR 1.085, 1.046-1.125, per year) were associated with higher mortality. Gender,DM,duration on dialysis, malignancy or CAD were not statistically significant. By multivariable (logistic regression) analysis: CKD4 (adjHR 3.9;1.75 – 8.92; p=.001)and age of recipient (adjHR 1.07; 1.025 – 1.117, p=.002) were the only factors associated with death within the first 2 years post transplant (model included DM, DD, donor age, CAD, years on dialysis).



Conclusions: Pts survival after kidney transplant seems related to early graft function ,older pts with CKD stage 4 post transplant have higher risk of death than other pts with better GFR 3 months post transplant , no specific cause of death was prevalent , this group of pts should be closely monitored.

SA-PO452

Economic Analysis of Survival for Patients Undergoing Kidney Transplant in Brazil Lucio Roberto Requiao-Moura,[1] Daniel Tavares Malheiro,[2] Silvia Regina Morgado,[3] Ana Carvalho Matos,[1] Alvaro Pacheco-Silva.[1] *[1]Renal Transplant Unit, Hospital Israelita Albert Einstein, Sao Paulo, Brazil; [2]Health Economy Dept, Hospital Israelita Albert Einstein, Sao Paulo, Brazil; [3]Management Dept, Hospital Israelita Albert Einstein, Sao Paulo, Brazil.*

Background: Brazil has one of the most important public programs of transplant in the world. However, there are few studies related to cost analysis in transplant in Brazil to support the maintenance of transplant as a therapy cost-effective. Aim: to perform an economic analysis of survival for kidney transplant patients in a philanthropic hospital.

Methods: We included in this study all admissions which resulted in cost related to kidney transplants, in all phases of transplant treatment (pre, transplant and post-transplant) of the year of 2014. Unit costs were associated to each health resource obtained from the hospital costing system. The unit costs of materials and medicines corresponded to the average direct costs of acquisition. For daily rates, tests and procedures unit costs corresponded to the fixed and variable costs associated with providing each service. Cost were collected in Brazilian Reais (R$) and converted to USD, considering the exchange rate from November 30th, 2014 (1USD=R$3.9). A survival analysis was done using the Cox model, using all kidney transplants performed since 2002 in our institution.

Results: The total cost used for kidney transplant program was U$ 6,015,160.77 in 2014. Considering the period of 2014, the cost was: in pre, transplant and post-transplant phases were $686,696.92, $1,283,362.56 and $4,045,201.28, respectively. The mean survival time was 4,497 days and the life expectancy calculated was 17 years in 922 patients included. Cost per patient per year of life-saved was $4,114.33.

Economic analysis	
Life expectation post transplant	17
Renal transplants performed in 2014	86
Life-saved years	1,462
Total cost of kidney transplant program in 2014	U$ 6,015,160.77
Cost per patient per year of life-saved	U$ 4,144.33

Conclusions: Kidney transplant was considered a cost-effective therapy since its value is lower than $50,000.00/year of life-saved, consumed in dialysis therapy.

SA-PO453

Evaluation of Baseline Allograft Biopsy and Long-Term Outcomes in Patients with Living-Donor Kidney Transplantation Takafumi Yamakawa,[1] Akimitsu Kobayashi,[2] Izumi Yamamoto,[2] Yasuyuki Nakada,[2] Takehiko Kawaguchi,[1] Toshiyuki Imasawa,[1] Takashi Yokoo,[2] Hiroshi Kitamura.[1] *[1]Nephrology, Chiba East Hospital, Chiba, Japan; [2]Nephrology, Jikei Univ, Minato-ku, Tokyo, Japan.*

Background: Donor shortage is a serious problem in kidney transplantation; consequently, increasing numbers of kidneys are from marginal donors or the elderly. Recent studies have shown that an evaluation of the baseline allograft biopsy may predict transplant outcomes in deceased-donor kidney transplantation. However, the pathology of the baseline allograft biopsy in living-donor kidney transplantation, including older donors, has not been fully validated.This study assessed the histological parameters of baseline allograft biopsy that affected the long-term graft survival in living-donor kidney transplantation.

Methods: Clinical data were examined in 192 patients who underwent living-donor kidney transplantation at Chiba East Hospital from April 2004 to April 2013. Patients experiencing rejection, BK virus nephropathy, and recurrent glomerular disease were excluded. All baseline biopsies were 1-hour biopsies and scored according to the Banff classification, and the relationship between the individual histological lesions and death-censored graft survival was assessed. Survival analysis was performed using Cox proportional hazards analysis and log-rank testing. We also evaluated the pathological findings in aging donor kidneys by stratification using donor age (under 50, 50 to 59, 60 to 69, over 70 years).

Results: The mean follow-up time after transplantation was 6.0 years. Arteriolar hyalinosis (HR, 2.16; 95% CI, 1.20–3.89; *P*=0.010) and glomerulosclerosis (HR, 3.64; 95% CI, 1.17–11.25; *P*=0.025) were significantly associated with death-censored graft survival, whereas interstitial fibrosis/tubular atrophy (IF/TA), and vascular intimal thickening were not. Although the prevalence of glomerulosclerosis, arteriolar hyalinosis, IF/TA, and intimal thickening were higher in the over-60 donor group, we could not predict graft survival using only donor age.

Conclusions: Arteriolar hyalinosis and glomerulosclerosis may be important pathological findings affecting long-term graft survival in living-donor kidney transplantation.

SA-PO454

Digital Quantification of Macrophage Abundance in a Cross Sectional Study of Native and Transplanted Kidneys Jessica Schmitz,[1] Abedalrazag Ahmad Khalifa,[1] Hermann G. Haller,[2] Hans Heinrich Kreipe,[1] Wilfried Gwinner,[2] Friedrich Feuerhake,[1] Jan H. Braesen.[1] *[1]Inst of Pathology, Hannover Medical School, Hannover, Germany; [2]Nephrology, Hannover Medical School, Hannover, Germany.*

Background: Standardized markers based on quantitative and qualitative evaluation and localization of immune cell density in kidney biopsies may improve diagnostic accuracy.

Methods: Kidney biopsies were stained for macrophages using a monoclonal CD68 antibody, scanned (Leica) and whole slide images were analyzed for immunopositively stained area using a digital approach (Definiens Tissue Studio). Results were obtained separately for cortex, medulla and extrarenal tissue. Kidney biopsies were clinically indicated biopsies (native: 100%, KTx 64%). KTx biopsies partly came from the Hannover Protocol Biopsy Program (36%).

Results: CD68-positively immunostained area (% of the respective cortex, medulla, extrarenal area) was higher in KTx (n=368) vs. native kidney (n=134) biopsies (cortex: 2.9 vs. 1.0, medulla: 2.8 vs. 0.8, extrarenal tissue: 2.2 vs. 0.8; p<0.001). 38% of the studied KTx biopsies revealed rejection (borderline 15%, cellular 8%, humoral 7%, combined cellular and humoral 9%). Humoral and combined rejection were correlated with significantly increased macrophage infiltration (no rejection: cortex 2.6%, medulla 2.4%; borderline: cortex 1.9%, medulla 1.5%; cellular: cortex 2.5%, medulla 2.6%; humoral rejection: cortex 4.4%, medulla 5.9%; combined rejection: cortex 6.2%, medulla 6.9%). The density of macrophages correlated significantly with the time between transplantation and biopsy: Highest mean values were measured when post-transplant time exceeded 1 year (cortex: 5.8% compared to <1year >90 days (4.1%), <90 days >8 days (1.3%), <8 days (1.5%)) Evaluation of IF/TA according to Banff 2013 consensus showed a significant increase of infiltrating macrophages with fibrosis progression both in native and transplanted kidneys.

Conclusions: The findings suggest that macrophages have an essential in active rejection, chronic allograft injury and fibrosis. Digital morphological approaches may facilitate the characterization of immune cell-mediated kidney injury in native kidneys and after KTx.

SA-PO455

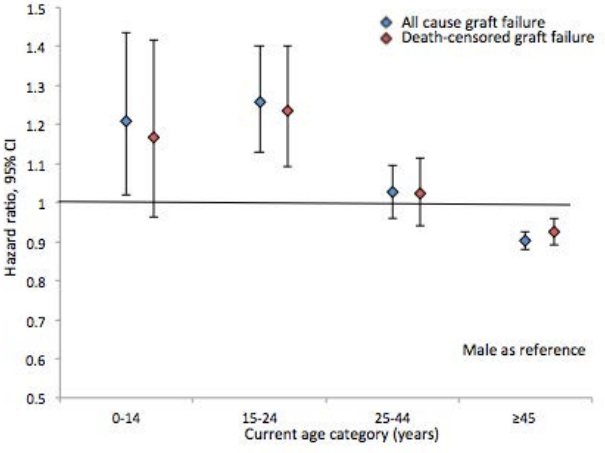
Sex Differences in Kidney Graft Outcomes Differ by Age Fanny Lepeytre,[1] Mourad Dahhou,[2] Xun Zhang,[2] Bethany J. Foster.[2] *[1]Hôpital du Sacré-Coeur de Montréal, Montréal, QC, Canada; [2]McGill Univ Health Centre, Montréal, QC, Canada.*

Background: Whereas studies of sex differences in graft survival among adult kidney transplant recipients showed conflicting results, several pediatric studies suggested poorer outcomes in females than males. We hypothesized that the impact of recipient sex on kidney graft survival differs by age.

Methods: We evaluated 159,417 patients recorded in the SRTR database who received a first deceased donor kidney transplant (1995-2013). We used time-dependent Cox models

to estimate the association between recipient sex and each of death-censored (DCGF) and all cause (ACGF) graft failure for patients of different ages. Models included a sex by current age (0 to 14, 15 to 24, 25 to 44, or ≥ 45 years) interaction term and the following covariates: race, primary disease, donor:recipient height ratio, donor age, donor sex, panel reactive antibody, and duration of dialysis pre-transplant.

Results: There were 66,562 graft failures and 37,564 deaths over a median of 4.9 years (IQR 2.0, 9.1). In multivariable models, females <25y had significantly higher risks of ACGF than males the same age (0-14y: HR 1.21 [95% CI 1.02, 1.43]; 15-24y: HR 1.26 [95% CI 1.40, 1.13]), and females ≥45y had significantly lower risks of ACGF than males the same age (HR 0.90 [95% CI 0.88, 0.93]). Compared with males of the same age, the risk of DCGF was significantly higher for females 15-24y (HR 1.24 [95% CI 1.09-1.40]) and lower for females ≥45y (HR 0.92 [95% CI 0.89-0.96]).



Conclusions: Female kidney transplant recipients <25y have a higher risk of poor outcomes than males of same age, whereas among those ≥45y, the risk of poor outcomes is higher for males than females. Differences in immune activation by sex, influenced by sex hormones, may play a role in these risk differences.

Funding: Clinical Revenue Support

SA-PO456

Opioid Use, Morbidity and Mortality in U.S. Kidney Transplant Patients

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Background: Pain is an important symptom for ESRD patients, linked to depression and diminished quality of life. Over the last 10 years, aggressive ESRD patient pain treatment has been advocated. The Medicare prescription drug benefit allows tracking ESRD prescriptions and linkage to outcomes. Few data exist on outcomes associated with pain and opioid medication prescription (OMP) in ESRD. The high prevalence of OMP and associated adverse events are increasingly evident. New Centers for Disease Control guidelines recommend caution in OMP. We assessed prevalence of OMP in kidney transplant patients, and associations between OMP and mortality and hospitalizations, with 2006–2010 USRDS data.

Methods: We limited our study sample to kidney transplant patients (≥365 d) with full Medicare Part A, B, and D coverage in each study year to ensure complete claim data. OMP was confirmed from Part D prescription claims. Cox proportional hazards regression models, controlled for demographic, ethnic, comorbidity and residence data examined associations of OMP in 2010 with subsequent all-cause death and hospitalization (2010 prevalent cohort; N=36,486).

Results: Approximately 14% of patients were prescribed 90 d opioids yearly. The most common OMPs in 2010 contained hydrocodone (6.4%) and oxycodone (3.8%). Patients with OMP for ≥90 d had increased death risk compared with those without (adjusted HR: 1.54 [95% CI, 1.38-1.71]). Short-term (1-89 d supply) and chronic OMP (≥90 d) also had increased hospitalization risk (1.20 [1.16-1.24] and 1.50 [1.44-1.57], respectively), compared with non-users. Rural transplant patients with OMP had higher mortality risk than their urban counterparts. Among individual opioids, hydrocodone, oxycodone, morphine, and hydromorphone were significantly associated with increased death risk.

Conclusions: Opioid drug prescription is associated with increased risk of death and hospitalization of ESRD transplant patients. While a causal relationship cannot be inferred, and opioid prescription may be an illness marker, efforts to treat pain effectively in ESRD transplant patients with less toxic interventions deserve consideration.

Funding: NIDDK Support

SA-PO457

Everolimus with Low-Dose Tacrolimus versus Standard Immunosuppressive Regimen: Subgroup Analysis of Renal Function at 12 Months in De Novo Renal Transplant Patients

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Background: Reduction of tacrolimus (Tac) levels after kidney transplantation has a beneficial impact on renal function. The US92 study determined if everolimus (EVR) with low-dose Tac (LTac) is non-inferior to mycophenolate mofetil (MMF) with standard-dose tacrolimus (STac) on measures of allograft function and safety in de novo renal transplant patients. This post-hoc analysis of US92 assessed renal function of subjects with/without treated biopsy-proven acute rejection (tBPAR) or delayed graft function (DGF), and by induction therapy.

Methods: Subjects were randomized 1:1 to receive EVR (0.75 mg BID, adjusted to maintain trough level 3–8 ng/mL) + LTac (C0h 0–2 Months [M]: 4–7 ng/mL, 2–6M: 3–6 ng/mL, 6–12M: 2–5 ng/mL) or MMF (2 g/day) + STac (C0h 0–2M: 8–12 ng/mL, 2–6M: 7–10 ng/mL, 6–12M: 5–8 ng/mL).

Results: Despite some differences at M1, mean eGFR (MDRD) at M12 was similar between treatments irrespective of tBPAR, DGF or induction therapy (Table). In both treatment groups, subjects with tBPAR had lower eGFR at M12 vs. those without tBPAR. Improved eGFR from baseline was numerically greater in subjects with DGF vs. those without.

Conclusions: Renal function as assessed by eGFR was generally consistent between the US92 EVR+LTac and MMF+STac groups, regardless of tBPAR, DGF or induction therapy.

Subgroup	eGFR, mL/min/1.73m^2 (n)					
	M1			M12		
	EVR+LTac	MMF+STac	P-value	EVR+LTac	MMF+STac	P-value
tBPAR						
Yes	55.1 (48)	53.2 (31)	0.450	54.9 (45)	53.0 (26)	0.691
No	64.5 (228)	58.5 (249)	0.010	64.9 (208)	64.2 (222)	0.931
DGF						
Yes	49.7 (38)	41.2 (33)	0.193	61.4 (34)	56.0 (29)	0.428
No	65.0 (238)	60.1 (247)	0.013	63.4 (219)	64.0 (219)	0.653
Induction therapy						
Thymoglobulin	60.8 (83)	54.7 (87)	0.131	61.3 (71)	59.4 (73)	0.562
Basiliximab	63.7 (193)	59.3 (193)	0.055	63.9 (182)	64.6 (175)	0.474

Funding: Pharmaceutical Company Support - Novartis Pharmaceuticals Corporation

SA-PO458

Follow-Up Results of HERAKLES Trial on Three Different Treatment Regimen and Switching off Effects in De Novo Renal Transplant Patients after 5 Years

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Background: To compare switching off effects from 3 different immunosuppressive (IS) regimen 5 years after renal transplantation (Tx).

Methods: 802 patients (pts) were included in this prospective, open-label, randomized, controlled multi-center study with observational follow-up (FU) to month (Mo) 60 post Tx. All pts received cyclosporine A (CsA), enteric-coated mycophenolate sodium (EC-MPS) and steroids; at 3 Mo post Tx 499 pts were randomized 1:1:1 to either a) continue standard CsA (100-180ng/ml) +EC-MPS(n=166) (STD) or convert b) to an everolimus (EVR)-based calcineurin inhibitor (CNI)-free regimen (EVR 5-10ng/ml) +EC-MPS(n=171) or c) to an EVR (3-8ng/ml) regimen with reduced CsA (50-75ng/ml;n=162). All pts continued on steroids.

Results: After 5 years post Tx from initial ITT population there were 29% in CNI-free and 50% in STD group still on their initial assigned treatment and available for Mo 60 analysis. Switch as reported due to AEs occurred in 6% of STD, 5% CNI-free and 2% CNI-reduced pts during FU. Switch was performed at investigator discretion and for STD group mostly towards mTORi (EVR 21%, SRL 13%), in CNI-free group mostly towards Tac(48%) or CsA(50%). In the CNI-reduced group EVR was given in 47%, CsA in 56%, Tac in 29 % pts [drug combinations, sum can be >100%]. eGFR (Nankivell) at Mo 60 was significantly improved by +14.4 mL/min in CNI-free non-switcher population (74.7mL/min) over STD group ($p<0.001$), in switcher population (switched from CNI-free) eGFR was still 64mL/min. BPAR rate was similar in all 3 groups during FU (7.9% STD, 7.6% CNI-free, 7.5% CNI-reduced).

Conclusions: Mo 60 HERAKLES data show that EVR with reduced-dose or without CNI-exposure reflect an efficacious, safe therapeutic approach offering the opportunity for an individualized IS to minimize CNI-exposure. Pts who never switched off the assigned EVR-based CNI-free regimen showed a strong and significant improved renal function, pts that were switched back to a CNI-regimen still showed improved GFR.

SA-PO459

Development of a Bioartificial Kidney Device Dimitrios Stamatialis,[1] Natalia V. Chevtchik,[1] Michele Fedecostante,[2] Jitske Jansen,[2] Milos Mihajlovic,[2] Martijn J. Wilmer,[3] Marieke Rueth,[4] Rosalinde Masereeuw.[2] *[1]Biomaterials Science and Technology - MIRA Inst, Univ of Twente, Enschede, Netherlands; [2]Pharmaceutical Sciences, Utrecht Inst for Pharmaceutical Sciences, Utrecht, Netherlands; [3]Pharmacology and Toxicology, Radboud Inst for Molecular Life Sciences, Radboud Univ Medical Center, Nijmegen, Netherlands; [4]excorlab GmbH, Obernburg, Germany.*

Background: A key component of a bioartificial kidney device (BAK) is a "living membrane" consisting of a tight renal cell monolayer on an artificial porous membrane. Recently, we showed the creation of such a membrane using conditionally immortalized human renal proximal tubular epithelial cells (ciPTECs) on a polyethersulfone (PES)-based flat and hollow fiber membrane (HFM). Here, we present the development of an upscaled BAK system with "living" HFMs bringing the BAK closer to clinical implementation.

Methods: HFMs were mounted in modules and coated with L-Dopa and Collagen IV (CIV). The culture of ciPTECs with organic cationic (OCT) transporters was performed under static conditions. The ciPTEC morphology and monolayer quality was investigated via expression of tight junction protein Zonula Occludens-1 (ZO-1), permeation of inulin-FITC, fluorescent OCT substrate 4-(4-(dimethylamino)styryl)-N-methylpyridinium iodide (ASP^+) and of organic cationic solutes.

Results: The upscaling of the L-Dopa/CIV coating and seeding of the ciPTECs on the membranes was successful. After one week of culture, reproducible cell monolayers were formed within modules containing 3 HFMs and surface area of 4 cm^2. Tight monolayer ciPTECs culture was achieved with limited inulin leakage when compared to modules without cells (301 ± 103 and 812 ± 2 $pmol \cdot min^{-1} \cdot cm^{-2}$ respectively, $p < 0.001$, unpaired t-test). The ASP^+ uptake by the cells was reduced by 60% in presence of uremic toxin mix or cimetidine, confirming the functional cell monolayer.

Conclusions: Upscaled HFM modules supporting a functional monolayer of renal cells were successfully developed. Future work will include detailed characterization of protein-bound uremic toxin transport.

Acknowledgement.This work is funded by the EU Marie Curie ITN Project BIOART (grant no.31669 EU-FP7-PEOPLE-ITN-2012).

Funding: Government Support - Non-U.S.

SA-PO460

Mixed Matrix Membranes for Removal of Protein-Bound Toxins from Human Plasma Dimitrios Stamatialis,[1] Denys Pavlenko,[1] Karin G. Gerritsen,[2] Esmée Van Geffen.[1,2] *[1]Dept of Biomaterials Science and Technology/MIRA Inst, Univ of Twente, Enschede, Netherlands; [2]Dept of Nephrology and Hypertension, Univ Medical Center Utrecht, Utrecht, Netherlands.*

Background: Protein-bound toxins (PBT) accumulate in uremic patients due to their poor removal by conventional hemodialysis. Their removal can be improved by a mixed matrix membrane (MMM), which combines adsorption and diffusion. In this work, we developed a low flux MMM and compared its performance to a conventional low-flux dialyzer used in the clinic.

Methods: The inner and outer layers of hollow fiber MMM were produced using a polymer blend of polyethersulfone/ polyvinyl-pyrrolidone. Activated carbon was loaded in the outer polymer matrix layer for adsorption of PBTs. The membranes were characterized by scanning electron microscopy (SEM), clean water flux experiments and dialysis/adsorption experiments with plasma spiked with uremic concentrations of the PBTs indoxyl sulfate (IS) and p-cresyl sulfate (pCS). Low flux dialyzer F8HPS (Fresenius) was used for comparison.

Results: By optimizing spinning conditions, we produced new MMM fibers with inner diameter of 450µm (inner diameter of F8HPS 200 µm) and inner membrane layer thickness of 21 µm. The MMM have a lower ultrafiltration coefficient (UC) in comparison to F8HPS (3.4±0.8 versus 10 $ml/h/m^2/mmHg$, respectively) and molecular weight cut-off of around 12 kDa. Despite this lower UC, the MMM showed improved removal of PBTs in comparison to F8HPS, due to the additional adsorption of toxins by the activated carbon (maximum removal of 367±14 versus 187±12 mg/m^2 for IS and 380±54 versus 225±3 mg/m^2 for pCS.

Conclusions: We developed MMMs with optimal characteristics offering superior ability in removing PBTs in comparison to a commercial dialyzer. Acknowledgment.This work is funded by the EU Marie Curie ITN Project BIOART (grant no.316690, EU-FP7-PEOPLE-ITN-2012).

Funding: Government Support - Non-U.S.

SA-PO461

Perfused Glomerular Microvascular Unit: A Glomerular Pathophysiology Model Claire Rigothier,[1,2] Killian Flegeau,[1] Sebastien Rubin,[1,2] Simon Mucha,[1,2] Raphael Devillard,[1] Jerome Kalisky,[1] Christian Combe.[1,2] *[1]BIOTIS, INSERM U1026, Univ de Bordeaux, Bordeaux, France; [2]Service de Néphrologie, Transplantation et Dialyse, CHU de Bordeaux, Bordeaux, France.*

Background: The development of an artificial glomerular unit may be pivotal for renal pathophysiology studies at a microscopic scale. Using a tissue engineering approach, the project will reproduce the glomerular architecture by performing a glomerular perfused microfiber.

Methods: Human immortalized glomerular cell lines: podocytes and endothelial cells (EC) were used. Cells and 3-dimensional (3D) matrix have been characterized by immunofluorescence (IF) with confocal analysis and Western blot (WB). Optical microscopy was performed to study microfiber compaction and contraction. We also analyzed cell viability and cell metabolism within the 3D construct. Femtosecond laser was used to create the central lumen of microfibers.

Results: Using the microfiber method developed in the unit, we repeatedly obtained a cellularized microfiber sorting human glomerular cells in 3D. Around a central structure made of collagen I, we successively found the internal layer composed by EC, the neoformed glomerular basement membrane rich in collagen IV and the external layer of podocytes. Cell concentration, optimal seeding time and role of physical stresses were appreciated and modulated to obtain the microfiber. Cell viability and cell phenotype were confirmed by IF and WB analysis: expression of specific proteins, vWF, PECAM and VEGFR2 for EC and nephrin, synaptopodin and podocin for podocytes. Cell characteristics were maintained after central lumen formation by femtosecond laser for planned microfiber perfusion.

Conclusions: In summary, with this microfiber technique, endothelial cells and podocytes were better differentiated than in culture dishes, and produced a differentiated GBM. Glomerular fluid stresses and glomerular pathophysiological conditions will be shortly simulated in the glomerular microfibers using the microperfusion method. A glomerular microvascular network will allow us to study cell interactions in a 3D system and increase our knowledge on the glomerular pathophysiology.

Funding: Private Foundation Support

SA-PO462

An Upscaled Bioartificial Kidney Device with an Apically Oriented Inflammatory Response upon LPS Exposure Michele Fedecostante,[1] Natalia V. Chevtchik,[2] Milos Mihajlovic,[1] Dimitrios Stamatialis,[2] Rosalinde Masereeuw.[1] *[1]Pharmacology, Utrecht Inst for Pharmaceutical Sciences, Netherlands; [2]Biomaterials Science and Technology, MIRA Inst for Biomedical Technology and Technical Medicine, UTwente, Netherlands.*

Background: The development of a bioartificial kidney (BAK) device for removal of protein-bound uremic toxins in plasma is needed to improve current therapy for end stage renal disease patients. Here, we investigated monolayer formation and immune response of human conditionally immortalized proximal tubule epithelial cell (ciPTEC) when cultured in an upscaled BAK device.

Methods: CiPTEC were cultured for 10 days on the outer surface of 3 assembled double-coated (L-DOPA (2 $mg \cdot ml^{-1}$) and collagen IV (25 $\mu g \cdot ml^{-1}$)) Polyethersulfone hollow fiber membranes (HFM, 4 cm^2 surface). Cell barrier integrity was investigated by immunostaining and inulin-FITC leakage. Immune response was assessed by ELISA measurements of IL-6 and IL-8 upon 24h lipopolysaccharide (LPS, 10 $\mu g \cdot ml^{-1}$) exposure.

Results: Tight monolayer of ciPTECs was achieved on HFM-BAK devices as shown by immunostaining and low inulin leakage compared to double-coated cell-free devices (244 ± 68 vs 1575 ± 128 $pmol \cdot min^{-1} \cdot cm^{-2}$, $p<0.001$, seeded vs. unseeded devices, resp.). Exposure of BAK devicesto LPS at the apical side resulted in pro-inflammatory cytokines release, which was more pronounced in the apical compartment (IL-6: 992 ± 53 *vs.* untreated: 17 ± 14; IL-8: 74 ± 10 *vs.* untreated: 5.8 ± 2.5; $ng \cdot cm^{-2}$) compared to the basolateral compartment (IL-6: 1.7 ± 1.4 *vs.* untreated: 2.0 ± 1.2; IL-8: 1.0 ± 0.5 *vs.* untreated: 0.4 ± 0.2 $ng \cdot cm^{-2}$). When BAK devices were exposed to LPS from the basolateral side, the cytokine response was 10.4±2.4- and 1.9±0.1-fold lower for IL-6 ($p<0.05$) and IL-8 as compared to apically exposed devices, respectively. This was also confirmed by immunostaining of Toll-like receptor 4 at the apical surface.

Conclusions: This study demonstrates an upscaled BAK device of renal epithelial cells on HFM with tight monolayer formation, good barrier function and polarized cytokine release upon LPS exposure. *Funding.* EU Marie Curie ITN Project BIOART (grant no.316690, EU-FP7-PEOPLE-ITN-2012).

Funding: Government Support - Non-U.S.

SA-PO463

Genome Engineering of Renal Epithelial Cells with the Goal of Improved Function in an Implantable Artificial Kidney Matthew H. Wilson,[1,2] Wentian Luo,[1] Rick C. Welch,[1] Shuvo Roy,[3] William Henry Fissell.[1] *[1]Nephrology and Hypertension, Vanderbilt Univ, Nashville, TN; [2]Nephrology, VA Medical Center, Nashville, TN; [3]Bioengineering and Therapeutic Sciences, Univ of California San Francisco, San Francisco, CA.*

Background: Development of an implantable artificial kidney (IAK) will require renal epithelial cells capable of reabsorption of salt and water. We are using genome engineering to bioengineer cells for improved Na+/H+ exchange and H20 reabsorption. The *piggyBac* transposon system offers a simple but highly efficient non-viral strategy for genome engineering cells to stably overexpress one or more transgenes simultaneously. The *piggyBac* transposase enzyme integrates transposon DNA containing one or more transgenes into the genomic DNA of cells via a cut-and-paste mechanism.

Methods: Standard molecular biology techniques were used to subclone the human sodium hydrogen exchanger 3 (NHE3) and aquaporin-1 (AQP1) cDNAs into *piggyBac* transposon vectors. The NHE3 transgene was engineered with a C-terminal hemagglutinin (HA) epitope tag. The AQP1 transgene contained flag and myc epitope tags. The *piggyBac* transposase was then co-delivered with these transposons to stably integrate and overexpress NHE3 or AQP1 in cultured renal epithelial cells.

Results: We generated MDCK cells stably expressing a cumate inducible NHE3 and confirmed cumate-induced overexpression via Western blot and immunofluorescence analysis of the HA tag. Confocal microscopy confirmed apical expression of NHE3 in polarized MDCK cells. We also generated MDCK cells stably overexpressing AQP1. Overexpression of AQP1 was confirmed using Western blot and immunofluorescence assays of the flag and myc tags.

Conclusions: We are currently also overexpressing NHE3 and AQP1 in cultured human renal proximal tubule cells (RPTECc). Cellular transport assays are ongoing to evaluate for increased capability in moving salt and water across a genome engineered cellular monolayer. These studies will allow us to determine the optimally genome engineered renal epithelial cell type for maximal function in the IAK.

Funding: Other NIH Support - NIBIB

SA-PO464

Transport by Renal Tubule Cell Bioreactor Is Dependent on Extracellualr Matrix Choice Harold D. Love,[1] Nicholas J. Ferrell,[1] Jin Cheng,[1] Shuvo Roy,[2] William Henry Fissell.[1] *[1]Nephrology and Hypertension, Vanderbilt Univ, Nashville, TN; [2]Bioengineering and Therapeutic Sciences, Univ of California, San Francisco, San Francisco, CA.*

Background: Renal tubule cell bioreactors are of interest for in vitro disease models, high-throughput drug and toxicity testing, and renal replacement therapy. The parameter space to be exploited in optimizing in vitro cell phenotype is extensive. There are several commercially available extracellular matrix preparations available to facilitate cell-scaffold attachment, leading to the question of whether any one matrix was associated with particular phenotypic features.

Methods: Primary human renal tubule cells (HRTC) were grown to confluence on Transwell inserts preincubated with Collagen IV, Collagen I, Laminin, Matrigel, or fibronectin, with and without 50 uM ascorbic acid. TEER and inulin leak rates were measured to verify confluence. Apicobasal volume transport was measured in the presence and absence of ouabain, an inhibitor of basolateral sodium-potassium ATPase.

Results: HRTC grew to confluence on all substrates. Inulin leak rates were not different from a control well bearing an impermeable substrate. Transport rates were different in the presence and absence of ouabain ($p = 5.6 \times 10^{-10}$ by ttest). Transport rates differed between matrices (p=0.006 by one-way ANOVA). Fibronectin and laminin displayed highest volume transport. When cells were cultured in the presence of ascorbic acid, transport was not significantly different between substrates ($p > 0.08$ by one-way ANOVA).

Conclusions: Choice of extracellular matrix substrates influences apicobasal transport in bioreactors, but adding cofactors for basement membrane synthesis to the culture medium abolishes differences arising from initial matrix choice.

Funding: Other NIH Support - NIBIB, Private Foundation Support

SA-PO465

Respiratory Capacities and Differentiation of Novel Gluconeogenic Renal Cell Lines Harold D. Love,[1] Jin Cheng,[1] Shuvo Roy,[2] William Henry Fissell.[1] *[1]Nephrology and Hypertension, Vanderbilt Univ, Nashville, TN; [2]Bioengineering and Therapeutic Sciences, Univ of California, San Francisco, San Francisco, CA.*

Background: The renal proximal tubule relies on oxidative phosphorylation to carry out metabolically intensive transport. Cultured primary cells rapidly switch to a less differentiated glycolytic phenotype characteristic of most immortalized renal cell lines. Glucose starvation of non-gluconeogenic cell lines can induce and select for cells that have switched on gluconeogenesis as a survival mechanism, as glucose is essential for the production of ribose-5-phosphate, a precursor for nucleic acid biosynthesis. The selective pressure of glucose starvation not only induces gluconeogenesis, but the cells also exhibit other unique features that are characteristic of renal proximal tubular epithelial cells.

Methods: LLC-PK1 cells were adapted to serum-free media and starved of glucose after the method of Gstraunthaler and Handler. Gluconeogenic colonies were isolated and expanded in glucose-free medium. Initial characterization of the mitochondrial oxidative capacity and glycolysis was carried out using a 96-well high throughput Seahorse Bioscience assay.

Results: Numerous colonies of cells growing in glucose-free medium appeared after 3-4 weeks, and were sub-cloned and expanded. The phenotypic appearance of the colonies was quite variable, with many showing a pronounced differentiation compared to the parental cells. Cells typically formed compact, very dense monolayers, with extensive dome formation, even in very small colonies. Cell proliferation was observed primarily in peripheral cells, while contact inhibited cells rapidly differentiated. Initial characterization of cell lines found significant differences in oxygen consumption rates and glycolysis, compared to parental control cells, with and without glucose.

Conclusions: Gluconeogenic cell lines were induced from LLC-PK1 cells by culturing in glucose-free media. Several cell lines had a more differentiated appearance and enhanced oxygen consumption with reduced glycolysis, compared to parental cells. Preliminary results suggest that cell lines with enhanced renal function *in vitro* can be obtained via forced gluconeogenesis.

Funding: Other NIH Support - NIBIB, Private Foundation Support

SA-PO466

Sugars Alter the Mechanical Properties of Renal Tubular Basement Membrane Nicholas J. Ferrell. *Div of Nephrology, Vanderbilt Univ Medical Center, Nashville, TN.*

Background: Diabetic nephropathy is characterized by loss of extracellular matrix (ECM) homeostasis in the kidney that results in thickening of the tubular basement membrane (TBM). In addition, hyperglycemia alters the biochemical structure of the ECM through formation of advanced glycation end-products that can crosslink the ECM and may alter the mechanical properties of the TBM. The mechanical properties of ECM play an important role in maintaining tissue function, and altered biophysical properties may affect disease progression. The goal of this work was to determine if incubation of renal tubules in sugars ex vivo alters the mechanical properties of TBM.

Methods: Tubules were manually dissected from the outer cortex of normal mouse kidneys. Tubules were incubated ex vivo in 100 mM glucose, 100 mM ribose, or PBS for four weeks. Stress-strain response of individual tubules was evaluated using a microcantilever-based tensile testing method. The stiffness (elastic modulus) of the tubular basement membrane was evaluated at strain ranges of 0-10%, 10-20%, and 20-30% strain by determining the slope of the linear regression of the strain-strain curves over those strain ranges.

Results: Glucose and ribose incubation resulted in a statistically significant ($p<0.05$) increase in the TBM stiffness over all strain ranges that were tested. Glucose incubated tubules had stiffness of 767±96 kPa, 1244±135 kPa, and 1944±200 kPa at strain ranges of 0-10%, 10-20%, and 20-30%, respectively. Ribose incubated tubules had stiffness of 1116±175 kPa, 2773±375 kPa, and 4342±413 kPa over the same strain ranges. This is a 2.2-2.6 fold increase in stiffness for glucose incubated tubules and a 3.8-5.2 fold increase in ribose incubated tubules compared to controls.

Conclusions: These data show that incubation of tubules with sugars is alone sufficient to alter TBM stiffness over a relatively short period of time. Both glucose and ribose increased TBM stiffness. Due to its higher reactivity, ribose had a more pronounced impact on TBM stiffness. These data suggest sugars may alter the biophysical properties of kidney extracellular matrix. These changes may play a role in disease progression in diabetic nephropathy.

Funding: NIDDK Support

SA-PO467

Evaluation of Renal Cells for In Vitro Modeling of Proximal Tubule Drug Transport Aishwarya Jayagopal, Shuvo Roy, Deanna L. Kroetz. *Bioengineering and Therapeutic Sciences, Univ of California, San Francisco, San Francisco, CA.*

Background: Active transport by renal proximal tubules plays a significant role in human drug disposition and is therefore important to model when developing drugs. Although several proximal tubule cell lines exist, limited data are available regarding their ability to act as acceptable models of the tubule. Here, several cell lines are compared with respect to monolayer formation, drug transporter expression and function, and cilia function.

Methods: hOCT2/hMATE1 double transfected (DT) MDCK cells, SV40 immortalized Human Proximal Convoluted Tubule (HPCT) cells, and hTERT immortalized Renal Proximal Tubule Epithelial Cells (RPTEC) were cultured on transwell inserts. Tight junctions and cilia were confirmed by immunofluorescence, monolayer tightness was measured by quantifying inulin leak through cells and RNA expression was measured by qRT-PCR. Transporter function was measured by quantifying cellular uptake and transport of substrates (+/- inhibitor). Cells were deciliated with 30 mM ammonium sulfate.

Results: All cells formed tight junctions as demonstrated by ZO-1 expression, but showed varying levels of monolayer tightness with MDCKs at ~1%, HPCTs at ~7%, and RPTECs at ~10% inulin leak. Both human cell types tested had comparable RNA expression levels of OCT2, MATE1, OAT3 and MRP4 (~ΔCT of: 14-15, 12-13, 15 and 5-9 respectively), while double transfected MDCK cells had high expression levels of OCT2 and MATE1 (~ΔCT of -2 and -4 respectively). Both DT-MDCK cells and HPCT cells showed inhibitable uptake and transport of ASP+ and Metformin. Lastly, both MDCK and HPCT cells grew cilia that could be removed without effects on tight junction formation, RNA expression of transporters and transporter function.

Conclusions: While overexpressing MDCK cells exhibit the best performance, both human proximal tubule cell lines show promise as potential models of human tubular function. Studies are ongoing to incorporate these cells into an engineered device to mimic renal drug elimination.

SA-PO468

Kidney-Specific Gene Transfer by Hydrodynamic Renal Pelvis Injection Lauren Elizabeth Woodard,[1] Jizhong Cheng,[2] Rick C. Welch,[1] Felisha M. Williams,[1] Wentian Luo,[1] Matthew H. Wilson.[1] *[1]Dept of Medicine, Div of Nephrology, Vanderbilt Univ Medical Center/Veterans Affairs, Nashville, TN; [2]Dept of Medicine, Div of Nephrology, Baylor College of Medicine, Houston, TX.*

Background: New breakthroughs in the treatment of kidney disease are desperately needed to address the increasing shortage of organs available for transplantation and high mortality associated with dialysis. The first commercial gene therapy products have recently become available. Gene transfer to the mouse kidney is desirable both in terms of providing proof-of-concept for gene transfer to address genetic diseases and for the creation of new disease models.

Methods: We found that a fast injection into the renal pelvis with a DNA solution of sufficient volume was effective for delivery of plasmid DNA to the adult mouse kidney, with no other organs expressing the transgene by live animal imaging for luciferase. We used the *piggyBac* transposon system to permanently integrate the luciferase transgene and found that the EF1alpha promoter provided superior long-term gene expression.

Results: Staining for TdTomato revealed expression in a variety of cell types, including proximal tubules, located in punctate areas of expression along the injection path as traced by fluorescent beads. In order to assess the degree of damage caused by the injection, we performed renal pelvis hydrodynamic injections on mice that had undergone a unilateral nephrectomy. We found mice receiving injections had a significantly increased B.U.N. as compared to sham controls at two days following surgery that resolved completely within

two weeks. To test the effect of the immune response on long-term gene expression, we treated mice with cyclophosphamide and observed increased levels of luciferase expression compared to sham controls.

Conclusions: Hydrodynamic renal pelvis injection of naked DNA produced transgene expression in many cell types. Higher levels of long-term expression were achieved with transposons for permanent integration and cyclophosphamide for immunosuppression. We are currently testing hydrodynamic renal pelvis injection of biologically relevant transgenes for treatment of cystinuria, acute kidney injury, and anemia.

Funding: NIDDK Support, VA Support, Private Foundation Support

SA-PO469

Targeting Kidney Pericytes with Adeno-Associated Virus: A Novel Method for Gene Therapy Yoichiro Ikeda,[1] Xiao Ru,[2] Luk Vandenberghe,[2] Benjamin D. Humphreys.[1] *[1]Div of Nephrology, Washington Univ in St. Louis, St. Louis, MO; [2]Schepens Eye Research Inst, Boston, MA.*

Background: Kidney perciytes are the major myofibroblast progenitor population and an important therapeutic target. There is no method to deliver genetic material to kidney pericytes, however. Recombinant adeno-associated virus (AAV) is non-integrating and infects both dividing and quiescent human cells and has emerged as a powerful viral vector for human gene therapy. Here we systematically evaluated the ability of AAV serotypes to transduce kidney pericytes.

Methods: We tested six different AAV capsid serotypes (2/2, 2/5, 2/6, 2/8, 2/9, 2/Anc80) with either the CMV or the synthetic 'CASI' promoter driving GFP or Cre recombinase. These were injected either into WT or R26TdTomato reporter mice and expression patterns evaluated in healthy and fibrotic kidneys.

Results: Among the 6 serotypes, AAV-2/8 and -2/Anc80 had the highest GFP expression in kidney. The CASI promoter drove higher per-cell expression than CMV, but the distribution was equivalent. Dose dependent expression was observed between the doses of 10^{10} - 10^{12} genome copies/mouse without toxicity. Expression was maximal 2-3 weeks after injection. Expression was limited to interstitial pericytes, mesangial cells and to SLC12A1+ macula densa epithelial cells. Since GFP expression was low in some cells, we used injected Cre recombinase AAV into R26TdTomato reporter mice to increase signal. At 10^{11} genome copies/mouse, we measured transduction of 17.6±12.4% of pericytes and 88.6±10.0% of mesangial cells. However at 10^{12} GC/mouse, 96.6±3.5% of PDGFRb+ pericytes were infected as well as 97.2±2.7% of mesangial cells. At the medium dose, AAV2/8-labeled pericytes differentiated into aSMA+ myofibroblasts after UUO, and 41.4±15.4% of aSMA+ interstitial area was TdTomato positive. Additional data validating this technique for knockout of floxed pericyte genes will be presented.

Conclusions: We demonstrate a novel AAV approach to deliver genetic material to nearly all kidney pericytes and mesangial cells. These results suggest the possibility of AAV-based gene therapies for kidney fibrosis.

SA-PO470

Immunoprotection of Renal Epithelial Cells by Silicon Nanopore Membranes Shuvo Roy,[1] William Henry Fissell.[2] *[1]UCSF, San Francisco, CA; [2]Vanderbilt Univ Medical Center, Nashville, TN.*

Background: Immunoisolation of macroencapsulated renal cells is a fundamental requirement for an implantable bioartificial kidney that will circumvent the need for immunosuppressants. Silicon nanopore membranes (SNM) with precisely engineered pore dimensions have exhibited superior mass transfer and molecular selectivity characteristics for implanted hemofiltration. In this study, we investigated SNM competence for the protection of renal epithelial cells from an inflammatory cytokine known to induce necrosis and apoptosis.

Methods: Four different types of renal epithelial cells (MDCK, HK2, LLC-PK1, and HPTCs) were grown to confluence on SNM with 7-nm wide slit pores. Transwell chambers were used as the control membranes. The cells were exposed to 500 ng/ml human tumor necrosis factor-α (TNFα) for 6 hours and the subsequent monolayer integrity was assessed via transepithelial electrical resistance (TEER), cell viability assay, and immunohistochemistry (IHC) techniques.

Results: Without TNFα, cells on both Transwell and SNM maintained their monolayer integrity by expressing zona occludens (ZO1) protein at the intercellular junctions. TEER values were 100-150 ohm-cm2 and 580-620 ohm-cm2 on Transwell and SNM, respectively. For Transwells, TNFα disrupted epithelial tight junctions resulting in a decrease in TEER and 10 fold increase of cell apoptosis. In contrast, with SNM, cells maintained monolayer integrity with minimal changes in TEER and cell viability.

Conclusions: SNM perform an immunoisolation function that can be adapted for the development of an implantable bioartificial kidney.

Funding: Other NIH Support - NIBIB Quantum Project

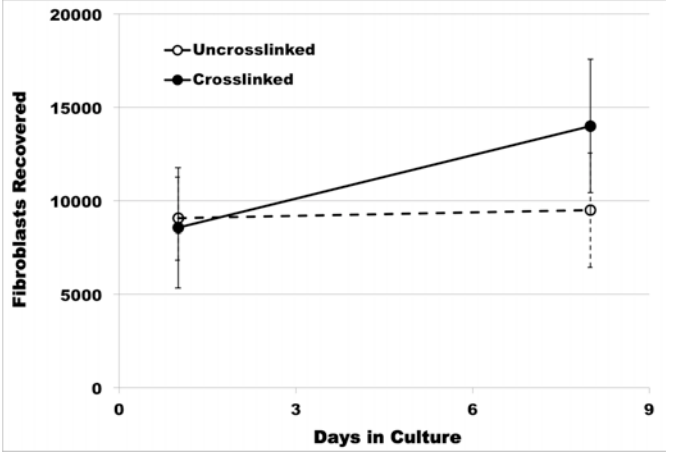
SA-PO471

Cell Proliferation on Crosslinked Perfusion-Decellularized Kidney Organ Scaffolds Edward A. Ross,[1] Alexey Goloubev,[1] Andres Rubiano,[2] Alicia R. Brown,[1] Chelsey Simmons,[2] Bradley J. Willenberg.[1] *[1]Univ of Central Florida, Orlando, FL; [2]Univ of Florida, Gainesville, FL.*

Background: The repopulation of decellularized whole kidneys is a tissue engineering approach to solve the shortage of donor organs for transplantation. A major challenge has been consistent adhesion and growth of seeded cells. We hypothesize that the problem is methodologic in that decellularization and sterilization protocols (e.g. chemical, radiation) can reduce tissue rigidity, making it a suboptimal substrate for cell attachment and proliferation; repopulation would be restored by stiffening the matrix by chemical crosslinking. Therefore, we prepared uncrosslinked and crosslinked sections of decellularized porcine kidneys and studied the growth of cells on the biomaterials.

Methods: Perfusion-decellularized kidney scaffolds were prepared as previously described. Cortex was sectioned to ~0.25cm^2 and crosslinked using *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC, 0.007M) and *N*-hydroxysulfo-succinimide (0.007M) at 4°C for 21h. A custom milli-indention system quantified stiffness. Human lung fibroblasts (1×10^5) were seeded and cultured on uncrosslinked and crosslinked sections. After days 1 and 8 cells were isolated using collagenase and mechanical dissociation, and then counted using a hemocytometer.

Results: Crosslinking with EDC increased tissue stiffness as we previously described, with increased steady-state elastic modulus of decellularized kidney scaffold sections ~4× compared to uncrosslinked sections. We now report day 1 to 8 culture results, showing fibroblast proliferation was greater on crosslinked scaffolds.



Conclusions: Growth of human lung fibroblasts is enhanced by EDC crosslinking, supporting our hypothesis that stiffer perfusion-decellularized organ scaffolds enhance the proliferation of anchorage-dependent cells.

SA-PO472

Visualizing and Quantifying the Luminescent Kidney in 3D Neal A. Paragas,[1] Alexander Klose.[2] *[1]Medicine, Univ of Washington, Seattle, WA; [2]In Vivo Analytics, Inc, New York, NY.*

Background: We have developed a platform system to monitor and quantify luminescence with the multispectral bioluminescence tomography (BLT) co-registered to a novel digital mouse atlas. Permitting for the first time quantification of a luminescent signal in a cell specific manner. This will allow us to non-invasively uncover the changes occurring temporally and spatially to tubular epithelial cells of the kidney.

Methods: We modeled different compartments of the kidney by creating a Podocin, Slc34a1, and HoxB7 luciferase reporter animals. First, we acquired bioluminescence images with a bioluminescent optical imager at six different spectral windows centered at 580, 600, 620, 640, 660, and 680 nm and with bandwidth of 20 nm. The multi-orientation images were acquired using a mirror gantry for simultaneous imaging of the dorsal, ventral and side views. The animal was placed in a fixed position into a novel body shape conforming animal mold, placed onto the mirror gantry and spectral images were acquired. The light intensity imaging data became input to a novel BLT reconstruction algorithm based on an expectationmaximization (EM) method and the simplified spherical harmonics (SP3) equations for modeling in vivo light propagation. Post reconstruction, we calculated the total photon emission density of a volume of interest (VOI).We then calculated cell specific luciferase expression co-registering it to a novel digital mouse atlas.

Results: Our new system using the EM method reconstructed the 3D photon emission of Podocin, SLC34a1 and Hb7-luciferase expressing animals and mapped the signal to a novel organ probability map. For the first time, we could demonstrate the feasibility of quantifying cell number non-invasively in the kidneys.

Conclusions: The ability to do non-invasive tomographic reconstruction of the kidney using bioluminescence will be a powerful tool to monitor segmental changes after renal injury.

Funding: NIDDK Support

SA-PO473

Isolation and Transcriptomic Analysis of Distinct Cell Populations from Mouse Renal Collecting Duct Lihe Chen,[1] Jae Wook Lee,[2] Chung-Lin Chou,[1] Susan M. Wall,[3] Dennis Brown,[4] Mark A. Knepper.[1] *[1]National Heart Lung and Blood Inst; [2]National Cancer Center, Korea; [3]Emory Univ School of Medicine; [4]Massachusetts General Hospital; [5]National Heart Lung and Blood Inst.*

Background: The renal collecting duct contains both principal cells (PCs) and intercalated cells (ICs). To better understand these cells, a reliable, high-yield isolation technique and systematic transcriptomic profiling are needed. To identify cell surface markers for ICs, we previously used transgenic mice that express GFP-driven by the

Atp6v1b1 promoter to enrich ICs. Transcriptomic analysis of these cells identified c-kit expression in these cells (confirmed by immunofluorescence microscopy). Previous studies have shown that *Dolichos biflorus* agglutinin (DBA) preferentially binds to mouse collecting duct principal cells.

Methods: We used DBA and an antibody to c-kit to isolate two populations of cells from mouse renal cell suspensions using FACS. The cell populations were characterized by RNA sequencing (RNA-Seq) using an Illumina HiSeq2500 platform.

Results: The average transcriptome depth was 11500 genes for DBA^+ cells (FPKM>1, n=2) and 11200 genes for c-kit^+ cells (FPKM>1, n=2). Based on mean c-kit/DBA FPKM ratio, the 10 top transcripts included several known IC markers, viz. Slc4a1, Oxgr1, Aqp6, Kit, Avpr1a, and Atp6v1g3, plus Tmem61, Dmrt2, Asb15 and Igkc, which have less well defined roles in ICs. Based on mean DBA/c-kit FPKM ratio, the 10 top transcripts included several known PC markers, viz Aqp4, Aqp2, and Fxyd4, plus Ptgds, C3, Ighj1, Epor, Ccl12 and Npnt, which have less well defined roles in PCs.

Conclusions: The profiling results confirmed that this flow-sorting method can isolate distinct cell populations that are enriched in PCs and ICs. The identification of additional IC and PC specific genes points to additional molecular functions of the two cell types.

Funding: Other NIH Support - NHLBI

SA-PO474

Identification of Biomarkers Associated with Progressive Fibrosis in Renal Transplant Patients Using High-Definition Fourier-Transform Infrared Imaging

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Background: Renal allografts are often lost due to progressive accumulation of chronic changes as a consequence of rejection and infection. Close monitoring of grafts by surveillance biopsies to detect subclinical complications and apply corrective measure may prolong the life of the graft. Here we identify biochemical markers associated with progression of interstitial fibrosis in renal transplant biopsies using label free chemical imaging technique, Fourier-transform infrared (FT-IR) imaging.

Methods: A pilot study focused on identifying 5 patients with no progression of interstitial fibrosis (non-progressors) and 5 patients with an increase in interstitial fibrosis over time (rapid progressors). Serial sections were acquired and stained with Masson trichrome stain and imaged using chemical imaging. An early (3-4 months) and a late (6-24 months) time point protocol biopsy for each patient was analyzed and the difference between the rapid progressors and non-progressors groups were analyzed using the chemical information extracted from areas of fibrosis. Clinical data and other relevant information was used to further increase our understanding of the biochemical signature obtained from FT-IR imaging.

Results: Multivariable analysis of the collected chemical data allows us to use early biopsies to segregate between rapid progressors vs non-progressors. The biochemical signatures between the early biopsies from the rapid progressors and non progressors cohorts were distinct suggesting different underlying biochemical reactions in the two groups. In addition, these changes were noted in late biopsies as well.

Conclusions: The data shows promise as we have identified a number of biochemical markers that are associated with the advancement of interstitial fibrosis. In addition, we have highlighted a 'biochemical-signature' that may be predictive of the later interstitial fibrosis, using baseline biopsies. Additional cases should allow us to validate these preliminary findings.

Funding: NIDDK Support

SA-PO475

Differential Urinary Proteome Analysis of IgA Nephropathy Using 2D-LC-MS/MS and iTRAQ Quantification

Ying Sun, Li Siqian, Xuemei Li, Mingxi Li. *Nephrology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China.*

Background: IgA nephropathy is a common primary glomerulonephritis, more accurate and non-invasive tests for its diagnosis and evaluation are urgently needed. Urinary proteome analysis has been applied to discovering biomarkers for kidney diseases. The aim of this study is to investigate the differential urinary proteome in various stages of IgA nephropathy.

Methods: Eighteen IgA nephropathy patients diagnosed by renal biopsy were recruited and were divided into three groups according to estimated glomerular filtration rate, IgA I (eGFR 90~120ml/min, n=6), IgA II (eGFR 60~89ml/min, n=6) and IgA III (eGFR 30~59, n=6).Six patients with membranous nephropathy were included as control (eGFR 90~120ml/min, n=6). Proteins from each group were digested by trypsin and then labeled with 4-plexiTRAQ regents. The pooled mixture of iTRAQ labeled samples were fractured and analyzed by LC-MS/MS. All MS/MS samples were analyzed using Mascot. Scaffold was used to validate MS/MS based peptide and protein identifications. Protein classification was performed based on functional annotations using Gene Ontology analysis.

Results: A total of 622 proteins were identified, 108 were found to be up or down regulated in a consistent trend from IgA I to IgA III. 13 of these108 proteins were highly up-regulated in IgA groups but down-regulated in control. Some inflammation-related, complement-activating and extracellular matrix proteins were found to be up-regulated in IgA groups, including tumor necrosis factor-binding protein-1, WNT1-inducible-signaling pathway protein 2 and Alpha-2-HS-glycoprotein chain A. Alpha-N-acetylglucosaminidase and other proteins turned out to be down-regulated in IgA groups. Selected differential proteins were validated by Western Blot.

Conclusions: This study established differential urinary proteome in various stages of IgA nephropathy. Some inflammation-related, complement-activating and extracellular matrix proteins, as well as proteins related to O-glycosylation defects may involve in the development and progression of IgA nephropathy, and could be potential biomarkers of IgA nephropathy.

SA-PO476

Bioinformatic Analysis of Differential Urinary Glycoproteome of Type 2 Diabetic Nephropathy

Zixuan Zhu, Ying Sun, Xuemei Li, Mingxi Li. *Dept of Nephrology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China.*

Background: Diabetic nephropathy(DN) is the leading cause of end-stage renal disease. The early detection and intervention may delay renal replacement therapy. The aim of this study is to identify the urinary glycoproteins during different stages of DN and find the potential biomarkers for early diagnosis of DN.

Methods: In our previous study, 72, 107 and 123 differential urinary glycoproteins were found from normoalbuminuria(n=7), microalbuminuria(n=8), and macroalbuminuria(n=8) patients. The differential proteins were classified into distinct clusters by hierarchical clustering, and Ingenuity Pathway Analysis (IPA) was performed to analysis the clusters altering most significantly during the disease progression.

Results: A total of 302 differential glycoproteins were hierarchically clustered into 9 clusters. In Cluster 2, 38 proteins were overrepresented in both microalbuminuria and macroalbuminuria, and increased progressively during disease progression. When IPA was performed, there was no difference between normal controls and normoalbuminuria. However, proteins involved in LXR/RXR activation pathway, FXR/RXR activation pathway and Acute Phase Response Signaling (APRS) pathway were significantly enriched. In cluster 4, 36 proteins presented a high level only in microalbuminuria, but down-regulated in other groups. IPA showed that the complementary pathway, APRS pathway, LXR/RXR activation pathway and Notch signaling pathway were enriched in this cluster.

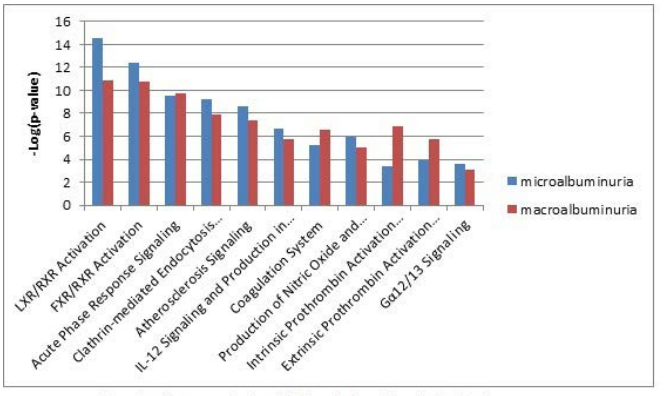

Figure1 pathway analysis of differential proteins in Cluster 2

Conclusions: The proteins involved in lipid metabolism, APRS, and complement activation significantly increased in the urine of DN patients along the disease progression, some of these proteins may become the candidate biomarkers for early diagnosis of DN.

SA-PO477

Immunomodulatory Therapy (Rx) Demonstrates Sustained Improvement in Myocardial Contractility in a Canine Model of Chronic Heart Failure (CHF)

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Background: Cardiorenal syndrome (CRS), the most severe subset of CHF patients, is characterized by diuretic resistance in a volume overload. Current therapy is limited and new innovative approaches are needed. CHF is characterized by a proinflammatory state. Monocytes and tissue macrophages are sources of systemic inflammation in CHF and cause a decrease in cardiac contractility. Systemic MO levels correlate with poor outcome. A novel leukocyte (LE) immunomodulating device (SCD), when placed in an extracorporeal circuit with regional citrate anticoagulation has been shown to be effective in acute multiorgan failure. The biomimetic membrane device (BMD) is based on the same LE processing premise as the SCD.

Methods: Impact of BMD_{Rx} was evaluated in a CHF dog model; 2 groups were evaluated: BMD treated (BT) and untreated control (UC), n=4-5 per group. Dogs were administered either 1-3 BMD_{Rx} or no Rx sessions over a week period, with study termination immediately (Ti) postBMD_{Rx} session (n=2-3) or 4 weeks (T4) postRx session (n=2).

Results: Data demonstrated left ventricle (LV) ejection fraction (EF) increased substantially in the BT group from 33.6±1.3 (n=5) to 43.3±2.5 (n=5; 6-48hrs postRx) and 37.0±0% (n=2; 4wks postRx) reflective of 28.9 and 10.2% increase, respectively. The UC group (n=4) EF% did not change. This effect was not due to a decline in systemic vascular resistance which was similar in both groups. Ventriculograms demonstrated BMD_{Rx} to convert viable but non-contracting myocardium to contracting myocardium. The renal effects were also substantive. In the Ti dogs, fractional excretion (FE) Na nearly doubled in the BT group vs. UC group, increasing from 2.2±0.8 to 5.3±0.8%. FE_{urea} went from 59±3.1 to 81±11.3%. T4 dog FE results are pending. No adverse events of arrhythmia or hypotension were observed during BMD_{Rx}.

Conclusions: Immunomodulation with the BMD improves myocardial contractility and natriuresis. Removal of the cardiodepressant effects of the chronic inflammatory state of CHF may be an innovative approach to CRS.

Funding: Other NIH Support - 1R43HL118792-01A1, Other U.S. Government Support

SA-PO478

Lack of Allostimulatory Potential of Conditionally Immortalized Proximal Tubule Epithelial Cells for Bioartificial Kidney Application Milos Mihajlovic,[1] Annemarie J.F. Westheim,[1] Joost Hoenderop,[2] Lambertus P.W.J. Van den Heuvel,[3] Wil Allebes,[4] Luuk Hilbrands,[5] Rosalinde Masereeuw.[1] *[1]Pharmacology, UIPS, Utrecht, Netherlands; [2]Physiology, Radboudumc, Netherlands; [3]Pediatrics, Radboudumc, Netherlands; [4]Laboratory Medicine, Radboudumc, Netherlands; [5]Nephrology, Radboudumc, Netherlands.*

Background: Novel renal replacement treatments, such as a bioartificial kidney (BAK), are needed to improve current hemodialysis. When developing a BAK, availability of functional cells and their safety are frequently encountered problems. Here, we evaluated the alloimmunization of readily available conditionally immortalized human proximal tubule epithelial cells (ciPTEC) for use in BAK.

Methods: Two ciPTEC lines (urine derived ciPTEC-U, tissue derived ciPTEC-T1) were characterized by flow cytometry for HLA-class I, HLA-DR, CD40, CD80 and CD86 expression, as well as pro-inflammatory cytokines and soluble HLA-class I production by ELISA, in various stimulatory conditions (n≥3). ciPTEC immunogenicity was assessed in direct co-culture experiments with peripheral blood mononuclear cells (PBMC) by measuring their proliferation using CFSE staining.

Results: IFN-γ (300 ng/ml; 48h) and LPS (10 µg/ml; 48h) exposure resulted in an increase of HLA-class I expression by 37±12%, $p<0.01$ and 29±9%, $p<0.05$ respectively. CD40 expression was increased by conditioned medium from aCD3/aCD28 activated PBMC (48h) 87±9%, $p<0.01$. Cells were negative for HLA-DR, CD80 and CD86 in all conditions. Cytokine production was induced by LPS (IL-6: 3.2±0.2, IL-8: 3.5±0.7 fold, $p<0.001$) and indoxyl sulfate (IL-6: 1.7±0.2 fold; IL-8: 1.3±0.4 fold, $p< 0.05$). Finally, ciPTEC were not able to induce PBMC proliferation after 5 days of co-culture, compared to positive controls (aCD3/aCD28 dynabeads; 77±8% dividing cells, $p<0.001$, n=4) and allogeneic PBMC (25.7%)). The results shown here refer to ciPTEC-T1, and are comparable to those obtained for ciPTEC-U.

Conclusions: Although ciPTEC might have an accessory role in inflammatory responses as shown by cytokine production, the cells are not immunogenic and, therefore, represent a safe choice for BAK application. **Acknowledgement:**This work is funded by the EU Marie Curie ITN Project BIOART (grant no.31669 EU-FP7-PEOPLE-ITN-2012).

Funding: Government Support - Non-U.S.

SA-PO479

Neointima Formation in Hemodialysis Grafts: A Role for Abnormal Vein Wall Dynamics? Yan-Ting E. Shiu,[1] Daniel Pike,[1] Yong He,[2] Timmy C. Lee,[3] Edgar A. Jaimes,[4] Scott A. Berceli,[2,5] Alfred K. Cheung.[1,6] *[1]U of Utah; [2]U of Florida at Gainesville; [3]U of Alabama at Birmingham; [4]MSKCC; [5]Malcom Randall VAMC; [6]VASLCHCS.*

Background: Hemodialysis arteriovenous grafts (AVGs) often fail due to neointimal hyperplasia (NH) at the graft-venous anastomosis (VA). Abnormal regional mechanical factors may play a role in the focal nature of NH formation, but previous work has largely focused on the role of wall shear stress (WSS), ignoring other mechanical factors including the dynamic motion and compression of the vein wall. This study used fluid structure interaction (FSI) modeling in a patient specific AVG to analyze and compare both WSS and wall dynamics at the NH-prone and resistant regions.

Methods: MRI scans were performed on one hemodialysis patient's AVG and used to reconstruct AVG's lumen geometry and obtain blood flow in the up- and down-stream artery and vein. Simulations of blood flow in the AVG lumen as well as the wall motion and compression were performed in ANSYS Workbench using arterial BP (120/80 mmHg) and MRI-measured blood flow as boundary conditions, as well as published values of the elastic properties of the artery and vein.

Results: While disturbed flow patterns (e.g., spiral and recirculating flow) occurred at both the NH-prone VA and NH-resistant proximal vein (PV) (**Fig. 1A**), peak WSS was about 3-fold higher at the VA than at the PV (**Fig. 1B**). The motion of the inner wall (i.e., the intimal layer) and the compression of the entire wall during a cardiac cycle were also greater at the VA than at the PV (**Fig. 1C-D**). At the VA, the maximum wall changes occurred at the maximum WSS. Wall motion and compression were very small at the PA.

Conclusions: Our finding that the NH-prone region of a human AVG has increased wall dynamics is novel. Future analyses in a large study will elucidate the relative contributions of WSS and wall dynamics to NH development, with the objective of improving AVG durability.

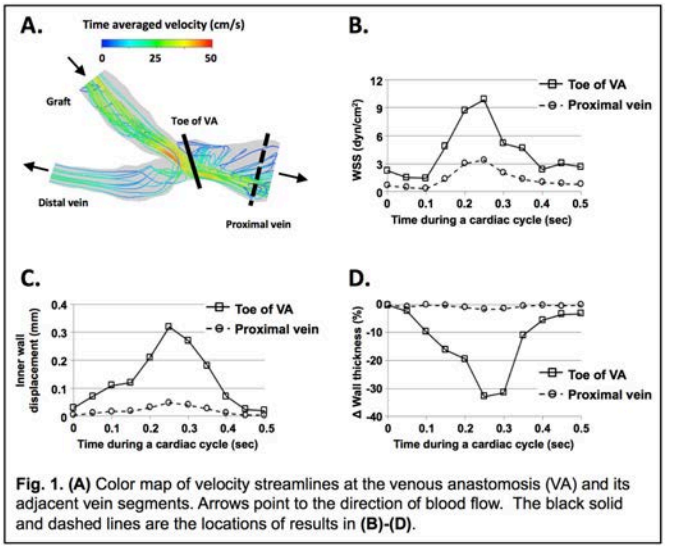


Fig. 1. (A) Color map of velocity streamlines at the venous anastomosis (VA) and its adjacent vein segments. Arrows point to the direction of blood flow. The black solid and dashed lines are the locations of results in **(B)-(D)**.

Funding: NIDDK Support

SA-PO480

AFE System Provides Improved Hemodynamic Conditions for Vein Maturation Compared to Conventional AVF Howard M. Loree,[1] Daniel Pike,[2] John S. Richardson,[1] Yan-Ting E. Shiu,[2] Larry W. Kraiss,[2] Nicholas Franano.[3] *[1]R&D, Flow Forward Medical, Inc., Lowell, MA; [2]U of Utah, Salt Lake City, UT; [3]Flow Forward Medical, Inc., Olathe, KS.*

Background: Cyclic stretching of the AVF outflow vein and suboptimal vein wall shear stress (WSS) may contribute to AVF failure. The Arteriovenous Fistula Eligibility (AFE) System™ from Flow Forward Medical is a small, temporary, external blood pump system designed to deliver non-pulsatile blood flow from the right atrium to a peripheral vein for 10–14 days. Flow rate is set to provide a mean WSS dose of 4 Pa in the vein, previously shown to promote dilation, with the goal of increasing AVF eligibility and AVF maturation rates. This computational study investigated WSS and cyclic wall stretching in the outflow vein during AFE System treatment and after conventional AVF creation.

Methods: Using fluid-structure interaction (FSI)-computational fluid dynamics (CFD), we studied blood flow and cyclic wall stretching in an idealized model of an AFE System outflow conduit anastomosed to a cephalic vein (**Fig. 1A**). FSI-CFD was also performed for a radiocephalic AVF at typical flow rates (**Fig. 1B**). Lumen diameter was 4 mm for all vessels and boundary conditions were set using flow or pressure values measured in mock flow loop studies.

Results: With the AFE System, when pump speed was set to provide a mean WSS of 4 Pa in the outflow vein, max WSS was about 20 Pa (**Fig. 1A**) and there was no cyclic wall motion. With a conventional AVF at peak systole, mean WSS was about 6.5 Pa in the vein and max WSS was about 300 Pa (**Fig. 1B**) with a 10-12% cyclic increase in lumen diameter.

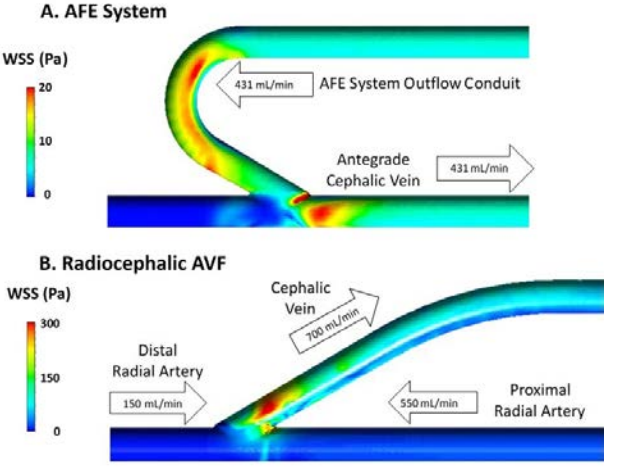


Fig. 1 Wall shear stress by FSI CFD in (A) AFE system outflow conduit & cephalic vein and (B) conventional radiocephalic AVF at peak systole. Arrows point to direction of blood flow at indicated mean flow rate.

Conclusions: The AFE System can provide a controlled dose of mean WSS to a peripheral vein without cyclic wall motion. A conventional AVF has cyclic stretching of the outflow vein, may not have ideal mean WSS, and may have very high peak WSS, all of which may contribute to failure.

Funding: NIDDK Support

SA-PO481

Loop Mediated Amplification Assay versus Culture for Detection of *Escherichia coli* in Urine: A Single Center Pilot Study Vinai Kumar Katragadda,[1] Aravindhan Arumugarajah,[1] Jennifer Sheyman,[1] Christopher J. Webster,[1] Kalathil K. Sureshkumar,[1] Richard J. Marcus,[1] Abhay N. Vats,[2] Michelangelo Di Giuseppe,[3] Swati Arora.[1] *[1]Dept of Medicine- Nephrology, Allegheny General Hospital, Pittsburgh, PA; [2]Univ of Pittsburgh, Pittsburgh, PA; [3]Atharva LLC Molecular Diagnostics, Cranberry, PA.*

Background: Urinary tract infection (UTI) is a common cause of morbidity in the adult population. Urine cultures could take up to 5 days, thereby, exposing patients to unnecessary broad spectrum antibiotics. Over 80% of outpatient UTIs and 50% of inpatient UTIs are caused by *Escherichia coli*. Newer assays, such as, loop-mediated amplification (LAMP) assay for detection of E.coli can provide results within 60 minutes. This can potentially be used for point of care (POC) testing in the ambulatory and hospital settings.

Methods: A prospective study was done comparing E.coli LAMP assay and urine culture to detect UTI. LAMP assay was conducted on urine samples using a thermal cycler with incubation for 60 minutes with E.coli DNA primers. E.coli LAMP products were detected using Sybr green dye under UV illumination.

Results: Mean age was 58 years and 73% were females. About 50% of the samples were from outpatient setting, 27% from inpatient and source was not recorded in the remainder. Out of 393 samples, 43 urine cultures were positive for E.coli. Comparison with LAMP assay is shown in table.

Comparison standard	Sensitivity	Specificity	Positive predictive value	Negative predictive value	p-value
LAMP vs. E.coli culture	91	24	0.73	0.54	< 0.001
LAMP vs. E.coli culture >100,000 cfu/ml	93	21	0.73	0.58	< 0.001
LAMP vs. E.coli culture < 100,000 cfu/ml	97	3	0.70	0.36	0.66

Conclusions: LAMP assay displayed good sensitivity and could be used as a screening tool to rule out UTI as a POC test. It is not specific and does not provide quantitative information or antibiotic sensitivities to guide management. LAMP assay would pick up even less than 10 copies of E.coli as a "positive" test which is clinically insignificant. Lastly, LAMP assay is designed for one specific organism only. More prospective studies are needed to evaluate utility of LAMP in clinical practice.

SA-PO482

Contribution of Vibrational Spectroscopy in Nephrology Vincent Vuiblet,[1,2,3] Philippe Birembaut,[2] Olivier Piot,[1,4] Philippe Rieu.[1,3] *[1]UMR CNRS 7369 MEDyC, URCA, Reims, France; [2]Nephropathology Dept of Biopathology Laboratory, CHU de Reims, Reims, France; [3]Nephrology Dept, CHU de Reims, Reims, France; [4]PICT, URCA, Reims, France.*

Background: Despite that renal histopathology is essential for diagnosis and prognosis in nephrology, it presents some limiting features. So, the development of more reliable techniques is open. Vibrational spectroscopy (VS) including Raman spectroscopy (RS) and Fourier-transformed infrared spectroscopy (FTIR) brings out some molecular and structural data from tissue analysis in a label-free manner. Our objective was to demonstrate VS is able to provide histologic data actually unattainable by conventional techniques.

Methods: Our investigations focused on 1) the detection of exogenous molecules, by considering more precisely Hydroxyethyl starch (HES) because of its renal toxicity and its high difficulty to be detected in renal biopsies; 2) the detection of endogenous molecules: we were particularly interested in the mapping of Advanced glycation end-product (AGEs). Indeed, there are many kinds of AGEs which are undetectable simultaneously on the same biopsy slide 3) the reproducible quantification of interstitial fibrosis and inflammation in renal grafts which is a valuable information due to its impact on the therapeutic and the prognosis.

Results: 1) We reported an accumulation of HES by RS in renal biopsies from patients exposed HES. Moreover, accumulation of HES in kidney exposed to HES was dependent on the good quality of graft defined by kidney donor risk index and renal function at 3 months. 2) 4 AGEs were mapped and quantified by RS in diabetic and normal glomeruli. Levels of each AGE were higher in diabetic glomeruli *vs* controls. In diabetic glomeruli, some AGEs were collocated with collagen that was not found in normal glomeruli. 3) Interstitial fibrosis (IF) and inflammation were quantified in 166 renal graft biopsies by an automated FTIR-based imaging technique. We assessed the robustness of this technique for discrimination of fibrosis and inflammation. We proved the clinical relevance of this technique by showing a good correlation of IF with renal graft function.

Conclusions: VS is a promising technique for nephrology both in basic research and in clinical practice.

SA-PO483

Remote Monitoring of Patients on Automated Peritoneal Dialysis Saves Healthcare Resources in a Simulation Study Suzanne Laplante,[1] Kimberly Mcleod,[2] Judy A. Danek,[1] Timothy L. Kudelka,[1] James A. Sloand,[1] Mary Gellens,[1] Leslie P. Wong.[3] *[1]Baxter Healthcare Corporation, Deerfield, IL; [2]XCenda, Palm Harbour, FL; [3]Cleveland Clinic, Cleveland, OH.*

Background: Remote monitoring is useful in chronic diseases, but evidence is scarce in home dialysis. A two-way data exchange platform with remote monitoring capabilities may enable earlier intervention and healthcare savings. This study estimates the nature and importance of the savings in USA.

Methods: Twelve (12) automated peritoneal dialysis (APD) patient profiles (therapy non-adherence, fluid overload, low drain/unidentified alarms, missing/factitious data entry) were used to simulate healthcare resource use with remote monitoring information (treatment data, blood pressure, weight) and without. Four US nephrologists (expert in managing APD patients) validated the "without remote monitoring" resources. The "with remote monitoring" resources were estimated by 7 APD teams (1 nephrologist, 1 nurse). A Monte-Carlo simulation (1,000 iterations) was run on resources avoided (resources "without remote monitoring" minus those with). US public reimbursement rates or medical literature were used for costing (3 perspectives: public healthcare payer, direct provider costs, provider opportunity costs).

Results: The Monte-Carlo simulation estimated that in these 12 patient profiles (average follow-up: 25 days; range: 7-60 days), remote monitoring could avoid 5.0±0.5 emergency room visits; 2.0±0.2 hospitalizations; 2.2±0.3 changes to hemodialysis for potential savings of $22,862±$1,384 to the public healthcare payer. Providers could avoid 0.8±0.3 repeat adequacy tests resulting in $19±$6 direct savings while their opportunity costs resulting mainly from avoidance of 6.7±2.5 unplanned clinic visits and 64±15 unplanned clinic calls would total $1,249±$237. The 12 profiles were estimated to be representative of 17.3-37% of the US APD patient population.

Conclusions: In a simulation, remote monitoring saved healthcare resources in APD patients with treatment non-adherence, fluid overload, volume depletion, low drain/unidentified alarms, or missing/factitious data entry by enabling earlier medical intervention, avoiding complications and treatment drop-out.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

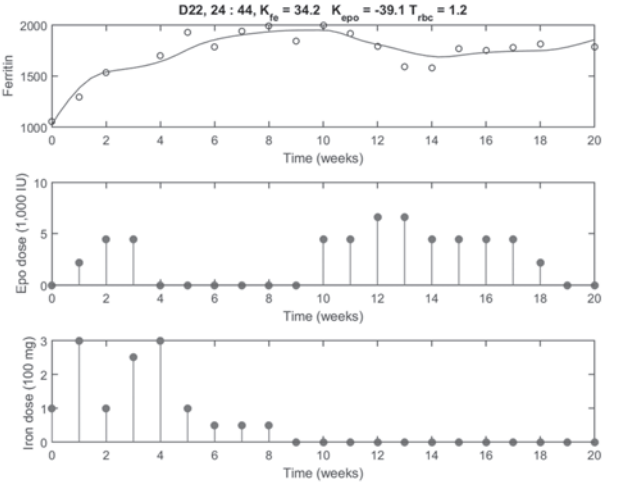
SA-PO484

Mathematical Modeling Approach to IV Iron Dosing in Hemodialysis Patients Adam E. Gaweda,[1] Yelena Z. Ginzburg,[3] Yossi Chait,[2] John Paul Middleton,[4] Michael J. Germain,[5] Michael E. Brier.[1] *[1]Univ of Louisville; [2]UMass Amherst; [3]New York Blood Center; [4]Duke Univ; [5]Renal and Transplant Associates of New England.*

Background: Coordinated dosing of Erythropoiesis Stimulating Agents (ESA) and Intravenous (IV) Iron is essential in anemia management of End Stage Renal Disease (ESRD). To aid physicians in this task we are developing a systems biology approach to modeling erythro- and ferrokinetic marker behavior. Here, we present a mathematical model of Ferritin (ferr) response to IV Iron and ESA.

Methods: A cohort of 23 hemodialysis patients was prospectively followed for 12 months at three dialysis centers in the United States. Data collected included weekly ferr concentration, ESA (Epogen), and IV Iron (Venofer) dose. We developed patient-specific models of comprising three parameters: 1) ferr sensitivity to iron dose, 2) ferr sensitivity to ESA dose, and 3) time constant, representing the time to reach 64% of steady state ferr response. We used a nonlinear least squares estimation to maximize the fit between model prediction and data.

Results: IV Iron doses greater than 100 mg/week result in a rapid increase of ferr . ESA dose increases in absence of IV Iron dose result in a decrease of ferr. We obtained the following model parameters: 1) ferr sensitivity to IV iron (median [min,max]): 42.6 [6.6, 135.2] ng/mL per 100 mg/week, 2) ferr sensitivity to ESA: -36.9 [-166.7, -3.2] ng/mL per 1,000 IU/week, 3) time constant: 5.4 [1.2, 16] weeks. The figure below shows an example of model prediction for a selected study subject.



Conclusions: Presented model reliably captures ferr response to IV Iron and ESA. The estimated model parameters are consistent with the physiology of erythropoiesis. Next steps involve addition of other ferrokinetic markers such as hepcidin and soluble transferrin receptor 1, and a validation of the model in a larger cohort of subjects.

Funding: NIDDK Support

SA-PO485

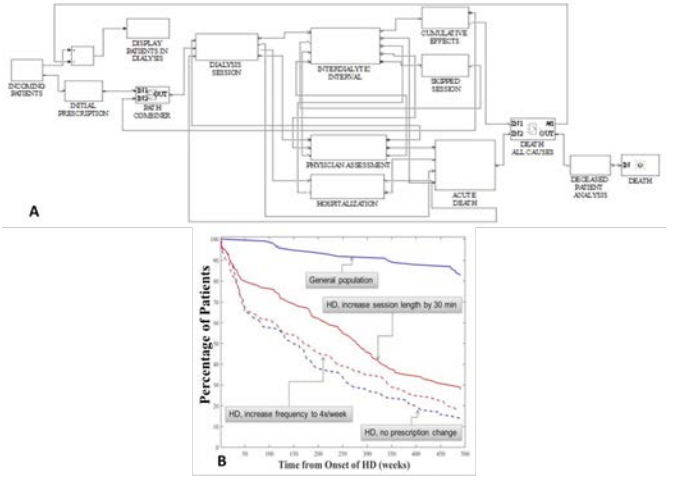
Discrete Event Model of Fluid Overload Complications in Hemodialysis

Victor Andreev,[1] Anca I. Stefan,[1] Michelle M.Y. Wong,[1] Jarcy Zee,[1] Robert Merion,[1] John Hartman,[2] Bruce M. Robinson.[1] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]Visonex Data Management, LLC, Green Bay, WI.*

Background: Fluid overload is one of the most common complications of hemodialysis (HD) and is associated with adverse clinical outcomes. We developed a discrete event simulation (DES) model of HD that simulates survival of a cohort of incident dialysis patients by incorporating the cumulative effects of fluid overload and intradialytic hypotension (IDH) in the context of excessive fluid removal.

Methods: The DES model was developed with the SimEvents tool (Mathworks), and consisted of a set of interconnected modules corresponding to various events and outcomes in the course of a patient's HD experience: initial HD prescription, the dialysis session, interdialytic interval, physician evaluation, acute complications, cumulative effects of fluid overload and IDH, skipped or shortened sessions, hospitalizations, and death (Figure A). The model uses patient-level and HD session-level (e.g. blood pressure and ultrafiltration rate) data for a cohort of 194 HD patients from multiple US facilities from 2010 to 2015.

Results: Figure B shows simulated survival curves for 4 scenarios: (1) HD, with an average session duration of 3.5 hours, (2) HD with 30 min added to each session upon detection of fluid overload, (3) HD with increased frequency to four times a week, and (4) natural aging in a control group.



Conclusions: Our novel DES model of the HD process simulates patient survival. Further validation of the model and incorporation of more modules (e.g., infections, protein-energy wasting) is in progress. Applying this methodology to model the mechanisms of HD complications and their management strategies at the patient level can be used to identify algorithms for prevention and treatment of fluid overload in HD patients.

SA-PO486

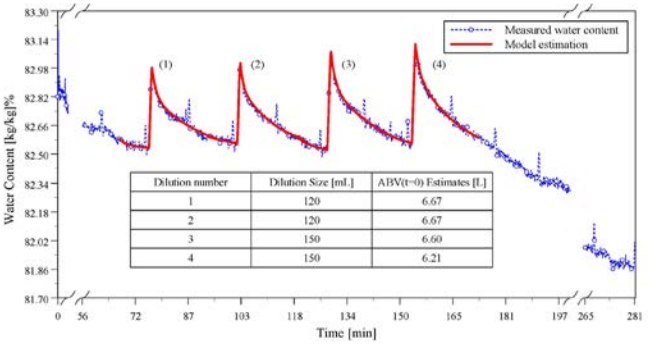
Estimating Absolute Blood Volume in Hemodialysis Patients

Hamed Samandari,[1] Joseph Horowitz,[1] Christopher V. Hollot,[1] Rammah M. Abohtyra,[1] Michael J. Germain,[2] Ravi I. Thadhani,[3] Daniel Schneditz,[4] Yossi Chait.[1] *[1]UMass; [2]WNERTA; [3]MGH; [4]Medical Univ of Graz.*

Background: Long- and short-term adverse outcomes have been associated with intradialytic hypotension, a common hemodialysis (HD) complication and significant cause of morbidity. It has been suggested that absolute blood volume (ABV) data is likely to significantly improve such outcomes.

Methods: Automatic on-line dialysate dilution and blood water concentration (BWC) measurement by blood volume monitor (BVM) were used to compare ABV estimation between classical single-pool (SP) back-extrapolation method and a new, physiological, intravascular BWC model (NM). The study included 3 arterio-venous (AV) and 3 central venous (CV) access patients, and multiple dilution tests (3-5) within each of several (2-6) HD treatments. Nested one-way ANOVA was used to compute intratreatment variability of estimates and Bland-Altman (BA) analysis was used to analyze agreement between the methods.

Results: A total of 84 bolus injections (60 to 210 mL) were performed over 21 HD treatments in 6 patients. Figure 1 shows measured BWC in a single treatment with 4 injections and the corresponding 4 distinct ABV estimations prior and post dilutions using NM. Intratreatment standard deviation (SD) of SP ABV estimates were 0.51L and 0.45L for CV and AV patients, respectively; the corresponding NM SD were 0.24L and 0.29L for CV and AV patients, indicating significant reductions in variability by 53% and 36%, respectively. BA agreement between the two methods was 0.12±1.14 and 0.09±0.84 L (bias±2SD) for AV and CV patients, respectively.



Conclusions: Our new model can successfully describe BWC dynamics during an on-line dialysate dilution protocol. The variability of ABV estimates using the new model is substantially smaller than that from SP estimates. The dilution protocol and the new ABV estimation method can be implemented within current HD technology.

Funding: NIDDK Support

SA-PO487

Characterization of Hemodialysis Patients Based on Systolic Blood Pressure Profiles

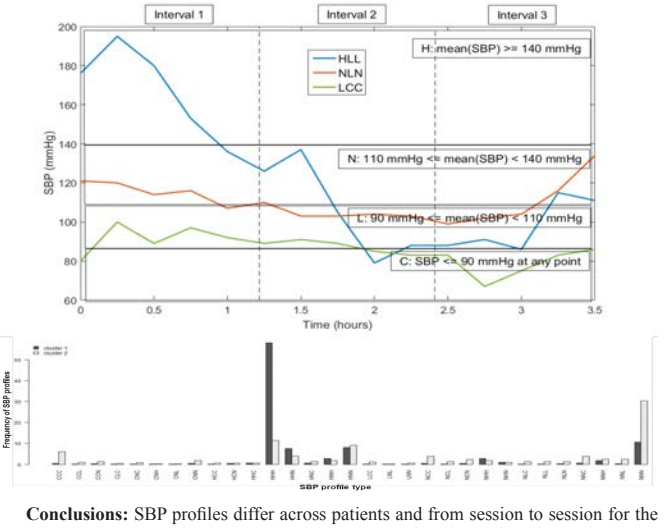
Anca I. Stefan,[1] Victor Andreev,[1] Michelle M.Y. Wong,[1] Gang Liu,[1] John Hartman,[2] Ronald L. Pisoni,[1] Bruce M. Robinson.[1] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]Visonex Data Management, LLC, Green Bay, WI.*

Background: Observational studies have revealed a complex relationship between systolic blood pressure (SBP) and mortality in end-stage renal disease (ESRD) patients. We present a classification of hemodialysis (HD) patients based on their intradialytic SBP profiles.

Methods: We analyzed intradialytic SBP data recorded every 15 minutes during HD sessions for a cohort of 194 HD patients from multiple US facilities from 2010 to 2015. To describe each patient's SBP profile, a vector was constructed by dividing each session into three equal time intervals and classifying each interval based on the corresponding SBP values. Thus, each session was assigned a three letter code. A "patient vector" was created by counting the number of sessions of each type. The table shows an example of a patient vector with high SBP during 316 sessions.

HHH	HHN	HNC	HNH	HNN	NHH	HNH	NNN
316	90	6	12	18	14	9	18

Results: Two major clusters of SBP profiles emerged. In Cluster 1, the predominant profiles of the average patient consisted of sessions in which SBP exceeded 140 mmHg during one or more intervals, with HHH being the most common profile (58% of sessions). In Cluster 2, the most common SBP profile was NNN (30% of sessions), along with 28% of sessions where hypotension occurred.



Conclusions: SBP profiles differ across patients and from session to session for the same patient. However, there are predominant SBP profiles for each patient, which may have prognostic implications. Future analyses will assess associations of the predominant SBP profiles with hospitalizations and cardiovascular complications which will be applied in discrete event simulation models of complications in HD.

SA-PO488

Accuracy of Contrast-Enhanced Ultrasound for Characterizing Kidney Lesions in Patients with and without CKD Emily H. Chang,[1] Sandeep Kasoji,[3] Paul Dayton,[3] Wui K. Chong,[2] W. Kimryn K. Rathmell.[4] *[1]UNC Kidney Center, UNC, Chapel Hill, NC; [2]Radiology, UNC, Chapel Hill, NC; [3]Biomedical Engineering, UNC, Chapel Hill, NC; [4]Lineberger Cancer Center, UNC, Chapel Hill, NC.*

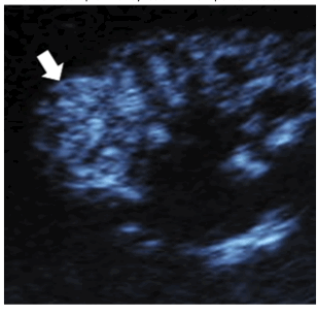
Background: Complex kidney lesions are often detected incidentally. Generally, lesions are further characterized by contrast-enhanced CT or MRI. However, these studies are often contraindicated in patients with chronic kidney disease (CKD). Contrast-enhanced ultrasound (CEUS; panel A), a new, non-nephrotoxic imaging technique, is a potential alternative for lesion surveillance among patients with CKD. We investigated the diagnostic accuracy of CEUS for malignancy or lesion progression prediction in patients with incidental kidney lesions.

Methods: CEUS was performed on 46 patients with known indeterminate or suspicious kidney lesions. Patients with and without CKD were evaluated to compare sensitivity in patients with vs without CKD. Results were independently interpreted by 2 blinded readers and risk-stratified by the Bosniak classification system. Using histologic diagnosis as the reference standard, CEUS sensitivity and specificity with 95% confidence intervals were calculated. As histology was available for resected lesions only, we performed secondary analyses considering histologic diagnosis *or* one-year follow-up imaging as the reference standard. The mean follow-up period was 18 months.

Results: In primary analyses, CEUS sensitivities ranged 95-100% for all patients and 100% for CKD patients (panel B). Specificities were low across all patients, in both primary and secondary analyses, ranging 0-68%.

Conclusions: CEUS has comparable sensitivity to CT and MRI and thus excellent potential as an alternative diagnostic tool for characterization of kidney lesions in patients with CT/MRI contraindications. The observed low specificity suggests that CEUS technique improvement is needed.

A. CEUS of complex kidney lesion. Arrow points out lesion.



B. Sensitivity and specificity with confidence intervals (CI) for reader 1 (R1) and reader 2 (R2) compared to tissue diagnosis and tissue diagnosis or follow-up imaging in all patients and those with CKD.

	All patients (N=46)				CKD (N=27)			
	Tissue Primary analysis (n=20)		Follow-up/Tissue Secondary analysis (n=46)		Tissue Primary analysis (n=5)		Follow-up/Tissue Secondary analysis (n=27)	
	R1	R2	R1	R2	R1	R2	R1	R2
Sensitivity (C.I.)	95% (85-100)	100%	88% (75-100)	100%	100%	100%	75% (45-100)	100%
Specificity (C.I.)	0%	0%	62% (41-83)	48% (26-69)	N/A	N/A	68% (48-89)	53% (30-75)

Funding: Other NIH Support - UNC NC TraCS; UNC Linebarger Cancer Center

SA-PO489

A Pilot Study of Nuclear Magnetic Resonance to Detect Volume Changes during Hemodialysis Kristin M. Corapi,[1] Lina Avancini Colucci,[2] Matthew Li,[2] Dihua Xu,[1] Andrew S. Allegretti,[1] Jimy Hanna,[1] Xavier F. Parada,[1] Dennis A. Ausiello,[1] Michael J. Cima,[2] Herbert Y. Lin.[1] *[1]Nephrology, Massachusetts General Hospital, Boston, MA; [2]Dept of Materials Science and Engineering, Massachusetts Inst of Technology, Cambridge, MA.*

Background: Patients treated with hemodialysis (HD) are prone to volume overload. Physicians rely on clinical examination and an assessment of interdialytic weight gain to assess volume status, but a more reliable and precise method is needed. We conducted a pilot study to explore the potential of nuclear magnetic resonance (NMR) to detect changes in volume status in HD patients.

Methods: Adult HD patients who were admitted to our hospital between April and Dec 2015 were recruited. Patients were excluded if they were initiating HD, had a limb amputation, or were being treated in the intensive care unit. The first NMR device was a single sided sensor designed to take measurements at the upper calf and the second was a bore-configured sensor designed to take measurements at the finger. The first measurements were obtained at initiation of dialysis. NMR measurements were repeated at hourly intervals and at the completion of dialysis. Pearson correlation was used to look for an association between change in NMR measurements and ultra-filtration volume.

Results: The demographics of the 22 participants are below.

Age (years)	66.6 (12.5)
% Male	72.7
% White	81.8
BMI (kg/m^2)	27.6 (5.6)
% with diabetes	59.1
% with hypertension	90.9
Ultrafiltration volume (L)	1.7 (1.2)

NMR measurements at the finger, but not the leg, were found to have a significant correlation with UF volume (r= 0.47, p=0.028 and r=0.07, p=0.77 respectively).

Conclusions: NMR may be a reliable and objective way to monitor volume status in ESRD patients. The finger sensor may be superior to the leg sensor because of differences in signal to noise or because of the differences in tissue compartments in the volumes sampled within the finger and leg. Further study and correlations with other measures of volume status are needed to determine the clinical role of portable NMR sensors.

Funding: Private Foundation Support

SA-PO490

Automation Optimizes Risk Stratification for Acute Kidney Injury: Pilot Study of Electronic Health Record Based Patient Screening Rajit K. Basu, Patricia A. Holshouser, Tara C. Terrell, Theresa A. Mottes, Ryan Knox, Hilary E. Pitner, Catherine Johnson, Bill Young, Stuart Goldstein. *Center for Acute Care Nephrology, Cincinnati Children's Hospital, Cincinnati, OH.*

Background: Earlier identification of patients at risk for AKI is hypothesized to improve outcomes. We previously validated a stratification methodology for AKI risk, termed the Renal Angina Index (RAI), in critically ill children for prediction of severe AKI. Screening for RAI elements requires extraction and calculation of objective data. We hypothesized that an automated electronic health record (EHR) screening algorithm would optimize the value of RAI screening compared to manual extraction and tabulation.

Methods: We integrated the RAI into our EHR to compare automated versus manual patient screening for AKI risk in two separate, single-center retrospective and prospective observational studies. The EHR-system and five practitioners with varying medical expertise (manual) screened 97 patients admitted to the pediatric intensive care unit (PICU) for RAI criteria 12 hours after ICU admission (time of eligibility). The primary outcome was "value", a composite of screening accuracy, time, and cost.

Results: Accuracy improved using automation in both the retrospective and prospective studies (auto: 91.1% and 92.2% vs. 75% and 77%, respectively). Median time required for screening individual patients was 00:07:25 (hr:min:sec) (range 00:04:18 – 00:14:27) and median time lag between patient eligibility and screening was 13:20:00 for the manual process (range 09:21:52 – 17:54:42). The automated process was instantaneous for both screening studies with no lag between first eligibility time and time of RAI reporting. Using average number of patients per day, required time for screening, and average hourly salary of researcher, the extrapolated daily cost for manual RAI screening alone would be $9,338.24/year/researcher or ~ $46,691.20 total.

Conclusions: Our data show that automation increases accuracy and decreases screening time, screening delay, and cost for using identifying patients at risk for AKI. Taken together, we suggest the EHR can be used to optimize the value of AKI risk screening for both research and clinical purposes.

SA-PO491

A Three-Dimensional Bioprinted Model of the Renal Proximal Tubule for Evaluation of Drug-Induced Nephrotoxicity Shelby King, Timothy Smith, James William Higgins, Celina Nino, Abigail Docuyanan, Alice Chen, Sharon Presnell, Deborah Nguyen. *Organovo, Inc., San Diego, CA.*

Background: Due to its exposure to high concentrations of xenobiotics, the proximal tubule (PT) is a primary site of nephrotoxicity and resulting drug attrition in drug development. Current pre-clinical methods using 2D cell cultures and animal models cannot fully recapitulate the *in vivo* human response to drugs.

Methods: Using Organovo's proprietary bioprinting platform, we have developed a human *in vitro* 3D tissue model of the PT to enable more accurate prediction of clinical outcomes.The tissue is composed of a thin interstitium supporting a basement membrane and polarized monolayer of primary human PT epithelial cells.

Results: The epithelial cells of the 3D tissues demonstrated formation of tight junctions, stable gamma glutamyl-transferase activity, and expression of renal transporters for at least 4 weeks in culture. The tissues also exhibited functional glucose transport via SGLT2, inhibited by the SGLT2 inhibitor canagliflozin, as well as P-gp mediated efflux of rhodamine 123 which was effectively blocked by the P-gp inhibitor zosuquidar. To validate the model for drug-induced toxicity assessment, the tissues were exposed to the nephrotoxin Cisplatin. Cisplatin induced a dose-dependent decrease in tissue metabolism and GGT activity and an increase in LDH release. Histologically, cisplatin induced a loss of epithelial nuclear and cellular morphology. The OCT2 inhibitor cimetidine almost completely reversed this damage, confirming the role of OCT2-mediated drug uptake and cytoplasmic drug accumulation as a mechanism for nephrotoxicity.

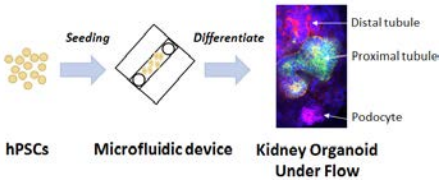
Conclusions: Together, these results support the use of this novel 3D tissue model of the PT for assessment of human renal toxicity over extended time in culture.

Funding: Pharmaceutical Company Support - Organovo, Inc.

SA-PO492

Organoid Differentiation under Flow: Bioengineering a Functional Kidney-on-a-Chip from Human Pluripotent Stem Cells Ramila E. Gulieva, Benjamin S. Freedman. *Div of Nephrology, Kidney Research Inst, and Inst for Stem Cell and Regenerative Medicine, Dept of Medicine, Univ of Washington, Seattle, WA.*

Background: Human pluripotent stem cells (hPSCs) have recently been differentiated into nephron-like kidney organoids, with important potential for kidney function. Microfluidic flow is an essential component of the kidney nephron, but is absent from existing kidney organoid cultures. We tested the ability of hPSCs to differentiate into kidney organoids under constant flow and perform kidney functions.



Methods: hPSCs were seeded in a multichannel microfluidic chamber and treated with specific growth factors to direct differentiation into kidney organoids under constant flow. Organoids were fixed and analyzed for kidney marker expression by immunofluorescence. Absorption of glucose and dextran probes was monitored live in kidney organoids under perfusion conditions.

Results: Over a two week period under constant flow, hPSCs seeded in microfluidic chambers differentiated efficiently into tubular kidney organoids (~15 organoids/cm^2). Each organoid contain segmented proximal tubules, distal tubules, and podocytes, which remained stable under flow. Organoid tubules exhibited functional ability to uptake glucose and dextran from the perfusate under flow.

Conclusions: Kidney organoid differentiation can be performed entirely under constant flow conditions, yielding a kidney-on-a-chip device capable of perfusion. Organoids arise intact in the chamber without disruption, preserving their complexity, and can perform functions of proximal tubules under flow. Bioengineering of this micro-physiological device, the first of its kind, represents an important step towards more functional organoid culture models for drug discovery and kidney regeneration. (Supported by an unrestricted gift from Northwest Kidney Centers to Kidney Research Institute).

Funding: NIDDK Support, Pharmaceutical Company Support - Northwest Kidney Centers, Private Foundation Support

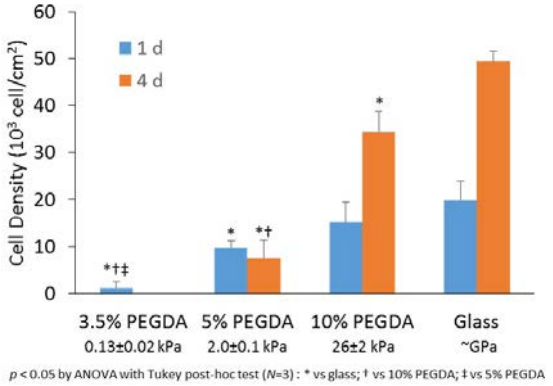
SA-PO493

Extracellular Matrix Mechanics Influence Proliferation and Cytoskeletal Organization of Cultured Renal Proximal Tubular Epithelium Jeffrey A. Beamish, Evan Chen, Andrew J. Putnam. *Univ of Michigan.*

Background: Chronic kidney disease (CKD) is associated with poor prognosis after acute kidney injury (AKI) and also is associated with changes in the mechanical properties of the kidney parenchyma. Recovery from AKI often requires proliferation of renal proximal tubular epithelial cells (RPTECs). In this study, we utilized a synthetic extracellular matrix (ECM) engineered with well-defined mechanical properties to investigate the influence of substrate mechanics on proliferation of human RPTECs.

Methods: Synthetic ECMs were prepared by photopolymerizing poly(ethylene glycol) diacrylate (PEGDA) hydrogel films with various compositions engineered to obtain a range of shear storage moduli. Human collagen IV was tethered to the gel surfaces using sulfo-SANPAH. Human primary cultured RPTECs were seeded on these matrices, cultured in expansion medium, and fixed 1 d and 4 d post-seeding. Cell density was measured by counting DAPI stained nuclei. The actin cytoskeleton was visualized with phalloidin. Focal adhesions were visualized by immunofluorescence staining for vinculin.

Results: RPTEC attachment to the synthetic ECMs increased as the modulus increased (Figure). At 1 d, a qualitative tendency toward more robust networks of basolateral stress fibers was observed on more rigid substrates. Well-developed focal adhesions formed on glass but were less prominent in cells seeded on the synthetic matrices. Proliferation over 4 d was enhanced on the firmer gels (Figure).



$p < 0.05$ by ANOVA with Tukey post-hoc test (N=3) : * vs glass; † vs 10% PEGDA; ‡ vs 5% PEGDA

Conclusions: Increased synthetic matrix rigidity enhanced attachment and proliferation of RPTECs. This effect was correlated with the qualitative enhancement of basolateral stress fibers and focal adhesions. These results suggest ECM mechanics modulate RPTEC proliferation and may influence the recovery of tubular cells from AKI.

Funding: Other NIH Support - Support for this work was provided by the University of Michigan O'Brien Kidney Center (DK-P30-081943). JAB was supported by T32DK007378

SA-PO494

Stable Filtration by Silicon Nanopore Membranes under Pulsatile Flow Joseph J. Groszek,[1] Shuvo Roy,[2] William Henry Fissell.[1] *[1]Nephrology and Hypertension, Vanderbilt Univ, Nashville, TN; [2]Bioengineering and Therapeutic Sciences, Univ of California, San Francisco, San Francisco, CA.*

Background: Silicon Nanopore Membranes (SNM) optimize permeability-selectivity factors in ultrafiltration membrane design. The efficiency of the membranes reduces package size and pressure requirements for filtration, enabling implanted renal replacement therapy. The failure characteristics of SNM are described by statistical likelihood of fracture due to the crystalline nature of the material, rather than gradual failure. Hydraulic permeability and macromolecular sieving by SNM were characterized using pulsatile flow of a blood surrogate.

Methods: SNM were manufactured by bulk and surface micromachining as previously described. Sample membranes were mounted in custom-made ultrafiltration cells and perfused with a 37% (v/v) glycerol-saline mixture spiked with a polydisperse fluorescently-tagged polysaccharide, Ficoll) with similar viscosity to blood. Pressure and flow waveforms simulating arterial flow were produced by a computerized pump control system. Filtration rates were monitored by mass accumulation on an analytical balance Serial aliquots of feed and filtrate were analyzed by size-exclusion chromatography and szie-dependent sieving coefficients calculated as the ratio of ultrafiltrate concentration to feed concentration.

Results: Hydraulic permeability was unchanged over 12 (n=2) and 16 (n=2) days. Sieving coefficients were unchanged over the same period. No membranes were fractured or leaked after 1.3 million pulsatile cycles.

Conclusions: Ultrathin crystalline silicon membranes are mechanically stable for over 10^6 pressure cycles in vitro. Permeability/selectivity performance does not significantly degrade over two weeks.

Funding: Other NIH Support - NIBIB

SA-PO495

Transcriptome Analysis of Three Progressive Models of Chronic Kidney Disease Identifies Pathways Implicated in Disease Progression Shannon Marie Harlan, Tao Wei, Zhonghua Qi, Martin S. Cramer, Dianna L. Jaqua, Matthew D. Breyer, Josef G. Heuer. *Lilly Research Labs, Eli Lilly and Company, Indianapolis, IN.*

Background: Publically available renal transcriptome data from patients with diabetic kidney disease (DKD) has served as a valuable resource for identification of genes and pathways upregulated in human DKD. Precisely how close animal models of DKD mimic many of the genetic features of human DKD remains unclear. The present studies explored gene expression profiles in three preclinical mouse models of renal disease, the remnant kidney, the *db/db*$^{-/-}$/*eNos*$^{-/-}$, and the ReninAAV *db/db* uNx model and compared them to published human DKD data sets.

Methods: Mice aged 20-26 weeks were used to isolate kidney RNA for microarray analysis (Asuragen, MOE-430 2.0 array). Differentially expressed genes (DEG) were defined as those with fold change >1.5, P value<0.05 and FDR <0.05. Results were compared to the published data set GSE30529 of human DKD.

Results: Clustering and pathway analysis of DEGs identified common pathways both up and down-regulated in the three mouse models with human DKD. Inflammation/immune and apoptosis/cell survival responses were both highly upregulated in all three models and in human DKD. Common pathways down-regulated in all three models and human DKD included amino acid metabolism and transporter activity. Comparing DEGs from the three models identified the highest concordance (84%) of DEGs to human DKD in the ReninAAV *db/db* uNx model consistent with this model most closely mimicking the pathophysiological characteristics of human DKD. KEGG analysis identified cytokine-cytokine receptor interaction as the top ranked pathway in this model, a pathway highly upregulated in human DKD.

Conclusions: Transcriptome data from the three mouse models of DKD supports the similarity of the models to human DKD, with the ReninAAV *db/db* uNx model having a molecular signature most closely resembling human DKD patients. In addition, inflammation which has been shown to be prominent feature of human DKD was highly upregulated in all models, suggesting a potential role of inflammation in the pathogenesis of DKD.

Funding: Pharmaceutical Company Support - Eli Lilly and Company

SA-PO496

Genomic and Proteomic Profiling Reveal Insights of Mesangial Cell Function in Patients with IgA Nephropathy Emelie Lassén,[1] Peidi Liu,[1] Wenjun Ju,[2] Matthias Kretzler,[2] Kerstin Ebefors,[1] Jenny C. Nystrom.[1] *[1]Neuroscience and Physiology, Univ of Gothenburg, Gothenburg, Sweden; [2]Computational Medicine and Bioinformatics, Univ of Michigan, Ann Arbor, MI.*

Background: To understand disease onset and to discover new drug targets for IgA nephropathy (IgAN) we need to more closely determine the role of the mesangial cells in disease development and progression. Using a systems biology approach involving *in silico* nanodissection (Ju W et al, Genome Res. 2013) we investigated the role of the mesangium in patients with IgAN and the effect of galactose deficient IgA (gd-IgA) on mesangial cells *in vitro*.

Methods: Transcriptomic profiles of glomeruli from patients diagnosed with IgAN (n=20) and healthy kidney donors (n=22) were obtained using the Affymetrix platform. Expression of mesangial and podocyte standard genes obtained by *in silico* nanodissection were compared between the groups and correlated to clinical parameters. Additionally, primary human mesangial cells were treated with gd-IgA to mimic IgAN in vitro and the proteome analysed using LC-MS/MS. This enabled identification of shared pathways between the patient glomerular transcriptome and the proteome in the *in vitro* model.

Results: By transcriptome analysis we found 736 significantly regulated genes. Mesangial cell standard gene expression separated IgAN patients from healthy donors, while no separation was seen for podocyte standard genes. Activation z-scores based on mesangial cell standard gene expression yielded a significant correlation with creatinine and eGFR, while no correlation was found based on podocyte standard genes. 22 significantly regulated pathways, mainly inflammatory, were shared between the glomerular transcriptome and the proteome of mesangial cells treated with gd-IgA.

Conclusions: Expression of mesangial cell standard genes determined by in silico nanodissection clusters IgAN patient samples separately from healthy controls. Correlation with eGFR and creatinine indicate their usefulness as predictive biomarkers. Shared regulated inflammatory pathways between the glomerular transcriptome and gd-IgA treated mesangial proteome give rise to new and exciting data useful for target exploration in IgAN.

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

SA-PO497

Quantitative Magnetization Transfer Imaging to Evaluate Renal Fibrosis in Mouse Diabetic Nephropathy Daisuke Katagiri,[1] Feng Wang,[1] Shinya Nagasaka,[1,2] Hua Li,[1] Suwan Wang,[1] Keiko Takahashi,[1] Ming-Zhi Zhang,[1] Akira Shimizu,[2] Raymond C. Harris,[1] Takamune Takahashi.[1] *[1]Vanderbilt Univ, Nashville; [2]NIppon Medical School, Tokyo, Japan.*

Background: Currently few non-invasive methods are available to evaluate fibrosis according with progressed kidney disease. MRI-based quantitative magnetization transfer (qMT), which provides indices describing the interactions between free water protons and immobile macromolecular protons, is applicable to evaluate tissue fibrosis. However, this technique has not been applied to kidney disease. This study was conducted to evaluate the utility of qMT in assessing fibrosis in advanced diabetic nephropathy (DN) by comparison with histological analysis.

Methods: 8, 24 weeks old db/db eNOS -/- (DN; 8wDN and 24wDN) and C57BL/6 (Wild type; WT) mice were imaged with a 7T MRI. Henkelman-Ramani's model was applied to derive qMT. Cortical and outer medulla regions with significant higher pool size ratio (PSR) values were detected and fibrosis level was evaluated by threshold PSR. Mice were sacrificed and median 50 % of each kidney was evaluated fibrosis determined by Picrosirius red and collagen IV (14 sections per mouse, and 3 - 4 mice per group).

Results: Localized changes of PSR were observed in cortex and outer medulla. 24wDN mice developed significant higher fibrosis in cortex than WT mice on histology (3.0 vs 0.5 %; Sirius red, 12.3 vs 4.4 %; collagen IV) and these fibrosis areas corresponded to high PSR region. Mean PSR values in cortex were increased with DN progression (0.09; WT, 0.10; 8wDN, 0.12; 24wDN). The observed longitudinal relaxation rate (R_{1obs}) and transverse relaxation rate of the free water pool (R_{2a}) correlated highly with the regional distribution of PSR. % Areas with higher than +2SD of PSR were significantly dominant in 24wDN mice than WT mice (14.4 vs 4.5 %; PSR>Mean+2SD, 7.7 vs 0.7 %; >+3SD, and 3.9 vs 0.0 %; >+4SD, $p<0.01$). The cortical fibrosis levels estimated using threshold PSR showed a significant correlation with the fibrosis indices determined with Sirius red and collagen IV ($p<0.05$).

Conclusions: The present study provides the first demonstration that renal fibrosis in DN can be non-invasively assessed with qMT-MRI technique and threshold PSR analysis.

Funding: NIDDK Support

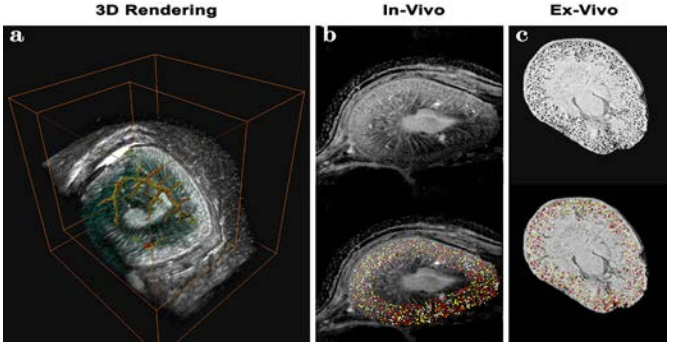
SA-PO498

In Vivo Detection of Glomerulus Number and Size in the Whole Kidney Using MRI Edwin Baldelomar,[1] Jennifer R. Charlton,[2] Kevin M. Bennett.[1] *[1]Univ of Hawaii at Manoa; [2]Univ of Virginia.*

Background: Nephron endowment is an important factor in susceptibility to renal insufficiency with development of acute or chronic kidney disease. Here we report a novel, non-invasive, approach to measure nephron endowment *in vivo* using MRI with use of the biocompatible contrast agent cationized ferritin (CF). We report glomerular number (N_{glom}) and individual glomerulus volume (IGV) in live animals.

Methods: Sprague-Dawley (SD) rats were given a total dose of 5.75mg/100g of CF through a tail vein catheter in 3 separate injections at 90-minute intervals. Animals were then imaged with *in-vivo* MRI on a Bruker 7T MRI using a T2* weighted 3D gradient recalled echo (GRE) sequence. Individual 3D MR images were acquired in less than one hour. Motion artifacts were readily mitigated by gating. After imaging, animals were transcardially perfused and kidneys resected for ex-vivo imaging using a T2* weighted 3D-GRE sequence for comparison. N_{glom} and IGV were measured using custom software.

Results: Whole kidneys were imaged *in-vivo* with MRI and images rendered in 3D to visualize gross anatomy, glomeruli, and vasculature. CF accumulation in glomeruli was visible as dark spots in the cortex in both in-vivo and ex-vivo images.



N_{glom} and IGV distributions measured in vivo compared well with measurements in ex vivo MRI; N_{glom} = 35446±2832(in-vivo), 39163±3604(ex-vivo); Mean-IGV = 5.49±1.48(in-vivo),4.90±0.70(ex-vivo) $*10^{-4}$ mm^3. Under the current protocol, a total scan time of ~50 minutes in length allows 3D detection of N_{glom} and V_{glom} in the rat. Further technical improvements should reduce this time significantly.

Conclusions: CF-enhanced MRI can be used to measure nephron endowment *in vivo* in small animals. Given its apparent lack of toxicity at these doses and ease of translation, this approach may be important for preclinical and clinical diagnostics in the future.

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SA-PO499

Beta Blocker Pharmacokinetics and Dialyzability in Chronic Hemodialysis Patients Alvin Tieu,[1] Thomas Velenosi,[1] Andrew S. Kucey,[1] Matthew A. Weir,[1,2] Brad Urquhart.[1,2] *[1]Dept of Physiology and Pharmacology, Western Univ; [2]Dept of Medicine, Div of Nephrology, Western Univ, London, ON, Canada.*

Background: There is a paucity of data available to describe drug dialyzability. Of the available information, most were obtained prior to implementation of modern hemodialysis (HD) membranes. This study aims to characterize the dialyzability of the four most commonly prescribed beta blockers in patients undergoing high-flux HD. Based on physicochemical properties, we hypothesize atenolol and metoprolol to be extensively removed by HD, while bisoprolol and carvedilol to be poorly dialyzed.

Methods: Chronic HD patients were recruited for a pharmacokinetic, 4-way crossover study. Atenolol, bisoprolol, carvedilol and metoprolol were administered separately to each patient over 4 HD sessions. Arterial and venous blood samples and total spent dialysate were collected. Beta blocker concentrations were measured by mass spectrometry and dialytic clearance was determined by the dialyzer and recovery clearance methods.

Results: After HD, 6.07, 1.11, 0.03 and 1.28 mg of atenolol, bisoprolol, carvedilol and metoprolol were recovered in spent dialysate. As a result, dialytic clearance rates for atenolol, bisoprolol and metoprolol were 117.1, 110.1 and 148.4 mL/min. These 3 beta blockers are significantly dialyzed as compared to carvedilol (17.8 mL/min). Other pharmacokinetic parameters that were calculated include non-dialytic clearance and post-dialysis doses required to maintain patients within a therapeutic window. For atenolol, bisoprolol and metoprolol, the fraction of elimination due to dialysis was 25, 19 and 13 % while the supplemental doses were 22.7, 2.88 and 1.39 mg. Only 4% of carvedilol was removed by dialysis.

Conclusions: Beta blocker efficacy can be hindered if substantial dialytic clearance occurs. Accordingly, atenolol and metoprolol are extensively cleared by HD, while carvedilol displays low dialyzability. Contrary to literature, our data indicates that bisoprolol is substantially eliminated by HD. With recent studies suggesting heightened mortality risk in HD patients prescribed highly dialyzed beta blockers, dialyzability data is critically important to optimize drug therapy in patients.

Funding: Government Support - Non-U.S.

SA-PO500

Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients Thomas Mavrakanas,[1,2] Caroline Samer,[3] Mark L. Lipman.[1] *[1]Div of Nephrology, Sir Mortimer Davis Jewish General Hospital, McGill Univ, Montreal, QC, Canada; [2]Div of General Internal Medicine, Geneva Univ Hospitals, Geneva, GE, Switzerland; [3]Div of Clinical Pharmacology & Toxicology, Geneva Univ Hospitals, Geneva, GE, Switzerland.*

Background: Atrial fibrillation increases the risk of ischemic stroke in patients with end-stage renal disease. Warfarin may not protect these patients against ischemic stroke. Apixaban is only 27% renally excreted and could be an option in dialysis patients. However, there are no data on apixaban pharmacokinetics at steady state in hemodialysis patients.

Methods: Five patients with atrial fibrillation, on hemodialysis (thrice weekly for >6 months) without any residual renal function, received apixaban 2.5 mg bid for 9 consecutive

days. Venous blood samples were collected immediately before (0) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 24 h after apixaban administration on days 1 and 8 (non dialysis days). On day 9, the dose was increased at 5 mg bid and administered for 7 more days. Pharmacokinetic sampling was repeated as above on day 15. Apixaban levels were measured in the plasma using the chromogenic anti-Xa method and apixaban-specific calibrators and controls.

Results: Apixaban exposure at steady state (day 7 for the 2.5 mg bid dose) was 3.7 fold higher as compared to day 1 (mean AUC 1783.6 vs 487.6 ng.h/mL). The 2.5 mg bid dose in hemodialysis patients achieved reasonable drug exposure and trough levels, comparable to the 5 mg bid dose levels in the general population. In hemodialysis patients, the 5 mg bid dose was associated with significantly higher exposure (mean AUC 6112 ng.h/mL) exceeding the expected 90th percentile in the general population and supratherapeutic peak levels (1.5 fold) in some patients.

Conclusions: In conclusion, apixaban 2.5 mg bid was associated with therapeutic drug levels in hemodialysis patients while the 5 mg bid dose led to supratherapeutic levels. Apixaban dose should therefore be halved in hemodialysis patients and a 2.5 mg bid dose considered for stroke prevention in atrial fibrillation patients.

SA-PO501

Paricalcitol Pharmacokinetics in Children Is Not Affected by Chronic Kidney Disease Stage Matthew B. Dufek,[1] Sven Stodtmann,[1] Nicholas J. Webb,[2] Denise Beck,[1] Peter Noertersheuser,[1] Ann Katherine Eldred,[1] Peter G. Linde,[1] Cheri E. Klein.[1] *[1]Abbvie Inc, North Chicago, IL; [2]Univ of Manchester, Manchester, United Kingdom.*

Background: Two studies were completed to evaluate the pharmacokinetics, efficacy, and safety of paricalcitol (Zemplar) in the reduction of intact parathyroid hormone (iPTH) in children 10-16 years with stage 3-5 CKD. Results from these studies were used to determine covariates that impact the exposure of paricalcitol in children with stage 3-5 CKD.

Methods: The first study evaluated the pharmacokinetics of paricalcitol following administration of 3 μg paricalcitol capsules to children (n=12) with stage 3/4 CKD. The safety and efficacy portion of the study (n=36) included a 12-week blinded and a 12-week open-period where all children received paricalcitol. In the second study, safety and efficacy of open-label paricalcitol capsules was evaluated in children (n=13) with stage 5 CKD (on dialysis) for 12 weeks. A population pharmacokinetic model was used to evaluate subject-specific covariates that explained the observed variability.

Results: In the stage 3/4 CKD study, the paricalcitol treatment group had 5 (27.8%) children with 2 consecutive reductions ≥30% in iPTH from baseline compared with none (0%) in the placebo group. No new safety signals were identified. With a single 3 μg paricalcitol dose mean C_{max} was 0.13 ng/mL and mean AUC_{∞} was 2.87 ng•h/mL. In the stage 5 CKD study, 8 (61.5%) children had 2 consecutive iPTH reductions ≥30% from baseline and 5 (38.5%) had 2 consecutive iPTH values between 150-300 pg/mL. Population pharmacokinetic analysis showed sex and body weight were significant covariates while CKD stage was not. Sex was not considered clinically relevant since dosing is individualized for iPTH response. The estimated apparent volume of distribution (22.9 L for males) and apparent clearance (19.1 L/day) increased 15.9% and 21.7% for every 10 kg increase in body weight over 46 kg, respectively.

Conclusions: Oral paricalcitol dosing in children 10–16 years with stage 3–5 CKD reduced iPTH levels and no new safety signals were identified. Population pharmacokinetic analysis showed that CKD stage does not influence the pharmacokinetics of paricalcitol in children.

Funding: Pharmaceutical Company Support - Abbvie Inc

SA-PO502

Population Pharmacokinetics Using Scavenged Samples II: Biostatistics and Modeling Matthew S. Shotwell,[1] Joseph J. Groszek,[2] William Henry Fissell,[2] Alexandra F. Chancellor.[3] *[1]Biostatistics, Vanderbilt Univ, Nashville, TN; [2]Nephrology and Hypertension, Vanderbilt Univ, Nashville, TN; [3]Clinical Pathology, Vanderbilt Univ, Nashville, TN.*

Background: Antibiotic dosing in critical illness complicated by AKI is incompletely understood. Traditional pharmacokinetic studies require large number of patients and repeated sampling that is impractical in postmarketing studies. We implemented a population pharmacokinetic analysis using blood left over from clinical samples.

Methods: Plasma concentration of target drug was modeled using a one-compartment linear differential equation model. Separate solutions to the homogeneous (between infusions) and nonhomogeneous equations (during infusions) were combined to describe the time course of drug concentration across multiple doses. Concentrations were modeled as the cumulative effect of all prior doses. Nonlinear mixed-effects (NLME) regression was used to fit the one-compartment model to measured drug concentrations. Both the volume of distribution and elimination rate parameters were modeled using fixed and random effects to account for between-subject heterogeneity, where the latter were assumed to be normally distributed with mean zero and unstructured covariance.

Results: 171 piperacillin plasma concentration measurements were collected from scavenged blood samples from 92 patient encounters. The number of scavenged samples per encounter varied from 1 (54%) to 8. The number of piperacillin doses per encounter varied from 1 to 49, with a median of 11. The figure below illustrates the fitted one-compartment model for a typical patient encounter. In these data, the estimated population average volume of distribution and elimination rate were 30.9 L (95% CI: 21.9, 43.5) and 0.15 h^{-1} (95% CI: 0.11, 0.22), respectively. However, there was substantial population heterogeneity in both parameters.

Conclusions: Pharmacokinetic (PK)models estimated from antibiotic concentrations measured in scavenged blood samples yield parameter estimates similar to estimates from PK.

Funding: Clinical Revenue Support

SA-PO503

Population Pharmacokinetic/Pharmacodynamic (PK/PD) Analyses of C.E.R.A. (Continuous Erythropoietin Receptor Activator - Methoxy Polyethylene Glycol-Epoetin Beta) in Both Adults and Pediatric Patients with Chronic Kidney Disease (CKD) Pascal Chanu,[1] Nicolas Frey.[2] *[1]Certara Strategic Consulting, France; [2]F Hoffmann-La Roche Ltd, Basel, Switzerland.*

Background: Objectives were to determine the PK/PD characteristics of C.E.R.A. in pediatric patients (pts) with anemia of CKD on hemodialysis (HD) and whether they differ from those in adults.

Methods: Serum C.E.R.A. concentrations and hemoglobin (Hb) levels in a 20-week open-label Phase II study of intravenous (IV) C.E.R.A. in pts aged 6–17 years on HD with stable chronic renal anemia were pooled with data collected during the clinical development of C.E.R.A. (IV and subcutaneous [SC]) in adult patients with CKD. Adult PK/PD structural models previously developed were used for the analyses. A non-linear mixed effect modeling approach was applied using NONMEM version 7.3.0.

Results: The pediatric PK/PD dataset consisted of 63 pts with 676 C.E.R.A. serum values and 1580 Hb levels. The adult PK/PD dataset (2 phase II, 3 phase III) consisted of 524 pts with 5883 C.E.R.A. serum values and 12786 Hb levels. The same structural PK model as the adult one (1-compartment model with first order absorption and elimination) adequately described the pediatric data. As already determined in adults, C.E.R.A. clearance increased with body weight and the volume of distribution increased with body weight and age. Once those covariate influences were taken into account, there was no difference in PK between adult and pediatric pts. The PK/PD model developed on adult phase 2/3 data could be applied successfully to pediatric data. The drug dependent parameters (S_{max} and SC50) were comparable in pediatric and adult pts indicating that the C.E.R.A. exposure–response relationship is similar in both populations. The predicted baseline Hb value in absence of any erythropoietin-stimulating agent therapy was found to increase with body weight. This effect is driven by the pediatric population and is in accordance with generally higher Hb levels observed in adults. No difference in PK/PD parameters was found between IV and SC formulation and between dialysis types (including pts not on dialysis).

Conclusions: The PK/PD characteristics of C.E.R.A. are similar between adult and pediatric populations.

SA-PO504

Pharmacokinetics and Safety of KBP-5074 in Phase 1 Single and Multiple Ascending Dose Studies Bin Zhang, Xiaojuan Tan, Shumao Ni. *KBP Biosciences USA Inc.*

Background: KBP-5074 is a new investigational mineralocorticoid receptor antagonist being developed for chronic kidney disease. The primary objective of these studies was to determine the safety, tolerability, and pharmacokinetic (PK) profileof KBP-5074 following single (SAD) and multiple (MAD) ascending oral doses in healthy subjects.

Methods: The SAD study was comprised of 5 sequential cohorts (0.5, 1.0, 2.5, 10, 30mg) and 1 food effect cohort (10mg). The MAD study was comprised of 2 cohorts (2.5, 5.0 mg) dosed for 14 days. PK parameters included C_{max}, T_{max}, $AUC_{0\text{-}24h}$, AUC_{last}, and $T_{1/2}$. Safety parameters included adverse events, vital signs, clinical laboratory results, ECG, and physical examination.

Results: 46 and 12 healthy adults were enrolled in the SAD and the MAD study, respectively. KBP-5074 was generally safe and well-tolerated at single doses up to 30.0 mg and multiple doses up to 5.0 mg. Adverse events were mostly mild and unrelated to study drug. No hyperkalemia (serum potassium >5.5 mmol/L) was reported in the SAD study and the 2.5 mg cohort in the MAD study (3 occurred in the 5.0 mg cohort in the MAD study). Dose proportional increases in plasma levels were observed within the tested dose range after single and multiple ascending doses of KBP-5074 and subsequently declined mono-exponentially. The half-life of KBP-5074 ranged from 59.70 to 72.42 hr in the SAD study, and 55.57 to 60.45 in the MAD study. Food appeared to delay T_{max} from 6 hr to 9 hr.

PHARMACOKINETIC RESULTS			
PK Parameter	SAD Study (Day 1)	SAD Study Food Effect (Day 1)	MAD Study (Day 14)
†C_{max}	9.370 (1.618) - 259.4 (151.4)	177.8 (18.31)	140.4 (38.97) – 321.8 (66.13)
†$AUC_{0\text{-}24h}$	162.5 (31.64) - 5016 (2754)	3154 (261.3)	2865 (821.2) – 6376 (1028)
†AUC_{last}	542.1 (80.85) - 26674 (11755)	15128 (3579)	12481 (4900) – 27686 (6131)
‡T_{max}	4.02 (4.0, 5.0) - 7.00 (4.0, 24.0)	9.00 (5.0, 12.0)	6.00 (2.0, 8.0) – 4.00 (2.0, 10.0)
‡$T_{1/2}$	59.70 (8.926) - 72.42 (17.36)	64.35 (13.75)	55.57 (15.08) – 60.45 (5.475)

† Mean (SD) ‡ Median (min, max).

Conclusions: KBP-5074 was generally safe and well-tolerated by healthy adults in these studies.The maximum repeated dose level in clinical practice may be less than 5.0 mg.

Funding: Pharmaceutical Company Support - KBP Biosciences USA Inc

SA-PO505

Pharmacokinetics and Pharmacodynamics of Eculizumab in Individualized Treatment of Atypical Hemolytic Uremic Syndrome Elena Volokhina,[1] Kioa L. Wijnsma,[1] Jack F. Wetzels,[1] Nicole Van De Kar,[1] Lambertus P.W.J. Van den Heuvel.[1,2] *[1]Radboud Univ Medical Center, Nijmegen, Netherlands; [2]Univ Hospitals Leuven, Leuven, Belgium.*

Background: The atypical hemolytic uremic syndrome (aHUS) is a devastating renal disease, caused by complement dysregulation. Approval of monoclonal complement inhibitor eculizumab/Soliris started a new era in the treatment for this disease. However, data on pharmacokinetics and pharmacodynamics of this drug remain limited.

Methods: Eculizumab was measured by in-house ELISA method. Complement activity was analyzed using Wieslab® complement screen assay. In total, 209 samples were taken from 11 patients before the eculizumab infusion in the induction (weekly), maintenance (2-weekly) and tapering (every 3, 4 and 5 weeks) phases of therapy.

Results: Our newly-developed eculizumab assay had variation coefficients of 2.9 % (intra-assay, 352 µg/mL) and 5.2 % (inter-assay, 328 µg/mL) and detection limit of 8 µg/mL. The samples with >50 µg/mL demonstrated <6 % of complement activity in classical and alternative complement pathways. The eculizumab levels had ranges of 36-459 µg/mL and 40-772 µg/mL during induction and maintenance phases, respectively, with 3 samples from 2 patients <50 µg/mL, required for efficient complement inhibition. During tapering, ranges of 61-367 µg/mL, 11-256 µg/mL and 13-161 µg/mL were measured at 3, 4 and 5 week infusion intervals, respectively.

Conclusions: Our data demonstrate large differences in attained eculizumab concentrations among patients at all treatment stages. In induction and maintenance, the detected concentrations were up to 9-15 fold higher than required for efficient complement inhibition (50 µg/mL), although 3 samples did not reach this target value. Thus, eculizumab therapy should be adjusted to meet the needs of individual patients and monitoring of eculizumab concentration is useful to guide the treatment schemes. We have shown that target eculizumab values (> 50 µg/mL) may be reached with infusion intervals extended beyond 2 weeks; extension of intervals for these patients may improve cost-effectiveness of therapy.

Funding: Government Support - Non-U.S.

SA-PO506

Pharmacokinetics (PK), Pharmacodynamics (PD), and Safety of Single and Multiple Oral Doses of Vadadustat in Healthy Japanese and Caucasian Subjects Gurudatt A. Chandorkar,[1] Stan Jhee,[2] David S. Han,[3] Jason Chan,[1] Karishma Manzur,[1] Ramin Farzaneh-Far.[1] *[1]Akebia Therapeutics, Inc., Cambridge, MA; [2]PAREXEL International Early Phase, Glendale, CA; [3]California Clinical Trials Medical Group in Affiliation with PAREXEL Early Phase, Glendale, CA.*

Background: Vadadustat is a novel, once-daily, oral, hypoxia-inducible factor prolyl-hydroxylase inhibitor and has been shown to increase and maintain hemoglobin (Hb) levels for the treatment of renal anemia in patients with chronic kidney disease. Vadadustat is currently being evaluated in global Phase 3 studies. This study evaluated PK, PD, safety, and tolerability of vadadustat in healthy Japanese and Caucasian subjects.

Methods: Healthy Japanese (n=24) and Caucasian (n=24) subjects were randomized to receive double-blind vadadustat (150, 300, or 600 mg/day) or placebo for 10 days (3:1 ratio). 24-hour serial blood samples (from Days 1 and 10) were analyzed for PK (vadadustat and metabolite concentrations) using validated LC/MS/MS methods. PD markers (EPO, reticulocytes, and iron indices) were also measured. Standard PK parameters (area-under-the-curve $AUC_{0\text{-}t}$, peak plasma concentration C_{max}, and clearance CL/F) were estimated. Data analysis included 95% confidence intervals of $AUC_{0\text{-}t}$ and C_{max}. Safety and tolerability were based on vital signs, clinical laboratory tests, electrocardiography, and adverse events (AEs).

Results: Vadadustat exposure was similar between the ethnicities following single and multiple doses, and overall exposure increased in an approximate dose-proportional manner. Change in EPO and reticulocytes as a function of vadadustat exposure were similar between the ethnicities. Mean Hb remained stable over time following multiple doses in both ethnicities. No dose-related or ethnicity-related trends were observed for the iron indices. No safety concerns were identified: Only 2 mild AEs were reported in vadadustat-treated subjects and both events resolved.

Conclusions: PK, PD, safety, and tolerability of vadadustat were similar between the healthy Japanese and Caucasian subjects. These results demonstrate that the vadadustat clinical data meets ICH E5 criteria for bridging in support of the global Phase 3 studies.

Funding: Pharmaceutical Company Support - Akebia Therapeutics, Inc.

SA-PO507

Pharmacokinetics of Sparsentan in Healthy Subjects: In Vitro Metabolism and Effects of Food, Gender, Age, and Multiple-Dose Escalation Xin-Ru Pan-Zhou, Kevin Leach, Maria Beconi. *Retrophin, Inc., Cambridge, MA.*

Background: Sparsentan (RE-021) is a first-in-class, dual endothelin A and angiotensin 1 receptor antagonist that is being evaluated in a clinical trial (DUET) to treat focal segmental glomerulosclerosis (FSGS). Here we report on in vitro hepatic metabolism and in vivo pharmacokinetic (PK) studies in healthy subjects.

Methods: In vitro metabolism was assessed by incubating sparsentan in human liver microsomes and hepatocytes. PK studies in healthy subjects included evaluation of the effects of food, gender, age, and multiple ascending dose administration (50-1000 mg/d for 14 days).

Results: Sparsentan was primarily metabolized by CYP3A4. Up to 29 metabolites, mostly products of oxidation, were detected in HLM and hepatocytes after incubation with ^{14}C-sparsentan**.** Sparsentan exhibited rapid absorption and dose-related increases in systemic exposure after once-daily ascending dosing. The half-life of ~15 hours supported adequate coverage for once-daily dosing. No accumulation of sparsentan was observed after 14-day oral dosing (accumulation ratio ≤ 1.3 for all doses). Similar exposures were observed in men and women (%mean ratio [90% CI] = 92.80 [75.95, 113.38] for C_{max} and 89.69 [72.24, 111.36] for AUC). There was an increase in exposure driven by food (20% in AUC and 50% in C_{max}), but this was not considered clinically relevant. An age effect was observed, with the AUC 65%-67% higher in subjects ≥ 65 years vs those aged 22 to 39 years.

Conclusions: Hepatic metabolism of sparsentan was mainly mediated by CYP3A4. In healthy subjects, sparsentan exhibited linear PK and no accumulation after multiple days of dosing. Sparsentan can be dosed without regard to food due to only a modest change in AUC. While plasma exposure of sparsentan was higher in elderly subjects, there was no gender effect on the PK of the drug. These PK results support further clinical development of a once-daily dosing regimen of sparsentan in patients with FSGS.

Funding: Pharmaceutical Company Support - Pharmacopeia, Inc. funded the human pharmacokinetic studies. Retrophin, Inc. acquired sparsentan from Ligand Pharmaceuticals, Inc. (formerly Pharmacopeia) and funded the in vitro metabolism studies. Retrophin participated in the study design, data collection and interpretation, writing, reviewing, and approving this abstract for submission

SA-PO508

Safety and Pharmacokinetics in Healthy Human Volunteers of RG-012: An Inhibitor of MicroRNA-21 Being Investigated for Treatment of Alport Syndrome John Stewart Grundy, Kai Liu, Jacqueline Blem, Paul C. Grint, Michael Huang. *Regulus Therapeutics, San Diego, CA.*

Background: RG-012 is a single-stranded chemically modified oligonucleotide being developed to treat patients with Alport syndrome (AS), which is characterized by loss of renal function associated with defects in specific collagen genes expressed in the kidney glomerular basement membrane. RG-012 inhibits miR-21, a microRNA target associated with renal dysfunction and increased expression during kidney stress.

Methods: Safety and clinical pharmacokinetics (PK) of RG-012 (parent drug), RG0005 (active metabolite), and SUM (RG-012+RG0005) were evaluated in a placebo-controlled single ascending subcutaneous dose study (0.5, 1, 2, 4, and 8 mg/kg of RG-012; n=8/cohort including 6 active and 2 placebo) in healthy volunteers, with urine and plasma PK sampling performed up to 24 and 672 hours post dose, respectively. Concentrations of RG-012, RG0005, and SUM up to 24–48hrs post dose were determined using HPLC-MS/MS (LLOQ=10 and 50 ng/mL in plasma and urine, respectively). Very low plasma concentrations of SUM seen at ≥72hrs post dose were determined using HPLC-FL (LLOQ=0.623 ng/mL) which cannot resolve RG-012 and RG0005.

Results: Subcutaneous administration of RG-012 up to 8 mg/kg appeared to be generally safe and well tolerated in this study (no SAEs, severe AEs, or subject discontinuations). RG-012 was the main analyte observed in plasma and urine, with RG0005 being the sole major metabolite detected (achieving up to 47% of parent drug exposure). The plasma profiles of the evaluated analytes were characterized by relatively rapid absorption/appearance (median T_{max} range: 4–8 hours), dose-dependent exposure, and rapid clearance ($MRT_{0\text{-}24h}$ range: 6.9–9.2 hours) presumably reflecting extensive distribution to tissues. The mean terminal elimination half-life values of SUM ranged from 4–13 days, likely reflecting long tissue half-lives. Combined urinary excretion of RG-012 and RG0005 over the first 24 hours post dose was less than 1% of the total administered dose.

Conclusions: In conclusion, favorable safety and clinical PK results in this study appear generally consistent with reported results from other similar compounds in this oligonucleotide class.

Funding: Pharmaceutical Company Support - Regulus Therapeutics; Genzyme

SA-PO509

Quantification of Cefepime, Meropenem, and Vancomycin Removal by Sustained Low-Efficiency Dialysis Joanna Q. Hudson,[1,2] Jagannath H. Saikumar,[2] Benjamin Duhart,[1] G. Morgan Jones,[3] Elvira Gosmanova.[4,5] *[1]UT Colleges of Pharmacy and; [2]Medicine, UT Health Science Center, Memphis, TN; [3]Methodist Univ Hospital, Memphis, TN; [4]Div of Nephrology, Albany Medical College; [5]Nephrology Section, Stratton VAMC, Albany, NY.*

Background: Adequate dosing of antibiotics is paramount for treating infections in critically ill patients undergoing renal replacement therapy. Little is known about antibiotic removal by sustained low efficiency dialysis (SLED). To address this knowledge gap, we quantified removal of cefepime (C), meropenem (M), and vancomycin (V) in intensive care unit (ICU) patients undergoing SLED.

Methods: Adult patients aged ≥18 years with acute kidney injury (AKI) or end-stage renal disease (ESRD) admitted to the ICU and receiving C, M and/or V while undergoing SLED were eligible for inclusion. Blood and dialysate flow rates were maintained at 250 and 100 mL/min, respectively. Simultaneous arterial and venous blood samples for analysis of C, M, and V concentrations were collected at time 0 and hourly for up to 8 hours during SLED (on-SLED). Arterial samples were collected every 2 hours for up to 6 hours while not receiving SLED (off-SLED) for calculation of SLED clearance (CL), half-life ($t_{1/2}$) on-SLED and off-SLED, and the fraction of removal by SLED (f_D). Antibiotic concentrations were measured by liquid chromatography/mass spectrometry.

Results: Sixteen patients completed the study: 56% male, mean age (±SD) 52±14 years, and mean weight 96±28 kg. Eighty-eight percent had AKI and 10 patients were receiving V, 9 M, and 4 C. A polysulfone dialyzer (F50 or F160) was used for all SLED sessions and the mean ultrafiltration rate was 96±49 mL/hr. Pharmacokinetic data for each drug are shown in the table (data shown as mean ±SD).

Drug	SLED CL, mL/min	On-SLED $t_{1/2}$, hr	Off-SLED $t_{1/2}$, hr	f_D, %
Cefepime	70±21	4.3±0.9	15.4±8.5	67±15
Meropenem	72±12	4.0±1.1	7.2±3.1	42±18
Vancomycin	33±12	12.3±6.6	N/A*	49±15

*No significant drop in concentration over sampling interval.

Conclusions: An 8-hour SLED session led to significant elimination of C, M, and V. If SLED is performed, additional doses of these antibiotics are warranted to avoid subtherapeutic concentrations.

Funding: Private Foundation Support

SA-PO510

Displacer-Enhanced Hemodialysis for Treatment of Intoxications with Highly Protein-Bound Drugs: A Model-Based Analysis Xia Tao, Vaibhav Maheshwari, Doris H. Fuertinger, Peter Kotanko, Stephan Thijssen. *Renal Research Inst, NY, NY.*

Background: Over 9 million intoxication cases involving drugs were reported in the US in 2014. Hemodialysis (HD) is an appropriate treatment in life-threatening situations. However, the inefficiency of HD to remove highly protein-bound drugs limits its use to treat intoxications with such substances. We previously showed that infusing binding competitors (displacers) into the dialyzer blood inlet enhances the dialytic removal of protein-bound uremic toxins in a HD model. Here we report simulations using a novel mathematical model to predict the efficacy of displacer-enhanced HD for treating intoxications with highly protein-bound drugs.

Methods: The model comprises a multi-compartmental representation of the patient and spatiotemporal representation of the dialyzer, accounting for dynamic equilibrium of drug, albumin and albumin-drug complex. Carbamazepine and phenytoin were chosen as model substances to evaluate the efficacy of displacer-enhanced HD. Ibuprofen (800 mg over 2.5h; optimized infusion profile) and aspirin (1000 mg over 2.7h; optimized infusion profile) were used as displacers for carbamazepine and phenytoin, respectively. Q_b and Q_d were 250 and 500 mL/min, respectively. Distribution volume was 44 L in 70 kg male.

Results: Compared to conventional HD, non-toxic drug levels were achieved in a substantial shorter time with displacer-enhanced HD.

Table 1. Time required to lower plasma levels to therapeutic range.

Drug	Carbamazepine	Phenytoin
Mean peak overdose level (mg/l)	46	70
Protein binding	75%	90%
Primary albumin binding site	II	I
Native elimination	~60h	~58h
HD	5.5h	9.3h
Displacer-enhanced HD	2.5h	2.7h

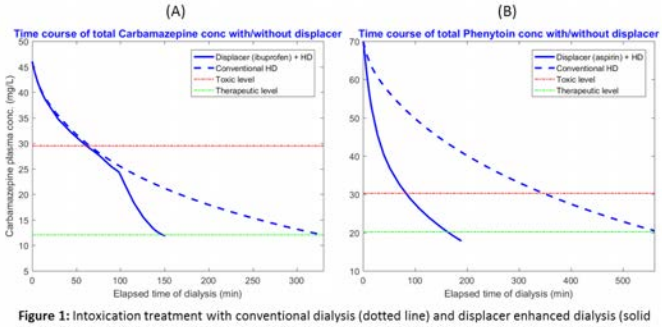

Figure 1: Intoxication treatment with conventional dialysis (dotted line) and displacer enhanced dialysis (solid line): (A) Carbamazepine removal with ibuprofen as displacer reduced HD duration by 180 min, (B) Phenytoin removal with aspirin as displacer reduced HD duration by 400 min. Time required by HD or Displacer enhanced HD denotes time to bring drug toxic concentration to therapeutic level.

Conclusions: Displacer-enhanced HD significantly improves the removal of highly protein-bound drugs. This efficacy gain may translate into resource savings and improved patient outcomes.

SA-PO511

Prediction and Validation of Hemodialysis Duration in Ethylene Glycol Poisoning Ioan-Andrei Iliuta,[1] Philippe Lachance,[2] Yannick Begin,[2] Fabrice Mac-Way,[2] Simon Desmeules,[2] Sacha A. De Serres,[2] Mohsen Agharazii.[2] *[1]Nephrology, Toronto General Hospital, Univ Health Network, Toronto, ON, Canada; [2]Nephrology, Hôtel-Dieu de Québec, Quebec City, QC, Canada.*

Background: Ethylene glycol (EG) poisoning is a fatal alcohol poisoning. Along with alcohol dehydrogenase (ADH) inhibition and supportive care, hemodialysis (HD) is required until correction of acidosis and serum EG level of < 3mmol/l. But, EG levels are not readily available, which could lead to under-dialysis or undue extension of HD. The aim of the present study is to define EG elimination half-life ($T_{1/2}$) during HD, use a training set to propose a $T_{1/2}$-based model for determining HD duration, and validate the model in a validation.

Methods: In a retrospective cohort study, we identified 26 episodes of EG in 24 subjects that met HD criteria. HD was performed using high-efficiency filters with a surface area > 2.0 m^2 , a blood flow of >350 ml/min and a dialysate flow of 750 ml/min. Using EG levels during HD, we calculated EG $T_{1/2}$ by one phase decay exponential regression analysis. Kinetic modelling was available for 21 cases, 2 of which were repeated poisoning. To predict HD duration, a training set used the 50th, 75th and 90th percentile of $T_{1/2}$ and target post-HD EG levels of 3, 2, 1 and 0.5 mmol/l. The optimal model was then validated in a validation set, and cross-validation was performed using leave-one-out approach.

Results: The overall elimination $T_{1/2}$ during HD, under ADH inhibition, was 158 min (95% CI 146-169). In the training set (n=12), the 50th percentile (165 min, 95% CI: 149-176 min) and a post-HD target level of 1 mmol/l provided the least difference in delivered versus predicted HD duration (13 min, 95% CI: -138 – 132 minutes), and assured a post-HD EG level of < 3mmol/l in all patients. In the validation set (n=7), all patients achieved a post-HD EG level of < 3 mmol/l and a difference between delivered versus predicted HD duration was -21 min (95%CI: -117 – 86). A cross-validation confirmed these findings.

Conclusions: Using an EG T1/2 of 158 min with high-efficiency HD, and a post-HD target EG level of 1 mmol/l, HD duration can be predicted accurately while assuring a safe post-HD EG level.

Funding: Government Support - Non-U.S.

SA-PO512

Cystatin C-Guided Vancomycin Dosing Improves Target Trough Achievement in the Critically Ill Compared to Standard Care with Creatinine Clearance Erin N. Frazee, Andrew D. Rule, John C. Lieske, Kianoush Banaei-Kashani, Jason N. Barreto, Abinash Virk, Philip Kuper, Ross Dierkhising, Nelson Leung. *Mayo Clinic, Rochester, MN.*

Background: A cystatin-C inclusive vancomycin dosing algorithm may improve target trough achievement compared to serum creatinine-guided therapy in critically ill patients.

Methods: Patients initiated on intravenous vancomycin in three intensive care units at a single tertiary medical center were studied. Dosing regimens were selected and implemented after an individualized target vancomycin trough (10-15mg/L or 15-20mg/L) was established. Between 01/2012-10/2013 vancomycin was dosed according to serum creatinine (historical controls). From 12/2013-05/2015 a novel vancomycin algorithm was implemented which used the $CKDEPI_{creatinine\text{-}cystatin\ C}$ eGFR to guide dosing (prospective intervention arm). Steady state target trough achievement was compared between the two study arms with and without adjustment for potential confounders.

Results: Patients in the intervention arm (N = 135) experienced significantly greater target trough achievement than historical controls (N = 264) [(50% vs. 28%; OR 2.53 (95% CI 1.65, 3.90); P < 0.001)]. Group differences persisted after adjustment for age, sex, APACHE III score, fluid balance, baseline creatinine clearance, operative admission diagnosis, presence of sepsis, and goal trough range [adjusted OR 2.79 (95% CI 1.76, 4.44); P < 0.001]. There was no difference in treatment failure, acute kidney injury, renal replacement therapy or death between treatment arms.

Conclusions: Use of a combined serum creatinine and cystatin C-based vancomycin dosing nomogram significantly improved target trough achievement among critically ill patients with stable renal function. Further studies are warranted to characterize the relationship between use of cystatin C-guided dosing and clinical outcomes.

SA-PO513

Nephrotoxicity Associated with Concomitant Vancomycin and Standard Infusion versus Extended Infusion Piperacillin-Tazobactam in Obese Patients Justin G. Horowitz, Roberto L. Collazo-Maldonado. *Nephrology, Methodist Health System, Dallas, TX.*

Background: Researchers have alluded to improved pharmacodynamic activity and clinical outcomes by extending the infusion time of piperacillin-tazobactam (PT) from 30 minutes to 4 hours. Over the past 2 years there has been discussion in the literature of a potential synergistic nephrotoxicity using PT with vancomycin (VANC). Therefore, it is prudent to identify if the infusion rate of PT may mitigate this synergistic effect.

Methods: This was a single-center, retrospective chart review. Patients were identified if they received VANC concomitantly with PT from September 2013 through August 2015. Patients were included if they received this antibiotic combination for >48 hours, a BMI ≥30 kg/m^2. Any patient with history of CKD or admitted to an ICU were excluded. Comparator arms both include VANC, however the standard infusion group received PT administered over 30 minutes as compared to the extended infusion receiving a 4 hour infusion. The primary outcome is incidence rate of acute kidney injury (AKI) defined as an increase in SCr by 0.5 mg/dL or 50% from baseline. Secondary outcomes include time to AKI, and identification of contributing risk factors.

Results: A total of 158 patients were included in total. Patients were predominately female (58%), and had a mean body mass index of 39.0 kg/m^2. The average daily dose of PT was 14.2 and 11.6 grams for standard versus extended infusion, respectively. For the primary outcome, 29% patients in the standard PT infusion arm and 32% of patients in the extended infusion arm experienced an AKI (p=0.68). Time to AKI was between 3-4 days in both cohorts (p=0.88). Univariate analysis shows that higher doses of PT may independently implicated in causing nephrotoxicity with vancomycin (OR 1.2, 95% CI 1.06-1.38; p<0.05).

Conclusions: Although there was no statistically significant difference in the incidence of AKI in patients receiving concomitant VANC and standard versus extended infusion PT, patients receiving higher doses of PT may be at greater risk of developing AKI. This is a concern when using standard infusion PT as it is dosed more frequently and therefore associated with higher daily doses.

SA-PO514

Chemotherapy Dosing prior to Hemodialysis in Cancer Patients with Kidney Failure Frieder Keller. *Innere 1, Univ Hospital, Ulm, Germany.*

Background: In cancer patients, the incidence of acute kidney injury is 15 – 45 % per year. Due to growing age, chronic kidney disease is prevalent with 20 – 50 % in this population. On the other side, the pharmacokinetics depend on kidney function in 31 of 68 essential anti-cancer drugs (46 %). To adjust for kidney function, the dose frequently is reduce. Independent from kidney function, chemo-therapy was underdosed in 30 % of cancer patients with a negative impact on survival [Br J Cancer 2002].

Methods: Only few case reports or small case series are published on dosing of chemotherapy in cancer patients with kidney failure. Most experts plead for chemotherapy administration after dialysis [Semin Dial 2015]. We have reviewed the literature and extracted the concept to administer the dialyzable anticancer drugs prior to hemodialysis. According to our own experience [Eur J Haematol 2005], the chemotherapy administration before hemodialysis might allow for a higher, near normal dose without inacceptable toxicity.

Results: We have found 28 PubMed cited papers where the concept to administer high and near normal standard dose chemotherapy prior to hemodialysis is proposed for 17 drugs. At least 30 % of these drugs is eliminatied by dialysis. To simulate normal kidney function, however, hemodialysis should start 2 hours after cessation of the chemotherapy infusion and hemodialysis should be repeated on a daily basis for 4 to 6 days.

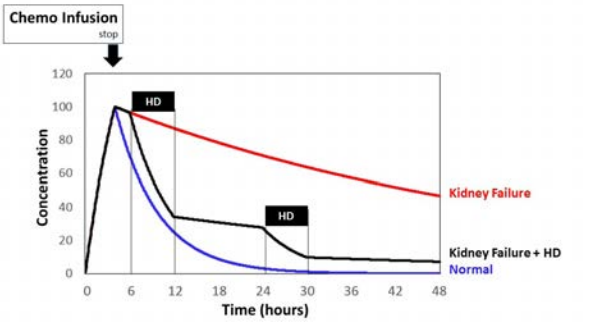

Figure 1: Concept of standard dose chemotherapy prior to hemodialysis (HD) in patients with kidney failure.

This concept has been reported for bleomycin, capecitabine (FBAL), carboplatin, cisplatin, cyclophosphamide, cytosine-arabinoside, fludarabine (2F-Ara-A), gemcitabine (dFdU), ifosfamide, iodine 131, irinotecan (SN-38), lenalidomide, methotrexate, oxaliplatin, pemetrexed, S-1 (tegafur), and topotecan.

Conclusions: Efficacy and safety of 17 essential chemotherapeutic agents could be improved by immediate post-infusion hemodialysis in patients with kidney failure.

SA-PO515

Cetuximab Prevents Methotrexate-Induced Nephrotoxicity Through Epidermal Growth Factor-Dependent Signaling Rosalinde Masereeuw,[1] Pedro Caetano Pinto,[1] Amer A. Jamalpoor,[2] Janneke Ham,[3] Carla Van Herpen,[3] Martijn J. Wilmer.[2] *[1]Pharmacology, Utrecht Inst for Pharmaceutical Sciences, Utrecht, Netherlands; [2]Pharmacology and Toxicology, Radboud Univ Medical Center, Nijmegen, Netherlands; [3]Medical Oncology, Radboud Univ Medical Center, Nijmegen, Netherlands.*

Background: A novel phase I/IIb study investigates the efficacy of combining methotrexate (MTX) with the epidermal growth factor receptor (EGFR) recombinant antibody cetuximab (CTX) in treatment of locally advanced head and neck squamous cell carcinoma. Here, we studied the effect of CTX on renal MTX handling by organic anion transporter 1 (OAT1), breast cancer resistance protein (BCRP) and multidrug resistance protein 4 (MRP4) in a renal cell model.

Methods: Conditionally immortalized proximal tubular epithelial cells over-expressing OAT1 (ciPTEC-OAT1) were used to examine activity and expression of OAT1, BCRP and MRP4 upon treatment with EGF (10 ng/ml), CTX (500 µg/ml) or the mitogen-activated protein kinase (MEK) inhibitor, U-0126 (2 µM). Nephrotoxic effects of MTX were determined using dimethylthiazol bromide (MTT) assay.

Results: MTX inhibited fluorescein uptake to 56±6% ($p<0.05$),decreased Hoechst33342 efflux to 71±5% ($p<0.05$) and chloromethylfluorescein-diacetate (CMFDA) to 58±5% ($p<0.05$), confirming the role of OAT1 in uptake and BCRP and MRP4 in renal efflux, resp. CTX reversed the EGF-increased expression of OAT1 to 32.2±1.3% ($p<0.05$) and BCRP to 32.0±9.7% ($p<0.05$), as well as their membrane expressions, while MRP4 was increased by 182±57% ($p<0.05$). This was supported by a decreased fluorescein uptake (to 68±1%; $P<0.01$) together with a decrease in Hoechst efflux (to 71±2%; $p<0.05$) and enhanced CMFDA efflux (by 133±6%; $p<0.05$). Furthermore, U-0126 decreased the functional expression of OAT1 (64±7%; $p<0.01$) and BCRP (67±7%, $p<0.05$) in EGF-stimulated cells, confirming EGFR-MEK signaling. Exposure of ciPTEC-OAT1 to MTX (100 µM) for 24h reduced viability to 40±3% ($p<0.05$), which was reversed by CTX or U-0126.

Conclusions: CTX downregulates OAT1 and BCRP while upregulating MRP4 via EGFR signaling. Further, CTX could prevent MTX-induced nephrotoxicity, which may open possibilities for nephroprotective co-medication therapies.

Funding: Government Support - Non-U.S.

SA-PO516

Peak Platinum Excretion Correlates with Novel Urinary Biomarkers in Cancer Patients Receiving Cisplatin-Containing Therapy Melanie S. Joy,[1] Blessy George,[1] Marie Madeleine Gomez,[1] Nickie Lee Mercke,[1] Xia Wen,[2] Brian Buckley,[2] Daniel Bowles,[1] Cindy L. O'Bryant,[1] Lauren Aleksunes.[1] *[1]Skaggs School of Pharmacy, Cancer Center, and Renal Diseases and Hypertension, Univ of Colorado, Aurora, CO; [2]Ernest Mario School of Pharmacy, Rutgers Univ, Piscataway, NJ.*

Background: Novel biomarkers are under investigation for detecting kidney injury. Given the limitation of measuring cisplatin in patient kidneys, urinary Pt may be a quasi-marker of exposures and toxicity. The current study determined Pt PK and urinary biomarkers.

Methods: Blood (0-6h) and urine (0-6h) were obtained from cancer patients (n=11) receiving cisplatin. Pt was quantified using ICP/MS. PK analysis was conducted using Phoenix®. Urinary biomarkers were measured using a multiplex assay at baseline, 3 and 10 days post-cisplatin.

Results: Patient characteristics were age 58±10 y, 11 Caucasian/2 other, 8 male/5 females, BSA 1.9 m^2, dose (53.5±19 mg/m^2). Pt PK parameters were C_{max} 2.8±1.0µg/mL, $AUC^{0-\infty}$ 28.6±19.5mg h/L, volume 55.3±15.7L, clearance 5.4±3.6L/h. No significant correlations between C_{max} (as the driving force for urinary excretion) and peak urinary biomarkers were observed. Peak Pt excretion (20.9±12.2 µg/mL) occurred in the 0-2 h urine collection. Significant relationships (R^2) were found between peak Pt excretion and urinary biomarkers.

Table 1. Correlations Represent R^2 Values	Urine Pt	P-value
KIM-1	0.6406	0.0048
TFF3	0.8106	0.0005
Osteopontin	0.7849	0.0007
NGAL	0.7974	0.0006
Cystatin C	0.7424	0.0014
B2M	0.8584	0.0002
Albumin	0.7968	0.0006
MCP-1	0.0268	0.3368
GST pi-1	0.5268	0.0134
Clusterin	0.5822	0.0084
Calbindin	0.7773	0.0008
IL-18	0.7424	0.0014

Conclusions: The results from this comprehensive study corroborate a high degree of agreement between peak Pt and biomarkers in urine. Given the high degree of exposure of proximal tubule cells to Pt through transporter pathways in the kidney, the results suggest a direct mechanism between kidney exposures and toxicity. Future studies will employ physiologically-based PK to fully understand the relationships between kidney exposures and toxicity.

Funding: NIDDK Support

SA-PO517

Effect of Experimental Kidney Disease on the Formation of TMAO by Flavin-Containing Monooxygenases Alexander J. Prokopienko,[1] Daniel P. Schrum,[1] Adam Fitch,[1] Alison Morris,[1] François A. Leblond,[2] Vincent Pichette,[2] Thomas D. Nolin.[1] *[1]Schools of Pharmacy and Medicine, Univ of Pittsburgh, Pittsburgh, PA; [2]Service de Néphrologie et Centre de Recherche, Hôpital Maisonneuve-Rosemont, Montréal, QC, Canada.*

Background: Cardiovascular disease (CVD) is the leading cause of death in kidney disease (KD) despite aggressive management of traditional risk factors. As such, non-traditional risk factors have received attention as potential therapeutic targets. Systemic exposure of the microbiota-derived metabolite trimethylamine-*N*-oxide (TMAO), which is associated with poor CVD outcomes, increases in KD disproportionately to reductions in renal clearance. Flavin-containing monooxygenases (FMO) oxidize trimethylamine (TMA) to form TMAO and are an important class of drug metabolizing enzymes. We hypothesize that FMO activity is increased in the setting of KD, leading to increased TMAO formation. Therefore, we aimed to assess the effect of experimental KD on FMO activity using TMA as a substrate.

Methods: Microsomes were isolated from liver tissue of KD (5/6thnephrectomized) and control rats (n=7 and 6, respectively). Microsomal incubation conditions were optimized, then enzyme kinetics were determined and compared between groups. TMAO was measured via LC-MS, and formation rate of TMAO was used as an indicator of hepatic FMO activity. Also, in a subset of rats (n=3 KD, n=4 control), serum TMAO concentrations were determined at sacrifice, and exploratory 16S DNA sequencing of intestinal scrapings was performed to compare TMAO exposure and microbiomes.

Results: Metabolic formation of TMAO was significantly increased by 25.6% in KD compared to control rats (Vmax 67.09 ± 1.87 vs. 53.41 ± 2.25 µM/mg protein/hr, $p<0.0001$). No significant differences in Km were observed. No differences in Alpha and Beta diversity metrics were observed in the 16S DNA sequencing between KD and control intestinal scrapings. The median TMAO concentration was increased 16-fold in KD compared to control (64.35 vs. 3.78 µM, $p<0.0385$).

Conclusions: These results suggest that FMO activity increases in kidney disease and may contribute to dramatically increased systemic exposure of TMAO.

Funding: NIDDK Support, Private Foundation Support

SA-PO518

First-in-Human Study of TP0463518, a Novel Oral Hypoxia Inducible Factor Prolyl Hydroxylase (HIF-PH) Inhibitor with Liver-Specific Erythropoietin Secretion Hidekazu Ochiai, Fumihiko Sato, Shota Tokuyama, Kunika Kikumori, Fuki Kurimoto, Noriko Takayama, Saeko Uchida, Tomohiro Sugimoto, Hiroyuki Tamaoki. *Taisho Pharmaceutical Co., Ltd., Tokyo, Japan.*

Background: TP0463518 is a novel potent HIF-PH inhibitor being developed for renal anemia treatment and induces endogenous erythropoietin (EPO) secretion. It is well-known that kidney is the dominant organ of EPO production. However, TP0463518 had a unique feature to induce liver-specific EPO secretion in bilaterally nephrectomized rats. The purpose of this human study is to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD: EPO) of TP0463518, a liver-specific EPO inducer after single oral administration.

Methods: In this first-in-human, double-blind, placebo controlled and single administration study, 40 Japanese healthy male subjects were randomized to TP0463518 (3, 6, 11, 20, and 36 mg) or placebo.

Results: C_{max} and $AUC_{0\text{-}72h}$ of plasma TP0463518 concentration increased in a dose-dependent manner after single oral administration of 3 to 36 mg of TP0463518. T_{max} and $T_{1/2}$ were 1.2 to 2.0 and 5.9 to 7.4 hours, respectively. Throughout the study, TP0463518 was well-tolerated and no remarkable adverse events occurred. Baseline EPO levels in serum were similar among all treatment groups (9.6±2.8 and 8.1±3.8 mIU/mL, respectively, N=6), which were all within reference range. TP0463518 increased serum levels of EPO in a dose-dependent manner. Serum levels of EPO after TP0463518 oral administration were 33.5±18.3 mIU/mL at 6 mg and 278.2±155.3 mIU/mL at 36 mg (respectively, N=6). The EPO levels returned to baseline level within 24 to 48 hours at all doses tested. Changes in levels of serum EPO after TP0463518 administration was correlated with C_{max} of plasma TP0463518 concentration (r=0.85). Moreover, a correlation between $AUC_{0\text{-}72h}$ of serum EPO and that of plasma TP0463518 was observed (r=0.82).

Conclusions: TP0463518 was well-tolerated, showed favorable PK profiles, and dose-dependently increased EPO levels in serum, possibly derived from the liver. These results indicate that TP0463518 will be a unique drug for the treatment of renal anemia.

SA-PO519

HTS Assay Based Discovery of Novel CD11b Agonists as Potential Therapeutics for Lupus Nephritis Xiaobo Li, Samia Khan, Vineet Gupta. *Rush Univ.*

Background: Systemic lupus erythematosus (SLE, lupus) nephritis is characterized by renal interstitial leukocytic recruitment that leads to chronic renal insufficiency in up to 30% of affected patients. Integrin CD11b/CD18 is critical for leukocyte adhesion and migration during inflammation and tissue injury. We previously used a cell-based, high-throughput screening (HTS) assay to identify small molecule CD11b agonists termed leukadherins that reduce leukocyte recruitment and inflammation in several disease models. Here we use this HTS assay to identify more novel CD11b agonists as potential therapeutics for lupus nephritis.

Methods: We used a cell-based HTS assay to screen a chemical library of >90,000 molecules for compounds that affected the adhesion of K562 cells that expressed CD11b/CD18 at the cell surface to the fibrinogen ligand. CD11b/CD18 K562 cells were exposed to titrating concentrations of molecules and the candidates with the lowest effective dose 50 (EC_{50}) were selected to investigate further.

Results: Using the HTS-adhesion assay, we screened a total of 90,000 molecules in a chemical library and determined 33 potential candidate molecules that bound to CD11b/CD18 K562 cells at $EC_{50} < 6\ \mu M$.

Conclusions: We will further investigate the anti-inflammatory properties of these newly selected candidates in vitro and in vivo. We will compare the efficacy of the new candidates, M1/70 a CD11b antagonist antibody, and CD11b agonist leukadherins in an anti-glomerular basement membrane nephritis model. We suggest that we can utilize this HTS assay to identify integrin-specific, small-molecule agonists that can provide effective therapeutics for lupus nephritis.

Funding: NIDDK Support

SA-PO520

Development of a Novel Drug Formulation to Enhance Mesangial Deposition in Glomerulonephritis Uma R. Fogueri,[1] Gavriel Roda,[1] Georgia Charkoftaki,[1] Michael F. Wempe,[1] Joshua M. Thurman,[2] Melanie S. Joy.[1,2] *[1]Skaggs School of Pharmacy and Pharmaceutical Sciences, Univ of Colorado, Aurora, CO; [2]Div of Renal Diseases and Hypertension, Univ of Colorado, Aurora, CO.*

Background: Optimal kidney mesangial deposition for drug delivery vehicles are size 10-100 nm and neutral to negative charge. The overall goals of this project were to develop a novel nanoemulsion of the tyrosine-kinase inhibitor, Imatinib Mesylate (ImM NE), and evaluate pharmacokinetics (PK) when dosing naked vs. NE formulations to MRL/lpr (lupus) and MRL/MpJ (control) mice.

Methods: ImM was dispersed in fish oil droplets via a protocol and filter extrusion was performed to achieve a desired particle size of 80 nm. The ImM NE physical characteristics were evaluated. A 200 µL volume (28 µg) of ImM NE or naked ImM was injected (tail vein) into MRL/lpr (n=11) and MRL/MpJ (n=12) mice. Serial blood samples (25 µL) were obtained and applied to dried blood spot (DBS) cards. An LC-MS/MS assay was developed to measure ImM from DBS. ImM PK analysis was performed using Phoenix®. Differences in PK between ImM naked and NE were evaluated by Instat®.

Results: The ImM NE exhibited optimal characteristics for enhanced mesangial deposition; particle size 60-80 nm and zeta potential -4.226 ± 0.496 mV. The ImM NE was stable at pH 7.4 for up to 72 h. ImM PK showed significantly higher Vd and plasma clearance with the NE, while the naked formulation showed higher plasma Cmax and $AUC^{0\text{-}\infty}$.

Table 1	ImM NE	Naked ImM	p-value
Cmax (ng/mL)	957±414	1622±455	0.0015
$AUC^{0\text{-}\infty}$ (µg min/mL)	77.3±33.2	106±24.1	0.0320
Vd (mL)	33.6±18.7	17.6±4.8	0.0121
Clearance (mL/min)	27.0±14.0	16.7±4.2	0.0367
Lambda (min^{-1})	0.014±0.002	0.016±0.001	0.0041

Conclusions: The formulation demonstrated optimal characteristics for enhanced mesangial deposition and stability. The ImM PK was significantly different between formulations and suggested higher tissue disposition with the NE. Tissue ImM data are pending to confirm enhanced deposition to kidney mesangium. Future studies will evaluate biodistribution of the NE via imaging and relationships to lupus outcomes (kidney biomarkers and ds-DNA).

Funding: Clinical Revenue Support

SA-PO521

Mouse Models Treated with Therapeutic Recombinant ACE2 with Long Plasma Half-Life Showed Potent Blood Pressure-Control Effects Pan Liu, Jan A. Wysocki, Minghao Ye, Daniel Batlle, Jing Jin. *Dept of Medicine-Nephrology/Hypertension, Feinberg School of Medicine, Chicago, IL.*

Background: Angiotensin-converting enzyme 2 (ACE2) is a plasma membrane anchored monocarboxypeptidase that potently degrades angiotensin II (Ang II) to form angiotensin-(1-7). Recombinant ACE2 enzymatic ectodomain (termed sACE2) has been shown to have protective effects in several mouse disease models caused by activation of renin-angiotensin system. However, due to the very short plasma half-life of sACE2, the therapeutic potential of such treatment is limited. To circumvent this problem, we made a recombinant fusion of sACE2 with the constant region (Fc) of human immunoglobulin IgG1 to increase its plasma stability.

Methods: We constructed a plasmid to express a fusion protein of ACE2 (amino acid 1-740) and Fc. We transfected HEK293 cells with the plasmid and established a stable cell line that produces this sACE2-Fc protein into the culture medium. The recombinant enzyme was purified from serum-free culture medium by chromatography and the enzyme activity was verified. Following a single i.v. injection of 50ug enzyme to mice, the pharmacokinetics of ACE2 activity in the plasma and the ability of this enzyme to prevent angiotensin II–induced hypertension was monitored. The untagged sACE2 was used as control.

Results: The recombinant sACE2-Fc has its enzymatic activity comparable to that of untagged sACE2 as measured by their catalysis rates of Ang II. Notably, the Fc fusion significantly extended the plasma half-life of sACE2 from less than 10 min to 9 days, representing an increase of over 1000 times in blood residence time. The single i.v. injection of sACE2-Fc showed long-lasting effect on preventing bolus angiotensin II-induced high blood pressure for up to 2 weeks. By contrast, as short as 4 hours after injection of the untagged sACE2 control, its effects on blood pressure no longer exist.

Conclusions: Our results suggest that fusion of Fc greatly increases recombinant sACE2 plasma stability. This feature could make sACE2 a more effective therapeutic agent for blood pressure control.

SA-PO522

In Vivo siRNA Knockdown of LRP2 (Megalin) in Mice Michael T. Eadon, Yinghua Cheng, Kelly J. Mason, Pierre C. Dagher. *Nephrology, Indiana Univ, Indianapolis, IN.*

Background: siRNA stabilized with 2'O-methylation is filtered and reabsorbed in the renal proximal tubule (PT) following IV administration, reducing gene expression temporarily in the PT. Prior siRNA efforts have focused on preventing up-regulation of candidate genes in response to injury or disease. We instead proposed to reduce gene and protein expression of *LRP2* (megalin), which is constitutively expressed, in order to better understand the molecular regulation of this protein.

Methods: 2'O-methylated siRNA targeting mouse *LRP2* (si*LRP2*) was commercially obtained. Using si*LRP2*, reduction of *LRP2* gene expression was confirmed as compared to scrambled siRNA (siSCR) in mouse S1 PT cells with RT-PCR. For *in vivo* use, C57bl/6 mice were obtained and tunneled intra-jugular catheters were placed. si*LRP2* administration was optimized for: dose, site of administration, carrier solution, frequency of administration, and duration of administration. Kidney cortex, liver, lung, and blood were collected upon animal sacrifice. Pharmacodynamic measures of gene and protein expression were compared by RT-PCR, western blot, and immunohistochemistry (IHC).

Results: Compared to siSCR, si*LRP2* reduced gene expression in S1 PT cells to 16.6% (SD 0.6%). Gene expression reduction *in vivo* varied considerably depending on conditions. Under optimized conditions measured 3 h after administration, si*LRP2* reduced gene expression in mouse kidney cortex to 22.8% (SD 25%) as compared to siSCR mouse kidney cortex expression. Time course studies indicate that gene expression remains reduced at 6 h post-si*LRP2*, but increased at 24 h (170%, SD 26%). No discernible decrement in megalin renal protein expression was observed by either western blot or IHC under any condition, even with a maximized twice daily dose for 4 days. si*LRP2* reduced liver *LRP2* expression; however, lung and whole blood expression did not change significantly due to the low expression of *LRP2* in these tissues at baseline.

Conclusions: Megalin is a protein with constitutive expression and a long half-life. Although *LRP2* renal gene expression reduction can be achieved with siRNA, siRNA as an intervention to reduce *in vivo* megalin protein expression is difficult and not cost effective at present.

Funding: Private Foundation Support

SA-PO523

A Predictive Modeling of Tacrolimus Pharmacokinetic Parameters Based on a High-Throughput Genetic Screening Approach Nicolas Pallet,[1] Margaux Luck,[2] Eric Thervet,[1] Cecilia Damon.[2] *[1]Hôpital Européen Georges Pompidou; [2]Inst Hypercube.*

Background: *CYP3A4* and *CYP3A5* variants explain only a part of the variation in Tacrolimus (Tac) metabolism suggesting the involvement of a wider network of candidate genes. Therefore, other candidates are likely to explain the genetic basis for interindividual variability in dose adjusted Tac concentrations (Tac C_0). Given the high level of inter-dependence between individual genes, we can assume that any biochemical reactions underlying drug responses could not depend on individual gene-drug correlations but rather on a group of genes.

Methods: Based on a high-throughput genetic screening approach, we aimed to identify a set of covariant germline polymorphisms predictive of the interpatients Tac pharmacokinetics variability in kidney transplantation. Tac C_0 of 229 kidney transplant recipients were monitored at each follow-up time after transplantation during three months. We developed a predictive multivariate approach integrating an ensemble features selection scheme based on Fisher's test and Mutual Information, and a temporal multivariate predictive modeling with Partial Least Squares regression.

Results: At days 60 and 90 and over all days, the predictive models explained 70.2%, 62.9% and 22.9% of total log(Tac C0/Dose) variability with 44, 33 and 16 genes, respectively (p-value<0.003 with a permutation test). As expected, these models included the *CYP3A4* and *CYP3A5* variants, and highlight molecular networks of drug metabolism and oxydoreductase activities. In addition, we have identified a variant of the gene encoding SLC28A3, a nucleoside transporter, as a potential candidate gene. Carriers of the SLC28A3 rs10868152, which is an intronic variant without linkage disequilibrium, have consistently lower Tac C_0/Dose, both in the discovery cohort, and in an independent validation cohort of 189 kidney transplant recipients.

Conclusions: Genes variants networks explain 30 to 70% of the inter-patient variability of Tac metabolism; genes interaction networks related to oxydoreduction functions and mono-oxygenase activity have a major impact on Tac metabolism; unexpectedly, purine transporters appear to be involved in Tac metabolism and biodisponibility.

SA-PO524

A Functional SNP at MiR-582-5p Binding Site in Calcineurin Subunit PPP3R1 Leads to Tacrolimus Resistance in Idiopathic Membranous Nephropathy Patients Ying Zhu, Jun Xue, Chuanming Hao. *Nephrology, Huashan Hospital.*

Background: Pharmacokinetic information alone appears to be insufficient to explain the variable drug response. The study explored the contribution of polymorphisms in the genes encoding tacrolimus drug target (calcineurin) on the interpatient variability of its efficacy in idiopathic membranous nephropathy (IMN) patients.

Methods: We searched for variants in the genes encoding calcineurin (PPP3CA, PPP3CB, PPP3CC, PPP3R1 and PPP3R2) by whole-exome sequencing in 8 IMN patients who received tacrolimus, including 4 with complete (CR) or partial remission (PR), 4 with no response (NR). The variants found were genotyped in another 12 patients (5 with CR or PR, 7 with NR). All patients had tacrolimus trough blood concentrations in the target range. The associations of these variants with the response to tacrolimus were analyzed. The functions of the meaningful variants were further investigated in human peripheral blood mononuclear cells (PBMCs) and other cell lines.

Results: A total of 19 variants were observed. Logistic regression analysis showed that the C allele of rs875 (a T-to-C nucleotide change in the 3'UTR of PPP3R1) was significantly associated with an increased risk of tacrolimus resistance (P=0.0205, OR=12.5, 95% CI: 1.089–143.421). As compared with the TT genotype in rs875 (n=25), the TC/CC genotype (n=58) had a higher PPP3R1 protein expression level in human PBMCs as assessed by immunoblot (P=0.0163). Bioinformatics analysis predicted that the C allele of rs875 disrupted a binding site for miR-582-5p. Co-transfection of miR-582-5p and PPP3R1 3'UTR luciferase reporter vector demonstrated that a significantly higher luciferase activity was observed in the rs875 CC construct when compared with the rs875 TT construct (P<0.05). MicroRNA mimics transfection showed that miR-582-5p suppressed PPP3R1 expression in cultured human podocytes with TT genotype, but not in cells with TC genotype (P<0.05).

Conclusions: Our findings suggest that rs875 may contribute to the risk of tacrolimus resistance in IMN patients through disrupting the regulatory role of miR-582-5p on PPP3R1 expression. Besides pharmacokinetics, pharmacodynamics should also be taken into account in improving tacrolimus therapy.

SA-PO525

CYP 3A5 Genotype and Race Association to Tacrolimus Pharmacokinetics Kathleen M. Tornatore,[1,4] Daniel Brazeau,[2] Gregory E. Wilding,[3] Louise M. Cooper,[1] Rocco C. Venuto.[4] *[1]School of Pharmacy; [2]School of Pharmacy; Univ of New England; [3]School of Public Health; [4]School of Medicine; Univ at Buffalo.*

Background: Variability in tacrolimus(TAC) dosing and pharmacokinetics(PK) between African American(AA) and Caucasian(C) renal transplant recipients(RTR) is attributed to cytochrome P450-3A5(CYP3A5) isoenzymes. The Clinical Pharmacogenetics Implementation Consortium(CPIC) TAC guidelines indicates CYP3A5*1*1 [Wild-type(W/T)] are Extensive Metabolizers(EM) and *3*3 [major variant] are Poor Metabolizers(PM) yielding racial differences in dose-normalized troughs and dosing. This study evaluated CYP3A5 genotype associations to TAC PK in AA and C RTR.

Methods: A 12-hr PK study determined trough(C12), C12/Dose(C12+), Area Under the Concentration Curve0-12(AUC12), AUC12/Dose(AUC*) and clearance(CL) in 32 C and 33 AA and C > 6 months post-transplant on steady-state TAC and mycophenolic acid. TAC dosages were adjusted to troughs of 4-9 ng/ml. CYP3A5 polymorphisms *1 and *3 *[rs776746]* were determined. CPIC defined phenotypes grouped by race were: **1*1(W/T)* [EM]; *1*3 [Intermediate Metabolizer (IM)] and *3*3[PM].

Results: EM-AA required twice the dosage compared to PM with comparable C12. EM-AA had 50% of the AUC* with rapid CL compared to PM. IM in AA and C had similar AUC* and CL while C had no EM.

TAC PK	Gr 1:EM-AA [n=12]	Gr 2:IM-AA [n=17]	Gr3:PM-AA [n=4]	Gr 4:IM-C [n=3]	Gr 5:PM-C [n=29]	P value	Pair wise comparison
Dose (mg)	5.4 (1.9)	3.9 (1.2)	2.8 (1.5)	3.3 (0.6)	2.3 (1.0)	<0.001	**Gr1 vs Gr2; Gr1 vs Gr3; Gr1 vs Gr5**
C12 (ng/ml)	7.0 (1.4)	8.3 (2.0)	7.9 (0.9)	6.2 (0.5)	6.7 (1.8)	0.045	None
C12+ (ng/ml/mg)	1.5 (0.7)	2.4 (0.8)	4.2 (3.4)	1.9 (0.2)	3.3 (1.4)	<0.001	None
AUC12 (ng.hr/ml)	125.6 (30.0)	146.6 (34.3)	130.5 (7.4)	106.0 (6.8)	115.5 (29.3)	0.016	**Gr1 vsGr3; Gr1 vs Gr5**
AUC* (ng.hr/ml/mg)	26.5 (11.2)	41.1 (12.6)	66.5 (48.7)	32.6 (6.80)	55.3 (21.4)	<0.001	**Gr1 vs Gr3; Gr1 vs Gr5**
CL (L/hr)	43.9 (16.5)	27.2 (10.6)	23.6 (15.2)	31.8 (7.4)	20.7 (7.2)	<0.001	**Gr1 vs Gr2; Gr1 vs Gr5**

Conclusions: Differences in TAC PK exist between race-CYP3A5 genotypes and support race-adjusted dosing requirements to individualize TAC regimens.

Funding: NIDDK Support, Pharmaceutical Company Support - Astellas

SA-PO526

Influence of Age and Race on Mycophenolic Acid Pharmacokinetics Post-Transplant Kathleen M. Tornatore,[1] Kris Attwood,[2] Louise M. Cooper,[1] Rocco C. Venuto.[3] *[1]Pharmacy, School of Pharmacy and Pharmaceutical Sciences; [2]Biostatistics, School of Public Health; [3]Nephrology/Medicine, School of Medicine and Biomedical Sciences; Univ at Buffalo.*

Background: Minimal data is available describing the influence of age on mycophenolic acid(MPA) pharmacokinetics (PK) in African American (AA) and Caucasian (C) renal transplant recipients (RTR) in spite of increased renal transplantation in the elderly. Our sub-study investigated the impact of age on MPA PK in stable AA and C RTR.

Methods: The 12-hour PK study of MPA were investigated in 35 AA and 32 C RTR receiving enteric coated MPA and tacrolimus. Validated gastrointestinal(GI) adverse effects(AE) ratings were assessed including diarrhea, dyspepsia and vomiting. Patients were categorized by age as follows: Young: >21 & ≤ 40 years; Middle Age: >40 &≤ 60 years and Elderly>60 years. Apparent clearance (CL), area under the concentration-time curve 0-12h(AUC12), dose-normalized AUC12 (AUC*), AUC 6-12 hours (AUC6-12), AUC6-12/AUC12 with GI AE were determined and analyzed with univariate ANOVA.

Results: Table summarizes the results. All groups were above the therapeutic MPA AUC12 guide of 60 mg.hr/L. The elderly exhibited the lowest C0, reduced enterohepatic recirculation(AUC6-12/AUC12) and greater GI AE.

Endpoints	Young (n=16)	Middle Age (n=38)	Elderly (n=13)	P Value*
e-GFR	57.06 (16.04)	52.97(14.26)	59.40 (19.26)	0.390
Dose (mg)	641.3 (185.5)	630.0(176.3)	595.4(135.2)	0.757
C0 (mg/L)	5.8(3.6)	4.8(5.2)	3.3(3.6)	0.019
AUC12 (mg.hr/L)	75.05(34.18)	66.84(30.68)	67.43 (28.54)	0.023
AUC*	0.12(0.06)	0.11 (0.05)	0.11(0.04)	0.076
CL (L/hr)	9.90 (4.32)	11.04(5.18)	10.21(3.83)	0.076
AUC6-12 (mg.hr/L)	30.96(16.81)	25.80 (21.03)	21.55 (12.96)	0.061
AUC6-12 / AUC12	0.40(0.12)	0.37(0.13)	0.30(0.11)	0.066
GI AE Score	2.31(1.62)	2.53(1.86)	2.62 (1.80)	0.054
* Race Adjusted Statistical Analysis				

Conclusions: These findings suggest that MPA dosing regimens need be individualized based upon age and race. Further evaluation of age-related changes in MPA exposure and relation to clinical responses(i.e. adverse effects) are important.

Funding: NIDDK Support, Pharmaceutical Company Support - Novartis Pharmaceuticals

SA-PO527

Micophenolic Acid Treatment in Long-Term Kidney Transplant Recipients

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Background: Therapeutic Drug Monitoring (TDM) of Micophenolic acid (MPA) has been clearly defined for the early post-transplant period while it has been less explored in the long-term follow-up. We evaluated TDM of MPA in long-term kidney transplant (KTx) recipients with immunosuppressive regimens combined with cyclosporine (Cya) or tacrolimus (FK).

Methods: We selected recipients with at least 2 years from KTx, on a stable dose of Myfortic (dMyf) and stable clinical conditions in the previous 6 months, not previously tested for MPA exposure. In these patients, for a maximum of 6 control visits, we collected: pro-drug MPA doses, MPA trough level concentrations (TLC) and exposure with limited sample strategy (AUC-LSS), hemoglobin (Hb), eGFR, albumin, TLC of metabolite 7-O-MPA-glucuronide (MPAG).

Results: We obtained a total of 180 samples (111 from patients on CyA and 69 from patients on FK). The CyA group had lower Hb (12,39±1,53 vs 14,17±1,16 g/dl), eGFR (44,8±15,9 vs 61,5±17,1 ml/min) and higher MPAG-TLC (94,28±38,68 vs 44,38±21,33 µg/ml) than FK group ($p<0,001$), and no significant difference in dMyf and MPA-TLC. In 15 volunteers (10 on CyA, 5 on FK) we performed AUC-LSS and 12 on 15 patients were in range 30-60 mg*h/L.

Conclusions: Despite CyA group was prone to increased clearance of MPA (e.g. type of calcineurin inhibitor, worst eGFR etc.), they presented the same dMyf and not different MPA-TLC than the FK group. This finding suggest that, in long-term KTx with decreased dose of CyA (C0 86,1±22,5 ng/ml), there may be a similar enterohepathic circulation for MPA with both CyA and FK immunosuppressive regimens. AUC-LSS of our study had a high percentage of patients in a proper MPA exposure, but this finding could be limited by estimation with LSS based on formulas for early KTx. Some patients in 30-60 mg*h/L range received very low dMyf (e.g. 360 mg/day in the CyA group). We speculate that there isn't a low limit dose, but only a proper or inadequate exposure to MPA.

SA-PO528

The Gut Microbiota and Drug Metabolism over Chronic Kidney Disease Progression

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Background: The hepatic drug metabolizing enzyme, cytochrome P450 3A (CYP3A), is downregulated in chronic kidney disease (CKD). The suspected cause is loss of renal clearance and subsequent retention of uremic toxins including indoxyl sulfate and p-cresyl sulfate. Differences in the gut microbiota between CKD and healthy patients further suggest that an increase in uremic toxin producing bacteria downregulates CYP3A. We aim to characterize the progression of CKD in terms of gut microbiota, uremic toxins and CYP3A expression to elucidate the mechanism of CYP3A regulation and potential targets for recovery.

Methods: Wistar rats were randomized into six groups defined by time of sacrifice (day 0, 3, 7, 14, 28 and 42). Each group (n=6) was pair-fed either control or CKD-inducing diet. mRNA expression of CYP3A and associated nuclear receptors (PXR/HNF4α) were determined by qPCR. CYP3A protein expression was determined by western blotting and the 16S rRNA gene from caecum swabs was amplified by Illumina sequencing. Metabolomics will be used to identify uremic toxins in plasma, tissues and feces.

Results: CKD significantly depleted CYP3A mRNA by day 14 (-83%, $P<0.001$) and persisted to day 42 (-83%, $P<0.001$). CYP3A protein expression followed a similar trend. PXR and HNF4α were decreased on days 14 and 28. Unsupervised principle component analysis of the cecum microbiota clearly separated CKD and control groups on day 14, 28 and day 42. Individual sequence analysis revealed an increase in bacterial genus *Turicibacter*, a novel finding in CKD.

Conclusions: Our model successfully indicated differences in bacterial composition across CKD progression. CYP3A expression is reduced in cohort with overt renal failure and occurs simultaneously as the observed bacterial changes, further supporting the hypothesised role of gut bacteria in CYP3A downregulation.

Funding: Government Support - Non-U.S.

SA-PO529

AZD9977 Is a Novel Mineralocorticoid Receptor (MR) Modulator with a Differentiated Mode of Action

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Background: Excess MR activation promotes target organ dysfunction, vascular injury and fibrosis. MR antagonists (eplerenone, spironolactone) improve outcomes in patients with heart failure, but their use in diabetic populations and in chronic kidney disease is limited by the target associated risk for hyperkalemia. Novel, potent and selective MR antagonists should ideally increase the therapeutic window by separation of organ protection from effects on electrolyte balance to avoid hyperkalemia. AZD9977 is a first in class, selective non-steroidal MR modulator that has been compared to eplerenone in preclinical studies.

Methods: Organ protection was studied in uni-nephrectomised (UNX) rats administered aldosterone via osmotic minipumps and fed a high-salt diet with compounds admixed for 4w. Acute effects of AZD9977 and eplerenone on aldosterone driven Na+ retention was tested in male rats on a low salt diet by administering a single dose and subsequent urine collection for 8h.

Results: In vitro, AZD9977 and eplerenone show similar potencies in competition binding experiments and in reporter gene assays. AZD9977 promotes nuclear translocation of MR in EA.hy926 cells expressing endogenous MR while eplerenone antagonises aldosterone mediated nuclear translocation. In UNX rats, 10, 30, 100 mg/kg AZD9977 or 10, 30 mg/kg eplerenone dose dependently reduced urine albumine to creatinine ratio in 24h urine after 4w and improved histopathology scoring of kidney and heart to similar extent. In acute testing, AZD9977 up to 100 mg/kg caused a minimal increase in urine Na+ while 3 to 100 mg/kg eplerenone led to a dose dependent substantially increased Na+ secretion. Co-administration of 100 mg/kg AZD9977 with 10 or 30 mg/kg eplerenone reduced eplerenone mediated Na+ secretion, suggesting a differentiated action for the two compounds in the same pathway.

Conclusions: AZD9977 is a novel differentiated MR modulator which in preclinical testing dissociates organ protective effects from effects on urine electrolytes, predicting a reduced risk for hyperkalemia compared to regular MR antagonists in the clinical setting.

Funding: Pharmaceutical Company Support - AstraZeneca R&D

SA-PO530

IgG/Creatinine Ratio in Spot Urine as a Prognostic Marker for Rituximab Therapy Outcome in Patients with Nephrotic Syndrome

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Background: Rituximab is a chimeric monoclonal antibody targeting CD20+ expressing B-cells and is used for a wide range of neoplastic and immune-mediated diseases. The nephrotic syndrome summarizes a group of syndromes such as proteinuria, edema, hyperlipidemia and hypoalbuminemia. As a second line option in therapy refractory patients, Rituximab is often successfully used to treat the nephrotic syndrome with dosages ranging from 375 mg/m² BSA to 1000 mg absolute. However, there are therapy resistant patients and we suspect the failure of therapy is caused by a urinary loss of Rituximab. Therefore we aim to find an association between proteinuria and the loss of Rituximab and therapy outcome.

Methods: Nephelometric analysis and flow cytometry was used to detect IgG and Rituximab concentration in urine probes of 11 nephrotic patients who were resistant to first line therapy and received either 375 mg/m² BSA or 1000 mg Rituximab. Therefore spot urine before and 24-hour urine collection samples within the first day of the therapy were examined. Daudi cells as a CD20 expressing B-cell line was used to determine the Rituximab concentration.

Results: The analysis of the urine samples revealed a loss of IgG before treatment and excretion of Rituximab within the first 24 hours of Rituximab infusion in all included patients, which was not observed in control patients, who also received Rituximab but displayed no proteinuria. The data indicates a correlation between IgG excretion before treatment and the level of reduction of proteinuria afterwards.

Conclusions: The preliminary results show that the determined IgG/creatinine ratio of spot urine before therapy may be a feasible and quick predictor of a Rituximab therapy success and might help for dosage adjustment.

SA-PO531

The Burden of Hepatorenal Syndrome (HRS)

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Background: This study evaluated the characteristics, medical visits, rates and days on dialysis, rates of liver and kidney transplants, and costs from the payer perspective of HRS patients covered by commercial and Medicare insurance in the United States.

Methods: Patients were identified from claims databases of commercially-insured (OptumHealth Reporting and Insights) and Medicare beneficiaries (5% Standard Analytic Files). At the time of their first inpatient admission with an HRS diagnosis ("index date") (ICD-9 code 572.4), commercially-insured patients were required to be age 18-64 and Medicare patients were required to be age 65+. Outcomes were assessed during the 30 days prior, and the 30, 60, and 90 days following index.

Results: 784 commercially-insured and 1,061 Medicare HRS patients met the sample selection criteria. Patients were primarily male (~60%) with a mean age of 54.1 among

commercially-insured and 74.1 among Medicare patients. After admission, median survival was short (commercial: 95 days; Medicare: 33 days). Within the first 30 days, the average stay was 11-12 days in both groups. Based on Kaplan-Meier analyses, 36% of commercially-insured and 26% of Medicare patients were readmitted within the next 30 days. Within the first 30 days, a substantial number of patients received dialysis (commercial: 30.5%; Medicare: 20.6%). Commercially-insured patients spent an average of 7.2 days on dialysis (not available in Medicare data). During follow-up, 10.7% of commercially-insured and 1.6% of Medicare patients received liver transplants while 1.4% and 0.2% received renal transplants, respectively. Average costs within the 90 day follow-up period were $157,665 for commercially-insured and $48,322 for Medicare patients, with most costs occurring within the first 30 days. The primary cost driver was inpatient visits (commercial: 90.3% of costs; Medicare: 83.1% of costs), with differences between the populations associated with lower mortality, higher transplant rates, and higher dialysis rates among the commercially-insured.

Conclusions: HRS is associated with high mortality and rates of nephrology-related healthcare resource utilization and imposes a significant economic burden.

Funding: Pharmaceutical Company Support - Mallinckrodt Pharmaceuticals

SA-PO532

Temporal Trends in the Rates of Acute Kidney Injury across Healthcare Settings in the Irish Health System

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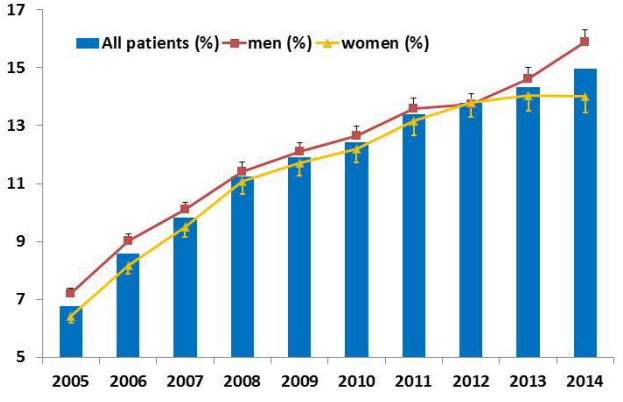
Background: Complete ascertainment of the true rates of acute kidney injury (AKI) and emerging trends are essential for the deployment of robust management within health systems. We determined the incident rates of first AKI and annual trends from 2005-2014 in the Irish Health System.

Methods: Health data from regional information systems were linked with mortality data from 2005 to 2014 (n=587,087). AKI events were identified as per KDIGO guidelines. Incidence rates (per 1000 patients) were calculated for each year, by county, geographic region, location of medical supervision [Emergency room (ER), General practice (GP), Inpatient (IP), Outpatient (OP) Outside facility (OF)]. Analysis were conducted using general linear modeling and logistic regression.

Results: Average age was 47.3 ±19 years and 47% were men. AKI incidence rates increased significantly from 6.78 (6.60, 6.96) in 2005 to 14.96 (14.55, 15.37) in 2014 per 1000 patients. Rates were higher in men than in women, increased with advancing age, varied by county of residence, by region and by location of medical supervision, P<0.001 for all. From 2005 to 2014, the rates of AKI increased in IP (35.76 to 52.25/1000), in ER (from 8.41 to 20.44/1000), in OP (7.23 to 22.16/1000), in OF (3.0 to 9.21/1000, P< 0.001), and in GP (1.01 to 4.13/1000), P <0.001 for all trends. The likelihood of AKI was substantially higher in 2014 (OR=4.74, 95% CI: 4.12, 5.45) vs 2005 (OR= 1.00, referent).



Conclusions: AKI rates have increased substantially in the Irish health system over time and in all healthcare settings. Given the scale of the problem, a national strategic plan is necessary to reduce AKI events and avoid adverse consequences.

Funding: Government Support - Non-U.S.

SA-PO533

Acute Kidney Injury Exerts Greater Impact on Mortality in Younger Men and Women Than among Older Patients within the Health System

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Background: Recent studies have shown that acute kidney injury (AKI) independently predicts mortality. However it is unclear whether the risks are equal for both men and women and across age groups. We investigated whether the impact of AKI on mortality differs by age and sex within the Irish Health System.

Methods: Health data from 2 regional information systems were linked with mortality data from 1999 to 2011 (n=533, 773). AKI events were identified per KDIGO guidelines. Transient AKI events were identified as acute elevations in creatinine which fell to below 1.1 times baseline within 48 hours of initial event. Multivariate Cox regression modelled the associations (Hazard ratios and 95% CI) with death and interaction terms tested for differences between gender and age groups (≤ 59, 60-80, and >80 years). Patients were censored at death, lost-to-follow-up, or end of study. Analyses were adjusted for demographic, facility characteristics, and laboratory variables.

Results: In the full multivariable Cox model, the interaction term for age* gender*AKI stage was very significant (P<0.001). The stratum-specific hazard ratios for each age and gender subgroup are shown.

Variable	No AKI	Transient AKI	Stage 1	Stage 2	Stage 3
Men					
< 59	1.00	2.90 (2.31-3.64)	4.74 (3.84-5.85)	5.63 (4.03-7.85)	5.00 (3.33-7.50)
60-80	1.00	1.93 (1.70-2.19)	2.78 (2.47-3.12)	3.46 (2.88-4.15)	3.15 (2.51-3.95)
> 80	1.00	1.69 (1.43-2.00)	2.29 (1.95-2.67)	2.75 (2.15-3.51)	3.65 (2.75-4.85)
Women					
< 59	1.00	5.12 (3.84-6.85)	7.70 (6.13-9.66)	11.73 (8.21-16.74)	12.08 (7.51-19.43)
60-80	1.00	2.16 (1.86-2.5)	2.85 (2.51-3.23)	3.37 (2.75-4.11)	4.83 (3.75-6.22)
>80	1.00	1.55 (1.35-1.77)	1.77 (1.57-2.00)	2.25 (1.85-2.72)	1.9 (1.37-2.64)

Conclusions: AKI events are more deleterious for younger than for older patients, with younger women having the greatest risk.

SA-PO534

Acute Kidney Injury in Primary and Secondary Care in England: Lessons and Initial Results from a National Registry

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Background: Acute Kidney Injury (AKI) is common and associated with considerable morbidity and mortality. This study aims to report progress and initial results from setting up a national AKI registry in England.

Methods: Since March 2015, NHS England has required all labs to 1) use a nationally agreed electronic detection algorithm to identify cases of potential AKI and 2) submit data on all cases, whether in primary or secondary care, to the UK Renal Registry. The algorithm looks back at local baseline creatinine results 1-7 and 8-365 days prior to the index result to produce a test result (AKI warning stage) 1, 2 or 3 based on an index to baseline ratio of 1.5-2.0, 2.0-3.0 or 3.0+ (or index >354 umol/L), respectively. For each AKI warning stage, patient identifiers, demographics and AKI stage are transmitted each month securely to the Registry and linked with the NHS spine for 30-day mortality tracing. Area-level social deprivation is assessed using the postcode-derived Index of Multiple Deprivation (IMD). This work is permitted without individual patient consent under the Registry's Section 251 support.

Results: In March 2015, 27 (21%) of an estimated 131 labs in England submitted data, increasing to 73 (56%) by March 2016. In that period, 569,375 AKI warning stage results were reported to the Registry in 184,354 individuals, 170,401 (92.4%) of whom had age, gender and IMD data and could be traced to the NHS Spine. The highest recorded AKI level for each individual was 1 in 65.2%, 2 in 18.5% and in 16.3%, with associated 30-day crude mortality rates of 14.3%, 29.7% and 31.5%, respectively. Compared to the least deprived decile, 30-day age- and sex-adjusted mortality was higher in people from the most deprived areas: 24.6%, 11.7% and 10.9% higher for AKI 1, 2 and 3, respectively.

Conclusions: Establishing a national registry of AKI in primary and secondary care is possible in England and has the potential to be a powerful quality improvement, public health and research tool.

Funding: Government Support - Non-U.S.

SA-PO535

Comparing Community and Hospital Acquired Acute Kidney Injury in a Population Based Study

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Background: Early recognition and management of acute kidney injury (AKI) is necessary to minimise preventable harm and high healthcare costs. The epidemiology of hospitalised AKI has been well described, but less is known about factors associated with community-acquired AKI (CA-AKI). Identifying those at risk of CA-AKI would be valuable

because approximately two-thirds of AKI originates in the community and some patients are not admitted to hospital. We aimed to describe the characteristics and associations of CA-AKI using a large, anonymised routine linked dataset.

Methods: Using data from the Hampshire Health Record (HHRA) UK, a data resource linking primary and secondary care (including laboratory) data, we applied KDIGO-based AKI criteria to identify AKI patients during 2014. Descriptive statistics and multivariate logistic regression models were used to compare characteristics of CA-AKI and hospital acquired AKI (HA-AKI) patients, adjusting for age, gender, socioeconomic status, co-morbidities and prescribed medication.

Results: 5,724 out of 643,039 eligible population generated at least one AKI alert: 61% (3469/5724) with CA-AKI and 39% (2255/5724) with HA-AKI. Being older, living in a deprived area, having hypertension, diabetes, chronic kidney disease, heart failure and being prescribed diuretics were risk factors for both CA-AKI and HA-AKI. Female gender and non-steroidal anti-inflammatory drugs (NSAIDS) were associated with CA-AKI but not HA-AKI. Renin angiotensin system inhibitors (RAASi) was associated with HA-AKI but not CA-AKI.

Conclusions: Incidence of CA-AKI was common (61% of all AKI) in our cohort. The study identified the characteristics of people at risk of CA-AKI in primary care who may benefit from targeted prevention, and indicates important differences in medication risk factors for CA-AKI and HA-AKI.

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SA-PO536

Community-Acquired Acute Kidney Injury (CA-AKI) Is Common and Correlates with Extended LOS across the 10 Most Common Diagnostic Categories in Emergency Department Admissions (ED) in a Large U.S. Integrated Delivery Network (IDN)

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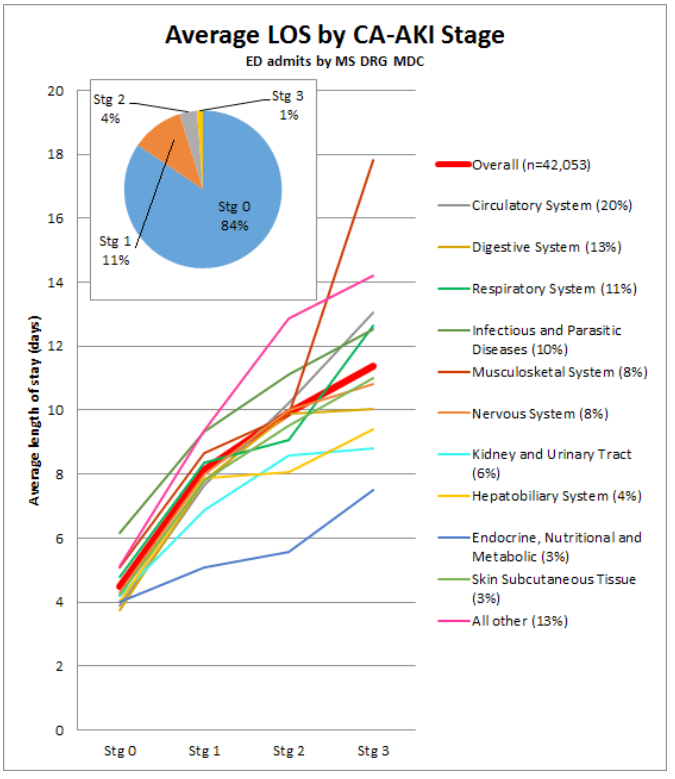
Background: In spite of increased global attention on AKI, including the 0by25 initiative, CA-AKI is not well understood in developed countries. CA-AKI, its associated diagnoses and impact on LOS were studied among patients admitted through EDs across a large IDN.

Methods: We identified all inpatient admissions over a 6 month period (10/15-3/16) that originated in the ED across 9 hospitals in urban and suburban settings in the Northeast US. Transfers from other acute care settings were excluded. CA-AKI was identified using KDIGO criteria from presenting creatinine values, using minimum values as the baseline. CA-AKI stage was correlated to diagnosis codes and LOS.

Results: 42,053 admissions met inclusion criteria. Mean patient age was 65.2y, and patients were 47.0% male. CA-AKI was identified in 6,494 admissions (15.4%), with stages 1, 2, and 3 present in 10.7%, 3.6% and 1.2%, respectively. The rate of CA-AKI varied from 12.5-18.3% across hospitals. The rate and distribution by stage were consistent across time. The MS-DRG Major Diagnostic Categories (MDCs) with the top 3 CA-AKI rates were infectious (34%), kidney & urinary tract (29%) and endocrine (28%) diseases. Average LOS (ALOS) was 4.5, 8.1, 9.9, and 11.4 days for stages 0-3 respectively, and demonstrated positive correlation for the top 10 most common MDC's (see fig). Sepsis was the most common DRG group with an ALOS by stage of 5.9, 8.5, 10.1 and 11.9 days, respectively. Regression demonstrated a 2.1 day increase in LOS for every 100% increase in creatinine.



Conclusions: Similar to low middle income countries, patients commonly present with CA-AKI in the developed world. Presentation with CA-AKI correlates with extended LOS across almost all MDCs, including circulatory, digestive, respiratory, infectious, as well as kidney disease.

SA-PO537

Epidemiology and Outcomes of Severe Septic Acute Kidney Injury Needing Renal Replacement Therapy – A Nationwide Population Based Study

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Background: Sepsis is the leading cause of hospital acquired acute kidney injury (AKI). Severe sepsis and septic AKI needing dialysis (AKI-D) are among the most lethal complications of sepsis. Population based epidemiology data are lacking, especially in the Asian ethnicity. Renal replacement therapy (RRT) is a potentially life-saving procedure for septic AKI. However, its roles in patients' outcomes are not clear, especially after adjustments for baseline comorbidities and illness. We use the Taiwan National Health Insurance Research Database (NHRID) to answer the questions.

Methods: From 1999 to 2007, a total of 2,619,534 patients was identifed. We defined severe sepsis using the diagnosis code with AKI, along with organ dysfunction. The cases undergoing RRT were identified using procedure codes. We calculated yearly incidence rates of AKI-D, along with mortality rates. A propensity matched cohort (1:4) was constructed with balanced profiles, to identify differences of 30 days' all-cause mortality rates after hospital discharge.

Results: A total of 312,686 (11.9%) patients was identified to have severe sepsis, while septic AKI-D developed in 4,977 (1.59%) patients, with the 30 days' mortality rate of 51.12%. The patients without AKI-D had a 30 days' mortality rate of 11.38% ($p<0.001$). Over the period, the yearly incidence of AKI-D in Taiwan increased from 1.45% to 1.75% (p for trend < 0.05). Yearly 30 days' mortality rates decreased from 53.0% to 48.1% (p for trend < 0.05). The incidence of respiratory tract (RTI) sepsis increased, while genitourinary tract infection (GUTI) sepsis decreased. The mortality rates of AKI-D decreased in both GUTI and RTI groups. Propensity matched cohort identified RRT to be an independent risk factor for 30 days' mortality (RRT: 2297 [52.30%] versus non-RRT: 6114 [34.8%)], $p <0.001$).

Conclusions: In the nationwide analysis, AKI-D incidence increased with time, but the associated mortality decreased. RRT has negative impacts on patients' outcome, but unidentified residual risks may account for the excessive risks.

SA-PO538

Redefining Neonatal Acute Kidney Injury: Insights from the Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) Cohort

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Background: Definitions of neonatal acute kidney injury (AKI) based on serum creatinine (sCr) derived from adult standards fail to incorporate confounders of gestational age (GA) and postnatal changes in sCr. Consequently, the incidence of neonatal AKI varies from 12-70% and its risks and long term morbidity have not been determined. The Neonatal Kidney Collaborative (NKC) represents 24 institutions from 4 countries and is dedicated to the study of neonatal AKI. Our objective was to refine the modified KDIGO definition of AKI by examining the effects of GA and rapid changes in sCr unique to the neonate.

Methods: Of 4273 NICU admissions screened retrospectively during the first 3 months of 2014, **2162** infants met inclusion/exclusion criteria of needing intravenous fluids ≥48 hours, no cardiac surgery and no severe kidney disease. Of these 1461(67%) had at least 2 sCr values and were included in the analysis. Receiver operating curve analyses were performed with area under the curve (AUC) for multiple parameters including maximum (Max) sCr, absolute and percent(%) rise in sCr for mortality (MORT) and length of stay (LOS).

Results: SCr parameters are summarized in the Table. AUC >0.7 is significant ($p<0.001$). Only Max sCr for LOS was not significant (AUC=0.59). SCr measures are in milligrams/deciliter (mg/dl).

Parameter		Overall Cohort	AUC	GA (<29 weeks)	GA (>29<36 weeks)	GA >36 weeks)
Max sCr	MORT	0.9	0.74	1.1	0.9	0.9
	LOS	0.8	0.59	0.9	0.8	0.8
Max sCr Rise	MORT	0.1	0.76	0.2	0.1	0.1
	LOS	0.1	0.74	0.2	0.0	0.0
Max %Rise sCr	MORT	35%	0.74	50%	25%	21%
	LOS	20%	0.73	50%	12%	10%

Conclusions: Diagnosis of neonatal AKI requires a definition based on GA and sCr rise in neonatal life. Future analyses will refine the sCr-based definition and provide a platform for prospective follow-up of this large neonatal cohort.

SA-PO539

A Phenome-Wide Association Study of Hospital-Acquired Acute Kidney Injury Nicolas Pallet, Eric Thervet, Anne Sophie Jannot. *Hôpital Européen Georges Pompidou.*

Background: Hospitalization Associated Acute Kidney Injury (HA-AKI) has been described in retrospective case-control studies but none has performed an exhaustive exploration of the dataset. Exhaustive methods hold a high explicative power, are easily understandable, and can generate a hierarchical classification of the risks factors associated with the outcome variable.

Methods: We extracted data from a French urban tertiary academic hospital (Georges Pompidou European Hospital, HEGP) I2B2 Clinical Data Ware House containing more than 700,000 single patients and more than 200,000,000 items and performed a Phenome-wide association study (PheWAS) to identify all of the ICD-10 diagnostic codes associated with HA-AKI (AKIN scores calculated during the first week after admission).

Results: We generated a database of 222,975 entries over a period of time of 10 years matched with 480 ICD-10 diagnostic codes. AKIN prevalence was 7.2%. The PheWas analysis generated 268 ICD-10 codes associated with AKI ($p<5.10^{-5}$), and the most important risk factor was post procedural disorders of the genitourinary system (N99) with an Odds Ratio (OR) of 17. The majority of the codes associated with an OR>5 were related to sepsis and infections, and also reflecting hemodynamic instability (shock, cardiac arrest, coma). Chronic kidney disease (N18) was positively associated with AKI with an OR of 4.5. Most of the codes negatively associated with AKI were related to follow-up examination (Z09, OR 0.06), screening (Z13, OR 0.08) and imaging (R93, OR 0.13). The most negatively associated code was Z56 (problems related to employment and non employment, OR 0.01). Interestingly, the ICD-10 code corresponding to AKI (N17) was found in less than 60% of the cases in which AKI was identified with the AKIN classification; conversely, AKIN "negative" patients received the N17 code in 30% of the cases, which might reflect misidentification of AKI by physicians.

Conclusions: The PheWas approach is a valuable mean to discover novel associations and to perform hierarchical classification of all the factors associated with HA-AKI. Our analysis delivers insights into how physicians identify AKI and its known risk factors, and might help to revise the current standard of care.

SA-PO540

Development and Validation of Acute Kidney Injury Risk Index in Patients with Abnormal Kidney Function Undergoing Non-Cardiovascular Surgery Lynette Espino Ilano, Shu-Yi Liao, Earl Ilano, Ali Motabar. *Univ of California, Riverside, Riverside Univ Health System Medical Center.*

Background: The authors sought to identify risk factors of Acute Kidney Injury (AKI) in patients with abnormal kidney function undergoing non-cardiovascular surgery and provide a risk index using a large representative national clinical data set.

Methods: The data from 2013-2014 American College of Surgeons–National Surgical Quality Improvement Program Participant Use Data File (ACS-NSQIP PUF) was used for analysis. AKI is defined as either ACS-NSQIP renal morbidity outcome of progressive renal insufficiency or acute renal failure necessitating dialysis. Patient's comorbidities and pre-operatives characteristics were evaluated as potential predictors in the model. A logistic regression model was used to build the scoring system to predict the risk of an event. The weighted risk score was constructed through the training set (75% of the whole data) and was evaluated by the area under curve (AUC). The final model was validated using the validation set (25% of the whole data).

Results: 1,195,825 operations between 2013 and 2014 were reviewed and 290,876 operations were included based on the inclusion/exclusion criteria. 2,450 subjects had AKI. Mechanical ventilation, hypertension requiring medications, ascites, sepsis, diabetes and abnormal kidney function stages were identified as potential predictors and were included in the final model. Each weight was assigned based on the estimate of coefficients. The full risk score ranged from 0 to 22 points. The AUC in the training set was 0.77 and was 0.79 using the validation set. People with a score of ≥ to 17 points had a 51.8 % risk of having AKI. People with a full score of 22 points had a 86.1% risk of having AKI compared to people with a score of 0 points who had a 0.3% risk of having AKI.

Conclusions: Our 22 points scoring systems with 6 variables were able to predict the risk of AKI in patient with abnormal kidney function stage 2-5. This tool is promising and may be used in the clinical setting for patients with abnormal kidney function undergoing non-cardiovascular surgery. External cohort that includes confirmed CKD patients is needed for further validation.

SA-PO541

Mild Postoperative Acute Kidney Injury: Incidence and Outcome Thorir E. Long,[1,2] Dadi Helgason,[1,2] Sólveig Helgadóttir,[2] Runolfur Palsson,[1,2] Tomas Gudbjartsson,[1,2] Gisli H. Sigurdsson,[1,2] Martin I. Sigurdsson,[3] Olafur S. Indridason.[2] *[1]Univ of Iceland; [2]Landspitali - the National Univ Hospital of Iceland, Reykjavik, Iceland; [3]Brigham and Woman's Hospital, Boston, MA.*

Background: A small rise in serum creatinine of 0.3 mg/dL over 48 hrs is currently included in the definition of acute kidney injury (AKI), yielding many mild cases of unknown significance. The aim of this study was to examine the incidence and outcome of individuals with mild AKI following surgical procedures.

Methods: This was a retrospective study of all adult patients who underwent abdominal, cardiothoracic, vascular or orthopedic surgeries at the National University Hospital in 2007-2015. Clinical data was extracted from electronic medical records. AKI was diagnosed according to the SCr component of the KDIGO criteria. The baseline characteristics and survival of patients with a mild AKI (only a rise in SCr of 0.3 mg/dL over 48 hrs, without 1.5 x baseline increase in 7 days) was compared with a propensity score matched control group (PSM,1:1) without AKI. This was performed for groups with and without preoperative reduction in kidney function (eGFR<60 mL/min//1.73 m^2).

Results: A total of 28,879 patients underwent 40,738 surgical operations during the study period. Both pre- and post-operative SCr was available for 19,072 operations. Median age at surgery was 68 yrs (IQR, 58-78) and 50% were female. AKI occurred following 1,557 operations (8%), 559 (3%) had mild AKI and 998 (5%) had more severe AKI. Patients with mild AKI were more likely to be male (66% vs. 54%, P<0.001), had a lower baseline eGFR, 48 (28-65) vs. 65 (47-83) mL/min/1.73 m^2 (p<0.001), and a higher comorbidity burden compared with patients with more severe AKI. Mild AKI patients with preoperative reduction in kidney function had worse 1-year survival than their PSM matched controls 76% vs 81%, (p<0.01). However, individuals with normal preoperative kidney function and mild AKI had similar 1-year survival as the PSM controls 89% vs 89% (p=0.5).

Conclusions: Our study suggests that mild AKI has a detrimental effect on outcome in patients with reduced kidney function, while those with preserved kidney function may tolerate mild AKI without adverse outcomes.

Funding: Government Support - Non-U.S.

SA-PO542

National Trends and Outcomes in Dialysis-Requiring Acute Kidney Injury in Patients with Septicemia Mihir Dave,[2] Harshil Shah,[1] Tushar Mishra,[2] Arpita Hazra,[2] Suman Khicher,[2] Abhishek Mishra,[4] Siddharth Mehta,[5] Kinsuk Chauhan,[1] Achint Patel.[3] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Detroit Medical Center, Detroit, MI; [3]Univ Of Arkansas For Medical Sciences, Little Rock, AR; [4]Univ of Iowa and Clinics; [5]Mount Sinai Beth Isreal.*

Background: National Trends and Outcomes in Dialysis-Requiring Acute Kidney Injury in patients with Septicemia.

Methods: We used the nationwide inpatient sample (NIS) database 2002-2013 to identify adults hospitalized with septicemia using Clinical Classification Software (CCS) developed by AHRQ. We defined AKI-D based on previously validated ICD-9-CM codes including 584.xx for AKI, v45.11, v56.0 and v56.1 for dialysis and procedure code 39.95 for the dialysis procedure. We excluded hospitalizations that had codes for dialysis but not for AKI, as these were likely for ESRD patients on dialysis. We used the multivariate regression to analyze changes in trends and outcomes and explore potential reasons explaining these changes.

Results: From 2002-2013, of the 8,10,8048 patients who were hospitalized with septicemia, 214185 (2.64%) developed AKI-D. Proportion of AKI-D increased from 1.4% hospitalizations in 2002 to 2.65% hospitalizations in 2013 (p<0.001) (Figure 1). This trend increased annually by 4.2% (OR 1.035; 95% CI 1.03-1.04;p<0.001). This rise was completely explained by changes in demographics and increase in co-morbidities. Percentage of in-hospital morality (40% v/s 15%) and discharge to specialized care (63% v/s 37%) were higher among the AKI-D patients. Odds of in-hospital mortality (OR 2.08; CI 2.02-2.14; p<0.001) and discharge to specialized care (OR 1.78; CI 1.72-1.84; p<0.001) remains high. Although the percent in-hospital mortality after AKI-D was decreased, the adjusted odds increased (OR 1.63 to 2.14). And also, the adjusted odds of requiring specialized care in a facility increased during study period (OR 1.42 to 1.91).

Conclusions: The incidence of AKI-D in patients admitted with Septicemia has increased over the period of time. Our results emphasize the need for better risk stratification and early recognition of kidney dysfunction in patients with septicemia.

SA-PO543

Epidemiological Study on the AKI-CKD Communication: A Single-Center Retrospective Database Analysis Taro Horino,[1] Yutaka Hatakeyama,[2] Hiromi Kataoka,[2] Tatsuki Matsumoto,[1] Yoshiko Shimamura,[1] Kosuke Inoue,[1] Yoshio Terada,[1] Yoshiyasu Okuhara.[2] *[1]Dept of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi Univ, Nankoku, Japan; [2]Center of Medical Information Science, Kochi Medical School, Kochi Univ, Nankoku, Japan.*

Background: Acute kidney injury (AKI) is a serious complication among hospitalized individuals and is closely associated with chronic kidney disease (CKD).This study investigated the extent of renal dysfunction progression after AKI events in both CKD and non-CKD patient groups.

Methods: This retrospective cohort study registered 131,358 individuals who visited Kochi Medical School hospital between October 19, 1981 and December 31, 2014. AKI and CKD was defined and staged according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria, using measured serum creatinine levels. This study evaluated 10,189 AKI patients meet KDIGO criteria.

Results: The incidence of AKI in this cohort was 7.8% (95% confidence interval: 7.7–8.0%). AKI stage 1, 2 and 3 were 7,803, 1,703, and 683, respectively. We finally analyzed data from 1,846 AKI patients, excluding patients who had proven post-renal AKI or whose baseline SCr was not defined. Final cohort included 1,051 (56.9%) men. Patients without CKD (group A), patients with CKD after AKI event (group B), and patients with patients with CKD on baseline (group C) were 820, 543, and 483, respectively. The mean eGFRs on baseline, on AKI, and after AKI event in group A were 90.8, 53.1, and 77.4 mL/min/1.73m^2, respectively. Those in group B were 72.9, 42.5, and 55.0 mL/min/1.73m^2, respectively. Those in group C were 38.8, 24.7, and 36.0 mL/min/1.73m^2, respectively. Interestingly, mean eGFRs after AKI event in all three groups were significantly reduced compared to those on baseline. Furthermore, this eGFR reduction tended to progress on AKI frequency-dependent manner.

Conclusions: We found that AKI was a risk factor for CKD progression. We showed that lower eGFR levels before AKI are and more frequently AKI events occur, more the incidence of CKD increase. We propose that physicians should pay attention to AKI-CKD communication.

SA-PO544

Acute Kidney Injury in the Tertiary Care Setting in Rwanda Marla D. McKnight,[3,4] Fredric O. Finkelstein,[2] Grace Igiraneza.[1] *[1]Dept of Medicine, Univ of Rwanda, Butare, Rwanda; [2]Yale Univ, New Haven, CT; [3]Renal Div, Dept of Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, MA; [4]Rwanda Human Resources for Health Program, Ministry of Health, Kigali, Rwanda.*

Background: Acute kidney injury (AKI) is a global health concern impacting both developed and developing countries. There is limited data from low-income settings on the epidemiology and outcomes of AKI.

Methods: In this observational, multi-centre study conducted in Rwanda between September 1, 2014 and January 31, 2015, patients ≥ age 16 admitted to a tertiary care hospital were screened for elevation of serum creatinine in both hospital and external labs. Patients meeting KDIGO definition of AKI, based on change in serum creatinine, had demographic and clinical information collected and were followed until discharge or in-hospital death. Length of stay (LOS) and in-hospital mortality in patients with AKI were compared to that of all inpatients and regression models performed to determine predictors of mortality.

Results: Of the 14,918 patients admitted, 427 patients met KDIGO criteria for AKI—8.2% stage 1, 41.9% stage 2, 49.9% stage 3. Mean age of patients with AKI was 47.2 ± 19.9; 50.8% were male. Infections (68.9%), cardiovascular disease (35.5%), pregnancy related conditions (12.4%), diabetes (11.5%) and cirrhosis (8%) were frequently associated with AKI. 10.3% of patients had a nephrology consult and 9.4% received renal replacement therapy. Mean LOS in patients with AKI was 17.4 ± 18.7 compared to 7.1 for all admitted patients (p<0.001). All-cause mortality among patients with AKI was 31.9% compared to an overall hospital mortality rate of 4.4% (p<0.001). Patients with cirrhosis (OR=5.59, p< 0.001), sepsis (OR=3.03, p<0.001) and cancer (OR=3.3, p=0.007) were at significantly higher risk of in-hospital mortality.

Conclusions: AKI in the tertiary care setting in Rwanda is associated with significantly increased mortality and length of hospital stay compared to patients without AKI. Further research is needed to understand the etiologies of AKI in Rwanda and other low income settings in order to guide strategies to prevent and/or reduce AKI related morbidity and mortality.

Funding: Private Foundation Support

SA-PO545

Acute Kidney Injury in Intensive Care Unit Patients: A Prospective Population-Based Study in Brazilian Amazon Fernando de Assis Ferreira Melo,[1] Etienne Macedo,[2] Ana Caroline Fonseca Bezerra,[3] Bruna Vitória Souza,[3] Bruna Cristina Meira Bruno,[3] Ravindra L. Mehta,[2] Emmanuel A. Burdmann,[1] Dirce M.T. Zanetta.[1] *[1]Univ of São Paulo, São Paulo, Brazil; [2]Medicine, Univ of California, San Diego, CA; [3]Medicine, Acre Federal Univ, Rio Branco, Acre, Brazil.*

Background: The Brazilian Amazon region is a resource constrained, impoverished area with limited health care facilities. The epidemiology of Acute Kidney Injury (AKI) in this region has not been described.

Methods: We performed a prospective study of the risk factors and incidence of AKI in patients admitted to all Intensive Care Units (ICU's) in Rio Branco (Acre), an Amazon region, from Feb 2014 to Feb 2016. Patients were screened at ICU admission and diagnosed with AKI based on modified KDIGO criteria and their course recorded through hospital discharge. AKI was characterized as community acquired (CAAKI) if AKI developed prior to hospital admission and hospital acquired (HAAKI) if developed during the hospital stay.

Results: Of 1494 patients admitted,1046 fulfilled selection criteria. A third of the patients developed AKI before ICU admission, only 6% were CAAKI. AKI incidence was 43.8%, with 61.9%, 19.5% and 18.6% Stage 1, 2 and 3 respectively and 5.4% received dialysis. Associated etiological factors for AKI included surgery (30.3%), hemodynamic instability (24%), and respiratory failure (19.2%). Only 1.7% had tropical diseases. Risk factors for AKI included use of nephrotoxic antibiotics (OR 8.6, p<0.001), anti-inflammatory drugs (OR 1.7, p=0.002), anemia (OR 3.8, p=0.001) and fluid balance over 1500 ml/24h (OR 1.6, p=0.003). AKI was associated with a higher ICU mortality (AKI 55.9% vs non AKI 13.9%, *p*<0.001). In a logistic regression model AKI mortality was associated with mechanical ventilation (OR 3.6, p<0.001), use of vasoactive drugs (OR 2.4, p=0.03) shock (OR 2.2, p<0.001), and use of antibiotics (OR 2.5, p<0.001).

Conclusions: AKI is common in ICU patients in the western Brazilian Amazon with few hospitalizations for tropical diseases and similar etiologies, risk factors and outcomes as developed countries; however with higher mortality rates that may represent the economic conditions and poor access to health care.

Funding: Government Support - Non-U.S.

SA-PO546

Delay on Acute Kidney Injury Diagnosis in Critically Ill Patient: A Snapshot on Brazilian Amazon Fernando de Assis Ferreira Melo,[1] Etienne Macedo,[2] Ana Caroline Fonseca Bezerra,[3] Magela Teodorio Melo Fernandes Magela,[3] Bruna Cristina Meira Bruno,[3] Bruna Vitória Souza,[3] Ravindra L. Mehta,[2] Emmanuel A. Burdmann,[1] Dirce M.T. Zanetta.[1] *[1]Univ of São Paulo, Sao Paulo, Brazil; [2]Univ of California-San Diego, San Diego, CA; [3]Acre Federal Univ, Rio Branco, Acre, Brazil.*

Background: There are deficiencies in the recognition and management of patients who developed Acute Kidney Injury (AKI) in Intensive Care Unit (ICU) that can result delay in treatment and inappropriate referral to nephrologist, leading to worse outcomes as need for dialysis, recovery and mortality rates.

Methods: We performed a prospective study of AKI incidence in patients admitted to all ICU's in Rio Branco, state capital of Acre, from Feb 2014 to Feb 2016. We used medical records to compare the performance of the clinician to make the diagnosis of AKI with the diagnosis made by KDIGO criteria.

Results: We studied 1046 patients. Among 43.8% of patients who developed AKI in ICU, there were agreement of the diagnosis day in only 14.5%, in 65% the clinician did not make the diagnosis and in 8.2% it was delayed. Thirty seven percent of the delayed diagnosis patients presented AKI grade III. Dialysis was offered to only 0.3% of non-diagnosed patients in contrast with 31.3% in those who had timely diagnosis (p <0.001). The APACHE II score was lower in those non-diagnosed compared with those who had timely diagnosis (17.5 vs. 27, p <0.001). ICU and hospital stay were higher when diagnosis was delayed compared with timely diagnosis patients (10 vs. 8, p <0.001 and 21 vs 16, p <0.001, respectively). Mortality was also higher in those non-diagnosed and delayed diagnosed patients, compared with those who had timely diagnosis (61.8% vs 68.3% vs 40%, p <0.001).

Conclusions: In the vast majority of our patients, the clinic diagnosis of AKI was not done or occurred later. This fact may have contributed to delay on completion of dialysis, increased length of ICU and hospital stay and higher mortality rates. It is necessary to increase awareness of AKI in ICU and disseminate knowledge about acute kidney injury stressing that small changes in renal function often contribute to serious adverse outcomes.

Funding: Government Support - Non-U.S.

SA-PO547

Epidemiology of Acute Kidney Injury in the Intensive Care Unit: A Systematic Review Fernando de Assis Ferreira Melo,[1] Etienne Macedo,[2] Ana Caroline Fonseca Bezerra,[3] Bruna Cristina Meira Bruno,[3] Bruna Vitória Souza,[3] Ravindra L. Mehta,[2] Emmanuel A. Burdmann,[1] Dirce M.T. Zanetta.[1] *[1]Univ of São Paulo, Sao Paulo, Brazil; [2]Univ of California-San Diego, San Diego, CA; [3]Acre Federal Univ, Rio Branco, Acre, Brazil.*

Background: AKI is commonly encountered in Intensive Care Unit (ICU) patients across the world; however, the epidemiology of Acute Kidney Injury (AKI) in the developed and developing world has not been systematically examined.

Methods: We conducted a systematic review of published studies (2005–2015) identified in PUBMED, CENTRAL, LILACS, and IBECs databases using the search terms "acute kidney injury" and "intensive care unit". We examined the differences in AKI incidence, severity (based on KDIGO criteria) and associated mortality and describe geographic variations based on the gross national income.

Results: We identified 94 studies: 60 from developed countries and 34 from developing countries. Of these, 75.5% used KDIGO-equivalent criteria; however, we found 10 different definitions for oliguria and 19 different definitions for baseline creatinine. The frequency of AKI was higher in studies using KDIGO-equivalent criteria (34.3% vs 24.3%), with lower mortality rates (median 29% vs median 42.5%). There were no differences in incidence of AKI between developed and developing countries. However, the need for RRT, ICU length of stay and mortality rates were higher in developing countries.

Conclusions: Despite the attempt to standardize the criteria for defining AKI, there is still no uniformity in the settings for "baseline creatinine" or "oliguria". Differences in ICU length of stay, need for RRT and mortality rates may reflect differences in the entry criteria and the social conditions, access to health care and hospital infrastructure.

Funding: Government Support - Non-U.S.

SA-PO548

Etiology and Outcome of Acute Kidney Injury – Study from Two Teaching Hospital from Nepal Sanjib Kumar Sharma.[1] *[1]Dept of Internal Medicine, B P Koirala Inst of Health Sciences, Dharan, Nepal; [2]Dept of Nephrology, College of Medical Sciences, Bharatpur, Nepal.*

Background: Most of the AKI occurs in developing nations. The etiologies and outcome is believed to be different in developed versus underdeveloped nations.

We conducted prospective observational study in two teaching hospital in Nepal to study the etiologies and the outcomes of acute kidney injury.

Methods: Consecutive patients attending out patient clinic or admitted in two teaching hospital in Nepal fulfilling AKIN criteria were enrolled and followed up for one year . The data were recorded in predefined validated case record form.

Results: The age distribution ranged from 15 years to 90 years. The most common etiology (31.38%, n=123) of the AKI was sepsis followed by community acquired pneumonia (71/392). However, significant number AKI patients had preventable causes of AKI like acute gastroenteritis (18.11%, n=46), obstructive uropathy (3.57%, n=14), malaria

(3.57%, n=14), and septic abortion (1.02%, n=4). The other etiologies were complicated UTI (19.13%, n= 75) and drug and toxins including herbal medicine (2.75%, n=19). Sixteen patients were of various etiologies and etiology of AKI could not be ascertain in 10 patients.

Sixty patients (15.3%) expired and 45 patients left against medical advised (LAMA). Among rest of the patients 84.69% patients recovered from AKI. Eight patients progressed to chronic kidney disease (0.98%+3.1%). Patients who were discharged from the hospital 12.5% were lost to follow up. The outcome of the AKI was significantly different in two centers (death and LAMA 44.44% Vs11.27%).

Conclusions: Though major etiology of teaching hospital setup remains similar to western world, there are still significant number of patients with AKI of preventable etiology. The mortality of even two teaching hospital set up differ significantly.

SA-PO549

Epidemiology of Acute Kidney Injury in an Intensive Care Unit of a Third Level Hospital in Mexico City Juan Reyna,[1] Sonia Hernandez,[3] Rodolfo Rincon-Pedrero.[2] *[1]Medicina Interna, Inst Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, INCMNSZ; [2]Nefrología y Metabolismo Mineral, INCMNSZ; [3]Nutriología, INCMNSZ.*

Background: Acute kidney injury (AKI) is one of the most common complications in critically ill patients and is associated with a high risk of death, length of stay and costs. We aimed to determine incidence, associated risk factors and outcomes of AKI in a general ICU from a medical center in Mexico City.

Methods: We retrospectively studied a cohort of 463 patients admitted to an ICU during 1 year. Exclusion criteria were chronic kidney disease with CKD-EPI <60mL/kg/1.73m^2 and kidney transplantation. We measured AKI by Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

Results: The overall incidence of AKI was 57%, distributed among the 3 stages: 22.7% stage 1, 33.7% stage 2 and 43.6% stage 3. Only 7.1% of AKI patients needed renal replacement therapy. Regarding the cause of AKI, septic shock, non surgical-associated hypovolemia, surgical-associated hypovolemia and nephrotoxic drugs contributed with 65.9, 27.3, 25 and 9%, respectively. Patients who developed AKI were more common men, had more diabetes, ischemic heart disease, hematological malignancies, septic shock and hypovolemia, stayed longer in the ICU, presented higher SAPS 2 score and more often needed mechanical ventilation (MV) and use of norepinephrine. The ICU mortality was 9% in patients without AKI, 15% in stage 1, 21.3% in stage 2 and 56.5% in stage 3. When adjusted for other variables; odds ratio of stage 1=1.12 (95% IC 0.40-3.09; p=0.8), stage 2=1.53 (95% IC 0.65-3.60; p=0.3) and stage 3=8.6 (95% IC 3.2-22.8; p=<0.001). Other independent risk factors for mortality included oligo-anuria, need for IMV, vasoactive therapy and SAPS 2 score, whereas a higher serum creatinine and body mass index (BMI) were associated with lower mortality risk.

Conclusions: There was a high incidence of AKI in this study. Only KDIGO stage 3 among other stages was considerably associated with mortality when adjusted for other variables. The strongest predictor of death was oliguria and we noted that lower serum creatinine levels were associated with an increased risk of death that could be related to volume overload or loss of muscle mass.

SA-PO550

The Effect of ICU System on Outcome of Critically Ill Patients with Acute Kidney Injury: Result from SEA-AKI Study Group Nattachai Srisawat, Warangkana Tantipornsinchai, Nobphathorn Mahamitra, Sadudee Peerapornratana, Kearkiat Praditpornsilpa, Somchai Eiam-Ong, Kriang Tungsanga. *Div of Nephrology, Dept of Medicine, Faculty of Medicine, Chulalongkorn Univ, Bangkok, Thailand.*

Background: Variation of ICU system may affect to the AKI outcome. To our best knowledge, there is no study which demonstrates the effect of ICU organization and AKI outcome. Our study aimed to explore the effect of Closed versus Open ICU to AKI outcome across adult ICUs.

Methods: The prospective multicenter observational study was conducted in 15 ICUs from 5 regions across Thailand from April 2014 to April 2015. We collected the data by registration in electronic web-based format. The Closed ICU model was defined as an ICU service led and managed by an intensivist. The Open model was an ICU service where critically ill patients were managed by primary physician; they may or may not choose to consult an intensivist. The main outcome was hospital mortality.

Results: Of fifteen ICUs, 12 ICUs and 3 ICUs were defined as Open ICU and Closed ICU, respectively. We have totally enrolled 5,381 patients and did the first half analysis in 2,480 patients (Closed ICU n=640 and Open ICU n=1,840 cases). AKI occurred in 1,271 patients (51.3%). Twenty eight percent of AKI patients were cared in Closed ICUs. The Closed ICU had significant higher percentage of nephrologists, intensivists, and certified critical care nurses than Open ICU (all p<0.001). There were comparable hospital mortality rate between Closed and Open ICU, 42.2% vs 42.7%, p=0.86. However, in multivariable linear regression adjusted for APACHE II, sepsis, ICU structure and process of care factors, we found hospital mortality of AKI patients was significantly lower in Closed ICU than Open ICU (p=0.001, OR=0.38, 95%CI 0.22-0.68). When using propensity score matching, we still found the same result. AKI patients in Closed ICU had significantly lower length of ICU stay than in Open ICU (p<0.001, OR=0.30, 95%CI 0.18-0.49).

Conclusions: In this large multicenter study, we demonstrated Closed ICUs had more favorable AKI outcome than Open ICU. Further study to explore the contributing factors in process of care is still warrant for improvement AKI outcome.

SA-PO551

National Trends and Outcomes in Dialysis-Requiring Acute Kidney Injury in Patients with Pneumonia: 2002-2013 Harshil Shah,[2] Achint Patel,[1] Mihir Dave,[3] Tushar Mishra,[3] Suman Khicher,[3] Kinsuk Chauhan,[2] Siddharth Mehta,[4] Chandra Kumar Mallick Kodavanti,[3] Abhishek Mishra.[5] *[1]Univ of Arkansas For Medical Sciences; [2]Icahn School Of Medicine at Mount Sinai; [3]Detroit Medical Center; [4]Mount Sinai Beth Isreal; [5]Univ of Iowa and Clinics.*

Background: Acute kidney injury requiring dialysis (AKI-D) is a serious and preventable complication in patients admitted with pneumonia. However, data on national trends in AKI-D after pneumonia are lacking after 2002.

Methods: We used the nationwide inpatient sample (NIS) database 2002-2013 to identify adults hospitalized with pneumonia using Clinical Classification Software (CCS) developed by AHRQ.We defined AKI-D based on previously validated ICD-9-CM codes including 584.xx for AKI, v45.11, v56.0 and v56.1 for dialysis and procedure code 39.95 for the dialysis procedure. We excluded hospitalizations that had codes for dialysis but not for AKI, as these were likely for ESRD patients on dialysis. We used the multivariate regression to analyze changes in trends and outcomes and explore potential reasons explaining these changes.

Results: From 2002-2013, of the 11,46,3481 patients who were hospitalized with pneumonia, 36975 (0.32%) developed AKI-D. Proportion of AKI-D increased from 0.27% hospitalizations in 2002 to 0.43% hospitalizations in 2013 (p<0.001). This trend increased annually by 6.1% (OR 1.06; 95% CI 1.05-1.07;p<0.001). Percentage of in-hospital morality (33% v/s 4%) and discharge to specialized care (49% v/s 26%) were higher among the AKI-D patients. Odds of in-hospital mortality (OR 2.08; CI 2.02-2.14; p<0.001) and discharge to specialized care (OR 1.78; CI 1.42-1.91; p<0.001) remains high even after adjusting the various confounding factors. Although the percent in-hospital mortality after AKI-D was decreased, the adjusted odds increased (OR 2.53 to 2.94). And also, the adjusted odds of requiring specialized care in a facility increased during the study period (OR 1.32 to 2.76).

Conclusions: The incidence of AKI-D in patients admitted with pneumonia has increased over the period of time. Our results emphasize the need for better risk stratification and early recognition of kidney dysfunction in patients with pneumonia.

SA-PO552

Rhabdomyolysis in Young Adults Asif Khan,[1] Lily Xu,[1] Saleha Riaz,[1] Jay Patel,[1] Doreen Chen,[1] Marianne Smith,[1] Elie El-Charabaty,[2] Suzanne E. El Sayegh.[2] *[1]Internal Medicine, Staten Island Univ Hospital, Staten Island, NY; [2]Nephrology, Staten Island Univ Hospital, Staten Island, NY.*

Background: Rhabdomyolysis (RB) is characterized by marked elevation of creatine phosphokinase (CK), myoglobinuria and aldolase in blood as the result of rapid skeletal muscle breakdown. The median age of RB is 47 years; however, there is a scarcity of the risk factors for RB in younger population. The current diagnostic criteria for RB include plasma markers that are non-specific and only detect muscle injury after it has already occurred. Researchers have been investigating neutrophil-Lymphocyte ratio (NLR) as an indicator of systemic inflammation; however to date its association with RB is limited.

Methods: This retrospective cohort study identified subjects aged between 18–49 years who were diagnosed with RB with a CK level of >1500 IU/L within the first 48 hours of admission. Frequency distribution or descriptive statistics for demographic and baseline disease characteristics were presented for all patients.

Results: A total of 331 subjects were included. 87.2% of the subjects were male and 12.8% were female. The median length of stay was 4 days with an overall mortality was 2.8%. The etiologies of 34.83% of the RB cases were due to illicit drugs; 16.47% of the cases were exercise induced, of which 94.7% were male and 72.7% related to severe intensity workouts, with a median CK of 8,840 IU/L. Illicit drug use was the major etiology in 28.1% of subjects with CK levels between 1,500-50,000 IU/L. Exercise was the major etiology (40%) in subjects with CK levels above 50,000 IU/L. There was a significant positive correlation between the NLR and the length of stay (p <0.0001).

Conclusions: The major etiologies of RB in adults <50 years old were illicit drug use (34.83%) and exercise (16.47%). S. CK was not an accurate prognostic indicator of RB in adults <50. Subjects with exercise induced RB had a much higher median serum CK, but their length of stay was less than the median. The NLR was shown to be positively correlated to the levels of serum CK and the total length of stay. This data suggests that the use of NLR can be an important prognostic indicator in RB.

SA-PO553

Acute Kidney Injury in Intensive Care Unit Patients: An International Registry Josee Bouchard,[1] Anjali Acharya,[2] Jorge Cerda,[3] Elizabeth R. Maccariello,[4] Rajasekara Chakravarthi Madarasu,[5] Ashita J. Tolwani,[6] Rolando Claure-Del Granado,[7] Andrew J.P. Lewington,[8] Enrico Fiaccadori,[9] Ravindra L. Mehta.[10] *[1]U de Montreal; [2]Jacobi Medical Center; [3]Albany Medical Coll; [4]Hosp Quinta d'Or; [5]CARE Hosp; [6]UAB; [7]U Mayor de San Simon; [8]Leeds Teaching Hosp; [9]U of Parma; [10]UCSD.*

Background: Acute kidney injury (AKI) is common and associated with increased morbidity and mortality.

Methods: We are conducting a prospective observational study to better characterize AKI in patients from 13 countries using AKIN criteria. We aim to highlight differences in AKI patients characteristics and outcomes over time, dividing our cohort by the median time of enrollment (Aug 2008-March 2011/April 2011-Nov 2015).

Results: Between 2008 and 2015, 2027 of 9780 patients (21%) had AKI during their 1st week of ICU, and we enrolled 1091 of them (54%). Over time, we observed several differences in patients characteristics, a decrease in the use of starches and diuretics, an increase in the number of kidney biopsies performed, and an earlier timing of initiation of dialysis. However, we did not observe significant changes in outcomes.

	2008-2011	2011-2015	p
Age (years)	62 (46-76)	59 (45-71)	0.03
Gender (male)	48.9	51.1	0.88
CKD	56.6	43.4	0.004
CAD	30.8	24.8	0.03
Sepsis	52.2	47.8	0.003
APACHE III	51 (35-72)	46 (32-64)	0.007
Mechanical ventilation	50.4	49.6	0.83
Pressors	53.2	46.8	0.13
Starches	8.2	3.7	0.001
Diuretics	56.3	43.7	0.001
Cumulative fluid balance (L)	2.3±6.9	1.9±6.5	0.43
AKI etiology			
ATN	14.7	21.8	0.002
GN	2.9	8.4	0.001
AIN	2.0	6.8	0.001
Prerenal	29.9	24.0	0.03
Biopsy	2.2	4.7	0.03
Dialysis requirement	23.2	22.1	0.68
Timing dialysis vs. ICU admission (days)	3 (1-7)	1 (0-4)	0.001
Duration dialysis (days)	5 (2-14)	6 (3-17)	0.63
Lengths of stay (days)	13 (6-27)	14 (6-28)	0.25
Mortality	21.4	18.2	0.28
Dialysis-dependence at discharge	11.9	12.1	0.77

Conclusions: Over the last 8 years, although we observed differences in patients characteristics and management, overall outcomes associated with AKI remained unchanged.

Funding: NIDDK Support

SA-PO554

A Nationwide Survey of Acute Kidney Injury in Patients with Malignancies in China

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Background: Patients with cancer are at a high risk of acute kidney injury (AKI), but the overall incidence of AKI in such patients and its severity remain largely unknown. The present study aimed to capture the current situation of AKI in patients with cancer in China and provide extensive information for prevention and management of AKI in such patients.

Methods: This nationwide multicenter retrospective cross-sectional study covered 82% of the population. In 2013, 2,223,230 adult patients from 22 academic and local hospitals each were screened for AKI via the Laboratory Information System using two screening criteria. To make the scope more manageable, we only examined the medical records of 26,086 patients with suspected AKI who were hospitalized in January or July. We recorded hospitalization data, all-cause in-hospital mortality, etc., and compared these data between patients with malignant tumor-related AKI (MR-AKI) and non-MR-AKI.

Results: We enrolled 1418 patients with MR-AKI and 6186 with non-MR-AKI. The detection rate of MR-AKI was significantly higher in academic hospitals versus local ones, mid-China versus south and north China, and affluent areas versus poor ones. However, the rate of MR-AKI non-recognition by the physicians in charge was very high in both academic and local hospitals. The all-cause in-hospital mortality rate among patients with MR-AKI was high at 19.2%, and another 18.6% with severe AKI withdrew from treatment. The rates of non-recognition and delayed recognition of AKI, all-cause in-hospital mortality, and treatment withdrawal and in-hospital costs were higher among patients with MR-AKI than those with non-MR-AKI.

Conclusions: To our knowledge, this study has the widest coverage of its kind thus far and accurately reveals the present situation of MR-AKI in China. Our findings could have clinical implications for patients with cancer in other developing countries as well.

SA-PO555

Phenotype of Vancomycin Associated Drug Induced Kidney Disease (DIKD): Results from the DIRECT Study

Linda Awdishu,[1] Rajasekara Chakravarthi Madarasu,[2] Stuart Goldstein,[3] Ashita J. Tolwani,[4] Melanie S. Joy,[5] Etienne Macedo,[1] Dinna Cruz,[1] Jorge Cerda,[6] David T. Selewski,[7] Andrew J.P. Lewington,[8] Michael Zappitelli,[9] Maria Ostermann,[10] Vivekanand Jha,[11] Ravindra L. Mehta.[1,12] *[1]Univ of California, San Diego; [2]Star Kidney Centers, India; [3]Cincinnati Children's Medical Center; [4]Univ of Alabama at Birmingham; [5]Univ of Colorado, Denver; [6]Albany Medical College; [7]Univ of Michigan; [8]Leeds Teaching Hospital, United Kingdom; [9]McGill Univ Health Center, Canada; [10]Guy's and St. Thomas' Hospital, United Kingdom; [11]Post Graduate Inst of Medical Education & Research, India; [12]On Behalf of DIRECT Investigators.*

Background: Vancomycin (VAN) is a frequently prescribed antibiotic in critically ill patients with conflicting published data on nephrotoxicity due to lack of phenotype standardization.

Methods: DIRECT is an international multi-center study which enrolled 634 patients with DIKD to identify drug-related polymorphisms by GWAS studies that were associated with standard phenotypes. Each case was adjudicated by 2 nephrologists.

Results: VAN associated AKI cases (N=171) were confirmed by adjudication (126 adult and 45 pediatric patients). Patients were 50% male with mean age of 47.7±18.2 years in adults and 12.3±4 years in pediatrics. Patients were 57% white, 24% hispanic, 13% black and 2% asian. Comorbidities included hypertension and diabetes in adults and asthma and cancer in pediatrics. AKI risk factors at baseline included diabetes 22%, hyperglycemia 28%, sepsis 21% and anemia 21%. The mean Scr increased from 0.78±0.34 to 4.42±2.46 mg/dL in adults and 0.46±0.19 to 2.5±1.95 mg/dL in pediatrics. Time to injury was 4(2-7) days. Biopsies were performed in 8% and dialysis was required for 17.5% cases. The initial VAN dose and serum concentration was 1991±899 mg/day and 26±18.4 mcg/mL in adults and 2191±1178 mg/day and 26.7±25.5 mcg/mL in pediatrics. Mortality was 5.4%, 9.4%, 19% at hospital discharge, 28 and 90 days and 27% of cases had elevations in Scr at 90 days.

Conclusions: VAN associated DIKD is a significant problem occurring in hospitalized patients receiving conventional dosing. Genome studies will further elucidate the mechanism of this injury.

Funding: Private Foundation Support

SA-PO556

Phenotype of NSAID Associated Drug Induced Kidney Disease (DIKD): Results from the DIRECT Study

Linda Awdishu,[1] Rajasekara Chakravarthi Madarasu,[2] Stuart Goldstein,[3] Ashita J. Tolwani,[4] Melanie S. Joy,[5] Etienne Macedo,[1] Dinna Cruz,[1] Jorge Cerda,[6] David T. Selewski,[7] Michael Zappitelli,[8] Andrew J.P. Lewington,[9] Maria Ostermann,[10] Vivekanand Jha,[11] Ravindra L. Mehta.[1,12] *[1]Univ of California, San Diego; [2]Star Kidney Centers; [3]Cincinnati Children's Medical Center; [4]Univ of Alabama at Birmingham; [5]Univ of Colorado, Denver; [6]Albany Medical College; [7]Univ of Michigan; [8]McGill Univ Health Centre; [9]Leeds Teaching Hospital; [10]Guy's and St. Thomas' Hospital; [11]Postgraduate Inst of Medical Education and Research; [12]On Behalf of the DIRECT Investigators.*

Background: Non-steroidal anti-inflammatory drugs can cause kidney injury by different mechanisms. Risk factors have been identified and include volume depletion and concurrent nephrotoxins.

Methods: DIRECT is an international multi-center study which enrolled 634 patients with DIKD to identify drug-related polymorphisms by GWAS studies that were associated with standard phenotypes. Each case was adjudicated by 2 nephrologists.

Results: NSAID associated AKI (N=64) and glomerular injury (N=2) were confirmed by adjudication (46 adult and 20 pediatric patients). Implicated NSAIDs were ibuprofen (N=39), indomethacin (N=2), ketorolac (N=16), ketoprofen (N=1) and naproxen (N=8). Patients were 44% male with mean age of 47.8±18.1 years in adults and 12.2±3.4 years in pediatrics. Patients were 45% white, 14% black, 14% hispanic and 27% asian. Co-morbidities included hypertension, diabetes and smoking in adults and asthma in pediatrics. The mean Scr increased from 0.91±0.31 to 4.48±2.84 mg/dL in adults and 0.49±0.18 to 3.04±2.76 mg/dL in pediatrics. Median (IQR) time to onset of injury was 4(2-7.5) days. Common risk factors were hyperglycemia, surgery and additional nephrotoxic exposures. Biopsies were performed in 17% with findings of interstitial nephritis in 64% of cases. Dialysis was required for 21.2% cases. Daily doses were ibuprofen 1131±654mg, ketorolac 58±36 mg and naproxen 974±402 mg. Mortality was 3.3%, 5.6% and 12.5% at hospital discharge, 28 and 90 days.

Conclusions: NSAIDs demonstrated significant increases in Scr across a range of risk factors, with infrequent definitive biopsies. Genome studies will further elucidate patient susceptibility to NSAID associated DIKD.

Funding: Private Foundation Support

SA-PO557

Vancomycin Induced Nephrotoxicity - Are We Over-Diagnosing

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Background: Vancomycin has been in use for more than half a century, but its extent of nephrotoxicity is still controversial. Most studies pertaining to vancomycin nephrotoxicity are observational and confounded by comorbidities, other nephrotoxins and, in studies considering achieved vancomycin concentrations as a risk factor, reverse causation. Purpose of this systematic review was to determine risk of acute kidney injury (AKI) attributable to intravenous (IV) vancomycin.

Methods: Pubmed, Cochrane Library were searched from 1990 through 2015 for randomized controlled trials (RCT) and cohort studies comparing IV vancomycin to a control group with a comparator antibiotic, in which kidney function or kideny injury outcomes were reported.Two reviewers extracted data and assessed risk of bias, one reviewer adjudicated assessments. We screened 1328 titles and abstracts, reviewed 115 articles and 7 RCT and 6 cohort studies were included in final analysis.

Results: All cohort studies were judged to have moderate or high risk of bias, so only qualitative synthesis was performed and did not provide strong evidence for vancomycin nephrotoxicity. Meta-analysis of 7 RCT suggested vancomycin was associated with increased risk of AKI (pooled RR 2.45, 95% CI 1.69-3.55). There was minimal heterogeneity between the studies (chi-square 3.67, $p = 0.72$, and $I^2 = 0\%$). Inspection of funnel plot showed no strong evidence of publication bias.However, evidence of vancomycin nephrotoxicity was judged to be indirect and of moderate strength as 12 of 13 studies compared vancomycin only to linezolid.

Conclusions: Vancomycin modestly increases risk of AKI; although substantial but still much lower compared to well-recognized nephrotoxins e.g. aminoglycosides (RR: 8-10) or amphotericin B (RR: 4-10). Nevertheless, in patients being treated with IV vancomycin that develop AKI, more than half of cases can be attributed to vancomycin (attributable fraction 0.59). A RCT of vancomycin designed to study renal outcome is needed to draw unequivocal conclusions.

SA-PO558

Comparative Incidence of Acute Kidney Injury between Vancomycin/ Cefepime and Vancomycin/Piperacillin-Tazobactam Combination Therapy

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Background: Acute kidney injury (AKI) is common during infections and may be potentiated by the use of nephrotoxic antibiotics. Combination of Vancomycin/ Piperacillin-Tazobactam (Vanc/Pip) has been associated with more AKI compared to Vancomycin/ Cefepime (Vanc/Cefe), though the mechanisms are unknown. We aim to compare rates of AKI after exposure to Vanc/Pip, Vanc/Cef, or Vanc/Pip/Cefe.

Methods: Multicenter retrospective cohort of adults exposed to >48 hours of (1) Vanc/Pip, (2) Vanc/Cefe or (3) Vanc/Pip/Cefe between January 2012 and January 2015. Participants in the Vanc/Pip/Cefe group were exposed to Cefepime either concurrently with Vanc/Pip, or within 90dys prior to admission. AKI was defined by AKIN criteria. Rates of AKI were analyzed using Chi-square tests and multivariable logistic regression.

Results: 5370 participants were included: 4,090 (76%) received Vanc/Cef, 997 (19%) received Vanc/Pip, and 283 (5%) received Vanc/Pip/Cefe.

Variable	Antibiotic Exposure			*P*
	Vanc/Cefe	Vanc/Pip	Vanc/Pip/Cefe	
Age, yrs, median (IQR)	65 (54, 75)	63 (51, 72)	63 (52, 73)	0.001
Male sex (%)	2283 (56)	576 (58)	163(58)	0.4
White race, (%)	3209 (78)	784 (79)	214 (76)	0.5
Hypertension (%)	2075 (51)	457 (45)	127 (45)	0.01
Diabetes (%)	1042 (26)	261 (26)	70 (24)	0.8
CKD (%)	1198 (29)	183 (18)	73 (26)	<0.001
LOS, days, median (IQR)	9 (5, 17)	9 (5, 15)	11 (6, 19)	0.001
Died during admission (%)	680 (17)	73 (7)	53 (18)	<0.001

Overall incidence of AKI was 24%. AKI was similar between Vanc/Pip and Vanc/Cef (24% vs. 23%; $P = 0.8$) but more common in the Vanc/Pip/Cefe group (31%; P=0.009). In multivariable analysis, compared to Vanc/Cefe, Vanc/Cefe/Pip use was associated with higher odds of AKI (OR 1.59 [95% CI 1.21, 2.10]), while Vanc/Pip use had similar odds of AKI (1.15 [95% CI 0.97, 1.40]).

Conclusions: Use of Vancomycin/Piperacillin-Tazobactam and Vancomycin/Cefepime resulted in similar rates of AKI. Use of all 3 antibiotics was associated with more AKI compared to either dual-regimen alone.

SA-PO559

Prescribing Patterns at the Time of Acute Kidney Injury: Opportunities to Improve Care

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Background: Currently, there is limited information about medication prescribing at the time of AKI and how this impacts on patient outcomes. We present a description of prescribing patterns at the time of AKI in the context of a prospective case-control study.

Methods: Participants were prospectively identified from a hospital-wide electronic AKI reporting system. Cases (hospitalised patients who sustained AKI) were matched 1:1 with controls (hospitalised patients without AKI) for age, baseline eGFR stage and diabetes. Electronic medical record was interrogated for complete prescribing details at sequential time points.

Results: 878 patients were successfully matched. Pharmacy confirmation of medication history occurred in 757 (87%) during admission.

At baseline, more cases than controls were prescribed ACE inhibitors/ARBs (206 (48%) vs 178 (41%), p=0.04) and NSAIDs (56 (13%) vs 30 (7%), p=0.003). There was no difference in prescription of statins, metformin or diuretics. At the time of AKI, 144 (33%) patients were administered ACEi/ARB and 37 (9%) cases received NSAIDs, suggesting suspension of medications in some cases.Within 24hrs of AKI onset, ACEi were stopped in 126 (88%) and NSAIDs in 34 (92%) of these. 188 cases were prescribed an antibiotic at the time of AKI; dosing was inappropriate in 61 (32%).

AKI diagnosis was communicated to primary care in 206 (47%) of cases at hospital discharge, and information regarding medication changes in only 123 cases (29%). At hospital discharge there was reduction in prescribing ACEi/ARB in both groups, but to a greater extent in AKI; 110 (26%) cases were prescribed ACEi/ARB at discharge, compared with 164 (37%) controls, p<0.001.

Conclusions: Whilst prescriber awareness of the importance of suspending nephrotoxic medications at time of AKI is evident, there are additional opportunities to reduce risk of AKI onset and to improve dose adjustment of common medications during AKI. Improving post-AKI care with consideration of restarting cardiovascular medications is another area in which benefits seem likely.

Funding: Private Foundation Support

SA-PO560

Carbapenem Antibiotics Are Associated with Significant Increases in Serum Creatinine after Contrast Administration

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Background: Carbapenem antibiotic use has been growing with the increase in resistant organisms. Imipenem, the initial drug in this class, was combined with cilastatin to reduce nephrotoxicity. Newer agents in this class are felt to be less nephrotoxic. Complete adverse effects of newer agents have not been fully defined. On this basis, the purpose of this study is to explore changes in serum creatinine (SCr) after contrast administration in patients on carbapenem antibiotics.

Methods: Patients receiving IV contrast with CT imaging over a 6 month period were identified. Dialysis subjects were excluded. Demographic data were obtained. All laboratory studies done on the day of imaging and SCr at 48hours were extracted. Vital signs and all medications administered on the day of the CT scan were noted. Change in creatinine from the day prior to CT imaging to 2 days after was calculated (Delta_SCr).

Results: Records for 2530 subjects were obtained. Delta_Scr for the cohort was -0.015+0.34mg/dl (-0.039+0.028mg/dl in those not receiving antibiotics). Delta_Scr for different antibiotic classes are shown below

Antibiotic administered on day of contrast	**Delta creatinine (mg/dl) at 48 hours (mean +/- SD)**	**p-value**
TMP/SMX	0.00 +/- 0.04	NS
Aztreonam	-0.05 +/- 0.06	NS
Linezolid	-0.03 +/- 0.05	NS
Aminoglycosides	0.07 +/- 0.05	NS
Vancomycin	0.04 +/- 0.02	0.013
Carbapenems	0.06 +/- 0.03	0.016

In univariate analysis, Delta_Scr was 0.064+0.027mg/dl (p=0.016) in patients receiving carbapenem antibiotics and IV contrast with 10% of subjects having SCr increase by >0.3mg/dl. Multivariate analysis showed the change in SCr was 0.059+0.027mg/dl (p=0.03).

Conclusions: Concomitant administration of carbapenem antibiotics and IV contrast was associated with a significant worsening of SCr in both univariate and multivariate analysis adjusting for demographic, hemodynamic, and other potential nephrotoxic variables. This study identifies a potentially novel risk factor for contrast induced nephropathy.

SA-PO561

Serum Vancomycin Levels Correlate with Significant Increases in Serum Creatinine after Contrast Administration Parker Lehmann,[1] Cheri Lehmann,[2] Udayan Y. Bhatt.[2] *[1]New Albany High School, New Albany, OH; [2]The Ohio State Univ Wexner Medical Center, Columbus, OH.*

Background: Vancomycin is commonly used in the treatment of drug resistant organisms. Rare nephrotoxicity has been reported with its use. However, vancomycin nephrotoxicity has not been fully characterized. On this basis, the purpose of this study is to characterize change in serum creatinine (SCr) in patients after IV CT contrast who are also receiving vancomycin.

Methods: After institutional approval, patients receiving intravenous contrast with CT imaging over a 6 month period were identified. Dialysis patients were excluded. Demographic data were obtained. All laboratory studies done on the day of imaging and SCr 48 hours after imaging were extracted. Vital signs and all medications administered on the day of the CT scan were obtained. Change in creatinine from the day prior to CT imaging to 2 days after was then calculated (delta_cr).

Results: Complete records for 2530 subjects were obtained. In univariate analysis, a significant linear relationship between serum vancomycin level and delta_cr was noted (slope = 0.015, p=0.001). Variables evaluated for multivariate model inclusion included demographic data, vital signs, and concomitant medications including vasopressor use, aminoglycoside use, and other potential nephrotoxins. A significant linear relationship between vancomycin level and delta_cr remained (slope=0.016, p=0.000). Multivariate quartile analysis was then performed.

Vancomycin Quartile Range	Increase in SCr (mg/dL)	p-value
0 to 10.45mcg/mL	Reference	Reference
10.45 to 14.4mcg/mL	0.075	0.321
14.4 to 19.85mcg/mL	0.121	0.116
Above 19.85mcg/mL	0.243	0.002

Conclusions: A significant linear relationship between vancomycin level and worsening SCr after IV contrast was noted. For every 10mcg/mL increase in vancomycin level, Scr would be expected to rise by 0.16mg/dl. Multivariate analysis found that vancomycin levels > 19.85mcg/mL were associated with a significant rise in SCr of 0.24mg/dl. This study demonstrates the additive nephrotoxicity of vancomycin and IV contrast. It also supports the clinical use of monitoring serum vancomycin levels.

SA-PO562

Incidence and Predictors of Acute Kidney Injury following the First Course of Cisplatin Shveta S. Motwani,[1,2] Sushrut S. Waikar,[1] Benjamin D. Humphreys,[3] Gary C. Curhan.[1] *[1]Brigham and Women's Hospital; [2]Dana-Farber Cancer Inst; [3]Washington Univ at St. Louis.*

Background: Cisplatin (Cis) associated acute kidney injury (C-AKI) has been reported in 25-30% patients after multiple courses. Knowledge regarding the risk factors comes from small studies with one type of cancer. We investigated the incidence and predictors of C-AKI, regardless of cause, following the first course of Cis across all cancer types.

Methods: Patients ≥18 yrs of age who received Cis from 2006-2014 at Massachusetts General Hospital and from 2001-2014 at Dana-Farber Cancer Institute/ Brigham and Women's Hospital were included in the study. Those with missing baseline (BL) or follow-up creatinine (Cr) or BL Cr >1.5mg/dl were excluded. C-AKI was defined as ≥0.3mg/dl rise in Cr over BL within 14 days of receiving the first dose. Demographic, clinical and laboratory data were extracted. Incidence rates were calculated. Exposures of interest were analyzed using multivariable logistic regression analysis with C-AKI as the primary binary outcome.

Results: Of the 5942 patients in the combined cohort, the mean ± SD of age was 56 ± 13 yrs, Cis dose 109 ± 54mg, bl Cr 0.9 ± 0.2mg/dl, serum albumin 4±0.5 g/dl, height 169±10 cm, weight 171±42 lbs, body mass index (BMI) 27±6 kg/m^2, with 56% being male, 88% white, 15% diabetic and 51% hypertensive. C-AKI occurred in 617 patients (10.4%). The results of regression analyses are presented in the table, with final model adjusted for BL Cr.

Variable	Univariate			Multivariable		
	OR	95% CI	P value	OR	95%CI	P value
Age,per 10 yrs	1.4	1.3,1.5	<0.0001	1.4	1.3,1.5	<0.0001
Male	1.6	1.3,1.9	<0.0001			
White	1.2	0.9,1.6	0.18			
Diabetes	1.5	1.2,1.9	<0.0001			
Hypertension	2.3	1.9,2.8	<0.0001	1.6	1.3,2.0	<0.0001
BLCr,per 0.3mg/dl	1.4	1.2,1.5	<0.0001	1.1	0.9,1.3	0.1
Albumin,g/dl	0.6	0.5,0.8	<0.0001	0.6	0.5,0.7	<0.0001
Dose,per 25mg	1.3	1.2,1.3	<0.0001	1.3	1.2,1.4	<0.0001
Ht,per 10cm	1.1	1.0,1.3	0.0002			
Wt,per 10 lbs	1.0	1.0,1.1	<0.0001			
BMI,kg/m^2	1.0	1.0,1.1	<0.0001			

Conclusions: C-AKI is frequent even after a single course. Hypertension and hypoalbuminemia are novel risk factors for C-AKI. These data may help identify those at high risk for kidney injury.

Funding: Other NIH Support - T32 training grant

SA-PO563

Acute Kidney Injury Biomarkers to Predict 3-Month Cisplatin Nephrotoxicity in Children Kelly McMahon,[1] Tom D. Blydt-Hansen,[2] Maury N. Pinsk,[3] Cherry Mammen,[2] Shahrad Rod Rassekh,[2] Ross T. Tsuyuki,[4] Prasad Devarajan,[5] Michael Zappitelli.[1] *[1]McGill U, Montreal; [2]U British Columbia, Vancouver; [3]U Manitoba, Winnipeg; [4]U Alberta, Edmonton, Canada; [5]Cincinnati Children's Hospital, Cincinnati.*

Background: Children often develop acute kidney injury (AKI) with cisplatin treatment. Late renal effects are common. Renal tubule injury markers neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) may help risk stratify for late cisplatin nephrotoxicity. Hypothesis: NGAL and KIM-1 predict chronic kidney disease (CKD) and hypertension (HTN).

Methods: Ongoing, 12-site, 3 year prospective study of cisplatin-treated children. Excluded: GFR<30 ml/min/1.73m^2. Protocol includes: Urine NGAL and KIM-1 measured at discharge of last (or second to last) cisplatin infusion; 3-month post-cisplatin visit outcomes: CKD: eGFR<90 by a)serum creatinine (SCr), b)cystatin C (CysC) equations ***or*** albumin-to-creatinine ratio>30mg/g; HTN: blood pressure≥95th percentile for age, gender, height. We compared cisplatin discharge NGAL&KIM-1 levels between subjects with/without 3-month CKD and HTN (Mann-Whitney) and calculated area under curve (AUC)[95%CI] for NGAL&KIM-1 to predict CKD, HTN.

Results: N=48 with complete 3-month data: median[IQR] age 6[3-12] years; 58% male. Table: Cisplatin discharge NGAL and KIM-1 were 2 to 8-fold higher in subjects with renal toxicity at 3 months. Table shows that cisplatin discharge NGAL predicted 3-month CKD or HTN more strongly (AUC 0.70-0.83) than KIM-1 did (AUC 0.60-0.70). AUCs for biomarkers to predict 3-month CKD were ~17% higher when CysC eGFR was used (Table).

Conclusions: Biomarkers measured near end of cisplatin therapy are associated with 3-month post-cisplatin CKD and HTN and may be useful to risk stratify for late renal effects screening and early cardiovascular risk reduction. CysC may be better at estimating GFR compared to SCr to define CKD in children.

Table: Urine NGAL and KIM-1 excretion and diagnostic characteristics for long-term renal outcomes 3 months post-cisplatin therapy completion. Comparison of patients with and without each late renal outcome. **Cisplatin Discharge**: last or before last cisplatin cycle of treatment plan (≥3rd infusion), biomarker measured at discharge.

	Cisplatin Discharge NGAL (ng)/ creatinine (mg) (median [IQR])		Cisplatin Discharge KIM-1 (pg)/creatinine (mg) (median [IQR])	
3-Month Renal Outcome	No Renal Toxicity	With Renal Toxicity	No Renal Toxicity	With Renal Toxicity
CKD (albuminuria *or* low SCr-eGFR)	15 [5.9-26] N=25	31 [12-121]* N=22 AUC 0.70 [0.54-0.85]	1024 [287-3389] N=25	2768 [876-4690] N=22 AUC 0.60 [0.44-0.77]
CKD (albuminuria *or* low CysC-eGFR)	13 [5.7-24] N=28	52 [28-153]* N=20 AUC 0.82 [0.70-0.94]	951 [225-3378] N=28	3259 [1287-7327]* N=20 AUC 0.70 [0.55-0.85]
Hypertension	14 [5.7-30] N=31	118 [23-175] N=3 AUC 0.83 [0.60-1.00]	1024 [242-2874] N=31	6963 [2.1-8240] N=3 AUC 0.61 [0.01-1.00]

Abbreviations: NGAL: Neutrophil gelatinase-associated lipocalin, KIM-1: Kidney injury molecule-1, IQR: Interquartile range, AUC: Area under the Curve, SCr: Serum creatinine, eGFR: Estimated glomerular filtration rate, CysC: Cystatin C, CKD: Chronic Kidney Disease.
Low eGFR: eGFR< 90ml/min/1.73m^2
SCr-eGFR: by updated Chronic Kidney Disease in Children (CKiD) equation
CysC-eGFR: by Zappitelli-CysC equation
Blood pressure: measured by an automated device. Mean of 2 lowest out of 3 readings is used.
Albuminuria: from random untimed urine sample at time of follow-up visit.
significant difference from no outcome group (p<0.05 by Mann-Whitney test)

Funding: Government Support - Non-U.S.

SA-PO564

Biomarkers of Cisplatin-Induced Kidney Injury in Children Kelly McMahon,[1] Tom D. Blydt-Hansen,[2] Maury N. Pinsk,[3] Cherry Mammen,[2] Shahrad Rod Rassekh,[2] Ross T. Tsuyuki,[4] Prasad Devarajan,[5] Michael Zappitelli.[1] *[1]McGill U, Montreal; [2]U British Columbia, Vancouver; [3]U Manitoba, Winnipeg; [4]U Alberta, Edmonton, Canada; [5]Cincinnati Children's Hosp, Cincinnati.*

Background: Acute kidney injury (AKI) and electrolyte abnormalities are common in children treated with cisplatin. Urine AKI biomarkers, neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1), may allow early AKI diagnosis and treatment. Hypothesis: urine NGAL and KIM-1 are diagnostic of cisplatin AKI.

Methods: 12-site, ongoing prospective study of cisplatin-treated children. Exclusion: GFR<30ml/min/1.73m^2. Study visits: Early Acute Visit ([AVE]: 1st or 2nd cisplatin infusion); Later Acute Visit ([AVL]:≥3rd infusion). Blood and urine sampling: pre-infusion, morning post infusion and discharge. Measures: serum creatinine (SCr), NGAL, KIM-1. Outcomes: a)Kidney Disease Improving Global Outcomes (KDIGO) AKI:≥50% SCr rise; b)Electrolyte-AKI:≥National Cancer Institute Grade 1 electrolyte abnormality (low serum potassium, phosphate or magnesium). We calculated % with AKI, compared AKI *vs.* non-AKI biomarkers at each timepoint (Mann-Whitney), characterized biomarker changes on treatment (Wilcoxon signed-rank), calculated area under curve (AUC)[95%CI] for NGAL and KIM-1 to diagnose AKI.

Results: N=95 with data: AVE median[IQR] age 5[2-13] years; hospital stay 5[3-15] days; %SCr rise of 73[60-125]; 54% male. KDIGO AKI: 21% AVE, 13% AVL. Electrolyte-AKI: 53% AVE, 75% AVL. Both: 13% AVE, 8% AVL. Especially for KIM-1, levels drop

immediately post cisplatin, then rise at discharge (Table). Table shows AKI biomarkers tend to be higher in AKI group(†). Biomarker AUCs for AKI diagnosis are higher at AVL (later cisplatin infusion) than AVE (Table, AVL AUCs range from 0.65-0.83).

Conclusions: Our novel data show that NGAL and KIM-1 are diagnostic of cisplatin-AKI, more so with later cisplatin infusions during cancer treatment.

Table: NGAL & KIM-1 excretion during cisplatin. At each timepoint, AKI *vs.* non-AKI biomarkers are compared for Early Acute Visit (AVE) and later AVL. Area under the curve (AUC) with 95%CI: In boxes, biomarker to diagnose AKI. LEFT: AKI defined by SCr KDIGO definition. RIGHT: AKI defined by KDIGO & Electrolyte NCI definition. Timepoints: pre-infusion, post-infusion and discharge. Median [interquartile range] biomarker levels shown.

	KDIGO AKI Definition		KDIGO & Electrolyte AKI Definition	
Timepoint	**Non-AKI**	**AKI**	**Non-AKI**	**AKI**
AVE NGAL (ng)/creatinine (mg)	**N=66**	**N=17**	**N=74**	**N=9**
AVE Pre	17 [6.1-30]	17 [6.6-60]	17 [6.6-31]	15 [6.3-62]
	AUC 0.55 [0.39-0.72]		**AUC 0.53** [0.30-0.77]	
AVE Post	15 [5.9-36]	11 [4.5-38]	15 [5.8-36]	11 [10-116]
	AUC 0.49 [0.31-0.67]		**AUC 0.54** [0.31-0.78]	
AVE Discharge	15 [6.6-56]	36 [9.7-108]#	16 [6.6-59]	36 [18-96]
	AUC 0.62 [0.45-0.79]		**AUC 0.63** [0.43-0.82]	
AVE KIM-1 (pg)/creatinine (mg)	**N=65**	**N=17**	**N=73**	**N=9**
AVE Pre	379 [174-835]	635 [217-3419]	389 [174-845]	635 [217-3419]
	AUC 0.60 [0.43-0.77]		**AUC 0.61** [0.40-0.83]	
AVE Post	193 [114-442]*	265 [102-610]	193 [114-447]*	213 [91-2585]
	AUC 0.55 [0.37-0.72]		**AUC 0.53** [0.27-0.78]	
AVE Discharge	924 [316-3028]	2228 [1307-4343]†	1105 [374-3031]	2019 [307-5278]
	* # **AUC 0.67** [0.53-0.81]		* # **AUC 0.60** [0.37-0.83]	
AVL NGAL (ng)/creatinine (mg)	**N=48**	**N=8**	**N=51**	**N=5**
AVL Pre	15 [5.1-30]	36 [18-84]	15 [5.0-32]	37 [35-91]
	AUC 0.66 [0.43-0.89]		**AUC 0.71** [0.43-0.98]	
AVL Post	9.9 [5.3-23]	41 [9.1-83]	10 [5.3-27]	32 [9.3-110]
	AUC 0.70 [0.50-0.90]		**AUC 0.72** [0.47-0.96]	
AVL Discharge	19 [6.0-30]	104 [6.7-274]	19 [6.0-31]	176 [34-371]†
	AUC 0.66 [0.37-0.95]		**AUC 0.82** [0.57-1.00]	
AVL KIM-1 (pg)/creatinine (mg)	**N=48**	**N=8**	**N=51**	**N=5**
AVL Pre	446 [150-1107]	697 [449-1694]	453 [153-1128]	939 [452-1818]
	AUC 0.65 [0.45-0.86]		**AUC 0.66** [0.37-0.96]	
AVL Post	204 [119-739]	6462 [306-15910]†	232 [123-784]	367 [257-18974]
	AUC 0.77 [0.60-0.93]		**AUC 0.71** [0.45-0.96]	
AVL Discharge	1178 [272-3286]	7003 [3074-10222]†	1325 [275-3420]	4079 [2069-10546]
	* # **AUC 0.83** [0.67-0.98]		* # **AUC 0.74** [0.51-0.98]	

† significant difference from Non-AKI group (p<0.05 by Mann-Whitney test)
* significant difference from pre timepoint (p<0.05 by Wilcoxon signed-rank test)
# significant difference from post timepoint (p<0.05 by Wilcoxon signed-rank test)
Additional information: 6/95 (6%) had KDIGO Stage 2 or 3 AKI at AVE; 3/63 (5%) at AVL.
AVE: 42% hypophosphatemia, 21% hypomagnesemia, 14% hypokalemia. Similar for AVL.

Funding: Government Support - Non-U.S.

SA-PO565

Association of Proton Pump Inhibitors with Acute Kidney Injury in Geriatric Population Zara Nisar. *Nephrology, Khyber Teaching Hospital, Peshawar, KPK, Pakistan.*

Background: Acute Kidney Injury in elderly patients presents with a wide range of clinical manifestations from an elevation in serum creatinine to anuric renal failure, arises from multiple causes, and occurs in a variety of clinical settings. The main objective of this study is to establish the relationship of use of Proton Pump Inhibitors as a risk factor for AKI in geriatric population.

Methods: A retrospective descriptive analysis was done from 31st December 2012-31st December 2015. Data was analyzed using SPSS (version 21). A total number of 18,668 outpatient prescriptions for PPIs were written.

Results: A total number of 18,668 outpatient prescriptions for PPIs were written. Among them were 9978 (53.44%) cases of Acute Kidney injury reported within 120 days of receiving the prescription. 5577 (55.89%) patients presented with decrease in urine output. 3678 (36.86%) cases reported with additional shortness of breath, swelling in the ankles/legs. 723 (7.24%) cases were presented with confusion and dizziness. Serum creatinine level was greater to or equal to 1.5mg/dl in 7892 (79.09%). In 2086 (20.90%) cases it was greater than or equal to 2.5mg/dl.

Conclusions: PPIs use is associated with an increased risk of Acute Kidney Injury in elderly patients. The study was limited by its retrospective nature, which hindered the its ability to draw conclusions regarding the connection between PPIs exposure and AKI onset. However, PPIs are perhaps the most common avoidable AKI risk to which elderly patients are regularly exposed. Doctors should continue to provide careful PPI education to the patients, and they should be regularly monitored for signs of Acute Kidney Injury.

SA-PO566

Renal Toxicities of Anti-Myeloma Agents Rimda Wanchoo, Valerie Suzanne Barta, Vipulbhai Sakhiya, Kenar D. Jhaveri. *Nephrology, Hofstra Northwell School of Medicine, Great Neck, NY.*

Background: Survival for patients with multiple myeloma(MM) has significantly increased in the last decade in large part due to development of proteasome inhibitors and immunomodulatory drugs. Drugs with novel mechanisms of action and targeted therapies are being explored both in the pre-clinical and clinical settings in myeloma. A possible limiting feature for these agents is their potential for nephrotoxicity.

Methods: We reviewed the FDA adverse event reporting system (FAERS) quarterly legacy data file 3rd quarter of 2011 to 2nd quarter of 2016 for all novel MM agents. Well established chemotherapy agents such as cyclophosphamide, melphalan and anthracyclines were excluded. The adverse event terms queried were: "hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, hypocalcemia, hypercalcemia, hyperkalemia, hypernatremia, hyperphosphatemia, proteinuria, renal failure acute, acute kidney injury, elevated creatinine, hypercreatinemia, hypertension and nephritis". We also reviewed the literature for case reports, case series and the primary studies of these agents for any known nephrotoxicities.

Results:

DRUG NAME	RENAL IMPAIRMENT*	HYPO-KALEMIA	HYPO-NATREMIA	HYPO-MAGNESEMIA	HYPER-KALEMIA	HYPOPHOSPHATEMIA	HYPER-NATREMIA	GRAND TOTAL
LENALIDOMIDE	881	136	61	33	25	28	8	1172
EVEROLIMUS	586	52	35	23	24	19	4	743
BORTEZOMIB	325	65	51	10	25	24	9	509
SIROLIMUS	249	8	13	2	9	7	0	288
VEMURAFENIB	176	11	18	2	4	0	0	228
POMALIDOMIDE	113	4	10	2	3	0	1	133
CARFILZOMIB	85	12	8	2	8	9	0	130
VORINOSTAT	44	26	26	0	10	16	2	124
DABRAFENIB	32	2	13	2	0	1	0	50
TRAMETINIB	28	1	11	3	0	1	0	44
NIVOLUMAB	20	5	14	2	4	1	0	44
PEMBROLIZUMAB	16	3	19	0	1	0	0	39
PANOBINOSTAT	11	2	3	1	2	2	0	22

Figure above summarizes the drugs studied and results found. Lenolidomide, everolimus and bortezomib were the top three offenders with AKI as the most common finding reported. Newer agents such as carfilzomib, BRAF inhibitors and PD-1 antagonists do have rare renal side effects. The review of literature found toxicities associated with lenolidomide, bortezomib and carfilzomib as top offenders. Importantly, the toxicities reported here are not just when these agents are used in MM but for other cancer treatments as well.

Conclusions: Novel targeted therapies being used in MM can be nephrotoxic. Knowledge of novel agents used in MM and their renal toxicities is important for the nephrologist and the hematologist.

SA-PO567

High-Dose Leucovorin as Sole Therapy for High-Dose Methotrexate Toxicity Carlos D. Flombaum,[1,2] Dazhi Liu,[1] Shirley Qiong Yan,[1] Amelia Chan,[1] Sherry Mathew,[1] Paul A. Meyers,[1,2] Ilya Glezerman,[1,2] Thangamani Muthukumar.[2,1] [1]*Memorial Sloan Kettering Cancer Center, New York, NY;* [2]*Weill Medical College of Cornell Univ, New York, NY.*

Background: High-dose MTX (HDMTX) therapy complicated by acute kidney injury is a medical emergency. Prolonged exposure to elevated MTX levels creates a high risk for severe mucositis, myelosuppression and death. High-dose leucovorin (HDLV) and alkalinization of the urine are the basis of support for these patients. More recently, glucarpidase (**G**) has been introduced to circumvent MTX toxicity. We aimed to investigate whether or not HDLCV and supportive therapy alone, without **G**, can prevent systemic toxicity from HDMTX.

Methods: To identify patients at high risk for severe MTX toxicity, we performed a retrospective review of all patients treated between 2000 and 2011 who had MTX levels 10 ≥ times of what are considered toxic levels at 48 and/or 72 hours after HDMTX (≥ 10 µmol/L at 48 hours and/or ≥ 1 µmol/L at 72 hours).

Results: 103 patients who received 113 courses of HDMTX were identified. Serum creatinine increased by a median of 2-fold from baseline (range 1–10 fold) but all patients recovered renal function. Median (range) MTX levels at 24, 48 and 72 hours post MTX administration were 69 (2. 2–410), 7.2 (1. 3–85) and 2.2 (0.0 5–26) µmol/L. MTX levels remained ≥0.1 µmol/L for a median of 9 days (range 0–19 days). There was a high correlation between MTX levels at 48, 72, 96 and 120 hours but not between 24 hours and subsequent time points. 83% of the patients received IV HDLCV, given within the first 48 hours in 84%. Myelosuppression was present in 39% of patients: grade≥III neutropenia in 27.4% and thrombocytopenia in 22%. Infectious complications, oral mucositis and diarrhea occurred in 19.5, 15 and 5.3 % of patients. There were 5 deaths, none directly attributed to complications from HDMTX.

Conclusions: We treated 113 episodes of HDMTX–associated renal dysfunction with a strategy that only included usual supportive measures and HDLV . We observed no HDMTX–associated mortality and the incidence of systemic complications was comparable to other studies where **G** was used. Glucarpidase is an extremely expensive drug and probably unnecessary in a significant number of patients.

SA-PO568

Renal Adverse Events of Immune Check Point Inhibitors Nupur N. Uppal, Valerie Suzanne Barta, Kenar D. Jhaveri, Rimda Wanchoo. *Nephrology, Hofstra Northwell School of Medicine, Great Neck, NY.*

Background: Enhancing anti-tumor T cell immunity with checkpoint inhibitor antibodies [anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-program death 1 (PD-1)] has shown significant clinical benefits in tumor regression and prolonged stabilization melanoma and other cancers. These agents are termed immune check point inhibitors(ICI).

Methods: To better understand recent published contributions related to ipilimumab, pembrolizumab and nivolumab induced renal toxicities, a Medline search of indexed manuscripts was conducted. The search terms 'renal failure' and 'acute kidney injury' with subheadings 'ipilimumab', 'pembrolizumab' , 'nivolumab' and 'nephrotoxicities' were employed. We also searched for 'hypokalemia, hypocalcemia, hyponatremia and hypophosphatemia'.Primary data from the initial studies of these agents and the FDA adverse reporting system(FAERS) database were also reviewed.

Results: A total of 18 citations were found. Acute interstitial nephritis, podocytopathy and hyponatremia are the three most common adverse renal findings related to the ICI. This figure compares the two reported classes of targeted therapies.The FAERS database had significant more reported renal toxicities with ipilimumab compared to the anti PD-1 agents.

Agents	CTLA-4 Antagonists(Ipilimumab)	PD-1 Inhibitors(Nivolumab and Pembrolizumab)
Onset of AIN	AIN appears 6-12 weeks	AIN appears 3 months – 12 months
Glomerular findings	Podocytopathy reported	No cases of podocytopathy reported
Gender	6/7 cases reported above were males	No gender preferences
Electrolyte disorders	Hyponatremia cases related to hypophysitis	Hyponatremia is rare
Transplant	In renal transplant patients, 2 cases reported no rejection when given as a solo agent.	When given lead to transplant rejection especially following use with CTLA-4 inhibitors(3 cases reported)

Conclusions: Renal injury appears to be part of the spectrum of immune-related adverse events. All agents are known to cause AIN. The renal insult related with ipilimumab appear to happen earlier in the course of the drug therapy (6-12 weeks following treatment) compared to events associated with PD-1 inhibitors appear around 6-10 months following initiation of treatment. Early recognition of immune mediated renal toxicities is important as treating with steroids promptly improves renal function. In kidney transplant patients, a preventive strategy might be needed to alleviate the chances of rejection.

SA-PO569

Incidence of AKI with Immune Checkpoint Inhibitors at a Single Center Jamie S. Hirsch,[1] Rimda Wanchoo,[1] Valerie Suzanne Barta,[1] Kenar D. Jhaveri,[1] Craig Devoe.[2] *[1]Nephrology, Hofstra Northwell School of Medicine; [2]Hematology/Oncology, Hofstra Northwell School of Medicine.*

Background: Immune checkpoint inhibitors (ICI) target the immune system and are increasingly being used to treat various cancers. Based on few published case reports, both anti-cytotoxic T lymphocyte protein-4 and anti-program death(PD-1) can lead to immune related adverse renal effects. We wanted to evaluate the incidence of AKI with these agents at a single center.

Methods: Data were obtained from Northwell Health's EHR, and included all patients receiving ipilimumab, nivolumab, or pembrolizumab at infusion centers between May 2011 & May 2016. Patients were included if they had at least one creatinine (Scr) measurement available prior to the first treatment and at least one Scr measurement following the first treatment. AKI was defined by KDIGO criteria. We compared data of the patients who developed AKI to those that didn't. Chi-squared testing was used to compare categorical variables and Student's t-test to compare continuous variables.

Results: Of 211 patients receiving ipilimumab (CTLA-4), nivolumab, or pembrolizumab at our center, 99 had Scr available for analysis. AKI Stage I developed in 29% (11/38) of CTLA-4 and 24.5% (15/61) of PD-1 patients, while AKI Stage II developed in 5% (2/38) and 10% (6/61), respectively. Table below summarizes the breakdown of patients that developed AKI vs no AKI, and no statistically significant differences were noted between the groups.

Ipilimumab	AKI	No AKI
Male (%)	82	70
Race (White) (%)	45	78
Mean SCr(mg/dl)	1.04	0.91
Melanoma diagnosis(%)	91	92.5
Median age(years)	66	64
Nivolumab/Pembrolizumab	**AKI**	**No AKI**
Male (%)	60	59
Race (White) (%)	47	61
Mean SCr (mg/dl)	0.96	0.98
Melanoma diagnosis(%)	13	21
Median age (years)	68	64

PD-1 were being used in cancers other than melanoma compared to CTLA-4 which was used primarily in melanoma.

Conclusions: In a single center study, the incidence of AKI in both CTLA- and PD-1 was high at 29% and 24.5%, respectively. No specific gender,age, or CKD differences were noted. Given the high incidence of AKI with ICIs,nephrologists & oncologists need to be aware of the nephrotoxicities.

SA-PO570

Gadolinium-Contrast Nephrotoxicity in Patients with Chronic Kidney Disease Stage 1 Shokichi Naito, Kouju Kamata, Kazuhiro Takeuchi, Tetsuya Abe, Haruka Takahashi, Yasuo Takeuchi. *Nephrology, Kitasato Univ School of Medicine, Sagamihara, Kanagawa, Japan.*

Background: Gadolinium (Gd)-contrast mediums (GCM) used in magnetic resonance imaging (MRI) have been traditionally considered non-nephrotoxic contrast materials. On the other hand, we have shown that an ionic contrast medium, Omniscan affected renal function transiently in patients with less than 1.6 mg/dl of serum creatinine (S-Cr) in ERA-EDTA 2012. However, there are no reports on the nephrotoxicity of GCM in early stages of chronic kidney disease (CKD). We investigated the effect of Gd-contrast medium on renal function in CKD stage 1 after MRI.

Methods: Patients aged 20–80 years, weighing 45–70 kg, and with CKD stage 1 in the 3 months prior to undergoing an MRI were enrolled. They were randomly divided into an ionic contrast medium (Omniscan) administration group (group O) and a nonionic contrast medium (Magnevist) administration group (group M). GCM (0.01 mmol/kg) was administered to all patients. We measured levels of S-Cr and serum cystatin C (S-Cys), as well as estimated glomerular filtration rate (eGFR) and estimated creatinine clearance rate (eCCr) using MDRD and the Cockcroft-Gault formula, respectively, just before and 24–72 h after the MRI. Mann-Whitney U-test and Wilcoxon signed-ranks test were employed for statistical analysis.

Results: There were no significant differences in the clinical background characteristics such as age, sex, and serum concentrations of albumin, S-Cr, S-Cys, eGFR, and eCCr between group O (n=21) and group M (n=32). There were no significant differences in S-Cr, eGFR, or eCCr before MRI and 24–72-h after MRI measurements of both groups. S-Cys levels increased significantly 24–72 h after MRI only in group O (0.69 ± 0.14 vs. 0.72 ± 0.11, P=0.047), whereas, there were no significant differences in S-Cys levels in group M (0.70 ± 0.18 vs. 0.69 ± 0.19, P=0.698).

Conclusions: The nonionic contrast medium, Magnevist, had no effect on renal function during MRI, while the ionic contrast medium, Omniscan, affected renal function transiently in the patients with CKD stage 1.

Funding: Pharmaceutical Company Support - Daiichi Sankyo Co., LTD., Tokyo, Japan

SA-PO571

Outcome of Patients with Acute Kidney Injury Secondary to p-Phenylenediamine (Kala-Pathar) Poisoning Syed A. Khalid,[1] Sidra Saleem,[1] Syed Rizwan A. Bokhari,[1] Hafiz I. Ahmad,[1] Arif Asif.[2] *[1]Nephrology, Allama Iqbal Medical College/ Jinnah Hospital Lahore, Pakistan; [2]Internal Medicine, Jersey Shore Univ Medical Center, NJ.*

Background: In the developing countries, household hair dye ingestion is emerging as a cheap and readily available compound to commit suicide. This Hair dye (known as "kala-pathar" in local language) contains p-Phenylenediamine having a molecular weight of 108.14112 g/mol and a host of other chemicals which lead to multi-organ dysfunction. Renal manifestations include metabolic acidosis and severe acute kidney injury. Previous studies have revealed high morbidity and mortality with PPD poisoning. No specific antidote or medicine for p-Phenylenediamine poisoning is available so far. We aimed to explore the clinical course and outcome of patients who developed AKI in this poisoning.

Methods: In this case series we observed patients with AKI secondary to p-Phenylenediamine poisoning admitted under nephrology service between 12-2015 to 05-2016. Patient demographic characteristics, clinical features and their outcomes were recorded. AKI was defined as per Acute Kidney Injury Network Group.

Results: Six patients, with AKI secondary to p-Phenylenediamine poisoning, were included in this study. Four (66%) were females with mean age 20.8 (range 14-25). Five (83%) were admitted to the medical floor and one (17%) patient was admitted in the ICU for ventilatory support. All of these patients ingested Kala-Pathar with suicidal intention. Oliguria, cervicofacial edema and dysphagia were the commonest presentations. All 6 patients had oliguria at presentation, whereas 4(66.7%) developed anuria during the first few

days of hospital admission. Four patients (66.7%) had rhabdomyolysis. All patients required hemodialysis with an average of 7 sessions (range 5-8). Five patients on medical floor made a full recovery from AKI in 7-8 weeks, while one patient admitted to the ICU expired.

Conclusions: Our study is the first to demonstrate promising results in majority of patients recovering from AKI due to p-Phenylenediamine poisoning, with timely hemodialysis and supportive care.

SA-PO572

Save the Kidneys: Using a Scoring System to Reduce Contrast Induced Nephropathy following Coronary Angiography Kelly M. Tierney,[1] Aaron Ho,[1] Mingxi Dennis Yu,[1] Laura J. Maursetter,[1] Todd L. Goldman,[1] Brad C. Astor,[1] Carol F. Otterson,[2] Mary K. Lease,[2] Mohun Ramratnam.[1] *[1]Univ of Wisconsin, Madison, WI; [2]William S. Middleton VA, Madison, WI.*

Background: Contrast-induced nephropathy (CIN) is a leading cause of hospital-acquired acute kidney injury. Though pre-hydration is commonly used to prevent CIN, there is significant variability in its use. The goal of this study was to evaluate the utilization and outcomes associated with a pre-hydration protocol for cardiac angiography based on the Mehran risk score (MRS) to achieve a lower rate of CIN compared to published incidence (5-15%).

Methods: All patients undergoing a coronary angiogram at the William S. Middleton VA Hospital between Feb 2014 and Dec 2015 were enrolled, excluding those on dialysis or vasoactive agents. Risk for CIN was assessed with the MRS and pre-hydration was ordered for those with a score ≥6 if they were not hypervolemic. CIN was defined as an increase in creatinine (Cr) of >50% or 0.3 mg/dL 48-72 hrs post-procedure.

Results: A total of 412 patients enrolled and had follow-up Cr values. Of these, 42.5% had diabetes, 25.7% had CHF, and 23.1% underwent PCI. The average pre-procedural Cr was 1.18 mg/dL. Patients with higher MRS were more likely to receive pre-hydration ($p<0.001$). A total of 14 (3.4%) patients developed CIN. Those with CIN had higher pre-procedural Cr ($p<0.01$) and higher MRS ($p<0.001$) than those without. The MRS components most strongly associated with CIN were anemia (IR=1.5;95%CI 1.1-2.1) and GFR <60 ml/min/1.73m^2 (IR=2.1;95%CI 1.1-3.8). Pre-hydration was associated ($p=0.05$) with a lower incidence of CIN after adjustment for MRS (OR=0.95;95%CI 0.90-0.99). All patients with CIN were followed by inpatient providers or referred to nephrology and 12/14 (86%) had complete resolution of their CIN.

Conclusions: Protocol-driven pre-hydration, based on the MRS, was associated with a lower incidence of CIN compared to published rates. Pre-hydration was associated with lower risk of CIN after adjusting for risk score. This supports the use of pre-hydration prior to coronary angiography. Further studies are needed to define the most effective protocol and assess the impact this interdisciplinary approach has on outcomes.

SA-PO573

Incidence and Risk Factors for Acute Kidney Injury following Coronary Angiography in the Era of Isosmolar Contrast Agents Dadi Helgason,[1,2] Thorir E. Long,[1,2] Sólveig Helgadóttir,[2] Runolfur Palsson,[1,2] Gisli H. Sigurdsson,[1,2] Tomas Gudbjartsson,[2] Martin I. Sigurdsson,[3] Ingibjorg J. Gudmundsdottir,[2] Olafur S. Indridason.[2] *[1]Univ of Iceland; [2]Landspitali - the National Univ Hospital of Iceland, Reykajvik, Iceland; [3]Brigham and Woman's Hospital, Boston, MA.*

Background: Acute kidney injury (AKI) remains a serious complication of coronary angiography (CA), despite less toxic contrast media and advances in imaging.We studied recent trends in incidence and risk factors of AKI following CA.

Methods: This was a retrospective study of all patients undergoing CA, with or without coronary intervention, in Iceland in 2008-2015. All procedures were performed using iodixanol, an iso-osmolar contrast agent. AKI was defined according to the serum creatinine (SCr) part of the KDIGO criteria. Data was collected from the Swedeheart/SCAAR database and hospital electronic records. Poisson regression was used to evaluate incidence changes and multivariate logistic regression to identify predictors of AKI.

Results: A total of 10,891 patients underwent 13,983 CAs and baseline SCr was available for 97.3% of the cases. AKI occurred in 281 cases (2.1%); 218 (1.6%), 33 (0.2%) and 30 (0.2%) classified as stage 1, 2 and 3, respectively. Annual incidence of AKI was 20.6/1000 CA/year and did not change significantly over the study period ($p=0.31$). AKI patients received higher doses of contrast media compared to non-AKI patients (163.9 mL vs. 128.7 mL, $p<0.0001$). In multivariate analysis, age (per year, OR=1.04, 95% CI=1.03-1.05), eGFR <60 mL/min/1.73 m^2 (OR=5.91, 95% CI=4.30-8.07), emergency CA (OR 6.37, 95% CI=4.82-8.43), disease found requiring CABG evaluation (OR=2.74, 95% CI=1.83-4.06), femoral access (OR=1.38, 95% CI=1.06-1.81), contrast dose (per 10 mL; OR=1.03, 95% CI=1.004-1.046), fluoroscopic time (per 10 min; OR=1.17, 95% CI=1.03-1.31), and procedural complications (OR=4.15, 95% CI=1.97-8.10) were associated with increased risk of AKI.

Conclusions: In this nationwide study, the incidence of AKI following CA was 2%; with similar rates during the 8-year period. In spite of use of iso-osmolar contrast agent its dose still associates with AKI along with emergency CA, procedural duration and complications and femoral access.

Funding: Government Support - Non-U.S.

SA-PO574

Preinterventional Kynurenine Predicts Long-Term Outcome after Contrast Media Exposure due to Coronary Angiography Christoph Reichetzeder,[1,2] Fabian Heunisch,[2] Gina Von Einem,[2] Markus Lukas Alter,[3,2] Karl-Heinz Kellner,[4] Thomas Bernd Dschietzig,[5,9] Axel Kretschmer,[6] Berthold B. Hocher.[1,7,8] *[1]Inst for Nutritional Science, Univ of Potsdam; [2]Center for Cardiovascular Research, Charité - Universitaetsmedizin Berlin; [3]Dept of Nephrology - CBF, Charité - Universitätsmedizin Berlin; [4]Neuroimmun GmbH, Karlsruhe, Germany; [5]Dept of Cardiology and Angiology - CCM, Charité - Universitätsmedizin Berlin; [6]Bayer Pharma AG, Wuppertal, Germany; [7]Inst for Laboratory Medicine, Berlin, Germany; [8]Dept of Basic Medicine, Medical College of Hunan Normal Univ; [9]Immundiagnostik AG, Bensheim, Germany.*

Background: Contrast media (CM) induced nephropathy (CIN) remains a serious complication of CM enhanced procedures. There is still a lack of established biomarkers that help to identify patients at high risk for long term complications. The current study aimed to evaluate plasma kynurenine as a predictive biomarker for long term complications of CM exposure due to coronary angiography.

Methods: 245 patients undergoing coronary angiography were analyzed in this prospective cohort study. Blood and urine samples were obtained at baseline/24h/48h after CM application to diagnose CIN. Patients were followed for 120 days for adverse clinical events. Long term outcome was measured by the combined endpoint "Major adverse kidney events" (MAKE) including death, the need for dialysis, doubling of plasma creatinine and rehospitalization.

Results: Preinterventional plasma kynurenine (PKYN) was not associated with CIN. Patients who later developed MAKE displayed significantly increased PKYN levels ($p<0.0001$). ROC analysis revealed that PKYN is highly predictive for MAKE (AUC=0.838; $p<0.0001$;). The optimal cutoff was found at ≥3.5 µmol/L. Using this cutoff, the Kaplan-Meier estimator demonstrated that concentrations of PKYN ≥3.5 µmol/L were significantly associated with a higher prevalence for MAKE until follow up (Chisquare=31.59; $p<0.0001$;) This association remained significant in multivariate Cox regression models adjusted for relevant factors of long term renal outcome.

Conclusions: Results of this study showed that preinterventional kynurenine might serve as a highly predictive biomarker for MAKE up to 120 days after coronary angiography.

SA-PO575

Incidence and Risk Factors for Contrast Induced Nephropathy (CIN) Among Cancer Patients Sheron Latcha,[1] Junting Zheng,[2] Andrew Plodkowski.[3] *[1]Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; [3]Radiology, Memorial Sloan Kettering Cancer Center, New York, NY.*

Background: Recent publications question the existence of AKI from intravenous contrast administration. Understanding the incidence and risk factors for CIN in cancer patients is important since these patients rely on CT imaging to establish cancer stage and response to chemotherapy.

Methods: Retrospective data was collected on all adult inpatients at Memorial Sloan Kettering Cancer who had a contrast (CON) or non contrast (NC) CT of the head, neck and chest from 1/1/2012-12/30/2014 with a creatinine (Cr) within 3D pre and post CT. Patients were excluded if a CON CT was done within 3D before a NC CT. Acute kidney injury (AKI) was defined as an increase in Cr > 0.3mg/dl or 1.5X baseline. ICD 9 codes were used to identify diagnoses and medications previously identified as risk factors for CIN (multiple myeloma (MM), diabetes, congestive heart failure (CHF), hypotension, liver metastases, chronic kidney disease (CKD), AKI, nonsteroidal anti inflammatory medications (NSAIDs), ACE inhibitors, ANGII receptor blockers, bisphosphonates, VEGF and immune checkpoint inhibitors, EGFR therapy, tyrosine kinase inhibitors, gemcitabine and cisplatin). Rao-Scott Chi-square test was used to examine AKI rate differences.

Results: 5178 NC CT and 2654 CON CT were included. The incidence of AKI was significantly greater in the NC group (11.5% vs 7.2% in CON group) and in those with GFRs <59ml/min, CHF, no liver metastases, CKD, AKI, chemotherapy within 60D of CT, EGFR therapy, leukemia, lymphoma, MM ($p<0.001$ for all above), male genital system tumors ($p=0.014$) and NSAIDs ($p=0.007$).

Conclusions: In this large cohort of cancer patients, IV contrast administration was not associated with increased AKI from CIN. Indeed, a significantly higher incidence of AKI was found in the NC group. The incidence was also higher in those with GFR <59ml/min, AKI, recent chemotherapy, EGFR therapy, NSAIDs, leukemia, lymphoma, male genital tumor and MM.

SA-PO576

Impact of Serum Uric Acid on Renal Outcome after Contrast Enhanced Computerized Tomography Ming-Ju Wu. *Div of Nephrology, Taichung Veterans General Hospital, Taichung, Taiwan.*

Background: The association between serum level of uric acid (sUA) and risk of acute kidney injury (AKI) after contrast-enhanced computerized tomography (CCT) is limited. The aim of this study was to determine whether elevated sUA could predict renal outcome after CCT.

Methods: We used a history cohort of 58106 non-dialysis adult patients who received non-ionic iso-osmolar CCT from June 1, 2008 to March 31, 2015 to evaluate the association of sUA and renal outcome. The exclusion criteria were patients with pre-existing AKI, multiple exposure, non-standard volume of contrast, and missing data for analysis.

Results: A total of 1440 patients were enrolled. Post-contrast-AKI (PC-AKI) occurred in 190 (12.5%) patients (18%) and the need of hemodialysis developed in 90 (6.3%) patients, both incidences were increased in patients with higher sUA. After adjusting for potential confounders, sUA was associated with an increased risk of PC-AKI [odds ratio (OR) of 2.62; 95% confidence interval (CI), 1.27~5.38, p=0.009] and the need of hemodialysis (OR, 5.40; 95% CI, 1.39~21.04, p=0.015). Comparing with sUA <8.0 mg/dL, patients with sUA ³8.0 mg/dL had higher incidence of PC-AKI (16.7% vs. 11.1%, p=0.012) and higher incidence of hemodialysis (12.1% vs. 4.3%, p<0.001). Additionally, 53.8% of patients with AKI had eGFR decreased ³20% after 3 months of CCT, compared to only 25.9% in patients without AKI (p<0.001).

Conclusions: Elevated sUA is associated with worse renal outcome after CCT. We suggest that elevated sUA may have potential as an independent risk factor for PC-AKI in patients scheduled to receive contrast-enhanced image study.

SA-PO577

Biomarkers for Diagnosis and Predicting Outcomes in Contrast Induced Nephropathy Justor Banda, Caroline Dickens, Saraladevi Naicker. *Internal Medicine, Univ of the Witwatersrand, Johannesburg, Gauteng, South Africa.*

Background: Serum creatinine is sub-optimal as a biomarker in the early diagnosis of contrast induced nephropathy (CIN). This study investigated a panel of novel biomarkers in the early diagnosis of CIN and in assessing patient outcomes.

Methods: This single centre, nested, prospective case-controlled study included 30 patients with CIN and 60 matched controls. Sera were collected pre-contrast; 24 hours (24h); 48h; and ≥5 days post contrast administration. Concentrations of NGAL, cystatin C, β_2M, IL18, IL10, and TNFα were determined using luminex and ELISA assays. Outcomes were biomarker diagnostic discrimination performance for CIN and mortality after generation of area under receiver operating characteristic curves (AUROC).

Results: Median 24h cystatin C and 48h β_2M levels were higher in CIN patients compared to controls (856.60ng/ml (IQR 620.75-1003.0) vs. 617.43ng/ml (533.11-805.21); p<0.001 and 5.3µg/ml (IQR 3.8-6.9) vs. 3.3µg/ml (2.7-4.5); p<0.001] with AUROCs of 0.75 and 0.78 respectively for early diagnosis of CIN. β_2M levels were higher at all time points. Baseline IL18 (p<0.001), β_2M (p=0.04) and TNFα (p<0.001) levels were higher in the non-surviving group and their AUROCs were all >0.80 for CIN+ mortality respectively. Baseline NGAL was superior for excluding patients at risk for CIN, with positive and negative predictive values of 0.50 and 0.81 respectively. Cystatin C (p=0.003) and β_2M (p=0.03) at 24h independently predicted CIN risk. β_2M predicted increased mortality of 40% at baseline and 50% at 24 hours.

Conclusions: Serum cystatin C was the best biomarker for CIN diagnosis, while IL18, β_2M and TNFα were best for predicting prognosis.

SA-PO578

Rapidly Reversible Contrast-Induced Acute Kidney Injury Does Not Increase the Risk for Worse Long-Term Renal Outcomes Darpan Gandhi,[1] Bhavna Bhasin,[1] Jorge Luis Castaneda,[2] Christopher D. Nielsen,[3] Juan Carlos Q. Velez.[1] *[1]Div of Nephrology, Medical Univ of South Carolina, Charleston, SC; [2]Div of Nephrology, Univ of Mississippi; [3]Div of Cardiology, Medical Univ of South Carolina.*

Background: Growing evidence indicates that contrast-induced acute kidney injury (CI-AKI) may increase the long-term risk for progression of chronic kidney disease (CKD) to end-stage kidney disease (ESKD). However, the duration of CI-AKI is highly variable and the impact of a sustained vs. a transient rise in serum creatinine (sCr) on long-term renal outcomes is not known. We hypothesized that recovery of CI-AKI within 7 days reduces the risk for worsening of long-term renal outcomes.

Methods: We reviewed records from non-ESKD patients with estimated glomerular filtration rate (eGFR) ≤ 45 ml/min who underwent coronary angiography (Cath) between 2008 and 2011 at MUSC. CI-AKI was defined as ≥ 25% rise in within 1-5 days post-Cath. CKD progression was defined as ≥ 30% fall in eGFR. Rapid recovery of CI-AKI was defined as improvement of sCr to a value < 25% above baseline within 7 days of Cath. Outcomes were assessed at 1 year.

Results: Of 2,098 subjects identified, 168 fulfilled the eGFR inclusion criteria, but 72 of them were excluded because of missing a sCr value after 24 hrs. The mean eGFR was 30.65 ± 9.9 ml/min, 58% were diabetics and the mean volume of dye was 107.2 ml. The incidence of CI-AKI was 29.2% (28/96). The composite endpoint of CKD progression, ESKD or death was reached by 50% (14/28) of those who developed CI-AKI compared to 17.6% (12/68) of those who did not develop CI-AKI [OR: 4.7 (95%CI: 1.7 – 12.3); p=0.002]. Eleven (39%) patients had a rapid recovery of CI-AKI, whereas the remaining 17 (61%) did not. Rapid recovery of CI-AKI was associated with a lower risk for the composite endpoint of CKD progression, ESKD or death [OR: 0.12 (95%CI: 0.02 - 0.75); p=0.023].

Conclusions: Although CI-AKI increases the long-term risk for worsening of renal outcomes, recovery within 7 days of the Cath is associated with a reduction in that risk, suggesting that severity of CI-AKI may impact its effect on long-term prognosis.

SA-PO579

Incidence and Risk Factors for Contrast-Induced Acute Kidney Injury in Patients Taking Trimethoprim-Sulfamethoxazole Hyun Seop Cho,[1,3] Tae Won Lee,[1] Eunjin Bae,[2] Hyun-Jung Kim,[1,3] Se-Ho Chang.[1,3] *[1]Internal Medicine, Gyeongsang National Univ Hospital, Jinju, Republic of Korea; [2]Internal Medicine, Gyeongsang National Univ Changwon Hospital, Changwon, Republic of Korea; [3]3 Inst of Health Sciences, Gyeongsang National Univ, Jinju, Republic of Korea.*

Background: Trimethoprim-sulfamethoxazole (TMP-SMX) is commonly used to prevent pneumocystis pneumonia and for wide range of infections in the outpatient setting. Previous studies have shown a relationship between TMP-SMX and acute kidney injury. The attributable risk for renal dysfunction from contrast medium in patients taking TMP-SMX not been well established.

Methods: We reviewed medical record database for all patients who received ≥3 days of treatment with TMP-SMX between from January 2009 to December 2015. Among these, we included patients underwent contrast-enhanced computed tomography (ECT) scan and for whom a baseline and follow-up determination of serum creatinine were available. CI-AKI was defined as an increase in serum creatinine (sCr) more than 25% of baseline value or 0.3 mg/dL at between 48 hours and 96 hours after ECT. We excluded patients who already had been receiving dialysis.

Results: Of 213 patients who met inclusion criteria, 18 (8.5%) had increases in sCr that met predetermined criteria for CI-AKI: The mean age was 58.81 ± 17.59 years. 45 patients (21.2%) had diabetes mellitus. Variables independently associated with CI-AKI included high potassium level (p=0.041), high potassium/sodium ratio (p=0.030), high Blood urea nitrogen level (p=0.027), high C-reactive protein(CRP) level (P=0.032), high HbA1c level (p=0.019), high CKD stage (p=0.023), concominant use of nephrotoxic drug (p=0.037). Multiple linear regression analysis shows hypoalbuminemia, hyperkalemia and concominant use of nephrotoxic drug to be significantly associated with CI-AKI (p=0.019, p=0.043 and p=0.013, respectively).

Conclusions: As it is well-known, the incidence of CI-AKI was higher in patients with high CRP level, advanced CKD satge and concominant use of nephrotoxic drug. Moreover, in high risk patients with hyperkalemia and hypoalbuminemia, TMP-SMX interruption should be considered to prevent the development of CI-AKI.

SA-PO580

Expression of Polycystins in LLC-PK1 Cells Does Not Increase Flow-Activated Calcium Fluxes Lindsey K. Stavola,[1] Helle A. Praetorius,[2] Michael J. Caplan.[1] *[1]Cellular and Molecular Physiology, Yale Univ, New Haven, CT; [2]Biomedicine, Aarhus Univ, Aarhus C, Denmark.*

Background: The primary cilium is thought to detect fluid flow in the kidney. The molecular basis of this mechanosensitivity is not fully elucidated. The polycystin 1 (PC1) and polycystin 2 (PC2) proteins, encoded by the genes that are mutated in Autosomal Dominant Polycystic Kidney Disease, localize in part to the primary cilium. PC1 is a ~450 kDa membrane protein with 11 membrane spans. PC2 belongs to the TRP family of Ca^{2+}-permeable channels. PC1 and PC2 form a complex, which is required for their trafficking to the primary cilium. It has been suggested that the ciliary pool of polycystins functions as a mechanosensitive ion channel that plays an obligate role in producing cilium-dependent flow-activated cytosolic Ca^{2+} transients.

Methods: We generated LLC-PK_1 renal epithelial cells stably expressing PC1 and PC2. Both proteins were abundantly present in the primary cilium. We conducted live cell imaging of the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) using these cells loaded with the Ca^{2+}-sensitive fluorescent dye Fluo4-AM.

Results: Overexpression of ciliary PC1 and PC2 did not increase the magnitude or duration of $[Ca^{2+}]_i$ transients elicited in response to increase in physiological fluid flow (10 µl/s corresponding to a linear velocity above the membrane of 70 µm/s). Thus, when expressed in this cell type, exogenous polycystins do not further add to the flow-activated $[Ca^{2+}]_i$ increase. Previous data suggested that TRPV4 forms a complex with the polycystins that confers mechanosensitivity on the cilium. To test this possibility, we co-expressed TRPV4 with PC1 and PC2 in LLC-PK_1 cells. Little or no TRPV4 protein was detectable in the primary cilium, but was found instead at the basolateral plasma membrane. Interestingly, expression of TRPV4 in LLC-PK_1 cells caused much larger flow-induced and ATP-induced $[Ca^{2+}]_i$ transients than was detected in cells expressing PC1 and PC2 alone.

Conclusions: These results demonstrate that exogenously expressed polycystins are not sufficient to further enhance ciliary mechanosensation and suggest that TRPV4 may play an indirect role in this process and in supporting cellular Ca^{2+} signaling.

Funding: Other U.S. Government Support

SA-PO581

Loss of Fluid Shear Stress as a Pathogenic Mechanism in Polycystic Kidney Disease Robin L. Maser. *Clinical Laboratory Sciences and The Kidney Inst, Univ of Kansas Med Ctr, KC, KS.*

Background: Formation and expansion of renal cysts compresses neighboring tubules leading to obstruction of urine flow in these tubules and in segments up- and downstream of isolated cysts. Tubular obstruction is evident in kidneys from rodent PKD models and in human ADPKD. Fluid shear stress (FSS) increases antioxidant gene expression in mouse M-1 cortical collecting duct cells, providing protection from oxidant-mediated damage.

Methods: To elucidate consequences of acute loss of urinary FSS, gene expression was analyzed in M-1 cells at an early timepoint after cessation of FSS. Cells subjected to physiological levels of laminar FSS for 4 hrs were either harvested (FSS; control), or placed

in static condition for an additional 4 hrs prior to harvest (FSS-stasis). Gene expression was examined via qRT-PCR using the PrimePCR Oxidative Stress panel (BioRad). Oxidative DNA damage (8-OH deoxyguanosine; 8OHdG) was assessed in sections of normal and cystic kidneys from the cpk mouse and the Cy rat models of PKD by immunostaining. Mitochondrial (mt) DNA damage was analyzed on denaturing agarose gels with mtDNA isolated from liver and kidney of cpk mice.

Results: Relative to FSS, FSS-stasis led to >2-fold change in expression level of 67 of the 88 genes assayed, and to *de novo* induction of 9 additional genes. Genes with increased expression were associated with renal injury, apoptosis, inflammation, and DNA damage. A gene whose expression was increased by acute loss of FSS in 3 independent experiments is Ogg1, which encodes 8-oxoguanine DNA glycosylase, an enzyme involved in response to and repair of oxidized DNA. 8OHdG staining was evident in nuclear and cytoplasmic compartments of cyst-lining cells and adjacent non-cystic tubules in cystic kidneys. mtDNA degradation was increased in cystic compared to normal kidneys of 2- and 3-week old mice, while liver mtDNA was unaffected.

Conclusions: Our studies demonstrate that acute loss of FSS initiates changes in renal tubular epithelial gene expression associated with oxidant stress/damage and may lead to an alteration in renal cell metabolism. Altogether, these results support a mechanism by which cyst-mediated tubule obstruction could contribute to PKD pathogenesis.

Funding: NIDDK Support

SA-PO582

Modeling Polycystic Kidney Disease in Human Kidney Organoids from Genome-Modified and Induced Pluripotent Stem Cells Nelly M. Cruz, Benjamin S. Freedman. *Div of Nephrology, Kidney Research Inst, and Inst for Stem Cell and Regenerative Medicine, Dept of Medicine, Univ of Washington, Seattle, WA.*

Background: Human pluripotent stem cells (hPSCs) can differentiate into nephron-like kidney organoids for disease modeling and regenerative medicine. Organoids derived from genome-modified *PKD1*$^{-/-}$ or *PKD2*$^{-/-}$ hPSCs form cysts from kidney tubules, but the penetrance of this phenotype is low. Using a variety of PKD hPSCs, we investigated the potential of differentiation protocol, culture conditions, and genetic background to modulate PKD organoid cystogenesis.

Methods: Induced hPSCs from four ADPKD and ARPKD patients or genome-modified *PKD1*$^{-/-}$ and *PKD2*$^{-/-}$ hPSCs were differentiated into kidney organoids using two different published protocols. Organoids were cultured under 2D or 3D conditions with or without forskolin, an agonist of adenylyl cyclase. PKD organoids and cysts were counted, measured, and analyzed for kidney tubule marker immunofluorescence, compared to non-PKD controls.

Results: Under novel conditions, *PKD1*$^{-/-}$ and *PKD2*$^{-/-}$ organoids formed translucent cysts with diameters approaching 1 cm over several months in culture. Penetrance of the cystogenesis phenotype was increased to ~ 80 % in *PKD1*$^{-/-}$ and *PKD2*$^{-/-}$ organoids, compared to < 10 % in isogenic control organoids. Cysts derived primarily from proximal tubular cells and expanded rapidly upon forskolin treatment. Differentiation efficiency was highly variable between induced hPSCs from different patients, independent of PKD mutations. By comparison, genome-modified hPSCs exhibited much greater uniformity.

Conclusions: *PKD1*$^{-/-}$ and *PKD2*$^{-/-}$ kidney organoids establish a high-penetrance system for human PKD cystogenesis *in vitro*. Genetic background is a confounding factor in organoid differentiation, necessitating the use of genome modification. Cyclic AMP signaling enhances human PKD cystogenesis, similar to mouse models. The modularity of kidney organoid cultures makes them a powerful new pre-clinical model in which to investigate PKD pathophysiology and evaluate candidate therapeutics. (Supported by an unrestricted gift from Northwest Kidney Centers to Kidney Research Institute.)

Funding: NIDDK Support, Pharmaceutical Company Support - Northwest Kidney Centers, Private Foundation Support

SA-PO583

Bioactive Lipid Alterations in the jck and pcy Mouse Models of Nephronophthisis Tamio Yamaguchi,[1] Nikhil Sidhu,[2] Jessay Gopuran Devassy,[2] Melissa Gabbs,[2] Amir Ravandi,[3] Masanori Kugita,[4] Shizuko Nagao,[4] Harold M. Aukema.[2] *[1]Dept of Clinical Nutrition, Suzuka Univ of Medical Science, Suzuka, Mie, Japan; [2]Dept of Human Nutritional Sciences, Univ of Manitoba, Winnipeg, MB, Canada; [3]Inst of Cardiovascular Sciences, St. Boniface Hospital Research Centre, Winnipeg, MB, Canada; [4]Education and Research Center of Animal Models for Human Diseases, Fujita Health Univ, Fujita Health Univ, Toyoake, Aichi, Japan.*

Background: Oxylipins are bioactive lipids formed via oxidative metabolism of polyunsaturated fatty acids by the cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP) pathways. We have previously shown that the renal oxylipin profile is altered in three orthologous models of polycystic kidney disease (PKD). To determine whether the changes in these bioactive lipids also occur in nephronophthisis (NPHP), we examined the oxylipin profile in the *jck* and *pcy* mouse models of NPHP, which have mutations in *Nphp9* and *Nphp3*, respectively.

Methods: Kidneys from 12 week-old C57BL/6-*jck/jck* (diseased) and C57BL/6-*jck/+* or +/+ (normal) mice, and from 20 week-old diseased (CD1-*pcy/pcy*) and normal (CD1-+/+) mice with established NPHP were studied. Oxylipin levels were quantified by HPLC/MS/MS using stable isotope dilution.

Results: Over 40 oxylipins were quantified in both models of NPHP. In both models, the levels of COX derived oxylipins (e.g. prostaglandins) were elevated by as much as 20 times, while the LOX derived (e.g. hydroxy fatty acids) and CYP derived (e.g. epoxy fatty acids) were present at levels as low as 10-20% of normal.

Conclusions: Oxylipins derived from COX were elevated, while those derived via the LOX and CYP pathways were markedly reduced in both models of NPHP. These lower levels of LOX and CYP metabolites contrasts with orthologous models of PKD that primarily display alterations in the COX metabolites. Inhibition of oxylipin biosynthetic pathways therefore may offer potential treatment strategies for NPHP. (Supported by the Natural Sciences and Engineering Research Council of Canada and the Children's Hospital Research Foundation of Manitoba, Japan Society for the Promotion of Science Grants-in-Aid for Scientific Research).

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SA-PO584

Inihibition of Bromodomain Protein BRD4 Ameliorates Renal Fiborsis in ADPKD Xia Zhou,[1] Xiaoyan Li,[1] Dorien J.M. Peters,[2] Xiaogang Li.[1] *[1]Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS; [2]Leiden Univ Medical Center, Leiden, Netherlands.*

Background: Bromodomain protein BRD4 recognizes and binds acetylated histones to regulate gene transcription. We found that therapeutic targeting of BRD4 with its inhibitor JQ1 delayed cyst growth in different ADPKD mouse models through inhibition of c-Myc transcription. Tubulointerstitial fibrosis is associated with the renal function decline during renal cyst progression. However, whether BRD4 regulates renal fibrosis in ADPKD remains unknown.

Methods: To understand the role of BRD4 in regulating renal fibrosis *in vivo*, we investigated renal fibrosis of *Pkd1*$^{nl/nl}$mice treated with JQ1.To explore the pathways underlying BRD4 mediated renal fibrosis, we treated renal fibroblasts with JQ1.

Results: We found that inhibition of BRD4 with JQ1 not only delayed cyst growth but also decreased renal interstitial fibrosis as examinedby Trichrome Masson and Picrosirus red staining. JQ1 treatment decreased the mRNA expression of fibrotic markers, Col1A1, Col3A1, α-SMA and Fibronectin as analyzed by qRT-PCR, and the protein expression of α-SMA as analyzed by immunohistochemistry staining in the kidneys from postnatal day 28 *Pkd1*$^{nl/nl}$ mice. TGF-β, the crucial cytokine in regulating fibrosis, and TGF-β/Smad signaling were elevated in cystic kidneys compared with the wild type kidneys. We further found that TGF-β1 treatment not only induced the expression of fibrotic markers (Col1A1, Col3A1, α-SMA and Fibronectin), but also increased the expression of BRD4 in rat kidney interstitial fibroblasts (NRK-49F). However, treatment with JQ1 plus TGF-β1 blocked the upregulation of fibrotic markers induced by TGF-β1 alone as analyzed by qRT-PCR and Western blot. BRD4 interacted with Smad3 but not Smad2 in NRF-49F cells as analyzed by co-IP. Inhibition of BRD4 with JQ1 decreased the cell proliferation of NRF-49F cells.

Conclusions: BRD4 promotes renal interstitial fibrosis in ADPKD. BRD4 plays an important role in TGF-β induced fibroblast activation through regulating the transcription of fibrotic markers, which may be mediated by its interaction with Smad3. BRD4 is a novel therapeutic target for renal fibrosis in ADPKD.

Funding: NIDDK Support

SA-PO585

Fibrosis Markers in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Wei Wang, Michel Chonchol, Berenice Y. Gitomer. *Univ of Colorado Denver.*

Background: In ADPKD patients the degree of renal fibrosis has been identified as the most significant and variable factor associated with progression to renal failure. However, there are no methods for direct assessment of fibrosis in ADPKD. Several tissue factors, including the matricellular proteins SPARC and periostin mediate fibrosis in pre-clinical models of ADPKD, but require renal tissue for measurement. However, changes in circulating micro RNA (miRNA) levels have been associated with fibrosis in liver, heart and kidneys. Thus we hypothesized that detection of fibrosis associated miRNAs in human serum from ADPKD patients might indicate fibrosis and serve as non-invasive biomarkers of disease progression.

Methods: Total RNAs were extracted from human ADPKD, chronic kidney disease (CKD) and normal control kidneys and mRNA levels of SPARC and periostin measured by RT-PCR. A total of 372 miRNAs were analyzed by microarray in the serum of 5 ADPKD patients with eGFR ≥60 ml/min/1.73m^2 and 3 age matched normal healthy controls at baseline. ADPKD patients were classified as fast (eGFR decrement> 3.4ml/min/1.73m^2/year) or slow (eGFR decrement ≤3.4ml/min/1.73m^2/year) progressors based on annualized eGFR change.

Results: Renal periostin mRNA expression was much higher in ADPKD patients compared to both in normal controls (0.093±0.047, n=5 vs 0.040±0.023, n=4, p=0.07) and in CKD patients (0.093±0.047, n=5 vs 0.023±0.027, n=4, p=0.02). Renal SPARC mRNA expression was also significantly higher in the kidneys from ADPKD patients than in normal controls (7.8±5.0, n=6 vs 2.2±1.1, n=5, p=0.049). Several serum miRNAs were differentially expressed in the fast disease progressors compared to slow progressors including the fibrosis related members of the miR-29 family (miR-29a, miR-29b, miR-29c) and miR-30.

Conclusions: Fibrosis in ADPKD kidney is indicated by increasedexpression of mRNAs for the matricellular proteins periostin and SPARC. The differential expression of several fibrosis related miRNAs measured at baseline in sera from patients with fast progressing disease indicates that a signature of fibrosis related circulating miRNAs might serve as a sensitive and non-invasive prognostic biomarker for more rapid disease progression.

Funding: NIDDK Support

SA-PO586

Disruption of Subcellular Sorting Regulators in a New 3D Cystogenesis Model for ADPKD Eryn E. Dixon, Owen M. Woodward. *Physiology, Univ of Maryland School of Medicine, Baltimore, MD.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common monogenic diseases worldwide. Loss of function mutations in *PKD1* or *PKD2* lead to deficiency of the polycystin-1 and -2 proteins, resulting in cystogenesis. However, many questions still remain about the mechanism of cyst formation, including effects of aberrant proliferation, mislocalization of growth signals, and alterations in fluid secretion machinery. Currently, cyst models are unable to demonstrate isolated, focal cysts, characteristic of ADPKD, with inactivation of *PKD1* or *PKD2*.

Methods: By employing a novel combination of culture techniques with an inducible cre model for *PKD1/2* inactivation, we have been able to demonstrate an increase in cystogenesis following heterogeneous inactivation of *PKD1* and *PKD2*. We have optimized the culturing of three dimensional organoids from primary postnatal mouse nephrons using a "sandwich" technique, where primary cells are seeded between two layers of polymerized Matrigel. This plating technique has promoted differentiation of organoids into more complex secondary structures. Finally, we have found a pulse of glial derived neurotrophic factor (GDNF) stimulates the mesenchymal to epithelial transition, activating tubulogenesis.

Results: This GDNF-induced epithelial switch, confirmed by expression of E Cadherin, is maintained after inactivation of *PKD1/2*, suggesting presence of epithelial organization in cystic structures. However, cystic fluid accumulation and expansion point to an altered localization of secretory machinery. To investigate, we looked closely at Ezrin and the phospho-Ezrin/Radixin/Moesin (p-ERM) complex, proteins important in organization of the membrane and cell structure. Here, we find that *PKD1/2* inactivation and cystogenesis disrupts Ezrin/p-ERM localization and activation, highlighting a potential mechanism of altered apical and basolateral sorting.

Conclusions: Our three dimensional cystogenesis model for ADPKD demonstrates persistence of epithelial characteristics with important defects in the membrane protein sorting mechanisms. **NIDDK 5P30DK090868 Baltimore PKD Center Pilot & Feasibility Grant**.

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SA-PO587

Functional Expression of CaSR in Conditionally Immortalized Proximal Tubular Epithelial Cells (ciPTEC) Deficient for Polycystin 1 or Derived from ADPKD1 Patients: CaSR as Possible Therapeutic Target Annarita Di Mise,[3] Grazia Tamma,[1] Marianna Ranieri,[1] Mariangela Centrone,[1] Giovanna Cinzia Baldelli,[1] Djalila Mekahli,[2] Elena N. Levtchenko,[2] Giovanna Valenti.[1] *[1]Univ of Bari Aldo Moro; [2]Univ of Cincinnati; [3]Albany Medical College.*

Background: Clinical and fundamental-research data suggest that altered Ca^{2+} and cAMP signaling might be two of the most proximal events in the pathogenesis of ADPKD. Cells from ADPKD cysts were reported to have a reduced resting cytosolic Ca^{2+} concentration and increased level of cAMP. CaSR is a G protein coupled receptor, which plays an essential role in regulating Ca^{2+} homeostasis whose activation is associated with an increase in intracellular calcium and decrease in cAMP making CaSR a possible candidate as therapeutic target.

Methods: Control human ciPTEC cells with stably down-regulated PKD1 (ciPTEC-$PC1_{KO}$) and ciPTEC generated from ADPKD1 patients (ciPTEC-$PC1_{Pt}$) were used as experimental tools.

Results: The expression of the endogenous CaSR in either ciPTEC-$PC1_{KO}$ and ciPTEC-$PC1_{Pt}$ was confirmed by Western blotting and by confocal analysis showing a clear apical localization of CaSR in the cells. CaSR functional expression was confirmed by studies with Fura2-AM showing that the calcimimetic NPS-R568, induced a significant increase in cytosolic calcium either in ciPTEC-$PC1_{KO}$ and in ciPTEC-$PC1_{Pt}$. Calibration of intracellular calcium demonstrated that resting cytosolic Ca^{2+} levels were significantly lower in ciPTEC-$PC1_{KO}$ with respect to ciPTECwt (93.4 nM vs 113.4 nM, P=0.0004) confirming calcium dysregulation in ciPTEC-$PC1_{KO}$. Conversely, as in native cells from cysts, significantly higher cAMP levels were found in ciPTEC$_{KO}$ with respect to ciPTEC-PC1wt. Of note, exposure of ciPTEC$_{KO}$ to the calcimimetic NPS-R568 significantly reduced intracellular cAMP levels.

Conclusions: We conclude that *i*. PKD1 mutation in humans preserves CaSR functionality *ii*. selective CaSR activation of human ciPTEC carrying PKD1 mutation increases intracellular calcium and reduces intracellular cAMP, improving the dysregulation of the two signaling molecules considered the most proximal events in the pathogenesis of ADPKD.

Funding: Government Support - Non-U.S.

SA-PO588

Phosphodiesterase Modulation of Renal Cystogenesis, and Effects of PKD2 on Development of Lateral Line Hair Cells Caroline R. Sussman, Raad B. Chowdhury, Madeline Rose Martell, Peter C. Harris, Vicente E. Torres. *Nephrology & Hypertension, Mayo Clinic, Rochester, MN.*

Background: cAMP is an important signaling molecule in Polycystic Kidney Disease (PKD), and PKD severity in animal models is affected by Phosphodiesterases (PDEs), which hydrolyze cAMP. We have shown using zebrafish that PDE1A modulates renal cystogenesis downstream of *Pkd2* and its product PC2. We explore here roles of zebrafish PDE3A in renal cystogenesis and effects of *Pkd2* mutation on development of lateral line hair cells (which express PC2), as a potential model for further studies of PDEs in PKD.

Methods: PDE3A levels were altered using morpholinos and RNA. PC2 effects were examined in *Pkd2* mutants.Phenotypes were examined using stereo-microscopy and immunofluorescence. Phenotypes were evaluated in at least 3 unique batches and significance tested using chi-square or t-test.

Results: Two splice-blocking *pde3a* morpholinos caused pronephric cysts and body curvature with dose dependence. The splice donor morpholino also caused hydrocephalus, otolith defects, and fin blistering with dose dependence. Co-injection of 125pg of mouse p*de3a* RNA with donor morpholino (5ng) rescued cysts (8% vs 33%; $p \leq 0.001$) and hydrocephalus (0% vs. 58%; $p \leq 0.001$). To examine the relevance of lateral line hair cells for further studies of PDEs and PKD, we assessed hair cell development in *Pkd2* mutant zebrafish (hi4166) by immunofluorescence of acetylated α-tubulin. Neuromasts were identified using DAPI and each was scored based on cilia appearance (normal (2), stunted (1), or missing (0)). Cumulative scores were calculated for lateral neuromasts. The average score for mutants was 30% lower than that of wild-type (1.1±0.15 vs. 1.5±0.18, $p < 0.01$). Additionally, *in situ* hybridization showed expression of *pde1a* in hair cells.

Conclusions: Morpholino and RNA studies further support involvement of PDE3A in renal cystogenesis and associated phenotypes, similar to PDE1A. Impaired development of lateral line cilia in *Pkd2* mutants suggest PC2 is involved in normal hair cell development. Expression of *pde1a* further suggests that lateral line hair cells may be an accessible model for studies of PDEs in PKD.

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SA-PO589

Hypermethylation of the MUPCDH Promoter as a Prognostic Biomarker for Cyst Growth in ADPKD Yu Bin Shin, Eun Ji Lee, Do Yeon Kim, Je Yeong Ko, Jong Hoon Park. *Biological Science, Sookmyung Women's Univ, Seoul, Korea.*

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a common genetic disease, which shows the formation of multiple fluid-filled cysts, and it finally results in renal failure. Still, early diagnosis and treatment of ADPKD have yet to be defined. In this study, we suggest a specific epigenetic condition as a prognostic biomarker.

Methods: 1. Renal tissue samples from subjects with ADPKD. Renal cyst tissue was obtained from patients with ADPKD undergoing nephrectomy. As controls, non-ADPKD renal tissue specimens were obtained from patients undergoing surgery for clear cell renal cell carcinoma; malignant cell infiltration was excluded by histology. 2. DNA methylation analysis. DNA methylation patterns were validated in two steps, using MS-HRM and EpiTYPER® analyses. For MS-HRM analysis, primers covered the region extending for 2 kb from the translation start ATG upstream to intron 1. Bisulfite-treated genomic DNA was amplified by PCR 3. ChIP-qPCR. ChIP was performed as previously described40, using antibodies specific for RNA polymerase II (ab817; Abcam, Cambridge, UK), AP-2α (sc-184; Santa Cruz Biotechnology), H3K4 me3 (17-614; EMD Millipore, Billerica, MA, USA), H3K9 me3 (ab8898; Abcam), and H3Ac (06–599; EMD Millipore).

Results: The promoter region of the gene encoding mucin-like protocadherin (MUPCDH) was hypermethylated in renal tissue of ADPKD patients compared to non-ADPKD controls. As the promoter region is hypermethylated, the expression of MUPCDH was significantly repressed in cyst-lining cells of ADPKD patients. So our results indicate that aberrant methylation of MUPCDH promoter CpG islands can be negatively correlated with reduced expression level of MUPCDH. Furthermore, this epigenetic silencing contributes to abnormal cell proliferation in ADPKD.

Conclusions: In this study, we suggested that hypermethylation of MUPCDH promoter induces the transcriptional repression and increased cell proliferation in ADPKD. Also, methylation level of MUPCDH promoter region in genomic DNA from urine can be used as the novel epigenetic biomarker for prognosis of ADPKD.

Funding: Government Support - Non-U.S.

SA-PO590

Repurposing of Targeted Cancer Therapies for Autosomal Dominant Polycystic Kidney Disease (ADPKD) Anna Nikonova, Vladislav Korobeynikov, Erica A. Golemis. *Molecular Therapeutics, Fox Chase Cancer Center, Philadelphia, PA.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disease that affects ~1 in 500 people. In ADPKD, mutations in *PKD1* and *PKD2* abnormally activate signaling pathways regulating cell proliferation, migration, and response to environmental cues. Some studies have suggested maintenance of cilia is critical for cyst development. Intriguingly, studies of the signaling defects associated with ADPKD have also identified defects paralleling many of those seen in cancer, in spite of the very different presentation of ADPKD and solid tumors.

Methods: We have been evaluating targeted signaling inhibitors in ADPKD models to probe biological similarities and differences between ADPKD and cancer, and to determine if cancer drugs are effective in ADPKD. We have explored the signaling interactions between PKD1 mutations, control of ciliary dynamics, and clinical agents with potential efficacy in ADPKD, with a goal of optimizing therapeutic options for patients with ADPKD.

Results: In initial studies, we found that HSP90 inhibition in conditional *Pkd1*$^{-/-}$ mice with the preclinical compound STA-2842 reduced initial renal cyst formation and slowed the progression of these phenotypes in mice with pre-existing cysts in animals up to 6 months of age. In ongoing work, we found treatment of *Pkd1*$^{-/-}$ mice with the clinical HSP90 inhibitor ganetespib controlled cyst growth for up to 50 weeks of treatment, extending survival in reference to vehicle treated mice. Suggestively, ciliation is reduced in the cysts of mice responding to ganetespib treatment relative to cysts found in control mice. Treatment of kidney epithelial cells with HSP90 inhibitors lead to the rapid resorption of primary cilia in the absence of serum.

Conclusions: These results support the idea that HSP90 inhibition and induced loss of cilia represent potentially useful therapeutic concepts for ADPKD. Extending the latter idea, we have now performed a screen of a library of targeted clinical candidates and agents to identify those regulating ciliary dynamics; assessment of additional candidates that cause ciliary resorption is in progress for in vivo control of Pkd1-dependent cyst formation.

Funding: NIDDK Support, Private Foundation Support

SA-PO591

High-Throughput, Comparative Variant Profiling Aids Molecular Diagnostics of ADPKD Vladimir Gainullin,[1] Christina M. Heyer,[1] Emilie Cornec-Le Gall,[1] Sarah L.R. Klein,[2] Vicente E. Torres,[1] Peter C. Harris.[1] *[1]Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [2]Macalester College, St. Paul, MN.*

Background: A high level of allelic heterogeneity at the two genes, *PKD1* and *PKD2*, characterizes ADPKD, with the pathogenicity and penetrance of many inframe variants often uncertain after *in silico* and family/population analysis. The PKD1 and PKD2 proteins, PC1 and PC2, interact while folding in the ER and PC1 maturation and surface localization requires the ER chaperone function of PC2. Hence, quantitatively assaying the surface localization of PC1 represents an unbiased approach to determine the significance of both PC1 and PC2 variants.

Methods: We developed a high-throughput, quantitative flow-cytometry-based assay utilizing exogenously coexpressed PC1 and PC2 to determine the level of surface localized PC1. Assays were performed on 45 PC1 and 45 PC2 missense variants (predicted to range from fully penetrant pathogenic to neutral) and compared to wildtype and truncation mutation controls.

Results: We found for 20% of PC1 and 50% of PC2 variants that no PC1 was surface localized (fully penetrant allele), while 10% of PC1 and 40% of PC2 variants behaved like wild type with full surface localization. A group of 70% of PC1 and 10% of PC2 variants showed reduced surface delivery, consistent with being incompletely penetrant (hypomorphic) alleles. For six PC1 variants this designation was consistent with early onset disease when co-inherited in trans with a fully inactivating allele, while in two cases combinations of two or more hypomorphic variants in cis generated a fully penetrant haplotype. A high level (70%, PC1; 50%, PC2) of fully or incompletely penetrant folding mutants were temperature-sensitive: completely or to some extent rescued by incubation at 30°C.

Conclusions: Our data indicates that the majority of ADPKD missense variants are folding mutations and that the pathogenicity and penetrance of each variant and a combination of variants can be precisely quantified. In addition, the temperature-sensitive nature of many missense mutations suggests the potential to treat some patients with molecular chaperone therapy.

Funding: NIDDK Support

SA-PO592

Determinants of Disease Variability in ADPKD: Insights from a Cohort of 1634 PKD1 Patients Emilie Cornec-Le Gall,[1] Berenice Y. Gitomer,[2] Arlene B. Chapman,[3] Alan S.L. Yu,[4] Dorien J.M. Peters,[5] Jon D. Blumenfeld,[6] York P. Pei,[7] Kyongtae Ty Bae,[9] Doris Rubio,[9] Christina M. Heyer,[1] Sarah R. Mauritz,[1] Vicente E. Torres,[1] Peter C. Harris.[1] *[1]Mayo Clinic; [2]U of Colorado; [3]U of Chicago; [4]U of Kansas; [5]Leiden; [6]The Rogosin Inst; [7]U of Toronto; [8]U of Maryland; [9]U of Pittsburgh.*

Background: ADPKD has marked clinical variability and extra-genic determinants remain poorly understood. ADPKD Modifier is a cross-sectional study designed to identify genetic, clinical, and environmental factors influencing renal disease severity and consists of mutation proven PKD1 caucasian patients.

Methods: The effect of possible modifying factors on renal survival was studied using Kaplan-Meier methods and Cox model, and their influence on square-root normalized eGFR and log-transformed height-adjusted total kidney volume (HtTKV) was analyzed using univariate and multivariate regression analyses.

Results: A total of 708 different *PKD1* mutations were identified in 1634 patients (727 males, 983 pedigrees). Median age at ESRD was 59.4y, but significantly earlier in males than females (55.8y vs. 62.3y, P<0.001), and in truncating vs. non truncating patients (58.1y vs. 61.3y, P=0.009). In addition, multivariate regression analysis showed that male gender, truncating mutations, diagnosis of hypertension before 35y and BMI or body weight were independently associated with lower eGFR and higher HtTKV (all P-values <0.005). As previously shown in the wider CKD population, alcohol consumption was associated with higher eGFR (P<0.001), however it had no influence on HtTKV. There was no apparent influence of smoking status, birth weight or caffeine intakes on HtTKV or eGFR. Intrafamilial correlation analysis estimated that heritability explained 12.2% and 30.9% of the variability of eGFR and HtTKV. Among the 40 patients with age and gender adjusted eGFR below the 2.5 percentile, 9 (22.5%) had severe associated conditions or nephropathies likely to account for the early progression to ESRD.

Conclusions: Beyond the effect of gender and mutation type, disease variability in ADPKD results from the combined effect of environmental factors and modifier genes. Early eGFR decline should prompt nephrologist to check for concomitant nephropathies.

Funding: NIDDK Support

SA-PO593

Using the PROPKD Score Can Enrich ADPKD Clinical Trials for Rapidly Progressive Patients Emilie Cornec-Le Gall,[1] Jaime Blais,[2] Christina M. Heyer,[1] Sarah R. Mauritz,[1] Frank S. Czerwiec,[2] John Ouyang,[2] Yannick Le Meur,[3] Vicente E. Torres,[1] Peter C. Harris.[1] *[1]Mayo Clinic; [2]Otsuka PDC; [3]CHU Brest, France.*

Background: The PROPKD score has been recently proposed to stratify the risk of progression to ESRD in ADPKD patients. We aimed to assess the prognostic value of this score in a subgroup of subjects from the TEMPO 3:4 trial.

Methods: The PROPKD score was calculated in 749 patients with an available DNA sample as the sum of the following factors: male: 1 pt; hypertension <35y: 2 pts; first urologic event <35y: 2 pts; *PKD2* mutation: 0 pt; nontruncating *PKD1* mutation: 2 pts; and truncating *PKD1* mutation: 4pts. Patients were classified into low risk (LR, 0-3 pts), intermediate risk (IR, 4-6 pts) and high-risk (HR, 7-9 pts) groups.

Results: HR patients (n=284, 36y) were significantly younger than IR (n=335, 40y) and LR (n=130, 45y) patients (p<0.001). While baseline renal function was similar across all 3 risk groups, baseline HtTKV significantly increased from the LR to the HR group (median values: 785 vs. 934 mL/m, P<0.001). In the placebo group, annual growth in TKV was highest in the HR group, and the rate of renal function decline was slowest in LR patients. Tolvaptan significantly slowed the rate of TKV growth in all 3 risk categories (LR: T=2.8 *vs.* P=5.0%, IR: T=2.2 *vs.* P=4.6 and HR: T=4.1 *vs.* P=6.6%, all P-values <0.005) and the rate of renal function decline in the IR and HR groups (IR: T=-2.4 *vs.* P=-3.5, P=0.01; HR: T=-2.7 *vs.* P=-3.8 ml/min/1.73m^2/y, P=0.01), but not in the LR group. In all subjects, tolvaptan reduced the rate of eGFR decline from -3.40 to -2.5ml/min/1.73m^2/y (p=0.0001) with a relative treatment effect (TE) of 27%. Excluding subjects in the LR group improved this difference (-3.6 to -2.5ml/min/1.73m^2/y, (p<0.0001), TE 33%). Similarly, while time to first renal event favored tolvaptan over placebo in the HR+IR (HR=0.39, P<0.0002), there was no difference in the LR group.

Conclusions: This study confirms the prognostic value of the PROPKD score and suggests that it will allow cost reduction of future trials and to maximize positive results by enriching the study population for rapidly progressing ADPKD subjects.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceutical

SA-PO594

Targeting Ciliogenesis by Modulating Tubulin Polymerization as a Therapeutic Approach for Polycystic Kidney Disease Sarah E. Moreno,[1] Herve Husson,[1] Laurie A. Smith,[1] Mandy M. Smith,[1] Ryan J. Russo,[1] Rose A. Pitstick,[2] Mikhail Sergeev,[3] Steven R. Ledbetter,[1] Nikolay Bukanov,[1] Monica Lane,[1] Kate Zhang,[1] George A. Carlson,[2] Jagesh V. Shah,[3] Laurent Meijer,[4] David Beier,[5] Oxana Beskrovnaya.[1] *[1]Sanofi-Genzyme, Framingham, MA; [2]McLaughlin Research Inst, Great Falls, MT; [3]Brigham and Women's Hospital, Boston, MA; [4]ManRos Therapeutics, Roscoff, France; [5]Seattle Children's Research Inst, Seattle, WA.*

Background: Polycystic kidney diseases (PKDs) are a class of genetic diseases that arise from abnormalities in the primary cilium and characterized by the continuous growth of renal fluid-filled cysts that leads to end-stage renal disease. Advancements in understanding the molecular mechanisms that drive cyst growth are crucial for the development of new therapeutic modalities.

Methods: Modulation of CDK5 was achieved through pharmacological inhibition or genetic inactivation in *jck* mice. Efficacy was measured by kidney to body weight ratio, blood urea nitrogen, and cystic volume. Effects of CRMP2 modulation on ciliary length and tubulin polymerization were assessed *in vitro*. Knockdown of CRMP2 *in vivo* was done using peptide-linked phosphorodiamidate morpholino antisense oligonucleotides (PPMO).

Results: We showed previously that inhibition of CDK5 *in vivo* leads to a reduction in ciliary length and attenuates progression of PKD. Mechanistic studies suggested that CDK5 may function through the regulation of tubulin dynamics by modulation of collapsing response mediator protein 2. Here we further expanded the role of CRMP2 on ciliogenesis. *In vitro* CRMP2 localizes to the primary cilium and *Crmp2* siRNA knockdown reduces tubulin polymerization leading to shortened cilia. *In vivo* we demonstrate that *jck* mice have increased microtubule stability and CRMP2 localizes to the primary cilium. *In vitro* modulation of CRMP2 with S-lacosamide results in decreased tubulin polymerization and reduces cilia length. *In vivo* knock down of CRMP2 in *jck* mice attenuated disease progression.

Conclusions: Taken together, our data supports targeting ciliogenesis as viable therapeutic approaches for the treatment of renal cystic diseases.

Funding: Pharmaceutical Company Support - Sanofi-Genzyme

SA-PO595

A Personalised Therapy for CEP290 Ciliopathy Syndrome John Andrew Sayer, Shalabh Srivastava, Simon Ramsbottom, Elisa Molinari, Colin Miles. *Inst of Genetic Medicine, Newcastle Univ, Newcastle, United Kingdom.*

Background: Mutations in CEP290 cause ciliopathy syndromes with a variety of clinical phenotypes. CEP290 is expressed in ciliary centrosomes; mutations are thought to affect the structure and function of the cilia. Over 130 different mutations have been described within CEP290. We present data concerning an affected boy aged 13 years, from consanguineous parents, with a cerebello-retinal-renal / Joubert syndrome phenotype.

Methods: Clinical features included ataxia, congenital amaurosis and progressive chronic kidney disease with renal cortical cyst formation. Mutation analysis (using a panel gene approach) revealed a homozygous nonsense mutation in exon 41 c.5668G>T (p.Gly1890X). This is a commonly reported mutation in CEP290.

Results: Using human urine derived renal epithelial cells (HuREC) from the patient we demonstrate loss of CEP290 protein and abnormalities in ciliary structure. Specifically we see elongated cilia (6.98 um vs 4.70 um in wild type controls) under scanning electron microscopy (SEM) and elongated cilia under immunofluorescence with a loss of acetylation of the axoneme at the distal end of the cilium. This ciliary abnormality could be rescued by treatment with the Hedgehog (Hh) agonist purmorphamine (2 micromolar) for 24 hours. As an alternative means of rescue we used a targeted morpholino oligonucleotide towards the intron-exon splice junction of exon 41. Using this approach we show, using RT-PCR, exon skipping and a rescue of expression of a near full-length CEP290 protein. Phenotypic rescue of elongated cilia was also confirmed.

Conclusions: In a patient with a homozygous truncating *CEP290* mutation, we have modelled the ciliary defect using HuRECs. The abnormal ciliary phenotype which included elongated cilia with abnormal axonemal acetylation was rescued by both Hh agonist treatment and targeted exon-skipping. This individualised approach offers new therapeutic options for the treatment of ciliopathies.

SA-PO596

Mutations in MAPKBP1 Cause Late Onset Cilia-Independent Nephronophthisis Maxence Macia,[1] Jan Halbritter,[2] Marion H. Delous,[1] Cecilie Bredrup,[3,4] Flora Silbermann,[1] Anne Elisabeth Christensen Mellgren,[3,4] Daniela A. Braun,[2] Heon Yung Gee,[2] Andreas W. Sailer,[5] Pierre Saint-Mezard,[5] Stephan Johansson,[4] Eyvind Rødahl,[3,4] Sophie Saunier,[1] Friedhelm Hildebrandt,[2] Alexandre Benmerah.[1] *[1]INSERM UMR1163, Imagine Inst, Paris Descartes Univ, Paris, France; [2]Div of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston, MA; [3]Dept of Ophthalmology, Haukeland Univ Hospital, Bergen, Norway; [4]Center for Medical Genetics and Molecular Medicine, Haukeland Univ Hospital, Bergen, Norway; [5]Novartis Insts for Biomedical Research, Basel, Switzerland.*

Background: Nephronophthisis (NPH), an autosomal recessive tubulointerstitial nephritis, is the most common cause of hereditary end-stage renal disease in the first three decades of life. Since most NPH gene products (NPHP) function at the primary cilium, NPH is classified as ciliopathy.

Results: We identified mutations in a novel candidate gene in 10 individuals from 6 families presenting late onset NPH with massive renal fibrosis. This gene encodes MAPKBP1, a poorly characterized scaffolding protein for JNK signaling. Immunofluorescence analyses showed that MAPKBP1 is not present at the primary cilium and that fibroblasts from affected individuals did not display ciliogenesis defects indicating that MAPKBP1 may represent a new family of NPHP not involved in cilia-associated functions. Instead, MAPKBP1 is recruited to mitotic spindle poles (MSPs) during the early phases of mitosis where it colocalizes with its paralog WDR62, which plays a key role at MSP. Detected mutations compromise recruitment of MAPKBP1 to the MSP and/or its interaction with JNK2 or WDR62. Additionally, we show increased DNA damage response signaling in fibroblasts from affected individuals and upon knockdown of *Mapkbp1* in murine cell lines, a phenotype previously associated with NPH.

Conclusions: In conclusion, we identified mutations in *MAPKBP1* as a genetic cause of late onset and cilia-independent NPH and propose "*NPHP21*" as an alias for *MAPKBP1*.

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

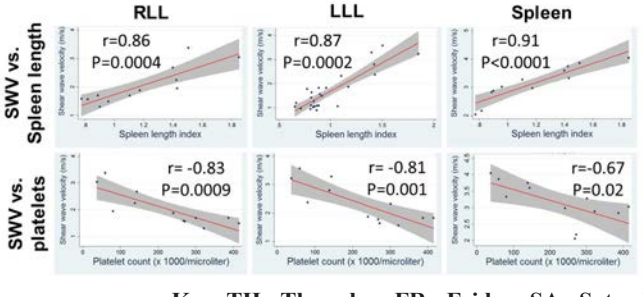
SA-PO597

Quantification of Liver Disease Severity in Autosomal Recessive Polycystic Kidney Disease (ARPKD) Using Ultrasound Elastography with Acoustic Radiation Force Impulse (ARFI) Erum A. Hartung,[1,2] Kassa Darge.[1,2] *[1]Children's Hospital of Philadelphia; [2]Univ of Pennsylvania, Philadelphia, PA.*

Background: We previously showed liver and spleen stiffness by ARFI is higher in ARPKD vs. controls, and in ARPKD pts with vs. without portal HTN. Aims of this study are 1) determine if ARFI liver and spleen stiffness can quantify severity of portal HTN; 2) explore cut-offs to detect presence of portal HTN.

Methods: Stiffness of right and left liver lobes (RLL, LLL) and spleen evaluated in 12 ARPKD pts ≤21y using Siemens Acuson S3000 to measure shear wave velocity (SWV, m/s). Splenomegaly defined as spleen length >90th%ile. Spleen length index calculated as actual/90th%ile. Low platelets (PLTs) defined as <150K. Linear fit plots and Pearson correlation performed between liver and spleen SWV, spleen length index, and PLTs. Receiver operating characteristic analysis used to explore cut-offs for liver and spleen SWV to distinguish pts with vs. without portal HTN (splenomegaly and/or low PLTs).

Results: Liver and spleen SWV positively correlated with spleen length (RLL: r=0.86, p=0.0004; LLL: r=0.87, p=0.0002; spleen: r=0.91, p<0.0001) and negatively correlated with PLTs (RLL: r= -0.83, p=0.0009; LLL: r= -0.81, p=0.001; spleen: r= -0.67, p=0.02).



Proposed cut-offs (% sensitivity, sensitivity) for RLL, LLL, and spleen SWV to differentiate pts with vs. without splenomegaly: 1.69 m/s (88% sens, 95% spec), 1.87 m/s (88% sens, 100% spec), and 3.27 m/s (75% sens, 100% spec) respectively; to differentiate pts with vs. without low PLTs: 1.95 m/s, 2.37 m/s, and 3.32 m/s respectively (100% sens, spec at all sites).

Conclusions: ARFI liver and spleen stiffness correlate with severity of portal HTN in ARPKD. The proposed cut-offs have high sensitivity and specificity to distinguish pts with vs. without portal HTN. ARFI appears useful to measure severity and progression of ARPKD liver disease.

Funding: Other NIH Support - NCATS

SA-PO598

Screening of UMOD/REN/HNF1B Gene Variations in a Chinese Cohort with Autosomal Dominant Tubulointerstitial Kidney Disease Kunjing Gong, Yaqin Wang, Min Xia, Ying Liu, Yuqing Chen. *Nephrology, Peking Univ First Hospital, Beijing, China.*

Background: Autosomal dominant tubulointerstitial kidney disease (ADTKD) is characterized by tubulointerstitial damage and progressive chronic kidney disease. Four genes, including UMOD, REN, HNF1B and MUC1 have been identified contributing to ADTKD. In the present study, we screened genetic variations of UMOD, REN and HNF1B in a Chinese ADTKD cohort.

Methods: 44 probands from 44 different families were recruited for this study. The mean age of the cohort was 30±11years, numbers of males and females were almost equal. ADTKD was diagnosed according to the KDIGO report. We first sequenced all of the three genes and confirmed the gross deletion of HNF1B by multiple ligation-dependent probe amplification (MLPA) assays.

Results: 61.4% of patients showed positive family history of renal disease. We detected 11 point mutations (10 in UMOD, 1 in HNF1B) in this cohort, and three of them (p.Cys35Tyr, p.Asn38Ile and p.Cys287Phe) were novel mutations of UMOD. Point mutation of REN and gross deletion of the HNF1B were not found. All the patients with mutation suffered hyperuricemia, and the patient with HNF1B mutation also presented hypohepatia and hypokalemia.

Conclusions: Almost 25% of patients in our ADTKD cohort were confirmed to have UMOD gene mutations. And three of them were novel mutation of UMOD. The result indicated that gene sequencing is one of the reasonable methods to diagnose ADTKD.

Funding: Government Support - Non-U.S.

SA-PO599

Rapamycin Treatment Improves the Cystic Kidney in the ADPKD Mouse Model via the Mtorc1 and Cell-Cycle-Associated CDK1/Cyclin Axis Ao Li,[1,2] Song Fan,[1] Yangyang Zhang,[1] Jialin Meng,[1] Xufeng Shen,[1] Jun Mao,[1] Yuchen Xu,[1] Li Zhang,[1] Xiansheng Zhang,[1] Chao Zhao Liang,[1] Guanqing Wu.[1,2] *[1]PKD Center, Dept of Urology, the First Affiliated Hospital of Anhui Medical Univ and Inst of Urology, Anhui Medical Univ, Hefei, Anhui, China; [2]State Key Laboratory of Molecular Oncology, Cancer Hospital and Inst, Chinese Academy of Medical Sciences, Beijing, China.*

Background: Recent studies showed that rapamycin treatment can improve the cystic phenotypes in mouse models of ADPKD, but direct link between polycystin dysfunction and mTOR signaling changes or ADPKD cystogenesis has not been clearly identified.

Methods: We employed our recently developed ADPKD animal model (*Vil*-Cre;*Pkd2*$^{f3/f3}$ mice) in which full spectrum of cystic phenotypes similar to human ADPKD patients are closely displayed in adulthood. Rapamycin treatment did predominately inhibit proliferation, but not affect apoptosis, in the cyst-lining epithelia of the disease kidney. To explore the molecular mechanism by which rapamycin suppresses epithelial proliferation, we have searched our previously established cDNA microarrays data between our E8 cell line (*Pkd2*-null) and its maternally derived D3 cell line (*Pkd2*$^{+/-}$) (Kim et al. AJSN 2009;20:2556). Of the signature genes, *Ccnd1* mRNA level encoding cyclin D1 showed 4-fold higher elevated in E8 than in D3 cells. We also used qPCR from mRNAs of E8/D3 cells and renal tissues from *Vil*-Cre;*Pkd2*$^{f3/f3}$ and its normal control *Pkd2*$^{f3/f3}$ mice.

Results: We found that downregulating PC2 not only significantly increased *Ccnd1* expression, but also elevated all cell-cycle-associated cyclins (namely cyclin A, B, D1, and E), and cyclin-dependent kinase 1 (CDK1). In addition, we also found that rapamycin treatment arrested aberrant epithelial-cell proliferation in the ADPKD kidney by downregulating these cell-cycle-associated cyclins and CDK1, but not other CDKs.

Conclusions: Our newly defined molecular mechanism, by which rapamycin suppresses proliferation via inhibiting abnormally elevated CDK1 and cycle-associated cyclins, revealed the involvement of the mTORC1–CDK1/cyclin axis in ADPKD, which will lead to new molecular targets for treating this disease.

Funding: Government Support - Non-U.S.

SA-PO600

Effects of Metformin on the AMPK Pathway and Metabolism in ADPKD Kidney Epithelial Cells Hui Li, Kirt Gill, Daniel Rivera, Kenneth R. Hallows. *Medicine, USC Keck School of Medicine, Los Angeles, CA.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations in polycystin-1 (PKD1) and polycystin-2 (PKD2) and presents with progressive development of renal cysts. In PKD1 mutant cells increased activity of cell proliferation pathways (e.g., mTOR and ERK) and decreased AMP-activated kinase (AMPK) activity

occur, along with dysregulated cellular metabolism. However, these factors are not well characterized for PKD2 mutants. Our goals were to examine and correlate effects on these pathways and cellular bioenergetics in normal and PKD2-deficient cells treated with and without cAMP agonists and the AMPK activator metformin. We hypothesized that metformin would dampen cAMP agonist-induced stimulation of cell growth pathways and correct the perturbed energy metabolism in PKD.

Methods: Immortalized kidney epithelial cells with inducible PKD2 knockout were used. AMPK, mTOR and ERK pathway markers and levels of key glycolytic enzymes were checked by immunoblotting and correlated with time- and dose-dependent effects of metformin treatment. 3-D Matrigel cultures were used to assess cyst growth after treatment with metformin and cAMP agonists (forskolin and IBMX). Seahorse XF Analyzer assays were used to evaluate the metabolic phenotype of cells under different conditions.

Results: Metformin (300 μM) effectively activated AMPK in polarized PKD2-deficient cells over 3 d. Unlike in PKD1-deficient cells, however, these cells displayed neither excessive activation of the mTOR pathway, inhibition of the AMPK pathway nor apparent metabolic dysregulation under baseline conditions. Nevertheless, metformin significantly inhibited cyst growth in 3-D cultures of these cells, both in the presence and absence of cAMP agonists. Metformin also inhibited oxidative metabolism in both PKD2-null and wild-type cells without significantly affecting glycolytic flux.

Conclusions: Cystogenesis may occur through differing signaling pathways depending on PKD mutation. Metformin may exert beneficial effects in PKD2 mutant cells by mechanisms distinct from those proposed in PKD1 mutant cells and may be in part AMPK-independent.

Funding: NIDDK Support, Other U.S. Government Support

SA-PO601

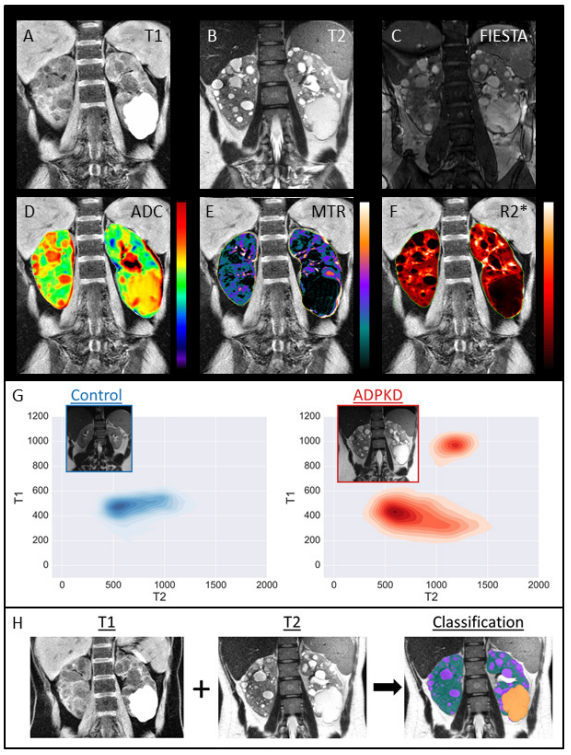
Advanced Magnetic Resonance Imaging and Image Analytics to Assess the Polycystic Kidney

Timothy L. Kline, Sudhakar K. Venkatesh, Maria V. Irazabal, Marie E. Edwards, Panagiotis Korfiatis, Peter C. Harris, Vicente E. Torres. *Mayo Clinic, Rochester, MN.*

Background: Advanced MR imaging and image analytics offer an opportunity to improve clinical monitoring and outcome prediction for PKD patients. These methods illuminate traditionally hidden features, such as: fibrotic tissue, restricted diffusion, increased stiffness, cyst heterogeneity, and changes in regional perfusion.

Methods: We performed a comprehensive MR imaging protocol (T1, T2, FIESTA, RBF, DWI, MT, BOLD, MRE) in 10 ADPKD patients (18-30 years old) and age and sex-matched control volunteers - all with normal renal function. Two exams were performed (on different days) on each volunteer to characterize repeatability of the measurements.

Results: The Figure shows examples of traditional MR imaging (A, B, C), and quantitative maps: apparent diffusion coefficient 'ADC' derived from DWI (D), 'MTR' derived from MT (E), and 'R2*' derived from BOLD (F). Quantitative MR imaging sequences were found to be repeatable. For the absolute difference between quantitative parameters measured at two different times, whole kidney MTR was 0.97 ± 0.76%, and whole kidney diffusivity was 0.086 ± 0.061. In addition, advanced multiparametric MR analysis techniques showed different pathologies, as well as the ability to perform tissue classification. Shown in 'G' is an example comparing T1/T2 values between an ADPKD patient vs an age and sex-matched control volunteer. Then, in 'H', an unsupervised clustering algorithm was used to perform cyst segmentation and classification of the PKD kidneys.



Conclusions: Quantitative and multiparametric MR imaging have strong potential for comprehensive characterization of the PKD kidney. It is likely that combining these techniques with other patient data will improve clinical decision making by providing new structural and functional information.

Funding: NIDDK Support

SA-PO602

Using T2- versus T1-Weighted MR Images to Assess Total Kidney Volume in Patients with ADPKD

Maatje D.A. van Gastel,[1] A. Lianne Messchendorp,[1] Merel Anouk Kaatee,[1] Marissa De Jong,[1] Shekar Mahesh,[2] Ron T. Gansevoort.[1] *[1]Nephrology, UMCG, Groningen, Netherlands; [2]Radiology, UMCG, Groningen, Netherlands.*

Background: In ADPKD patients, measurement of total kidney volume (TKV) by MR imaging is performed to select patients for treatment with disease modifying drugs and to evaluate efficacy of novel treatments. Historically T1-weighted images were used, but the methodology of T2-weighted imaging has evolved, making T2-weighted imaging also suitable for TKV measurement. We studied the performance of T2- versus T1-weighted images to assess TKV and growth rate in TKV.

Methods: 30 patients with ADPKD were randomly selected. Patients underwent a standardized abdominal MRI-protocol on a 1.5-Tesla or 3.0-Tesla MRI-scanner at baseline and follow-up. TKV was measured by manual tracing with Analyze Direct 9.0 and 11.0 software (Inc. Overland Park, KS, USA). Three readers measured 12 scans to establish intra- and interreader coefficients of variation (CV). Correlations between T1 and T2 measured TKV and growth rates in TKV were tested with ICC and Bland-Altman analyses.

Results: Average age of the participants was 49.5±7.0 years, 46.7% were female, and estimated GFR was 48.4±10.8 mL/min/1.73m^2. Intra- and interreader CVs were low and comparable for T2- and T1-weighted images (intra: 0.83 (7.03) versus 1.15 (5.03)%, p=0.9, and inter: 2.18 (4.05) versus 1.69 (7.27)% , p=0.9, respectively). TKV was significantly higher for T2 images compared to T1 images, but numerically similar: 1938.6 [1257.1-2960.7] versus 1957.1 [1255.8-2788.5] mL, resp. (p=0.001) with a mean difference of only 1.6% and excellent agreement (ICC 0.996). Growth in TKV during a follow-up of 2.2±0.4 years was similar for T2- and T1-weighted images (9.2±10.5 versus 7.7±8.9%, p=0.1, respectively), with high agreement (ICC 0.849). Bland-Altman analysis showed no systematic under- or overestimation of TKV growth rate when using T2 instead of T1 weighted images.

Conclusions: In patients with ADPKD measurement and growth rate of TKV using T2-weighted images perform similarly compared to using T1-weighted images. Both methods can therefore be used in clinical practice.

Funding: Pharmaceutical Company Support - Ipsen Pharmaceuticals, Private Foundation Support

SA-PO603

Imaging Techniques for Estimating Total Kidney Volume in Children with Autosomal Dominant Polycystic Kidney Disease: 3D-US versus MRI

Stephanie Le De Rechter,[1] Luc Breysem,[2] Marleen Smet,[2] Frederik De Keyzer,[2] Raymond H. Oyen,[2] Elena N. Levtchenko,[1] Djalila Mekahli.[1] *[1]Pediatric Nephrology, Univ Hospitals Leuven, Leuven, Belgium; [2]Radiology, Univ Hospitals Leuven, Leuven, Belgium.*

Background: Total kidney volume (TKV) has been shown in adult Autosomal Dominant Polycystic Kidney Disease (ADPKD) to be an independent and strong predictor for disease progression. In the current interventional clinical trials, TKV measurement by magnetic resonance (MR) imaging has been shown to be more accurate, reproducible and able to detect small changes over a short period of time than ultrasound (US). Since future therapies in ADPKD could be extended to include children, we aimed to examine whether the high-resolution 3D-US TKV measurements might be used as an alternative method to MR measurements in ADPKD children.

Methods: Prospective evaluations of renal MR, 2D- and 3D-US were performed, whereby TKV was calculated by means of manual delineations (MR, 3D-US) or by the ellipsoid method (2D-US). Correlations and differences between parameters were evaluated using Pearson r and Wilcoxon signed rank tests. After correction using the optimal linear regression, the variability of the measurements was examined using in Bland-Altman plots.

Results: We included 29 patients (17 male, 12 female) with a median age (SD) of 14.0 (3.4) years and eGFR 111 (17) ml/min/1.71m² leading to 58 evaluated kidneys. Although both US methods showed significantly lower TKV compared to MR (In ml, 3D-US: 181 (111); 2D-US 158 (101); MR 205 (132); all p<0.001), both showed a strong correlation to the MR TKV (2D-US: r=0.963; 3D-US: r=0.941). After correcting for the lower values in US, Bland-Altman plots showed slightly lower variability and error in 3D-US measurements compared to 2D-US in kidneys with a TKV below 200 ml (on average 15.5 ml error on 2D-US compared to 12.9 ml on 3D-US), although not reaching significance (p=0.23).

Conclusions: In children, 3D-US represents a good alternative for MR to measure TKV in ADPKD.Compared with MR, US TKV was prone to underestimation. After correcting for these, 3D-US tended to be slightly more comparable to MR in small TKV (<200 ml) than 2D-US.

Funding: Government Support - Non-U.S.

SA-PO604

In Vivo Functional Genomics Screen to Identify Genetic Disease Modifier Driving Autosomal Dominant Polycystic Kidney Disease Phenotypic Heterogeneity Raphael A. Nemenoff, Kenneth H. Marsh, Emily K. Kleczko, Michel Chonchol, Katharina Hopp. *Univ of Colorado Denver, Anschutz Medical Campus.*

Background: ADPKD is characterized by significant phenotypic heterogeneity even within families, suggesting that factors other than the specific *PKD1/PKD2* mutation influence ADPKD severity. One explanation for this is the existence of additional mutations to other loci that modify ADPKD pathomechanisms and hence alter disease progression. Identification of such modifier genes, however, has been proven difficult in the past.

Methods: Here, we utilized the conditional Sleeping Beauty (SB) transposon mutagenesis mouse (SB11;T2/Onc3) driven by *Cdh16* cre-recombinase to identify PKD modifiers in a *Pkd1* haploinsufficient mouse model. Generally, $Pkd1^{+/-}$ mice do not develop cysts; however, since a small change of *Pkd1* gene product function beyond 50% is enough to drive cystogenesis, genes disrupted or overexpressed by T2/Onc3 integration that directly or indirectly function in *Pkd1* pathways will trigger a cystic phenotype.

Results: We generated experimental mice ($Pkd1^{del2/+}$;Ksp-$cre^{Tg/+}$;Rosa-26-$SB11^{Tg/+}$;T2/$Onc3^{Tg/+}$) and confirmed kidney specific cre-recombinase and SB11 expression. Additionally, we found SB11 to primarily be localized to the collecting duct and Loop-of-Henle, nephron segments thought to be key to ADPKD pathogenesis. Importantly, by MRI, US, and histology we show that our experimental mice develop several cysts as early as one month of age, while none were found in genetic littermate controls (negative for *Cdh16* or SB11). These cysts stained positive for SB11 by immunofluorescence, demonstrating proof-of-concept. Experiments to capture cystic lesions by laser micro-dissection, identify T2/Onc3 integration sites through next-generation sequencing, and pathway map common insertion sites are ongoing.

Conclusions: In summary, we developed a model that can in an unbiased fashion functionally identify genetic modifiers of ADPKD. Our preliminary findings indicate that mutations to additional genomic loci can trigger cystogenesis in a non-cystic background. These modifier loci will provide insight into ADPKD pathomechanisms, highlight novel therapeutic targets, and aid in patient management.

Funding: NIDDK Support

SA-PO605

Serum Bicarbonate Levels and Total Kidney Volume in Children and Young Adults with Autosomal Dominant Polycystic Kidney Disease Kristen L. Nowak, Zhiying You, Berenice Y. Gitomer, Michel Chonchol, Melissa A. Cadnapaphornchai. *Univ of Colorado Anschutz Medical Campus.*

Background: Enhanced renal production of ammonia has been linked to cyst formation, and alkali administration has been found to reduce cystic tubular dilatation in animal models of autosomal dominant polycystic kidney disease (ADPKD). Whether lower serum bicarbonate concentrations are associated with an increased rate of total kidney volume (TKV) growth is unknown.

Methods: Participants were 85 children and young adults (8-22 years) participants with ADPKD and normal kidney function receiving lisinopril who were randomized to treatment with pravastatin or placebo for a 3-year period with evaluation of height-corrected TKV (HtTKV) at baseline, 18 and 36 months. The study population was divided into tertiles based on serum bicarbonate levels. We used Generalized Estimating Equations (GEE) models to examine the association between serum bicarbonate levels with repeat measures of HtTKV categorized as below and above the median level.

Results: Participants had a mean age of 15 ± 4 years. Mean serum bicarbonate level and estimated glomerular filtration rate were 24.4 ± 2.1 mEq/L and 115 ± 20 mL/min/1.73m^2, respectively. The median (IQR) HtTKV was 288 (221-394) ml/m. Compared to the first (lowest) tertile, the OR (95% CI) for a HtTKV above the median value during the course of the study were as follows: second tertile, 1.004 (0.73-1.38) and third tertile, 0.84 (0.72-0.97) after adjustment for age, gender, randomization group, body-mass index, systolic blood pressure, estimated glomerular filtration rate, and urine albumin excretion.

Conclusions: In a cohort of children and young adults with ADPKD with normal kidney function, higher serum bicarbonate concentrations were associated with a lower risk of increase in HtTKV.

Funding: NIDDK Support

SA-PO606

Design of a Phase I Clinical Trial with 2-Deoxy-D-Glucose in Autosomal Dominant Polycystic Kidney Disease Francesca Testa,[2] Marco Busutti,[2] Marco Chiaravalli,[1] Marco Leonelli,[2] Mariano Capistrano,[3] Francesco SCOLARI,[3] Donatella Spotti,[4] Alessandra Boletta,[1] Riccardo Magistroni.[1,2,4] *[1]Div of Genetics and Cell Biology, Molecular Basis of Polycystic Kidney Disease Unit, San Raffaele Scientific Inst, Milan, Italy; [2]Div of Nephrology, Univ of Modena and Reggio Emilia, Modena, Italy; [3]Second Div of Nephrology, Azienda Spedali Civili di Brescia, Brescia, Italy; [4]Div of Nephrology, San Raffaele Scientific Inst, Milan, Italy.*

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a life-threatening Mendelian disease. The epidemiology is controversial and an accurate estimation in a small region of the North of Italy is ongoing. The hallmark of ADPKD is bilateral renal cysts formation. Several deregulated pathways have been described and in recent studies we have shown that defective glucose metabolism is a feature of ADPKD. Others and we showed that the glucose analogue 2-deoxy-D-Glucose (2DG) slowed down disease progression in animal models. Few previous clinical trials describing the use of 2DG as antineoplastic agent suggest low side effects. We are now about to initiate a Phase I Clinical Trial in ADPKD.

Methods: The aim is to perform a Phase I Clinical Trial to assess 2-DG tolerability. With a combined effort involving preparation of the active compound ready for human administration and selection of a small number of patients, an exploratory study will be initiated.

Results: This is a single center, open label, one arm trial in adult subjects. The study will follow a modified accelerated titration model. After determining eligibility and recording baseline parameters, 2DG will be titrated from lowest (2mg/die) to highest tolerated levels. Preliminary data suggest a prevalence comprised between 4.2 and 4.6 : 10000 inhabitants. Based on this we defined a recruiting population supplied by three Nephrology Centers. A limited number of ADPKD patients, with large kidneys but not severely reduced function will be exposed to 2DG and clinically monitored.

Conclusions: This first exploratory study will provide information to design a long-term evaluation in a relatively small patient population to measure markers of potential efficacy of 2DG.

Funding: Government Support - Non-U.S.

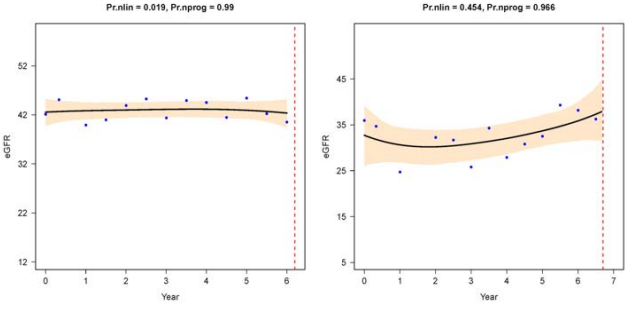
SA-PO607

Patterns of Renal Function Decline in the HALT PKD Trials Godela M. Brosnahan,[1] Kaleab Z. Abebe,[2] Frederic F. Rahbari-Oskoui,[3] Charity G. Moore,[2] Kyongtae Ty Bae,[2] Jared J. Grantham,[4] Robert W. Schrier,[1] Arlene B. Chapman,[5] Ronald D. Perrone,[6] Vicente E. Torres.[7] *[1]Univ Colorado; [2]Univ Pittsburgh; [3]Emory Univ; [4]Univ Kansas; [5]Univ Chicago; [6]Tufts Medical Center; [7]Mayo Clinic.*

Background: Renal function loss in autosomal dominant polycystic kidney disease (ADPKD) is generally believed to be steady and rapid once the limit of compensatory hyperfiltration has been reached. However, a detailed examination of individual patterns of renal function decline has not been performed.

Methods: Using data from the HALT trials we calculated the probabilities of linear or nonlinear trajectories of estimated glomerular filtration rate (eGFR) decline, as well as the probability of nonprogression for each participant using a previously validated Bayesian model. Twenty-six subjects with early disease and persistently high eGFR were excluded.

Results: The majority of participants (88% in Study A; 94% in Study B) experienced a progressive decline in eGFR during up to 8 years of follow-up, including those with well preserved renal function at baseline.A proportion (25% in Study A and 14% in Study B) of subjects with progressive decline had a nonlinear pattern. Interestingly, 12% of participants in Study A and 6% in Study B experienced a prolonged period of stable eGFR.



These individuals (Study A) had significantly smaller total kidney volumes, higher renal blood flow, lower urinary albumin excretion and lower body mass index than the majority; in Study B subjects with reduced but stable eGFR were older than the progressors but otherwise similar. Nontruncating weak *PKD1* mutations were enriched among participants with stable eGFR in both Study A and B.

Conclusions: Although the course of renal function loss is progressive in most individuals with ADPKD, 6 to 12% experience prolonged intervals during which GFR decline is no faster than expected of ageing alone. Maintaining a healthy body weight may help to preserve GFR in ADPKD.

Funding: NIDDK Support, Pharmaceutical Company Support - Merck donated Lisinopril and Boehringer Ingelheim Pharmaceuticals donated Telmisartan and matched placebo, Private Foundation Support

SA-PO608

Serum Uric Acid, Total Kidney Volume and Disease Progression in Autosomal Dominant Polycystic Kidney Disease (ADPKD): Results from the HALT PKD Trial Godela M. Brosnahan, Berenice Y. Gitomer, Wei Wang, Zhiying You, Kristen L. Nowak, Diana I. Jalal, Michel Chonchol. *Univ Colorado, Aurora, CO.*

Background: Hyperuricemia has been implicated in the progression of chronic kidney disease (CKD) in clinical studies. We tested the hypothesis that higher serum uric acid levels may be associated with greater total kidney volume (TKV) and progression to end-stage renal disease (ESRD) in ADPKD.

Methods: We measured uric acid levels in stored serum samples in 766 patients who participated in the HALT-PKD randomized controlled trial of two different blood pressure

control strategies. Participants in HALT-Study A had abdominal MRI for total kidney volume measurement. We used mixed effect models (HALT- Study A; N=410) and Cox proportional-hazards models (HALT-Study B; N=356) to examine the associations between uric acid modeled as a continuous variable with repeated measures of height-corrected total kidney volume (HtTKV) during the course of the study and time to a 50% reduction in eGFR or ESRD, respectively.

Results: The mean age, serum uric acid level and eGFR in HALT-A were 37±8 years, 6±2 mg/dL and 90±17 ml/min/1.73m^2. The median (IQR) for HtTKV was 593 (409, 896) ml/m. In HALT-B the mean age, uric acid level and eGFR were 49±8 years, 7±2 mg/dL and 48±11 ml/min/1.73m^2. The b estimates (TKV) and hazard ratio (50% reduction in eGFR or ESRD) are summarized in table 1.

	Unadjusted	Adjusted
	HALT Study A	HALT Study A
ß estimate; 95% CI (per mg/dL increase)	-3.9 (-20.66 to 12.86; p=0.65)	-11.26 (-31.43 to 8.92; p=0.27)
	HALT Study B	HALT Study B
Hazard ratio; 95% CI (per mg/dL increase)	1.21 (1.11 to 1.29; p<0.0001)	1.10 (1.01 to 1.19; p=0.02)

Adjusted for age, gender, race, randomization group, body mass index, systolic blood pressure, eGFR, urine albumin excretion and genotype.

Conclusions: Higher serum uric acid levels are associated with increased hazard for kidney function decline and ESRD but not with larger kidney volume. Randomized interventional studies will be necessary to examine whether treating hyperuricemia has a protective role in ADPKD.

Funding: NIDDK Support, Pharmaceutical Company Support - Merck donated Lisinopril and Boehringer Ingelheim Pharmaceuticals donated Telmisartan and matched placebo, Private Foundation Support

SA-PO609

Variability of PKD1-PKD2 in Autosomal Dominant Polycystic Kidney Disease (ADPKD): A 643 Patients Italian Experience

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Background: ADPKD is the most common hereditary kidney disease.

Methods: We analysed PKD1 and PKD2, in a large cohort of 440 unrelated Italian patients with ADPKD and 203 relatives by direct sequencing and MLPA. Molecular and detailed phenotypic data have been collected and submitted to the PKD1/PKD2 LOVD database.

Results: We describe 701 variants, 249 (35.5%) already associated with ADPKD and 452 (64.5%) novel. According to the criteria adopted, the overall detection rate was 80% (352/440). Novel variants with uncertain significance were found in 14% of patients. Among patients with pathogenic variants, in 301 (85.5%) the disease was associated with PKD1, 196 (55.7%) truncating, 81 (23%) non truncating, 24 (6.8%) IF indels, and in 51 (14.5%) with PKD2. Enrichment of the cohort in subjects with an uncertain clinical diagnosis (21.8%) may explain the lower detection rate.

Conclusions: This is the first large retrospective study in Italian patients: our results outline the high allelic heterogeneity of variants, complicated by the presence of variants of uncertain significance and of multiple variants in the same subject. To this point, databasing (www.LOVD.nl/PKD1-PKD2) of both clinical and molecular data is crucial to improve the assessment of variant pathogenicity. Molecular analysis helped us to offer genetic counselling in at risk families: in relatives of probands with a pathogenic variant, we were able to prove 97 individuals to be free of the disease and 91 diagnosed with ADPKD.

Funding: Government Support - Non-U.S.

SA-PO610

Bone Mineral Density Is Reduced in Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: We previously identified low bone turnover in young patients with ADPKD and normal kidney function. Histomorphometric measurements are characterized by decreased indices of bone formation and resorption in trabecular bone and increased thickness of cortical bone. While fracture rates have not been reported in patients with ADPKD, we hypothesized that the abnormalities in bone turnover are associated with low bone mineral density (BMD) determined by dual energy x-ray absorptiometry (DEXA).

Methods: All patients provided informed consent and the protocol that was approved by the Colorado Multiple Institution Review Board. BMD was assessed, by DEXA scan in 15 patients with ADPKD and normal kidney function at 3 sites: lumbar spine L1-L4, neck of the femur and distal ⅓ of the radius. Z scores were calculated as standard deviations above or below normal age and sex matched participants from the National Health and Nutrition Examination Study.

Results: : BMD was assessed in 8 women and 7 men with ADPKD. Mean age of the patients was 33 ± 12 years; mean estimated glomerular filtration rate (eGFR) 93.1 ± 30.7 ml/min/1.73m^2. Bone density was lowest at the lumbar spine as shown in the table of Z scores.

Region (Z Score)	Spine L1-L4	Left Femoral Neck	Right Femoral Neck	Distal Third Radius
Mean	-0.55	-0.07	-0.08	0.16
Standard deviation	1.19	0.79	0.79	0.7

Thirty six percent of patients had a lumbar bone density ≤1 S.D. below normal age- and sex-matched healthy subjects.

Conclusions: We describe for the first time lower BMD in patients with ADPKD and normal kidney function. Lowest bone density was detected in the lumbar spine consistent with the higher proportion of trabecular/cortical bone in this region. Further studies are need to better understand clinical implications of these findings.

Funding: NIDDK Support

SA-PO611

Introduction of Tolvaptan for ADPKD: Implications for Renal Services

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Background: ADPKD is the most common hereditary renal disease. Following the TEMPO 3:4 trial, tolvaptan was approved by EMA in May 2015 for adults with ADPKD, eGFR >30 ml/min and 'rapidly progressing disease' (not defined further). In the USA, the FDA did not approve tolvaptan in this indication but requested further evidence – another randomised controlled trial will be completed in 2017. Glasgow Renal and Transplant Unit serves a population of 1.5 million. The aim of this study was to establish the number of patients who may be eligible for treatment and the implications for our service.

Methods: Adults with ADPKD attending Glasgow Renal and Transplant Unit were identified. Most recent, 1 year and 5 year values for eGFR using the CKD-EPI equation were collected. Rapid disease progression was defined as decline in eGFR ≥5ml/min in 1 year or ≥12.5ml/min over 5 years. Patients without evidence of rapid disease progression by eGFR were further evaluated by family history and imaging criteria. Numbers qualifying for treatment or requiring further imaging according to UK Renal Association guidelines (which include criteria for rapid progression by eGFR decline or kidney size increase) were calculated.

Results: 645 patients with ADPKD and attending Glasgow Renal and Transplant Unit were identified. Point prevalence of ADPKD was 430 per million population. 353 met age and renal function criteria and 185 also met criteria for rapid disease progression by declining eGFR. 168 did not have rapid disease progression by eGFR decline. 73 had no recent measurement of kidney length and require US. 12 had mean kidney length >16.5cm on US and require MRI to establish kidney volume. 64 had mean kidney length <16.5cm, requiring follow-up US every 2-3 years.

Conclusions: The introduction of Tolvaptan therapy for ADPKD will have significant implications for renal services. Many patients will require imaging by US and/or baseline and follow-up MRI. Treated patients require monthly blood tests for the first 18 months of therapy. Our data, derived from a population of defined size, will help renal units estimate the implications for their services.

SA-PO612

Implications of Transporter Studies on Development of Tesevatinib for Polycystic Kidney Disease: Multidrug and Toxin Extrusion (MATE)1/2-K Inhibition

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Background: Tesevatinib is a tyrosine kinase inhibitor in clinical development for the treatment of autosomal dominant PKD (ADPKD) based on its demonstrated ability to target EGFR, Src and HER2. Testing for inhibition of membrane transporters is required to determine drug-drug interaction potential.

Methods: P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2-K were screened for inhibition by tesevatinib *in vitro*. Tesevatinib concentration in EDTA-plasma from treated ADPKD subjects was determined by LC/MS/MS.

Results: Mean steady state plasma C_{min} and C_{max} was 111 and 136 nM in ADPKD patients treated QD with 50 mg tesevatinib. Total plasma tesevatinib C_{max}/IC50 for transporter inhibition was only >0.1 for MATE1 and MATE2-K (IC_{50} = 80nM and 68nM). MATE1/2-K inhibitors such as cimetidine may increase serum creatinine due to the reduced tubular creatinine secretion into ultrafiltrate, without clinically meaningful alteration in renal function. Consistent with this, ADPKD subjects receiving tesevatinib experienced non-progressive elevations of serum creatinine, without corresponding elevations in cystatin C that would indicate an impact on renal function. The median increase in creatinine from screening for 24 subjects receiving tesevatinib were 11.1, 14.3 and 10.0% on Days 3, 7 and 28 of treatment, while that for cystatin C was 0, 1.9, and -1.7%. Seven subjects with elevated serum creatinine during tesevatinib treatment had interruptions in drug administration

ranging in duration from 11 days to 32 days. All seven subjects exhibited a reduction in serum creatinine following the interruption in drug treatment ranging from 0.03 mg/dL to 0.20 mg/dL (mean reduction 0.13 mg/dL).

Conclusions: MATE inhibition by tesevatinib may explain serum creatinine increases associated with treatment, indicating the need for innovative approaches to eGFR assessment when conducting ADPKD clinical trials.

Funding: Pharmaceutical Company Support - Kadmon Corporation

SA-PO613

Haematologic Phenotype of Hereditary Polycystic Kidney Disease

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Background: Hereditary polycystic kidney disease (PKD) has a complex phenotype including not only renal cyst formation leading to end-stage kidney disease (ESKD) but also vascular abnormalities and endothelial dysfunction. Patients with PKD tend to have a higher susceptibility for urinary and respiratory infections and develop more skin cancer after transplantation.

Methods: We compared lymphocyte counts in patients with and without PKD at the time of transplantation in a cohort with follow-up until December 31, 2014. We analyzed flow cytometric immuno-phenotyping data if available. We also conducted a multicenter age-matched case-control study in a cohort including 202 patients with and 202 without PKD across comparable CKD strata with follow-up until February 1, 2016. We used multiple linear regression analysis to adjust for potential confounders in both models. We also recorded and analyzed other hematological characteristics.

Results: In a population of 700 patients with ESKD, total lymphocyte counts (and particularly $CD8^+$ T and B lymphocytes) were significantly lower in the 126 patients (18%) with versus without PKD ($p<0.001$ for both). After adjustment for age, sex, lnCRP and eGFR (in the CKD cohort only), PKD was associated with a lower lymphocyte count of 264/µL (95%CI 164 to 384; p<0.001) and 345/µL (95%CI 245 to 445; p<0.001) in the ESKD and CKD cohort respectively. Also, thrombocyte and monocyte counts were independently lower in patients with versus without PKD in both cohorts (p<0.001 for both cell types within each of the cohorts).

Conclusions: PKD is characterized by distinct haematological abnormalities and more particularly lymphopenia, independent of kidney function. A genetic basis for increased apoptosis of lymphoid cells and their precursors in PKD is conceivable.

SA-PO614

Smoking Worsens the Renal Phenotype of Pkd1-Deficient Cystic Mice

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Background: Smoking is a risk factor for progression to stage 5 chronic kidney disease in males, including the autosomal dominant polycystic kidney disease (ADPKD) scenario. To elucidate this matter, we analyzed the effects of smoking on the renal phenotype of a mouse model orthologous to ADPKD.

Methods: *Pkd1*-deficient cystic mice ($Pkd1^{cond/cond}$:$Nestin^{cre}$) and noncystic animals ($Pkd1^{cond/cond}$) were exposed to cigarette smoking from conception to 18 weeks of age, 2 times a day, 30-min cycles (CYS and NCS, respectively). Additional controls included cystic and noncystic mice not exposed to smoking (CY and NC, respectively). Serum urea nitrogen (SUN), renal cystic index by ultrasonography, cell proliferation, area of renal fibrosis and body weight (BW) were evaluated at 16-18 weeks in all groups.

Results: CYS mice had higher SUN than CY (57.2±32.4 *vs* 35.7±6.0 mg/dL, p<0.05) and NC animals (*vs* 32.0±3.1 mg/dL, p<0.001). NCS mice also showed higher SUN than NC animals (48.6±19.1 *vs* 32.0±3.1 mg/dL, p<0.01). No difference in SUN was detected, however, between CYS and NCS mice and between CY and NC animals. The cystic index was increased in CYS kidneys compared to CY [17.4% (6.0-31.7) *vs* 4.6% (2.7-8.4), p<0.05] while BW was lower in CYS than CY mice [24.2 (23.4-25.0) *vs* 28.3 g (27.1-29.4), p<0.0001]. Cell proliferation rate was increased in NCS kidneys compared to NC [0.9% (0.7-1.0) *vs* 0.2% (0.1-0.2), p<0.0001] and higher in CYS than CY cystic epithelia [2.1% (0.9-4.3) *vs* 1.1% (0.5-1.6), p<0.05]. Renal fibrosis was also higher in CYS mice than CY [1.1% (0.8-2.0) *vs* 0.3% (0.2-0.8), p<0.0001], NCS [*vs* 0.1% (0.09-0.2), p=0.01] and NC animals [*vs* 0.05 % (0.03-0.09), p<0.0001]. Increased fibrosis was also detected in CY kidneys compared to NCS and NC (p<0.0001) and in NCS kidneys compared to NC (p<0.05).

Conclusions: Our data revealed that smoking aggravated the renal phenotype of cystic mice, increasing the cystic burden, cell proliferation and fibrosis, and reducing kidney function. Deleterious effects were also observed in noncystic kidneys. Our findings support an accelerating effect of smoking on the progression of ADPKD.

Funding: Government Support - Non-U.S.

SA-PO615

Effect of Dietary Salt of the Progression of ADPKD in the HALT PKD Clinical Trials

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Background: The Consortium for Renal Imaging Studies in PKD (CRISP) found that 24 hours urinary sodium excretion (UNaE) associates with the rate of total kidney volume (TKV) increase. Whether sodium restriction can slow the progression of ADPKD is not known.

Methods: This post-hoc analysis of the HALT-PKD randomized clinical trials of renin-angiotensin blockade in ADPKD used linear mixed models to examine whether dietary sodium (reflected by UNaE) affected rates of TKV or eGFR change in patients with eGFR >60 ml/min/1.73 m^2 (Study A) or the risk for a composite endpoint of 50% reduction in eGFR, ESRD or death, or the rate of eGFR decline in patients with eGFR 25-60 ml/min/1.73 m^2 (Study B). Patients were instructed to follow a <100 mEq sodium diet.

Results: During the trial UNaE declined by 0.25 ± 0.04 and 0.41 ± 0.04 mEq/24 hr per month of follow-up in studies A and B (both P<0.001). In Study A, averaged and time varying UNaE were associated with kidney growth (2.4%/yr and 0.48%/yr for each 100 mEq UNaE, P<0.001 and P=0.005, respectively) and averaged UNaE was marginally associated with faster eGFR decline (-0.37 ml/min/1.73m^2/yr for each 100 mEq UNaE, P=0.09). In Study B, averaged but not time varying UNaE associated with increased risk for 50% reduction in eGFR, ESRD or death (HR 1.56 for each 100 mEq UNaE, P=0.01) and faster eGFR decline (-0.48 ml/min/1.73m^2/yr for each mEq 100 mEq UNaE, P<0.001).

Conclusions: These results reinforce the important role of moderate sodium restriction in the management of patients with ADPKD.

Funding: NIDDK Support, Other NIH Support - CRISP

SA-PO616

Prediction of GFR Slopes in Autosomal Dominant Polycystic Kidney Disease Patients with Normal Renal Function

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Background: The Irazabal classification represents a major advance in prediction of renal function decline among patients with autosomal dominant polycystic kidney disease (ADPKD). Since this classification includes a limited number of predictors, we sought to improve the prediction of GFR decline by using a sequence of predictive models and taking the advantage of both the longitudinal HALT-A and CRISP data.

Methods: To improve prediction of GFR in ADPKD with normal renal function, we analyzed data from the HALT-A and CRISP cohorts; 558 and 241 ADPKD adults followed for 8 and 12 yrs respectively in these prospective, multicenter studies. We have developed statistical models of GFR linear trajectories over the duration of the HALT study and replicated the utility of this approach to predict GFR decline over time in the CRISP study.

Results: We built multilevel linear models of GFR trajectories by progressive addition of physical findings, laboratory data, PKD mutation type/severity and imaging studies (height-adjusted total kidney volume; htTKV). In the HALT-A cohort the final model explained 50% of variability of initial GFR and 31% of variability in GFR change over time (vs 41% and 22% explained by htTKV by age interaction only as used in the Irazabal classification). The best model includes variables and indices based on age, blood pressure, body surface area, hemoglobin, serum potassium, BUN, alkaline phosphatase, urine sodium, potassium and albumin, PKD mutation strength and htTKV. Most of these variables were replicated as significant predictors and explained 54% of variability of the initial GFR and 50% of the GFR slope in the CRISP cohort (vs 47% and 35% explained by the htTKV by age interaction).

Conclusions: HtTKV and age are important predictors of GFR decline in ADPKD patients with normal GFR. However, addition of selected physical findings and laboratory data further improves the model.

Funding: NIDDK Support

SA-PO617

Development of a Customized Diagnostic Panel for Targeted Exome Sequencing of Polycystic Kidney Diseases Takuya Fujimaru, Takayasu Mori, Shintaro Mandai, Motoko Chiga, Hiroaki Kikuchi, Fumiaki Ando, Yutaro Mori, Naohiro Nomura, Shotaro Naito, Tomokazu Okado, Tatemitsu Rai, Shinichi Uchida, Eisei Sohara. *Nephrology, Tokyo Medical and Dental Univ, Bunkyo-ku, Tokyo, Japan.*

Background: Polycystic kidney disease (PKD) is an inherited kidney disorder. Genetic diagnosis is crucial for genetic counseling and the clinical management of patients and their families. However, especially among the child population, it is often difficult to make a precise diagnosis based on clinical features and imaging findings. Additionally, the increasing number of causative genes makes it difficult to perform DNA sequencing using conventional Sanger sequencing. Therefore targeted multiple genome resequencing using next-generation sequencing enables rapid and precise DNA diagnosis at a large scale.

Methods: With reference to Human Gene Mutation Database (HGMD^R), articles, opinion of experts, we created a custom capture RNA probe library (SureSelect Custom, Agilent Technologies) for 66 genes that cause nine types of hereditary PKD, such as autosomal dominant polycystic kidney disease (ADPKD), autosomal recessive polycystic kidney disease (ARPKD) and nephronophthisis. MiSeq sequencing was performed with 150 bp SE reads and each downstream analyses were conducted by using BWA, SAMtools, GATK, VEP, and GEMINI software. Copy number variations (CNVs) were evaluated with CONTRA.

Results: Provisional sequencing for four human subjects who were clinically diagnosed with PKD using this newly created panel secured 96.5% enough coverages (depth>10) for all the targeted genes with mean depth of 457.1. Of these, likely-pathogenic heterozygous variants in PKD1 are detected in a patient diagnosed with ADPKD. In another patient diagnosed with ARPKD, disease- causing compound heterozygous variants in PKHD1 are found with trio-based analysis.

Conclusions: We succeeded in developing a custom diagnostic panel specialized in PKD. In the situation that many responsible genes for PKD have been reported increasingly, comprehensive approach for genetic diagnosis will enable fast and efficient diagnosis of PKD in future.

Funding: Government Support - Non-U.S.

SA-PO618

Epithelial Morphogenesis of Urine-Derived Renal Epithelial Cells from Children with Autosomal Recessive Polycystic Kidney Disease: An Ex Vivo Study Wolfgang H. Ziegler, Margarita E. Georgiadis, Kathrin Swolana, Birga Soetje, Dieter Haffner. *Dept of Pediatric Kidney, Liver, and Metabolic Diseases, Hannover Medical School, Hannover, Germany.*

Background: Autosomal recessive polycystic kidney disease (ARPKD) is caused by mutation of the *Pkhd1* gene, which encodes fibrocystin (FPC), a type I membrane protein of largely unknown function. Among other functions, FPC affects adhesion signaling of cells and their ability to orientate correctly towards one another. Recently, we established a link between loss of FPC function and defective epithelial morphogenesis in 3D cell culture using a canine cell line. Data in humans are lacking. Therefore, we set up assays for analyzing epithelial cells from ARPKD patients and healthy controls.

Methods: We take urine-derived renal epithelial cells (URECs) of ARPKD patients and respective controls in culture. The patients must have their original kidney(s) and still secrete urine. Populations of primary cells obtained within 14 days of culture are being characterized by different criteria and also tested in 3D cell culture conditions, which induce formation of epithelial spheroids with defined polarity, lumen and cilia.

Results: Using 2D and 3D-culture conditions, we observe URECs of three different phenotypes, spindle, patch, and cobblestone-like epithelial cells. While all different cell morphologies stain positively for the collecting duct marker aquaporin 2, only cobblestone-like cells give rise to a strong epithelial barrier as verified by impedance measurements and form spheroids in 3D culture conditions. Thus, cells of this phenotype are being studied preferentially to establish characteristic cell parameters with respect to growth rates, adhesion to micropatterned surfaces and spheroid formation. Cell of the suitable phenotype can be collected from all ARPKD patients, whereas it is restricted in samples from controls (10-20%) requiring a larger control cohort to distinguish cell properties from patients and controls.

Conclusions: By establishing methods allowing us to characterize the URECs of ARPKD patients, we aim to provide specific read-outs for future *ex vivo* analysis of the illness and for testing options of personalized pharmaceutical intervention.

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

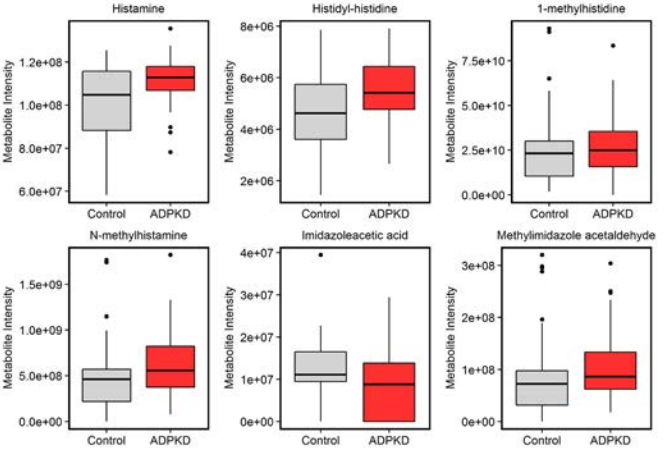
SA-PO619

Early Changes in Histidine Metabolism in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Sophia A. Banton,[1] Ken H. Liu,[1] Shuzhao Li,[1] Dean P. Jones,[1] Peili Chen,[2] F. Gary Toback,[2] Arlene B. Chapman.[2] *[1]Emory Univ; [2]Univ of Chicago.*

Background: Autosomal dominant polycystic kidney disease (ADPKD), the most common inherited kidney disease, is characterized by expansive cyst growth, leading to increased total kidney volume (TKV), a decline in kidney function and ultimately end-stage renal disease. Evidence suggests that common cellular and molecular mechanisms are responsible for cystogenesis in ADPKD regardless of the genes mutated.

Methods: To further understand the pathophysiology and unique metabolomic features of early ADPKD, we used untargeted high-resolution metabolomics to analyze paired urine and plasma samples in a case-control framework comparing ADPKD patients (n=42, mean TKV 1,253.07±1,053.32 mL, mean eGFR 88.95± 31.08) to age and gender-matched healthy controls (n=18, eGFR 107.89±15.48).

Results: Among metabolic pathways that were different between ADPKD patients and controls, the most highly represented were histidine and purine metabolism. Complementary analyses that explored the relationships between renal function (eGFR) and disease severity (TKV) also showed differences in histidine metabolism. Plasma histamine (p=0.01) and histidyl-histidine (p=0.02) and urinary 1-methylhistidine (p=0.01), N-methylhistamine (p=0.02), and methylimidazole acetaldehyde (p<0.001) were elevated in ADPKD. Urinary imidazoleacetic acid (p=0.02) levels were lower in ADPKD patients. Histamine, histidyl-histidine, 1-methylhistidine and N-methylhistamine are associated with increased odds of ADPKD, and metabolome-wide association studies of these metabolites revealed that additional histidine metabolites are highly enriched in the urine and plasma of ADPKD patients.



Conclusions: ADPKD promotes dysregulation of the histidine pathway in PKD patients, which results in a metabolic profile that resembles clinical histidinemia.

Funding: NIDDK Support

SA-PO620

Next Generation Sequencing of an Extensive Kidney-Disease Gene Panel for a Comprehensive Genetic Diagnosis of Cystic and Glomerular Inherited Kidney Diseases Elisabet Ars,[1] Gemma Bullich,[1] Iván Vargas,[2] Patricia Ruiz,[1] Laura Lorente,[1] Gema Ariceta,[3] Jose Ballarin,[1] Roser Torra.[1] *[1]Molecular Biology Laboratory and Nephrology Dept, Fundacio Puigvert, Barcelona, Spain; [2]Informatics Dept, Inst de Diagnostic per la Imatge (IDI), Barcelona, Spain; [3]Pediatric Nephrology Dept, Hospital Vall d'Hebron, Barcelona, Spain.*

Background: The advent of next generation sequencing (NGS) has enabled the creation of comprehensive multi-gene panels, and served to broaden the phenotypic spectrum of inherited kidney diseases (IKD). Genetic diagnosis of cystic and glomerular IKD is complicated by their high genetic heterogeneity and phenotypic variability, with clinical manifestations that can be mimicked by mutations in several genes. We aimed to develop a comprehensive approach for genetic diagnosis of cystic and glomerular IKD.

Methods: NGS of 132 genes causative or associated with cystic or glomerular IKD was performed in 232 patients, a pilot study of 116 patients and a diagnostic cohort of 116 patients, consisting of 87 cystic and 29 glomerular IKD patients.

Results: In the pilot study, 134 out of 135 previously known mutations (99%) were identified, demonstrating similar sensitivity than Sanger sequencing. In the diagnostic cohort, disease-causing mutations were found in 86 out of 116 patients (74%), including 64 out of 87 cystic IKD patients (74%) and 22 out of 29 glomerular IKD patients (76%). Mosaic mutations were detected in 3 in the tuberous sclerosis patients and 2 ADPKD patients. Structural variants in *HNF1B*, *COL4A5* and *COL4A3* were found in 7 patients. Complex inheritance patterns were identified in a total of 5 patients, 3 ADPKD patients and 2 Alport syndrome patients. Mutations in low-frequency mutated genes such as *NPHP3*, *CUBN*, or *OFD1* were also identified.

Conclusions: Targeted sequencing of our kidney-disease gene panel is a comprehensive, efficient and cost-effective tool for genetic diagnosis of cystic and glomerular IKD.

Funding: Government Support - Non-U.S.

SA-PO621

Developmental Switch for Polycystic Hepatic and Kidney Disease (PKD) Treatment: Unmasking the Signaling Pathways That Temporally and Spatially Drive Cyst Initiation and Cyst Progression Olaya Lamas-Gonzalez,[1] Adrian Cordido,[1] Susana Bravo,[3] Ana Belen Sanz,[2] Alberto Ortiz,[2] Candido Diaz-Rodriguez,[1] Miguel A. Garcia-Gonzalez.[1] *[1]Group of Genetics and Developmental Biology of Renal Diseases, Health Research Inst of Santiago de Compostela (IDIS), Spain; [2]Fundación Jiménez Díaz, Spain; [3]Proteomic Unit, (IDIS), Spain.*

Background: Different mechanisms have been related to the pathogenesis of Polycystic Kidney Disease (PKD). This make hard to understand the principal mechanism underlying cystogenesis as well as the identification of therapeutic approach for complete and specific inhibition of cystogenesis.Although, strong evidences in cystic volume reduction and cystic progression have been described.

Methods: We have previously shown the identification of the differential proteome related to the developmental window identified for PKD progression, as well as the proteome related to cystic progression under inflammatory respond.

Results: In this study, we further explore the effect of therapeutic targeting our list of candidates (n=16) identified for ADPKD prevention and control. We previously described several proteins underlying altered cell morphogenesis, ECM-cell interactions and cell metabolism during cystogenesis. By drug targeting of several of those pathways, we blocked cystogenesis from distal nephron segment, reduced/delayed global cystic progression, as well as inhibited polycystic liver phenotypecompletely recovering kidney and liver function. These effects were potentiated in combination with Tolvaptan, although unexpected phenotypical effects were identified.

Conclusions: In conclusion, we have first described the ADPKD related proteome that help us to puzzle out the different signaling cascades that temporally and spatially play a role in cyst initiation and progression. Moreover, we also identified an effective treatment for both PKD and PLD controlling both cystic origin and progression, although more studies are need for the understanding of phenotypic side effects. Finally, our work unmasks the necessity of a multidrug cocktail strategy for the treatment of PKD, by the target of specific nephron segment cystic origin as well as blockage of the mechanisms underlying cystic progression and expansion.

Funding: Government Support - Non-U.S.

SA-PO622

Autosomal Dominant Tubulointerstitial Kidney Disease: The Spanish Cohort Nadia Ayasreh,[1] Gemma Bullich,[1] Monica Furlano,[1] Rosa Miquel,[2] Xavier Fulladosa,[3] Miguel A. Garcia-Gonzalez,[4] Jose Ballarin,[1] Elisabet Ars,[1] Roser Torra.[1] *[1]F. Puigvert; [2]H.U. Canarias; [3]H.U.Bellvitge; [4]C.H. Santiago de Compostela; [5]H. Reina Sofia, Spain.*

Background: Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD) is a rare cause of end stage renal disease. It is caused by mutations in at least four different genes: *MUC1*, *UMOD*, *HNF1B* and *REN*. In this study we describe the clinical features of patients with *MUC1* and *UMOD* mutations.

Methods: Inclusion criteria were: autosomal dominant inheritance, renal failure without haematuria, and absent or minimal proteinuria, and exclusion of other causes of nephropathy. We have analyzed 59 families from different Spanish hospitals. We have collected clinical, laboratory, radiological and anatomopathological data, and performed the genetic study. Genetic analysis of *MUC1* insC mutation was optimized by SNaPshot.

Results: 24 of 59 families (40.6%) had genetic diagnosed: 9 families with *UMOD* mutations, 15 families with *MUC1* mutations and 1 family with *HNF1b* mutation. 124 individuals diagnosed, 39 *UMOD* (31.4%), 85 *MUC1* (68.5%) and 1 HNF1b (0.8%) Of the 60 individuals who developed ESRD, the median age of onset was 45.21 years (SD 11.52) for those with *MUC1* mutation vs 54.17 years (SD 13.46) for those with *UMOD* mutation ($p<0.05$). The prevalence of hyperuricemia was higher in patients with *UMOD* mutation (80.8% vs 56.6%, $p<0.05$) with a mean age at onset hyperuricemia similar in both groups. There were no statistical differences in proteinuria or imaging (cysts were present in 15% of patients with available data). Renal biopsies showed tubular atrophy and interstitial fibrosis.

Conclusions: The *MUC1* gene is responsible for the greatest percentage of ADTKD (21%), followed by *UMOD* gene (10%) and *HNF1B* (3%) With the data analyzed in the present study, the clinical difference between *MUC1* and *UMOD*, lies in the age of onset ESRD, which is almost 9 years before in patients with *MUC1*. Another interesting difference is the higher prevalence of hyperuricemia among *UMOD* patients. There is a great variability among and within families on the age of ESRD The analysis of the insC *MUC1* mutation is difficult which hampers routine implementation. We have optimized its analysis by SNaPshot.

SA-PO623

Effect of Renal Transcatheter Arterial Embolization on Quality of Life in Patients with Autosomal Dominant Polycystic Kidney Disease Tatsuya Suwabe, Yoshifumi Ubara, Akinari Sekine, Masayuki Yamanouchi, Junichi Hoshino, Masahiro Kawada, Kenmei Takaichi. *Toranomon Hospital, Dept of Nephrology, Minato-ku, Tokyo, Japan.*

Background: Patients with autosomal dominant polycystic kidney disease (ADPKD) and massive kidneys have various symptoms related to abdominal distension and renal dysfunction, which impair quality of life (QOL). However, current strategies for improving the QOL of ADPKD patients are very limited. Renal transcatheter arterial embolization (TAE) is effective for reducing kidney volume, but its impact on the QOL of ADPKD patients is unknown. This study aimed to clarify the influence of renal TAE on the QOL of ADPKD patients with enlarged kidneys.

Methods: All patients with ADPKD who undergo renal TAE at our hospital between 2010 and 2014 were enrolled. The short form-36 (SF-36) questionnaire and our original 15-item questionnaire about specific symptoms of patients with ADPKD were used to evaluate QOL. To estimate the mean values of the SF-36 physical component summary (PCS), mental component summary (MCS) and role/social component summary (RCS) and the answers to our 15-item questionnaire at each time point, the least squares mean (95% CI) were calculated using linear mixed model.

Results: A total of 188 patients on hemodialysis (92 men and 96 women, mean age: 56.7 ± 9.1 years, median total kidney volume: 4497 cm^3) were enrolled. The least squares mean of PCS, MCS and RCS before renal TAE were 38.21 (95%CI; 36.50 to 39.91), 48.45 (47.05 to 49.86), and 43.04 (40.70 to 45.37), respectively. These values improved to 42.0 (40.22 to 43.77: $p<0.001$ vs. before renal TAE), 51.25 (49.78 to 52.71: $p=0.001$), and 49.67 (47.22 to 52.12: $p<0.001$) at one year after renal TAE, respectively. Abdominal fullness, poor appetite, and heartburn showed marked improvement. Scores for fever, bodily pain, gross hematuria, and sleep disorder also improved slightly, but significantly. Scores for snoring, constipation, and use of analgesics/hypnotics/purgatives did not improved significantly after renal TAE.

Conclusions: Renal TAE was effective for improving abdominal fullness, appetite, heartburn, and SF-36 MCS and RCS scores, but not enough for improving sleep disturbance, constipation, and physical strength (PCS score).

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

SA-PO624

Development of Cost/Effective Strategies for Genetic Diagnosis of Polycystic Kidney Disease Based on the Population Mutagenesis Rate or Specific Needs M. Lara Besada-Cerecedo,[1] Lisbeth Silva,[1] Beatriz Sobrino,[2] Jorge Amigo,[2] Patricia Regueiro Casuso,[1] Ana Barcia de la Iglesia,[1] Manuel Fidalgo,[1] Carmen Vazquez,[1] Angel Carracedo,[2] Candido Diaz-Rodriguez,[1] Miguel A. Garcia-Gonzalez.[1] *[1]Group of Genetics and Developmental Biology of Renal Diseases, Health Research Inst of Santiago de Compostela (IDIS), Spain; [2]Galician Public Foundation of Genomic Medicine, Galician Public Foundation of Genomic Medicine, Spain.*

Background: Genetic tests have the benefit of ensuring an accurate diagnosis, is done one time in life and it can anticipate the disease, band the limitation of a high cost to be used in diagnostic routine. With the incorporation of the new generation sequencing (NGS), genetic tests have reduced dramatically the costs getting closer to the diagnosis by magnetic resonance imagen, and the advantage that it costs 100 times cheaper for the rest of family members.

Methods: We developed three strategies: T1)NGS panel for the genetic region responsible of the most polycystic kidney disease in the population (the replicated region of *PKD1,* exons 1-34), T2) NGS Panel for common polycystic disease (8 genes), and T3) NGS Panel for common, rare and ultra-rare polycystic kidney disease (all 72 known cystic genes).

Results: By analyzing a total of 252 PKD families (2150 patients), we identify the associated mutation in 90 families by using the T1, 128 by using T2 and 34 by using T3. In addition we reanalyzed all genetic variants identified to the moment, that help us to establish a PKD database of a total number of 3260 reclassified variants in four categories: 1174 class-I/definitely pathogenic (832 *PKD1*, 155 *PKD2* and 187 *PKHD1;* "stop codon", "frameshift insertions/deletions" and "canonical splice site alterations"); 141 class-II/probably pathogenic (107 *PKD1*, 12 *PKD2* and 22 *PKHD1;* "inframe deletion/insertions", "non canonical splice site mutations" and "amino acid substitutions"); 1594 class-III/uncertain significance (1119 *PKD1*, 85 *PKD2* and 390 *PKHD1)* and 351 SNPs (199 *PKD1*, 21 *PKD2* and 131 *PKHD1).* A total of 29 *PKD1* variants, 8 *PKD2* and 15 *PKHD1* were novel PKD mutations.

Conclusions: Here we describe the first cost/effective strategy applied for the diagnosis of all patients belonging to Local Health System for ADPKD.

Funding: Government Support - Non-U.S.

SA-PO625

Periostin Overexpression in Collecting Ducts Accelerates Polycystic Kidney Disease Archana Raman, Stephen C. Parnell, Aditi Khanna, Yuqiao Dai, Gail Reif, Darren P. Wallace. *Kidney Inst, Univ of Kansas Medical Center, Kansas City, KS.*

Background: Aberrant expression of extracellular matrix molecules and secreted factors contributes to cyst growth and fibrosis in polycystic kidney disease (PKD). Periostin, a matricellular protein involved in tissue development and repair, is overexpressed by cyst-lining epithelial cells and accumulates within the matrix adjacent to renal cysts. We found that periostin increased the activity of integrin-linked kinase (ILK) downstream signaling pathways, including the Akt-mTOR pathway and induced proliferation of human PKD cells. Cilengitide, an αVβ3- and αVβ5-integrin antagonist, blocked periostin-induced cell proliferation. Genetic knockout of periostin in pcy/pcy (pcy) mice, a slowly progressive model of cystic disease, reduced renal cell proliferation, cystic index and interstitial fibrosis, and improved the survival of the mice.

Methods: We generated periostin transgenic mice (Postntg) using a floxed STOP cassette in front of the periostin gene under the control of the ROSA26 promoter. Postntg mice were bred to Pkhd1-Cre mice to selectively overexpress periostin in collecting ducts (CD), a predominant site for cyst formation. To determine if periostin accelerates cystic disease, Postntg: Pkhd1-Cre mice were bred with pcy mice to generate pcy: Postntg: Pkhd1-

Cre mice. In addition, we determined if ILK knockdown in CD slowed PKD progression by generating pcy: ILK(floxed/+): Pkhd1-Cre mice. Both groups of mice were sacrificed at 10 weeks of age for tissue analysis.

Results: We found that overexpression of periostin increased CD staining for phosphorylated S6, a downstream target of mTOR, and significantly increased renal cell proliferation, cystic area and interstitial fibrosis. In contrast, heterozygous loss of ILK in the CDs of pcy mice significantly reduced renal cell proliferation, cystic area and interstitial fibrosis, and reduced levels of blood urea nitrogen consistent with improved renal function.

Conclusions: These results indicate that aberrant expression of ECM molecules, including periostin, contributes to elevated mTOR activity and cell proliferation, suggesting that the integrin-ILK signaling pathway may be a potential therapeutic target for PKD.

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SA-PO626

Collecting Duct-Specific Inactivation of HNF-1β Leads to Fibrocystic Disease and Impaired Urinary Concentration

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Background: Hepatocyte nuclear factor-1β (HNF-1β) is an essential transcription factor that regulates tissue-specific gene expression in the kidney. In humans, mutations of *HNF-1β* cause renal cysts and diabetes (RCAD) and congenital anomalies of the kidney and urinary tract (CAKUT).

Methods: We used Pkhd1/Cre mice to delete *Hnf-1β* specifically in renal collecting ducts. Water and solute excretion were measured using metabolic cages. HNF-1β targets were identified using ChIP-seq and gene expression profiling.

Results: *Hnf-1β* mutant mice survived long-term and developed slowly progressive cystic kidney disease, renal fibrosis, and hydronephrosis. *Hnf-1β* mutants had higher urine volume and lower urine osmolality than wild-type littermates. These abnormalities were present prior to the development of kidney cysts and hydronephrosis, suggesting a primary defect in urinary concentration. Circulating ADH levels were similar in wild-type and mutant mice. NR1H4 (FXR), a transcription factor known to regulate water homeostasis, was identified as a novel HNF-1β target. HNF-1β was bound to the FXR promoter *in vivo*,and FXR mRNA was downregulated in mutant mice. FXR protein localized to collecting ducts in wild-type mice and was diminished in the cysts of mutant mice. mIMCD3 cells exposed to hypertonic medium robustly upregulated FXR mRNA levels. This upregulation was lost in *Hnf-1β* mutant cells.

Conclusions: These findings reveal a new role for *Hnf-1β* in urinary concentration by regulating the transcription of FXR in the renal collecting duct.

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SA-PO627

Kcnn4 Dysregulation in Pkd1 Dosage-Dependent Mouse Models of ADPKD

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Background: The relentless increase of renal cyst number and size in ADPKD kidneys is governed in part by *PKD1*/PC1 gene dosage-dependent mechanisms.Cyst enlargement is regulated by epithelial cell secretion and proliferation, associated with tissue remodeling. Cyst fluid secretion is mediated by apical Cl^- channels requiring sustained basolateral Cl^- loading accompanied by basolateral K^+ recycling. The Ca^{2+}-activated K^+ channel, Kcnn4, provides a major pathway for K^+ recycling, consistent with PC1's role in epithelial Ca^{2+} homeostasis. We investigated Kcnn4's role in disease progression in both dosage-reduced $Pkd1^{F/F}$;*Ksp-Cre* and dosage-increased $SBPkd1_{TAG}$ mouse models of ADPKD.

Methods: Therenal-specific, *Pkd1* dosage-increased $SBPkd1_{TAG}$ mouse model develops severe renal cystic disease by age 5-6 months, whereas severe disease is evident by P10-18 in *Pkd1* dosage-reduced $Pkd1^{flox/flox}$;*Ksp-cre* mice. Epithelial cell proliferation, apoptosis, fibrosis and cilia length were respectively assessed by Ki67, TUNEL, Sirius red staining and acetylated tubulin; cAMP by ELISA, mRNA levels by qPCR and protein levels by immunoblot.

Results: Renal Kcnn4 mRNA was upregulated ~5-fold in $SBPkd1_{TAG}$ mice (n=12) and ~2-fold in $Pkd1^{flox/flox}$;*Ksp-cre* mice (n=7) vs age-matched controls (n=11 and 5). Levels of kidney cAMP were increased 4-fold in $SBPkd1_{TAG}$ mice (n=4) and 13-fold in $Pkd1^{flox/flox}$;*Ksp-Cre* mice (n=5) relative to age-matched controls (n=6 and 5). pERK1/2 was dramatically increased in $SBPkd1_{TAG}$ mouse kidney, suggesting MAPK pathway activation. $SBPkd1_{TAG}$ mice also showed 2-fold increased proliferative index in non-ectatic, "normal appearing" tubules, and 5-fold increased proliferative index in ectatic tubules and cysts. Consistent with increased cAMP, cilia were elongated in both $SBPkd1_{TAG}$ mice (n=5) and $Pkd1^{flox/flox}$;*Ksp-cre* mice (n=11).

Conclusions: Our study identified Kcnn4 as a pro-secretory and probably pro-cystogenic risk modifier in both *Pkd1* dosage-increase and dosage-decrease mechanisms, supporting Kcnn4 as a therapeutic target to retard cyst enlargement and disease progression in ADPKD.

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

SA-PO628

Low Dose Rituximab Therapy in Resistant Idiopathic Membranous Nephropathy: Single Center Experience

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Background: 10-30% patients with idiopathic membranous nephropathy(IMN) progress to End Stage Kidney Disease in 10 years. The modified Ponticelli regimen(MPR) and Calcineurin inhibitors achieve remission in 60% patients. Most studies have used standard dose Rituximab in IMN: 375m/m2 weekly(4 doses) or 1g on day 1 and 15.Using this dose is expensive with high risk of infections. Few studies have used lower doses. Our study aims to do a preliminary assessment of the efficacy and safety of low dose Rituximab (LDR) in Indian patients with resistant IMN.

Methods: 17 patients with immunosuppression(IS) resistant IMN treated with LDR therapy from April 2015 to January 2016 were included.Treatment resistance was defined as no decrease in proteinuria after treatment with Modified Ponticelli regimen(MPR) and/or Tacrolimus(Tac) with Steroids for atleast 6 months.They received 2 doses of Rituximab(500mg each),7-10 days apart. A 3rd dose(500mg) was repeated if B cells were not depleted at 4 weeks after LDR or if no reduction in proteinuria by 12 weeks.

Results: 64.7% were males and their mean age was 35.1±13.9 years. Prior IS received by these patients were: 6-MPR, 2-Tac, 4- MPR then Tac, 2-Tac then Mycophenolate Mofetil(MMF)+Steroids and 3- MPR, Tac and then MMF. Proteinuria before therapy was 6.4±3.1g/day and serum creatinine was 0.9±0.4mg/dl. Four patients received a third dose:three for persistent proteinuria and one for inadequate B cell depletion. 12(70.6%) patients achieved remission(10-partial remission, 2- complete remission). Pre treatment serum Phospolipase A2 Receptor(PLA2R) levels were available in 11 patients-5 were negative. 2/5 PLA2R negative and 5/6 PLA2R positive patients achieved remission. Median time to remission was 2.1(0.7-6.1)months. Serum creatinine at follow up after 6.8(4.1-12.4) months was 1.0±0.5mg/dl. There were no adverse effects in any patient.

Conclusions: LDR therapy is effective and safe in IS resistant IMN.Further follow up is needed to determine relapse rates and long term outcome.

SA-PO629

Immunosuppressive Treatment for Elderly Membranous Nephropahty Patients

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Background: Primary membranous nephropathy (MN) is one of the most common nephrotic syndrome (NS) in elderly (age≥65yrs) patients. The number of people aged 65 or older is increasing annually. The aim of this study is to evaluate the use of immunosuppressant (IS) in elderly primary MN patients.

Methods: We retrospectively recruited 311 biopsy proven primary MN patients from 6 centers between 1990 and 2015. The endpoints were all-cause mortality, infection, doubling of the baseline serum creatinine or renal replacement treatment (RRT) and remission.

Results: To compare the baseline characteristics according to age, we divided into two groups of age ≥65 years (elderly, n=130) and <65 years (young, n=181). Of the 130 elderly patients, 104 (79.4%) presented with NS and of these, 25 (24%) had conservative treatment, 17 (16.3%) had steroid only therapy and 62 (59.6%) had steroid combination with other IS treatment. Yong group received higher rate (n=85, 66.9%) of steroid combination with other IS treatment than elderly group. The infection, death and renal outcome rate was higher with elderly group than young group, while remission rate was lower in elderly group. In elderly group, 73 (70.2%) patients achieved remission, 11 (10.3%) patients had RRT or doubling of serum creatinine, 9 (8.7%) patients were death and 17 (16.3%) patients were hospitalized because of infection. Treatment options of NS were not significantly associated with outcomes except infection. In elderly group, multivariate cox hazard models identified steroid only (HR 16.4, 95% CI 1.94-138.90, P=0.010), steroid combination with other IS treatment (HR 5.17, 95% CI 0.65-40.94) were significantly associated with infection. However, treatment options of NS in <65 years group were not significantly associated with composite outcomes.

Conclusions: Conservative therapy or steroid combination with other IS therapy are preferred than steroid only therapy in elderly patients at risk of infection. Prospective study is warranted to compare the efficacy and complications of treatment in elderly MN patients.

SA-PO630

Differences between Anti-PLA2R ELISA and IFT Assays in Idiopathic Membranous Nephropathy (iMN) during Therapy Anne-Els van de Logt,[1] Julia M. Hofstra,[2] Renate G. Van der Molen,[3] Jack F. Wetzels.[1] *[1]Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; [2]Interne Geneeskunde, Gelderse Vallei, Ede, Netherlands; [3]Laboratory Medicine, Radboud Univ Medical Center, Nijmegen, Netherlands.*

Background: In our center patients with iMN are treated with cyclophosphamide and steroids until disappearance of anti-PLA2R antibodies (aPLA2R) measured by indirect immunofluorescence (IFT). We previously showed excellent concordance (94 % agreement, kappa 0.85) between aPLA2R measured by IFT and ELISA in patients with iMN at diagnosis. We have assessed agreement in samples obtained during treatment.

Methods: We selected 31 aPLA2R positive patients. In all available serum samples aPLA2R were measured using IFT and ELISA, both obtained from Euroimmun®.

Results: Twenty patients were male, mean age was 56 ± 13 years, median serum creatinine level was 1.3 g/dl (1.1-1.6) and median protein creatinine ratio 7.3 g/g (5.0-11.2). We observed a more rapid disappearance of aPLA2R measured by ELISA compared to IFT.

	Baseline	8 weeks	8 weeks	16 weeks	16 weeks	24 weeks	24 weeks
IFT	pos	pos	neg	pos	neg	pos	neg
Elisa titer RU/ml (range)	94 (15-776)	13 (4-47)	2 (2-6)	14 (6-61)	2 (2-5)	12 (5-46)	-
pos	29	3	2	2	0	1	0
borderline	2	0	**1**	**1**	0	**1**	0
neg	0	**5**	**3**	**3**	5	**3**	0

After 8 weeks of therapy discordance was 24 %. There were no clear differences in laboratory parameters between patients with concordant and disconcordant results.

Conclusions: Our study demonstrates that the time course of disappearance of aPLA2R during therapy is dependent on the assay that is used. We speculate that the introduction of an ELISA assay might lead to a shorter duration of therapy. Additional studies are needed to evaluate if the ELISA assay allows more accurate prediction of clinical outcome. Of note, two of three patients with positive aPLA2R by IFT and negative aPLA2R by ELISA after 24 weeks were in partial remission at this time point.

SA-PO631

Anti-PLA2R Antibody (aPLA2R) Levels at Baseline Do Not Predict Response to Immunosuppressive Therapy in Patients with Idiopathic Membranous Nephropathy (iMN) Anne-Els van de Logt,[1] Julia M. Hofstra,[2] Renate G. Van der Molen,[3] Jack F. Wetzels.[1] *[1]Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; [2]Internal Medicine, Gelderse Vallei, Ede, Netherlands; [3]Laboratory Medicine, Radboud Univ Medical Center, Nijmegen, Netherlands.*

Background: In our center patients with iMN are treated with cyclophosphamide and steroids until disappearance of aPLA2R measured by indirect immunofluorescence (IFT). Recently ELISA assay was introduced, which allows quantitative measurements. It has been shown that patients with iMN and high aPLA2R levels did not respond to treatment with rituximab. We have evaluated the relationship between baseline aPLA2R levels and clinical response of patients treated with our antibody guided treatment regimen.

Methods: We included 30 anti-PLA2R positive (IFT) patients. In stored baseline samples aPLA2R were measured with ElISA (Euroimmun®).

Results: Nineteen patients were male, mean age was 56 ± 13 years, median serum creatinine level was 1.3 g/dl (1.1-1.6) and median protein creatinine ratio 7.7 g/g (5.5-11.3) . All patients tested positive with ELISA. When grouped in tertiles of aPLA2R, there were no differences in baseline characteristics.

aPLA2R titer	Lowest tertile	Middle Tertile	Highest Tertile	P value
Male/Female	7/3	5/5	7/3	ns
Elisa titer RU/ml (range)	15-67	86-134	136-776	0.000
Follow-up from start of therapy (IQR)	11.8 (2.8-25.9)	11.0 (5.4-29.8)	14.1 (3.4-20.4)	ns
IFT neg after 8 weeks	8	8	2	0.024
Remission	6	10	7	ns
Relapse	3	5	0	ns

In patients in the highest tertile the disappearance of aPLA2R was slower and as a consequence more prolonged immunosuppression was given. At the end of follow-up there were no differences in remission rate. Relapse rate was numerically lower in this group, however this might be related to the longer duration of therapy.

Conclusions: Patients with higher levels of aPLA2R often need more prolonged immunosuppressive therapy. However, with the use of antibody guided therapy clinical outcome is comparable.

SA-PO632

Low-Dose of Rituximab for Membranous Nephropathy Dario Roccatello, Roberta Fenoglio, Savino Sciascia. *Nephrology and Dialysis Unit and Center of Research of Immunopathology and Rare Diseases (CMID), San Giovanni Hospital and Univ of Turin, Turin, Italy.*

Background: The key role of B cells in the pathogenesis of idiopathic membranous nephropathy (IMN represents the rationale of the B-cells depletion therapy with Rituximab (RTX). Traditional protocols proved to be effective in several open studies. A single-dose of RTX (sdRTX) has been reported to be as effective as the lymphoma protocol in some cases of immune-mediated diseases. Data on IMN patients (pts) treated with sdRTX as a front-line treatment are limited. In this study, the efficacy of the sdRTX in IMN was compared with a standardized therapy (Ponticelli protocol, PP).

Methods: 9 pts (mean age 64.7, 35-81 yrs) with nephrotic syndrome(NS) and major risk factors precluding conventional immunosuppressive therapy were perspectively treated with a single dose of 500 mg RTX. Pts were matched with those of the last 10 pts (mean age 59.9; 38–80 yrs) treated with PP in our Unit .

Results: In sdRTX-treated pts, proteinuria (uP) decreased from 11.0(IQ 6.5-24) to 2.4(IQ 2.3-21.2) g/24 hrs after 6 months ($p<0.05$). Among these sdRTX-treated pts, 1 became uP-free (< 0.5 g/24 hrs) within 6 months, 2 pts, who had a partial response (> 50% uP decrease) at 6 months, became uP-free in 12 months. 2 pts were unresponsive. The remaining 4 pts had a partial response, but 1 of these received an additional single dose of RTX for uP relapse. Creatinine (Cr) remained stable: 1.1 (range 0.7-1.7) mg/dl at 6 months vs 1.1(range 0.8-1.7) mg/dl at baseline. In PP-treated pts, uP decreased from 7.4(IQ 5.7-20.0) to 3.0(IQ 0.9-28) g/24 in 6 months ($p<0.05$). 6 pts had either complete (# 2) or partial (# 5) response. 3 pts were unresponsive. Cr remained stable: 1.1 (0.5-2.5) mg/dl at 6 months vs 1.2(0.7-3.5) mg/dl at baseline. There were no differences as regard to uP values and uP decrease in 6-month, between sdRTX and PP.

Conclusions: Current protocols of RTX treatment in immune-mediated diseases, were mainly derived from hematologic experience. Our data suggest that low doses of RTX are as effective as a standardized immunosuppressive treatment in the management of IMN pts. This sdRTX scheme could be especially indicated in pts with co-morbidities.

SA-PO633

Childhood and Adolescent Phospholipase A2 Receptor Related Primary Membranous Nephropathy: A Prospective Study on Prevalence and Treatment Outcome Harbir Singh Kohli,[1] Raja Ramachandran,[1] Ritambhra Nada,[2] Vivekanand Jha,[1] Krishan Lal L. Gupta.[1] *[1]Nephrology, PGIMER; [2]Histopathology, PGIMER, Chandigarh, India.*

Background: Primary membranous nephropathy (PMN) accounts for <5 and 10% of nephrotic syndrome in children and adolescents respectively. Autoantibodies to M-type phospholipase A2 receptor (aPLA2R) are seen in 70% of adult PMN . There are no prospective studies evaluating the prevalence of aPLA2R, its association with treatment outcome in PMN in this age group , hence the study was undertaken.

Methods: Children and adolescents (up to 19 yrs) with biopsy proven MN were included. Patients with positive viral makers, antinuclear factor or dsDNA antibodies were excluded. Blood for aPLA2R was drawn prior to immunosuppressive therapy. Patients were followed on monthly basis with proteinuria, serum albumin and creatinine. Serum $aPLA_2R$ (ELISA, EUROMMUN, value ≥ 20RU/ml considered positive) was done at baseline,6 and 12 months of treatment. Staining for PLA2R in the glomeruli was done. PLA2R related PMN was defined as presence of either enhanced glomerular staining or aPLA2R.

Results: A total of 20 patients were enrolled. Mean age was 15.25±3.90 (5-19) years. The mean proteinuria and serum albumin was 4.39±1.89 (2.4-9.2) g/day and 2.02±0.65 g/dL. Sixteen (80%) patients had PLA2R related PMN. Enhanced staining for PLA2R and aPLAR positivity was seen in 14 (70%)patients each. The median aPLA2R level in seropositive cases was 232.49 RU/mL. Twelve (75%) of 16 had both enhanced staining and serological positivity, with good association between the two ($p=0.03$). Patients were initiated on cyclical therapy of oral prednisolone (GC) and cyclophoshamide or tacrolimus (TAC) and GC. Of these two did not complete therapy. Remission was achieved in 11 (55%) patients at 1 year. Seven (35%) had complete and 4 (20%) partial remission. Those in remission had lower baseline aPLA2R (65.5RU/ml) as compared to resistant patients (358.53RU/ml). There was a parallel reduction in decrease in aPLA2R titre and proteinuria.

Conclusions: Childhood and adolescent onset PMN is PLA2R related in 80%. The response to therapy is seen in one half of patients. aPLA2R monitoring is clinically relevant and should be incorporated in the management of PMN.

SA-PO634

CD19 Targeted Rituximab Therapy in Adult Calcineurin Inhibitor Resistant,Dependent or Intolerant Nephrotic Syndrome due to Idiopathic Minimal Change Disease and Focal Segmental Glomerulosclerosis Harbir Singh Kohli,[1] Raja Ramachandran,[1] Indu R. Rao,[1] Ritambhra Nada,[2] Krishan Lal L. Gupta.[1] *[1]Nephrology, PGIMER; [2]Histopathology, PGIMER, Chandigarh, India.*

Background: Calcineurin inhibitors (CNIs) are first line agents in the management of steroid dependent (SD) and resistant (SR) nephrotic syndrome (NS) due to minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). CNI use is limited by relapses and nephrotoxicity. Rituximab is a potential alternative, this prospective study was done to evaluate the efficacy and safety of targeted rituximab therapy in CNI intolerant/ dependent/resistant SD or SR MCD/FSGS.

Methods: A total of 24 adult patients of SDNS or SRNS (MCD/FSGS), who were CNI resistant/dependent/ intolerant were enrolled. All patients received rituximab 375mg/m^2 to target CD19 levels < 1% (48 hrs post infusion). CD 19 counts were monitored monthly and those with CD-19>1% received additional dose of rituximab. Patients were followed up monthly for at least 6 months. Study outcomes were remission rates and side effects. Definitions: CNI resistant: no response with 24 weeks, CNI dependent: relapse during or after CNI taper, CNI intolerant: irreversible nephrotoxicity or uncontrolled diabetes.

Results: Mean age was 23.2.±7.9 (16-46) years. The study included 17 (71%) and 7 (29%) cases of FSGS and MCD respectively. SR and SD was seen in 11 (46%) and 13 (54%) respectively. CNI dependence, intolerance and resistant were in 13 (54%), 4 (17%) and 7 (29%) patients respectively. All achieved CD19 depletion with 1 dose of Rituximab. Of 24, 10 (42%) needed 1 dose while 14 (58%) 2 doses during 6 months. By 12 months 3 or 4 doses were required in majority. At 6 months, 21 (87.5%) were in remission (13 complete, 8 partial). Three subjects had relapse despite CD 19 depletion and required additional threapy, CNIs in 2, low dose prednisolone in 1. Remission in SRNS was 73% vs 100% in SDNS. Remission in CNI dependent, intolerant and resistant was 100, 75 and 71% respectively. Rituximab was well-tolerated, with mild infusion reactions in 5 and pneumonia in 1.

Conclusions: CD-19 targeted rituximab therapy is a safe and effective in the management of adults with CNI resistant/dependent/intolerant MCD/FSGS.

SA-PO635

Clinicopatholgical Manifestation in Patients of Idiopathic Membranous Nephropathy with Nephrotic Syndrome Shinji Kitajima,[1] Akihiro Sagara,[1] Tadashi Toyama,[1] Akinori Hara,[1] Yasunori Iwata,[1] Norihiko Sakai,[1] Miho Shimizu,[1] Kengo Furuichi,[1] Hitoshi Yokoyama,[2] Takashi Wada,[1] Yasutaka Kamikawa.[1] *[1]Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Japan; [2]Div of Nephrology, Kanazawa Medical Univ Hospital, Kanazawa, Japan.*

Background: The 20-year renal survival of Idiopathic membranous nephropathy (IMN) in Japanese adults with nephrotic syndrome was reported around 60%. In this study, we evaluated the predisposing clinicopathological factors for IMN patients with nephrotic syndrome.

Methods: One hundred five patients of nephrotic syndrome (62 males and 43 females; mean age 47.4 years) with biopsy proven IMN from 1965 to 2012 in Kanazawa Universitiy Hospital were evaluated in this study. The patients were followed for more than three years, or until renal or patient death. Clinicopathological factors, which might affect renal death and patient death were evaluated.

Results: Seventy out of 105 patients (67%) achieved complete remission(CR) or incomplete remission I(ICRI) (proteinuria < 1 g/day and plasma albumin concentration > 3.0g/dl) after initial treatments. Renal death was observed 14 out of 105 patients (13,3%). The group of renal death showed lower remission rate (CR or ICRI;renal death group; 21.4%, renal survive group; 73.6%). Based on the electron microscopic findings, the patients were assigned to two distinct types, homogeneous type and heterogeneous type (synchronous electron dense deposits or various phases of dense deposits in basement membrane, respectively) as we previously published in Kidney International in 2004. The rate of heterogeneous type was higher in renal death group (renal death group; 92.3%, renal survive group; 36.5%). Patients death was observed 23 four out of 105 patients (21.9%). The rate of death due to infection was higher in non-remission group (non-remission group; 33%, remission group; 21%).

Conclusions: These findings suggest that electron microscopic findings demonstrating heterogeneous type and no-remission of nephrotic syndrome was susceptible to renal death in patients with nephrotic IMN.

SA-PO636

Rituximab versus the Modified Ponticelli Regime in the Treatment of Primary Membranous Nephropathy: A Health Economic Model Patrick Hamilton,[1] Durga A.K. Kanigicherla,[1] Michael Venning,[2] Paul E. Brenchley,[1] David M. Meads.[3] *[1]Central Manchester Univ Hospitals, United Kingdom; [2]Univ of Manchester, United Kingdom; [3]Univ of Leeds, United Kingdom.*

Background: Membranous Nephropathy (MN) is among the most common causes of nephrotic syndrome worldwide with a high healthcare burden. Treatment using the modified Ponticelli regime (mPR) has remained the standard of care for decades, but newer therapies such as Rituximab are offering promising results with a reduced side effect profile. The cost of this treatment however can be a barrier to widespread use especially in resource limited healthcare systems.

Methods: We developed a decision-analytic model using a stochastic Markov model to estimate the cost-effectiveness of Rituximab versus the mPR over a one year horizon and from the perspective of the NHS. The primary outcome was cost of treatment at one year. Secondary outcomes were cost per treatment and incremental quality adjusted life years (QALY) over 5 years and a lifetime. The median age of patients at diagnosis is 53 years old; we therefore extended the lifetime over 47 years. Transition probabilities, costs and utility values to inform the model were obtained from published data following a systematic review.

Results: At one-year Rituximab is cheaper than mPr with an incremental cost of -£47.53, and with a better quality of life as shown by an incremental QALY of 0.02. At one-year Rituximab therapy is both cheaper and more effective (ie dominates) than mPR and is therefore the preferred option. The probability of Rituximab dominating at one year is 63%. Over five years, Rituximab remains the preferred option with an incremental cost of -£428.28 and an incremental QALY of 0.026. Over a lifetime the cost of Rituximab remains the cheaper option with an incremental cost of -£915.44.

Conclusions: This work indicates that the high single dose cost of Rituximab should not be a barrier to its use in the treatment of primary MN and highlights the need for a high quality clinical trial investigating the efficacy of Rituximab versus the current standard of care.

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SA-PO637

Comparative Effectiveness and Tolerance of Treatments for Idiopathic Membranous Nephropathy: A Network Meta-Analysis Daqing Hong, Li Wang, Guisen Li. *Renal Div and Inst of Nephrology, Sichuan Provincial People's Hospital, Chengdu, Sichuan, China.*

Background: Immunosuppressive treatment in general was shown to prevent renal progression and all-cause mortality in idiopathic membranous nephropathy (IMN) patients with nephrotic syndrome, however, the efficacy and safety of different immunosuppressive treatments have not been systematic assessed. A network meta-analysis was performed to compare different immunosuppressive treatment in IMN.

Methods: Cochrane library, MEDLINE, EMBASE and trial register system were searched for randomised controlled trials reporting the treatments for IMN to May, 2016. Composite endpoint of End-stage renal disease (ESRD) or mortality, complete or partial proteinuria remission and withdrawal because of treatment adverse events were compared combing direct and indirect comparison using network meta-analysis., Ranking different immunosuppressive treatment in the outcomes were analyzed by using SUCRA and MDS-ranking method.

Results: 36 randomised controlled trials were included. Compared with non-immunosuppressive treatment, only cyclophosphamide (CTX) and chlorambucil significantly reduced the risk of composite outcome of ESRD or mortality when combining the direct and indirect comparison (RR=0.31, 95%CI: 0.12-0.81 and RR=0.33, 95%CI: 0.12- 0.92). CTX increased the composite outcome of CR or PR (RR=4.29, 95%CI: 2.30-8.0) while chlorambucil did not (RR=1.58, 95%CI: 0.80-3.12) as compared with non-immunosupppressive treatment, chlorambucil also significantly increased withdrawal risk (RR=3.34, 95%CI: 1.37- 8.17) as compared to CTX. Both tacrolimus (RR=3.10, 95%CI: 1.36-7.09) and cyclosporine (RR=2.81, 95%CI: 1.08-7.32) also significantly increased the rate of CR or PR as compared with non-immunosuppressive treatment (without significant difference as compared with CTX), while ranking results showed that cyclosporine or tacrolimus was with less possibility of drug withdrawal as compared to CTX or chlorambucil.

Conclusions: Only alkylating agents can reduce risk of ESRD or mortality, however, they both had higher risk of drug withdrawal. Tacrolimus and cyclosporine can increase increase the possibility of proteinuria remission with less drug withdrawal.

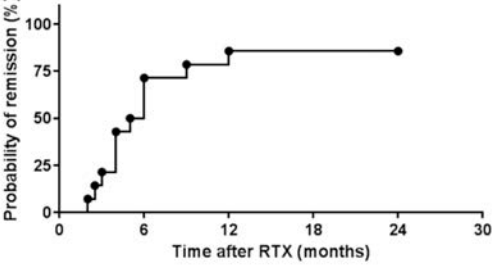
SA-PO638

Rituximab as Monotherapy for Pure Membranous Lupus Nephritis Nathalie Chavarot,[1,9] David Verhelst,[2,9] Agathe Pardon,[3,9] Valérie Caudwell,[3,9] Lucile Mercadal,[4,9] Antoinette Sacchi,[5] Jean-Marc Roger Dueymes-Laporte,[8] Veronique Le Guern,[6] Alexandre Karras,[7,9] Eric Daugas.[1,9] *[1]Nephrology, APHP, Bichat Hospital, Paris, France; [2]Nephrology, CH, Avignon, France; [3]Nephrology, CHSF, Corbeil-Essonnes, France; [4]Nephrology, APHP, Pitié Salpêtrière Hospital, Paris, France; [5]Internal Medicine, CH, Mantes la Jolie, France; [6]Internal Medicine, APHP, Cochin Hospital, Paris, France; [7]Nephrology, APHP, HEGP, Paris, France; [8]CH, Cayenne, French Guiana; [9]French Cooperative Group on Lupus Nephritis.*

Background: Optimal treatment for pure membranous lupus nephritis (MLN) remains undetermined. Rituximab constitutes a treatment option in lupus nephritis and is currently evaluated for idiopathic membranous nephropathy.

Methods: We retrospectively investigated patients with biopsy-proven pure class V lupus nephritis and protein-to-creatinine ratio (PCR) ≥ 2g/g and treated with Rituximab as monotherapy (1g infusion at day 1 and day 15, or 4 weekly infusions of 375mg/m^2) +/- low dose of steroids (≤20mg/day) +/- hydroxychrloroquine. Complete remission was defined as PCR <0.5 g/g with normal eGFR, and partial remission as ≥50% reduction in PCR to subnephrotic levels and normal eGFR. Treatment failure was considered when an additional immunosuppressive therapy or steroids > 20 mg/day were prescribed during the first 12 months.

Results: In 14 patients (13 women) median PCR ratio was 4.4g/g, median serum albumin 25.5g/L, and median eGFR (CKD-Epi) 121.5 mL/min/1.73m^2. The median follow-up was 29 months. Two patients experienced treatment failure. Remission was recorded in the remaining 12 (86%, complete remission in 8) within a median time of 5 months.



PCR decreased to 0.16g/g at month 12 and to 0.11g/g at month 24. All had serum albumin over 30g/L at month 12. eGFR remained stable in all. Three patients had relapse of proteinuria (at 12, 29 and 34 months). No patients experienced serious adverse event.

Conclusions: Rituximab as monotherapy might be an effective treatment for pure MLN.

SA-PO639

PLA2R Positive Membranous Nephropathy Associated with Viral Infection

Aikaterini K. Nikolopoulou, Megan Griffith, H. Terence Cook, Charles D. Pusey. *Imperial College London, United Kingdom.*

Background: Membranous Nephropathy (MN) can be associated with hepatitis infection and less commonly with HIV infection. The significance of anti-phospholipase A2 receptor (PLA2R) antibodies in this setting is not known.

Methods: A retrospective study of biopsy proven MN from January 2006 to January 2015 was undertaken. A total of 11 patients with MN and Hepatitis B (HBV), C (HCV) or HIV infection were identified. The biopsies were stained for PLA2R antigen and results were correlated to viral activity and clinical outcomes.

Results: The cohort consisted of 11 patients, 4 women and 7 men, mean age 39.9 years. HIV was detected in 5 patients, HBV in 4 and HCV in 3 (one patient HIV/HBV coinfection).

PLA2R staining was positive in 6 biopsies: 1 with HIV, 2 HBV, 3 HCV. Circulating anti-PLA2R antibodies were detected in 3 patients at time of biopsy. Viral load was undetectable at the time of biopsy in all but one patient with HBV. In the PLA2R negative group 3 patients had HIV, 1 HBV and 1 HIV/HBV coinfection. Viral load was detectable in 1 patient with HBV and 1 with HIV.

Mean proteinuria was higher in the PLA2R positive compared to the PLA2R negative group (mean uPCR= 801.6 vs 374.4mg/mmol) although this was not statistically significant. Electron microscopy in both groups showed predominantly subepithelial electron dense deposits (EDD). EDDs of all stages were present but stage II were the more frequent. Tubuloreticular inclusion bodies (TRI) were seen in 2 patients with interferon treated HCV in the PLA2R positive group; no TRIS were seen in the PLA2R negative group.

Follow up was available for 10 patients. At 24 months 9 had preserved renal function. One PLA2R and HCV positive progressed to ESRD. One patient with PLA2R positive MN and HIV went into spontaneous partial remission, others received tacrolimus (n=7), rituximab (n=2) or cyclophosphamide with high dose steroids (n=1).

Conclusions: PLA2R positivity can be found in MN associated with hepatitis infection and we describe a rare case of PLA2R positive MN and HIV. It is possible that the viral infection triggers immunological activity leading to the anti-PLA2R antibody response. MN can present even when infection is controlled and viral load undetectable.

SA-PO640

Membranous Glomerulonephritis with Crescents

Aikaterini K. Nikolopoulou, Isabel Huang-Doran, Stephen Paul McAdoo, Megan Griffith, H. Terence Cook, Charles D. Pusey. *Imperial College London, United Kingdom.*

Background: The coexistence of membranous glomerulonephritis (MGN) with necrotising and crescentic glomerulonephritis (NCGN) is rare. We examined the incidence and outcomes of patients with MGN and NCGN treated at our centre and the association with anti-neutrophil cytoplasm antibodies (ANCA) or anti-glomerular basement (anti-GBM) antibodies.

Methods: We report the clinical and pathological findings of 10 patients with MGN and NCGN, identified from our renal biopsy database from January 2004 to January 2015.

Results: The cohort consisted of 3 women and 7 men with a mean age of 58.8 years. ANCA and anti-GBM positivity was tested by ELISA. ELISA was positive in 9 patients (4 MPO-ANCA, 1 PR3-ANCA, 4 anti-GBM); one patient was negative and the biopsy showed IgA deposition. Clinical presentation included heavy proteinuria (mean urinary protein:creatinine ratio 1,731mg/mmol), microscopic haematuria and acute kidney injury (mean creatinine 390μmol/L (4.4mg/dL). Pathologic evaluation revealed MGN and NCGN with crescents involving a mean of 25% of glomeruli. Immunohistology available in 8 cases showed granular IgG deposits with linear IgG in anti-GBM cases. Electron microscopy showed stage I or II MGN changes in the majority of cases. PLA2R staining was negative in 8 available biopsies and no causes of secondary MGN were identified. One patient had a biopsy that showed MGN alone 6 months prior to anti-GBM disease. One patient had pre-existing p-ANCA vasculitis 2 years prior to MGN. Follow up was available for all 10 patients, and all were treated with steroids, together with cyclophosphamide (n=6), plasma exchange (n=1),rituximab (n=3) and MMF (n=2), alone or in combination. At a mean follow up of 48.1 months, 4 patients progressed to ESRD and 6 had stabilisation or improvement of renal function. One patient with ESRD died during the follow up period. The only independent predictor of progression to ESRD was serum creatinine at presentation.

Conclusions: MGN combined with NCGN is a rare dual glomerulopathy in which anti-PLA2R antibodies are not generally detected. Presentation is with proteinuria, haematuria and acute kidney injury. Prognosis is variable and seems to be related to renal function at presentation.

SA-PO641

The Concentration of Cyclosporine in the Treatment of Idiopathic Membranous Nephropathy (IMN) in Chinese Patients

Rui Zhang, Jiafan Zhou, Mengjun Liang, Yajuan Huang, Qianhui Zhang, Jiang Zongpei. *Nephrology, The Sixth Affiliated Hospital of Sun Yat-Sen Univ, Guangzhou, Guangdong, China.*

Background: CNI-based regimen is recommended in K-DIGO in IMN but causes severe pneumonia. There is no definitely safe and effective cyclosporine concentration that K-DIGO recommended. The concentration usually regarded nontoxic is 125~175ng/ml in many reports. We observed curative effect of cyclosporine in IMN patients in our department.

Methods: There were 53 patients with IMN in our department in 2012.10~2015.12. 30 patients were given cyclosporine plus prednisone, 16 males and 14 females. The age range was 28 to 69(mean age 47.5). Prednisone was given 0.25~0.5mg/kg.d, cyclosporine was 3.0~4.5mg/kg.d and adjusted to the concentration. We defined 6 months as the longest time to induce remissions.

Results: The remission rate was 70.0% (21/30) in 6 months, included complete remission rate 28.6%(6/21) and partial remission rate 53.6%(15/21). In the remission group, there were significant differences before and post treatment in plasma albumin(25.81±5.17g/L vs 33.19±3.47g/L, $p<0.01$), proteinuria(5.58±3.02g/d vs 1.68±0.81g/d, $p<0.01$). The average time of remissions was 125.75±95.67d. The eGFR(81.59±16.86ml/min/1.73m^{2}vs 84.18± 23.27ml/min/1.73m^2, p=0.539) was no significant change. We recorded 5 cases of severe pneumonia. The average concentration of cyclosporine of these patients was 134±53.7ng/ml. The cyclosporine concentration in the patients free of severe pneumonia was 77.04±26.65ng/ml, $p<0.01$ compared with patients with severe pneumonia. The average cyclosporine concentration was 78.51±25.02ng/ml and the average cyclosporine dose was 3.04±0.46mg/kg.d that induced remission in our department.

Conclusions: Cyclosporine plus prednisone is an effective regimen in IMN in our department. High concentration of cyclosporine is one of the reasons for severe pneumonia. We recommend 80±20ng/ml concentration of cyclosporine plus prednisone may be safty and effectively in treatment for Chinese patients with IMN.

SA-PO642

Prevalence of Circulating Anti-THSD7A Autoantibody in Patients with Membranous Nephropathy in Japan

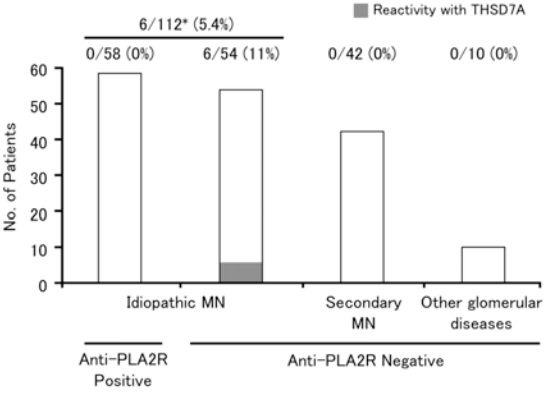
Shin'ichi Akiyama, Shoichi Maruyama. *Nephrology, Nagoya Univ Graduate School of Medicine, Nagoya, Aichi, Japan.*

Background: Circulating autoantibody against phospholipase A2 receptor (PLA2R) and thrombospondin type 1 domain containing 7 A (THSD7A) were well known as valuable biomarkers for idiopathic membranous nephropathy (iMN), and they were found in approximately 70% and 5%, respectively, of patients with iMN in Caucasian cohort. We previously reported the anti-PLA2R IgG was found in approximately 50% of patients with iMN in Japan; however the prevalence of anti-THSD7A IgG in Japanese patients is unclear.

Methods: We studied serum samples from biopsy-proven 112 patients with iMN, who consisted of 58 anti-PLA2R IgG positive patients and 54 anti-PLA2R negative patients, and 42 patients with secondary MN (sMN), and as controls, 5 each of patients with IgA-N, MCNS. All serum samples were collected before treatments. The anti-THSD7A IgG was analyzed by Western blot and indirect immuno fluorescence test cell-based assay (IIFT-CBA, EUROIMMUN). Western blot was performed under non-reducing condition with recombinant full-length THSD7A protein.

Results: As shown in Fig.1, the anti-THSD7A IgG was only detected in 6 out of 54 patients with anti-PLA2R IgG negative iMN, and was not detected in any of patients with anti-PLA2R positive iMN, sMN or other glomerular diseases. The major subclass of anti-THSD7A IgG was IgG4. Moreover, hyper-expressed THSD7A on podocytes were observed by immunofluorescent antibody technique using biopsy samples from patients with anti-THSD7A IgG positive iMN.

Conclusions: In Japanese cohort, the circulating anti-THSD7A was found in 6 (5.4%) out of 112 patients with iMN. No patients had both anti-THSD7A IgG and anti-PLA2R IgG. The prevalence and predominant IgG subclass of anti-THSD7A IgG and an expression manner of THSD7A on podocytes in Japanese patients with iMN are similar to those in Caucasian patients with iMN.



*No. of anti-THSD7A positive patents / No. of total patients.

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

SA-PO643

Serum Fibrinogen as a Predictive Biomarker of Response to Treatment in Patients with Membranous Nephropathy Hua Zhou, Ya Li, Congcong Jiao, Hairong Tang, Lizhi Li, Kong Weiwei, Lining Wang. *Dept of Nephrology, The First Hospital of China Medical Univ, China.*

Background: Membranous Nephropathy (MN) typically needs long time of treatment with steroid and immunosuppressants. A biomarker that predicts the response to treatment will likely help clinicians better manage MN. We aim to investigate whether serum fibrinogen (Fg) can predict response to steroid and immunosupressants.

Methods: 137 patients with MN proven by renal biopsy were treated with steroid and cyclophosphamide (CTX) at China Medical University from 2013 to 2014 (male: female is 89:48). The serum Fg, albumin (sAlb), low-density lipid cholesterol (LDL-C), and 24hour urinary protein excretion (uTP) were observed up to 9 months. The correlations between Fg before treatment and severity of nephrotic syndrome (uTp, sAlb, and LDL-C) before treatment, 3, 6, 9 months after treatment were analyzed.

Results: After 9 months' treatment of steroid and CTX, uTP excretion decreased (7.08±0.29 vs 2.50±0.42 g/24hr, p<0.01), sAlb increased (22.25±0.44 vs 34.35±0.78 g/L, p<0.01), and LDL-C reduced (6.08±0.22 vs 4.15±0.20 mmol/L, p<0.01). Fg was corrected to normal level (5.76±0.17 vs 3.80±0.36 g/L, p<0.01). The level of Fg before treatment positively correlated with uTp and LDL-C before and after treatment (uTP at 9 months and LDL-C at 6 months). Fg negatively correlated with sAlb pretreatment and 9 months post-treatment (see table).

Fg (g/L)	uTP (g/24hr)	sAlb (g/L)	LDL-C(mmol/L)
pretreat vs.pretreat	r=0.26(p<0.01) n=135	r=−0.41(p<0.01) n=135	r=0.55(p<0.01) n=133
pretreat vs.3m post-treat	r=0.27(p<0.01) n=106	r=−0.24(p<0.01) n=119	r=0.31(p<0.01) n=102
pretreat vs.6m post-treat	r=0.27(p<0.01) n=90	r=−0.21(p<0.05) n=93	r=0.31(p<0.01) n=88
pretreat vs.9m post-treat	r=0.36(p<0.01) n=74	r=−0.23(p<0.05) n=76	r=0.15(p=ns) n=68

Conclusions: The degree of hypercoagulation at the onset of MN correlates with the changing severity of nephrotic syndrome. Our data suggest that the level of serum fibrinogen before treatment might be a useful biomarker to predict the response to steroid and CTX. Thus, early correction of hypercoagulation might improve the outcome of membranous nephropathy.

Funding: Government Support - Non-U.S.

SA-PO644

Effects of Immunoadsorption and Immunoadsorption plus Rituximab on Circulating Phospholipase A2-Receptor Antibodies in Idiopathic Membranous Nephropathy Ammon Handisurya,[1] Renate Kain,[2] Elion Hoxha,[3] Thomas Perkmann,[4] Kurt Derfler,[1] Alice Schmidt.[1] *[1]Dept of Medicine III, Medical Univ of Vienna, Austria; [2]Dept of Pathology, Medical Univ of Vienna, Austria; [3]III. Dept of Internal Medicine, Univ Medical Center Hamburg-Eppendorf, Germany; [4]Dept of Laboratory Medicine, Medical Univ of Vienna, Austria.*

Background: 70% of all subjects with idiopathic membranous nephropathy (iMN) feature serum phospholipase A2-receptor-antibodies (PLA2R-Ab) which are linked to pathogenicity and course of the disease.

Methods: To evaluate whether immunoadsorption (IAS) effectively removes circulating PLA2R-Ab and results in a reduction of proteinuria, 4 subjects with biopsy-proven iMN, positive serum PLA2R-Ab and nephrotic range-proteinuria were treated with IAS (22-42 sessions within 68-366 days, 8000 ml total plasma volume per IAS) followed by 6 cycles of IAS combined with rituximab (Rtx; 2xIAS + 1xRtx 375 mg/m² body surface within 3 consecutive days; 4 weeks between each cycle) and a follow-up period of up to 500 days. Patients (pat.) 1-3 had iMN in their native kidneys, pat.4 a recurrence of iMN after renal transplantation. Pat.3 and 4 had received Rtx before, however without marked effect on disease activity.

Results: All pat. achieved partial remission (PR) according to the KDIGO-definition at the end of the study with reductions of serum PLA2R-Ab between -69.0 and -99.2% and urinary protein-creatinine-ratio (uPCR) between -49.3 and -82.6%. IAS-treatment alone removed serum PLA2R-Ab (-30.1 to -91.4%) only in pat.2-4, resulting in an attenuated uPCR (-25.7 to -82.9%) but PR only in pat.2. In pat.1, uPCR decreased by 24.9% but serum PLA2R-Ab interestingly increased by 2047.3%. PLA2R-Ab were detected in the eluate of pat.1-3 (not measured in pat.4). The combination of IAS with Rtx effectively reduced serum PLA2R-Ab by >90% in all but pat.4 (+13.6%) and resulted in PR of pat.1-3. During follow-up, PR was maintained in pat.1-3 and also pat.4 achieved PR 2 months after the final Rtx-administration.

Conclusions: Our data show that IAS removes PLA2R-Ab from circulation and sustains antibody removal in combination with Rituximab suggesting that IAS may improve rituximab-effects in known rituximab non-responders with iMN.

SA-PO645

Factor H Autoantibodies and Membranous Nephropathy Claudia Seikrit, Pierre M. Ronco, Hanna Debiec. *INSERM UMR-S1155, Tenon Hospital, Paris, France.*

Background: About 80% of patients with primary MN have autoantibodies against phospholipase A2 receptor (PLA2R), predominantly of IgG4 subclass. C3 and C5b-9 occur in glomerular immune deposits, implicating complement activation as a putative effector mechanism. Why 30% of patients will reach end-stage renal disease remains elusive. Here we report the case of a patient with PLA2R-related MN who later developed anti FH autoantibodies and degraded renal function.

Methods: Serum samples from patient were tested in parallel for the presence of PLA2R and FH autoantibodies using ELISA assays. To localize the binding domain of the FH autoantibodies, reactivity with recombinant FH fragments was measured.

Results: In 2009, histologically confirmed MN with circulating anti-PLA2R antibodies and normal renal function was diagnosed in a 64-year old male patient. A few months later and during the follow-up until 2016, he developed progressive renal insufficiency (serum creat: 103µmol/l (2009)- 296µmol/l (2015). He was not treated with immunosupressors. Circulating PLA2R antibodies were no longer detected after 2009. Instead a high titer of IgG3 isotype antibody reactive with FH was found in the serum between 2010 and 2015. This autoantibody recognized FH on Western blot only in non reduced conditions. IgG binding on immobilized FH was inhibited by pre-incubation with purified FH or rFH fragments containing a region that comprised the C terminal domains SCR15-20 but not the N-terminal domains SCR1-4. Plasma FH antigenic level was normal and genetic analysis revealed no abnormality in FH and FHRP1-5. Analysis of 84 sera from a retrospective cohort of patients with MN revealed that 3 additional patients had anti-FH antibodies, albeit at a lower titer than the index patient.

Conclusions: This is a first case of MN where autoantibodies targeting the C-terminal domains of FH were detected. Because FH is a major regulator of the alternative complement pathway, inhibition of FH activity by autoantibodies at podocyte cell surface might contribute to the overshooting of this pathway and accelerate disease progression. Patients with MN should be screened for anti-FH autoantibodies.

SA-PO646

Initial Anti-Phospholipase A2 Receptor Antibody Levels Predict Clinical Outcome in Patients with Idiopathic Membranous Nephropathy Jennie Lonnbro-Widgren,[1] Kerstin Ebefors,[3] Christine Payre,[4] Gerard J. Lambeau,[4] Johan C. Molne,[2] Borje Haraldsson,[1] Jenny C. Nystrom.[3] *[1]Univ of Gothenburg, Medicine, Gothenburg, Sweden; [2]Univ of Gothenburg, Biomedicine, Gothenburg, Sweden; [3]Univ of Gothenburg, Neuroscience and Physiology, Gothenburg, Sweden; [4]CNRS and Univ of Nice, Molecular and Cellular Pharmacology, Nice, France.*

Background: The clinical outcome in patients with idiopathic membranous nephropathy (iMN) is difficult to predict. PLA_2R antibodies are associated with persistence of nephrotic range proteinuria, and recent studies have provided evidence for epitope-spreading in the PLA_2R in patients with a less favorable clinical outcome.

Methods: In 25 patients with iMN and a mean follow-up of 63 months, levels of serum PLA_2R antibodies were measured at the time of renal biopsy, and correlated with the clinical outcomes. Additional glomerular staining for PLA_2R and THSD7A was performed, as well as measurement of serum epitope-specific titers and THSD7A antibodies at the time of renal biopsy.

Results: A statistically significant correlation (r=0.6, p<0.01) between a high serum PLA_2R antibody level at diagnosis and a less favorable clinical outcome was found. Patients with high autoantibody levels were more frequently exposed to immunosuppressive therapy, compared to patients with low autoantibody levels, and epitope spreading was seen among patients with higher PLA_2R antibody levels. In this study, 19 of 25 (76%) patients had a PLA_2R-associated iMN. One of the six PLA_2R-negative patients had detectable serum THSD7A autoantibodies and a positive glomerular staining for THSD7A. Moreover, THSD7A antibodies were not detected in any patient with PLA_2R-associated disease.

Conclusions: A high serum PLA_2R antibody level at presentation indicates a less favorable clinical outcome, and a higher risk of renal deterioration during follow-up. We therefore propose that these autoantibodies may be used as a prognostic marker for treatment decisions. In addition, the reactivity against three domains of PLA_2R, where the severity of the disease seems to be coupled to epitope spreading, may also be a tool to predict outcome of iMN.

Funding: Private Foundation Support

SA-PO647

A Retrospective Analysis of Patients with Idiopathic Membranous Nephropathy Treated with Steroids and Intravenous Cyclophosphamide. A Single Centre Experience Hannah E. Wilkinson, Robin Ramphul, David Makanjuola, Hugh Gallagher, Bhrigu Raj Sood, Rebecca Suckling, Marie B. Condon. *Renal Unit, St. Helier Hospital, Surrey, United Kingdom.*

Background: The use of steroids and oral Cyclophosphamide is a well recognised treatment for patients with idiopathic membranous nephropathy (IMN). However, long term effects of high dose cytotoxic agents have been well established. Taking this into account we adopted a less toxic regimen with lower dose intravenous pulsed Cyclophosphamide as an alternative to higher dose oral Cyclophosphamide.

Methods: 20 patients were treated with oral Prednisolone and IV Cyclophosphamide between 2003 and 2015. All patients had biopsy proven IMN. Decision to treat was based

on persistent nephrotic syndrome +/- deterioration in renal function despite ACEI+/-ARB and maximal BP control. Treatment consisted of Prednisolone 40 mg/day for 30 days on month 1, 3 and 5. Cyclophosphamide was dosed according to bodyweight and renal function on day 1 of month 2, 4 and 6. 4 patients received IV Methylprednisolone pulses.

Results: All patients were male, mean age 61 yrs. 19 patients completed the treatment protocol. 11 patients (57.9%) achieved remission (either partial or complete). Average time to remission was 6.6 months. 6 went on to achieve CR (31.6%), average time to CR was 13.8 months. The treatment regimen significantly reduced uPCR (p=0.0025), increased serum albumin (p= 0.00287) and stabilised creatinine (p=0.0402) in the 48 months following treatment compared to the 6 months preceding therapy when censored for second line therapy. 2 (18%) patients relapsed, both treated with Tacroliums and achieved PR. 3 patients received Tacrolimus due to failure to achieve CR, all patients achieved PR or CR with Tacrolimus. 4 patients progressed to ESRF, 4 patients died during follow up with mean age 71 years, average time to death was 64.12 months after starting treatment. The mean cumulative dose of Cyclophosphamide in our study was 3284mg (range 2160-4500mg).

Conclusions: In our low toxicity protocol we have achieved remission rates approaching 60%. Furthermore this protocol has low relapse rate with less than 25% cumulative dose of Cyclophosphamide than would be received with the modified Ponticelli regimen.

SA-PO648

Primary Nephrotic Syndrome Independently Increases the Risk of Developing End-Stage Renal Disease in Adults Alan S. Go,[1] Dongjie Fan,[1] Thida Tan,[1] Janet M. Wojcicki,[2] David Law,[1] Leonid V. Yankulin,[1] Sijie Zheng,[1] Kenneth K. Chen,[1] Glenn Matthew Chertow,[3] Juan Daniel Ordonez.[1] *[1]Kaiser Permanente Northern California; [2]Univ of California, San Francisco; [3]Stanford Univ.*

Background: Few studies have systematically evaluated the independent association of primary nephrotic syndrome (NS) with the risk of end-stage renal disease (ESRD) within representative populations. We identified a cohort of adults with primary NS and a matched cohort without NS in a large integrated healthcare system and examined characteristics associated with development of ESRD.

Methods: Within Kaiser Permanente Northern California, we identified adults aged >=18 years between 1996-2012 who had nephrotic range proteinuria (UACR>3500 mcg/mg, PCR>3.5 mg/mg, 24-hr protein>3500 mg or dipstick>300 mg/dL) or diagnosed NS (ICD-9 581.x) in electronic records and lab databases. Of these, nephrologists reviewed health records for clinical presentation, labs and biopsy results to confirm primary NS. Compared with a matched cohort of patients without NS during the study period matched on age (+/- 1 month), active membership and having known kidney function, we examined the independent association between NS and the risk of developing ESRD after adjustment for potential confounders (gender, race, comorbidities, baseline estimated glomerular filtration rate, baseline hemoglobin level) using multivariable extended Cox regression models.

Results: We identified 907 adults with confirmed primary NS and 89,593 matched adults without NS. The annual incidence of ESRD was 4.65 per 100 person-years in NS patients vs. 0.03 per 100 person-years in matched non-NS patients (P<0.001). After adjustment for potential confounders, NS was independently associated with a substantially higher rate of ESRD (adjusted hazard ratio 14.6, 95% CI: 9.6-22.3).

Conclusions: Among a large, diverse community-based population, primary nephrotic syndrome was a strong, independent risk factor of developing ESRD.

Funding: Private Foundation Support

SA-PO649

Tacrolimus in the Treatment of Pediatric Steroid Resistant Nephrotic Syndrome (SRNS) Ankana Daga, Avi Traum. *Div of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston, MA.*

Background: Data on tacrolimus use in the treatment of pediatric SRNS is limited and biopsy findings are variable. Given the focal nature of glomerulosclerosis, whether Minimal Change Disease (MCD) in SRNS patients is a different disease or an effect of biopsy sampling continues to generate controversy. Thus, the aims of this study were to characterize the response rate to tacrolimus in pediatric SRNS, and to further describe the response rate based on biopsy findings.

Methods: This was a single-center, retrospective study of children with SRNS treated with tacrolimus. SRNS was defined as no improvement in proteinuria after 8 weeks of full dose steroids. Complete Response (CR) was defined as a urine protein-to-creatinine ratio (UPC) ≤ 0.2 and Partial Response (PR) as ≥ 50% reduction in proteinuria. Biopsy findings were recorded as MCD vs. Focal Segmental Glomerulosclerosis (FSGS).

Results: In 47 patients who met inclusion criteria, 57% were male, 45% were Caucasian, with the average age at diagnosis of 7.2 ± 5.6 years. Thirty-six (77%) patients responded to therapy after 6 months of tacrolimus (32% CR, 45% PR). Twenty-eight (60%) patients responded to therapy after 12 months of tacrolimus (28% CR, 32.6% PR). Acute kidney injury was the most common side effect, occurring in 17 (36%) patients. FSGS was detected on biopsy in 27 patients while 16 patients had MCD. The average number of glomeruli per biopsy sample was 16.7 ± 9.8. Of the 27 patients with FSGS, 67% responded to therapy (15% CR, 52% PR) at 6 months. Interestingly, of the 16 patients with MCD, 88% responded (50% CR, 38% PR) at 6 months. The response rate at 12 months of treatment with tacrolimus was 67% in the FSGS group versus 56% in the MCD group. The MCD group at 12 months included 2 lost to follow up and 2 with <12 months of therapy, while among FSGS patients, 3 had therapy discontinued, which included 2 who developed ESRD, and 1 who was diagnosed with cancer.

Conclusions: Tacrolimus is an effective therapy in children with SRNS irrespective of histologic findings. Biopsy revealing MCD in SRNS patients should not preclude use of tacrolimus. Multi-center studies are needed in the future to validate these findings.

SA-PO650

Rituximab Treatment for Frequently Relapsing Nephrotic Syndrome or Steroid-Dependent Nephrotic Syndrome Mika Sonoda, Eiji Ishimura, Shuko Ueda, Shinya Nakatani, Mitsuru Ichii, Yoshiteru Ohno, Akihiro Tsuda, Katsuhito Mori, Masaaki Inaba. *Osaka City Univ Graduate School of Medicine, Osaka, Japan.*

Background: Frequently relapsing nephrotic syndrome (FRNS) and steroid-dependent nephrotic syndrome (SDNS) requires long-term corticosteroid therapy and/or immunesupressive agents, which cause significant adverse effects. Recently, rituximab, a chimeric monoclonal antibody against the CD20 antigen, has been expected for the treatment of FRNS /SDNS in children in some countries. However, there are few reports on the treatment for adult patients with childhood-onset FRNS and/or SDNS.

Methods: Six patients (24.6 +/- 5.9 year-old, 2 males and 4 females) of FRNS/SDNS were treated by rituximab. All patients had nephrotic syndrome of childhood-onset, which relapsed more than fifteen times. They had been orally taking prednisolone and/or cyclosporine. After premedication, such as acetoamiophen and chlorphenamine, to prevent infusion reaction, 500 mg rituximab was intravenously administered. Effect of rituximab on inhibition of relapse and changes in B cell counts in blood were examined up to ten months.

Results: All patients could receive intravenous 500mg rituximab, without any infusion reaction and adverse events. In the follow-up period, oral predonisolone and/or cyclosporine could be reduced gradually without relapse of nephrotic syndrome. B cells in blood significantly decreased. Changes in B cell counts in all patients were as followings; before administration, CD 19 cells were 8.5 +/- 4.1%, and CD 20 cells 10.1 +/- 3.6%; after 6 months: 2.8 +/- 3.3% (CD19) and 2.8 +/- 3.5% (CD20). In one patient, rituximab was re-administered because increase of B cells were seen.

Conclusions: Intravenous rituximab treatment is effective against relapse of nephrotic syndrome in adult patients with childhood-onset FRNS /SDNS. It is safely administered with appropriate anti-allergic pretreatment. It causes significant decrease in B cell counts in blood. It can reduce the dose of corticosteroid in adult patients with childhood-onset FRNS/SDNS. Long-term observation is currently undergone.

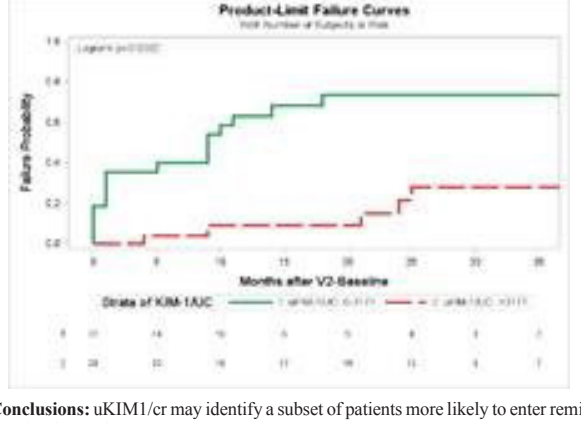
SA-PO651

Urine KIM-1/Creatinine as a Marker of Glomerular Disease Severity and Treatment Response in the Nephrotic Syndrome Study Network Qiaoyuan Wu,[1] Jonathan P. Troost,[2] Tiane Dai,[1] Boxian Wei,[2] Peter X.K. Song,[2] Debbie S. Gipson,[2] Cynthia C. Nast,[1] Matthias Kretzler,[2] Sharon G. Adler.[1] *[1]Div of Nephrology & Hypertension, Los Angeles Biomedical Research Inst, Torrance, CA; [2]Div of Nephrology, U Michigan, Ann Arbor, MI.*

Background: We tested whether at baseline (BL) the proximal tubule injury marker urine KIM-1/creatinine (uKIM1/cr) correlated with BL disease severity and/or improved a remission prediction model.

Methods: uKIM1/cr was measured on BL protease-protected spot urine from non-immunosuppressed patients (Minimal change (MC), n= 7; Focal segmental glomerulosclerosis (FSGS), n= 24; Membranous nephropathy (MN), n= 12; and other glomerulopathies (OG), n= 12). Urine protein/creatinine (UPCR) was measured at BL, and Q4-6 mos. Correlations with BL uKIM1/cr and UPCR, morphometrically measured histopathologic features, and renal outcomes were assessed. Associations between uKIM1/cr and time to first complete remission were tested using a Kaplan-Meier analysis and Cox proportional hazards models adjusting for baseline proteinuria, diagnosis, and subsequent treatment. Subgroup variation by diagnosis in the effect of uKIM1/cr on reaching remission was tested using interaction terms.

Results: Median follow-up was 24 mos; 16 of 55 patients were subsequently treated (steroids, n=9; calcineurin inhibitors, n=4; mycophenolate mofetil, n=3). BL uKIM1/cr correlated with UPCR (r=0.45; p<0.001), but not with eGFR. uKIM1/cr was lower in MC than FSGS, MN, and OG (p=0.006) and correlated with foot process effacement but not with global or segmental sclerosis, interstitial fibrosis, tubular atrophy, or acute tubular injury. After adjusting for BL proteinuria, pathologic diagnosis, and treatment, uKIM1/cr was a significant predictor of time to complete proteinuria remission.



Conclusions: uKIM1/cr may identify a subset of patients more likely to enter remission from nephrotic syndrome.

Funding: NIDDK Support, Other NIH Support - Office of Rare Diseases, Private Foundation Support

SA-PO652

Effect of Tacrolimus on Endothelial-Derived Microparticles in Pediatric Patients with Nephrotic Syndrome Howard Trachtman,[1] Laura Jane Pehrson,[1] Suzanne M. Vento,[1] Laura Malaga-Dieguez,[1] Brandon Renner,[2] Jennifer Laskowski,[2] Joshua M. Thurman.[2] *[1]Pediatrics, NYU Langone Medical Center, New York, NY; [2]Medicine, Univ of Colorado School of Medicine, Aurora, CO.*

Background: Tacrolimus (TAC) causes direct injury to endothelial cells that in kidney transplant recipients is characterized by increased circulating levels of endothelial-derived microparticles (EDMP). The objective of this study was to determine the effect of TAC on EDMP in pediatric patients receiving the drug to treat nephrotic syndrome (NS), a cohort without longstanding kidney disease and fewer comorbid conditions.

Methods: Children with NS due to minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS) treated with TAC were recruited in the Fink Ambulatory Care Center or Bellevue Nephrology Clinic. The following material was obtained from the medical record: age, gender, TAC dose, BP, eGFR, proteinuria, and trough TAC level. A plasma sample was obtained every 6 months for measurement of EDMP by flow cytometry using antibodies to CD31, CD44 and complement C3. Results were compared to those from a cohort of 30 healthy control subjects.

Results: 13 patients (9M: 4F), 11.7±4.9 yr old, were enrolled in the study. The underlying disease was MCD in 6 and FSGS in 7 cases. The initial eGFR was 142±100 and 112±50 ml/min/1.73 m^2 at 6 months. The TAC dose was 0.1±0.5 mg/kg/day and the trough drug level was 3.7±1.3 ng/ml. The number of EDMP in the patients with NS was 1,605±170/ml at entry and 1,381±97/ml after 6 months of follow-up (P = NS) and both values were compared with healthy controls (1,178±69/ml; P < 0.05). C3 deposition on the EDMP was similar in children with NS compared to healthy controls (86±11 vs. 80±41 RFU; P = NS) and did not increase after 6 months of TAC treatment (95±12 RFU).

Conclusions: Administration of TAC to pediatric NS patients is associated with an increased number of EDMP that is steady over 6 months. The number of EDMP in patients with NS was significantly higher than in healthy controls, suggesting that NS itself is associated with increased EDMP generation. EDMP may be a useful biomarker to monitor vascular injury in patients with NS treated with TAC.

Funding: NIDDK Support

SA-PO653

Assessing Patients' Interest and Barriers to Clinical Research Participation in Nephrotic Syndrome Laura H. Mariani,[1,2] Chelsey Fix,[3] Kathleen Broderick,[3] Julie Abramson,[3] Abigail L. Swan,[3] Lauren Lee,[3] Elizabeth L. Cope.[1] *[1]Arbor Research Collaborative for Health; [2]U. Michigan; [3]NephCure Kidney International.*

Background: Recruitment for clinical research studies in primary Nephrotic Syndrome (NS) is hindered by the rarity of the disease, diverse care settings and geographic spread of affected patients. Better understanding of the level of interest and barriers to participation from a diverse group of patients with NS is critical to successful recruitment and study design.

Methods: The NephCure Kidney Network (NKN) is a web-based patient opt-in registry for primary NS. Participants provide data including kidney disease history, demographics and research participation preferences. Logistic regression models were fit to identify predictors of willingness to participate.

Results: As of May, 2016, 587 participants from 32 countries have been recruited. Mean(SD) age is 26(12) yrs, 50% female, 22% non-Caucasian and 10% Hispanic. 38% have FSGS, 23% MCD, 2% IgAN, 2% MN and 2% MPGN. 62% are currently on immunosuppression. 45% had achieved remission, 17% had been on dialysis and 13% had a transplant prior to enrollment. Only 15% reported having participated in a clinical trial, yet 56% reported being interested in a study testing "an experimental therapy that may or may not help him or her." Increasing age was associated with higher odds of being interested (OR 1.3 per 10 years, p 0.001), but there was no association with sex, race, ethnicity, prior medication exposure or remission status. Figure 1 describes interest by study requirements and participation barriers.

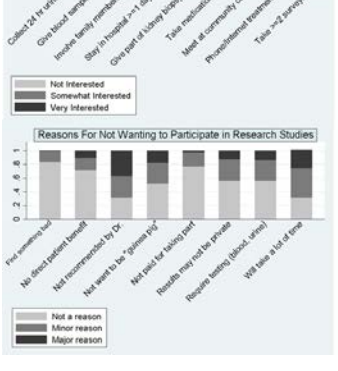


Figure 1: Patient reported interest and barriers to research participation in Nephrotic Syndrome

Conclusions: While the majority of NKN participants indicate a high interest in many types of clinical research, few reported previously participating. Designing studies around topics of high value to the patient, engagement from their primary nephrologist, ensuring appropriate data privacy and limiting time burden may help to increase participation.

Funding: Private Foundation Support

SA-PO654

Serum 1,25-Dihydroxyvitamin D Better Reflects Renal Parameters Rather Than 25-Hydoxyvitamin in Patients with Biopsy-Proven Glomerular Disease Yu Ah Hong, Hyeon Seok Hwang, Yoon-Kyung Chang, Suk Young Kim, Cheol Whee Park, Sungjin Chung. *Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.*

Background: Impaired vitamin D metabolism may contribute to the development and progression of chronic kidney disease (CKD). The purpose of the study was to determine associations of circulating vitamin D metabolites with the degree of proteinuria and impaired estimated glomerular filtration rate (eGFR) in patients with biopsy-proven glomerular disease.

Methods: Blood samples for 25-hydroxyvitamin D (25D) and 1,25-dihydroxyvitamin D (1,25D) levels were collected from 173 patients who admitted for renal biopsy. All clinical and laboratory data were obtained at the time of the renal biopsy, and therapeutic medication after renal biopsy was collected.

Results: As serum 1,25D levels declined, renal function was significantly decreased ($p<0.001$). However, serum 25D levels were not different according to the change of eGFR ($p=0.786$). Serum albumin was significantly increased and total cholesterol and 24hr urine protein were significantly decreased in patients with the higher levels of 25D and 1,25D than in those with the lower values. The prevalence of nephrotic range proteinuria and moderate to severe renal dysfunction (eGFR ≤ 60ml/min/1.73m^2) progressively increased with declining 1,25D, but not 25D. Multiple linear regression analysis showed that 25D was significantly correlated with serum albumin and total cholesterol ($\beta=0.224$, $p=0.006$; $\beta=-0.263$, $p=0.001$) and 1,25D was significantly correlated with eGFR, serum albumin and serum phosphorus ($\beta=0.202$, $p=0.005$; $\beta=0.304$, $p<0.001$; $\beta=-0.161$, $p=0.024$). In adjusted multivariable linear regression, eGFR and 24hr proteinuria were independently correlated only with 1,25D ($\beta=0.154$, $p=0.018$; $\beta=-0.171$, $p=0.012$), but not 25D. The lower level of 1,25D was associated with the frequent use of immunosuppressive agents after renal biopsy ($p<0.001$).

Conclusions: According to these results, it is noteworthy that circulating 1,25D may be superior to 25D as an indicative marker of disease severity in patients with biopsy-proven glomerular disease.

SA-PO655

Rituximab Therapy for Idiopathic Nephrotic Syndrome Montserrat M. Diaz Encarnacion,[1] Iara Karlla Dasilva,[2] Luis F. Quintana,[4] Manuel Praga,[5] Juliana Bordignon Draibe,[6] Jose Ballarin.[7] *[1]Fundacio Puigvert; [2]Fundacio Puigvert; [3]Hospital Puerta de Hierro; [4]Hospital Clínic; [5]Hospital Univ 12 de Octubre; [6]Hospital Univ de Bellvitge; [7]Fundacio Puigvert.*

Background: Steroids continue to be the main treatment at idiopathic nephrotic syndrome (INS). Approximately 40%–50% of patients are steroid-dependent (SD) and require repeat courses of prednisone and/or the addition of other immunosuppressive (IS) medications. Rituximab (RTX) is effective for the treatment of SD or frequently relapsing (FR) in pediatric patients, but this efficacy in adult patients is not established. **The aim** our study was to evaluate the effects of RTX in adult with a diagnosis of difficult-to-treat INS, and to compare the outcomes with control patients treated with steroids in combination with other IS, excluding RTX.

Methods: We reviewed 50 patients with SD and FR INS, 28 patients received RTX between 2008-2015, and 22 control group patients in 6 Spanish hospitals. The minimal follow up is 8 month post-RTX. Data are expressed as means ± standard deviation. Comparisons before and after RTX treatment (baseline vs last follow up) were assessed by the paired Student's parametric *t*-test (significant=$p<0.05$).

Results: 23 patients (82%) responded to RTX with complete remission, 20 patients (71%) had no relapses after RTX and 13 without IS. 8 patients (29%) experienced at least one relapse of NS after RTX. We observed a highly significant reduction in the total number of relapses ($p<0.001$) and a decline in proteinuria (p 0,03) after RTX. The mean follow-up of 31±26 m (8–86) after RTX. We observed a significant reduction in frequency of relapses/ year in the RTX group compared with control group. There were differences in the final dose of steroid and tacrolimus needed to obtening sustained remission between both groups.

Conclusions: RTX treatment is safe and well tolerated and effectively reduced the incidence of recurrences and need for maintenance IS in adult patients with difficult-to-treat INS, but a few data is available about the long-term in adult.

Funding: Government Support - Non-U.S.

SA-PO656

Rituximaab in the Treatment of Children with Steroid Dependent/ Resistant Nephrotic Syndrome Sooraj Yesudas Santhakumari. *Cochin Kidney Centre, Kochi, Kerala, India.*

Background: About 10 -20 percent of children with nephrotic syndrome are steroid resistant/dependent. Though a variety of treatment modalities including cyclophosphamide, Calcineurin inhibitors (CNIs), mycophenolate, azathioprine etc are available for these children, still a small percentage remains refractory to these medicines. Rituximab is a

chimeric antibody directed against the CD 20 receptors of B cells. There are studies which have shown that it is useful in Steroid dependent Nephrotic Syndrome (SDNS)/Steroid Resistant Nephrotic Syndrome (SRNS).

Methods: 15 children who satisfied the criteria for SDNS/SRNS were involved in the study. All had undergone treatment with Cyclophosphamide, CNIs and mycophenolate but were not able to achieve sustained remission and also was unable to withdraw steroids. Renal biopsy was done whenever possible. All the children were given 2 doses of Rituximab 375 mg/sq.m 2 weeks apart. They were then followed up for a period of minimum 8 months. Steroids and other immunosuppressents were withdrawn whenever possible.

Results: There were 15 children - 9 males and 6 females. The average age was 8.4 +/- 2.4 years. The average duration of nephrotic syndrome was 30.46 +/- 8.61 months. All had received treatment with steroids and other immunosuppressives. 6 patients had undergone renal biopsy out of which 5 were minimal change disease and one was FSGS. All of them received 2 doses of Rituximab 375 mg/sq.m 2 weeks apart. The average followup was 12.46 +/- 2.92 months. The minimum followup was 8 months and maximum followup was 18 months. 14 patients responded to the treatment (93%) and we were able to stop immunosuppression. One child continues to be on steroid and CNIS. All children tolerated the drug well. There were no major adverse events except one episode of Herpes Zoster in a child which responded to treatment.

Conclusions: We conclude that Rituximab is a safe and effective treatment option in children with Resistant Nephrotic Syndrome. However more studies and more followup is required.

SA-PO657

Short-Acting Natural ACTH Induces Rapid Remission of Steroid-Dependent Nephrotic Syndrome Followed by Delayed-Onset Resistance: Implications of Newly Formed Neutralizing Antibodies Pei Wang,[1,2] Minglei Lu,[1] Xianhui Liang,[1] Yan Ge,[1] Zhangsuo Liu,[2] Rujun Gong.[1] *[1]Nephrology, Brown Univ; [2]The First Affiliated Hospital of Zhengzhou Univ, China.*

Background: There is increasing evidence supporting the use of adrenocorticotropic hormone (ACTH) as an alternative treatment for refractory proteinuric glomerulopathies. The efficacy of short-acting ACTH, however, remains unknown and was tested here.

Methods: A 21-year-old man with a 5-year history of steroid-dependent nephrotic syndrome due to minimal changes disease developed Cushing's syndrome and was recently afflicted with severe cellulitis. He was weaned off all immunosuppressants, including corticosteroids, and this resulted in a relapse of generalized anasarca, associated with massive proteinuria and hypoalbuminemia. ACTH monotherapy was subsequently initiated.

Results: The initial regimen consisted of subcutaneous injections of 25 IU of short-acting animal-derived natural corticotropin given daily at 09:00 AM with reference to the Columbia ACTH gel therapy regimen. Short-acting ACTH treatment induced a rapid response, marked by massive diuresis, substantial reduction in body weight and partial remission of proteinuria. Ten days later, the patient developed mild skin rash and subcutaneous nodules at injection sites. A relapse followed despite doubling the dose of corticotropin, consistent with delayed-onset resistance to treatment. Immunoblot-based antibody assay revealed *de novo* formation of antibodies in the patient's serum that were reactive to natural ACTH. In cultured melanoma cells known to intensely express melanocortin receptors, addition of the patient's serum strikingly mitigated dendritogenesis and cell signaling triggered by natural ACTH like the extracellular signal-regulated kinase (ERK) and glycogen synthase kinase (GSK)3β pathways, denoting neutralizing properties of the newly formed antibodies.

Conclusions: Short-acting ACTH was likely effective in inducing remission of steroid-dependent nephrotic syndrome. The delayed resistance might be attributable to the formation of anti-ACTH neutralizing antibodies. The experimental protocols established here may aid in determining the cause of resistance to ACTH treatment in future studies.

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

SA-PO658

Novel Paradigm for Categorizing Subtypes of Focal Segmental Glomerulosclerosis: A Pilot Study Thomas Kitzler,[1] Nadezda Kachurina,[2] Martin M. Bitzan,[3] Elena Torban,[2] Paul R. Goodyer.[3] *[1]Medical Genetics, McGill Univ Health Centre, Montreal, QC, Canada; [2]Dept of Medicine, McGill Univ and McGill Univ Health Centre, Montreal, QC, Canada; [3]Dept of Paediatric Nephrology, McGill Univ Health Centre, Montreal, QC, Canada.*

Background: Focal segmental glomerulosclerosis (FSGS) is found in the majority of children with steroid resistant nephrotic syndrome (SRNS), many of whom progress to end-stage renal disease despite second-line treatment with immunosuppressive agents. About half of these children harbour mutations in genes relevant for podocyte structure and integrity, whereas of the other half, some appear to have a circulating, yet to be identified, cytotoxic "FSGS factor" that directly causes damage to the podocyte ultrastructure. Children with genetic podocyte defects tend to fare well on treatment with renal transplant, while children with a circulating factor are at high risk of recurrence of FSGS on renal allograft, but may benefit from novel targeted therapeutic approaches instead. Here we present a novel approach on how to distinguish these subgroups.

Methods: This is an analysis of 16 patients with clinically confirmed SRNS. We employed a combined approach of Next Generation Sequencing of 37 known FSGS genes and a functional assay, which indirectly tests for the presence of a podocyte-toxic factor in patients' sera by use of cultured human podocytes. Toxicity of sera is evidenced by disassembly of podocyte focal adhesion complexes (Kachurina et al., Am J Physiol Renal Physiol, 2015).

Results: Preliminary analysis of patients' sera demonstrated absence of podocyte-toxicity in patients with identifiable genetic podocyte defects, whereas indirect evidence for a circulating factor (i.e., podocyte-toxicity) could only be detected in patients without identifiable genetic defects.

Conclusions: Based on these preliminary observations, we propose that SRNS comprises three subgroups: 1) patients with genetic causes of SRNS who fare well after renal transplantation; 2) patients without genetic causes with high risk of recurrence in the allograft, as evidenced by serum podocyte-toxicity; and 3) patients without genetic causes and low recurrence risk, i.e., absence of podocyte-toxicity.

SA-PO659

A Prospective, Open Label Study of the Safety and Treatment Efficacy of ACTHar Gel for Fibrillary Glomeruloneprits James A. Tumlin,[1] Brad H. Rovin,[4] William G. Paxton,[2] Isabelle Ayoub,[4] Salem Almaani,[4] Dawn J. Caster,[5] Alice Sue Appel,[3] Gerald B. Appel.[3] *[1]Renal Div, Univ of Tennessee College Medicine, Chattanooga, TN; [2]Georgia Nephrology Associates, Atlanta, GA; [3]Renal Div, Columbia Univ, New York, NY; [4]Renal Div, Ohio State Univ, Columbus, OH; [5]Renal Div, Univ of Louisville, Louisville, KY.*

Background: Fibrillary glomerulonephritis (FGN) is a rare glomerular disease characterized by randomly deposited Congo-red negative fibrils within the mesangium and glomerular basement membranes. The therapeutic options for FGN are poor, with more than 50% of patients progressing to ESRD within 5 years. ACTHar gel has shown benefit in the treatment of multiple forms of proteinuria glomerular diseases. To determine its therapeutic efficacy in FGN, we retrospectively reviewed 14 patients treated with ACTHar gel.

Methods: A total of 14 patients with biopsy proven FGN were reviewed. Mean age was 59+4 yrs with 93% Caucasian and 57% female. The FGN subtypes included 3-MGN, 8-Mesangial, 2-MPGN, and 1 Crescentic. Seven (50%) received prior immunosuppression; Pred-4, CNI-5, Rituximab-2. All patients but one received 6 mths ACTHar; dose range (80-240 units 2-3 inj/wk)(mean dose 174+9 units) (range 2-24 mths). Complete responses were defined as UP/Cr ratio < 0.30; partial responses were defined as a > 50% reduction in pre-ACTH UP/Cr ratios.

Results: A complete response was achieved in 1 patient (7%), partial remissions in 6 (43%) and no response in 7 (50%). Responsive patients did not differ in FGN subtypes or prior treatment. Patient responses are shown in Table-1. (Proteinuria-UP/Cr gm/gm) *(p=0.009).

Table-1	Number	Age	Prior Tx	Peak UP/ Cr ratio	Pre-ACTH UP/Cr ratio	Post-ACTH UP/Cr ratio
Responders	7	57.1±6	4/7 (57%)	7.53+1.0	5.43+0.67	1.34+0.31*
Non-Responders	7	61.0±3	3/7 (43%)	6.44+1.0	4.93+1.2	5.81+0.87

Conclusions: FGN is a rare and refractory form of glomerular disease with a high rate of progression to ESRD. We have shown that a prolonged course of ACTHar gel (8+months) leads to a complete or partial remission in 50% of patients. ACTHar gel may be an alternative therapy for FGN.

Funding: NIDDK Support, Private Foundation Support

SA-PO660

Hypothyroidism Secondary to Severe Nephrotic Syndrome Anna Matyjek,[1] Aleksandra Rymarz,[1] Slawomir Literacki,[1] Dorota Brodowska-Kania,[1] Tomasz Rozmyslowicz,[2] Stanislaw Niemczyk.[1] *[1]Military Inst of Medicine, Warsaw, Poland; [2]Univ of Pennsylvania, Philadelphia.*

Background: The issue of clinically significant hypothyroidism secondary to urine loss of free hormones, TBG and albumin is currently widely discuss in paediatric population with nephrotic syndrome. In adults, however, the data are limited. The aim of the study was to estimate the thyroid function in severe nephrotic syndrome in adults, defined as serum albumin level *(SA)* ≤ 2.5 g/dl.

Methods: The 25 adult patients (mean age 45±18 years, 68% men) with severe nephrotic syndrome and eGFR >30 ml/min/1.73m^2 were included into the prospective pilot study. The thyroid hormone profile was assessed using electrochemiluminescence immunoassay *(ECLIA)*. The Spearman correlation coefficient was used to statistical analysis *(Statistica 12, StatSoft)*.

Results: The mean values of measured parameters were: SA 1.8±0.4 g/dl, TP 4.2±0.6 g/dl, daily proteinuria 11.5±6.0 g, daily albuminuria 8.9±6.7 g, urine albumin-to-creatinine ratio *(ACR)* 4.77±1.9 g/mgSCr, TSH 4.1±2.2 µIU/ml, fT4 12.7±3.2 pmol/l, fT3 3.4±0.8 pmol/l, antithrombin activity 75±20%. The study revealed the impaired thyroid hormone profile in 76% subjects, in 81% with SA <2.0 g/dl and in 67% with SA 2.0-2.5 g/dl. The main abnormality was overt hypothyroidism (28%) and euthyroid sick syndrome (*ESS*, characterized by decreased level of serum fT3 or fT4, or both, accompanied by normal TSH range) (28%), followed by subclinical hypothyroidism (20%). TSH level inversely correlated with SA (r=-0.415, p=0.007) and antithrombin activity (r=-0.58, p=0.009). The significant negative correlations were observed between free hormones and daily proteinuria (for fT3 r=-0.255, p=0.043; for fT4 r=-0.528, p=0.029) and ACR (for fT3 r=-0.495, p=0.028; for fT4 r=-0.559, p=0.016). The ACR >4.0 g/mgSCr was associated with 77% risk of thyroid free hormone deficiency.

Conclusions: Severe nephrotic syndrome causes significant disturbances in the thyroid function. In most of the patients hypothyroidism or ESS was observed. The thyroid function monitoring in patients with severe nephrotic syndrome seems to be necessary to avoid possible clinical consequences.

Funding: Clinical Revenue Support

SA-PO661

Collapsing Glomerulopathy in Kidney Allografts: Donor Ethnicity and Clinical Course Ndidiamaka O. Obadan, Evelyn Bruner, Girish K. Mour, Juan Carlos Q. Velez. *Nephrology, Medical Univ of South Carolina, Charleston, SC.*

Background: Collapsing glomerulopathy (CG) is a variant of focal segmental glomerulosclerosis (FSGS). In native kidneys, almost all affected individuals are African American (AA), 75% of whom carry 2 *APOL1* risk alleles. However, in kidney allografts, CG can also affect non-AAs. The largest published series of allograft CG involved 10 patients and did not report donor race. We hypothesized that a larger series that includes donor race data could provide insights about the pathogenesis and clinical course of this entity.

Methods: Kidney allograft biopsies performed at our institution from 2001-2016 were reviewed for cases of CG. Clinical data were extracted from medical charts. Outcomes were assessed by donor race.

Results: Among 116 cases of allograft FSGS, we identified 22 as CG (19%). Donor race was AA in 13 (59%) and white (W) in 9 (41%) cases. No difference was found in recipient's mean age (56 vs. 47 yrs), gender (23% vs. 33% female), race (23% vs. 55% AA), time from transplant to CG (35 vs. 19 months) or cold ischemia time (13 vs. 16 hrs) for AA-CG and W-CG, respectively. Among AA-CG cases, native nephropathy were diabetic (DN) (6), hypertensive (5) and FSGS (2), suggesting possible recurrence in 2 cases. On the other hand, all W-CG cases were possibly *de novo* (native nephropathy: DN in 4, IgA in 2, lupus, ADPKD and aHUS in 1). DNA for CMV and BKV was found in 2 AA-CG cases, whereas CMV, parvo, coxsackie and EBV viremia were found in 4 W-CG cases. No difference was found in mean serum creatinine (4.2 vs. 2.6 mg/dL) or urine protein-to-creatinine (7.6 vs. 4.8 g/g) at the time of diagnosis, although there was a trend for a greater incidence of nephrotic syndrome in AA-CG (83% vs. 55%, p=0.17). More importantly, graft loss occurred in 12 (95%) AA-CG vs. in 4 (44%) W-CG cases (p=0.02).

Conclusions: CG is a form of FSGS with increased relative incidence in kidney allografts that presents frequently as *de novo* disease. Viremia is detectable in about 25% of cases. CG affecting kidneys from AA donors appear to have a more ominous outcome; Whether *APOL1* risk alleles account for the difference remains to be determined.

SA-PO662

Apoptosis Inhibitor of Macrophage (AIM) Expression in the Kidney Was Associated with Increased Proteinuria and Decline in Renal Function Yasunori Iwata, Megumi Oshima, Kengo Furuichi, Norihiko Sakai, Miho Shimizu, Akinori Hara, Tadashi Toyama, Yasuyuki Shinozaki, Yasutaka Kamikawa, Shinji Kitajima, Akihiro Sagara, Takashi Wada. *Nephrology, Kanazawa Univ.*

Background: Apoptosis inhibitor of macrophage (AIM) expressed on macrophages prolongsinflammation by protecting macrophages from apoptosis. Most circulating AIM co-exists with immunoglobulin M (IgM). AIM's pathophysiological role in relation to IgM remains unclear. Here we evaluated the glomerularexpression/deposition of AIM and IgM in the kidney using immunohistochemistry and its associations with clinical manifestations in 43 patients with biopsy-confirmed kidney diseases.

Methods: Kidney biopsy tissue from all patients was immunostained for AIM and IgM. Staining patterns and percent stained areas within the glomeruli were determined. Cells expressingAIM were identified by co-staining with macrophage and endothelial cell surface markers. Correlations between stainingresults and clinical parameters were evaluated using univariate and multivariate analyses.

Results: AIM was deposited in various areas, such as mesangial and capillary area. A part of AIM expressionwas localized to CD68-positive macrophages in the glomerulus. Amount of glomerular expression was positivelycorrelated with urinary protein in patients with severe proteinuria andkidney dysfunction. Urinaryprotein was higher in patients exhibiting overlapping glomerular expression of AIM and IgM. Annual eGFR decline ratenegatively correlated withAIM-positive area. AIM-positive area and initial serum creatinine were independently associated with decreased kidney function.

Conclusions: AIM expression in the kidney was associated with urinary protein and decline in renal function.Co-expression with IgM appeared to exacerbate AIM's deleterious effects on renal function. Combined glomerular AIMand IgM expression is a candidate prognostic index for kidney disease.

Funding: Government Support - Non-U.S.

SA-PO663

Natural History of Lithium Nephropathy: Cross-Sectional Analysis of a Cohort of Li-Treated Bipolar Disorder Patients Martin Flamant,[1,3] Emmanuelle Vidal-Petiot,[1,3] Fideline Serrano,[1,3] Pedro Fernandez,[1,3] Frank Bellivier,[2,3] Francois Vrtovsnik.[1,3] *[1]Bichat Hospital, APHP, Paris, France; [2]Center for Bipolar Disorder, APHP, Paris, France; [3]Paris Diderot Univ, Paris Diderot Univ, Paris, France.*

Background: Lithium (Li) therapy may lead to secondary renal disease including diabetes insipidus, hypercalcemia and chronic microcystic nephropathy but the natural history of these disorders in this setting is still unclear.

Methods: measured GFR (clearance of ^{51}Cr-EDTA), maximal urinary osmolality following 12h of water restriction and injection of 0.4 µg ddAVP (UOsm-max, in mosm/kg), osmotic load (OsmL, mosm/d), ionized calcium, PTH before and after iv calcium load were measured in 87 consecutive patients (pts) referred by the Center for Bipolar Disorder and treated with Li for 0-1y (G1, n=17), 1-5y (G2, n=21), 5-15y (G3, n=24), >15y (G4, n=25). Kidney microcysts were counted by MRI imaging in 37 pts.

Results: In the whole cohort (36% men), mean(SD) age and GFR, were 50.2 (15.3) years and 73.7 (22.6) mL/min/1.73m². GFR was independently correlated (multiple regression) with both duration of Li exposure (-0.98ml/min/1.73m²/y, p<0.0001) and age (-0.55ml/min/1.73m²/y, p<0.001). Polyuria (>3L/day) was found in 25% of pts and associated with a higher OsmL (p<0.05) and decreased UOsm-max (p<0.001) in pts from G1 to G4. Hypercalcemia (HCa) was present in 23 pts and associated with high PTH in 9, all in G4. PTH decrease following iv Ca load was blunted with longer therapy (p<0.05). Prevalence of microcysts increased from G1 to G4 (p<0.002) but lacked in 25% of G4 pts.

	GFR (ml/mn/>1.73m²)	diuresis > 3L/d (%)	UOsmax if P (if w/o P)	OsmL if P (if w/o P)	HCa (%)	ΔPTH>50% after iv Ca	>2 microcysts (%)
G1	94.7	20	776 (738)	999 (560)	12	86	8
G2	79.6	24	616 (717)	803 (580)	6	76	20
G3	73.7	28	519 (627)	726 (610)	40	55	56
G4	54.4	29	296 (530)	699 (663)	44	42	75

Conclusions: Li-induced diabetes insipidus occurs early during the course of Li therapy. Microcysts are frequent but not systematic in long-term treated pts. In this cohort, GFR decrease is highly correlated with length of exposure to Li and reaches -1.5 ml/min/1.73m/y, with 1/3 attributable to aging and 2/3 to Li.

SA-PO664

Interstitial Nephritis Associated with Programmed Cell Death-1 Inhibitors Samer Mohandes, Vahagn A. Zakaryan, Jason Prosek. *Ohio State Univ Wexner Medical Center, Columbus, OH.*

Background: Programmed Cell Death-1 (PD-1) inhibitors are immune checkpoint inhibitors used to treat malignancies= by blocking inhibition to T-cell activation. Current PD-1 inhibitors include nivolumab and pembrolizumab. Acute interstitial nephritis (AIN) has been described with ipilimumab but not well described with PD-1 inhibitors. Here we report 6 cases of suspected AIN due to use of PD-1 inhibitors.

Methods: Six patients who underwent treatment with PD-1 inhibitors in whom AIN was clinically observed are presented. PD-1 inhibitors were used for RCC, melanoma and urothelial carcinoma. AKI attributed to AIN was observed within 3 days to 5 months. AIN was proven by biopsy in 2 cases. Clinical features are summarized in Table 1. One patient developed hypercalcemia with elevated 1,25-OH vitamin D level suggesting granulomatous AIN. All of the patients who received prednisone achieved remission. 5 patients were rechallenged, 3 remained on low dose prednisone. Recurrent AIN was not observed after rechallenge.

Results:

Case	1	2	3	4	5	6
Age	59	63	66	44	56	53
Malignancy	Melanoma	Urothelial Ca	RCC	RCC	RCC	Melanoma
Anti-PD1	Pem	Niv	Niv	Niv/Ax	Ipi/Niv	Ipi/Niv
Time to AKI	5 weeks	3 days	5 months	6 weeks	4 weeks	10 days
Enlarged Kidneys	Yes	Yes	N/A	No	N/A	Yes
Aseptic Leukocyturia	Yes	N/A	Yes	Yes	No	Yes
Eosinophilia	none	13%	none	19%	none	none
Response to Steroids	Yes	N/A	Yes	Yes	Yes	Partial
Anti-PD1 resumed?	Yes	N/A	Yes	Yes	Yes	N/A

Clinical features and course of the 6 cases. Pem - pembrolizumab, Niv - nivolumab, Ax - axitinib, Ipi - ipilimumab, RCC - renal cell carcinoma.

Conclusions: The above demonstrates an association of PD-1 inhibitors with AIN. A kidney biopsy is the gold standard for diagnosis of AIN however this option is limited for patients with RCC, many whom are left with a solitary kidney after nephrectomy. Thus clinicians will need to feel comfortable making this diagnosis on clinical grounds to initiate therapy. Rechallenging patients with anti-PD1 therapy after resolution of AIN appears to be a safe option with close monitoring.

SA-PO665

Renal Involvement in Primary Sjögren's Syndrome Duvuru Geetha, Andreas Goules, Alan N. Baer. *Johns Hopkins Univ.*

Background: Renal disease is rare in Primary Sjögren's syndrome (PSS) and manifests as interstitial nephritis and glomerulonephritis. This single center study aims to describe the clinico-pathologic features and treatment outcome of renal disease in PSS.

Methods: PSS patients with renal disease were identified from PSS database retrospectively and clinical features, renal biopsy findings, treatment details and renal outcome were recorded.

Results: Twenty patients with a diagnosis of PSS and renal disease were included. Of the 20 patients, 14 had interstitial nephritis (IN), 3 had glomerulonephritis (GN) and 3 had both entities and were classified as having GN. IN occurred before the onset of glandular manifestations in 3 and after their onset in 11 patients (median SS duration 4.5 yrs, range: 0-9). In the IN group, 3 patients presented with chronic kidney disease (CKD), 4 with renal tubular acidosis (RTA), 2 with symptomatic hypokalemia, 4 with renal

colic and 1 with hematuria/proteinuria. Eight of 14 patients with IN received systemic immunosuppression (prednisone, mycophenolate mofetil, azathioprine, rituximab and anti-TNF agents) during the renal disease course but in 7 patients no beneficial effect was observed on renal function, hypokalemia and RTA. Six of 14 patients with IN developed CKD (median duration of renal disease 6 yrs, range: 1.5-17) while 5 of them preserved normal renal function during follow up (median follow up duration: 14 yrs, range: 5-20).GN occurred later during PSS course (median SS duration 8 yrs, range: 0-14.5) and 2 patients presented with CKD, 3 with proteinuria/hematuria and 1 with nephrotic proteinuria. In the GN group, renal biopsy findings revealed membranoproliferative (MPGN) (n=3), focal segmental glomerulosclerosis (n=1) and fibrillary glomerulopathy (n=1). All 3 MPGN patients had cryoglobulinemia and in 1 patient cryoglobulinemic MPGN was clinically diagnosed. All GN patients were treated with immunosuppressive therapy with stabilization or improvement of renal function in the 4 MPGN patients only.

Conclusions: IN occurs early in disease course in PSS and does not improve with systemic immunosuppression. On the contrary, GN appears as a late complication of PSS and a favorable treatment response is seen in those with MPGN pathology.

SA-PO666

Study on the Mechanism of Renal Tubular Proteinuria in Children with OCRL Gene Mutations

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Background: The oculocerebrorenal syndrome of Lowe (*OCRL*) gene is located on Xq25-26 and encodes a phosphatidyl inositol 4,5 bisphosphate ($PI(4,5)P_2$) phosphatase (OCRL-1). Mutations in this gene cause Lowe syndrome (LS) or type 2 Dent disease (T2D) in which low molecular weight (LMW) proteinuria is a cardinal finding. It is considered that megalin plays an important role in the development of renal tubular proteinuria. Megalin is expressed on the luminal side of proximal tubular cells (PTCs) and is involved in the reabsorption and metabolism of LMW proteins, such as α_1-microglobulin (AMG), β_2-microglobulin (BMG) and retinol-binding protein. Recently, it was revealed that two fractions of megalin are excreted into the urine: full-length megalin (C-megalin) and megalin ectodomain (A-megalin). This study was conducted to explore the mechanisms of LMW proteinuria in patients with *OCRL* mutations by determining the urinary megalin fractions.

Methods: Using spot urine samples obtained from five male patients with *OCRL* mutations (median age: 9 years), A- and C-megalin were measured with enzyme-linked immunosorbent assays and corrected for excreted creatinine. The data were compared with those of 50 control subjects.

Results: All patients demonstrated normal levels of urinary C-megalin. However, patients with *OCRL* mutations showed abnormally low levels of urinary A-megalin, except a 5-year-old boy, who was the youngest subject of the present study.

Conclusions: Considering the decreased excretion of urinary A-megalin in 4 out of 5 patients with *OCRL* mutations,LMW proteinuria may be caused by impairment of megalin recycling within the PTCs while a homologous enzyme, such as INPP5B, may compensate for the defective OCRL-1 function to some extent during early childhood.

SA-PO667

Persistent B Cell Depletion and Recurrent Neutropenia: A Rare Complication of Rituximab

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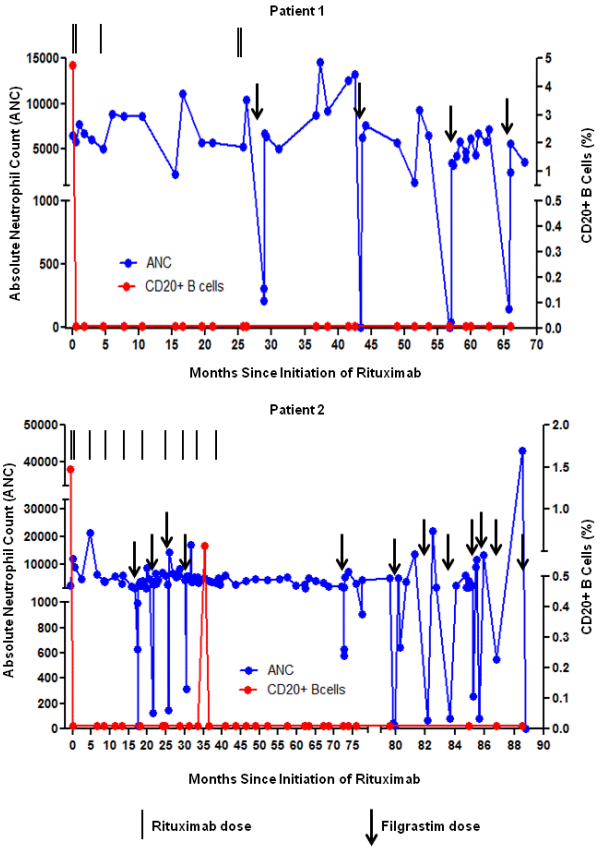
Background: B cell depletion with rituximab (RTX) is an important therapeutic strategy in the treatment of glomerular diseases. We describe a syndrome of persistent of B cell depletion and recurrent neutropenia (NTP) in 2 patients with ANCA vasculitis who received RTX for maintenance of remission.

Methods: We performed a retrospective analysis of clinical data in patients who had persistent B cell depletion for at least 2 years after their last RTX dose in conjunction with recurrent episodes of NTP.

Results: Two of 519 (0.3%) patients in our cohort receiving RTX for ANCA vasculitis or other glomerular diseases developed a syndrome of persistent B cell depletion and recurrent NTP.

Characteristic	Pt 1	Pt 2
Age at first RTX	27	60
Sex	F	F
ANCA serotype	MPO	MPO
Induction therapy	CYC, Pred	CYC, Pred
Prior maintenance therapy	Aza, Pred	Aza, Pred
Total RTX (gm)	5	10
Episodes of NTP	4	12

Patient 1 received 5, 1gm doses of RTX (horizontal lines) and continues to have B cell depletion 40.0 months after her last RTX dose. She developed 4 episodes of NTP, the last occurring 39.6 months after her last RTX dose. Each episode of NTP was treated successfully with filgrastim (arrows). Patient 2 received 10, 1 gm doses of RTX and had B cell depletion on her last check 51.4 months after her last RTX infusion. She developed 12 episodes of NTP, all treated with filgrastim. The last episode of NTP, occurring 51.6 months after her last RTX infusion, was complicated by a fatal infection.



Conclusions: RTX rarely leads to a syndrome of persistent B cell depletion and neutropenia that can be fatal. Clinicians treating glomerular diseases with RTX should be aware of this complication.

Funding: NIDDK Support

SA-PO668

Study of Risk Factors for Valproate-Induced Fanconi Syndrome

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Background: In recent years, there has been an increase in reports of proximal renal tubular impairment caused by valproate (VPA), VPA-induced Fanconi syndrome (FS). The etiology is presumed to be a malfunction in the mitochondria in the cells of the proximal renal tubules stemming from a carnitine deficiency caused by VPA though there remain many points to be addressed. Delayed diagnosis of VPA-induced FS may cause pathological bone fracture. In order to achieve early diagnosis, this study was conducted to elucidate the risk factors for development of VPA-induced FS.

Methods: The subjects were 91 cases (median age 16 years, interquartile range 11-26 years, 55 males) for whom detailed data could be obtained among 312 cases taking VPA to control seizures at our institution. Cases with a urinary BMG of at least 230 μg/L were classified in the FS group (15 cases), cases with less than 230 μg/L were in the non-FS group (76 cases), and the patient backgrounds and laboratory findings were compared between them.

Results: There was no difference in age, duration of administration and blood levels of VPA, or number of drugs used together between the two groups. However, the FS group had a significantly higher proportion of male children compared to the non-FS group (73% vs. 36%), and more bedridden cases (47% vs. 17%, p=0.029) and cases of total enteral nutrition (40% vs. 5%, p<0.001). Also, among the clinical test values, we found depressed serum uric acid levels (FS vs. non-FS median value: 3.1 vs. 5.3 mg/dl, p<0.001), serum phosphorus levels (3.4 vs. 4.1 mg/dl, p=0.26), and decreased serum free carnitine concentrations (27.7. vs. 44.2, p<0.01), and an elevated urinary BMG (287.0 vs. 102.0 μg/L, p<0.001).

Conclusions: Patients with being bedridden, having total enteral nutrition, a depressed serum uric acid level,and a decreased serum free carnitine concentration have higher risk for VPA-induced FS. In such cases, a carnitine preparation should be administered when using VPA, and it is necessary to switch from VPA to another anti-convulsant in cases with elevated urinary BMG suggesting renal tube impairment.

SA-PO669

Anti-Brush Border Antibody Disease in Humans: Clinicopathological Features and a Putative Common Autoantigen Christopher Patrick Larsen,[1] Paige A. Coles,[3] A. Bernard Collins,[2] Michael Merchant,[4] Jon B. Klein,[4] Ivy A. Rosales,[2] Robert B. Colvin,[2] Laurence H. Beck.[3] *[1]Arkana Laboratories, Little Rock, AR; [2]Massachusetts General Hospital, Boston, MA; [3]Boston Univ Medical Center, Boston, MA; [4]Univ of Louisville, Louisville, KY.*

Background: Primary tubulointerstitial disease caused by antibodies to proximal tubule brush border antigens (ABBA) with tubular basement membrane (TBM) immune complex deposition was described in experimental animals in the 1960s. Human cases with similar pathologic findings were reported in the early 1970s and the finding of serum anti-brush border antibodies (ABBA) was reported in 1981. More recently, a case report described a patient with recurrence of this disease in a transplant. Despite this long history, little is known about the disease.

Methods: Sera from patients with idiopathic TBM deposits on biopsy were screened by indirect IF (IIF) for the presence of ABBA in two renal biopsy laboratories. Sera from cases positive for ABBA were then tested by western blot (WB) and immunoprecipitation (IP) using human tubulointerstitial extract.

Results: We identified 8 ABBA+ cases by IIF. The patients (7M:1F) were 68-78 years old and had a mean serum Cr of 5.3 mg/dl at diagnosis. All renal biopsies showed acute tubular injury (ATI) and 3/8 also had interstitial inflammation. Granular IgG deposits were along the TBM, Bowman's capsule, and segmentally in the GBM in all cases. IgG4 was the predominant or co-dominant IgG subclass in 6/8. Despite treatment, none of the 6 patients with follow-up (mean 4.8 mo) had evidence of remission. Remarkably, WB revealed a common high molecular weight Ag detected by all 8 patients. IP and mass spectrometric analyses, as well as confocal co-localization studies using patient serum on normal kidney, have been performed to identify and characterize candidate Ags.

Conclusions: We present the largest case series to date of renal disease due to ABBA. This disease primarily affects elderly males and presents with acute renal failure. Pathologic findings include ATI with granular basement membrane IgG staining, often with minimal inflammation. WB and IP analysis suggests a common autoantigen.

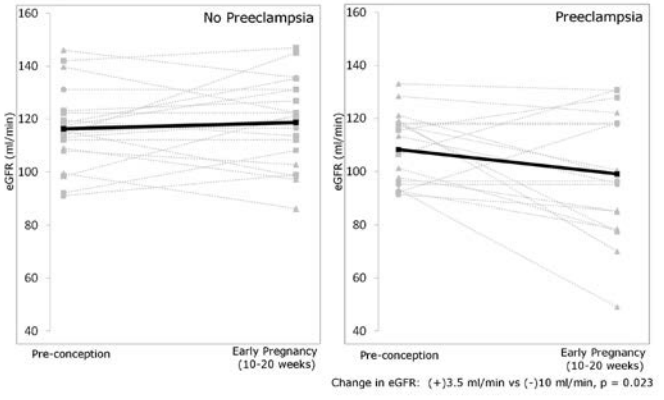
SA-PO670

Impaired Glomerular Hyperfiltration in Early Pregnancy and Adverse Pregnancy Outcomes Jessica Sheehan Tangren, Camille Elise Powe, Ravi I. Thadhani. *Massachusetts General Hospital, Boston, MA.*

Background: Glomerular hyperfiltration, an early marker of renal disease, is a normal phenomenon that begins early in pregnancy. The role of gestational hyperfiltration (GH) in maintaining a healthy pregnancy is unknown. We determined if impairments in gestational hyperfiltration in early pregnancy predict the development of adverse outcomes in women with early stage CKD.

Methods: We studied women with CKD stage I who delivered infants between 1998 and 2007 at the Massachusetts General Hospital. eGFR (CKD-EPI) was calculated at baseline (pre-conception) and in early pregnancy (<20 weeks gestation). Outcomes in women whose eGFR declined during early pregnancy (impaired GH, iGH, n=21) were compared to women whose eGFR increased during early pregnancy (preserved GH, pGH, n=22). We defined a composite adverse outcome of delivery by cesarean section, preeclampsia, small for gestational age offspring and progression to CKD III within 5 years of delivery.

Results: Baseline serum creatinine, age, blood pressure and BMI were similar between the groups. Women with iGH had higher rates of preeclampsia (62% vs 32%, p=0.048). In women with iGH, 90% met the composite adverse outcome versus 59% with pGH (p=0.02). In women who developed preeclampsia, the eGFR decreased on average in early pregnancy while in women who did not develop preeclampsia, the eGFR increased (Figure 1).



Conclusions: In women with CKD I, impaired hyperfiltration in early pregnancy is associated with poor maternal outcomes, including preeclampsia.

Funding: NIDDK Support

SA-PO671

Kidney Biopsy Has Significant Clinical Utility in Advanced Chronic Kidney Disease Amit J. Joshi, Ambarish Athavale, Radhika Jaiswal, Albert M. Osei, Peter D. Hart. *Dept of Nephrology, John H. Stroger Hospital of Cook County, Chicago, IL.*

Background: Kidney biopsy is not commonly performed in advanced CKD (ACKD) with eGFR of ≤ 30 ml/min due to perceived non-diagnostic utility and higher complication rate. Therefore, we assessed the clinical utility and safety of native kidney biopsy in patients with ACKD with negative ANA and ANCA serology.

Methods: Retrospective review of our biopsy database from Jan 2010-Dec 2015 identified 97 cases. Mean age was 46.5 (±12.7) years and women accounted for 42% of the study cohort. African Americans constituted 51%, Hispanics 31%, Caucasians 8%, and other races 10%. Mean S. Creatinine was 4.3 (±2.0) mg/dL with eGFR of 18.5(±7.1) ml/min. Mean proteinuria was 5.2 (±5.5) g/g of Cr and 62% cases had hematuria on urinalysis. Diabetes, paraproteinemia, HIV and hepatitis C antibody were present in 28.6%, 6.1 %, 19.4%, and 9.2% of cases respectively.

Results: Biopsy ascertained renal diagnosis in a majority (84.5%) of which the most common were IgAN, FSGS and Diabetic nephropathy. 10% had unsuspected diagnosis namely Fibrillary GN, Necrotizing GN, Amyloidosis and Sarcoidosis. 15.5% had advanced glomerulosclerosis and 48.5% had severe (>50%) tubulointerstitial disease. Based on biopsy findings, disease specific therapy was initiated in 37.1% and non-diabetic renal disease was identified in 46% of cases with diabetes.

Table 1: Biopsy diagnoses (number, %)

Advanced glomerulosclerosis: 15 (15.5%)	IgAN: 14 (14.4%)	FSGS: 13 (13.4%)
Diabetic nephropathy: 13 (13.4%)	Membranous nephropathy: 6 (6.1%)	Tubulointerstial nephritis: 6 (6.2%)
HIV associated nephropathy: 4 (4.1%)	Hypertensive nephrosclerosis: 4 (4.1%)	Membranoproliferative GN: 4 (4.1%)
Amyloidosis: 3 (3.1%)	Minimal change disease: 3 (3.1%)	Thrombotic microangiopathy: 3 (3.1%)
Necrotizing GN: 3 (3.1%)	Fibrillary glomerulonephritis (GN): 2 (2.1%)	Mesangioproliferative GN: 2 (2.1%)
Sarcoidosis: 2 (2.1%)		

Complications: Major (PRBC transfusion ±intervention): 1%, Minor (hematoma not requiring any intervention): 8 %.

Conclusions: Kidney biopsy remains an important diagnostic tool even in patients with advanced CKD. It guides clinical management and can be done safely.

SA-PO672

Renal Biopsy - Specimen Adequacy and Safety: A Performance Improvement (PI) Project Abhisekh Sinha Ray,[1] Sri G. Yarlagadda,[1] Neville Irani.[2] *[1]Nephrology and Hypertension, Kansas Univ Medical Center, Kansas City, KS; [2]Radiology, KUMC, Kansas City, KS.*

Background: Renal biopsy in this era is shared by nephrologists and interventional radiologists (IR). Available literature suggests wide variability in bleeding risk (0.5-7%) and specimen adequacy. Increasing needle size has been attempted to improve adequacy of biopsy sample, however, bleeding risk increases. There is also concern for significant inter-operator variability. We therefore undertook a PI project to assess sample adequacy, bleeding risk, analyze risk factors and effect of change in needle size.

Methods: We collected data from 454 patients who had renal biopsy from 2014 to April 2016. All patients were observed for 24hrs to monitor for complication. Bleeding complication was defined as radiologic demonstration of hematoma, need for transfusion or embolization by IR. Biopsy sample was considered adequate if it had at least 10 glomeruli. In May 2014, we downsized biopsy needle to 18gauze and in March 2015, we restricted operator pool to find any effect of these interventions on outcome measures.

Results: We found thrombocytopenia (<100,000/cmm, Odds ratio [OR] 5.28), hemoglobin <8.5g/dl (OR 5.24), advanced renal failure (eGFR <30ml/kg/min, OR 3.99) and INR >1.5 (OR 3.2) are associated with increased bleeding; however, hypertension and type of kidney biopsy (native or transplant) didn't significantly alter the risk. Decreasing needle size didn't affect sample adequacy or bleeding risk. There is no significant variability observed between trainee physicians and experienced operators. Limited number of biopsies performed in our institution might have culminated into significant monthly variation in outcome without any identifiable factor and also restricted ability to detect whether specific etiologies leading to renal dysfunction contribute to any increase in post-procedural bleeding risk.

Conclusions: In our tertiary care center with medium volume of renal biopsies done, sample adequacy was not impacted by decreasing needle size. We didn't find any significant inter-operator variability. Patients with anemia, thrombocytopenia, advanced renal failure or coagulopathy are at significantly increased risk for procedural bleed.

SA-PO673

Successful Use of Renal Denervation (RDN) in Patients with Loin Pain Hematuria Syndrome- The Prairie LPHS Study Bhanu Prasad, Jennifer St. Onge, Shelley Giebel. *Nephrology, Regina Qu Appelle Health Region, Regina, SK, Canada.*

Background: Loin pain hematuria syndrome (LPHS) is a painful and incapacitating condition that typically afflicts young women. Attempts to relieve pain by dorsal rhizotomy, renal capsulectomy, and thoracolumbar sympathectomy have been unsuccessful. Surgical transection of the renal nerves by auto transplantation of the kidney leads to recurrence of pain after variable periods. Bilateral nephrectomy has been associated with complete pain relief but at the burden of ongoing need of renal replacement therapy.

Methods: Four patients with LPHS from southern Saskatchewan, with LPHS and intractable pain unresponsive to conservative measures underwent endovascular ablation of the renal nerves between July and November 2015 using the Vessix™ renal denervation system. The number and frequency of pain medications, and responses to the EQ-5D, McGill Pain Questionnaire, Geriatric Depression Score, Short Form Health Survey (SF-36), and Oswestry Disability Index were measured at baseline and at 3 and 6 months post-procedure to evaluate changes in pain, disability, quality of life and mood. Renal denervation (RDN) was performed after seeking Health Canada approval for this indication.

Results: There were significant improvements in pain (McGill Pain Questionnaire), disability (Oswestry disability index), and quality of life (EQ-5D and SF-36) from baseline to 6-months post-procedure. Two out of four patients were off all pain medications; the remaining two had a 75% reduction in the dose of pain medications.

Conclusions: We present four successful cases of RDN, a novel treatment of intractable pain in patients with LPHS. Reduction in pain was accompanied by considerable improvement in functionality and quality of life. All the patients in our study post-RDN, reported less absenteeism, remarkably fewer trips to ER and hospitalizations, relief of caregiver burden, and considerable reduction in number, dose and frequency of pain medications.These results suggest that percutaneous catheter based renal nerve ablation with radiofrequency energy is a safe and rapid treatment option that should be considered in all patients with LPHS.

SA-PO674

Impact of Percutaneous Endovascular Ablation of the Renal Nerves (RDN) on Central Blood Pressures in Patients with Chronic Kidney Disease (CKD): Prairie RDN Study Bhanu Prasad,[1] Jennifer St.Onge.[2] *[1]Nephrology, Regina Qu Appelle Health Region, Regina, SK, Canada; [2]Research and Performance Support, Regina Qu Apelle Health Region, Regina, SK, Canada.*

Background: Central aortic blood pressures (CBP) in comparison to brachial blood pressures more accurately reflect loading of the left ventricular myocardium, coronary arteries, and cerebral vasculature and thereby, better relate to cardiovascular target organ damage and to cardiovascular events.We investigated the impact of minimally invasive catheter based renal denervation (RDN) on central blood pressures and vascular stiffness in patients with stage 3 and 4 CKD with resistant hypertension.

Methods: Twenty-six patients with resistant hypertension from our multidisciplinary chronic kidney disease (CKD) clinic underwent either unilateral or bilateral RDN from February 2013 to August 2014. CBP, 24-hour ambulatory blood pressures, average of 6 office BP readings on BP Tru, along with carotid-femoral pulse wave velocities were measured at 3,6,12 and18 months. Radial arterial pressure waveforms were obtained by applanation tonometry using a solid transducer; central arterial waveforms and pressures were calculated by the use of the SphygmoCor device.

Results: Baseline (mean ± standard deviation) central systolic/diastolic blood pressures (mm Hg) were 131±22.57/ 77.09±16.36 and at 18 months were 120.16±14.67/ 70.58±14.35 respectively. In contrast the 24-hr ambulatory blood pressures (mm Hg) at baseline and 18 month were 142.8±16.27/65.63± 11.59 and 145.34± 13.99/66.53±13.36. Central pulse pressures (mm Hg) at baseline and 18-month post-RDN were 55.59±25.17 and 49.54±20.07 respectively. Similarly, the augmentation pressures at baseline and 18 month were: 14.09±11.35 and 11.32±11.52 mm Hg respectively. Augmentation index (%) was 22.86±11.98 at baseline and 18.45±12.63 at 18 months. Pulse wave velocity was 15.95 (14.15) at baseline and 15.03 (4.93) at 18 months.

Conclusions: We conclude that RDN is associated with modest improvement in aortic pulse pressure, augmentation pressure, and augmentation index relative to the brachial ambulatory blood pressures in patients with stage III and IV CKD. There was no negative impact on renal status post procedure.

SA-PO675

Tyrosine Kinase Inhibitor-Induced Hypertension in Patients Diagnosed with Renal Cell Carcinoma Is Associated with Decreased Urinary Excretion of Nitrogen Oxide Metabolites Kirsten Madsen,[1,2] Anne Robdrup Tinning,[1] Niels Viggo Jensen,[3] Lars Bastholt,[3] Boye Jensen.[1] *[1]Dept of Cardiovascular and Renal Research, Univ of Southern Denmark, Odense, Denmark; [2]Dept of Pathology, Odense Univ Hospital, Odense, Denmark; [3]Dept of Oncology, Odense Univ Hospital, Odense, Denmark.*

Background: Tyrosine kinase inhibitors (TKIs) are important in the pharmacological treatment of several malignant diseases. A common side effect is hypertension due to a yet unknown mechanism. Most TKIs target the receptors of VEGF, a vascular growth factor known to stimulate NO production. We hypothesize that TKIs increase blood pressure by impaired renal NO bioavailability.

Methods: 22 patients (11 males and 11 females) diagnosed with renal cell carcinoma (RCC) undergoing treatment with the TKI pazopanib were included in the study. Home blood pressure measurements were recorded and blood and urine samples collected at baseline and at two follow-up visits (FU) 4 and 8 weeks after initiation of treatment.

Results: At baseline, mean systolic and diastolic blood pressure was 137±3/76±2 mmHg. After 4 weeks of treatment, both systolic and diastolic blood pressure was significantly increased compared to baseline (150±4/89±2 mmHg, P<0.05) whereas after 8 weeks, systolic but not diastolic blood pressure had returned to baseline values (137±4/81±2 mmHg). Five patients initiated or intensified ongoing antihypertensive treatment before 1st FU and additionally 4 patients before 2nd FU. No changes in eGFR were observed during treatment. Urinary protein/creatinine ratio increased significantly after 4 weeks compared to baseline. A transient decrease in plasma NO metabolites (NOx) was seen at 1st FU, whereas plasma cGMP was significantly reduced at both FU visits. Moreover, a significant reduction in both urinary NOx and cGMP excretion normalized to creatinine was seen at both 1st and 2nd FU.

Conclusions: Pazopanib treatment in RCC patients leads to hypertension associated with decreased urinary excretion of NO metabolites suggesting an important role of reduced renal NO bioavailability in TKI-induced hypertension.

Funding: Private Foundation Support

SA-PO676

Can We Prevent Recurrent Pre-Term Preeclampsia? Line Malha, Franco B. Mueller, Phyllis August. *Div of Nephrology and Hypertension, Weill Cornell Medicine, New York, NY.*

Background: Preterm preeclampsia (PTPE) (< 34 weeks of gestation) is a life-threatening complication of pregnancy with a high recurrence rate (20-60%). Low dose aspirin (ASA) may prevent recurrence, and some trials suggest that low molecular weight heparin (LMWH) and ASA together is more effective but results are inconclusive. We report the recurrence rate of PE in women with prior PTPE and the impact of therapy on fetal birth weight (BW) and gestational age at delivery (GA).

Methods: We prospectively followed 41 women with PTPE in a prior pregnancy throughout 53 subsequent pregnancies. Women were screened for genetic and acquired thrombophilias and treated with either ASA or LMWH and ASA as determined by treating physicians. Maternal and fetal outcomes in subsequent pregnancies were ascertained including preeclampsia (PE), GA, and BW.

Results: The mean (±SD) age of the women was 36±5 years at the time of their subsequent pregnancy, and BMI was 25.6±5.4kg/m^2. 66% were white, 5% black and 15% Hispanic. Genetic thrombophilias were detected in 91% and acquired thrombophilias in 36%. Thirteen women (25%) were not treated with ASA or LMWH, 12 (23%) received ASA alone, and 27 (52%) received LMWH±ASA. PE recurred in 6 pregnancies (11%) and PTPE in 5 (9%). In subsequent pregnancies BW was higher (1473±743 grams prior pregnancy vs. 2880±778 grams in the subsequent pregnancies, p<0.001), and GA at delivery was later (29±4 weeks vs. 36±4 weeks, p<0.001). PE recurrence was numerically higher in the untreated group compared to those treated with ASA alone, or LMWH ±ASA (3/13 vs., 1/12 or 2/27). BW and GA increased similarly in subsequent pregnancies in all groups although women treated with LMWH±ASA had a greater increase in GA (8.8 vs 4.4 weeks, p=0.021).

Conclusions: The risk of recurrent PE or PTPE in women with prior PTPE was lower than reported in prior studies. BW and GA at delivery were significantly better in subsequent pregnancies. We found a trend towards a decreased incidence of PE and greater prolongation of pregnancy in those treated with LMWH±ASA compared to no treatment or ASA alone. We propose an appropriately designed clinical trial to determine the benefits/ risks of LMWH in women at risk for PTPE.

SA-PO677

Renin-Angiotensin-Aldosterone Profiles Predictive of Superimposed Preeclampsia Line Malha,[1] Cristina P. Sison,[2] Phyllis August.[1] *[1]Div of Nephrology and Hypertension, Weill Cornell Medicine, New York, NY; [2]Biostatistics Unit, Feinstein Inst for Medical Research, Northwell Health, Manhasset, NY.*

Background: Women with preexisting, or chronic hypertension (CHT) in pregnancy are at heightened risk for significant morbidity and death, primarily due to further elevations in blood pressure (BP) and development of superimposed preeclampsia (SPE). The pathophysiology for the elevations in BP remains unresolved.

Methods: We performed a prospective, longitudinal trial of 108 women with CHT and investigated the hypothesis that renin-angiotensin aldosterone profiles (RAAS) are associated with BP and SPE. We measured plasma renin activity (PRA), 24h urine Na, K and aldosterone (UA) at 12, 20, 28, and 36 weeks gestation and post-partum to investigate the association between these potentially pathophysiologic parameters and elevations in BP and SPE.

Results: Mean Arterial Pressure (MAP) was inversely related to PRA (r=-0.23, p<0.0001) and UA (r=-0.11, p=0.047). PRA and UA were significantly and positively associated with each other (r=0.5327, p<0.0001). Whereas PRA, and UA increased similarly in the first and second trimesters of pregnancy in women who did or did not develop SPE, the levels of both PRA (P=0.005) and UA (P=0.039) were significantly lower at 28 weeks in those who developed SPE compared to those who did not develop SPE. Interestingly, PRA was significantly lower in black women compared to other racial groups (p = 0.026 at 36 weeks and <0.003 at all other time points including postpartum) and UA was also significantly lower in black women at 36 weeks (p<0.03). After adjusting for MAP, urine

Na, urine K and serum K, both UA (0.0001) and race (P=0.0018) were significant predictors of PRA, while gestational age (P<.0001), PRA (P=0.0001), urine K (P<.0001) and urine Na(P=0.0005) were predictors of UA.

Conclusions: We conclude that renin-angiotensin- aldosterone profiles, ascertained in the third trimester of pregnancy, foretell the development of SPE in pregnant women with CHT. The RAAS profiles characterized in our investigation, in addition to serving as prognostic biomarkers, advance sodium retention as the primary mechanism for the elevation in BP in women with SPE.

SA-PO678

Pathway Analysis and Targeted Proteomics of Human Urinary Exosomal Proteins during Aldosterone Administration James M. Luther,[1] Kristie Rose,[2] Bing Zhang,[2] Kevin Schey.[2] *[1]Medicine, Vanderbilt Medical Center; [2]Vanderbilt Univ.*

Background: Exosomes are microvesicular bodies which are secreted from all cell types. Urinary exosomes contain >3,000 identifiable proteins which may provide insight into human disease, but their physiologic regulation remains undefined.

Methods: To test the hypothesis that the urinary proteome is dynamically regulated by exogenous hormones, we analyzed urine exosomes from 10 healthy subjects in a cross-over study after vehicle and aldosterone infusion (0.7 µg/kg/hr for 10 hrs) while on a standardized diet (160mmol Na/d for 5 days). Urinary exosomes were isolated by a two-step centrifugation method after reduction of the Tamm-Horsfall protein (uromodulin) with DTT. After isolation by ultracentrifugation, proteins underwent trypsin digestion and were subjected to MudPIT analysis. Statistical analysis was performed using a quasi-likelihood analysis with Benjamini & Hochberg correction for multiple comparisons. Validation was performed by targeted multiple-reaction-monitoring analysis for selected peptides quantified with stable-isotope peptide standards.

Results: Aldosterone infusion increased plasma aldosterone (55.9±5.5 vs 7.8±1.5 ng/dL; P<0.001) without acutely altering blood pressure or serum potassium. At a False Discovery Rate <0.05, 101 proteins were identified as up-regulated in the ALDO group, while 189 proteins were down-regulated. Gene ontology enrichment analysis of significantly altered proteins revealed that aldosterone altered small GTPase-mediated signal transduction, GTP binding, protein binding, and GTPase activity. In particular, aldosterone treatment altered pathways involving regulation of the actin cytoskeleton, which could be implicated in sodium channel trafficking. In separate validation samples, changes in RAC3 and TAO3 were verified using multiple-reaction monitoring mass spectrometry targeting with isotopic standards.

Conclusions: These data demonstrate that aldosterone dynamically alters the urinary exosome content in humans, including those involved in actin-cytoskeleton regulation. Furthermore, exosomal protein assays may provide a useful physiologic biomarkers in future clinical studies.

Funding: NIDDK Support

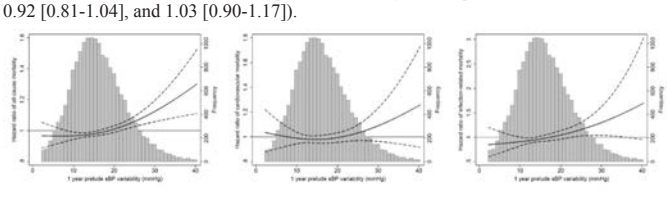
SA-PO679

Higher Pre-ESRD Visit-to-Visit Variability in Systolic Blood Pressure Is Associated with Increased Post-ESRD Mortality in Advanced CKD Patients Transitioning to Dialysis Keiichi Sumida,[1,2] Miklos Zsolt Molnar,[1] Praveen Kumar Potukuchi,[1] Fridtjof Thomas,[1] Jun Ling Lu,[1] Elani Streja,[3] Kunihiro Yamagata,[2] Kamyar Kalantar-Zadeh,[3] Csaba P. Kovesdy.[1,4] *[1]Univ of Tennessee Health Science Center, Memphis, TN; [2]Univ of Tsukuba, Ibaraki, Japan; [3]Univ of California, Irvine, CA; [4]VA Medical Center, Memphis, TN.*

Background: Higher systolic blood pressure visit-to-visit variability (SBV) is associated with higher mortality. However, little is known about the association of pre-ESRD SBV with outcomes after dialysis initiation.

Methods: We identified 17,994 US veterans with advanced CKD transitioning to dialysis between 10/2007-9/2011 who had at least 3 outpatient BP measurements to calculate SBV using the intraindividual standard deviation (SD) of all SBP values during the last 1 year before dialysis initiation. Associations of SD quartiles (<11.6, 11.6-15.6, 15.7-20.3, ≥20.4 mmHg) with post-ESRD all-cause and cause-specific mortality were examined using Cox (for all-cause) and competing risk (for cause-specific mortality) regressions and cubic splines with adjustment for potential confounders.

Results: Greater SBV was linearly associated with higher all-cause and infection-related mortality, and showed a U-shaped association with CV mortality (Figure). The multivariable adjusted hazard/subhazard ratios [95% CI] for the highest (vs. lowest) quartile of SBV were 1.11 [1.04-1.19] and 1.39 [1.08-1.79] for all-cause and infection related mortality, respectively. The middle quartiles of SBV were associated with the lowest CV mortality (subhazard ratios [95% CI] for SBV quartiles 2 through 4 (vs. quartile 1); 0.98 [0.87-1.11], 0.92 [0.81-1.04], and 1.03 [0.90-1.17]).



Conclusions: High pre-ESRD SBV is associated with increased post-ESRD mortality. The lowest SBV is associated with higher CV mortality, the mechanisms of which (e.g. autonomic dysfunction) need further elucidation.

Funding: NIDDK Support, VA Support

SA-PO680

Patterns of Blood Pressure Response during Intensive BP Lowering in the Secondary Prevention of Small Subcortical Strokes (SPS3) Trial Elaine Ku,[1] Rebecca Scherzer,[1] Michelle Odden,[2] Michael Shlipak,[1] Carole White,[3] Oscar Benavente,[3] Pablo E. Pergola,[4] Carmen A. Peralta.[1] *[1]UCSF; [2]Oregon State Univ; [3]SPS3 Coordinating Center; [4]Univ of Texas.*

Background: Whether there are identifiable,discrete patterns of concomitant responses of systolic (SBP) and diastolic (DBP) blood pressure during intensive BP lowering, and the associations of these patterns with risk of mortality, major vascular events (MVEs), and stroke are not well known.

Methods: We used an unsupervised, group-based cluster procedure (machine learning) to identify distinct patterns of BP change among 1,331 participants in the Secondary Prevention of Small Subcortical Strokes (SPS3) Trial previously randomized to intensive anti-hypertensive therapy (target SBP <130 mm Hg) after lacunar stroke.

Results: Among persons undergoing active, aggressive BP lowering, the cluster procedure partitioned subjects into three groups, according to BP response during the active intensification period: 1) mildly elevated baseline mean SBP and minimal visit-to-visit BP variability (mild reducers); 2) moderately elevated baseline mean SBP and moderate visit-to-visit BP variability (modest reducers); and 3) very elevated baseline mean SBP with very large visit-to-visit BP variability during intensification (large reducers). Compared to mild reducers, modest reducers had a higher adjusted risk of death, MVE, and stroke.

Outcome	Cluster	Event Rate per 1000 PY	Demographic-adjusted[a] HR (95% CI)	Multivariable-adjusted[b] HR (95% CI)
Mortality	1	11.2 (7.8, 16.0)	ref	ref
	2	20.0 (14.7, 27.1)	1.71 (1.07, 2.75), p=0.026	1.64 (1.01, 2.67), p=0.046
	3	27.3 (17.2, 43.3)	2.30 (1.25, 4.21), p=0.0071	2.30 (1.20, 4.42), p=0.012
MVE*	1	18.0 (13.3, 24.3)	ref	ref
	2	41.1 (32.6, 51.9)	2.28 (1.55, 3.34), p<.0001	2.13 (1.44, 3.15), p=0.0002
	3	28.0 (17.1, 45.7)	1.51 (0.82, 2.77), p=0.18	1.67 (0.89, 3.11), p=0.11
Stroke**	1	12.3 (8.5, 17.7)	ref	ref
	2	34.3 (26.6, 44.2)	2.76 (1.77, 4.31), p<.0001	2.63 (1.67, 4.13), p<.0001
	3	18.9 (10.5, 34.2)	1.45 (0.69, 3.05), p=0.32	1.62 (0.76, 3.46), p=0.21

[a]Model 1 = age, sex, race, and education level.
[b]Model 2 adjusts for model 1 plus cardiovascular risk factors (smoking, baseline cholesterol, baseline diabetes, baseline cardiovascular disease (congestive heart failure or coronary heart disease), body mass index).
[a,b] For MVE and stroke, Fine-Gray competing-risk analysis accounts for competing risk of death
* MVE = stroke, myocardial infarction, or vascular death
** Stroke = Ischemic or hemorrhagic stroke (primary study outcome)

Large reducers had the highest risk of death. Risk of MVE and stroke was also higher for large reducers compared with mild reducers, but this finding did not reach statistical significance.

Conclusions: Among persons with prior lacunar stroke, baseline SBP and large SBP and DBP variability during anti-hypertensive treatment intensification can identify discrete groups of persons at higher risk of adverse outcomes.

SA-PO681

Threshold Value of Blood Pressure before 20 Weeks' Gestation for the Prediction of Preeclampsia Development in Healthy Pregnant Women: A Cohort Study in Korea Sung Woo Lee,[1] Eunjeong Kang.[2] *[1]Internal Medicine, Eulji General Hospital, Seoul, Republic of Korea; [2]Internal Medicine, Seoul National Univ Hospital, Seoul, Republic of Korea.*

Background: Preeclampsia is a dangerous pregnancy-related complication. Blood pressure (BP) during early pregnancy could be a good marker for preeclampsia development. However, the threshold values have not been evaluated. Therefore, we performed the current cohort study.

Methods: Among 11,059 pregnant women who delivered a baby in a tertiary care hospital between 2003 and 2015, 3925 who had BP and dipstick proteinuria data, and did not have comorbidities were included. BP before 20 weeks' gestation was used as the main factor to determine preeclampsia development. For visual evaluation of non-linear associations, a restrictive cubic spline curve was used. For threshold evaluation, the area under the receiver operator curve was used with the Youden index.

Results: For the 3925 women, mean age was 32.6 years; 65.7% of women were nulliparous and 12.1% had a multifetal gestation. Mean systolic BP and diastolic BP before 20 weeks' gestation were 113.2 mm Hg and 63.9 mm Hg, respectively. The calculated threshold values were 118.3 mm Hg for systolic BP (sensitivity 0.50 and specificity 0.70) and 66.9 mm Hg for diastolic BP (sensitivity 0.53 and specificity 0.69). In a multivariate logistic regression analysis, systolic BP ≥118.3 mm Hg or diastolic BP ≥66.9 mm Hg was independently associated with preeclampsia development (adjusted odds ratio, 2.151; 95% confidence interval, 1.400 – 3.306; $P < 0.001$).

Conclusions: The threshold values of systolic BP and diastolic BP for preeclampsia development were 118.3 mm Hg and 66.9 mm Hg, respectively. Clinicians need to care for women more intensively if their BP is above these levels. Future prospective studies are needed to confirm our study results.

SA-PO682

Profiles of Systolic Blood Pressure Patterns in Patients Who Died in the First Year of Hemodialysis

Marta Reviriego-Mendoza,[1] Peiran Yu,[1] Dugan Maddux,[1] Danqing Xu,[1] Jochen G. Raimann,[2] Xiaoling Ye,[2] Hanjie Zhang,[2] John W. Larkin,[1] Jeroen Kooman,[3] Frank van der Sande,[3] Len A. Usvyat,[1] Peter Kotanko,[2,4] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, MA; [2]Renal Research Inst, NY; [3]Maastricht Univ Medical Center, Netherlands; [4]Icahn School of Medicine at Mount Sinai, NY.*

Background: Previous studies indicate that lower predialysis systolic blood pressure (SBP) is a risk factor for short term mortality in HD patients (pts) (Maddux D, et al., ASN 2014 & 2015). We aimed to understand the profiles of SBP in pts who died during the incident year of HD.

Methods: Data from 192,379 Fresenius Medical Care North America pts during 2008 to 2014 was analyzed. Pts were grouped according to mean SBPs at 0-15, 30-45, and 90-105 days after HD initiation. SBP groups included low (LSBP; <110mmHg), normal (NSBP; 110 to <140mmHg), high (HSBP; 140 to ≤180mmHg), and very high (VHSBP; >180mmHg) in each of the periods. The respective percent (%) mortality in each SBP group for periods of 0-29, 30-89, and 90-364 days from the start of HD was computed. The % mortality relative to NSBP was calculated to compare the relative difference in % mortality between SBP groups.

Results: SBP profiles of pts who died during the incident year of HD are shown in Figure 1. We observed two major findings: i) The 2nd and 3rd months after initiating HD were the timeframe where the % mortality is highest for all SBP groups, particularly for the LSBP group (Figure 1A). ii) When compared to NSBP, the relative difference in % mortality appears to be 2.8 to 4 times higher in patients with LSBP, and lowest in pts with HSBP and VHSBP (Figure 1B).

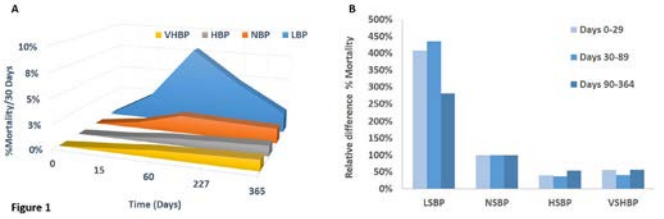


Figure 1

Conclusions: Our findings indicate that relative mortality rates are highest in pts with LSBP in the first year on HD, particularly during the first 90 days of HD. Pts with SBP 140 to ≤180mmHg appear to have lower relative mortality compared to other SBP groups.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

SA-PO683

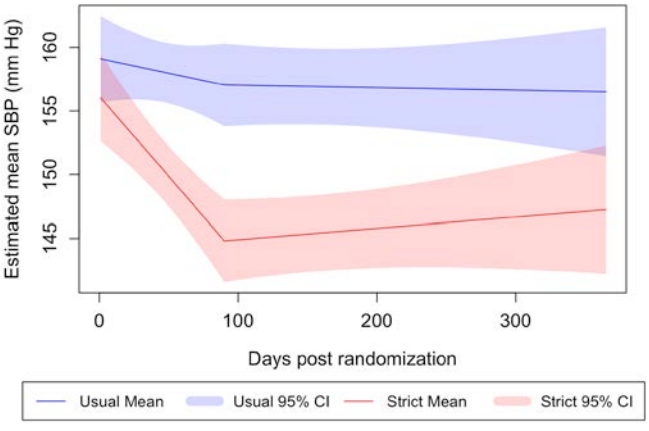
Results of the BID Pilot Study

D. Miskulin,[1,8] R. Schrader,[8] Jennifer J. Gassman,[2] Manisha Jhamb,[3] David W. Ploth,[4] Mahboob Rahman,[5] Lavinia A. Negrea,[5] Raymond Y. Kwong,[6] Philip Zager.[7,8] *[1]Tufts; [2]Cleveland Clinic; [3]UPMC; [4]MUSC; [5]CWRU; [6]BWH; [7]UNM; [8]DCI.*

Background: Optimal predialysis systolic blood pressure (SBP) for hemodialysis (HD) patients is unknown. The current KDOQI guideline is SBP <140 mm Hg. However, SPRINT results suggest that lower SBP may be beneficial. The BID Pilot assessed feasibility and safety of conducting a full-scale RCT of usual vs. strict SBP control.

Methods: We randomized 126 HD patients to a predialysis SBP of 110-140 (n=62) or 155-165 (n=64) mm Hg for 1 year. Primary outcomes were feasibility and safety. We estimated mean SBP in each arm throughout the study from a linear mixed model. We assessed the relationship of SBP to interdialytic weight gain (IDWG), expressed as percent estimated dry weight. We compared the frequency of serious adverse events (SAEs) across arms. The secondary outcome was change in left ventricular mass (LVM) by MRI.

Results: Over the last 9 months mean separation in SBP between arms was 12.9 mm Hg. Only 31.8% and 43.8% of patients in the strict and usual arms, respectively, sustained the target SBP.



There was a trend in each arm for IDWG to be higher in those with SBP above vs. in the respective targets. Overall and in each arm there were no statistically significant relationships between IDWG and SBP. The number of hospitalizations (H) and vascular access thromboses (T) was higher in the strict (H 85, T 20) vs. usual arm (H 47, T 7), both P<0.05. However, the number of patients with H and T was similar in the strict (H 29, T 10) and usual arms (H 25, T 7) (NS). In an intent-to-treat analysis the median change in LVM was similar in the strict (-0.8 g) vs. usual arm (1.5g) (NS). In an as-treated analysis, the median change in LVM was greater in the strict (-11.1 g) vs. usual (-1.2g) arm (p=0.03).

Conclusions: It is feasible and safe to conduct a full-scale RCT to explore the hypothesis that intensive control of SBP in hypertensive HD patients may improve clinical outcomes.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clininc, Inc. (DCI)

SA-PO684

Effect of the DASH Diet on Nocturnal Dipping and Nighttime Blood Pressure: Moderating Role of Race and Albumin Excretion Rate

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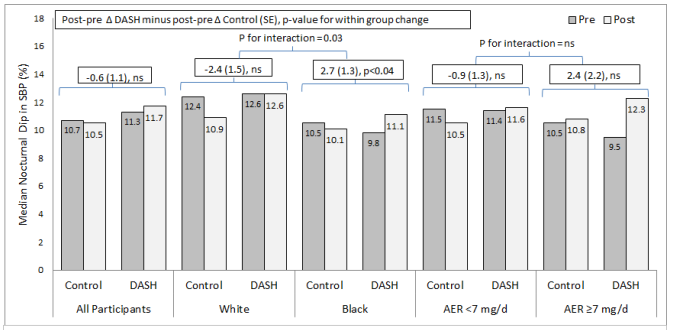
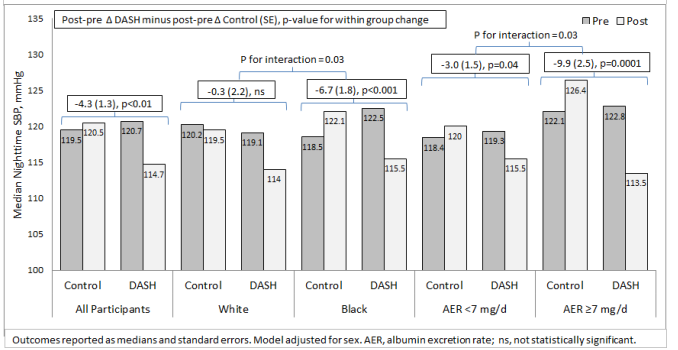
Background: Blunted nocturnal dip in blood pressure (BP) and elevated nighttime BP are independently associated with increased cardiovascular mortality. The effect of the DASH diet on nocturnal dip in BP is not known, nor is whether response differs by race or presence of low-grade albuminuria, which may be a marker for subclinical kidney disease.

Methods: DASH multicenter, randomized controlled feeding trial data were used to examine whether the DASH diet, compared to a control diet, enhances nocturnal dip in SBP and lowers nighttime SBP. A total of 202 pre-hypertensive and hypertensive adults randomized to 8 weeks of the DASH diet or control diet had pre- and post-intervention ambulatory BP data and pre-intervention 24-hour urine samples. Nocturnal change in SBP was defined as daytime mean SBP minus nighttime mean SBP expressed as a percentage of daytime mean SBP. We report a negative nocturnal change value as "dip". Median regression was used to compare pre-post changes in nocturnal dip in SBP and nighttime SBP between treatment arms. We also tested for interaction effects between diet, race (black versus white), and albumin excretion rate ([AER] ≥7 mg/day versus <7 mg/day) on changes in SBP.

Results: Mean age was 45±10 years, 51% were men, 59% were black, and 26% had AER ≥7 mg/day.



Outcomes reported as medians and standard errors. Model adjusted for baseline hypertension (yes/no). AER, albumin excretion rate; ns, not statistically significant.



Outcomes reported as medians and standard errors. Model adjusted for sex. AER, albumin excretion rate; ns, not statistically significant.

Conclusions: DASH enhanced nocturnal dip in SBP and reduced nighttime SBP in blacks but not whites and caused larger reductions in nighttime SBP in subjects with AER ≥7 mg/day than <7 mg/day. Our study suggests the DASH diet may improve nocturnal dipping and nighttime BP in blacks and adults with low-grade albuminuria.

Funding: NIDDK Support

SA-PO685

Antihypertensive Effects of Sparsentan, a Dual Angiotensin II and Endothelin Type A Receptor Antagonist Radko Komers,[1] Alvin Shih,[1] Rene Belder.[2] *[1]Retrophin, Inc., Cambridge, MA; [2]Sanofi, Bridgewater, NJ.*

Background: Two randomized, controlled, double-blind, Phase 2 studies evaluated the efficacy and safety of sparsentan as a treatment for Stage I and II hypertension.

Methods: Study 1 (NCT00522925) randomized 113 patients (1:1:1) to receive sparsentan 200 or 500 mg/day or placebo (PBO) for 4 weeks and compared mean change from baseline in 24-hour ambulatory systolic (SBP) and diastolic blood pressures (DBP). Study 2 (NCT00635232) randomized 261 patients (1:1:1:1:1) to receive sparsentan 200, 400, or 800 mg/day, irbesartan (IR) 300 mg/day, or PBO for 12 weeks to evaluate the change in sitting SBP and DBP. Both studies assessed the rates of treatment-emergent adverse events (TEAEs).

Results: In study 1, sparsentan-treated patients had greater reductions in SBP and DBP compared with PBO-treated patients (SBP: 200 mg, -12.2 mmHg; 500 mg, -14.8 mmHg PBO, -0.4 mmHg; $P<.001$). TEAEs were similar for all groups (200 mg, 21%; 500 mg, 26%; PBO, 25%). Edema was noted in 3% of PBO and 0% and 5% of sparsentan 200- and 500-mg treated patients. In study 2, sparsentan 200- and 400-mg doses resulted in greater reductions in BP than PBO ($P<.001$), and was similar to IR-treated patients. SBP and DBP reductions in patients on sparsentan 800-mg doses were greater than in patients on IR (SBP: -23.4 vs -10.7 mmHg; $P=.009$). The proportion of responders (BP <140/90 mmHg) on 400- and 800-mg doses (52% and 62%), but not the 200-mg dose (36%), were greater than in patients on IR (32%) and PBO (9%). TEAE rates were dose-dependent with sparsentan, but the TEAE rates at the 2 lower doses did not differ from PBO or IR. Edema occurred in 3%, 7%, and 11% of patients who received sparsentan 200, 400, and 800 mg, respectively, compared with 3% in IR-treated and 2% in PBO-treated patients, and resulted in 2 study withdrawals in the SP 800-mg group.

Conclusions: In the setting of Stage 1 and 2 hypertension, sparsentan reduced BP compared with PBO, and provided better BP control at 400- to 800-mg doses compared with IR. Both sparsentan 200 and 400 mg had a favorable safety profile, while sparsentan 800 mg showed an increased number of TEAEs including edema and early study withdrawals.

Funding: Pharmaceutical Company Support - Ligand Pharmaceuticals, Inc., funded this study and participated in the study design, study research, data collection, analysis, and interpretation of data. Retrophin, Inc., acquired sparsentan from Ligand and participated in the writing, reviewing, and approving this abstract for presentation

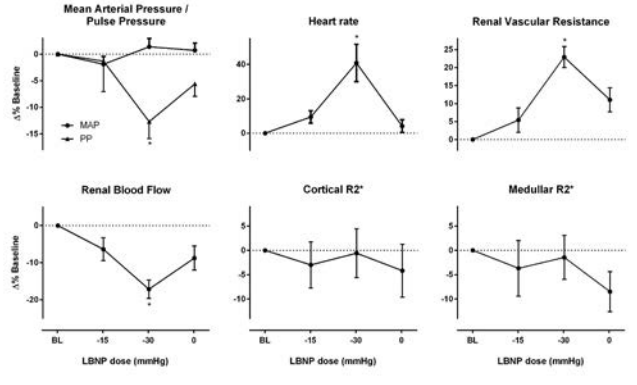
SA-PO686

Renal Blood Flow and Oxygenation during Systemic Sympathetic Activation by Lower Body Negative Pressure René van der Bel,[1] Jasper Verbree,[2] Oliver J. Gurney-Champion,[3] Erik Stroes,[1] Aart J. Nederveen,[3] C.T.P. (Paul) Krediet.[1] *[1]Internal Medicine, Academic Medical Center at the Univ of Amsterdam, Netherlands; [2]Physiology, Academic Medical Center at the Univ of Amsterdam, Netherlands; [3]Radiology, Academic Medical Center at the Univ of Amsterdam, Netherlands.*

Background: In kidney disease, renal hypoxia and systemic sympathetic activation are thought to augment each other, but direct observations in humans are lacking. To explore the relation between renal oxygenation and systemic sympathetic activity we studied the effects of Lower Body Negative Pressure (LBNP) on renal blood flow (RBF) and RO in healthy humans. LBNP induces systemic sympathetic activation, sodium retention and decreases GFR and renal plasma flow.

Methods: After a 15 min baseline, 8 healthy volunteers (age 19-31 years) were subjected to LBNP at -15 and -30 mmHg for 15 minutes per dose. RO and RBF were assessed by BOLD and phase contrast MRI, respectively. Off-line, R2* values were calculated for cortex and medulla, via mono-exponential fitting to multi-echo 2-dimensional fast field-echo data. RBF was calculated in the proximal renal artery after manual vessel segmentation.

Results: Mean arterial blood pressure (proxy of renal perfusion pressure) did not change, pulse pressure (proxy of stroke volume) decreased from 50±10 to 43±7 mmHg. Heart rate and renal vascular resistance increased dose dependently (by 28±15% and 23±8%, p<0.05, respectively), while RBF decreased from 9.6±1.9 to 7.9±1.6 ml/s(p=0.02). There was no change in cortical or medullary R2*.



Conclusions: These data do not support the widely held view that systemic sympathetic hyperactivity causes renal hypoxi a per se. Either renal oxygen demand and supply are equally suppressed during sympathetic activation or the changes in RO are below the detection threshold of BOLD MRI.

Funding: Private Foundation Support

SA-PO687

Non-Lateralizing Aldosterone-Producing Adenoma Benefited by Unilateral Adrenalectomy George Thomas. *Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH.*

Background: Current guidelines recommend adrenal vein sampling (AVS) in patients with primary aldosteronism (PA) to differentiate bilateral from unilateral disease when the patient desires surgical cure and there are no contraindications. There are no reports of non-lateralizing aldosterone producing adenomas (APA) that benefit from unilateral adrenalectomy. The objective of this study is to describe clinical outcomes of patients with APA who undergo unilateral adrenalectomy despite non-lateralization by AVS.

Methods: This is a single center, prospective, observational study. We included patients with PA who underwent dedicated adrenal CT scan followed by AVS. Sequential bilateral AVS was done with continuous ACTH (50 micrograms/hour) infusion. A selectivity index (adrenal vein cortisol/ peripheral vein cortisol) of 4:1 and cortisol-corrected aldosterone lateralization index of 5:1 were the criteria set for lateralization. We report the outcomes of 6 patients who underwent adrenalectomy despite non-lateralization. The primary outcome was decrease in PA to ≤ 10 ng/dl and serum potassium (K) increase to ≥ 3.8 mEq/L without treatment. The secondary outcome was blood pressure (BP) ≤ 140/90 mm Hg without treatment or the use of less anti-hypertensive medication.

Results: Of 50 patients with solitary APA who underwent AVS, 8 had lateralization index of less than 5:1 (range: 0.43 to 3.03). Six with solitary adenomas ranging between 1.9 to 3.0 cm chose surgery despite non-lateralization. Post-operatively, PA decreased from an average of 62 ng/dl (range: 37 to 145) to 5.5 ng/dl (range: 2.3 to 9.1). Serum K increased to ≥ 3.8 meq/l without treatment in all patients. BP significantly decreased from a mean of 137/86 mm Hg to 119/76 mm Hg. Anti-hypertensive medication use decreased from a mean of 4.5 to 0.8.

Conclusions: The management of a solitary APA should not rely solely on findings of AVS but should include patient preference and the clinical setting (drug intolerance, resistant hypertension, hypokalemia leading to adverse cardiovascular events, or progressive renal disease). We show that patients with biochemical evidence of PA and clear-cut solitary APA on imaging benefit from unilateral adrenalectomy irrespective of findings of AVS.

SA-PO688

Racial Differences in Nocturnal Dipping Status in Diabetic Kidney Disease (DKD): Results from the STOP-DKD Study Leah L. Zullig,[1] Clarissa Jonas Diamantidis,[1] Manjushri V. Bhapkar,[2] Huiman Barnhart,[3] Megan M. Oakes,[1] Hayden Bosworth,[1] Uptal D. Patel.[1] *[1]Dept of Medicine, Duke Univ, Durham, NC; [2]Duke Clinical Research Inst, Duke Univ, Durham, NC; [3]Biostatistics & Bioinformatics, Duke Univ, Durham, NC.*

Background: Abnormal nocturnal blood pressure (BP) dipping is associated with higher cardiovascular risk, progressive kidney disease and death, potentially contributing to racial differences in outcomes. We sought to determine the association of race with dipping status among STOP-DKD study participants with type 2 diabetes and kidney disease (DKD).

Methods: STOP-DKD is a randomized, controlled trial evaluating the impact of a multifactorial clinical pharmacist-administered telehealth intervention on progression of DKD compared to an education control in patients with DKD recruited from Duke Primary Care clinics in 2015. Eligible patients had: annual averaged glomerular filtration rates (eGFR) > 45 mL/min/1.73m^2; evidence of nephropathy and/or retinopathy; and uncontrolled hypertension (HTN; > 140/90 mmHg). 24-hour ambulatory blood pressure monitoring (ABPM) values were collected at baseline, and analyzed by wake and sleep-periods. Nocturnal non-dipping was defined as a fall in sleep-period BP of ≥0% to <10% compared to waking BP.

Results: Of 281 participants, 117 (42%) completed 24-hour ABPM, about half of whom were black (n=56, 48%). Participants were predominantly male (n=64, 55%), married (n=73, 63%), and had completed high school (n=106, 91%). Average daytime and nocturnal DBPs were higher in blacks than whites (76.8 vs.73.4, p=0.02; and 71.7 vs. 66.8, p=0.004, respectively) while the average SBPs did not differ significantly. Black participants were less likely to have a ≥10% SBP dip than whites (15.1% vs. 31.5% respectively; p=0.067). Males and black patients were less likely to have a ≥10% dip in diastolic BP (31.3% vs. 57.4% for male vs. female, p=0.007; 30.2% vs. 53.7% for blacks vs. whites, p=0.019).

Conclusions: Non-dipping status is more common among black patients with DKD than their white counterparts. Interventions targeting BP in black patients may minimize such differences, and in turn, improve outcomes in this high-risk group.

Funding: NIDDK Support, VA Support

SA-PO689

Lateralization Index of Adrenal Vein Sampling Is a Predictor of Blood Pressure Improvement after Adrenalectomy for Primary Aldosteronism

Miho Tagawa,[1] Muriel Ghosn,[2] Scott O. Trerotola,[2] Heather Wachtel,[2] Debbie L. Cohen,[2] Raymond R. Townsend.[2] *[1]Nara Medical Univ; [2]Univ of Pennsylvania.*

Background: Adrenal Vein sampling (AVS) is recommended in primary aldosteronism (PA) to determine if lateralization occurs. Lateralization index (LI) > 4 is considered a positive result. It is unclear however what LI value predicts BP response.

Methods: This is a retrospective observational study on patients who underwent AVS and adrenalectomy for PA at Penn from 1997 to 2015. Improvement of BP was defined as reduction in systolic BP (SBP)>10mmHg with same number of antihypertensives, or SBP within 10mmHg with reduction in number of antihypertensives. Data were analyzed using multivariable logistic regression analyses.

Results: There were 169 patients who underwent AVS and adrenalectomy. Mean age was 53 (46-60) years, 64 % were male, 34% were African American, 55 % were Caucasian. LI of AVS was 11.9 (8.1-22.2) and 8.0 (5.1-18.5) for patients with or without BP improvement at 0-6 months, respectively (p=0.16). After adjustment for known predictors of BP improvement after adrenalectomy, LI >9 was independently associated with BP improvement at 0-6 months.

	OR for improvement in BP	95 % (CI)
Age	1.0 7	0.94-1.22
Male sex	4.48	0.40-49.9
Duration of hypertension (years)	0.79	0.65-0.96
Body mass index	0.80	0.66-0.98
estimated glomerular filtration rate	0.95	0.89-1.00
Family history of hypertension	3.56	0.45-28.3
Plasma aldosterone concentration/plasma renin activity	1.00	1.00-1.01
Systolic blood pressure	1.14	1.03-1.27
Diastolic blood pressure	0.91	0.81-1.01
African American	1.65	0.17-16.4
LI > 9	17.2	1.30-229.5

At 12-24 months, LI>9 was associated with modest tendency for BP improvement [OR (95% CI) was 5.7 (0.3-96.6)].

Conclusions: LI >9 was independently associated with improvement in BP at 0-6 months after adrenalectomy. LI > 9 may be a useful predictor for short-term improvement in BP after adrenalectomy for PA.

SA-PO690

Split Renal Function in Patients with Unilateral Atherosclerotic Renal Artery Stenosis - Effect of Renal Angioplasty

Aso Saeed, Elzbieta Nowakowska-Fortuna, Gert Jensen, Hans V. Herlitz, Gregor S. Guron. *Sahlgrenska Univ Hospital/ Sahlgrenska Academy, Dept of Molecular and Clinical Medicine, Inst of Medicine/Nephrology, Gothenburg, Sweden.*

Background: The objective of the study i to evaluate the effect of percutaneous transluminal renal angioplasty (PTRA) on split renal function (SRF) in patients with unilateral atherosclerotic renal artery stenosis (ARAS).

Methods: Retrospective analysis of all consecutively examined patients at our Centre with significant ARAS undergoing PTRA during 2002-2007. A significant ARAS was defined as a lesion with a trans-stenotic mean arterial pressure gradient (MAPG) of at least 10 mmHg or a diameter stenosis ≥ 60%.Ambulatory (24 h) SBP (ASBP) and DBP (ADBP) and calculated SRF using ^{99m}Tc-DTPA renal scintigraphy were evaluated before (baseline) and 4 weeks after PTRA.

Results: ASBP and ADBP were significantly lower 4 weeks after PTRA compared to baseline levels (Table 1). Although total estimated glomerular filtration rate (eGFR, 4-variable MDRD) had not changed by PTRA, analysis of SRF showed significantly increased eGFR in stenotic kidneys and comparable decreases in eGFR in non-stenotic kidneys 4 weeks after PTRA (Table 1).

Table 1. Effect of PTRA on ambulatory blood pressure, kidney function and split renal function.

	Baseline (n=52)	4 weeks after PTRA (n=52)	P-value
ASBP, mm Hg	145±14	138±16	0.005
ADBP, mm Hg	80±9	77±11	0.005
S-Creatinine, µmol/l	116±39	117±41	0.81
eGFR (MDRD) ml/min/1.73m2	57±21	58±21	0.77
% stenotic renal function	38±19	41±19	<0.0001
% non-stenotic renal function	62±19	59±19	<0.0001
eGFR stenotic kidney, ml/min/1.73m2	22±14	26±17	0.004
eGFR non-stenotic kidney, ml/min/1.73m2	37±16	34±15	0.026

Conclusions: In patients with unilateral ARAS, PTRA significantly improved eGFR in stenotic kidneys and decreased filtration in contralateral, non-stenotic kidneys. These potentially beneficial effects may not be apparent when total kidney function remains stable. The clinical significance of these findings needs to be evaluated further.

Funding: Government Support - Non-U.S.

SA-PO691

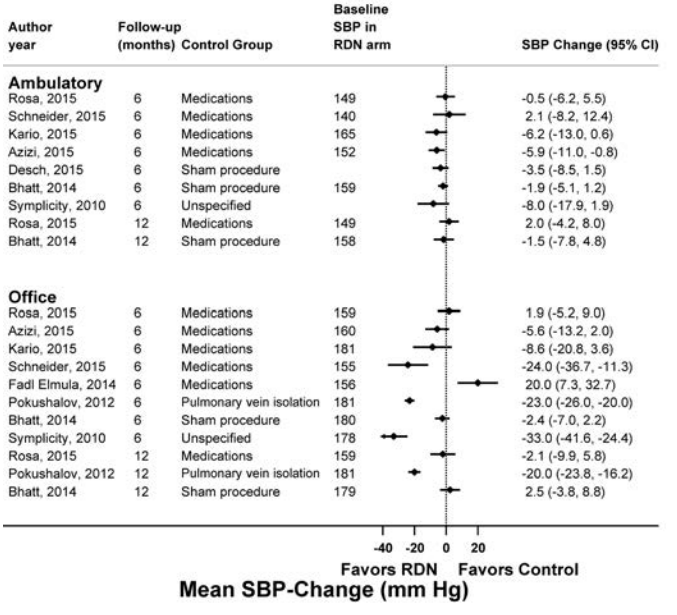
Renal Denervation for Resistant Hypertension: A Systematic Review

Tariq Shafi, Matt Chacko, Zackary Berger, Lisa M. Wilson, Jessica L. Gayleard, Eric B. Bass, Stephen M. Sozio. *Johns Hopkins Univ.*

Background: Renal denervation (RDN) may reduce blood pressure (BP) in patients with resistant hypertension, but data on its effectiveness are conflicting.

Methods: ***Studies:*** We reviewed studies published through March 2016 if they reported a randomized controlled trial (RCT), a comparative cohort with ≥10 patients in each arm, or a non-comparative cohort with ≥25 patients. ***BP:*** We abstracted systolic BP (SBP) measured by 24-hour ambulatory BP monitoring (ABPM) or in office. ***Changes in SBP:*** Defined as follows: 1. Within-group change: the absolute change in SBP during follow-up within either the RDN or control/sham group. 2. Between-group change: within-group change in RDN group minus within-group change in control/sham group. ***Primary metric for effectiveness of RDN:*** Between-group SBP change measured by ABPM.

Results: We retrieved 1,233 unique citations. 83 studies met inclusion criteria; 9 (11%) were RCTs, 8 (10%) were comparative cohorts, and 66 (80%) were non-comparative cohorts. The between-group ABPM SBP change with RDN was small in RCTs (range: -8 mm Hg to +2 mm Hg). The within-group change in office SBP with RDN was higher in RCTs and comparative cohorts (-42 mm Hg to -8 mm Hg) as well as in non-comparative cohorts (range -58 mm Hg to +12 mm Hg), suggesting potential observer bias. Data were scant on clinical endpoints, such as hospitalization or death. Adverse effects were uncommon but potentially serious, and included hematomas, pseudoaneurysms, and renal artery interventions.



Conclusions: Renal denervation may lower systolic BP in patients with treatment-resistant hypertension, but the results are highly variable. Further research is needed to clarify its role in improving clinical outcomes. *Primary Funding Source:* Agency for Healthcare Research and Quality.

Funding: Other NIH Support - Agency for Healthcare Research and Quality

SA-PO692

Systolic Blood Pressure Patterns during the Incident Year of Hemodialysis

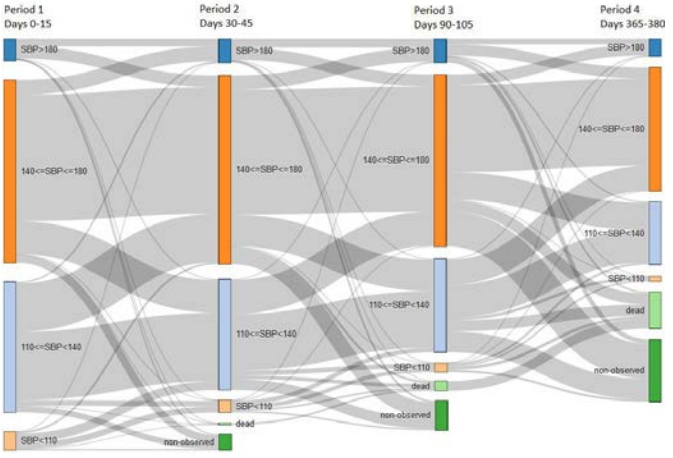
Peiran Yu,[1] Dugan Maddux,[1] Danqing Xu,[1] Jochen G. Raimann,[2] Marta Reviriego-Mendoza,[1] John W. Larkin,[1] Jeroen Kooman,[3] Frank van der Sande,[3] Len A. Usvyat,[1] Peter Kotanko,[2,4] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America; [2]Renal Research Inst; [3]Maastricht Univ Medical Center, Netherlands; [4]Icahn School of Medicine at Mount Sinai.*

Background: KDOQI guidelines recommend managing systolic blood pressure (SBP) in hemodialysis (HD) patients to achieve a pre-HD SBP <140/90mmHg and post-HD SBP <130/80mmHg. Despite this, previous studies suggest that lower pre-HD SBPs are associated with increased risks for mortality (Robinson BM, et al. Kidney Int. 2012 Sep;82(5):570-80). We aimed to understand SBP patterns in those who survived or died during the first year of HD.

Methods: Data from 192,379 incident HD patients during 2008 to 2014 was analyzed. Patients were grouped by SBP level at 0-15, 30-45, 90-105, and 365-380 days after the initiation of HD. SBP groups included low (LSBP; <110mmHg), normal (NSBP; 110 to

<140mmHg), high (HSBP; 140 to ≤180mmHg), and very high (VHSBP; >180mmHg). Changes in SBP groups were tracked in those who survived or died utilizing a Sankey diagram (river plot).

Results: We observed three key findings that are shown in Figure 1: i) there appeared to be the greatest number of patients in the HSBP group during the incident year, as compared to other SBP groups. ii) Compared to patients in the NSBP group, mortality rates appeared higher for patients in the LSBP group, and lowest for the HSBP and VHSBP groups. iii) The proportion of patients with fluctuations in SBP groups between time points appeared more noticeable in the LSBP and VHSBP groups, followed by patients in the NSBP group.



Conclusions: While the majority of patients in the first year on HD have high pre-HD SBP (140 to ≤180mmHg), our findings indicate considerable SBP fluctuations. The mortality appeared to be highest in patients with SBP <110 mmHg.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

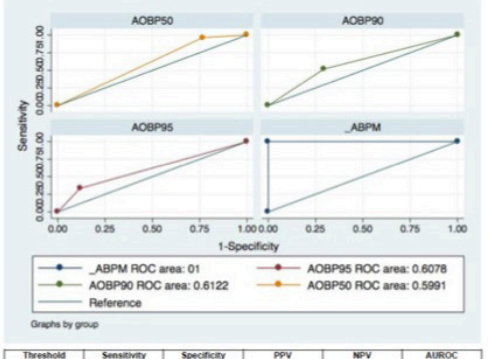
SA-PO693

Accuracy of Half Hour Automated Office Blood Pressure in the Diagnosis and Monitoring of Hypertension in Pediatrics Sally Anne Kellett, Samuel R. Crafter. *Nephrology Dept, Women's and Children's Hospital, Adelaide, SA, Australia.*

Background: This study was designed to determine the accuracy of half hour automated office blood pressure ($AOBP_{30}$) compared to 24 hour ambulatory blood pressure (BP) monitoring (ABPM), the gold standard test. Currently, the majority of patients referred to the Adelaide Women's & Children's Hospital for diagnosis or monitoring of hypertension (HTN), undergo $AOBP_{30}$ before ABPM. In adults, AOBP correlates with ABPM, but the relationship in pediatrics is unknown.

Methods: A single centre retrospective cohort study of 46 patients who received both BP tests between 2012-2014. Both tests classified patients as hypertensive or not based on the mean systolic and/or diastolic BP during the day and/or night, relative to the 95th centile. ABPM was conducted in accordance with AHA Guidelines using Meditech ABPM-04. For $AOBP_{30}$, BP was recorded at 3 minute intervals using the Welch Allyn Vital Signs Monitor 6000 series, and compared to Fourth Report normative data. The data was also re-analysed post-hoc using lower BP thresholds for $AOBP_{30}$ (90th and 50th centiles). Accuracy was assessed by sensitivity, specificity, positive and negative predictive values (PPV/NPV) and area under the receiver operating curve (AUROC).

Results: The sensitivity, specificity PPV, NPV and AUROC [95% confidence interval] were 32%, 89%, 82%, 46% and 0.6078 [0.49-0.721] respectively. 42% of false negatives on $AOBP_{30}$ were nocturnal HTN on ABPM.



Threshold	Sensitivity	Specificity	PPV	NPV	AUROC
95th centile	32%	89%	82%	46%	0.608
90th centile	50%	72%	74%	48%	0.612
50th centile	96%	22%	64%	80%	0.599

Conclusions: $AOBP_{30}$ in its current format shows poor accuracy compared with ABPM across a range of patient subgroups and diagnostic thresholds. Based on this study we recommend not using $AOBP_{30}$ as a screening test for the diagnosis and monitoring of hypertension outside of a study setting. Future studies could consider altering the format of the AOBP by increasing the frequency of measurements and/or including algorithms to deal with outlying data.

SA-PO694

Renal Artery and Parenchymal Changes after Renal Denervation Margreet F. Sanders,[1] Pieter Jan Van Doormaal,[2] Peter J. Blankestijn.[1] *[1]Dept of Nephrology & Hypertension, Univ Medical Center Utrecht, Utrecht, Netherlands; [2]Dept of Radiology, Univ Medical Center Utrecht, Utrecht, Netherlands.*

Background: Renal denervation (RDN) is a treatment for difficult to control hypertension, with the intent to disrupt sympathetic renal nerves and lower blood pressure. Relatively little is known about the incidence of renal injuries after RDN. The aim of this study was to investigate the incidence of renal artery and parenchymal changes after RDN with contrast enhanced magnetic resonance angiography (MRA).

Methods: The present study is an initiative of the European Network COordinating research on Renal Denervation (ENCOReD), a collaboration of hypertension expert centers performing RDN. Patients treated with endovascular radiofrequency RDN and with available MRA both before and after RDN were included. Pre and post scans were evaluated in random order by two independent, blinded radiologists. Primary outcome was the change in renal artery and parenchyma after RDN.

Results: Ninety-six patients were included. Indication for RDN was treatment resistant hypertension in all patients. After a median time of 366 days (IQR 185) post RDN, MRA showed a new stenosis (25-49% lumen reduction) in two patients. Furthermore, there was progression of pre-existing lumen reduction (from <25% to 50-74%) in one patient. In one of the three patients, we concluded from procedural angiography that ablations were applied near the location of the observed stenosis. The incidence of vascular changes 12 months after RDN was 3.1% (95% confidence interval -0.4; 6.7%). No other renal vascular or parenchymal changes were observed.

Conclusions: Twelve months after RDN, the incidence of new or progression of pre-existing vascular abnormalities is 3.1%, when assessed by MRA. Ablations were applied near the observed stenosis in only one patient. No renal parenchymal changes were found.

SA-PO695

Serum Irisin Levels and Urotensin II Levels Are Independent Determinant Factors of Blood Pressure in Patients with Preeclampsia Li Jie Zhang, Ai Hua Zhang. *Dept of Nephrology, Peking Univ Third Hospital, Beijing, China.*

Background: Irisin is a newly identified myokine secreted from skeletal muscle that can promote energy expenditure and alleviate insulin resitant. The aims of this study were to observe irisin level and urotensin II (UII) in serum and placenta in normal pregnant and preeclamptic women, investigate the relationship between serum irisin and UII, and their association with blood pressure.

Methods: A total of 71 pregnant subjects were recruited, including 32 healthy and 39 preeclamptic pregnant women. Serum irisin were measured by using enzyme-linked immunosorbent assay, and serum UII concentrations were measured by radioimmunoassay analysis. Expressions of fibronectin type III domain-containing protein 5 (FNDC5) (irisin precursor) and UII in placenta specimens were performed using immunohistochemistry (IHC) and western blot.

Results: There was no difference of serum irisin levels between preeclamptic patients with normal controls (157.78±21.96ng/ml vs. 159.88±16.94ng/ml, P>0.05). While serum UII was significantly higher in preeclamptic women than normal pregnancy (35.59±21.27pg/ml vs. 24.64±14.20pg/ml, P=0.041). FNDC5 and UII expressions were both upregulated in placental tissue of preeclamptic pregnancy by IHC and western blot analysis. In patients with preeclampsia, serum irisin was negatively associated with systolic and diastolic blood pressure (r=-0.340, P=0.005; r=-0.304, P=0.012), while serum UII was positively associated with systolic blood pressure (r=0.286, P=0.033). There was no relationship between serum UII and irisin level in normal pregnancy and preeclampsia patients.Serum irisin and UII, urinary protein level, BMI and serum creatinine are independent determinants of blood pressure in preeclampsia by multiple regression analysis.

Conclusions: Serum irisin and UII are independent determinants of blood pressure in preeclampsia.

SA-PO696

Comparison of Efficacy of Atenolol versus Lisinopril in Hypertensive Patients on Hemodialysis: A Randomized Control Trial Zara Nisar. *Nephrology, Khyber Teaching Hospital, Peshawar, KPK, Pakistan.*

Background: The Aim of this study is to establish the efficacy of these drugs in terms of cardiovascular events in Hypertensive patients on hemodialysis, and maintenance of Blood Pressure.

Methods: 50 patients were randomized to open-label Atenolol group and 50 patients were randomized to open-label Lisinopril group, each administered 2 times per week after dialysis. Blood pressure was monitored and recorded and was controlled to less than 140/90 mmHg with medications and sodium restriction. The primary outcome was to look for serious cardiovascular events within 12 months.

Results: Serious Cardiovascular events occurred in 20 patients who had 26 episodes in the Atenolol group as compared with the lisinopril group in which 35 patients nearly had 61 episodes. The serious cardiovascular events Myocardial Infarction, heart failure, ventricular arrhythmias and stroke were found in 12 patients in atenolol group with 16

episodes where as 21 patients in Lisinopril group with 26 episodes . Patients on Atenolol were found to recover better in hospital setup as compared to those on lisinopril in these cardiovascular events. The ambulatory 24-h BP was found to be similar in both groups. However, the monthly measured BP was found to be higher in Lisinopril group.

Conclusions: Atenolol has better coverage for BP maintenance and preventing Cardiovascular events in hemodialysis patients as compared to Lisinopril in our setup. Note: This study is done in Khyber teaching hopsital, Peshawar, Pakistan and here 2 times dialysis regime is followed.

SA-PO697

A Novel Method of Determining Adiposity and Its Relationship with Blood Pressure in the Modification of Diet in Renal Disease Study

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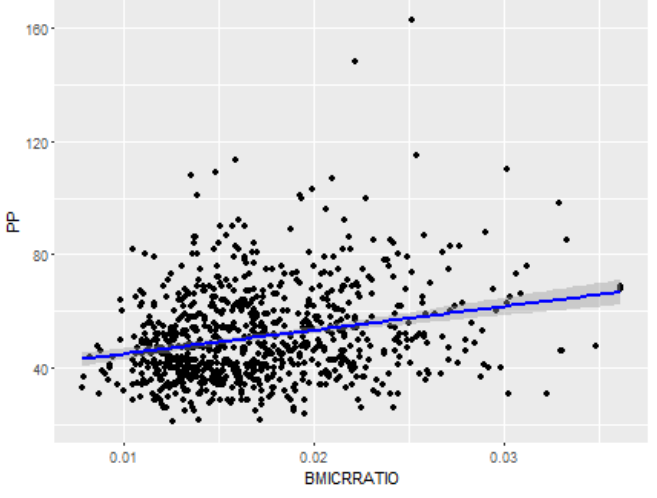
Background: Obesity is a known risk factor for hypertension and other diseases. The Body Mass Index (BMI, kg/m^2) is the most commonly used method of assessing obesity, yet this approach does not directly measure the quantity of fat. Because urinary creatinine excretion (UCrV) is believed to be a marker of skeletal muscle mass, we hypothesized that a ratio of the BMI to UCrV (BMI/UCrV) might provide a better index of adiposity. Specifically, we developed this ratio to attempt to emphasize non-muscular body size by normalizing for UCrV. We next chose to examine whether this ratio might correlate more strongly with systolic (SBP), diastolic (DBP) and pulse pressure (PP) within participants of the Modification of Diet in Renal Disease (MDRD) Study.

Methods: A retrospective analysis of the MDRD data identified 840 unique patients, ages 19-71. Data was extracted and imported into R Studio Correlational analysis between recorded components of blood pressure (Systolic, Diastolic, and Pulse Pressure) and the BMI/UCrV ratio was executed.

Results: We found that although systolic (SBP) and diastolic blood pressure (DBP) was predicted similarly by the BMI/UCrV ratio and BMI, the BMI/UCrV ratio predicted pulse pressure (PP) better than either BMI or UCrV alone.

	SBP	DBP	PP
BMI	0.0205**	0.0029	0.0139**
UCrV	0.0083	0.0334**	0.0242**
BMI/UCrV	0.0181**	0.0229**	0.0580**

Data shown as adjusted R2. * p<0.05, ** p<0.01.



Conclusions: We found that a novel indicator of adiposity, the BMI/UCrV ratio, correlated better with pulse pressure than either BMI or UCrV alone. If validated, this may be a useful clinical parameter to track and address.

Funding: Other NIH Support - NHLBI, Private Foundation Support, Clinical Revenue Support

SA-PO698

Dietary Sodium and Potassium Intake in a Referred Population with Difficult to Control Hypertension

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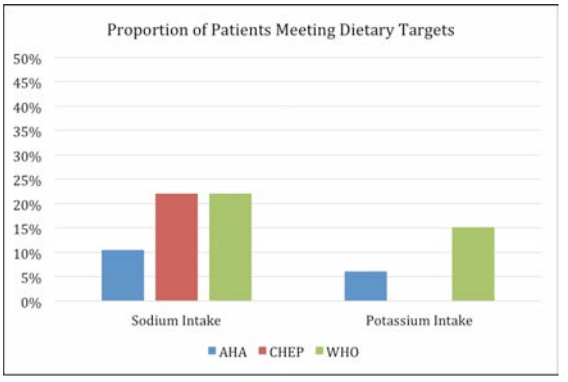
Background: High sodium intake and low potassium intake in the diet are important risk factors for the development and persistence of hypertension. NHANES and Health Canada data report higher than recommended consumption of sodium in the general population, but little data exists examining sodium intake in referred patients with difficult to control hypertension (DCHT). In this chart review, we report the dietary sodium and potassium intake in such a population.

Methods: This retrospective observational study included patients over 18 years of age referred to The Ottawa Hospital Renal Hypertension Clinic for management of DCHT. Patients were included if they had a documented 24 hour urinary electrolyte measurement, which was used to estimate daily sodium and potassium intake. We used current guidelines from American Heart Association (AHA, <65 mmol/day Na, >120 mmol/day K), Canadian Hypertension Education Program (CHEP, <87 mmol/day Na), and World Health Organization (WHO, <87 mmol/day Na; >90mmol/day K) for dietary goals.

Results: Of the 556 patients screened for inclusion, 95 (17.1%) had a 24 hour urinary sodium documented, with a mean intake of 142 mmol/day. 10 patients (10.5%) met the AHA target and 21 patients (22.1%) met the CHEP and WHO target for sodium intake. 33 patients had a 24 hour urinary potassium documented, with a mean of 60.7 mmol/day. 2 patients (6.1%) met the AHA target while 5 patients (15.2%) met the WHO target for potassium intake.



Conclusions: Even in a referred population of patients with DCHT, the dietary sodium intake is at an acceptable threshold for only a minority of patients, with the dietary potassium intake being acceptable for an even smaller proportion. While this may represent a selection bias, where poor intake results in higher blood pressure, it does represent a promising opportunity for intervention.

SA-PO699

Hypotension and Vasopressor Use during Elective Surgery in Patients Advised to Continue Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Medications on the Day of Surgery

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Background: Continued use of angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) on the day of surgery is associated with intraoperative hypotension requiring vasopressor therapy. Here we assess the efficacy of the recommendation to hold ACE-I/ARB medications in preventing intraoperative hypotension. We hypothesized that the recommendation to continue as well as the patient's report of having taken an ACE-I/ARB medication on the day of surgery would be associated with increased intraoperative hypotension and vasopressor use.

Methods: We retrospectively studied 629 patients aged 50-75 on ACE-I/ARB therapy undergoing elective surgery with general anesthesia. Independent variables were (a) whether the patient was *advised* to hold or continue their ACE-I/ARB medication and (b) whether the patient *reported* having taken an ACE-I/ARB medication on the day of surgery. We also assessed invasiveness of surgery. Outcomes included (a) intraoperative vasopressor use and (b) lowest systolic blood pressure (SBP) during surgery.

Results: The advice to hold ACE-I/ARB was associated with intraoperative severe hypotension (SBP <65) (OR: 0.0977; CI: 0.043 – 0.221). A patient's report of taking an ACE-I/ARB was associated with vasopressor use (OR:1.663; CI: 1.183 – 2.340) and moderate hypotension (SBP <85) (OR: 1.5; CI: 1.069 to 2.105). Both vasopressor use and intraoperative hypotension were associated with surgery invasiveness (P<0.001).

Conclusions: Severe hypotension is associated with the recommendation to hold ACE-I/ARB therapy; however, a patient's report of having held the treatment was not. As hypotension correlated to surgery invasiveness, we postulate that the recommendation to hold the medications was most commonly made to patients planned for invasive surgery and thus at higher risk for hypotension; this recommendation, however, was unable to prevent it.

SA-PO700

Neurocognitive Function in Children with Primary Hypertension

Marc Lande,[1] Donald Lee Batisky,[2] Juan C. Kupferman,[3] Joshua A. Samuels,[4] Stephen R. Hooper,[5] Bonita E. Falkner,[6] Shari R. Waldstein,[7] Peter G. Szilagyi,[8] Hongyue Wang,[1] Jennifer Staskiewicz,[1] Heather Adams.[1] *[1]Univ of Rochester; [2]Emory Univ; [3]Maimonides Medical Center; [4]Univ of Texas at Houston; [5]Univ of North Carolina; [6]Thomas Jefferson Univ; [7]Univ of Maryland, Baltimore County; [8]Univ of Califonia at Los Angeles.*

Background: While young hypertensive adults have lower neurocognitive test (NT) performance compared with normotensive controls, data on neurocognition in pediatric primary hypertension (HTN) are limited. Our objective was to compare NT performance of children with primary HTN to that of normotensive controls. We also explored potential interactions of HTN with disordered sleep, a highly comorbid condition.

Methods: 75 children (10–18 y) with newly diagnosed, untreated HTN and 75 frequency matched normotensive controls had baseline NT for a prospective multicenter study of cognition in primary HTN. Subjects completed tests of general intelligence, attention, memory, executive function, and processing speed. In addition to medical and demographic variables, parents completed the Pediatric Sleep Questionnaire (PSQ).

Results: By design, the HTN and control groups did not differ significantly in sex, maternal education, or obesity. They were also found to be similar in age, income, race, ethnicity, anxiety, depression, cholesterol, glucose, insulin, and C-reactive protein.

HTN subjects had higher PSQ scores (p=0.04). In multivariate analyses, HTN was independently associated with worse performance on the Rey Auditory Verbal Learning Test (p=0.012), CogState Groton Maze Learning Test delayed recall (p=0.002), Grooved Pegboard (p=0.045), and Wechsler Abbreviated Scales of Intelligence Vocabulary (p=0.016). Results also indicated a significant interaction between PSQ score and HTN (p=0.04), such that HTN heightened the association between increased disordered sleep and worse executive function in the HTN group.

Conclusions: Youth with primary HTN demonstrated significantly lower NT performance compared with normotensive controls, particularly on measures of memory, attention, and executive functions. Further study is needed to determine if these performance differences will reverse with antihypertensive therapy.

Funding: Other NIH Support - NHLBI

SA-PO701

Extracellular Water Is an Independent Determinant of Uncontrolled and Resistant Hypertension in CKD: The Nephrotest Cohort Study

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Background: Hypertension is highly prevalent during chronic kidney disease (CKD) and in turn worsens CKD prognosis. We aimed to describe the determinants of uncontrolled and resistant hypertension, including extracellular water (ECW) during CKD.

Methods: We analysed baseline data from the Nephrotest cohort study. Patients with CKD stage 1 to 5 underwent thorough renal exploration including measurements of GFR (clearance of ^{51}CrEDTA) and of extracellular water (ECW, volume of distribution of the tracer). Hypertension was defined as blood pressure (BP, average of three office measurements) above 140/90 mmHg or the use of antihypertensive drugs. Resistant hypertension was defined as uncontrolled BP (>140/90) despite 3 drugs including a diuretic or the use of 4 or more drugs, regardless of BP level.

Results: In 2015 patients (mean age 59±15 years, 67% male, mean GFR 42±15 mL/min/1.73m²), prevalence of hypertension was 88.4%. In hypertensive patients, the mean number of treatments was 2.7±1.4, and prevalences of uncontrolled and resistant hypertension were 44.1 and 32.4%, respectively. In multivariable analysis, older age, higher albuminuria, diabetic nephropathy and the absence of aldosterone blockers were independently associated with uncontrolled BP. Older age, lower GFR, higher albuminuria, and BMI, African origin, diabetes and diabetic and glomerular nephropathies were associated with resistant hypertension. In addition, ECW was independently associated with both uncontrolled BP [OR for 1L increase, 1.06, 95% confidence interval (CI) 1.02-1.11] and resistant hypertension [OR 1.08, 95% CI 1.03-1.14].

Conclusions: A lower GFR is associated with hypertension severity but not with BP control. ECW is an independent determinant of both resistant and uncontrolled hypertension during CKD, which advocates for the large use of diuretics in this population.

SA-PO702

Plasma Peptidomics Based Multivariable Model for Identification of Mediators Involved in Hypertension

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Background: Hypertension is a major risk factor for cardiovascular disease and is also a risk factor for other end-organ diseases. Despite of advancements in lowering blood pressure, the best approach to lower it, remains controversial due to the lack of information on its development. We therefore, performed plasma proteomics to identify the markers discriminating hypertensive from normotensives.

Methods: Plasma samples from hypertensive and normotensive subjects were used for the study. We performed LC-MS/MS analyses of the plasma samples. Hypertension specific plasma peptides were identified and a model was developed using least absolute shrinkage and selection operator logistic regression. The underlying peptides were identified and to get an insight in to the mechanisms, pathway analysis was performed.

Results: By comparison of plasma samples, 27 biomarkers were identified discriminating hypertensives from normotensives. 70% of the features selected were found to occur less likely in hypertensive patients. A cross-validated predictor model was developed with the overall R square of 0.434 and the area under the ROC curve was 0.891 with 95% confidence interval 0.8482 to 0.9349, P<0.0001. The mean value of the cross-validated predictor score of normotensive and hypertensive patients was found to be -2.007 ± 0.3568 and 3.383 ± 0.2643, respectively. Phosphtidylinositol 3 kinase regulatory, humanin, anoctamin 10, NIK related protein kinase, Mannose-6- phospho isomerase, tryptophan, erythrocyte membrane glycopeptide, transcription factor Dp-2, pleckstrin homology domain-containing family O member 1, cardiac phospholamban, osteocalcin or sarcolipin, ras-related protein Rab-13, protein prune homolog, nexilin and palladin were the identified peptides. The pathway analysis revealed that these proteins had mostly cardiac related functions.

Conclusions: Plasma proteomics model was able to predict the hypertensive-normotensive status based on 27 molecular features. After validation in other cohorts for reproducibility, the identified markers may be useful to clarify the causes of hypertension and to predict the development of hypertension and hence of cardiovascular events.

SA-PO703

The Long Term Prognosis of IgA Nephropathy with Malignant Nephrosclerosis Patients

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Background: This study is aimed to investigate the correlation between clinicopathological characteristics and long term prognosis of IgA nephropathy with malignant nephrosclerosis patients (IgAN-MHN) and essential malignant nephrosclerosis (EMHN).

Methods: This is a retrospective cohort study of 34 IgA-MHN patients and 82 EMHN patients confirmed by renal biopsy in Peking Union Medical College Hospital (PUMCH). IHC staining of CD34 and CD68 were used to evaluate the area of peritubular capillaries (PTC) and macrophage infiltration respectively. The primary end point were defined as renal replacement therapy, kidney transplant as well as death. Kaplan-Meier analysis and Cox regression was used to detect factors related to prognosis.

Results: Among 1765 cases of IgA nephropathy from 2003 to 2012, there were 550 patients (31.2%) with hypertension and 34 patients (1.9%) with MHT. Compared with EMHN patients, the IgAN-MHN patiens were younger (31.6±8.6 vs 35.7±8.5, *P*=0.042), and less rate of males (71% vs 92% male, *P*=0.008) with lower blood pressure (211.4±28.8/142±20.5 vs 224.2±25.8/149.8±23.6, *P=0.038 or 0.15*). IgAN-MHN patients showed higher urinary proteins (3.69±3.55 vs 2.00±1.33, P= 0.006) and lower serum albumin (39.45±4.24, 34.66±5.24, P<0.001) and serum creatinine (Scr) levels than EMHN patients(410.80±237.07 vs 311.86±177.30, P=0.042).The PTC proportion was decreased in both IgAN-MHN and EMHN patients compared with the glomerular minor lesion group, which correlated well with eGFR. After 5ys follow up,no significant difference of kidney survival rate was observed between IgAN-MHT and EMHT groups (59% vs 63%, p>0.05). Except PTC injury and CD68 staining, the eGFR at biopsy and the poor controlled blood pressure were risk factors of the ESRD.

Conclusions: PTC injury correlated well with eGFR of MHN patients. No significant difference of long term kidney survival was observed between IgAN-MHN and EMHN patients.

SA-PO704

Assessing the Validity of the OMRON HEM-907XL Oscillometric Blood Pressure Measurement Device in Non-Hemodialysis Chronic Kidney Disease Patients

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Background: An integral component of chronic kidney disease (CKD) care is the management of hypertension, requiring accurate blood pressure measurement. Automated blood pressure devices that use oscillometry to determine blood pressure (BP) are commonly employed in BP measurement, but operate on the assumption that oscillometric signals are similar between patients with and without co-morbidities like CKD. The OMRON HEM-907XL is a commercial device that measures BP oscillometrically and was the device used in SPRINT, in which 28% of participants had chronic kidney disease. This device has been validated in the general population, but not in patients with non-dialytic CKD. The objective of this study was to validate the accuracy of the OMRON HEM-907XL in non-dialytic CKD patients.

Methods: Patients were recruited from SPRINT and CRIC trial follow-up visits as well as the nephrology clinic at the University of Pennsylvania. 87 patients met inclusion criteria, defined as estimated glomerular filtration rate <60 mL/min/1.73m² or the presence of albuminuria. The measurement protocol was developed according to the Association for the Advancement of Medical Instrumentation guidelines for validation of blood pressure devices, with one observer recording measurements from the OMRON device and two clinicians obtaining simultaneous aneroid values.

Results: There was a 5 mmHg (+/- 7.5) difference in mean systolic blood pressure between the OMRON and aneroid values, and a 0.3 mmHg (+/-5.3) difference in mean diastolic blood pressure, which met criteria for validation based on the Association for the Advancement of Medical Instrumentation guidelines.

Conclusions: In conclusion, the OMRON HEM-907XL oscillometric blood pressure device provides consistent readings in comparison to aneroid measurements, and appears valid for use in patients with chronic kidney disease.

Funding: NIDDK Support

SA-PO705

Effects of Blood Pressure Control in Uncomplicated Grade 1 Hypertension

Xianhui Qin,[1] Youbao Li,[1] Binyan Wang,[1] Yong Huo,[2] Genfu Tang,[3] Mingli He,[4] Delu Yin,[4] Xiping Xu,[1] Xin Xu,[1] Fan Fan Hou.[1] *[1]Nanfang Hospital, Southern Medical Univ; National Clinical Research Center for Kidney Disease; [2]Peking Univ First Hospital; [3]Anhui Medical Univ; [4]First People's Hospital, Lianyungang.*

Background: Effects of blood pressure(BP) control(<140/90mmHg) in patients with grade 1 hypertension are unclear. We aimed to examine the effect of BP control in prevention of cardiovascular events and deaths in patients with grade 1 hypertension in the China Stroke Primary Prevention Trial(CSPPT).

Methods: A total of 3187 patients, with a median antihypertensive treatment duration of 4.6 years, were divided into subgroups according to (1)the percentage of on-treatment visits in which BP was controlled(<140/90mmHg); or (2) the time-averaged mean SBP/DBP levels achieved throughout the treatment period or up to the occurrence of an event.

Results: Compared with those with BP control <25% of the on-treatment visits(3.7%), the incidence of first stroke decreased progressively as the percentage of BP control increased(25-<50%, 1.8%; HR,0.47;95%CI:0.21-1.07; 50-<75%, 1.3%; 0.34;0.16-0.73; ≥75%, 1.3%;0.36;0.16-0.83; P for trend=0.019).

Proportion of visits with BP control	Outcome, No(%)	HR(95%CI)	Adjusted HR(95%CI)
First stroke			
<25%	11(3.7)	ref	ref
25-<50%	13(1.8)	0.46(0.20-1.02)	0.47(0.21-1.07)
50-<75%	16(1.3)	0.32(0.15-0.69)	0.34(0.16-0.73)
≥75%	12(1.3)	0.33(0.15-0.76)	0.34(0.16-0.73)
P for trend		0.010	0.019

Consistently, compared with patients with time-averaged SBP≥140 or DBP≥90mmHg, the risk of first stroke was reduced in patients with SBP<140mmHg(1.1% vs 2.9%; 0.40;0.22-0.70) or DBP<90mmHg(1.5% vs 2.7%; 0.42;0.18-1.02). Similar results were observed for the composite cardiovascular events and all-cause death. The beneficial results were consistent across the age(<60 vs ≥60years), sex, baseline SBP(<150 vs ≥150mmHg) and hypertension subtypes(isolated systolic hypertension or systolic-diastolic hypertension). Furthermore, only 1.5% of the patients discontinued the treatments due to adverse events.

Conclusions: The control of BP(<140/90mmHg) had significant beneficial effects on stroke and all-cause death in patients with grade 1 hypertension.

Funding: Government Support - Non-U.S.

SA-PO706

Nocturnal Blood Pressure Variability Is Associated with Renal Arteriolar Hyalinosis Suffering from IgA Nephropathy

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Background: Abnormal blood pressure (BP) variability (BPV) occurring on beat-to-beat, within 24-hour and day-to-day is related to target organ damage. However, the association between abnormal BPV and renal structural damages has not been clearly investigated.

Methods: We investigated the 24-hour, daytime and nighttime BP standard deviations (SDs) which reflect very short-term BPV, nighttime to daytime (N/D) ratio of SBP and 7-day BPV in 27 IgA nephropathy patients (age 41.7 ± 15.2 years, 9 men and 18 women, estimated glomerular filtration rate (eGFR) 69.2 ± 17.2 ml/min/1.73m^2, urinary protein excretion (UP) 0.64 ± 0.46 g/gCr). Renal biopsy tissues were scored as follows: the levels of arteriolar hyalinosis; the proportion of arterioles affected (0: absent, 1: 1-25%, 2: 26-50%, 3: 51-100%), the levels of arteriosclerosis in arcuate and interlobular arteries (0: normal, 1: intima thickness and less than media thickness, 2: intima thickness and more than media thickness), and percentages of global sclerosis (GS) and tubulointerstitial fibrosis.

Results: The levels of arteriolar hyalinosis were positively correlated with age, body mass index (BMI), 24-hour SBP, SBP, DBP and SD of SBP in nighttime, N/D ratio of SBP and SBP in 7-day and were negatively correlated with eGFR. The levels of arteriosclerosis were positively correlated with age, UP, N/D ratio of SBP and SD of SBP in nighttime and negatively correlated with eGFR. Percentages of GS and tubulointerstitial fibrosis were not correlated with BP parameters. Multiple liner regression analysis revealed that the levels of not arteriosclerosis but arteriolar hyalinosis were associated with SD of SBP in nighttime, when age, sex, BMI, eGFR and SBP in nighttime were adjusted (b= 0.441, p= 0.008). No significant correlations were found between the levels of arteriolar hyalinosis and N/D ratio of SBP or SD of SBP in 7-day after multiple liner regression analysis.

Conclusions: In IgA nephropathy patients, short term BPV in nighttime was associated with arteriolar hyalinosis.

SA-PO707

Complement in Renal Disease-Potential Effect during Pathogenesis of Hypertension?

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Background: Complement deposition is frequently observed in kidney biopsies of patients with hypertensive renal disease, but an association of hypertension and complement deposition or involvement of complement in the pathogenesis of hypertensive nephropathy has not been investigated.

Methods: In this retrospective study archival human renal biopsies from 230 patients with known hypertension and 80 control patients with non-hypertensive renal diseases were investigated using immunohistochemistry and semi-quantitative scores and the results were correlated with renal function. To address whether complement was only passively deposited on or also actively expressed by renal cells, complement deposition as well as C1 and C3 mRNA expression was analyzed in a rat model of hypertension i.e. the 5/6-nephrectomy rat (n=12) and controls (n=10).

Results: Glomerular C1q and C3c complement deposition was significantly higher in hypertensive patients and rats than in non-hypertensive controls. Mean arterial blood pressure in 5/6-nephrectomy rats correlated well with the amount of C1q (r=0.790; p<0.0001) and C3c deposition (r=0,697; p<0.0003) and also with left ventricular weight (C1q: r=0.819; C3c: r=0.621; both p<0.002). C3 were not only deposited but also actively produced by renal cells of hypertensive rats as assessed by quantitative mRNA analysis. Of note, in hypertensive patients renal function as measured by creatinine clearance correlated significantly negative with the intensity of C1q staining (r=-0.322; p=0.001), but not with that of C3c.

Conclusions: Hypertensive nephropathy, but not other non-hypertensive renal diseases, was significantly associated with in-situ expression and deposition of complement. Since complement activation is known to have multiple disease promoting effects further investigations are needed to identify whether it is involved in the pathogenesis or progression of hypertensive nephropathy.

SA-PO708

Preeclampsia and Severe Proteinuria during Pregnancy and Postpartum Follow-Up: Results from a High Risk Center in Brazil

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Background: Preeclampsia (PE) is a disease of pregnancy and puerperium and a leading cause of morbidity and mortality worldwide. Women with PE must be followed after delivery to evaluate long term complications as cardiovascular and renal diseases. The kidney injury may remain after delivery and the long term consequences of massive proteinuria are still unclear.

Methods: Retrospective cohort of pregnant women with proteinuria≥2g/24h followed at UNICAMP from January 2009 to December 2013. Exclusion criteria: previous nephropathy, delivery in other center or absence of PE diagnosis. Data on demographic characteristics, laboratory findings, maternal and fetal/neonatal outcomes were recorded and analyzed with Epi-Info 7.

Results: 254 women screened and 196 met the criteria for review. Of those, 32 had normal proteinuria (during pregnancy <0.3g/24h) prior to the onset of PE and were further studied. The mean age was 31±6.1 years, majority white (72%) and more than a half were multiparous. The mean proteinuria first evaluated during pregnancy (gestational age 25 weeks±7.7) was 0.16g/24h (±0.07) and after onset of PE, which happened around 33 weeks (±4.1), it rose to 3.7g/24h(±2) and 81% had severe PE. Gestational age at delivery was 33(±4.1) and 75% delivered by cesarean. Less than half showed up for a postpartum visit and only 12 women had quantification of proteinuria after delivery and among those, 4 had normal proteinuria (<0.15g/24h), while 8 remained proteinuric (1,3±1.7g/24h). None had further then 3 months follow-up.

Conclusions: PE is a severe disease with impact in outcomes during pregnancy and childbirth but also with possible long term consequences. Women who develop massive proteinuria during pregnancy may remain proteinuric, and a few may develop chronic disease and must be diagnosed and referred. An accurate long term follow-up of those women is mandatory. Future studies must address follow-up of those women after puerperium, onset of other hypertension-related diseases and impact in future pregnancies.

Funding: Government Support - Non-U.S.

SA-PO709

Changes of Blood Pressure Patterns and Target Organ Damage in Patients with Chronic Kidney Disease: Results of the APrODiTe-2 Study

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Background: Blood pressure (BP) control is the most established practice for preventing the progression of chronic kidney disease (CKD). We examined the BP control and nocturnal dipping pattern changes in hypertensive patients with CKD and their effects on target organ damages.

Methods: We recruited 378 hypertensive CKD patients from 4 centers in Korea. The patients underwent clinic and ambulatory BP monitoring at the time of enrollment and 1 year later. High clinic and ambulatory BP were defined as > 140/90 mmHg and > 135/85 mmHg (daytime)/ > 120/70 mmHg (nighttime), respectively.

Results: The BP control states at the 2 time points were as follows: true controlled (16.5, 17.5%), white-coat (2.9, 0.4%), masked (50.0, 53.3%), and sustained uncontrolled (30.6, 28.8%) hypertension. The dipping states at 2 time points were as follows: extreme-dipping (11.4, 10.8%), dipping (22.2, 20.5%), non-dipping (31.3, 34.7%), and reverse-dipping (35.0, 34.0%). Better changes (to true controlled and white-coat) of BP control status were associated with initially lower levels of serum uric acid, urea nitrogen, and proteinuria and higher estimated GFR (eGFR). When we divided the patients according to the median eGFR and proteinuria changes, more stable changes in eGFR and proteinuria were associated with better initial and follow-up BP control statuses. Moreover, better BP control and dipping (to dipper) changes were also associated with more stable eGFR and proteinuria changes. Good initial and follow-up BP control statuses were associated with less LVH. And masked and sustained uncontrolled hypertension was associated with more cardio-cerebrovascular events in the univariate analysis.

Conclusions: A large majority of Korean hypertensive CKD patients had uncontrolled BP and abnormal dipping patterns. Furthermore, better BP control and dipping status changes were associated with better renal function and proteinuria as well as less cardio-cerebrovascular damages.

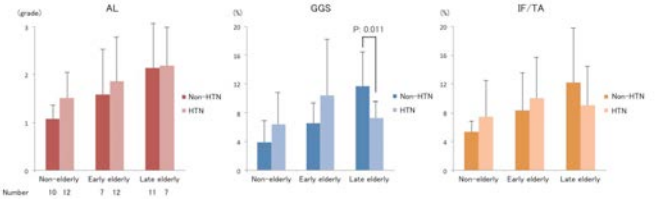
SA-PO710

Aging vs. Hypertension: An Autopsy Study of Sclerotic Renal Histopathologic Lesions in Non-CKD Adults Yusuke Okabayashi, Nobuo Tsuboi, Go Kanzaki, Takaya Sasaki, Kotaro Haruhara, Kentaro Koike, Yoichi Miyazaki, Tetsuya Kawamura, Makoto Ogura, Takashi Yokoo. *Div of Nephrology and Hypertension, The Jikei Univ School of Medicine, Tokyo, Japan.*

Background: Both renal ischemic arteriosclerosis and arterial hyperperfusion co-exist in elderly hypertensive patients. Thus, the two conflicting purposes of renal tissue perfusion maintenance and reduction of pressure overload have to be achieved for renal protection in such patients. In this study, we aimed to clarify the impacts of aging and/or hypertension in the development of sclerotic renal lesions in non-CKD adults.

Methods: Fifty-nine Japanese non-CKD autopsies, with or without hypertension, were analyzed to compare the clinicopathologic features among age groups. Arteriosclerotic lesions (AL), interstitial fibrosis/tubular atrophy (IF/TA), global glomerulosclerosis (GGS), and the mean glomerular volume (GV) were evaluated in both juxtamedullary and superficial cortexes (about 50 glomeruli for each).

Results: The studied kidneys had an average age of 66 years and an average eGFR of 98 ml/min/1.73 m^2; 47% had hypertension. In the non-elderly group (<65 years) and early elderly group (65–74 years), the degree of IF/TA and GGS in hypertensives were higher than those of normotensives. In the late elderly group (>75 years), the degree of GGS was significantly lower in hypertensives than those in normotensives.



Multivariate analysis revealed that age but not hypertension was identified as an independent factor that associated with AL, GGS, and IF/TA. In contrast, hypertension was a factor independently associated with GV.

Conclusions: In non-CKD adults, it is likely that normal aging plays a major role in the development of sclerotic renal histopathologic lesions. In contrast, hypertension may be protective against these lesions in the very elderly.

SA-PO711

Comparison of Salt Taste Thresholds and Salt Usage Behaviors between Adults in Myanmar and Korea Jae Wan Jeon, Soon Bae Kim, Hyosang Kim. *Internal Medicine, Nephrology, Asan Medical Center, Seoul, Republic of Korea.*

Background: Excessive oral salt intake can induce hypertension. According to previous studies, the prevalence of hypertension is higher in Myanmar than in Korea. We postulated that Myanmar adults had higher salt taste thresholds and eat much saltier food. This study aimed to compare salt taste thresholds and salt usage behavior scores between adults in Myanmar and Korea.

Methods: This cross-sectional study enrolled patients who visited volunteer medical service clinics at Ansung in Korea and Hlegu and Bago in Myanmar in August 2014. We measured the vital signs, heights, and weights of each patient and evaluated detection thresholds, recognition thresholds, and salt preferences. All patients underwent urinalysis and spot urine Na tests. Additionally, they each completed a salt usage behavior questionnaire.

Results: A total of 131 patients were enrolled, including 64 Myanmarese patients and 67 Korean patients. Blood pressure was significantly higher in the Myanmarese than in the Koreans. Detection and recognition thresholds, salt preferences, and spot urine sodium and salt usage behavior scores were also higher in the Myanmarese than in the Korean subjects. We calculated correlation coefficients between systolic blood pressure and parameters that were related to salt intake. The detection and recognition thresholds were significantly correlated with systolic blood pressure.

Conclusions: All parameters related to salt intake, including detection and recognition thresholds, salt preference, salt usage behavior scores and spot urine sodium concentrations, are significantly higher in Myanmarese than in Korean individuals.

SA-PO712

Nationwide Multicenter Kidney Biopsy Study of Japanese Patients with Type 2 Diabetes Kengo Furuichi,[1] Yukio Yuzawa,[2] Yoshifumi Ubara,[3] Miho Shimizu,[1] Tadashi Toyama,[1] Yasunori Iwata,[1] Norihiko Sakai,[1] Takashi Wada.[1] *[1]Div of Nephrology, Kanazawa Univ, Kanazawaa, Japan; [2]Dept of Nephrology, Fujita Health Univ Hospital, Toyoake, Japan; [3]Nephrology Center, Toranomon Hospital, Tokyo, Japan.*

Background: The pathological manifestations of diabetic nephropathy in Type 2 diabetes are diverse. However, pathological study with large scale and long observation is very limited. In this nationwide multicenter, retrospective study, we demonstrated the impacts of pathological findings as predictors for kidney events in Japanese patients with Type 2 diabetes in detail.

Methods: Kidney biopsy was performed for and clinical data were collected of 600 patients with Type 2 diabetes from 13 centers across Japan. In this study, thirteen pathological findings were clearly defined and scored.

Results: The mean observation period was 72.4 months. Three hundred and four composite kidney events (dialysis, doubling of Cr or halving of eGFR), 31 kidney deaths, 76 cardiovascular events, and 73 deaths occurred during the observation period. One hundred three cases, 149, and 348 were in Green and Yellow, Orange, and Red categories of CKD heat map, respectively. Even in cases of Green and Yellow categories, diffuse lesion, polar vasculosis and subendotherial space widening were commonly detected (positive cases; diffuse lesion 81.6%, polar vasculosis 42.6%, subendotherial space widening 35.1%). Cox proportional hazards analysis revealed that presence of nodular lesion, exudative lesion, and mesangiolysis in cases of Green and Yellow categories in CKD heat map were significantly high impacts on composite kidney events after adjustment for clinical risk factors (HR, 95% CI; nodular lesion: 21.1 , 5.3 to 84.6, exudative lesion: 5.1, 1.3 to 20.3, mesangiolysis: 7.6, 2.0 to 28.8).

Following points were limitation of this study; only evaluated by light microscopy, retrospective study, limited to cases with kidney biopsies, no evaluation of the therapeutic interventions.

Conclusions: In summary, this nationwide kidney biopsy study of 600 cases with Type 2 diabetes revealed that pathological findings (presence of nodular lesion, exudative lesion, and mesangiolysis) were strong predictors of kidney events in low-risk CKD heat map patients.

Funding: Government Support - Non-U.S.

SA-PO713

Nodular Lesions in Diabetic Nephropathy: Collagen Staining and Renal Prognosis Koki Mise,[1,2] Toshiharu Ueno,[1] Junichi Hoshino,[1] Masayuki Yamanouchi,[1] Noriko Hayami,[1] Jun Wada,[2] Hirofumi Makino,[2] Kenmei Takaichi,[1] Yoshifumi Ubara.[1] *[1]Nephrology Center, Toranomon Hospital, Tokyo, Japan; [2]Dept of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama Univ Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.*

Background: Nodular lesions are one of the most characteristic pathological changes of advanced diabetic nephropathy (DN). Previous studies have demonstrated that the pattern of both routine and collagen staining of nodular lesions changes during their development. However, the association between such changes of staining and the renal prognosis remains unclear.

Methods: Among 252 patients with biopsy-proven DN, 67 met the selection criteria and were enrolled to investigate this relationship. In all patients, staining of nodular lesions with periodic acid Schiff (PAS), periodic acid methenamine silver (PAM), Masson trichrome, and collagens I, III, IV, V, and VI was performed. The endpoint was commencement of dialysis due to end-stage renal disease. The Cox proportional hazard model was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for the death-censored endpoint.

Results: At least one mesangiolytic nodular lesion (MNL) that showed faint staining for PAS and PAM was found in 61% of the patients. Type IV collagen was decreased in these lesions, whereas type VI collagen was markedly increased, consistent with previous reports. In patients with at least one MNL, the HR for the endpoint was significantly higher than in patients without MNL after adjusting for known promoters of renal progression (HR: 2.94, [95% CI: 1.24-7.07]).

Conclusions: MNL may reflect characteristic changes of collagen and could be a useful prognostic indicator that should be assessed in patients with nodular lesions. Further investigation of the mechanism underlying this change could contribute to finding new therapeutic targets for DN.

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

SA-PO714

Paratubular Basement Membrane Insudative Lesions Predict Renal Prognosis in Patients with Type 2 Diabetes and Biopsy-Proven Diabetic Nephropathy Koki Mise,[1,2] Yutaka Yamaguchi,[3] Junichi Hoshino,[1] Akinari Sekine,[1] Toshiharu Ueno,[1] Noriko Hayami,[1] Masayuki Yamanouchi,[1] Hitoshi Sugiyama,[2] Hirofumi Makino,[2] Jun Wada,[2] Kenmei Takaichi,[1] Yoshifumi Ubara.[1] *[1]Nephrology Center, Toranomon Hospital, Tokyo, Japan; [2]Dept of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama Univ Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; [3]Yamaguchi's Pathology Laboratory, Matsuo, Japan.*

Background: Glomerular insudative lesions are a pathological hallmark of diabetic nephropathy (DN). However, paratubular basement membrane insudative lesions (PTBMIL) have not attracted much attention, and the association between such lesions and the renal prognosis remains unclear.

Methods: Among 142 patients with biopsy-proven DN and type 2 diabetes encountered from 1998 to 2011, 136 patients were enrolled in this study. Patients were classified into 3 groups (Group 1: mild, Group 2: moderate, Group 3: severe) according to the extent of cortical and medullary PTBMIL. The endpoint was a decline of the estimated glomerular filtration rate (eGFR) by ≥ 40% from baseline or commencement of dialysis for end-stage renal disease. The Cox proportional hazard model was employed to calculate hazard ratios (HRs) and 95% confidence interval (CIs) for the death-censored endpoint.

Results: During a median follow-up period of 1.8 years (IQR: 0.9-3.5 years), the endpoint occurred in 104 patients. Baseline mean eGFR was 43.9 ± 22.8 ml/min/1.73 m^2, and 125 patients (92%) had overt proteinuria. After adjusting for known indicators of DN progression, the HR for the endpoint was 2.32 (95% CI: 1.20-4.51) in PTBMIL Group 2 and 3.12 (1.48-6.58) in PTBMIL Group 3 versus PTBMIL Group 1. Furthermore, adding the PTBMIL Group to a multivariate model including known promoters of DN progression improved prediction of the endpoint (c-index increased by 0.02 [95% CI: 0.00-0.04]).

Conclusions: PTBMIL may be useful for predicting the renal prognosis of patients with biopsy-proven DN, but further investigation of these lesions in various stages of DN is needed.

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

SA-PO715

Interstitial Fibrosis and Tubular Atrophy Are Dominantly Associated with Progressive Renal Decline in Patients with Type 2 Diabetes and Biopsy Proven Diabetic Nephropathy Masayuki Yamanouchi,[1] Toshiharu Ueno,[1] Junichi Hoshino,[1] Koki Mise,[2] Yoshifumi Ubara,[1] Kenmei Takaichi.[1] *[1]Okinaka Memorial Inst for Medical Research, Tokyo, Japan; [2]Okayama Univ Graduate School of Medicine.*

Background: Which histological lesions (glomerular, tubulointerstitial, and/or arterial lesions) of diabetic nephropathy are dominantly associated with progressive renal decline is unknown.

Methods: 223 individuals with Type 2 diabetes and biopsy proven diabetic nephropathy were identified between 1985 and 2011 in the Toranomon Hospital (Tokyo, Japan). Histological classification was performed by two pathologists based on the Tervaert's Pathologic Classification of Diabetic Nephropathy. The rate of eGFR loss in these patients was determined by serial measurements of eGFRcre using linear regression model. The primary outcome was to become a decliner who has an eGFR rate loss >= 3.3 mL/min/year. Clinical data as well as laboratory data such as HbA1c, eGFR, and urinary protein were collected at the date of renal biopsy.

Results: The median follow up, after excluding the first one-year observation period, was 4.3 years. The majority of individuals have a linear eGFR trajectory and 124 decliners were identified among them. With IFTA (interstitial fibrosis/tubular atrophy) score 1 as reference, Odds Ratios of IFTA score 2 and 3 were; 8.0 (95%CI, 3.4-18.9) and 5.4 (95%CI, 2.5-12.0) in unadjusted model; 6.2 (95%CI, 2.5-15.6) and 5.2 (95%CI, 2.2-12.5) in the model adjusted for clinical variables (age, sex, duration of diabetes, and BMI); and 4.7 (95%CI, 1.3-17.0) and 9.6 (95%CI, 1.7-53.9) in the model adjusted for clinical variables plus baseline HbA1c, eGFR, and urinary protein levels with other histologic lesions. Though other histologic lesions including glomerular lesions reveal significant in unadjusted analysis, none of them remain significant in adjusted analysis.

Conclusions: Although glomerular lesion is important for diagnosis of diabetic nephropathy, our finding suggests that interstitial fibrosis/tubular atrophy may be more strongly associated with progressive renal decline than other histological lesions.

SA-PO716

Polar Vasculosis Is Early Morphological Change in Diabetes Noriko Uesugi,[1] Kengo Furuichi,[2] Michio Nagata,[1] Takashi Wada.[2] *[1]Renal Vascular Pathology, Univ of Tsukuba, Tsukuba, Ibaraki, Japan; [2]Nephrology, Kanazawa Univ Hospital, Kanazawa, Japan.*

Background: Aggregation of neovascular arterioles with hyalinosis around glomerular poles (porlar vasulosis (PV)) is hallmark of advanced diabetic nephropathy(DN) and is usually associated with prominent afferent arteriolar (AA) hyalinosis, but can be seen in very early stage of DN. PV might occur in diabetes (DM) with no DN and no prominent AA hyalinosis. To clarify this, we analyzed paraffin embedded human surgical kidney specimen of non-tumor parts of renal carcinoma.

Methods: We analyzed PAS, PAM, MT, EVG, HE staining sections from 22 Japanese cases including 12 DM with no urinary abnormalities (65y.o, S-Cre 1.0 mg/dl) and 10 control without hypertension or renal disease(64y.o, S-Cre 0.8 mg/dl) and investigated frequency of PV, % hyalinosis of AA and % of glomerular global sclerosis(GS). Origin of PV was determined by serial sections double stained by endothelial marker, CD34, and vascular medial marker SMA, followed by PAS staining.

Results: No definite glomerular abnormalities was observed in all except two DM cases. The two showed mildly expanded mesangial area with a few small nodules. Average 548(380-750) and 551(390-824) glomeruli were analyzed in control and DM,respectively. Percentage of GS and hyalinosis of AA showed no difference in control (10±8, 25±20,respectively) and in DM (11±7, 30±25, respectively). PV was found in all DM cases (1-52/specimen), but not in control. PV was observed in glomeruli with no or mild AA hyalinosis and was frequently seen in cases with glomerular change and severe arteriosclerosis. Serial immunostained sections confirm the PV was originated from efferent arteriole.

Conclusions: PV is representative early damage of glomerular microcirculation in DM before overt diabetic nephropathy clinically.

Funding: Other U.S. Government Support

SA-PO717

Diffuse and Intense Glomerular C4d Staining Reflects Endothelial Injury in Diabetic Nephropathy Shigeo Hara,[1] Shinichi Nishi.[2] *[1]Dept of Diagnostic Pathology, Kobe Univ, Kobe, Hyogo, Japan; [2]Dept of Nephrology, Kobe Univ, Kobe, Hyogo, Japan.*

Background: Endothelial injury plays a critical role in the disease progression in diabetic nephropathy (DN). Recent study has reported C4d as a common denominator in thrombotic microangiopathy (JASN 2015). The aim of the present study was to examine the utility of C4d as an indicator of endothelial damage in DN.

Methods: The study consists of 12 cases of histologically-proven diabetic nephropathy without concurrent glomerulonephritis and tubulointerstitial nephritis. According to the glomerular C4d staining on frozen section, the cohort was divided into two groups with intense (Group I; n = 9) or weak (Group W; n = 3) C4d staining. Clinical and pathological characteristics were examined between both groups.

Results: Group I was clinically characterized by more severe level of proteinuria compared to Group W (6.85 g/gCr vs. 0.32 g/gCr, $p < 0.01$), whereas serum creatinine levels, eGFR and HbA1c levels at the time of biopsy were not significant. Pathologically, all but one case in Group I showed nodular lesion corresponding to class III, whereas two cases and one case in Group W were assigned class IIa or IIb, respectively. Exudative lesions including capsular drop and subepithelial widening of renal tubules were noted in the four cases in group I. In Group W, however, only capsular drop was found in one case. The degree of interstitial fibrosis, tubular atrophy, arteriosclerosis and arteriolar hyalinosis were comparable between both groups. C4d staining in Group I was almost confined to the glomeruli without diffuse positivity in peritubular capillaries. In addition to linear IgG staining, IgM were positive in 5 cases of Group I, but none of Group W. In Group I, electron microscopy revealed marked subendothelial widening which was not observed in Group W.

Conclusions: C4d staining can be a reliable ancillary test to designate glomerular endothelial damage in DN.

Funding: Clinical Revenue Support

SA-PO718

Differential Diagnostic Models of Diabetic Nephropathy and Non-Diabetic Renal Diseases Meijun Si, Zengchun Ye, Wenbo Zhao, Xun Liu. *Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China.*

Background: Non-diabetic renal diseases(NDRD) could be detected among patients with type 2 diabetes mellitus(T2DM) and chronic kidney disease(CKD).The treatment and prognosis of NDRD is different from diabetic nephropathy(DN), which makes the differential diagnosis of great importance. We aim to build up diagnostic models for differentiating NDRD from DN.

Methods: Patients with T2DM and CKD who had performed renal biopsies between 2004 and 2013 were enrolled.Renal pathology was regarded as the gold standard for the diagnosis of DN and NDRD. A logistic regression model was built by multiple regression analysis while artificial neural network (ANN) models were constructed by MATLAB 2011A software.

Results: Among the103 patients enrolled,49 had DN while 54 had NDRD. 36 multicenter subjects with T2DM and CKD were applied as the external validation. Through univariate and multivariate regression analysis, four significant factors : diabetic retinopathy(DR), diabetes duration, hemoglobin(Hb) and urinary protein(Upro) were included in logistic regression model: $P(DN) = \exp(3.682* DR+0.227Diabetes\ duration-0.043*Hb +0.207*Upro+0.350)/[1+ \exp(3.682* DR+0.227\ Diabetes\ duration\ -0.043*Hb +0.207*Upro+0.350)]$.We built up an artificial neural network based on the same four parameters.103 subjects were randomly divided into the training set (N=69) and the internal validation set (N=34). In the external validation, the optimized genetic algorithm GA-MLP-6-7-1 harvested preferably predictive effect(consistency 91.7%,sensitivity 91.0% and specificity 61.6%),which is significantly greater than the regression model (consistency 75.0%,sensitivity 55.0% and specificity 100.0%).The kappa test indicated that the reliability of the ANN GA-MLP-6-7-1 was greater than the logistic regression model($P<0.05$).

Conclusions: Both logistic regression model and artificial neural network could help with the clinical differentiation between DN and NDRD. ANN GA-MLP-6-7-1 based on DR, diabetes duration, Hb and Upro could differentiate NDRD from DN more efficiently than the regression model.

Funding: Government Support - Non-U.S.

SA-PO719

Evaluation of Renal Pathological Classification in Patients with Diabetic Nephropathy Meijun Si, Zengchun Ye, Wenbo Zhao, Xun Liu, Hui Peng, Tan-Qi Lou. *Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China.*

Background: In 2010,a pathological classification of diabetic nephropathy(DN) mainly based on mesangial expansion and Kimmelstiel–Wilson nodules was proposed by Professor Tervaert. We classified the biopsy specimen of patients with type 2 diabetic nephropathy according to Tervaert's classification to assess the relationship between pathological classification and prognosis.

Methods: We retrospectively analyzed the pathological features of patients diagnosed with DN between January 2004 and December 2013. Tervaert's classification was applied to the specimens. All patients enrolled were censored by telephone calls or out-patient clinic by the deadline on 31 December 2014. The end point was defined as doubling of serum creatinine or introduction of dialysis.We further conducted the survival analysis to evaluate the impact of pathological classification on the prognosis of DN.

Results: 49 Patients enrolled were divided into four categories of IIa(N=5), IIb(N=8), III(N=21) and IV(N=15) according to Tervaert's classification.The eGFR in III was significantly lower than II,while the serum albumin in II was significantly higher than III(all $P<0.05$). The proportion of glomerular and segmental sclerosis and the score of interstitial fibrosis and tubular atrophy(IFTA) was higher in III than II($P<0.05$). The longest diabetes duration, highest level of SBP, urinary protein and serum creatinine were detected in IV. The mesangial expansion is more severe in IV than II and III($P<0.05$). There was significant difference of prognosis among the four groups($P<0.05$). The cumulative survival rate for five years in IIa, IIb, III and IV was 100%, 85.7% ,32.5% and 26.7% respectively. II has a better prognosis than IV($P<0.05$).

Conclusions: Our results indicated that clinical and pathological findings and renal outcomes in four DN groups classified by Tervaert's classification were different. IV might suggest the terminal stage of DN while IIa presented with the mildest clinical leisions and better prognosis compared with IV, which was important for early diagnosis and treatment of DN. Terveart's pathological classification could help predict the prognosis of DN.

Funding: Government Support - Non-U.S.

SA-PO720

Clinical Features and Prognosis of Patients with Type 2 Diabetes Melitus and Chronic Kidney Disease Meijun Si, Wenbo Zhao, Zengchun Ye. *Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China.*

Background: The renal pathology type in patients with type 2 diabetes mellitus and chronic kidney disease (CKD) could be diabetic nephropathy (DN), non-diabetic renal diseases (NDRD) and DN with NDRD. We aim to investigate the clinical characteristics and prognosis of type 2 diabetic patients with different types of renal pathology.

Methods: We conducted a retrospective investigation of type 2 diabetic patients with CKD who had performed renal biopsies between 2004 and 2013. According to the pathological diagnosis, patients were categorized into three groups: DN group, NDRD group and DN with NDRD group(MIX group). All patients were censored by telephone calls or out-patient clinic by the deadline on 31 December 2014. The end point was defined as doubling of serum creatinine or introduction of dialysis.

Results: Among 110 patients enrolled, 49(44.5%) patients had DN alone, 54(49.1%) patients had NDRD while 7(6.4%) patients had concurrent DN and NDRD. Compared with NDRD, DN patients had a longer diabetes duration and a higher diabetic retinopathy(DR) rate(all P<0.05).The prevalence of having both nephrotic range proteinuria and kidney function decrease (eGFR<60ml/min) was higher in DN than NDRD(P<0.05). The mean follow up time was 41 months. 25 patients reached the endpoint with 18 in DN,5 in NDRD and 2 in MIX group. The prognosis of NDRD is better than DN(P=0.013) and MIX group(P=0.037), while the 5 year renal survival rate of NDRD, DN and MIX group was 87% , 63% and 33% respectively. Among the clinical indicators, Multiple linear regression model indicated the independent risk factors for endpoint event were urinary protein(OR1.277,95%CI 1.102-1.479), hemoglobin(OR0.963,95% CI 0.940 -0.987) and serum creatinine(OR1.005,95%CI1.001 -1.009).

Conclusions: Our results indicated that type 2 diabetic patients with CKD had different pathologic features and clinical manifestations. The short duration of diabetes and the absence of DR were factors associated with NDRD. The poorest prognosis was observed in patients with concurrent DN and NDRD.

Funding: Government Support - Non-U.S.

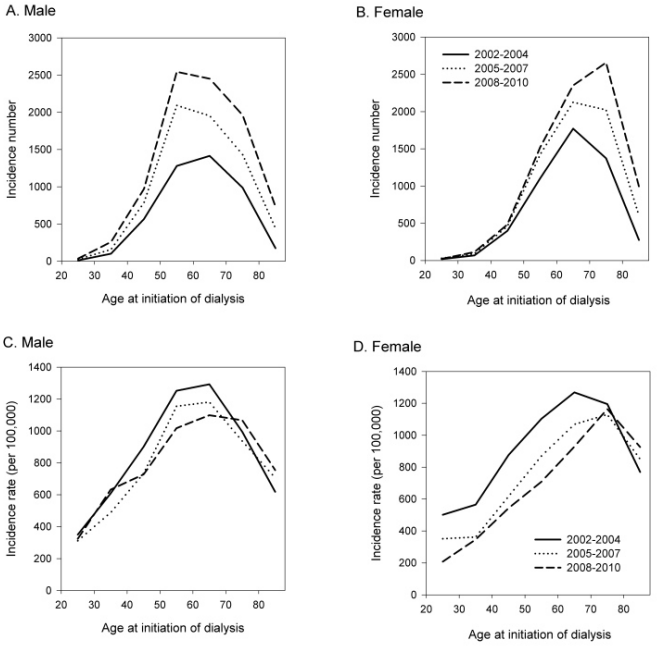
SA-PO721

Time Trends and Gender Differences in Incidence of Diabetes-Related Dialysis – A 2002-2010 Population-Based Study in Taiwan Jinn-Yang Chen,[1] Pei-Hung Chuang.[2] *[1]Div of Nephrology, Taipei Veterans General Hospital, Taipei, Taiwan; [2]Foundation for Poison Control, Taipei, Taiwan.*

Background: The prevalence of type 2 diabetes increases worldwide. Understanding burden of diabetes-related dialysis is important in order to allocate health resources, and to encourage measures to counteract trends for increasing prevalence.

Methods: Data were retrieved from 2001-2010 Taiwan National Health Insurance claim records. The gender and age-specific incidence rate of long-term dialysis was calculated for type 2 diabetes patients in the periods of 2002-2004, 2005-2007 and 2008-2010, seperately. Poisson regression was performed to evaluate the effects of age, gender and period with a log (person-year) off-set term and a deviance scale parameter adjustment. All statistical analyses were conducted using the SAS statistical software, Version 9.2.

Results: There were 20,397 male and 19,933 female diabetes-related dialysis occurring between 2002 and 2010. The incidence number of diabetes-related dialysis increased from 2002 to 2010 in every age group. During 2008-2010, the numbers of male patient peak at the age-range of 50-59 years and those of female patients peak at the range-range of 70-79 years. There was a decreasing trend of incidence rate from 2002 to 2010 in female patients younger than 70 years old. In contrast, there was an increasing trend of incidence rate in female patients older than 80 years old from 2002 to 2008.



Initially, Poisson regression model showed that the relative risk (RR) of diabetes-related dialysis in 2002-2004 was higher than that in the other two periods. However, this period effect disappeared after adding interaction terms gender&age and period&age into the model.

Conclusions: For adult female patients younger than 70 years, there was a decreasing trend of diabetes-related dialysis incidence rate from 2002 to 2010 in Taiwan.

Funding: Government Support - Non-U.S.

SA-PO722

Association between Renal Function and Diabetic Foot Ulcer in Type 2 Diabetic Patients Haitham Ezzat, Abd el Basset El Shaarawy, Amr Mohab. *Nephrology Dept, Ain Shams Univ, Cairo, Egypt.*

Background: Diabetic nephropathy and diabetic foot syndrome (DFS) are two major complications of diabetes. The aim of this study was to evaluate renal function in patients with diabetic foot ulcers and to identify a potential association between them.

Methods: In this cross sectional study 75 adult patients with type 2 DM were enrolled. They were divided into 2 groups , group 1 included 50 patients with diabetic foot ulcer (DFU) (25 male & 25 female) and group 2 included 25 patients without DFU (12 male & 13 female).The stages of DFU were recorded according to Wagner and Armstrong grading. Demographic data was collected from all subjects. Laboratory parameters included s.creatinine, serum urea, HbA1C, lipid profiles, urinalysis, urinary microalbumin and albumin/creatinine ratio (ACR). The eGFR was estimated using the Modification of Diet in Renal Disease equation (MDRD).

Results: Compared with type 2 patients without DFU, those with DFU were significantly older ($P < 0.001$), exhibited a higher HbA1c (8.42%±1.02 vs 7.58%±0.57, P<0.001) , had a longer duration of diabetes (18.0±10.74 years vs 4.327±2.497 years , $P < 0.001$),higher mean systolic blood pressure (135.40±19.91 vs 126.00±15.81 mmgH; P=0.043) , higher serum creatinine levels (2.46 mg/dl ±1.005 vs 1.68 mg/dl ±0.516, $P < 0.001$), and had a lower eGFR (41.196 ml/min ±25.542 vs 61.856 ml/min ±24.641, $P = 0.001$). There was increase in the prevalence of foot ulcers by increasing the degree of renal impairment (14% with CKD stage 2, 30% with CKD stage 3 and 56% with CKD stage 4). Also there was increase in the prevalence of foot ulcers with increasing degree of albuminuria (12% with normo-albuminuria ,26% with microalbuminuria and 62% with macro-albuminuria). In group 1, there was significant correlation between the Wagner stages of DFU and eGFR ($P < 0.001$) as well as Armstrong stages of DFU and eGFR ($P < 0.001$).

Conclusions: There was a strong association between the degree of renal function impairment and DFU. Thus diabetic patients with CKD should regularly screened for the presence of DFS with early preventive strategies.

SA-PO723

Detection of Early Renal Function Decline in Type 1 Diabetes: Comparison of eGFR Slopes Based on Serum Creatinine versus Cystatin C Adam Smiles, Melissa Major, John J. Tsay, Jan Skupien, Monika A. Niewczas, James Warram, Andrzej S. Krolewski. *Joslin Diabetes Center, Boston, MA.*

Background: The second Joslin Kidney Study is an observational study of the natural history of Early Renal Function Decline (ERFD) in type-1 diabetes.

Methods: A cohort of patients with normo- or micro-albuminuria (ALB) was recruited from among patients of the Joslin Diabetes Center. Serial measurements of creatinine (Cre) and cystatin C (Cys) were collected over 3.5 to 11 years. CKD-EPI equations were used to calculate eGFRcre and eGFRcys. Slopes of decline of eGFRcre and eGFRcys were estimated using generalized linear models.

Results: ERFD was defined as an eGFR loss greater than 3 mL/min/1.73 m^2 per year. The table shows the proportion of patients with ERFDcre or ERFDcys according to their respective estimates of baseline eGFR.

	Normo-ALB n=451		Micro-ALB n=304	
Baseline eGFR	Creatinine ERFD	Cystatin C ERFD	Creatinine ERFD	Cystatin C ERFD
120+	21% (20/95)	12% (17/145)	27% (16/59)	22% (19/86)
90-119	10% (31/300)	13% (35/272)	23% (43/184)	35% (58/167)
60-89	9% (5/56)	23% (8/34)	21% (13/61)	39% (20/51)
TOTAL	12% (56/451)	13% (60/451)	24% (72/304)	32% (97/304)

While detection of ERFD by eGFRcre and eGFRcys was similar in Normo-ALB (12% for Cre and 13% for Cys), it was higher for eGFRcys in Micro-ALB (24% and 32%, p=0.02). Interestingly, the proportion of patients with ERFDcys was independent of baseline eGFRcys in both Normo-ALB and Micro-ALB (p=0.2 and 0.06). eGFRcys slope was also better correlated with covariates than the eGFRcre slope. The most striking were ACR (–0.25 Cys vs. –0.15 Cre, p=0.04) and serum TNFR1 (–0.20 vs –0.15, p=0.3).

Conclusions: In conclusion, cystatin C may be a more sensitive tool to identify ERFD, especially in a population with micro-ALB. Further investigation is required into any trends in rates of ERFD across baseline eGFR groups.

Funding: Private Foundation Support

SA-PO724

Real World Analyses of Urinary Albumin and eGFR Decline in 329,841 Diabetic Patients Michael Cressman,[2] Jennifer L. Ennis,[1] Dajie Luo,[4] Barry Goldstein,[2] George L. Bakris.[3] *[1]Litholink/LabCorp, Chicago, IL; [2]Covance, Princeton, NJ; [3]Medicine, Univ of Chicago, Chicago, IL; [4]LabCorp, Durham, NC.*

Background: Renal outcome trials in diabetic kidney disease (DKD) have generally used severely increased albuminuria as an eligibility criterion to enrich kidney disease progression risk. However, this approach can hinder recruitment, particularly when reduced estimated glomerular filtration rate (eGFR) is also required.

Methods: In order to estimate prevalence and renal prognostic significance of lesser degrees of albuminuria, we analyzed renal laboratory data obtained at LabCorp testing facilities in a cohort of 18-75 year old diabetic patients who had urinary albumin to creatinine ratio (ACR) and at least 3 eGFR results over a period of at least 1 year (n=329,841) between November 2011 and August 2015. Individual eGFR linear regression coefficients were calculated to assess annual rates of eGFR decline across the entire population and in subsets classified according to initial eGFR (>90, 60-89, 30-59 or 15-29 mL/min/1.73m^2) and ACR category (<30, 30-99, 100-299, 300-2999 or > 3000 mg/g).

Results: Mean (SD) age, initial eGFR and duration of follow-up were 59 (10) years, 81 (21) mL/min/1.73m^2, and 2.6 (0.7) years, respectively. Mean (SD) number of eGFR results was 8 (4). ACR was >30, >100, >300, or >3000 mg/g in 29%, 14%, 7% and 1%, respectively, across the entire population with a shift toward higher levels among patients with lower initial eGFR. Although the overall mean rate of eGFR decline was low (2.17 mL/min/year), 21% had reductions > 5 mL/min/yr. Among patients with initial eGFR 30-59 mL/min/1.73m^2 who were followed for at least 2 years (n=40,454), the proportion of patients with eGFR decline > 40% (initial vs last eGFR) was 7.3% in patients with ACR < 30 mg/g but increased progressively with higher ACR levels (ACR 30-99 mg/g: 12.3%, ACR 100-299 mg/g: 18.8%, ACR 300-2999 mg/g: 44.4%, ACR > 3000 mg/g: 81.1%).

Conclusions: These findings support inclusion of patients with lower ACR levels in large DKD outcome trials and the utility of a current, large clinical laboratory database to optimize renal entry criteria and derive sample size estimates for these studies.

Funding: Pharmaceutical Company Support - LabCorp, Covance

SA-PO725

Prevalence of Proteinuria and Albuminuria in Obese Patients Undergoing Bariatric Surgery Max R. Pommier, Satyam Patel, David Selzer, Jordan L. Rosenstock. *Nephrology, Lenox Hill Hospital, NYC, NY.*

Background: Obesity is recognized as a risk factor for kidney disease and both proteinuria and albuminuria have been associated with obesity. The actual prevalence of albuminuria and proteinuria in obese patients in the US has not been clearly described. Furthermore, obesity is associated with risk factors of kidney disease such as diabetes and hypertension and the prevalence excluding these risk factors is uncertain. In this study, we sought to determine the prevalence of albuminuria and proteinuria with and without diabetes and hypertension.

Methods: Consecutive patients undergoing bariatric surgery were recruited. Urine samples were collected from each patient prior to surgery and sent for urine albumin/creatinine and urine protein/creatinine. Albuminuria was defined as an albumin to creatinine ratio of more than 30 mg and proteinuria as a protein to creatinine ratio of greater than 300 mg.

Results: The study included 219 patients. The mean age was 42 years and mean BMI was 44. Diabetes (DM) was present in 25%. Hypertension (HTN) was present in 47%. The prevalence of proteinuria and albuminuria was 7.5% (95% CI: 4.3-11.9%) and 19.7% (95% CI: 14.2-26.2%) respectively. Among those without DM but who had HTN, 3.2% (95% CI: 0.4-11.2) had proteinuria and 17% (95% CI 8.4-30.9) had albuminuria. Of patients with neither DM nor HTN, 3% (95% CI: 0-6%) and 11% (95% CI: 5-17%) had proteinuria and albuminuria respectively. Diabetics had more proteinuria and albuminuria than the non-diabetic groups. The non-diabetic groups did not differ significantly from each other in terms of prevalence of proteinuria and albuminuria. The BMI for diabetics did not differ from non-diabetics. On multivariate analysis, only the presence of DM was associated with proteinuria and albuminuria.

Conclusions: In conclusion, we found a relatively high prevalence of microalbuminuria and proteinuria in an urban, obese population. When diabetics were excluded, there was a much lower prevalence. Patients who had neither DM nor HTN had less microalbuminuria than those with hypertension, but still had much more than seen in the general US population, likely reflecting an adverse effect of obesity itself on renal physiology.

SA-PO726

Effects of Bariatric Surgery on Albuminuria and Estimated Glomerular Filtration Rate in Obese, Diabetic Patients Pei Loo Tok,[1] Chieh-Suai Tan,[1] Meifen Zhang,[2] Kwang Wei Tham.[2] *[1]Renal Medicine, Singapore General Hospital, Singapore, Singapore; [2]Endocrinology, Singapore General Hospital, Singapore, Singapore.*

Background: Bariatric surgery is an established treatment for patients who have obesity with BMI more than 35kg/m2 and type two diabetes mellitus (T2DM) not achieving recommended targets with medical therapy. However, renal outcomes after bariatric surgery are not well studied. The aim of our study is to determine the impact of bariatric surgery on urine albumin creatinine ratio (UACR), serum creatinine and estimated glomerular filtration rate (eGFR) in our multi-ethnic population in Singapore.

Methods: This is a single centre retrospective study of obese T2DM patients who underwent bariatric surgery from 2008 to 2013. Comparison was made between serum creatinine and UACR before surgery and at the last follow up visit. Estimated glomerular filtration rate was calculated by substitution of adjusted body weight (ABW) into the Cockcroft gault equation. Secondary outcomes of weight, glycemic control and blood pressure (BP) were also recorded.

Results: A total of 83 patients (Age 45+/- 9 years; 55% females) with BMI 42 +/- 9 kg/m2 and HbA1c 8.5+/-1.6% underwent bariatric surgery (78.3% laparoscopic gastric bypass and 21.7% laparoscopic sleeve gastrectomy). UACR results done preoperatively and on follow up was done for 82% of the patients (68/83). Of the patients who were microalbuminuric, 69% (20/29) regressed to normoalbuminuria (p<0.01). Of the patients who were macroalbuminuric, 50% (6/12) patients regressed to microalbuminuria but none to normoalbuminuria. The mean creatinine at baseline and at last follow up was 87+/- 48 umol/L and 79+/- 49 umol/L. The eGFR at baseline and at last follow up was 128 +/- 55 ml/min and 137 +/- 61 ml/min (p<0.001). At last follow up, the BMI was 32 +/- 8 kg/m2 and the HbA1c was 6.1 +/- 0.9 %.

Conclusions: There is significant improvement of UACR in obese T2DM patients after bariatric surgery in addition to benefits of weight loss and improved glycemic control.

SA-PO727

Glomerular Hyperfiltration and Increased Efferent Arteriolar Resistance Are Present in Subjects with Impaired Fasting Glucose and/or Impaired Glucose Tolerance Akihiro Tsuda, Eiji Ishimura, Hideki Uedono, Mitsuru Ichii, Shinya Nakatani, Masaaki Inaba. *Dept of Nephrology, Dept of Metabolism, Endocrinology and Molecular Medicine, Osaka City Univ Graduate School of Medicine, Osaka, Japan.*

Background: Glomerular hyperfiltraton is known to be present in subjects with impaired fasting glycaemia (IFG)(Melsom T, et al. Diabetes Care, 2011). However, little is known about the precise intrarenal hemodynamic abnormalities in subjects with with IFG and/or impaired glucose tolerance (IGT). The aim of the present study is to evaluate intrarenal hemodynamics in subjects with normal glucose tolerance (NGT) and in those with IFG and/or IGT.

Methods: 36 subjects (57.1 ± 12.1 years, 17 males and 19 females), who were planned to provide a kidney for transplantation, were enrolled. 75g oral glucose tolerance test (75g-OGTT), measured GFR (inulin clearance;C_{in}) and renal plasma flow (para-aminohippurate clearance) were performed in all subjects. Intrarenal hemodynamic parameters (R_e; efferent arteriolar resistance, R_a; afferent arteriolar resistance, P_{glo}; intraglomerular hydrostatic pressure) were calculated by Gomez's formulae.

Results: Of 36 subjects, 25 showed NGT, and 11 showed IFG and/or IGT by 75g-OGTT. eGFR of IFG and/or IGT was not significantly different from that of NGT. C_{in} (100.0±28.4 vs.78.7±17.1, p=0.065), FF (0.26±0.08 vs. 0.22±0.04 %;p=0.09), R_e (3574.7±1573.0vs.2423.7±536.3, p=0.0078) and P_{glo} (59.6±9.0vs.54.6±5.5, p=0.025) of IFG and/or IGT subjects were higher than those of NGT subjects. R_e (r=0.642, p<0.0001) and FF (r=0387,p=0.0197) were significantly, positively associated with fasting plasma glucose (FPG). In multiple regression analyses after adjustments of age, gender, and body mass index, FPG (R_e : β=0.59, p<0.0001, FF: β=0.300, p=0.077), 2-hr average glucose levels in 75g-OGTT (R_e : β=0.45, p=0.019, FF: β=0.430, p=0.015) and HbA1c (R_e : β=0.35, p=0.065, FF: β=0.440, p=0.009) were significantly associated with R_e and FF.

Conclusions: eGFR cannot be used in evaluation of glomerular hyperfiltration in IFG and/or IGT subjects. Hemodynamic abnormalities, possibly caused by increased R_e, associated with poor glycemic control are present even in IFG and/or IGT subjects.

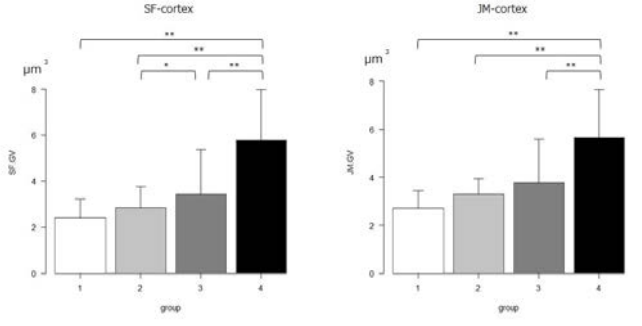
SA-PO728

Diabetes and Hypertension Synergistically Exacerbates Glomerular Hypertrophy Takaya Sasaki, Kentaro Koike, Kotaro Haruhara, Nobuo Tsuboi, Go Kanzaki, Yusuke Okabayashi, Yoichi Miyazaki, Tetsuya Kawamura, Makoto Ogura, Takashi Yokoo. *Nephrology and Hypertension, The Jikei Univ School of Medicine, Minato-ku, Tokyo, Japan.*

Background: Glomerular hypertrophy is an early histopathological finding in diabetic nephropathy that precedes the development of diabetes-specific glomerular lesions. Although hypertension is a major clinical feature associated with a poor renal outcome in diabetes, no previous study has analyzed diabetic glomerular hypertrophy in relation to hypertension in humans.

Methods: Autopsied kidneys without renal dysfunction (eGFR >60 ml/min/1.73 m^2) were analyzed to estimate the glomerular volume (GV) in different parts of the renal cortex. The mean GV was calculated from a formula involving the glomerular surface area (approximately 50 glomeruli measured per cortex).

Results: We analyzed a series of 80Japanese autopsy specimens. The average values were age of 70 years and estimated glomerular filtration rate (eGFR) of 98 ml/min/1.73m^2. The autopsied specimens were obtained from normotensive non-diabetes patients (n=31), hypertensive non-diabetes patients (n=28), normotensive diabetes patients (n=13), and hypertensive diabetes patients (n=8). The mean GV in the diabetic hypertensive patients was markedly higher than in the other groups in both superficial (SF) and juxtamedullary (JM) cortices (figure).



*:p<0.05, **:p<0.001
Group 1: non-diabetic normotensive group, Group 2: non-diabetic hypertensive group
Group 3: diabetic normotensive group, Group 4: diabetic hypertensive group

The factors independently associated with the mean GV were a low glomerular density, diabetes and hypertension in the SF cortex, and diabetes and hypertension in the JM cortex. In contrast, neither age nor renal function nor degree of glomerulosclerosis were found to be related to the mean GV in either cortex in multivariate analyses.

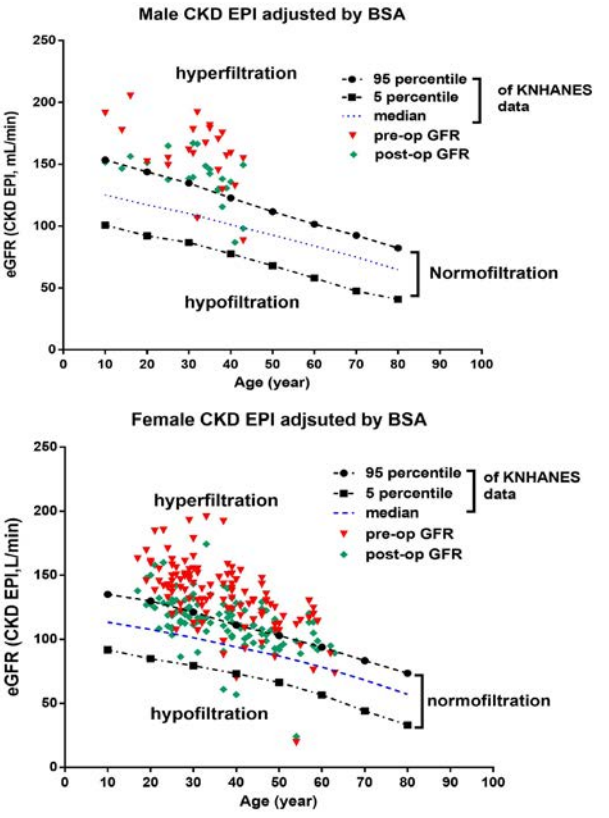
Conclusions: These results suggest that diabetes and hypertension may synergistically exacerbate glomerular hypertrophy across all layers of the human renal cortex.

SA-PO729

Predictors of Resolution of Glomerular Hyperfiltration in Obese Patients following Bariatric Surgery Sinae Lee,[1] Suyeon Park,[2] Hye Ran Kang,[1] Jin Seok Jeon,[1] Hyunjin Noh,[1] Dong-Cheol Han,[1] Soon Hyo Kwon.[1] *[1]Div of Nephrology, Dept of Internal Medicine, Soonchunhyang Univ Seoul Hospital, Seoul, Korea; [2]Dept of Biostatistics, Soonchunhyang Univ Seoul Hospital, Seoul, Korea.*

Background: Obesity is associated with increased glomerular filtration rates (GFR). Bariatric surgery is efficient to improve glomerular hyperfiltration. The aim of this study was to elucidate the predictors of resolution in glomerular hyperfiltration.

Methods: We prospectively enrolled obese patients who underwent bariatric surgery and had follow up more than one-year.Glomerular hyperfiltration was defined as estimated GFR (eGFR) above 95 percentile of GFR values in age, sex-matched cohorts extraced from the Korea National Health and Nutrition Examination Survey (KNHANES) Database. GFR was estimated using a body surface area (BSA)-adjusted Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (mL/min) at the time of surgery and annually during follow-up period.



Results: Among total 136 of eligible patients, ninety-nine patients with glomerular hyperfiltration (age range, 14-58; 16 men; 83 women) were analyzed. Median follow-up period was 2 years (range, 1 to 4 years). 44 Diabetic (32%) and 45 hypertensive (33%) patients were included. Bariatric surgery decreased eGFR (150.0±18.5 vs. 126.5±16.7 mL/min; p<.0001). Among them, eGFR of 49 (50%) patients returned to the normofiltration range (5-95 percentile of eGFR in KNHANES). Multivariate analysis identified pre-operation BMI (p=0.001, OR=0.80; 95% CI= 0.70-0.92) and age (p=0.01, OR=1.12; 95% CI=1.02-1.21) as independent factors of resolution of glomerular hyperfiltration at surgery.

Conclusions: The predictive factors for resolution of increased GFR following bariatric surgery include BMI and age at surgery time.

SA-PO730

Urinary Angiotensinogen (AOG) Is Increased in Type I Diabetes with Microalbuminuria Minghao Ye, Jan A. Wysocki, Ahmed Mohamed Khattab, Hasan Issa, Matthew Adam Gutterman, Mark E. Molitch, Daniel Batlle. *Nephrology/Endocrinology, Feinberg School of Medicine, Chicago, IL.*

Background: An increase in urinary AOG, a key component of the RAS, has been reported in CKD patients including some with type 1 and 2 diabetes. These patients usually had macroalbuminuria and were receiving RAS blockers which may alter AOG. At the stage of macroalbuminuria AOG, like albumin, can be filtered as alterations in glomerular permeability have developed since both proteins have a similar molecular weight. We evaluated urinary AOG in biosamples from patients with mild elevations in albumin excretion rate (AER) from a cohort where hypertension was an exclusion criteria and RAS blockers were not used.

Methods: Biosamples were obtained from NIDDK repositories from participants in the Diabetes Control and Complications Trial (DCCT). AOG in patients with microalbuminuria was compared to a group of normoalbuminuric participants matched for the following: GFR, SBP, DBP, HbA1C, age, gender, diabetes duration and allocation to intensive or conventional insulin therapy. (Table)

Results: Urine AOG was increased in biosamples from the group with microalbuminuria as compared to those with normoalbuminuria and similar GFR, HbA1C blood pressure and disease duration (Table). There was no significant correlation between AOG and UAE (R=0.2) within the low range of UAE examined. This suggests that the source of increased AOG is not only filtered AOG from the circulation but also AOG formed intrarenally.

Variable	AER (mg/24hr)	eGFR (ml/ min/1.73m^2)	SBP (mmHg)	HbA1c (%)	Diabetes Duration (months)	Insulin (standard/ intensive)	Urine AOG/ Creatinine (ng/mg)
Controls (n=44)	8 (2-18)	123 (98-150)	112 (96-150)	8.2 (5.4-11.7)	82 (22-172)	24/20	4.0 (0.22-48)
Micro (n=39)	41 (30-88)	126 (97-147)	118 (92-140)	8.3 (6.0-11.7)	99 (26-180)	18/21	9.7 (1.38-393)
p value	0.0001	NS	NS	NS	NS	NS	0.004

With exception of insulin treatment, all other values represent median (range).

Conclusions: Urinary AOG is increased in persons with type 1 diabetes who have microalbuminuria in the absence of hypertension or RAS blocker therapy for albuminuria. Urinary AOG is a potential early biomarker of diabetic kidney disease and possibly overactivity of the kidney RAS.

Funding: NIDDK Support

SA-PO731

Urinary Prorenin Is Increased in Patients with Type 1 Diabetes and Nephropathy Jan A. Wysocki,[1] Johannes Rein,[1] Maryam Afkarian,[2] Daniel Batlle.[1] *[1]Northwestern Univ, Chicago, IL; [2]Univ of Washington.*

Background: Prorenin is increased in patients with T1D and T2D with complications, whereas plasma renin activity is not. Recent studies have shown that the soluble prorenin receptor can activate non-enzymatically prorenin, and therefore activate RAS. There is no information on urinary prorenin from patients with diabetes, and the levels are very low in subjects without diabetes. Proteolytic and non-proteolytic activation of prorenin may be important in kidney RAS overactivity in DN. We evaluated urinary prorenin as well as active renin in biosamples from subjects with T1D who have developed DKD and controls who had not, despite longstanding diabetes (>25 years).

Methods: Biosamples and clinical data from people with T1D were obtained from the Kidney Research Institute DKD Repository of the University of Washington. DKD was defined as either a urine ACR ≥300 mg/g or an eGFR <60 mL/min per 1.73 m^2 and ACR ≥30 mg/g. People with longstanding diabetes but no evidence of DKD had≥30 years of T1D, estimated eGFR>90 mL/min per 1.73 m^2, and ACR <300 mg/g. Samples for active renin were first concentrated before applying to ELISA. Urinary prorenin was measured using ELISA detecting prorenin only.

Results: Prorenin was detectable in 81% (30/37) of samples from the cases but only in 51% of the urines (22/43) from the controls with diabetes who did not have diabetic kidney disease. Median urine Prorenin/Cr (IQR) was significantly higher in DKD biosamples 99 (33,303) pg/mg than in biosamples from those without DKD 39 (21, 84) pg/mg, p<0.005. Median urine active renin/Cr was also increased in subjects with DKD 2.9 pg/mg (1.8,7.5) as compared to those without it 1.4 pg/mg (0.9, 3.6), p<0.05. There was a significant positive correlation between urinary prorenin and active renin protein (0.676, p<0.001).

Conclusions: Urinary prorenin could be a source of increased urinary active renin in persons with type 1 diabetes. Both prorenin and active renin are increased in patients with DKD as compared to those who have escaped this complication after longstanding diabetes. Prospective studies are needed to examine the potential predictive value of urinary prorenin and active renin for the development of DKD.

Funding: NIDDK Support

SA-PO732

Urinary Excretion of Podocyte mRNA Is an Early Diagnostic Biomarker in Diabetic Nephropathy Akihiro Fukuda, Akihiro Minakawa, Yuji Sato, Kazuo Kitamura, Shouichi Fujimoto. *First Dept of Internal Medicine, Univ of Miyazaki, Miyazaki, Japan.*

Background: Albuminuria is used for early diagnostic assessment of diabetic nephropathy but does not always reflect disease activity. Recent studies suggest that podocyte injury has already begun at the early stage of diabetic nephropathy. Podocyte cell lineage-specific mRNA can be recovered from urine pellets. The study examined whether urinary excretion of podocyte mRNA can be used as an early diagnostic biomarker in diabetic nephropathy.

Methods: We examined both animal models of diabetic nephropathy and human urine samples. The leptin-deficient Zucker diabetic Fatty (ZDF-fatty) rat model of type 2 diabetes was compared with heterozygous ZDF rats as a control. From January 2015 to June 2015, spot urine samples from out-patients at various stages of diabetes (normoalbulinuria group: n=99, microalbuminuria group: n=38, macroalbuminuria group: n=37) and healthy controls (n=41) without diabetes or hypertension, were taken. We examined urinary excretion of podocyte mRNA and urine albumin/creatinine ratio, and measured glomerular volume, and podocyte number and density in the rat model.

Results: ZDF-fatty rats became diabetic with increased blood glucose and glycosuria by 10 weeks. Albuminuria significantly increased by 10 weeks, however, urinary excretion of podocyte mRNA increased by 8weeks in ZDF-fatty rats. At 6 weeks, podocyte numbers had not decreased, while glomerular volume significantly increased and podocyte density significantly decreased compared to controls, suggesting that podocyte stress had begun at the early stage of diabetes. Similar results were observed in human participants. Urinary excretion of podocyte mRNA increased dependent on albuminuria level in diabetes patients *vs.* controls (normoalbuminuria: 4.3-fold; microalbuminuria: 4.2-fold; macroalbuminuria: 16.7-fold). Urinary excretion of podocyte mRNA in the normoalbuminuria group at the interquartile range of the control level of albuminuria significantly increased *vs.* controls (6.7-fold).

Conclusions: Urinary excretion of podocyte mRNA begins to increase much faster than albuminuria in both animal models and humans, and could be an early diagnostic biomarker in diabetic nephropathy.

Funding: Government Support - Non-U.S.

SA-PO734

Impaired Leukocyte Glucose 6-Phosphate Dehydrogenase (G6PD) Response to Hyperglycemia Is Associated with Rapidly Progressive Kidney Disease in Individuals with Diabetes Matthew R. Lynch,[1,2] Robert C. Stanton.[1,2] *[1]Div of Nephrology, Beth Israel Deaconess Medical Center, Boston, MA; [2]Kidney and Hypertension Section, Joslin Diabetes Center, Boston, MA.*

Background: Mechanisms of diabetic kidney disease (DKD) progression are unclear. An appropriate response to oxidative stress is an increase in G6PD activity, the source of the essential antioxidant NADPH. Impaired G6PD activity occurs in animal models of DKD and in leukocytes from animals and persons with diabetes, suggesting that leukocyte G6PD activity correlates with kidney GP6D activity. We hypothesized that leukocyte G6PD activity response would be impaired in patients with progressive DKD.

Methods: 45 patients with DKD were recruited; those with at least a 3.3 ml/min/year loss in eGFR since establishing care were deemed to be rapid progressors. Rapid progressors with an uninterrupted decline in eGFR were judged linear rapid progressors (LRP), while the rapid progressors with at least one period of at least one year of stable eGFR were called non-linear rapid progressors (NLRP). Non-rapid progressors (NRP) included all remaining patients. The change in leukocyte G6PD activity to high glucose stress was measured. Leukocytes were isolated from whole blood and incubated in normal (5.5 mM glucose) or high glucose (25 mM) conditions for one hour at 37°C. Serum glucose, hemoglobin A1C, creatinine, hemoglobin, albuminuria and medications were abstracted from medical records.

Results: Compared to baseline, leukocyte G6PD activity changes to high glucose stress were decreased in LRP (-19.52±13.85%), unchanged in NLRP (1.9±10.3%), and increased in NRP (18.2±6.47%; p=0.035 versus LRP). There was no difference between the groups' baseline leukocyte or erythrocyte G6PD activity. Albuminuria was higher in LRP than in the other groups (LRP: 3815±1310 mg/g, NLRP: 724.9±569.9 mg/g, and NRP: 454.5±165.8 mg/g; p=0.01 and p<0.001, respectively).

Conclusions: Leukocyte G6PD activity response to high glucose stress was significantly impaired in patients with linear rapidly progressive DKD. Leukocyte G6PD response may act as a surrogate for renal G6PD activity, suggesting that G6PD may be both a biomarker and potential therapeutic target in human DKD.

SA-PO735

Proteomic Analysis Suggests Role of TGF-β Regulatory Proteins in Development of Diabetic Kidney Disease Elwaleed Elnagar,[1] Christian Herzog,[1] Maria Lopes-Virella,[2] Kelly J. Hunt,[2] Michael G. Janech,[2] Ricky Edmondson,[1] John M. Arthur.[1] *[1]Univ of Arkansas for Medical Sciences; [2]Medical Univ of South Carolina.*

Background: Diabetic nephropathy is the leading cause of ESRD in the US but a relatively small percentage of patients with type 2 diabetes have reduced renal function after 15 years. Albuminuria is used to predict decline in renal function but it is neither sensitive nor specific. The goal of this study is to identify novel predictive biomarkers and pathways involved in development of diabetic kidney disease.

Methods: Urine from 10 subjects enrolled in the VA Diabetes Trial who had normal serum creatinine (SCr) and normoalbuminuria at enrollment, but doubled their SCr during follow up, were matched to 10 that had no increase in SCr. Urine proteins were digested with trypsin and analyzed by liquid chromatography/tandem mass spectrometry. Identified proteins were quantified using spectral counting and differences between progressors and nonprogressors were identified using a t-test with Benjamini-Hochberg correction for multiple comparisons.

Results: We identified 888 proteins with a decoy false discovery rate of 0.08%. After removing proteins primarily expressed in bladder or skin, 20 had p values ≤0.05. Vasorin had the smallest p value (0.001) and was lower in progressors. Vasorin binds TGF-B preventing its stimulation of the receptor. Among the 20 proteins with p≤0.05, 7 (vasorin, plasma serine protease inhibitor, gamma-glutamylcyclotransferase, oxidized low-density lipoprotein receptor 1, angiotensinogen, kallikrein-1 and L-selectin) were involved in TGF-B signaling and the directional changes in five are consistent with increased TGF-B signaling. Observed changes in other mediators with slightly higher p values also would result in an increase in TGF-B (MMP-9, latent TGF binding protein 2, activin receptor).

Conclusions: A high percentage of differentially abundant urine proteins in patients that will develop diabetic kidney disease are involved in regulation of TGF-B signaling and most of the differentially abundant proteins in the pathway should lead to an increase in TGF-B. This is an intrarenal pro-fibrotic signal that can potentially be used to predict patients that will develop CKD.

Funding: NIDDK Support, VA Support

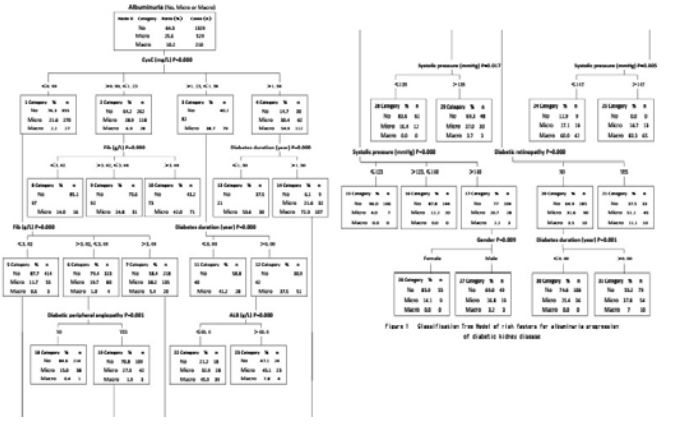
SA-PO736

Classification Tree Model Analysis on Related Factors of the Incidence and Degree of Albuminuria of Diabetic Kidney Disease Wenbo Zhao,[1] Meijun Si,[1] Hui-Qun Li,[1] Zhouqing Gan,[2] Weiming Han,[2] Tan-Qi Lou.[1] *[1]Dept of Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China; [2]Zhongshan School of Medicine, Sun Yat-sen Univ, Guangzhou, Guangdong, China.*

Background: To analyze the impact factors for the degree of albuminuria of diabetic kidney disease by the classification tree model.

Methods: A total of 2068 hospitalized patients with type 2 diabetes were enrolled. According to glomerular filtration rates and urine albumin quantification,the patients were divided into type 2 diabetes group (1329 cases) , early diabetic renal damage group (529 cases) and macroalbuminuria group(210 cases) . The clinical data of the patients were recorded to analyze the main influential factors for the microalbuminuria of type 2 diabetic patients using the Exhaustive CHAID classification tree algorithm.

Results: Eight important explanatory variables were screened out by the classification tree model from the 30 candidate variables related to microalbuminuria and macroalbuminuria., including Cys C levels, fibrinogen,SBP , retinopathy, sex, diabetes peripheral vascular disease, diabetic duration, serum albumin . CysC was the main factor of DKD,CysC > 1.58 mg/L and diabetes duration of 1.50 years or less appear microalbuminuria is a 53.6% chance;CysC > 1.58 mg/L, diabetes duration > 1.50 years and SBP > 147 mmHg have 83.3% chance of macroalbuminuria.



Conclusions: Classification tree model can effectively analyze the different levels of albuminuria related influencing factors, and identify people at high risk characteristics, is conducive to early prevention and treatment.

SA-PO737

Fibrinogen May Be an Independent Predictor of Diabetic Kidney Disease Wenbo Zhao,[1] Hui-Qun Li,[1] Zengchun Ye,[1] Ming Li,[1] Meijun Si,[1] Zhouqing Gan,[2] Weiming Han,[2] Tan-Qi Lou.[1] *[1]Dept of Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China; [2]Zhongshan School of Medicine, Sun Yat-sen Univ, Guangzhou, Guangdong, China.*

Background: Analysis of the correlation of fibrinogen and different stages albuminuria in diabetic kidney disease.

Methods: As a Cross-sectional study,we collected hospital clinical data of 1152 cases for type 2 diabetes, without albuminuria group (785 cases), microalbuminuria group (285 cases) and macroalbuminuria group (112 cases),analying albuminuria progress related influence factors for multiple factors regression.

Results: The levels of fibrinogen was in the three groups respectively for(3.46±1.33) g/L, (4.16±1.32)g/L, and(4.85±1.28)g/L(P=0.000). In the without albuminuria group and microalbuminuria group, the multi-factor Logistic regression analysis showed fibrinogen (Fib) (β= 0.463, P = 0.000, OR = 1.589), and retinopathy, CysC, systolic blood pressure into the model. In microalbuminuria group and macroalbuminuria group, the multi-factor Logistic regression analysis showed fibrinogen (Fib) (β=0.463,P=0.000, OR=1.589), and retinopathy, CysC, Waist-to-hip ratio into the model.

Conclusions: Fibrinogen associated with different stages albuminuria , that could be independent predictors of diabetic kidney disease.

SA-PO738

Non-Alcoholic Fatty Liver Disease Is Not Related to the Incidence and Degree of Albuminuria of Diabetic Kidney Disease Wenbo Zhao, Zengchun Ye, Ming Li, Meijun Si, Hui-Qun Li, Tan-Qi Lou. *Dept of Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzou, Guangdong, China.*

Background: To analyze the association between non-alcoholic fatty liver disease (NAFLD) and the Incidence and degree of albuminuria of diabetic kidney disease in patients with type 2 diabetes.

Methods: the incidence of diabetic nephropathy was assessed in 2068 type 2 diabetic patients. The NAFLD was diagnosed based on liver ultrasound. The difference in diabetic nephropathy incidence between patients with and without NAFLD was tested by $\chi 2$. Multinomial logistic regression analysis was used to assess the factors associated with degree of albuminuria of diabetic kidney disease.

Results: The incidences of NAFLD and diabetic nephropathy in participants were approximately 44% (910/2068) and 35.7% (739/2068) respectively, microalbuminuria and macroalbuminuria in participants were approximately 25.6% (529/2068) and 10.1% (210/2068) respectively, and there were difference in the prevalence of degrees of albuminuria of diabetic kidney disease between patients with and without NAFLD (p= 0.000). The incidences of NAFLD was highest in Patients without albuminuria (64.3%, 628/1329), in Patients with microalbuminuria (25.6%, 225/529), in Patients with macroalbuminuria (10.2%, 57/210). In multinomial logistic regression analysis, Fasting blood-glucose, BMI, Waist–hip ratio, fibrinogen, peripheral neuropathy, diabetic retinopathy, CysC, history of hypertension were significantly associated with Patients with microalbuminuria, whereas age of onset, high blood pressure, fibrinogen, diabetic retinopathy, CysC, triglyceride (TG), high-density lipoprotein, low density lipoprotein were significantly associated with were significantly associated with Patients with macroalbuminuria. NAFLD were not associated with the degree of albuminuria of diabetic kidney disease.

Conclusions: The present results suggest that NAFLD is not related to the the Incidence and degree of albuminuria of diabetic kidney disease .

SA-PO739

Glomerular IgM Deposition Predicts Renal Outcome in Patients with Type 2 Diabetes Xi Tang, Li Li, Yu Han Li, Fang Liu. *Nephrolgoy, West China Hospital, Sichuan Univ, Chengdu, Sichuan, China.*

Background: Immunofluorescent staining reveals IgG, IgM, C3 deposits in renal tissue of some patients with type 2 diabetes. However, the clinical implication of such immune complex deposition is unclear.

Methods: A retrospective study was carried out in the west china hospital, Sichuan university, China. Among the 347 patients with diabetes who underwent renal biopsy from 2001 to 2015, 190 cases had pure diabetic nephropathy. According to the classification of Tervaert et al, 108 patients (glomerular class I to III) with at least 12-month follow-up were enrolled in this study. Clinical and pathological data were collected. Immunofluorescent staining was classified into three categories according to the intensity (0=none, 1=weekly positive, and 2=positive).Renal survival was estimated by the Kaplan-Meier method. The Cox proportional hazards model was employed to identify the risk parameters associated with renal survival.

Results: The number of cases with positive glomerualr IgG, IgM and C3 staining were 29, 40, and 28, respectively. Over a median follow-up of 32 months, 38 cases developed into ESRD, 19 cases died. The Median time of renal survival 60(47.40,72.60)months. The renal survival rates at5 years after biopsy were 41.7%. By multivariate Cox proportional analysis, smoking [HR, 2.775(1.281, 6.010), *P*=0.010], eGFR [HR, 0.981(0.962, 0.999),*P*=0.045], and positive glomerular IgM deposit [1.997(1.095,4.269),*P*=0.039] were independent predictors of ESRD. According to the intensity of IgM deposits, patients were divided into three groups. Compared with those with none renal IgM deposits, patients with positive staining of glomerular IgM had significant lower baseline eGFR (45.78±18.08 *v.s.* 66.69±30ml/min/1.732m2). Age, gender, duration, hypertension, BMI, diabetic retinopathy , diabetic peripheral neuropathy, 24 hour proteinuria, serum IgG, IgM, C3 and albumin, glomerular class were similar among the groups.

Conclusions: Glomerular IgM deposits as well as smoking and eGFR at the baseline of renal biopsy were the independent risk factors of ESRD in the patients with type 2 diabetic nephropathy.

SA-PO740

Impact of Anti-Erythropoietin Receptor Antibodies in Diabetic Patients with Chronic Kidney Disease Akinori Hara, Akihiko Koshino, Yasunori Iwata, Norihiko Sakai, Miho Shimizu, Kengo Furuichi, Takashi Wada. *Div of Nephrology, Kanazawa Univ Hospital, Kanazawa, Japan.*

Background: To examine the clinical significance of autoantibodies to the erythropoietin receptor (EPOR) in diabetic patients with chronic kidney disease (CKD).

Methods: One hundred and twelve type 2 diabetic patients with CKD who have been followed up until 2014 (mean age, 62.9±12.5 years) were enrolled in this study. Anti-EPOR antibodies in sera from these patients were measured using enzyme-linked immunosorbent assay.

Results: Anti-EPOR antibodies were detected in 26 (23%) of the 112 diabetic patients enrolled. Patients with anti-EPOR antibodies were older and had lower estimated GFR (eGFR) than those without. In addition, in patients with anti-EPOR antibodies, hemoglobin concentration was lower than those without. During follow-up period, end-stage renal failure (ESRF) requiring dialysis therapy was more frequently observed in patients with anti-EPOR antibodies than in those without, and presence of the antibodies were significant risk factors for progression of ESRF. In 52 patients who had undergone renal biopsy, positivity for anti-EPOR antibodies was associated with the extent of interstitial inflammation.

Conclusions: These results suggest that anti-EPOR antibodies might be involved in the progression of CKD through interstitial inflammation, and the presence of the antibodies may be a predictor for renal dysfunction in type 2 diabetic patients.

Funding: Government Support - Non-U.S.

SA-PO741

Novel Tubular Biomarkers Predict Renal Progression in Type 2 Diabetes Mellitus: A Prospective Cohort Study Kasemsan Aramsaowapak, Bancha Satirapoj, Theerasak Tangwonglert, Naowanit Nata, Amnart Chaiprasert, Prajej Ruangkanchanasetr, Ouppatham Supasyndh. *Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand.*

Background: Estimated glomerular filtration rate (GFR) and albuminuria are routine for assessing renal progression. Tubulointerstitial injury is both a key feature of diabetic nephropathy and an important predictor of renal dysfunction. Novel tubular biomarkers that relate to renal injury in diabetic nephropathy could improve risk stratification and prediction.

Methods: A prospective cohort study, a total of 303 type 2 diabetes patients were followed up. The baseline values of urine Cystatin-C to creatinine ratio (UCCR), urine angiotensinogen to creatinine ratio (UANG), urine NGAL to creatinine ratio (UNGAL) and urine KIM-1 to creatinine ratio (UKIM-1) were measured. The primary outcome was a decline in estimated GFR of ≥25% per year from baseline.

Results: The median follow-up period was 12.5 months, and the primary outcome was noted in 13.5%. Urine tubular biomarkers of UCCR, UANG, UNGAL and UKIM-1 were significantly higher according to the degree of albuminuria and all of them had significant higher in patients with the rapid decline in estimated GFR of ≥25% per year from baseline. All biomarkers predicted primary outcome with ROC for UCCR = 0.72; 95% CI 0.64-0.79, UANG = 0.71; 95% CI 0.63-0.79, UNGAL = 0.64; 95% CI 0.56-0.72. In multivariate COX regression analysis, the number of patients with rapid renal progression was higher in those in the upper quartiles of all biomarkers than in those in the lower quartiles.

Conclusions: The study supported that type 2 diabetic patients with high levels of urine tubular biomarkers (Cystatin-C, angiotensinogen, KIM-1 and NGAL) had more rapid decline in renal function. These tubular biomarkers may be independent predictors of the progression of type 2 diabetic nephropathy.

SA-PO742

p66Shc: A Novel Biomarker of Tubular Oxidative Injury in Patients with Diabetic Nephropathy Xiaoxuan Xu,[1,3] Xuejing Zhu,[1] Yachun Han,[1] Chun Hu,[1] Chang Wang,[1] Shuguang Yuan,[1] Yuan Yang,[1] Li Xiao,[1] Fu-You Liu,[1] Yashpal S. Kanwar,[2] Lin Sun.[1] *[1]Second Xiangya Hospital, China; [2]Depts of Pathology & Medicine, Northwestern Univ, Chicago; [3]Health Management Center, Xiangya Hospital.*

Background: Increased p66Shc expression has been associated with diabetic nephropathy (DN). However, whether p66Shc can serve as a potential biomarker for tubular oxidative injury in DN is unknown.

Methods: We measured the expression of p66Shc in peripheral blood monocytes (PBMs) and renal biopsy tissues from DN patients and then analysed the relationship between p66Shc expression and the clinical characteristics of patients with DN. Patients were divided into 4 groups (class IIa, class IIb, class III and the control group). qPCR, Western blotting and immunohistochemistry were performed.

Results: The results showed that both p66Shc and p-p66Shc expression significantly increased in PBMs and kidney tissues of DN patients. Moreover, Spearman's correlation and multiple regression analyses were carried out. A positive relationship between the p66Shc expression and oxidative stress was found. p66Shc and oxidative stress were significant predictors of the degree of tubular damage. In addition, p66Shc expression was positively correlated with the concentrations of β-NAG, UACR and 8-OHdG, low-density lipoprotein and blood glucose levels, and duration of diabetes in patients with DN from class IIa to class III.

Conclusions: These data indicated that increased expression of p66Shc may serve as a therapeutic target and a novel biomarker of DN.

Funding: Government Support - Non-U.S.

SA-PO743

APX-501 Protein as a Novel Biomarker for Diabetic Nephropathy in Type 2 Diabetes Jin Joo Cha,[1] Young Sun Kang,[1] Gyu Sik Choi,[1] Hye Sook Min,[2] Ji Eun Lee,[2] Hyunwook Kim,[3] Jungyeon Ghee,[1] Ji Ae Yoo,[1] Kitae Kim,[4] Sang Youb Han,[5] Kum Hyun Han,[5] Sewon Oh,[5] Dae R. Cha.[1] *[1]Korea Univ; [2]Wonkwang Univ; [3]Yonsei Univ; [4]Dong-A Univ; [5]Inje Univ, Republic of Korea.*

Background: Excess production of reactive oxygen species in many tissues leads to tissue injuries through inflammation and fibrosis. Recently, we identified that APX-501 protein was synthesized from endothelial cells and is involved in oxidative stress in the kidney. Therefore, we investigated the role of APX-501 as a new biomarker for diabetic nephropathy in type 2 diabetic patients.

Methods: Preliminary animal and in vitro expriments were performed to identify the expression of APX-501 protein in renal tissues and cells in diabetic condition. For human study, 171 type 2 diabetic patients and 65 healthy control subjects participated in the study. The study subjects were divided into 1) nondiabetic healthy controls with normoalbuminuria (n=65), 2) normoalbuminuric diabetic group (n=66), 3) microalbuminuric diabetic group (n=52) and 4) overt proteinuria group (n=53). Plasma levels of APX-501 were measured by ELISA.

Results: In type 2 diabetic db/db mice, plasma level and renal expressions of APX-501 were increased according to age compared with those in nondiabetic db/m mice. In cultured murine podocytes and mesangial cells, high glucose condition markedly increased APX-501 synthesis and secretion. In type 2 diabetic patients, plasma APX-501 concentrations were significantly higher compared to healthy controls. Plasma APX-501 levels were the highest in patients with overt proteinuria. APX-501 levels were inversely correlated with body mass index (BMI) and positively correlated with systolic blood pressure, postprandial glucose levels, HOMA-IR, plasma retinol binding protein 4 (RBP-4) and urinary albumin(UAE) excretion. UAE, RBP-4 and BMI were independent determinants of plasma APX-501 concentration. APX-501 levels were not correlated with estimated glomerular filtration rate and we could not detect urinary excretion of APX-501 even in the overt proteinuria group.

Conclusions: These findings suggest that APX-501 synthesis may be activated in early stage of diabetic environment, may be a new biomarker for diabetic nephropathy in type 2 diabetic patients.

SA-PO744

Longitudinal Associations of Urinary Sodium and Potassium Excretion with eGFR and Albuminuria in Type 1 Diabetes Jessica B. Kendrick,[1] Leila R. Zelnick,[2] Michael Steffes,[3] Michel Chonchol,[1] Ian H. De Boer.[2] *[1]Univ of Colorado; [2]Univ of Washington; [3]Univ of Minnesota.*

Background: Patients with type 1 diabetes are at high risk of renal complications. Whether dietary sodium or potassium intake affects the development of kidney disease remains unclear.

Methods: We performed a cohort study of 1391 participants with type 1 diabetes in the Diabetes Control and Complications Trial and its observational follow-up, the Epidemiology of Diabetes Interventions and Complications Study. We measured urinary sodium and potassium excretion in 4-hour timed urine samples collected between 1989-1996. Up to 3 measurements were made per participant and averaged. Over the subsequent 14 years, we ascertained the development of incident reduced eGFR (sustained eGFR <60 ml/min/1.73m^2), ≥30% decline in eGFR and incident albuminuria (sustained albumin excretion rate (AER) ≥30 mg/d). Cox proportional hazards models were used to examine associations of tertiles of urinary sodium and potassium excretion with each outcome, excluding participants who had developed the outcome of interest prior to follow-up.

Results: Baseline mean (SD) age and eGFR were 38 (7) years and 109 (15) ml/min/1.73m^2. After adjustment for demographics, BMI, smoking, SBP, DBP, baseline eGFR and AER, duration of diabetes, HbA1c and use of ACEi/ARBs, lower urinary excretion of sodium and potassium tended to be associated with lower and higher estimated risks of renal outcomes, respectively, but none of these associations was statistically significant (Table).

	Sustained eGFR <60 ml/min/1.73m^2 N=63 HR (95% CI)	≥ 30% decline in eGFR N=70 HR (95% CI)	Sustained AER ≥ 30 mg/d N=319 HR (95% CI)
Urinary Sodium Exretion (mg/d)			
<4122	0.63 (0.33-1.20)	0.79 (0.49-1.28)	0.97 (0.74-1.29)
4122-5843	0.79 (0.41-1.49)	0.62 (0.37-1.04)	0.94 (0.70-1.26)
≥5844	1.0 (REF)	1.0 (REF)	1.0 (REF)
Urinary Potassium Excretion (mg/d)			
<3180	1.22 (0.62-2.41)	1.19 (0.72-1.98)	1.21 (0.90-1.61)
3180-5281	1.25 (0.62-2.41)	0.93 (0.56-1.55)	1.08 (0.81-1.45)
≥5282	1.0 (REF)	1.0 (REF)	1.0 (REF)

Conclusions: Urinary sodium and potassium excretion were not significantly associated with incident kidney disease in type 1 diabetes.

Funding: NIDDK Support

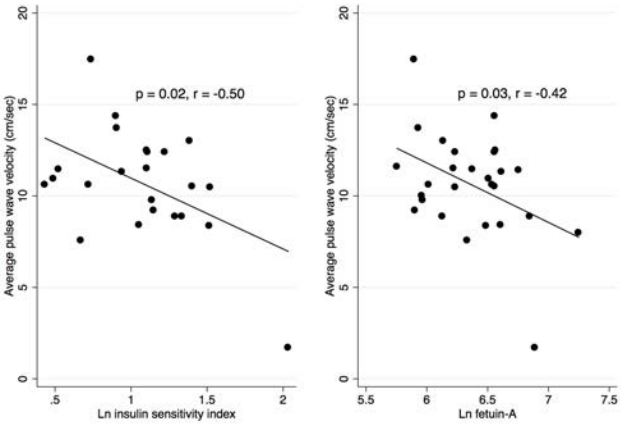
SA-PO745

Fetuin-A and Insulin Resistance Measured by Hyperinsulinemic Euglycemic Clamp Are Independent Determinants of Aortic Stiffness in Patients with CKD Stages 3 and 4 Sudipa Sarkar,[1] Serpil Muge Deger,[1] Leon Hsueh,[3] Ian H. De Boer,[4] Brijesh Patel,[1,2] Edward D. Siew,[1,2] Talat Alp Ikizler,[1,2] Adriana Hung.[1,2] *[1]Vanderbilt Univ, TN; [2]Nashville VA; [3]Univ of Illinois; [4]KRI, Seattle.*

Background: Both increased arterial stiffness and insulin resistance (IR) are highly prevalent and closely associated with cardiovascular disease in chronic kidney disease (CKD). Fetuin-A is a hepatic protein that inhibits arterial calcification and insulin action. In this study, we evaluated whether IR and fetuin-A are important determinants of arterial stiffness.

Methods: In this cross-sectional study, we enrolled 33 individuals with nondiabetic CKD stages 3 and 4 from the Nashville VA Hospital and Vanderbilt. Insulin sensitivity was measured by hyperinsulinemic euglycemic clamp (HEGC). Arterial stiffness was assessed by aortic pulse wave velocity (aPWV). Fetuin-A was measured by ELISA. Pearson correlation was used for univariate analysis and linear regression was used for both univariate and multivariate analyses.

Results: The mean age was 65±11 years, 74% were male, and 27% were African Americans. The mean BMI was 31±5 kg/m^2. Both fetuin-A and insulin sensitivity index (ISI) were negatively correlated with aPWV (r=-0.42, p=0.03 and r=- 0.50 p=0.02, respectively). In the multivariate analysis, ISI (β=-3.54 cm/sec per ln ISI, p=0.02), fetuin-A (β=-3.69 cm/sec per ln fetuin-A, p=0.05), and age (β=0.14 cm/sec per year, p<0.01) were significantly associated with aPWV, but truncal fat (β=-0.01 cm/sec per kg, p=0.34) and creatinine (β=1.57 cm/sec per ln creatinine, p=0.57) were not.



Conclusions: Lower fetuin-A and decreased insulin sensitivity are associated with increased aPWV and may contribute to increased CV risk in patients with CKD. Larger studies are needed to further evaluate the beneficial effect of higher levels of fetuin A in arterial stiffness in CV outcomes in CKD.

Funding: VA Support

SA-PO746

NGAL and C-Cystatin Association with Albumin-Creatinine Relation in Type 1 Diabetes Patients Marcelo Rodrigues Bacci, Priscila Fernandes Alfieri, Francisco Winter Dos Santos Figueiredo, Fernando Luiz Affonso Fonseca. *General Practice, ABC Medical School, Santo Andre, São Paulo, Brazil.*

Background: Type 1 diabetes(T1DM)renal disease is well known because of its histological findings and stablished timeline since the beginning.Early injury kidney biomarkers are well studied in acute status however in chronic conditions as diabetes their relationship with albuminuria is not known.The aim of the study was analyse early kidney injury biomarkers between patients with T1DM and type 2 diabetes(T2DM)with the same pattern of glycemic control.

Methods: It is a cross-sectional study.Patients with the diagnosis of diabetes(type 1 and type 2)were recruited in order to compare the following kidney injury biomarkers:NGAL,C cystatin,creatinine,HbA1C,urinary beta trace protein and urinary albumin/creatinine relation(ACR).Exclusion criteria included patients with end stage renal disease in dialysis, cancer and hospitalized for any reason in the previous 30 days of blood collection.The modified diet of renal disease equation was used in adults to estimate glomerular filtration rate and the modified Schwartz equation to estimate eGFR in children.

Results: A total of 77 patients were included.Of them,56 with T2DM and 21 with T1DM.T1DM had 56.7% of females and a mean age of 23.9 years.T2DM were composed by 69.6% of females and a mean age of 63.5 years. The mean eTFG was 89.76 ml/min/1.73m2 for T1DM patients and 76.8 ml/min/1.73m2 for T2DM.Adjusting the analysis for the same HbA1C level for both groups they did differ with the following parameters:ACR, NGAL and C cystatin.T1DM had a median value of 4.69 for c cystatin and T2DM 4.07 with a $p< 0.001$.Also,ACR was different between them with a $p< 0.001$.The mean value for T1DM was 40.86 mg/g and for T2DM 157.98 mg/g.NGAL mean value was 1.19 in T2DM and 0.19 in T1DM with a $p<0.001$.Groups did not have a statistically significant difference for urinary beta trace protein.

Conclusions: For a same glycemic level, patients with T1DM and T2DM had different patterns of biomarkers of renal dysfunction eve3n with a normal eGFR.NGAL was associated with worse ACR and eGFR in T2DM. C Cystatin was associated inversely with ACR in T1DM. Despite same glycemic control, T2DM had worse ACR than T1DM.

Funding: Private Foundation Support

SA-PO747

Examination of Glycemic Control Index in Diabetic Dialysis Patients under On-Line Hemodiafiltration Yukie Kitajima,[1] Toru Hyodo.[2] *[1]Tokyo Healthcare Univ, Setagaya, Tokyo, Japan; [2]Eijin Clinic and Kurata Hospital Dialysis Center, Hiratsuka, Kanagawa, Japan.*

Background: Glycohemoglobin (HbA1c) of diabetic dialysis patients has been reported to underestimate diurnal blood sugar fluctuations as it is affected by red cell survival, erythropoietin, etc. Therefore, it is recommended in Japan that glycoalbumin (GA) should be used for glycemic control index of diabetic dialysis patients. However, recently in Japan, on-line hemodiafiltration (o-HDF) with high albumin (Alb) leakage has been widely used in dialysis treatment methods due to the reimbursement in the national insurance system since 2012. As GA is affected by albumin metabolism, evaluation of GA values needs to be reexamined for diabetic dialysis patients under HDF. In this study, we examined GA values for different dialysis treatment methods.

Methods: The subjects were 156 diabetic dialysis patients (99 males and 57 females) with an average age of 69.2 ± 12.7 years. Those with Hb of less than 8.0 g/dL, hepatic dysfunction, and transfusion history, were excluded. [Methods] The subjects were divided according to treatment types: a hemodialysis (HD) group (23 patients) and an o-HDF group (133patients). We examined the correlation of GA and HbA1c in comparison with known correlation, and the amount of Alb removed in the HDF group.

Results: A significant positive correlation was observed between GA and HbA1c in the HD group ($R2 = 0.809$ and $p < 0.0001$). Inaba et al. reported a similar result ($r = 0.777$ and $p < 0.001$: J Am Soc Nephrol, 2007). However, the correlation in the o-HDF group was lower than in the HD group ($R2 = 0.316$ and $p < 0.0001$). In the o-HDF group, average of GA, HbAlc and Hb is 20.4 ± 4.7%, 6.0 ± 0.9% and 10.6 ± 1.0g/dl. The mean amount of Alb removed in the effluent in the o-HDF group (24 diabetic dialysis patients) was 2.5 ± 2.17 g per a session. [Discussions] It is possible that GA value is underestimated in the o-HDF group due to the effect of Alb leakage. If Hb value is stable by the therapy, HbA1c may be the golden standard of the diabetic estimation even also in dialysis patients.

Conclusions: For glycemic control index of diabetic dialysis patients, GA and HbA1c need to be used along with the dialysis treatment method.

SA-PO748

Don't Hang Your Hat on Retinopathy in Diabetic Kidney Disease Ambarish Athavale, Amit J. Joshi, Radhika Jaiswal, Albert M. Osei, Peter D. Hart. *Nephrology, Stroger Hosp of Cook County, Chicago, IL.*

Background: In ethnic minorities with type II Diabetes (DM) and "atypical" kidney disease, the frequency of non-diabetic glomerular disease is unknown and whether retinopathy correlates with Diabetic nephropathy (DN) is undetermined. Aim: 1.To describe prevalence of non-diabetic glomerular disease in patients with DM. 2.Correlate retinopathy with Diabetic nephropathy in patients with DM with atypical features.

Methods: Retrospective review of the medical records of 94 patients with DM who had kidney biopsy at our hospital between 01/2010 and 12/2015.

Results:

Age	54.5 ±9.5 yrs	
Gender (M: F)	45:49	
African American Hispanic White Asian/Pacific islander Other	49 36 4 4 1	
Diabetes duration	10 ±7.08 yrs	
Creatinine	2.5±2.1 mg/dl	
A1C	7.06±1.7	
Proteinuria	5.09±4.07 g/day	
Hematuria	49	
Atypical features that prompted kidney biopsy		
Unexplained rise in creatinine	25 (26.5%)	
Nephrotic syndrome, no retinopathy	24 (25.53%)	
Hematuria	9 (9.57%)	
Positive ANA	14 (14.89%)	
Low complements	4 (4.25%)	
Hepatitis C	7(7.44%)	
+ ANCA	4(4.25%)	
Monoclonal band	6(6.38%)	
	Retinopathy	No Retinopathy
DM Nephropathy	19	12
Non Diabetic glomerular disease	14	36
	33	48 (P<0.0001)

60% had non-diabetic glomerular disease and the most common were IgAN (14%) and FSGS (13%), 31% had Diabetic nephropathy and 9% had Diabetic nephropathy and another primary glomerular disease (most commonly arteriolar nephrosclerosis). Retinopathy information was available in 81/94 patients. 33/81 had retinopathy and 48/81 had no retinopathy. Presence of retinopathy did not accurately predict Diabetic nephropathy. Of 33 patients with retinopathy, 14/33 (42.42%) had a non-diabetic glomerular disease while 12/48 (25%) patients with no retinopathy also had Diabetic nephropathy.

Conclusions: Non-diabetic kidney disease is very common in Diabetic ethnic minorities with atypical features. Retinopathy did not reliably predict Diabetic nephropathy. Thus, atypical features, with or without retinopathy warrants kidney biopsy.

SA-PO749

Incidence of Peripheral Arterial Disease in Hemodialysis Patients in 2 Separate Dialysis Units David H. King,[1] Philip Davis,[2] Viyaasan Mahalingasivam,[1] Amrita Ramnarine,[1] Sumith C. Abeygunasekara,[1] Abdelgalil Abdelrahman Ali,[1] Iain C. Macdougall.[2] *[1]Renal Unit, Broomfield Hospital, Chelmsford, Essex, United Kingdom; [2]Renal Dept, Kings College Hospital, London, United Kingdom.*

Background: The true incidence of Peripheral Arterial Disease (PAD) in Chronic Kidney Disease (CKD) is unknown. Conventional Ankle/Brachial (ABI) screening is inaccurate in the presence of severe medial artery wall calcification as seen in CKD and diabetic patients. We have used a new instrument *BlueDop*^{TM},capable of achieving accurate PAD triaging in the presence of calcification.

Methods: *BlueDop™* Vascular Expert Technology was employed in the PAD screening role. This system does not require external compression of the calf arteries as used in conventional ABI systems. Dialysis patients were screened in two units A (City) and B (Urban), some 50 miles apart. Patients underwent a 4 minute test involving application of non-invasive Doppler Ultrasound to each leg with automatic PAD recognition by *BlueDop™*.

Results:

Number Pts/ Limbs	% Female Gender	% Caucasian Ethnicity	Mean Age yrs	% diabetic	% PAD	%diabetic +PAD	% non-diabetic +PAD
A 53/103	64	62	65	24	63	33	10
B 45/90	18	91	70	20	31	39	11

Conclusions: Incidence of PAD in the diabetic group in this study was 3.3 to 3.5 times that in the non-diabetic group. This was remarkably consistent between the 2 dialysis units despite large differences between them in gender mix, ethnicity and PAD incidence. Interestingly, although much has been published on the incidence of PAD in hospitalized diabetic patients, the data are subject to selection bias since, by definition, these patients have been referred as a result of ischemic symptoms. The strength of this study is that the findings are 'incidental' and not related to the reason for hospital attendance. Further work should be aimed at ascertaining whether early detection of PAD in this high-risk population may allow earlier intervention and treatment of this devastating condition.

Funding: Pharmaceutical Company Support - Bluedop Medical Ltd

SA-PO750

Cross-Sectional Study of Chronic Kidney Disease Prevalence in Association with Monoinfected Patients Hepatitis C Virus in ANRS CO-22 Hepather Cohort

Eric Thervet,[1,2] Vincent Bonnemains,[2] Laurent Alric,[2,4] Jean-Jacques Boffa,[2,5] Philippe Mathurin,[6] Benedicte Stengel,[2] Fabrice Carrat,[2] Stanislas Pol,[1,3] Carole Cagnot,[7] Linda Wittkop.[2,8] *[1]Nephrology, HEGP, Paris05, France; [2]UMR970,U1223,UMR1136,UMR152,U1219, INSERM, France; [3]Hepatology, Cochin, Paris 05, France; [4]InternalMed-Dig, CHUToulouse3, France; [5]Nephrology, Tenon, Paris6, France; [6]Hepatology, CHULille, France; [7]ANRS, France; [8]ISPED, France.*

Background: Patients with chronic HCV infection have an increased risk of CKD. HCV is also more common in CKD patients than in the general population. The purpose of this study was to estimate the prevalence of ≥ stage3CKD in HCV patients and to look for correlation with the liver disease severity.

Methods: We analyzed the eGFR using CKDEPI formula in patients with a positive virus C serology in a multicenter observational prospective national cohort Hepather CO-22 (n = 20802). Exclusion criteria was kidney transplant recipients.

Results: The analysis included 8571 patients (pts). The characteristics were: 56% men;57 ± 20 years;30% hypertensive;HCV since 17 ± 13 years;detectable HCV RNA in 96%;genotype 1, 2, 3, 4 and 5/6/7 in 66%, 6%, 13%, 13% and 2%, respectively;40% of cirrhotic patients (96% Child A and MELD average 8 ± 3);and 59% previously treated with anti-viral (interferon and ribavirin in 67%). The prevalence of an eGFR≤60 ml/min was 6.3%. In univariate analysis, risk factors were sex, age, BMI, duration of infection, HCV treatment, diabetes, hypertension, high cholesterol, level of education, a history of heart disease, liver transplantation, the genotype but not the stage of fibrosis, cirrhosis and Child score. In multivariate analysis, predictors of CKD were:

Covariate	OR (CI 95%)	p
Age (10 yrs)	1,7 (1,6-1,9)	<0.01
HBP	4,4 (3,4-5,6)	<0.01
Diabetes	1,8 (1,0-2,4)	<0.03
Cardiopathy	1,6 (1,0-2,4)	<0.03
Hypercholesterolemia	1,4 (1,0-1,9)	<0.04

Conclusions: In our cohort, the CKD prevalence was 7.3% and was associated with age, hypertension, diabetes, hypercholesterolemia, and history of cardiac disease but not the severity of the liver disease. Longitudinal analysis will analyze the effect of anti-viral combinations on long-term renal function based on the usual nephropathy risk factors.

Funding: Private Foundation Support

SA-PO751

Constipation and Incident Chronic Kidney Disease

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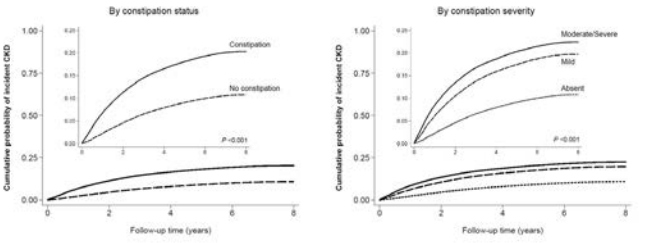
Background: Constipation is one of the most prevalent conditions in primary care settings, and it increases the risk of cardiovascular disease, potentially through inflammation by altered gut microbiota. Little is known about its association with incident CKD.

Methods: In a nationwide cohort of 3,504,732 U.S. veterans with eGFR ≥60 mL/min/1.73 m^2 between 2004 and 2006 and follow-up through 2013, we examined the association of constipation status and its severity (absent, mild, or moderate/severe), defined using ICD9 codes and laxative use, with incident CKD and ESRD, and change in eGFR in Cox (for time-to-event analyses) and multinomial logistic (for eGFR slope) regressions, with adjustment for sociodemographics, comorbidities and medications.

Results: The mean (SD) age was 60.0 (14.1) years; 93% were male; and 25% were diabetic. Patients with (vs. without) constipation had a higher multivariable adjusted risk of CKD (HR, 1.25; 95% CI, 1.24-1.27) and ESRD (HR, 1.17; 95% CI, 1.08-1.26), and experienced faster eGFR decline (multinomial ORs [95% CI] for eGFR slope <-10, -10 to <-5, and -5 to <-1, vs. -1 to <0 mL/min/1.73 m^2/year, 1.12 [1.10-1.15], 1.07 [1.05-1.09], and 1.03 [1.02-1.05], respectively). More severe constipation was associated with incremental risk for all renal outcomes.



Conclusions: Constipation status and its severity are independently associated with higher risk of incident CKD and ESRD, and with progressive eGFR decline. Further studies are needed to elucidate the underlying mechanisms and to determine whether the amelioration of constipation can prevent adverse renal outcomes.

Funding: NIDDK Support, VA Support

SA-PO752

External Validation of the Framingham Risk Score for Incident Chronic Kidney Disease at 10 Years in a Thai General Population

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Background: A risk score for incident CKD has been developed for the general population using the Framingham Heart Study (FHS) Offspring cohort. This score has been validated in Caucasians, African-Americans, but has not in an Asian population. Thailand has among the highest rise in ESRD in the world. The ability to identify patients at high risk of CKD may be essential to reduce ESRD rates. We aim to assess the performance of the FHS CKD risk predictors for incident CKD at 10 years follow-up in a Thai general population cohort.

Methods: Employees of EGAT (The Electric Generating Authority of Thailand) were studied prospectively in 2002 and followed up in 2012 (n=2568). Incident CKD refers to subjects without CKD at baseline who develop CKD (GFR <60) at follow up. CKD was defined alternatively by MDRD or CKD-EPI. The performance of the FHS simplified risk score (developed using MDRD) and the FHS 5 variable algorithms (separate algorithms for MDRD or CKD-EPI) for predicting incident CKD were assessed. Differences between predicted and observed rate were compared using Hosmer-Lemeshow test. Discrimination was quantified by c statistic. Recalibration was performed to correct for differences in CKD and risk factors prevalence.

Results: After excluding CKD at baseline, 10.4% of subjects developed incident CKD by MDRD, and 10.0% developed incident CKD by CKD-EPI. For the original simplified risk score, the agreement between predicted and observed rates were not high (MDRD: $\chi2$ =30, P<0.001; CKD-EPI: $\chi2$ =256, p<0.001), and the discrimination were modest (AUC:MDRD, 0.69;CKD-EPI, 0.63). The observed versus predicted probability of CKD using the recalibrated FHS algorithm were fair: (MDRD $\chi2$ =19, p=0.015; CKD-EPI $\chi2$ = 20, p=0.01) with CKD-EPI having better discrimination (AUC: MDRD, 0.67; CKD-EPI, 0.75).

Conclusions: The CKD-EPI FHS algorithm performs well in estimating a Thai individual's 10-year probability of developing chronic kidney disease using clinical factors readily accessible in primary care.

Funding: Government Support - Non-U.S.

SA-PO753

Association of Urine Sulfate with Death and Kidney Outcomes in Hypertensive Chronic Kidney Disease

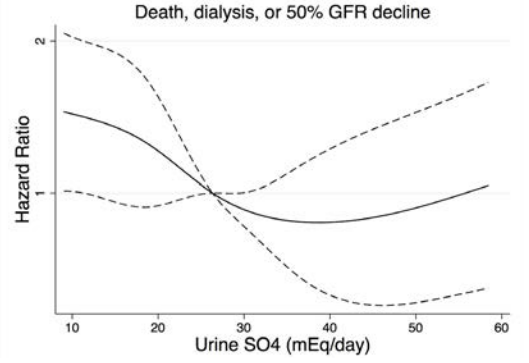
Kalani L. Raphael,[1] Jennifer L. Murray,[2] David J. Carroll,[1] Srini Beddhu.[1] *[1]Univ of Utah; [2]Colorado College.*

Background: The type of dietary protein, plant or animal, might be an important determinant of outcomes in chronic kidney disease (CKD) patients. We examined the association between urine sulfate excretion, an indicator of animal protein intake, with CKD progression and death in the African American Study of Kidney Disease and Hypertension (AASK).

Methods: Baseline urine [sulfate] (mEq/L) was measured by the barium precipitation method (n=1057). Daily sulfate excretion was calculated from 24-hour urine volumes. Participants were divided into tertiles of urine sulfate excretion (mEq/day). Cox and spline regression models related baseline urine sulfate excretion to the AASK primary composite outcome (death, dialysis or GFR reduction by 50%). Models were adjusted for demographics, randomized group, protein intake, urine potassium excretion, body mass index, measured GFR (mGFR), proteinuria, and serum bicarbonate at baseline. The lowest tertile was the reference group in the Cox model. The median sulfate excretion value was the reference in the spline model.

Results: Baseline characteristics were: age 54 years, 61% male, mGFR 47 ml/min per 1.73m^2, median proteinuria 81 mg/gm, and median urine sulfate excretion rate 26.3 (95%

CI 9.02-58.4) mEq/day. After adjustment, the hazard ratios of the composite outcome were 0.73 (95% CI, 0.56-0.96) in the middle tertile and 0.57 (95% CI, 0.39-0.85) in the highest tertile compared to the lowest tertile of sulfate excretion. Results were similar after adding blood pressure, heart disease, and smoking status in the model. Adjusted spline regression model showed higher risk of the composite outcome with lower urine sulfate excretion.



Conclusions: Lower urine sulfate excretion was associated with a higher risk of death and CKD progression in African Americans with hypertensive CKD independent of mGFR, proteinuria, protein intake, and other factors.

Funding: VA Support, Private Foundation Support

SA-PO754

High Prevalence of Chronic Kidney Disease and Hypertension in the First 3 Years after Pediatric Cardiac Surgery Michael Zappitelli,[1] Chirag R. Parikh,[2] Steven G. Coca,[3] James S. Kaufman,[4] Paul L. Kimmel,[5] Marva M. Moxey-Mims,[5] Vernon M. Chinchilli,[6] Alan S. Go,[7] Prasad Devarajan.[8] *[1]Montreal Children's Hosp, McGill U, Montreal; [2]Yale U, New Haven; [3]Icahn School of Med Mount Sinai, New York; [4]VA New York Harbor Healthcare System, New York; [5]National Inst of Diabetes, Digestive and Kidney Disease, NIH, Bethesda; [6]Penn State Coll of Med, Hershey; [7]Kaiser Permanente Northern California, Oakland; [8]Cincinnati Children's Hosp, Cincinnati.*

Background: Late chronic kidney disease (CKD) and hypertension (HTN) outcomes after pediatric cardiac surgery (CS) are unclear. We determined CKD and HTN prevalence in the 3 years post-pediatric CS.

Methods: The **AS**sessment, **S**erial **E**valuation and **S**ubsequent **S**equelae in **AKI** study includes a prospective cohort of children having CS at Montreal and Cincinnati Hospitals. Children were recruited pre-CS, followed post-operatively (postop) and at 3, 12, 24 and 36 m post-discharge. AKI definition: ≥50% or ≥0.3 mg/dL serum creatinine (SCr) rise from baseline or dialysis. Follow-up included blood pressure (BP), SCr and Cystatin C-glomerular filtration rate (eGFR), urine albumin to creatinine ratio (ACR). HTN definition: systolic (Sys) or diastolic (Dia) BP ≥95th percentile for height, gender, age. CKD definition: eGFR< or ACR> normal for age. HTN and CKD prevalence was calculated in the whole cohort and in AKI *vs*.non-AKI groups.

Results: 124 children (52% boys, 46% AKI) were enrolled (11% loss/death over 3 years). In the whole cohort, CKD prevalence at 3, 12, 24, 36 m was 22, 32, 33, 34%, respectively. Similarly-defined CKD prevalence in the US general child population ranges from <2-12%. Follow-up HTN prevalence was 31, 28, 16, 22%, respectively, compared to general child population HTN prevalence of 1-4% (US/Canada population data). CKD or HTN prevalence did not significantly differ between AKI groups at any visit (p>0.05).

Conclusions: Within 3 years of pediatric CS, about one-third and one-fifth patients have CKD and HTN, respectively. This warrants close follow-up of children after CS, for renal and cardiovascular risk reduction.

Funding: NIDDK Support

SA-PO755

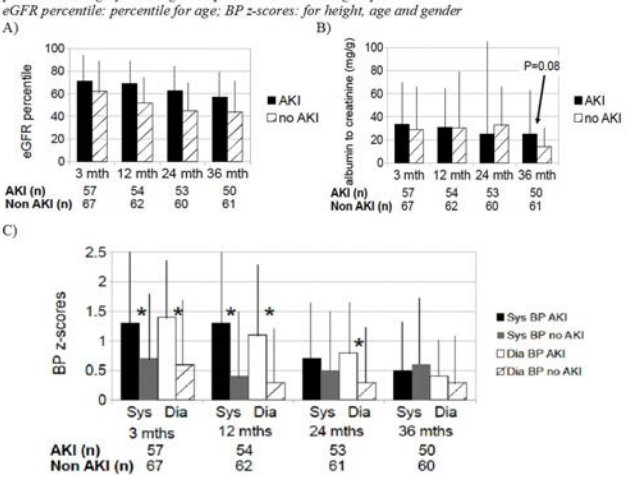
Renal Function and Blood Pressure Recovery 3 Years after Pediatric Cardiac Surgery-Associated Acute Kidney Injury: A Two-Center Study Michael Zappitelli,[1] Chirag R. Parikh,[2] Steven G. Coca,[3] James S. Kaufman,[4] Paul L. Kimmel,[5] Marva M. Moxey-Mims,[5] Vernon M. Chinchilli,[6] Alan S. Go,[7] Prasad Devarajan.[8] *[1]Montreal Child Hosp, McGill U, Montreal; [2]Yale U, New Haven; [3]Icahn School of Med Mount Sinai, New York; [4]VA New York Harbor Healthcare System, New York; [5]NIDDK, NIH, Bethesda; [6]Penn State Coll Med, Hershey; [7]Kaiser Permanente Northern California, Oakland; [8]Cincinnati Child Hosp, Cincinnati.*

Background: Long-term acute kidney injury (AKI) outcomes of pediatric cardiac surgery (CS) are unknown.

Methods: **AS**sessment, **S**erial **E**valuation and **S**ubsequent **S**equelae in **AKI** Study includes children having CS at Montreal and Cincinnati Hospitals, recruited pre-CS, followed postop and 3, 12, 24, 36m post-discharge. AKI definition: ≥50% or ≥0.3 mg/dL serum creatinine (SCr) rise from baseline or dialysis. Follow-up included SCr+Cystatin C-eGFR (age-adjusted percentile), urine albumin to creatinine ratio (ACR), systolic (SBP) and diastolic (DBP) blood pressure (age-gender-height z-scores). AKI *vs* non-AKI follow-up eGFR percentile, ACR and BP z-score were compared.

Results: Of 124 enrolled children undergoing CS, 11% died or were lost to follow-up in 3 years. 57(46%) had AKI. AKI patients were younger (median 7 *vs* 47m), had higher preop eGFR (mean 138 *vs* 110 ml/min/1.73m^2) and longer hospital stay (12 *vs* 10d)(p<0.05). eGFR percentile was higher in AKI patients at each follow-up (Fig). At 3, 12, 24m, AKI *vs.* non-AKI ACR were similar (Fig). At 36m ACR was within normal in both groups (Fig). AKI BP z-scores were significantly higher at 3 and 12m. AKI DBP was higher at 24m (Fig). By 36 m, BP z-scores were similar in both groups (Fig). In both groups, there was a reduction in eGFR, ACR and BP over time (Fig).

Figure. AKI *vs.* non-AKI eGFR percentile (A), ACR (B) and BP z-score(C) at 3, 12, 24 and 36 months post cardiac surgery discharge. * = p<0.05 between AKI groups.
eGFR percentile: percentile for age; BP z-scores: for height, age and gender



Conclusions: Although CS children experiencing AKI had elevated BP up to 24m post-CS, we observed no significant impact of AKI on eGFR or ACR at 36 m. AKI effects on BP resolved by 36m suggesting resilience to AKI in this population.

Funding: NIDDK Support

SA-PO756

Charles Comorbidity Index and the Progression of Renal Disease Filipa B. Mendes,[1] Joao Santos,[2] Luisa H. Pereira,[1] Ana Paula Silva,[1,2] Ana Marreiros,[3] Pedro Neves.[1,2] *[1]Nephrology Dept, Algarve Hospital Centre; [2]Dept of Biomedical Science, Algarve Univ; [3]Algarve Univ.*

Background: With the worldwide ageing of population, associated with the consequent comorbidities, chronic kidney disease (CKD) prevalence is progressively increasing. These conditions multiply the dependence on health care units and increase costs. Because comorbidities could be expected to worse the kidney function, the Charlson Comorbidity index (CCI) may have a role in the prediction of renal survival. In this study we evaluated the degree of comorbidities in a pre-dialysis population and investigated the relationships between the CCI and the renal progression disease.

Methods: A retrospective observational study included 693 patients, with an eGFR< 30 ml/min/1.73m^2, followed in a pre-dialysis clinic during a four years period (2008-2012). The population was divided into four groups according to the CCI: G1 (n=172)- CCI ≤ 5.2; G2 (n=162)- CCI 5.4-6.4; G3 (n=177)- CCI 6.5-7.4 and G4 (n=182)- CCI ≥ 7.5. Descriptive statistics, the ANOVA and the chi-square tests were used for comparison between groups. *Bonferroni* test was used as a post-hoc test. Multivariate and univariate logistic regressions for relationship between CCI and the other variables.

Results: The mean age of patients was 70.09 years, 54% (371) male gender and the mean eGFR (MDRD) was 20.17 ± 9.16 ml/min. When compared with the other groups, G1 showed lower age (p<0.001) and higher hemoglobin (p<0.001), eGFR (p=0.025), calcium (p=0.033) and albumin (p<0.001). In a multivariate logistic regression model adjusted to gender, phosphorus, eGFR, albumin and blood pressure, we found that CCI (OR= 1.297, 95% CI, 1.103–1.525 p=0.002), female gender (OR= 2.046, 95% CI, 1.272-3.292, p=0.003), phosphorus (OR=2.212; 95% CI, 1.576-3.105 p<0.001) and eGFR (OR=0.868 95% CI, 0.823-0.915 p<0.001) were independent risk factors for renal disease progression and renal replacement therapy. By the univariate logistic regression, G4 was a predictive factor for the progression of renal disease, when compared with G1 (OR: 1.622; 95% CI: 1.002–2.623 p=0.049).

Conclusions: In our study CCI was a strong predictor of renal disease progression in patients with chronic kidney disease stages IV-V.

SA-PO757

Oral Medicinal Charcoal Adsorbent Ameliorates Uremic Serum-Induced Intestinal Epithelial Barrier Disruption Shanshan Liang, Hongli Jiang. *Dialysis Dept of Nephrology Hospital, First Affiliated Hospital of Medicine School, Xi'an Jiaotong Univ.*

Background: Chronic kidney disease (CKD) causes intestinal barrier dysfunction which by allowing influx of endotoxin and other noxious products. Oral activated charcoal has been shown to markedly reduce plasma concentration of uremic toxins like indoxyl sulfate and p-cresol sulfate which are produced by the gut microbial flora.This study determined whether CKD-associated disruption of intestinal tight junction is mediated by activated charcoal adsorptive removal retained uremic toxins/ metabolites.

Methods: The human intestinal epithelial cells Caco2 were seeded on the Transwell plates and utilized when transepithelial electrical resistance (TEER) exceeded 500Ω*cm2 to ensure full polarization and TJ formation. The cells were then incubated for 24 h in media containing 10% serum from healthy individuals, 10% serum from regular hemodialysis patients(HD) or patients taking medicinal charcoal tablets(MCT) 2.7g/day, 3 times/day for 3 months also receive hemodialysis (HD-MCT). The serum of HD and HD-MCT were both collected after hemodialysis. TER was then measured and cells were processed for MTT assay and Western blot analyses.

Results: Compared with the controls, incubation in media containing serum from regular hemodialysis patients for 24h and 48h both resulted in a marked drop in TEER pointing to increased epithelial permeability. This was also accompanied by significant reductions in claudin-1, occluding, and ZO-1 protein abundance. The severity of TJ damage and dysfunction was significantly less in cells exposed to the HD as well as HD-MCT patients in comparison to HD serum. Cell viability and proliferation ability decreased significantly after treatment with HD serum compared with the HD-MCT and control group. These results point to the presence of as-yet unidentified product(s) in the uremic serum capable of depleting epithelial TJ and administration of medicinal charcoal tablets resulted in partial restoration of the epithelial TJ proteins.

Conclusions: Uremic milieu can impair the intestinal epithelial TJ and its barrier function, and administration of oral medicinal charcoal tablets attenuated uremia-induced disruption of intestinal epithelial TJ.

Funding: Government Support - Non-U.S.

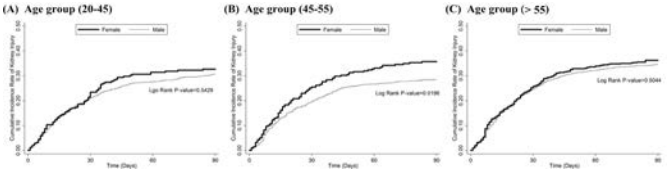
SA-PO758

The Nephrotoxicity of Cisplatin May Have Gender Difference Chia-Chun Wu, Hsien-Yi Wang, Wei-Chih Kan. *Dept of Medicine, Div of Nephrology, Chi Mei Medical Center, Tainan, Taiwan.*

Background: Gender difference is reported in various diseases, in general, women seems have less common and less severe acute kidney injury and chronic kidney disease compare to men. However, female animals have more susceptibility of cisplatin induced nephrotoxicity(CIN) were reported.Herein, we want to know if the CIN has gender difference in human based on nation-wide population database.

Methods: The National Health Insurance Research Database in Taiwan was used to identify patients received cisplatin treatment for cancer therapy. Patients have any history of acute or chronic kidney disease before using cisplatin, have multiple cancer or sex organ cancer and younger than 20 years old were excluded. Outcome is defined as diagnosis of either acute or chronic kidney disease within 3 months after first cisplatin administration. Age, non-steroid anti-inflammatory disease, treatment with aminoglycoside or exposure of contrast media were regarded as confounding factors and adjusted. Subgroups according to age of childbearing, perimenopause and post menopause in women were further analysed.

Results: A total of 3973 male and 1154 female patients with cisplatin treatment were analysed. The mean age was 56.15±12.85 and 56.31±12.40 in male and female separately without significant difference. Overall, 37.4% of patients who treated cisplatin had CIN without significant difference between men and women. Age older than 55 years old, history of diabetes mellitus, higher Charlson comorbidity score and treated with aminoglycoside after cisplatin were risk factors of CIN. In different age groups, women in perirenopause stage have a 1.28 times higher risk of CIN compare with men in the same age.



Conclusions: Women in perimenopause stage have a greater risk of CIN compared with men. Estrogen level is higher in the stage of perimenopause, which might imply the the role of oestrogen in gender difference of CIN.

SA-PO759

The Renal Response to an Acute Protein Load Strongly Predicts Outcome in Chronic Kidney Disease Amelia Rita Bernasconi,[1] Ricardo M. Heguilen.[2] *[1]Medicine, Hospital Juan A Fernandez Univ de Buenos Aires, Buenos Aires, Argentina; [2]Nephrology, Hospital Juan A Fernandez Univ de Buenos Aires, Buenos Aires, Argentina.*

Background: Chronic kidney disease (CKD) characterizes by its progressive nature. In clinical studies, outcome measures include –among others-doubling serum creatinine (DSC), and/or the need for renal replacement therapy (RRT) but a single and reliable predictor has not been identified yet. The aim of this study was to evaluate the role of renal reserve (RR) as an early predictor of outcome in patients with CKD.

Methods: Consecutive adults with recent diagnosis of CKD whose RR was evaluated through an acute oral protein challenge were included in this study. They were grouped according to its RR index (RRI) in RR1 (RRI >1.3) or RR0 (RRI <1.3). The main outcome measure was DSC

Continuous variables are expressed as mean (sd) and categorical variables as frequency. Unpaired t-test, chi2 or Fischer's exact test were used as appropriate. Cox proportional hazard regression was used to estimate the hazard ratio (HR) for DSC, comparing RR0 with RR1, adjusting for age, sex, diabetes, hypertension, tobacco use, the presence of hyperuricemia or lipid abnormalities, baseline creatinine, urinary albumin etc. The Kaplan-Meier survival estimate along with the log-rank test to compare survival to DSC was calculated. p values < 0.05 were considered significant.

Results: 78 stages 1-3 CKD individuals (39 male) aging 21 to 72 years were assessed. Both groups were similar with regard to age, gender distribution, as well as baseline characteristics. There was a tendency for a higher baseline Scr in individuals from the RR0 group. The median survival to DSC was 51mo and 72mo in RR0 and RR1 respectively (p 0.03). After adjusting for potential covariates and confounders, the HR in RR0 was 2.75 (95%CI 1.02 – 7.43).

Conclusions: The inclusion of RR studies may help to generate an accurate model to predict outcome in CKD.

SA-PO760

Kidney Disease Progression and Associated Factors in HIV+ Patients Pedro Pereira Campos,[1] Iola Pinto,[3] Ana Luisa Papoila,[2] Karina Soto.[1,2] *[1]Nephrology, Hospital Fernando Fonseca, Lisbon, Portugal; [2]Bioestatistics, FCM, Univ Nova de Lisboa, Lisbon, Portugal; [3]Matematicas, ISEL, Lisbon, Portugal.*

Background: Chronic kidney disease is more prevalent in HIV+ patients than in the general population. Large studies have shown that the improved management of these patients has decreased HIV-related causes of CKD. We aimed to determine the evolution of kidney function in HIV infected patients, searching for early kidney dysfunction and its risk factors. Additionally, we studied the influence of serum Cystatin C on the eGFR of this cohort.

Methods: A longitudinal analysis was performed in 1761 consecutive HIV+ outpatients. Clinical data and laboratory analysis were registered prospectively at admission and biannually during 3y of follow-up. The primary endpoint was decreased kidney disease (eGFR ≤90 ml/min estimated by using the CKD-EPI based on serum creatinine (SCr-eGFR) and serum cystatin C (SCysC-eGFR). Univariable and multivariable mixed regression models were used.

Results: Among 1761 patients (mean age 45 CI38.0-53.0); 54.5% were male; 44% African ancestry 92.2% HIV type1; 24.4% Hypertension; 7.0% Diabetic. Mean CD4 count 477 (CI 326-649)cels/μL; viral load 68.2% <20 copies/mL. In univariable regression, the variables associated with significantly eGFR increase were: age (<0.001); DM (0.001); HT (<0.001); HVC (0.121); CVD (0.007); abacavir (0.039); atazanavir (0.200); and ritonavir (0.010). Multivariable results in table 1.

eGFR	OR	SE	z	P>z	95%CI	
AGE	1.116	0.015	8.00	0.000	1.08	1.14
Hipertension	2.098	0.512	3.03	0.002	1.30	3.38
HVC	2.282	0.782	2.41	0.016	1.16	4.46
ARV Ritonavir	1.783	0.397	2.60	0.009	1.15	2.75

CD4, viral load were not significant, whereas age, hypertension, virus C hepatitis, and only ritonavir among antiretroviral therapy were significantly associated with decreased eGFR. For each 0.1 mg/L of Cystatin C the eFGR decrease 3.10 mL/min.

Conclusions: Decreased kidney function in HIV patients remains frequent and is associated with traditional factors as age and hypertension, of those related to HIV only was associated with VCH and among antiretroviral therapy only ritonavir was determinant for kidney disease progression.

SA-PO761

Predicting Progression to Dialysis in Patients with Advanced Chronic Kidney Disease Wael F. Hussein, Rossana Rocco. *Dept of Nephrology, Tallaght Hospital, Trinity Health Kidney Centre, Dublin, Ireland.*

Background: Identifying patients at high risk for progression to dialysis initiation helps triaging care. The Kidney Failure Risk Equation (KFRE) developed using data from Canadian patients, and validated in multiple trial cohorts, gives a risk estimate for progression to dialysis. We aimed to validate the KFRE in patients with advanced chronic kidney disease in a clinical non-trial cohort.

Methods: Retrospective observational study on nephrology clinic patients in a large teaching hospital between Jan 2010 and Dec 2013. Patients with a stable eGFR between 15 and 20 ml/min/1.73 m^2 were included. Two year risk of progression was calculated using the eight variable (age; gender; eGFR; serum albumin, calcium, phosphate, and bicarbonate; and urinary albumin:creatinine ratio) KFRE. Kidney failure was defined as commencement of dialysis within 2 years from the inclusion date. Patients who received a pre-emptive kidney transplant, were lost to follow up or died before development of kidney failure were excluded. Performance of the KFRE was evaluated by comparing the predicted and the observed risk, Brier's score, and the area under the receiver operating characteristic curve (ROC-AUC).

Results: Of 3,901 nephrology patients, 199 satisfied the inclusion criteria. Of those, 1(0.5%), 8(4.0%) and 29 (14.6%) were excluded because of pre-emptive transplantation, loss to follow up and death respectively. Of 161 patients included in the final analysis, the median age was 70 years (IQR: 57 – 78), 78 (48%) were female, and 64 (32%) had diabetes. During the observation period, 33 patients (20%) required dialysis. Calibration of observed versus predicted risk of kidney failure across quartiles of predicted risk is shown in Table 1. Brier score was 0.13. The ROC-AUC was 0.761 (95% CI: 0.660 – 0.863).

Quartile of predicted risk	n	Mean predicted risk	Mean observed risk	n predicted	n observed
2.1 - 5.6%	42	3.9%	7.1%	2	3
- 11.1%	39	8.1%	10.3%	3	4
- 23.7%	40	18.0%	18.0%	7	7
- 79.6%	40	40.9%	47.5%	16	19

Conclusions: Among patients with advanced CKD, KFRE can identify high risk patients, and may be used to triage these patients to prepare for renal replacement therapy.

SA-PO762

Association between GSTM1 Copy Number and Incident End-Stage Renal Disease in the Atherosclerosis Risk in Communities (ARIC) Study Adrienne Tin,[1] Morgan Grams,[1] Robert B. Scharpf,[1] Michelle M. Estrella,[1] Megan Grove,[2] Dan Arking,[1] Eric Boerwinkle,[2] Josef Coresh.[1] *[1]Johns Hopkins Univ; [2]The Univ of Texas Health Science Center at Houston.*

Background: Glutathione S- transferase mu 1 (*GSTM1)* catalyzes the conjugation of glutathione with a range of electrophiles. Having 0 copies of *GSTM1* (*GSTM1-0*) has been associated with chronic kidney disease (CKD) progression in African American patients in the AASK trial. Whether *GSTM1-0* is associated with ESRD in the general population independent of hypertension and diabetes is unknown.

Methods: In the African American cohort of the ARIC study, we estimated *GSTM1* copy number using whole exome sequencing reads and ascertained ESRD events using linkage to the US Renal Data System (USRDS). We evaluated the association between *GSTM1* copy number and ESRD using Cox regression controlling for age, sex, baseline eGFR, prevalent diabetes and hypertension. We estimated the association between *GSTM1* copy number and ESRD in participants with and without 2 *APOL1* renal risk alleles.

Results: Of the 1924 African Americans in this study, 52% had hypertension and 16% had diabetes. The mean baseline eGFR was 112 mL/min/1.73 m^2. The median follow-up time was 23 years. *GSTM1-0* was significantly associated with 1.72-fold higher risk of ESRD compared with those with 2 copies of *GSTM1* (table, p-trend=0.04). When stratified by *APOL1* risk, *GSTM1-0* vs. 2 copies was associated with 2.43-fold higher risk of ESRD in those with 2 *APOL1* risk alleles and 1.6-fold high risk in those with 0/1 copy of the *APOL1* risk allele (p for interaction 0.70).

Conclusions: *GSTM1* was significantly associated with ESRD independent of traditional risk factors. These results are consistent with those reported from the AASK trial and extend the association between *GSTM1* and CKD to a population-based cohort. Our results suggest *GSTM1* is a potential treatment target for the prevention of CKD progression.

	Overall	*APOL1* 2 risk alleles	*APOL1* 0/1 risk allele
n (event)	1924 (125)	263 (20)	1661 (105)
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
GSTM1 0 copy	1.72 (1.03, 2.86)	2.43 (0.56, 10.6)	1.60 (0.93, 2.76)
GSTM1 1 copy	1.45 (0.92, 2.29)	2.19 (0.61, 7.86)	1.34 (0.82, 2.19)
GSTM1 2 copies	1.00	1.00	1.00

SA-PO763

Phosphate Balance and Outcome in Advanced CKD Antonio Bellasi,[1] Lucia Di Micco,[2] Domenico Russo,[3] Luca Di Lullo,[4] Andrea Galassi,[5] Mario Cozzolino,[6] Biagio Raffaele Di Iorio.[2] *[1]ASST-Lariana; [2]PO Landolfi; [3]Federico II Univ, Napoli; [4]Ospedale Parodi Delfino; [5]ASST Monza - Desio; [6]Univ of Milan.*

Background: Perturbation of phosphate homeostasis portends unfavorable outcome in CKD. Although some lines of evidence suggest an association with mortality, serum levels of phosphate poorly reflect phosphate balance. A considerable effort is devoted to definine new markers of phosphate homeostasis. We investigated the association of fraction excretion of phosphate (FeP) with relevant outcome in advanced CKD.

Methods: Retrospective, longitudinal study of 407 CKD subjects (age 66 years, 43% female, mean creatinine clearance 32 ml/min) receiving Nephrology care in Italy. Demographic and clinical characteristics were obtained at the time of referral. Routine laboratory and 24-urine collection were used. Risk of CKD progression to ESRD, all-cause mortality as well as the composite of the 2 were regarded as outcome of interest. ANOVA, logistic regression and survival analysis were used to compare patients' characteristics across quartiles of FeP, detect predictors of FeP and the association of FeP with the outcome of interest.

Results: Higher FeP was associated with older age, higher azotemia and PTH levels as well as lower creatinine clearance, serum phosphate and 24-h urine potassium excretion (all p-values<0.01). After adjustment for confounders, abnormal FeP (>20%) was inversely associated with creatinine clearance (B-0.03, p=0.006), diastolic blood pressure (B-0.04, p=0.01) and serum phosphate (B-0.43, p=0.008). Independent of multiple adjustments, a graded and independent association between quartiles of FeP and ESRD but not all-cause mortality was detected.

Risk/quartile of FeP	Low	Mid-Low	Mid-High	High
ESRD	ref	3.28(0.87-12.3)	7.33(2.13-25.1)	12.3(3.64-41.7)
Mortality	ref	1.44(0.83-2.48)	1.68(0.98-2.88)	1.33(0.72-2.45)
Composite	ref	2.01(1.22-3.31)	2.29(1.41-3.70)	2.39(1.44-3.99)

Conclusions: FeP is associated with ESRD but not all-cause mortality risk in a large cohort of advanced CKD patients. Future efforts are required to validate FeP as a marker of phosphate balance and if CKD progression explains the risk burden of phosphate imbalances in this high-risk population.

Funding: Government Support - Non-U.S.

SA-PO764

Acute Kidney Injury, Proteinuria, Glycemic Control, and Kidney Disease Progression in Diabetes Mellitus Mollie Y. Sands, Anthony C. Leonard, Charuhas V. Thakar. *Univ of Cincinnati, Cincinnati, OH.*

Background: Acute kidney injury (AKI), proteinuria (PU), and glycemic control (A1c), are each known to influence the risk of chronic kidney disease (CKD) in diabetics. The relationship between these risk factors and CKD progression is not well studied.

Methods: In a de-identified Veterans Affairs cohort of 3,679 type 2 diabetics (T2D) with baseline glomerular filtration rate (eGFR) > 30ml/min (followed between 1999 and 2008, inpatient and outpatient), we examined relationships between PU, AKI (during hospitalizations), and mean A1c > 7 (averaged for study period) as major predictors. CKD progression outcomes were: annualized mean glomerular filtration rate (eGFR) decline; rapid decline (eGFR decline > 5 ml/min/year); and reaching Stage IV CKD. Logistic regression and Cox models (adjusted for demographics, co-morbidities and baseline eGFR) generated risk estimates expressed as odds and hazard ratios (OR, HR) with 95% confidence intervals (CI). The sample was 97.7% male (mean age of 61.7 yr), with mean baseline eGFR of 79.7 ml/min.

Results: Linear rates of eGFR decline across 3 risk groups [High (N = 421) mean A1c > 7, PU, and AKI; Medium (N=2,134) 1-2 of these risk factors present; Low (N=1,124) 0 present] showed a mean annual rate of decline of 4.33, 2.88 and 2.29 ml/min respectively (ANOVA p = 0.005; adjusted ANOVA p = 0.002). Overall, 14% (N=503) reached Stage IV CKD; compared to low-risk, the high-risk group was more likely to do so (adjusted OR, 7.2, 95% CI 5.1 – 10.1). For the rapid decliner outcome (N=903) logistic regression models showed significant positive interactions between PU and mean A1c >7 (p = .005), and between PU and AKI (p = .007). The crude mortality rate was higher in rapid decliners (27.2% vs others 20.1%; p< .0001); as well as in those reaching Stage IV CKD (36.2% vs 19.8% in others; p < .0001).

Conclusions: Diabetics with AKI, PU, and mean A1c > 7 experience faster rates of linear eGFR decline, and are 7-fold more likely to reach Stage IV CKD than those without these risk factors. The effect of two risk factors at once (AKI and PU, or PU and mean A1c > 7) imparts more than respective additive effects on the rapid decliner outcome.

Funding: VA Support

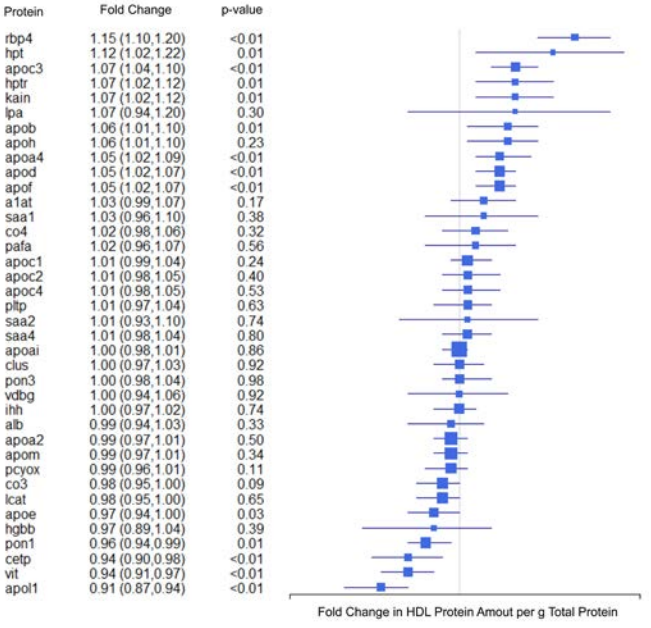
SA-PO765

Protein Composition of High Density Lipoprotein Varies with Progression of Chronic Kidney Disease Andrew N. Hoofnagle, Cassianne Robinson-Cohen, Ian H. De Boer, Bryan R. Kestenbaum. *Univ of Washington, Seattle, WA.*

Background: High density lipoprotein (HDL) particles contain a heterogeneous composition of proteins of humoral and cellular origin and serve important anti-atherosclerotic functions. HDL particles from chronic dialysis patients are enriched in several proteins involved in inflammation, vitamin binding, and lipoprotein metabolism. We used novel mass spectrometric methods to characterize the protein composition of HDL particles across the spectrum of kidney function.

Methods: We analyzed plasma samples of 507 participants from the Seattle Kidney Study, a clinic-based prospective study of chronic kidney disease (CKD). We used sequential density gradient ultracentrifugation to isolate the HDL fraction. HDL proteins were quantified using trypsin digestion and liquid chromatography-tandem mass spectrometry. We used linear regression to estimate associations of each 15 ml/min/1.73m^2 lower estimated glomerular filtration rate (GFR) with the log transformed concentration of each HDL protein after adjustment for age, race, sex, diabetes, body mass index, smoking, and statin use.

Results: Mean participant age was 58 ±14 years, 24% were African American, 33% were female, and 50% had diabetes. The mean estimated GFR was 45 ±26 ml/min/1.73m^2 and the mean plasma HDL cholesterol concentration was 42 ±17 mg/dL. Lower estimated GFR was associated with significant differences in the concentration (per g total HDL protein) of multiple proteins within HDL. After full adjustment and accounting for multiple comparisons, lower estimated GFR was significantly associated with higher HDL concentrations of retinol binding protein 4, apoC-III, apoF, and lower HDL concentrations of vitronectin and apoL1.



Conclusions: In CKD patients not requiring dialysis, decreased kidney function is associated with significant differences in the amounts of several proteins within HDL.

Funding: NIDDK Support, Other NIH Support - NHLBI

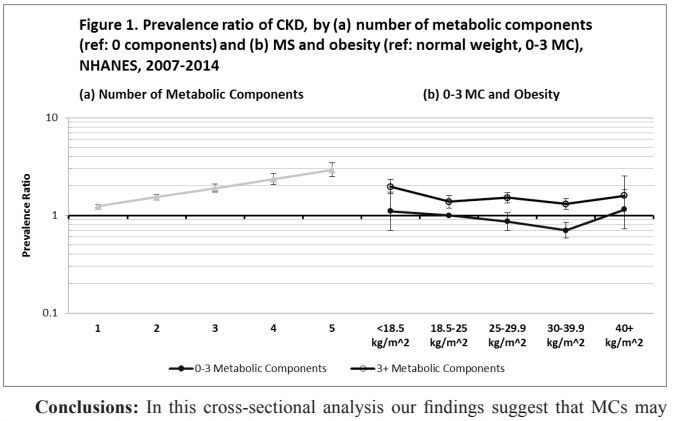
SA-PO766

Metabolic Components and Chronic Kidney Disease (CKD) Prevalence in the United States Patrick J. Albertus,[1] Jennifer L. Bragg-Gresham,[1] Hal Morgenstern,[1] Chi-Yuan Hsu,[2] Neil R. Powe,[2] Rajiv Saran.[1] *[1]KECC, Univ of Michigan; [2]Univ of California San Francisco.*

Background: Obesity is thought to affect CKD risk. We examined the association between the metabolic components (MC) related to obesity and CKD in a national sample.

Methods: The analysis included participants ≥20 years old in the National Health and Nutrition Examination Survey 2007-14. CKD was defined as eGFR<60 ml/min/1.73^2 or urine albumin-to-creatinine ratio≥30 mg/g. We measured 5 binary MCs: fasting glucose≥100 mg/dL or diabetes (HbA1c≥7%, self-reported diagnosis, or medication); high density lipoprotein<40 mg/dL for men or <50 mg/dL for women; triglycerides≥150 mg/dL; systolic blood pressure>130 mmHg or diastolic blood pressure>85 mmHg, or hypertension medication; and waist circumference>40" for men or >35" for women. Modified Poisson regression was used to estimate the association (prevalence ratio [PR] and 95% CI) between MCs and CKD prevalence, adjusting for age, sex, race/ethnicity, family income, education, serum albumin, and (with/without) body mass index (BMI).

Results: Among 9,673 subjects, the proportion with ≥3 MCs was 37.8%. Compared with subjects with <3 MCs, in those with ≥3 MCs the adjusted PR of CKD was 1.6 (1.5, 1.8) without BMI adjustment and 1.6 (1.4, 1.7) with BMI adjustment. A higher number of MCs was associated with higher prevalence of CKD (Fig 1.a). Additionally, adjustment for the number of MCs resulted in little association between BMI and CKD prevalence (Fig 1.b).



Conclusions: In this cross-sectional analysis our findings suggest that MCs may incrementally increase the risk of CKD and that there may be little or no effect of BMI on CKD beyond these MCs.

Funding: Other U.S. Government Support

SA-PO767

ErbB4 Deletion Induced Metabolic Syndrome in Mice on a High Energy Diet Fenghua Zeng, Lance A. Kloepfer, Raymond C. Harris. *Medicine, Vanderbilt Univ Medical Center, Nashville, TN.*

Background: Patients with obesity and diabetes have a higher risk to develop chronic kidney diseases. Although reports have indicated a possible relationship between decreased ErbB4 expression and diabetic nephropathy, its role in the development of diabetes has not been previously examined.

Methods: Heart rescued ErbB4 deletion (ErbB4^{del}ht$^+$) and wild-type (WT) mice were fed a high energy diet (HED) that contains 11% fat. Body weight, blood glucose, and lipid profile were measured. Insulin sensitivity were studied using IPGTT and IPITT.

Results: ErbB4^{del}ht$^+$ and WT mice were fed the HED after weaning when they had similar body weight. At 20-week of age compared to WT mice, ErbB4^{del}ht$^+$ mice developed metabolic syndrome manifested by increased body weight and fat weight; hyperglycemia; abnormal IPGTT, IPITT, and increased HOMA-IR index; and dyslipidemia shown by elevated levels of free fatty acid, cholesterol, triglycerides, and LDLcholesterol. Even though serum leptin levels were significantly increased in ErbB4^{del}ht$^+$ mice, there were no differences in food intake from controls. Serum adiponectin tended to be reduced in ErbB4^{del}ht$^+$ mice. Pathologically, ErbB4^{del}ht$^+$ mice developed severe liver steatosis, and larger adipocytes with large lipid droplets. Severe inflammation was predominantly detected in epididymal white adipose tissue (eWAT) demonstrated by increased F4/80 immunoreactivity and widely spread crown-like structures, with increased mRNA levels of iNOS, an M1 macrophage marker, with no significant changes of Arg1 expression, a marker for M2 macrophage. The mRNA levels of proinflammatory cytokines, TNF-α, MCP1/CCL2, and CXCL1, were significantly increased in the eWAT of ErbB4^{del}ht$^+$ mice. There was no significant changes in the mRNA levels of IL-10 and IL-4, the antiinflammatory cytokines.

Conclusions: Our findings suggested ErbB4 is involved in energy homeostasis possibly through regulating insulin sensitivity and inflammation in adipose tissues, and may constitute a novel therapeutic target for the treatment of obesity and diabetes.

Funding: NIDDK Support, VA Support

SA-PO768

Obesity Predicts Steeper Measured Glomerular Filtration Rate Decline in a Non-Diabetic General Population Vidar T.N. Stefansson,[1] Jørgen Schei,[1,2] Trond G. Jenssen,[1,3] Toralf Melsom,[1,2] Bjorn Odvar Eriksen.[1,2] *[1]Metabolic and Renal Research Group, UiT The Arctic Univ of Norway, Tromsø, Norway; [2]Section of Nephrology, Univ Hospital of North Norway, Tromsø, Norway; [3]Dept of Organ Transplantation, Oslo Univ Hospital, Oslo, Norway.*

Background: Obesity is associated with an increased risk of end-stage renal disease. Hypertension and diabetes are established mediators of the effect of obesity on kidney function. Whether obesity also contributes directly to the wide variation in age-related decline in the glomerular filtration rate (GFR) seen in healthy persons, is unknown. Previous studies of obesity and GFR decline have shown mixed results, depending on whether creatinine or cystatin C was used to estimate GFR. These estimates are confounded by non-GFR-related factors, and are inaccurate in the normal and high ranges of GFR. We aimed to explore the relationship between obesity and the measured GFR (mGFR) decline rate.

Methods: GFR was measured using iohexol clearance in 1594 non-diabetic middle-aged subjects without cardiovascular or renal disease from the general population. The study was repeated after a median observation time of 5.6 years in 1324 (83%) subjects in the Renal Iohexol Clearance Survey Follow-Up (RENIS-FU) study. Obesity was measured using the body mass index (BMI), waist circumference, the waist-hip ratio, and estimated body fat percentage (BFP). The mGFR decline rate was analyzed using multivariable adjusted linear mixed models, and non-linear relationships were explored using fractional polynomial transformations.

Results: The mean (SD) mGFR decline rate was -0.95 (2.23) ml/min/year. The obesity variables were not linearly associated with a change in the mGFR decline rate in multivariable adjusted linear mixed models. However, statistically significant non-linear relationships were found between the mGFR decline rate and both BMI and estimated BFP in separate models ($p<0.05$). For BMI, the mGFR decline rates were -0.93, -0.94, -1.13, -1.60 and -2.44 mL/min/year at 25, 30, 35, 40 and 45 kg/m^2, respectively. A similar pattern was observed in relation to BFP.

Conclusions: Severe obesity contributes to a steeper age-related mGFR decline in the non-diabetic general population.

Funding: Pharmaceutical Company Support - Boehringer-Ingelheim, Government Support - Non-U.S.

SA-PO769

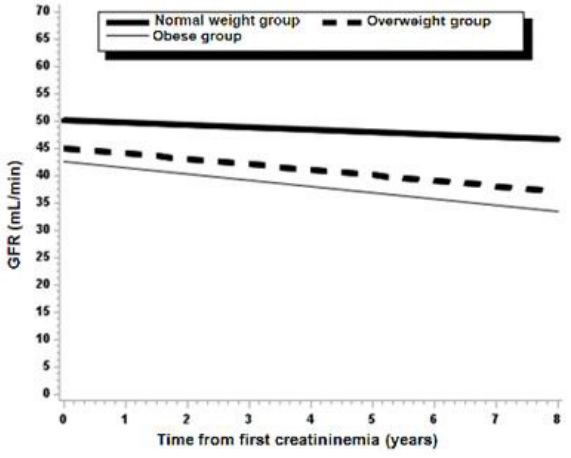
Overweight Is Associated with Chronic Kidney Disease Progression Louis De Laforcade,[1] Christelle Maurice,[3] Maurice Laville.[1,2,3] *[1]Dpt of Nephrology, Hospices Civils de Lyon, Pierre Bénite, France; [2]INSERM Unit 1060 CarMeN, Univ Lyon I Claude Bernard, Oullins, France; [3]TIRCEL Renal Care Network, Lyon, France.*

Background: Obesity and overweight are frequent in patients suffering from chronic kidney disease (CKD). Previous studies are discordant about the link between CKD progression and body mass index (BMI). We examined the database of our renal care network to study CKD course according to BMI.

Methods: We analyzed patients followed in the renal care network. All patients with two serum creatinine (Scr) values at an interval of 6 months or more were included. Patients with glomerular filtration rate (eGFR, MDRD equation) below 15 mL/min were excluded.

Standard demographic data, SCr, eGFR, and main comorbidities were recorded. Patients were divided into three groups: normal weight (NW : BMI < 25kg/m²), overweight (OW : BMI 25 - 30 kg/m²) and obesity (OB : BMI > 30 kg/m²). The slope of eGFR decrease was compared between the 3 groups using a mixed-model approach.

Results: 1203 patients were included, with a maximal follow-up of 8 years. Men accounted for 53% of the study population, median age was 67 years, 11% of the patients were diabetic. According to BMI, 44% were in the NW group, 36% in the OW group and 20% in the OB group. eGFR ranged between 60 and 30 mL/min in 58 % patients, between 30 and 15 mL/min in 20%. The slope of eGFR decrease was significantly lower in NW (- 0.43mL/min per year) than in OW (-1mL/min per year) or OB group (- 1.15 mL/min per year ; p = 0.002 between three groups). This difference persisted after adjustement on sex, age, systolic blood pressure and weight changes in our mixed-model approach.



Conclusions: Obesity and overweight are associated with a faster decrease of renal function in CKD patients. This relationship had been previously studied Asiatic or North American patients, but our study is the first to show this association in Continental Europe.

SA-PO770

Psoriasis as a Systemic Disease: Kidney Involvement Lisa Giovannini,[1] Andrea Conti,[2] Gianni Cappelli.[1] *[1]Dept of Surgery, Medical and Dentistry, Univ Hospital of Modena, Modena, Italy; [2]Dept of Specialist Surgery, Unit of Dematology, Univ Hospital of Modena, Modena, Italy.*

Background: Studies to date examining kidney disease in patients with psoriasis have primarily small sample sizes and have yielded conflicting results. However, renal involvement in course of psoriasis could not be an infrequent event.

Methods: We determined prevalence of CKD by estimating GFR (CKD-EPI GFR) and albuminuria in moderate-severe psoriatic patients, according to KDIGO guidelines. Urinary albumin was detected by turbidimetric immunoassay. Student's t and Chi squared tests were used to compare continuous or categorical data. Forward multiple linear regression analysis assessed possible influences on microalbuminuria. ROC analysis tested the variable "duration disease" to microalbuminuria occurrence.

Results: 219 patients gave informed consent and entered the study. Prevalence of AUCR>30mg/gr was 17,35%. Indeed, 17,35%, 5,02%, 3,66% of our population showed a moderately increased, a high, and a very high risk of CKD respectively. Cumulative Cyclosporine dose explained significantly AUCR according to multiple regression analysis (p<0,0001). In the adjusted cohort of CKD risk-factors free pts, prevalence of microalbuminuria was 12.79%. Presence of arthritis (p<0,0001), disease duration (p<0.0001) and actual PASI score (p<0,001) demonstrated a positive correlation with microalbuminuria. Patients with psoriatic arthritis had 14 times more probability to show a microalbuminuria than psoriatic patients without arthritis (p=0.0001; OR 14,25; 95%CI: 2,815 to 72,12). A long time psoriasis higher than 21 years added 106.5 time risk to present microalbuminuria (p<0,0001; OR 106.5; 95%CI 5.902 to 1921) with comparable age, BMI and eGFR. At the same time, long time psoriasis (>21years) arthritic patients have OR 1,88 to present microalbuminuria.

Conclusions: Duration of disease and psoriatic arthritis have a strong independent association with microalbuminuria. Patients with psoriatic arthritis, especially with a disease duration longer than 21 years, should be routinely screened for microalbuminuria for a more comprehensive management.

SA-PO771

Estrogen Receptor b Hinders Renal Fibrosis in Obstructive Nephropathy by Selectively Inhibiting Snail 1-Induced Renal Tubular Epithelial Cells Epithelial to Mesenchymal Transition Rong Cao, Yongcheng He. *Dept of Nephrology, The First Affiliated Hospital of Shenzhen Univ, Shenzhen, Guangdong, China.*

Background: Renal fibrosis is the final common pathway of virtually all kinds of progressive CKD(Chronic Kidney Disease) leading to ESRD(End-Stage Renal Disease). Estrogen Receptor β (ERβ) is a nuclear transcription factor, and increasing evidence suggests that ERβ can delay the progress of a variety of tissue fibrosis, but the role of ERβ in renal fibrosis is still unknown. The purpose of this study is to investigate the effect of ERβ in renal fibrosis and its underlying mechanism.

Methods: 40 biopsy-proven CKD patients were collected .The model of unilateral ureteral obstruction (UUO) was used in vivo, and mouse primary renal tubular epithelial cells(PTECs)were treated with TGFβ1 in vitro.

Results: 1)The expression of ERβ and snail 1were significantly down-regulated in fibrotic renal tissues among the 40 biopsy-proven CKD patients. Besides, both ERβ mRNA and protein were decreased in UUO mice,compared with the sham group. 2)ERβ was widely expressed in mouse kidney, highest in the cortex, followed by the outer medulla and inner medulla.Moreover, ERβ was also expressed in mouse primary renal tubular epithelial cells . 3)UUO mice exhibited marked interstitial inflammation and fibrosis in renal tissue stained with hematoxylin and eosin and Masson's trichrome. However, treatment with DPN, a specific agonist of ERβ, 5 days after UUO operation, significantly reduced inflammatory cell infiltration and interstitial fibrosis score. What's more, UUO-induced renal fibrosis was aggravated in ERβ knockout mice, compared with the WT mice. 4)DPN can significantly decrease collagen production in PTECs and reduce TGFβ1-induced PTECs EMT. Consistent with this, treated with ERβ-siRNA, collagen production and cell migration were increased in PTECs. 5) Over expression of snail 1 by plasmid can increase collagen production in PTECs and reduce TGFβ1-induced PTECs EMT.

Conclusions: ERβ hinders renal fibrosis in obstructive nephropathy by selectively inhibiting snail 1-induced renal tubular epithelial cells Epithelial to Mesenchymal Transition.

Funding: Government Support - Non-U.S.

SA-PO772

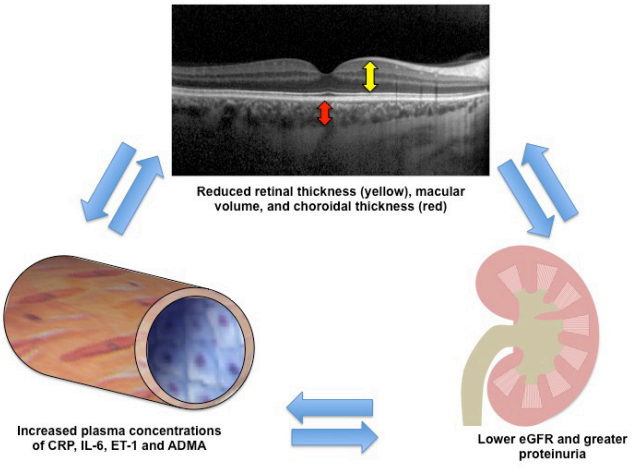
Chorioretinal Thinning in Chronic Kidney Disease Links to Inflammation and Endothelial Dysfunction Neeraj Dhaun. *Centre for Cardiovascular Sciences, Univ of Edinburgh.*

Background: Chronic kidney disease (CKD) is strongly associated with cardiovascular disease (CVD) and there is an established association between vasculopathy affecting the kidney and eye. Optical coherence tomography (OCT) is a novel, rapid method for high-definition imaging of the retina and choroid. Its use in patients at high CVD risk remains unexplored.

Methods: We used the new SPECTRALIS OCT machine to examine retinal and retinal nerve fibre layer (RNFL) thickness, macular volume and choroidal thickness in a prospective cross-sectional study in 150 subjects – 50 patients with hypertension, 50 with CKD and 50 matched healthy controls. The same, masked ophthalmologist carried out each study. Plasma IL-6, TNFα, ADMA, and ET-1, as measures of inflammation and endothelial function, were also assessed.

Results: Retinal thickness, macular volume and choroidal thickness were all reduced in CKD patients compared to hypertension and health (p<0.001 for CKD *vs.* both hypertension and health for each). RNFL thickness did not differ between groups. Interestingly, a thinner choroid was associated with a lower eGFR (p<0.0001) and, in CKD, with greater proteinuria as well as increased plasma concentrations of CRP, IL-6, ADMA and ET-1 (all p<0.05). Finally, choroidal thickness associated inversely with renal histological inflammation and arterial stiffness. In a model of hypertension, choroidal thinning was seen only in the presence of renal injury.

Conclusions: The decreases in chorioretinal thicknesses in CKD are associated with lower eGFR and higher proteinuria but not blood pressure. Larger studies, in more diverse groups of CKD patients, are now warranted to clarify whether these eye changes reflect kidney pathology and the natural history of CKD. Similarly, the associations with measures of arterial stiffness, inflammation and endothelial dysfunction should be examined further.



SA-PO773

Nuclear Phosphatase, SCP4 Interacts with the FOXOs Transcriptional Factors Contributing to Muscle Wasting in Chronic Kidney Disease

Xinyan Liu,[1] Yanlin Wang,[2] William E. Mitch,[2] Zhaoyong Hu.[2] *[1]Nephrology Div, The 2nd Hospital of Shanxi Medical Univ, Tianyuan, Shanxi, China; [2]Nephrology Div, Balyor College of Medicine, Houston, TX.*

Background: Chronic kidney disease (CKD) and related inflammatory cytokines stimulate protein-energy wasting (PEW), a complication which manifests sustainably loss of muscle mass. The mechanisms leading to muscle wasting are complex but primarily resulting from accelerated protein degradation and activation of autophagic/lysosomal and proteasomal pathways. However, the regulation of these proteolysis pathways during muscle wasting remains unclear. We examined how a novel nuclear phosphatase, SCP4 (Small C-terminal Phosphatase 4) influences muscle protein metabolism by regulating FoxO transcription factors.

Methods: We measured protein synthesis and degradation in C2C12 cells with knockdown or forced-expression of SCP4 and examined the signaling pathway by which SCP4 regulates muscle protein metabolism. In muscles of CKD mice, we tested if knockdown of SCP4 ameliorates the loss of muscle protein.

Results: In muscle cell cultures, overexpression of SCP4 stimulates muscle proteolysis; conversely, knockdown SCP4 prevent cytokines and serum starvation induced muscle protein loss. SCP4 overexpression causes FOXO1/3a accumulation in nuclei and this response is accompanied by induction of atrogin-1/MuRF-1 and activation of autophagic pathway. Treatment of myotubes with proinflammatory cytokines stimulates SCP4 expression and NF-κB mediates this response. In muscle of CKD mice, SCP4 is up-regulated. Similar results are also observed in muscles of patients with CKD. Mice with SCP4 knockout or knocking down SCP4 by electroporation of SCP4 shRNA in muscle decrease FoxO1/3a nuclear accumulation and transcription activities despite of CKD. These led to suppression of protein degradation and maintain muscle mass.

Conclusions: SCP4 expression stimulates muscles proteolysis in CKD. Targeting SCP4 may prevent muscle wasting in CKD and perhaps other catabolic conditions.

Funding: NIDDK Support

SA-PO774

Magnetic Resonance Imaging Sensitive to Hypoxia and Fibrosis in a Multi-Center Study of Chronic Kidney Disease

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Background: Renal hypoxia and interstitial fibrosis are key contributors to CKD progression according to chronic hypoxia theory [PMID: 9551436]. Phosphate and FGF23 excess have been linked to accelerated CKD progression. COMBINE (CKD Optimal Management with Binders and Nicotinamide) is a multicenter trial to test whether nicotinamide and lanthanum carbonate will safely lower serum phosphate and FGF23 levels in an attempt to prevent cardiovascular and progressive renal disease compared to placebo. In this study, we evaluated both renal cortical oxygenation and diffusion coefficients using blood oxygenation level dependent (BOLD) and diffusion MRI at baseline in subjects participating in COMBINE and compared them to measures in a cohort of healthy subjects with no known renal disease.

Methods: To-date data was available for a total of 98 subjects with CKD (age=65.8±11.9 years; eGFR=33.0±7.1 ml/min/1.73m^2) and 29 healthy controls (age=41.3±18.9 years; eGFR=99.3±17.4 ml/min/1.73m^2). BOLD and Diffusion MRI data was acquired on a 3.0 T scanner. BOLD MRI measurements were repeated following administration of 20 mg *i.v*. of furosemide. Large cortical and whole kidney regions of interest (ROI) were used for analysis [PMID: 26193455]. Lower oxygenation should result in higher R2* values and presence of fibrosis should result in lower apparent diffusion coefficient (ADC).

Results: Both cortical R2* (20.6±3.4 *vs*. 18.0±1.62 s^{-1}; p<0.0001) and ADC (1460.0±165.5 *vs*. 1715.5±92.0 mm^2/s; p<0.0001) were significantly different in CKD compared to controls. Further the response to furosemide was significantly reduced in CKD (1.0±0.9 *vs*. 2.3±1.1 s^{-1}; p<0.0001). All the three MRI measures showed significant correlation with eGFR (ρ(R2*)=-0.34 (p=0.0003); ρ(ADC)= 0.41 (p<0.0001); ρ(Kid_Delta_R2*=0.48 (p<0.0001)). Even though age was found to be a confounder, in an age matched subset, all three parameters were significantly different between the two groups.

Conclusions: The lower cortical oxygenation and decrease in cortical diffusion coefficients in CKD are consistent with increased hypoxia and presence of fibrosis and support the chronic hypoxia hypothesis.

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SA-PO775

Urinary Human L-Type Fatty Acid Binding Protein on Chronic Phase Reflects the Degree of Chronic Tubular Loss after Ischemia-Reperfusion Renal Injury

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Background: AKI is an important risk factor for onset of CKD and notable detector of chronic tubular loss after AKI is needed for monitoring the CKD after AKI. The aim of this study is to elucidate that urinary human L-type fatty acid binding protein (hL-FABP) on chronic phase is associated with the degree of tubular loss on chronic phase after AKI.

Methods: Male hL-FABP chromosomal transgenic (Tg) mice were subjected to ischemic reperfusion (I/R) model. The Tg mice were divided into three groups: short duration ischemia group (short-I/R) received procedure of renal ischemia induced by left renal artery clamping for 10 min; long duration ischemia group (long-I/R) received ischemia for 20 min; and the sham operated group. Contralateral nephrectomy was performed at the same time of tissue reperfusions. Kidneys were obtained 20 days after last I/R.

Results: Although serum creatinine levels at 1 and 20 days after I/R in the short-I/R mice were similar to those in the control mice, these levels in the long-I/R mice were significantly higher than in the short-I/R and control mice. Urinary hL-FABP levels at 1 day after I/R were significantly higher in the long-I/R mice than in the short-I/R and control mice, and in the short-I/R than in the control mice. Urinary L-FABP levels at 20 days after I/R in the long-I/R mice were significantly higher than those in the control mice, and tended to be higher than those in the short-I/R mice. The degree of MCP-1 protein expression, macrophage infiltration, tubular damage and renal fibrosis at 20 days after I/R were significantly more severe in the long-I/R than in the short-I/R and the control mice, and in the short-I/R than in the control mice. Urinary L-FABP levels at 20 days after I/R were significantly correlated with the degree of renal damage.

Conclusions: Urinary L-FABP on chronic phase reflects the degree of chronic tubular loss after I/R and, therefore, may be useful for monitoring the CKD after AKI in clinical practice.

SA-PO776

Relationships of Dietary Phosphate Intake and Serum Phosphate with Clinical Outcomes in Chronic Kidney Disease Stages 3-5: Findings from the KoreaN Cohort Study for Outcome in Patients with Chronic Kidney Disease (KNOW-CKD) Study

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Background: We investigated the relationships of dietary phosphate intake and serum phosphate with clinical outcomes in chronic kidney disease (CKD) stages 3-5.

Methods: We collected the data of 849 CKD stage 3-5 non-dialysis patients from a prospective cohort study (KNOW-CKD). A renal event is defined by a >50% decrease inestimated glomerular filtration rate (eGFR) from the baseline values, doubling of serum creatinine, or end stage renal disease. CV event is defined myocardial infarction (fatal and nonfatal), coronary revascularization, stroke and new onset or aggravation of congestive heart failure. We used multivariate logistic regression models to assess associations of baseline 24-h urine phosphate excretion and serum phosphate with clinical outcomes (renal and CV event).

Results: Among the 849 participants in this study, the mean age ± SD was 56.5 ± 11.2 years (range 20–75), 61.7% were male. 24-h urine phosphate excretion was not correlated with serum phosphate concentrations after eGFR adjusted (r=-0.073, P=0.034). Models were adjusted for age, sex, primary renal disease (glomerulonephritis, diabetes, hypertension, polycystic kidney disease and others), eGFR, 24-h urine protein and nitrogen excretion, body mass index, smoking, use of phosphate binder and coronary artery disease. There was no association of 24-h urinary phosphate excretion with renal event, CV event and total event. Whereas, higher serum phosphate concentrations were not associated with renal (oddi ratio [OR] 1.839, 95% confidence interval [CI] 0.839-4.028, P=0.128) and CV event (OR 1.491, 95% CI 0.566-3.925, P=0.419). But, strongly associated with total event (OR 1.957, 95% CI 1.008-3.800, P=0.047).

Conclusions: There was no evidence that dietary phosphate intake assessed by 24-h phosphate excretion is associated with clinical outcomes. On the other hand, higher serum phosphate was associated with clinical outcomes in CKD stages 3-5.

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SA-PO777

Patient Awareness of Target Blood Pressure and Hypertension Control in Chronic Kidney Disease

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Background: Patient awareness of treatment goals may help improving risk factor control in CKD. We assessed awareness of target blood pressure (BP) among CKD patients and its associations with BP control.

Methods: We used baseline data from the CKD-REIN/CKDOPPS study, a prospective cohort study of patients enrolled with CKD stage 3 and 4 in a nationally representative sample of 40 nephrology clinics in France. We compared patients who reported target systolic BP (SBP) values <140 (or <130) mm Hg to those who did not. We performed separate analyses with achieved BP <140/90 or <130/80 mm Hg as dependent variable.

Results: Of 2850 patients, 86% had a diagnosis of hypertension registered in medical records. Median age was 69 [IQR 62-77] years, 66% were men, 41% had stage 4 CKD, 91% were aware of their hypertensive condition. Among 37% who reported "to have been told about target BP", 94% reported target SBP <140 (including 67% reporting target SBP value <130), 5% reported target SBP value ≥140, and 1% did not remember their target. Fewer patients (75%) reported a diastolic BP target value. Overall, 40% of the patients had office BP <140/90, and 17%, office BP <130/80. Awareness of target SBP was associated with younger age, higher education level, CKD awareness, and self-BP monitoring. After adjusting for potential confounders, patients reporting target SBP values <140 did not have

better BP control, whatever the threshold. Those who reported target SBP <130 were more likely to have BP <140/90 (OR 1.34 95% CI 1.09-1.65, p 0.006), but not <130/80 (OR 1.16 95% CI 0.90-1.51, p 0.26).

Conclusions: Both awareness of BP target and achievement of BP <140/90 mm Hg are low among CKD patients. Given the importance of hypertension control in preventing CKD progression and cardiovascular complications, setting lower SBP targets (<130) may be a strategy to achieve minimally acceptable BP control (<140/90).

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SA-PO778

Geographic Variation in Rapid Kidney Function Decline

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Background: Geographic variation in the prevalence of CKD and incidence of ESRD has been previously reported. However, the geographic epidemiology of rapid eGFR decline has not been examined. We aimed to characterize the spatial epidemiology of rapid eGFR decline using a national longitudinal cohort of United States Veterans.

Methods: We built a cohort of 2,107,570 US veterans and investigated the prevalence of rapid eGFR decline (defined as eGFR slope <-5 ml/min/1.73 m^2/year) and potential ecologic risk factors using mixed effect logistic regression models. To examine possibility of clustering, cluster analysis was performed.

Results: : Prevalence of rapid eGFR slope adjusted for age, race, gender, diabetes, and hypertension varied by county from 4.10-6.72% in the lowest prevalence quintile to 8.41-22.04% in the highest prevalence quintile (p for heterogeneity <0.001). Examination of adjusted prevalence by diabetes and hypertension status showed that while these conditions were major drivers of rapid eGFR decline, substantial geographical variation was present in those with and without diabetes and those with and without hypertension. Compared to rural areas, living in metropolitan neighborhoods was associated with increased odds of rapid eGFR decline (OR: 1.09; CI: 1.03-1.14). Residents of counties with higher proportion of people living in poverty, and higher percentage of African Americans exhibited highest odds of rapid eGFR decline (OR: 1.05; CI: 1.01-1.10; and OR: 1.20; CI: 1.16-1.27; respectively). Spatial analyses suggest the presence of cluster of counties with high prevalence of rapid eGFR decline.

Conclusions: In conclusion, our findings show substantial geographic variation in rapid eGFR decline among United States veterans; the variation persists in analyses stratified by presence of diabetes and hypertension; results also suggest ecologic factors associated with rapid eGFR decline.

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SA-PO779

Optimizing Timing of Pre-Emptive AV Access Creation: Results from the CRIC Study

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Background: Scant data exist to guide clinicians regarding optimal timing of pre-emptive AV access surgery (surgery) in preparation for chronic dialysis. We hypothesized that using a trigger based on predicted likelihood of developing ESRD would be a superior strategy compared with using a static GFR threshold (and superior to current clinical practice).

Methods: We studied Chronic Renal Insufficiency Cohort (CRIC) enrollees with eGFR <30 ml/min/1.73m^2 after 8/2010 (N=608). We compared 3 potential strategies: i) current practice, captured by patient self-report of surgery; ii) hypothetically triggering surgery when eGFR <20 ml/min/1.73m^2; iii) hypothetically triggering surgery when Kidney Failure Risk Equation (KFRE)(Tangri JAMA 2011) estimated likelihood of developing ESRD within 1-yr >20% (thresholds chosen *a priori*). We calculated sensitivity as the probability of appropriately undergoing/correctly triggering surgery among those who actually developed ESRD within a year. Specificity is the probability of correctly not undergoing/not triggering surgery among those who did not develop ESRD within a year.

Results: Mean age of the study population was 66 years, 49% were female, 40% non-Hispanic whites and 41% non-Hispanic blacks. 118 cases of chronic hemodialysis were observed. A strategy guided by likelihood of developing ESRD within the next year had the best disease odds ratio (DOR) at 27.9 (Table 1).

Current practice (patient self-report of AV access surgery)	Specificity (95% CI)	0.987 (0.980, 0.992)
	Sensitivity (95% CI)	0.118 (0.072, 0.187)
	DOR (95% CI)	10.4 (5.0, 21.5)
Scenario if AV access surgery triggered by eGFR <20 ml/min/1.73m^2	Specificity	0.831 (0.806, 0.853)
	Sensitivity	0.787 (0.659, 0.876)
	DOR	18.1 (9.2, 35.4)
Scenario if AV access surgery triggered by likelihood of ESRD within 1-yr >20%	Specificity	0.932 (0.913, 0.947)
	Sensitivity	0.672 (0.548, 0.776)
	DOR	27.9 (15.5, 50.3)

Conclusions: Using predicted likelihood of ESRD to guide pre-emptive AV access surgery may be a promising strategy.

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SA-PO780

The Expression of VDR in Renal Tissue of Lupus Nephritis and Its Association with Renal Injury Activity

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Background: The incidence of systemic lupus erythematosus is closely related to the polymorphism of vitamin D receptor (VDR). To further explore the role of VDR in lupus nephritis (LN), we observed the expression of VDR in renal tissue of LN and evaluated the renal pathological index.

Methods: 20 renal biopsy specimens were collected from 35 patients with LN according to ISN/RPS2003 lupus nephritis type standards pathological type and carrying out the activity index (AI), chronic index (CI). 5 tissue specimens over 2cm far from kidney tumor of renal cancer patients were used as normal control. The expression of VDR were detected by immunohistochemistry in renal tissue of two groups. The relationship between VDR expression and histological injure index, proteinuria and SLICC renal activity scores were analyzed.

Results: 1, Compared with the control group, the expression of VDR in the lupus nephritis were lower(P <0.05). 2,The expression of VDR were negatively correlated with AI (r=-0.548, P =0.012), and no correlation were observed between VDR level and CI (P >0.05). 3,The expression of VDR in renal tissue is negatively correlated with SLICC renal activity scores. (r=-0.470, P =0.037) .

Conclusions: Down-regulation of VDR in renal tissue of lupus nephritis were associated with renal activity injury severity.

SA-PO781

Renal Outcomes in Patients with Colorectal Cancer and Repeated Intravenous Contrast Exposure

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Background: Renal function in cancer patients is affected by exposure to various nephrotoxins. Its preservation is important for effective cancer treatment and surveillance. Contrast-induced nephropathy is a well-recognized acute complication in this population, but the long-term effects of repeated contrast exposure are unknown. We analyzed the association of the number of contrasted computed tomographies (cCT) and other clinical factors with the reduction of eGFR in colorectal cancer (CRC) survivors after CRC resection.

Methods: We retrospectively queried a prospective surgical CRC database to identify 592 patients with stage I or II CRC who underwent resection in 2007-2012 and were alive for at least 3 years. CKD-EPI equation was used to calculate eGFR, and >20% decline in eGFR relative to baseline was defined as significant and used as the primary outcome. The association of clinical factors with the primary outcome at 1 and 3 years was analyzed using logistic regression.

Results: At 1 year, 313 patients had creatinine (Cr) available for eGFR calculation. Significant eGFR decline was observed in 51 (16%) of these patients. In multivariable analysis, cardiovascular disease (CVD) was independently associated with significant eGFR decline [OR=2.4, 95%CI (1.18-4.89), p=0.02]. At 3 years, 208 patients with measured Cr were available with 34 (16%) demonstrating significant eGFR decline that was associated with comorbid hypertension, CVD and operation time. Exposure to ≥4 cCTs was marginally associated with significant eGFR decline.

Figure 1. Univariate analysis of eGFR decline

	eGFR decline by 1 year		eGFR decline by 3 years	
Characteristic	OR (CI)	p-value	OR (CI)	p-value
CVD (Yes vs. No)	**2.87 (1.44-5.71)**	**0.003**	**2.49 (1.03-6.02)**	**0.04**
Diabetes (Yes vs. No)	**2.04 (1.08-3.86)**	**0.03**	1.66 (0.74-3.69)	0.22
HTN (Yes vs. No)	1.34 (0.71-2.52)	0.37	**2.42 (1.00-5.86)**	**0.05**
Nephrotoxic chemotherapy (Yes vs. No)	**0.45 (0.22-0.94)**	**0.03**	1.15 (0.53-2.49)	0.72
OR time (per10 min increase)	1.03 (1.00-1.06)	0.06	**1.04 (1.00-1.07)**	**0.03**
Number of cCTs by 3 years (≥4 vs. <4)	*NA*		2.09 (0.94-4.63)	0.07

Conclusions: Cumulative contrast exposure was marginally associated with a >20% eGFR decline at 3 years after surgical resection in patients with early stage CRC. This trend calls for further studies to elucidate the long-term effects of contrast exposure in cancer patients. CVD was found to be a consistent risk factor of post-operative eGFR decline.

SA-PO782

The Tissue Expressions of Tubular Injury Marker, NGAL and KIM-1, Are Associated with Renal Function Decline in Diabetic Nephropathy

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Background: The tubular injury may be involved in the pathogenesis and progression of renal dysfunction in addition to glomerular damage in diabetic nephropathy (DN). This study was conducted to examine whether tubular expressions of neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) predict the subsequent decline of renal function in human DN.

Methods: We identified 122 patients with diabetes who underwent renal biopsy from 2000 to 2014 and confirmed to have DN. After exclusion of patients with coexisting other renal disease, estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2, 35 subjects were included in the analyses. Annual decline of eGFR (GFR slope) was calculated by linear regression analysis. We assessed tissue tubular expressions of NGAL and KIM-1 by immunohistochemistry.

Results: Overall, GFR slopes were linear. The median baseline urinary protein to creatinine ratio (PCR) was 6.76 (2.18 - 7.61) mg/mgCr, the median baseline eGFR was 50.4 (42.6 - 66.4) ml/min per 1.73m^2, and median GFR slope was -15.6 (-32.9 - -4.4) ml/min per 1.73m^2 per year. In linear regression analyses, tubular expressions of NGAL were correlated with GFR slope and interstitial fibrosis and tubular atrophy score (P = 0.012, P = 0.088, respectively). Those of KIM-1 were correlated with GFR slope and PCR (P = 0.002, P = 0.003, respectively). In multivariate analyses, tubular expressions of NGAL remained as an independent predictor of GFR slope (P = 0.011). However, the association between KIM-1 expressions and GFR slope was dependent on PCR.

Conclusions: Tissue expressions of tubular injury marker, NGAL were closely associated with GFR decline, independently of PCR. These findings suggest that tubular injury might play an independent role in the pathogenesis of DN.

SA-PO783

Age at Onset, Complement Abnormality and Renal Survival in Patients with aHUS Enrolled in a Global Registry

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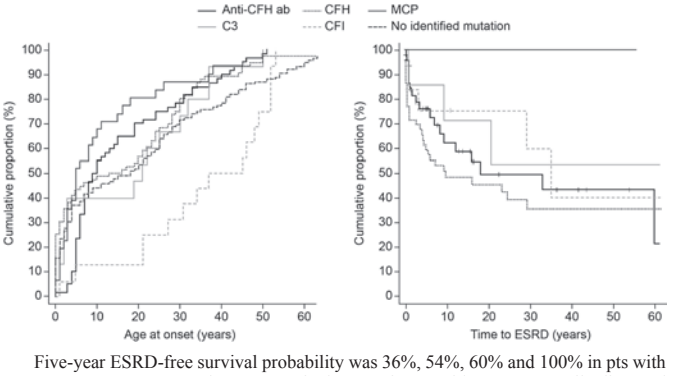
Background: Atypical hemolytic uremic syndrome (aHUS) is a rare, genetic, life-threatening disease of chronic, uncontrolled complement activation that leads to thrombotic microangiopathy with severe organ damage. Here we characterize renal survival in patients (pts) with aHUS enrolled in the global aHUS Registry.

Methods: All pts diagnosed with aHUS are eligible for enrolment. Exclusion criteria: Shiga toxin *Escherichia coli*-positive HUS or ADAMTS13 activity <5%. Data are collected at enrolment and every 6 months thereafter. Data are reported prior to treatment with eculizumab.

Results: As of November 2015, 851 pts were enrolled (387 childhood, 464 adult onset). Prior dialysis was recorded for 56% of pts, while 19% had received a kidney transplant. Five year end-stage renal disease (ESRD)-free survival probability was 73% and 57% for pediatric and adult pts respectively. Cox proportional hazard regression analysis shows age of onset associated with ESRD risk (p<0.001). Gender, race, family history of aHUS, and time from onset to diagnosis, were not associated with ESRD risk. Pts with CFI mutations had their first aHUS manifestation later than pts with other complement abnormalities.

Figure: Age of onset and ESRD survival probability by individual complement abnormality



Five-year ESRD-free survival probability was 36%, 54%, 60% and 100% in pts with CFH, C3, CFI, MCP mutations, respectively, 49% in pts with CFH autoantibodies, and 67% in pts with no identified complement abnormality.

Conclusions: Our data suggest pts with aHUS who have disease onset in adulthood or a CFH mutation are at highest risk of ESRD. These pts may especially benefit from rapid initiation of eculizumab, which has been shown to be effective in the treatment of aHUS.

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SA-PO784

Associations of Blood Pressure with End Stage Renal Disease in Chronic Kidney Disease

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Background: Hypertension is a risk factor for kidney disease progression, but the optimal blood pressure for CKD patients is undetermined. We studied the associations of systolic and diastolic blood pressure with ESRD among non-dialysis dependent CKD patients.

Methods: We included 31,280 patients with eGFR <60 ml/min/1.73m^2 (twice 90 days apart) and on at least one antihypertensive agent. ESRD details were ascertained from the US Renal Data System. We fitted competing risk regression models for ESRD to evaluate various SBP (<110, 110-119, 120-129, 130-139, 140-149, and ≥150 mmHg) and DBP (<50, 50-59, 60-69, 70-79 80-89 mmHg) targets. The competing event was all-cause mortality. The model was adjusted for age, gender, race, insurance group, diabetes, hyperlipidemia, BMI, albumin, hemoglobin, malignancy, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, ACE/ARB, beta blocker, smoking, and CKD stage.

Results: During a median follow-up of 2.2 years, 915 patients developed ESRD. In multivariate models, SBP <110 and 110-119 mmHg were associated with lower risk of ESRD, while SBP ≥150 mmHg was associated with greater risk of ESRD. DBP was ≥90 mmHg was associated with higher risk of ESRD.

Baseline SBP vs. ESRD		
	Unadjusted ESRD SHR (95%CI)	Adjusted ESRD SHR (95%CI)
<110	0.87 (0.66, 1.15)	0.54 (0.40, 0.72)
110-119	0.80 (0.61, 1.03)	0.65 (0.50, 0.85)
120-129	0.87 (0.69, 1.08)	0.97 (0.77, 1.2)
130-139	Ref	Ref
140-149	1.22 (0.98, 1.52)	1.10 (0.87, 1.4)
≥150	2.27 (1.87, 2.74)	1.7 (1.4, 2.1)
Baseline DBP vs. ESRD		
	Unadjusted ESRD SHR (95% CI)	Adjusted ESRD SHR (95%CI)
<50	1.37 (0.77, 2.44)	0.70 (0.36, 1.35)
50-59	1.00 (0.77, 1.31)	0.77 (0.59, 1.02)
60-69	0.87 (0.73, 1.04)	0.86 (0.72, 1.04)
70-79	Ref	Ref
80-89	1.11 (0.93, 1.33)	1.07 (0.89, 1.29)
≥90	2.77 (2.28, 3.38)	1.50 (1.20, 1.86)

Conclusions: In a non-dialysis dependent CKD population, SBP <120 mmHg was associated with a lower risk of ESRD. SBP ≥150 mmHg and DBP ≥90 mmHg were associated with a higher risk of progression to ESRD.

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SA-PO785

The Effect of Calcitriol and Cholecalciferol Supplementation on Proteinuria in CKD Stage 3-4

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Background: Vitamin D deficiency is associated with an increased risk of proteinuria and kidney disease progression in patients with chronic kidney disease (CKD). The effect of vitamin D supplementation on proteinuria has not been well studied. We examined the effect of calcitriol vs. cholecalciferol supplementation on proteinuria in a randomized double-blind, direct head-to-head comparison.

Methods: In a randomized trial to evaluate the effect of calcitriol vs. cholecalciferol on vascular endothelial function, 128 patients with CKD stage 3-4 (estimated GFR 15-44 ml/min/1.73m^2) with vitamin D deficiency, defined as serum 25-hydroxyvitamin D level < 30 ng/mL, and proteinuria < 3.5 g/day, were randomly assigned to receive either cholecalciferol (4000 IU daily x 4 weeks then 2000 IU daily x 20 weeks) or calcitriol (0.25 mcg daily x 4 weeks then 0.5 mcg daily x 20 weeks). Urinary albumin to creatinine ratio (ACR) was measured at baseline and end of study. We examined the change in ACR from baseline to end of study in the calcitriol group vs. cholecalciferol group.

Results: 115 patients completed the study. The mean (SD) age and eGFR was 58.1 ± 12.5 years and 33.2 ± 10.0 ml/min/1.73m^2, respectively. The use of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) was similar between the two groups (69.6% in the calcitriol group vs. 68.5% in the cholecalciferol group). The baseline median (IQR) ACR was 222.0 (39.7-846.8) mg/g in the calcitriol group and 158.8 (29.2-585.6) mg/g in the cholecalciferol group. Over the 6 month time period, the ACR decreased from baseline in the calcitriol group by 14.6%, p=0.02 and increased in the cholecalciferol group by 5.8%, p=0.35. The change in ACR during the follow-up period between the two groups was significant (-3.96, 95% CI -7.25 to -0.62, p=0.02). The between group difference in ACR remained after adjustment for age, gender, race, systolic blood pressure and use of ACEi/ARB. Incidence of hypercalcemia and adverse events was similar between the two groups.

Conclusions: Treatment with calcitriol but not cholecalciferol results in a significant decrease in albuminuria in patients with CKD stage 3-4.

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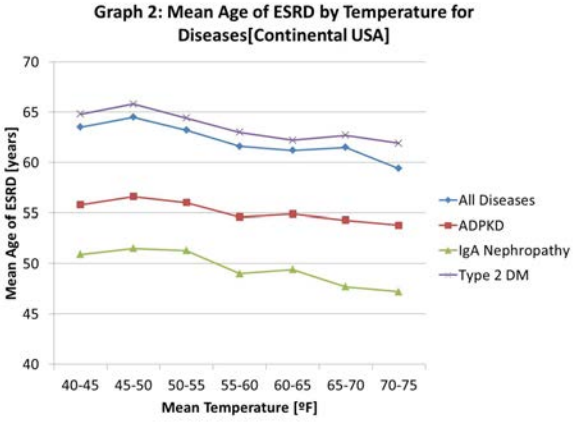
SA-PO786

Increasing Climate Temperature Is Associated with Earlier Age of Onset of End Stage Renal Disease Michael E. Bleyer, Ebunoluwa Esther Taylor, Gregory B. Russell, Anthony J. Bleyer. *Section of Nephrology, Wake Forest Baptist Health, Winston-Salem, NC.*

Background: Global temperature is increasing, and there has been a rising concern that high climate temperatures may be associated with chronic kidney disease such as Meso-American Nephropathy. To explore the relationship between climate temperature and age of ESRD, we evaluated data from the United States Renal Data System (USRDS). US data is particularly useful because of a relatively standard approach to when dialysis is started and because of a broad range in climate temperature in the US.

Methods: We obtained data for all patients with new onset ESRD between ages 30 and 90 in the continental United States. We were particularly interested in where individuals were likely to have spent most of their life rather than where they lived when dialysis was initiated. We therefore obtained from the USRDS the state where each patient obtained his social security number. In the US, social security numbers are usually obtained before or at the age of 18 years. We obtained median annual temperature data from the US National Oceanographic and Atmospheric Association. A multivariate linear regression model was developed with age of ESRD as the outcome variable, and gender, race, median income, and median annual state temperature as independent variables.

Results: 2.3 million individuals were included in the analysis. There was an inverse linear relationship between age of onset of ESRD and climate temperature.



This relationship was found with autosomal dominant polycystic kidney disease, IgA nephropathy, and type II diabetes. The relationship remained significant after adjusting for race, gender, and median income.

Conclusions: Higher climate temperatures are associated with a younger age of onset of ESRD. This could significantly contribute to ESRD incidence in developing countries, and could be affected by climate change.

Funding: Clinical Revenue Support

SA-PO787

Estimation of Nephron Number of Japanese CKD Patients Toshiyuki Imasawa,[1] Takehiko Kawaguchi,[1] Kensei Yahata,[2] Takashi Nakazato.[3] *[1]Kidney Center, National Hospital Organization Chiba-East Hospital, Chiba-city, Chiba, Japan; [2]Dept of Nephrology, National Hospital Organization Kyoto Medical Center, Kyoto-City, Kyoto, Japan; [3]Dept of Medical Information Management, National Hospital Organization Chiba Medical Center, Chiba-city, Chiba, Japan.*

Background: Previous studies showed that nephron number is a good predictor of CKD progression. However, all these results were based on animal studies or on autopsied human kidneys (retrospective studies). Because nephrologists cannot count nephron number of CKD patients, this knowledge is unavailable at a real clinical place. Recently, we established an estimation formula for nephron number in CKD patients who were received kidney biopsies (BMC Nephrol 2012, 13:11).

Methods: Patients were from PRONEP (Predicting the Outcome of Chronic Kidney Disease by the Estimated Nephron Number) study (protocol: BMC Nephrol 2012). In this analysis, 573 Japanese patients were included. By the estimation formula, we calculated nephron numbers of Japanese CKD patients. In addition, nephron numbers of IgA nephropathy, diabetic nephropathy, and FSGS (focal segmental glomerulosclerosis) due to hemodynamic factor were individually calculated. Because sclerosed glomeruli might be absorbed, we also calculated nephron numbers of cases whose eGFR were over 45ml/min/1.73m^2.

Results: All results are in Table.

	Japanese CKD patients	IgAN	DMN	FSGS (hemodynamic)
n	573 (386)	216 (170)	45 (24)	15 (7)
eGFR	64.4 +/- 38.9 (85.7 +/- 34.9)	74.1 +/- 37.8 (88.9 +/- 33.0)	45.8 +/- 21.4 (66.3 +/- 11.4)	55.2 +/- 29.2 (79.0 +/- 25.8)
nephron number /kidney	667,460 +/- 310,730 (712,366 +/- 287,733)	680,702 +/- 302,604 (723,997 +/- 294,190)	821,262 +/- 280,784 (818,819 +/- 237,968)	557,340 +/- 322,246 (472,928 +/- 113,628)

In parentheses, data of cases over eGFR 45ml/min/1.73m^2. Values are shown as mean+/-SD.

Conclusions: Nephron numbers of Japanese are expected to be lower than Caucasian. Interestingly, nephron numbers of FSGS due to hemodynamic factor (mostly perihilar variant) were significantly lower than those of other CKD patients. Now, we are prospectively following these patients and will analyze whether these estimated nephron numbers can predict CKD progression.

Funding: Government Support - Non-U.S.

SA-PO788

The Association of Sleep Duration and Quality with Chronic Kidney Disease Progression Ana C. Ricardo, Kristen Knutson, Jinsong Chen, Lawrence J. Appel, Lydia Bazzano, Manjula Kurella Tamura, Mahboob Rahman, Susan P. Steigerwalt, John Thornton, Matthew R. Weir, Eve Van Cauter, James P. Lash. *On Behalf of the Chronic Renal Insufficiency Cohort (CRIC) Study Group.*

Background: Although there is increasing evidence that sleep disorders are common in individuals with chronic kidney disease (CKD), its association with CKD progression is not known. We examined the association of sleep duration and quality with CKD progression and all-cause death.

Methods: We conducted a prospective longitudinal study of 432 adults (mean age 60 years, 48% women, and mean estimated glomerular filtration rate [eGFR] 38 ml/min/1.73m^2) enrolled at two participating sites of the CRIC Study. Participants wore a wrist actigraph for 5-7 days to measure sleep duration and quality. Subjective sleep quality, apnea risk and daytime sleepiness were self-reported using validated questionnaires. We used Cox proportional hazards models to evaluate the association of sleep measures with incident end stage renal disease (ESRD) and all-cause death, and linear mixed-effects models to assess differences in eGFR slope.

Results: Participants slept an average of 7.4 hours/night, and the mean sleep fragmentation was 21%. Over median follow-up of 5 years, we observed 70 ESRD events and 48 deaths. In analyses adjusted for sociodemographic factors, body mass index, blood pressure, diabetes, cardiovascular disease and baseline kidney function, longer sleep duration was associated with 19% lower risk of ESRD (HR 0.81, 95% CI 0.67-0.99 per hour increase in sleep duration), and higher sleep fragmentation was associated with 4% increased ESRD risk (HR 1.04, 95% CI 1.01-1.07 per 1% increase in fragmentation). In adjusted mixed effects regression models, higher sleep fragmentation was associated with significant eGFR decline (-0.17 ml/min/1.73m^2/year, p = .016). Self-reported daytime sleepiness was associated with 10% increased risk for all-cause death in the fully adjusted model (HR 1.10, 95% CI 1.02-1.18, per 1 unit increase). We found no significant association between sleep start time, self-reported sleep quality or apnea risk with outcomes.

Conclusions: These findings suggest that short and poor quality sleep are unappreciated risk factors for CKD progression.

Funding: NIDDK Support

SA-PO789

The Association of Histopathological Lesions with Renal Function Decline and Mortality in Biopsy-Confirmed Kidney Disease Anand Srivastava,[1] Arnaud Djou Kaze,[1] Isaac Ely Stillman,[3] Helmut G. Rennke,[2] Sushrut S. Waikar.[1] *[1]Renal Div, Brigham & Women's Hospital, Boston, MA; [2]Pathology Dept, Brigham & Women's Hospital, Boston, MA; [3]Pathology Dept, Beth Israel Deaconess Medical Center, Boston, MA.*

Background: Kidney biopsy is the gold standard for diagnosing many kidney diseases, and may also provide prognostic information. No study to our knowledge has tested whether histopathologic lesions independently predict outcomes across a variety of kidney diseases.

Methods: We enrolled 654 patients undergoing kidney biopsy at three tertiary care hospitals in Boston, MA into a prospective observational cohort study. We fit multivariable-adjusted Cox proportional hazards models to test the association of histopathological lesions involving the mesangium, vessels, and tubulointerstitium with the composite endpoint of renal function decline (doubling of serum creatinine or need for renal replacement therapy) or mortality.

Results: The most common diagnoses were lupus nephritis (13.6%), IgA nephropathy (11%), and diabetic nephropathy (10.4%). 38.3% had other primary glomerular diseases and 37.1% had non-glomerular diseases. 127 patients reached the primary endpoint over a median follow-up time of 21.9 [IQR 10.9–42.8] months. Table shows the associations of histopathological findings with the composite endpoint, adjusted for age, race, sex, log(proteinuria), and estimated glomerular filtration rate (eGFR).

	Adjusted HR [95% CI]
Mesangial Expansion*	
Mild	2.36 [1.33-4.17]
Moderate	2.60 [1.41-4.80]
Severe	2.38 [1.23-4.58]
Glomerulosclerosis*	
11-25%	1.05 [0.59-1.86]
26-50%	1.47 [0.87-2.46]
>50%	2.02 [1.18-3.44]
Interstitial Fibrosis/ Tubular Atrophy*	
11-25%	1.88 [0.97-3.65]
26-50%	2.12 [1.08-4.19]
>50%	3.39 [1.77-6.46]
Arterial Sclerosis+	
Moderate	0.96 [0.58-1.59]
Severe	1.28 [0.79-2.07]
Arteriolar Sclerosis+	
Moderate	1.53 [0.93-2.50]
Severe	1.86 [1.13-3.06]
*Reference is None/0-10% of cortical volume +Reference is None/Mild	

Conclusions: Across a diverse group of kidney diseases, histopathological lesions on kidney biopsy provide independent prognostic information even after adjusting for known risk factors including proteinuria and eGFR.

Funding: NIDDK Support

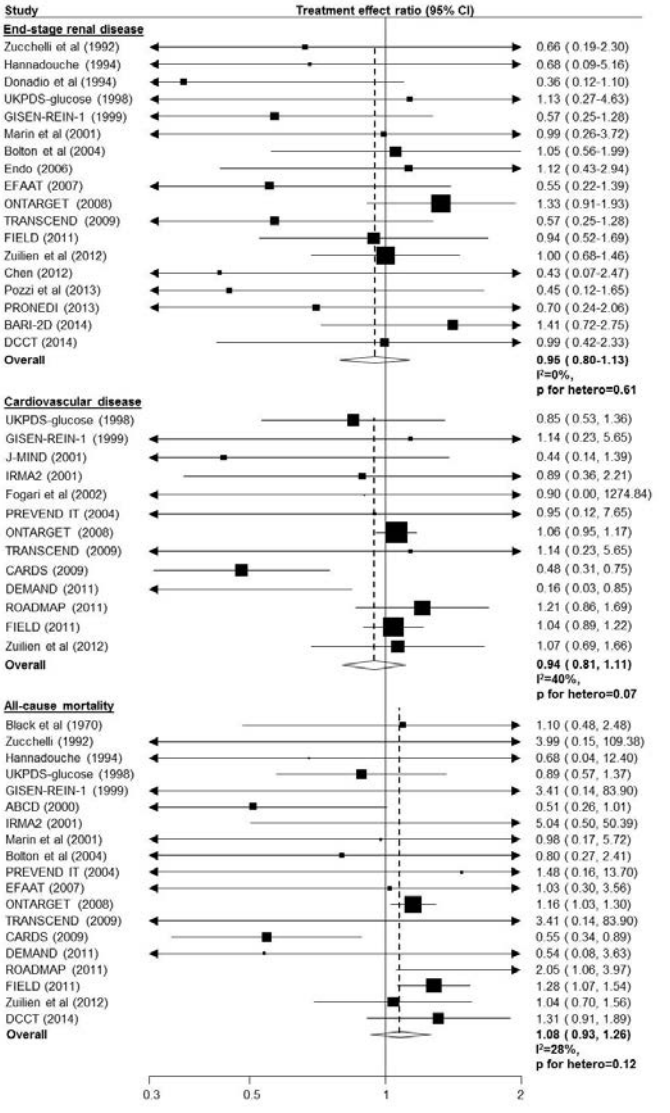
SA-PO790

Assessing the Association between Change in Albuminuria and Clinical Outcomes: A Systematic Review and Meta-Analysis Tyrone Harrison, Helen Tam-Tham, Brenda Hemmelgarn, Min Jun. *Univ of Calgary, Calgary, AB, Canada.*

Background: Albuminuria is a significant predictor of kidney disease progression, cardiovascular morbidity, and mortality among patients with diabetes and/or established chronic kidney disease. However, there is limited information on the prognostic value of albuminuria change on clinically important outcomes. We aimed to assess the association between albuminuria progression and adverse clinical outcomes (all-cause death, cardiovascular disease [CVD], and end-stage renal disease [ESRD]) in adults based on a systematic review of the literature.

Methods: CENTRAL, EMBASE, and MEDLINE were systematically searched for randomized controlled trials (1946-January 2015) that reported change in albuminuria and at least 1 of the 3 clinically important outcomes. Two reviewers abstracted trial characteristics and and outcome data independently. To determine the association between change in albuminuria and clinical outcomes, we determined the treatment effect ratio (TER), defined as the ratio of the treatment effects on clinical outcomes and the effects on the change in albuminuria.

Results: We identified 27 trials (50300 patients) that met the inclusion criteria. 18 reported data on ESRD, 13 on CVD, and 19 on all-cause death. Treatment effects on albuminuria and ESRD were consistent with minimal heterogeneity (TER 0.95 [0.80-1.13), while relatively similar levels of consistency were observed for the outcomes of CVD and all-cause death, however, with evidence of greater heterogeneity (I^2=40% and 28%, respectively).



Conclusions: This review identifies a potentially important correlation whereby progression of albuminuria may be a valid surrogate for ESRD. However, greater heterogeneity was observed for the outcomes of CVD and death. Assessment of the surrogacy of albuminuria in large prospective trials is needed.

SA-PO791

U-Shaped Relationship between Serum Uric Acid Levels and Intrarenal Hemodynamic Parameters in Healthy Subjects Hideki Uedono, Akihiro Tsuda, Eiji Ishimura, Mitsuru Ichii, Shinya Nakatani, Masaaki Inaba. *Dept of Nephrology, Dept of Metabolism, Endocrinology and Molecular Medicine, Osaka City Univ Graduate School of Medicine, Osaka, Abeno-ku, Asahi-machi, Japan.*

Background: Hyperuricemia has been reported to affect renal hemodynamics (Uedono H, et al. Kidney Blood Press Res 2015). However, it is recently reported that low levels, as well as high levels, of serum uric acid are associated with the loss of kidney function (Kanda E, et al. PLOS One 2015). In the present study, we evaluated the relationship between serum uric acid levels and intrarenal hemodynamic parameters in healthy subjects, utilizing plasma clearance of para-aminohippurate (C_{PAH}) and inulin (C_{in}).

Methods: Renal and glomerular hemodynamics were evaluated by simultaneous measurements of C_{PAH} and C_{in} in 40 healthy subjects (17 males and 23 females, 55.3±12.4 years). Intrarenal hemodynamic parameters, including efferent arteriolar resistance (R_e), afferent arteriolar resistance (R_a), and intraglomerular hydrostatic pressure (P_{glo}), were calculated by Gomez's formulae. Serum uric acid levels were compared with these intrarnal hemodynamic parameters.

Results: In a quadratic regression analysis, serum uric acid levels had a significant, inverse U-shaped relationship with C_{in} and with C_{PAH} (p=0.0068, R^2=0.237 and p=0.0335 R^2=0.160, respectively), and U-shaped relationship with R_a (p=0.0005, R^2=0.340). In a multiple regression analysis, in which normal uric acid levels (between 3.0 to 6.4 mg/dL) and abnormal uric acid levels (less than 3.0 or more than 6.4) were entered as dummy variables

of 0 and 1, respectively, abnormal uric acid levels were demonstrated to be significantly and independently associated with R_a (β= 0.315, p = 0.0254) after adjustment of age, gender, body mass index, and systolic blood pressure. (R^2=0.550, p<0.0001).

Conclusions: These findings suggest, for the first time in human, that both mild hyperuricemia (> 6.4 mg/dL) and mild hypouricemia (< 3.0 mg/dL) are significantly associated with increased R_a in healthy subjects with C_{in} > 60 ml/min. The increase in R_a in subjects with hyperuricemia as well as hypouricemia, even in mildly abnormal levels, may be related to renal hemodynamic abnormalities in human.

SA-PO792

Abstract Withdrawn

SA-PO793

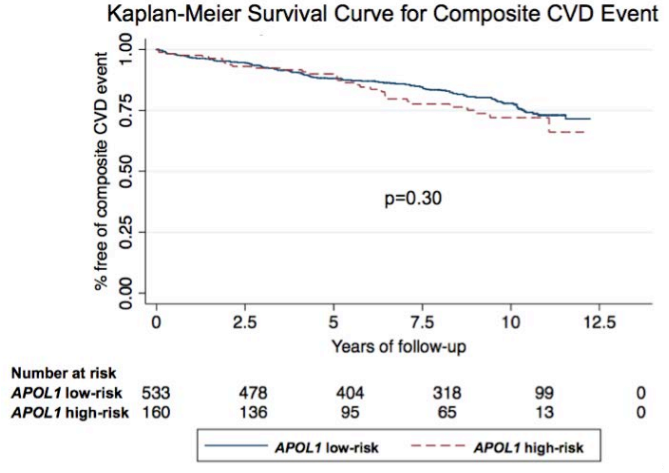
APOL1 Variants and Cardiovascular Disease: Results from the African American Study of Kidney Disease and Hypertension (AASK)

Teresa K. Chen, Lawrence J. Appel, Adrienne Tin, Michael J. Choi, Michelle M. Estrella. *Johns Hopkins Univ.*

Background: Studies on the association between *APOL1* risk variants and cardiovascular disease (CVD) have been conflicting thus far. We aimed to determine whether *APOL1* high-risk variants are associated with increased risk for adverse CVD outcomes in the context of established hypertension-attributed chronic kidney disease (CKD).

Methods: Using data from the trial and cohort phases of AASK (mean follow-up 7.7 years), we constructed Cox proportional hazards models to estimate the relative hazard of experiencing a composite CVD outcome (cardiac revascularization procedure, nonfatal myocardial infarction, heart failure exacerbation, stroke, or cardiovascular death) among African Americans with the *APOL1* high-risk (2 alleles) vs. low-risk (0-1 allele) genotypes. We adjusted for age, gender, ancestry, smoking, body mass index, total cholesterol, randomized treatment groups, and baseline and longitudinal estimated glomerular filtration rate (eGFR), systolic blood pressure, and proteinuria. Censoring occurred at ESRD, death, lost to follow-up, or administrative censoring.

Results: Among the 1094 AASK trial participants, 693 had *APOL1* genotyping available (23% high-risk genotype) and were included in our study. At baseline, the *APOL1* high-risk group had a lower mean eGFR (44.7 vs. 50.1 ml/min/1.73 m^2) and more proteinuria (median 0.19 vs. 0.06) compared to the low risk group. In both unadjusted (HR: 1.23; 95% CI: 0.83 to 1.81; p=0.31) and fully adjusted (HR: 1.14; 95% CI: 0.76 to 1.72; p=0.53) models, individuals with the *APOL1* high-risk genotype had similar risk for the composite CVD outcome as those with the low-risk genotype. Use of additive or dominant genetic models yielded similar findings.



Conclusions: Among African Americans with hypertension-attributed CKD, *APOL1* high-risk variants are not associated with an increased risk for cardiovascular disease.

Funding: NIDDK Support, Pharmaceutical Company Support - Norman S. Coplon Extramural Grant Program by Satellite Healthcare (a not-for-profit renal care provider)

SA-PO794

High Erythropoiesis-Stimulating Agent Dose Is Associated with Increased Healthcare Resource Utilization and Risk of Adverse Events in Non-Dialysis-Dependent Chronic Kidney Disease Patients

David T. Gilbertson,[1] Suying Li,[1] Yi Peng,[1] Haifeng Guo,[1] Shaum Kabadi,[2] Sean Zhao,[2] Trudy Pendergraft,[2] Louise Janice Sargent Heuer,[2] Wendy L. St. Peter.[1] *[1]Chronic Disease Research Group, Minneapolis Medical Research Foundation, Minneapolis, MN; [2]AstraZeneca, Wilmington, DE.*

Background: High-dose ESA (HDE), a measure of ESA resistance, is associated with increased comorbidities, adverse events, and healthcare resource utilization (HRU) in hemodialysis patients. Little is known about this association in non-dialysis-dependent chronic kidney disease (NDD-CKD) patients.

Methods: We investigated this association in stage 3-5 NDD-CKD patients with anemia using 2011-2013 Medicare data. A baseline period was used to define CKD, anemia, and comorbidities from diagnosis codes, and ESA use from drug codes. A 1-year follow-up period was used to define HRU and adverse events. HDE as a measure of ESA resistance was defined by an average monthly ESA dose >90th percentile of monthly doses. Analyses were adjusted for patient characteristics, IV iron use, RBC transfusion, and CKD stage.

Results: A total of 12,901 stage 3-5 NDD-CKD patients with anemia receiving ESAs were included. HDE cut-points were ≥75,630 units for erythropoietin and ≥351 mcg for darbepoetin. HDE use was associated with a significantly increased burden of cardiovascular and thromboembolic events. Furthermore, the risk of death was 60% higher among HDE patients (HR 1.60, [1.43-1.79]), and the risk of major adverse cardiac event (MACE) was 46% higher (1.46, [1.31-1.62]) (Table). Medicare payments were 52% higher for HDE patients (1.52, [1.41-1.63]).

Outcome	Hazard Ratio (95% CI)
All-cause death	1.60 (1.43-1.79)
Major adverse cardiac event	1.46 (1.31-1.62)
Hypertensive emergency	0.95 (0.37-2.45)
Deep vein thrombosis	1.42 (1.18-1.72)
Pulmonary embolism	1.64 (1.22-2.20)
Hospitalization	1.36 (1.26-1.47)
Emergency department visit	1.14 (1.04-1.26)
Hospice	1.55 (1.34-1.80)
Outpatient visits	1.34 (1.33-1.36)
Medicare payment	1.52 (1.41-1.63)

Conclusions: Anemia requiring HDE use in stage 3-5 NDD-CKD patients is associated with increased death, MACE, cardiovascular events, thromboembolic events and HRU. Further research is needed to confirm these associations in other cohorts that include more precise data on hemoglobin measurement and ESA dose.

Funding: Pharmaceutical Company Support - AstraZeneca

SA-PO795

Unexpected Medical Consequences of Revised ESA Label in Non-Dialysis-Dependent Chronic Kidney Disease Patients with Anemia

Suying Li,[1] Haifeng Guo,[1] Shaum Kabadi,[2] Sean Zhao,[2] Trudy Pendergraft,[2] Louise Janice Sargent Heuer,[2] Yi Peng,[1] Wendy L. St. Peter,[1] David T. Gilbertson.[1] *[1]Chronic Disease Research Group, Minneapolis Medical Research Foundation, Minneapolis, MN; [2]AstraZeneca, Wilmington, DE.*

Background: In 2011, the US Food and Drug Administration (FDA) revised labeling for erythropoiesis-stimulating agent (ESA) treatment in non-dialysis-dependent chronic kidney disease (NDD-CKD) patients, and a Hb target of 10-12 g/dL was replaced by guidance to initiate therapy when Hb fell to <10 g/dL. This study aimed to examine changes in anemia treatment, comorbidities, and outcomes after the ESA label change.

Methods: Stage 3-5 NDD-CKD patients with anemia were selected from a 20% Medicare random sample. Two study cohorts were created: the "2008 cohort," consisting of patients identified from the 2007-2009 claims, and the "2012 cohort," based on the 2011-2013 claims. Use of ESAs, intravenous (IV) iron, red blood cell (RBC) transfusions and cardiovascular (CV) comorbidities were defined in a 1-year baseline period, and outcomes (major adverse cardiac events [MACE] including all-cause death, hypertensive emergency [HE], deep vein thrombosis [DVT], and pulmonary embolism [PE]) were defined in a 1-year follow-up period for each study cohort. Results were unadjusted.

Results: ESA use in NDD-CKD patients with anemia declined in 2012 relative to 2008, while use of IV iron and transfusions remained stable (Table). Although the prevalence of baseline comorbidities was similar between the two cohorts, rates of HE, DVT, and PE increased in the 2012 cohort by 100%, 31%, and 45%, respectively. In addition, all-cause death and MACE incidence did not decline.

	2008 cohort	2012 cohort
n	71,744	109,251
Anemia treatment, %		
ESA	29.4	12.7
IV iron	6.3	6.7
RBC transfusion	21.3	22.2
Baseline comorbidities, %		
Atherosclerotic heart disease	51.7	52.7
Congestive heart failure	43.0	43.0
Cerebrovascular accident/transient ischemic attack	21.9	24.1
Peripheral vascular disease	34.2	36.8
Other cardiac-related comorbidities	33.6	36.6
CV Outcomes, rate per 100 patient-yrs (unadjusted)		
All-cause death	15.4	15.2
MACE (including all-cause death)	23.2	22.4
HE	0.3	0.6
DVT	18.7	24.5
PE	7.6	11.0

Conclusions: After the 2011 ESA label change, a reduction in all-cause death and MACE was not observed, while HE, DVT and PE rates increased. Adjusted risk of these unexpected medical outcomes warrants further investigation.

Funding: Pharmaceutical Company Support - AstraZeneca

SA-PO796

Hyperkalemia and Prescription of Antihypertensive Medications: Early Findings from the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) Francesca Tentori,[1,2] Charlotte Tu,[1] Lindsay Zepel,[1] Brian Bieber,[1] Michelle M.Y. Wong,[1] Friedrich K. Port,[1] Christian Combe,[3,4] Benedicte Stengel,[5] Danilo Fliser,[6] Ricardo Sesso,[7] Ichiei Narita,[8] Bruce M. Robinson.[1] *[1]Arbor Research; [2]Vanderbilt U.; [3]CHU de Bordeaux; [4]U. Bordeaux; [5]Inserm U1018; [6]Saarland U. Med. Ctr.; [7]UNIFESP; [8]Niigata U. Grad School of Med. and Dental Sci.; [9]CKDOPPS and CKD REIN Investigators.*

Background: Current guidelines identify renin angiotensin system inhibitors (RASi) as a key element in the treatment of patients with chronic kidney disease (CKD). However, these drugs may be limited in the presence of hyperkalemia. We postulated that prescription of antihypertensive medications in CKD patients varies according to serum potassium (SK) levels, and that these practices vary across countries.

Methods: We leveraged early data from the CKDopps (2013-2016), a prospective cohort study of patients (pts) with eGFR <60 ml/min/1.73m2 from national samples of nephrology clinics in Brazil (BR), France (FR), Germany (GER) and the US to provide descriptive analyses of prescription of anti-hypertensives and K-binding resins by country and SK.

Results: Among 5,104 pts, mean age by country was 66 to 73 yrs; 35-48% were female; 41-58% had diabetes; 46%-67% had eGFR < 30. RASi use was less common in the US and BR than GER and FR; no large differences were seen between diabetics and non-diabetics. RASi use in the US was less common at SK>5 than SK≤5. Prescription of K-binding resins in pts with SK>5 was common in FR and GER, but almost absent in BR and US (Table 1).

Table 1. Selected anti-hypertensive medications and potassium-binding resins prescription, by country and potassium level

	Brazil[a]		France[b]		Germany[c]		US[a]	
Serum Potassium (mEq/L)	**≤ 5**	**> 5**	**≤ 5**	**> 5**	**≤ 5**	**> 5**	**≤ 5**	**> 5**
% of patients*	72%	28%	84%	16%	79%	21%	82%	18%
RASi prescription								
Non-Diabetics	37%	63%	69%	80%	72%	86%	51%	51%
Diabetics	49%	56%	78%	89%	71%	76%	59%	45%
Diuretic†	61%	68%	--	--	72%	68%	60%	52%
K-binding resins‡	0%	0%	10%	25%	5%	16%	1%	4%

* among patients with non-missing serum potassium value: 242, 2913, 1276 and 673 in Brazil, France, Germany and US, respectively
† loop or other diuretics
‡ Na-based (e.g. Kayexalate) or Ca-based (e.g. Calcium Resonium)
a. data from the first interval in which both labs and meds data were available
b. data from the values at enrollment
c. data from the most recent interval

Conclusions: Among pts with advanced CKD, prescription patterns vary across countries. Pharmacological treatment of hyperkalemia, especially in FR and GER, may allow for more liberal prescription of RASi. There is a substantial opportunity for improvement in management of diabetic pts, especially in the US where only half were prescribed a RASi and use of K-binding resins was exceedingly rare.

Funding: Pharmaceutical Company Support - AbbVie, Amgen, Baxter Healthcare, F. Hoffmann-LaRoche, Hexal, Keryx, Kyowa Hakko Kirin, Merck, Proteon, Relypsa, Sanofi, Shire, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, WiNe Institute, Societies for Nephrology in Germany, Italy, & Spain. All grants are made to Arbor Research Collaborative for Health and not to Dr. Tentori directly

SA-PO797

Asymmetric Dimethyl Arginine Modifies the Relationship between High Soluble Urokinase-Type Plasminogen Activator Receptor (suPAR) and the Risk of Death and Cardiovascular (CV) Events in Stage 2-5 CKD Patients Carmine Zoccali, Patrizia Pizzini, Graziella D'arrigo, Daniela Leonardis, Claudia Torino, Maurizio Postorino, Giovanni Tripepi, Francesca Mallamaci. *CNR-IFC, Nephrol Dial Transplant, Reggio Calabria, Reggio Calabria, Italy.*

Background: suPAR is an innate immunity/inflammation biomarker strongly related with plaque instability and atherosclerotic events in patients with cardiovascular disease and in chronic kidney disease (CKD). Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide (NO), is substantially raised in CKD patients and predicts mortality and cardiovascular events (CV) in CKD. Inflammation powerfully activates NO synthesis and there may be a biological interplay between suPAR and ADMA in CKD.

Methods: We measured serum suPAR levels (R&D ELISA) and ADMA (ELISA (DLD Diagnostika GMBH, Hamburg, Germany) in 753 stage G2-5 CKD patients with a 31+10 months follow-up.

Results: suPAR was strongly and independently related with ADMA (r=0.22, P<0.001) as well as with major biomarkers of inflammation (IL-6 r=0.27, P<0.001; Procalcitonin r=0.21 P<0.001; CRP r=0.137, all P<0.001). During follow-up 130 patients developed the combined end point death-CV events and in an adjusted model suPAR predicted this end-point (P<0.001). In further analyses a strong competitive interaction emerged between ADMA and suPAR and a 0.1 uMol/L increase in ADMA signalled a 33% risk excess for the end-point in patients in the first suPAR tertile (HR 1.33; 95% CI: 1.08-1.64, p=0.006) while no risk excess by ADMA was registered in the second and third suPAR tertiles.

Conclusions: suPAR robustly associates with ADMA and biomarkers of innate immunity in CKD and shares a pathogenic pathway whereby ADMA competitively interacts with suPAR for the risk of death and cardiovascular events. ADMA and suPAR should be jointly considered in mechanistic and in clinical studies.

Funding: Government Support - Non-U.S.

SA-PO798

APOL1 Risk Variants and Subclinical Cardiovascular Disease (CVD) in HIV+ and HIV- Men Tessa Kimberly Novick,[1] Ruibin Wang,[1] Sudhir Penugonda,[2] Michael Shlipak,[3] Carl Grunfeld,[3] Adrienne Tin,[1] Jeremy J. Martinson,[4] Matthew Jay Budoff,[5] Rulan S. Parekh,[6] Wendy S. Post,[1] Michelle M. Estrella.[1] *[1]Johns Hopkins; [2]UCSF; [3]Northwestern Univ; [4]Univ of Pittsburgh; [5]UCLA; [6]Univ of Toronto.*

Background: HIV is associated with increased CVD risk and augments adverse effects of *APOL1* risk variants. We assessed whether the *APOL1* variants are associated with subclinical CVD in HIV+ and HIV- blacks in the Multicenter AIDS Cohort Study (MACS).

Methods: We conducted a cross-sectional analysis of men who were genotyped for the *APOL1* G1 and G2 variants and took part in the CVD substudy which enrolled men aged 40-70, weighed <136kg and had no prior coronary revascularization. We used Poisson regression to compare associations of high-risk (2 variants) vs. low-risk (0/1 variant) genotypes with prevalence of coronary artery calcium (CAC), coronary artery plaque and if present, type of coronary artery plaque (non-calcified, mixed and calcified) on CT imaging.

Results: Mean age and eGFR were 52 and 93 ml/min/1.73m^2, respectively, and were similar by *APOL1* genotype. Of 214 HIV+ and 95 HIV- men, 15% had 2 risk variants, 39% had CAC and 69% had coronary artery plaque present. Overall, high- vs. low-risk genotypes were associated with lower prevalence of CAC, but there was little difference in the presence of coronary artery plaque or its subtypes (Table). Stratified analyses showed a stronger association of *APOL1* variants with less CAC and greater non-calcified plaque presence in HIV+ than in HIV- men, though the interactions did not reach statistical significance.

Table. Associations of *APOL1* high- vs. low- risk genotypes with prevalence of subclinical CVD in HIV+ and HIV- black men

	Prevalence ratio (95% CI)	P-value
Overall*		
CAC	0.53 (0.30-0.92)	0.02
Any coronary plaque	1.09 (0.87-1.37)	0.46
Non-calcified plaque	1.14 (0.88-1.48)	0.33
Mixed plaque	1.21 (0.64-2.31)	0.56
Calcified plaque	1.03 (0.54-1.94)	0.94
HIV+ black men**		
CAC	0.37 (0.15-0.92)	0.03
Any coronary plaque	1.12 (0.84-1.48)	0.44
Non-calcified plaque	1.32 (0.98-1.78)	0.07
Mixed plaque	0.71 (0.26-1.97)	0.51
Calcified plaque	0.67 (0.26-1.72)	0.40
HIV- black men**		
CAC	0.81 (0.42-1.56)	0.53
Any coronary plaque	1.04 (0.71-1.52)	0.85
Non-calcified plaque	0.82 (0.50-1.35)	0.44
Mixed plaque	2.29 (0.85-6.15)	0.10
Calcified plaque	1.81 (0.65-5.03)	0.26

*Adjusted for age, CT scanning center, cohort status, ancestry, HIV serostatus, CVD risk factors, eGFR and proteinuria.
**Adjusted as above except for HIV serostatus. P-interactions for HIV x *APOL1* >0.05 for all models.

Conclusions: *APOL1* risk variants are associated with lower CAC burden in blacks. This association is particularly robust and may be driven by presence of non-calcified plaque in HIV+ men. Studies are needed to delineate underlying mechanisms and further evaluate if associations of *APOL1* variants with subclinical CVD indicators differ by HIV serostatus.

Funding: NIDDK Support, Other NIH Support - NIAID, NCI, NIDA, NIMH, NHLBI, NIDCD, JHU-ICTR

SA-PO799

Serum Magnesium and Mortality Risk in Patients with and without CKD in the Dallas Heart Study Silvia Ferrè, Xilong Li, Beverley Adams-Huet, Naim M. Maalouf, Robert D. Toto, Orson W. Moe, Javier A. Neyra. *UT Southwestern, Dallas, TX.*

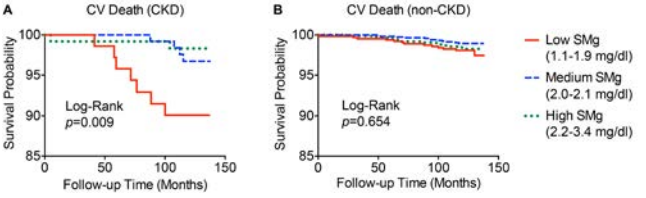
Background: Low serum magnesium (SMg) has been linked to increased mortality in hemodialysis patients and cardiovascular disease (CVD) in the general population. We examined whether similar associations exist in patients with prevalent CKD in the multiethnic population-based Dallas Heart Study (DHS) cohort.

Methods: The whole cohort, CKD and non-CKD subgroups were analyzed. The independent variable was SMg as a continuous variable and divided into tertiles. Study outcomes were all-cause and CV death evaluated using multivariable Cox regression hazards models adjusted for demographics; comorbidity; anthropometric and biochemical parameters including albumin, phosphorus, and PTH; use of diuretics; and their interactions. Median follow-up=12.3 yrs.

Results: Among 3550 participants, 404 (11.4%) had prevalent CKD. Mean SMg (mg/dl) was 2.07 (SD=0.18) in the whole cohort, 2.08 (0.19) in the CKD and 2.07 (0.18) in the non-CKD subgroups. All-cause and CV death occurred in 135 (4.4%) and 52 (1.7%) participants, respectively. SMg was independently associated with all-cause death in the whole cohort (adjusted HR, 1.9; 95% CI, 1.3–2.6; for low vs high tertile). Every 0.2 mg/dl increase in SMg reduced the adjusted hazard for all-cause death by 80%. These

observations were observed in both CKD and non-CKD subgroups. In contrast, SMg was only associated with CV death in the CKD subgroup (adjusted HR, 8.4; 95% CI, 1.6–43.6; for low vs high tertile).

Figure 1. Kaplan-Meier curves for CV death in (A) CKD and (B) non-CKD participants stratified by SMg tertiles.



Conclusions: Low SMg was independently associated with all-cause death in both CKD and non-CKD participants, and with CV death only in CKD participants. The pathophysiologic mechanisms of the effect of Mg on CVD and whether Mg supplementation may impact the CVD burden in CKD patients warrants further investigation.

Funding: Other NIH Support - UL1 TR001105; P30 DK079328-06

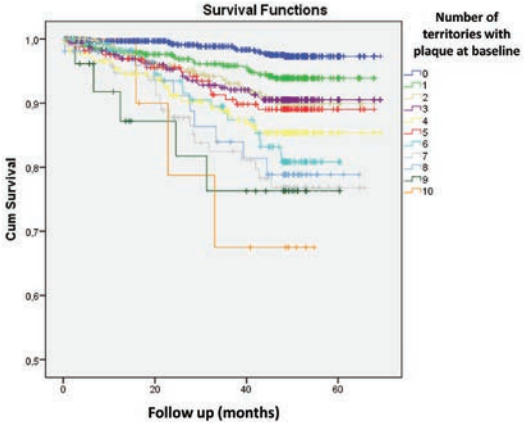
SA-PO800

Subclinical Atheromatosis Detection by Arterial Ultrasound Predicts the Time Free from Cardiovascular Events in Chronic Kidney Disease. Results of the NEFRONA Study Jose M. Valdivielso, Montserrat Martinez-Alonso, Angels Betriu, David Arroyo, Maria Abajo, Elvira Fernandez. *IRBlleida, Lleida, Spain.*

Background: Cardiovascular disease remains the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD).

Methods: The NEFRONA study enrolled 2445 CKD patients without previous cardiovascular disease and 559 subjects with normal renal function. The aim of the study was to assess the value of ultrasound detection of subclinical atheromatosis in the prediction of cardiovascular risk. This study shows the competing risk regression analysis of cardiovascular events (CVE) at the end of the study.

Results:



There have been 216 CVE (48 fatal and 168 nonfatal), 110 non-cardiovascular deaths and 588 renal transplants (both considered competing events). The number of missing patients is 99. The cumulative incidence of CVE is of 7.19% (69.4% men and 30.6% women) with a median of follow-up of 48.09 months. Kaplan Meier curves of survival free from CVE show that it decreases gradually and progressively with increases in the number of territories with plaque. The competing event regression analysis of the whole population shows that the factors significantly predicting CVE incidence are age in non-diabetic subjects, the number of territories with plaque, being a CKD patient in any stage, diabetes and low 25OH vitamin D in CKD stage 3. The stratified analysis showed that factors affecting survival in CKD stages 3-4 were age in non-diabetics, the number of territories with plaque, the levels of 25OH vitamin D, potassium levels over 5 and cholesterol over 240. In dialysis the number of territories, the dialysis vintage, the levels of phosphate, sex and diabetes significantly affected survival.

Conclusions: The severity of arterial atheromatosis estimated by ultrasound predicts the time free from CVE in CKD. Arterial ultrasound is a useful tool to predict cardiovascular risk in CKD patients.

Funding: Pharmaceutical Company Support - Abbott

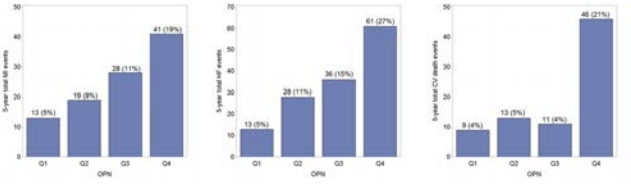
SA-PO801

Osteopontin and Cardiovascular Outcomes in Patients with Stable Coronary Disease Meyeon Park, Debbie Huang, Rakesh Mishra, Michael Shlipak, Mary Whooley. *UCSF.*

Background: Osteopontin (OPN) is an adhesion molecule upregulated by cardiac myofibroblasts and synthesized by endothelial cells in atherosclerotic plaques. OPN promotes hypoxia-induced proliferation of kidney mesangial cells and is stimulated by angiotensin II. We investigated the association between OPN and cardiovascular outcomes in patients with stable ischemic heart disease and variable levels of kidney function assessed by eGFR and ACR.

Methods: OPN was measured in 985 patients with stable coronary disease enrolled in the Heart and Soul Study between 9/2000-12/2002. Poisson regression models were used to examine the relationship between baseline OPN and myocardial infarction (MI), heart failure hospitalization (HF), and all-cause death. Five-year mortality rates were stratified by quartile of OPN.

Results: Spearman correlations between OPN and eGFR and ACR were -0.40 and 0.23. In unadjusted models, risks of MI and HF were significantly higher for participants in Q4 OPN compared to the lower 3 quartiles [incident rate ratio (IRR) 2.48 (95% CI 1.71, 3.60) and 2.96 (2.17, 4.03)] (Fig. 1). Adjusting for demographics and clinical risk factors, participants in Q4 OPN had a higher risk of HF [IRR 1.56 (1.08, 2.25)], while risk of MI was not different between OPN quartiles after adjustment [IRR 1.39 (0.90, 2.16)]. The association between OPN and HF was no longer significant after adjusting for eGFR and ACR [IRR 1.35 (0.90, 2.03)]. Risk of death was highly significant in unadjusted models [IRR 3.59 (2.61, 4.94)] and remained so even after adjustment for eGFR and ACR [IRR 1.83 (1.23, 2.71)].



Conclusions: Higher levels of OPN were associated with risk of HF after adjusting for demographic/clinical factors, but eGFR and ACR attenuated these associations. Higher levels of OPN were nevertheless associated with risk of death independent of eGFR and ACR. OPN may mediate CV risk via angiotensin II-dependent pathways in both kidneys and heart.

Funding: NIDDK Support

SA-PO802

Plasma Dephosphorylated Uncarboxylated Matrix Gla Protein Associate with Vascular Calcification and Vascular Stiffness in Chronic Kidney Disease Paweena Susantitaphong, Sipanan Thamratnopkoon, Pisut Katavetin, Nattachai Srisawat, Khajohn Tiranathanagul, Kearkiat Praditpornsilpa, Somchai Eiam-Ong. *Div of Nephrology, Dept of Medicine, Chulalongkorn Univ, Bangkok, Thailand.*

Background: Vascular calcification causes cardiovascular morbidity and mortality in chronic kidney disease (CKD) patients. Matrix Gla protein (MGP) is a potent inhibitor of vascular calcification and needs vitamin K–dependent phosphorylation and carboxylation for its activity. Therefore, the plasma level of "inactive" dephosphorylated uncarboxylated MGP (dp-ucMGP) which would reflect vitamin K status might associate with vascular calcification. This study was conducted to investigate the association between plasma dp-ucMGP and vascular calcification as well as vascular stiffness in CKD patients.

Methods: Eighty-three CKD stage 3-5 patients were enrolled in this study. Vascular calcification was determined using abdominal aorta calcification (AAC) score from lateral lumbar film, vascular stiffness was assessed by cardio-ankle vascular index (CAVI), and plasma dp-ucMGP levels were measured using ELISA method, Maastricht,The Netherlands.

Results: The mean age was 62.9±13.9 years. The plasma dp-ucMGP levels in CKD stage 3, and CKD stage 4&5 were 604.0 (457.5-925.0) and 1,056 (523.3-1,663.5 pmol/L, respectively (normal <500 pmol/L). The prevalence of vascular calcification (AAC score≥1) was 63.4% and that of vascular stiffness (CAVI≥9) was 46.3%. Multivariate logistic regression analysis to predict vascular calcification showed that age and plasma dp-ucMGP were significantly associated with vascular calcification (OR 1.23;95%CI 1.09-1.37);p<0.001 and OR 1.003 95%CI 1.001-1.005;p=0.002,respectively). In contrast, there was no association between plasma dp-ucMGP and vascular stiffness.

Conclusions: Plasma dp-ucMGPlevels increase progressively with more advance stage of CKD. Plasma dp-ucMGP associated with vascular calcification could be the marker for vascular calcification in CKD patients. Since vitamin K supplement is the readily available treatment to reduce of dp-ucMGP, the effect of vitamin K supplement on vascular calcification in CKD patients should be further explored with the long-term randomized clinical trial.

SA-PO803

Need for Insulin Is Associated with Increased Risk of All-Cause Mortality (ACM) in Various CKD Stages in Type 2 Diabetes Mellitus (T2DM) Rabia Nadeem Kiani,[1] R. E. Boucher,[1] Guo Wei,[1] Debra Lynn Simmons,[1] T. S. Bjordahl,[1] Linda F. Fried,[2] Tom Greene,[1] Srini Beddhu.[1] *[1]Univ of Utah, SLC, UT; [2]VA, Pittsburgh, PA.*

Background: In more advanced CKD, insulin use might reflect insulin resistance and/or contraindication to oral hypoglycemic agents. Therefore, we examined the relationship between the need of insulin and ACM at various stages of CKD in a national cohort of 1,561,876 veterans with serum creatinine and serum HDL-cholesterol measured within 3 months of each other from Jan 1, 2000 to Dec 31, 2008.

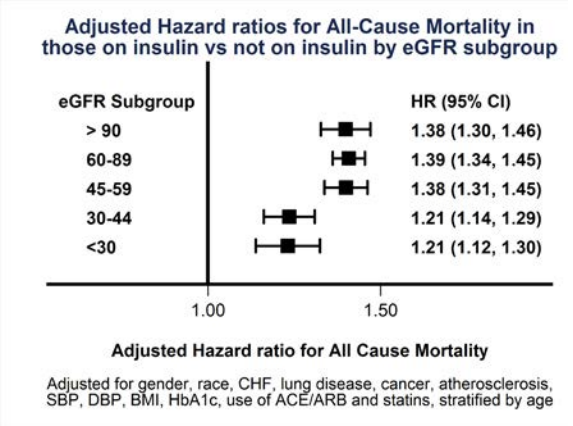
Methods: There were 188,544 veterans with T2DM (defined by ICD9 codes). Data on filled medications were obtained from outpatient pharmacy database. Laboratory data were

obtained from routine clinical labs. Mortality data were from vitals files. Within each eGFR subgroup, the risk for ACM in those on insulin vs. those not on insulin were examined in separate Cox regression models.

Results: Mean age was 65± 11 yrs. 97.4 % were males and 18.4% were black. 20.4% were using insulin. The mean eGFR was 73 ± 23 ml/min/1.73 m^2.

eGFR group	N		ACM / 100 person years (# deaths/total follow-up years)		HR (95% CI)*
	Not on insulin	On insulin	Not on insulin	On insulin	
>90	36,085	9,635	1.1 (4708/420,923)	1.6 (1736/106,479)	1.41 (1.34, 1.49)
60-89	75,227	15,333	1.7 (14,408/846,149)	2.4 (3805/161,675)	1.38 (1.33, 1.42)
45-59	24,761	6,844	2.7 (6802/255,966)	3.6 (2340/65,659)	1.32 (1.26, 1.38)
30-44	11,001	4,374	4.2 (4156/99,969)	4.8 (1809/37,331)	1.13 (1.08, 1.19)
<30	4,006	2,528	7.0 (2053/29,312)	7.2 (1302/18,186)	1.03 (0.97, 1.10)

*Unadjusted HR for comparison of those on insulin vs. not on insulin within each GFR group



Conclusions: Need for insulin in more advanced CKD is associated with elevated mortality risk in adjusted models. Interventions that decrease the need for insulin might decrease mortality in advanced CKD.

Funding: NIDDK Support, VA Support

SA-PO804

Brain Deep and Subcortical White Matter Hyperintensity in Predialysis CKD Patients Hideaki Shima,[1] Tatsuhiko Mori,[1] Hajime Hirano,[1] Mika Sonoda,[2] Mikio Okamura,[3] Tetsuo Shoji,[2] Eiji Ishimura,[2] Masaaki Inaba.[2] *[1]Nephrology, Osaka Medical College, Takatsuki, Japan; [2]Internal Medicine 2, Osaka City Univ, Osaka, Japan; [3]Nephrology, Kayashima-Ikuno Hospital, Kadoma, Japan.*

Background: CKD patients have higher risk for stroke than the general population. Magnetic resonance imaging (MRI) of brain is highly sensitive for detecting ischemic lesions such as deep and subcortical white matter hyperintensity (DSWMH). DSWMH reported to be a risk factor for future stroke and dementia in non-CKD population. In this study, we investigated the prevalence of DSWMH and its relation to clinical severity in predialysis CKD patients without prior stroke.

Methods: The participants of this cross-sectional study included 505 CKD patients and 100 Non-CKD subjects who underwent brain MRI without enhancement to evaluate DSWMH between January 2008 and December 2011.

Results: DSWMH was more prevalent in the CKD (58.4%) than in the Non-CKD (27.0%) groups. In Non-CKD group, those with DSWMH had higher age (66.0±12.0 vs. 56.2±11.6 years), higher systolic blood pressure (125.0±14.3 vs. 116.5±11.2mmHg), and higher proportion of smokers (53.9% vs. 21.0%).In addition to these factors, lower eGFR(27.9 ± 22.2vs.55.4 ± 34.5 ml/min/1.73m²), higher proteinuria (3.09 ± 3.47 g/gCre vs. 2.45 ± 3.18 g/gCre), anemia (Hb11.4 ± 2.4 vs. 12.4 ± 2.4 g/dl) and diabetes (44.7% vs. 29.0%) were associated with the presence of DSWMH in the CKD group. Multivariate logistic regression analysis revealed that eGFR (p<0.01) but not proteinuria (p=0.79) was a significant factor associated with the presence of DSWMH independent of age, sex, diabetes and blood pressure. Moreover, the severity of DSWMH evaluated by the Fazekas scale was significantly and positively correlated with CKD stages.

Conclusions: DSWMH was more prevalent and severer in more advanced stages of CKD. A lower eGFR, rather than proteinuria, was the factor associated with the presence of DSWMH independent of age, sex, diabetes mellitus, and blood pressure. DSWMH may explain the higher risk of stroke in this population.

SA-PO805

Determinants of Long-Term Outcomes in Patients with Atherosclerotic Renovascular Disease and High-Risk Clinical Features Diana Vassallo, James Ritchie, Constantina Chrysochou, Darren Green, Philip A. Kalra. *Dept of Renal Medicine, Salford Royal NHS Foundation Trust, Salford, United Kingdom.*

Background: Although most patients with atherosclerotic renovascular disease (ARVD) remain stable on multitargeted vascular protective therapy, a small but important proportion of patients present with a 'high-risk' clinical phenotype and do not respond to conservative management. In this study we aimed to identify determinants of long-term outcomes in such a selected high-risk subgroup.

Methods: Patients with a radiological diagnosis of ARVD were recruited into our single-center study between 1986 and 2014. Patients with >70% unilateral or bilateral ARVD together with one or more of these presentations were designated 'high-risk': flash pulmonary edema (FPE), severe hypertension, rapidly deteriorating renal function. Patients who did not meet these criteria were designated 'low-risk'. Univariate Cox regression analysis was used to explore the association between individual variables and the following end-points: death, end-stage kidney disease (ESKD), cardiovascular event (CVE) and the first of any of these events.

Results: Out of a total of 843 patients who met inclusion criteria, 131 (15.5%) were designated high-risk.

	Low-risk patients n=712	High-Risk patients n=131	p-value
Median age (years)	71.9	73.3	0.4
Diabetic (%)	27.5	36.6	0.04
Macrovascular disease (%)	68.8	79.4	0.02
Congestive heart failure (%)	17.6	33.3	<0.001
Renin-angiotensin blockade (%)	47.2	59.5	0.01
Statin (%)	52.1	67.9	0.001
Median baseline eGFR	32.6	32.7	0.6
Revascularized (%)	12.8	42.0	<0.001

In the high-risk group, multivariate analysis showed that renin-angiotensin blockade was associated with reduced risk of death (HR 0.42 [95% CI 0.23-0.77], p=0.004), CVE (HR 0.65 [95% CI 0.42-0.99] p=0.046) and any event (HR 0.64 [95% CI 0.41-0.94] p=0.024). Revascularization conferred protection against ESKD (HR 0.58 [95% CI 0.36-0.92] p=0.02) and CVE (HR 0.63 [95% CI 0.41-0.97] p=0.037).

Conclusions: Both intensive vascular protective therapy and revascularization may optimize clinical outcomes in patients with ARVD and 'high-risk' clinical features.

SA-PO806

The Effect of Revascularization in Patients with Atherosclerotic Renovascular Disease and High-Risk Clinical Features - A Single-Center Observational Study Diana Vassallo, James Ritchie, Constantina Chrysochou, Darren Green, Philip A. Kalra. *Dept of Renal Medicine, Salford Royal NHS Foundation Trust, Salford, United Kingdom.*

Background: There is evidence that certain patients with atherosclerotic renovascular disease (ARVD) may benefit from revascularization. In this study we explored the effect of revascularization on long-term clinical outcomes in patients with specific clinical presentations who would meet current criteria for revascularization.

Methods: Patients with a radiological diagnosis of ARVD were recruited into our single-center study between 1986 and 2014. Patients with >70% unilateral or bilateral ARVD together with one or more of the following presentations were designated 'high-risk': flash pulmonary edema (FPE), severe hypertension, rapidly deteriorating renal function. Outcomes in these patients, those specifically with bilateral ARVD and those with <1g proteinuria at baseline were compared to 'control' patients who had the same degree of RAS but did not exhibit these high-risk features. Multivariate Cox regression was used to investigate the effect of revascularization on death, progression to end-stage kidney disease (ESKD), cardiovascular event (CVE) and the first of any of these events in this selected population.

Results: Of 872 patients recruited, 131 (15%) had a 'high-risk' presentation while 144 (16.5%) were designated 'controls'. Revascularization was associated with reduced risk of death in patients presenting with FPE (HR 0.38 [95% CI 0.15-0.96], p=0.04) and reduced risk of ESKD in patients with rapidly deteriorating renal function (HR 0.44 [95% CI 0.24-0.82], p=0.009). In patients with bilateral ARVD, revascularization reduced the risk of both death (HR 0.45 [95% CI 0.20-0.99], p=0.047) and ESKD (HR 0.49 [95% CI 0.27–0.89] p=0.019). High-risk patients with <1g proteinuria at baseline had reduced risk of ESKD (HR 0.56 [95% CI 0.34-0.94] p=0.029), CVE (HR 0.54 [95% CI 0.33-0.89] p=0.016) and any event (HR 0.61 [95% CI 0.38-0.98] p=0.042) following revascularization.

Conclusions: Our results indicate that revascularization may be of benefit in patients with FPE, rapidly deteriorating renal function, severe bilateral renal artery disease and those with <1g/day proteinuria.

SA-PO807

Kidney Dysfunction and Left Ventricular Hypertrophy in Population-Based Autopsy Samples: The Hisayama Study Kensuke Izumaru,[1] Jun Hata,[2] Yutaka Nakashima,[1] Toshiaki Nakano,[3] Kazuhiko Tsuruya,[3] Yoshinao Oda,[4] Takanari Kitazono,[3] Yutaka Kiyohara,[5] Toshiharu Ninomiya.[2] *[1]Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan; [2]Dept of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; [3]Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; [4]Dept of Anatomic Pathology, Pathological Sciences, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; [5]Hisayama Research Inst For Lifestyle Diseases, Fukuoka, Japan.*

Background: Growing evidence has suggested that subjects with kidney dysfunction develop left ventricular hypertrophy (LVH) with the progression of renal disease. However, there are limited studies addressing pathologically the association between kidney dysfunction and LVH.

Methods: In 334 population-based autopsy samples, we investigated the thickness of left ventricular wall according to estimated glomerular filtration rate (eGFR) levels. In 95 sample selected randomly from these samples, the sizes of cardiac cell and the percentages of fibrosis in left ventricular wall were also estimated.

Results: The thickness of left ventricular wall increased significantly with eGFR levels of ≥60, 45-59, 30-44, and <30ml/min/1.73m^2, being 9.1, 9.5, 9.8, and 10.3 (mm), respectively (p for trend <0.05). Lower eGFR levels were associated significantly with greater mean values of cardiac cell size in left ventricular wall after adjusting for confounding factors: 15.3, 16.1, 16.4, and 17.4 (μm) in eGFR levels of ≥60, 45-59, 30-44, and <30ml/min/1.73m^2,(p for trend <0.001). Likewise, subjects with lower eGFR had significantly higher multivariable-adjusted mean values of percentage of fibrosis in left ventricular wall, being 3.22, 4.33, 3.83, and 6.14 (%) in eGFR levels of ≥60, 45-59, 30-44, and <30ml/min/1.73m^2 (p for trend <0.001).

Conclusions: Our findings suggest that renal dysfunction is associated with the cardiac hypertrophy and fibrosis of left ventricle via cardiac cell enlargement and cardiac fibrosis.

SA-PO808

Utility of High-Sensitivity Troponin I in Patients with Impaired Renal Function Eve Victoria Miller-Hodges. *Centre for Cardiovascular Science, Univ of Edinburgh, Edinburgh, United Kingdom.*

Background: Cardiovascular disease remains the leading cause of death in Chronic Kidney Disease. The optimal diagnosis and exclusion of acute myocardial infarction is limited in these patients by the uncertain role of cardiac biomarkers such as Troponin. We investigated whether low serum High-Sensitivity Troponin I (hsTnI) continued to identify those at low risk of cardiac events in the presence impaired renal function (eGFR<60).

Methods: Patients with impaired renal function (eGFR<60) were identified from two prospective cohorts of patients presenting to emergency departments with suspected acute coronary syndrome (Shah AS, *Lancet* 2015 & Shah AS, *BMJ* 2015; n=5050). Serum hsTnI was measured at presentation. The negative predictive values for a range of hsTnI concentrations were established for a composite outcome of myocardial infarction or cardiovascular death at 30 days and at 1 year, compared to the normal population (eGFR >60).

Results: 1160/5050 [23%] patients had an eGFR<60. 302 [26%] had a diagnosis of myocardial infarction at presentation compared to 478 [12.3%] of those with an eGFR>60 (p<0.01). These patients were at significantly higher risk of subsequent myocardial infarction or cardiac death at 30 days (104 [9%] *vs.* 55 [1.4%]) and at 1 year (302 [26%] *vs.* 478 [12.3%]). Serum hsTnI concentration at admission was higher in patients with impaired renal function (median 15.5ng/L [IQR 6-53] *vs.* 4.00ng/L [IQR 2-10]) but the majority of patients were below the 99th centile threshold (702 [61%]). As in health, a low hsTnI threshold at presentation (<5ng/L) continued to identify those patients with impaired renal function at very low risk of myocardial infarction or death within 30 days (negative predictive value 99.4% [98.4-99.9]).

Conclusions: In this large representative cohort of patients presenting with suspected acute coronary syndrome, patients with impaired renal function were at the highest risk of myocardial infarction and cardiac death. A low serum hsTnI concentration identified those at very low risk of myocardial infarction and cardiac death.

SA-PO809

Evaluation of Clinical Outcomes among Nonvalvular Atrial Fibrillation Patients Treated with Warfarin or Rivaroxaban Stratified by Renal Function Matthew R. Weir,[1] Lloyd P. Haskell,[2] Jeffrey S. Berger,[3] Veronica Ashton,[2] François Laliberte,[4] Concetta Crivera,[2] Kip Brown,[4] Patrick Lefebvre,[4] Jeff R. Schein.[2] *[1]Univ of Maryland School of Medicine, Baltimore, MD; [2]Janssen Scientific Affairs, LLC, Raritan, NJ; [3]New York Univ School of Medicine, NY, NY; [4]Groupe d'Analyse, Ltée, Montréal, QC, Canada.*

Background: Renal impairment is linked to increased risk of thromboembolic and bleeding events in NVAF patients.This study compares these events for patients treated with warfarin or rivaroxaban stratified by renal function.

Methods: Patients with first dispensing of warfarin or rivaroxaban after 11/2011 from IMS PharMetrics Plus data (05/2011-6/2015) were included. Ischemic stroke, major bleeding, VTE, and MI outcomes, stratified by estimated creatinine clearance (eCrCl from Cockcroft-Gault formula), were analyzed with hazard ratios. Confounding adjustments were made with inverse probability of treatment weights.

Results: Analyses included 874 rivaroxaban and 1,069 warfarin users. Baseline characteristics for weighted cohorts were similar. Outcomes are reported in table.

Renal Function	Outcomes	Unweighted Incidence Rate (per 100 person-year)		Adjusted HRs (95% CI)	P-Values
		Rivaroxaban	Warfarin		
Overall	Ischemic stroke	0.9	2.6	0.69 [0.23-2.04]	0.5020
rivaroxaban=874	Major bleeding	4.4	6.4	1.18 [0.72-1.94]	0.5166
warfarin=1,069	Composite	7.0	15.0	0.69 [0.46-1.05]	0.0850
eCrCl < 80 mL/min	Ischemic stroke	2.0	4.1	1.21 [0.23-6.48]	0.8201
rivaroxaban=201	Major bleeding	10.2	8.7	1.51 [0.77-2.95]	0.2323
warfarin=406	Composite	9.9	16.6	1.17 [0.53-2.61]	0.6954
eCrCl ≥ 80 mL/min	Ischemic stroke	0.5	1.6	0.56 [0.14-2.18]	0.4040
rivaroxaban=673	Major bleeding	2.8	4.8	0.92 [0.47-1.81]	0.8164
warfarin=663	Composite	6.2	14.0	0.58 [0.36-0.93]	0.0230
Composite = VTE, MI, or stroke					

Conclusions: Rivaroxaban-treated patients with eCrCl ≥ 80 mL/min had significantly lower risk for the composite measure. Ischemic stroke and major bleeding rates were not statistically different between rivaroxaban and warfarin, in patients with or without renal impairment. Further research is warranted to corroborate these findings.

Funding: Pharmaceutical Company Support - Janssen Scientific Affairs, LLC

SA-PO810

Early Mortality and Late Outcomes for Coronary Revascularisation in Chronic Kidney Disease - A Systematic Review and Meta-Analysis Robin Ramphul, Debasish Banerjee. *Renal and Transplantation Unit, St. George's Univ Hospitals NHS Foundation Trust, London, United Kingdom.*

Background: Despite the high prevalence of coronary artery disease in patients with chronic kidney disease (CKD), the optimal method of coronary revascularisation remains unclear. We conducted a systematic review and meta-analysis of the available literature comparing early mortality and long-term outcomes of percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) in patients with CKD.

Methods: We reviewed contemporary studies, conducted after the year 2000 as PCI therapy have improved, comparing PCI to CABG in CKD patients, using Review Manager 5.1 for statistical analysis and PRISMA guidelines for reporting. Clinical end-points compared were early (in-hospital or 30-day) and late (> than 1 year) mortality; repeat revascularisation, occurrence of major adverse cardiovascular events (MACE) and myocardial infarction (MI) after revascularisation.

Results: 4 studies investigated early mortality. The pooled analysis showed similar early deaths for PCI and CABG (4% v 6%, p=0.44, Figure 1a). In 6 studies reporting late mortality, CABG was associated with less deaths compared to PCI (26% v 30%, p<0.001, Figure 1b). Repeat revascularisation was reported in 3 studies with CABG less likely to lead to further revascularisation compared to PCI (2% v 14%, p=0.01, Figure 1c). The occurrence of MACE was reported in 3 studies. CABG was associated with significantly less events compared to PCI (18% v 28%, p=0.01, Figure 1d) and although MI alone occurred less often with CABG than PCI this was not statistically significant (4% v 10%, p=0.41). There existed a selection bias with PCI preferred to CABG in single vessel disease and CABG for multivessel or left main disease.

Conclusions: The results favour CABG for late mortality, repeat revascularisation and MACE whilst PCI is marginally beneficial for early mortality.

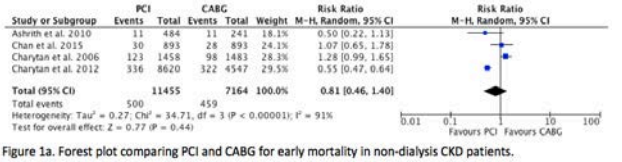


Figure 1a. Forest plot comparing PCI and CABG for early mortality in non-dialysis CKD patients.

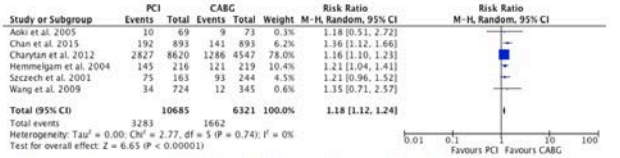


Figure 1b. Forest plot comparing PCI and CABG for late mortality in non-dialysis CKD.

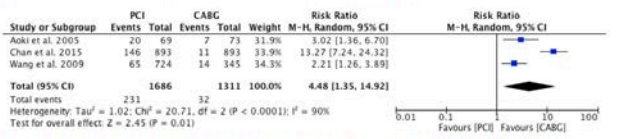


Figure 1c. Forest plot comparing PCI to CABG for need for repeat revascularisation in non-dialysis CKD.

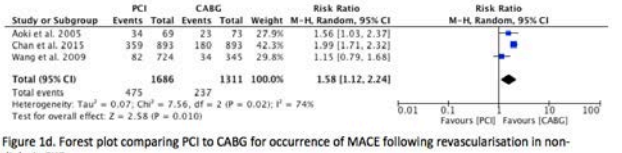


Figure 1d. Forest plot comparing PCI to CABG for occurrence of MACE following revascularisation in non-dialysis CKD.

SA-PO811

Role of TCF7L2 Gene and PPARG2 Gene Polymorphism on Renal and Cardiovascular Complications in Patients with Type 2 Diabetes: A Cohort Study Pamila Tasanavipas, Bancha Satirapoj, Amnart Chaiprasert, Naowanit Nata, Theerasak Tangwonglert, Prajej Ruangkanchanasetr, Ouppatham Supasyndh. *Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand.*

Background: The emerging renal and cardiovascular complications of type 2 diabetes genetics involves differently assembled gene variants including transcription factor-7-like-2 (TCF7L2) and peroxisome proliferated activated receptor gamma 2 (PPARG 2) polymorphism. However, the relevance of these genes for complications prediction has not been extensively tested.

Methods: We analyzed the SNPs rs7903146 in TCF7L2 and PPARG2 gene polymorphism for their contribution to incidence of CKD and CVD complications in the prospective cohort study. All type 2 diabetes patients were followed the estimated glomerular filtration rate (eGFR) and CV outcomes. Cox proportional hazards regression models were used to estimate the genotype effect on the incidence of CKD and CV complications.

Results: A total of 422 patients with mean age of 62±11.8 years and eGFR of 72.8±31.8 mL/min/1.73 m^2 were included. SNPs rs7903146 in TCF7L2 gene were classified into 3 groups: C/C 385patients (91.2%), C/T 32patients (7.6%) and T/T 5 patients (1.2%) and PPARG2 gene were classified into 2 groups: Pro12Pro 404 patients (95.7%) and Pro12Ala 18 patients (4.3%). The prevalence of CKD, CV disease and death at the end of the 5-year follow-up was 16.8%, 29% and 7.9%, respectively. The Pro12Ala variant of PPARG2 gene was significantly was associated with increased CKD risk at the end of the study (adjusted HR 3.45 [95% CI 1.01–11.77, p = 0.046), it did show significant association with increase stroke risk, but not CV diseases and mortality. Whereas, no genotype effect of rs7903146 in TCF7L2 gene was apparent on renal and CV complications in type 2 diabetes over time except that it increased coronary artery disease risk.

Conclusions: The findings of our study are that Pro12Ala variant in PPARG2 gene is associated with risk of developing CKD in Asian type 2 diabetes in the prospective cohort. Further investigations are warranted to understand the pathway-based functional implications of the important loci in PPARG2 gene.

SA-PO812

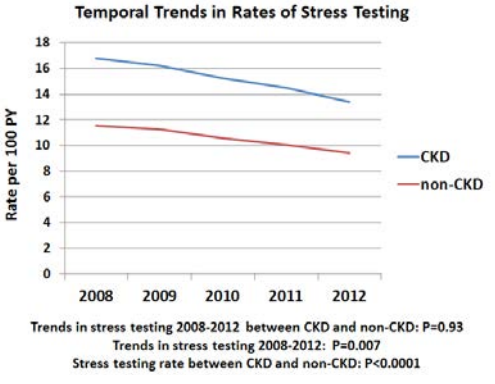
Cardiac Stress Testing in U.S. Patients with Chronic Kidney Disease: Is the Epoch of Nihilism and Renalism Ancient History? Charles A. Herzog,[1,2] Tanya Natwick,[1] Shuling Li,[1] David M. Charytan.[3] *[1]MMRF, Chronic Disease Research Group, Mpls, MN; [2]HCMC, Univ of MN; [3]Brigham & Women's Hospital, Boston, MA.*

Background: A "nihilistic approach" to coronary artery disease (CAD) in pts with chronic kidney disease (CKD) has previously been reported. We have revisited this "truism" in the context of cardiac stress testing in the modern era (2008-12).

Methods: The 20% Medicare sample was searched by single cohort yrs (2008-12) to identify pts age 65+ with no CKD (n = 4,232,080 in 2012) and Stages 1-5D CKD (n= 332,058 in 2012). Incidence rates of non-invasive CAD testing (Stress: Echo, Nuclear, MRI, and ECG and CT: angiography or Calcium score) were estimated within each cohort by yr.

Results: Demographics of pts receiving tests (2012): **non-CKD**: 35% age 75-84, 6% age 85+, 88% white, 7% black, 48% male; **CKD**: 44% age 75-84, 10% age 85+, 80% white, 13% black, 54% male, 7% CKD stages 1 & 2, 67% 3,4,5ND, 8% ESRD and 17% unknown stage. The rate of stress testing (per 100 pt-yrs) was 11.5 for non-CKD and 16.8 for CKD pts in 2008, declining to 9.4 and 13.4 respectively in 2012 (see figure). Stress nuclear testing was dominant: 80.3% (non-CKD) and 88.2% (CKD) of all stress tests in 2008 and 77.7% (non-CKD) and 87.1% (CKD) in 2012 vs stress echo: 11.6% (non-CKD) and 7.4% (CKD) in 2008 and 12.6% (non-CKD) and 7.4% (CKD) in 2012. There was a trend towards higher rates (per 100 pt yr) of stress testing with worse kidney function: No CKD (9.4), Stage 1-2 (13.0), Stage 3-5ND (14.0), ESRD (18.4) in 2012.

Conclusions: There has been a progressive decline in rates of stress testing in both non-CKD and CKD pts from 2008 to 2012. Stress nuclear imaging accounts for more than three-fourths of all stress tests. CKD pts have consistently higher rates of stress testing compared to non-CKD pts in 2008-12. Commonly held perceptions of under-utilization of stress testing for CAD in CKD pts are false in the current era.



Funding: Other NIH Support - NHLBI, Private Foundation Support

SA-PO813

Efficacy of Statin Therapy in Early-Stage Chronic Kidney Disease Han Ro,[1] Sun Moon Kim,[2] Yun Jung Oh,[3] Ae Jin Kim,[1] Jae Hyun Chang,[1] Hyun Hee Lee,[1] Wookyung Chung,[1] Ji Yong Jung.[1] *[1]Dept of Internal Medicine, Gachon Univ Gil Medical Center, Incheon, Republic of Korea; [2]Dept of Internal Medicine, Chungbuk National Univ Hospital, Cheongju, Republic of Korea; [3]Dept of Internal Medicine, Cheju Halla General Hospital, Jeju, Republic of Korea.*

Background: Chronic kidney disease (CKD) is a major risk factor for the development of cardiovascular disease (CVD), and statin treatment can reduce the risk of CVD. However, whether statin treatment affects renal progression and outcomes in CKD patients remains unclear.

Methods: We retrospectively reviewed CKD patients who visited to Gachon University Gil Medical Center with renal problems from 2003 to 2013. From a total 14497 CKD patients, 858 statin users were paired with 1:1 with non-users for analysis using propensity score matching. The outcomes of this study were creatinine doubling, renal death, all-cause mortality, and interactive factors for composite outcomes.

Results: Statins were prescribed to 13.5% of the study subjects. Statin treatment-associated hazard ratios (HRs) [95% confidence intervals (CIs)] for the doubling of serum creatinine levels were significant only in patients with an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2, and were 0.744 (0.635–0.873) in the unmatched cohort and 0.767 (0.596–0.986) in the matched cohort. In analyses of secondary outcomes, the HRs (95% CIs) for all-cause mortality were 0.655 (0.502–0.855) in the unmatched cohort and 0.537 (0.297–0.973) in the matched cohort. The HRs (95% CIs) for composite outcomes among patients with and without eGFR ≥30 mL/min/1.73 m^2 were 0.764 (0.613–0.952) and 1.232 (0.894–1.697), respectively (P for interaction, 0.017).

Conclusions: Statin treatment in the early stages of CKD may be related to renal progression and the all-cause mortality rate.

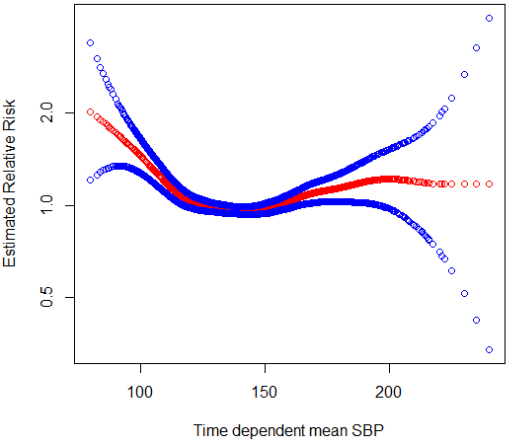
SA-PO814

Low Systolic Blood Pressure during the Follow-Up Period Is Associated with Increased Risk of Cardiovascular Disease in Patients with Type 2 Diabetes and Renal Impairment with and without Heart Failure - The Swedish National Diabetes Register (NDR) Hanri Afghahi,[1] Maria K. Svensson.[2] *[1]Nephrology, Skaraborg Hospital, Skövde, Sweden; [2]Medical Sciences, Uppsala Univ, Uppsala, Sweden.*

Background: Current guidelines recommend a SBP target of <140 mmHg in patients with diabetes and renal impairment (RI) and <130 mmHg when albuminuria is presence . The aim of this study was to further evaluate the relationship between SBP and risk of cardiovascular events (CVEs) in patients with type 2 diabetes (T2D) and (RI), with or without a history of chronic heart failure (CHF) using time-updated mean SBP.

Methods: 27 732 patients with T2D and RI (eGFR< eGFR 60ml/min/1.73m^2 according to MDRD) were followed for mean 4.7 years. The relationships between SBP and CVEs were examined by time-dependent Cox models, to estimate hazard ratios (HR), adjusting for cardiovascular risk factors and medications.

Results: The patients were mean age of 75±9 years, their diabetes duration was 10±8 years, 43% were male, mean SBP at baseline was 138±18 mmHg and 15% had a history of CHF. Patients were classified into 4 groups by time-updated mean SBP (<130, 130-140, 141-160 and >160 mmHg). A time updated mean SBP between 130 and 140 mmHg was used as a reference group. All patients with a time updated mean SBP <130 mmHg had a higher risk of CVEs (HR 1.23, 95% CI 1.19-1.34). In patients without a history of CHF a time-updated mean SBP <130 mmHg was also associated to a higher risk of CVEs (HR 1.23 95% CI 1.14-1.32).



Conclusions: In patients with type 2 diabetes and renal impairment a systolic blood pressure <130 mmHg over the time was associated with a higher risk of cardiovascular events. This association was also found in patients without a history of CHF.

SA-PO815

Trimethylamine-N-oxyde (TMAO) Accumulates in Patients with Chronic Kidney Disease (CKD): Correlation with the Measured Glomerular Filtration Rate (mGFR) Caroline C. Pelletier,[1,2] Mikael Croyal,[3] Michel Krempf,[3] Laurent Juillard,[1,2] Christophe O. Soulage.[2] *[1]Nephrology, Hospices Civils de Lyon, France; [2]Univ Lyon, INSA-Lyon, INSERM U1060, CarMeN Lab, France; [3]INRA, UMR 1280, CRNH, Mass Spectrometry Area, Nantes, France.*

Background: TMAO is associated with poor cardiovascular outcomes in the general population. Significant higher TMAO levels has been ever been reported in patients with CKD. However, these observations were only based on estimated GFR. We wanted to further confirm plasma TMAO accumulation and its relationship with kidney function in a cohort of CKD patients characterized by measured GFR.

Methods: Control and CKD patients were recruited in the E.Herriot university hospital, in Lyon (France) to perform a measurement of GFR by an inuline clearance and plasmatic TMAO determination by LC-MS/MS.

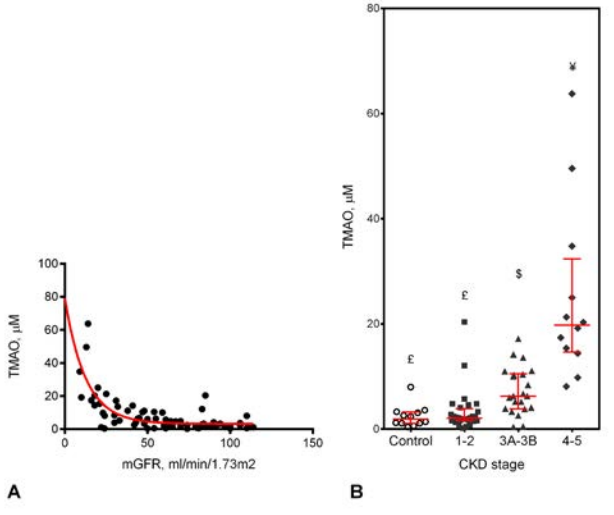
Results: TMAO was measured in 75 patients and was stronlgy associated with the level of mGFR.

Characteristics of healthy volunteers and CKD patients.

	Healthy volunteers	CKD patients			P-value
		Stage 1-2	Stage 3	Stage 4-5	
Effective	12	27	22	14	
Age, y	41.2±10.5	47.3±14.8	63.8±15.5	51.5±21.0	***
Creatinin, µM	64.3±14.7	83.1±17.6	122.5±40.6	275.3±114.6	****
UAlb/UCreat, mg/mmol	1.2±1.0	12.0±28.1	59.5±195.7	52.7±67.1	****
mGFR, ml/min/1.73m^2	102±8.2	76.1±10.6	43.4±8.9	18.4±5.3	****
TMAO, µg/L	2.4±2.1	3.3±4.1	7.3±4.5	21.5±17.7	****

Means were compared with ANOVA test with a significant p<0.05.

We observed a significant differences between the stages 4-5 and the stage 3 as well as between the stage 3 and all the other patients with better renal function.



Conclusions: Plasma TMAO is increased in patient with CKD and negatively associated with the stages of CKD, defined by mGFR. We confirmed that TMAO accumulates in CKD as a result of the decreased GFR suggesting that TMAO could be considered as a novel uremic toxin.

Funding: Clinical Revenue Support

SA-PO816

The Predictive Value of Serum Triglyceride to High-Density Lipoprotein Cholesterol Ratio According to Renal Function in Patients with Acute Myocardial Infarction (From the Korea Acute Myocardial Infarction Registry) Jin Sug Kim, Yu Ho Lee, Da Rae Kim, Chun-Gyoo Ihm, Tae Won Lee, Kyung-Hwan Jeong. *Kyung Hee Univ Hospital.*

Background: Serum triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio has been reported as an independent predictor for cardiovascular events in general population. However, the prognostic value of this ratio is unclear in patients with renal dysfunction. We examined the association of TG/HDL-C ratio and major adverse cardiovascular events (MACEs) according to renal function in patients with acute myocardial infarction (AMI).

Methods: This study was based on the Korea Acute Myocardial Infarction Registry database. Among 13,897 patients who diagnosed AMI from November 2005 to July 2008, 7,016 patients were enrolled. Patients were stratified into three groups by estimated glomerular filtration (eGFR) and TG/HDL-C ratio was categorized into tertiles based on the distribution of TG/HDL-C ratio. We investigated the 12-month MACEs, including cardiac death, MI, and repeated percutaneous coronary intervention or coronary artery bypass grafting.

Results: During follow up period, 593 patients (8.5%) had MACEs. There was a significant association between the TG/HDL-C ratio and MACEs (p<0.001). The Cox regression analysis shows that high tertile of TG/HDL-C ratio was an independent factor for 12-month MACEs (HR 1.64, 95% CI 1.26-2.14, p<0.001). Then we performed subgroup analyses according to renal function. In patients with normal renal function (eGFR≥90 ml/min/1.73 m^2) and mild renal dysfunction (eGFR 60≤to<90 ml/min/1.73 m^2), higher TG/HDL-C ratio was significantly associated with increasing risk of MACEs (hazard ratio [HR] 1.65, 95% confidence interval [CI] 1.04-2.49, p=0.018; HR 1.60, 95% CI 1.16-2.19, p=0.004, respectively). However, in patients with moderate renal dysfunction (eGFR<60 ml/min/1.73 m^2), higher TG/HDL-C ratio lost predictive value(HR 1.25, 95% CI 0.84-1.86, p=0.274).

Conclusions: Among patients with AMI, the TG/HDL-C ratio is a useful independent predictor of 12-month MACEs. However, this ratio lost predictive power in subgroup with moderate renal dysfunction. Further studies are needed to investigate underlying mechanism.

SA-PO817

A Predictive Model for Development of Peripheral Artery Disease among Patients with Chronic Kidney Disease Jing Chen, Wei Yang, Jason Roy, Xiaoming Zhang, Damodar R. Kumbala, Pranav S. Garimella, Mahboob Rahman, Raymond R. Townsend, Bernard G. Jaar, Edward J. Horwitz, Madhumita J. Mohanty, Esteban A. Cedillo-Couvert, Stephen M. Sozio, Harold I. Feldman, Emile Mohler, L. Lee Hamm, Jiang He. *Tulane Univ.*

Background: Patients with chronic kidney disease (CKD) have an increased risk of peripheral artery disease (PAD). A predictive model may help evaluate risk before significant changes in ankle-brachial index (ABI) to provide early detection, prevention, and treatment.

Methods: A total of 3,146 adult CKD patients in the Chronic Renal Insufficiency Cohort Study without PAD at the baseline visit were included in this analysis. Incident PAD was defined as a new onset ABI of <0.9 or clinical PAD confirmed by an endpoint assessment committee. Models were developed using Cox proportional hazards regression methods and evaluated using C statistics. The LASSO approach was used to select predictors, where the best fitting model is the one that minimizes the deviance in cross-validation.

Results: 635 individuals developed PAD over 6 years of follow-up. The hazard ratios for selected risk factors in the predictive models are presented in the table.

Variables	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Log ABI	0.60 (0.54, 0.66)	0.61 (0.55, 0.68)
Log age	1.27 (1.16, 1.39)	1.21 (1.09, 1.34)
Female	1.37 (1.17, 1.61)	1.28 (1.08, 1.52)
Black	1.53 (1.31, 1.79)	1.19 (1.01, 1.42)
Current smoker		2.01 (1.63, 2.48)
Diabetes		1.28 (1.02, 1.59)
Log pulse pressure		1.16 (1.05, 1.28)
Log alkaline phosphatase		1.10 (1.01, 1.20)
Log C-reactive protein		1.12 (1.03, 1.22)
Log fibrinogen		1.08 (0.97, 1.19)
Log hemoglobin		0.99 (0.90, 1.09)
Log Hemoblobin A1c		1.11 (1.01, 1.23)
Log eGFR		0.90 (0.82, 0.99)
C-Statistics	0.67 (0.69, 0.74)	0.72 (0.65-0.70)

The final model 2 was significantly (P<0.001) more accurate than the model 1.

Conclusions: A model using readily available clinical and laboratory tests can improve the risk prediction over ABI for development of PAD in CKD patients. Further studies should validate this predictive model.

Funding: NIDDK Support

SA-PO818

Efficacy and Safety of Warfarin Therapy in Chronic Kidney Disease Patients with Atrial Fibrillation Priscilla P. How,[1,4] Timothy Koh,[1] Xin Yi Wong,[2] Doreen Tan,[2] Ying-Ying Seow,[3] Hersharan Sran.[4] *[1]Dept of Pharmacy, National Univ of Singapore; [2]Dept of Pharmacy, Khoo Teck Puat Hospital; [3]Dept of Renal Medicine, Khoo Teck Puat Hospital; [4]Dept of Medicine (Nephrology), National Univ Hospital.*

Background: While anticoagulation of atrial fibrillation (AF) patients without chronic kidney disease (CKD) to reduce stroke risk is well-established, it is less straightforward in patients with both conditions due to their increased bleeding and stroke risk. This study aimed to determine warfarin's efficacy and safety in local AF patients with varying degrees of renal impairment.

Methods: Patients who filled warfarin prescriptions at two acute care hospitals in Singapore between June 2010 and May 2012 were included if they were ≥ 21 years old, received warfarin for AF for ≥ 3 months prior to study entry (target INR 2-3), and for 2 continuous years or until discontinuation due to an event or death. The patients were classified by CKD stages into 4 groups. Risk of major adverse cardiovascular events (MACE) and major bleeding were estimated using time-dependent Cox regression analyses.

Results: Of the 250 patients recruited, 81 (32.4%) had stage 3 CKD, 32 (12.8%) had stage 4-5 CKD and 16 (6.4%) had end-stage renal disease (ESRD) and were receiving dialysis. Compared to patients with no CKD (eGFR>60 ml/min/1.73m^2, reference group), risk of MACE was similar among stage 3 CKD (hazard ratio [HR] 0.55; 95%CI 0.09–3.26), stage 4-5 CKD (HR 1.81; 95%CI 0.26–12.51) and ESRD patients (HR 3.66; 95%CI 0.33–40.34). Risk of major bleeding was similar among those with stage 3 (HR 0.60; 95%CI 0.21–1.68) and stage 4-5 CKD (HR 3.31; 95%CI 0.70–15.79), while a trend of increased bleeding risk was observed among ESRD patients (HR 9.21; 95%CI 1.00–84.71). Proportion of patients with labile INR was also highest among ESRD patients (68.8% vs. 47.1-53.1%, P=0.407).

Conclusions: Similar risk of MACE and major bleeding was observed among our local AF patients with varying degrees of renal impairment receiving warfarin. However, ESRD patients may be at increased risk of major bleeding.

SA-PO819

Impact of Updated Recommendations for Aspirin Use for the Primary Prevention of Cardiovascular Disease Fanny Lepeytre, Myriam Khalili, Stephan Troyanov, Josee Bouchard, Francois Madore. *Nephrology, Hôpital du Sacré-Coeur de Montréal, Montréal, QC, Canada.*

Background: Newly updated guidelines of the U.S. Preventive Services Task Force (USPTF) recommend initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) in adults aged 50-59 yrs who have a ≥ 10% 10-yr CVD risk. In adults aged 60-69 yrs or at increased risk of bleeding, the decision to initiate aspirin use should be individualized. The impact of these new recommendations remains largely unknown especially for patients with CKD.

Methods: We studied 20,004 randomly selected individuals from the general population aged 40-69 yrs to estimate the number and the characteristics of individuals with and without aspirin therapy. We evaluated CVD history and risk factors, Framingham score, medication use and kidney function.

Results: Among participants aged 50- 59 yrs with no history of CVD and a ≥10% 10-yr CVD risk, 15.5% (n=462) were currently taking aspirin or another platelet aggregation inhibitor. For individuals aged 60-69 yrs, this proportion was higher (28.3%). Factors independently associated with current aspirin use in patients with no history of CVD and increased risk are shown below.

Characteristics	OR	95% CI	P-Value
Age	1.06	1.05, 1.08	<0.001
Male gender	1.37	1.16, 1.61	<0.001
Obesity (BMI, kg/m^2)	1.20	1.03, 1.40	0.02
Regular medical visits *	1.92	1.28, 2.88	0.01
Diabetes *	1.60	1.07, 2.41	0.02
Diabetes treatment	2.84	1.87, 4.33	<0.001
Dyslipidemia *	1.29	1.08, 1.54	0.01
Statin use	3.30	2.74, 3.98	<0.001
Anti-hypertensive treatment	3.36	2.88, 3.91	<0.001
CKD EPI < 60ml/min	0.71	0.54, 0.95	0.02

No association was found with hypertension*, income, education, ethnicity, tobacco use. *: self reported.

Conclusions: Current aspirin use for primary CVD prevention is low (15.5%) and is associated with CVD risk factors and corresponding treatments. Patients with chronic kidney disease are less likely to receive aspirin. Implementation of updated USPTF guidelines will require significant practice changes.

Funding: Clinical Revenue Support

SA-PO820

Quantitative Evaluation of Antihypertensive Adherence in Chronic Kidney Disease Lee Lee Zhu, Thuy Hoang, Linda Awdishu. *Skaggs School of Pharmacy and Pharmaceutical Sciences, Univ of California, San Diego, La Jolla, CA.*

Background: Adherence to ACEI and ARB therapy is important to reduce blood pressure (BP) and proteinuria in patients with chronic kidney disease (CKD). No studies to date has reported measurements of antihypertensive concentrations in biological fluids to assess medication adherence.

Methods: This is a prospective medication reconciliation and adherence study of 492 patients at University of California, San Diego Health System. Adult patients taking ACEI or ARB who were able to provide urine or saliva sample were included in the study. Medication reconciliation and adherence by patient interview was conducted by a pharmacist or student pharmacist. Urine and saliva were analyzed for ACEI and ARB concentrations using liquid chromatography-mass spectrometry. Patients with CKD (eGFR<60 ml/min/1.73m2) were compared to those without CKD for ACEI or ARB and/or metabolite concentrations in the urine or saliva as well as office and home BP measurements. Fisher's exact test was used to compare count data and student's t-test was used to compare continuous data.

Results: A total of 135 patients were included with 62 and 73 in the CKD and non-CKD groups, respectively. Self-reported adherence was high in both groups with 97-100% of patients reporting missing or being late on 0-5 doses/month. CKD patients reported better accuracy in self reporting (somewhat accurate 94% vs 88%, p=0.003). In CKD, urine and saliva detection of parent drug was: lisinopril 90%, losartan 92%, olmesartan 100%, ramipril 0%, valsartan 91% and metabolites: benazeprilat 75%, enalaprilat 100%, losartan carboxylic acid 100%, ramiprilat 100%. There was no difference in the detection of drugs or metabolites in CKD vs non-CKD patients. Office BP readings were lower in the CKD group (SBP 123 vs 130 mmHg, p=0.015). There was no difference in home BP readings or serum potassium concentration.

Conclusions: Adherence to ACEI and ARB therapy was similar between CKD and non-CKD patients. CKD patients had lower blood pressures without evidence of elevated serum potassium concentrations. Detection of ACEI or ARB drug concentrations in the urine provides a quantitative measure of adherence to support self-reporting.

Funding: Pharmaceutical Company Support - Millennium Research Institute

SA-PO821

Effects of CKD on Survival Who Were Screened for Sleep Apnea Syndrome Kunitoshi Iseki.[1] [1]*Clinical Research Support Center, Tomishiro Central Hospital, Tomigusuku, Okinawa, Japan;* [2]*Internal Medicine, Nakamura Clinic, Urasoe, Okinawa, Japan.*

Background: Sleep Apnea Syndrome (SAS) is common in CKD patients, but the prognosis is not precisely examined based on the overnight polysomnography (PSG).

Methods: We enrolled all subjects (n=10,856) who were evaluated by PSG during September 1990 to December 2010 at the Nakamura Clinic, Okinawa, Japan (the ONSLEEP registry). Among them, serum creatinine (SCr) at the time of PSG examination was available in 3,676 patients (70.7% men; mean age 48.9 years). Survival was confirmed by medical charts, letters, and telephone calls. Follow ups were from the date of PSG to the last visit of 2014 or the dates of response to mail or telephone call. Outcomes were starting dialysis (ESRD) or death, whichever came first. We excluded those age <20 years old and those were already on dialysis. CKD was defined as eGFR<60 ml/min/1.73m^2 which was estimated using Japanese formula. SAS was diagnosed when the apnea-hypopnea index (AHI) ≥5. Cox analysis was done to examine the risk of SAS, CKD, and the combination on survival.

Results: Prevalence of CKD increased with AHI; 14.8% in AHI<5 (N=704), 18.9% in AHI 5 to <15 (N=773), 22.7% in AHI 15 to <30 (N=706), and 20.3% in AHI≥30 (N=1,493). The total follow-up period was 16,358 patient-years and the mean observation period was 4.5 years. The number of death and ESRD was 89 and 19. The outcome rate per 1,000 patient-years was 6.6 (combined), 5.4 (mortality) and 1.2 (ESRD), respectively. The event rate was as 0.5% in SAS (-)/CKD (-), 2.4% in SAS (+)/CKD (-), 4.8% in SAS (-)/CKD (+), and 7.1% in SAS (+)/CKD (+). The hazard ratio (95% confidence interval) was 1.82 (0.67 to 7.45) in SAS (+) & CKD (-), 5.74 (1.41 to 28.04) in SAS (-) & CKD (+), 3.78 (1.37 to 15.61) in SAS (+) & CKD (+) when the group of SAS (-) & CKD (-) was taken as a reference. Limitations are the limited number of SCr measurements and lack of details of SAS treatment such as continuous positive air pressure (CPAP) and medications.

Conclusions: The present study supports the notion to evaluate CKD among SAS patients.

Funding: Private Foundation Support

SA-PO822

Circulating ACE2 as a Biomarker of Cardiovascular Outcomes Lidia Anguiano,[1] Marta Riera,[1] Julio Pascual,[1] Sergi Clotet-Freixas,[1] Angels Betriu,[2] Jose M. Valdivielso,[2] Clara Barrios,[1] Elvira Fernandez,[2] Maria Jose Soler.[1] [1]*Nephrology, Hospital del Mar-Inst Hospital del Mar d'Investigacions Mèdiques, Barcelona, Spain;* [2]*Nephrology, Hospital Arnau de Vilanova, Lleida, Spain.*

Background: ACE2 activity from human EDTA-plasma samples directly correlated with the classical CV risk factors namely older age, diabetes and male gender and with atherosclerosis progression at 2 years of follow-up. In a CKD population without previous history of CV disease. **Aim**: To study circulating ACE2 activity as a biomarker of CV outcomes in CKD stages 3-5(CKD3-5) patients at 4 years of follow-up.

Methods: Prospective study of 1237 CKD3-5 patients. Circulating ACE2 activity was analyzed. Variables assessed: non-fatal and fatal CV event, non-CV mortality, all-cause mortality (CV and non-CV), and the composite all-cause mortality + non-fatal CV event. For the overall survival analysis, stratified baseline circulating ACE2 activity (low-level ACE2: <24.9 RFU/μL/h and high-level ACE2: ≥24.9 RFU/μL/h) was used.

Results: Non-fatal and fatal CV events was higher in the high-level ACE2 group (9.4%) as compared to the low-level group (5.1%, p=0.008). Estimated mortality was also assessed in patients with the composite all-cause mortality and non-fatal CV event and in patients with all-cause mortality. In both cases, estimated mortality was higher in the high-level ACE2 group (14.1% and 8.5%, respectively) as compared to the low-level ACE2 group (8.7% and 4.8%, respectively; p=0.008 and p=0.024, respectively). Multivariate logistic regression was adjusted for 10 variables (see Table).

Conclusions: In CKD3-5 patients without history of CV, circulating ACE2 may help to detect patients at risk for CV event and non-CV mortality at 4 years of follow-up.

		Adjusted analysis	
		HR (95% CI)	p-value
Non-fatal and fatal CV event	Age, <65 vs ≥65 years	1.51 (1.03-2.23)	0.036
	Diabetes, yes vs no	2.30 (1.57-3.38)	<0.001
	Baseline circulating ACE2 activity, <24.9 vs ≥24.9 RFU/µL/h	1.62 (1.01-2.60)	0.046
Non-CV mortality	Age, <65 versus ≥65 years	4.46 (2.41-8.24)	<0.001
	Creatinine, mg/dL	1.34 (1.10-1.64)	0.003
	Baseline circulating ACE2 activity, RFU/µL/h	1.01 (1.00-1.01)	0.002
All-cause mortality and non-fatal CV event	Age, <65 versus ≥65 years	2.30 (1.66-3.20)	<0.001
	Current smoker, yes vs no	1.53 (1.10-2.12)	0.012
	Diabetes, yes vs no	1.91 (1.40-2.61)	<0.001
	Creatinine, mg/dL	1.26 (1.12-1.42)	<0.001
	Baseline circulating ACE2 activity, <24.9 vs ≥24.9 RFU/µL/h	0.26 (0.85-1.79)	0.261
All-cause mortality	Age, <65 versus ≥65 years	2.63 (1.68-4.12)	<0.001
	Gender, men vs women	2.20 (1.35-3.59)	0.002
	Diabetes, yes vs no	1.67 (1.09-2.55)	0.018
	Hemoglobin, g/dL	0.73 (0.64-0.84)	<0.001
	Baseline circulating ACE2 activity, <24.9 vs ≥24.9 RFU/µL/h	1.23 (0.74-2.05)	0.429

Funding: Government Support - Non-U.S.

SA-PO823

Prognostic Value of Reverse Dipper Blood Pressure Pattern in Patients with Non-Dialysis Chronic Kidney Disease: A Prospective Cohort Study

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Background: Reverse dipper blood pressure(BP) pattern has been studied among the general and hypertensive population. However, the prognosis of reverse dipper BP pattern in chronic kidney disease (CKD) patients remains unknown.

Methods: We monitored BP throughout the day and followed health outcomes in 588 CKD patients admitted to our hospital. Time to all-cause mortality, to cardiovascular mortality, to renal and to cardiovascular events was recorded. Multivariate-adjusted Cox regressions were carried out to detect the prognostic value of reverse BP pattern for total mortality, cardiovascular mortality, renal events and cardiovascular events.

Results: The prevalence of dippers, non-dippers and reverse dippers was 34.69%, 43.54% and 18.03% respectively. Patients with reverse dippers had higher incidence of total mortality, cardiovascular mortality, renal and cardiovascular events than patients with dippers (P<0.05), and also had higher incidence of total mortality, cardiovascular mortality and events than patients with non-dippers (P<0.05). Multivariate-adjusted Cox regression analyses showed that reverse dippers (*versus* dippers) was associated with a higher risk of total mortality (HR=5.085, P=0.002), cardiovascular mortality (HR=4.437, P=0.013), renal events (HR=3.291, P<0.001) and cardiovascular events (HR=4.259, P=0.006) even adjusted by 24h systolic BP (SBP).

Conclusions: In conclusion, we have provided the first evidence that reverse dipper BP pattern, independent of 24-hour SBP levels, had prognostic value in Chinese patients with non-dialysis chronic kidney disease. Further prospective randomized clinical trials are needed to clarify whether correcting blood pressure pattern by administration of antihypertensive drugs at night has a beneficial effect in improving the prognosis and attenuating the progression of cardiovascular and renal disease in CKD patients.

Funding: Government Support - Non-U.S.

SA-PO824

Testosterone Replacement Therapy (TRT) to Normalize Serum Total Testosterone (T) Levels Is Associated with Delayed Progression of CKD and Lower All-Cause Mortality

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Background: The effect of TRT on the progression of CKD is not known. We used data from a large cohort to retrospectively determine whether TRT has adverse effects on patients with CKD.

Methods: The Veterans Administration Informatics and Computing Infrastructure (VINCI) data were extracted using SAS Enterprise Guide 7.1 and analyzed using SPSS. Serum creatinine (mg/dl) as a measure of renal function was compared between groups of Veterans with low total testosterone (T). (Gp1) who normalized with TRT (N=38729, creatinine 1.06 ±0.001, FU 6.1 years) and (Gp2) untreated subjects who maintained low T levels (Gp2, N=9755, creatinine 1.11 ± 0.004, FU 5.1 years). Change was defined by time to various plasma creatinine concentration thresholds and all-cause mortality.

Results: Table 1A shows that increase in serum creatinine levels from <1.5 to ≥1.5, <3 to ≥3 and <6 to ≥6 was significantly (P<0.001) delayed in Gp1. Table 1B shows that all-cause mortality in individuals <50 years and those ≥50 years was significantly lowered in Gp1 (P<0.001).

TABLE 1A			
	N	**Final Creatinine**	**Days to event±SEM (P, Normalized *vs.* untreated)**
Creatinine from <1.5 to ≥1.5		mg/dL±SEM	
Normalized	8042	1.72±0.01	899±10 (P<0.001)
Untreated	1815	1.70±0.01	757±19
Creatinine from <3 to ≥3			
Normalized	1146	3.92±0.04	1315±32 (P<0.001)
Untreated	335	3.76±0.08	1053±54
Creatinine from <6 to ≥6 (ESRD)			
Normalized	280	7.19±0.09	1317±64 (P<0.001)
Untreated	66	7.40±0.22	1059±107

TABLE 1B			
Death, all-cause			
Age (yr)		**N**	**Median survival days ±SEM (P, Normalized *vs.* untreated)**
<50	Normalized	102	1596±96 (P<0.001)
	Untreated	30	1369±210
≥50	Normalized	1407	1681±27 (P<0.001)
	Untreated	786	1343±35

Conclusions: Normalization of T levels does not hasten decline in renal function and may lower all-cause mortality.

Funding: VA Support, Private Foundation Support

SA-PO825

Thyroid Hormone Replacement May Decrease the Risk of Cardiovascular Events in Diabetic Nephropathy Patients with Subclinical Hypothyroidism

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Background: Recent studies have revealed that subclinical hypothyroidism is associated with several adverse cardiovascular outcomes in diabetic nephropathy. Although thyroid hormone replacement therapy (THRT) could restore these conditions in general population, the effectiveness of THRT in diabetic nephropathy combined with subclinical hypothyroidism is not investigated.

Methods: From 2000 to 2014, we identified 257 patients who diagnosed with diabetic nephropathy combined with subclinical hypothyroidism. Subclinical hypothyroidism was defined as normal free thyroxine (fT4) with elevated thyroid stimulating hormone (TSH). THRT was defined as the replacement of thyroid hormone at least 60 days. The primary outcomes are defined as all-cause mortality and incident major cardiovascular events.

Results: The mean age was 65.6±12.5 years. Among 257 diabetic nephropathy combined with subclinical hypothyroidism patients, 83 (32.3%) were classified as the THRT group. THRT group showed significantly high TSH level (7.10±1.53 vs 6.16±1.21, P < 0.001). During a mean follow-up duration of 38.0±29.2 months, all-cause mortality and incident major cardiovascular events were observed in 21 and 98 patients, respectively. In multiple Cox analysis, THRT did not reduce all-cause mortality (hazard ratio [HR], 1.833; 95% confidence interval [CI], 0.440-7.642, P = 0.406), while was independently associated with the lower risk of incident major cardiovascular events (HR, 0.558; 95% CI, 0.332-0.939, P = 0.028) even after adjustment for age, sex, TSH, HbA1c and estimated glomerular filtration rate.

Conclusions: These findings suggest that THRT in patients with diabetic nephropathy combined subclinical hypothyroidism might be considered the therapeutic options.

SA-PO826

The Subclinical Fluid Overload Is Significantly Associated with Coronary Artery Calcification in Patients with Chronic Kidney Disease

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Background: The aim of this study is to identify the relationship between fluid status and underlying renal function, and to elucidate the association between fluid overload and coronary artery calcification in patients with chronic kidney disease (CKD).

Methods: The data was retrieved from the prospective observational cohort for Cardiovascular and Metabolic Disease Etiology Research Center-High Risk (CMERC-HI, NCT02003781). Fluid status was measured by bioimpedance analysis and extracellular water was adjusted by total body water (ECW/TBW). The subjects were excluded from the study if they had severe overhydration (ECW/TBW≥0.40). Finally, 1,148 CKD patients were eligible in present analysis.

Results: The mean age of the study subjects was 60.0±10.9 years, and 656 (57.1%) patients were male. The fluid overload valued by ECW/TBW was gradually intensified according to CKD stages. The participating individuals were divided into four groups according to the quartiles of ECW/TBW. Age, prevalence of diabetes, peripheral and central pulse pressure, and coronary calcium score (CCS) increased in accordance with increasing quartiles of ECW/TBW. In multiple linear regression analysis, age, diabetes, serum albumin, C-reactive protein, and eGFR were independently associated with ECW/TBW. In addition, ECW/TBW was found to be independently associated with CCS after adjustment for multiple confounding factors (per 0.001 increase in ECW/TBW; odds ratio=1.06, 95% confidence interval=1.02-1.10, P=0.003) in multiple logistic regression analysis. Subgroup analysis in patients with CKD stage 1-3a also demonstrated the significant association between ECW/TBW and CCS.

Conclusions: Extracellular volume status is significantly associated with coronary artery calcification in patients with CKD throughout all stages.

SA-PO827

High-Normal Albuminuria Is Associated with Subclinical Atherosclerosis in a Nondiabetic Population without Chronic Kidney Disease Toshinori Ueno, Ayumu Nakashima, Shigehiro Doi, Aki Sanada, Takao Masaki. *Dept of Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan.*

Background: Low-grade albuminuria is considered to be a predictor of cardiovascular mortality, while little is known about the relationship between high-normal albuminuria and subclinical atherosclerosis in the general population without diabetes mellitus.

Methods: In this cross-sectional study, 2137 non-diabetic, Japanese middle-aged men (mean age, 53 years), who attended general health checkups between April 2012 and March 2015, underwent blood sampling, urinalysis, and carotid ultrasonography. Presence of chronic kidney disease (CKD) was diagnosed by the clinical criteria, estimated glomerular filtration rate <60 ml/min per 1.73m^2 or urine albumin to creatinine ratio (UACR) ≥30 mg/g. Carotid intima-media thickness (IMT) and the number of focal atheromatous plaques were used as indicators of subclinical atherosclerosis. To assess independent predictors of IMT and carotid plaque formation in the non-CKD subpopulation, multivariate stepwise analysis was used.

Results: Among 2137 participants, 324 (15.2%) had CKD. Both IMT (0.68±0.13 vs. 0.64±0.13 mm, p<0.01) and the presence of plaques (71.0 vs. 59.0%, p<0.01) were significantly higher in the CKD than in the non-CKD subjects. In subjects without CKD (n=1813), mean UACR was 5.1 (range 0.0–29.8) mg/g, and a significant positive trend across UACR quartiles was observed for IMT and the number of carotid plaques. Age, body mass index, and hypertension were independentlyassociated with thickened IMT, whereas UACR did not show a significant correlation. In contrast to IMT, UACR was independently associated with the number of carotid plaques.

Conclusions: Our results indicate that high-normal albuminuria is associated with carotid plaque formation in a nondiabetic population without CKD.

SA-PO828

Endogenous Ouabain as a Biomarker of Heart Failure and a Predictor of Mortality after Cardiac Surgery in CKD Patients Marco Simonini, Simona Pozzoli, Nunzia Casamassima, Chiara Lanzani, Lorena Citterio, Simona Delli Carpini, Elisabetta Messaggio, Stefano Tentori, Elena Bignami, Paolo Manunta. *San Raffaele Scientific Inst, Milan, Italy.*

Background: Cardiovascular diseases remain the main cause of mortality and morbidity worldwide and, in particular, in patients with Chronic Kidney Disease (CKD). The identification of subjects with increased risk of developing new cardiovascular events remains a priority in order to guide treatments and determine individual prognosis. Biomarkers are useful tools that are able to help physicians in decision-making. Our aim is to investigate Endogenous Ouabain (EO), an adrenal stress hormone with hemodynamic effects, as a valuable biomarker of heart failure in patients with impaired renal function.

Methods: From a population of more than 800 patients undergoing elective cardiac surgery, we selected those patients with impaired renal (eGFR < 90 ml/min/m^2) function at baseline. In this subset of patients (550) have investigated the relationships between EO with well known and codified markers of heart failure. We also explored the predictive power of this biomarker for 30-days morality after cardiac surgery.

Results: EO was found to be correlated negatively with left ventricular EF (p=0.011), positively with Cardiac End Diastolic Diameter (p=0.05) and positively with plasmatic NT-proBNP level (p=0.001). Moreover, a different plasmatic EO level (both preoperative and postoperative) was found according to NYHA class (p=0.005). Finally, a higher EO level in the immediate post-operative time was indicative of a more severe cardiological condition and it was associated with increased perioperative mortality risk (p=0.041 for 30-days morality). All data were corrected for sex, age, BMI, basal eGFR, and EuroSCORE. All correlation remains significant if we consider the whole population (802 subject) for the analysis.

Conclusions: Our data suggest that in CKD population preoperative and post-operative plasmatic EO level identifies patients with a more severe cardio-vascular presentation at baseline. These patients have a higher risk of morbidity and mortality after cardiac surgery.

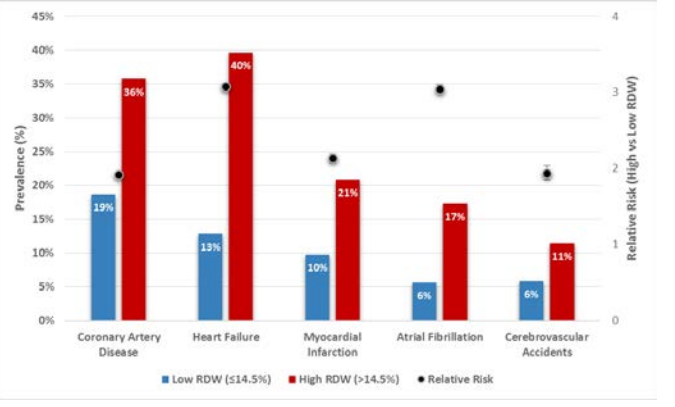
SA-PO829

Red Cell Distribution Width as a Biomarker of Cardiovascular Disease in Patients with Chronic Kidney Disease Nissreen Elfadawy, Chang H. Kim, Sadeer Al-Kindi. *Internal Medicine, Case Medical Center - Univ Hospitals - Case Western Reserve Univ, Cleveland, OH.*

Background: Cardiovascular risk stratification in patients with CKD is required to direct prevention and intervention strategies. Anisocytosis, as measured by Red Cell Distribution Width (RDW) has been linked to adverse cardiovascular outcomes in patients with heart failure. It is unknown whether higher RDW is associated with increased prevalence of cardiovascular disease (CVD) in CKD population. The aim of the study is to evaluate the association between high RDW and prevalence of CVD in patients with CKD.

Methods: Using Explorys database, we identified patients with CKD (age 18-65 years) and have active records between 1999 and 2016. Patients were stratified into normal RDW (≤14.5%) and high RDW (>14.5%). We studied the frequency of CVD, namely: coronary artery disease (CAD), heart failure (HF), myocardial infarction (MI), atrial fibrillation (Afib), and cerebrovascular accident (CVA), based on the ICD diagnoses, in the 2 groups. Statistical comparison between the normal and high group was performed with chi-square test, and risk ratio (RR) of the CV adverse events was calculated.

Results: A total of 231,390 CKD patients (stages I- V) were included. The proportion of the CKD patients with CVD was significantly higher in the RDW high group compared to the RDW normal group. The RR was greater in the HF (3.1 [3.0-3.1]) and A fib (3 [2.9-3.1]). When patients were stratified by CKD stage, the RR was highest in the early CKD stages and decreased with advancing stage.



Conclusions: In this large cohort of CKD patients, elevated RDW was associated with significantly increased CVD prevalence specially in early CKD stages I-II. RDW could identify patients for CVD prevention trials in this high risk population.

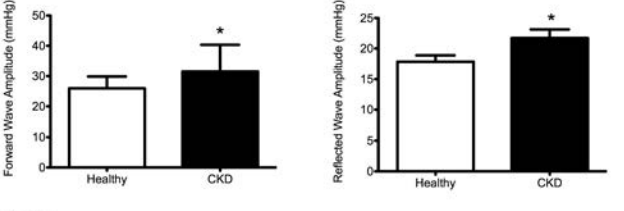
SA-PO830

Arterial Wave Reflection and Cardiorespiratory Fitness in Mild to Moderate CKD Danielle L. Kirkman,[1] Bryce J. Muth,[1] Raymond R. Townsend,[2] David G. Edwards.[1] *[1]Univ of Delaware; [2]Univ of Pennsylvania.*

Background: Cardiorespiratory fitness levels are reduced in Chronic Kidney Disease (CKD) patients and are associated with a poor quality of life, increased cardiovascular disease (CVD) risk and premature death. Disease related structural and functional cardiac and vascular changes provide central limitations to exercise tolerance. Increased arterial wave reflection amplitude may contribute to increased left ventricular pulsatile load and thus hamper oxygen delivery during activity. The relationship between arterial wave reflection and cardiorespiratory fitness in CKD is unknown.

Methods: Cardiopulmonary exercise testing (CPX) and assessment of central aortic pressure with wave separation analysis were carried out in 27 stage 3-5 CKD patients (Mean±SD, age 60±13yrs; eGFR 44±13ml/min/1.73^2) and 20 healthy controls (57±5yrs). VO_{2peak} was measured by expired respiratory gas analysis during graded CPX. Aortic pressure waves were synthesized from radial artery waveforms acquired by applanation tonometry and use of a generalized transfer function. Augmentation Index (AI) was calculated and the central pressure waveform was separated into forward and reflected waves using a physiologic flow waveform.

Results: VO_{2peak} was reduced in CKD patients (27±7 *vs.* 18±5ml/kg/min, p<0.01). Central aortic systolic pressure was increased in CKD patients (134±21 *vs.* 119±14mmHg, p=0.01). AI was similar between groups (29±11 *vs.* 27±14%, p=0.5), however both forward and reflected wave amplitudes were higher in CKD.



* p < 0.05

In CKD patients, moderate to strong inverse relationships were shown between VO_{2peak} and both forward (r=-0.68, p<0.01) and reflected (r=-0.55, p<0.01) wave amplitudes.

Conclusions: Forward and reflected wave amplitudes are increased in CKD, which may contribute to the high CVD risk in these patients. Increased arterial wave amplitudes may pose a central limitation to exercise tolerance in CKD.

Funding: Other NIH Support - NIH National Heart Lung and Blood Institute: HL11351401

SA-PO831

Clinical Value of Natriuretic Peptides in Predicting Short- and Long-Term Dialysis in Stage 4 and 5 Chronic Kidney Disease Patients

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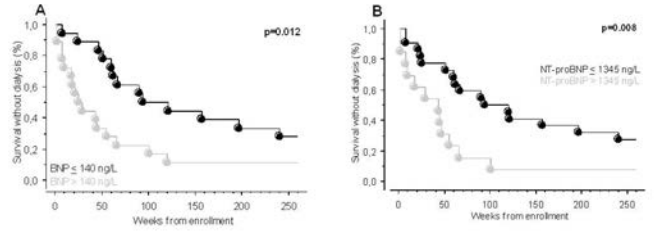
Background: Anticipating the time to renal replacement therapy (RRT) in chronic kidney disease (CKD) patients is an important but challenging issue. Natriuretic peptides are biomarkers of ventricular dysfunction related to poor outcome in CKD. We comparatively investigated the value of B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) as prognostic markers for the risk of RRT in stage 4 and 5 CKD patients within a 5-year follow-up period.

Methods: Baseline plasma BNP (Triage, Biosite) and NT-proBNP (Elecsys, Roche) were measured at inclusion. Forty-three patients were followed-up during 5 years. Kaplan-Meier analysis, with log-rank testing and hazard ratios (HR), were calculated to evaluate survival without RRT.

Results: During the first 12-month follow-up period, 16 patients started RRT. NT-proBNP concentration was higher in patients who reached endpoint (3221 ng/L vs 777 ng/L, p=0.02). NT-proBNP concentration > 1345 ng/L proved significant predictive value on survival analysis for cardiovascular events (p=0.04) and dialysis within 60 months follow-up (p=0.008 ; Figure). BNP concentration > 140 ng/L was an independent predictor of RRT after 12 months follow-up (p<0.005), and of significant predictive value for initiation of dialysis within 60 months follow-up.



Conclusions: Our results indicate a prognostic value for BNP and NT-proBNP in predicting RRT in stage 4 and 5 CKD patients, regarding both short- and long-term periods. NT-proBNP also proved a value in predicting cardiovascular events. Natriuretic peptides could be useful predictive biomarkers for therapeutic guidance in CKD.

SA-PO832

Sodium/Urea Nitrogen in Second Urine Is the Best Tool in Predicting 24-Hour Urinary Sodium

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Background: Determining daily salt intake is important in predicting public health. Sodium intake has been calculated based on using spot urine to estimate sodium intake instead of 24-hour urine due to inadequate collection. However, it is still unclear what is best to estimate daily sodium intake. We measured sodium and other electrolytes for each samples collected as every episode of urination during 24 hours, and examined any correlation to represent 24-hour urinary sodium.

Methods: Fifteen male adults(age: 33.7±6.43) were participated. They had only 3 meals per day which includes total of 2.0g of sodium and no restriction to water intake. The 24-hour urine was collected starting from second urine of the first day to first urine of the second day. The 24-hour sodium intake was estimated using Tanaka's equation. Urine sodium, potassium, chloride, urea nitrogen, creatinine, and specific gravity were measured from the spot urine. We used ratio of Na to other parameters to analyze any correlation to total 24-hour urinary sodium. Each urine samples were compared in three sets; first morning urine of the second day, second urine of the first day, and every 88 collected urine samples of 15 enrolled participants.

Results: The 24-hour urinary sodium (24UNa) was 143.9±42.1mg. The 24UNa was significantly correlated with Na/urea nitrogen(r=0.56), Na/Osm (r=0.51), age (r=0.548), Na/Cr (r=0.392) and estimated sodium using Tanaka's equation (Tanaka's Na, r=0.463). Most significant correlation was seen in second urine of the first day: 24UNa was correlated with Na/urea nitrogen (r=0.710), Na/Osm (r=0.680), Na/Cr (r=0.589), age (r=0.544), Na/Cr (r=0.589), and Tanaka's Na (r= 0.666). However, first morning urine of the second day showed unexpected poor correlation: Na/urea nitrogen (r=0.322), Na/Osm (r=0.308), age (r=0.544), Na/Cr (r=0.202) and Tanaka's Na (r=0.375).

Conclusions: In conclusion, second urine sample is more suitable than first morning urine to estimate 24UNa. The Na/urea nitrogen had significant correlation with 24UNa in second urine in all participants. Further studies are necessary to validate valuable index and optimal time for urine sample in predicting 24-hour urinary sodium.

SA-PO833

Association of Serum Aldosterone Levels with Clinical Outcomes in the Elderly

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Background: Elevated serum aldosterone levels have been associated with adverse outcomes in persons with hyperaldosteronism and cardiac disease. We investigated the relationship between serum aldosterone and clinically important outcomes in a healthy elderly cohort.

Methods: Serum aldosterone was measured at baseline in the Health ABC Study, a cohort of well-functioning adults aged 70-79 years. Using a case-cohort study design, cases were selected for kidney disease progression (30% reduction in eGFR), incident heart failure (HF), incident cardiovascular disease (CVD), and all-cause mortality. Weighted Cox proportional hazards models, sequentially adjusted for cardiovascular and kidney factors, were used to examine the associations of serum aldosterone with each clinical outcome.

Results: Mean (SD) age was 73.6 (2.8) years; 49% were women, and 61% were white. Median (25th, 75th) serum aldosterone was 5.12 (3.15, 8.85) ng/dL. There was no association between serum aldosterone with kidney disease progression, incident HF, or all-cause mortality. After adjustment for cardiovascular and kidney factors, medication use and urine sodium, there were significant lower atherosclerotic CVD events with high serum aldosterone levels.

	Event Rate*	Unadjusted†	Adjusted Model 1†	Adjusted Model 2†
Progression of Kidney Disease	2.85	1.00 (0.91, 1.09)	1.00 (0.92, 1.10)	1.01 (0.92, 1.10)
Incident HF	1.92	1.08 (0.97, 1.22)	1.04 (0.93,1.16)	1.03 (0.92, 1.17)
Incident CVD	2.63	0.92 (0.79, 1.07)	0.0.86 (0.73, 1.01)	0.85 (0.72, 0.99)
All-Cause Mortality	4.73	0.98 (0.92, 1.05)	1.01 (0.92, 1.06)	0.99 (0.91, 1.07)

Legend:
*Event rates per 100 person-years
†Model outcomes are reported as HR (95% confidence intervals). Hazard ratios are reported per doubling serum aldosterone
Adjusted Model 1 = Adjusted for age + race + gender + BMI + prevalent diabetes mellitus + prevalent HTN + systolic BP + LDL + smoking + eGFR + ACR
Adjusted Model 2 = Model 1+ RAS blockade + any diuretic + urine sodium excretion

Conclusions: There was no relationship between high serum aldosterone and kidney disease progression, incident HF, or all-cause mortality. Higher aldosterone levels were associated with lower CVD risk after adjustment for urine sodium excretion and medications. Additional studies are needed to confirm these relationships in healthy, younger people.

SA-PO834

Association of Urine Sodium with Clinical Outcomes in the Elderly

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Background: Recent studies in persons at high cardiovascular risk suggest a U-shaped relationship between sodium intake and cardiovascular outcomes. We assessed the relationship of urine sodium, as a proxy for sodium intake, to clinical outcomes in healthy older adults. Because aldosterone levels may increase with low sodium intake, we evaluated whether aldosterone is an important confounding variable.

Methods: Baseline spot urine sodium and serum aldosterone were measured in the Health ABC Study, a cohort of well-functioning adults aged 70-79 years. 24-hr urine sodium excretion was estimated by the Kawasaki formula. Using weighted cox proportional hazards models in a case cohort study design, we evaluated the association of urine sodium with kidney disease progression (30% decrease in eGFR), incident heart failure, incident atherosclerotic cardiovascular disease (CVD), and all-cause mortality. Sequential adjustments for cardiovascular and kidney factors as well as aldosterone were performed.

Results: Mean (SD) 24-hr urine sodium excretion was 4174 (1546) mg. Lower levels of urine sodium were associated with CVD but not kidney disease progression, heart failure, or all-cause mortality. Aldosterone did not attenuate the relationship of low urine sodium with CVD. There was no interaction between aldosterone and urine sodium for CVD (p-interaction=0.6).

	Unadjusted*	Adjusted Model†	Adjusted Model + Aldosterone‡
Kidney Disease Progression			
Quartile 1	0.78 (0.50, 1.22)	0.77 (0.50, 1.20)	0.77 (0.50, 1.20)
Quartile 2	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Quartile 3	0.84 (0.54, 1.33)	0.78 (0.50, 1.22)	0.78 (0.50, 1.22)
Quartile 4	1.18 (0.76, 1.81)	0.89 (0.58, 1.38)	0.89 (0.58, 1.38)
Incident Heart Failure			
Quartile 1	1.37 (0.85, 2.21)	1.34 (0.80, 2.24)	1.39 (0.83, 2.33)
Quartile 2	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Quartile 3	1.05 (0.65, 1.71)	0.91 (0.54, 1.55)	0.88 (0.52, 1.49)
Quartile 4	1.24 (0.76, 2.00)	1.10 (0.65, 1.86)	1.02 (0.60, 1.74)
Incident Atherosclerotic CVD			
Quartile 1	1.33 (0.80, 2.21)	1.88 (1.03, 3.32)	2.00 (1.14, 3.52)
Quartile 2	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Quartile 3	1.31 (0.80, 2.17)	1.33 (0.76, 2.34)	1.29 (0.73, 2.27)
Quartile 4	1.20 (0.72, 2.00)	1.17 (0.66, 2.06)	1.11 (0.63, 1.96)
All-Cause Mortality			
Quartile 1	0.91 (0.63, 1.32)	0.90 (0.61, 1.32)	0.90 (0.61, 1.32)
Quartile 2	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Quartile 3	1.04 (0.72, 1.51)	0.91 (0.62, 1.33)	0.91 (0.62, 1.33)
Quartile 4	1.38 (0.97, 1.98)	1.21 (0.85, 1.75)	1.22 (0.84, 1.75)

Legend:
Models are reported as Hazard Ratios (95% confidence intervals):
*Unadjusted: urine sodium excretion per SD increase (SD = 1,546 mg/day)
†Adjusted Model: Adjusted for age, race, gender, BMI, DM, HTN, SBP, LDL, smoking, eGFR, urine ACR, RAAS blockade, any diuretic use
‡Adjusted Model + Aldosterone: Adjusted for all variables above + serum aldosterone

Conclusions: Lower levels of urine sodium were associated with higher risk of CVD in healthy adults, but not with heart failure, kidney disease progression, or mortality. Aldosterone did not attenuate the relationship between low urine sodium excretion and CVD.

SA-PO835

Growth Arrest-Specific Gene 6 May Be a Biomarker of Non-Complicated Atherosclerotic Plaque Burden Rachel M. Holden,[1] Laura E. Couture,[1] Michael A. Adams.[2] *[1]Medicine, Queen's Univ, Kingston, ON, Canada; [2]Biomedical and Molecular Sciences, Queen's Univ, Kingston, ON, Canada.*

Background: Growth arrest-specific gene 6 (Gas6) belongs to the family of vitamin K-dependent proteins. Gas6 is not detected in normal vessels but is expressed by vascular smooth muscle cells at all stages of human atherosclerosis and is markedly higher in non-complicated plaques than in complicated (i.e. vulnerable) plaques. Gas6 may act as a protective factor, in part, by reducing the pro-inflammatory phenotype of VSMCs. The objective of this study was to determine the association of Gas6 with measures of atherosclerosis quantified by carotid ultrasound.

Methods: In 204 patients referred for coronary angiography, blood was collected and maximum plaque height and carotid intima media thickness (CIMT) was assessed in the internal carotid arteries (ICA) and carotid bulbs by ultrasound. Gas6 and FGF-23 were measured in plasma via ELISA (Immunotopics Inc). Multi-variable models evaluated independent predictors of maximum plaque height, CIMT and the difference between maximal plaque height and CIMT (PH-CIMT).

Results: In bivariate analysis, Gas6 was significantly higher in females (p=0.019), diabetics (p=0.010) and those with BMI > 30 kg/m^2 (p=0.004). There was a significant correlation between gas6 and FGF-23 (r=0.262, p<0.001). There was no association between gas6 and CIMT. In multivariate models adjusted for age, sex, and diabetes, a higher level of gas6 was associated with lower plaque height and lower PH-CIMT. This significant relationship remained robust after adjustment for smoking, hypertension, hyperlipidemia, phosphate and FGF-23.

Conclusions: Although Gas6 levels were higher in diabetics and obese subjects, there was a significant and inverse association between Gas6 and plaque height. Gas6 is anti-inflammatory and its expression is markedly higher from non-complicated plaques. Therefore, gas6 could be a biomarker reflecting the presence of less vulnerable plaques in humans. Whether vitamin K is a significant mediator of this process is not known.

SA-PO836

Social Support and Health Outcomes in Hispanics with Chronic Kidney Disease Anna C. Porter,[1] Jesse Yenchih Hsu,[2] Eunice Carmona,[1] Clarissa Jonas Diamantidis,[3] Michael J. Fischer,[1] Edward J. Horwitz,[6] Marie Krousel-Wood,[4] John W. Kusek,[5] Claudia M. Lora,[1] Eva Lustigova,[4] Bhavik P. Patel,[1] Ana C. Ricardo,[1] Anne M. Slaven,[4] Xue Wang,[2] James P. Lash.[1] *[1]Univ of IL; [2]Univ of PA; [3]Duke; [4]Tulane; [5]NIDDK; [6]MetroHealth OH.*

Background: Low social support is a predictor for negative health outcomes in the general population and in patients with chronic disease. However, less is known about social support in patients with chronic kidney disease (CKD), particularly in Hispanics. We evaluated the association of social support with CKD progression, cardiovascular (CV) events, and all-cause mortality in Hispanic adults with CKD.

Methods: We conducted a prospective observational study of 322 Hispanic adults with CKD enrolled in the Hispanic Chronic Insufficiency Cohort Study. Social support was measured at baseline with the Medical Outcomes Study Social Support instrument. Depression was measured with the Beck Depression Inventory. Outcomes included CKD progression (50% loss of eGFR or incident ESRD), CV events (heart failure, stroke, myocardial infarction, peripheral arterial disease), and death. Low social support was defined as a score > 1 standard deviation below the cohort mean.

Results: The mean age was 57 years, 62% were men, 17% had low social support, and the mean eGFR was 38 ml/min/1.73 m^2. Compared with individuals in the highest quartile of social support score, individuals in the lowest quartile had a demographic-adjusted OR for depressive symptoms of 3.11(1.59-6.07). Over a median follow-up of 5 years, the event rate per 100 person-year was 8.6 for ESRD, 4.6 for CV events, and 3.7 for death. Cox regression analyses adjusted for sociodemographics, diabetes, eGFR, and proteinuria are shown in the Table.

	ESRD	CV Events	Death
Adjusted HR (95% CI)			
Social support score > 1 SD below mean	0.63(0.34-1.18)	0.53(0.24-1.21)	0.61(0.27-1.42)

Conclusions: Despite the strong association between low social support and depressive symptoms, low social support was not associated with ESRD, CV events, or mortality in this cohort. Further work is needed to understand the role of social support in this population.

Funding: NIDDK Support

SA-PO837

Sensory and Motor Nerve Deficits in Patients with Pre-Existing Chronic Kidney Disease in the Health, Aging and Body Composition (Health ABC) Study Ranjani N. Moorthi,[1] Simit Doshi,[1] Linda F. Fried,[2,7] Ann Schwartz,[3] Mark J. Sarnak,[4] Suzanne Satterfield,[5] Anne B. Newman,[6] Michael Shlipak,[3,7] Sharon M. Moe,[1,7] Elsa S. Strotmeyer.[6] *[1]Indiana Univ, Indpls; [2]VA Pittsburgh; [3]UCSF, San Francisco; [4]Tufts Medical Center, Boston; [5]Univ of Tenessee; [6]Univ of Pittsburgh; [7]Veterans Administration.*

Background: Neuropathy is prevalent in the elderly and associated with loss of functional independence. We hypothesize that pre-existing CKD in the elderly predisposes to worsening sensory and motor nerve deficits over time.

Methods: The Health ABC Study is a longitudinal cohort of community-dwelling white and black Medicare beneficiaries with initial enrollment in 1997-98 (year 1). Subjects underwent sensory and motor nerve testing at years 4 and 11. We examined the relationship between CKD (eGFR < 60 ml/min in 1999/2000 or year 3) with new nerve deficits that were detected at year 11 but were not present at year 4. Sensory deficit was defined as insensitivity to light (1.4g) or standard (10g) touch and motor deficit was defined as compound peroneal motor action potential < 1mV or nerve conduction velocity (NCV) < 40 m/s. Multivariable regression was used to compare odds of developing a new sensory and/or motor deficit at year 11, excluding those with existing deficits, in pre-existing CKD.

Results: Mean (SD) age of participants at year 11 was 82(3) years, 45.2% were men, 34.6% were black and 13.8% had CKD based on eGFR at year 3. After excluding existing nerve deficits, participants with CKD at year 3 had worsening monofilament insensitivity at year 11 (p<0.01) and developed more NCV decreases (p<0.05). Presence of CKD was associated with a 1.9 higher odds (1.1-3.7) of having one or more new nerve deficits (sensory and/or motor) at year 11, adjusted for age, race, gender and diabetes.

Nerve Function (at year 11 compared to year 4)	eGFR>60 year 3	eGFR<60 year 3	p value
SENSORY			
New or worsening deficit (from light to standard touch) in monofilament insensitivity	49.8% (456)	62.0% (106)	0.004
MOTOR:			
CMAP< 1mV New Deficit	15.4% (110)	18.8% (22)	0.35
NCV<40 m/s New Deficit	22.2% (138)	32.7% (32)	0.02

Conclusions: CKD is associated with future development of sensory and motor nerve deficits.

Funding: NIDDK Support

SA-PO838

A Prospective Study of Peripheral Neuropathy in Chronic Kidney Disease and Electrophysiological-Pathological Correlation Pinaki Mukhopadhyay. *Nephrology, NRS Medical College, India.*

Background: The present study aims to study the spectrum and severity of peripheral neuropathy in CKD patients and correlate electrophysiological findings with estimated GFR and to establish electrophysiological and pathological correlation in assessment of the progression of peripheral neuropathy with progression of CKD.

Methods: A prospective cross-sectional observation study where 60 consecutive patients with CKD (eGFR<60 mi/min) were enrolled excluding patients with neuropathy due to any other causes except diabetes.Detail history and clinical examination including neurology symptom score (NSS) score and electrophysiological examinations were done. Sural nerve biopsy was done and correlated with severity and progression of CKD using suitable statistical tool.

Results: Out of 60 CKD patients,29 were diabetic CKD.About 81.66% of subject had distal symmetric polyneuropathy and NS Score was 1.75(+-)1.36.In 25% mononeuropathy, 3.33% (CTS) Cranial Neuropathy and 11.6% autonomic involvement were found. Among 49 neuropathy positive patients, 48.97%had sensory motor polyneuropathy while 51.02% had pure sensory polyneuropathy.Neuropathic group were more symptomatic and had higher s. creatinine level(p- 0.012) compared to non-neuropathy group. Hyperkalemia was seen more in neuropathic group with mean serum.K+ level of 5.39 compared to non-neuropathy group (mean s.K+ 4.93) (p-0.17). Diabetes patients were at higher risk of neuropathy with odds ratio of 6.89 compared to non-diabetic in CKD subjects. Paresthesia and/or dysesthesia were the most common symptoms in 40(66.66%),while most common abnormality in examination was abnormal vibration sensitivity in 37(61.66%) subjects. Nerve conduction study revealed sural sensory action potential (81.66% abnormal) was the most common abnormal parameter, while tibial motor action potential and peroneal distal latency were second most common findings. Sural nerve biopsy revealed mostly axonopathy in advanced CKD and in few cases demyelination which closely correlated with EP study.

Conclusions: 1.Peripheral neuropathy is common and linearly correlated with severity of CKD. 2. Axonopathy is common in advanced CKD and there is a clear relationship between electrophysiological – pathological study.

SA-PO839

Factors Predicting Renal Events among Chronic Kidney Disease Patients Including Post-Kidney Transplantation Cases

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Background: Increase in urinary biomarkers of tubular injury is associated with poor renal outcome among patients with chronic kidney disease (CKD) but relative significance of each biomarker remains elusive. Much less is known about utility of those biomarkers in post-kidney transplantation (KT) cases. We carried out single-center, prospective, observational study among 250 out-patient CKD subjects including KT cases.

Methods: Urine albumin, alpha1-microglobulin (a1MG), liver-type fatty acid binding protein (L-FABP) and N-acetyl glucosaminidase were measured in 250 CKD subjects. Cox proportional hazards models were used to examine association of creatinine (Cr)-normalized urinary biomarker levels with renal events defined by serum Cr doubling, end-stage renal disease (ESRD) or death. Decline rate of renal function was also studied by comparing serum Cr changes after 2 years.

Results: Ages of participants were 59.0±16.1 (mean± SD) years, 61% were men, 11% had diabetes mellitus and 20% were KT cases. Median follow-up period was 4.5 years. Among patients who did not develop renal events within 2 years, relative serum Cr values after 2 years were 129±73% (diabetic nephropathy, n=14), 111±29% (nephrosclerosis, 36), 96±21% (chronic glomerulonephropathy, 37), 87±10% (lupus nephritis, 15) and 104±28% (KT, 48), reflecting response to treatment. After post hoc analysis using stepwise method, independent variables predicting renal events were male gender [hazard ratio (HR) 2.2, P<0.05), eGFR (HR per SD increase 0.285, P<0.001), urinary albumin (1.51, P<0.001) and a1MG/Cr (1.33, P<0.05). Urinary L-FABP/Cr was not independently associated with renal events, likely because it was highly proportional to urinary a1MG/Cr (r=0.89).

Conclusions: In addition to classical risk factors for ESRD, urinary a1MG was independently associated with increased risk of renal events in individuals with CKD including KT cases.

SA-PO840

Understanding Pharmaceutical Care Needs of Living Kidney Donors Through Linked Transplant Registry and Pharmacy Claims Data

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Background: Limited data are available on pharmaceutical care needs of living kidney donors (LKD).

Methods: We integrated 1) national US Scientific Registry of Transplant Recipients data for LKD (1987-2012) with 2) pharmacy fill records from a nationwide pharmacy claims clearinghouse to examine utilization patterns of diabetes treatments, antihypertensive medications, and antidepressants as measures of these conditions before and after donation.

Results: The linked data captured 32,065 LKD actively filling in the first year before, and 36,597 actively filling in the first year after donation **(Table).** A very small but surprising fraction of LKD were treated with insulin or an oral hypoglycemic agent in the 3 years prior to donation. In year 10 yrs after donation, 0.4% received insulin and 2.3% received an oral glucose-lowering agent. Angiotensin converting enzyme inhibitors comprised the most common class of antihypertensive agent used in the years after donation, with use in 11.3% by year 10. Among the sample, 8.6% received a diuretic by year 10. The most common antidepressant prescriptions filled before and after donation were selective serotonin reuptake inhibitors (SSRI). 9.3% of LKD filled an SSRI prescription in the year before donation, and 8.7% in the year after donation.

Prescription fills among living kidney donors, before and after donation.

Type of Prescription	Percentage of Donors with Prescription Fills in Given Years Before and After Donation								
	Year Before Donation			Year After Donation					
	Year -3 (N=23,749)	Year -2 (N=27,730)	Year -1 (N=32,065)	Year 1 (N=36,597)	Year 2 (N=32,726)	Year 4 (N=29,961)	Year 6 (N=26,765)	Year 8 (N=22,354)	Year 10 (N=16,834)
Diabetes Treatment									
Diabetic supplies	0.28%	0.26%	0.24%	0.26%	0.36%	0.58%	0.89%	1.25%	1.51%
Insulin	0.10%	0.08%	0.06%	0.07%	0.09%	0.12%	0.19%	0.31%	0.37%
Oral hypoglycemic agents	0.30%	0.37%	0.35%	0.23%	0.35%	0.66%	1.12%	1.82%	2.29%
Antihypertensive Medications									
Diuretics	2.47%	2.56%	2.62%	2.26%	2.82%	3.93%	5.45%	6.84%	8.64%
Calcium channel blockers	0.62%	0.65%	0.74%	1.16%	1.37%	1.90%	2.66%	3.31%	3.57%
Beta-blockers	1.58%	1.72%	1.87%	2.05%	2.52%	3.38%	4.35%	5.56%	6.69%
ACE inhibitor	1.72%	1.71%	1.91%	2.38%	3.22%	5.08%	6.86%	9.18%	11.33%
Other antihypertensives	0.23%	0.29%	0.28%	0.29%	0.31%	0.48%	0.67%	0.82%	0.97%
Antidepressant Medications									
Tricyclic antidepressants	1.58%	1.72%	1.46%	1.63%	1.89%	1.92%	2.12%	2.17%	2.26%
SSRIs	9.66%	9.86%	9.29%	8.68%	9.70%	9.38%	9.65%	9.37%	8.96%
SNRIs	2.21%	2.30%	2.18%	2.02%	2.38%	2.44%	2.66%	2.80%	2.92%
MAOs	0.00%	0.01%	0.01%	0.00%	0.00%	0.01%	0.01%	0.03%	0.01%
New generation antidepressants	3.41%	3.54%	3.66%	3.21%	3.74%	3.82%	3.93%)	4.15%	4.22%

Denominators = Number of donors having *any* medication prescription filled in that given year.

Abbreviations: ACE, angiotensin converting enzyme inhibitor; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; MAO, monoamine oxidase inhibitor.

Conclusions: Use of antihypertensive and diabetes medications increase over time after live kidney donation, while antidepressant use appears stable. These data demonstrate the rich potential for linked transplant registry data and pharmacy claims data to examine the incidence and prevalence of medically-treated conditions before and after donation. Future work should compare pharmaceutical care needs of living donors to that of controls with similar baseline good health.

SA-PO841

Diagnostic Utility of Stored sFlt-1 for Future Renal Deterioration

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Background: Soluble fms-like tyrosine kinase-1 (sFlt-1), produced by alternative splicing of Flt-1 pre-mRNA is an endogenous antagonist as VEGF and placental growth factor signaling. We have already demonstrated that in the baseline condition, the majority of sFlt-1 is stored in the endothelial cell surface, with an extremely small amount in the circulation, and that stored sFlt-1 is significantly decreased in patients with advanced CKD, as verified by heparin-stimulation; however the relationship between stored sFlt-1 and renal deterioration clinically remains unknown.

Methods: We recruited 104 participants undergoing heparin-loading test, defined as blood collection before and 5 minutes after intravenous heparin injection at a dose of 0.4 IU/kg.

Results: Estimated stored sFlt-1 levels were calculated by subtracting pre-heparin from post-heparin levels of sFlt-1. Heparin injection significantly increased median (interquartile range) sFlt-1 levels from 93 (68-117) pg/mL to 273 (213-383) pg/mL, showing stored sFlt-1 levels of 189 (108-276) pg/mL. Pre-heparin sFlt-1 levels were inversely correlated with eGFR (r=–0.372), but the relationship of post-heparin and stored sFlt-1 levels with eGFR was reversed, resulting in a highly direct correlation (r=0.420 and r=0.597, respectively). Decreased post-heparin and stored sFlt-1 levels but not pre-heparin sFlt-1 levels were significantly associated with the severity of proteinuria (p<0.001, ,p<0.001, respectively). During study period, 42 renal events including all-cause mortality, end-staging renal disease or doubling of baseline creatinine levels were occurred. A univariate hazard ratio [95% confidence interval] of above versus below median levels of pre-heparin, post-heparin and stored sFlt-1 for adverse events was 2.52 [1.32-5.15], 0.66 [0.34-1.25], 0.38 [0.17-0.77], respectively. The c-statistics of pre-heparin, post-heparin and stored sFlt-1 levels was 0.758, 0.678 and 0.798, respectively, suggesting that stored sFlt-1 had more predictive accuracy in renal deterioration than other sFlt-1.

Conclusions: Decreased stored sFlt-1 is significantly associated with renal events.

SA-PO842

CKD Pregnant Patients in Jalisco, Mexico: Maternal and Perinatal Outcomes

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Background: Medical indications to start RRT during pregnancy have been established by international studies, but risk factors for RRT initiation have not been determined yet. Hospital Civil de Guadalajara (HCG) is a tertiary care facility responsible for managing pregnant patients with CKD without social security in the Western region of the country. Our objective was to determine risk factors for RRT among pregnant CKD patients at HCG.

Methods: Prospective, descriptive maternal-fetal outcome analysis among pregnant CKD patients at HCG from June 2013 to September 2015. CKD was defined as kidney damage for ≥3 months (KDIGO guidelines) before pregnancy. Data was recorded at first visit and 3 months after delivery. Clinical complications and perinatal outcomes were evaluated: need for RRT, preeclampsia, anemia (WHO, Hb<11g/dL), preterm delivery (newborn <37 weeks) and need for Neonatal Intensive Care (NIC). Dialysis was initiated when blood urea nitrogen (BUN) was ≥45 mg/dL or if the classic criteria for RRT were met.

Results: 27 pregnant women with known CKD were included and followed from June 2013 to September 2015. Ten patients (37%) required RRT (HD). 2 patients in the CKD-HD group (both with CKD stage 3 at first visit) showed recovery of renal function and were free of hemodialysis in the follow up period (3 months after delivery).

Baseline characteristics	CKD	CKD and HD	p
	n= 17	n=10	
Age, years	23.88 ± 8.05	20 ± 3.23	0.423
< 18 years old, (%)	6	3	0.4022
Single, (%)	3 (18)	3 (30)	0.2495
Chronic HTN, (%)	8 (47)	6 (60)	0.2746
SBP ≥ 140 mmHg, (%)	5 (29)	3 (30)	0.4834
DBP≥ 90 mmHg, (%)	8 (47)	3 (30)	0.2116
Urinary Tract Infection, (%)	2 (18)	4 (40)	0.06342
Anemia (Hb < 11mg/dL), (%)	3 (18)	9 (90)	0.0002034
Average Hb, mg/dL	11.54 ± 1.08	8.3 ± 1.66	0.1281
Average sCr, mg/dL	1.72 ± 0.72	5.3 ± 3.89	0.00001748
Average Proteinuria, gr/24 hrs (range)	2.17 ± 1.95 (0.14-5.7)	2.88 ± 1.62 (1.1-6.92)	0.5831
Average BUN	22.96 ± 10.48	58.8 ± 39.29	0.00001021
Average GFR ml/min (range)	50.41 ± 40.09 (18-181)	21.8 ± 19.3 (9.6-63.4)	0.045
Average serum Albumin mg/dL	2.83 ± 1.09	2.64 ± 1.03	0.8953
CKD categories: Stages 1-2, (%) Stages 3a-3b, (%) Stage 4, (%) Stage 5, (%)	 4 (24) 7(41) 6(35) 0	 0 2 (20) 4 (40) 4 (40)	 0.016
Diabetes Mellitus Type 1	2	1 (10)	0.697
Gestational age by last menstrual period, weeks (range)	19.83 ± 9.18 (7.4-36)	21.21 ± 8.32 (7.5-31.1)	0.7885
Gestational age by ultrasound, weeks (range)	20.31 ± 9.02 (6.5-35.5)	20.3 ± 6.36 (13.2-31)	0.2889
Uresis, ml/24 hrs	2477 ± 704.2*	1433 ± 451.9	0.1776
First time pregnancy, (%)	6 (35)	7 (70)	0.05212
Average previous pregnancies (range)	2.2 (1-6)	1.4 (1-3)	1.04
Maternal outcomes	**CKD**	**CKD and HD**	**p**
Preclampsia or eclampsia, (%)	7 (41)	4 (40)	0.3725
Vaginal delivery, (%)	6 (35)	2 (20)	0.224
C-section delivery, (%)	11 (65)	8 (80)	0.224
Serum Creatinine (3m after delivery)	2.43±1.27	5.39±3.25	0.020

Perinatal outcomes	CKD	CKD and HD	p
	n= 17	n=10	
Still born, (%)	0	1 (10)	0.1852
Spontaneous abortion, (%)	1 (5.9)	1 (10)	0.3704
Polyhydramnios, (%)	0	1 (10)	0.1852
Oligohydramnios, (%)	1 (5.9)	0	0.3148
Programed C-section, (%)	11 (69)	2 (22)	0.01709
Urgent delivery, (%)	1 (6)	5 (56)	0.007946
Labor, (%)	4 (25)	2 (22)	0.4318
Gestational Age (Capurro)	37±2.15	31.22 ± 3.76	0.005
Premature baby, (%)	7 (44)	5 (63)	0.667
Weight at birth, mg	2460 ±693.65	1837 ±684.17	0.049
Need for NIC, (%)	4 (25)	4 (40)	0.2036
Died after birth, (%)	0	0	NA

Conclusions: CKD stage and anemia at first visit were risk factors for RRT during pregnancy. Urgent pregnancy cessation due to eclampsia, preeclampsia and polyhydramnios was more frequent in the HD group. As expected, babies from the HD group had lower gestational age and lower weight at birth when compared to babies of CKD mothers that did not require HD. Renal recovery after delivery remains low, but perinatal and maternal outcomes are improving.

SA-PO843

Pregnancy in Mexican, Low-Income, Chronic Kidney Disease Patients

Maria de la Luz Alcantar Vallin, Angela Maria Soto Cruz, Karina Renoirte, Guillermo Garcia-Garcia. *Nephrology, Hospital Civil Guadalajara, Guadalajara, Jalisco, Mexico.*

Background: CKD is a global public health problem and it is linked to adverse outcomes in pregnancy. The prevalence of CKD in childbearing age may reach 3%. However, few settings offer an integrated nephrological and obstetric follow up in this population. We report outcomes in CKD low-income, pregnant women, followed at our Pregnancy & CKD Clinic.

Methods: This is a prospective observational study at the Hospital Civil de Guadalajara. From July 2013 to September 2015, 27 pregnant patients with eGFR < 60 ml/min/1.73 m2 and/or markers of kidney damage ≥ 3 months previous to conception were included. The group was compared to a historic cohort of pregnant women without CKD. Chi-square and t-test were used when appropriate. Multivariate logistic regression analysis was used to estimate odds ratios and 95% CI. Significance was assessed at p <0.05.

Results: 89% of pregnancies had a live birth. Pre-eclampsia (OR 13.53, 95% CI 2.69-68.15, p < 0.001), pre-term delivery (OR 8.27, 95% CI 2.56-26.74, p < 0.001), low-birth weight (OR 8.27, 95% CI 2.56-26.74, p < 0.001), and admission to NICU (OR 9.47, 95% CI 1.79-50.16, p < 0.001) where more frequently seen in the CKD group.

Characteristics	Control n= 48	CKD n= 27	p
Age (y)	27.5 ± 7.04	22.5 ± 6.86	0.004
Teenage (%)	3 (6.3)	6 (22.3)	0.002
DM (%)	1 (2.1)	3 (11.1)	0.09
HTN (%)	1 (2.1)	14 (51.9)	< 0.001
SCr (mg/dL)	0.52 ± 0.103	3.3 ± 2.94	< 0.001
GFR (ml/min/1.73m^2)	145.9 ± 45.2	39.7 ± 36.2	< 0.001
GFR < 60 ml/min/1.73 m^2 (%) Stage 3 Stage 4 Stage 5		23 (85) 9 (33) 10 (37) 4 (15)	
Required HD (%)		10 (37)	
Hgb (g/dL)	12.5 ± 1.28	10.3 ± 2.03	< 0.001
Pre-eclampsia/eclampsia (%)	2 (5)	12 (44)	< 0.001
Live birth (%)	48 (100)	24 (89)	0.13
Birth weight (g)	3022 ± 455	2253 ± 739	< 0.001
Birth weight < 2,500 g (%)	6 (12.24)	13 (54.16)	< 0.001
Pre-term delivery (%)	7 (14.28)	13 (48.14)	< 0.001
Admission to NICU (%)	2 (4)	7 (29)	0.006

Conclusions: Low-income, CKD pregnant women, have a higher rate of adverse materno-fetal outcomes. Our study supports an integrated, multidisciplinary, approach and follow-up for pregnant patients with all stages of CKD. Multi-center studies are needed to establish standard protocols for the appropriate management of this condition.

SA-PO844

Renal and Obstetric Outcomes of Pregnant Women with CKD 3-5

Philip Webster,[1] Matt Hall,[2] Louise Webster,[1] Sue Carr,[2] Nigel J. Brunskill,[2] Liz Lightstone.[1] *[1]Imperial College Renal and Transplant Centre, Imperial College Healthcare NHS Trust, London, United Kingdom; [2]John Walls Renal Unit, Leicester General Hospital, Leicester, United Kingdom.*

Background: Chronic Kidney Disease (CKD) affects up to 6% of women of childbearing age & women with more advanced CKD are now rarely advised to avoid pregnancy. There are variable data on the effect of pregnancy on CKD & this observational study is the largest to our knowledge to look at both renal & obstetric outcomes in women with CKD 3-5.

Methods: Women with an MDRD eGFR below 60ml/min/1.73m^2, either prior to pregnancy or by 12 weeks of gestation, from 2 tertiary centres were included. Women already on dialysis or with early fetal loss were excluded. Outcomes analysed included a 25% increase in serum creatinine (SCr), requirement for renal replacement therapy (RRT) & gestation at delivery.

Results: 88 women (2003-2012) were identified & followed up for a median 1408 days. 12 had a renal transplant, 3 of whom had pancreas transplants. Median age: 32.2yrs (IQR 29.3, 35.8). Median baseline SCr: 128µmol/l (IQR 113, 149). A 25% increase in SCr was seen in 21% (18/88) & this was in the 3rd trimester in 15 of the 18. Baseline eGFR did not predict those with a 25% rise in SCr during pregnancy. During follow up, 16% (14/88) went on to require RRT (1 during pregnancy) & this was more likely in those with a baseline eGFR <30 ml/min/1.73m^2 (46% *vs* 12%, p=0.013). Preterm delivery (<37 weeks) was common (58% (51/87)) & median gestation was lower in women with CKD 3b (35 weeks; IQR 32, 37; n=36; p=0.011) or CKD 4/5 (34 weeks; IQR 33, 37; n=11; p=0.013) than those with CKD 3a (37 weeks; IQR 35, 39; n=41). Obstetric outcomes available on 47/88 women showed 100% live births. Mode of delivery (13 (28%) emergency caesarean section, 18 (38%) elective caesarean section, 16 (34%) vaginal delivery) was not affected by baseline renal function.

Conclusions: Women with CKD 3-5 are at risk of adverse renal and obstetric outcomes, with renal decline most commonly occurring in the 3rd trimester. The worse the renal function at conception the greater the risk of requiring RRT and preterm delivery.

SA-PO845

Secular Trends in the Incidence of End–Stage Renal Disease and Its Risk Factors in IgA Nephropathy

Shigeru Tanaka,[1] Toshiharu Ninomiya,[2] Ritsuko Katafuchi,[3] Kosuke Masutani,[2] Akihiro Tsuchimoto,[2] Masanori Tokumoto,[1] Hideki N. Hirakata,[4] Hiroaki Ooboshi,[1] Kazuhiko Tsuruya,[2] Takanari Kitazono.[2] *[1]Div of Internal Medicine, Fukuoka Dental College, Fukuoka, Japan; [2]Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; [3]Kidney Unit, National Fukuoka–Higashi Medical Center, Fukooka, Japan; [4]Fukuoka Renal Clinic, Fukuoka, Japan.*

Background: There are limited data on the secular trends in the incidence of end–stage renal disease (ESRD) and frequencies of its risk factors and treatment modalities in patients with IgA nephropathy (IgAN).

Methods: This study divided 1259 patients with IgAN into three groups according to the timing of renal biopsy: 1979–1989 (n=232), 1990–1999 (n=574) and 2000–2010 (n=453). The mean follow–up periods of these three cohorts were 37.4, 43.4 and 48.4 months, respectively.

Results: A total of 63 (5.0%) developed ESRD. The age–adjusted incidence of ESRD decreased significantly over time, from 12.5 per 1000 person–years (95% confidence interval [CI)], 2.5–24.6) in 1979–1989, to 6.5 per 1000 person–years (95% CI, 1.7–25.2) in 1990–1999; to 4.2 per 1000 person–years (95% CI, 1.8–17.5) in 2000–2010. The proportions of patients with preserved renal function and acute inflammatory histologic changes (i.e. endocapillary hypercellularity, extracapillary proliferation, and acute crescentic lesion) at the timing of biopsy increased over time, as did the rates of prescriptions of renin–angiotensin system inhibitors and corticosteroids (all P for trend<0.001). The impacts of acute inflammatory histologic lesions on renal prognosis were drastically reduced with the times.

Conclusions: These findings suggest that early diagnosis in the acute inflammatory phase and subsequent aggressive treatment may have contributed to the significant downward trends over three decades in the incidence of ESRD in Japanese patients with IgAN.

SA-PO846

Hospitalization Burden of Chronic Renal Insufficiency Cohort (CRIC) Study Participants Amanda Hyre Anderson,[1] Jason Roy,[1] Eugene Lin,[2] Michael J. Fischer,[2] L. Lee Hamm,[2] James P. Lash,[2] Eva Lustigova,[2] Emile Mohler,[1] Akinlolu O. Ojo,[2] Mahboob Rahman,[2] Julia J. Scialla,[2] Susan P. Steigerwalt,[2] Harold I. Feldman.[1] *[1]Univ of Pennsylvania; [2]The CRIC Study.*

Background: Patients with chronic kidney disease (CKD) experience a substantial burden of morbidity requiring hospitalization. However, hospitalizations prior to development of end-stage renal disease (ESRD) are not well characterized.

Methods: Participants of the multi-center prospective observational CRIC Study (N=3,939; mean estimated glomerular filtration rate (eGFR): 45 mL/min/1.73m²; age range: 21-75 years; 48.4% with diabetes). Over a median of 6.9 years, hospitalizations were ascertained by patient reports, confirmed by queries of local hospitals, and categorized by ICD-9 codes. Hospitalization rates (unadjusted and adjusted for age, gender, race/ethnicity, clinical center, education, eGFR, and proteinuria in Poisson regression models) were compared across sub-groups.

Results: Through mid-2013, 14,794 hospital stays were confirmed pre-ESRD with a mean duration of 2.8 days. Prior to ESRD, the mean time spent in the hospital per participant per year was 2.6 days, with 50% and 10% of participants spending 0.5 days and nearly one week hospitalized annually, respectively. Unadjusted hospitalization rates (95% CI) were 61.5 (60.5-62.5), 49.3 (48.2-50.5), and 77.3 (75.6-79.0) per 100 person-years among those overall, without and with diabetes, respectively. Unadjusted rates were highest among older participants, non-Hispanic blacks, and those with lower levels of education, higher levels of proteinuria, higher SBP, history of CVD, and lower eGFR. Multivariable-adjusted rates were significantly higher with lower baseline eGFR, higher proteinuria, diabetes, and higher systolic blood pressure. The top three primary ICD-9 codes included those for congestive heart failure, chest pain, and acute kidney injury.

Conclusions: The burden of pre-ESRD hospitalizations among individuals with CKD is substantial and varies by sociodemographic and clinical factors.

Funding: NIDDK Support

SA-PO847

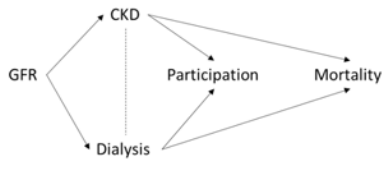
Chronic Kidney Disease and All-Cause Mortality: The Influence of Selection Bias in a National Health Survey Seth P. Kuranz. *Decision Resources Group, Burlington, MA.*

Background: The National Health and Nutrition Examination Survey (NHANES) collects biologic measures to assess CKD among participants who travel to mobile examination centers. NHANES likely under-ascertains severe cases of CKD due to issues of patient mobility. We assess the influence of potential selection bias due to under-ascertainment of severe cases on the association between CKD and all-cause mortality.

Methods: NHANES data (cycles 2005-06, 2007-08, and 2009-10) linked to NCHS mortality files were assessed the association between CKD (GFR < 60 ml/min, calculated using both the CKD-EPI and MDRD equations, or self-reported dialysis) and all-cause mortality among US adults aged 20+, using Cox Proportional Hazards models. Findings from the literature, and a directed acyclic graph were used to identify parameters necessary to conduct a quantitative bias analysis addressing the relationship between CKD, all-cause mortality, dialysis, and participation in the NHANES laboratory examination.

Results: Crude and age-adjusted models found CKD was associated with all-cause mortality (HR=7.51 (7.50-7.53)). Accounting for selection bias, due to conditioning on participation (Figure 1), attenuated the association between CKD and all-cause mortality (HR=4.11 (3.39-4.91)). Attenuation was smaller in the age-adjusted analyses. Only small differences were observed between the MDRD and CKD-EPI GFR equations.

Figure 1. Directed Acyclic Graph



Conclusions: Restriction is a commonly employed strategy to control for confounding in epidemiologic research. Unintentional restriction arising from differential participation may induce relationships between unmeasured/uncontrolled variables and both the exposure and outcome. Although NHANES is a well conducted nationally representative survey, this particular form of selection bias should be considered in studies that use NHANES data to assess associations between CKD and other health outcomes.

Funding: Pharmaceutical Company Support - Decision Resources Group

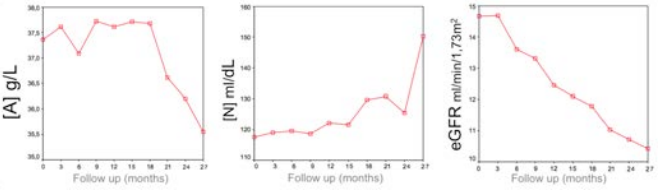
SA-PO848

Prolonged Conservative Therapy in End Stage Renal Disease: A Therapeutic Option? The Verona Experience Vincenzo De Biase, Alfredo Petrosino, Alessandra Dalla Gassa, Giuseppina Pessolano, Isabella Squarzoni, Chiara Branco, Antonio Lupo. *Renal Unit, Univ Hospital of Verona, Verona, VR, Italy.*

Background: The prolonged conservative therapy (CT) of End Stage Renal Disease (ESRD) ameliorates uremic symptoms and postpones the initiation of renal replacement therapies (RRTs). There is no evidence of survival advantage from early initiation of dialysis, thus CT could be considered as a common path for ESRD patients, both in "palliative care" as well as in those intended to RRTs.

Methods: We observed 144 ESRD patients in CT in our low-clearance clinic, followed up in the period 01/2013–05/2016 and enrolled as they reached a eGFR (CKD-EPI)<15±4 ml/min/1,73m². The observation ended at the initiation of RRTs (haemo [HD] or peritoneal [PD] dialysis or kidney transplant [T]) or in case of death. RRTs where started when indicated, in according to KDIGO 2012 guidelines. The duration of follow up [FU] was the main end point. We further evaluated serum albumin [A] and azotaemia [N], as indexes of dietary adequacy, and eGFR variations.

Results: The mean FU at the end point was 20.2 months (CI 16.50-23.86), with no differences between those who initiated RRTs and those who did not. 37 patients (60.7%) started HD, 4 (6.6%) PD, 3 (4.9%) received a T. 12 patients (19.7%) died without RRTs. 88 patients continued the FU. Mean eGFR at the endpoint was 10.43 ml/min/1,73m2. [A] did not change within 21 months (p<0.027, quadratic regression) and [N] showed a similar but opposite trend (p<0,066, quadratic regression); eGFR slightly declined (p<0.0001).



In a general linear model, [A] and eGFR only were positively related to FU.

Conclusions: CT in ESRD patients seems to confer a stable nutritional status, as assessed by [A] and [N], within 21 months of treatment. Moreover, it allows postponing the beginning of RRTs of nearly 2 years, proving RRTs to be avoidable in many cases.

SA-PO849

Factors Affecting Secondary Care Referral of Older People with Advanced Chronic Kidney Disease and Their Outcomes: An Observational Cohort Study Anirudh Rao,[1,2] Stephanie J. MacNeill,[1,2] Yoav Ben-Shlomo,[2] Fergus J. Caskey.[1,2] *[1]UK Renal Registry, Bristol, United Kingdom; [2]Univ of Bristol, Bristol, United Kingdom.*

Background: Aim of this study was to identify patient characteristics and outcomes associated with advanced chronic kidney disease (CKD) being managed solely in primary care rather than co-managed in primary and secondary care as current evidence is limited.

Methods: The Health Improvement Network (THIN) primary care database was used to identify patients aged ≥65 years with new advanced CKD(eGFR ≤20mls/min/1.73m²) managed solely by a general practitioner(GP)(Primary care cohort) or co-managed with a nephrologist(Secondary care cohort). Multivariable regression models were used to explore cohort differences in baseline demographics, clinical & laboratory markers, and survival in the 12 months following the index eGFR. Cohort differences in GP consultations and proportion having ≥4 hospitalisations was assessed using Mann Whitney and Chi-square tests respectively.

Results: There were 632 and 2,464 patients in the Primary and Secondary care cohorts, respectively. In a multivariable logistic model, older patients (65-69yrs (ref); 70-74yrs: OR 0.5, 95% CI 0.2-1.8; 75-79yrs: 2.2, 0.8-6.0; 80-85yrs: 3.3, 1.3-8.7; >85 yrs 10.6, 4.1-27.1), women(OR 2.2, 95% CI 1.6-3.1), those living in rural areas(OR 2.1,95% CI 1.5-3.1), cardiovascular disease(OR 1.7, 95% CI 1.2-2.4) and cancer(OR 1.6, 95% CI 1.1-2.4) were more likely in the Primary care cohort. Patients in this cohort had fewer GP consultations(median (IQR) 7(3-13) vs 9(5-15), p<0.001) and a lower proportion required ≥4 hospitalisations(3.6% vs 9.8%, p<0.001) in the first year when compared to those in secondary care. Mortality remained higher in primary care cohort despite adjustment for sociodemographic, clinical measures and Charlson Index(HR 1.6, 95% CI 1.1-2.2, p=0.008).

Conclusions: People with advanced CKD are more likely to be managed solely in primary care if they are older, female and have a co-existing diagnosis of cardiovascular disease or cancer. They have a higher mortality rate, but are less likely to consult their GP or be admitted to hospital. Further study is required to understand the reasons for and appropriateness of these referral decisions.

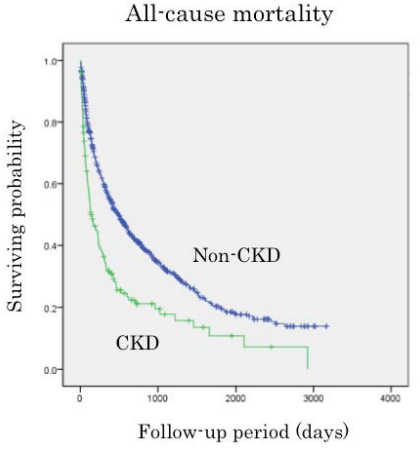
SA-PO850

Chronic Kidney Disease Is Associated with Mortality in Stage IV Cancer Patients Taisuke Ishii,[1,2] Takuya Fujimaru,[1] Gautam A. Deshpande,[3] Eriko Nakano,[2] Yasuhiro Komatsu.[1] *[1]Nephrology, St. Lules International Hospital, Chuo-ku, Tokyo, Japan; [2]Medical Oncology, St. Lules International Hospital, Chuo-ku, Japan; [3]Center for Clinical Epidemiology, St. Lules International Univ, Chuo-ku, Tokyo, Japan.*

Background: The prevalence of chronic kidney disease (CKD) is increasing among cancer patients. However, the impact of CKD on the prognosis of patients with advanced cancer is unknown. The aim of this study is to examine the association between CKD and mortality in stage IV cancer patients.

Methods: In this single-center, retrospective cohort study, we collected data from all patients with newly diagnosed stage IV solid cancer from April 2009 to December 2014, with follow-up through December 2015. CKD was defined as eGFR ≤ 60 ml/min/1.73m^2 at the time of diagnosis. The primary endpoint was all-cause mortality. The secondary endpoint was cancer-specific mortality. Log-rank test and Cox proportional hazard analysis were used for analysis.

Results: Of 962 patients (age 69±10, 51.8% of males) meeting inclusion criteria, 150 patients (16%) had CKD. During follow-up (median 293 days, IQR 79-751 days), 639 patients (66.4%) died. On Kaplan-Meier survival analysis, patients with CKD showed significantly poorer survival compared to those without CKD (log-rank test, $p < 0.001$). After adjusting for age, gender, BMI, type of cancer, anticancer therapy, baseline serum sodium, glucose, WBC, hemoglobin, CRP, and ECOG Performance Status, CKD remained significantly associated with all-cause mortality (HR 1.63, 95% CI 1.26-2.10). For cancer-specific mortality, CKD was also correlated with poorer survival (log-rank test, $p < 0.001$) and was identified as an independent risk factor in multivariate analysis (HR 1.67, 95%CI 1.26-2.22).



Conclusions: This study is the first to report CKD as an independent predictor of mortality in patients with advanced cancer.

SA-PO851

Canadian Child Multi-Centre ABLE Study: Long-Term Renal Outcomes 3 Months Post-Cisplatin Kelly McMahon,[1] Tom D. Blydt-Hansen,[2] Maury N. Pinsk,[3] Cherry Mammen,[2] Shahrad Rod Rassekh,[2] Ross T. Tsuyuki,[4] Prasad Devarajan,[5] Michael Zappitelli.[1] *[1]McGill U, Montreal; [2]U British Columbia, Vancouver; [3]U Manitoba, Winnipeg; [4]U Alberta, Edmonton, Canada; [5]Cincinnati Children's Hosp, Cincinnati.*

Background: Acute kidney injury (AKI) during cisplatin therapy is common in children. Cisplatin may cause late kidney disease (chronic kidney disease [CKD] or hypertension [HTN]). The late cisplatin renal outcome phenotype remains unclear. ABLE is a pan-Canadian study on biomarkers of late child cancer treatment effects, including nephrotoxicity. Aim: Describe CKD and HTN 3 months post-child cisplatin therapy.

Methods: Ongoing 12-site prospective study of cisplatin-treated children. Exclusion: GFR<30 ml/min/1.73m^2. Protocol: 2 acute visits (AV) at an early (1st or 2nd - AVE) and later (≥3rd - AVL) cisplatin infusion; 3 follow-ups (FU): 3, 12, 36 months post-cisplatin with urine/blood, blood pressure(BP) collection. AKI: serum creatinine rise≥50% from baseline at AVE or AVL. FU outcomes: CKD: eGFR<90ml/min/1.73m^2 [by 1) serum creatinine, 2) cystatin C] ***or*** albumin-to-creatinine ratio (ACR)>30 mg/g; HTN: BP≥95th percentile for age, gender, height. We calculated % with low eGFR, albuminuria or HTN at 3 months. We compared AKI *vs.* non-AKI groups (chi-square or non-parametric tests).

Results: Of 56/110 with 3-month data (median[IQR] age 6[3-12] years; 53% male), HTN (7%) and albuminuria (39%) were very common (Table, "All"). Albuminuria was more common in AKI patients (though not significant); eGFR was higher in AKI (not significant, Table). 3-month HTN was more common in AKI patients ($p<0.05$) due to higher diastolic BP (Table).

Conclusions: ABLE will be the largest renal follow-up of cisplatin-treated children. 3-month post-cisplatin CKD and HTN prevalence is high overall. HTN is more common in patients with cisplatin-AKI. Patients with AKI may have relative hyperfiltration 3 months post-cisplatin.

Table: Long-term renal abnormalities 3 months after cisplatin treatment end in all patients, AKI patients and non-AKI patients.

Outcome	All	AKI	Non-AKI	P-value
Albuminuria	23/59 (39%)	10/20 (50%)	13/39 (33%)	0.21
Systolic BP percentile (median [IQR])	39th [26th-50th] N=41	41st [34th-50th] N=16	39th [15th-50th] N=25	0.30
Diastolic BP percentile (median [IQR])	50th [40th-73rd] N=41	61st [47th-80th] N=16	46th [39th-67th] N=25	**0.03**
Hypertension (HTN)	3/42 (7%)	3/16 (19%)	0/26 (0%)	**0.049**
SCr-eGFR (median [IQR] mL/min/1.73 m^2)	136 [115-158] N=49	144 [115-172] N=20	135 [115-152] N=29	0.38
SCr-eGFR<90 mL/min/1.73m^2	5/49 (10%)	2/20 (10%)	3/29 (10%)	1.00
CysC-eGFR (median [IQR] mL/min/1.73 m^2)	124 [105-145] N=62	131 [110-144] N=20	122 [104-148] N=42	0.34
CysC-eGFR<90 mL/min/1.73m^2	5/62 (8%)	2/20 (10%)	3/42 (7%)	0.52
CKD (low SCr-eGFR *or* albuminuria)	27/61 (44%)	11/21 (52%)	16/40 (40%)	0.36
Low SCr-eGFR *or* albuminuria *or* HTN	28/62 (45%)	12/21 (57%)	16/41 (39%)	0.18

Abbreviations: AKI: Acute kidney injury, IQR: Interquartile range, BP: Blood pressure, HTN: Hypertension, eGFR: Estimated glomerular filtration rate, SCr: Serum creatinine, CysC: Cystatin C.
SCr-eGFR: estimated by updated Chronic Kidney Disease in Children (CKiD) formula;
CysC-eGFR: estimated by Zappitelli CysC equation;
Blood pressure: measured by an automated device; mean of 2 lowest out of 3 readings is used.
Albuminuria: using random untimed urine sample at time of follow-up visit.
Additional information: 3/59 (5%) had severe albuminuria (ACR>300 mg/g)

Funding: Government Support - Non-U.S.

SA-PO852

Risk of Metformin-Associated Lactic Acidosis in Chronic Kidney Disease Benjamin Lazarus,[1] Aozhou Wu,[1] Yingying Sang,[1] Josef Coresh,[1] Alex R. Chang,[2] Morgan Grams.[1] *[1]JHU, Baltimore, MD; [2]Geisinger Health System, Danville, PA.*

Background: Metformin is a first-line treatment for diabetes mellitus, but is frequently avoided in those with CKD due to the risk of metformin-associated lactic acidosis (MALA). The FDA recently expanded the metformin label to allow for use at eGFR 30-60 ml/min/1.73m^2, but limited data exists regarding the risk of MALA in this range of kidney function.

Methods: Using Poisson regression and a new-user, active comparator design, we evaluated the risk of acidosis events, defined by an ICD-9 code of 276.2, in 12,437 new metformin users compared to 6,541 new sulfonylurea users in the Geisinger Health System from 2004-2014, by categories of baseline eGFR.

Results: Overall, there were 366 acidosis events over a mean 2.6 years of follow-up. Metformin and sulfonylurea users were similar in age, sex, race, baseline serum bicarbonate concentration, HbA1c, smoking status and BMI. Cardiovascular disease and hypertension were more prevalent in sulfonylurea users, whereas concomitant use of insulin, statin, renin-angiotensin system inhibitors, diuretics and NSAIDs were more frequent in metformin users. The demographic-adjusted incidence of acidosis for metformin users was 5, 6, 8, 17 and 84 events per 1,000 person years for baseline eGFR >90, 60-89, 45-59, 30-44 and <30 ml/min/1.73m^2, respectively. The corresponding incidence for sulfonylurea users was 7, 7, 15, 10 and 45 events per 1,000 person years. Overall, there was no significant difference in acidosis risk between metformin and sulfonylurea users, but there was a trend toward increased risk at eGFR <30 ml/min/1.73m^2.

Table 1. Risk of lactic acidosis for metformin users versus sulfonylurea users.

eGFR (ml/min/1.73m^2)	Incidence rate ratio*	95% CI
>90	0.75	0.49-1.15
60-89	0.87	0.59-1.28
45-59	0.55	0.30-1.00
30-44	1.16	0.45-2.98
<30	2.24	0.51-9.88

*Adjusted for age, sex, race, serum bicarbonate, HbA1c, smoking status, BMI, cardiovascular disease, hypertension and concomitant medication use.

Conclusions: Patients with eGFR >30 ml/min/1.73m^2 who use metformin do not appear to be at greater risk of acidosis than those who use sulfonylureas, supporting the FDA label expansion.

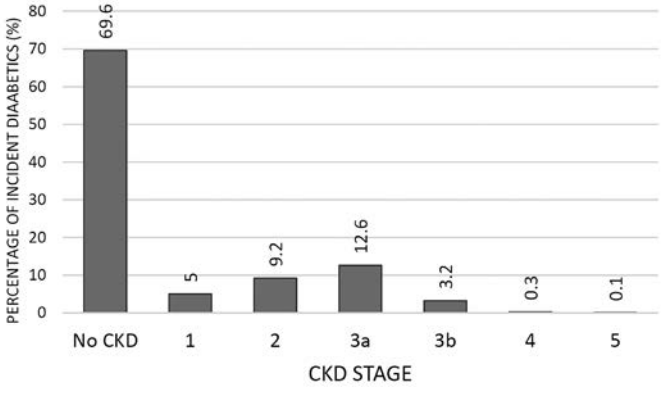
SA-PO853

Evidence of Chronic Kidney Disease in Veterans with Diabetes prior to Treatment Justin Gatwood,[1,3] Marie Chisholm-Burns,[1] Robert L. Davis,[2] Fridtjof Thomas,[2] Praveen Kumar Potukuchi,[2,3] Adriana Hung,[4] Csaba P. Kovesdy.[2,3] *[1]College of Pharmacy, Univ of Tennessee Health Science Center, Memphis, TN; [2]College of Medicine, Univ of Tennessee Health Science Center, Memphis, TN; [3]Nephrology, Memphis VA Medical Center, Memphis, TN; [4]Nephrology, Vanderbilt Univ School of Medicine, Nashville, TN.*

Background: Diabetes mellitus (DM) is a growing public health threat, and its impact on chronic kidney disease (CKD) remains of paramount importance. This study evaluated the extent of CKD in a national cohort of US veterans prior to initiating oral antidiabetic (OAD) therapy for incidence cases of DM.

Methods: The VA Corporate Data Warehouse was used to identify the first diagnosis for uncomplicated DM and the presence of disease was confirmed by an accompanying prescription for an OAD agent during 2002-2014. CKD was measured using estimated glomerular filtration rates (eGFR) and urine albumin-to-creatinine ratios as recorded nearest to the initial DM diagnosis and up to the date of the first OAD prescription fill.

Results: A total of 41,658 patients were analyzed, and most were White (77.7%) and male (96%). At DM diagnosis, mean (SD) age and hemoglobin A1C were 61.4 (10.18) and 7.4% (1.37), respectively, and 69.9% exhibited normal kidney function (UACR <30 and eGFR ≥60). However, 30.1% had CKD and 16.2% exhibited at least moderately reduced eGFR (CKD Stages 3a-5, Figure). The odds of any CKD stage (vs. no CKD) increased with age and hemoglobin A1C (p <0.0001 for both). Self-identified Asian (OR = 1.45, CI: 1.12-1.88) or African American race (OR = 1.12, CI: 1.05-1.20) was associated with a higher risk of CKD compared to White race.



Conclusions: CKD is common in veterans with incident DM, especially among older patients and certain minorities. Efforts to diagnose CKD should be made in conjunction with attempts to lower blood sugar early in the treatment process.

SA-PO854

Evaluation of Non-Prescribed Opioid and Illicit Drug Use in Chronic Kidney Disease Patients Thuy Hoang, Linda Awdishu, Lee Lee Zhu. *Pharmacy, Univ of California, San Diego Skaggs School of Pharmacy & Pharmaceutical Sciences, La Jolla, CA.*

Background: Over 58% of CKD patients experience pain and 49% of patients report their intensity of pain to be moderate to severe. Neuropathic and musculoskeletal pain are among the most common types of pain experienced by this population. The objective of this study was to determine the prevalence of non-prescribed pain medication or illicit drug use in patients with and without CKD using urinary and saliva samples.

Methods: This was a sub-study from a larger prospective medication reconciliation and adherence study of 493 patients at UCSD Health System and ambulatory care clinics. Medication reconciliation was conducted by a pharmacist or student pharmacist for each patient. Urine and saliva specimens were collected at the time of medication reconciliation and analyzed using triple quad liquid chromatography with tandem mass spectrometry (LC-MS/MS) for the presence of opioids and illicit drugs. Patients with a GFR <60mL/min/1.73m^2 (by MDRD equation) were defined as CKD. We hypothesized that patients with CKD were more likely to use non-prescribed pain medications and illicit drugs than patients without CKD. A Fishers's exact test was used to compare the occurrence of non-prescribed pain medications and illicit drug use detected in biological samples between CKD and non-CKD groups.

Results: A total of 251 patients were included in this study, 145 in non-CKD group and 106 in the CKD group. The detection of a prescribed pain medications were similar between CKD and non-CKD patients (p=0.60) indicating similar rates of adherence. Illicit drug use in CKD and non-CKD patients were overall low. No difference was found between the two groups (6.2% vs 2.9%, p=0.37) regarding illicit drug use. Patients without CKD were more likely to use non-prescribed pain medications, mostly consisting of opioids, than CKD patients (40% vs 10.6%, p= 0.0001).

Conclusions: Urine and saliva testing provides an objective measurement of medication reconciliation and adherence. Despite current knowledge that CKD patients are under-treated for pain, we found that CKD patients are less likely to use non-prescribed pain medications compared to non-CKD patients.

Funding: Pharmaceutical Company Support - Millennium Research Institute

SA-PO855

Renoprotective Effect of Dipyridamole in Pre-Dialysis Advanced Chronic Kidney Disease -A Nationwide Database Analysis Ko-Lin Kuo,[1] Szu-Chun Hung,[1] Jia-Sin Liu,[2] Chih-Cheng Hsu,[2] Der-Cherng Tarng.[3] *[1]Taipei Tzu Chi Hospital, Taiwan; [2]National Health Research Insts, Taiwan; [3]Taipei Veterans General Hospital, Taiwan.*

Background: Dipyridamole decreases proteinuria and improves renal function progression in patients with glomerular disease through its inhibition of platelet activation and enhanced nitric oxide expression. Whether the effects of dipyridamole on renal outcome or survival is unclear in CKD stage 5 patients who have not yet received dialysis (CKD 5 ND).

Methods: A prospective cohort study was conducted based on the Taiwan National Health Insurance Research Database. From January 1, 2000 to June 30, 2009, we enrolled 28497 CKD 5 ND patients with serum creatinine levels >6 mg/dL and hematocrit levels <28% and who were treated with erythropoiesis-stimulating agents (ESAs) but not yet received renal replacement therapy. All patients were further divided into two groups with or without dipyridamole within 90 days after starting ESA therapy (index date). Patient follow-up took place until long-term dialysis, death before initiation of dialysis or December 31, 2009.

Results: With a mean follow-up of 12 months, 20,152 patients (70.7 %) required long-term dialysis and 5,697 (20.0%) died before progression to end-stage renal disease requiring dialysis. After propensity score-matching, use of dipyridamole was associated with a lower risk for long-term dialysis (HR, 0.96; 95% CI, 0.93-0.99) and pre-dialysis death (HR, 0.89; 95% CI, 0.84-0.95) as compared with nonusers.

Conclusions: Dipyridamole exhibited a protective effect in reducing the risk for long-term dialysis and pre-dialysis death in CKD 5 ND patients. Randomized studies are needed to validate this association.

SA-PO856

Effect of Rituximab on Malignancy Risk in Patients with ANCA-Associated Vasculitis Emma Van Daalen,[1] Raffaella Rizzo,[2,3] Andreas Kronbichler,[3,4] Ron Wolterbeek,[5] Jan A. Bruijn,[1] David R.W. Jayne,[3] Ingeborg M. Bajema,[1] Chinar Rahmattulla.[1,3] *[1]Pathology, Leiden Univ Medical Center; [2]Nephrology, Dialysis and Hypertension Unit, St. Orsola-Malpighi Univ Hospital; [3]Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge Univ Hospitals; [4]Internal Medicine IV (Nephrology and Hypertension), Medical Univ of Innsbruck; [5]Medical Statistics and Bioinformatics, Leiden Univ Medical Center.*

Background: Patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) who are treated with cyclophosphamide have an increased malignancy risk compared to the general population. We investigated whether treatment with rituximab instead of cyclophosphamide has decreased the malignancy risk in patients with AAV.

Methods: The study included patients with AAV treated at a tertiary vasculitis referral centre between 2000 and 2014. The malignancy incidence in these patients was compared to the incidence in the general population by calculating standardized incidence ratios (SIRs). Malignancy incidence was compared between rituximab- and cyclophosphamide-treated patients.

Results: Of the 323 included patients, 33 developed a total of 45 malignancies during a mean follow-up of 5.6 years. This represented a 1.89-fold increased (95% confidence interval [CI], 1.38 to 2.53) malignancy risk compared to the general population. Cyclophosphamide-treated patients had an increased malignancy risk compared to the general population (SIR, 3.10; 95% CI, 2.06 to 4.48). In contrast, rituximab-treated patients had a malignancy risk similar to the general population (SIR, 0.67; 95% CI, 0.08 to 2.43). The malignancy risk in patients treated with cyclophosphamide was 4.61-fold higher (95% CI, 1.16 to 39.98) than the risk in patients treated with rituximab.

Conclusions: The malignancy risk in patients with AAV was lower in patients treated with rituximab than in patients treated with cyclophosphamide. Notably, rituximab treatment was not associated with an increased malignancy risk compared to the general population. Rituximab may therefore be a preferable alternative therapy to cyclophosphamide.

SA-PO857

Malignancy in Membranous Nephropathy: Evaluation of Incidence Basil Alnasrallah. *Nephrology, Auckland City Hospital, Auckland, New Zealand.*

Background: Membranous Nephropathy (MN) is known to be associated with malignancy. However, the exact risk remains unclear. In addition, the number of inflammatory cells in the glomeruli has been reported to be associated with malignancy in MN and has been suggested to direct screening; this has not been further validated.

Methods: We looked for the association of malignancy and MN in a cohort of 201 MN patients in Auckland region; we systemically reviewed the clinical records and linked them to the New Zealand Cancer Registry. We calculated the expected risk of a matched population by gender and age taking into account the annual change of risk. We also examined the pathology of renal biopsies of 17 MN patients with malignancies and compared the number of inflammatory cells per glomerulus with matched controls.

Results: 40 malignancies were identified. 28 after the MN diagnosis, the standardized incidence ratio (SIR) was 2.1 (95%CI, 1.3 - 2.85) which was similar between patients ≥60 years and <60 years. The SIR was higher in the first 5 years at 2.3 (95%CI, 1.29 - 3.4) but diminished and lost significance after that. The median number of inflammatory cells per glomerulus didn't differ between MN patients with and without malignancies at 1.86 (IQR, 1.17-2.7) and 2.07 (IQR, 1.17-3.65), respectively (*p*-value 0.56).

Conclusions: The relative risk of malignancy in MN patients was similar across different age groups at 2.1; this risk was most prominent in the first 5 years. The number of inflammatory cells per glomerulus did not differentiate between MN patients with and without malignancies.

SA-PO858

Risk of Renal Progression Is Higher in Upper Tract Urothelial Carcinoma Than in Renal Cell Carcinoma after Unilateral Nephrectomy - A Population-Based Study Huei-Lan Lee,[1] Ming-Yen Lin,[1] Wei-Ming Li,[2,4] Sheng-Wen Niu,[1] Chun-Nung Huang,[2,4] Wen-Jeng Wu,[2,4] Li-Tzong Chen,[3] Shang-Jyh Hwang.[1,4] *[1]Nephrology, Kaohsiung Medical Univ Hospital; [2]Urology, Kaohsiung Medical Univ Hospital; [3]National Inst of Cancer Research; [4]Faculty of Medicine, Kaohsiung Medical Univ.*

Background: Impairment of renal function in patients at diagnosis as upper tract urothelial carcinoma (UTUC) seemed more frequent than in renal cell carcinoma (RCC), which influenced renal outcome and also resulted in a worse clinical outcome. Limited information is available to compare the risk of progression of preexisted renal impairment to end-stage renal disease (ESRD) in patients of UTUC and RCC, respectively. The aim of study was to compare risk of renal progression in patients with UTUC and RCC after receiving unilateral nephrectomy.

Methods: We conducted a population-based cohort study through Taiwan National Health Insurance Research Dataset. Incident UTUC and RCC patient who underwent nephrectomy from 2002 to 2007 was identified from Taiwan Cancer Registry Dataset and linked to claim data.Primary endpoint was defined aspostoperative dialysis 3 months after surgery. Differences of characteristics between UTUC and RCC patients were described as mean ± standard deviation or percentage and tested by independent t test and chi-square test. Competing risk approach was used for estimating cause-specific hazard ratio (CSHR) and 95% confidence interval (CI).

Results: Totally, 1571 UTUC and 1910 RCC patients were included and traced until dialysis or end of the 3-years follow-up. Similar prevalence of CKD stages in UTUC (48.7%) and RCC (45.8%) patients was represented at the baseline. UTUC patients were significantly older, more female, and had more diabetes and stroke than RCC patients. After adjusting factors of age, sex, tumor grade, and co-morbidities, patient with UTUC was significantly associated with excessive risk of postoperative dialysis (CSHR: 2.09, 95%CI: 1.61-2.69, p<0.01) than that of patient with RCC.

Conclusions: UTUC is associated with increased risk of dialysis than RCC. Base on this finding, the strategy of renal function screen after nephrectomy should depend on the type of urinary tract cancer.

Funding: Government Support - Non-U.S.

SA-PO859

Prevalence and Outcomes of Chronic Lung Disease in Patients with Chronic Kidney Disease: A Systematic Review and Meta-Analysis Chung-Jiah Justin Chen, Sreedhar A. Mandayam, Wolfgang C. Winkelmayer, Sankar D. Navaneethan. *Baylor College of Medicine, Houston, TX.*

Background: Chronic lung diseases and CKD are both major public health issues. The burden and impact of chronic lung diseases in the CKD population has not been systematically studied. Hence, we conducted a systematic review and meta-analysis to study the prevalence of chronic lung disease and its impact on all-cause mortality in those with CKD.

Methods: We searched MEDLINE (1966-May 2016) using appropriate MESH terms to identify relevant observational studies reporting obstructive or restrictive lung disease prevalence in CKD patients and mortality outcomes in CKD patients with lung disease. Prevalence rates of chronic lung disease (obstructive and restrictive lung disease separately) and all-cause mortality risk estimates were extracted from individual studies and pooled using a random effects model.

Results: Seven studies were included (n = 839,736). Overall, prevalence of COPD was 18.4% (6 studies, 95% CI: 11.7%, 27.6%) in CKD population. Prevalence was significantly higher among studies that used spirometry to diagnose COPD (3 studies, prevalence rate:34%, 95% CI: 14.6%, 60.9%) than the prevalence among studies that used chart review (ICD-9 codes, medication use etc.) for diagnosing COPD (3 studies, prevalence rate:9%, 95% CI: 5%, 13%). There was an increased risk for all-cause mortality in CKD patients with COPD (vs. without COPD) (Hazard ratio: 1.26, 95% CI: 1.09, 1.41). One study reported prevalence rate of 10% for restrictive lung disease in CKD population. Further, restrictive lung disease was inversely associated with albuminuria and eGFR.

Conclusions: Obstructive and restrictive lung diseases are highly prevalent and are significantly associated with higher all-cause mortality in CKD. Prevalence rates of COPD in CKD patients who underwent spirometry are significantly higher than those of CKD patients with COPD identified by medical records, suggesting that chronic lung diseases are probably underdiagnosed in CKD patients. Even though restrictive lung disease appears to be common in CKD population, formal studies are lacking. Further studies are required to characterize pathogenic mechanisms between lung disease and CKD.

SA-PO860

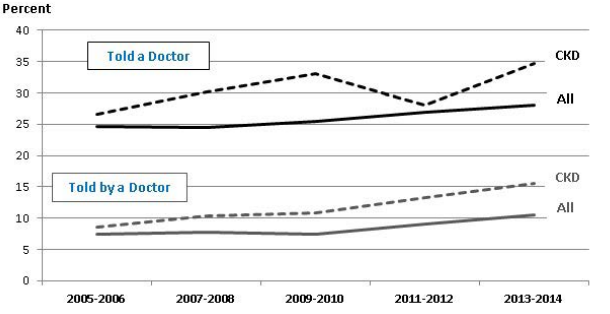
Trends in Self-Reported Communication of Sleep Problems between U.S. Adults with CKD and Their Doctors Jennifer L. Bragg-Gresham,[1] Monica Shieu,[1] Hal Morgenstern,[1] Neil R. Powe,[2] Delphine S. Tuot,[2] Sharon Saydah,[3] Deborah Rolka,[3] Rajiv Saran.[1] *[1]Univ of Michigan, Ann Arbor, MI; [2]UCSF, San Francisco, CA; [3]CDC, Atlanta, GA.*

Background: Given sleep's importance for health, we explored trends in the prevalence of self-reported communication of sleep problems between US adults with CKD and their doctors.

Methods: A sample of 25,255 adults aged 20+ from the 2005-2014 National Health and Nutrition Examination Survey was used to estimate the prevalence of (1) having ever told a doctor about having trouble sleeping, and (2) having ever been told by a doctor s/he had a sleep disorder. Prevalence was estimated for each 2-year survey interval. CKD was defined as eGFR <60 ml/min/1.73 m² or UACR >30 mg/g. Logistic regression was used to assess unadjusted and age-sex-BMI-adjusted trends over time among adults with CKD and all adults.

Results: From 2005 to 2014, the crude and adjusted prevalence of each sleep outcome increased in both adults with CKD and all adults (all *p* for trend <0.02). The crude prevalence of both outcomes was greater in adults with CKD than in all adults throughout the 10-year period. Adults with CKD had a greater absolute increase than all adults in the percentage told by a doctor they had a sleep disorder (8.0% vs. 3.0%). In both groups, age and BMI were positively associated with poor sleep outcomes, women were more likely to tell a doctor of their sleep problems, and men were more likely to be told they had a sleep disorder (all p<0.0001).

Crude Prevalence (%) of each sleep outcome in US adults with CKD and all adults, by 2-year interval



Conclusions: The frequency of sleep problems communicated between adults with CKD and their doctors increased in the US in the past decade and were consistently greater in adults with CKD than all adults.

Funding: Other U.S. Government Support

SA-PO861

The Rise of Kidney and Related Chronic Diseases in Remote Living Aboriginal People in the Context of the Epidemiologic and Health Transitions Wendy E. Hoy,[1,2] Susan A. Mott,[1] Cheryl E. Swanson,[1] Suresh Kant Sharma,[1,2] Jennifer J. Nicol.[1] *[1]CKD.CRE, The Univ of Queensland, Herston, Brisbane, QLD, Australia; [2]Menzies School of Health Research, Darwin, Northern Territory, Australia.*

Background: The increase in chronic diseases in Aboriginal communities is poorly understood. We describe the emergence of chronic disease and CKD in one remote community since 1960 in the context of epidemiologic and health transition.

Methods: We analysed deaths and renal replacement records (RRT) records (deaths=1,166, RRT=91) for the Tiwi Aboriginal community in the Northern Territory from 1960 to 2010, inspected birthweights since 1956 and used population estimates in 1957 and census data since 1986.

Results: In the early 1960s, >50% of Tiwi deaths were in infants or children: >45% of newborn were low birthweight (LBW, <2.5 kg), and infant mortality rate was about 130/1000 live births, higher in LBW subjects, Deaths in infants and children fell by >95% by the late 1980s, with a greater absolute and relative reduction for LBW persons. Now nearly all babies survive to adult life, with nearly all deaths occurring in adults, and increasingly in adults >45 years old. Most adult natural deaths are from pulmonary, cardiovascular, renal and liver disease, with a >2-fold increase in LBW persons-- evidence of the "Barker hypothesis". As treatment postpones pulmonary and CV deaths, and people are ageing, renal deaths are increasing. However, age at renal failure has risen by 20 years since the 1970s. The Tiwi population has tripled since 1957, and the age-structure is maturing from a third world to an intermediate pattern. A pressing current concern is deaths from misadventure (often suicide) of young adults.

Conclusions: Emergence of chronic disease is a consequence of triumphs in public health and healthcare delivery in the last 5 decades. Such phenomena are most certainly echoed in the developing world, although it is unlikely that many other populations have experienced these events in such a compressed way. As birthweights continue to increase and chronic disease management improves further, longevity will continue to increase.

Funding: Pharmaceutical Company Support - The Colonial Foundation Australia, Amgen Australia, Government Support - Non-U.S.

SA-PO862

Negative Psychosocial Factors and Chronic Kidney Disease (CKD) Outcomes among African Americans Clarissa Jonas Diamantidis,[1] Nrupen Anjan Bhavsar,[1] Mario Sims,[2] Julia J. Scialla,[1] Clementina A. Davenport,[1] Rasheeda K. Hall,[1] Crystal C. Tyson,[1] Wei Wang,[2] Adolfo Correa,[2] L. Ebony Boulware.[1] *[1]Duke Univ School of Medicine; [2]Univ of Mississippi Medical Center.*

Background: Established CKD risk factors do not fully account for the renal outcomes of African Americans. We studied the association between negative psychosocial factors and CKD prevalence, incidence and progression in the Jackson Heart Study (JHS).

Methods: We used factor analysis to identify common domains of 12 baseline psychosocial factors (perceived daily, lifetime, and burden of discrimination; anger in, anger out, hostility, pessimism, stress, John Henryism, spirituality, perceived social status, social support). We quantified the association of identified factor domains with baseline CKD prevalence (estimated glomerular filtration rate [eGFR] <60 mL/min/1.72m^2 or urine albumin-to-creatinine ratio of ≥ 30 mg/g) and CKD progression (annualized rate of eGFR decline), or incident CKD (new eGFR <60 mL/min/1.72m^2 at follow-up and 25% eGFR decline from baseline, or new onset albuminuria) in multivariable models adjusted for sociodemographics and comorbidity. Those missing key CKD or psychosocial variables were excluded.

Results: Of 3390 (64%) participants with baseline CKD status available, 656 (19%) had CKD. Those with CKD (vs. no CKD) had lower perceived daily, lifetime and burden of discrimination; lower hostility, stress, and perceived social status; less John Henryism; higher pessimism, all $p < 0.05$. Factor analysis identified 3 psychosocial domainsfor CKD prevalence: 1) stressors (perceived discrimination, stress), 2) moods (anger, hostility), and 3) coping strategies (John Henryism, spirituality, social status, social support). After adjustment, those with greater stressors were less likely to have prevalent CKD (OR 0.76 [0.65-0.89]). Psychosocial domains were not associated with CKD incidence or progression.

Conclusions: Negative psychosocial attitudes were less common among those with CKD and not associated with CKD incidence or progression. Our study, limited to a single US area, may not be generalizable. Further study should explore the role personal expression of negative attitudes plays in engagement in care among African Americans.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO863

Level of C-Reactive Protein Is Associated with the Progression of Diabetic Nephropathy in African Americans in the Jackson Heart Study Cohort Satyesh K. Sinha,[1] Keith C. Norris,[2] Susanne B. Nicholas.[2] *[1]Internal Medicine, Charles R Drew Univ of Science and Technology, Los Angeles, CA; [2]David Geffen School of Medicine, Univ of California Los Angeles, Los Angeles, CA.*

Background: The reasons for the disparities in the prevalence and incidence of diabetic nephropathy (DN) and end stage renal disease (ESRD) in African Americans (AA) remain unclear but may involve complex inflammatory mechanisms that contribute significantly to the development and progression of DN. We recently reported a strong association between C-reactive protein (CRP) and urinary albumin excretion (UAE). The level of CRP and UAE both were significantly higher in AA compared to whites, suggesting that inflammatory processes of DN may be influenced by ethnicity. However, the association of CRP with progression of DN in the longitudinal follow-up data has not been examined. In this study, we tested the hypothesis that circulating inflammatory markers, such as CRP, are associated with the progression of DN in AA.

Methods: We analyzed longitudinal follow-up data from Exam 1 (2000-2004), Exam 2 (2005-2008) and Exam 3 (2009-2012) at the JHS to determine the role of inflammation in the development of DN in AA using the inflammatory marker, high sensitive CRP (hs-CRP), and kidney function (measured by UAE). We analyzed data using Cox regression to estimate the hazard ratio (HR) for DN according to tertile of hsCRP, controlling for demographics. Data are presented as HR, and 95% confidence interval (CI); $p<0.05$ was statistically significant.

Results: In the fully adjusted model, the elevated hsCRP (>4.24 mg/L) was associated with DN (HR= 2.34, 95% CI 1.1-5.01, $p<0.05$) compared to the reference group (hsCRP <1.46 mg/L). The mean survival time was significantly reduced with hsCRP >4.24mg/L compared to low hsCRP (<1.46mg/L), $p<0.001$.

Conclusions: We conclude that elevated hsCRP is associated with progression of DN and mortality in AA.

Funding: Other NIH Support - U54-MD-008149

SA-PO864

Rapid Changes in Estimated GFR Associates with All-Cause Mortality: A Prospective Cohort Study from Chinese Community-Based Populations Yang Luo. *Dept of Nephrology, Beijing Shijitan Hospital, Capital Medical Univ, Beijing, China.*

Background: Reduced kidney function is an independent risk factor for all-cause mortality and cardiovascular events, but data from longitudinal studies about the association of decline of estimated GFR (eGFR) with clinical outcomes are limited.

Methods: We investigated whether 4 year annual changes in eGFR associated with the risk of all-cause mortality and cardiovascular events in the next 2 consecutive years in a Chinese community-based population, 36404 qualified participants of the Kailuan study were included in this analysis.

Results: After adjustment for baseline covariates including age, gender and eGFR in Cox proportional hazards models, the participants with the rapid decline in eGFR (annual decline greater than 4ml/min.1.73m^2) were at significantly greater risk for all-cause mortality (hazard ratio 1.56[95% confidence interval 1.22 to 1.99]), but not at cardiovascular events (0.96 [95% confidence interval 0.78 to 1.18]) compared with the non-rapid change participants (annual decline less than 4ml/min.1.73m^2). We also observed that the first quartile of decline of eGFR (annual decline from 0.81to 21.19ml/min.1.73m^2) associated with all-cause mortality but not with cardiovascular events in Cox proportional hazards models with the same adjustment baseline covariates when we made the second quartile of decline of eGFR as reference; the third and fourth quartile of the decline of eGFR didn't showed association with all-cause mortality and cardiovascular events, perhaps as a result of clinical instability.

Conclusions: In conclusion, a rapid decline in eGFR associates with a higher risk for all-cause mortality but not cardiovascular disease. Increases in eGFR among participants don't associate with similar clinical outcomes.

SA-PO865

HBV and HCV Prevalence and Incidence among ESRD Patients in France Corinne Isnard-Bagnis,[1] Cécile Couchoud,[4] Luc Haudebourg,[2] Gilbert Deray,[1] Patrice Cacoub,[5] Sophie Tezenas du Montcel.[2,3] *[1]Nephrology, Hopital Pitié Salpetriere APHP, Paris, Ile de France, France; [2]Biostatistics, Hopital Pitié Salpetriere APHP, Paris, Ile de France, France; [3]UMR_S1136 and INSERM UMR_S 1136 Inst Pierre Louis d'Epidémiologie et de Santé Publique, Sorbonne UPMC Univ Paris 06, Paris, Ile de France, France; [4]REIN Registry, Agence de la Biomédecine, Saint Denis La Plaine Cedex 93212, Ile de France, France; [5]Internal Medicine-Immunotherapy Dept i2B and UMR_s959, Hôpital Pitié Salpetriere APHP and Sorbonnes Univ, Paris, Ile de France, France.*

Background: Risk for HBV and HCV is increased in ESRD patients. New HCV treatments have prompted us to generate updated epidemiological data.

Methods: In a multi center cohort study, using the REIN National French prospective registry (ESRD), we extracted data for patients who initiated dialysis/had been put down on the kidney transplant waiting list (Jan, 2005 to Dec, 2013). We extracted records related to: "inclusion in REIN", "annual dialysis follow-up", "dialysis after graft failure", "registration on the kidney transplant waiting list " and "kidney transplant". A positive HBsAg and a positive HCV RNA defined HBV and HCV infections.

Results: 72,948 patients started dialysis or were preemptively transplanted, 45,591 men (62.5%), (mean age 66.9±16.1 yrs).13,609 (18.7%) patients received a kidney graft, (mean age 50.9±15.5 yrs). At inclusion, 615 patients were HBV and 1,026 HCV infected. The prevalence of HBV and HCV infections were 0.84% (95% PI: 0.78 – 0.91) and 1.41% (95% PI: 1.32 – 1.49). Prevalence of HBV and HCV infection by age group increased progressively until a maximum rate of 1.80% (95% PI: 1.46 – 2.20) and 3.14% (95% PI: 2.68 – 3.65) in the 4th decade, then regularly decreased. During follow up, we identified new HBV or HCV infections in 117 and 81 patients, respectively. Overall incidence for HBV and HCV infections between 2005 and 2013 were 0.076% (95% PI: 0.062 – 0.090) and 0.053% (95% PI: 0.041 – 0.065) respectively. During the 1st year of dialysis, the incidence of HBV infection was 0.35% (95% PI: 0.28 – 0.43) and that of HCV 0.22% (95% PI: 0.16 – 0.29).

Conclusions: Our data highlights the need for HCV therapy for over 1000 patients and persistence of nosocomial cases.

SA-PO866

Heterogeneity of Chronic Kidney Disease with Age in a Major Metropolitan Renal Service Usman Mahmood,[1] Wendy E. Hoy,[2] Helen G. Healy,[1,2] Andrew John Mallett,[1,2] Adrian Lawrence Kark,[1,2] Anne Cameron (Salisbury),[1,2] Zaimin Wang,[2] Rajitha Asanga Abeysekera.[1] *[1]Royal Brisbane & Women's Hospital, Australia; [2]Univ of Queensland, Australia.*

Background: Aim of the study is to describe the characteristics of disease and outcomes with increasing age in people with CKD.

Methods: 1,265 patients enrolled into the CKD.QLD registry at Royal Brisbane and Women's Hospital were grouped according to age into <25, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, 85+ years at consent and followed till start of renal replacement therapy (RRT), death, discharge or November 2015. Characteristics were described as mean (SD), proportions as percentage (%) and outcomes defined as mortality, start of RRT, hospitalization and progression of kidney disease.

Results: 651 of the cohort were male and 614 were female, mean ages of 66.7 and 65.6 years respectively. Reno-vascular disease (including hypertension) (RVD) was the leading primary diagnosis in both genders, followed by diabetic nephropathy. Proportions with RVD progressively increased from undetectable in the <25 year to 69.4% in the 85+. A single diagnosis was recorded in 76% of <25 years, compared to 58% in > 85 years, with remainder having two or more etiologies listed. In the youngest and older age group, proportions with CKD stage 3A to 5 were 27.6% and 98% respectively. Up to 8 comorbidities were documented per patient, with means of 0.5 in <25 and 2.9 in 85+ age groups. All comorbidities were more common in males than females (mean 2.8 (1.7) vs. 2.2 (1.5)). Mortality rates increased from 1.6 to 17.4 per 100 person years, whilst RRT rates decreased from 1.7 to 0.4 per 100 person years in the 35-44 to 85+ age groups. Rates of hospitalization, length of stay and cost progressively increased from the youngest to eldest groups. The proportion of patients who lost more than 5 mls/min of eGFR during follow up increased from 10.5% in the youngest age group to 29.2% in the eldest.

Conclusions: The characteristics of CKD patients differ by age. Older people more likely have vascular and metabolic disease, have less conversion to dialysis, higher deaths rates and are more likely to access acute hospital services. There is opportunity to personalize CKD care delivery taking this heterogeneity into account.

Funding: Government Support - Non-U.S.

SA-PO867

The Association of Monocyte Count and eGFR with All-Cause Mortality

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Background: Chronic kidney disease (CKD) is associated with a high all-cause mortality risk. Elevated monocyte count has been associated with increased risk of death in the general population, however, data in CKD is limited. Whether monocyte count modifies the association of estimated glomerular filtration rate (eGFR) and mortality is not known.

Methods: We built a national cohort of 1,706,589 U.S. veterans and followed them over a median of 9.16 years to examine the association of monocyte count with eGFR categories:15-30 ml/min/m^2, 30-45 ml/min/m^2, 45-60 ml/min/m^2, 60-90 ml/min/m^2, 90-105 ml/min/m^2 (reference) and >105 ml/min/m^2, and with all-cause mortality risk. Monocyte count was divided into quartiles: 0.00-0.40 k/cmm (reference) 0.40-0.56 k/cmm, 0.56-0.70 k/cmm and >0.70 k/cmm. Interaction analyses were undertaken to test whether monocyte count modifies the risk of mortality associated with eGFR.

Results: A high monocyte count (>0.56 k/cmm) was associated with increased risk of death overall and across each eGFR category. A high monocyte count was associated with high (>90 ml/min/m^2) and low (<45 ml/min/m^2) eGFR; eGFR levels that were associated with higher mortality risk. The maximum joint mortality risk was noted in the lowest eGFR and highest monocyte category (HR = 2.68, CI = 2.59-2.79). The mortality risk associated with high monocyte count and low eGFR exhibited a significant negative interaction on both additive and multiplicative scales.

Conclusions: To our knowledge this is the first study to investigate the interactions between monocyte count, eGFR and their association with death. Increased monocyte count and both low and very high eGFR were associated with higher all-cause mortality risk. Monocyte count modified the risk of death associated with eGFR at low eGFR levels and is a valuable parameter in determining the prognosis of patients with CKD.

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SA-PO868

Infection as a Major Cause of Death in Japanese Elderly Chronic Kidney Disease: The Gonryo Study

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Background: Chronic kidney disease (CKD) *is increasing in* Japan, based on the *rapidly* growing ageing-population. Infection is a major complication by ageing, and the second cause of death in Japan under the dialysis population. However the cause specific death except cardiovascular disease (CVD)is limited, and the clinical feature who died by infection inCKD before dialysis is not fully known.

Methods: We prospectively followed up 2,694 outpatients, who satisfied estimated glomerular filtration rate <60 ml/min and/or presenting proteinuria, under the care of nephrologists. Patients were stratified by age at 65 years to 1,495 of non-elderly and 1,199 of elderly. And elderly divided into 65-74, 75-85 and over 85 years old. Deaths, censored for RRT, were recorded for a follow-up time of 5 years. Cause of death was classified as CVD, infection, malignancy or other reported using International Classification of Diseases codes.

Results: Among 2,694 patients, the median age 62 (qurtile 51– 72) years, males 53% and a median eGFR 53.7 (qurtile 33.4 – 74.0) ml/min, and 118 died and 308 patients started RRT during a median follow-up of 4.5 (qurtile 1.9 – 5.0) years. Among 118 deaths, the most common cause was CVD (28.0%) followed by infection (19.5%) and malignancy (17.8%). While the CVD and malignancy observed in all generation, infection-related death was observed only in elderly, and in over 75 years infection-related mortality (22.9%) was as frequent as CVD (24.3%). In elderly population, the survival risk before developing ESKD associated significantly with high age, low body mass index (BMI), and history of cardiovascular disease. In those,increased the risk of infection-related mortality was associated with the lower BMI.

Conclusions: Infection is the second leading the cause of death in our CKD population, especially is that in elderlies.

SA-PO869

The Interplay between *Clostridium difficile* Infection (CDI) and Renal Disease: Epidemiology, Treatment Management and Outcomes

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Background: Despite increased risk of CDI among patients (pts) with renal impairment, there is limited data evaluating treatment and outcomes in these pts. We evaluate the impact of CDI along the continuum of renal impairment.

Methods: Retrospective, observational study of consecutive cases of CDI, verified by positive PCR at UCLA (12/2013-12/2014). Pts were stratified into two groups: renally impaired (acute kidney injury, chronic kidney disease, end stage renal disease) (renal) and no renal impairment (non). Charts were reviewed for demographics, comorbidities, CDI therapy and clinical outcomes.

Results: Overall, 222 pts had CDI, 90% were considered first CDI episode. 89 (40%) pts were renal (24.7% on dialysis) and 133 (60%) pts were non. Baseline demographics displayed in mean (standard deviation) or n (%); age: 67 years (16) vs. 60 years (20); admitted from community: 60 (67.4) vs. 99 (74.4); private insurance: 16 (18) vs. 48 (36); medicare: 50 (56.2); 64 (48.1). Most common comorbidities included chronic pulmonary disease (36 vs. 27.1%), acute coronary syndrome (37.1 vs. 25.6%), and diabetes mellitus (39.3 vs. 23.3%). CDI-related shock was most common in renal (15.7 vs. 3.8%). Most pts were initially treated with metronidazole (metro) (75.2 renal and 76.8% non). Renal were more likely to receive both metro then vancomycin than non (38.2 vs. 24.8%). Hospitalists were the most common prescribers of CDI therapy. Length of hospital and ICU stay was longer in renal; 24 (33) vs. 22 days (24), and 9 (24) vs. 3 days (8), respectively. Readmission and CDI recurrence were more frequent in renal: 36.9% vs. 27% and 20.2% vs. 16.7%, respectively.

Conclusions: 40% of pts with CDI were renal and almost half of these received various CDI treatments, with most pts initially treated with metro. Recurrence and readmission rates were frequent in these pts. Renal pts are at high risk for CDI and poor outcomes and require aggressive treatment management.

Funding: Pharmaceutical Company Support - Merck & Co, INC

SA-PO870

Increased Serum Alkaline Phosphatase Predicts Rapid Decrease of Glomerular Filtration Rate in Patients with Normal Renal Function/Early Chronic Kidney Disease

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Background: High alkaline phosphatase has been associated with increased mortality and coronary calcification in many subgroups, but the impact of alkaline phosphatase on decline in glomerular filtration rate (GFR) is unknown.

Methods: We retrospectively included patients with normal renal function or early chronic kidney disease who underwent cardiac CT angiography (CCTA) from March 2008 to June 2013 in a single medical center. We gathered available medical records of patients as follows; demographics, baseline laboratory findings at the time of CCTA scan, serum creatinine data of 0, 3, 6, 12, and 24 month (±3 weeks). The latest serum creatinine level, any mortality events and major cardiovascular events were retrieved till February 2016.

Results: Of 2,132 patients, there were 110 (5.2%) patients who showed decreases in GFR above 30% within a median 3.1 years. In multivariate Cox regression analysis, high alkaline phosphatase (>120 IU/L) was a definite predictor for GFR decrease even after adjusting following variables; age, gender, comorbidities, CRP, liver enzyme, coronary calcium score (CCS) and GFR at the time of CT scan (HR 2.20, 95% CI 1.08-4.51, *P*=0.031). For subgroup analysis, subjects with lower arterial calcification (CCS<100), non-diabetes, male, high-GFR (≥60ml/min/1.73m^2), and lesser age (age<70 years) revealed significant increased risk of GFR decline by high alkaline phosphatase level, while the opponents did not. On the other hand, high alkaline phosphatase (>120 IU/L) had little influence on major cardiovascular events (OR 1.106, 95% CI 0.516-2.373, *P*=0.795), and CCS was not related to elevation of serum alkaline phosphatase (*P*=0.367).

Conclusions: We found that elevated serum alkaline phosphatase in normal renal function/early chronic kidney disease can predict more decrease in GFR, which mechanism may not related to arterial calcification.

SA-PO871

Associations of Liver Histopathology with Inflammatory Markers in Non-Uremic and Uremic Hepatitis C Positive Patients

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Background: The aim of this study is to investigate the association between hepatic activity index (HAI) and fibrosis score (FS) with inflammation in non-uremic hepatitis C positive patients.

Methods: Fifty chronic hepatitis C (CHC) positive patients, 15 with end-stage renal disease (ESRD), having a liver biopsy were included in this study. 25 patients with similar age and gender were also enrolled as control group. Liver biopsies were scored according

to modified ISAAC scoring system: mild and severe according to fibrosis observed in the biopsy. Serum YKL-40, neutrophil/lymphocyte ratio (NLR), trombocyte/lymphocte ratio (PLR), CRP and Immunglobulin (Ig)G, A, and M levels were used to determine inflammation. AST to Platelet Ratio Index (APRI) score was also evaluated.

Results: Patients with CHC had increased inflammation compared to the controls (NLR, 2.52±1.26,1.91±0.92;P<0.05), (IgG,1491±491mg/dL,1143±229mg/dL;P<0.001), (YKL-40, 134±170 ng/mL,18±9.1 ng/mL; P<0.001). ESRD patients had lower HCV RNA levels IU/mL (p=0.201), HAI (p=0.01) and FS (p=0.007) compared to non-uremics. Patients with ESRD and high FS were older (40±7.7, 53±10 years old; p=0.01) and had higher APRI score (0.28±0.21,0.53±0.21, p=0.06). In adjusted models, APRI score (t value:3.98, p=0.002) was an independent predictor for FS. In non-uremic cHepC patients with higher FS, AST (p=0.005), ALT (p=0.01), Ig G (p<0.001), YKL 40 levels (p=0.02) and APRI score (p=0.002) were significantly higher. In adjusted analysis, YKL 40 levels (t value: 3.48; p=0.001) and APRI score (t value:4.57, p<0.001) were found as independent predictors of FS.

Conclusions: In non-uremic CHC patients, serum Ig G and YKL 40 levels may be valuable markers of HAI. In ESRD patients, there is not sufficient data for prediction of HAI and FS. In these patients, APRI score may provide better information.

SA-PO872

Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Cystatin C as Predictors of Undiagnosed Kidney Injury in Diabetic African American Men Elimelda Moige Ongeri,[1] Olugbemiga E. Jegede,[2] Susan Sumner,[3] Lakmini S. Premadasa,[1] Scott H. Harrison,[1] Robert H. Newman.[1] *[1]Biology, North Carolina A&T State Univ, Greensboro, NC; [2]Community Health & Wellness Clinic, Cone Health, Greensboro, NC; [3]Eastern Regional Comprehensive Metabolomics Resource Core, RTI International, Research Triangle Park, NC.*

Background: Diabetic nephropathy (DN) is the leading cause of end stage renal disease (ESRD). Ethnic minorities disproportionately bear the burden of complications of diabetes, yet minorities, especially African American men, are underrepresented in research studies that serve to develop biomarkers for diagnosis and therapeutics. Traditional tests for DN lack sensitivity and are often inaccurate. As a result, DN is underdiagnosed in patients in the early stages of the disease, making it difficult to implement interventions to slow progression to ESRD. Assays for recently developed protein-based biomarkers such as NGAL, Cystatin C, and kidney injury molecule-1 (KIM-1) are more sensitive and thus suitable for early diagnosis of kidney injury. However these assays are not widely available in clinical settings.

Methods: Enzyme-linked immunosorbent assays (ELISA) were used to determine the levels of creatinine, NGAL, Cystatin C, and KIM-1 in 67 African American men from three groups: 1) diabetics without diagnosed DN, 2) diabetics with diagnosed DN, and 3) non-diabetic controls.

Results: The levels of serum NGAL and Cystatin C were significantly higher ($p \leq 0.0001$) in patients with diagnosed DN compared to non-diabetic controls. However, there was no significant difference in the levels of urine KIM-1. Importantly, a substantial proportion (17%) of the diabetic patients without diagnosed DN exhibited both NGAL and Cystatin C levels that were ³ 2 SD above the mean levels found in non-diabetic controls.

Conclusions: A combination of NGAL and Cystatin C could be used to predict early stage DN in African American men. The data will serve as a basis for the development of educational material to engage African American men in community participatory research to prevent and/or manage diabetes and slow progression to DN and to encourage collection of biological samples for biomarker development.

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SA-PO873

The Effect of Annual Income on the Progression of CKD in Japan Naohiko Fujii,[1] Takayuki Hamano,[2] Tadao Akizawa,[3] Seiichi Matsuo,[4] Hirofumi Makino,[5] Enyu Imai,[6] Tsuyoshi Watanabe,[7] Kosaku Nitta,[8] Shoichi Maruyama,[4] Masafumi Fukagawa,[9] Akira Hishida.[10] *[1]Hyogo Prefectural Nishinomiya Hospital, Japan; [2]Osaka Univ, Japan; [3]Showa Univ, Japan; [4]Nagoya Univ, Japan; [5]Okayama Univ, Japan; [6]Nakayamadera Imai Clinic, Japan; [7]Fukushima Medical Univ, Japan; [8]Tokyo Women's Medical Univ, Japan; [9]Tokai Univ, Japan; [10]Yaizu City Hospital, Japan.*

Background: The effect of socioeconomic status on the disparity in medical treatment and healthcare should not be overlooked as an interventional target. However, such evidences are limited in CKD. We assessed the association between income levels and eGFR trajectory over time, by using the dataset from the Japanese CKD prospective cohort study (CKD-JAC, N=2977, mean eGFR 28.7 ± 12.2 mL/min/1.73m^2).

Methods: We enrolled 1849 (62%) participants that responded to the questionnaire on annual household income at baseline, which were stratified into quartiles. We evaluated eGFR change by using a joint model analysis, incorporating both random-effects and survival models to take into account fewer observations due to worse outcomes. We first adjusted for demographics and renal function at baseline (Model 2), and then for other possible confounders, such as systolic BP, administration of ACEI/ARB, and CRP (Model 3).

Results: The income quartiles were defined as Low (Q1, N=456), Middle (Q2, N=506), High (Q3, N=434), and Q4 (Highest, N=453) for the subjects with annual household income of <$30,000, $30,000-49,999, $50,000-79,999, and ≥$80,000, respectively. The subjects with lower income were likely to be significantly older, female, diabetic, and hypertensive. They also had a lower renal function, a higher prevalence of CVD, and a higher prevalence of inflammation. When we adjusted for demographic factors and renal function at baseline, the overall time-interaction term of income quartiles became significant (overall P=0.029), where we observed the fastest eGFR decline in income Q3 (-0.43 [0.86, 0.01], P=0.055); however, the further adjustment for other covariates diminished the significance of time-interaction by income quartiles (Model 3).

Conclusions: The annual household income level was not associated with eGFR decline among CKD patients in Japan.

Funding: Pharmaceutical Company Support - Kyowa Hakko Kirin

SA-PO874

Application of Group-Based Trajectory Modeling (GBTM) in Renal Research Zhiying You, Jessica B. Kendrick, Michel Chonchol. *Medicine, Univ of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: In epidemiological studies of chronic kidney disease (CKD) and autosomal dominant polycystic kidney disease (ADPKD), kidney function and total kidney volume and other variables are repeatedly or longitudinally measured. The group-based trajectory modeling (GBTM) is a powerful approach that summarizes such data collected across the study period and divides the subjects into groups based on their trajectories or pattern of change over time. The identification of clinical variables associated with trajectories may help identify new risk factor and novel therapeutic targets. In the published renal literature there is a lack of use of GBTM. Here we report two examples of GBT application.

Methods: We used GBTM to identify five trajectory groups of plasma fibroblast growth factor 23 (FGF23) levels among patients with end stage renal disease (ESRD) in the first example, using data from the Hemodialysis (HEMO) study. In the second example, we identify four trajectory groups of serum calcium levels among patients with CKD of stage IIIB and IV and with vitamin D insufficiency or deficiency, using data from a randomized controlled trial titled "Vitamin D and arterial function in patients with chronic kidney disease" that was funded by NIH/NIDDK (5K23DK087859). All analyses were performed by using SAS procedure TRAJ under SAS version 9.4 (SAS Institute, Cary NC).

Results: Five trajectory group of FGF23 were considered reasonable based on consideration of (1) the criterion of the Bayesian information and Akaite information, (2) sample size, and (3) the patterns of the identified trajectory groups and their percent. The five groups were stable lower and higher level, going up from low and stable low level, and going down from high level. Similarly, four trajectory groups of blood calcium were considered appropriate and they were stable low, moderate and high level, and going up from high level.

Conclusions: The SAS TRAJ procedure is user friendly and is easy to use. Exploratory analysis is necessary because GBTM was developed to empirically examine what trajectory groups present in a target population.

SA-PO875

Slope of Renal Decline as an End-Point for Intervention Trials to Prevent End-Stage Renal Disease Jan Skupien,[1,2] James Warram,[1] Adam Smiles,[1] Robert C. Stanton,[1] Andrzej S. Krolewski.[1] *[1]Joslin Diabetes Center, Boston, MA; [2]Jagiellonian Univ Medical College, Krakow, Poland.*

Background: Clinical trials of interventions to prevent ESRD enroll high-risk patients with impaired renal function. Recently validated surrogate end-points include a 40% or a 30% decline from baseline eGFR within 1-3 years, predicting ESRD occurrence several years later. However, no end-points have been proposed for early intervention studies, enrolling patients whose ESRD develops after 10 years of follow-up. We examined data from patients in whom ESRD developed and whose eGFR had been followed since it was normal. Our aim was to investigate the relationship between validated end-points and the slope of eGFR decline.

Methods: We analyzed data from 264 Joslin Clinic patients (49% women) participating in natural history studies of diabetic nephropathy who developed ESRD 2-25 years after their enrolment with normal eGFR. Median duration of follow-up and rate of renal decline were 7 years and 9 ml/min/year, respectively. At entry, median age was 32 years, diabetes duration 18 years, glycated hemoglobin 9.7% and baseline eGFR 84 ml/min.

Results: The frequencies of alternative end-points according to year of follow-up were:

Time (years)	ESRD	Doubling serum creatinine	40% loss	30% loss
1	0%	0%	6%	10%
2	2%	11%	24%	40%
3	10%	26%	47%	62%

For 90% of patients with ESRD within 3 years, the slope of renal decline was 21 ml/min/year or more. For 90% of those with a doubling of serum creatinine, a 40% loss or a 30% eGFR loss within 3 years, the slope of decline was ≥14, ≥10 and ≥8 ml/min/year, respectively. Among the 38% who were not detected by any surrogate endpoint, in > 95% the time to ESRD was 8-18 years, and the rate of renal decline ≥4 ml/min/year.

Conclusions: Currently approved surrogate end-points develop during a clinical trial only in high-risk patients with rapid renal decline or significantly impaired renal function. It limits external validity of such trials. Early intervention trials should enroll patients whose renal decline is 4-8 ml/min/year. We urge diligent efforts to validate slope of renal decline as a surrogate end-point for intervention trials to postpone or prevent ESRD.

Funding: Private Foundation Support

SA-PO876

Vitamin D Associates with Higher Physical Activity and Comorbidities in Chronic Kidney Disease: Result from the KoreaN Cohort Study for Outcomes in Patients with Chronic Kidney Disease (KNOW-CKD)

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Background: Although vitamin D (Vit D) is known to be related the physical activities and comorbidities, there was a lack of evidence of their relationship in chronic kidney disease (CKD) patients.

Methods: Data were collected from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD, NCT01630486 at http://www.clinicaltrials.gov). Baseline serum 25-OH Vit D concentration was measured using chemiluminescence immunoassays in the central laboratory. Vit D insufficiency was defined by 25-OH vit D below 20ng/mL. We categorized patients into 3 groups (low, moderate, high physical activity level) according to their physical activity, quantified by the International Physical Activity Questionnaire. We used age-adjusted Charlson comorbidity index (CCI) for assessment of comorbidities, and divided into 2 groups based on ≥ 4 points of CCI or below. The associations were assessed by multivariate linear regression analyses with log-transformed 25-OH Vit D because of skewed distribution of 25-OH Vit D.

Results: A total number of patients with measurement of 25-OH Vit D was 1,133, among whom 925 patients reported physical activity. Median 25-OH vit D was 16.5 ng/mL in overall patients, 17.2 ng/mL in male, and 15.0 ng/mL in female. The proportion of 25-OH vit D insufficiency was 33.6%. Physical activity (P = 0.026) and age-adjusted CCI (P = 0.037) was independently associated with log 25-OH Vit D after adjustment for age, sex, diabetes, CKD stages, albumin, and season, respectively.

Conclusions: The results of this study suggest that 25-OH Vit D concentration is independently associated with self-reported physical activity and age-adjusted CCI in CKD patients.

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SA-PO877

Clinical Characteristics of Age Distribution in 496 Severe Secondary Hyperparathyroidism Patients Undergoing Parathyroidectomy

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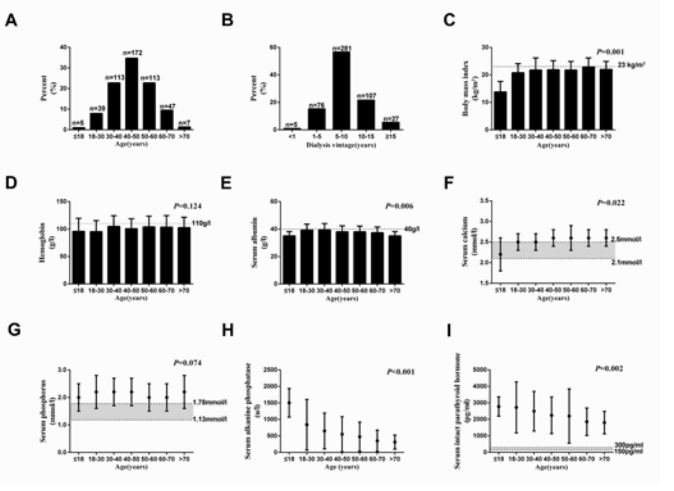
Background: Severe secondary hyperparathyroidism(SHPT) patients are characterized by systematic clinical manifestations and parathyroidectomy(PTX) is recommended for treatment, the relationships between age and clinical characteristics of severe SHPT are unknown.

Methods: Clinical baseline data were analyzed according to the stratification of age in retrospective study of 496 PTX patients from single centre.

Results: Clinical characteristics of patients were shown in table 1.

	Total (n=496)
Age(years)	46.0±11.4
Male/Female(n)	274/222
Body mass index(BMI, kg/m²)	21.8±3.6
Causes of ESRD(n,%)	
Chronic glomerulonephritis(CGN)	457(92.1%)
Diabetic nephropathy	6(1.2%)
Others	33(6.7%)
Dialysis mode(n,%)	
Hemodialysis	461(92.9%)
Peritoneal dialysis	35(7.1%)
Dialysis vintage(years)	7.7±3.6
Laboratory values	
Hemoglobin(g/l)	102.3±19.4
Hematocrit(%)	31.9±6.0
Glucose(mmol/l)	4.3±1.3
Creatinine(μmol/l)	877.3± 276.2
Urea(mmol/l)	22.4±8.3
Total cholesterol (mmol/L)	4.2±1.0
Triglyceride(mmol/l)	1.6±1.1
Albumin(Alb,g/l)	38.3±4.4
Calcium(Ca,mg/dl)	10.2±0.9
Phosphorus(P,mg/dl)	6.7±1.6
Alkaline phosphatase(ALP,u/l)	360.6(176.8-805.9)
Intact parathyroid hormone(iPTH,pg/ml)	2134.1(1512.4±2964.2)
Weight of resected parathyroids(g)	4.2±2.6

BMI, hemoglobin, and serum Alb levels in each group were <23 kg/m², <110g/L, and <40 g/L, respectively. Serum Ca, ALP, and iPTH levels were different among groups, while serum P wasn't. Serum iPTH and ALP were lower in elderly patients.



Higher serum iPTH were related with lower BMI and serum Alb in study population.

Conclusions: Young and middle aged groups are the major component of severe SHPT patients. Their majority etiology is CGN and serum iPTH level is a risk factor for malnutrition.

Funding: Government Support - Non-U.S.

SA-PO878

A Real-World Cost-Effective Analysis of Sevelamer versus Calcium-Based Binders for the Treatment of Hyperphosphatemia in Korean Dialysis Patients

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Background: Sevelamer, a non-calcium based phosphate binder, has been shown to attenuate the progression of vascular calcificationand improve survival in dialysis patients compared with calcium-based binders (CBBs). We conducted a cost-effectiveness analysis (CEA) comparing sevelamer with calcium acetate in dialysis patients using real-world data from the Health Insurance Review Agency (HIRA) database in Korea.

Methods: Data from 4674 patients enrolled in Korean multicenter prospective cohort study between Sep. 2008 and Dec. 2012 were linked to the HIRA database. After propensity score matching, the final dataset used in the CEA comprised 501 sevelamer-treated and 501 calcium acetate-treated patients. A Markov model was used to estimate costs, life years (LY), quality-adjusted life years (QALYs), and cost effectiveness. Forty-month treatment-specific survival was analyzed.

Results: Patients receiving sevelamer had lower mortality compared with patients receiving calcium acetate (HR, 0.64; 95% CI, 0.45–0.91; p=0.012). In the base case analysis, treatment with sevelamer was associated with a gain of 1.758 in LYs and 1.108 QALYs per patient compared with calcium acetate. The incremental cost effectiveness over a lifetime horizonwas acceptable at KRW (South Korean Won,₩) 6,966,350 per LY gained and ₩ 11,057,699per QALY gained for sevelamer compared with calcium acetate. One-way sensitivity analyses demonstrated that sevelamer was cost effective compared with calcium acetate across a wide range of alternative assumptions. Probabilistic sensitivity analysis showed that sevelamer was cost effective in 100% of the model iterations, using a willingness-to-pay threshold of ₩ 31,355,740 per QALY gained.

Conclusions: Sevelamer was associated with better survival and acceptable cost effectiveness in dialysis patients compared with calcium acetate. Treatment of hyperphosphatemia with sevelamer could serve as a cost-effective alternative treatment option to CBBs in dialysis patients in Korea.

SA-PO879

Shotgun Lipidomics Reveals Alteration of Acyl Chain Carbon Number and Unsaturation with Advancing Chronic Kidney Disease

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Background: Alteration in carbon number and double bonds in complex lipids are linked with poor outcome. Impact of chronic kidney disease (CKD) on such alterations has not been studied. We systematically determined abundance of lipids across different stages of CKD using mass spectrometry based shotgun lipidomics.

Methods: In a cross sectional observation, 214 CKD patients from stage 1 to 5 with available baseline clinical characteristics were selected from the Clinical Phenotyping Resource and Biobank Core (CPROBE). Lipids from plasma was extracted with modified Bligh-Dyer method carrying the extraction in a 2:2:2 volume ratio of water/methanol/dichloromethane, spiked internal standards, reconstituted in Buffer B (10% ACN and 90% IPA in 10mM ammonium acetate) and injected in ABSciex 5600 quadrupole time

of flight mass spectrometer. MS/MS spectra were obtained in electrospray positive and negative modes with Analyst TF software and processed with MultiQuant 1.1.0.26. Data were normalized, log2 transformed and z-score standardized. Mixed linear models were applied to test independent alteration of lipid abundance by acyl chain carbon number of double bond across various stages of CKD.

Results: The selected patients included 36 (16.8%), 99 (56.3%), 61 (28.5%), and 18 (8.4%) participants from stage 1 to stage 5, respectively. Using shotgun lipidomics we identified 330 compounds from 17 lipids. In stage 2, there was a significant linear increase in abundance of free fatty acids by number of double bonds and carbon numbers in acyl chains ($p=0.006$), a trend which was reversed in CKD stage 5, independent of any covariates ($p=0.002$). On the other hand there was a significant linear decrease in abundance of triacylglycerols, phosphotidylcholines, phosphtidylethanolamines (PE), LysoPE, cardiolipins, and cholesteryl esters by number of double bonds and carbon numbers is stage 2 ($P\leq0.02$), a trend which was revered in stage 5 ($p\leq0.035$), independent of other covariates.

Conclusions: We conclude that CKD stage is associated with dynamic alteration of acyl chain carbon number and double bonds which may have mechanistic implications on outcomes which should be studied in future investigation.

Funding: NIDDK Support

SA-PO880

Diffusion Tensor Imaging Demonstrated White Matter Structural Abnormalities in Hemodialysis Patients

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Background: Patients treated with dialysis have high rates of clinical stroke and structural brain disease. There are limited data regarding the presence of more subtle damage to white matter integrity.

Methods: In the Boston Dialysis Study, we compared brain magnetic resonance imaging (MRI) using a diffusion tensor imaging (DTI) protocol in hemodialysis (HD) patients to community dwelling persons without known kidney disease who underwent the same MRI protocol. Using a tract based spatial statistics (TBSS) software package, significant differences in Fractional Anisotropy (FA) and Mean Diffusivity (MD) between patients and controls were placed on a three dimensional skeleton highlighting white matter fiber tracts. Statistical comparison of each overlaid voxel was age controlled, using a permutation based corrected p value of <0.05.

Results: Thirty HD patients and twenty six controls had adequate imaging for analysis. Mean age was similar (52 vs 49 years for HD vs control). The HD group had fewer women (38% vs 23%), more African Americans (38% vs 23%), and a higher rate of diabetes (29% vs 8%). Hemodialysis patients had significantly lower FA across multiple white matter fiber tracts, with fronto-temporal lobes, genu of the corpus callosum and fornix more significantly affected than posterior parts of the brain.

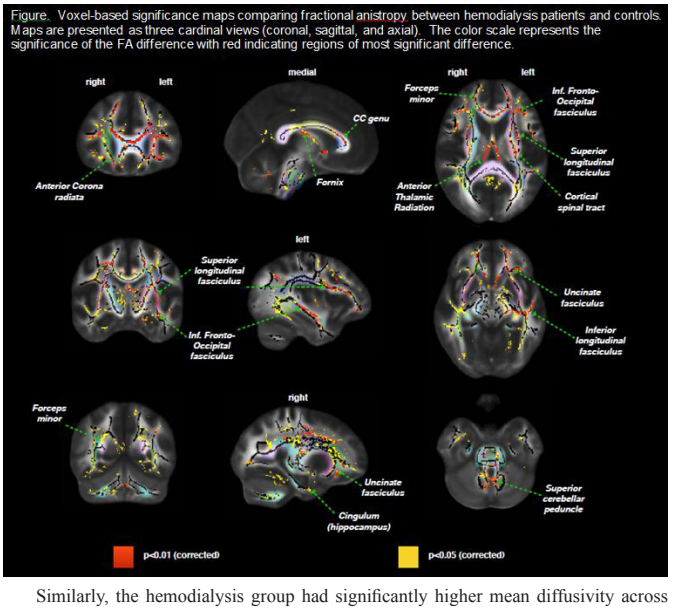

Figure. Voxel-based significance maps comparing fractional anistropy between hemodialysis patients and controls. Maps are presented as three cardinal views (coronal, sagittal, and axial). The color scale represents the significance of the FA difference with red indicating regions of most significant difference.

Similarly, the hemodialysis group had significantly higher mean diffusivity across multiple anterior brain regions.

Conclusions: Hemodialysis patients show loss of white matter integrity on DTI, more anterior than posterior, compared to those without known kidney disease. The pattern of injury may imply accelerating aging as it is most similar to that seen in elderly adults.

Funding: NIDDK Support

SA-PO881

Renal SCAN-ECHO and Renal e-Consults Improve Care and Value for Rural and Highly Rural Veterans Who Live Distant to Veterans Affairs Renal Specialty Care

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Background: Renal Specialty Care Access Network-Extension for Community Health Outcomes (SCAN-ECHO) is a provider-to-provider telemedicine program linking primary care providers (PCPs) with specialists. In 2010 the VA launched a form of consultations (i.e. non-visit consults or NVC) involving reviews of the electronic medical records by specialists. We evaluated differences in SCAN-ECHO, NVC, and traditional in-clinic consults (ICC) in a geographic area of the Pacific Northwest.

Methods: We reviewed patient demographics and characteristics of patients served through either renal SCAN-ECHO consults (n=105), NVCs (n=350) or ICCs (n=380). Patient rurality and driving distance to specialty clinic were established.

Results: Veterans served by SCAN-ECHO lived the furthest away and were more likely to be highly rural, followed by NVC, and ICC Veterans (see Table). The total number of round trip driving miles saved by SCAN-ECHO was 98,280, which represented $40,786 saved in travel reimbursement compared to 127,824 miles saved NVCs ($53,045).

VISN 20 Renal Consults FY15	SCAN-ECHO (n = 105)	Non-Visit (n = 350)	In Clinic (n = 380)
Average distance of patient to VA nephrologist	468 miles	182 miles	54 miles
% of patients living more than 300 miles from a VA nephrologist	43%	12.5%	1%
Total number of round trip miles saved ($ saved (0.415/mile))	98,280 ($40,786.20)	127,824 ($53,045.96)	N/A
% Rural/Highly Rural Veterans	68%/3%	40%/3%	32%/0%
% Female Veterans	11%	6%	4%
% Black Veterans	3%	11%	22%

Conclusions: VISN 20 Renal SCAN-ECHO and renal NVCs serve a more rural patient population that live further away from VA specialty care compared to ICCs. VA VA Telemedicine efforts improve specialty care access for rural veterans and save money. Future research should be directed towards assessing the impact of telemedicine initiatives on patient outcomes.

Funding: VA Support

SA-PO882

Telenephrology May Improve Rural Primary Care Provider (PCP) Satisfaction and Nephrology Care within Veterans Affairs

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Background: PCPs practicing in rural areas have more difficulty accessing specialty care for their patients and have been shown to report professional isolation, lack of access to professional development. As part of the Veterans Affairs (VA) Specialty Care Access Network-Extension for Community Health Outcomes (SCAN-ECHO) we launched a provider-to-provider Nephrology telemedicine consultation service to provide mentoring for PCPs who treat predominantly rural Veterans with renal disease.

Methods: We conducted an e-mail survey of VA-based PCPs (n=55) in the rural Pacific Northwest who attended a longitudinal Nephrology telemedicine program. We used a validated survey to assess provider measures.

Results: Most PCPs reported that the program increased their knowledge and competencies (92.8%), improved the quality of care for their patients (85.4%), improved coordination of care between PCPs and Nephrologists (72.7%), was useful in treating patients not discussed in the program (83.7%), felt that their participation was rewarding (94.5%) and felt more integrated into their local clinical team (54.5%). The majority of PCPs felt that Renal SCAN-ECHO increased their overall job satisfaction (67.3%) and they felt more connected to a community of practice (83.7%). 92% stated that they would recommend the program to a colleague. 60% of PCPs felt that SCAN-ECHO improved access to nephrology care for their patients. Participation in SCAN-ECHO led to an improvement in job satisfaction in 90% of rural PCPs vs 70% of urban PCPs. 80% of rural PCPs felt that SCAN-ECHO improved the quality of care for their patients (as compared to 58% urban PCPs).

Conclusions: A renal provider-to-provider Nephrology telemedicine service can be a rewarding experience that improves provider self reported knowledge, job satisfaction and quality of nephrology care in more rural areas. Future research is needed to study the effect of such an intervention on patient outcomes.

Funding: VA Support

SA-PO883

Telenephrology: An Effective Strategy for Improving Access and Opportunity of Nephrologist Evaluation of Primary Care Chronic Kidney Disease Patients Carlos Zuniga,[1,2,3,4] Maria Cecilia Riquelme,[1] Hans K. Müller,[2,3] Camila Andrea Astorga Parra,[1] Francisco J. Albornoz.[2,5] *[1]Health Service, Concepcion; [2]Health Service, Talcahuano; [3]Med School, Univ de Concepcion; [4]Medical School, Univ Catolica Sma Concepcion; [5]Medical School, Univ Andres Bello.*

Background: Chronic Kidney Disease (CKD) is a significant public health problem in Chile, leading to a great demand of unsatisfied renal consultations, which is worsened by a workforce shortage of nephrologists. This study assessed the impact of telenephrology (TN) to improve access and opportunity of care by renal specialist in a public health care network.

Methods: A retrospective cohort of TN asynchrony consults between 55 primary care providers (PCP) and 3 nephrologists in two cities of southern Chile, between Oct 2012 and May 2016 were analyzed. The main analyzed variables were: 1. Average response time versus historical response for in person consult; 2. Average invested time per consult/nephrologist; 3. Identification of patients in need of advanced care 4. User satisfaction questionnaire among PCP.

Results: 2256 consultations were included, (59 % females), mean age 69 years (15-96), CKD stage III (57%), IV (24%), V (4.5%). Average historical response time for traditional in person consult diminished from 195 days to 1 day for electronic consult; Invested time per consult/nephrologist diminished from 20 minutes for in person to 10 minutes for electronic consult. Following consultation, 1268 patients (56,2%) were sent back by the nephrologist to primary care with treatment advice and 988 patients (43,8%) were sent to renal outpatient evaluation for CKD predialysis stage and complex nephropathy. Additionally, at six month of TN implementation we reach No waiting list of referred renal patients. PCP rated 85% approval of the electronic model, highlighting the decreasing waiting time for consult, health network integration and continuous education.

Conclusions: The tele-consult model is an efficient method for improving access to nephrologist assessment, prompt treatment, selection of patients for specialized and complex care and optimizes the available time of nephrologist in an integrated network with PCP.

Funding: Government Support - Non-U.S.

SA-PO884

Implementation and Evaluation of Electronic Consultation in Nephrology Mallika L. Mendu, Gearoid M. McMahon, Sushrut S. Waikar. *Brigham and Women's Hospital, Harvard Medical School, Boston, MA.*

Background: The care of kidney disease patients is fragmented and poorly coordinated between referring primary care providers (PCPs) and nephrologists. Nephrology is a specialty that could embrace an electronic consultation (e-consult) model to improve the process of referral by facilitating communication and determining the need and urgency of a referral.

Methods: We conducted a pilot study to examine the impact of an e-consult system for patients with kidney-related conditions over the course of 15 months. Nephrologists (n = 2) reviewed questions submitted by PCPs (n = 49), and provided recommendations within an EHR-based platform. We sought to determine what types of kidney-related conditions were best suited for e-consults, as well as PCP and nephrologist satisfaction.

Results: 74 total nephrology e-consults were completed during the study period. The median time required for completion was 10 minutes for both provider groups. The most common kidney conditions leading to an e-consult were stage 3 CKD (16.2%), medication-related questions (13.5%), abnormal imaging findings (10.8%), electrolytes (9.5%), and proteinuria (8.1%). Satisfaction with the e-consult model was high among both nephrologists and PCPs (see Figure 1).

Figure 1. Nephrology and PCP satisfaction with e-consult tool

Survey Question	Nephrologists' Responses (N, %)	PCPs' Responses (N, %)
Did you feel that was an appropriate e-consult?		
Yes	60 (84.5%)	NA
No, in-person referral preferred	9 (12.7%)	NA
No, neither e-consult or in-person referral was warranted	2 (2.8%)	NA
Did the e-consult answer the clinical question you posed?		
Yes	NA	47 (95.9%)
No	NA	2 (4.1%)
If e-consult did not exist do you believe PCP would have sought informal or formal nephrology care?		
Yes	59 (83.1%)	NA
No	12 (16.9%)	NA
If e-consult did not exist would you have referred your patient to see a nephrologist?		
Yes	NA	27 (55.1%)
No	NA	22 (44.9%)
If e-consult did not exist would you have sought any informal nephrology advice via email or telephone?		
Yes	NA	29 (59.2%)
No	NA	20 (40.8%)
Do you feel confident that the patient can be managed without an in-person referral?		
Yes	46 (64.8%)	34 (69.4%)
No	5 (7.0%)	4 (8.2%)
In-person referral was recommended	20 (28.2%)	11 (22.4%)
How many minutes did you spend utilizing the e-consult for the patient?		
Median	10 (IQR 10, 15)	10 (IQR 5, 10)
Did you feel the e-consult was efficient?		
Yes	70 (98.6%)	47 (95.9%)
No	1 (1.4%)	2 (4.1%)

Conclusions: In this pilot of an e-consult for patients with kidney conditions, we found that utilizing e-consults was efficient, well received by both nephrologists and PCPs, and could improve the appropriateness of in-person nephrology referral.

SA-PO885

iConnect Care - A Web Based Chronic Kidney Disease Virtual Consultation Program Vishwas Raghunath,[1,2] Ivor Jonathan Katz.[1,2] *[1]Renal Medicine, St. George Hospital and Community Services, Sydney, New South Wales, Australia; [2]Univ of New South Wales, Sydney, New South Wales, Australia.*

Background: Specialists are overwhelmed with chronic kidney disease (CKD) patients, who can be managed in primary care (PC). Opportunistic screening of high risk (HR) CKD patients and follow-up in PC is the most sustainable form of CKD care. The iConnect Care CKD program provided a 'virtual consultation' (VC) instead of face to face (F2F) consultation.

Methods: A total of 70 patients were recruited from GP sites and Hospital clinics and followed for one year. The HR patients (eGFR< 30ml/min/1.73m^2 +/- albuminuria >30mg/mmol/L) were randomised to either VC or F2F. Patients were monitored every 6 months by a Clinical Nurse Specialist (CNS). The specialist team providing VCs comprised a Nephrologist, Endocrinologist, Cardiologist and a Palliative care Physician.

Results: Sixty one (87%) patients were virtually tracked or consulted with 14 (23%) of these being HR. At 12 months there was no difference in progress or outcomes in VC versus F2F groups nor a difference in low risk (LR) patients followed by CNS or GP. All were successfully followed. Software integration was challenging affecting enrolment. GPs reported high level of satisfaction and patients found the system attractive. VC consults occurred within a week and a second specialist opinion within another two.

Conclusions: The program allowed safe, quick and efficient consultation from multiple specialists. VC has a role to play in future patient care and ongoing evaluation is necessary.

Funding: Pharmaceutical Company Support - AMGEN Australia Research Grant

SA-PO886

Source and Content of Chronic Kidney Disease Videos on YouTube®: Stream with Caution Elizabeth Ortiz, Claudia M. Lora. *Univ of Illinois at Chicago.*

Background: Many individuals with chronic diseases use the internet to obtain health information. Recently, concerns have been raised about the content of this information on YouTube; the second most globally used internet site. YouTube videos related to pre-dialysis chronic kidney disease (CKD) have not been evaluated.

Methods: We identified 362 videos using the following search terms: "chronic kidney disease," "chronic kidney failure," "chronic renal failure," "chronic renal insufficiency," "kidney disease" and "kidney failure." We excluded videos that were not in English, did not relate to CKD in humans or were duplicates. We examined the source, target audience, the number of views and comments, and the content.

Results: We excluded 211 videos. Of the remaining 151, 20% were uploaded by universities and professional societies, 50% by commercial organizations, 7% by individuals without clear credentials, and 23% by individuals with CKD. Target audiences were patients (66%), students (5%), health care personnel (2%), or were unspecified (27%). The mean number of views was 96,323, and the mean number of comments was 20. Table 1 summarizes the content of the videos. A total of 36 (24%) videos contained misleading or incorrect information, and 73 (48%) videos marketed a non-evidenced based treatment for CKD. Specifically, 12 (8%) advertised an herbal supplement for CKD.

Conclusions: Most YouTube videos on CKD are uploaded by commercial organizations and target a patient audience. A large number of videos included misleading information or advertised treatments that could be harmful in CKD. Patients should be cautioned about using YouTube as a source of health information. Future studies need to examine YouTube as an intervention aimed at improving knowledge of CKD.

Table 1. Content of YouTube Videos Related to CKD, n=151

Topic	n(%) of videos
Kidney Functions	41 (27)
Diagnosis	25 (17)
Symptoms	29 (19)
Treatment	75 (50)
Dietary Modification	53 (35)
Complications	90 (60)

Funding: NIDDK Support

SA-PO887

Tracking Health Behavior Using Google Analytics: A New Clinical Investigative Tool Stephanie W. Ong,[1] Kelly Min,[1] Akib Uddin,[2] Sarbjit Vanita Jassal,[1] Emily Seto,[2] Alexander G. Logan.[1] *[1]Nephrology, Univ Health Network, Toronto, ON, Canada; [2]Centre of Global eHealth Innovation, Univ Health Network, Toronto, ON, Canada.*

Background: We have developed and tested an integrated smartphone app system for advanced CKD, which allows patients to track blood pressure (BP), medications, symptoms and lab tests and have access to CKD care resources and provider contact information. Results suggest improved outcomes; however its effect on health behaviors remains unknown. Google Analytics (GA) can track interactions with electronic devices, and thus evaluate health behaviors. In this study we evaluated the app's features using GA.

Methods: GA was used to determine the frequency of visits to each feature and the pattern of use over a 6-month period. At exit, participants were interviewed about usability and feasibility of the app, and the results were correlated with GA usage.

Results: Patients (n=45) used the app consistently throughout the study. There were 33,085 unique views with the total time spent per person averaging 8.1 hours. BP was the most utilized feature, followed surprisingly by laboratory results as most participants had tests done at baseline and once or occasionally twice during the study, and then by medications. The use of the symptom feature was infrequent, even though patients were asked to complete the symptom checklist at a minimum month and more often if symptomatic. The CKD resources and contact features were rarely used. Pattern analysis revealed multiple unexplained spikes in use of the BP feature. In exit interviews (n=38) patients stated that BP and labs were most useful features due to their interactive nature and supportive feedback, while many questioned the value of tracking symptoms as it lead to few changes in treatment.

Conclusions: GA is a valuable and inexpensive tool that may help clinicians track, and better understand, changes in health behaviors over time. Apart from tracking feature use, GA provides insights into which features patients are most likely to use and which do not provide enough value and may require redesign. It also raises questions about clinical correlates to changes in the pattern of use.

Funding: Government Support - Non-U.S.

SA-PO888

Racial Disparities in Cardiopulmonary Resuscitation Knowledge in Chronic Kidney Disease Patients due to Low Health Literacy

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Background: Patients (pts) with chronic kidney disease (CKD) experience poor survival after receiving cardiopulmonary resuscitation (CPR). Minority CKD pts also receive CPR more often than other racial groups. Low health literacy (HL) affects one's ability to understand health information to make appropriate health decisions and disproportionately affects minorities. As low HL affects up to 32% of CKD pts, we investigated whether HL mediates racial disparities in CPR knowledge.

Methods: Cross-sectional study of CKD pts in nephrology clinics affiliated with two academic centers in Boston, MA. Inclusion: age ≥ 45 years, English-speaking, Black or White race and, Stage 4 or 5 CKD (defined by eGFR < 30 ml/min/1.73m^2). Exclusion: listed for kidney transplantation or history of dementia. An 8-item multiple choice CPR knowledge survey was administered. HL was assessed via the Rapid Estimate of Adult Literacy in Medicine (REALM).

Results: 149 pts completed the study.

	Total (N=149)	Black (N=62)	White (N=87)	P - value
Mean age,years (± SD)	68 (± 11)	66 (± 11)	70 (± 10)	0.02
Low HL	34	63	14	<0.01
CPR knowledge items (% pts with correct responses)				
Cardiac arrest	46	39	52	0.12
CPR purpose	84	77	89	0.07
Physical trauma	43	34	49	0.06
Respiratory failure	**48**	**31**	**60**	**<0.01**
Mechanical ventilation	81	77	83	0.42
Speaking while intubated	**44**	**31**	**54**	**<0.01**
Post-CPR survival	6	8	5	0.38
Daily activities post-CPR survival	60	60	60	0.99
Mean summary percentage score (± SD)	**51 (± 20)**	**45 (± 19)**	**56 (±20)**	**<0.01**

Blacks and Whites differed on HL and CPR knowledge in unadjusted and multivariate analyses adjusted for age, education, income, and comorbidities. The addition of HL to this model revealed mediation with HL - and not race - that was related to CPR knowledge.

Conclusions: Overall CPR knowledge is low among CKD pts. CPR knowledge is lower for Blacks than for Whites, but this difference is mediated by HL. Future CPR educational interventions should target HL barriers to improve decision-making and decrease racial disparities for CKD pts.

Funding: NIDDK Support, Private Foundation Support

SA-PO889

The Portal Patient in Kidney Disease: One Center's Experience on Who Uses Health Portals and How

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Background: Patient health portals are increasingly promoted to facilitate chronic disease management. It remains unclear which patients routinely access portals and what information they seek as most relevant to chronic kidney disease (CKD) care.

Methods: Adults with CKD Stages 1-5 were enrolled to take a cross-sectional survey from April 2015-May 2016. We asked patients if they used the Internet to learn about kidney disease, whether they used the patient health portal, and if so, which features they utilized. To examine for associations between demographics and item responses we used logistic regression.

Results: 202 patients enrolled with a mean (SD) age 59 (16) years. 48% were men, 78% Caucasian, 17% African American (AA), 73% CKD Stage 3-5, 51% had an annual income > $50K, and 95% had ≥ H.S. education. 128 (63%) used the Internet to learn about CKD. 127 (63%) utilized the portal to: 89% - check lab results, 76% - view/request appointments, 74% - send messages to providers, 74% - view personal health history, and 59% - review/request prescription changes. Patients with income >$50K were more likely (OR 2.50 p<0.01) to use the portal compared to those of lower income. After adjustment for age, sex, race, income, education, and CKD stage, this association was diminished and older patients were found less likely to use the portal (OR 0.97 p=0.02). Older patients (OR 0.97 p<0.01) were less likely, and patients with annual income > $50K (OR 3.27 p<0.01) and more advanced CKD (OR 2.42 p=0.02) more likely, to use the Internet to learn about CKD. In adjusted analysis, these associations remained significant [older (OR 0.94 p<0.01), annual income > $50K (OR 6.90 p<0.01) and more advanced CKD (OR 3.54 p=0.02)].

Conclusions: Portals offer benefits to communication and care, but older patients and those of lower income may be less likely to reap these benefits. Future work must ensure health portals are useful and accessible to all patients with CKD.

Funding: NIDDK Support

SA-PO890

Disparities in Patient Reported Barriers to Optimal Self-Management for Chronic Kidney Disease

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Background: Patient self-care is critical to chronic kidney disease (CKD) management. The study goal was to determine barriers that impact patients' ability to practice healthy behaviors.

Methods: 202 adults with CKD Stages 1-5 completed a cross-sectional survey between April 2015-May 2016. Patients rated how often barriers got in the way of keeping their kidneys healthy; scale from 0=never to 3=almost all the time. Topics included: lack of psychosocial support, poor communication with providers, lack of resources/motivation for healthy behaviors, and low knowledge. We used linear regression to examine associations between demographics and ratings.

Results: Mean (SD) age was 59 (16) years, 48% were male, 78% Caucasian, 17% African American (AA), 73% had CKD Stage 3-5, 51% had an annual income > $50K, and 95% ≥ H.S. education. Ratings ranged from mean (SD) 0.28 (0.63) [poor communication with doctor(s)] to 1.10 (0.96) [not having motivation to exercise]. 31% rated not having motivation to exercise and 29%, not being healthy enough to exercise, as most frequent barriers. In univariate analysis, annual income < $25K was significantly associated with 9 out of 10 barriers and many remained significant after adjusting for age, sex, race, income, CKD stage, and education: lack of social support (β=0.40 p=0.04), insurance situation (β=0.37 p=0.04), poor access to fresh foods (β=0.25 p=0.01), low income (β=0.91 p<0.01), low motivation to exercise (β=0.53 p<0.01). Although most felt poor communication with doctors was not a barrier, AA race (β=0.31 p<0.01) and income < $25K (β=0.21 p=0.04) were associated with perceiving this as a barrier more often, and were significant after adjustment [AA race (β=0.45 p<0.01), income < $25K (β=0.36 p=0.02)].

Conclusions: Barriers to healthy behaviors are reported more often in those most vulnerable to CKD progression. Future efforts must focus on more support and improved communication for minority and low income patients.

Funding: NIDDK Support

SA-PO891

Quantitative Analysis: What Patients Want from Kidney Disease Education

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Background: Chronic kidney disease (CKD) patients often lack understanding of their disease, treatment options, and the potential for disease progression. The study purpose was to understand patients' wants and needs for CKD education.

Methods: 202 adults with CKD Stages 1-5 completed a cross-sectional survey between April 2015-May 2016. Questions focused on: Barriers to using current education materials (10 sub-topics with yes/no response), desired educational content (21 sub-topics rated 0=less important to 4=more important), preferred timing to use materials, and design of materials (4 sub-topics rated 0=not a helpful to 4=extremely helpful).

Results: Mean (SD) age was 59 (16) years. 48% were male, 78% Caucasian, 17% African American, 73% had CKD Stage 3-5, 51% had an annual income > $50K, and 95% had ≥ H.S. education. The most common barriers to using current education materials included too little information provided (36%) and content perceived as too general (33%). Topics rated most important to include in future materials were medications that can hurt kidneys [mean (SD) rating 3.7 (0.7)], foods to avoid with advanced CKD [3.6 (0.7)], treatment options for kidney failure [3.6 (0.7)] and explanations about how CKD progresses [3.6 (0.8)]. Descriptions of other patients' experiences with CKD was ranked

lowest [2.5 (1.3)]. 28% wanted to review education materials prior to doctor visits and 46% wanted to use them in combination (before, during and after visits). Suggestions from providers was rated highest to include in material design [mean (SD) rating 3.3 (0.8)], followed by tips for communicating with doctors [3.2 (1.1)], use of charts/graphs/tables [2.2 (1.3)] and descriptions of others' experiences [2.2 (1.3)]. 53% were willing to review materials for ≤ 30 minutes.

Conclusions: This study suggests current education materials are deficient in patient individualization and details. Improved education materials should strive not to be too burdensome on patients' time.

Funding: NIDDK Support

SA-PO892

Illness Experience of Undocumented and Emergently Dialyzed Hispanics

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Background: Undocumented US patients with end-stage renal disease (ESRD) do not have access to routine dialysis in Colorado. At Denver Health, undocumented patients with ESRD are admitted to the hospital for two consecutive days of emergency-only dialysis when they present critically ill. The purpose of our study was to describe their illness experience.

Methods: We conducted a qualitative, descriptive study, using semi-structured interviews with undocumented Hispanic adults with ESRD. The interview guide utilized open-ended questions to elicit the symptom burden and personal impact of emergency-only dialysis. Interviews were audio-recorded, transcribed verbatim, and analyzed by three members using an inductive approach.

Results: We interviewed 20 undocumented Hispanics with ESRD between August 2015 and March 2016. Participants speak primarily Spanish, live below the poverty line, and have resided in the US for over three years. Four themes were described: escalating symptoms, imminence of death, burden of being undocumented, and family. Patients go an average of 6-7 days between dialysis sessions and thus describe the escalating symptoms during the last 3 days of the week leading up to their emergency department visit. Patients risk being turned away and not receiving dialysis when they present before they are critically ill so they must wait for the sensation of 'drowning.' Patients also describe the sense that death is imminent because they suffer several near death experiences with many describing previous cardiopulmonary resuscitation for arrhythmias. Expressing fears that they will not survive, many say their 'last goodbye' to their family prior to each hospital admission. Patients describe a great burden in being undocumented because they do not receive pre-dialysis care and have a willing family kidney donor yet no transplant benefits. Their lack of access to care also impacts their family such that they describe protecting their family by hiding their escalating symptoms to prevent further distress.

Conclusions: Patients describe significant personal and family distress as a result of lack of access to care.

Funding: Private Foundation Support

SA-PO893

High Moral Distress in Health Care Providers Providing Care to Undocumented Immigrants Needing Dialysis

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Background: No national standards exist for chronic dialysis in undocumented immigrants posing a unique ethical dilemma for providers.

Methods: Cross Sectional Internet Survey in April 2016 of Nephrology, ICU, ER, IM, Palliative Care nurses and physicians at a safety-net hospital. Survey was developed in collaboration with center for Ethics; it employed the Moral Distress thermometer to score moral distress on a scale of 1 to 10, with 10 representing higher distress. Predictors:Specialty, Age, Years in practice, patient encounters, and Education in Bioethics.

Results: 299 out of 765 participants completed the survey. 47% were nurses; the remaining were physicians from multiple specialties. 48% had >20 patient encounters with undocumented immigrants needing dialysis in the last year. Score distribution was skewed: 48% reported intense to severe moral distress and 33% none to mild. This pattern was observed across each specialty; median score for the entire cohort was 6 (95%- 2,9). Younger providers (<40 years old) and trainees reported a significantly higher score. No differences were found between nurses and physicians, specialties, gender, no. of patient encounters and education in bioethics. More than 70% of respondents attributed their distress to suffering of patients due to inadequate dialysis and tension between what is considered ethical and what the law allows or forbids; 78% quoted the patients' quality of life to be worse than the average citizen with ESRD. Among Nephrologists, caring for these patients led to moral distress levels similar to that of dealing with a violent dialysis patient. Venting, team approach to patient care and withdrawing from situation were predominant coping mechanisms.

Conclusions: Provision of inadequate dialysis causes significant moral distress in providers from all specialties involved in the care of undocumented immigrants; younger providers and trainees being particularly at risk for burnout and detachment. Legal and fiscal policies need to be balanced with the strong ethical and moral commitments providers have for ensuring quality standard of care to all patients.

SA-PO894

Gender Disparities in Cardiovascular Outcomes and Mortality in Persons with Chronic Kidney Disease

Ana C. Ricardo, Wei Yang, Lawrence J. Appel, Esteban A. Cedillo-Couvert, Jing Chen, Rajat Deo, Marie Krousel-Wood, Anne Frydrych, Mahboob Rahman, Sylvia E. Rosas, Daohang Sha, Jackson T. Wright, Martha L. Daviglus, James P. Lash. *On Behalf of the Chronic Renal Insufficiency Cohort (CRIC) Study Group.*

Background: Data from general populations indicate that cardiovascular events are less common in women than men, but studies of individuals with chronic kidney disease (CKD) are limited and less conclusive. We evaluated gender-related disparities in cardiovascular events and all-cause mortality in adults with CKD.

Methods: This was a prospective, longitudinal study of 1778 women and 2161 men enrolled in the CRIC Study (mean age 58 years, 42% non-Hispanic white, 42% non-Hispanic black, 13% Hispanic, and mean estimated glomerular filtration rate [eGFR] 45 ml/min/1.73m^2 at entry). Using Cox-proportional hazards models, we investigated the association of gender (women vs. men) with adjudicated atherosclerotic events (myocardial infarction, stroke or peripheral arterial disease), incident heart failure and all-cause mortality.

Results: Over a median follow-up of about seven years, we observed 585 atherosclerotic, 638 heart failure, and 853 death events. The table below summarizes multivariable analyses results.

Outcome	HR (95% CI)* Women vs. Men	P value interaction Gender*Age	P value interaction Gender*Diabetes
Atherosclerotic events	0.64 (0.52-0.79)	0.13	0.77
Heart failure		0.23	0.04
Diabetes	0.86 (0.69-1.09)		
No Diabetes	0.58 (0.40-0.82)		
All-cause mortality	0.59 (0.48-0.72)	0.19	0.92

*Adjusted for clinical site, age, race/ethnicity, education, marital status, nephrology care, health insurance, systolic blood pressure, diabetes, history of cardiovascular disease, smoking status, physical activity, body mass index, LDL cholesterol, ACEi/ARB, aspirin and statin use, baseline eGFR, proteinuria, serum FGF23, calcium and phosphorus.

Conclusions: In this large and diverse CKD cohort, women had lower risk of atherosclerotic events and death than men. Among participants without diabetes, women were less likely to experience a heart failure event.

Funding: NIDDK Support

SA-PO895

A Mapping Study of Dialysis Patients' Perceptions of Kidney Transplantation

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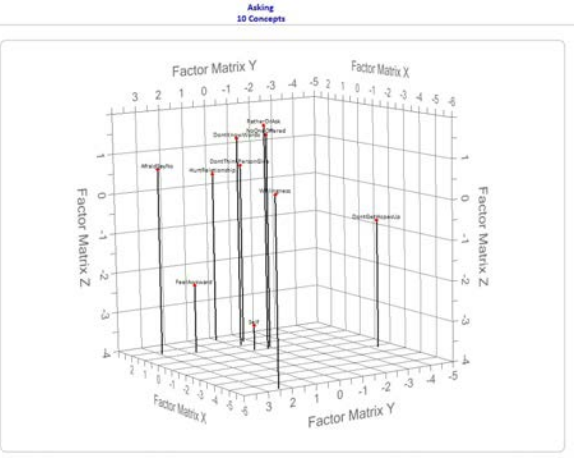
Background: Kidney transplantation remains the preferred treatment modality for patients with end stage renal disease, but continues to be underutilized. While previous studies have identified barriers to transplantation, to date no research has explored the relationships between patients' unique perceptions of transplant-related barriers and facilitators.

Methods: We employed perceptual mapping techniques (multidimensional scaling and vector modeling) to understand and visualize patient-level barriers and facilitators to living and deceased donor kidney transplantation. These methods generate 3-dimensional maps of transplant-related concepts, which can be used to inform message strategies aimed at increasing patients' interest in transplantation and pursuit of living donors.

Results: Preliminary findings of data collected via an online survey suggest that patients (n=30) consider themselves well informed, and understand the pros, cons and long-term effects of transplantation. However, patients were most concerned by the anticipated pain associated with the transplant surgery and the potential for being placed back on dialysis. With regard to living donation, perceptual maps revealed fears of troubling and feeling indebted to the donor as well as fears of becoming hopeful and having potential donors decline to donate.



Conclusions: Although data collection is ongoing, interim findings indicate that certain concepts may be instrumental to moving patients along the path to kidney transplantation. Specifically, messages highlighting the severity of kidney disease and countering the emotional aspects of making requests for living donation with instruction on how to effectively pursue this treatment option are needed.

SA-PO896

Patient Preferences for End-Stage Renal Disease Management Eric Finkelstein,[1] Semra Ozdemir,[1] Chetna Malhotra,[1] Lina Choong,[2] Gan Sheryl Shien Wen,[2] Lydia Lim Wei Wei,[2] Andy Sim Gim Hong,[2] Tazeen H. Jafar.[1] *[1]Duke-NUS Medical School, Singapore; [2]Singapore General Hospital, Singapore.*

Background: For very elderly (age 75+) end-stage renal disease (ESRD) patients with multiple comorbidity, there is little expected survival and quality of life (QoL) benefits for dialysis compared to conservative management (CM). Dialysis is also costlier compared to CM. Despite this, dialysis is the most common management option for very elderly ESRD patients including those with co-morbidities in Singapore. To better understand the high dialysis uptake rate, we aimed to investigate the patient level factors influencing decision to choose dialysis or CM.

Methods: We administered a discrete choice experiment survey to 250 Stage 3b-5 chronic kidney disease (CKD) pre-dialysis patients aged >65 years visiting outpatient clinics of the Renal Medicine Department of the largest hospital in Singapore. Prior to the DCE, patients were asked to provide their best estimate of survival for a hypothetical patient with similar health problems as themselves, and their expected QoL and cost if they undergo dialysis and CM. They were then asked a series of hypothetical choice tasks that varied by expected survival, QoL, out-of-pocket cost, and treatment type and asked to choose the one that most appealed to them should they be faced with this decision.

Results: Patients were on average aged 74 (SD=6) years, mostly males (65%) and with average CKD-Epi eGFR of 23.7 (SD=10.5) ml/min/1.73m^2. Over 60% of patients could not provide an estimate of expected survival under any treatment option. Over 40% could not provide an estimate of the expected costs of dialysis or CM, although 66% expected dialysis to be costlier. 60% reported that CM offers better QoL. Expected survival, QoL, cost and treatment type were significant predictors of patient treatment choices. On average, CM was preferred over a form of dialysis for the management of ESRD.

Conclusions: Findings suggest that most elderly patients with advanced CKD were unaware of key factors that should be considered in the decision making process for dialysis or CM. However, despite this knowledge gap, a majority had a clear preference for CM. Future efforts should be made to inform patients on these factors.

SA-PO897

Identifying Factors That Influence Physicians' Recommendations for Dialysis and Conservative Management Eric Finkelstein,[1] Semra Ozdemir,[1] Chetna Malhotra,[1] Tazeen H. Jafar,[1] Lina Choong.[2] *[1]Duke-NUS Medical School Singapore, Singapore; [2]Singapore General Hospital, Singapore.*

Background: For elderly end-stage renal disease (ESRD) patients with multiple comorbidities, dialysis may offer little survival benefits compared to conservative management (CM). Dialysis patients also incur greater costs and greater rates of hospitalization, and lower life satisfaction. Yet, many elderly ESRD patients receive dialysis when it is available. This might be partly due to physician recommendations on treatment choice. Yet the factors that influence these recommendations remain largely unknown.

Methods: We surveyed physicians who attended the 9th Asian Forum of Chronic Kidney Disease Initiative conference to understand factors that influence physicians' recommendations for managing ESRD. We used vignettes that vary by age and comorbidity status, and asked physicians to predict survival of hypothetical patients undergoing dialysis or CM. We then asked them to choose whether they would recommend dialysis or CM for a hypothetical patient with that profile. We also compared the physician's recommendations for patients to what they would recommend for themselves if they were diagnosed with ESRD.

Results: On average, physicians believe that dialysis extends life relative to CM. Yet, many believe that CM confers *greater* survival. Estimates range from 17.3% (for a vignette depicting a 65 year old with diabetes and CHF) to 50% for vignettes depicting patients with advanced cancer. Results further reveal high discordance in treatment recommendations. For a 65 year old with diabetes, 62% recommended dialysis. For those with advanced cancer, 25% recommended dialysis. Those who were more optimistic about the ability of dialysis to extend life were far more likely to recommend it to their (hypothetical) patients. Physicians were far *more* likely to recommend dialysis for themselves than for their patients.

Conclusions: This study suggests that physicians would benefit from a greater understanding of the survival benefits of dialysis and CM for elderly patients with different comorbidity profiles. This information could then be used to better inform patients to ensure that they receive treatment most consistent with their preferences for care.

SA-PO898

Barriers and Facilitators to Chronic Kidney Disease Patient Education as Perceived by Primary Care Physicians: A Qualitative Study Varun Agrawal, Sandeep S. Soman, Clarissa Jonas Diamantidis, Michelle M. Estrella, Kerri L. Cavanaugh, John Sperati, Khaled Abdel-Kader, Bernard G. Jaar, Michael J. Choi, Mark A. Perazella, Yang Liu, Raquel C. Greer. *NKF Education Committee, NY.*

Background: Education of patients with chronic kidney disease (CKD) in nephrology practice is associated with improved dialysis readiness. Little is known as to how primary care physicians (PCPs) view their role in education of CKD patients.

Methods: We conducted 4 focus group interviews of PCPs in 4 US cities to determine challenges and possible solutions to providing CKD education in primary care. A questionnaire was administered to assess comfort with education of patients with CKD. A trained moderator conducted group discussions using standardized open-ended questions. Two independent abstractors coded the transcribed recorded interviews and identified major themes.

Results: 32 PCPs were interviewed and most (85%) were in private practice. While many PCPs felt comfortable educating patients about CKD (84%), only about half had resources to assist with education on CKD (56%) or hypertension (50%). Even fewer had patient education tools for CKD complications such as anemia (25%), bone disorders (25%), or hyperkalemia (28%). PCPs identified numerous barriers to CKD education at various levels of healthcare, including the patient level (low public awareness of CKD, lack of CKD-specific symptoms and patient's fear of dialysis) and the provider and healthcare system levels (complexity of CKD educational concepts, lesser emphasis on CKD as compared to other medical conditions at the clinic visit, lack of ancillary support to provide CKD education and limited time). Strategies suggested by the PCPs to facilitate CKD patient education included raising public awareness of CKD, better tools to facilitate patient involvement in CKD care, and nephrology referrals.

Conclusions: While many PCPs felt comfortable educating patients about CKD, they identified numerous barriers to CKD education. Education programs in primary care that enhance patient awareness and knowledge of CKD in the non-dialysis stage, possibly with effective educational tools and nephrologist collaboration, may improve patient's self-management and outcomes.

Funding: NIDDK Support, Private Foundation Support

SA-PO899

Abstract Withdrawn

SA-PO900

Primary Care Providers' Perceptions of Barriers to Management of Chronic Kidney Disease: A Qualitative Study John Sperati, Sandeep S. Soman, Michelle M. Estrella, Yang Liu, Clarissa Jonas Diamantidis, Mark A. Perazella, Khaled Abdel-Kader, Kerri L. Cavanaugh, Varun Agrawal, Bernard G. Jaar, Michael J. Choi, Raquel C. Greer. *NKF Education Committee, NY, NY.*

Background: Primary care providers (PCPs) care for the majority of patients with chronic kidney disease (CKD), yet there are missed opportunities for optimal care. This study aims to further identify the causes.

Methods: We conducted 4 PCP focus groups (n=32) (Baltimore, MD, St. Louis, MO, Raleigh, NC, & San Francisco, CA) to identify barriers to PCP management of CKD. A questionnaire was administered to obtain PCPs' demographics, practice characteristics, and comfort with management of patients with CKD. Standardized, open-ended questions developed by the authors were used to identify PCPs' perceived barriers to management of CKD, as well as tools to facilitate improved CKD care. Groups were audiotaped and transcribed verbatim. Two investigators independently coded concepts addressed during the discussions, which were categorized into major themes.

Results: 45% (n=14) of PCPs surveyed reported not following CKD guidelines. Most PCPs (n=27, 84%) felt comfortable managing patients with CKD, but many were uncomfortable managing specific complications of CKD such as anemia (n=14, 44%), bone disorders (n=16, 50%), and acidosis (n=22, 69%). PCPs cited a lack of tools to manage specific complications of CKD (19-69%) and a lack of educational resources for patients (44-78%). Other significant barriers identified spanned patient (*e.g.*, low awareness of CKD and poor adherence to treatment recommendations), provider (*e.g.*, staying current with CKD guidelines), and system levels (*e.g.*, limited time and reimbursement for complex patients). PCPs desired electronic prompts, lab decision support, medical homes, concise guidelines, PCP education, improved compensation, patient access to self-monitoring tools, and better insurance coverage as tools to facilitate CKD management.

Conclusions: PCPs experience substantial barriers in providing care to patients with CKD. Interventions to address these barriers and increase implementation of facilitative tools may improve PCPs effectiveness and capacity to care for CKD patients.

Funding: NIDDK Support, Private Foundation Support

SA-PO901

Advantages of Nutrition Counseling in CKD Patients by a Professional Dietician on the Physical or Psychological State Atsushi Ueda,[1] Aki Hirayama,[2] Kunihiro Yamagata.[3] *[1]Hitachi General Hospital, Japan; [2]Tsukuba Univ of Technology, Japan; [3]Univ of Tsukuba, Japan.*

Background: In Japan, most of chronic kidney disease (CKD) patients go to a clinic. However, it is frequently observed that the patients going to a clinic don't have access to good nutrition counseling. This lack of opportunity is usually due to the absence of a national registered dietician the clinic. To solve this problem, we dispatched a national registered dietician to a clinic and subjected CKD patients to nutrition counseling. This study evaluates the advantages of this nutrition counseling method.

Methods: The studies group consisted of 46 (male31, female15) patients with CKD stage2~4, age 54-87 (average 70). Nutrition counseling was performed twice within 3 months, and each session lasted 30 minutes. A dispatched a national registered dietician used an iPad including original nutrition counseling software and a textbook. During the session, we first identified the main issues such as obesity, salt restriction, protein restriction or potassium restriction, according to the patients' health. We then accordingly issued specific nutrition instructions. Finally, we examined the patient's status, several laboratory data and the behavior modification stage (BMS) by using the transtheoretical model. The previous factors were examined before the first session of counseling and also two months after the second session of counseling. Furthermore, we linked the different BMS to the patient's status and various laboratory data.

Results: Obesity counseling (34%, 16/46), salt restriction (23%, 10/46), protein restriction (11%) or potassium restriction (5%) counseling were issued. In general after counseling, the BMS improved remarkably. Body mass index (BMI) and HbA1c decreased significantly in the group with improved BMS. BMI also decreased significantly in the group with diabetic nephropathy.

Conclusions: This counseling method using an iPad and a textbook by professional dieticians is effective in improving the stage of behavior change, BMI and HbA1c in CKD patients. Therefore, our study demonstrates that the delivering on-demand of nutritional counseling may be useful for preventing the physical or psychological deterioration in CKD patients.

SA-PO902

Utilization of Medical Nutrition Therapy in Patients with Non-Dialysis Chronic Kidney Disease Jennifer K. Bond, Ruth Kafenztok, Kavitha Vellanki, David J. Leehey, Vinod K. Bansal, Anuradha Wadhwa, Julia Schneider, Benjamin Ling, Holly J. Kramer. *Nephrology and Hypertension, Loyola Univ Medical Center, Maywood, IL.*

Background: Medical nutrition therapy (MNT) has been associated with slower progression of chronic kidney disease (CKD). As of January, 1 2011 the Patient Protection and Affordable Care Act allows Medicare to fully cover recommended preventive services that were only previously covered through cost-sharing, including MNT. Medicare beneficiaries with diabetes and non-dialysis CKD stage 3-5 may receive MNT with no out of pocket costs. Many private insurers also cover MNT services with no out of pocket patient costs. The objective of this study was to examine the utilization of MNT services by a cohort of patients with non-dialysis CKD receiving care at Loyola clinics from 2009-2015 and determine if MNT utilization increased after implementation of the Affordable Care Act.

Methods: Data were obtained from Loyola University Medical Center's EMR. The patient population was limited to adults with non-dialysis CKD (ICD-9 codes 585.3-585.4) receiving continued care in Loyola nephrology clinics. Utilization of MNT for each year was identified by billing codes: 97802-97804, G0270, G0271, G0447, G0473, S9449, S9452, S9470, G0108 paired with a charge (58139510) or procedure code (5110403) for MNT. Co-morbid conditions identified by ICD-9 codes. Generalized estimating equation models were used to assess temporal differences in MNT utilization (years 2009-2010 vs. 2011-2015) adjusting for the demographics.

Results: A total of 334 adults with CKD, mean age of 69.3 years, were identified. Overall, 56.0% male , 26.7% black, 6.9% Hispanic, 65.3% white. Obesity, diabetes and coronary artery disease were present in 46.7%, 56.6% and 37.4%, respectively. Medicare and private insurance was primary insurance for 63.2% and 31.1%, respectively. During the 6 year follow-up, 80.2% had no MNT, 8.7% had 1 MNT visit and 11.1% had 2 or more MNT visits. No significant difference in MNT utilization was noted by time period (p=0.3).

Conclusions: In conclusion, MNT utilization is low at our institution. Future studies should examine potential barriers for MNT utilization in patients with non-dialysis dependent CKD.

SA-PO903

Diabetes and Kidney Disease Specific Health Literacy in Urban and Reservation Based Native Americans Vallabh O. Shah,[1] Stephens Lancer,[2] Chistopher Aston,[2] Donica M. Ghahate,[1] Jeanette Bobelu.[1] *[1]Univ of New Mexico; [2]Univ of Oklahoma.*

Background: Health literacy (HL) is a measure of a patients' ability to read, comprehend, and act on medical information to make appropriate health decisions. Poor HL is disproportionately burdensome on vulnerable populations, such as Native Americans. Little is known about the extent to which HL affects clinical health outcomes including diabetes and kidney disease in reservation based vs non-reservation based Native Americans (NA).

Methods: We conducted a HL survey using validated instrument in Zuni reservation based (n=200) and Oklahoma (n=200) non-reservation based Urban NAs.

Results: HL regarding diabetes and kidney disease was significantly higher in NM (reservation) compared to OK (non-reservation) NAs. However it did not differ between diabetics and non-diabetics. HL varied significantly with age, education and work status both within state and within diabetic status, but not with gender, or with propensity to speak a tribal language. HL was significantly higher in younger participants, those with higher levels of education, and those employed rather than unemployed. Those with complications due to diabetes, such as kidney disease, neuropathy or eye disease, tended to have lower HL than those that did not have complications, suggesting lower HL may lead to poorer preventive care. On the other hand, those with one or more family members with complications due to diabetes tended to have higher HL than those that did not have such family members, suggesting affected family members were a motivation for improving HL.

Conclusions: Reservation based NAs had significantly higher health literacy regarding diabetes and kidney disease than non-reservation based NAs, however, this did not translate into improved (lower) prevalence of diabetes or its associated complications. Higher health literacy appeared to be a consequence rather than a preventative of diabetes or its associated complications.

Funding: Other NIH Support - NIGMS, Other U.S. Government Support

SA-PO904

Veterans Affairs (VA) eKidneyClinic: Addressing Chronic Kidney Disease Health Literacy Gap Devasmita Choudhury,[1] R. Brooks Robey,[2] Rose Mary M. Pries,[3] Dorian R. Schatell,[4] Susan T. Crowley.[5] *[1]Medicine, Salem Veterans Affairs Medical Center, Salem, VA; [2]Medicine, White River Junction Veterans Affairs Medical Center, White River Junction, VT; [3]Veterans Health Education & Information Program, Veterans Health Administration, Durham, NC; [4]MEI INC, Madison, WI; [5]Medicine, Veterans Affairs Connecticut Health Care System, West Haven, CT.*

Background: Chronic kidney Disease (CKD) health literacy can be critical in preventing CKD progression. CKD literacy gap is high amongst CKD patients despite clinic education. Well designed, interactive education improves education/outcomes. To address CKD literacy gap, VA developed a comprehensive, freely available VA eKidneyClinic (http://ckd.vacloud.us) web-tutorial detailing at 5th grade reading level (using Flesch-Kincaid formula), basic disease process, nutritional, laboratory, social, pharmacy, and treatment aspects of all CKD stages in written & graphical format, with video narrative vignettes. Pre-/ post-tutorial questions engage, test, reinforce understanding through action planning. Additional Internet links allow further knowledge acquisition.

Methods: To gain understanding of eKidney tutorial usefulness, basic metrics were obtained using Google analytics resources.

Results: Users: 40% US, 60% worldwide (all continents). No users- middle east, developing African nations; Male 54%, female 46%. 89% <55 years age. Web access:18% VA network; 82% other (i.e. broadband). > 500 active users /30 day: 82% new, 18% repeat. Of repeat users, 11.4% visit site >1/ 30 days. Of multi- session users: 34% new, 66% return.

Conclusions: VA eKidneyClinic provides novel, patient-centered, readily accessible Internet resource to address gaps in CKD education. eKidney use is worldwide by veterans & non-veterans in countries with internet availability. Young & middle age populations are common users. Nearly 20% are repeat users of eKidney. Early data suggests usefulness of eKidney in addressing the CKD literacy gap. Web-education familiarity for those >55 years may be a limiting factor. Further research is important to correlate and validate utility of eKidneyClinic in addressing CKD literacy.

Funding: VA Support

SA-PO905

Physical Activity and Kidney Function in U.S. Hispanics/Latinos: Findings from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Bhavik P. Patel, Ana C. Ricardo, Nora Franceschini, Marc D. Gellman, David X. Marquez, Neil Schneiderman, Daniela Sotres-Alvarez, Gregory A. Talavera, Elizabeth Vasquez, Denise C. Vidot, Martha L. Daviglus, James P. Lash. *HCHS/SOL Investigators.*

Background: Hispanics/Latinos are disproportionally affected by chronic kidney disease (CKD). We evaluated the association of physical activity with kidney function in a representative sample of US Hispanic/Latino adults.

Methods: HCHS/SOL is population-based cohort of 16,415 Hispanics/Latinos aged 18-74 yr at baseline (2008-2011) enrolled using a probabilistic sample from 4 US cities. Analyses include individuals with at least 3 days (≥10 hours/day) of accelerometer-measured physical activity, and kidney function measures (n=11622). Using 2008 Physical Activity (PA) Guidelines for Americans we classified PA as high (moderate PA ≥300 min/wk and/or vigorous PA ≥150 min/wk), medium (moderate PA 150-<300 min/wk and/or vigorous PA 75-<150 min/wk), and low/inactive (not meeting above criteria). Kidney function was measured via estimated glomerular filtration rate (eGFR) using the CKD-EPI creatinine-cystatin C equation, and urine albumin-to-creatinine ratio (UACR). Complex survey linear regression analyses were conducted adjusting for sociodemographic and clinical variables.

Results: Mean eGFR for Hispanics/Latinos in the high, medium and low/inactive categories were 111, 109 and 103 ml/min/1.73m^2 respectively. The corresponding UACR medians were 5.8, 6.1 and 7.1 mg/g. Compared with high PA, Hispanics/Latinos in the low/inactive category were significantly ($p<0.05$) more likely to be older (mean age, 45 years vs 37 years), female (60% vs 33%), foreign born (83% vs 69%), and Spanish-speaker (81% vs 65%). They were also more likely to have diabetes (20% vs 9%), and hypertension (28% vs 15%). After adjustments, low/inactive and medium PA were associated with significantly ($p<0.05$) lower eGFR (β -2.5 and -1.5 ml/min/1.73m^2, respectively) compared with high PA. There was no significant association between PA and UACR.

Conclusions: US Hispanic/Latino adults not meeting PA recommendations had lower kidney function compared to individuals with high PA. Longitudinal studies are needed to further evaluate the association of PA and incident CKD.

Funding: NIDDK Support, Other NIH Support - National Heart, Lung, and Blood Institute (NHLBI)

SA-PO906

Differences in the National Prevalence of Chronic Kidney Disease (CKD) in Urban versus Rural Veterans within the U.S. Department of Veterans Affairs (VA)

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Background: Little is known regarding rural versus urban differences in prevalence of CKD among Veterans. Our objective was to determine the prevalence of CKD from a national sample of rural and highly rural (R/HR) compared to urban Veterans, and to further evaluate treatable risk factors for CKD progression and adverse outcomes prior to program implementation.

Methods: We created a 10% stratified sample from over the 5.3 million enrolled Veterans with at least one primary care outpatient (PC) visit from fiscal year (FY) 2011-2015 with proportional allocation by facility from VA's Corporate Data Warehouse (CDW). Rurality status was based on the CDW geospatial information using the patient's primary address. We determined prevalence of CKD stage using estimated glomerular filtration rate (eGFR) by three different methods: 1) CKD-EPI, 2) Modification of Diet in Renal Disease (MDRD), and 3) VA clinical result (MDRD). Standard stages of CKD were defined; additional comorbid conditions were determined using standard ICD-9 codes.

Results: From FY2011-FY2015, R/HR Veterans comprised 35-38% of all Veterans who received PC within VA. Almost 95% of R/HR Veterans were male and older as compared to urban Veterans. R/HR Veterans had greater prevalence of comorbid conditions vs. urban Veterans, including diabetes (22% vs. 20%), hypertension (48% vs. 43%), congestive heart failure (3.9% vs. 3.7%) respectively. The mean creatinine was similar among R/HR vs. urban Veterans (1.1 (SD=0.49) vs 1.1 (0.61) mg/dl). The estimates of CKD stage showed R/HR Veterans had Stage 1 CKD (32.9 vs 37.1%), Stage 2 (48.6 vs 45.2%), Stage 3 (16.8 vs 15.7%), Stage 4 (1.3 vs1.4%), and Stage 5 (0.4 vs0.6%) CKD, respectively.

Conclusions: Compared to urban Veterans, R/HR Veterans had a greater prevalence of latter stage CKD (3-5). Data are needed to determine how risk factor treatment compares in urban and rural settings prior to Nephrology program implementation.

Funding: VA Support

SA-PO907

The Spectrum of Chronic Kidney Disease in Public Renal Services of Queensland, Australia: Data from the CKD.QLD Registry

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Background: We describe the spectrum of CKD from 13 renal services in a state of 4.6 million people, and an area of 1.85 million km^2, covering urban, regional and remote regions. Service areas have emphases on farming, mining, and tourism (F, M and T), a retirement area (R), two city-hospital referral services (C1, C2), and a large, multiethnic disadvantaged urban population (L).

Methods: Data were extracted from the CKD.QLD registry, which embraces all public renal services in Queensland. Patient enrolment began in May, 2011.

Results: 6,534 patients have been enrolled, and followed for 17,147 years. Median age was lowest (63yr) in F, M and T and highest (74yr) in R. Males ranged from 58% in F and M to only 35% in R. Proportions in the lowest three SES deciles were 45% for L, 20% for C1 and zero for R. In all sites >80% of patients were overweight/obese/very obese. Among nonIndigenous patients, proportions with diabetic nephropathy ranged from 9% in T to 37% in L, while renovascular diagnosis ranged from 8% at M to 25% at R, and GN ranged from 9% at C2 to 20% at T. About 30% of subjects generally lacked micro or macro-albuminuria. The number of comorbidities was age-related. Indigenous people constituted 3.5%: they were more often female, about 15 years younger, more often had diabetic nephropathy (32% and 51% at two sites), and had higher death rates. In all sites, only 25% of persons progressed (eGFR loss of >5ml/min/yr) over one and two years. Proportions who progressed were higher with diabetic nephropathy and renovascular disease, and least in those with GN. Incidence of RRT with stage 5 CKD was 37/100 person years, while deaths without RRT rose by stage, peaking at 21/100 person.

Conclusions: There is marked variation among patients with CKD in the public health sector in Queensland. This should influence regional health care policies and resource consumption. Surveillance might ultimately allow calculation of regional prevalence and incidence rates.

Funding: Pharmaceutical Company Support - Amgen Australia, Government Support - Non-U.S.

SA-PO908

Socioeconomic Status Shows Stronger Association for Risk of ESRD Than Incidence of CKD in the ARIC Study

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Background: Low socioeconomic status (SES) is strongly associated with ESRD but associations with CKD are less certain and comparing the two will provide insight into whether disparities are wider in early or late in CKD.

Methods: 13,515 participants with eGFR ≥60 at baseline (1987-1989) in the ARIC Study with household income and educational attainment data were examined for their association with subsequent CKD incidence (eGFR<60 and ≥25% decline in eGFR or CKD hospitalization or ESRD) and ESRD (dialysis, transplantation or death due to kidney disease). We performed seemingly unrelated regression to compare the association of SES measures with CKD and ESRD.

Results: During a median follow-up of ~23.2 years, 3,300 participants developed CKD and 385 participants developed ESRD. In a demographically adjusted model, with high household income as reference, low household income was associated with increased incidence of CKD (HR=1.27, CI: 1.14–1.42) and ESRD (HR=2.31, CI: 1.74–3.07) (Table). After additional adjustment for major CKD risk factors, the association across three levels of SES did not reach statistical significance for CKD but did for ESRD ($p<0.001$; stronger association with ESRD vs. CKD). Similar results were obtained for educational attainment, although its association was attenuated for both CKD and ESRD when adjusted for risk factors. No significant interaction was observed between SES measures and race for CKD or ESRD.

Conclusions: Low SES was associated with increased risk of CKD and ESRD, with stronger association for ESRD. Our results suggest that interventions to reduce disparities are at least as important late in CKD as early.

Table: Hazard ratios for CKD and ESRD events by SES categories

	Overall			
	High	Medium	Low	p-trend
Household income (N)	**8,544**	**2,997**	**1,974**	
CKD, % (n)	22.9 (1,958)	25.6 (773)	28.8 (569)	
Model 1 (HR, 95% CI)	Ref.	1.06 (0.97 – 1.16)	**1.27 (1.14 – 1.42)**	<0.001
Model 2 (HR, 95% CI)	Ref.	1.00 (0.91 – 1.09)	1.04 (0.93 – 1.17)	0.56
ESRD, % (n)	1.8 (153)	3.6 (107)	6.3 (125)	
Model 1 (HR, 95% CI)	Ref.	**1.51 (1.16 – 1.96)**	**2.31 (1.74 – 3.07)***	<0.001
Model 2 (HR, 95% CI)	Ref.	1.29 (0.99 – 1.69)	**1.52 (1.14 – 2.04)***	0.01
Educational attainment (N)	4,921	5,584	3,010	
CKD, % (n)	22.7 (1,117)	23.2 (1,295)	29.5 (888)	
Model 1 (HR, 95% CI)	Ref.	1.05 (0.97 – 1.14)	**1.25 (1.14 – 1.37)**	<0.001
Model 2 (HR, 95% CI)	Ref.	0.98 (0.90 – 1.06)	1.04 (0.94 – 1.15)	0.52
ESRD, % (n)	2.0 (100)	2.2 (120)	5.5 (165)	
Model 1 (HR, 95% CI)	Ref.	1.10 (0.84 – 1.44)	**1.82 (1.40 – 2.36)***	<0.001
Model 2 (HR, 95% CI)	Ref.	0.90 (0.69 – 1.18)	1.16 (0.88 – 1.52)*	0.24

Income (in 2016 US$): high (>$50,000), medium ($25,000-$50,000), low <$25,000); Education: high (>High School, HS), medium (HS), low (<HS)

*p<0.05 for ESRD stronger than CKD. Model 1: Adjusted for age, gender and race-center; Model 2: Model 1 + smoking status, alcohol intake, physical activity, body mass index, high blood pressure, diabetes, total cholesterol and high density lipoprotein

Interactions were not significant for race-income (p=0.45 for CKD and 0.11 for ESRD),or race-education (p=0.68 for CKD and 0.12 for ESRD)

SA-PO909

The Association between Socioeconomic Status and Risk Factors for Cardiovascular Mortality in Chronic Kidney Disease: Result from the KoreaN Cohort Study for Outcomes in Patients with Chronic Kidney Disease (KNOW-CKD)

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Background: Although cardiovascular (CV) disease is a major cause of death in chronic kidney disease (CKD) patients, a relationship between socioeconomic status (SES) and risk factors of CV mortality in CKD are less well known.

Methods: Data were collected from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD, NCT01630486 at http://www.clinicaltrials.gov). SES was characterized on the basis of monthly income and education attainment, which were divided into 3 categories, respectively. Left ventricular hypertrophy (LVH) was defined as left ventricular mass index (LVMi) >115g/m^2 for male, or >95g/m^2 forfemale. Anemia was defined as hemoglobin <13mg/dL for male, or <12mg/dL for female. Mean brachial-to-ankle pulse wave velocity (baPWV) and coronary calcium score (CCS) were divided into higher or lower groups based on their median values. We conducted logistic regression to evaluate the association between SES - categorized into the tertiles of education level or monthly income - and cardiac surrogate markers or anemia. Age, sex, diabetes, CKD stage, body mass index, blood pressure were included as covariates.

Results: Total 1,661 patients were enrolled. The lowest education level was independently associated with LVH (adjusted odds ratio [OR] 1.75, 95% confidence interval [CI] 1.26-2.42, *P*=0.001), higher baPWV (adjusted OR 1.54, 95% CI 1.09-2.17, *P*=0.014) and anemia (adjusted OR 1.559, 95% CI 1.11-2.20, *P*=0.011). The lowest monthly income was independently associated with LVH (adjusted OR 1.48, 95% CI 1.03-2.12, *P*=0.034), but not with anemia or higher baPWV. Neither education attainment nor income level showed a significant relationship with CCS.

Conclusions: In the CKD population, lower SES defined by education attainment exhibited a significant association with LVH, arterial stiffness, and anemia, while monthly income was associated with only LVH. Further efforts are warranted to improve the outcomes for CKD patients in the lower SES.

Funding: Government Support - Non-U.S.

SA-PO910

Association of Comorbidity with Late Nephrology Referral - A Population-Based Study Ming-Yen Lin, Yiwen Chiu, TengHui Huang, Huei-Lan Lee, Shang-Jyh Hwang. *Div of Nephrology, Dept of Internal Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung Medical Univ, Kaohsiung, NA, Taiwan.*

Background: Timely referral to nephrology can ensure adequate care, reduce mortality and medical expenses in patient with chronic kidney disease. However, factors associated with timely nephrology referral are not systematically explored. We hypotheses patient's comorbidity can contribute to timing of nephrology referral.

Methods: One retrospective population-base cohort study was conducted to include patient newly underwent long-term dialysis from 2000 to 2008 year through Taiwan National Health Insurance Research Databases. The early referral (ER) and late referral group (LR) were defined as patients who were referred to a nephrologist more than or less than half year prior to dialysis initiation, respectively. The suggested 29 comorbidities by previous study for claim data within three years before dialysis were applied for these patients.

Results: A total of 24,846 (38.1%) patients and 40,442 (61.9%) patients were ER and LR group. A proportion of ≥3 comorbidities was higher in ER group than in LR group (57.3% vs 50.8%, p<0.001). In multiple logistic regression adjusting age, sex, insurance amount, urbanization, and various comorbidities demonstrated that patients with alcohol misuse (odds ratio 1.23, 95% confidence interval 1.06-1.43), asthma (1.12, 1.03-1.21), cancer with metastatic (1.26, 1.03-1.54), chronic heart failure (1.19, 1.14-1.23), dementia (1.30, 1.15-1.47), and stroke or transient ischemic attack (1.07, 1.02-1.13) were more likely to have late nephrology referral than those without. However, patients with pain (0.82, 0.73-0.91), chronic viral hepatitis B (0.63, 0.52-0.76), depression (0.78, 0.72-0.86), hypertension (0.53, 0.50-0.55), hypothyroidism (0.71, 0.62-0.81), irritable bowel syndrome (0.80, 0.72-0.88), peptic ulcer disease (0.89, 0.85-0.93), psoriasis (0.77, 0.62-0.95), severe constipation (0.84, 0.80-0.88) were negative associated with late nephrology referral.

Conclusions: Various comorbidity in patient with chronic kidney disease determines the timing of nephrology referral. However, the complex relationship between comorbidity and adequate pre-dialysis care needs further study.

SA-PO911

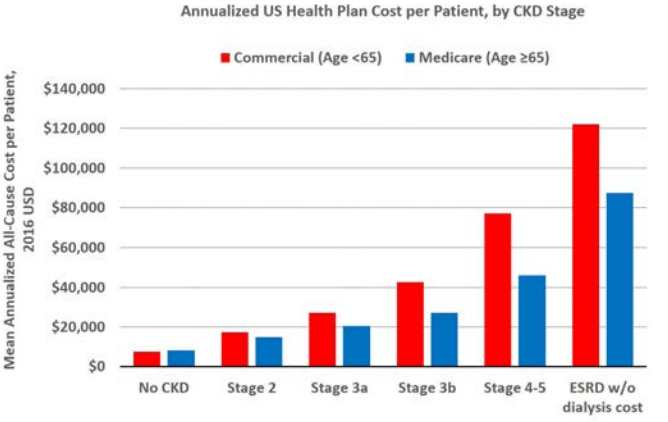
Healthcare Cost Rises Exponentially by Stage of Chronic Kidney Disease Ladan Golestaneh,[1] Paula J. Alvarez,[2] Nancy Reaven,[3] Susan Funk,[3] Karen J. Mcgaughey,[4] Cristine A. Sproles,[2] Wade Benton,[2] Macaulay A. Onuigbo.[5] *[1]Albert Einstein College of Medicine; [2]Relypsa, Inc; [3]Strategic Health Resources; [4]California Polytechnic State Univ; [5]Mayo Clinic, Rochester.*

Background: Prevalence of chronic kidney disease (CKD) is rising, but the economic impact of CKD progression on US health plans is not well known.

Methods: A large electronic medical record (EMR) database (Humedica) was queried to identify patients (pts) with renin-angiotensin-aldosterone system inhibitor prescription (Rx) history. Pts with 90+ days of ≥1 CKD stage (by GFR or diagnosis), plus CKD-free controls, were studied. Since the EMR database did not contain claims data, mean claims costs to US Commercial (Comm) and Medicare (Medi) plans for specific services and Rxs were obtained (OptumInsight) and applied to services and Rxs in EMR data of pts <65 and ≥65 years of age, respectively. Dialysis in ESRD, rarely reported in EMRs, was excluded. Annualized all-cause cost was computed per pt in each CKD stage, and ESRD, and summed. Payer-specific means were compared between CKD stages (Chi-square).

Results: 93,912 pts <65 years (41,737 with CKD/ESRD; 52,175 controls) and 81,829 pts ≥65 years (77,243 with CKD/ESRD; 4586 controls) were evaluated. Mean annualized all-cause cost per pt in 2016 USD rose exponentially from $7500 (no CKD) to $27,200 at Stage 3a and $77,000 by Stages 4-5 (Comm) and from $8100 (no CKD) to $20,500 at Stage 3a and $46,100 by Stages 4-5 (Medi); all p<0.0001 (figure). Mean cost per pt in ESRD pts, excluding dialysis was $122,000 for Comm and $87,300 for Medi plans (p<0.0001 vs Stages 4-5). In each stage, inpatient care was the largest contributor to total costs and its relative contribution increased as CKD progressed.

Conclusions: All-cause health plan costs rise exponentially at each stage of CKD progression for both Medi and Comm health plans in the US. ESRD patients cost more even without the burden of dialysis procedure expenses.



Funding: Pharmaceutical Company Support - Relypsa, Inc.

SA-PO912

Costs of Chronic Kidney Disease during Transitions between Stages of CKD among U.S. Veterans David W. Hutton,[1] Debabrata Ray,[1] Hal Morgenstern,[1] Anca Tilea,[1] Joel Segel,[1] Diane Steffick,[1] Aaron Pearson,[1] Michael J. Fischer,[2] Denise M. Hynes,[2] Chuan-Fen Liu,[2] Edward D. Siew,[2] Daniel F. Balkovetz,[2] Susan T. Crowley,[2] Rajiv Saran.[1] *[1]Univ of Michigan; [2]VA Healthcare System.*

Background: While CKD becomes more expensive with advancing stage, how costs change as individuals transition across stages is unknown. We sought to estimate cost of care for Veterans transitioning the CKD continuum to inform prioritization of VA CKD prevention efforts.

Methods: We analyzed existing data in the VA Renal Information System (VA REINS), an internal national data system that informs the VA about CKD in its population.An operational definition of a VA user (≥1contact with VA in 3yrs) was used. All users were categorized as CKD stages 3a-5 based on their outpatient eGFR and followed 2010-2011 to determine how the cost of care changed with CKD stage shift. Total annual inpatient, outpatient, and pharmacy costs were aggregated from VA internal cost accounting, external fee-based service, and linked Medicare payments to calculate VA spending on CKD as well as mean annual costs by CKD stage.

Results: In 2011, combined (VA + Medicare) aggregate cost for VA users with ≥1 eGFR<60 (n= 845,610) was over $18 billion. Average annual per patient (PP) costs increased by CKD stage: stage3a $17,742; stage3b $23,084; stage4 $33,564; stage5 $85,177. Among users whose CKD stage changed 2010 to 2011, worsening CKD conferred an increased cost; for those with improving CKD status a downward cost. For patients who died in 2011, the change in cost depended on their 2010 stage.

Figure1: Change in annual PP cost among VA users with CKD (2010-2011)

		CKD stage in 2011					
		3a	3b	4	5	ESRD	Dead
CKD stage in 2010	3a	**$1,650**	$5,170	$18,290	$32,220	$26,670	$7,360
	3b	-$570	**$2,450**	$8,070	$27,960	$23,900	$3,520
	4	-$8,200	-$1,550	**$2,970**	$12,010	$22,990	-$2,120
	5	-$16,790	-$17,070	-$7,150	**$1,620**	$5,070	-$31,190

Negative numbers = decreased cost, Positive numbers = increased cost

Conclusions: Total cost of caring for US veterans with CKD is high, and change in costs with shift in CKD stage has implications for gauging cost effectiveness of VA CKD prevention strategies.

Funding: VA Support

SA-PO913

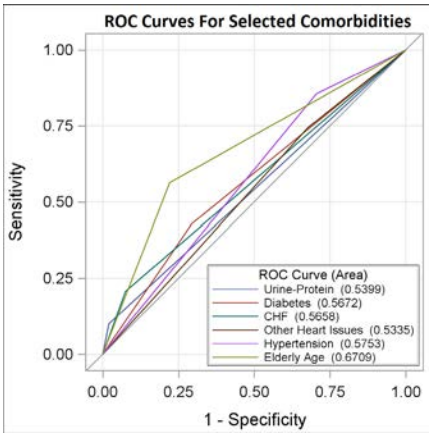
Billing Codes Are Not Reliable in the Detection, Staging, and Progression of Chronic Kidney Disease Kabir Jalal,[1] Edwin J. Anand,[2] Rocco C. Venuto,[2] Pradeep Arora.[3] *[1]Biostatistics, Univ at Buffalo, Amherst, NY; [2]Nephrology, Erie County Medical Center, Buffalo, NY; [3]Nephrology, Veterans Affairs, Buffalo, NY.*

Background: Billing codes are not only used for reimbursement, but are also used by administrators and investigators for population health management and therefore need to be reliable. The accuracy of administrative coding was studied, using Chronic Kidney Disease (CKD) as the condition of interest. Clinical progression was compared to progression assessed by coding changes.

Methods: Data from a large third party payer, with an average annual enrollment of 1.3 million, from 2007- 14. Patients with eGFR readings less than 60 for 2 months or having proteinuria were identified as CKD cases. ROC analysis examined the sensitivity/specificity of billing codes in capturing CKD. Analysis was stratified based on demographic and comorbid factors. The correlation of CKD severity data from billing codes with eGFR was analyzed. Longitudinal mixed model analysis identified rapid progressors (eGFR loss greater than 4 per year), and changes in coding were examined for disease progression.

Results: 38,857 CKD cases were identified. 46% were male and 54% were females. CKD stages 3, 4 and 5 were found in respectively 50, 28, and 9%. Billing codes identified

10,567 patients, giving a sensitivity of 27.19%.The specificity was 97%. With regards to severity, the accuracy of the codes for CKD stage 3 was 69.58%; stage 4, 46.14%; and stage 5, 46.77%. Changes in coding alone identified only 11.95% of rapid progressors.



Conclusions: 1. Inaccuracies in billing codes preclude use of this data for identifying patients with a disease of interest. 2. Administrative codes have poor sensitivity in the identification of patients with CKD, but are highly specific 3. Billing codes inaccurately identify rapid progressors 4. Physician education on accurate coding is crucial in the EHR era.

SA-PO914

Trends in the Timing of a Second GFR after a First GFR Lower than 60 in a Primary Care Setting Claudine T. Jurkovitz, Richard Caplan, Sarahfaye Heckler, James Thomas Laughery, Edward Ewen. *Christiana Care Health System, Newark, DE.*

Background: The KDOQI guidelines recommend 2 measurements of glomerular filtration rate (GFR) <60 mL/min/1.73m^2 at 3 months intervals or more to establish the diagnosis of chronic kidney disease (CKD). We examined the timeline of measuring a second GFR in an outpatient primary care setting.

Methods: We used the CKD-Epi equation to assess GFR from the serum creatinine records of patients seen in a large network of primary care offices from 2007 to 2015. Our study population was defined as patients 18 or older with at least one GFR<60. We excluded patients whose first GFR was <15. Followup began at the time of the first GFR<60. We calculated the time interval between the first GFR<60 and the second GFR and stratified the patients according to their first GFR into 3 categories (GFR 15-<30; 30-<45; 45-<60). We used Analysis of Variance test for linear contrast to assess the trend of the time interval according to GFR categories and the Cochran-Mantel-Haenszel for linear association for the trend in the proportion of patients who had a second GFR within 3 months, between 3-12 months, and more than 12 months after the first GFR.

Results: A total of 13,320 patients had at least one GFR<60, 1,880 patients who did not have any followup serum creatinine and 353 with GFR<15 were excluded. Of 11,087 patients, 62% were female, 81% white, 18% black, 6% had a first GFR 15-<30, 20% had a first GFR 30-<45 and 74% a first GFR 45-<60. Mean age was 69. Overall, 39% had a second GFR within 3 months, 44% between 3 and 12 months, and 17% after 12 months. Among patients with first GFR 15-<30, 30-<45, 45-<60 respectively, the median time intervals between GFR measurements were 82, 105, and 140 days (p <0.0001); 52%, 46% and 36% had a second measurement within 3 months, 37%, 40% and 46% had a measurement between 3 and 12 months, and 11%, 14% and 18% had a measurement after 12 months (p<0.0001).

Conclusions: In a primary care setting, the timing of the second GFR depends primarily on the level of the first GFR. It is likely that at low levels of GFR, physicians are concerned about ruling out acute kidney injury and choose to re-measure serum creatinine closer to the first measurement.

Funding: Other NIH Support - Work supported by an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institute of Health under grant number U54-GM104941 (PI: Binder-Macleod)

SA-PO915

Using Primary Care Database to Understand the Generalizability of the European QUALity (EQUAL) Study in the UK Anirudh Rao,[1,2] Stephanie J. MacNeill,[1,2] Yoav Ben-Shlomo,[2] Fergus J. Caskey.[1,2] *[1]UK Renal Registry, Bristol, United Kingdom; [2]Univ of Bristol, Bristol, United Kingdom; [3]On Behalf of EQUAL Investigators.*

Background: The EQUAL Study is an ERA-EDTA funded cohort study looking at the timing of dialysis start in elderly patients with advanced CKD. Most observational studies are likely to recruit a selected sub-sample of eligible participants which could affect the generalizability. The aims of the study were 1.Quantify selection biases by identifying factors that were associated with participation/non-participation in EQUAL 2.Describe differences in outcomes between patients participating & not participating in EQUAL.

Methods: EQUAL data(UK) from first 250 patients was compared to patients identified from The Health Improvement Network(THIN) database, under a nephrologist meeting EQUAL inclusion criteria(2,464). Descriptive statistics and regression models were used to examine differences in baseline demographics, clinical & laboratory markers, hospitalization and mortality between the two cohorts.

Results: In a multivariable logistic model, older patients(every 5-year age band,OR 0.7, 95%CI 0.6-0.8), women(OR 0.6, 95%CI 0.5-0.9); those with cardiovascular disease(OR 0.6, 95%CI 0.4-0.9), vascular disease(OR 0.5, 95%CI 0.3-0.9) & rheumatological disease(OR 0.3, 95%CI 0.2-0.7) were less likely to be in EQUAL cohort. Greater proportion of patients started renal replacement therapy in EQUAL in the first year after reaching eGFR ≤20 mls/min when compared to THIN cohort(8% vs 2%,p<0.001). Patients in THIN had worse outcomes compared to EQUAL cohort; 7% vs 1.6%(p=0.001) required ≥4 hospitalisations in the first year and relative mortality was increased(HR 1.7, 95%CI 1.1-2.6,p=0.02),this was moderately attenuated after adjustment for various confounders(HR 1.5, 95%CI 0.92.3,p=0.10).

Conclusions: This study provides empirical evidence regarding factors associated with participation in an cohort study of elderly people with advanced CKD: older and sicker patients were less likely to be recruited and this was supported by follow up data on health outcomes. This selection pattern is likely in most observational studies of chronic diseases and needs consideration when generalizing the results to a wider population.

SA-PO916

In Their Own Words: Symptoms and Impacts on the Lives of Patients with Anemia Associated with Chronic Kidney Disease Vanja Sikirica,[1] Susan Mathias,[2] Steven I. Blum,[1] Kirsten L. Johansen.[3] *[1]GlaxoSmithKline, Afghanistan; [2]Roivant Sciences; [3]Nossuli Research.*

Background: We conducted qualitative interviews with patients with anemia associated with Chronic Kidney Disease (aCKD) to identify and explore the most relevant symptoms and impacts from the patient's perspective.

Methods: One-on-one interviews were conducted with aCKD patients recruited from dialysis centers in the US. Patients were ≥18 years of age, with a confirmed diagnosis of CKD, and hemoglobin (Hgb) level <12.0 g/dL. Patients receiving dialysis (≥3 times/week) also: 1) received an erythropoietin stimulating agent (ESA) for ≥12 weeks; or 2) initiated dialysis within the past 4 weeks. Non-dialysis aCKD patients had to either: 1) have been receiving an ESA for ≥12 weeks; or 2) not within the prior 12 weeks. Protocol was IRB approved; all patients provided consent.

Results: Twenty-eight aCKD patients (mean age 60±17.2) were interviewed. Most were female (75%), and receiving treatment with an ESA (82%) or IV Iron (54%). Most were CKD Stage 5 or receiving dialysis (68%). Mean Hgb was 9.6 g/dL (SD=0.9, range: 7.2-11.5 g/dL). Patients with aCKD reported (spontaneously or probed) a range of symptoms and related impacts, which were mostly similar across the different sub-groups (dialysis or ESA status or Hgb level). Frequently mentioned concerns included: difficulty remembering things (n=12 out of the 12 patients that were asked; 100%); feeling weak/lacking strength (n=10/10 patients with Hgb <10g/dL; 100%); feeling tired/exhausted/fatigued (n=27/28; 96%); interference with daily activities (n=19/20; 95%); shortness of breath (n=16/17; 94%); GI symptoms (n=11/15; 73%); difficulty sleeping (n=10/16; 63%); emotional (n=10/16; 63%) and social impacts (n=9/21; 43%); and difficulty concentrating (n=9/24; 38%). Non-dialysis patients were more likely to have difficulty remembering things (n=5/9; 56% vs n=7/15; 47%) or difficulty sleeping (n=5/7; 71% vs n=5/9; 56%).

Conclusions: Regardless of treatment with dialysis and ESAs, aCKD patients experienced a wide range of symptoms and impacts. Some differences were noted between patients based on dialysis status and Hgb level. This study captures the burden and unmet needs associated with aCKD.

Funding: Pharmaceutical Company Support - This study was funded by GlaxoSmitKline

SA-PO917

Development of a Patient Reported Outcome Symptoms Measure for Use with Patients with Anemia Associated with Chronic Kidney Disease Susan Mathias,[1] Steven I. Blum,[2] Vanja Sikirica,[2] Kirsten L. Johansen.[3] *[1]Health Outcomes Solutions, Winter Park, FL; [2]GlaxoSmithKline, Collegeville, PA; [3]Univ of California, San Francisco, CA.*

Background: To develop a new disease-specific patient-reported outcome (PRO) measure to capture relevant symptoms and impacts of anemia associated with Chronic Kidney Disease (aCKD).

Methods: Development included an iterative approach following best practices for PRO development. An initial literature review was conducted to identify the existence of relevant PRO measures and concepts to explore during qualitative research with patients with aCKD (≥18 years old; hemoglobin <12 g/dL). Concept elicitation (CE) interviews were conducted using an Interview Guide developed specifically for this study to identify symptoms and impacts associated with aCKD reported with high frequency. Based on analyses of these transcripts, draft measures were developed, further evaluated and refined based on clinical input and cognitive debriefing (CD) interviews with patients. The study received IRB approval; all patients provided informed consent.

Results: Eight dialysis [5 hemodialysis (HD); 3 peritoneal dialysis (PD)] and 6 non-dialysis (ND) patients (71% female; mean age 65±18) completed the initial CE interviews. Interview transcripts were coded and analyzed which led to the development of draft questions to assess the most relevant symptoms and impacts. Draft questions were subsequently revised in an iterative fashion, based on CD interviews with an additional 22 aCKD patients (9 HD, 3 PD and 10 ND; 68% female; mean age 61±17), and clinician input. The final questionnaire, the Chronic Kidney Disease and Anemia Questionnaire (CKD-AQ), containing 23 items, assesses severity and frequency of the most relevant

symptoms and impacts identified by aCKD patients, including: tiredness, energy levels, weakness, shortness of breath, chest pain, and impacts on cognition and daily activities. The CKD-AQ has been translated into 72 languages for use in future studies.

Conclusions: The CKD-AQ is a new PRO measure which captures frequency and severity of the most relevant symptoms and impacts associated with CKD-related anemia. Future studies will evaluate its psychometric properties.

Funding: Pharmaceutical Company Support - This study was funded by GlaxoSmithKline

SA-PO918

Adherence to Anemia Management Guidelines among Kidney Transplant Candidates Meteb M. AlBugami,[1,2] Fahad Eid Alotaibe,[1,2] Khalid Bel'eed-Akkari.[1] *[1]Multi-Organ Transplant Center, King Fahad Specialist Hospital, Dammam, Saudi Arabia; [2]Dept of Internal Medicine, College of Medicine, Univ of Dammam, Dammam, Saudi Arabia.*

Background: Anemia is one of the major comorbidities of chronic kidney disease (CKD). It is linked to cardiovascular disease (CVD), and low quality of life. Achieving target levels of hemoglobin requires replenishing iron stores and supplemental erythropoiesis stimulating agents. Overshooting could happen and is associated with unwanted complications. This study aimed to measure the extent to which kidney transplant (KT) candidates complied with the National Saudi Anemia Guidelines.

Methods: All potential KT recipients evaluated at the Kidney and Pancreas Transplant Department at King Fahad Specialist Hospital-Dammam, between January 2009 and December 2012 were reviewed. Data were collected from electronic database. Blood samples were obtained during patients' initial visit to the pre-transplant evaluation clinic. For patients on hemodialysis, pre-dialysis samples were obtained.

Results: A total of 678 candidates were evaluated, with a mean age of 43±13.7 years, and 396 (58%) of the subjects were males. Data were missing in 81 (12%) of the cases. Mean hemoglobin level was 11.7±1.8 gm/dL, and 20% achieved the guideline target. Median ferritin level was 260 ng/mL (IQR 111 – 519), and 26% had level more than 500 ng/mL. Mean transferrin saturation 30±19%, and 30% had level less than 20%. 347 (58%) subjects had hemoglobin 11.5 gm/dL and above.

Conclusions: Substantial proportion of KT candidates referred for pre-transplant evaluation failed to meet the national Saudi guideline targets of anaemia management. moreover, overshooting target hemoglobin is common. This should prompt us to place greater and more rigorous emphasis on adherence measures to the guidelines in order to improve the cardiovascular risk and quality of life.

SA-PO919

Geographic Variation in Access among Adults with Kidney Disease: Evidence from Medical Expenditure Panel Survey, 2002-2011 Mukoso N. Ozieh,[1] Kinfe Gebreegziabher Bishu,[2] Rebekah J. Walker,[2] Jennifer A. Campbell,[2] Leonard Egede.[2] *[1]Nephrology, MUSC, Charleston, SC; [2]Center for Health Disparities Research, Internal Medicine, MUSC, Charleston, SC.*

Background: To understand geographic variation in access to care over time in patients with kidney disease.

Methods: We analyzed 4,404 (weighted sample of 4,251,129) adults with kidney disease from the Medical Expenditure Panel Survey over 10 years. Three dependent variables were created to investigate variation in access: usual source of care (USC), overall medical access to care, which took into account usual source of care, ability to get care, and delay in care, and prescription access, which took into account ability to get prescriptions and delay in getting prescriptions. Multiple logistic regression was used with geographic region as the main independent variable, adjusting for relevant covariates.

Results: Compared to the Northeast region, adults living in the Midwest (OR=0.56; 95% CI 0.35–0.89), South (OR=0.48; 95% CI 0.32–0.72) and West (OR=0.53; 95% CI 0.34–0.84) had significantly lower odds of reporting a USC. For the combined access measure, compared to Northeast, adults in Midwest (OR=0.60; 95% CI 0.40–0.88), South (OR=0.62; 95% CI 0.44–0.88) and West (OR=0.50; 95% CI 0.34–0.72) had significantly lower odds of medical access to care. Region was not significantly associated with the odds of having prescription access, though a significant increase in prescription access was observed over time.

Conclusions: Geographic variation in access to care among adults with kidney disease exists independent of income, education, insurance and comorbid conditions, with those in the South least likely to have a USC and those in the West least likely to have overall access to care.

SA-PO920

Factors Shaping the CKD Awareness among the University Nephrology Patients Emma Rebecca Segal,[1] Colin A. Hinkamp,[1] Xuerong Wen,[1] Ashutosh M. Shukla.[1,2] *[1]Medicine, Univ of Florida; [2]NF/SG VHS, Gainesville, FL.*

Background: CKD awareness is known to be poor among patients with CKD. Factors influencing this are not well understood and are a major hindrance to interventional approaches.

Methods: We conducted a cross sectional study in a university nephrology practice, aimed to assess the effects of patient related factors on their CKD awareness. After consent, subjects were administered a survey packet that included assessment of demographics, health literacy (REALM-SF), KD-QoL, and Charlston Comorbidity Index. A novel 45-item survey adjusted for a grade 5 literacy was developed after initial checks for reproducibility, to assess CKD knowledge.

Results: Preliminary findings of an ongoing study with the first 108 enrollees is presented. Participants were 67% Caucasians, 44% women, 60±17 years, had eGFR of 36±20 ml/min/1.73m^2, and renal care for 5.3±5.9 years. Majority lived in a two-person household (48%) with household income (57.7%) below the median for general population. Subjects displayed poor matrices of CKD awareness (19.6 ± 9.2, Range: 0-36). Univariate analyses showed CKD awareness had significant zero phase correlations with age (ρ=-0.33, P=0.0004), eGFR (ρ=-0.19, P=0.04), duration of renal care (ρ=0.21, P=0.03), physical composite of QoL (ρ=0.28, P=0.006), health literacy (ρ=0.18, P=0.06), and household income (ρ=0.35, p=0.0002). The multivariate model after Mallow's Cp selection showed: Awareness is positively influenced by household income, physical QoL and comorbidities but is negatively influenced by age and severity of renal dysfunction.

	Significant Risk Factors	Estimates ± SE	p
CKD Awareness (transformed)	KDQoL-Physical	6.4 ± 2.7	0.02
	eGFR (transformed)	-39 ± 17	0.03
	Charlston Comorbidity Index	36 ± 14	0.01
	REALM score	40 ± 26	0.13
	Household Income	235 ± 58	0.0001
	R^2	0.43	

Conclusions: The results will provide a preliminary validation for our CKD questionnaire, showing significant correlations between CKD awareness and known parameters of health awareness. Ongoing prospective evaluations will be needed to determine if this correlates with hard outcomes including dialysis modality choice, and future importance of educational interventions.

SA-PO921

A Quality Improvement Project to Increase Transplant Referrals in Chronic Kidney Disease Patients in Nephrology Fellows' Continuity Clinic Lori- Ann M. Fisher, Haldane Porteous, Daphne Harrington Knicely. *Nephrology, Johns Hopkins Univ, Baltimore, MD.*

Background: Kidney transplantation remains the optimal treatment for patients with advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD). Pre-emptive and/or early renal transplantation is associated with optimal outcomes in terms of patient and graft survival. In the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for the management of CKD, living donor pre-emptive renal transplant in adults should be considered when the GFR < 20 mL/min/1.73m^2 and there is progressive and irreversible CKD over the preceding 6-12 months. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend that patients with an eGFR < 30 mL/min/1.73m^2 be prepared for dialysis and transplantation. The aim of this quality improvement project was therefore to increase the number of transplant referrals in patients with an eGFR < 20mL/min/1.73 m2 to more than 80% in the nephrology fellows' continuity clinic.

Methods: Charts of patients with CKD stages G3a to G5 in the nephrology fellows' continuity clinic at Johns Hopkins Bayview Medical Center from May 2015 to August 2015 were audited by peer review. The data was obtained from review of the clinic notes. A transplant documentation template or "smart phrase" was made available in the electronic medical record (EMR) for use in all patients with CKD stage G4 or greater. It was implemented into use in November 2015. Reminders were sent to the nephrology fellows every month for continued use of the transplant smart phrase. Charts were audited from November 2015 to January 2016.

Results: A total of 208 charts were reviewed pre-intervention, and 118 charts were reviewed post-intervention. Of the pre-intervention charts, 43 were seen with an eGFR < 20 mL/min/1.73m^2 versus 23 in the post-intervention charts. The total number of transplant referrals increased from 21% to 48% after the intervention.

Conclusions: Simple documentation reminders or smart phrases in the EMR may improve overall compliance with transplant referral and improve coordination in care as exemplified in this quality improvement project. This model could be applied to other CKD quality measures.

SA-PO922

Acceptability of a Multi-Level Intervention to Improve Health Outcomes among Safety-Net Patients with Chronic Kidney Disease Adrienne Strait, Alexandra Velasquez, Karen Leong, Neil R. Powe, Adriana Najmabadi, Delphine S. Tuot. *Univ of California, San Francisco, San Francisco, CA.*

Background: The Kidney Awareness Registry and Education (KARE) trial tested the impact of a multi-level intervention to improve blood pressure control among low-income patients with CKD. KARE consisted of a primary care CKD Registry with point-of-care provider notifications and quarterly feedback on care provision and a patient CKD self-management support (CKD-SMS) program that included low literacy educational materials, automated telephone administered self-management (ATSM) modules, and live telephone health coaching. We explored acceptability of KARE interventions among providers and patients.

Methods: At trial conclusion, we surveyed participating primary care providers (PCPs) and conducted focus groups (n=4) among non-PCP staff to assess acceptability of the registry. We conducted 8 focus groups with English and Spanish-speaking patients to evaluate their experience with the CKD-SMS program. Focus group transcripts were analyzed using grounded theory analysis.

Results: Nearly 60% of PCPs completed the survey (n=61/105). Most (93.8%) PCPs believed the point-of-care notifications benefited clinic workflow and agreed that quarterly feedback enhanced their ability to identify (88.9%) and manage (72.2%) CKD. Staff focus groups confirmed that point-of-care notifications were helpful to order overdue diagnostic studies (i.e. microalbuminuria) and noted that better communication among health team members would enhance the registry's uptake. Patient focus groups suggested the ATSM system was impersonal, though easy to use; that frequent (i.e., weekly) automated calls were preferred to reinforce self-management behaviors; that content should include more dietary advice; and that the convenience of telephone (vs. in-person) health coaching was a program strength. There were diverse opinions about adding mobile text messages to the program but no desire to include Skype functionality.

Conclusions: A registry is acceptable to healthcare provider teams and has the potential to enhance identification and management of CKD in safety-net primary care clinics. A telephone based CKD-SMS program is appreciated by low-income patients.

Funding: NIDDK Support

SA-PO923

Assessing Literacy Skills Related to NSAID Medication Labeling in Primary Care Amy Barton Pai,[1] Nelson Polanco,[2] Mara Garfinkel,[2] Verina Mansour.[2] *[1]Univ of Michigan College of Pharmacy, Ann Arbor, MI; [2]Albany College of Pharmacy and Health Sciences, Albany, NY.*

Background: In primary care, NSAID prescriptions account for up to 20% of prescriptions. Both prescription (Rx) and OTC NSAIDs have medication guides and/or labeling that vaguely describe kidney risks of these products. The purpose of this study was to evaluate the performance of a medication label health literacy tool focused on NSAIDs (MedLit-NSAID).

Methods: The study recruited patients from a large primary care practice in upstate NY. The MedLit NSAID questions assess locating, calculating integrating literacy. Two MedLit-NSAID questions query participants regarding kidney risks using the FDA medication guide (for Rx) and the OTC label to answer the questions. The Newest Vital Sign (NVS) health literacy assessment tool was also administered for comparison. Participants scores were analyzed in the following strata: male/female, age <65 year, age > 65 years, eGFR > or < 60 mL/min/1.73m^2. Data on age, ethnicity, education, number and management of medications was collected.

Results: The study enrolled 145 patients (mean (SD)) age 56 (15) with the majority being white and self-reporting they manage their own medications. Analysis of total MedLit-NSAID scores in the gender, age and eGFR strata showed that male participants and those with eGFR < 60 had significantly lower scores ($p<0.05$ for all comparisons). There was no difference in total MedLit-NSAID scores between participants aged < or > 65 years. A higher proportion of participants with eGFR < 60 vs. eGFR > 60 had some or completed high school (47% vs. 24%, respectively). Participants with eGFR < 60 scored similarly on the Rx question related to NSAIDs, however 61% incorrectly answered the OTC question compared to only 11% with eGFR > 60 ($p<0.01$). The total NVS score was positively correlated with total MedLit-NSAID score (r=0.52).

Conclusions: There is variability in literacy related to NSAID medication labeling in the primary care setting. Literacy among those with eGFR < 60 regarding NSAIDs appears to be poor compared to people with intact kidney function. Labeling for NSAIDs should be re-evaluated and better educational initiatives should be developed.

Funding: Other U.S. Government Support

SA-PO924

Factors Affecting Medication Management among Patients with Chronic Kidney Disease Katie E. Cardone,[1] Sabrina Daoui,[2] Rachid Daoui,[2] Kirsten M. Donato,[1] Wendy M. Parker.[1] *[1]Albany College of Pharmacy and Health Sciences, Albany, NY; [2]Div of Nephrology, Saratoga Hospital, Saratoga Springs, NY.*

Background: Patients with chronic kidney disease (CKD) have complex medication regimens and are at high risk for medication-related problems including non-adherence. Effective medication management strategies are required to optimize outpatient treatment of CKD and/or its underlying conditions. Few data exist regarding medication management in patients with CKD. The primary objective of this study was to identify factors affecting medication management skills and strategies in CKD.

Methods: Patients of an outpatient nephrology office were surveyed during regularly-scheduled appointments. Patients completed a series of validated survey tools, including the Short Test of Functional Health Literacy in Adults (S-TOFHLA), the Medication Adherence Rating Scale (MARS), and the Self-Efficacy for Appropriate Medication Use Scale (SEAMS). Additional questions about medication management strategies and demographic factors were also included. Correlations between demographic, health literacy and performance on medication management scales were performed using SAS.

Results: Twenty-nine patients participated. Most participants had "adequate" health literacy (S-TOFHLA). N=26 (90%) participants were adherent based on MARS and most were highly confident in their abilities to manage medications (SEAMS). Despite indicating they were organized and managing their care appropriately, nearly half (48%) indicated they forget to take their medications at times and only half (56%) indicated they ask a pharmacist questions on their medications. Aging and female gender were positively associated with use of a pill box.

Conclusions: Lessons learned from this highly literate patient population highlight opportunities to improve medication management and adherence. Medication management strategies should be explored in more diverse cohorts of patients with CKD.

Funding: Private Foundation Support

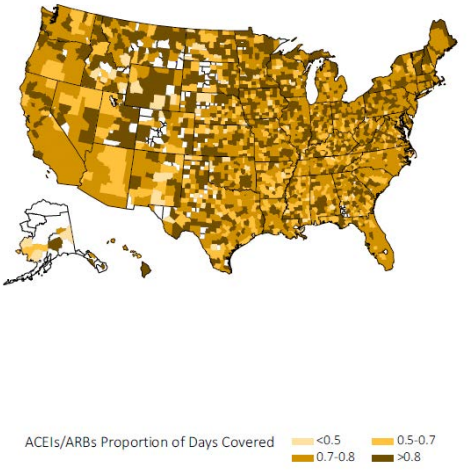
SA-PO925

Environmental and Individual Predictors of Medication Adherence among Elderly Patients with Hypertension and Chronic Kidney Disease (CKD): A Geospatial Approach Yun Han,[1] Steven Erickson,[1] R. Hirth,[1] Rajiv Saran,[1] Rajesh Balkrishnan.[2] *[1]U of Michigan; [2]U of Virginia.*

Background: Few studies have assessed geographical variation in medication adherence across different regions. This study aimed to explore local variations in medication adherence and examine environmental and individual influences on adherence to ACEIs and ARBs among elderly hypertensive CKD patients in the United States.

Methods: This retrospective cohort study utilized a linked dataset from Medicare 5% sample claim data (2006-2013), American Community Survey 5-Year Data (2005-2009) and the Primary Care Service Area (PCSA) data (2007). We included hypertensive CKD patients who were aged 67 and above, continuously enrolled in Medicare Part D and had at least one ACEIs/ARBs pharmacy claim. Patients' 1-year adherence to ACEIs/ARBs was measured using Proportion of Days Covered (PDC), and then aggregated at county level. The geographically weighted regression and the linear mixed-effects models were applied to investigate the relationship between environmental, individual factors and medication adherence.

Results: Significant spatial autocorrelation was observed in ACEIs/ARBs adherence, as the West North Central and New England region had higher adherence rate than the East South Central and West South Central regions. Residing in Medically Underserved Areas (MUAs) and a higher deprivation score were related with lower average PDC. Patients, who were female, white, enrolled in Part D Low-income-Subsidy program, having diabetes and atrial fibrillation were associated with better adherence.



Conclusions: Medication adherence is geographically differentiated across the United States. Residing in MUAs, county deprivation score, and having Part D LIS are potentially modifiable factors that could improve medication adherence. Such factors may be helpful in the design of interventions focused on improving patient outcomes.

Funding: NIDDK Support

SA-PO926

Receipt of Nephrology Care and Clinical Outcomes among Veterans with Advanced Chronic Kidney Disease Enrica Fung,[1] Tara I. Chang,[1] Glenn Matthew Chertow,[1] I-Chun Thomas,[1] Steven M. Asch,[1,2] Manjula Kurella Tamura.[1,2] *[1]Stanford Univ; [2]Palo Alto VA.*

Background: Clinical practice guidelines recommend referral to nephrology once estimated glomerular filtration rate falls (eGFR) below 30 ml/min/1.73m^2; however evidence for benefits of nephrology care remains conflicting.

Methods: We assembled a national cohort of veterans with advanced CKD, defined by anoutpatient eGFR ≤25 ml/min/1.73m^2 between January 1, 2010 to December 31, 2010 and a prior eGFR <60 ml/min/1.73m^2, using administrative and laboratory data from the Department of Veterans Health Affairs and the United States Renal Data System. We used landmark analysis to determine the associations among the receipt of outpatient nephrology care over a 12-month period, survival and progression to ESRD, defined as receipt of dialysis or kidney transplantation.

Results: Of 11,489 patients included in the cohort, 37.2% received nephrology care. Older age, prior hospitalization, more than 4 outpatient visits to non-nephrology providers, heart failure, dementia, cancer, depression, post-traumatic stress disorder, and rapidly declining kidney function were independently associated with the absence of nephrology care. Over a mean follow up of 1.8 years, 17.0% of patients died and 10.1% progressed to ESRD. In models adjusting for demographics, comorbidities, and trajectory of kidney function, nephrology care was associated with a lower risk for death (HR 0.85, 95% CI 0.78-0.95) but a higher risk for ESRD (HR 1.21, 95% CI 1.05-1.40). Patients who received nephrology care were more likely to have serum phosphate within recommended ranges, but less likely to have blood pressure within recommended ranges.

Conclusions: Among patients with advanced CKD, nephrology care was associated with lower mortality but did not dampen the risk for progression to ESRD.

Funding: NIDDK Support, VA Support

SA-PO927

International Variations in the Frequency of the Types of Patient-Physician Contact for CKD Patients: Early Findings from CKDopps

Elodie Speyer,[1] Benedicte Stengel,[2] Koichi Asahi,[3] Brian Bieber,[1] Antonio Alberto Lopes,[4] Ronald L. Pisoni,[1] Nidhi Sukul,[5] Francesca Tentori.[1,6] *[1]Arbor Research, Ann Arbor, MI; [2]UMRS 1018, Paris Sud Univ, Villejuif, France; [3]Fukushima Medical Univ, Fukushima, Japan; [4]Faculdade de Medicina da Bahia, Univ Federal da Bahia, Salvador, Brazil; [5]Dept of Nephrology, Univ of Michigan, Ann Arbor, MI; [6]Vanderbilt Univ, Nashville, TN.*

Background: Regular patient-physician contact by multiple caregivers is recommended in CKD to manage complications and improve outcomes.

Methods: CKDopps is an ongoing prospective cohort study of patients with stage 3-5 CKD from national samples of nephrology clinics. The frequency of visits to different health care providers during the year prior the enrollment was self-reported by patients and described by country [Brazil (BR), France (FR), the United States (US)], CKD stage, and patient's characteristics.

Results: As of May 2016, 3496 patients (mean age=67.1 (SD 12.9); 61% male; 41% diabetics) completed a questionnaire (67% of enrolled patients). 31% of patients in BR reported that they had not seen a general practitioner in the year prior the enrollment (vs. 2-8%), while not seeing a cardiologist was more common in the US (49% vs. 32-37%). Although the proportion of patients having not seen a dietician or social worker decreased with CKD progression, it still remained high in CKD Stage 5 (59-75%, and 77-94%, respectively). Among diabetics, 32-46% according to the country, reported having not seen a diabetes doctor, and 43% in BR had not seen an ophthalmologist (vs 13-17%)**.** Practices were similar among men and women and across age groups.

Table1: Patients reporting to have not seen the following health care professionals during the past year, by country, CKD stage and diabetes status

	Brazil				France				United States			
	Stage 3-5	Stage 3	Stage 4	Stage 5	Stage 3-5	Stage 3	Stage 4	Stage 5	Stage 3-5	Stage 3	Stage 4	Stage 5
N patients	405	139	190	76	2596	1416	1073	107	495	195	247	53
Health professional												
Internist/General Practitioner	31%	43%	23%	25%	2%	2%	3%	3%	8%	10%	6%	9%
Heart doctor	37%	37%	34%	45%	32%	33%	32%	26%	49%	51%	52%	31%
Dietician	59%	60%	62%	51%	75%	77%	74%	66%	73%	81%	70%	60%
Social Worker	77%	81%	75%	75%	94%	95%	92%	91%	90%	95%	89%	80%
Among diabetics (n=1,409)												
Diabetes doctor	42%	48%	39%	50%	32%	28%	37%	44%	46%	51%	50%	40%
Foot doctor	91%	93%	91%	94%	80%	78%	81%	91%	53%	97%	51%	46%
Eye doctor (Ophthalmologist)	43%	47%	39%	47%	13%	10%	16%	19%	17%	20%	15%	17%
Dietician	61%	56%	66%	57%	68%	69%	67%	56%	71%	78%	66%	63%

Conclusions: These early findings based on patient self-report suggest an underuse of specialist care for advanced CKD patients internationally. Additional work is needed to gain further understanding of specialist use, integration of care, and association with outcomes, which may eventually inform optimal practice.

Funding: Pharmaceutical Company Support - AbbVie, Amgen, Baxter Healthcare, F. Hoffmann-LaRoche, Hexal, Keryx, Kyowa Hakko Kirin, Merck, Proteon, Relypsa, Sanofi, Shire, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, WiNe Institute, Societies for Nephrology in Germany, Italy, & Spain

SA-PO928

Geography, Life Expectancy, and Age of Mortality in Dialysis Patients

Peiran Yu, Yue Jiao, Marta Reviriego-Mendoza, John W. Larkin, Len A. Usvyat, Franklin W. Maddux. *Fresenius Medical Care North America.*

Background: Dialysis patients (pts) have an estimated life expectancy ranging from 30 to >50% lower than the general population depending on age (USRDS 2015 Annual Data Report). We aimed to compare the age of mortality in dialysis pts in differing geographies versus the life expectancy in the general population.

Methods: We analyzed data from the Fresenius Medical Care Knowledge Center on all pts with records of a death date, birthday and home zip code. Pts were assigned to a commuting zone according to their zip code, and the largest 50 commuting zones were selected based on regions with the largest number of female and male pts. Average age of death, geographical location, and the life expectancies of the general population within those locations were calculated. Income levels were adjusted to represent the dialysis population using an estimated income assignment in weighted quartiles: 40% quartile 1 (lowest income), 30% quartile 2, 25% quartile 3, and 5% quartile 4 (highest income).

Results: We studied data from 193,630 pts who died (92,309 female & 101,321 male). We observed that the age of death in dialysis pts to life expectancy in the general population was distinguishable between females and males overall and in the differing geographic commuting zones (individual points). Dialysis pts had a life expectancy about 12-20 years shorter than those in the general population in differing geographies (Figure 1). The age of death was positively correlated to life expectancies in the general population for females (correlation coefficient (r) =0.560) and males (r =0.667).

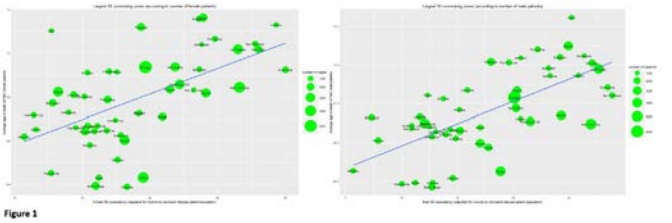


Figure 1

Conclusions: Our findings illustrate that age of mortality in dialysis pts is lower than the life expectancies in the general population, and vary considerably for differing geographies in a gender specific manner. These observations may be important to consider how to improve longevity of dialysis pt population.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

SA-PO929

Family History of Kidney Disease and Diabetic Nephropathy among Remote Canadian Indigenous Peoples - Results from the FINISHED Screen/Triage/Treat Project

Stephanee Ophey,[1] Paul Komenda,[1] Thomas W. Ferguson,[1] Navdeep Tangri,[1] Caroline D. Chartrand,[2] Lorraine L. Mcleod,[2] Audrey Gordon,[1] Allison Dart,[1] Claudio Rigatto,[1] Barry Ad Lavallee.[1,2] *[1]Max Rady College of Medicine, Univ of Manitoba, Winnipeg, MB, Canada; [2]Diabetes Integration Project, Winnipeg, MB, Canada.*

Background: Indigenous Canadians have a high prevalence of Chronic Kidney Disease (CKD). We aimed to determine the relationship between family history of kidney disease and current kidney disease status among remote Canadian Indigenous. We accomplished this using a subset of data from The First Nations Community Based Screening to Improve Kidney Health and Prevent Dialysis (FINISHED) project, a CKD screening initiative in remote First Nations communities in Manitoba, Canada between 2012 and 2015.

Methods: An interdisciplinary team screened for CKD using both urine-albumin-to-creatinine ratio (ACR) and eGFR in 630 adults from 4 remote First Nations communities. Our primary outcome of interest was the association between reported family history of kidney disease and current diabetic nephropathy (defined as hemoglobin A1C $\geq$ 6.5% and urine ACR $\geq$ 3mg/mmol or eGFR < 60 ml/min/1.73m^2) or non-diabetic nephropathy (defined as elevated urine ACR or low eGFR without elevated hemoglobin A1C).

Results: 402 of the 587 respondents provided information on family history of kidney disease (first degree relatives and grandparents). Of those with a reported family history of kidney disease (n = 156), 31.4% were found to have diabetic nephropathy, in comparison to 21.1% in those with no family history (p = 0.02). No statistically significant relationship was observed between family history and presence of non-diabetic nephropathy (13.5 vs. 14.2%; p=0.83).

Conclusions: Remote dwelling Indigenous Canadians have a high prevalence of CKD. Family history is a risk factor for diabetic CKD, but not for non-diabetic CKD. The high incidence of non-diabetic CKD requires further study to establish etiology and improve outcomes.

SA-PO930

Mortality in Patients with Chronic Kidney Disease in New South Wales – A Cohort Study 2000-2010

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Background: Patients with CKD have a higher mortality, but there is limited local data onhow this effect differs with the use of renal replacement therapy (RRT – dialysis or transplant) and geographical remoteness. This study compares chronic kidney disease (CKD) progression and survival for hospitalised patients in NSW.

Methods: The NSW Admitted Patient Data Collection identified all patients with an ICD-10 AM code for CKD on any admission between 1/7/2000 and 31/07/2010. Patients were linked to the death registry and ANZDATA. We defined RRT using the ANZDATA Registry and rural status using residential postcode and by ARIA scores. Competitive risk regression was conducted comparing rural versus urban populations.

Results: 165,901 people with CKD were admitted to hospital in NSW (982,887 patient years) and had a median follow up of 6.3 years. Only 16% (n=26,412) of patients lived rurally. During the study follow up period, 6285 (4.2%) people received RRT and 85163 (51.3%) died. Of those that received RRT, 1027 (3.9%) were rural and 5868 (4.2%; p=0.02) were urban. Of those that received RRT, 2979 (43.1%) died by the end of the study compared to 82,190 (51.7%) of those that did not receive RRT (p<0.001). Competitive risk regression showed minimal difference in the risk of receiving RRT between rural and urban residents (HR 0.93 95%CI 0.87-1.00; p=0.04).

Conclusions: The presence ofICD-10 codes for CKD in administrative data is associated with very high mortality, greater than that seen in dialysis patients. The frequency of CKD codes and the subsequent mortality far outstrips the burden of requirement for RRT.Further exploration of stages of CKD, differences in baseline characteristics will enhance understanding further.

SA-PO931

Engaging Kidney Disease Patients and Family Members as Co-Investigators in Patient Centered Outcomes Research Teri Browne,[1] Gary Green,[2] Katina Lang-Lindsey,[3] Patti Ephraim,[4] Patty Danielson,[5] Suzanne Ruff,[6] Holly St. Clair,[5] Lana Schmidt,[5] Amy Swoboda,[6] Peter Woods,[5] Tara Smith Strigo,[7] L. Ebony Boulware.[7] *[1]College of Social Work, Univ of South Carolina, Columbia, SC; [2]American Association of Kidney Patients, Tampa, FL; [3]Univ of Mississippi, Jackson, MS; [4]Johns Hopkins Univ, Baltimore, MD; [5]Patient with Kidney Disease; [6]Family Member; [7]School of Medicine, Duke Univ.*

Background: While often patients and family members are engaged peripherally in patient centered outcomes research (PCOR), our novel model includes them as fully engaged co-Investigators in a currently funded Patient-Centered Outcomes Research Institute (PCORI) kidney disease clinical trial.

Methods: Patients and family members partnered with researchers to develop an intervention, establish outcomes and write a PCORI proposal. We transcribed our meeting discussions, identified common themes, and refined our ideas prior to funding.

Results: Patients and family members were leading participants in all pre-award discussions and contributed to more than 5 major study design revisions. The study intervention evolved from a simple education program into a comprehensive health system intervention including provider tools and educational, behavioral, and psychosocial support for patients to improve kidney care. Patients and family members identified their most important research outcomes as: control, empowerment, acceptance, grief, anxiety, depression and CKD knowledge. Patients and family members are active and full co-Investigators on this project. They meet at least monthly with all investigators, provide feedback on all components of the study protocol, revise all recruitment and communications materials, and ensure all aspects of the intervention respond to patient and family members' needs.

Conclusions: Patients and family members can be fully engaged in research projects, thereby substantially improving the relevance and quality of PCOR studies. Our example could serve as a model to improve kidney disease PCOR studies and outcomes.

Funding: Other U.S. Government Support

SA-PO932

Can-SOLVE CKD: A Pan-Canadian Patient-Oriented Research Network Adeera Levin,[1] Braden J. Manns,[3] Mila Tang,[2] Helen Chiu,[2] Heather A. Harris.[2] *[1]Dept of Medicine, UBC; [2]PHCRI, BC; [3]Dept of Medicine & Community Health Sciences, U of Calgary, AB.*

Background: The optimal conduct of patient-oriented research (POR), a priority for many research funding agencies, is uncertain. The Canadian nephrology community has been working for 4 years to develop an integrated POR network—Canadians Seeking Solutions and Innovations to Overcome (Can-SOLVE) CKD. The network's vision: By 2020, every Canadian with, or at high risk for CKD will receive the best recommended care, experience optimal outcomes and have the opportunity to participate in studies with novel therapies, regardless of age, sex, gender, location or ethnicity.

Methods: Using James Lind Alliance methodology and workgroups including patients and policy-makers, we identified the top research questions for early and advanced CKD. Key research questions identified by patients were formulated into a comprehensive research program. Partnerships with patients, researchers and policy-makers were leveraged to co-build a pan-Canadian patient-oriented research network.

Results: A research program with 3 themes and 19 projects spanning basic science, clinical and population health research was formed. National core infrastructure resources were developed.

A Patient Council and Indigenous Peoples' Engagement and Research Council are at the core of the network. Universities, provincial renal programs, and >100 researchers from multiple disciplines (e.g nursing, pharmacy, epidemiology etc.) from across Canada are involved. Peer-reviewed federal funding aimed at POR has been secured for this network, as part of the strategy to improve health of patients with chronic diseases.

Conclusions: Can-SOLVE CKD is a novel POR network, aimed at overcoming challenges that thwart the translation of discoveries into clinical research, and uptake of evidence into practice. Lessons learned can be shared with researchers from other countries seeking to partner with patients in research.

Funding: Government Support - Non-U.S.

SA-PO933

Multi-Disciplinary Care Is Cost-Effective in Chronic Kidney Disease Eugene Lin,[1] Glenn Matthew Chertow,[1] Jeremy D. Goldhaber-Fiebert.[2] *[1]Internal Medicine - Nephrology, Stanford Univ; [2]Centers for Health Policy and Primary Care and Outcomes Research, Stanford Univ.*

Background: End-stage renal disease (ESRD) accounts for 5.6% of total Medicare expenditures, though patients on dialysis make up 1.6% of its beneficiaries. Multi-disciplinary care (MDC) has been proposed as a way to mitigate the morbidity and costs associated with the transition from chronic kidney disease (CKD) to ESRD.

Methods: To evaluate the cost-effectiveness of MDC relative to usual care, we developed a Markov model of progressing from CKD to ESRD. Unlike previous models, ours captures patient heterogeneity. We assumed that CKD progression depended on age, gender, CKD stage, and level of albuminuria. We calibrated progression probabilities to published data on risks of death and of developing ESRD. The cost-effectiveness analysis adopted the Medicare payer perspective. Using data from a recent systematic review, the model assumes that MDC decreased mortality rates by 15% and progression rates to ESRD by 55%. We modeled a typical MDC program which involved four nurse practitioner (NP) visits per year. We obtained ESRD mortality rates and costs from the United States Renal Data System (USRDS). Sensitivity analyses focused on potentially lower efficiency and higher costs of MDC and on clinical characteristics of the target CKD population.

Results: Compared to usual care, MDC costs $24,613 per QALY gained. MDC remained below $35,000 per QALY gained over a wide range of severities of CKD (from stage 3 to 5), ages (25 to 75 years), and albuminuria (100 mg/g to 1000 mg/g). Cost-effectiveness estimates were robust to changes in the efficiency of MDC. An MDC program that decreased mortality and progression rates by only 2% cost $84,916 per QALY gained. Likewise, an expensive MDC program of 12 NP visits a year cost $44,285 per QALY gained.

Conclusions: Even if deployed inefficiently, MDC programs would likely be cost-effective in CKD patients in the United States.

Funding: NIDDK Support

SA-PO934

The Cost-Effectiveness of Community Health Workers: A Chronic Kidney Disease Markov Model David N. van der Goes,[1] John P. Ney,[2] Rajan Bishwakarma,[1] Kristina Nicole Piorkowski,[1] Mark L. Unruh.[3] *[1]Dept of Economics, Univ of New Mexico, Albuquerque, NM; [2]Dept of Neurology, Boston Univ, Boston, MA; [3]Dept of Internal Medicine, Univ of New Mexico, Albuquerque, NM.*

Background: Given the rise in rate of CKD and the increase in number of Americans over 60, there is a clear need to improve outcomes for patients with CKD earlier in the disease; early intervention may be the answer. We explore the use of community health workers (CHW) as an add-on intervention for patients with Stage 3 CKD and Stage 4 CKD to reduce costs and enhance quality of life by slowing the rate of progression and increasing the interval between diagnosis of CKD and ESRD. CHWs and care coordinators have been shown to be effective in educating patients about both their health state and the health care system.

Methods: We constructed a six health state cost-utility Markov model: 1) CKD 3a, 2) CKD 3b, 3) CKD4, 4) ESRD, 5) Transplant, and 6) Death to compare the current standard of care to care with CHWs. We use payer (Medicare) perspective and lifetime time horizon. We estimate transition probabilities and costs from publicly available data. Our CHW program is theoretical and its impacts are based on the current literature. We ran a baseline model and evaluate uncertainty through probabilistic sensitivity analysis.

Results: The model shows that CHWs reduce costs and improve quality of life. CHWs reduce lifetime costs by about 1 percent and increase quality adjusted life years (QALY) by about 1% compared to current standard of care. The model is most sensitive to, in order, the cost of dialysis, the cost of Stage 4 CKD, and CHW program costs.

Conclusions: Adding CHWs to standard care would reduce costs and improve quality of life for patients with CKD. CHWs should be considered as part of the CKD care team.

Funding: Private Foundation Support

SA-PO935

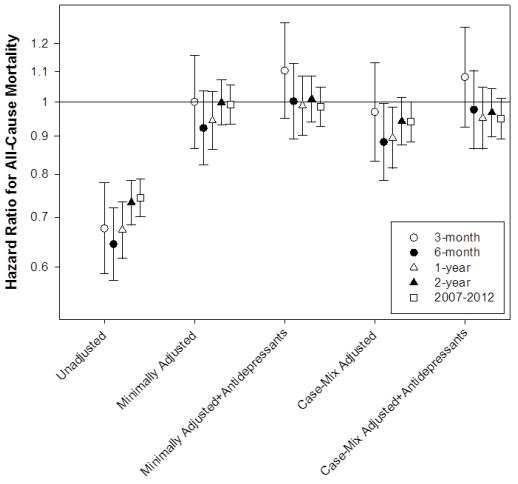
Posttraumatic Stress Disorder and Mortality in Veterans with Advanced CKD: A Transition of Care in CKD Study Elani Streja,[1] Melissa Soohoo,[1] Joline L.T. Chen,[3] Daniel L. Gillen,[1] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Univ of Tenn.; [3]VA Long Beach.*

Background: End stage renal disease (ESRD) patients starting dialysis treatment often experience worse mental health and quality of life. It is not known whether posttraumatic stress disorder (PTSD) has any impact on outcomes in these patients. A previous study in veterans showed that late-life PSTD was associated with increased cardiovascular (CV) disease, yet the association of PTSD and outcomes remains unknown in veterans who transition to ESRD.

Methods: We investigated a cohort of 34,681 US veterans who initiated dialysis between 10/2007-9/2011 and utilized the VA healthcare system. We used Cox proportional

hazard models to examine the association of pre-ESRD (prelude) PTSD (identified by ICD9 codes) with all-cause mortality occurring in the first 3 months, 6 months, 1 year, 2 years post transition to dialysis and over a 6 year period (2007-2012). We minimally adjusted for demographic covariates and additionally adjusted for comorbidities and prior prescription of antidepressants.

Results: Patients were 70±12 years old, among whom 25% were African-Americans, 6% Hispanic and 52% were ever prescribed antidepressants; 2,592 (7.5%) of the cohort was diagnosed with PTSD prior to dialysis initiation. PTSD was associated with lower crude post-ESRD mortality. However, after adjustment for demographics, this association was nullified, and further adjustment for antidepressants did not modify the association.



Conclusions: Pre-ESRD PTSD does not exhibit a clear associative pattern with early dialysis mortality in veterans transitioning to ESRD after adjustment for demographics, comorbidities and antidepressant use. Whether this is a result of better and more focused treatment and management of PTSD in veterans remains to be seen.

Funding: NIDDK Support

SA-PO936

Depression and Factors Affecting It in Patients of Chronic Kidney Disease at a Tertiary Care Public Teaching Hospital: Evidence from a Cross Sectional Study Sanjay D'Cruz,[1] Pramil Tiwari,[2] Rajiv Ahlawat.[2] *[1]General Medicine, Government Medical College and Hospital, Chandigarh, India; [2]Pharmacy Practice, NIPER, SAS Nagar, Punjab, India.*

Background: Chronic kidney disease (CKD) is progressive disease and known to cause premature mortality. CKD patients are at increasing risk of depressive disorder because of considerable psychological stress due to physical and social changes brought on by disease. The presence of depression in patients of CKD can lead to poor outcomes. The present study was conducted to assess the prevalence of depression and the factors influencing it in patients of chronic kidney disease.

Methods: This cross-sectional study was carried out in 408 patients diagnosed with CKD over a one year from Sept 2014 to Sept 2015 at our tertiary care hospital. CKD was defined according to KDIGO guideline. Nine-item Patient Health Questionnaire (PHQ-9) from PRIME-MD was used to assess the presence of depression. Depression was classified further on the basis of score as minor, moderate and major. Unpaired Student's t-Tests and multiple logistic regression test were used for analysis.

Results: Of all the patients, 41.1% had no depression on the basis of PHQ. Mild depression was found to affect 29% of the patients followed by moderate depression (14%), moderately severe depression (11%) and severe depression in 5%. None of the patients were receiving any antidepressant. The likelihood of depression was significantly higher with age >60 (OR 1.10, 1.12-1.53; P<0.05). Depression was found to be associated with duration of CKD >2 yrs (OR 1.92, 0.80-1.43; P<0.001) lack of reimbursement (OR 0.55, 0.45-1.12; P<0.05), Anemia Hb ≤10 (OR 1.87 (0.86-1.25; P<0.05)), GFR ≤30 (OR1.55, 0.99-1.86; P<0.001, and Hb1Ac ≥7 (OR 1.73, 0.82-2.42; P<0.05). The risk of depression was not significant for gender, duration of diabetes, area of residence, education status, dialysis status and BMI of the patients.

Conclusions: Fifty nine percent of all patients were found to be affected by depression. Age, duration of kidney disease, lack of medical bill reimbursement, hemoglobin, GFR and Hb1Ac levels were found to be significant risk factors for depression.

SA-PO937

Prevalence and Correlates of Sexual Dysfunction in Women on Hemodialysis: A Multinational Cross-Sectional Study Valeria M. Saglimbene,[1,2] Suetonia Palmer,[3] Giovanni F.M. Strippoli.[1,2,4] *[1]Diaverum Medical Scientific Office; [2]Univ of Sydney; [3]Univ of Otago Christchurch; [4]Univ of Bari, on behalf of the CDS Investigators.*

Background: Sexual dysfunction may affect 80% of women with chronic kidney disease, however the specific domains of sexual function most affected and the clinical correlates of sexual dysfunction remain poorly described. We assessed the prevalence and correlates of the domains of sexual dysfunction among women with ESKD treated with hemodialysis.

Methods: We conducted a prospective multinational, cross-sectional study involving 1309 women treated with hemodialysis. Individual domains of sexual dysfunction were assessed using the self-reported Female Sexual Function Index (FSFI).Women provided responses anonymously with lower scores in each domain representing greater sexual dysfunction. The individual domain scores were then totaled and multiplied by a predetermined factor to weigh each domain equally. Correlates of each domain were identified using stepwise multivariable linear regression. Sensitivity analyses considered women who reported being sexually active.

Results: Of 1309 enrolled women, 659 (50.3%) provided complete responses to FSFI survey questions and 35% reported being sexually active. Overall, most respondents reported either no sexual activity or high sexual dysfunction in all measured domains (orgasm 75.1%; arousal 64.0%; lubrication 63.3%; pain 60.7%; satisfaction 60.1%; sexual desire 58.0%). Respondents who were waitlisted for a kidney transplant reported scores consistent with less sexual dysfunction, while older respondents reported scores consistent with greater dysfunction. The presence of depression was associated with worse lubrication and pain scores [mean difference for depressed versus non-depressed women (95% CI) -0.42 (-0.73 to -0.11), -0.53 (-0.89 to -0.16), respectively] while women who had experienced a previous cardiovascular event reported higher pain scores [-0.77 (-1.40- to -0.13)].

Conclusions: Women with ESKD report marked sexual dysfunction across a range of domains, which appear to be associated with medical comorbidity.

SA-PO938

The Association of Albuminuria and Kidney Dysfunction with the Risk of the Major Dementia Subtypes in a Japanese Community-Based Population: The Hisayama Study Keita Takae,[1] Jun Hata,[1] Tomoyuki Ohara,[1] Masaharu Nagata,[2] Kazuhiko Tsuruya,[1] Takanari Kitazono,[1] Yutaka Kiyohara,[3] Toshiharu Ninomiya.[1] *[1]Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; [2]Shin-eikai Hospital, Kitakyushu, Fukuoka, Japan; [3]Hisayama Research Inst for Lifestyle Diseases, Fukuoka, Japan.*

Background: Several prospective studies have reported that albuminuria and kidney dysfunction are both risk factors for cognitive impairment and dementia. However, few studies have assessed this issue considering dementia subtypes in Asian populations.

Methods: A total of 1,651 community-dwelling Japanese subjects aged ≥60 years without dementia were followed for 10 years. The hazard ratios (HRs) for the development of all-cause dementia and its subtypes, namely, Alzheimer's disease (AD), and vascular dementia (VaD), were estimated according to the levels of urine albumin-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) using a Cox proportional hazards model.

Results: During the follow-up, 358 subjects developed all-cause dementia (238 ADs and 93 VaDs). Compared with those with UACR of ≤6.9 mg/g, multivariable-adjusted HRs (95% confidence intervals [CI]) for the development of all-cause dementia were 1.12 (0.78-1.61), 1.64 (1.17-2.30), and 1.55 (1.10-2.17) in subjects with UACR of 7.0-12.7, 12.8-29.9, and ≥30.0 mg/g, respectively, after adjustment for age, sex, educational level, history of stroke, systolic blood pressure, anti-hypertensive treatment, diabetes, total cholesterol, body mass index, eGFR, smoking habits, alcohol intake, and regular exercise.Likewise, higher albuminuria levels were associated with greater adjusted risks of AD(HR [95% CI]: 1.22 [0.79-1.89], 1.74 [1.15-2.63], and 1.57 [1.03-2.40], respectively) and VaD (HR [95% CI]: 1.03 [0.46-2.29], 1.94 [0.96-3.95], and 2.19 [1.10-4.38], respectively). However, kidney dysfunction (eGFR ≤60 mL/min/1.73m^2) was not associated with the development of AD or VaD after adjustment for confounding factors.

Conclusions: Albuminuria is a significant risk factor for the development of both AD and VaD, but kidney dysfunction was not in a Japanese community-based population.

SA-PO939

Renal Metabolic Factors and MRI Findings in CKD: The BRain IN Kidney Disease Study Anne M. Murray,[1] Yelena Slinin,[2] Cynthia S. Davey,[3] Prashanthi Vemuri.[3] *[1]Hennepin County Medical Center, Minneapolis, MN; [2]Mayo Clinic, Rochester, MN; [3]Univ of Minnesota, Minneapolis, MN.*

Background: The extent that renal metabolic factors beyond eGFR contribute to the recognized increased risk of MRI pathology in CKD patients has not been adequately measured. We previously identified elevated phosphorus, anemia, and low cholesterol as factors associated with cognitive impairment in our BRain IN Kidney disease (BRINK) study cohort.

Methods: We included non- dialysis BRINK CKD participants with eGFR <60 mL/min/1.73 m^2. We assessed the cross- sectional relation between baseline hemoglobin, serum phosphorus, and cholesterol and baseline brain MRI outcomes using linear regression models adjusted for age, gender, race, education, eGFR, stroke and diabetes.All MRI scans were acquired on a 1.5 T Phillips Ingenia scanner. We used structural MRI (MPRAGE), to measure gray matter regional cortical thickness, FLAIR to measure cerebrovascular disease, T2* GRE imaging for microhemorrhage, and diffusion tensor imaging (DTI) for microstructural changes.

Results: 166 CKD BRINK patients with baseline MRI were included in analyses: mean age = 70, mean eGFR = 32.4 (± 10.4), 8.4% Black race, mean education 14.2 years, 48% with diabetes, 15% previous stroke, mean phosphorous 3.6 (± 0.7) mg/dL, mean hemoglobin 12.9 (±1.8) g/dL,and mean cholesterol 176(± 44) mg/dL. Lower hemoglobin (-1 mg/dL) was associated with a) lower occipital thickness (-0.04 [0.02], P = 0.025), parietal thickness (-0.08 [0.04], P = 0.027), and mean whole brain cortical thickness (-0.014 [0.01], P = 0.045) and with (b) higher DTI medial diffusivity in the gray matter temporal lobe (5.5 [2.3], P=0.021) and white matter occipital lobe (3.5 [1.7],P= 0.043). Higher phosphorus (1 mg/dL) was associated with increased subcortical infarcts (0.21 [0.09], P=0.025).

Conclusions: We identified anemia and elevated phosphorus as potential mechanisms of MRI pathology in CKD, but 3 year follow up MRIs are needed to confirm these results and their association with cognitive impairment.

SA-PO940

Association between Brain Magnetic Resonance Imaging Pathology and Cognitive Performance in Patients Receiving Maintenance Hemodialysis David A. Drew,[1] Rafeeque Bhadelia,[2] Hocine Tighiouart,[1] Tammy Scott,[1] Sarah M. Duncan,[1] Daniel E. Weiner,[1] Mark J. Sarnak.[1] *[1]Tufts; [2]BIDMC.*

Background: Although hemodialysis (HD) patients have high rates of clinical stroke and cognitive impairment, there are limited data on the association between subclinical structural brain pathology and cognitive function.

Methods: In the Boston Dialysis Study, we obtained brain magnetic resonance imaging (MRI) in 45 HD patients without clinical history of stroke. We assessed the severity of white matter disease and cerebral atrophy (sulcal and ventricular prominence) using a semi-quantitative scale (0 to 9) and determined hippocampal size (0 to 3) as well as prevalence of small and large vessel infarcts. A comprehensive battery of cognitive tests was administered, with individual test results reduced into two summary scores, representing memory and executive function. Summary scores have a mean of zero and standard deviation of one. Using multiple linear regression, we determined the association between each MRI finding and summary scores, adjusting for demographics, education, vascular access type, and history of cardiovascular disease.

Results: Mean age (SD) was 55 (17) years, with 50% women, 43% African American, 49% with at least some college education, and median dialysis vintage (25^{th} – 75^{th}) of 20 months (7 – 39). Both greater ventricular and hippocampal atrophy were associated with worse memory in unadjusted analyses but were non-significant in fully adjusted analyses. More severe white matter disease, cerebral atrophy and presence of subclinical infarcts were all associated with worse executive function. After adjustment, sulcal prominence remained significant, while ventricular prominence showed a trend.

MRI findings	Memory Function Summary Score				Executive Function Summary Score			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	SD difference (95% CI)	p	SD difference (95% CI)	p	SD difference (95% CI)	p	SD difference (95% CI)	p
White Matter Grade	-0.07 (-0.23, 0.10)	0.4	0.07 (-0.11, 0.25)	0.5	**-0.14 (-0.27, -0.01)**	**0.04**	-0.03 (-0.18, 0.13)	0.7
Sulcal Grade	-0.08 (-0.24, 0.08)	0.3	0.18 (-0.03, 0.39)	0.09	**-0.23 (-0.35, -0.12)**	**<0.001**	**-0.23 (-0.40, -0.06)**	**0.01**
Ventricular Grade	**-0.14 (-0.28, -0.01)**	**0.04**	-0.04 (-0.21, 0.14)	0.7	**-0.17 (-0.28, -0.06)**	**0.002**	-0.14 (-0.28, 0.01)	0.06
Hippocampal Grade	**-0.53 (-0.92, -0.13)**	**0.01**	-0.19 (-0.66, 0.27)	0.4	-0.29 (-0.64, 0.07)	0.1	-0.21 (-0.60, 0.19)	0.3
SVI or LVI	0.11 (-0.48, 0.70)	0.7	0.48 (-0.13, 1.08)	0.1	**-0.51 (-0.98, -0.04)**	**0.04**	0.02 (-0.52, 0.57)	0.9

SD = standard deviation, SVI = small vessel infarct, LVI = large vessel infarct
Bold = statistically significant findings
White Matter, Sulcal and Ventricular Grades scored from 0-9, with 9 indicating worse pathology. Hippocampal grade scored from 0-3, with higher scores indicating greater atrophy. Effect size is per 1 point increase in scale for all predictors, except for SVI or LVI which is binary
*Adjusted for age, sex, race, education, vascular access, and history of cardiovascular disease

Conclusions: Structural brain pathology in patients treated with hemodialysis is associated with worse cognitive function. Demographics, including age and cardiovascular disease may in part explain these associations.

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SA-PO941

Chronic Kidney Disease in Patients with Alzheimer Disease Wieslawa Janczak, Jolanta Malyszko. *2nd Dept Nephrology, Medical Univ, Bialystok, Poland.*

Background: Elderly people suffer from physiological or pathological ageing. The prevalence of both dementia and CKD increases in age above 65 years. It is important to assess CKD prevalence in elderly patients with dementia.

Methods: We analyzed retrospectively a group of n=188 elderly (aged 80.6 years) people with Alzheimer disease hospitalized in Geriatric Department, Medical University for whom renal function had been evaluated using three following formulas: CKD-EPI, Cockcroft-Gault (CG) and MDRD. All of the patients has normal serum creatinine according to the hospital central laboratory (IDMS validated Jaffe method). Neurocognitive functions had been tested with use of Mini-Mental State Examination (MMSE). For all of selected patients MMSE score was less than 24.

Results: For analyzed group with Alzheimer disease obtained mean value of eGFR/creatinine was different depending on evaluation method.

eGFR ml/min/1.73m^2	eGFR > 90	eGFR 60-89	eGFR 30-59	eGFR 15-29	eGFR <15
CG	1.06%	17.55%	70.74%	10.64%	0.00%
MDRD	6.38%	50.00%	42.02%	1.60%	0.00%
CKD-EPI	0.53%	44.68%	53.19%	1.60%	0.00%

Mean serum creatinine in the studied group was 1.01 mg/dl. CKD was defined when level of eGFR was less than 60ml/min/1.73m^2 and it was diagnosed in 81.38% of the group according to CG, in 43.62% according to MDRD and in 54.79% according to CKD-EPI. Despite normal serum creatinine CKD was found in more than half of the studied population. Mean BMI was 25 kg/m^2. MMSE score did not correlate with eGFR/creatinine.

Conclusions: CKD frequently occurs among group of elderly people with Alzheimer disease. However it is determined for different percentage of the group depending on estimation method (CKD-EPI, C-G, MDRD). This may lead to uncertainty of diagnosis for some patients. As patient with Alzheimer disease hardly cooperates, it is important to emphasis the presence of impaired kidney function on patient's and caregiver's education on renal function and its consequences. The difference between CG- and other two formulas may be due to nutrition status and body mass. Assesment of kidney function is of utmost importance for drug dosing, as they are subjected for polypharmacy.

Funding: Government Support - Non-U.S.

SA-PO942

Depressive Symptoms and Cognitive Impairment in Adults with Chronic Kidney Disease Michael J. Fischer,[1] Dawei Xie,[2] Melissa Lamar,[1] Qiang Pan,[2] Lydia Bazzano,[4] Alan S. Go,[5] Edward J. Horwitz,[6] Manjula Kurella Tamura,[3] Eva Lustigova,[4] Akinlolu O. Ojo,[7] Ana C. Ricardo,[1] Stephen L. Seliger,[8] Jonathan J. Taliercio,[9] Kristine Yaffe,[3] James P. Lash.[1] *[1]U. Illinois; [2]U. Penn; [3]UCSF; [4]Tulane; [5]Kaiser Permanente; [6]MetroHealth; [7]U. Michigan; [8]U. Maryland; [9]Cleveland Clinic.*

Background: Depression and cognitive impairment are common in adults with chronic kidney disease (CKD), and are associated with worse health outcomes. While the relationship between depression and cognitive impairment has been studied in end-stage renal disease, it has not been examined in earlier stages of CKD.

Methods: We conducted cross-sectional and longitudinal analyses of depressive symptoms (DS) and cognitive function among adult participants with CKD in the prospective multicenter Chronic Renal Insufficiency Cohort (CRIC) Study. Elevated DS were defined by a Beck Depression Inventory (BDI) score >= 11. Global cognitive function was assessed by the Modified Mini-Mental State Exam (3MS) where scores range 1-100. At baseline, linear regression was used to examine the relationship between elevated DS and 3MS scores. During follow up, mixed linear models were used to evaluate the relationship between baseline elevated DS and change in 3MS scores over time. All analyses were adjusted for center, sociodemographic, comorbidity, laboratory, kidney function, and proteinuria covariates.

Results: Among 3863 adults with CKD, 27% had elevated DS at baseline. Mean (SD) 3MS score was 89.4 (0.3) and 93.2 (0.3) in those with and without elevated DS at baseline, respectively (p < .0001). In fully adjusted analyses, mean 3MS score was significantly lower among those with elevated DS [beta coefficient = -0.81 (-1.34 to -0.29)] at baseline. During a median follow up of 5.9 years, the overall mean annual change in 3MS score was -0.03. In fully adjusted analyses, the relationship between baseline elevated DS and change in 3MS score over time was not significant (p=0.92).

Conclusions: In a large diverse adult cohort with CKD, elevated depressive symptoms are independently associated with worse cognitive function at baseline but not with changes in cognitive function over time. Whether treatment of depression leads to improvement in cognitive function warrants further study.

Funding: NIDDK Support, VA Support

SA-PO943

Depression and Suicidal Ideation Is Associated with Renal Function in Predialysis Chronic Kidney Disease Patients Hae-Ryong Yun, Jong Hyun Jhee, Min-Uk Cha, Hyoungnae Kim, Seung Hyeok Han. *Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.*

Background: Depression including suicidal ideation is prevalent mental health problems in patients with end-stage renal disease (ESRD). Uremia related factors have been suggested as causes of this increased prevalence in ESRD patients. Although uremic toxicity is known to be increased even in early chronic kidney disease (CKD) patients, the relationship between depression and renal function is not well elucidated. Therefore, the association between renal function and depressive symptoms including suicidal ideation was investigated in predialysis patients with CKD.

Methods: Subjects whoparticipated in the Korea National Health and Nutritional Examination Survey (KNHANES) from 2010 to 2014 were evaluated. Subjects younger than 18 years or older than 75 years and CKD stage 5 patients were excluded. Depression was screened using the Korean version questionnaire. Suicidal ideation was assessed by a positive answer to the question 'In the last 12 months, have you ever thought about committing suicide?'.

Results: A total of 21,250 subjects were evaluated.Suicidal ideation was found in 2518 (11.8%) patients, and 5235 (24.6%) patients had depressive symptoms. Suicidal ideation was reported in 101 (11.5%), 86 (12.9%), 63 (18.4%), and 6 (33.3%) of each CKD stage 1, 2, 3 and 4 respectively (P for trend <0.001). Depressive symptoms were reported in 193 (21.9%), 170 (25.4%), 111 (32.5%), and 8 (44.4%) of each CKD stage 1, 2, 3 and 4 respectively (P for trend 0.002). When the relationship between renal function and mental health problems was evaluated, lower eGFR showed a significant relationship with having suicidal ideation (OR 0.95, 95% CI 0.97-0.99, P=0.02) even after adjustments with confounding factors.

Conclusions: Depressive symptoms and suicidal ideation were significantly more common in advanced CKD stage patients. Evaluation and management strategies for mental health issues should be considered in predialysis CKD patients.

SA-PO944

Qualitative Study of Coping Strategies Used by Patients with Advanced Kidney Disease Lalita Subramanian,[1] Martha Quinn,[2] Junhui Zhao,[1] Jarcy Zee,[1] Laurie Lachance,[2] Francesca Tentori.[1,3] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]The Center for Managing Chronic Disease, Univ of Michigan, Ann Arbor, MI; [3]Vanderbilt Univ Medical Center.*

Background: Chronic kidney disease (CKD) and its treatment impact patients' physical and mental health, as well as identity, lifestyle and relationships. Strategies used by patients to cope with these are not well elucidated. Using data from the Empowering Patients on Choices for Renal Replacement Therapy (EPOCH-RRT) Study, coping strategies were explored.

Methods: CKD patients with eGFR <25 mL/min/1.73 m^2 were interviewed in 2013, using a protocol developed in collaboration with patients, caregivers and healthcare

professionals. Data from 65 CKD not on dialysis (CKD-ND), 76 hemodialysis (HD), 38 peritoneal dialysis (PD) patients on how they cope with their kidney problems were analyzed to identify thematic categories, and then classified based on the Hierarchical Factor Structure of the Coping Strategies Inventory (CSI, Tobin et al., Cog. Ther. Res. 1989).

Results: 17 of the 38 themes that emerged were common to HD, PD and CKD-ND patients, while some were specific to each group. "Take care of myself and follow doctor's orders" and "rely on family and friends for support and encouragement" were among the top three themes for all three groups.

Table 1: Top themes classified using primary, secondary and tertiary CSI subscales

Top Themes	CSI Subscales	Sample Quotes
Take care of myself and follow doctor's orders	1° Problem solving 2° Problem focused 3° Engagement	"I just make sure I stay on my diet and try not to cheat very much! (*laughs*) And, uh, and, and keep up with my blood work and stuff." (CKD-ND patient)
Accept it	1° Cognitive restructuring 2° Problem focused 3° Engagement	"Uh, just, uh, I have no choice! I have to accept it, for what it is. If I was railing against it, that's not gonna get me anywhere! (*laughs*) So, I just, I accept it and, uh, try to live a productive life." (PD patient)
Rely on family or friends for support and encouragement	1° Social support 2° Emotion focused 3° Engagement	"I have an amazing support system of family and friends that, that I would not be able to, to deal with everything that's, as well as I do without them. They, they keep me sane." (HD patient)
Positive attitude	1° Cognitive restructuring 2° Problem focused 3° Engagement	"I just keep attempting to re-direct. If I do go into a negative space, I just keep attempting to re-direct, stay positive, think about what I do have, do what I can do, not focus on what I can't do" (HD patient)

Conclusions: CKD patients use a variety of coping strategies to deal with their disease. Some strategies were more commonly reported according to the stage of disease and treatment type. Overall, engagement strategies were more diverse and more frequently cited than disengagement strategies. Awareness of effective coping strategies used by others could improve coping and result in better health outcomes for CKD patients.

Funding: Private Foundation Support

SA-PO945

Physical Activity Level Impacts Life Quality in Patients with CKD

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Background: The aim was to investigate the relationship between the main lifestyle-related factor, physical activity (PA) and health-related quality of life (HRQoL) in a samples of patients (pts) with chronic kidney disease (CKD), with chronic conditions (CC) and controls with respect to the age, gender or body mass index (BMI) differences in groups.

Methods: A cross-sectional study was conducted on 1006 pts (322 male and 684 female pts, age range 18.9–89.1 years) recruited at primary health care centers and the university hospital. The patient's age, self-reported smoking status and BMI were used as independent variables to predict PA level (MET-mins/week, assessed by International Physical Activity Questionnaire, IPAQ), the physical component scores (PCS) and mental component scores (MCS) of HRQoL (assessed by SF-36).

Results: Mean SF-36 score among pts with low PA was 113.5 (95% CI: 105.3…121.8), median PA 122.2 (95% CI: 117.9…126.5) and high PA 123.2 (95% CI: 119.0…127.4; p = 0.1144. After adjustment for age, gender, disease status, smoking, or BMI no statistical differeneces were found (p = 0.0737). However, among CKD pts similar analysis revealed a statistically significant result: mean score 110.9 (95% CI: 102.6…119.2; p = 0.0000). PA impact to SF-36 score was statistically different between studied pts groups (p=0.014). Low, median and high PA unadjusted mean score was in CKD pts accordingly 70.7, 115.6, 120.9, in CC pts 104.0, 124.1, 131.6. After the adjustment p = 0.0064. Mean TOTAL_MET in CKD pts 3773.8 (95% CI: 2678.8…4868.8). Pts with low PA formed 17.1% (95% CI: 10.5…25.7%), mean PA 44.8% (95% CI: 35.0…54.8%) and high PA 38.1% (95% CI: 28.8…48.1%). Interestingly, there was no statistically significant differences in distribution of PA levels between CKD and CC pts (p = 0.1642); CKD pts and controls (p = 0.5494) or CKD pts with eGFR >45 and < 45 ml/min.

Conclusions: PA level impacts life quality in patients with CKD. The distribution of PA level is similar among CKD pts irrespectively the kidney function.

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SA-PO946

Membranous Nephropathy (MN): Baseline Health Related Quality of Life (HRQOL) in Patients with Severe Nephrotic Syndrome (SNS) in the Membranous Nephropathy Trial of Rituximab (MENTOR) RCT

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Background: HRQOL is an important patient reported outcome compromised in people with kidney failure. MN with SNS has potential physical and emotional consequences for patients but its impact on HRQOL has not been studied.

Methods: Baseline HRQOL data were collected from 130 patients (77% male; age 52 + 12.5 years) with MN and SNS (Uprotein 10.4 gm +4.7; CrCl 89.6 +32.6 ml/min/BSA; Salbumin 2.6 +0.5g/dL) participating in MENTOR. HRQOL was measured with the KDQOL-SF™1.3 (modified by removing dialysis questions and adding symptoms unique to MN).

Results: Scores for Effects of Kidney Disease (m=72 .7+ 21.8) and Symptom burden (m=76.5 + 15.5) showed only moderate impact with swelling of the feet/ankles and feeling washed out being the most burdensome symptoms. Whereas Burden of Kidney disease (m=52.7 + 28.5) and Overall Health (62.8 + 18.4) scores were more severely effected and only marginally better than reported for dialysis patients. On generic items, Role Limitations-Physical (55.1 + 45,4) and Energy/fatigue (47.9 +24.8) were considerably worse than healthy controls and only slightly better than dialysis patients. Physical Health Composites (PCS) (42.5 +11.1) were better than dialysis populations but worse than healthy controls, while Mental Health Composites (MCS) (48.8+9.7) were only marginally different than people on dialysis (better) and healthy controls (worse). Regression models were calculated to predict PCS and MCS by selected demographic and clinical variables. Male sex (p=0.002) and higher CrCl (p=0.02) were significant predictors of better PCS scores. None of the variables significantly predicted MCS.

Conclusions: MN impacts HRQOL, particularly physical functioning, burden of kidney disease and overall health. Women and those with worsening kidney function are at particular risk for poor physical functioning. Given the association between HRQOL and clinical outcomes (e.g.morbidity and mortality), it is essential for clinicians to assess the impact of MN on HRQOL and to develop strategies to help patients minimize the burden of their disease.

Funding: Pharmaceutical Company Support - Genentech, Private Foundation Support

SA-PO947

Quality of Life Progression during Dialysis Initiation

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Background: Dialysis initiation is associated with emotional distress and poorer quality of life (QOL). Reduced internal (resilience) and external (emotional support) resources may predict which patients are at greater risk of QOL decline.

Methods: This prospective enrolment study assessed QOL parameters (see below) in relation to Connor-Davidson Resilience Scale and Emotional Support scores at 3 time periods: 183 ± 154 (mean ± SD) days prior to dialysis initiation, and 19 ± 14, and 104 ± 13 days after dialysis initiation. The repeated QOL measurements were analyzed using a longitudinal mixed effects model with either resiliency or emotional support, at enrolment, included as independent predictors, adjusting for temporal and patient level factors.

Results: In the 49 patients who successfully completed the three QOL assessments, the resiliency and emotional support scores were 84.7 ± 9.2 (score range 0-100), and 44.7 ± 21.0 (score range 0-60), respectively. All QOL parameters tended to drop significantly with the initiation of dialysis, and then rising towards baseline at the last assessment. Resiliency and emotional support had a strong positive association with nearly all the QOL parameters included in this study before, during, and after dialysis initiation.

Quality of Life (QOL) Parameters	Estimate (p-value) Resiliency*	Estimate (p-value) Emotional Support*
KDQOL-36:		
Physical Component	0.33 (0.004)	NS
Mental Component	0.32 (<0.001)	0.11 (0.016)
Kidney Disease Burden	1.07 (<0.001)	0.39 (0.005)
Symptoms/Problems	0.25 (0.026)	0.13 (0.004)
Effects of Daily Life	0.29 (0.003)	0.12 (0.005)
PROMIS:		
Global Physical Health	0.13 (<0.001)	0.04 (0.016)
Global Mental Health	0.18 (<0.001)	0.06 (0.001)
Applied Cognitive Abilities	0.87 (<0.001)	0.25 (0.040)

**Estimated effect of a 1-point change in Resiliency/Emotional Support on QOL parameters.*

Conclusions: During sequential measurements, QOL declines during dialysis initiation and returns to baseline in most patients. Lower levels of internal (resiliency) and external (emotional support) resources are associated with lower QOL scores, suggesting a possible modifiable relationship during this vulnerable period.

Funding: Private Foundation Support

SA-PO948

Survey Questionnaire on Improved Quality of Life (QoL) in Chronic Kidney Disease (CKD) Patients with One or More Co-Morbid Conditions Using Renadyl™, a Pro and Prebiotic Dietary Supplement

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Background: Probiotics and Prebiotics are widely used for digestive and immune health. Recent scientific advances, in the field of "Gut Microbiome" and its modulation using Pro/Prebiotics beyond gut health is growing in various diseases including gut-brain connection and gut-kidney connection. Renadyl™; a Pro/Prebiotic dietary supplement has demonstrated its potential to reduce serum uremic toxins in a pharma like validation with *in vitro* and clinical studies in animals and humans. This case study aimed to collect information on QoL and health status through modulation of gut microbiome in CKD patients using Renadyl™.

Methods: 834 patients using Renadyl™ were sent survey questionnaires. Results were analyzed using SAS V9.2 and MS Excel.

Results: 168 responses were received (20% response rate, 42% female, 47% male, aged 12-98 years). 85% were over 51 years of age, 58% in stage III/IV of kidney disease with 77% having at least one comorbid condition, and 48% were retired. 61% experienced improvement since taking Renadyl™. Statistical analysis indicated a significant difference ($p<0.0001$) in distributions of QoL responses before and after taking the product. Multivariate analysis indicated that duration of administration ($p<0.0001$), employment ($p<0.012$), comorbidity ($p<0.012$), and GFR ($p<0.0015$) were significant factors influencing the reported QoL. Even disabled respondents reported significant improvement.

Conclusions: This patient/consumer survey showed the ability of Renadyl™to provide benefit to patients in all stages of CKD and dialysis and with a variety of comorbid conditions. It appears to have a stabilizing effect on the overall health status and QoL, maintaining or improving kidney health in particular. Further, adequately powered studies that could establish a clearer correlation between this supplement and its impact on GFR are warranted.

Funding: Pharmaceutical Company Support - Kibow Biotech Inc

SA-PO949

Differences in Patient and Renal Provider Assessment of Physical Symptoms, Quality of Life, General Health, and Depressive Symptoms in Chronic Kidney Disease Fredric O. Finkelstein,[1] Juan Calderon,[1] Alan S. Kliger,[1] Bridget A. Forbes,[2] Monica Cimini.[2] *[1]Nephrology, Yale School of Medicine, New Haven, CT; [2]Metabolism Associates, New Haven, CT.*

Background: Wide discrepancies in symptom burden perception between dialysis patients and their renal providers have been previously well documented. This can result in significant undertreatment of dialysis patients' symptoms. Providers' ability to recognize physical symptoms (PS) and perceptions on general health (GH) and quality of life (QoL) in patients with chronic kidney disease (CKD) has not been studied yet. The aim of this study is to examine the degree of patient-provider concordance in terms of their perceptions of PS, GH, and QoL in patients with CKD.

Methods: A standardized questionnaire was administered synchronously to each patient and the treating renal provider at the time of their routine clinic appointment. The survey was comprised of eighteen questions addressing PS, overall GH and QoL. We used a Likert scale to grade severity of symptoms. We compared the net sum of all rated physical symptoms, PHQ2 score, GH and QOL between patients and providers and analyzed discrepancies based on CKD stages.

Results: A total of eighty patients and providers completed the survey. Providers underscored severity of PS in 27% of cases and overscored them in 18% of cases. Net sum of PS severity across the entire sample was 1150 points for providers versus 1301 points for patients. Agreement in severity of physical symptoms occurred in 55% of cases. Underrecognition of PS was highest at stage 5. The percentage of concordance when assessing perception of GH was 34%, with highest percentage of concordance in advanced stages of CKD. For QoL analysis, providers underestimated their patients QoL in 36% of cases and both had concordant scores in only 44% of cases.

Conclusions: Underrecognition of the severity of PS and underestimation of perception of quality of life in CKD patients by renal providers, particularly in more advanced CKD, is problematic. In contrast, both providers and patients' perception of general health have increased concordance, particularly at more advanced CKD stages.

SA-PO950

Is Caregiver Burden Associated with Chronic Kidney Disease (CKD) Patients' Quality of Life? Tara Liaghat, Khaled Iskandarani, Nasrollah Ghahramani. *Penn State College of Medicine, Hershey, PA.*

Background: The kidney disease quality of life 36 (KDQOL36) is an instrument developed to measure several components related to the quality of life of patients with CKD, while the burden interview survey (BIS) is an instrument developed to measure caregiver burden. The aim of this study was to investigate whether caregiver burden indicated by BIS total score is associated with patients' quality of life components as measured by the KDQOL36.

Methods: Stage 4 and 5 CKD patients were paired/ matched to a caregiver. The patients completed the KDQOL36 instrument, while their respective caregivers completed the BIS. A multivariable linear regression model of caregiver BIS total score predicted by patients' scores on each of the 5 subcomponents was fit while adjusting for age, sex, and Hispanic ethnicity of caregiver.

Results: The sample consisted of 62 patient-caregiver pairs. Lower scores indicating worse performance on the KDQOL36 subscales with the exception of physical composite were statistically significantly associated with higher scores on the BIS, indicating increased care giver burden.

KDQOL36 Subcomponent	Estimate	Standard Error	P-value
KD Symptoms Lists	-0.2683*	0.1181	**0.0272**
KD Effects	-0.2400*	0.08727	**0.008**
KD Burden	-0.1524*	0.04991	**0.0036**
KD Physical component	-0.1569*	0.1481	0.2947
KD Mental component	-0.4903*	0.1476	**0.0017**

*All estimates were adjusted for age, sex, race, and ethnicity. Bolded p-values are statistically significant at $\alpha<0.05$.

Conclusions: Caregiver burden is associated with CKD patients' quality of life, whereby improvements in the patients' quality of life reduce caregiver burden.

Funding Disclosure:Dr. Nasrollah Ghahramani is funded by CDR-1310-07055 from the Patient-Centered Outcomes Research Institute (PCORI).

Funding: Other U.S. Government Support

SA-PO951

Peer Mentoring for Patients with Chronic Kidney Disease and Their Caregivers: A Qualitative Study Tara Liaghat, Eugene Lengerich, Nasrollah Ghahramani, Jennifer Kraschnewski. *Penn State College of Medicine.*

Background: Peer mentorship may enhance patient engagement for those with advanced chronic kidney disease (CKD) (stages 4 and 5); yet, the approaches and qualities (i.e., online vs in-person) that make a good mentor are unclear. This study sought to determine these qualities by conducting focus groups with mentees from the mentorship program in a randomized peer-education study.

Methods: Seven focus group meetings were conducted with mentees (n=20). Mentees were patients with advanced CKD and their caregivers who were matched with trained patient and caregiver peer mentors for in-person or online mentorships. Meetings were audio-recorded, transcribed, and thematically analyzed by three facilitators who concurred with the significant results.

Results: Three important themes emerged, which were: (1) in-person meetings facilitated meaningful partnerships, more than phone or online communication: "But she knows how I'm feeling when I'm saying it versus when I'm typing it."; (2) good mentors were relatable and good listeners: "They have to be a caring person about other people. Be able to relate. I guess they can relate because they are in the same predicament or already was in that predicament… a good listener too."; and (3) mentorship program provided support: "It changed a whole lot. Him giving me support and also outside my family…so that's been a big positive change for me. A lot of support for the last year and a half since I started."

Conclusions: A mentorship program for patients with advanced CKD may provide them with substantial support, particularly when mentorship is conducted in-person and the mentor is a relatable, empathetic listener. **Funding Disclosure:** Dr. Nasrollah Ghahramani is funded by CDR-1310-07055 from the Patient- Centered Outcomes Research Institute (PCORI).

Funding: Other U.S. Government Support

SA-PO952

Assessment of Quality of Life in Children with Chronic Kidney Disease Based on First 5 Years Data of the Pediatric CKD Cohort Min Hyun Cho,[1] Hee Sun Baek,[1] IL-Soo Ha,[2] Hee Gyung Kang,[2] Hae Il Cheong,[2] Hyun-Jin Choi,[2] Young Seo Park,[3] Joo Hoon Lee,[3] Heeyeon Cho,[4] Jae Il Shin,[5] Kyoung Hee Han,[6] Seong Heon Kim.[7] *[1]Pediatrics, Kyungpook National Univ Children's Hospital; [2]Seoul National Univ Children's Hospital; [3]Asan Medical Center Children's Hospital; [4]Samsung Medical Center; [5]Severance Children's Hospital; [6]Jeju Univ Hospital; [7]Pusan National Univ Children's Hospital.*

Background: Quality of life (QOL) is an essential subject in children with chronic kidney disease (CKD) and their family. In Korea, a 10-year longitudinal study on the patient and renal survival by specific causes of CKD (KNOW-CKD study) has been pursued from 2011 and pediatric cohort is one of subgroups in the groups of KNOW-CKD study.

Methods: We performed a cross-sectional investigation of QOL in children with CKD (Pediatric cohort) using the PedsQL 4.0 Generic Core Scale Module. During 5 years, total 381 pediatric patients with CKD aged 2-18 year old were enrolled from five Korean university hospitals.

Results: The male to female ratio was 259:122 and mean age was 10.1 years old. According to CKD staging, patients were distributed as follows; stage I 72, stage II 75, stage III 124, stage IV 67, stage V 43. Patients with higher CKD stage had significantly lower QOL score in all domains of the parent-proxy reports, but not child-self reports. According to gender, boys had a tendency to present better QOL than girls in the child-self reports, especially in emotional functioning, psychosocial health summary score and total score, but, in the parent-proxy reports, there was no significant difference between these two groups. Age discrepancy was not a significant factor to decide QOL in children with CKD. In addition, there was significant difference between parent-proxy reports and child-self reports and QOL scores in the child-self reports was significantly higher than in the parent-proxy reports.

Conclusions: Residual renal function and gender in children with CKD can be important factors to decide QOL, but there was a significant difference of these results between parent-proxy and child-self reports. Therefore, we need systemic, individualized supporting tools to improve QOL of children with CKD and their families.

Funding: Government Support - Non-U.S.

SA-PO953

The Association of Depression, Perceived Health Status, and Quality of Life between Individuals with and without Chronic Kidney Disease: An Analysis of the National Health and Nutrition Examination Survey 2011-2012 Hoang Anh Nguyen, Cheryl A. Anderson, Cynthia Miracle, Dena E. Rifkin. *UCSD, San Diego, CA.*

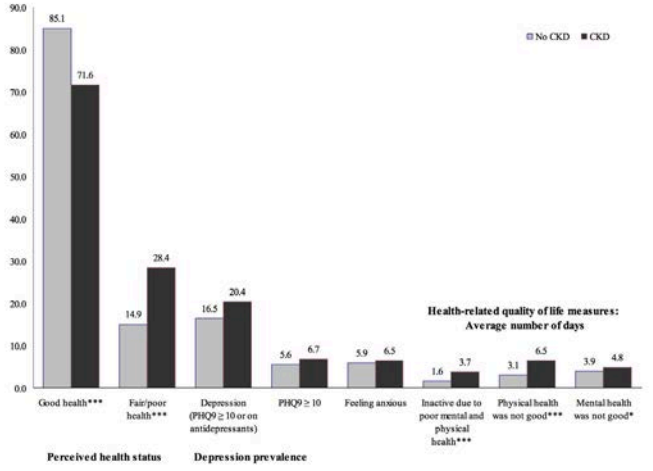
Background: Depression is the most common mental health disorder among those with ESRD, with prevalence of 15-40%. However, the association between CKD and depression is more variable in the literature. We examined associations of CKD with depression, perceived health status, and quality of life in the National Health and Nutrition Examination Survey (NHANES) 2011-12.

Methods: This study included 5,364 adults. Depression was defined by a Patient Health Questionnaire score ≥ 10, or reported antidepressant use. Overall health status was self-rated. Reduced quality of life was defined by the average number of days having poor mental and physical health, or feeling anxious. We calculated odds ratios for the associations

between CKD and depression and self-perceived health status, and used linear regression to examine the associations between CKD and the average number of days of poor health and self-reported anxiety.

Results: The prevalence of CKD was 15.5% and of depression was 16.9%. Figure 1 shows unadjusted results. Those with CKD were not more likely to be depressed vs those without CKD after multivariate adjustment. Although they were 1.8 times more likely to have fair/poor health status after adjusting for demographic characteristics, this was non-significant after adjusting for both demographic and clinical confounders. Those with CKD reported 2 more days of poor physical health and being inactive due to poor health in the past month (p-values < 0.01), after multivariate adjustment. No differences were found for self-reported anxiety.

Figure 1: Perceived health status, depression prevalence, and quality of life among U.S. adult population with chronic kidney disease in NHANES 2011-2012.



Student t-tests were used in the analysis.
***p-value < 0.001, **p-value < 0.01, *p-value < 0.05

Conclusions: Our findings suggest that NHANES participants with CKD have more days of poor health, but are not more likely to be depressed or anxious. This may reflect differences between clinical CKD populations and community-based samples.

Funding: Other NIH Support - T32 Grant

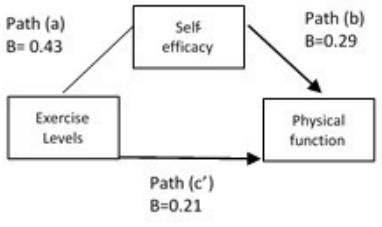
SA-PO954

Exercise and Physical Function in Patients with CKD: The Mediating Role of Self-Efficacy Amy L. Clarke,[1] Joseph Chilcot,[2] Alice C. Smith.[1] *[1]Leicester Kidney Exercise Team, Univ of Leicester, United Kingdom; [2]Inst of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom.*

Background: Chronic kidney disease (CKD) is characterized by low physical functioning (PF), associated with increased mortality. Exercise (EX) may help to retain independence but CKD patients are sedentary. Self-efficacy (SE) is both a determinant and an outcome of EX and may explain the relationship between EX and PF. This study explored if the direct effect of EX levels on PF was, in part, mediated by an indirect effect of SE.

Methods: A survey of non-dialysis CKD patients was conducted between 2012 and 2015. This included 3 validated questionnaires: Duke Activity Status Index to estimate PF, Leisure Time Exercise Question to explore EX levels, and EX Self-Efficacy Questionnaire to explore confidence to EX. Mplus path models were used to estimate the total and indirect effects (with bootstrapped confidence intervals), using maximum likelihood estimation. Standardised model estimates are reported.

Results: 966 patients (age 61SD±18, 57%male, eGFR 39SD±24) were evaluated. EX levels were an independent predictor of PF(B= 0.21, p<.01) and SE(B=0.43, p<.01) after adjustment for age, eGFR and co-morbidity. SE significantly predicted PF after adjusting for above factors and controlling for EX levels(B=0.29, p<.01). There was a significant indirect effect between EX and PF, through SE(Beta = 0.12, 95% CI 0.10, 0.14, p<.05) which accounted for ~37% of the total effect. Overall 54% of the variance in PF was explained.



Conclusions: EX levels are positively associated with PF. Patients who engage in greater levels of EX are more efficacious which may positively impact PF. SE is a modifiable construct important for EX behavioural interventions. Interventions should target processes to enhance SE such as mastery experiences, vicarious learning, social persuasion and physiological/emotional responses.

SA-PO955

Collecting Patient Reported Outcomes in Chronic Kidney Disease: The UK Renal Registry Experience Fergus J. Caskey,[1,2] Retha D. Steenkamp,[1] Rachel May Gair,[1] Sabine Van der Veer,[3] Richard J. Fluck,[4] Claire Louise Corps.[5] *[1]UK Renal Registry, United Kingdom; [2]Univ of Bristol, United Kingdom; [3]Univ of Manchester, United Kingdom; [4]Royal Derby Hospital, United Kingdom; [5]Univ of Leeds, United Kingdom.*

Background: Renal registries are starting to collect patient reported outcomes. This study explores the feasibility of collecting such data in people with CKD in secondary care in England and presents initial results.

Methods: Ten of the 52 adult renal units in England participated. The survey consisted of i) 5 questions on overall health (EQ-5D-5L), ii) 17 questions on symptoms (iPOS-S renal) and iii) 13 questions on the patient's ability to manage their health (PAM). A paper copy of the survey was given to outpatients with pre-dialysis CKD or a transplant and those on maintenance haemodialysis/peritoneal dialysis. Completed surveys were returned to the Registry and scanned into the database. The EQ-5D-5L and iPOS-S renal questions use scales from '0' representing no problems/concerns to '4' representing the highest level of severity/concern. These were recoded to absent/mild (0,1) and moderate/severe/overwhelming (2, 3, 4). PAM was classified from 1 (least) to 4 (most) activated.

Results: In round 1, 334 patients returned surveys from 6 units. The majority (83%) were on haemodialysis. Most completed the survey on their own (49%); the remainder were helped by friends (24%) or clinical staff (27%). They did so at the renal unit (69%), at home (24%) or in clinic (7%). In all patient groups, at least moderate impairments in mobility, self-care, usual activities, pain/ discomfort, anxiety/ depression were reported in 52%, 30%, 54%, 42%, 31%, respectively. The presence of at least moderate symptoms ranged greatly from 12% for vomiting and 15% for diarrhoea to 45% for difficulty sleeping, 54% for poor mobility and 60% for weakness/lack of energy. Amongst respondents, 30% and 10% had activation levels 3 and 4, respectively.

Conclusions: The routine national collection of patient reported outcomes poses practical and logistic challenges. The high burden of symptoms and low activation levels of the majority of patients highlights the importance of capturing these alongside traditional markers of quality of care.

Funding: Government Support - Non-U.S.

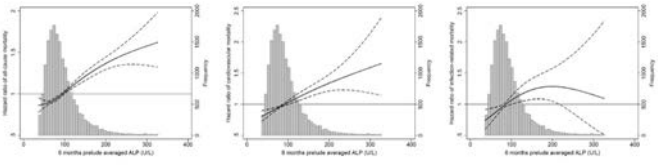
SA-PO956

Prognostic Significance of Pre-ESRD Serum Alkaline Phosphatase for Post-ESRD Mortality in Late-Stage CKD Patients Transitioning to Dialysis Keiichi Sumida,[1,2] Miklos Zsolt Molnar,[1] Praveen Kumar Potukuchi,[1] Fridtjof Thomas,[1] Jun Ling Lu,[1] Yoshitsugu Obi,[3] Connie Rhee,[3] Elani Streja,[3] Kunihiro Yamagata,[2] Kamyar Kalantar-Zadeh,[3] Csaba P. Kovesdy.[1,4] *[1]Univ of Tennessee Health Science Center, Memphis, TN; [2]Univ of Tsukuba, Ibaraki, Japan; [3]Univ of California, Irvine, CA; [4]VA Medical Center, Memphis, TN.*

Background: Higher serum alkaline phosphatase (ALP) has been associated with increased mortality in both non-dialysis dependent CKD and ESRD patients. However, little is known about the impact of ALP levels in advanced CKD on outcomes after dialysis initiation.

Methods: We examined the association of the averaged ALP levels over the last 6 months preceding transition to dialysis, with all-cause and cause-specific mortality during the two-year period following dialysis initiation in 17,985 US veterans transitioning to dialysis between 10/2007-9/2011. ALP levels were categorized into quartiles (<66, 66-85, 86-111, ≥112 U/L). Associations were examined using Cox (for all-cause) and competing risk (for cause-specific mortality) regressions and cubic splines with adjustment for demographics, comorbidities, medications, pre-ESRD 6-month averaged serum albumin and eGFR levels, and access type at dialysis initiation.

Results: Higher ALP levels were associated with increased risk of all-cause, CV, and infectious mortality (Figure). The adjusted hazard/subhazard ratios [95% CI] for ALP quartiles 2 through 4 (vs. quartile 1) were 1.10 [1.04-1.17], 1.12 [1.05-1.19], and 1.42 [1.33-1.51] for all-cause; 1.07 [0.95-1.21], 1.12 [0.99-1.26], and 1.30 [1.15-1.47] for CV; and 1.20 [0.93-1.55], 1.24 [0.96-1.59], and 1.39 [1.09-1.78] for infectious mortality, respectively.



Conclusions: Higher pre-ESRD ALP is associated with increased post-ESRD mortality risk. Further studies are needed to determine if interventions that lower pre-ESRD ALP levels reduce mortality in incident dialysis patients.

Funding: NIDDK Support, VA Support

SA-PO957

Low Serum Levels of Alkaline Phosphatase Are Associated with Greater Total Kidney Volume in Patients with Early Autosomal Dominant Polycystic Kidney Disease

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Background: We have previously identified a low bone turnover state in patients with early autosomal dominant polycystic kidney disease (ADPKD) characterized by decreased bone formation, resorption and low serum levels of alkaline phosphatase (AP). While increased levels of serum AP have been associated with progression in chronic kidney disease (CKD), we sought to determine whether serum AP levels are related to the risk of total kidney volume (TKV) progression in ADPKD.

Methods: Serum AP levels were measured in 524 ADPKD patients with stage 1 and 2 CKD. The data were collected from the HALT- PKD study A, a randomized, placebo-controlled trial to determine whether the combination of an angiotensin converting enzyme inhibitor (ACEI) and angiotensin II-receptor blocker was superior to the ACEI alone, and whether intense blood pressure lowering was superior to standard blood pressure in delaying height-corrected TKV (HtTKV) measured at baseline, 24, 48, and 60 months. AP was modeled as a categorical variable derived from the median value (<56 vs. > or =56 IU/L). We used Generalized Estimating Equation models to examine the association between serum AP levels with repeat measures of HtTKV categorized as below and above 800 ml/m.

Results: At baseline, participants had a mean age and CKD-EPI eGFR, of 37 ± 8 years and 91.4 ± 17.4 ml/min/1.73m^2, respectively. The median (IQR) for AP and HtTKV were 56 (45-69) IU/L and 589 (405-860) ml/m, respectively. After adjustment for age, gender, race, randomization group, body mass index, systolic blood pressure, eGFR, urine albumin excretion, serum calcium, phosphate and parathyroid hormone level a lower AP (< 56 IU/L) serum level was independently and significantly associated with increased odds of a higher HtTKV (OR:149; 95% CI: 1.02-2.18; p=0.04).

Conclusions: Low serum AP, is independently associated with a higher HtTKV in patients with early ADPKD. These findings suggest that altered bone biology in patients with ADPKD may be related to renal disease progression.

Funding: NIDDK Support

SA-PO958

Association between Serum Alkaline Phosphatase and Mortality in Maintenance Haemodialysis Patients

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Background: Studies mainly from the developed countries have revealed higher levels of intact parathyroid hormone (iPTH), calcium, phosphate and alkaline phosphatase as independent predictors of mortality in haemodialysis patients. Data on the existence of this link in African haemodialysis patients are sparse. Therefore, the aim of this study was to assess the impact of serum total alkaline phosphatase (TAP) on mortality in maintenance haemodialysis (MHD) patients.

Methods: This study enrolled a total of 223 patients on MHD from two dialysis centers in Johannesburg between January 2009 and March 2016. Patients were categorized into low TAP group (<112 U/L) versus high TAP group (≥112 U/L) based on median TAP of 112 U/L. By multivariate Cox regression analysis the impact of serum TAP on primary outcome (Death) was assessed.

Results: The MHD patients (147 men, 76 women) had a mean age of 54.5±15.6 years with a median dialysis vintage of 24 months (IQR, 12-48) and a mean kt/V (single pool) of 1.4±0.3. During a period of 7 years there were 52 (23.3%) deaths. After adjusting for cofounders such age, makers of bone disorder (calcium, iPTH, phosphate)and co morbidity (DM); patients in the high TAP group had significant higher risk of death compared to patients in the low TAP group (hazard ratio,2.6;95% CI 1.23-5.45, p=0.01). Similarly, corrected calcium <2.75mmol/L was associated with a lower risk of death compared to patients with calcium ≥ 2.75 mmol/L(HR=0.18, 95%CI 0.04-0.95 ; p=0.04). TAP correlated significantly with iPTH (r=0.3; P<0.001).

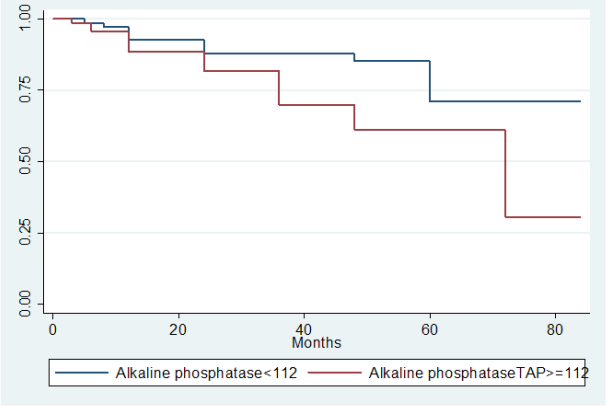

Figure1. Kaplan – Meier survival curves comparing patients with total alkaline phosphatase (<112U/L) to those with total alkaline phosphatase (≥112 U/L).

Conclusions: High levels of serum alkaline phosphate are associated with an increased risk of death in MHD patients. This relatively inexpensive test may be utilized as a surrogate marker for monitoring treatment in End Stage Renal Disease.

SA-PO959

Serum Bone-Specific Alkaline Phosphatases/Total Alkaline Phosphatases Ratio as a Risk Factor for Mortality in Hemodialysis Patients

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Background: The aim of our study was to determine the association between b-ALP,t-ALP, b-ALP/t-ALPand theall-cause mortality in hemodialysis patients.

Methods: The study included226 maintenance hemodialysis patients. Levels of serum b-ALP were measured by ELISA. Survival rates were analyzed using Kaplan–Meier survival curves. A Cox regression model was used to access the possible influence of variables on all-cause mortality.

Results: Study patients had an median age of 58 (48-68) yr-old, with dialysis vintage of 41 (21-72.3) mo, 11.1% with diabetes,and 63.7% male. The respective concentrations of b-ALPandt-ALPwere 19.71(14.85-26.72)U/L and 63.0(50.0-80.5)U/L.The b-ALP/t-ALP ratio ranged from 0.09 to 0.64(median 0.336).B-ALP / t-ALP ratio were significantly lower inhemodialysis patientsversus health controls(P=0.035),whereas there were no differences in serumb-ALPand t-ALPlevel.Significant correlations were found between serum b-ALP and t-ALP,b-ALP / t-ALP ratio,iPTHand P.Patients were followed-up prospectively from the first day of the laboratory measurement for a maximum of 36 monthsor until death. A total of 50 patients died.Kaplan–Meier survival analysis showed higher mortality in the first tertile of b-ALP / t-ALP than in the third tertile (P = 0.042). Cox regression hazard analysis identified lowerb-ALP / t-ALP as a significant predictor [HR 2.39 (95%CI:1.16–4.90)] for all-cause mortality, After adjustment for various factors,this effect is moderate[HR 1.90(95%CI:0.759–4.751)].

Figure1. The association between serum b-ALP ,t-ALP, b-ALP / t-ALP, PTH and P

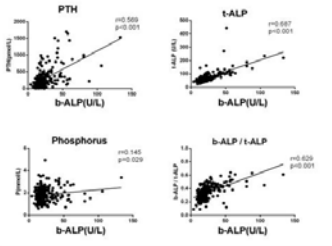

Figure2. The Kaplan-Meier analysis of all-causemortality

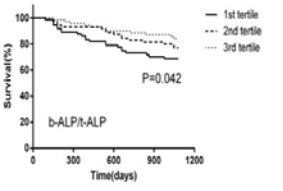

Table1.Hazardratios with 95% confidence intervals for all-cause mortality according to tertiles of b-ALP,t-ALP and b-ALP/t-ALP

		Model1			Model2			Model3		
		HR	95%CI	P	HR	95%CI	P	HR	95%CI	P
b-ALP	First tertile	1.46	0.64-3.32	0.371	1.36	0.60-3.10	0.402	1.37	0.60-3.12	0.442
	Second tertile	3.09	1.50-6.40	0.002	2.74	1.32-5.69	0.008	2.52	1.21-5.25	0.013
	Third tertile	1			1			1		
t-ALP	First tertile	0.60	0.29-1.24	0.164	0.88	0.40-1.89	0.733	0.79	0.34-1.85	0.584
	Second tertile	0.97	0.51-1.85	0.919	0.85	0.44-1.63	0.619	0.84	0.42-1.70	0.627
	Third tertile	1			1			1		
b-ALP/t-ALP	First tertile	2.39	1.16-4.90	0.018	1.41	0.65-3.07	0.381	1.09	0.49-2.43	0.814
	Second tertile	1.5	0.69-3.22	0.304	1.14	0.51-2.56	0.742	0.84	0.36-1.93	0.66
	Third tertile	1			1			1		

Model 1 :unadjusted.
Model 2 :adjusted by sex ,age ,dialysisduration, DM
Model3 :adjusted by sex ,age ,dialysisduration, DM, Hb, ALB, PTH, CA, P

Conclusions: In patients undergoing hemodialysis, lower b-ALP/t-ALP ratiois associated with higher mortality.

SA-PO960

Severity of Secondary Hyperparathyroidism Is Associated with Higher Baseline Bone Markers and Greater Reductions in Calcium in Etelcalcetide-Treated Subjects

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Background: Etelcalcetide (ETL), a novel IV calcimimetic, has been shown to reduce parathyroid hormone (PTH) and corrected calcium (cCa) in adults on hemodialysis (HD) with secondary hyperparathyroidism (SHPT). Bone-specific alkaline phosphate (BSAP) and collagen type 1 cross-linked C-telopeptide (CTx) have also been studied in this population.

Methods: Adult subjects (N=1023) on HD with baseline PTH>400pg/mL were randomized to 26 wks ETL or placebo. ETL was initiated at 5mg IV per dialysis session and titrated every 4 wks (max 15 mg) to achieve PTH<300pg/mL. Results are shown for the ETL arm only (total and by baseline PTH strata) for proportion of subjects with cCa<8.3 mg/dL or <7.5mg/dL and % change in mean PTH and cCa during the efficacy assessment phase (EAP) at wks 20 to 27 compared to baseline values. BSAP and CTx are shown for wks 12 and 27 compared to baseline values.

Results: Table 1 shows baseline laboratory values by baseline PTH strata. The highest PTH stratum demonstrated greater reduction in cCa and included the highest proportion of subjects with <7.5mg/dL despite comparable PTH reduction across strata. Reductions in CTx were observed at wks 12 and 27, which were similar across PTH strata. Conversely, BSAP increased at wk 12 similarly across strata, but decreased at wk 27, which was most pronounced in the highest baseline PTH stratum. Mean ETL dose during EAP increased with SHPT severity.(Table 2)

Conclusions: Following initiation of ETL, early decreases in CTx were observed whereas BSAP actually increased, potentially driving net bone calcium influx. With

increased SHPT severity, there were higher baseline biomarkers of bone metabolism (BSAP and CTx), a greater percentage reduction in cCa, and a higher proportion of subjects with low calcium.

Table 1. Baseline Laboratory Values by baseline PTH

	Entire Cohort (N = 509)	Stratum A PTH < 600 pg/mL (n =172)	Stratum B PTH 600 - 1000 pg/mL (n = 225)	Stratum C PTH > 1000pg/mL (n = 112)
PTH pg/mL	846.9 (492.6)	509.8 (71.0)	780.6 (120.6)	1497.6 (679.1)
cCa mg/dL	9.64 (0.66)	9.57 (0.63)	9.64 (0.68)	9.74 (0.64)
*BSAP µg/L	23.3 (15.4, 34.6)	17.5 (13.0, 24.6)	23.8 (15.9, 33.8)	34.6 (23.6, 54.1)
*CTX ng/L	2950 (1970, 4160)	2310 (1680, 2930)	3130 (1960, 4240)	4280 (3310, 5390)

BSAP = bone specific alkaline phosphatase; cCa = corrected calcium; CTX = cross-linked C-telopeptide (CTx); PTH = parathyroid hormone
*Median (Q1, Q3); All other values are mean (SD)

Table 2. Reduction in Calcium Levels and Change in Bone Biomarkers by Baseline PTH

	Entire Cohort (N=509)	Stratum A PTH < 600 pg/mL (N=172)	Stratum B PTH 600 – 1000 pg/mL (N=225)	Stratum C PTH > 1000 pg/mL (N=112)
[a]PTH, % Change	-56.3% (1.4)	-54.2% (2.3)	-58.2% (1.9)	-55.5% (3.2)
[a]Ca, % Change	-7.0% (0.4)	-5.1% (0.6)	-7.5% (0.6)	-8.9% (0.9)
*cCa < 8.3 mg/dL (% patients)	78.6%	75.3%	80.5%	79.5%
*cCa < 7.5 mg/dL (% patients)	27.1%	23.5%	25.8%	34.8%
[b]BSAP % change (wk 12)	9.9% (2.3)	10.3% (4.9)	9.5% (2.9)	10.3% (4.1)
[b]BSAP % change (wk 27)	-18.5% (2.3)	-11.0% (4.8)	-20.9% (3.0)	-24.5% (4.0)
[b]CTx % change (wk 12)	-26.6% (1.5)	-24.5% (2.9)	-27.1% (2.1)	-28.9% (3.0)
[b]CTx % change (wk 27)	-38.5% (1.9)	-35.6% (4.5)	-39.7% (2.2)	-40.5% (3.4)
Mean (SD) ETL dose (mg/wk), EAP	21.5 (13.4) mg	17.2 (11.7) mg	22.3 (13.4) mg	26.1 (13.8) mg

BSAP = bone specific alkaline phosphatase; cCa = corrected calcium; CTx = cross-linked C telopeptide (CTx); EAP = efficacy assessment phase; PTH = parathyroid hormone
*Based on number of patients with at least one post-baseline cCa value
[a]Mean (SE) % change during EAP; [b]Mean (SE) % change

Funding: Pharmaceutical Company Support - Amgen Inc.

SA-PO961

Effects of Etelcalcetide by Severity of Secondary Hyperparathyroidism

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Background: Etelcalcetide (ETL), a novel IV calcimimetic, has been shown to reduce levels of parathyroid hormone (PTH), corrected calcium (cCa), phosphate (P) and fibroblast growth factor (FGF-23) in adults on hemodialysis (HD) with secondary hyperparathyroidism (SHPT).

Methods: Adult subjects on HD with SHPT (PTH>400pg/mL) were randomized to 26 wks ETL or placebo. ETL was started at 5mg IV per HD session and titrated every 4 weeks (max 15 mg) to achieve PTH≤300pg/mL. The efficacy of ETL was evaluated post hoc by baseline disease severity. Results shown are for the ETL arm only for % change in mean PTH, cCa, or P during the efficacy assessment phase (EAP, wks 20-27) and FGF-23 at wk 27 compared with baseline and % of subjects achieving PTH≤300pg/mL, P<5.5 mg/dL, and combination of PTH≤300 and P<5.5 during EAP.

Results: Subjects with higher baseline PTH levels had higher baseline levels of cCa, P, and FGF-23.(Table 1) %PTH reduction did not differ across strata. However, % reductions in cCa, P, and FGF-23 were greatest in the higher PTH strata. Achievement of PTH, P and PTH+P targets was highest in subjects in the lowest PTH stratum. Subjects in the lowest PTH stratum had the lowest dose of ETL during EAP. (Table 2)

Conclusions: ETLwas effective in reducing PTH levels regardless of baseline SHPT severity though achievement of targets was greatest and mean dose was the least in those with lesser disease severity. Subjects with the most severe SHPT at baseline had both the highest levels of cCa, P and FGF-23 at baseline and the greatest reductions during treatment with ETL.

Table 1. Baseline Laboratory Values by baseline PTH

	Entire Cohort (N = 509)	Stratum A PTH < 600 pg/mL (n =172)	Stratum B PTH 600 – 1000 pg/mL (n = 225)	Stratum C PTH > 1000 pg/mL (n = 112)
PTH pg/mL	846.9 (492.6)	509.8 (71.0)	780.6 (120.6)	1497.6 (679.1)
cCa mg/dL	9.64 (0.66)	9.57 (0.63)	9.64 (0.68)	9.74 (0.64)
P mg/dL	5.86 (1.59)	5.51 (1.35)	5.94 (1.65)	6.21 (1.73)
*FGF-23 pg/mL	4206 (1070, 15061)	2677 (744, 10711)	5437 (1101, 18301)	5844 (1842, 21061)

*Median (Q1, Q3); All other values are mean (SD)

Table 2. Efficacy of Etelcalcetide by Baseline PTH

	Entire Cohort (N=509)	Stratum A PTH < 600 pg/mL (N=172)	Stratum B PTH 600 – 1000 pg/mL (N=225)	Stratum C PTH > 1000 pg/mL (N=112)
[a]PTH, % Change	-56.3% (1.4)	-54.2% (2.3)	-58.2% (1.9)	-55.5% (3.2)
[b]PTH ≤ 300 pg/mL	51.5%	69.2%	48.9%	29.5%
[b]P < 5.5 mg/dL	55.6%	58.1%	54.2%	54.5%
[b]PTH ≤ 300 pg/mL and P < 5.5 mg/dL	34.4%	44.8%	34.7%	17.9%
[a]cCa, % Change	-7.0% (0.4)	-5.1% (0.6)	-7.5% (0.6)	-8.9% (0.9)
[a]P, % Change	-8.7% (1.4)	-5.4% (1.9)	-8.2% (2.4)	-14.6% (2.3)
[c]FGF-23, % Change	-56.1% (-84.7, -7.1)	-42.8% (-74.1, 17.0)	-52.8% (-84.9, -15.5)	-77.6% (-90.3, -44.9)
Mean(SD) dose (mg/wk), EAP	21.5 (13.4) mg	17.2 (11.7) mg	22.3 (13.4) mg	26.1 (13.8) mg

[a]Mean (SE) % change during EAP; [b]Proportion achieving endpoint during EAP; [c]Median (Q1, Q3) % change at wk 27

Funding: Pharmaceutical Company Support - Amgen Inc.

SA-PO962

WELCOME - Web-Based Evaluation of the Clinical Benefit of Cinacalcet (MIM) in End-Stage Renal Disease (ESRD) in Central and Eastern Europe (CEE)

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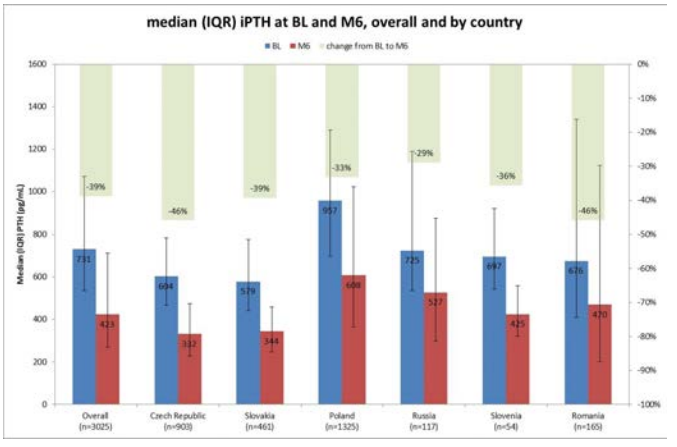
Background: This multicenter, observational study was conducted from 01/07 to 10/15. Aims: describe changes in CKD-MBD parameters after MIM start overall and before (BGR) *vs* after (AGR) KDIGO guideline release; describe characteristics of patients (pts) initiating MIM.

Methods: Eligibility: ESRD pts, MIM use according to SmPC. Data collected at baseline (BL=first MIM dose) and up to 6 months (M6). Endpoints: achieving PTH ≤300 pg/mL [primary]; KDOQI target for calcium (Ca) or phosphorus (P); vitamin D (Vit D) and P binder (PB) use; MIM dose; adverse drug reactions (ADR).

Results: 3025 pts were eligible; 2680 (89%) completed study; 345 discontinued (death 28%; transplantation 26%; adverse events 15%; loss to follow-up 11%; other 20%); 2582 (85%) completed ≥144 days of MIM.

	N=3025	
	BL, n (%)	**M6, n (%)**
PTH ≤300 pg/mL	58 (2)	884 (29)
PTH 150-300 pg/mL	50 (2)	664 (22)
Ca 8.4-9.5 mg/dL	1504 (50)	1584 (52)
P 3.5-5.5 mg/dL	938 (31)	1234 (41)
PB use	2528 (84)	1721 (57)
Vit D use	1736 (57)	1199 (40)

Median (IQR) MIM dose: 30 (30-42) mg/day. PTH varied between countries.



BGR *vs* AGR comparison was inappropriate: not all countries enrolled pts in both periods. 114 pts (4%) reported ADR (incl. gastrointestinal disorders, n=72; hypocalcemia, n=26); 1 pt had 2 serious ADR (cholecystitis, cholelithiasis). All-cause mortality: 3%.

Conclusions: MIM substantially reduced PTH and improved target achievement for PTH, Ca, and P; PTH values varied across countries.

Funding: Pharmaceutical Company Support - Amgen GmbH, Headoffice for CEE, Vienna, Austria

SA-PO963

Parathyroidectomy Achieves KDIGO Targets for Mineral and Bone Metabolism on Hemodialysis Patients?

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Background: Secondary hyperparathyroidism (SHP) is a common complication of chronic kidney disease. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines provides target ranges for serum calcium, phosphorus and parathyroid hormone levels. Parathyroidectomy (PTX) is indicated for patients with refractory SHP despite clinical treatment. The aim of this study was to evaluate how PTX impacts KDIGO targets for CKD-MBD.

Methods: A retrospective review of patients on dialysis that underwent PTX was performed. Total calcium (Cat), phosphorus (P) and intact parathyroid hormone (iPTH) levels were analyzed immediately before PTX and after 6 and 12 months and compared with KDIGO targets. The PTX was indicated if the patient had untreatable SHP with medications or major complications of SHP (bone fracture, brown tumor, calciphylaxis).

Results: Between january 2004 and april 2015, 79 patients underwent PTX, 64.6% women with a mean age of 45.8 years and mean time on dialysis of 9.7 years. Total PTX with autotransplantation was the most common surgical technique. Laboratory tests are shown in Table 1.

	Baseline	6 months	12 months	p
Cat (mg/dL) *	10.55 ± 1.16[a,b]	8.96 ± 1.78[a]	8.76 ± 1.27[b]	<0.001
P (mg/dL) *	6.3 ± 1.81[a,b]	4.21 ± 1.82[a]	4.55 ± 1.38[b]	<0.001
iPTH (pg/mL) #	2046[a,b]	72,5[a]	81.2[b]	0.006
*values in mean±sd;# median; (a) baseline vs 6 months; (b) baseline vs 12 months.				

The percentage of patients that, after 6 months, had laboratory values of P, Cat and iPTH in agreement with KDIGO targets were 50.9%, 37.3% and 9.1%, respectively. After 12 months the percentage were 61.7%, 50% and 22.6%, respectively. When analyzed the three parameters together, no patient had laboratory values in target range defined by KDIGO at 6 months and, after 12 months, only 6.7% of patients. After 1 year, 64.5% of patients had iPTH < 150 pg/mL.

Conclusions: PTX is useful in the control of calcium and phosphorus, however keeps the level of iPTH off target level. Additionally, PTX determines high prevalence of hypoparathyroidism.

SA-PO964

Long-Term Mortality and Bone Safety in Patients with End-Stage Renal Disease Receiving Lanthanum Carbonate

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Background: This was a phase 4, long-term, observational, safety study of patients with ESRD treated with lanthanum carbonate (LaC) in the USA (NCT00567723).

Methods: The exposed group, comprising patients (≥18 years) who had received ≥12 consecutive weeks of LaC treatment, included patients from clinical trials of LaC and patients prescribed LaC as part of normal clinical practice. A matched comparator group, comprising patients treated with any other phosphate binder, was identified from the USRDS (1:4 matching). Both groups were on dialysis and were observed for up to 5 years using the USRDS. Primary endpoints were time to all-cause mortality and bone fracture rates requiring hospitalization. Secondary endpoints were time to gastrointestinal disease; liver disease; malignancy; and major infectious episodes requiring hospitalization.

Results: Of the 2136 exposed patients enrolled, 2027 were included in the analysis. Using 2014 USRDS data, a Kaplan–Meier analysis showed that median 5-year survival (95% CI) was 51.6 (49.1, 54.2) and 48.9 (47.3, 50.5) months for patients in the exposed (n=2027) and comparator groups (n=8103), respectively. Bone fracture rates were 5.9% and 6.7%, respectively. A Cox proportional hazards model was fitted to adjust for patient baseline characteristics. LaC was not associated with an increased risk of any of the safety endpoints; however, in one of the secondary endpoints, LaC had a significant 17% reduced risk of time to major infectious episodes (P<0.001).

Primary endpoints	Hazard ratio (95% CI)
All-cause mortality	0.96 (0.90, 1.03) P=0.262
First bone fracture	0.91 (0.74, 1.11) P=0.351
Secondary endpoints	
Gastrointestinal disease	0.90 (0.79, 1.02) P=0.090
Liver disease	0.85 (0.68, 1.07) P=0.163
Malignancy	1.20 (0.72, 2.01) P=0.488
Major infectious episodes	0.83 (0.77, 0.90) P<0.001

Conclusions: These data support the long-term safety of LaC in patients with ESRD.

SA-PO965

Effect of Kidney Donation on Bone and Mineral Metabolism: The KARMA Prospective Controlled Observational Study

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Background: Chronic Kidney Disease (CKD) is an independent risk factor for cardiovascular disease. Unilateral nephrectomy for live transplant donation represents an ideal model to study the effects of an acute decrement in GFR in the absence of renal pathology. Recent evidence suggests detectable differences in cardiac morphology early after kidney donation. We sought to determine the effect of kidney donation on bone and mineral metabolism.

Methods: We enrolled pre-donation living transplant kidney donors and healthy controls in this single-centre prospective cohort study. Biochemical parameters were determined before and after donation and after 12 months, and at baseline and 12 months in the control group.

Results: Between 2012-2015, we enrolled 34 donors (male=20, 59%) and 34 controls (male=16, 47%). The mean donor age was 53±10 years, vs controls 50±14 years (p=0.33). Most patients were Caucasian (94% and 97% respectively). Baseline eGFR was similar between groups (donor 83±15 mL/min, control 88±21 mL/min, p=0.21). In the control group, biochemical parameters did not change significantly over time. In contrast, kidney donation reduced eGFR significantly to 56±10 mL/min after 6 weeks (p<0.0001), and remained lower than baseline after 12 months 63±13 (p<0.0001). Alkaline phosphatase increased from 99±21 IU/L to 106±22 IU/L after 6 weeks (p=0.01), but after 12 months had reduced to significantly below baseline (83±22 IU/L, p=0.0003). PTH increased from 4.7 pg/mL (3.4-5.8) at baseline to 5.8 pg/mL (4.6-8.6, p=0.0007) after 12 months. Soluble α-klotho decreased markedly from 931 pg/mL (663-1145) at baseline to 721 pg/mL (562-957, p=0.0004) after 12 months. 1,25-Dihydroxyvitamin D concentrations decreased from 50±12 pg/mL at baseline to 42±13 pg/mL (p=0.0046) after 12 months.

Conclusions: Kidney donation results in a decrement in eGFR with incomplete recovery. This reduction in renal function results in persistently abnormal markers of bone mineral metabolism. Together with a lower ALP after 12 months, this suggests reduced bone turnover and may contribute to cardiovascular sequelae of reduced kidney function.

SA-PO966

Efficacy of Microwave Ablation for Severe Secondary Hyperparathyroidism in Subjects Undergoing Hemodialysis

Zongli Diao, Wenhu Liu, Guo Weikang. *Dept of Nephrology, Beijing Friendship Hospital, Capital Medical Univ, Beijing, China.*

Background: Severe secondary hyperparathyroidism is a serious problem in patients undergoing hemodialysis. The efficacy of microwave ablation, a minimally invasive treatment, for severe secondary hyperparathyroidism is as yet unclear. In this study, we studied its efficacy for patients with severe secondary hyperparathyroidism.

Methods: This was a prospective, single-arm, clinical trial. We enrolled patients with severe secondary hyperparathyroidism attending our hemodialysis center who met the inclusion and exclusion criteria. We then assessed primary outcome measures: serum concentrations of intact parathyroid hormone (iPTH).

Results: Twenty-six patients were enrolled in this study, 10 of whom (38.46%) were responsive to microwave ablation and 16 (61.54%) of whom were not. In response group patients, serum iPTH concentrations declined to within the target range (124–558 pg/mL) immediately after microwave ablation, the changes compared with baseline values being statistically significant (1272.02±440.34 vs. 176.09±75.84 pg/mL, P<0.001). During follow-up, the iPTH concentrations of seven of these patients remained within the target range; however, the remaining three patients experienced recurrences at the 15, 19, and 21-month follow-up. Sixteen patients with No Response stopped follow-up at 3 months (when they were identified as having No Response). Compared with baseline values (1691.42±354.48 pg/mL), iPTH concentrations declined significantly immediately after microwave ablation (1022.02±427.05 pg/mL), and at the 1-week (1161.82±437.21 pg/mL) and 1-month (1210.61±505.34 pg/mL) follow-ups, P values being <0.001, 0.005 and 0.013, respectively. However, iPTH concentrations did not decline to the target range. Furthermore, they started to increase from immediately after microwave ablation, increasing by the 3-month follow-up to concentrations that did not differ significantly from those at baseline. The main complication was recoverable hypocalcemia (10 cases, 38.46%).

Conclusions: Microwave ablation is relatively ineffective in patients with severe secondary hyperparathyroidism and should not be the initial therapy in such cases.

SA-PO967

Microwave Ablation for Mild-to-Moderate Secondary Hyperparathyroidism Patients on Hemodialysis

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Background: Secondary hyperparathyroidism (SHPT) is a common complication in hemodialysis patients. The main treatment for mild-to-moderate SHPT is calcitriol, but as the control rate is low. Microwave ablation (MWA) has been used for severe SHPT, and shows its unique advantages, such as little trauma. As MWA may be useful for mild-to-moderate SHPT, this study examined efficacy of the procedure.

Methods: In this prospective, randomized, controlled study, we compared efficacy of MWA plus calcitriol and calcitriol in patients with mild-to-moderate SHPT. All SHPT patients with iPTH 300–800 pg/mL at our hemodialysis center were eligible. Serum iPTH was recorded at month 0, 1, and 2 and then at 2-month intervals until month 12. Primary end points were: (1) overall rate to achieve iPTH target; (2) iPTH change after MWA; and (3) rate at which participants developed severe SHPT. The secondary end point was weekly calcitriol dosage.

Results: Twenty-eight patients were enrolled in this study. There was no statistical difference in rate to achieve iPTH target between MWA and calcitriol groups (23.33% *vs.* 20.73%; P=0.72). Rate of iPTH <150 pg/mL (lower limit of target range) in the MWA group was higher than the calcitriol group (23.33% *vs.* 8.54%; P=0.01). iPTH after MWA was significantly lower than the calcitriol group. iPTH of the MWA group was higher than the calcitriol group at baseline (610.24±210.69 *vs.* 521.68±164.9 pg/mL; P=0.227), but lower during follow-up. Maximum difference between MWA and calcitriol groups was 275.11 pg/mL at month 8 (554.66±289.78 *vs.* 279.55±172.78 pg/mL; P=0.02). Minimum difference was 58.06 pg/mL at month 2 (572.58±387.72 *vs.* 514.52±453.13 pg/mL; P=0.66), which was considered clinically significant. Only one case (7.14%) developed severe SHPT in the MWA group and six (42.86%) in the calcitriol group (P=0.038). Weekly calcitriol dosage of the MWA group was lower than the calcitriol group (1.56±1.49 *vs.* 4.72±4.72 μg; P=0.03).

Conclusions: MWA decreases iPTH levels significantly for mild-to-moderate SHPT and prevents development into severe SHPT. It is worthwhile attempting to treat mild-to-moderate SHPT with MWA.

SA-PO968

Calciphylaxis New Aspects of an Old Entity Enrique Morales, María Fernández Vidal, Eduardo Hernández-Martinez, Eduardo Gutierrez-Martinez, Manuel Praga. *Nephrology, Hospital Univ 12 de Octubre, Madrid, Spain.*

Background: Calcific uraemic arteriolopathy (CUA), also called calciphylaxis, is a rare but disastrous and life-threatening disease mostly affecting patients with chronic kidney disease treated with dialysis. There is little information about the incidence of this entity in patients with a functioning kidney transplant (KT) and patients with normal kidney function (NKF). The aim of this study was to analyze risk factors (RF) and treatment of CUA in different types of patients.

Methods: Retrospective study that includes patients diagnosed with CUA from December 1999 to December 2015. Clinical features, laboratory evaluation, treatment and outcome were investigated.

Results: Twenty-eight patients (53.6% women) were included. The mean age was 67.2 ± 11.8 (38-88) years. The prevalence of diabetes mellitus and obesity (BMI>30 kg/m2) was 46.4 and 42% respectively. At the time of diagnosis, 53.6% were on hemodialysis (HD), 25% were KT patients and 21.4% had NKF. Skin biopsy confirmation was reported for 78.6% and the remaining were diagnosed clinically. 82.1% of cases showed peripheral CUA. The vitamin K antagonists (VKA) (68.7%) and steroids (100%) were considered a significant RF in patients with KT. The multimodal treatment (66.7% bisphosphonates, 58.3% intravenous sodium thiosulfate and 42.9% cinacalcet) was used in patients. The resolution of CUA was present in 62.5% patients. The mean follow-up time was 26.3 ± 45.2 (1-192) months. The 1-year patient survival in patients with CUA was 23, 56, 100% in the KT, HD and NKF patients respectively (log rank 6.8, p .032). Eleven patients died (39.3%) during the CUA, 6 cases (40%) of HD and 5 cases (71.4%) in patients with KT. The presence of renal insufficiency (p .03), Charlson's index (CI)> 7 (p .06), central CUA lesion (p .04) and hypoalbuminemia (p .02) were the significant RF of mortality in patients with CUA.

Conclusions: Although the incidence of CUA remains low in our population, the mortality is extremely high, mainly in the KT. The VKA should be considered as new and significant RF in the majority of groups. The identification of RF before CUA development and standard therapy should be the main objectives to conduct randomized clinical trials.

SA-PO969

The Role of Calciprotein Particles in the Mineralisation Paradox in Chronic Kidney Disease Michael Ming Xin Cai,[1,2] Edward R. Smith,[1] Sven-Jean Tan,[1,2] Nigel David Toussaint,[1,2] Timothy D. Hewitson,[1,2] Stephen G. Holt.[1,2] *[1]Royal Melbourne Hospital, Australia; [2]Univ of Melbourne, Australia.*

Background: Vascular calcification in chronic kidney disease (CKD) is often accompanied by a paradoxical reduction in bone mineralisation. In CKD, a fraction of serum calcium (Ca) and phosphate (Pi) circulates as colloidal nanocrystals stabilised by a protein shell, termed calciprotein particles (CPPs). CPPs are associated with arterial stiffness, coronary calcification and mortality. This study tested the differential effect of CPP on vascular smooth muscle cell (VSMC) and osteoblast mineralisation.

Methods: Saos-2 (an osteosarcoma cell line) and MOVAS-1 (murine VSMC) were treated for 7 days with either control media (CM), osteogenic media (OM, +3mM Pi), CM supplemented with secondary CPP (CPP) or OM supplemented with CPP (OM+CPP). Mineralisation was detected with alizarin red and von Kossa staining, and quantified as Ca corrected for protein. Cell viability was determined by the ratio of live/total cell count. Alkaline phosphatase (ALP) activity was assayed using p-nitrophenyl phosphate based method.

Results: OM treatment increased Saos-2 mineralization, but not MOVAS-1. OM+CPP treatment yielded a dose-dependent *decrease* in Saos-2 mineralisation. In contrast, treatment of MOVAS-1 with OM+CPP resulted in a *synergistic increase* in mineralisation compared to OM and CPP respectively. OM+CPP but not OM or CPP reduced MOVAS-1 viability(P<0.01). ALP activity was similar between treatment groups in both cell lines. Compared to freshly prepared OM+CPP, media pre-incubation for 24 h at 37^{o}C reduced monolayer mineralisation in both cell lines despite an increase in CPP bound calcium.

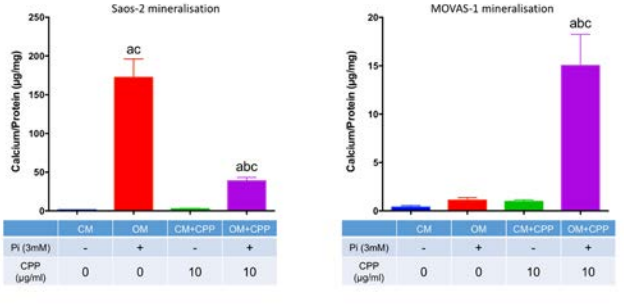


Figure 1: Differential effects of Pi and CPP on Saos-2 and MOVAS-1 cell monolayer mineralisation over 7 days.
Legend: a, P<0.01 vs CM; b, P<0.01 vs OM; c, P<0.01 vs CM+CPP.

Conclusions: In high Pi, CPP reduce mineralisation of an osteoblast-like cell but increase mineralisation of a VSMC cell line. Our findings suggest circulating CPP in CKD serum may be a novel mediator of the calcification paradox in CKD.

Funding: Government Support - Non-U.S.

SA-PO970

Cortical Unlike Trabecular Bone Is Not Associated to Coronary Artery Calcification Progression in Chronic Kidney Disease Patients Larissa Rodrigues,[1] Amandha Bittencourt,[1] Aluizio B. Carvalho,[1] Raul Santos,[2] Carlos Eduardo Rochitte,[2] Maria Eugenia F. Canziani.[1] *[1]Nephrology, Federal Univ of Sao Paulo, Sao Paulo, Brazil; [2]Heart Inst Univ of Sao Paulo Medical School Hospital, Sao Paulo, Brazil.*

Background: Vascular calcification progression has been associated with loss of trabecular bone in chronic kidney disease (CKD) patients. There are few data evaluating the relation between cortical bone and vascular calcification in this population. The aim of this study was to analyze cortical bone density (BD) from vertebral tomographic images and its association with coronary artery calcification (CAC) progression in non-dialyzed CKD patients.

Methods: Over time changes of cortical and trabecular bone were analyzed by using vertebral tomographic images at the level of the aortic root from a previous prospective study. Automatic delineation of cortical bone layer was performed by *Image J* software, and trabecular bone was determined by selecting a region of interest placed at mid-vertebral body including only trabecular bone using Vitrea2 workstation software. Cortical and trabecular BD were expressed in Hounsfield Units (HU). Coronary artery calcium score was expressed as Agatston Units (AU). The presence of CAC was considered when calcium score was equal or higher than 10 AU.

Results: 70 asymptomatic patients (57.8 ± 10.2 years, 63% males, 20% diabetics, estimated glomerular filtration rate (eGFR) = 37.3 (24.8 – 51.3) ml/min/1.73m^2) were followed for 24 months. Cortical bone density was 400.0 ± 89.9 and 404 ± 94.8 HU (p= 0.41), at baseline and at 24 months, respectively. During follow-up, 29 (41.4%) patients reduced their cortical BD. Changes in cortical BD were not associated to age, gender, diabetes and baseline or changes of eGFR and mineral bone parameters. There was no association between cortical and trabecular BD changes (r=0.19; p=0.12). CAC was observed in 33 (46%) patients at baseline, and 30 (91%) of them showed CAC progression. Cortical bone changes were not associated with CAC progression (r=0.18; p=0.34).

Conclusions: Despite a substantial number of patients showed cortical bone loss there was no association between changes in cortical BD and coronary calcification progression.

SA-PO971

Trabecular Bone Score and Incident Fragility Fracture Risk in Adults with Reduced Kidney Function Kyla Lynn Naylor,[1] Jerilynn C. Prior,[2] Amit X. Garg,[1,3] Claudie Berger,[4] Lisa Langsetmo,[5] Jonathan D. Adachi,[6] David Goltzman,[4] Christopher S. Kovacs,[7] William Leslie.[8] *[1]Inst for Clinical Evaluative Sciences; [2]Univ of British Columbia; [3]Univ of Western Ontario; [4]McGill Univ; [5]Univ of Minnesota; [6]McMaster Univ; [7]Memorial Univ; [8]Univ of Manitoba.*

Background: Trabecular bone score (TBS) is a gray-level textural measure obtained from dual energy X-ray absorptiometry (DXA) lumbar spine images which provides information independent of areal bone mineral density (BMD). The association between TBS and incident fractures in adults with reduced kidney function, and whether this association differs from adults with normal kidney function, is unknown.

Methods: We included 1426 participants aged ≥40 years (mean age 67 years) in the community-based Canadian Multicentre Osteoporosis Study. We stratified participants at cohort entry by estimated glomerular filtration rate (eGFR <60 [n=199, 72.4% stage 3a, 25.1% stage 3b, and 2.5% stage 4] versus ≥60 ml/min/1.73 m^2 [n=1227]). TBS was obtained from lumbar spine (L1-L4) DXA images, with a lower TBS representing worse bone health. Over an average of 4.7 years follow-up we documented incident fragility (low-trauma) fracture events (excluding craniofacial, foot, and hands). We used a modified Kaplan-Meier estimator to determine the 5-year probability of fracture. Cox proportional hazard regression per standard deviation decrease in TBS expressed the gradient of fracture risk.

Results: Individuals with an eGFR <60 mL/min/1.73 m^2 who had a TBS value below the median (<1.277) had a significantly higher 5-year fracture probability than those above the median (18.1% versus 6.2%; *P*=0.01). The association between TBS and fracture was independent of BMD and other clinical risk factors in adults with reduced and normal kidney function (adjusted hazard ratio [aHR] per standard deviation decrease in TBS: eGFR <60 ml/min/1.73 m^2,aHR 1.62, 95% confidence interval [CI] 1.04-2.51; ≥60 ml/min/1.73 m^2, aHR 1.44, 95% CI 1.13-1.83).

Conclusions: Lower lumbar spine TBS is independently associated with a higher fracture risk in adults with reduced kidney function.

SA-PO972

Association of Bone Mineral Density with Fractures across the Spectrum of Chronic Kidney Disease - The Prairie DXA Study Bhanu Prasad,[1] Jennifer St.Onge.[2] *[1]Nephrology, Regina Qu Appelle Health Region, Regina, SK, Canada; [2]Research and Performance Support, Regina Qu Apelle Health Region, Regina, SK, Canada.*

Background: Bone mineral density (BMD) by dual energy x-ray absorptiometry (DXA) scans predict fractures rather robustly in otherwise healthy men and women, but its role in CKD patients has been less defined. DXA quantifies areal bone mineral content, which measures bone density but it does not pick up derangements of bone quality or architecture which are inevitable in CKD.Impaired architecture may present as low BMD on DXA scans.Therefore, DXA may not be the most robust instrument to accurately predict the risk of fracture. We wanted to examine the relationship of BMD with fracture risk across the spectrum of CKD.

Methods: We conducted a retrospective review of 410 consecutive patients who underwent DXA scan at the point of entry into our multidisciplinary chronic kidney disease (CKD) program. BMD data, T score and Z scores were collected at four sites: the lumbar spine, total hip, mean of left and right femoral neck, and the proximal radial region (radius 33%). We collected data on demographic, lab markers of mineral metabolism and fractures.

Results: 35.9% stage III CKD, 28.4 % stage IV CKD, and 32.4% stage V CKD patients experienced a clinical fracture during the study period. On multivariate analysis, a decline of 1.0 SD in total Hip BMD T-score was associated with a statistically significant increase in the risk of fracture (OR= 1.36, 95% CI: 1.02, 1.72, p=.04) while controlling for parathyroid hormone, alkaline phosphatase, calcium and phosphorus and GFR of <30. Compared to a GFR of ≥30 mls/ minute, the OR of identifying a fracture was 1.54 in comparison to OR of 1.14 in patients with GFR <29 mls/minute.

Conclusions: This is the largest Canadian cohort of CKD patients with DXA scans to our knowledge.We were able to show that T-scores predict fractures across stage III, but had a modest ability in stage IV. As fractures lead to significant morbidity and mortality, we believe there is a role for DXA scans which, are inexpensive, non-invasive, safe, and readily available have a role in clinical practice for identifying patients at risk for fractures in different stages of CKD.

SA-PO973

Association of Dialysate Calcium Concentration, Vitamin D Use, and Hip Fracture in Hemodialysis Patients Miho Tagawa,[1] Takayuki Hamano,[2] Shinichi Sueta,[3] Seiji Hashimoto,[2] Satoshi Ogata.[2] *[1]Nara Medical Univ; [2]Patient Registration Committee of Japan Renal Data Registry; [3]Kyoto Univ.*

Background: The effects of dialysate calcium concentration (D[Ca]) on bone and mineral markers have been studied, however, the association between D[Ca] and fracture has not been studied. In Japan, most dialysis facilities use central supply system for dialysate.

Methods: This was a longitudinal study based on the Japan Renal Data Registry from 2008 to 2010. Hemodialysis patients without prior hip fracture were enrolled. Predictor variable was D[Ca] (≥3.0 vs 2.5 mEq/L). Use of active vitamin D (VitD) in each D[Ca] category was also considered. Outcome variable was incidence of hip fracture during 2 years. Statistical analyses were performed using multivariate logistic regression model, adjusted for potential confounders.

Results: Among 301,649 patients on the database, data for 47,352 patients were available after excluding missing data. There were 979 events of hip fracture during 2 years. Adjusted OR for D[Ca]≥3.0mEq/L was 0.89 (0.78-1.02), 0.93 (0.77-1.12), 0.89 (0.69-1.14), and 0.75 (0.52-1.08) for total cohort, patients with intact parathyroid hormone (PTH) <150, 150-300, and >300 pg/mL, respectively. Among patients with PTH 150-300 pg/mL, VitD use was associated with significant reduction in hip fracture for both D[Ca] categories and D[Ca] of 2.5 mEq/L with VitD use was associated with lower incidence of hip fracture compared to D[Ca]≥3.0 mEq/L without VitD. Among patients with PTH>300 pg/mL, the use of D[Ca] of 2.5 mEq/L without VitD was associated with significant increase in hip fracture.

	PTH<150 pg/ml	PTH 150-300 pg/ml	PTH > 300 pg/ml
D[Ca]≥3.0, Vit D (-)	1 (reference)	1 (reference)	1 (reference)
D[Ca]>3.0, Vit D (+)	0.85 (0.68-1.07)	0.68 (0.49-0.95)	1.39 (0.74-2.63)
D[Ca]2.5, Vit D (-)	1.20 (0.92-1.57)	1.37 (0.91-2.06)	2.37 (1.11-5.08)
D[Ca]2.5, Vit D (+)	0.83 (0.65-1.07)	0.69 (0.49-0.98)	1.57 (0.83-2.96)

Conclusions: The effects of D[Ca] of 2.5 mEq/L on incident hip fracture is dependent on PTH levels and concomitant VitD use. The results suggest that vitamin D should be prescribed not to increase the risk of fracture when using D[Ca] of 2.5 mEq/L.

SA-PO974

The Prevalence and Risk Factors of Low Bone Mineral Density in Chinese Chronic Kidney Disease Patients Ying Qian, An Jin Chang, Xiaonong Chen. *Nephrology, Ruijin Hospital Affiliated to Shanghai Jiaotong Univ School of Medicine, Shanghai, China.*

Background: Bone and mineral disorder is one of the most common clinical complications in CKD patients. Since Chinese research in this field is only at the beginning, we need more data to analysis the prevalence and risk factors of low bone mineral density in Chinese CKD patients.

Methods: We selected CKD inpatients from 2009 to 2015.Patients were excluded if they used glucocorticoid and calcitriol. GFR was estimated using MDRD formula for Chinese. All patients were classified into 5 CKD stages according to K/DOQI guideline and were measured BMD at lumbar spine, femoral neck and total hip by dual energy X-ray absorptiometry (DXA). Osteoporosis was defined by BMD according to the reference values suitable for Chinese population. Clinical characteristics of all patients were also collected. The correlation between BMD and detection indexes was analysed and the independent risk factors for low BMD in CKD patients were also explored.

Results: A total of 429 patients were enrolled in the study.Mean age of the patients (221 males and 208 females) was 53.89±16.14 years. Totally 43.59% of all patients were diagnosed as low BMD (including osteopenia 23.31% and osteoporosis 20.28%). The number of patients in CKD1-5 was 127, 72, 75, 39 and 116, respectively. And the prevalence of low BMD in CKD1-5 were 33.1%,41.7%,40%,38.5%,60.3%. Simple linear regression analysis showed that BMD at femoral neck and total hip (g/cm^2) were positively associated with BMI, eGFR, CO2-CP, Ca and 25(OH)D_3, but negatively associated with age, Scr, AKP, iPTH and P. The BMD of lumbar spine (L1-L4) were only positively associated with BMI, and negatively associated with age, AKP. Multiple linear regression analysis showed that femoral neck BMD or total hip BMD was independently associated with Scr after adjusting potential confounding factors. Multiple logistic regression analysis revealed that serum creatinine was the independent risk factor for low BMD in CKD.

Conclusions: The prevalence of low BMD was high in Chinese CKD patients. And the femoral neck BMD and total hip BMD decreased with the decline of renal function.

SA-PO975

Improvement of Reduced Bone Mineral Density after Total Parathyroidectomy in the End-Stage Renal Disease Patients with Severe Secondary Hyperparathyroidism Li Fang, Junwei Yang. *Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: The ESRD patients with secondary hyperparathyroidism (SHPT) usually display reduced bone mass which might lead to a substantial increase in osteoporosis and fracture. Despite the development of new therapeutic agents, a majority of patients still require parathyroidectomy (PTX). However, the effect of total PTX on bone mass changes in SHPT is not well understood yet. The aim of this study was to evaluate whether BMD changes after total PTX and identify which factor contributes most to bone changes.

Methods: 34 patients undergoing total PTX because of severe secondary hyperparathyroidism were included. Preoperative and postoperative bone mineral density (BMD) values measured by dual energy X-ray absorptiometry (DEXA) and some other clinical parameters were collected.

Results: Before PTX, we found that the prevalence of osteopenia and osteoporosis at different lumbar vertebra sites vary greatly. Osteoporosis at L1 was revealed in11.8%, while at L4 was 32.5%. Osteopenia at L1 was in 32.5%, while at L4 was in 32.3%. For the hip, DEXA showed osteopenia in 55.9% and osteoporosis in 23.5% at femoral neck, and 61.7% and 5.9% at trochanter. After PTX, lumbar spine BMD significantly increased from 0.92±0.157 g/cm2 to 1.04±0.171 g/cm2 and femoral neck BMD increased from 0.69±0.127 g/cm2 to 0.79±0.131 g/cm2. Accordingly, the prevalence of osteoporosis and osteopenia were decreased (Osteoporosis: L1 5.9%, L4 5.9%, femoral neck 0%, trochanter 0%; Osteopenia: L1 26.5%, L4 32.3%, femoral neck 55.9%, trochanter 61.8 %). At the most affected site L4, 91.2% had significant improvement (>5%), 2.9% moderate improvement (0.1-5%) and 5.9% declining bone mineral density. Patients who significantly improved usually had lesser preoperative BMD values (P =0 .001), greater preoperative levels of parathyroid hormone (P = .002), and higher parathyroid gland weight (P = 0.008).

Conclusions: Bone mineral density signicantly improves after surgery, which support total PTX in ESRD patients with severe secondary hyperparathyroidism. The hip and lumbar spine had similar response to PTX, especially in the load-bearing trabecular bone.

Funding: Government Support - Non-U.S.

SA-PO976

The Characteristics of Bone Mineral Density Changes in the End-Stage Renal Disease Patients with Severe Secondary Hyperparathyroidism Through Separate Analyses Li Fang, Junwei Yang. *Center for Kidney Disease, Second Affiliatted Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Bone mineral density (BMD) measurement using dual-energy X-ray absorptiometry (DEXA) was still controversial in screening for and monitoring of renal osteodystrophy in end-stage renal disease (ESRD) patients. However, considering the significance of secondary hyperparathyroidism (SHPT) in the pathogenesis of renal osteodystrophy, the purpose of this study was to evaluate the characteristics of BMD changes in the ESRD patients with severe secondary hyperparathyroidism.

Methods: 126 patients who were hospitalized for severe secondary hyperparathyroidism were included in this cross-sectional study. BMD values and some other clinical parameters were collected.

Results: We found that BMD values decreased significantly from L1 to L4 in the lumbar spine and the prevalence of osteoporosis seemed to be much higher in the lumbar spine but lower in the hip, which indicating that the bone loss seemed predominant in the load-bearing trabecular bone. Correlation analysis revealed that parathyroid hormone (PTH) was negatively correlated with the BMD Z-scores of the lumbar spine and hip. To further investigate the impact of PTH on BMD changes, we stratified the patients according to their i-PTH levels (500-1000, 1000-2000, and >2000pg/ml, respectively). We found that along with the increase of parathyroid hormone, the loss of bone mineral content was prior to the loss of bone area for the lumbar spine, especially in the load-bearing bones. However, for the hip, the changes of bone mineral content were not significantly, while the bone area at intertrochanter was even significantly increased in the group with PTH above 2000 pg/ml.

Conclusions: Bone densitometry reveals pronounced decrease in bone mineral density in severe secondary hyperparathyroidism and the significance of PTH induced bone abnormalities would actually be diverse depending on the sites. BMD measurement by DEXA might be of major clinical relevance in the evaluation of bone loss in ESRD patients with severe secondary hyperparathyroidism.

Funding: Government Support - Non-U.S.

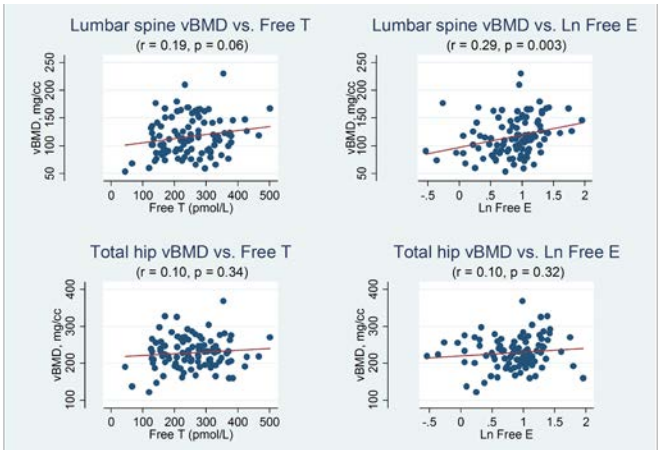
SA-PO977

Free Testosterone Is Positively Associated with Bone Mineral Density in Kidney Transplant Candidates Hanne Skou Joergensen,[1] Simon Winther,[2] Lars Rejnmark,[3] My Svensson,[4] Per R. Ivarsen.[1] *[1]Nephrology, Aarhus Univ Hospital, Aarhus, Denmark; [2]Cardiology, Aarhus Univ Hospital, Aarhus, Denmark; [3]Endocrinology, Aarhus Univ Hospital, Aarhus, Denmark; [4]Nephrology, Akerhus Univ Hospital, Oslo, Norway.*

Background: Hypogonadism is common in CKD. Both testosterone (T) and estradiol (E) decrease bone resorption and are positively associated with bone mineral density (BMD) in healthy elderly, but little is known of the effects of sex hormones on bone health in CKD. We investigated associations between free T, free E and BMD in male kidney transplant candidates.

Methods: Volumetric BMD (vBMD) of lumbar spine and total hip were measured by quantitative computed tomography. Total T, total E, sexual hormone binding protein (SHBG), intact parathyroid hormone (iPTH) and albumin were analyzed from fasting morning blood samples. Free T and free E were calculated based on constants for protein binding to SHBG and albumin.

Results: Analyses included 107 patients. Free T correlated to age (r= -0.20, p=0.04), weight (r= -0.25, p=0.01), Ln Free E (r=0.42, p<0.001) and dialysis treatment (r=0.47, p<0.001). Ln Free E correlated to Free T, type 1 diabetes (r=0.22, p=0.03) and ln-iPTH (r=0.20, p=0.04). Figure 1 shows the association between sex hormones and vBMD. In the multiple linear regression model, both hormones were significant predictors at lumbar spine and Free T was significant at total hip (Table 1).



	Lumbar spine (Adj. R^2=0.23)		Total hip (Adj. R^2=0.21)	
	β	*p*	*β*	*p*
Age	-0.975	0.004	-0.304	0.46
Weight	-0.188	0.47	-0.003	0.99
Dialysis	-19.69	0.009	-27.52	0.003
Type 1 diabetes	-5.70	0.52	-35.29	0.001
Type 2 diabetes	13.90	0.17	29.21	0.02
Ln iPTH, pmol/L	-9.59	0.01	-13.14	0.007
Free T, pmol/L	0.094	0.049	0.137	0.02
Ln Free E, pmol/L	17.24	0.04	10.75	0.30

Conclusions: Sex hormones may play an important part in bone health in men with late stage CKD.

Funding: Private Foundation Support

SA-PO978

Large Variations between Four Methods for Sclerostin Determination in Patients Undergoing GFR Measurement and in Hemodialyzed Patients before and after a Single Dialysis Session Etienne Cavalier,[1] Pierre Delanaye.[2] *[1]Clinical Chemistry, Univ of Liege; [2]Nephrology, Univ of Liege.*

Background: Sclerostin (SCL) is a promising biomarker for bone research. It has also been associated, in some studies, with mortality in hemodialyzed (HD) patients. However, literature is conflicting on that point and some authors have pointed out that assays used for SCL might explain these discrepancies. Also, the impact of renal function on SCL levels remains poorly studied.

Methods: We have measured SCL concentration in 150 healthy and CKD patients who had undergone GFR determination with the iohexol method. We have also measured SCL before and after a single dialysis session in 44 patients. Each sample has been measured with 4 different ELISA: Biomedica (B), MSD (M), R&D (R) and Teco (T).

Results: Median [IQR] SCL concentration in the non-HD patients were very different according to the method: B : 1017 [546], M : 36 [21], R : 160 [101] and T : 629 [325] pg/mL. We did not observe any systematic differences between the methods. In univariate analysis, we observed a significant and inverse relation between GFR and SCL when measured by B, R and T but not with M. The different assays also showed a wide variation in HD patients. With B and R methods, HD patients presented median values higher than those whose GFR was >45 mL/min, but were similar with those presenting GFR <45 mL/min. With T method, the median observed in HD patients was higher than in non-HD patients, whatever the GFR. On the contrary, median SCL was lower in HD than in non-HD patients with the M method. After a dialysis session, a significant decrease was observed in HDF, but not in HD mode and was always more important if SCL was measured with T, B and R methods, compared to the M one.

Conclusions: SsCL determination in CKD patients is challenging and any conclusion is method-depending. Previously described relations between GFR and SCL levels may be an analytical artifact with inactive SCL fragments that would accumulate when GFR decreases and would be recognized by T, B and R, but not M method. In conclusion, method for SCL determination clearly impacts findings previously observed in CKD and HD patients.

SA-PO979

Sclerostin – A Debutant on the Autosomal Dominant Polycystic Kidney Disease Scene? Magdalena Jankowska,[1,2] Abdul Rashid Tony Qureshi,[1] Bengt Lindholm,[1] Peter Stenvinkel,[1] Pieter Evenepoel.[3] *[1]Div of Renal Medicine and Baxter Novum, Karolinska Univ Hospital at Huddinge M99, Karolinska Inst, Stockholm, Sweden; [2]Dept of Nephrology, Transplantology and Internal Medicine, Medical Univ of Gdansk, Gdansk, Poland; [3]Dept of Immunology and Microbiology, Laboratory of Nephrology, Katholieke Univ Leuven, Leuven, Belgium.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disease originating from a mutation in genes encoding polycystin 1 and 2. Recent evidence suggests that these polycystins mediate mechanosensation not only in the primary cilium of kidney cells but also in bone cells. The Wnt/β-catenin signaling pathway plays a central role in mechanotransduction in osteocytes. Mechanical unloading causes the upregulation of the Wnt inhibitor sclerostin. We tested the hypothesis that ADPKD associates with higher circulating sclerostin levels.

Methods: Circulating levels of sclerostin and other laboratory parameters of mineral and bone disease, including intact parathyroid hormone (PTH), calcium, phosphate, magnesium, 25(OH)D-vitamin, 1.25(OH)D-vitamin and bone specific alkaline phosphatase (bALP) were assessed in 503 patients with end stage renal disease recruited from ongoing longitudinal cohort studies in Stockholm, Sweden (**cohort 1**; n=100, 19% ADPKD) and Leuven, Belgium (**cohort 2**; n=403, 19% ADPKD).

Results: Patients with ADPKD had higher sclerostin levels and lower bALP levels as compared to patients with other primary renal disease. In multivariate analysis, ADPKD associated with circulating sclerostin levels, independent of the established determinants including age, gender, body mass index, diabetes, phosphate, PTH, and 1,25(OH)D-vitamin.

Conclusions: Circulating sclerostin levels are increased in ADPKD, possibly reflecting impaired mechanosensation. The clinical relevance of this finding, e.g. with regard to vascular and bone health, remains to be investigated. Our finding draws attention to etiology of kidney disease as an important, yet neglected, confounder or the association between renal failure and mineral and bone disease.

SA-PO980

Bone Marrow Adipocyte after GH Supplementation in Pediatric ESKD Patients Ornatcha Sirimongkolchaiyakul, Renata C. Pereira, Katherine Wesseling-Perry, Isidro B. Salusky. *Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA.*

Background: Mesenchymal stem cells are precursors for both osteoblasts and adipocytes. Marrow adipogenesis is associated with osteoporosis in adults with normal kidney function. GH increases osteoblast proliferation and differentiation and is commonly used to promote growth in children with CKD. The effects of GH on bone marrow adipogenesis; however are unknown.

Methods: 24 pediatric peritoneal dialysis patients age 10.3 + 4.6 (SD) years with high (n=14) or low/normal (n=10) bone turnover were randomly assigned to treatment with GH or not. Patients with high bone turnover group also received intraperitoneal Calcitriol. Bone biopsy was performed at baseline and after 8 months of therapy.

Results: Marrow adipocytes/tissue area did not change with therapy in patients with either high turnover or low/normal bone turnover, irrespective of treatment with GH versus standard therapy.

Table 1 Biochemical and marrow adipocyte

	High Bone Turnover			Low/normal Bone Turnover		
	Baseline	Calcitriol + GH (N = 6)	Calcitriol + no GH (N = 8)	Baseline	GH (N = 6)	Nothing (N = 4)
S-Ca (mg/dl)	9.66 ± 0.89	8.98 ± 0.48	6.55 ± 1.49	10.10 ± 0.72	9.7 ± 0.26	9.45 ± 0.41
S-PTH (pg/ml)	602 ± 373	1045 ± 154	291 ± 169	127 ± 75	500 ± 130	381 ± 343
N. adipocyte	1748 ± 898.87	1498.17 ± 1079.13	1717.75 ± 777.55	1866.70 ± 788.79	1624.5 ± 1115.19	2101.75 ± 562.06
N. adipocyte/T. Ar (/mm2)	145.98 ± 62.85	122.09 ± 78.15	144.89 ± 50.82	178.84 ± 63.48	147.56 ± 87.39	183.81 ± 55.72

Table 2 Changes of marrow adipocyte in patients received GH or noting

	GH (N = 12)	no GH (N=12)	p-value
N. adipocyte/T.Ar (/mm2)	25.93 ± 57.14	39.77 ± 37.30	0.48

Table 3 Changes of marrow adipocyte in high and low/normal bone turnover

N. adipocyte/T. Ar (/mm2)	High Bone turnover (N = 14)	Low/normal bone turnover (N = 10)	p-value
GH	41.46 ± 66.68	10.39 ± 40.01	0.39
no GH	12.09 ± 61.89	-26.35 ± 16.56	0.29

Conclusions: Marrow adipocity did not change in response to GH therapy in this sample of pediatric ESKD patients.

Funding: NIDDK Support

SA-PO981

Canonical Wnt Signaling May Contribute to Altered Pre-Osteoblast Maturation Characteristics in CKD Renata C. Pereira,[1] Richard Bowen,[2] Isidro B. Salusky,[1] Katherine Wesseling-Perry.[1] *[1]Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA; [2]Orthopedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA; [3]Dentistry, UCLA, Los Angeles, CA.*

Background: Bone disease in chronic kidney disease (CKD) has been traditionally defined by changes in bone turnover stemming from altered circulating parathyroid hormone (PTH) concentrations. However, we have shown that primary pre-osteoblasts from CKD patients have increased proliferation and decreased mineralization rates *ex vivo*, suggesting that CKD induces intrinsic changes to osteoblast biology that are independent of circulating PTH concentrations.

Methods: To understand potential mechanisms mediating these changes, primary pre-osteoblasts from 6 adolescent dialysis patients (3 with high and 3 with low bone turnover) and 3 healthy adolescent controls were plated at 10,000 cell/cm^2 and cultured in the presence of growth media (10% fetal bovine serum and 100 μg/ml ascorbic acid) until achieving confluence. Maturation/mineralization was promoted by the addition of 10mM β-glycero-phosphate and cells were grown for 7 days after which time RNA was harvested from cultures for RNA Seq analysis (Genewiz). Parallel cultures were grown for 14 days after which time total protein was isolated.

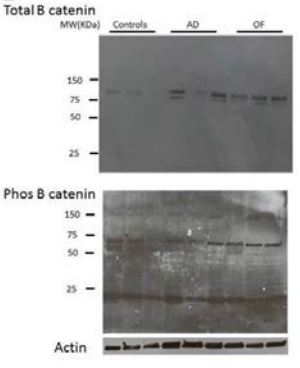
Results: RNA Seq analysis revealed marked differences in expression of genes of the *Wnt* signaling pathway; thus, beta-catenin expression was evaluated in protein extracts. Beta catenin protein was increased in CKD as compared to healthy control cells.

A

Gene	Protein	Control (RPMBP)	ESKD (RPMBP)	ESKD/Control (Reads/Reads)
DKK1	Dikkopf1	55.82	116.17	2.08
DKK2	Dikkopf2	0.04	0.19	4.86
DKK3	Dikkopf3	18.29	84.26	4.61
SOST	Sclerostin	0	0.06	
WISP1	Wnt1 inducible signaling protein 1	51.80	17.57	0.34
WISP2	Wnt1 inducible signaling protein 2	22.75	5.42	0.24
WISP3	Wnt1 inducible signaling protein 3	3.20	7.00	2.19
WNT16	Wnt family member 16	0.94	0.05	0.06
WNT2B	Wnt family member 2	0.25	0.40	1.60
WNT3	Wnt family member 3	0.08	0.55	6.91
WNT5A	Wnt family member 5a	66.66	27.89	0.42
WNT5B	Wnt family member 5b	16.38	33.10	2.02
WNT7B	Wnt family member 7b	0.02	0.01	0.523
WNT9A	Wnt family member 9a	0.02	0.11	4.98
FRZB	Soluble frizzled related protein 3	0.52	10.20	19.77
SFRP1	Soluble frizzled related protein 1	0.68	1.98	2.91

RPMBP: reads per million base pairs read

B



Conclusions: Increased proliferation and decreased mineralization rates in pre-osteoblasts from CKD patients suggests that increased canonical *Wnt* signaling may contribute to this phenotype.

Funding: NIDDK Support, Pharmaceutical Company Support - Genzyme

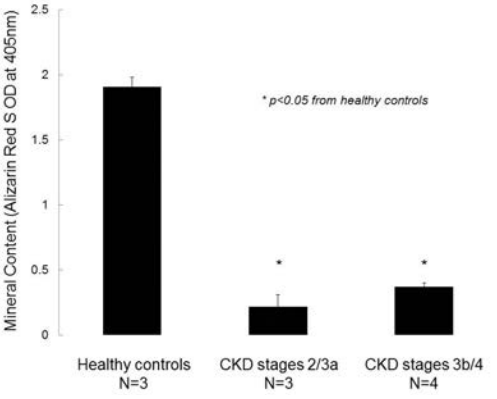
SA-PO982

Pre-Osteoblast Maturation Failure Is a Feature of Early Chronic Kidney Disease Renata C. Pereira,[1] Kathleen Noche,[1] Richard Bowen,[2] Isidro B. Salusky,[1] Katherine Wesseling-Perry.[1] *[1]Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA; [2]Orthopedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, CA.*

Background: Primary pre-osteoblasts from ESKD patients have decreased mineralization rates *ex vivo* (Pereira RC, KI 2015) suggesting that CKD induces intrinsic changes to osteoblast biology resulting in maturation failure.

Methods: To evaluate whether this phenotype is a feature of early CKD, pre-osteoblasts from 7 adolescent patients with CKD stages 2-4 with normal serum calcium, phosphorus, and PTH levels and from 3 healthy adolescent controls were plated at 10,000 cell/cm^2 and cultured in 10% fetal bovine serum and 100 μg/ml ascorbic acid until achieving confluence. Cells were stimulated to mineralize with 10 mM β-glycero-phosphate for 21 days then washed with PBS, fixed with 10% formalin, and stained with 2% Alizarin Red S. Mineral content was measured by acetic acid-extracted Alizarin Red S dye OD at 405 nm. Subsequently, the potential of CKD and healthy control pre-osteoblasts to transition to an adipocyte-like phenotype was examined by culturing confluent cells in the presence of insulin (1μM), dexamethasone (10^{-6}M), and isobutylmethylxanthine (0.5mM) for two weeks. Cells were then stained with Oil Red O; fat was extracted using 100% isopropanol for 30 minutes and absorbance measured at 490 nm.

Results: Cells from pre-dialysis CKD patients with all stages of pre-dialysis CKD mineralized more slowly (figure 1) and transitioned to an adipocyte-like phenotype more readily than healthy controls (Oil red O OD: 0.28+0.06 v. 0.18+0.03, respectively; p<0.05 between CKD and healthy controls).



Conclusions: Decreased mineralization rates and an increased propensity for pre-osteoblasts to transition to an adipocyte-like phenotype may represent bone cell maturation failure in early CKD.

Funding: NIDDK Support, Pharmaceutical Company Support - Genzyme, Private Foundation Support

SA-PO983

Bone Biopsy Results in Chronic Kidney Disease Orfeas Liangos,[1] Silvia Kirchhoff,[2] Joachim Buchholz,[1] Markus Ketteler.[1] *[1]Nephrology, Klinikum Coburg, Coburg, Germany; [2]Faculty of Medicine, Univ of Wuerzburg, Wuerzburg, Germany.*

Background: Although bone histology remains the gold standard in the differential diagnosis of renal osteodystrophy, biomarkers are more commonly used for diagnosis and to guide therapy. However, their predictive value may be questionable. Notwithstanding these facts, data comparing bone biopsy results and biomarkers of bone metabolism remain sparse.

Methods: Here we present a retrospective analysis of bone biopsy results from a single center comprising N=109 patients, categorized according to renal function and compared with intact parathyroid hormone (iPTH), alkaline phosphatase and other biomarkers. We tested associations of these markers with renal osteodystrophy (ROD) class IIIb according to Delling's classification. Results are shown in mean (SD) or percent, as appropriate. Comparisons are made using the Mann-Whitney test due to skewed distribution of values.

Results: Mean (SD) age was 69 (13) years, 55% were women, 25% diabetic, 76% hypertensive, 34% had vertebral fracture. Mean alkaline phosphatase (AP) and bone-specific AP were 112 (83) and 21 (14) U/l, respectively, and iPTH 16 (19) pmol/l. 12% of patients had normal renal function, 37% were in CKD stage 3-5 not on dialysis and 50% were in CKD stage 5D (ESRD). iPTH values were significantly higher in ESRD with high-turnover mixed uremic osteodystrophy (ROD IIIb), 29 (18) pmol/l, if compared to patients without, 9 (9) pmol/l (p<0.001). No significant associations were found for AP or bone-specific AP serum levels. In CKD patients not on dialysis, the finding of ROD IIIb was associated with elevated iPTH, 37 (50) versus 9 (10) pmol/l (p=0.008), bone-specific AP, 55 (44) versus 17 (7) U/l (p=0.04), and decreased blood pH, 7.36 (0.05) versus 7,44 (0.06) (p=0.04). As expected, no phenotypes of RA were found in patients with normal renal function.

Conclusions: While in ESRD patients, presence of high-turnover renal osteodystrophy on iliac crest biopsy was associated with elevated iPTH and serum urea level but not with bone-specific or total AP; the same diagnosis in patients with CKD not on dialysis was also associated with iPTH but, in addition, with elevated bone specific AP and decreased blood pH.

SA-PO984

Osteitis Fibrosa versus Mixed Disease: What Are the Differences? Teg Marcos Veiga,[1] Adriana Belo Lopes Prazeres,[1] Amadeu de Assis Marinho Neto,[1] Jose Edevanilson Gueiros,[1] Ana Paula Gueiros,[1] Vanda Jorgetti.[2] *[1]Nephrology, UFPE, Recife, Pernambuco, Brazil; [2]Nephrology, USP, Sao Paulo, Brazil.*

Background: Bone mineralization is fundamental for the formation of healthy bone and various factors contribute to this process. In high bone turnover, it is the mineralization deficiency present in mixed disease (MD) that distinguishes it from osteitis fibrosa (OF). The aim of this study was to identify clinical and laboratory parameters capable of clinically distinguishing between these two conditions.

Methods: Retrospective analysis of 166 patients on dialysis with a histological diagnosis of high bone turnover. The clinical data examined were age, sex, underlying disease, time on dialysis, fractures, vascular calcification on radiography and the presence of osteoporosis in the bone biopsy. Laboratory tests consisted of total calcium (Cat), phosphorus (P), intact parathyroid hormone (iPTH) and alkaline phosphatase (AP).

Results: The mean age and time on dialysis were equivalent between OF and MD of 47.5 vs 50.1 years and 9.4 vs 9.9 years, respectively. Female were more prevalent in both groups (61% vs 62.3%). No difference in the occurrence of fractures and the presence of vascular calcification. Laboratory tests are shown in table 1.

	OF	MD	p
Cat (mg/dL)*	9.99 ± 1.08	9.74 ± 1.13	0.13
P (mg/dL)*	6.34 ± 1.65	5.5 ± 1.7	0.002
AP (U/L)#	214	355	0.023
iPTH (pg/mL)#	1240	1352	0,92
*values in mean±sd; # median			

Osteoporosis was present in 29.5% of the patients with OF and 47.5% with MD (P= 0.02). Aluminum toxicity (AT) was more prevalent in OF group (51.4% vs 34.4%; P= 0.03).

Conclusions: In the absence of BB and the presence of hyperparathyroidism, higher levels of AP in combination with lower levels of P suggest diagnosis of MD and may be of assistance in clinical management of CKD-MBD. Even in patients with high bone turnover, AT is still very prevalent. The deficiency in bone mineralization contributes to the occurrence of osteoporosis.

SA-PO985

The Profile of Renal Osteodystrophy at a Single Brazilian Center: 12-Year Register Amadeu de Assis Marinho Neto,[1] Ana Paula Gueiros,[1] Jose Edevanilson Gueiros,[1] Vanda Jorgetti,[2] Adriana Belo Lopes Prazeres,[1] Teg Marcos Veiga.[1] *[1]Nephrology, UFPE, Recife, Brazil; [2]Nephrology, USP, São Paulo, Brazil.*

Background: Clinical and laboratory parameters are not always sufficient for diagnosis of CKD-MBD and bone biopsy (BB) is thus the gold standard. The aim of this study was to evaluate the clinical and laboratory profile of patients who underwent BB.

Methods: A retrospective analysis of 200 patients undergoing BB between August 2003 and December 2015. The clinical data examined were age, sex, underlying disease and time on dialysis. Laboratory tests consisted of total calcium (Cat), phosphorus (P), intact parathyroid hormone (iPTH) and alkaline phosphatase (AP). BB specimens were classified histologically as osteitis fibrosa (OF), mixed disease (MD), adynamic bone disease (ABD) or osteomalacia (OM). Aluminum intoxication (IAL) was defined when more than 20% of the trabeluar bone surface were covered by metal. Comparative analysis was performed according to the histological diagnosis.

Results: The mean age of patients was 48.8 years and 58.7% were women. The mean time on dialysis was 9.4 years. Only 7% of the population was diabetic. OF was the most prevalent histologic type (52.2%), followed by MD, present in 30.3% of patients. ABD and OM were found in 13.9% and 3.0%, respectively. Table 1 shows the comparative analysis of the histological types.

	0F	MD	ABD	OM	p
Cat (mg/dL)*	9.9±1.1	9.7± 1	9.6± 1	9.1 ± 0.7	0.052
P (mg/dL)*	6.34±1.6[a,c]	5.5±1.7[a]	5.6±1.8[f]	2.3±1.4[c,f]	< 0.001
AP (U/L)#	214[a,b]	355[a,d,e]	108[b,d]	154[e]	<0.001
iPTH (pg/mL)#	1240[b,c]	1352[d,e]	107[b,d]	313[c,e]	<0.001
*values in mean±sd; # median; (a) OF vs MD; (b) OF vs ABD; (c) OF vs OM; (d) MD vs ABD; (e) MD vs OM; (f) ABD vs OM.					

IAL was present in 47.8% of patients, who had lower iPTH (p<0.001) and AP (p<0.001) compared to patients without IAL. Osteoporosis was found in 37.3% of the BB.

Conclusions: The data show a high prevalence of high bone turnover diseases and indicate that IAL is still an undesirable reality in this setting. AP and iPTH are good markers of bone remodeling. Osteoporosis is highly prevalent in patients on dialysis, even in the case of a young population.

SA-PO986

Relationship between Osteoclast Released Clastokines and Parathyroid Hormone in Hemodialysis Patients Cai-Mei Zheng,[1,2,3] Chien-Lin Lu,[1] Jing-Quan Zheng,[1,2,4] Wenya Ma,[5] Wen-Chih Liu,[1,5] Yung-Ho Hsu,[1,2,3] Jia-Fwu Shyu,[1,6] Yuh-Feng Lin,[1,2,3] Kuo-Cheng Lu.[1,5] *[1]Graduate Inst of Clinical Medicine, College of Medicine, Taipei Medical Univ, Taipei, Taiwan; [2]Dept of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical Univ, Taipei, Taiwan; [3]Div of Nephrology, Dept of Internal Medicine, Shuang Ho Hospital, Taipei Medical Univ, New Taipei, Taiwan; [4]Div of Critical Care Medicine, Dept of Emergency Medicine-Critical Care Medicine (EM-CCM), Shuang Ho Hospital, Taipei Medical Univ, Taipei, Taiwan; [5]Div of Nephrology, Dept of Internal Medicine, Cardinal Tien Hospital, School of Medicine, Fu-Jen Catholic Univ, New Taipei, Taiwan; [6]Dept of Biology and Anatomy, National Defense Medical Center, Taipei, Taiwan.*

Background: Patients on long-term dialysis may develop bone loss due to imbalance in bone formation and bone resorption. We believed that changes in osteoclast released clastokines occur according to different levels of parathyroid hormone in dialysis patients and responsible for bone changes in these patients.

Methods: A total of 223 patients under maintenance dialysis for more than 3 months were enrolled. Patients were grouped according to PTH levels (PTH<150, PTH 150-300, PTH ≥ 300). Serum FGF 23, procollagen type 1 amino-terminal propeptide (P1NP), TRAP 5b, Wnt 10b, Wnt 16, osteoprotegerin (OPG), RANK-L, beta-catenin, DKK-1, sclerostin (SOST) and total alkaline phosphatase (ALP) were measured and compared the changes according to PTH levels among three groups.

Results: Among 128 patients with PTH level ≥300 pg/mL, higher Wnt10b (p< 0.0001), P1NP (p=0.006) and higher OPG (p=0.003) than those of lower PTH groups (PTH< 150 pg/mL and PTH=150-300 pg/mL) were noted. Serum FGF 23 was higher (p=0.005) and DKK1 was lower (p=0.02) among higher PTH group (PTH ≥300 pg/mL) than lower PTH group (PTH< 150 pg/mL). No significant changes in Wnt 16 (p=0.08), RANK-L (p=0.19), beta-catenin (p=0.11),SOST (p=0.91) and TRAP 5b (p=0.15) with PTH levels were noted.

Conclusions: Our results suggest that osteoclast released clastokine Wnt 10b is increased in relation with higher PTH levels, which might be explanation for the compensatory role of clastokine mediated bone formation among dialysis patients.

SA-PO987

Comparison of Calcimimetic R568 and Calcitriol in Mineral Homeostasis in Hyp Mice: An Animal Model of X-Linked Hypophosphatemia Maren Leifheit-Nestler,[1] Julia Kucka,[1] Geert J. Behets,[2] Patrick C. D'Haese,[2] Dieter Haffner.[1] *[1]Dept of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; [2]Laboratory of Pathophysiology, Univ of Antwerp, Belgium.*

Background: We studied the calcimimetic R568 and calcitriol in *Hyp* mice, an animal model of X-linked hypophosphatemia, which is characterized by elevated levels of FGF23, renal phosphate wasting, 1,25-dihydroxyvitamin D (1,25D) deficiency, and rickets. Current medical treatment with oral phosphate and 1,25D is inefficient, associated with side effects, and secondary hyperparathyroidism (sHPT). We hypothesized that mineral homeostasis is differentially affected by R568 and 1,25D in *Hyp* mice with respect to the PTH-vitamin D-FGF23-Klotho axis and skeletal function.

Methods: Male *Hyp* mice aged 28 days received R568 (3 and 10 ng/kg BW/d), 1,25D (150 ng/kg BW/d) or vehicle for 4 weeks. Vehicle-treated wildtype mice served as controls. Blood C-term/intact FGF23, and PTH were measured. Kidneys were analyzed for Cyp24, Cyp27, and Klotho by qPCR and immunoblotting. Bones were investigated by mCT, histomorphometry, and qPCR.

Results: R568 and 1,25D prevent sHPT, yet only 1,25D raises serum phosphate levels in *Hyp* mice. Diminished tubular phosphate reabsorption was unaffected by either treatment. 1,25D increases calciuria and further enhances FGF23 synthesis in bone and circulating FGF23 levels. By contrast, R568 lowers bone *FGF23* expression and serum C-term FGF23 concentration. Renal 1,25D production is further suppressed by 1,25D treatment and improved by R568. *Hyp mice* showed reduced renal Klotho levels, which were normalized by 1,25D and unaffected by R568 treatment. 1,25D but not R568 improved femur length and weight gain, and restored mineralized growth plate and mineralized bone area. R568 significantly improved trabecular but not cortical bone parameters. By contrast, 1,25D improved cortical but not trabecular bone parameters.

Conclusions: R568 reduces PTH and skeletal/circulating FGF23, improves renal vitamin D synthesis, but only partially corrects skeletal abnormalities in *Hyp* mice. 1,25D improves body growth, and defective mineralization despite further enhancement of skeletal FGF23 synthesis.

SA-PO988

Renin-Angiotensin System Inhibition Ameliorates Bone Fragility Through Blocking Both Osteocytic and Osteoblastic Actions in Uremic Rats Takuya Wakamatsu,[1] Yoshiko Iwasaki,[2] Suguru Yamamoto,[1] Akemi Ito,[3] Yoshimitsu Takahashi,[1] Fumitake Gejyo,[1] Junichiro James Kazama,[4] Masafumi Fukagawa,[5] Ichiei Narita.[1] *[1]Div of Clinical Nephrology and Rheumatology, Niigata Univ Graduate School of Medical and Dental Sciences, NIigata, Japan; [2]Dept of Health Sciences, Oita Univ of Nursing and Health Sciences, Oita, Japan; [3]Ito Bone Histomorphometry Inst, Niigata, Japan; [4]Dept of Nephrology and Hypertension, Fukushima Medical Univ, Fukushima, Japan; [5]Div of Nephrology and Metabolism, Tokai Univ School of Medicine, Isehara, Japan.*

Background: Chronic kidney disease (CKD) patients are at an extremely high risk of bone fracture regardless of parathyroid function. Osteocyte apoptosis is elevated in uremic conditions, leading to the deterioration of elastic mechanical properties in weight-bearing bones. The pharmacological use of renin-angiotensin system (RAS) inhibitors is associated with approximately 30% reduction of fracture risk in hemodialysis patients. However, the mechanism remains unknown.

Methods: Sprague-Dawley rats undergone subtotal nephrectomy were administered olmesartan (Nx-O, n=7) or hydralazine (Nx-H, n=6) for 6 weeks. The direct effects of RAS on osteoblasts were observed using MC3T3-E1 cells and primary osteocytes obtained from the mouse femur.

Results: Comparable levels of kidney damage and blood pressure were observed in the Nx-O and Nx-H rats. Compared to Nx-H,Nx-O showed less osteoclast activity (erosion depth; 8.47±1.01 μm vs Nx-H 12.39±2.37 μm, *p<0.01)*, increased mineralization (MAR; 2.43±0.17 μm/day vs Nx-H 0.76±0.88 μm/day, *p<0.01*), raised bone elasticity (storage modulus; $3.01\times10^9\pm1.00\times10^9$ Pa vs Nx-H $1.19\times10^9\pm0.79\times10^9$ Pa, *p=0.046*), and reduced osteocyte apoptosis (empty lacunae; 36.6±12.2N/mm^2 vs Nx-H 67.9±13.6 N/mm^2, *p<0.01*). Angiotensin II (AII) significantly increased the expression of RANKL in MC3T3-E1 cells. AII also increased ROS production and DNA fragmentation in cultured primary osteocytes. These changes were inhibited by olmesartan.

Conclusions: AII modulates bone metabolism through both direct action on osteoblasts and pathways via the promotion of osteocytic apoptosis leading to deteriorated bone mechanical properties, which were improved by AII receptor-1 blockade.

SA-PO989

The Rapid Down-Regulation of Klotho in an Obstructed Kidney Is Not Accompanied by a Compensatory Up-Regulation in the Contralateral Kidney

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Background: The anti-ageing hormone, Klotho, is a renoprotective protein alleviating acute kidney injury and promoting kidney regeneration. The kidney is a major source of Klotho. In the present study the time course of Klotho changes in experimental unilateral ureter obstruction (UUO) and in the contralateral kidney (CK) was followed.

Methods: UUO rats (n=37) were studied at 0, 1, 2, 3, 4, and 10 days (D) and the results of the obstructed kidney were compared to those of CK and to kidneys from unilateral nephrectomized (UNX) control rats (n=35) as well as normal kidneys. Kidney Klotho, the renoprotective BMP7 and LGR5 together with markers of fibrosis, TGF-β and Periostin, gene expressions were examined.

Results: Unilateral ureter obstruction resulted in significantly decreased Klotho expression already at day 1, which decreased further progressively to day 10. Baseline: 1.91±0.30; D1: 0.91±0.18 ($p<0.01$), D10: 0.21±0.02 ($p<0.01$). LGR5 was reduced from 0.80±0.30 at baseline to 0.19±0.03 at D1 ($p<0.01$) in the obstructed kidney, suggesting stem cell depletion. The decrease in Klotho expression in UUO kidney was associated with a decreased expression of BMP7 (Baseline: 0.87±0.11, D1: 0.57±0.07, D10: 0.63±0.08, $p<0.01$) and an increased expression of TGF-β (Baseline: 0.51±0.07, D1: 0.69±0.11, D10: 1.51±0.17, $p<0.01$) and induction of Periostin (0.09±0.10 to D1: 0.67±0.40, $p<0.05$). The expressions of BMP7, TGF-β, Periostin and LGR5 were similar in contralateral, UNX and normal kidneys. The contralateral kidney had similar expression of Klotho (D1: 2.20±0.27 and D10: 1.80±0.15) compared to normal and UNX kidneys (D1: 1.91±0.28 and D10: 2.05±0.83).

Conclusions: In an unilateral ureter obstruction model a very rapid and significant decrease in the expression of Klotho took place already at day 1 in the obstructed kidney. The unilateral ureter obstruction was associated with upregulation of pro-fibrotic genes and down-regulation of anti-fibrotic BMP7. The contralateral kidney did not respond with a compensatory increase in Klotho.

SA-PO990

Comparison of the Two Types of Iron-Based Phosphate Binders, Sucroferric Oxyhydroxide and Ferric Citrate, on Lowering Serum Phosphate Effects in Patients on Hemodialysis

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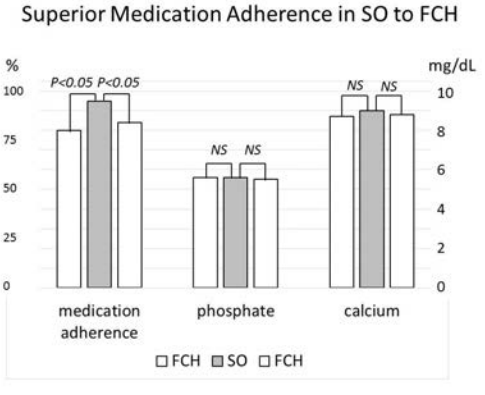
Background: Sucroferric oxyhydroxide(SO), a new type of iron-containing phosphate binder, is reported to exerts stronger phosphate lowering effect compared with ferric citrate hydrate (FCH) in equivalent dose resulting in lower pill burden.

Methods: To compare the effects of SO and FCH on medication adherence as well as serum phosphate-lowering effects in patients on hemodialysis (HD) in a crossover study. Thirty-two subjects were already treated with 1500 mg to 2250 mg of FCH daily. Subjects were switched to 750 mg to 1000 mg of SO daily for 4-6 weeks, then previous treatment with FCH. Measurement of plasma bone mineral parameters including phosphate and calculation of the medication adherence (total actual number of tablets taken during a period / number of tablet expected to be taken during a period x 100) were achieved at the end time point of each arm.

Results:



As shown in figure 1, there was no significant difference in serum phosphorous concentration in SO or FCH (FCH: 5.6 ± 1.3 – SO: 5.6 ± 1.4 – FCH: 5.5 ± 1.1 mg/dL). A significant increase was observed in medication adherence in SO compared to FCH (FCH: 79 ± 10 - SO: 95 ± 14 - FCH: 84 ± 14%). No significant difference was observed in other bone mineral parameters.

Conclusions: Thus, SO can potentially exert similar phosphate-lowering effects to FCH with better medication adherence and lower pill burden in patients on maintenance HD.

Funding: Private Foundation Support

SA-PO991

Bone Biopsy Findings and Biochemical Markers before and after Two Years of Renal Transplantation

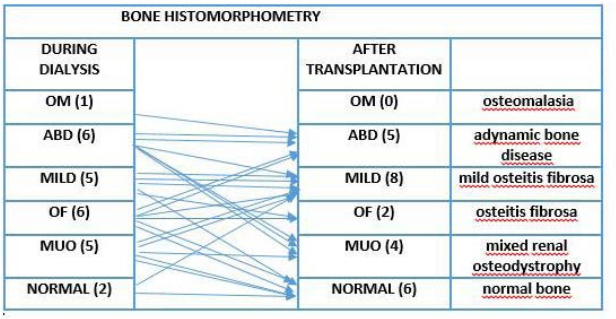
Satu Keronen,[1] Leena Martola,[1] Patrik Finne,[1] Inari S. Burton,[2] Tobias E. Larsson,[3] Heikki Kroger,[4] Eero Honkanen.[1] *[1]Abdominal Centre, Nephrology, Helsinki Univ Central Hospital and Helsinki Univ, Helsinki, Finland; [2]Univ of Eastern Finland, Terveystalo Jyväskylä, Jyväskylä, Finland; [3]Astellas Pharma, Sweden; [4]Kuopio Univ Hospital, Kuopio, Finland.*

Background: There are only few studies on bone biopsies before and after renal transplantation (RTX). The aim of this study was to investigate the changes in histomorphometric pattern of bone disease after RTX.

Methods: Bone biopsy was taken from the iliac crest and analyzed using the turnover -mineralization -volume classification on 25 consecutive dialysis patients (80% men, 48 % on PD) at baseline and 25 (24- 26) months after RTX. The median time on dialysis prior to RTX was 24 (15-42) months. Median GFR was 64 (41-70) ml/min per1.73 m^2 (MDRD). Immunosuppressive therapy comprised CNI, MMF, and prednisone. Serum markers of bone turnover were obtained.

Results: The changes in bone histomorphometry before and after RTX are shown in Figure 1. Bone biopsy findings were divided into three subgroups based on bone turnover. Biochemical findings after RTX are shown in Table 1. At baseline, 44% of dialysis patients had OF or MUO, 28% mild OF or normal turnover and 28% of patients had OM or ABD. After two years of RTX 24%, 56% and 20% of patients had OF/MUO, mild OF/normal or OM/ABD, respectively. Following RTX osteocalcin and bone alkaline phosphatase (BAP) were significantly higher in OF+ MUO group.

Fig.1 The changes in bone histomorphometry before and after renal transplantation



Variables	All n = 25 (median + IQR)	OM + ABD n=5	Mild OF + normal n=14	OF + MUO n=6	P
GFR ml/min per 1.73m²	64 (41-70)	48	68	35	0.19
osteocalcin ug/l	41 (35-74)	37	39	86	<0.05
BAP ug/l	15 (11-27)	14	14	36	<0.05

Conclusions: After two years of renal transplantation bone turnover normalized in almost 80% of the patients. Lower GFR might explain higher osteocalcin and BAP seen in OF + MUO group.

Funding: Pharmaceutical Company Support - Shire Pharmaceuticals

SA-PO992

Kidney Transplantation Alters the Association between Serum Sclerostin and Bone Sclerostin Expression

Mathias Haarhaus,[1] Henrik Boltenstål,[1] Abdul Rashid Tony Qureshi,[1] Geert J. Behets,[2] Bengt Lindholm,[1] Peter Stenvinkel,[1] Patrick C. D'Haese.[2] *[1]Div of Renal Medicine and Baxter Novum, Karolinska Univ Hospital at Huddinge, Karolinska Inst, Stockholm, Sweden; [2]Laboratory of Pathophysiology, Dept of Biomedical Sciences, Univ of Antwerp, Antwerp, Belgium.*

Background: The osteocyte derived protein sclerostin inhibits bone turnover. Serum sclerostin rises early in chronic kidney disease (CKD) but to what extent this reflects osteocyte sclerostin production is not clear. We investigated associations between serum sclerostin, bone sclerostin expression and different types of renal osteodystrophy.

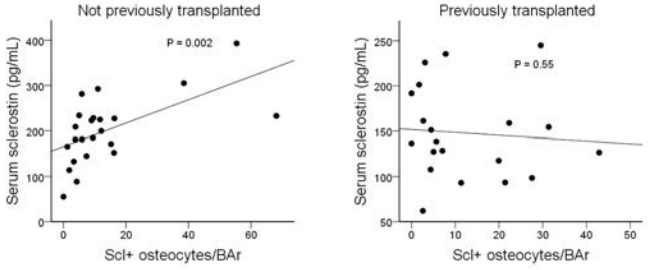
Methods: Immunohistochemical staining of sclerostin was performed in bone biopsies from 43 CKD patients (pts), including 15 pts undergoing dialysis and 20 pts who had received a kidney transplant. Bone sclerostin expression was correlated to bone histomorphometric parameters and serum sclerostin levels.

Results: Pts with low bone formation rate (BFR < 97µm²/mm²/day) had higher serum and bone sclerostin expression than pts with normal or high BFR.

	Low BFR (N=13)	Normal + high BFR (N=28)	P
	median (range)	median (range)	
Serum sclerostin (pg/mL)	224.7 (126.5-393.0)	141.7 (55.3-392.9)	0.004
Scl+ /BAr (number/mm²)	12.1 (1.3-68.1)	5.0 (0-38.6)	0.008

Whereas a strong association between serum and bone sclerostin expression was observed in non-transplanted pts (figure 1) no such association was observed in transplanted

pts, independent of kidney graft function. Females had higher bone sclerostin expressions than males (P=0.046), despite similar serum sclerostin levels and bone histomorphometric parameters.



Conclusions: Serum sclerostin and bone expression of sclerostin are inversely associated with bone turnover in CKD. In non-transplanted CKD pts, serum sclerostin reflects bone sclerostin expression. Bone sclerostin expression is affected by gender in CKD.

Funding: Government Support - Non-U.S.

SA-PO993

Kidney Transplantation Increases Bone Esclerostin Expression

Maria Julia C.L.N. Araujo, Igor Marques, Fabiana Graciolli, Wagner Dominguez, Luciene dos Reis, Ivone Braga de Oliveira, Rosilene M. Elias, Vanda Jorgetti, Elias David-Neto, Rosa M.A. Moyses. *Nephrology Div, Univ of Sao Paulo, Brazil.*

Background: Most of the metabolic disorders improve after kidney transplantation (Tx), although bone metabolism can remain compromised, which is evidenced by high rates of bone loss, fractures and vascular calcification. Osteocytic bone protein expression is dysregulated in CKD, and this seems to contribute negatively to bone health in these patients. It has been described that FGF-23 and sclerostin (Scl) expression is increased in children after solid organ transplantation. Nonetheless, little is known about bone-related proteins expression in adult recipients, which were analyzed prospectively in this study.

Methods: Transiliac bone biopsies were obtained from 30 adult patients one week before and one year after Tx. Bone fragments were used for histomorphometric analysis, as well as for bone proteins, measured by immunohistochemistry and MILLIPLEX® MAP.

Results: Patients were relatively young (41 ± 11 yrs), with a pre Tx dialysis vintage of 30 (15-55) months. After a successful Tx, there was an increase in serum calcium and a decrease in PTH and alkaline phosphatase. No changes were seen in bone DKK1, whereas a decrease was observed in bone osteoprotegerin (OPG) and FGF-23. Although serum Scl decreased after KTx [1.2 (0.6-1.9) vs. 0.5 (0.4-0.6) ng/ml; p = 0.001)], an increase of this protein in bone was observed with both methods.

	Pre-Tx	1 year after Tx	p
MILLIPLEX® (mg/g protein)			
DKK1	2.94 (2.23-3.68)	2.87 (2.05-4.28)	0.954
OPG	0.62 (0.43-0.76)	0.38 (0.29-0.63)	0.037
Scl	531 (371-941)	760 (482-1,395)	0.059
FGF-23	5.97 (4.19-12.49)	4.73 (3.74-6.89)	0.005
Immunohistochemistry (%+/total osteocytes)			
Scl	5.6 (2.0-13.8)	24.5 (6.7-44.5)	0.008
FGF-23	7.7 (1.5-25)	11.4 (3.8-40.7)	0.215

Conclusions: Kidney function recovery after Tx is accompanied by significant changes in most bone proteins expression. Contradictory to the decrease in levels of serum Scl, its bone expression, actually, has increased. This finding may explain the persistence of Tx-related bone disease.

SA-PO994

Cinacalcet Hydrochloride Increases Sharpey Fiber Area in Patients with Secondary Hyperparathyroidism

Aiji Yajima,[1,2] Ken Tsuchiya,[2] Kosaku Nitta.[2] *[1]Biomedical Engineering, Indiana Univ, Indianapolis, IN; [2]Medicine, Kidney Center, Tokyo Women's Medical Univ, Tokyo, Japan.*

Background: Bone formation without prior bone resorption, namely, minimodeling is increased in patients with hypoparathyroidism (Ubara Y. Kidney Int 2005) or those who received parathyroidectomy (Yajima A. Kidney Int 2008). Skeletal muscle interaction is quite important in thinking about bone formation through the osteocyte (Bonewald LF. J Bone Miner Res 2013). Sharpey fiber connects periosteal surface with muscle layer and it is very important for the transmission of mechanical loading. And little is known about sharpey fiber in the field of bone disease. We investigated sharpey fiber as one of the causes of reduced fracture rate in patients treated with ciacalcet hydrochloride (Moe SM. J Am Soc Nephrol 2015).

Methods: Hemodialysis patients suffering from secondary hyperparathyroidism (n=14, Age; 61.8±7.3 yrs, Dialysis duration; 8.7±5.2 yrs) were treated with cinacalcet hydrochloride (HCL) and concomitant administration of low doses of oral or intravebous vitamin D for one year. The dose of cinacalcet HCL was ranged from 25 to 100 mg/day. Serum intact parathyroid hormone (i-PTH) and sharpey fiber area (Sharpey fiber surface/periosteal surface; %) was measured before and after the treatment with cinacalcet HCL in these patients.

Results: Serum i-PTH level was decreased from 857.3±213.0 to 184.6±50.4 pg/mL. Sharpey fiber area was increased from 42.5±15.7 to 75.3±16.5 % (p<0.001, Wilcoxon signed rank test) after the treatment with cinacalcet HCL in patients with secondary hyperparathyroidism.

Conclusions: Cinacalcet hydrochloride is a potential candidate to increase sharpey fiber, which increases minimodeling volume through the osteocyte (Tatsumi S. Cell Metab 2007). It is possible that one of the causes of reduced fracture rate in patients receiving cinacalcet hydlochloride is an increased sharpey fiber area in dialysis patients.

SA-PO995

Sclerostin Is a Good Predictor of Marrow Adipocyte in Dialysis Patients

Aiji Yajima,[1,2] Ken Tsuchiya,[2] Kosaku Nitta.[2] *[1]Biomedical Engineering, Indiana Univ, Indianapolis, IN; [2]Medicine, Kidney Center, Tokyo Women's Medical Univ, Tokyo, Japan.*

Background: Some papers regarding the relationship betweem sclerostin (Scl) and bone turnover and osteocytic perilacunar/canalicular remodeling was published (Poole KE. FASEB 2005, Kogawa M. J Bone Miner Res 2013, Nakashima T. Nat Med 2011, and etc.). However, only one basic paper regarding the relationship between Scl and marrrow adipocyte has been published (Ukita M. Sclerostin enhances adipocyte differentiation in 3T3-L1 cells. J Cell Biochem 2016). And parathyroidectomy increased marrow adipocyte differentiation in dialysis patients (Yajima A. presented). We analyzed the relationship between serum Scl or i-PTH and marrow adipocyte parameters in hemodialysis patients.

Methods: We measured serum Scl (ELISA, Biomedica Medizinprodukte, Vienna, Austria) and intact parathyroid hormone (iPTH) (Electrochemiluminescence immunoassay, Elecsis PTH, Roche Diagnostics GmbH, Mannheim, Germany) levels in 23 hemodialysis patients (Age; 60.5±6.0 yrs, dialysis duration; 10.7±7.3 yrs). At the same time, iliac bone biopsy specimens were obtained from the patients to measure (1) adipocyte volume/marrow volume (Ad.V/Ma.V (%)), (2) Number of adipocyte/Ma.V (N.Ad/Ma.V (N/mm^2) and (3) mean adipocyte volume (Ad.V/N.Ad (μm^2)). The relationship between serum parameters and adipocyte parameters were analyzed by linear regression analysis.

Results: I, 1, Serum Scl was 70.6±44.3 ng/mL, ranging from 25.0 to 172.2 and i-PTH was 589.3±479.2 pg/mL, ranging from 5 to 1430. Ad.V/Ma.V was 37.8±18.5 %, N.Ad/Ma.V was 212.6±57.8 N/mm^2 , and Ad.V/N.Ad was 1815.6±644.3 μm^2. II, 1, Serum Scl was positively associated with Ad.V/Ma.V (r=0.752, p<0.001) and Ad.V/N.Ad (r=0.582 (p<0.005)). But Scl was not associated with N.Ad/Ma.V. 2, Serum i-PTH was negatively associated with Ad.V/Ma.V (r=0.526, p<0.01) and Ad.V/N.Ad (r=0.511 (p<0.01)). But i-PTH was not associated with N.Ad/Ma.V.

Conclusions: In dialysis patients, marrow adipocyte parameters were strongly associated with serum Scl as compared with i-PTH levels. It is highly possible that sclerostin regulates the metabolism of marrow adipocyte. Sclerostin is important because adipocyte suppresses osteoblast function.

Funding: Private Foundation Support

SA-PO996

Increase of Bone Marrow Adiposity Is Associated with Decrease of Bone Formation and Volume in Pre-Dialysis Chronic Kidney Disease Patients

Joao Victor Salgado, Maria Dalboni, Aluizio B. Carvalho, Maria Eugenia F. Canziani. *Discipline of Nephrology, Federal Univ of São Paulo, São Paulo, São Paulo, Brazil.*

Background: Metabolic disorders and accumulation of uremic toxins might contribute to bone fat deposition and skeletal fragility in CKD patients. We aimed to investigate the relationship between bone marrow adiposity and bone Turnover, Mineralization and Volume (TMV system) in CKD patients not yet in dialysis.

Methods: Twenty-two transiliac bone biopsy specimens obtained in a cross-sectional study previously performed in 2-5 stages CKD patients (52±11 yrs, 59% male, 32% diabetes, 33±17 ml/min/1.73m^2) were evaluated by quantitative histomorphometry to assess bone and marrow adipocyte parameters. For TMV system, bone formation rate (BFR/BS) was considered as Turnover, mineralization lag time (MLT) as Mineralization and trabecular bone volume (BV/TV) as Volume. Adipocyte number (Ad.N) and adipocyte volume / total volume (Ad.V.TV) was used as adipocyte parameters. Serum bone and biochemical markers were measured.

Results: Ad.N and Ad.V.TV did not differ significantly with regards to age, gender, diabetes mellitus and CKD stages. Ad.N correlated negatively with LDL-cholesterol (r= -0.48, p=0.02) and BV/TV (r= -0.58, p=0.005). Ad.V.TV correlated negatively with BV/TV (r= -0.61, p=0.002) and BFR/BS (r= -0.46, p=0.03). Adipocyte parameters, Ad.N and Ad.V.TV, did not correlate with MLT.

Conclusions: Increase of bone marrow adiposity seems to be associated with decrease of bone formation and volume but not with mineralization in pre-dialysis CKD patients.

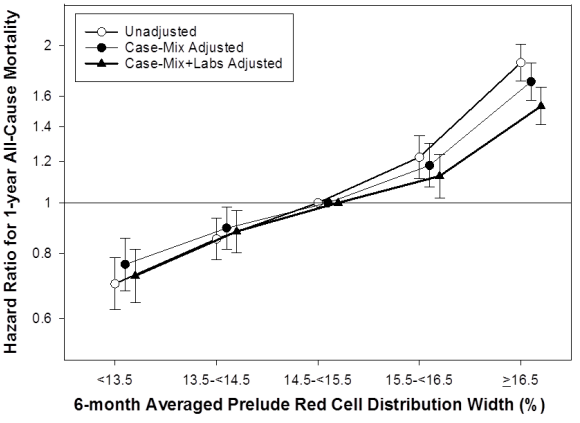
SA-PO997

Association of Pre-ESRD Red Cell Distribution Width and Early Dialysis Mortality: A Transition of Care in CKD Study Melissa Soohoo,[1] Miklos Zsolt Molnar,[2] Elani Streja,[1] Connie Rhee,[1] Daniel L. Gillen,[1] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Univ of Tenn.*

Background: Recent studies have shown that red blood cell distribution width (RDW), a marker of red blood cell size and variability and likely an iron store marker, is a predictor of mortality in the hemodialysis population. However, the association of RDW in the prelude period prior to transitioning to end-stage renal disease (ESRD) and post-ESRD mortality is unknown.

Methods: We examined a cohort of 18,924 US Veterans transitioning to ESRD between 2007-2011 with RDW measured in the 6 months prior to dialysis initiation (prelude period). We analyzed the association of RDW with all-cause and cardiovascular mortality in a cohort using Cox proportional hazards and Fine & Gray competing risk regression models, respectively. Each analysis was adjusted for case-mix (demographics and comorbidities) and laboratory measurements. RDW was divided into 5 categories <13.5, 13.5-<14.5, 14.5-<15.5, 15.5-<16.5, and ≥16.5 %.

Results: The mean age (mean±SD) of the cohort was 68±11years old and included 2% females, 71% diabetics and 25% African Americans. Across all levels of adjustment, higher 6-month prelude RDW was linearly and incrementally associated with higher all-cause mortality compared to the reference group (14.5-<15.5%). This association was consistent for 3-, 6-, 12 and 24-month all-cause mortality. In addition, 6-month prelude RDW was also linearly associated with post-ESRD cardiovascular mortality, although the magnitude was somewhat attenuated.



Conclusions: In very advanced CKD patients, higher RDW is associated with higher all-cause and cardiovascular mortality in patients transitioning to ESRD independent of comorbidities and laboratory measures. Future studies are needed to confirm these findings as well as to further understand the mechanism underlying these RDW associations.

Funding: NIDDK Support

SA-PO998

Correlates of Red Blood Cell Life Span in Chronic Hemodialysis Patients Jie Ma,[1,3] Yanna Dou,[1] Hanjie Zhang,[1] Stephan Thijssen,[1] Schantel Williams,[1] Viktoriya Kuntsevich,[2] Nathan W. Levin,[2] Peter Kotanko.[1,2] *[1]Research Dept, Renal Research Inst, New York, NY; [2]Mount Sinai Beth Israel, New York, NY; [3]Nephrology, Peking Union Medical College Hospital.*

Background: The pathogenesis of anemia in hemodialysis (HD) patients is multifactorial, with decreased red blood cell life span (RBC-LS) being a significant contributor. The impact of reduced RBC-LS is recognized but not well researched. The objective of this study was to investigate the relationship between RBC-LS and EPO dose and inflammatory markers in HD patients.

Methods: The RBC-LS (calculated from measured alveolar carbon monoxide concentrations), inflammatory markers IL-6, IL-18, IL-10 (measured by LuminexÔ) and hsCRP were assessed at baseline and during follow up.Monthly hemoglobin (Hgb) levels, weekly EPO dose and clinical parameters were obtained from electronic health records. The association between RBC-LS, weekly EPO dose and inflammatory biomarkers was evaluated by using linear mixed effects models.

Results: Forty-five HD patients were enrolled with an average age of 58.5±13.9 years, 71% male, 46.7% diabetics, and a mean HD vintage 47 ± 46 months. In 22 patients up to 5 repeated RBC-LS measurements were available. RBC-LS was 74± 23 days (range 30 to 125). RBC-LS was inversely correlated with the EPO requirement.

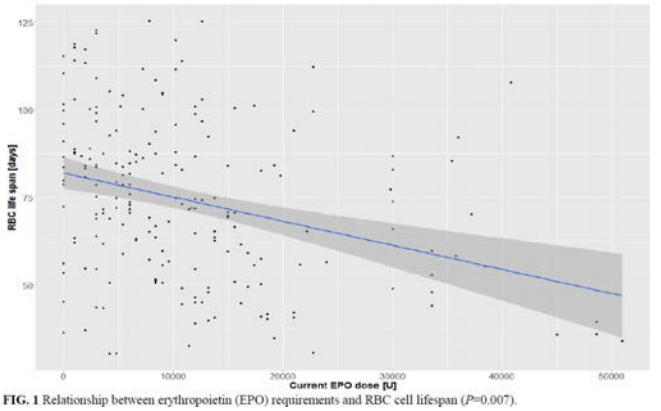


FIG. 1 Relationship between erythropoietin (EPO) requirements and RBC cell lifespan (P=0.007).

While RBC-LS was positively correlated with uric acid (P=0.018), no correlation was found with any of the inflammatory biomarkers, Kt/V, β_2-microglobulin, ferritin, RBC and reticulocyte counts, PTH, and HbA_1C.

Conclusions: In chronic HD patients RBC-LS is markedly reduced and inversely correlated with EPO dose. The positive correlation with uric acid raises the possibility that its anti-oxidant effects may protect RBCs. The lack of an association between levels of inflammatory biomarkers and RBC-LS suggests a limited role of inflammation as a determinant of premature RBC death.

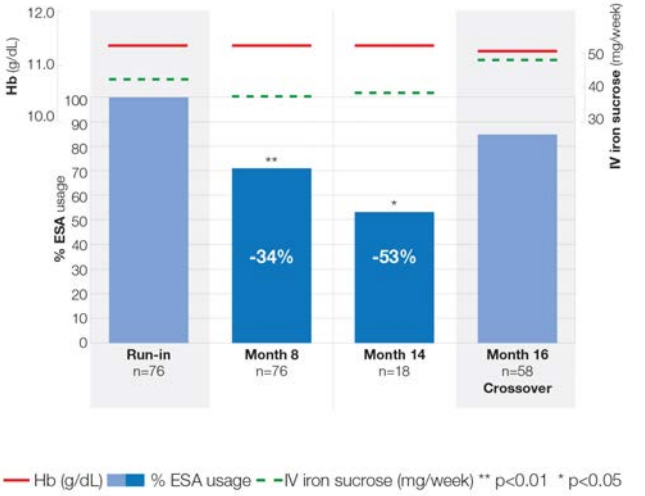
SA-PO999

Improving Anemia Therapy in Hemodialysis Patients Iain C. Macdougall,[1] Antonio Sousa,[2] Thomas Ryzlewicz,[3] Franz-Ferdinand Becker,[4] Amelia Fairburn-Beech,[4] William Kilgallon.[4] *[1]Renal Unit, King's College Hospital, London, United Kingdom; [2]Fundação Renal Portuguesa, Portuguesa, Portugal; [3]Via Medis Nierenzentren, Riesa, Germany; [4]Oxyless Ltd, London, United Kingdom.*

Background: Hemodialysis (HD) patients have a shortened red cell survival, partly due to hemolysis associated with uremia, and partly due to the HD process itself. Blood-air contact within the extra-corporeal circuit contributes to the latter problem. A novel bloodline (Oxyless) which reduces the blood-air contact by 99.1% has been shown to reduce Erythropoiesis-Stimulating Agent (ESA) dose requirements in HD patients. We now report data over a longer treatment period (14 months).

Methods: 142 patients (>18 years, HD > 3 months via an A-V fistula), in two cohorts, were selected for treatment with Oxyless bloodlines, in an open label, prospective, audit following a 3 month run-in period. After 8 months, cohort 1 (109 patients) reverted to the control bloodlines (Nikkiso/Gambro) in the crossover phase for a further 8 months. Cohort 2 (33 patients) remained on the Oxyless bloodlines for 14 months without crossover.

Results: Mean ESA dose fell by 34% (p<0.01) by Month 8, further reducing to 53% (p<0.05) by Month 14. Hemoglobin (Hb) levels were stable throughout at 11.5g/dL. IV iron dose fell by 12% (Month 8) and 25% (p<0.05) by Month 14 each compared to baseline.



By Month 16 (Cohort 1), ESA doses increased to 82% of their baseline levels. Hb levels were 11.3g/dL. Iron dose returned to 120% of pre-treatment levels. Patients of a shorter dialysis vintage (<4 years, n=45) showed a greater reduction in ESA usage at Month 8 (-47%, p<0.01) compared with patients of a longer vintage (4-17 years, n=31, -16%), irrespective of their diabetic status.

Conclusions: These results provide further evidence that this bloodline can optimise anemia management, increasing confidence in the data validity, and suggesting clinical and economic benefits from the use of this technology.

Funding: Pharmaceutical Company Support - Oxyless Ltd

SA-PO1000

Modeling Outcomes by Dopps-Identified Modifiable Dialysis Practices in the Monitor-CKD5 Study Christian Combe,[1] Johannes F. Mann,[2] Gerard M. London,[3] David Goldsmith,[4] Philippe Zaoui,[5] Frank Dellanna,[6] Michael Gorray,[7] Nadja Hoebel,[7] Karen Macdonald,[8] Ivo Abraham.[8,9] *[1]Centre Hospitalier de Bordeaux, Univ of Bordeaux, Bordeaux, France; [2]Friedrich Alexander Univ Erlangen-Nürnberg, Erlangen, Germany; [3]Centre Hospitalier FH Manhés, Fleury-Mérogis, France; [4]Guy's and St. Thomas' NHS Foundation Hospital, London, United Kingdom; [5]Univ de Grenoble-Aples, Grenoble, France; [6]Dialysezentrum, Düsseldorf, Germany; [7]Sandoz/Hexal AG, Holzkirchen, Germany; [8]Matrix45, Tuscon, AZ; [9]Univ of Arizona, Tuscon, AZ.*

Background: Six modifiable hemodialysis (HD) practices were found to be predictive of mortality in the DOPPS (Port et al. *Blood Purif* 2004). We assess associations between the 6 modifiable practices and 4 outcomes in MONITOR-CKD5, a prospective 2-year real-world study of 2023 HD patients with renal anemia in 10 European countries.

Methods: Exploratory analysis between 6 modifiable HD practices (adequate dialysis dose, partial correction of serum albumin, phosphate control, reduced interdialytic weight gain, use of fistula, anemia correction) at baseline and 4 outcomes: chronic hypo-response to erythropoiesis stimulating agents (ESAs), thrombo-embolic event (TEE), hospitalization, and mortality. Each outcome was modeled with each HD practice using multi-level logistic regression corrected for center effect.

Results: Table 1 presents modeling results. Rates of modifiable HD practices and outcomes are also listed.

Table 1.

Modifiable Practices		Chronic hypo-response to ESA^ (8.0%)		TEE (14.4%)		Hospitalization (17.1%)		Mortality (14.2%)	
	% Yes	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Kt/V ≥ 1.2*	82.9%			0.593	0.358–0.983				
Serum albumin ≥ 3.5 g/dL*	82.5%			0.508	0.294–0.877			0.527	0.285–0.976
Phosphate ≤ 5.5 mg/dL*	61.5%			0.699	0.489–0.999				
Interdialytic weight gain ≤5.7%*	92.2%	0.265	0.156–0.451						
Fistula*	83.4%					0.438	0.272–0.705	0.458	0.279–0.754
Baseline Hb (1 g/dL)	11.1±1.1*	0.608	0.516–0.717			0.778	0.652–0.928		

^ ≥4 consecutive months of ESA Resistance Index >15 (IU/kg/wk)/(g/dL)
* yes vs. no
* Mean±SD
Only results with p< 0.05 shown

Conclusions: Two or more modifiable HD practices were related to each of the 4 outcomes in this real-world study. The desired state of each practice had an odds-lowering association with all outcomes. Given their strong association with significant clinical outcomes, these 6 modifiable HD practices should be monitored in each center.

Funding: Pharmaceutical Company Support - SANDOZ

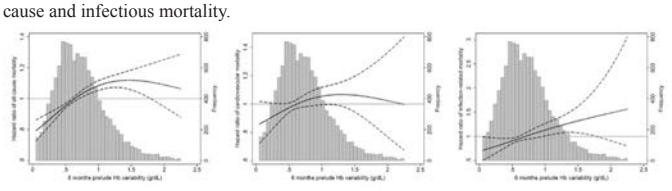
SA-PO1001

Association of Pre-ESRD Hemoglobin Variability with Post-ESRD Mortality in Advanced CKD Patients Transitioning to Dialysis Charles Dyer Diskin,[1] Keiichi Sumida,[1,2] Miklos Zsolt Molnar,[1] Praveen Kumar Potukuchi,[1] Fridtjof Thomas,[1] Jun Ling Lu,[1] Connie Rhee,[3] Elani Streja,[3] Kunihiro Yamagata,[2] Kamyar Kalantar-Zadeh,[3] Csaba P. Kovesdy.[1,4] *[1]Univ of Tennessee Health Science Center, Memphis, TN; [2]Univ of Tsukuba, Ibaraki, Japan; [3]Univ of California, Irvine, CA; [4]VA Medical Center, Memphis, TN.*

Background: Hemoglobin variability (Hb-var) has been associated with increased mortality both in non-dialysis dependent (NDD)-CKD and ESRD patients, however, the impact of Hb-var in late-stage NDD-CKD on outcomes after dialysis initiation remains unknown.

Methods: We analyzed a cohort of 12,016 US veterans with advanced CKD transitioning to dialysis between 10/2007-9/2011 who had at least 3 Hb measurements in the last 6 months before dialysis initiation. Hb-var was defined by residual standard deviation of all Hb values in the 6 months before dialysis initiation using within-subject linear regression models. Associations of Hb-var quartiles (<0.46, 0.46-0.69, 0.70-0.96, ≥0.97 g/dL) with all-cause and cause-specific mortality after dialysis initiation were examined using Cox (for all-cause) and competing risk (for cause-specific mortality) regressions and cubic splines with adjustment for demographics, comorbidities, medications, CV medication adherence, pre-ESRD 6-month averaged eGFR levels, and Hb-var parameters (Hb intercept and slope).

Results: Higher Hb-var was associated with increased risk of all-cause and infectious mortality, but not for CV mortality (Figure). The adjusted hazard ratios [95% CI] for the highest (vs. lowest) quartile of Hb-var were 1.20 [1.11-1.29] and 1.49 [1.11-2.00] for all-cause and infectious mortality.



Conclusions: Pre-ESRD Hb-var is associated with higher post-ESRD mortality, and especially with infectious mortality. Further research is needed to clarify the underlying mechanisms and true causal nature of the observed association.

Funding: NIDDK Support, VA Support

SA-PO1002

Transfusion Practice for Incident Dialysis Patients in Canada: A Prospective Observational Study Aminu K. Bello,[1] Christine M. Ribic,[2] Serge Cournoyer,[3] Mercedeh Kiaii,[4] Martine Leblanc,[5] Melanie Poulin-Costello,[6] David N. Churchill,[2] Norman Muirhead.[7] *[1]Univ of Alberta, Edmonton, AB; [2]McMaster Univ, Hamilton, ON; [3]Univ de Sherbrooke, Sherbrooke, QC; [4]Univ of British Columbia, Vancouver, BC; [5]Univ de Montréal, Montréal, QC; [6]Amgen Canada Inc.; [7]Univ of Western Ontario, London, ON.*

Background: KDIGO guidelines in 2012 recommended conservative ESA use. Study objectives were to identify blood transfusion (BT) rates in incident dialysis patients in Canada after 2012, factors associated with BT and the clinical context.

Methods: Data were obtained by monthly chart review. Transfusion data were recorded as units transfused and as transfusion episodes (≥ 2 units within 24 hrs.)

Results: 314 patients were enrolled; 80% completed 12 months follow-up. 65% were male and 75% were Caucasian with mean age of 64 yrs. 75% received pre-dialysis care for > 12 months. Overall, 30% received at least 1 unit during follow-up. During the first 90 days, 168 units were transfused over 76 patient-years (PY) (221 units/100 PY). From day 91-365, there were 215 units transfused over 208 PY (104 units/100 PY). Expressed as transfusion episodes, the rates per 100 PY were 148 for the first 90 days and 63 for days 91-365. Univariate Cox regression for time to first transfusion showed an association with older age, no pre-dialysis care, BT prior to starting HD, use of a temporary dialysis catheter and starting dialysis as an inpatient ($p < 0.05$). The most common reason for transfusion was a low hemoglobin value (92%) with concurrent clinical reasons being gastrointestinal bleeding (10%) and peri-surgical blood loss (9%). The mean Hb values before the first 3 transfusion episodes were 78.6, 75.3 & 75.9 g/L and 88-91% had Hb < 90 g/L. Univariate Cox regression for time to first hospitalization showed an association with in-patient start of dialysis and receiving a BT before hospitalization ($p < 0.05$).

Conclusions: The transfusion rate was higher in the first 90 days. The time to first transfusion was associated with age and factors associated with pre-dialysis care. The most common indication was a low haemoglobin value rather than clinical factors.

Funding: Pharmaceutical Company Support - Amgen

SA-PO1003

Effect of Altitude on Dosage Requirement of C.E.R.A. (Continuous Erythropoietin Receptor Activator) to Correct Hemoglobin (Hb) Levels in Chronic Kidney Disease (CKD) Patients (pts) Maria Guadalupe Suarez,[1] Alfredo Chew-Wong,[2] Raymundo Alfredo Aviles,[3] Luis E. Morales-Buenrostro,[4] Francisco Eduardo Quintana,[5] Sandro Avila Pardo,[6] Manuel Avendano Garcia,[7] Octavio Cabrera-Anaya.[8] *[1]Hosp Angeles Lindavista, Mexico City, Mexico; [2]Clinica San Cosme, Aguascalientes, Mexico; [3]Hosp San Javier Marina, Pto Vallarta, Mexico; [4]Nefros Investigacion S.C., Mexico City, Mexico; [5]Hosp Star Médica, Morelia, Mexico; [6]Hosp Reg Alta Esp, Veracruz, Mexico; [7]Centro de Hemodiálisis del Norte, Mexicali, Mexico; [8]Roche Servicios de México SA de CV, Mexico City, Mexico.*

Background: Severe anemia in CKD pts is associated with increased risk of adverse clinical events and mortality. Iron and erythropoiesis-stimulating agents (ESAs) are the standard of care for dialysis pts. Hemodialysis (HD) pts living at higher altitudes have higher Hb levels and lower ESA requirements.The long half-life, low binding affinity and low systemic clearance of C.E.R.A. allow once-monthly dosing. The primary objective of the multicenter Phase IV ALTITUDE trial (NCT01519947) was to determine the C.E.R.A. dose needed to achieve an Hb of 11–12g/dL in ESA-naïve CKD pts living either <50m above sea level (masl) or ≥1800masl.

Methods: C.E.R.A. was administered according to label to 86 pts (29 <50masl; 57 ≥1800masl) with stage III–V CKD (34 pre-dialysis; 52 HD).

Results: Mean age was 56 yrs, 44% were male, and etiology of CKD was diabetes in 57 pts and hypertension in 28. All had an adequate iron profile. At baseline, in the <50 and ≥1800 masl groups, mean Hb values were 9.4 and 9.0g/dL and mean C.E.R.A. doses were 71 and 52.2µg, respectively. 66 pts completed the study (4 lost to follow-up, 4 withdrew for protocol violation, 3 for adverse events and 9 for other reasons). 64 pts achieved target Hb, with mean C.E.R.A. doses of 160.5 and 70.0µg in the <50 and ≥1800 masl groups, respectively. The significant difference between groups was largely driven by the HD population. Safety was consistent with the known profile for C.E.R.A.

		C.E.R.A. dose required (µg)			
	Patients	Mean	SD	Median	Range
<50masl	22	160.5*	107.7	150	50-442
≥1800masl	42	70.0*	33.9	59	30-175

*p<0.05.

Conclusions: Lower C.E.R.A. doses are required to correct Hb in CKD pts living at altitude than at sea level.

SA-PO1004

Efficacy of Continuous Erythropoietin Receptor Activator (CERA) on End-Stage Renal Disease Patients with Renal Anemia before and after Peritoneal Dialysis (PD) Initiation Daisuke Fujimoto, Masataka Adachi, Yushi Nakayama, Hideki Inoue, Yutaka Kakizoe, Takashige Kuwabara, Yuichiro Izumi, Teruhiko Mizumoto, Masashi Mukoyama. *Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan.*

Background: There have been few reports on the management of renal anemia using CERA throughout the period from pre- to post-PD initiation. We investigated the usefulness of CERA in PD patients to examine its efficacy and dosage before and after PD initiation.

Methods: 16 patients (6 males; mean age, 59.9 years) who started PD between 2011 and 2015 were investigated. Hemoglobin (Hb) levels, iron parameters (transferrin saturation and ferritin), CERA dosage, and erythropoietin resistance index (ERI) (CERA amount μg/body weight kg/Hb (g/dL)/4) for 24 weeks were examined retrospectively before and after PD initiation.

Results: The mean Hb levels were 10.4 g/dL at 24 weeks prior to PD initiation, 10.2 g/dL at PD initiation and 11.7 g/dL at 4 weeks after that, showing a significant increase after PD initiation. The proportion of patients whose Hb levels were 11g/dL or higher increased from 40.0% to 81.2% after PD initiation. The mean CERA dosage was 73.3 μg/month(M) at 24 weeks prior to PD initiation, 87.5 μg/M at initiation, and 71.9 μg/M at 4 weeks after that. Thus, CERA dosage tended to increase just before PD initiation and then decreased after that. In non-diabetic patients, CERA dosage to maintain Hb levels decreased after PD initiation by approximately 25% compared to that prior to PD initiation. In contrast, it did not change after PD initiation in diabetic patients. ERI was 0.027 at 8 weeks prior to PD initiation, 0.036 at initiation, and 0.026 at 8 weeks after that, indicating that it tended to increase just before initiation and decreased significantly after that. With regard to iron metabolism, no significant changes in TSAT or ferritin levels were observed, suggesting relatively stable iron metabolism with CERA treatment during PD initiation.

Conclusions: Treatment with CERA prior to PD initiation resulted in fair anemia management for both diabetic and non-diabetic patients. Our data also suggest that CERA dosage might be reduced in non-diabetic patients after initiation of PD.

SA-PO1005

Dosing Penalty after Switching from ESA Originator to Biosimilar: Matched Cohort Study in Stable Hemodialysis Patients Roberto Minutolo,[1] Piergiorgio Bolasco,[2] Domenico Santoro,[3] Maurizio Mb Borzumati,[4] Alberto Santoboni,[5] Stefano Sposini,[6] Carlo Mura,[7] Oliviero Filiberti,[8] Fulvio Fiorini,[9] Gianni Carraro,[10] Luca De Nicola,[1] Domenico Russo.[11] *[1]Nephrology Div, Hospitals of II Univ of Naples; [2]ASL Cagliari; [3]Univ of Messina; [4]Verbania; [5]Colleferro; [6]Massa; [7]Montevarchi; [8]Vercelli; [9]Rovigo; [10]Padova; [11]Univ Federico II, Italy.*

Background: In hemodialysis (HD), switch from ESA originator to biosimilar associates with dosing penalty (DP) of about 10% according to industry-driven studies. However, DP in daily clinical practice is ill-defined.

Methods: From 12 non-profit centers, we selected consecutive ESA treated HD patients (2011-14) receiving stable i.v. ESA dose and not transfused in the previous 3 months. Patients switched from originators to biosimilars (BIO, n=153) were matched with those persisting with ESA originator (CON, n=153) to evaluate DP (difference of ESA dose between BIO and CON).

Results: Age (70±13y), males (63%), diabetes (30%), history of CVD (40%), BW (68±15 kg) and vascular access (87% AV fistula) did not differ in the two groups. Biosimilars were HX575 (Binocrit, 79%) or SB309 (Retacrit, 21%).

	Basal	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24
CON							
Hb (g/dL)	11.2 ±0.8	11.3 ±1.0	11.3 ±0.9	11.3 ±0.8	11.2 ±0.8	11.2 ±0.8	11.3 ±0.8
ESA (IU/w)	7,729 ±5,160	7,379 ±5,379	7,557 ±5,188	7,291 ±5010	7,101 ±5,089	7,192 ±5,004	7,118 ±4788
BIO							
Hb (g/dL)	11.2 ±0.9	11.1 ±1.0*	11.1 ±1.0*	11.1 ±1.0	11.0 ±0.9	11.1 ±1.0	11.2 ±0.9
ESA (IU/w)#	7,740 ±5,388	8,515 ±5,793	8,815 ±5,728*	9,369 ±6,334*	9,647 ±6,392*	9,716 ±6,484*	9,807 ±6,663*

Mean±SD. #P<0.001 for trend; * P<0.05 vs CON. At week-24, DP was 2,690 IU/wk, 95%CI 1,384-3,995, equal to 35% (95%CI 21-49). In CON and BIO, TSAT (25±11 and 28±13%, respectively) and ferritin (398±244 and 382±282 ng/mL, respectively) were similar at each visit and unchanged versus baseline. The same held true for iron therapy, Kt/V, CRP, albumin and PTH.

Conclusions: In controlled conditions, switch from ESA originator to biosimilar requires doses higher than expected to maintain constant Hb. Besides economic issue, these data call for long-term studies to assess whether the lower efficacy of biosimilars poses a safety threat.

SA-PO1006

A U.S. Phase III Trial to Compare HX575 (Proposed Biosimilar Epoetin Alfa) with Epogen®/ Procrit® in Renal Anemia Patients Matthew R. Weir,[1] Rajiv Agarwal,[2] Jeffrey C. Fink,[1] Nelson P. Kopyt,[3] Susanne Schmitt,[4] Gregor Schaffar,[4] Jim Mckay,[5] Radmila Kanceva,[4] Pablo E. Pergola.[6] *[1]Univ of Maryland School of Medicine, Baltimore, MD; [2]Indiana Univ School of Medicine, Indianapolis, IN; [3]Lehigh Valley Hospital, Allentown, PA; [4]Sandoz/Hexal AG, Holzkirchen, Germany; [5]Sandoz Inc, Princeton, NJ; [6]Univ of Texas Health Science Center at San Antonio, San Antonio, TX.*

Background: This study aimed to show biosimilarity of HX575 (Sandoz/Hexal AG) with the licensed reference product Epogen®/Procrit® (Amgen/Janssen), following subcutaneous (sc) administration.

Methods: Randomized, double-blind, parallel-group, multicenter (n=49) study consisting of a 4-wk screening period followed by a 52-wk treatment period. Patients (pts; n=435) on dialysis and treated with a stable dose of Epogen®/Procrit® sc at least once per wk were included and randomized to treatment with HX575 (n=217) or Epogen®/Procrit® (n=218). Primary endpoint was mean absolute change in hemoglobin (Hb) level between the screening (wk -4 to -1) and evaluation periods (wk 21 to 28). The incidence of Ab formation against epoetin was a secondary endpoint.

Results: Patient demographics were comparable between the 2 groups. Mean Hb level at baseline and evaluation period was comparable for HX575 and Epogen®/Procrit® treated pts. Mean (SD) change in Hb level from baseline to evaluation period was -0.11 (1.001) g/dL for HX575 and 0.01 (0.953) g/dL for Epogen®/Procrit® treated pts. ANCOVA analysis found the estimated difference in Hb level was -0.0926 g/dL with a 90% CI (-0.2264, 0.0413) entirely within the pre-specified equivalence limits (-0.5 g/dL, 0.5 g/dL). 9 pts tested positive (transiently) for anti-epoetin antibodies by radioimmunoprecipitation assay (2 pts were already positive at baseline); no patient tested positive for neutralizing Abs. Exposure-related incidence rates of anti-epoetin Abs were similar between the 2 groups (HX575, 0.036; Epogen®/Procrit®, 0.011).

Conclusions: SC administration of HX575 in pts with renal anemia was therapeutically equivalent to Epogen®/Procrit® in terms of maintaining stable Hb levels and immunogenic potential.

Funding: Pharmaceutical Company Support - SANDOZ

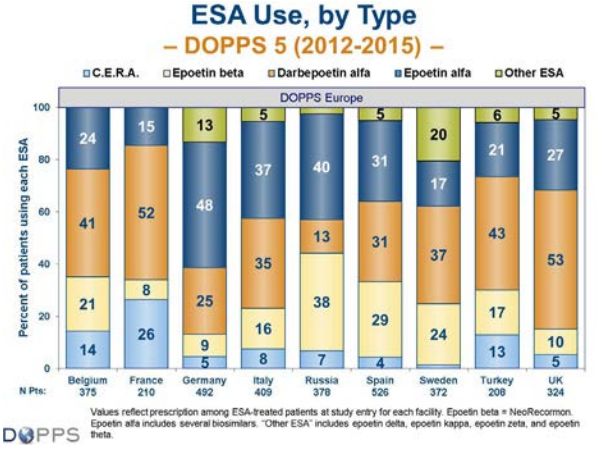
SA-PO1007

Prevalence and Dosing Patterns of ESAs Used in 9 European Countries: DOPPS Douglas S. Fuller,[1] Bruce M. Robinson,[1] Boris Bikbov,[2] Francesco Locatelli,[3] Ronald L. Pisoni.[1] *[1]Arb Res Collab Hlth, Ann Arbor, MI; [2]Moscow St. Univ of Med and Dent, Moscow, Russian Federation; [3]A. Manzoni Hosp, Lecco, Italy.*

Background: C.E.R.A. (methoxy polyethylene glycol-epoetin beta), darbepoetin alfa (DA), and epoetin beta (EB) are erythropoiesis-stimulating agent (ESA) alternatives to epoetin alfa (EA) commonly used in Europe. C.E.R.A. is now available in the US; availability of EA biosimilars is anticipated in coming years.

Methods: We provide prevalence and dosing patterns for C.E.R.A., DA, EB, and EA using weighted analyses of data from 9 European countries (Belgium, France, Germany, Italy, Russia, Spain, Sweden, Turkey, UK; 167 facilities (fac); 4230 pts) in the Dialysis Outcomes and Practice Patterns Study (DOPPS) phase 5 (2012-2015).

Results: Overall prevalence was 8% C.E.R.A., 35% DA, 19% EB, and 31% EA. The % of facs using C.E.R.A. ranged from 20% (UK) to 58% (Fra); for DA: 30% (Rus) to 87% (Tur); for EB: 15% (UK) to 53% (Ita/Tur); for EA: 17% (Fra) to 86% (Ger). In facs using C.E.R.A., median % ESA-treated pts using C.E.R.A. was 13% [IQR=6-38%, mean=28%]; for DA: 43% [IQR=17-85%, mean=49%]; for EB: 33% [IQR=15-90%, mean=47%]; for EA: 48% [IQR=26-89%, mean=54%]. Common C.E.R.A. dosing frequencies were 1x/mo (81%) and 2x/mo (12%); for DA: 1x/wk (66%) and 2x/mo (22%); for EB/EA: 3x/wk (39%), 2x/wk (27%), and 1x/wk (30%). Median dose for C.E.R.A. was 109 mcg/mo [IQR=69-162, mean=157]; for DA: 121 mcg/mo [IQR=64-211, mean=171]; for EB: 5.6 ku/wk (IV, 57%) and 5.1 ku/wk (SC); for EA: 5.8 ku/wk (IV, 81%) and 4.2 ku/wk (SC). Achieved mean hemoglobin (Hb) levels were similar (11.1-11.2 g/dl) among pts prescribed C.E.R.A., DA, EB, or EA.



Conclusions: Combinations of C.E.R.A., DA, EB, and EA are used in European facs to maintain Hb at recommended levels. As C.E.R.A. and EA biosimilars become available in the US, this real-world practice data can provide useful insight for US clinicians interested in the use of these medications.

Funding: Pharmaceutical Company Support - AbbVie, Amgen, Baxter Healthcare, F. Hoffmann-LaRoche, Hexal, Keryx, Kyowa Hakko Kirin, Merck, Proteon, Relypsa, Sanofi, Shire, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, WiNe Institute, Societies for Nephrology in Germany, Italy, & Spain. All grants are made to Arbor Research Collaborative for Health and not to Mr. Fuller directly

SA-PO1008

Serum Concentration of Non-Transferrin Bound Iron in HD Patients Is Higher Than Normal Control and Is Increased after Intravenous Iron Administration

Noriko Saito,[1] Shigeru Miyazaki,[2] Kazuhide Saito,[2] Tetsuo Morioka,[1] Hisaki Shimada,[1] Kozo Ikarashi,[1] Yutaka Tsubata,[1] Kazuhiro Yoshita,[1] Yutaka Kohgo.[3] *[1]Shinraku-en Hospital, Niigata, Japan; [2]Niigata Univ, Niigata; [3]International Univ of Health and Welfare Hospital, Nasushiobara, Japan.*

Background: Non-transferrin bound iron (NTBI), which appears in the serum under iron overload, is associated with organ damage through free radical production.intravenous iron administration (IVIA) is a common treatment for renal anemia in hemodialysis(HD) patients.

Methods: NTBI, Hepcidin25, soluble Tf receptor(sTfR), 8-oxo-2'-dehydroguanosine, high sensitive CRP, serum iron, TSAT and ferritin were evaluated in 44 HD patients who were not recieved iron administration nor erythropoietin stimulating agents (ESA) for at least 2months and as a control 30 healthy volunteers. NTBI was measured by recently described assay system(Clin Chim Acta 437(2014) 129). 23 HD patients without any iron load within 2 weeks were administered saccharated ferric oxide (Fe 40mg) intravenously after HD session. 19(83%) patients had received ESA. We evaluated the NTBI and above markers before and at 0.5, 1, 2, 4, 6, 20, 44 hours after IVIA.

Results: The NTBI levels in HD patients was higher than that in control (3.3(3.0~3.9) vs 2.7(2.5~3.0) μg/ml p<0.001). In HD patients NTBI correlated with Tf and the predictor of NTBI was Tf by stepwise analysis(β=0.328, p=0.030, R^2=0.107). TSAT before IVIA was 20(14~27)%, and increased to 81(65~100%) at 0.5hours after IVIA and then decreased to the level before IVIA at 44hours. NTBI before IVIA was 1.5(1.1～2.25)μg/dL, increased to 2.2(1.8～2.7)μg/dL at 4 hours (p=0.021) and decreased to 1.8(1.2～2.25)μg/dL at 44 hours. Maximum increase rate of NTBI((NTBI at peak - NTBI before IVIA) x 100 / NTBI before IVIA) was 80(50~146)%. By stepwise analysis, sTfR before IVIA was a negative predictor for NTBI (β=-0.494, p=0.016, R^2=0.244). (Medians (interquartile range) or numbers(%)).

Conclusions: NTBI in HD patient was higher than healthy control, correlates to Tf and significantly increase at 4 hours after IVIA. The predictor of NTBI maximum increase rate was sTfR of before IVIA. NTBI could be a novel marker to assess iron metabolism in HD patients.

Funding: Private Foundation Support

SA-PO1009

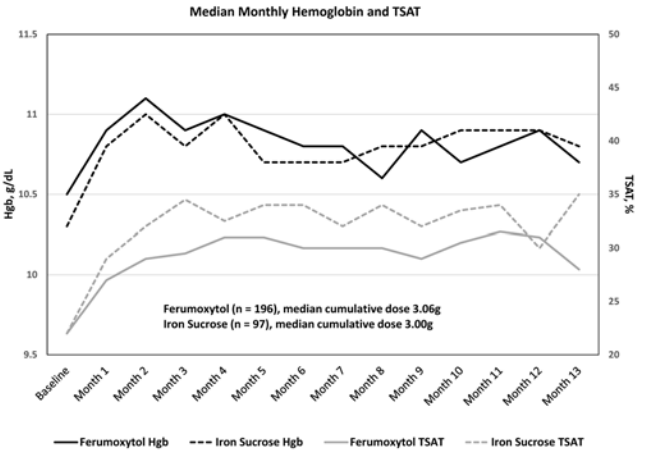
The FACT-Study: A Randomized Controlled Trial of Repeated Doses of Ferumoxytol or Iron Sucrose in Patients on Hemodialysis

William Strauss, Naomi V. Dahl, Kristine Bernard, Zhu Li. *AMAG Pharmaceuticals, Inc., Waltham, MA.*

Background: Data from prospective randomized controlled trials comparing different IV iron formulations over a period of >1 year are lacking. The purpose of this study was to gain a better understanding of the long-term safety, efficacy, and frequency of use of IV iron in the episodic treatment of iron deficiency anemia (IDA) in CKD-HD patients.

Methods: This open-label multicenter, prospective study (NCT01227616) conducted at 35 sites in 3 countries, randomized patients with Hgb<11.5 and TSAT<30% 2:1 to ferumoxytol (FER) (2 X 510 mg, 2-8 days apart) or iron sucrose (IS) (10 X 100 mg at consecutive HD sessions), administered by infusion or injection. Patients with persistent or recurrent IDA (Hgb<11.5 g/dL and TSAT <30%) at any monthly observation visit over the following 12 months were treated again with an additional course of their randomized treatment. Safety was continuously monitored.

Results: Demographics were balanced between the two treatment groups (196 FER; 97 IS). Mean age was 58.8 (SD 13.96), 58.4% were male, 50.5% were White, and 30% were Black or African American. Over the 13-month study period, adverse events (AEs) were reported in 158 (80.6%) of FER and 81 (83.5%) of IS patients. These were considered treatment related by the investigators in 9 (4.6%) of FER and 4 (4.1%) of IS patients. Serious AEs were reported in 93 (47.7%) of FER patients and 49 (50.5%) of IS patients, none of which were considered treatment related by the investigators. For both treatment arms, the median month-by-month change in ESA dose remained zero throughout the study.



Conclusions: Ferumoxytol and iron sucrose demonstrated comparable efficacy and AE profiles during episodic treatment over a 13-month period in CKD patients undergoing HD.

Funding: Pharmaceutical Company Support - AMAG Pharmaceuticals, Inc.

SA-PO1010

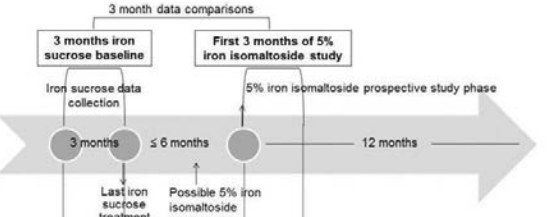
An Observational Study of Iron Isomaltoside 5% in Haemodialysis: A Novel Intravenous Iron for Dialysis

Ashraf I. Mikhail,[1] Staffan Schön,[2] Jorgen B.A. Hegbrant,[2] Christopher Brown,[1] Inger Nilsson,[2] Gert Jensen,[3] Jason Moore,[4] Lennart D. Lundberg.[5] *[1]ABMU HB, United Kingdom; [2]Diaverum Sweden AB; [3]Sahlgrenska Univ Hospital, Sweden; [4]Royal Devon & Exeter Hospitals, United Kingdom; [5]Norrland Univ Hospital, Sweden.*

Background: Iron isomaltoside 5% (Diafer®) is a recently approved IV iron for dialysis patients. The controlled-release matrix minimises labile (free) iron. Minimising labile iron may be important to reduce iron toxicity which may carry long term risks. The tight iron binding also allows for fast push injection. This study aims to determine the effectiveness and safety of iron isomaltoside in clinical practice in a haemodialysis (HD) cohort.

Methods: This interim analysis includes data from 95 patients for the first 3 months of an ongoing 12 month study of 209 HD patients in Sweden and the UK. Patients entering the study had to have 3 month data for iron sucrose within month -9 to 0 from the start of the prospective phase. Data for iron sucrose are compared to cross-over data for iron isomaltoside. The primary endpoint is comparison of Hb levels.

Results:



Iron sucrose	Iron isomaltoside	Clinical data over 3 months
111	**114**	**Mean Hb (g/L)**
54	**40**	**Patients with all Hb values in range 100-120 g/L (%)**
21	17	Patients with at least one Hb <100 g/L but no Hb >120 g/L (%)
25	41	Patients with at least one Hb >120 g/L but no Hb <100 g/L (%)
420	**434**	**Mean ferritin (microgram/L)**
53	45	Patients with mean ferritin in range 200-500 micrograms/L (%)
29	39	Patients with mean ferritin > 500 micrograms/L (%)
26	**26**	**Mean TSAT (%)**
40	36	Patients with mean TSAT in range 20-30% (%)
33	32	Patients with mean TSAT < 20% (%)
		Drug data over 3 months
6	6	Mean number of iron doses/patient
544	**648**	**Mean cumulative iron dose/patient (mg)**
181	216	Mean cumulative iron dose/patient/month (mg)
93	90	Patients on ESA (%)
8151	7707	Mean cumulative ESA dose/patient/week (IU)
not collected	2	Patients with ADRs (%)
not collected	0	Patients with serious ADRs (%)
28	1	Patients with metallic taste (%)

Iron isomaltoside maintains Hb levels and adequate iron status in patients converted from iron sucrose. Higher Hb values with iron isomaltoside are the result of higher (16%) elemental iron doses; with a consequential reduction in ESA requirement of 6%. Iron isomaltoside is well tolerated. One patient experienced headache and one patient metallic taste (1%). In comparison, 28% experienced metallic taste with iron sucrose. Logistical benefits were enabled by fast push injection requiring less than 3 minutes for preparation and intradialytic administration of iron isomaltoside.

Conclusions: Iron isomaltoside 5% safely and effectively maintains Hb levels for CKD patients on HD. By optimising the iron dose, ESA use can be reduced. This novel formulation that reduces labile iron may have potential benefit to patient outcomes but this requires determination.

Funding: Pharmaceutical Company Support - Pharmacosomos A/S

SA-PO1011

Comparison of Hb Levels and Dose of Iron Associated with Adverse Events between Younger and Elderly Hemodialysis Patients Takahiro Kuragano, Takeshi Nakanishi. *Dept of Internal Medicine Div of Kidney and Dialysis, Hyogo College of Medicine, Nishinomiya, Japan.*

Background: We recently demonstrated that high dose of ESA and iron were associated with higher risk of death and/or adverse events in maintenance hemodialysis patients(MHD) in TRAP study (Kidney Int. 2014). Elderly MHD are increased and the optimal renal anemia treatment for them should be examined. We performed a secondary analysis of the patients enrolled in the TRAP study.

Methods: In 1095 MHD, we compared the relation of anemia, nutritional and inflammatory markers to adverse events between younger (<65 yo) and elderly (≥65 yo) during 3 years. The composite events (CEs) were defined as cerebro-cardio vascular disease, infection, hospitalization, and death. A time dependent cox hazard model was applied to the evaluation of the association between these clinical factors and CEs.

Results: Compared with younger MHD, serum albumin level and body mass index were significantly lower (P<0.05) and high sensitive CRP was higher (p<0.05) in elderly MHD. In elderly MHD, Hb levels was significantly lower (p =0.02), and ferritin (p=0.01) and the index of ESA hypo-responsiveness 'ESA/Hb' (p=0.01) were higher than those of younger MHD. In the elderly MHD, the risk of CEs was significantly smaller in only the patients Hb levels with 10-11g/dL (HR:0.67, P=0.035), but not in those >11g/dL. In younger MHD, compared to the patients with Hb <10g/dL, the risk of CEs was significantly decreased in higher Hb levels (10-11g/dL (HR:0.47, p=0.02), 11-12g/dL (HR:0.31, p=0.01), and >12g/dL (HR:0.12, p=0.04)). Both of younger and elderly MHD, higher ESA/Hb levels (≥400) was significantly associated with higher risk for CEs (HR:2.24, p=0.01, HR:1.90, p=0.01). Dose of intravenous iron was significantly associated with higher risk of CEs in both younger (HR:1.2, p=0.02) and elderly (HR:1.2, p=0.02) MHD.

Conclusions: The elderly MHD might have the higher ESA hypo-responsiveness and iron storage which could be related to chronic inflammation and malnutrition. In elderly MHD, targeting higher Hb level similar to younger might not be necessary for the prevention of adverse events. Further studies for examining the adequate anemia management for elderly MHD are needed.

SA-PO1012

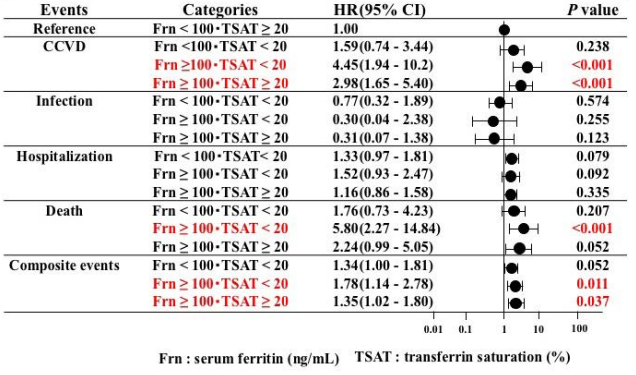
The Relationship between Iron Dysutilization for Erythropoiesis and Adverse Events or Survivals in Patients Undergoing Hemodialysis Takahiro Kuragano, Takeshi Nakanishi. *Dept of Internal Medicine Div of Kidney and Dialysis, Hyogo College of Medicine, Nishinomiya, Japan.*

Background: Patient with high serum ferritin and low transferrin saturation(TSAT) levels could be considered as dysutilization of iron for erythropoiesis in which iron administration might increase TSAT and Hb levels. Long-term safety of iron administration to these patients has not been well studied.

Methods: Study design was the observational multicenter study for period of 3 years. We defined dysutilization of iron for erythropoiesis as the patients with lower TSAT(<20%) and higher ferritin(≥100ng/mL) levels. In 805 patients with maintenance hemodialysis (MHD), the association between dysutilization of iron for erythropoiesis and adverse event was investigated with the time dependent cox hazard model.

Results: Compared with low TSAT(≤ 20%) level, patient with normal TSAT(20-30%) was significantly lower risk for cerebrovascular and cardiovascular disease(CCVD) (HR:0.25, P=0.04), and patients with higher TSAT(≥30%) were lower risk for death(HR:0.12, P=0.01). Male, younger patients, without diabetes, low high sensitive(h) CRP, and low β2microglbulin were selected as significant predictors of high TSAT. Compared with low ferritin(<100ng/mL) and high TSAT(≥20%), patients with high ferritin(≥100ng/mL) and low TSAT, and with high ferritin and high TSAT had a significantly higher risk of CCVD. Patients with high ferritin and low TSAT had a significantly higher risk of death than low ferritin and high TSAT.

Fig. 1 Relationship between TSAT and ferritin levels and adverse events



Conclusions: Although patients with low TSAT levels had a significantly higher risk of CCVD or death, higher TSAT level was not associated with iron administration or iron storages. Patients who were suspected as dysutilization of iron for erythropoiesis had a higher risk of CCVD and death. The administration of iron should be cautious to the patients with dysutilization of iron for erythropoiesis.

SA-PO1013

Dysregulated Iron Metabolism in Bone Marrow of a Mouse Model of Chronic Kidney Disease Tomoko Kimura, Kiyoko Yamamoto, Yuki Morikami, Takanori Nagai, Masayoshi Nanami, Yasuyuki Nagasawa, Yukiko Hasuike, Takahiro Kuragano, Takeshi Nakanishi. *Div of Kidney and Dialysis, Dept of Internal Medicine, Hyogo College of Medicine, Japan.*

Background: Causes of anemia in CKD are thought to be primarily caused by inadequate EPO synthesis,shortened erythrocyte life span,and failure in bone marrow(BM) due to chronic inflammation. But the major mechanism has not been well clarified. In the present study,we examined the differentiation pattern of erythroid in the BM using flow cytometry(FACS),renal EPO production and hepatic hepcidin expression using mouse model of adenine-induced renal failure(RF).

Methods: RF was induced by the administration of 0.15 to 0.3% adenine-containing chow for 8weeks to male C57BL/6J mice. Liver,kidney,BM,and blood were obtained from control(C) and RF mice. Then Hb,serum iron and ferritin levels were measured. Serum hepcidin levels were quantified using LC-MS/MS methods. Hepatic hepcidin(Hamp),renal EPO and BM Fam132b(erythroferrone)mRNA from C and RF were semi-quantified using RT-PCR. To evaluate the maturation of erythron,BM erythroid precursors were analyzed using CD71(Transferrin receptor) and Ter119 markers by FACS.

Results: We confirmed that Hb levels were significantly lower(8.8±0.3vs13.4±0.1g/dL) and serum ferritin levels were higher(2.6±0.6vs1.1±0.1μg/mL) in RF than C. Renal EPOmRNA expression in RF was increased compared to C(2.5:1). FACS analysis showed the percentages of Pro EB(CD71+/Ter119-) and Baso EB(CD71+/Ter119+) in the BM were decreased in RF compared to C. Hepatic Hamp mRNA expression was increased(2.4:1) and serum hepcidin levels were also higher(397.6±79.4vs99.6±6.9ng/dL) in RF compared to C. Serum iron(105.4±5.1 vs121.4±3.8μg/dL) and TSAT(37.2±1.1%vs43.0±1.2%) were lower in RF than C. Further,BM Fam132b mRNA expression was significantly decreased(0.6:1) in RF compared to C.

Conclusions: Erythroblast maturation was affected in the steps of late differentiation,those are the decrease in CD71+cells. In RF,erythroferrone might be decreased,which could cause the increase in hepcidin although renal EPO expression was increased.Finally we presumed that the increase in hepcidin expression could be associated with the dysregulated erythroblast differentiation in RF model.

SA-PO1014

Disturbance of Iron Utilization in Erythropoiesis of Presensitized High-Risk Kidney Transplant Recipients Treated by Non-Antigen-Specific Immunoadsorption Sebastian Markus Schaefer, Martin G. Zeier, Matthias Schaier. *Div of Nephrology, Heidelberg Univ Hospital, Heidelberg, Germany.*

Background: Non-antigen-specific immunoadsorption (IA) is an established method for desensitization of presensitized high-risk kidney transplant recipients. Despite of concomitant intravenous iron and erythropoietin substitution, patients under IA treatment regularly show significant decrease in haemoglobin levels. We hypothesised that IA influences systemic iron homeostasis and subsequently affects the erythropoiesis. Hepcidin is the key regulator of systemic iron homeostasis that coordinates iron uptake, storage and release to the blood stream. High erythroid iron demand inhibits hepcidin secretion from hepatocytes, thus increasing the intestinal iron uptake and iron levels in blood.

Methods: In a pilot study in eight presensitized high-risk transplant recipients, differnt parameters of iron homeostasis were measured.

Results: Haemoglobin levels decreased over the course of IA treatment (Δhaemoglobin ±SD: after 6 treatments 0.55 ±0.90, after 10 treatments 1.16 ±1.29). In pre-post-treatment comparison, hepcidin levels in blood were reduced following an IA treatment cycle, suggesting direct elimination through adsorption. Hepcidin levels increased until next treatment cycle, however did not reach baseline levels. Despite hepcidin depletion as well as iron and erythropoietin substitution, the percentage of hypochromic erythrocytes constantly increased during the entire IA treatment. Conversely, transferrin and ferritin levels as indicators of iron deposits remained unchanged during the course of IA. Furthermore, continuously declining levels of soluble transferrin receptor indicated sufficient erythroid iron deposit.

Conclusions: Collectively, our data indicate clinically relevant disturbed iron utilization in erythropoiesis of IA treated patients leading to hypochromic anaemia despite of sufficient iron and erythropoietin substitution.

Funding: Pharmaceutical Company Support - Fresenius AG

SA-PO1015

Discriminative Effect of Oral and Intravenous Iron Administration on the Fibroblast Growth Factor-23 and Inflammatory Cytokines in Patients on Maintenance Hemodialysis with Iron Deficiency Anemia Yukiko Hasuike,[1] Wataru Fukao,[1] Soshi Yorifuji,[1] Yuki Morikami,[1] Tomo Yamakawa,[2] Kazuhiro Toyoda,[2] Takeshi Nakanishi.[1] *[1]Div Kidney and Dialysis, Dept Internal Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan; [2]Dept Kidney and Dialysis, Meiwa Hospital, Nishinomiya, Hyogo, Japan.*

Background: FGF-23, a bone-derived hormone, plays an important role in the pathogenesis of several complications in patients with chronic kidney disease. The effect of iron supplementation, oral vs intravenous (IV), on fibroblast growth factor-23 (FGF-23) and inflammatory cytokines were examined in maintenance hemodialysis (MHD) patients with iron deficiency anemia (IDA).

Methods: MHD patients with absolutely iron deficiency (n=61, serum ferritin <50 ng/ml) treated with erythropoiesis stimulating agents (ESA) were enrolled. Oral iron (ferric citrate hydrate 50 mg daily, Oral group, n=29,) or IV iron (saccharated ferric oxide 40 mg weekly, IV group, n=32) were administrated for 10 weeks. Iron supplementation was halted when serum ferritin level was >100 ng/ml. Factors related to anemia, iron metabolism, inflammation, oxidative stress (pentosidine), and FGF-23 (ELISA, Kinos) were measured at the start and after 3 months of iron supplementation.

Results: Mean age of 68.6±11.1 years, mean dialysis vintage 7.3±6.7 years, and serum ferritin levels of 11.3±7.2 ng/ml. In both the 2 groups, Hb, MCV, serum ferritin, TST, hepcidin, IL-6 (Oral: 5.71 to 8.20 pg/ml, IV: 5.17 to 5.45 pg/ml, median), and TNF-α (Oral: 34.8 to 42.0 pg/ml, IV: 36.4 to 47.9 pg/ml, median) were significantly increased and ESA resistance index was decreased by the iron supplementation. Soluble transferrin receptor of only the Oral group was decreased (p=0.0058), and FGF-23 of only the IV group was increased compared with at the start (1800 [614-4300] pg/ml to 2850 [659-6850] pg/ml, p=0.0004). There was no change of high-sensitivity CRP and pentosidine levels of the 2 groups.

Conclusions: Iron supplementation might stimulate the production of inflammatory cytokines. Iron administered intravenously could induce the elevation of serum FGF-23 level.

SA-PO1016

Association between Fibroblast Growth Factor 23 and Iron Metabolism in Hemodialysis Patients Hirokazu Honda,[1] Tetsuo Michihata,[2] Kanji Shishido,[3] Takanori Shibata.[4] *[1]Div of Nephrology, Dept of Medicine, Showa Univ Koto Toyosu Hospital, Tokyo, Japan; [2]Ebara Clinic, Tokyo, Japan; [3]Dept of Dialysis, Kawasaki Clinic, Kawasaki, Japan; [4]Div of Nephrology, Dept of Medicine, Showa Univ School of Medicine, Tokyo, Japan.*

Background: Recent study demonstrated the association among inflammation, iron metabolism and fibroblast growth factor (FGF) 23 (KI. 2016;89:135). The present clinical study aimed to assess associations between anemia, iron metabolism and FGF23 in hemodialysis (HD) patients.

Methods: This prospective observational study examined a cohort of prevalent HD patients (n=282). Blood samples were obtained before dialysis session at baseline to measure levels of hemoglobin (Hb), transferrin saturation (TSAT), ferritin, albumin-adjusted calcium (Ca), phosphate (P), intact (i)-PTH, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, FGF23, and high sensitive (hs)-CRP. After the baseline measurement, study patients were followed-up for 6 months. Levels of Hb, TSAT and ferritin, and hs-CRP were measured every 1 month, 2 months and 3 months, respectively. Doses of ESAs, epoetin or darbepoetin-alfa, and intravenous iron supplementation during 6 months were recorded.

Results: FGF23 were positively correlated with Ca, P, i-PTH and inversely correlated with TSAT and ferritin. Whereas levels of Hb and hs-CRP and doses of ESAs during 6 months did not differ among FGF23 tertiles, levels of ferritin and TSAT in higher FGF23 tertile were continuously lower than those in middle to lower FGF23 tertiles. Higher FGF23 tertile was independently associated with repeated measurements of TSAT and ferritin by a univariate repeated measures analysis, however, the association of ferritin with higher FGF23 tertile, but not of TSAT, was only confirmed by multivariate repeated measures analysis. Doses of intravenous iron supplementation were significantly increased in higher FGF23 tertile in multivariate models.

Conclusions: High FGF23 levels may be associated with prolongation of low levels of ferritin, resulting in increased doses of iron supplementation to manage anemia in HD patients.

SA-PO1017

Association between Intact Parathyroid Hormone and Soluble Klotho Levels on Iron Metabolism in Anemic Hemodialysis Patients Miguel Uriol Rivera,[1] Gonzalo Gómez Marqués,[1] Manuel Luque-Ramírez.[2] *[1]Dept of Nephrology, Son Espases Univ Hospital, Palma de Mallorca, Islas Baleares, Spain; [2]Dept of Endocrinology, Ramón y Cajal Univ Hospital, Madrid, Spain.*

Background: High intact parathyroid hormone (iPTH) levels and soluble a-klotho (s-klotho) deficiency are two conditions associated to renal anemia. We evaluate in hemodialysis patients: i) the influence of iPTH on s-klotho levels; ii) the potential association of s-klotho levels with ferrokinetics and ESA needs.

Methods: This is a *post-hoc* analysis from the MIR-EPO study (EudraCT: 2009-015511-40). Patients were divided in 3 groups according to baseline iPTH: group A (n:5; <150 pg/ml), group B (n:8; 150-300 pg/ml), and group C (n:15; >300 pg/ml). ESA and iron supplements were administered to maintain hemoglobin levels between 10.5 and 12.0 g/dl and transferrin saturation(TSAT) ≥20%. s-klotho were measured after 3 months of ESA titration at 2 time points (month 3 and 6). We assessed s-klotho changes throughout the study and the differences among its mean changes as a function of iPTH subgroups.

Results: In the Group A, s-klotho did not change throughout the study [+0.01pg/ml$_{log}$; P=0.81], whereas decreased in groups B and C [-0.12pg/ml$_{log}$ (P=0.01), and -0.06pg/ml$_{log}$ (P<0.01), respectively]. Percentage mean change of s-klotho between groups A and B was significantly (28%, P=0.01). No significant differences among other groups were found. As a whole, a positive correlation between changes in s-klotho and serum iron, TSAT, and transferrin plasma levels were observed. A log-lineal regression model determined that increased s-klotho levels in group A were associated with a decrease in iron supplementation and ESA needs (X^2:5.0, P=0.02, and X^2:3.9, P=0.04, respectively).

Conclusions: In haemodyalisis patients, lower iPTH levels have a beneficial impact on iron metabolism.This effect may be mediated by s-klotho levels.

Funding: Private Foundation Support

SA-PO1018

Differences between 25-OH Vitamin D, 1,25-$(OH)_2$ Vitamin D and Paricalcitol on the Erythropoietic Response of Anemic Hemodialysis Patients Miguel Uriol Rivera,[1] Sheila Cabello Pelegrin,[1] Angel Garcia-Alvarez,[2] Manuel Luque-Ramírez.[3] *[1]Nephrology, Son Espases Univ Hospital, Palma de Mallorca, Islas Baleares, Spain; [2]Pharmacy, Inca Hospital, Palma de Mallorca, Islas Baleares, Spain; [3]Endocrinology, Ramón y Cajal Univ Hospital, Madrid, Spain.*

Background: Vitamin D(VD) deficiency is associated to renal anemia. However, it is not well-known if there are differences between 25(OH)-VD or 1,25-$(OH)_2$ VD, and the potential interaction of paricalcitol(PRC) use, on the erythropoietic response. We evaluate the association of 25VD, 1,25VD levels and paricalcitol use on the iron metabolism and hematologic parameters in hemodialysis patients.

Methods: This is a *post-hoc* analysis from the MIR-EPO study(EudraCT: 2009-015511-40). Erythropoietic stimulating agents(ESA) and iron supplements were administered to maintain haemoglobin(Hb) between 10.5 and 12.0 g/dl and transferrin saturation ≥20%. Calcifediol(n:17) was given to achieve 25VD ≥30ng/ml. PRC was used for secondary hyperparathyroidism(n:23). The relationships between the changes(Δ:month6 – month0) in 25VD or 1,25VD with iron supplements, ESA doses, hematologic and iron metabolism parameters were assessed by correlation analysis.

Results: Thirty-one patients were analysed. Direct correlation between Δ25 and Δ1,25VD levels were found (r:0.50, P<0.01) and inverse between Δferritin with Δ25VD and Δ1,25VD was found. Δ1,25VD showed an inverse correlation with ΔHb levels. Those patients who achieved 25VD levels ≥ 30ng/ml needed higher ESA doses (49%, P=0.01). In those patients on PRC, ferritin and ESA doses decreased significantly at the end of the study with respect to baseline.

Conclusions: PRC therapy is associated with decreasing iron stores and ESA doses. 25VD and 1,25VD are also associated to iron stores. However, current recommended 25VD levels seems not to be beneficial for erythropoietic response.

Funding: Private Foundation Support

SA-PO1019

A Negative Impact of Calcium on Hematopoiesis in Hemodialysis Patients Takahito Ito. *Kataguilli Medical Center, Shibata, Niigata, Japan.*

Background: In hemodialysis patients, efficient hematopoiesis is crucial. We retrospectively studied an effect of calcium on hemoglobin level.

Methods: As of June 1, 2015, we had 106 Japanese patients on maintenance hemodialysis. Thereafter, doses of oral calcium carbonate, cinacalcet, and intravenous maxacalcitol were adjusted to maintain serum albumin-corrected calcium concentration (C-Ca) within the target range. In parallel, doses of intravenous erythropoiesis stimulating agents (ESA) and saccharated ferric oxide were adjusted to optimize hemoglobin level (Hb). Six months after, 98 patients were analyzed (63.5 ± 10.9 y, 59 males, 21 diabetics, dialysis vintage 13.0 y [Q1-Q3, 5.0-23.25]). Eight patients were excluded from the analysis because of insufficient blood analysis or patient loss.

Results: Decrease of calcium carbonate and/or increase of cinacalcet lowered C-Ca (P=0.0010 and =0.0007), respectively. Adjustment of maxacalcitol did not significantly change C-Ca. Intact PTH increased from 204.3 ± 127.7 to 251.3 ± 143.2 (P=0.0042). Hb and transferrin saturation changed from 10.78 ± 1.34 g/dL and 32.0 ± 13.1% to 11.1 ± 1.31 and 28.2 ± 13.0, respectively (P=0.0319 and 0.0128). In univariate analysis, Hb at baseline, C-reactive protein (CRP) at baseline, increment of serum albumin concentration during 6 months (ΔAlb), and increment of C-Ca (ΔC-Ca, -0.02 ± 0.87 mg/dL) were associated with ΔHb (0.37 ± 1.84 g/dL). Multivariate analysis with ΔHb as the dependent variable revealed that lowering C-Ca, but not CRP or ΔAlb, linked with the increase of Hb (table1). Similar results were obtained in the patients (N=54) who had received stable or reduced doses of ESA and ferric oxide during the 6 months (table1).

Conclusions: Our results imply that calcium level may be responsible for hematopoiesis or red blood cell survival, regardless of ESA or ferric oxide.

Model	R^2	Independent Variable	Standard β	95% Confidential Interval
All Patients (N=98)	0.509	Hb at Baseline	-0.668	-1.128 — -0.730
		ΔC-Ca	-0.274	-0.881 — -0.277
Subset (N=54)	0.533	Hb at Baseline	-0.621	-1.171 — -0.616
		ΔC-Ca	-0.338	-1.138 — -0.312
Subset: In these 54 patients, doses of ESA and ferric oxide remained unchanged or decreased during the study period.				

Funding: Clinical Revenue Support

SA-PO1020

Cholecalciferol Supplementation and Serum Hepcidin-25 Concentrations in Hemodialysis Patients - A Randomized Controlled Trial

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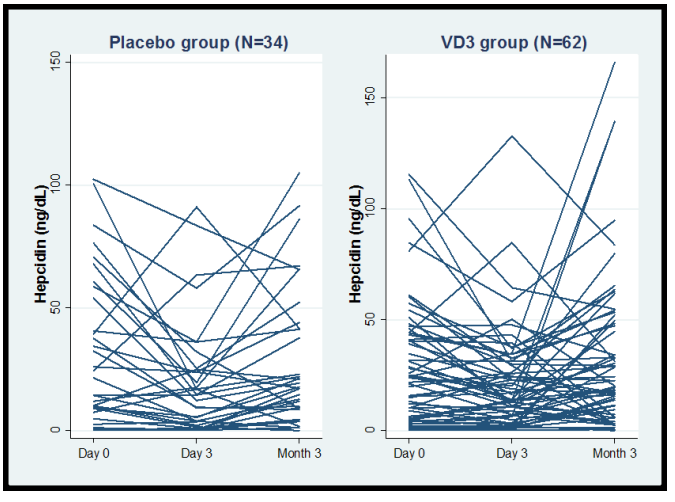
Background: A previous study demonstrated that nutritional vitamin D supplementation decreased serum hepcidin levels in healthy subjects. However, it still remains unknown whether it is also true with maintenance hemodialysis (MHD) patients.

Methods: This is a double-blind RCT of cholecalciferol (VD_3) supplementation in MHD patients. Patients were randomly assigned to either thrice-weekly (TW) 3,000 IU VD_3, once-monthly (OM) VD_3 (equivalent to 9,000 IU/week), TW placebo, or OM placebo. The primary outcomes were log-transformed serum hepcidin levels at Day 3 and Month 3. Based on the intention-to-treat principle, we compared VD_3 vs. placebo by using *a priori* defined generalized linear model ignoring the administration intervals. We also examined the differences between TW vs. OM VD_3.

Results: Out of 96 participants, 3 dropped out between Day 3 and Month 3. Median (IQR) serum 25(OH)D levels at baseline and Month 3 were 13 (10–15) and 13 (11–17) ng/mL in the placebo group and 10 (8–13) and 24 (20–29) ng/mL in the VD_3 group, respectively. Likewise, median (IQR) hepcidin levels at baseline, Day 3, and Month 3 were 18 (8–54), 13 (2–25), and 18 (9–42) ng/mL in the placebo group, and 23 (5–43), 15 (6–31), and 22 (9–50) ng/mL in the VD_3 group, respectively (Figure). After baseline adjustment, VD_3 was associated with 1.7 (95%CI, 1.2–2.4) times higher hepcidin levels at Day 3, which lost significance at Month 3 [1.1 (95%CI, 0.7–1.9)]. There were no significant differences in serum levels of TNF-α, IL-6, hemoglobin, or ferrodynamics. Any indices did not show differences between TW and OM VD_3.



Conclusions: Contrary to the previous study in healthy subjects, cholecalciferol supplementation increased serum hepcidin-25 levels in the short term among MHD patients.

Funding: Pharmaceutical Company Support - Molecular Physiological Chemistry Laboratory, Inc., Private Foundation Support

SA-PO1021

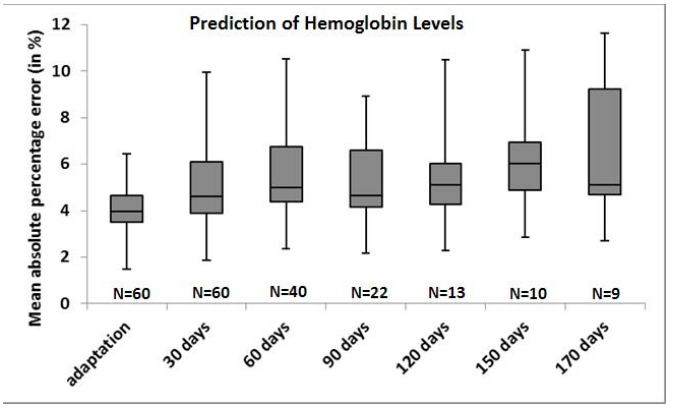
Prediction of Hemoglobin Levels in Individual Hemodialysis Patients by Means of a Mathematical Model of Erythropoiesis

Doris H. Fuertinger, Stephan Thijssen, Peter Kotanko. *Renal Research Inst, NY.*

Background: Prediction of hemoglobin levels in individual hemodialysis (HD) patients treated with erythropoietin (EPO) is highly desirable but challenging. The non-linear dose responsive curve differs between patients and is influenced by multiple factors, such as iron status and inflammation. We adapt a complex mathematical model of erythropoiesis to individual HD patients and predict their hemoglobin (Hgb) response to EPO therapy for up to 24 weeks.

Methods: A mathematical model of erythropoiesis (Fuertinger et al, J Math Biol 2013) is adjusted to individual HD patients treated with EPO. Crit-Line® monitors provided Hgb measurements. Hgb data measured during a 150 days baseline period together with the model are used to estimate a patient's individual erythrocyte lifespan, bone marrow response to EPO, endogenous EPO production, and EPO half-life. Model predictions are compared to measured Hgb data. Boxplots are used to present the mean absolute percentage error (MAPE). Depending on the availability of follow-up data we predict individual Hgb levels for up to 170 days.

Results: We studied 60 chronic HD patients with an age of 59.4 ± 14.7 years, 29 males, 30 Blacks, 37 with diabetes, and a body mass index of 27.9 ± 6.7 kg/m^2. Figure 1 shows the quality of the model adaptations (left boxplot) and Hgb predictions made by the individualized model. Median MAPE is ~4.2% and remains stable for up to 170 days, while MAPE interquartile range increases from ~1.2% in the first 150 days to ~4.5% at 170 days.



Conclusions: The individualized erythropoiesis model predicts individual Hgb levels for up to 21 weeks with clinically satisfactory accuracy and precision. These findings indicate that the mathematical model is able to capture patient-level hemoglobin dynamics, a necessary requirement for its intended use as an individualized anemia management tool.

SA-PO1022

Optimal Hemoglobin Level in Patients with Chronic Kidney Diseases on Hemodialysis in High Altitude Cities

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Background: In patients with anemia due to chronic renal disease, it is recommended in order to avoid complications, to maintain hemoglobin levels between 10-12 g/dl, according to studies conducted at sea level; however, the optimal value allowed in patients residing in high altitude cities is still unknown.

Methods: A descriptive study was conducted in the Renal Unit of the Austro (UNIREAS) Cuenca, Ecuador, (altitud: 2,560mts) during the period January 2010 to December 2011, obtaining data from physical medical records of each patient.

Results: A total of 3,423 measurements of hemoglobin in patients with chronic renal disease stage 5D was obtained, of which 57% were women and 43% men. The complications were divided int different ranges of hemoglobin, from 10 to 12 gr/dl (31.2%), from 12.1 to 13g/dl (45.5%), from 13.1 to 14g/dl (30.3%), from 14.1 to 15 g/dl (21.2%) and over 15g/dl (3%). Additionally, the distribution of complications according to the chronic pathologies assessed was evaluated. Arterial Hypertension (43.7%), Arterial Hypertension plus Diabetes Mellitus type 2 (34.3%), Diabetes Mellitus type 2 (6.25%), Diabetes Mellitus type 1 (1.5%) and others (14%).

Conclusions: The complications increase as the value of hemoglobin increases. However, from the total of measurements greater than 12 g/dl only 1.84% showed compiications. In addition, the complications rate found int he groups with a range of 10 to 12 g/dl hemoglobin was 1.49% compared with a rate of 1.62% found in the group with a wader range of 10 to 13 g/dl.

SA-PO1023

Achievement of Renal Anemia KDIGO Targets by Two Different Strategies - A European Hemodialysis Multicenter Analysis

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Background: Hemoglobin target levels can be achieved through more frequent i.v. iron use with less ESA or vice versa. ESA therapy to correct anemia may result in adverse clinical outcomes and i.v. iron may exacerbate oxidative stress, potentiate atherogenesis and increase the propensity to infections. By tradition, anemia treatment strategies differ significantly between Portugal and Poland.

Methods: We included 1,247 patients on hemodialysis from Portugal (n=730) and Poland (n= 517) in an analysis of the achievement of KDIGO renal anemia targets and focused on treatment strategies.

Results: In Poland, the use and doses of i.v. iron were 35% higher than in Portugal ($p<0.001$) while the use and doses of ESA were 17% higher in Portugal (5034 vs 3133 IU [adjusted]/week, $p<0.001$). Hb 10-12 g/dl was achieved in 70% of pts in Poland and in 66% of pts in Portugal (NS, Chi-2). In Poland vs Portugal, 74% and 78% of pts had ESA ($p=0.056$), 87% vs 83% had ferritin>200 ug/l ($p=0.08$), 36% vs 16% had ferritin>800 ug/l ($p<0.001$), 89% vs 76% had TSAT ≥20% ($p<0.001$), and 15% vs 8% had TSAT≥50% ($p<0.001$). Comorbidity index <7 (Poland 52%, Portugal 39%) vs 7-12 (45% and 58%) vs >12 (3% and 4%) were significantly different between countries ($p<0.001$).

	Age	Vint	BMI	Kt/V	TT ..	Hb	TSAT	Ferri	Alb	Ca	P	iPTH	CVC	AVF
Poland	67	53 m	27	1.6	737	11	35	757	41	8.7	4.7	565	19%	76%
Portugal	69	66 m	25	2.0	724	11	29	498	40	8.9	4.1	561	15%	77%
p	**	***	***	***	***	NS	***	***	NS	***	***	NS	***	NS

t-test **=0.01, ***=0.001

Conclusions: The KDIGO hemodialysis anemia target was achieved in the two countries through different treatment strategies in terms of ESA use and doses of i.v. iron. These differences may have clinical implications: future evaluations will show how these differences in treatment strategies correlate with the future risks of complications, hospitalization and mortality.

Funding: Pharmaceutical Company Support - DaVita

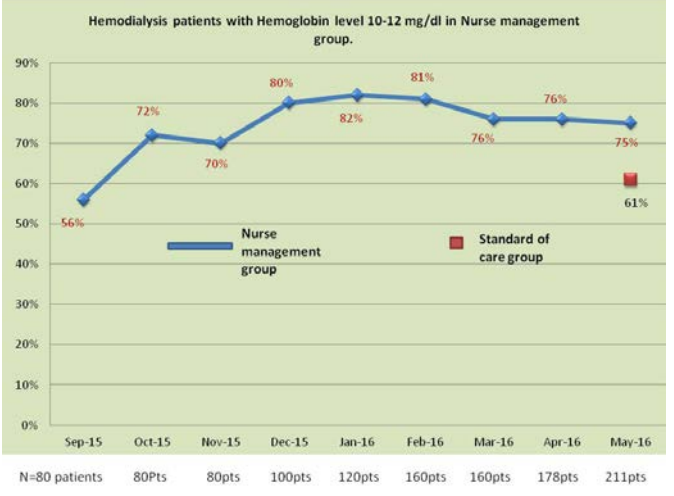
SA-PO1024

Nurse Based Anemia Management in Hemodialysis: An Observational Prospective Study Abdullah Hamad, Fatma Ahmed Ramadan, Nadiya Noor Khan, Hany Ezzat Ismail, Tarek Abdellatif Ghonemy, Sahar Aly, Fadwa S. Al-Ali. *Nephrology, Hamad General Hospital, Doha, Qatar.*

Background: The concept of anemia nurse manager (ANM) was explored because of her availability in the dialysis unit which provides a chance to address management swiftly and timely. We did a prospective observational study to compare our new ANM model to our standard of care (SOC) in regard to achieving hemoglobin (Hg) in target (10-12 g/dL) and avoid extreme Hg (below 9 or above 13).

Methods: ANM team consisted of two part-time nurses under supervision of an expert nephrologist who provided extensive training for them for 2 months. We randomly selected and gradually included all patients located in 1st floor (our center is the largest in Qatar and has 380 patients in 2 floors). They were followed for 8 months (September 2015 to May 2016). We followed Hg, iron sat and ferritin per our protocol. Nurses reviewed the results one day after blood draw with the nephrologist and prescriptions for erythropoietin stimulating agents (ESA) and iron were written simultaneously (physician prescription is mandatory per health authority in Qatar). Patients who did not have any Hg values during this period were excluded.

Results: We started with 66 patients and gradually reached 211 patients by May 2016. Percentage of patients with Hg within target range steadily improved.



There was a statistically significant difference in the number of patients in target range in the new model (1st floor) versus SOC (2nd floor, n=147) (75% versus 60.5%) (pValue 0.005 fisher exact test). Number of patients with extreme Hg has improved from 10.7% in Sep. 2015 to 6.4% in May 2016 (censored for ESA naïve patients) compared to 12% in SOC group (p 0.08). The two groups did not differ in iron parameters.

Conclusions: Our ANM model designed to fit local requirements in Qatar significantly improved percentage of Hg in target and decreased extreme Hg levels compared to SOC.

SA-PO1025

Trajectories of Hemoglobin Levels before and after Initiation of Dialysis Dugan Maddux,[1] Frank van der Sande,[2] Jeroen Kooman,[2] Jennifer A. Vosburgh,[1] Marta Reviriego-Mendoza,[1] John W. Larkin,[1] Len A. Usvyat,[1] Terry L. Ketchersid,[1] Peter Kotanko,[3,4] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Maastricht Univ Medical Center, Maastricht, Netherlands; [3]Renal Research Inst, New York, NY.*

Background: Anemia affects about 82% of stage 5 chronic kidney disease (CKD) patients (Pts) (Shaheen FA, et al. Saudi J Kidney Dis Transpl 2011). As reported by the USRDS these Pts exhibit a drop in mean hemoglobin levels (Hgb) from about 13g/dL to <11g/dL in the 5 years prior to end stage renal disease (ESRD). We studied Hgb trajectories in Pts who transitioned from CKD to ESRD by survival status in the first year of dialysis.

Methods: We analyzed data from the Fresenius Medical Care CKD Data Registry on 14,095 Pts with Hgb results in the 12 months pre-dialysis who transitioned to ESRD between 2008 and 2016. Changes in mean monthly Hgb were analyzed by survival status in the 12 months after starting dialysis.

Results: Two main observations are notable: i) Hgb gradually declined in the year prior to dialysis initiation, more precipitously in the final 2 months (Figure 1A); compared to those who survived the first year of dialysis, the Hgb decline is more pronounced in those who die (Figure 1B). ii) Hgb rapidly rose after dialysis initiation; by month 2 after dialysis start, mean Hgb was similar to levels 12 months prior to dialysis start. (Figure 1A). In Pts who died in the first year of dialysis, the Hgb increase was lower than, and never reached Hgb levels of survivors.

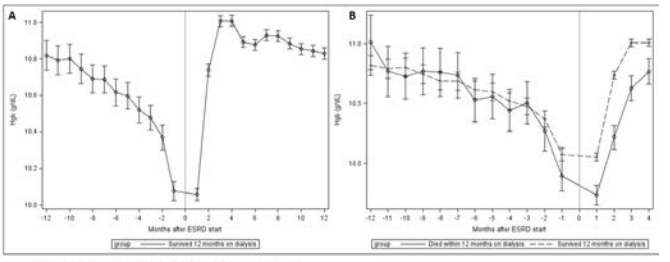


Figure 1. Error bars represent the 95% confidence intervals.

Conclusions: We found Hgb declines during the 12 months before transition from CKD to ERSD. Hgb rebounds during the incident dialysis period exceeding levels 12-months before dialysis initiation. The drop in Hgb is most pronounced in Pts who die within the first year of dialysis. Our study is limited since ESA doses prior to dialysis are not available in this dataset.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

SA-PO1026

Effect of Ultrapure Dialysate on Erythropoietin Response in Hemodialysis Patients Chai L. Low, Calantha K. Yon, Meili Chang. *Pharmacy, VA San Diego Healthcare System, San Diego, CA.*

Background: Chronic inflammation often leads to resistance to treatment with erythropoietin (EPO) in hemodialysis patients. Cytokines such as IL-6 and TNF- α are known to inhibit response to EPO. The presence of endotoxins in dialysate can induce proinflammatory cytokines. Currently, endotoxin level not exceeding 0.50 unit/ml in dialysate is recommended by AAMI. Preliminary studies have shown that ultrapure dialysate (endotoxin <0.03 unit/ml) may be associated with less resistance to EPO and decreased EPO requirement in hemodialysis patients. The aim of this study was to evaluate the effect of ultrapure dialysate on EPO response in hemodialysis patients at VASDHS.

Methods: This prospective study was conducted from Aug 1, 2015 to Mar 31, 2016. Nephros® Dual-Stage ultrafilters were installed in Oct 2015. Inclusion criteria:hemodialysis patients at least 18 years old who were clinically stable and receiving standard ESRD care at VASDHS for at least 3 months prior to enrollment. Exclusion criteria:(1)acute or chronic infection;(2)chronic inflammatory disease states;(3)bleeding disorders, or(4)newly diagnosed malignancies. Erythropoietin Resistance Index (ERI), defined as EPO dose/kg/Hemoglobin, was used to compare intra and inter individual changes in EPO response. Outcome measures were changes in CRP levels, EPO dose, and ERI. Repeated measures ANOVA and Wilcoxon signed rank test were used for statistical analysis.

Results: 39 patients included in data analysis. There were 38 males and 1 female, mean age 65.6±9.01, and average duration on hemodialysis 5.4±3.8 years.

N=39	Baseline	With Ultrafilters	P
CRP (mg/L)	1.57 ± 2.56	1.68 ± 2.05	0.67
Weekly Epo dose (unit)	7778	7789	0.84
ERI	10.17 ± 8.48	10.54 ± 10.28	0.55
Endotoxin (unit/ml)	<0.01	<0.01	NA
Hemoglobin (g/dl)	10.30 ± 0.71	10.47 ± 0.11	0.42
Ferritin (ng/ml)	588.41 ± 242.19	593.18 ± 180.49	0.90
TSAT (%)	24.46 ± 8.93	25.31± 9.52	0.69

Conclusions: There were no statistically significant differences in all outcome measures after the installation of ultrafilters. At baseline endotoxin of 0.01 unit/ml, lowering endotoxin levels further does not affect EPO responsiveness in our hemodialysis patients.

Funding: VA Support

SA-PO1027

Impact of Dialysis Adherence on Anemia Management Vibha S. Nayak, Kausar Hamiduzzaman, Adam E. Gaweda, Michael E. Brier. *Nephrology and Hypertension, Univ of Louisville, Louisville, KY.*

Background: The impact of patient dialysis adherence on anemia management has not been evaluated recently. We tested the hypothesis that nonadherence to dialysis treatment results in a significant decrease in hemoglobin achieved.

Methods: Data were retrospectively collected from the University of Louisville dialysis facility for the years 2004 to 2015. Patient adherence was noted in the EMR. Data were cleaned to remove duplicate records and treatments were marked as complete if

erythropoietin and/or iron was administered. 516 patients data were used for the analysis with a minimum of 90 schedule treatments during the calendar year. The following information was calculated: percentage of completed treatments, total ESA and iron administered, and the yearly mean run time, ultrafiltration, hemoglobin, T sat, and ferritin achieved. ESA and iron doses were adjusted by dry weight and reported as weekly dose. Statistical analysis was by decision tree classification technique.

Results: Results of the decision tree analysis are shown in the following table.

	Population Mean Hemoglobin 11.4 ± 1.3						
Nodes	1	2	3	4	5	6	7
ESA U/ week/kg	0	0 to 1.5	1.5 to 3.3	3.3 to 11.3	11.3 to 15.3	15.3 to 35.1	>35.1
Hb g/dl	13.1	11.5	10.9	11.0	11.2	11.4	11.0
Ferritin ng/ ml (nodes 8-18)	<523, >523			<737, 737-1149, >1149	<977, >977	<1148, >1148	<849, >849
Hb g/dl	13.6, 12.5			11.4, 10.9, 10.6	11.4, 10.8	11.6, 10.7	11.2, 10.7
% Adhearance (nodes 19-26)				(<737) 95% | (737-1149) 96% | (>1149) 95%		(<1148) 92%	
Hb g/dl				11.2, 11.6 | 10.6, 11.2 | 10.3, 10.9		11.3, 11.8	

The analysis resulted in 26 decision points (nodes), with 7 nodes related to ESA dose shown as the dose range included and mean Hb for that node. In nodes 1,4,5,6, and 7 ferritin significantly added 11 further nodes and is shown as a single break point or range with the corresponding mean Hb for that node. In nodes 4 and 6 adherence significantly added 8 additional nodes. All p values were < 0.012.

Conclusions: Adherence less than 92 to 95% resulted in significantly decreased Hb ranging from 0.4 to 0.6 mg/dl. Higher ferritin resulted in lower Hb ranging from 0.5 to 1.1 mg/dl.

Funding: NIDDK Support

SA-PO1028

Reducing Blood Volume Waste from Dialysis Central Venous Catheters (CVCs) Emily Xue,[1] Bette J. Gilmartin,[2] Virginia L. Hood.[1,2] *[1]Univ of Vermont College of Medicine, Burlington, VT; [2]Univ of Vermont Medical Center, Burlington, VT.*

Background: Anemia is a major complication of end stage renal disease. As treatment is costly and associated with risks, it is important to reduce unnecessary blood loss in this population, including during hemodialysis (HD). Under the current protocol for HD in patients with CVCs, the first 10mL of blood is discarded to "clear the line" before sampling blood for labs or connecting the patient to the HD machine, leading to a yearly blood loss of approximately 1.5L per patient. We propose a protocol to reduce the blood discarded without affecting standard laboratory measurements by comparing values in samples drawn after less blood is discarded with those using the current protocol.

Methods: Eight patients with CVCs undergoing HD gave informed consent to have two samples of blood taken from CVCs for monthly tests. The first sample (S1), experimental, was drawn after 3mL of blood per CVC lumen was discarded; the second (S2), control, was drawn after 5-7mL per lumen was discarded. Results of hemoglobin, Na, K, Cl, BUN, Ca, Phos, albumin, and CO2 from S1 and S2 samples were analyzed using paired t-tests and Bland Altman plots constructed.

Results: For each of the values measured, there was no significant difference between the experimental and control values. P-values ranged from 0.12 to 0.50. Predetermined power to detect a 1-4% difference was 95%. There was no systematic bias suggesting lower values in S1 compared with S2 that would indicate dilution in the first sample.

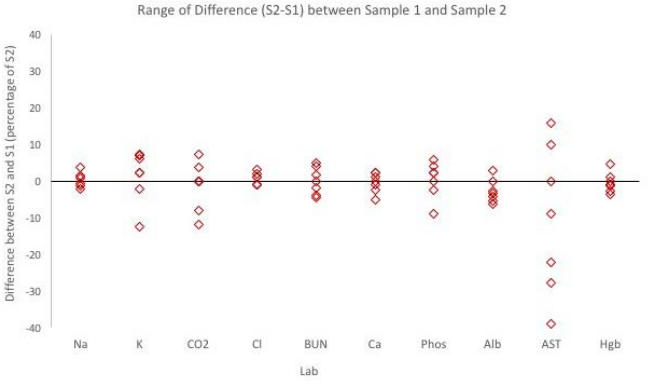


Figure 1. Plot of calculated differences between sample 2 and sample 1 for each parameter. Differences are normalized as percentage of sample 2 ([S2-S1]/S2).

Conclusions: Discarding 6 versus 10mL blood from CVCs did not change values of standard pre-dialysis blood values in any way that would affect clinical care. The proposed protocol of discarding less blood when accessing CVC lines could save at least 600mL blood/HD patient/year and may be generalizable to non-dialysis patients with CVCs.

SA-PO1029

Hemodialysis Patient Plasma Trace Metals Associate with Dialysis Incidence versus Prevalence, Gender, and Response to Erythropoiesis Stimulating Agents Michael Merchant,[1] Michael E. Brier,[1] Jessica Gooding,[2] Susan Sumner,[2] Susan Mcritchie,[2] James M. Harrington,[2] Jason P. Burgess,[2] Brad H. Rovin,[3] Jon B. Klein,[1,4] Jonathan Himmelfarb.[5] *[1]Univ of Louisville; [2]NIH Eastern Regional Comprehensive Metabolomics Resource Core at RTI International; [3]Ohio State Univ; [4]Robley Rex VAMC; [5]Univ of Washington, Seattle.*

Background: Uremic toxins can form blood metal binding protein-adducts, that are associated with mortality and response to erythropoiesis stimulating agents (ESAs). Knowledge of trace metal levels associating with hemodialysis (HD) patient response to ESA dosing might improve anemia management. We tested the hypothesis that plasma trace metal concentrations correlate with markers of anemia and response to ESA treatment.

Methods: EDTA-Plasma from 110 HD patients (77 prevalent, 33 incident) participating in the NIDDK funded study (R01-01DK091584) were analyzed by ICP-MS for the plasma concentration of As, Cd, Co, Cr, Cu, Mn, Mo, Ni, Pb, Sb, Se, Sn, V, and Zn. Associations were determined between trace metals and gender, race, HD status, monthly hemoglobin (Hgb) values, total ESA dose for the month the sample was collected, erythropoietin response index (ERI), transferrin percent saturation, ferritin, iron, hepcidin and c-reactive protein (CRP).

Results: Cd(p-value<0.001)*, Sn*, Ni(p-value<0.05)**, and Mo** concentrations were significantly higher in prevalent patients, as was detection of V*. Conversely, Mn* concentrations were lower in prevalent patients. Spearman correlations of trace metals in prevalent plasma samples revealed: Cd concentrations were inversely correlated with Hgb levels, and positively correlated with EPO and ERI. Sn was positively correlated with EPO. Zn was negatively correlated with ERI. Cd** concentrations were significantly higher in females compared to males. Cu* and Se** were positively and Mo** was negatively correlated to CRP by multivariable regression. V** was negatively correlated with hepcidin.

Conclusions: Plasma trace metal concentrations associate with dialysis vintage, gender, correlate with ESA response, and may be useful in guiding HD patient specific approaches to anemia management. We hypothesize specific trace metals may play a causal role in ESA resistance.

Funding: NIDDK Support, Other NIH Support - R01-01DK091584 (MM/MB). RTI RCMRC NIH Common Fund Program grant U24 DK097193 (SS). NIH Common Fund Program grant K01 GM109320 (JG). This research was supported by an unrestricted gift from the Northwest Kidney Centers to the Kidney Research Institute, VA Support

SA-PO1030

Levocarnitine Injections Decrease the Need for Erythropoiesis Stimulating Agents in Hemodialysis Patients with Renal Anemia Seishiro Baba, Tomoyasu Otsuki, Kazuyoshi Okada, Masanori Abe. *Nephrology, Hypertension and Endocrinology, Nihon Univ School of Medicine, Tokyo, Japan.*

Background: Patients with chronic kidney disease often develop anemia, which can be treated with erythropoiesis stimulating agents (ESAs). However, there are concerns about the negative side effects of ESA treatment, including an increased risk of an adverse cardiovascular event and death. Therefore, it is desirable to minimize ESA use. Carnitine is thought to be associated with the maintenance of red blood cells, including their numbers, substrate storage capacity, membrane lipid turnover, and protein construction. In hemodialysis patients, carnitine imbalance or deficiency can result from insufficient intake, a decrease in carnitine biosynthesis, or removal of carnitine from the body during dialysis. In the study, we gave levocarnitine injection to the hemodialysis patients to evaluate its efficiency for anemia in renal disease.

Methods: We randomly assigned maintenance dialysis patients at our hospital to receive levocarnitine injections (n = 30) or no injection (n = 30), and monitored the patients during 12 months of treatment. The treatment group was injected with levocarnitine doses of 1000 mg three times each week after hemodialysis. All patients received recombinant human erythropoietin as an erythropoiesis stimulating agent (ESA). Response to ESA therapy was determined by calculating the erythropoiesis resistance index (ERI; ESA dose/kg/g/dL/week).

Results: (1) The target levels of hemoglobin and hematocrit were maintained during the period of the study in both levocarnitine group and control group. (2) The quantity of ESAs required to maintain these levels decreased gradually in levocarnitine group, and was significantly lower during study initiation than at months 6 and 12 and was also significantly lower than the levels required in the control group at these time points. (3) ESIs showed a significant decrease at months 6 and 12 in levocarnitine group, with a significant difference between the two groups at months 6 and 12.

Conclusions: The results suggest that levocarnitine can reduce the quantity of ESAs used in renal anemia patients on hemodialysis and improve the response to therapy with ESAs.

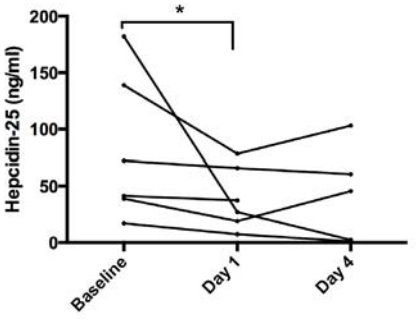
SA-PO1031

Glucocorticoids Inhibit HAMP mRNA in HEPG2 Cells and in CKD Patients with Vasculitis Adam Rumjon, Iain C. Macdougall. *Dept of Renal Medicine, King's College Hospital, London, United Kingdom.*

Background: Hepcidin is the master regulator of iron homeostasis encoded for by the *HAMP* gene, and CKD patients have increased circulating levels of the hormone. Knowledge on factors controlling its production is expanding, and previous studies showed that hepcidin is suppressed by oestrogen and testosterone. There are no data on the effect of glucocorticoids on hepcidin, and the aim of this study was to investigate the effect of steroids on *HAMP* gene expression in vitro, as well as on hepcidin levels in CKD patients with acute vasculitis.

Methods: HepG2 cells were exposed to increasing doses of dexamethasone from 1.25 to 80 ng/mL, for a period of 18 hours. HepG2 cells were pre-treated with dexamethasone (10ng/mL) or vehicle for 4 hours before the addition of 12.5 ng/ml of interleukin-6 or vehicle, for 2 hours. Total cellular RNA was extracted and reversed transcribed; quantitative rt-PCR was then performed and amplification was performed using Taqman *HAMP* and GAPDH (housekeeping) primers. Serum hepcidin-25 levels were measured using mass spectrometry in 6 patients admitted with suspected ANCA-positive vasculitis before and after the administration of 500mg IV methylprednisolone.

Results: The dexamethasone-HAMP dose-response curve showed suppression of HAMP at concentrations ≥20 ng/mL. IL-6 stimulated HepG2 cells not pre-treated with dexamethasone showed an 11-fold rise in HAMP compared to only a 7.5-fold increase in cells pre-treated with dexamethasone. Hepcidin-25 levels in all 6 patients were lower 24 hours post-administration of methylprednisolone.



Conclusions: These data suggest that the glucocorticoid dexamethasone suppresses *HAMP* expression *in vitro*, and this may be IL-6-mediated. Administration of methylprednisolone reduced levels of circulating serum hepcidin within 24 hours. The consistency of both the in vitro and human in vivo data increases confidence in the validity of this effect.

SA-PO1032

A Single Center Retrospective Review of Incident Catheter Rates in an Academic Outpatient Dialysis Unit Eric Loman, Thurein Kyaw, Brendan T. Bowman. *Nephrolgy, Univ of Virginia, Charlottesville, VA.*

Background: K/DOQI guidelines recommend an Arteriovenous Fistula (AVF) rate of 68% in prevalent End Stage Renal Disease (ESRD) patients and at least 50% in incident ESRD patients. We reviewed data of all incident ESRD patients initiating hemodialysis (HD) in a University based outpatient unit to identify factors associated with catheter starts.

Methods: We conducted a chart review of all 78 incident HD patients (Nov 2012–Aug 2015). Data included: demographics, ESRD cause, pre-dialysis nephrology care, documented episodes of AKI, eGFR drop preceding ESRD, and time to access placement referral.

Results: 65 patients (83.3%) initiated HD with a catheter versus 13 patients (16.7%) with AVF or AVG. There were no major differences in demographics or cause of ESRD between the two groups. The main factor associated with a catheter start was AKI, occurring in 62% of patients. The catheter group had a profound loss of GFR in the 12 months preceding ESRD: nearly 80% of the group experienced a GFR loss of 50% or more compared to the gradual decline in the AVF/AVG group. 73.3% of the catheter group had a CKD diagnosis at HD start, with only 61.5% seen by a Nephrologist previously. In the AVF/AVG group, all patients were followed for at least 3 years by a Nephrologist prior to HD. 83% of patients starting with an AVF/AVG were seen by a surgeon 6 months or longer before initiating HD vs 40% in the catheter group. Less than half of catheter patients changed to an AVF or AVG.

Conclusions: Previous studies have shown high incident catheter rates associated with late diagnosis of CKD, lack of pre-dialysis nephrology care, and AKI. Our study confirms this. In addition, our study demonstrates the importance of rapid loss of GFR from prior stable moderate CKD on incident catheter rates. This suggests focusing access placement in outpatients with gradual GFR loss will not prevent high incident catheter rates. Further emphasis should be also placed on inpatients with rapid GFR loss/AKI leading to ESRD; ideally during the index hospitalization.

SA-PO1033

The Associations between Vascular Access Care and Mortality Rates in Hemodialysis Patients Hao Han,[1] Marta Reviriego-Mendoza,[1] Sheetal Chaudhuri,[1] Karen G. Butler,[1] Sophia Rosen,[1] Jane Brzozowski,[1] John W. Larkin,[1] Walead Latif,[2] Elsie Koh,[2] Len A. Usvyat,[1] Gregg Miller,[2] Melvin Rosenblatt,[2] Murat Sor,[2] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Fresenius Vascular Care, Berwyn, PA.*

Background: Fresenius Vascular Care (FVC) offers outpatient vascular access (VA) care for Fresenius Medical Care North America (FMCNA) hemodialysis (HD) patients. We studied the associations in mortality rates for FVC outpatient VA care versus other VA providers that are mostly in a hospital setting or no VA care received at all.

Methods: We analyzed data from 4,691 HD patients who visited FVC at any time during calendar year 2014. Control patients were selected by 1:1 matching exactly for concurrent year of FVC care, state of residence, gender, race, and access type, as well as, nearest neighbor matching on the logit of the propensity score for age, dialysis vintage, albumin, body mass index, and Kt/v. Further analysis was performed for 4,376 FVC patients with a preexisting arteriovenous fistula or graft (AVF/AVG). Six month mortality rates per 100 patient years were compared between study groups after 1/1/2015.

Results: Data from a total of 9,382 HD patients was analyzed for this study. Compared to matched control patients, mortality rates in FVC patients were decreased by 33%($p<0.001$; Figure 1A). Similarly, in patients enrolled in FVC with a preexisting AVF/AVG showed a 28% reduction in mortality when compared to controls ($p<0.001$; Figure 1B).

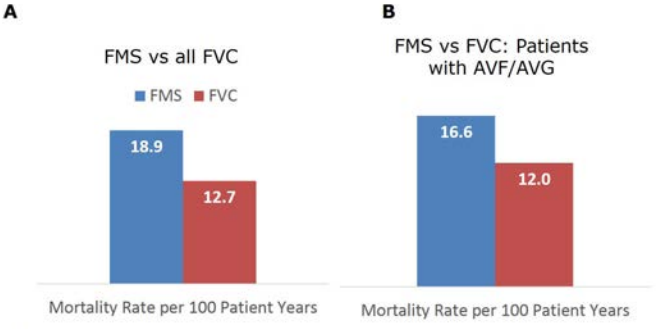


Figure 1

Conclusions: The results of this analysis suggest that outpatient VA care may have the potential to reduce mortality rates in HD patients when compared to patients receiving VA care in other settings or no care at all. Ongoing studies are warranted to determine the long term mortality outcomes associated with FVC VA care.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

SA-PO1034

Analysis of 5,000 Cases of Vascular Access Interventional Therapy for Vascular Access Failure at a Single Facility – How Well Were the AVG Maintained? Teruhiko Maeba, Shigeru Owada. *Internal Medicine, Asao Kidney Clinic, Kawasaki, Kanagawa, Japan.*

Background: Sustaining a functional vascular access (VA) is one of the most important factors in the maintenance of an HD modality. The application of vascular access interventional therapy (VAIVT) for VA trouble is increasing recently but the effectiveness of VAIVT has not been entirely satisfactory because of the relatively high rate of re-stenosis.

Methods: We have experienced 5,028 cases (in 947 patients) of VA trouble treated with VAIVT over the last twelve years in which primary assisted and secondary assisted rates were analyzed.

Results: 1. We have used a noncompliant type of balloon catheter for 98.6% of cases and primary assisted patency rates were 99.2%. 2. Secondary assisted patency rates were 72.3% at two years, 64.3% at 4 years, 72.0% at 6 years, 51.0% at 8years and 47.7% at 11years in all patients. 3.In diabetic patients, assisted patency rate was 47.4% at 11years and it was 47.6% in non-diabetic patients ($p=0.82$, Log rank). There were no significant differences found between the arteriovenous fistulas (AVF) and the arteriovenous grafts (AVG) ; 49.8% and 37.0% at 11 years, respectively. 4. Failure of secondary assisted patency was observed in 517 patients. In these, a new AVF was made on the same side in 38.0% of the patients, a contralateral side AVF was made in 6.0% and an AVG in34.0%, superficialized reposition of brachial artery in 4.0% and death occurred in 18.0%.

Conclusions: The results for the initial clinical success rate and secondary assisted patency rates were excellent. It was possible to reduce the economic burden for patients by using a noncompliant type of balloon catheter. Long-term maintenance of AVG was possible by the use of VAIVT.

SA-PO1035

Outcomes of Multi-Disciplinary Interventional Nephrology Service in Singapore General Hospital Chee Yong Ng, Swee Ping Teh, Ru Yu Tan, Chieh-Suai Tan. *Renal Medicine, Singapore General Hospital, Singapore.*

Background: Singapore General Hospital (SGH) has established an interventional nephrology suite (INS) for management of vascular access issues. This is a multidisciplinary set-up comprising of interventional nephrologists (IN), interventional radiologists (IR) and vascular surgeons (VS).

Methods: This study reports the outcome of thrombolysis / thrombectomy of haemodialysis access performed in INS from 1st March 2015 to 29th February 2016.

Results: A total of 198 patients with thrombosed access had interventions done in INS during this period. Of these, 104(52.5%) were arteriovenous fistula (AVF). Mean age of study subject was 63.5±11.9, predominantly Chinese (62.6%), and of male gender (51%). Majority of patient in this study develop End Stage Renal Disease(ESRD) from diabetes mellitus (58.6%). Procedures performed by IN, IR and VS were 38.9%, 51.6% and 9.5% respectively. 96.5% of patient had reestablishment of flow in the vascular access radiologically, while 94.9% had successful haemodialysis post procedure. There was no significant difference in baseline characteristics among patients who underwent procedure done by the 3 groups of proceduralist. Radiological success rate of procedures done by IN, IR and VS were 98.7%, 94.1% and 100% (p=0.176) and clinical success rate was 98.7%, 92.2%, 94.7% (p=0.141) respectively. Complications occurred in 4.5% of patients but there's no significant difference in complications rate among the 3 groups of proceduralist. 3 months patency recorded for intervention done by IN were 40.3%, IR 33.5% and VS 26.3% respectively (p=0.433).

Conclusions: There was no statistically significant difference in the radiological and clinical success rate of interventional nephrologists, interventional radiologists and vascular surgeons. The centre's 3 month primary patency after percutaneous thrombectomy and clinical success rate of intervention for AVGs are in keeping with NKF KDOQI guideline standards of 40% and 85% respectively.

SA-PO1036

Vascular Access (VA) Triage and Clinical Events in Haemodialysis (HD) Sandro Mazzaferro,[1] Maria Luisa Muci,[2] Lida Tartaglione,[1] Luciano Carbone,[2] Silverio Rotondi.[2] *[1]Scienze Cardiovascolari, Respiratorie, Nefrologiche, Anestesiologiche e Geriatriche, Sapienza Univ, Rome, Italy; [2]Nephrology and Dialysis Unit, ICOT Hospital, Latina, Italy.*

Background: VA type (AVF vs CVC) affects morbidity and mortality in HD, but its performance is not routinely evaluated. We developed a system of VA triage representative of its monthly performance. We report here on the relationship between this VA triage and clinical events.

Methods: Nurses report each session data (weights, BP, HR, Blood flows, VA pressures, symptoms, clots and KT/V) on a data sheet. Pathologic values generate a score that, with empiric thresholds, flags the VA green, yellow or red. We retrieved clinical events (admissions and deaths) of those patients whose VA had been triaged for >3 months between 1/1/2014 and 12/31/2015. For each patient we considered the average triage of the available follow-up, separately for different VA types.

Results: 111 patients (62 AVF and 49 CVC), followed for 18±7 months, experienced 12 deaths and 170 hospital admissions which lasted 16±26 days. Prevalence of events was greater in CVC as compared to AVF patients (75% vs 51%,p<.02). Based on average triage, patients were separated into groups that resulted different for prevalence of events (36, 68 and 100% in the green, yellow and red groups respectively; p<0.001), but not for age, dialysis duration or diabetes. This difference was confirmed in the subgroup with AVF (30, 62 and 100% respectively, p<0.01) but not in patients with CVC.

Triage		Green	Yellow	Red	p<
Case,n°		50	57	4	
Age,y		68±13	71±11.7	73±11.6	n.s.(^)
Dialysis age,months		21±19	20.3±31.5	18±28.7	n.s.(^)
Diabetes,n°		16 (32%)	19 (33%)	0	n.s.(*)
AVF/CVC,n°		23/27	37/20	2/2	
Patients with events	AVF and CVC n°(%)	18 (36%)	39 (68%)	4 (100%)	<.001(*)
	AVF only, n°(%)	7 (30%)	23 (62%)	2 (100%)	<.02(*)
	CVC only, n°(%)	19 (70%)	16 (80%)	2 (100%)	n.s.
Events= admission/deaths. Data are mean±SD;(^) ANOVA;(*)X^2					

Conclusions: We confirm the role of VA type as a risk factor for events and suggest that a triage system evaluating the performance of each type of VA could represent, in particular for AVF, a useful sensor of increased clinical risk.

Funding: Private Foundation Support

SA-PO1037

Twelve-Month Patency Rate after a First PTA for Failed Arteriovenous Fistula: Comparison between Low- and High-Pressure Balloon Dilation (YOROI Study) Koki Wakamoto, Kensuke Sasaki, Toshinori Ueno, Ayumu Nakashima, Shigehiro Doi, Takao Masaki. *Dept of Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan.*

Background: Low-pressure balloon dilation for failed hemodialysis fistulas has recently exhibited a better patency rate in comparison with conventional strategy in achieving complete balloon expansion, even in patients with residual stenosis. In this study, we investigate the 12-month patency rates for low- and high-pressure dilation in patients who underwent their first percutaneous transluminal angioplasty (PTA) for failed arteriovenous fistula.

Methods: This study was a multicenter, prospective, randomized, two-comparison, non-inferiority trial. The YOROI balloon (Kaneka Medics, Osaka, Japan), with a diameter of 4 mm, was used for dilation of stenotic lesions. Balloons were inflated to a pressure of 8 atm (low-pressure group), or to a pressure of up to 30 atm to achieve complete expansion (high-pressure group). The 12-month patency rate after balloon angioplasty was analyzed by Kaplan–Meier analysis and a log-rank test. We also investigated the incidence of complications.

Results: A total of 71 patients who received their first PTA were enrolled. One patient in the low-pressure group dropped out due to peripheral ischemia after PTA, and one patient in the high-pressure group died during the observation period. 12-month patency rates did not show a significant difference between the low- and high-pressure groups. In addition, the patency rate of the group with incomplete expansion was not significantly lower than that of the group with full balloon expansion.

Conclusions: Full expansion of the balloon using high pressure was highly probable. However, with no significant difference noted in the 12-month patency rate, our results suggest that complete balloon expansion does not affect patency rates.

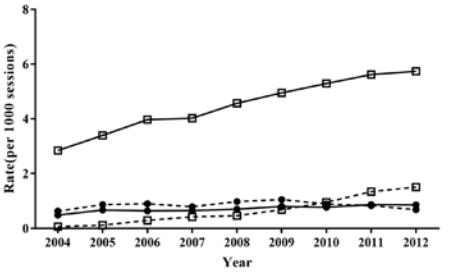
SA-PO1038

Hemodialysis Center of Frequent Percutaneous Transluminal Angioplasty Use Is Not Associated with Fewer Vascular Access Recreation-A Nationwide Population Study at Taiwan Yiwen Chiu, Feng-Xuan Jian, Ming-Yen Lin, Shang-Jyh Hwang. *Div of Nephrology, Dept of Internal Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung Medical Univ, Kaohsiung, NA, Taiwan.*

Background: The percutaneous transluminal angioplasty (PTA) frequency increased dramatically but its effect on vascular access (VA) recreation was not so clear.

Methods: Prevalent patients under maintenance hemodialysis (HD) at Taiwan from 2004 to 2012 were included. The demographics, baseline clinical characteristics, number of PTA and VA recreation for each patient were collected. The mean/media/portion/frequency which appropriate for all the variables above was assigned annually to each center as its characteristics. Generalized estimating equation was used to test the association between center's PTA frequency and VA recreation rate.

Results: Total 81,225 patients were included (mean age 61.8(±13.9) y/o, male 50 %, DM 49 %, mean HD vintage 5.2(±3.9) y) as well as 820 HD centers. PTA frequency increased by 3 times from 1.10 at 2004 to 3.57 at 2012 (per 1000 HD sessions) and VA recreation rate were kept around 0.80 (per 1000 HD sessions). Compared with the HD centers of infrequent use of PTA (annual lowest quartile, range: 0-2.19 per 1000 HD sessions), the ones of frequent use (annual highest quartile, range: 2.12-29.41 per 1000 HD sessions) didn't have lower VA recreation.



PTA (●) and VA recreation (□) rate at centers of frequent (—, highest quartile of PTA rate) and infrequent (---, lowest quartile of PTA rate) PTA use.

The independent predictors for HD center of lower VA recreation rate were those with more female, at earlier time cohort, fewer myocardial infarction history history, shorter HD vintage, and lower mortality (all p<0.05), but not frequent PTA use (p=0.37).

Conclusions: Frequent use of PTA seems not improve VA patency at center level for no significant association identified with lower VA recreation. The indication of PTA in daily practice should be re-evaluated with regard to its efficiency in term of lowering VA recreation.

SA-PO1039

Diagnostic Accuracy of Computed Tomography Angiography and Magnetic Resonance Angiography in the Detection of Hemodialysis Arteriovenous Fistula Dysfunction: A Meta Analysis

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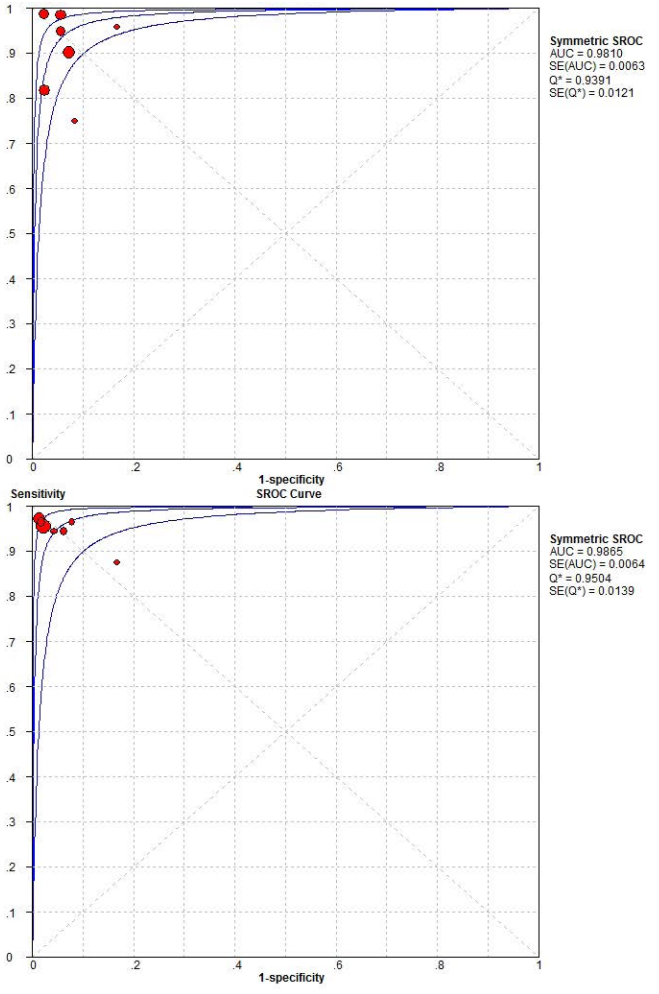
Background: We sought to evaluate the diagnostic accuracy of computed tomography angiography (CTA) and magnetic resonance angiography (MRA) compared with invasive digital subtraction angiography (DSA) or surgery for the detection of ateriovenous fistula dysfunction in hemodialysis patients.

Methods: PUBMED, MEDLINE, Cochrane library, and EMBASE searches were performed until May 31th, 2016 for potential related articles. Inclusion criteria were 1) at least one of the following diagnostic methods: CTA or MRA were included as a diagnostic test for hemodialysis AVF; (2) >50% diameter stenosis or occlusion selected as the cut-off criteria; (3) DSA or surgery as the standard of reference; (4) absolute numbers of true positive, false positive, true negative, and false negative results could be derived. Standard meta-analyses were applied.

Results: Seven studies reported the diagnostic accuracy for detection of AVF malfunction by CTA. They indicated a pooled sensitivity of 95% (90% to 97%), specificity of 96% (93% to 97%), positive likelihood ratio of 17.01 (11.40 to 25.36) and negative likelihood ratio of 0.09 (0.04 to 0.19) with a sDOR of 207.32 (97.85 to 473.12) and AUC of 0.9810. Seven studies reported the diagnostic accuracy for detection of AVF dysfunction by MRA. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, sDOR and AUC of were 97% (93% to 99%), 98% (96% to 99%), 27.21 (14.68 to 50.43), 0.05 (0.03 to 0.09), 788.21 (350.38 to 1773.15) and 0.9865 respectively.

Research	Country/ District	Subjects	Type	TP	FP	FN	TN	CTA Sensitivity	Specificity
Hey 2009	Belgium	162	64-MD CTA	46	8	5	103	0.90 (0.79-0.97)	0.93 (0.86-0.97)
Dimopoulou 2011	Sweden	92	16-MD CTA	37	3	2	50	0.95 (0.83-0.99)	0.94 (0.84-0.99)
Wasinrat 2010	Thailand	147	64-MD CTA	32	6	0	109	1.00 (0.89-1.00)	0.95 (0.89-0.98)
Ko 2005	Taiwan	62	4-MD CTA	37	1	0	62	1.00 (0.91-1.00)	0.98 (0.91-1.00)
Cavagna 2000	Italy	13	CTA	11	0	0	2	1.00 (0.72-1.00)	1.00 (0.16-1.00)
Rooijens 2008	Netherland	136	4-slice CTA	9	3	2	122	0.82 (0.48-0.98)	0.98 (0.93-1.00)
Lin 1998	Taiwan	9	CTA	4	0	1	5	0.80 (0.28-0.99)	1.00 (0.48-1.00)

Research	Country/ District	Subjects	Type	TP	FP	FN	TN	MRA Sensitivity	Specificity
Froger 2005	Netherland	282	1.5-T 3D CE-MRA	68	3	2	209	0.97 (0.90-1.00)	0.99 (0.96-1.00)
Doelman 2005	Netherland	433	1.5-T 3D CE-MRA	106	7	5	315	0.95 (0.90-0.99)	0.98 (0.96-0.99)
Han 2003	Netherland	10	1.5-T 3D CE-MRA	13	2	0	29	1.00 (0.75-1.00)	0.94 (0.79-0.99)
Pinto 2006	the US	80	1.5-T 3D CE-MRA	8	4	0	68	1.00 (0.63-1.00)	0.94 (0.86-0.98)
Duijm 2006	Netherland	101	1.5-T 3D CE-MRA	13	1	0	87	1.00 (0.75-1.00)	0.99 (0.94-1.00)
Cavagna 2000	Italy	13	0.5T MRA	10	0	1	2	0.91 (0.59-1.00)	1.00 (0.16-1.00)
Waldman 1996	Netherland	42	0.5T MRA	8	1	0	33	1.00 (0.63-1.00)	0.97 (0.85-1.00)



Conclusions: CTA and MRA have a good diagnostic accuracy for detection of AVF dysfunction in hemodialysis patients.

SA-PO1040

Dynamic Access Pressure Surveillance Predicts Venous Needle Dislodgment

Stanley Frinak,[1] Jerry Yee,[1] Anatole Besarab,[2] Gerard Zasuwa.[1] *[1]Nephrology, Henry Ford Hospital, Detroit, MI; [2]Nephrology, Stanford Univ, Palo Alto, CA.*

Background: Venous needle dislodgment (VND) incidents may be as high as 200/day with 2 serious adverse outcomes/day. Venous pressure (VP) measured during dialysis is variable > 130 mmHg. Recent data showed 56% of fistulas (AVF) and 6% of grafts had intraccess pressures (AP) ≤ 30 mmHg; 39% of AVF had AP ≤ 20 mmHg. Therefore, the current alarm threshold (T) for VND must be lower T"VP – (20 to 30 mmHg) yet not produce excessive false alarms. Low AP could place patients at greater risk for VND. We evaluated a Dynamic access pressure surveillance (DAPS) algorithm which continuously monitors AP for used as a more sensitive detection device for VND.

Methods: A Fresenius 2008 K dialysis machine (DM) was tested. A DAPS alarm for VND was implemented using LabVIEW software from National Instruments . VP data was obtained using an A to D converter connected to the analog output of the VP module, TX data was read every 2 sec from the DM serial port. A sham dialysis circuit with an artificial access site, QB = 800 ml/min and AP variable 40 to 0 mmHg was used for testing. DAPS alarm threshold was AP < 5 mmHg and the DM asymmetric VP limit was 25 mmHg. Circuit was filled with blood, QB=400 and the height of a 1L blood reservoir was adjusted to set the AP to 40mmHg. Reservoir height was decreased to set AP = 0 mmHg and alarms recorded. Procedure was repeated for QB=400 and 300. AP values of 30, 20, 15 and 10 were also tested for all QB values.

Results: Figure shows the results of the study. The DM alarm was only activated when the AP was decreased from 40 to 0 mmHg. In contrast, DAPS alarm was consistently positive even down to AP of 10 mm Hg. Tests repeated at QB=500 showed variable results for the DM alarm. In total 75% of studies produced no DM alarm.

Conclusions: The DAPS alarm implemented in a DM could be used for a more sensitive alarm system to detect VND.

Access Pressure Reduced to Zero to Determine Alarm Status

QB	AP	Venous Alarm Status DM Alarm	DAPS Alarm
500	10	FALSE	TRUE
500	15	FALSE	TRUE
500	20	FALSE	TRUE
500	30	FALSE	TRUE
500	40	TRUE	TRUE
400	10	FALSE	TRUE
400	15	FALSE	TRUE
400	20	FALSE	TRUE
400	30	FALSE	TRUE
400	40	TRUE	TRUE
300	10	FALSE	TRUE
300	15	FALSE	TRUE
300	20	FALSE	TRUE
300	30	FALSE	TRUE
300	40	TRUE	TRUE

(Tests repeated at QB=500)

QB	AP	Venous Alarm Status DM Alarm	DAPS Alarm
500	20	TRUE	TRUE
500	20	FALSE	TRUE
500	30	TRUE	TRUE
500	30	FALSE	TRUE
500	40	FALSE	TRUE

SA-PO1041

An Increase in Mean Platelet Volume/Platelet Count Ratio Is Associated with Vascular Access Failure in Hemodialysis Patients Dong Ho Shin, Eunjung Kim, Jung-Woo Noh, Ja-Ryong Koo. *Hallym Univ College of Medicine.*

Background: After stenosis of arteriovenous vascular access in hemodialysis patients, platelets play a crucial role in subsequent thrombus formation, leading to access failure. In a previous study, the mean platelet volume (MPV)/platelet count ratio, but not MPV alone, was shown to be an independent predictor of 4-year mortality after myocardial infarction. However, little is known about the potential influence of MPV/platelet count ratio on vascular access patency in hemodialysis patients.

Methods: A total of 143 patients undergoing routine hemodialysis were recruited between January 2013 and February 2016. Vascular access failure (VAF) was defined as thrombosis caused by stenosis after having undergone thrombectomy, or as greater than 50% stenosis on angiography requiring either surgical revision or percutaneous transluminal angioplasty. Platelet indices, including MPV/platelet count ratio and their changes were compared in patients with and without VAF by using linear mixed model analysis. Additionally, Cox proportional hazards model analysis ascertained that the change of MPV/platelet count ratio between baseline and 3 months [Δ(MPV/platelet count ratio)$_{3mo\text{-}baseline}$] had prognostic value for VAF.

Results: Of the 143 patients, 38 (26.6%) were diagnosed with VAF. During a median follow-up of 26.9 months, Δ(MPV/platelet count ratio)$_{3mo\text{-}baseline}$ significantly increased in patients with VAF compared to that in patients without VAF [6.7 (3.1–18.9) vs. 3.9 (-0.2–9.9), $P = 0.02$]. Moreover, a liner mixed model revealed that there was a significant difference in the increased MPV/platelet count ratio over the first 3 months in patients with VAF compared to those without VAF ($P = 0.003$). In multivariate analysis, Δ(MPV/platelet ratio count)$_{3mo\text{-}baseline}$ was an independent predictor of VAF (hazard ratio, 1.04; 95% confidence interval, 1.00–1.08; $P = 0.03$).

Conclusions: An increase in MPV/platelet count ratio was an independent risk factor for VAF. Therefore, continuous monitoring of the MPV/platelet count ratio may be useful to stratify the risk of VAF in patients undergoing routine hemodialysis.

SA-PO1042

The Effect of Vascular Access Type on the Variation of Intra-Access Flow Volume during Hemodialysis Younhee Lee, Hoon Suk Park. *The Catholic Univ of Korea, Seoul, Korea.*

Background: The current surveillance protocol for vascular access (VA) recommends intraaccess flow volume (Qac) should be measured within the first one and a half hours during hemodialysis (HD) to avoid errors. Several previous studies access resistance, which may cause Qac variation, was different among VA types. Therefore, we investigated Qac variation according to VA types.

Methods: Qac was measured at 30, 120, and 240 minutes in each HD session in 144 VA for comparison. 58 VA were lower arm arteriovenous fistula (AVF), 14 were lower arm arteriovenous graft (AVG), 27 were upper arm AVF and 45 were upper arm AVG. The other Qac (%) were expressed as the percentages of Qac at 30mins (100%). The variation of Qac over time was analyzed using repeated measures ANOVA.

Results: Repeated measures ANOVA revealed that the time factor significantly affected access flow ($p < 0.001$), which decreased over time. With regard to group effect, there was significant difference among Qac (%) by VA types ($p < 0.001$). Qac (%) of lower arm AVG at 240 minutes was 75.8 ± 11.3 whereas Qac (%) of upper arm AVF at 240 minutes was 99.5 ± 7.8. There also existed a significant interaction between the effects of time and VA type ($p < 0.001$) suggesting that VA type affected Qac variation during HD. Post hoc analysis revealed Qac variation during HD was significantly different in lower arm AVG.

Conclusions: Our study suggested that Qac of lower arm AVG should be measured according to the current surveillance protocol, but Qac of the other VA types, especially upper arm AVF one, can be measured at anytime during HD.

Funding: Clinical Revenue Support

SA-PO1043

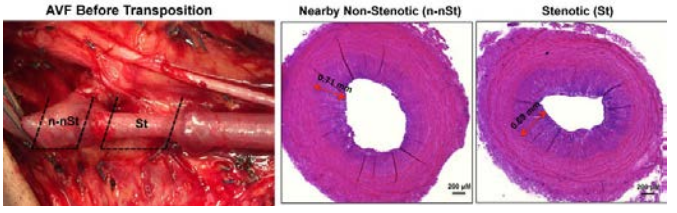
Intimal Hyperplasia Does Not Explain Focal Stenosis in Two-Stage Arteriovenous Fistulas Marwan Tabbara,[1] Laisel Martinez,[1] Juan Camilo Duque Ballesteros,[2] Angela Paez,[1] Guillermo Selman,[1] Loay H. Salman,[3] Roberto I. Vazquez-Padron.[1] *[1]DeWitt Daughtry Family Dept of Surgery, Leonard M. Miller School of Medicine, Univ of Miami, Miami, FL; [2]Dept of Medicine, Miller School of Medicine, Univ of Miami, Miami, FL; [3]Section of Interventional Nephrology, Miller School of Medicine, Univ of Miami, Miami, FL.*

Background: Intimal hyperplasia has been historically recognized as the cause of venous stenosis. Recently, we have revealed that IH is not associated with two-stage arteriovenous fistula (AVF) maturation failure. The purpose of this study is to compare the degree of IH in stenotic and nearby non-stenotic segments collected from the same AVF.

Methods: Focal areas of stenosis were detected in the operating room in seven patients (n=7) during the second stage basilic vein transposition procedure. The entire vein was inspected prior to the transposition and the areas of stenosis were visually located with the aid of manual palpation and hemodynamic changes in the vein peripheral and central to the narrowing. Close up photography was used for documentation before tissue collection (7 tissue pairs). Intimal area, thickness and intimal to media ratio were assessed in hematoxylin and eosin stained cross-sections, followed by pairwise statistical comparisons.

Results: The intimal area in stenotic and non-stenotic segments ranged from 1.25 to 5.57 mm^2 and 0.16 to 5.30 mm^2, respectively. There was no significant difference between these two groups (p=0.8). The intimal thickness (p=0.6) and intima/media area ratio were also similar between both segments (p=0.8).

Conclusions: Although a higher number of patients are needed to confirm these findings, our results concur with our previous study and suggest that IH does not explain focal venous stenosis in two-stage brachiobasilic fistulas.



Funding: NIDDK Support

SA-PO1044

Overexpression of Cathepsins in Arteriovenous Fistula Stenosis in Maintenance Hemodialysis Patients Shang Guo Piao,[1] Jian Jin,[2] Can Li.[1] *[1]Nephrology, YanBian Univ Hospital, YanJi, JiLin, China; [2]Nephrology, The Catholic Univ of Korea, Seoul, Korea.*

Background: Increasingevidence has demonstrated that cathepsins (Cats), a family of lysosomal cysteine proteases, play a critical role in various cardiovascular diseases. However, their role and expression in arteriovenous fistula (AVF) dysfunction are undetermined. The present study was undertaken to examine the expression of Cats and extracellular matrix (ECM) components in maintenance hemodialysis patients with AVF stenosis.

Methods: A total of 38 maintenance hemodialysis patients in YanBian University Hospital were enrolled. Of these, 18 subjects with AVF occlusion or severe stenosis served as AVF stenosis group, and 20 subjects with end-stage renal disease served as control group. Tissue samples were obtained from vein segments undergoing surgical AVF repair or creation. Basic parameters, histopathology, oxidative stress (MnSOD), and expression of Cats (K and S) and ECM components (PIA-1, TIMP-1, and βig-h3) were examined by immunohistochemistry and immunoblotting. In addition, the pearson-single-correlation coefficient analysis were used to compare Cats expressions withβig-h3 and MnSOD expression.

Results: Compared with the control group, serum CatK and CatS levels were increased in the AVF stenosis group. These increases in serum Cats levels were accompanied by upregulation of CatK and CatS protein expressions in the intima and medial layers of vein segments by approximately of 3-folds and 2.5-folds. In parallel, expression of TIMP, PAI-1 and βig-h3 was significantly increased in the AVF stenosis group compared with the AVF control group. Immunoblotting of oxidative stress biomarker revealed that MnSOD protein expression was enhanced in the AVF stenosis group. The upregulation of Cats expression was positively correlated with βig-h3 and MnSOD ($r=0.69$, $r=0.57$; $r=0.61$; $P<0.01$).

Conclusions: Our observations indicate that an increase in Cats expression, along with ECM components upregulation, is closely associated with AVF stenosis in maintenance hemodialysis patients.

Funding: Other NIH Support - National Natural Science Foundation of China, Other U.S. Government Support, Government Support - Non-U.S.

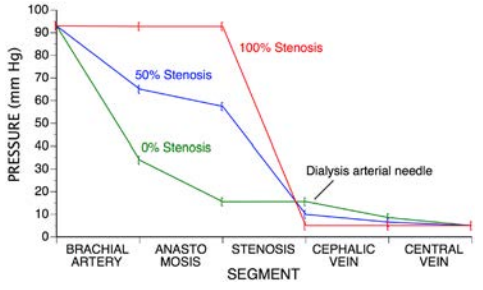
SA-PO1045

Stenosis at Arteriovenous Anastomosis of Fistula: A Challenge for Dialysis Pressure Surveillance William D. Paulson,[1] Kim Hirschman,[2] Sulav Bastola,[3] John Jason White,[1] Steven A. Jones.[4] *[1]Medicine, Augusta Univ, Augusta, GA; [2]Vasc-Alert LLC, Lafayette, IN; [3]Charu Polyclinic and Diagnostic Center, Kathmandu, Nepal; [4]Biomedical Engineering, Louisiana Tech Univ, Ruston, LA.*

Background: Dialysis pressure surveillance is widely recommended for detection of stenosis in vascular accesses. However, the native fistula (AVF) is problematic in that dialysis needles are downstream to the arteriovenous (AV) anastomosis, where stenosis often develops. We used a mathematical model of the brachiocephalic AVF and clinical dialysis arterial pressures to determine the limitations in detecting AV anastomosis stenosis.

Methods: The model used engineering equations to determine influence of stenosis at the AV anastomosis on dialysis arterial pressure. The model included cephalic V. anastomosed end to side to brachial A., radial & ulnar A., palmar arch, and vein that drains the hand and connects to cephalic V. Mean arterial pressure = 93 mmHg, central venous pressure = 5 mmHg. Luminal diameter of inflow artery was less than outflow vein (0.6 vs. 0.8 cm). We used data from 49 patients with trouble-free AVFs in the Vasc-Alert on-line surveillance program to determine variability of arterial needle pressures with blood pump running.

Results: Model predicts AVF pressures at stenosis = 0%, 50%, 100% are 15.7, 10.0, 5.0 mmHg, respectively. Thus, stenosis causes only small pressure changes. The SD for differences in pressure between 2 measurements with similar blood pump speed = 14.1 mmHg, so that change in pressure must be >28.3 mmHg to be significant at P <0.05.



Conclusions: Stenosis at the AV anastomosis causes a decrease in pressure that may be too small to detect when the dialysis pump is running. Static pressure measurements or on-line surveillance programs that apply trend analysis and adjust for the effect of blood pump speed on pressure may compensate for this problem.

Funding: Clinical Revenue Support

SA-PO1046

Treatment of Arteriovenous Fistula Complications Using Far Infrared Therapy: Cambridge Experience Regin Lagaac,[1] Nicholas Pritchard.[2] *[1]Renal Medicine, Cambridge Univ Hospitals NHS FT, Cambridge, United Kingdom; [2]Renal Medicine, Cambridge Univ Hospitals NHS FT, Cambridge, United Kingdom.*

Background: It is vital that Arterio Venous Fistulas (AVF) will continue to function efficiently. Complications of AVF includes pain of the AVF site, bruises and infiltration, underdeveloped AVF with weak thrill and bruit due to small calibre of veins, calcified arteries with reduced blood flow leading to thrombosis. There are limited treatment options for patients presenting with these problems. Increasing evidence shows that far infrared radiation has beneficial effects on tissue healing and endothelial function, this has led to its use in the treatment of skin necrosis and wound healing. The application of Far Infrared therapy to AVFs in HD patients has been studied as a way to improve fistula blood flow, thereby reducing complications of fistula thrombosis and improving dialysis clearance and adequacy.

Methods: A protocol has been developed by the Cambridge renal team to decide which patient will undergo the FIR treatment: It should be used for patients with the following characteristics: just undergone AVF surgery, with a maturing AVF, with steal syndrome, with low access blood flow, showing early signs of stenosis, and AVF bruises due to infiltration from previous cannulation. FIR therapy is a 40 minutes applications during each haemodialysis session for 4 to 6 weeks. Discontinuation of the treatment based on clinical discretion.

Results: 22 patients received FIR therapy. In summary, 6 patients had an improvement of pain score on needling of AVF, 14 patients AVF needle-site haematomas resolved quicker and 2 AVFs matured with demonstrably better blood flow rates on doppler.

	Number of patients
Improvement of AVF pain score	6
Haematomas resolved quicker	14
Better blood flow rates	2

Conclusions: We have found FIR therapy to be of use in the maturation of AVFs, particularly in patients with challenging access, as well as in the treatment of problems such as haematoma formation and those experiencing AVF pain during HD. It is a safe and effective treatment modality that has been shown to reduce complications and improve the efficiency of AVFs through its direct anti-inflammatory properties.

SA-PO1047

Statin Treatment Improves Vascular Access Outcome among Diabetic Hemodialysis Patients Manabu Kanda, Satoru Sanada, Yasunori Miyasaka, Atsuhiro Kanno, Kozo Sato, Mitsuhiro Sato, Yoshio Taguma, Toshinobu Sato. *Dept of Nephrology, Japan Community Health Care Organization Sendai Hospital, Sendai, Miyagi, Japan.*

Background: An effective therapeutic approach to reduce the risk of hemodialysis vascular access dysfunction is still unclear despite previous studies. Prior research has shown conflicting results of statin treatment probably because the pathogenesis of vascular access dysfunction is multifactorial and some confounding factors such as underlying causes of end-stage kidney diseases or type of vascular access could influence the results. In this study, we focused on diabetic hemodialysis patients and evaluated the impact of statin treatment on vascular access patency.

Methods: A retrospective cohort study of 243 consecutive patients who newly started hemodialysis due to diabetic nephropathy between January 2011 and December 2013 at Japan Community Health Care Organization Sendai Hospital was performed and the patients were followed for two years. The primary outcome was vascular access dysfunction. Effect of statin treatment was examined using Kaplan Meier analysis and Cox proportional hazard, after adjusting for covariates.

Results: The mean follow-up period was 426.7 days, and 131 (53.9%) patients developed vascular access dysfunction. Vascular access survival was significantly longer among statin users (547.9±29.9 versus 430.6±21.2 days, log-rank: P =0.008). The two-year patency rate was 58.7% among statin users and 38.6% in non-users. In multivariable analysis, statin treatment is significantly associated with better vascular access outcomes, in which the hazard ratio was 0.73 (95%CI, 0.54 to 0.97; P=0.03) in the unadjusted model and 0.63 (95%CI, 0.46 to 0.87; P =0.004) after adjustment for covariates.

Conclusions: The present study provided better vascular access outcomes among statin users in diabetic hemodialysis patients, which was only performed with diabetic hemodialysis patients. Native radiocephalic arteriovenous fistula was mainly used as a vascular access. This could account for the difference between our results and those of previous studies.

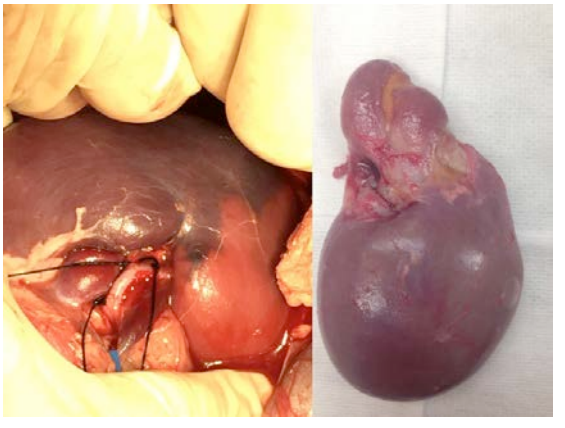
SA-PO1048

Creation of a Pig Model of Chronic Renal Insufficiency Diego Celdran-Bonafonte,[1] Begoña Campos,[2] Aous Jarrouj,[1] Sanjay Misra,[3] Matthew Kurian,[2] Sukit Raksasuk,[1] Prabir Roy-Chaudhury.[1] *[1]Univ of Arizona; [2]Univ of Cincinnati; [3]Mayo Clinic.*

Background: Uremia is an important contributor to the huge increase in the incidence of cardiovascular morbidity and mortality in CKD and ESRD patients; as a result of inflammation, oxidative stress and endothelial dysfunction. Despite this, we do not at the present time, have a reliable large animal model that replicates the uremic milieu. The objective of the current study was to develop a pig model of uremia with a GFR between 15-30 ml/min.

Methods: 4 Yorkshire pigs were used in this study. Renal insufficiency was induced through a total nephrectomy of the right kidney followed by selective ligation of the vascular supply of the contralateral kidney under direct vision. 2 animals were left with 15% remnant renal mass (caudal pole of the left kidney was left perfused), while the other two animals were left with 7% remnant renal mass (ventral aspect of the mid hilum was left perfused). Blood samples were collected sequentially over a 42 day period for BUN and creatinine. Samples were stored for future measurement of inflammatory markers and also for genomic, proteomic and metabolic analyses.

Results: Animals with 15% of remnant renal mass (left panel in Figure 1) had an initial increase in the creatinine to 4-5mg/dL followed by a stabilization at 1-2mg/dL by 2 weeks. In contrast, animals with only 7% of remnant renal mass had an initial increase in creatinine to greater than 8mg/dL followed by a stabilization between 3-4 mg/dL by 2 weeks. A macroscopic post mortem evaluation of the animal with the caudal pole left unligated demonstrated significant hypertrophy of this region with ischemic necrosis of the upper pole (right panel in Figure 1).



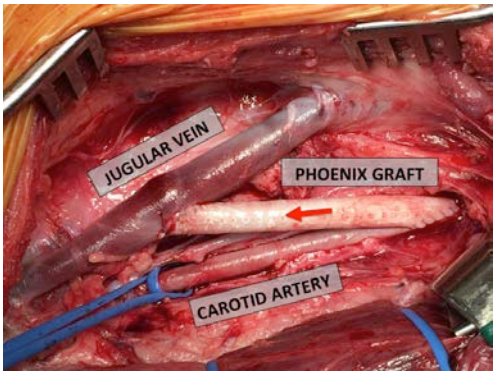
Conclusions: Our data describe the development of a reproducible large animal model of uremia (7% remnant renal mass) that could be used for mechanistic and therapeutic investigation.

SA-PO1049

Cellular Integration and Early Cannulation Potential in a Bioengineered Arteriovenous Vascular Access (Phoenix) Diego Celdran-Bonafonte,[1] Chelsea Elizabeth Stowell,[3] Begoña Campos,[2] Aous Jarrouj,[1] Sukit Raksasuk,[1] Peter L. Jernigan,[2] Yadong Wang,[3] Prabir Roy-Chaudhury.[1] *[1]Univ of Arizona; [2]Univ of Cincinnati; [3]Mayo Clinic.*

Background: Hemodialysis vascular access dysfunction continues to be the Achilles heel of hemodialysis. The objective of our study was to develop a bioengineered scaffold (the Phoenix), which when placed *in-situ* would allow for both early cannulation *and* rapid cellular integration.

Methods: Porous vascular graft cores were electrospun from a blend of polyglycerol sebacate (PGS) prepolymer and polyvinyl alcohol (PVA). Cores were reinforced with polycaprolactone (PCL) and a non-porous synthetic sealant layer. Phoenix grafts of varying sizes were surgically placed between the carotid artery and jugular vein in four Yorkshire Cross pigs.



Results: Reinforcement significantly improved structural tensile strength and suture retention load. Ultrasound examination documented flow and patency until sacrifice at 2 weeks. Movat staining revealed an active cellular repopulation of the scaffold (progressing radially outward from the lumen upto 2/3 of the wall thickness) with muscle cells and ECM deposition. Endothelial (CD31 positive), and possible intimal and medial layers were identified. No such repopulation was evident in a contralateral PTFE graft. Successful cannulation of the Phoenix was performed *in-vivo,* and *ex-vivo* attempts at cannulation revealed rapid closure of the needle site.

Conclusions: Our results indicate that the Phoenix appears to combine the autogenous benefits (note active host cell repopulation of the scaffold) of an AVF, with the early cannulation benefits (downstream reduction of catheter complications) of an AVG. Patency studies are currently in progress but these initial data suggest that the Phoenix could significantly reduce the morbidity and mortality currently associated with dialysis vascular access dysfunction.

Funding: Other NIH Support - NIH/NCATS

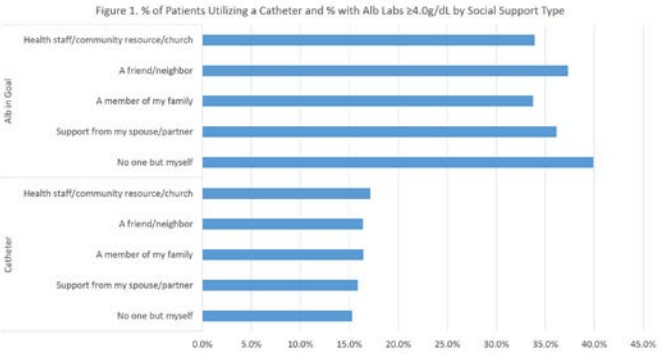
SA-PO1050

Impact of Social Support Types on Nutritional Status and Catheter Utilization in Hemodialysis Patients John W. Larkin, Yue Jiao, Marta Reviriego-Mendoza, Dugan Maddux, Joy R. Lutz-Mizar, Stephanie Johnstone, Len A. Usvyat, Franklin W. Maddux. *Fresenius Medical Care North America.*

Background: The associations between outcomes and the type of social support dialysis patients (Pts) receive from family, friends, or caregivers have not been widely studied. We aimed to investigate whether social support types in hemodialysis (HD) Pts are associated with nutritional status. Also, we studied catheter utilization, since it was hypothesized that stronger family support may help patients have a permanent access placed.

Methods: We analyzed data from Jan 2014 to Dec 2015 on 168,688 Pts at Fresenius Medical Care North America who completed a social work questionnaire. We captured responses to the question "when you have a big problem, can you usually rely on?", which has choices for support types of: "no one but myself", "support from my spouse/partner", "a member of my family", "a friend/neighbor", or "health staff/community resource/church". We compared support types to the proportion (%) of Pts achieving mean albumin (Alb)≥4.0g/dL and the % of Pts with a catheter during the 6 month period prior to completing the questionnaire.

Results: We observed that Pts who received social support from no-one or a friend/neighbor were found to have a higher % of Pts with an Alb ≥4.0g/dL, as compared to others. Those who received support from no-one had the lowest % of Pts with a catheter (Figure 1).



Conclusions: The findings indicate the social support type that Pts receive may have a small impact on their nutritional status and use of catheters. Although we found that support from no-one was associated with the most Pts meeting Alb≥4.0g/dL and least Pts utilizing catheters, these observations could potentially be representing a healthier or younger sub-population. Further analyses are needed controlling for differences in demographic and clinical parameters.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

SA-PO1051

Epidemiology of Dialysis Catheter-Associated Bloodstream Infections in an Emergent Dialysis Cohort Hal Zhang,[3] Maulin Shah,[1] Nicolas Cortes-Penfield,[2] Jingbo Niu,[1] Eric Wu,[3] Roya Zamani,[3] Daniel Chen,[3] Sreedhar A. Mandayam.[1] *[1]Nephrology, Baylor College of Medicine, Houston, TX; [2]Infectious Disease, Baylor College of Medicine, Houston, TX; [3]Internal Medicine, Baylor College of Medicine, Houston, TX.*

Background: Dialysis catheter-related bloodstream infections (CRBSIs) cause significant morbidity and mortality in end-stage renal disease (ESRD) patients. Harris Health in Houston provides dialysis to hundreds of undocumented immigrants on an emergent basis and is often unable to support fistulas, leaving these patients chronically dependent on tunneled dialysis catheters. The epidemiology of CRBSI in this population has not been described until now.

Methods: We performed a retrospective chart review of all ESRD patients who receive hemodialysis solely on an emergent basis through Harris Health System in Houston, Texas between 1/1/2012 and 12/31/2015. We recorded patient demographics, comorbidities, and all CRBSIs that occurred during the study period. We defined CRBSI as a positive blood or catheter tip culture and treated as catheter-related infection by the treatment team. We assessed the association between potential risk factors and the number of CRBSIs using negative binomial regression. The magnitude of the association for risk factors significantly related to CRBSIs in the crude model were assessed in a multivariate model adjusting for each other.

Results: Of the total 342 ESRD patients, 78 patients had 120 CRBSIs. The infection rate was about 1/1000 catheter days. 23 patients had multiple CRBSIs and there were 17 recurrent infections (recurrence rate 16.5%). The risk of CRBSIs was 1.7 (95% CI: 0.7, 3.9), 2.8 (95% CI: 1.2, 6.4), 1.8 (95% CI: 0.7, 4.7) and 0.5 (95% CI: 0.2, 1.7) among patients with age 40-49, 50-59, 60-69 and 70 years older compared with patients younger than 40 years. Patients with hemodialysis frequency≥6 sessions per month had 2.3 (95% CI: 1.0, 5.6) times higher risk of CRBSI than those with frequency≤3.

Conclusions: In our cohort of emergent HD patients, CRBSI was less frequent than the CDC national average and is more frequent in the 50-59 age group and in patients receiving more frequent dialysis.

SA-PO1052

Hemodialysis Infection Prevention Using Polysporin Ointment with Shower Technique in Satellite Centres (HIPPO-SAT): A Pilot Randomized Control Trial Sarah Daisy Kosa,[1,2] Amiram Gafni,[2] Gabrielle Ene,[1] Andrew A. House,[3] Julieann L. Lawrence,[3] Louise M. Moist,[3] Paul Y. Tam,[5] Lehana Thabane,[2] George G. Wu,[6] Charmaine E. Lok.[1,2] *[1]Toronto General Hospital; [2]McMaster Univ; [3]London Health Sciences Centre; [4]Mackenzie Health Hospital; [5]The Scarborough Hospital, Scarborough, ON, Canada; [6]Credit Valley Hospital.*

Background: We developed the Toronto Hemodialysis Catheter Shower Technique protocol (STP) to permit HD patients with catheters to shower without increase infection risk. The study objective was to determine the feasibility of conducting a definitive parallel randomized controlled trial (RCT) called HIPPO-SAT that will evaluate the impact of STP on catheter-related bacteremia (CRB) in adult satellite HD patients.

Methods: Adult HD patients using catheters were recruited from 3 in-centre and 8 satellite HD units, randomized to receive STP or standard care, and followed for 6 months (Registration:NCT02002169). The primary outcome of study feasibility was based on 5 outcome measures, each with its own statistical threshold for success (threshold), of which 4 must be achieved for HIPPO-SAT to be deemed feasible. Secondary exploratory outcomes included CRB rates and patient-reported satisfaction with their vascular access care.

Results: 68 patients were randomized (33 in STP group) and 4/5 feasibility measures of feasibility were achieved: 1) accurate CRB rate documented (threshold: kappa level

>0.80), 2) 97.8% (279/285) of satellite patients with catheters screened (threshold: >95%), 3) 88% (23/26) in the STP arm successfully educated by 6 months (threshold: >80%), and 4) 0% (0/29) patients in the control arm using STP (threshold: <5%). However, only 44.2% (72/163) of eligible patient consented to participate (threshold: >80%). The rate of CRB was similarly excellent in STP and control groups (0.68 vs. 0.88/1000 CVC-days), and patients showed high levels of satisfaction in both groups.

Conclusions: This HIPPO SAT pilot study demonstrated feasibility of the larger HIPPO SAT study, especially due to the high levels of education success with the STP arm, and low levels of STP use in the control arm.

Funding: Private Foundation Support

SA-PO1053

Prevention of Hemodialysis Catheter-Associated Bloodstream Infection: A Single Center Experience Yo Komatsuzaki, Izumi Yamamoto, Mayuko Kawabe, Ai Katsuma, Yasuyuki Nakada, Taketo Uchiyama, Yukio Maruyama, Yudo Tanno, Ichiro Ohkido, Nobuo Tsuboi, Keitaro Yokoyama, Takashi Yokoo, Nanae Matsuo. *Dept of Internal Medicine, Div of Nephrology and Hypertension, The Jikei Univ School of Medicine, Tokyo, Japan.*

Background: Central-line-associated bloodstream infection (CLABSI) is a dangerous health care-associated infection that increases hospital costs and length of stay. Several reports have shown that using a multidisciplinary team and "prevention bundles(PB)" approach, which includes staff education, hand hygiene, the use of maximum sterile barrier precautions, the use of chlorhexidine gluconate (CHG), and catheter checklists, has markedly reduced the infection rate. However, there are limited data on CLABSI in dialysis access. This study investigated the efficacy of PB in patients using dialysis access in our dialysis center.

Methods: We retrospectively evaluated the incidence of CLABSI before (October 2012 to March 2013) and after (April 2013 to April 2015) the intervention PB were adopted for patients with dialysis access using the formulae of the Dialysis-related Infections Surveillance Research Consortium (DRISRC) in Japan: [infection cases/dialysis session×1000]. The PB included hand hygiene, maximum sterile barrier precautions, the use of 1% CHG, avoiding the femoral vein, and checklists for dialysis access. The checklist for dialysis access included the date and place of insertion, type of catheter (short- or long-term), reason for insertion and withdrawal, and appearance of the insertion site. We then checked the compliance status and obtained feedback from staff members.

Results: Overall, four patients developed CLABSI in the 6 months before adopting the PB versus only two cases per year after the intervention. The incidence of CLABSI in dialysis access before intervention was 6.97 (4/575×1000), which was comparable with the value of 6.96 from DRISRC in Japan. After the intervention, the incidence decreased to 3.19 (2/626×1000), 2.52 (2/793×1000), and 3.3 (2/606×1000) in 2013, 2014, and 2015, respectively.

Conclusions: PB effectively reduced CLABSI in dialysis access. Checking the compliance with technique and methods, and feedback from staff are important for maintaining the PB system.

SA-PO1054

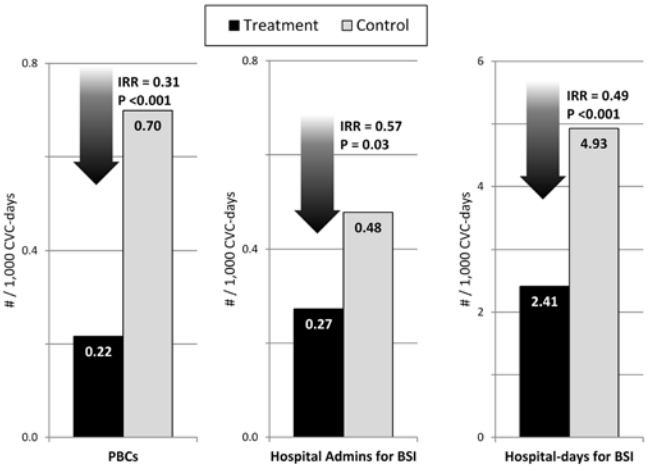
A Novel Device for Reducing Catheter-Related Bloodstream Infections: A Multi-Center, Controlled, Randomized Clinical Trial of the ClearGuard HD Antimicrobial Barrier Cap Jeffrey L. Hymes,[1] Ann Mooney,[2] Carly R. Van Zandt,[2] Laurie Lynch,[3] Robert Ziebol,[3] Douglas Killion.[3] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Frenova Renal Research, Waltham, MA; [3]Pursuit Vascular, Inc., Maple Grove, MN.*

Background: Bloodstream infections (BSIs) have been a significant problem for hemodialysis catheter patients for decades, leading to poorer outcomes such as death and hospitalization, and increased cost to the healthcare system. This clinical trial studied use of antimicrobial central venous catheter (CVC) caps intended to prevent BSI.

Methods: 12-month, prospective, cluster-randomized, multi-center, pragmatic, open label clinical trial conducted at 40 Fresenius Medical Care North America dialysis facilities. We matched facilities by positive blood culture (PBC) rate and number of CVC patients. Patients were randomized in a 1:1 ratio to use ClearGuard HD Antimicrobial Barrier Caps® or standard CVC caps. 2,470 patients participated in the study, accruing approximately 350,000 CVC-days. The primary endpoint was PBC rate as an indicator of BSI rate. PBCs, hospital admissions for BSI, hospitalization-days for BSI, IV antibiotic starts, and CVC-days were measured.

Results: The treatment and control groups were well matched. Use of ClearGuard HD CVC caps was associated with a 55% reduction in PBC rate compared to standard CVC caps during the 12-month study (0.27 vs. 0.60/1,000 CVC-days, P<0.001). Sustained use of ClearGuard HD CVC caps (last 6 months of study) demonstrated a 69% reduction in PBC rate (0.22 vs. 0.70/1,000 CVC-days, P<0.001), a 43% reduction in hospital admissions for BSI (0.27 vs. 0.48/1,000 CVC-days, P=0.03), and a 51% reduction in hospitalization-days for BSI (2.41 vs. 4.93/1,000 CVC-days, P<0.001). No device-related adverse events were reported.

Conclusions: Use of ClearGuard HD Antimicrobial Barrier Caps significantly reduced BSIs, hospital admissions for BSI, and hospitalization-days for BSI.



Funding: Pharmaceutical Company Support - Pursuit Vascular

SA-PO1055

A New Dialysis Catheter Dressing (Cath Dry) Significantly Reduces Catheter Infections Omaran Abdeen,[1] Alexander J. Martos.[2] *[1]Kidney Consultants Medical Group, Inc., Kidney Consultants Medical Group, Inc., Mission Hills, CA; [2]Dept of Public Health, Columbia Univ Mailman School of Public Health, New York, NY.*

Background: Dialysis catheter infections are a significant cause of morbidity/mortality and adversely impacts quality of life. We evaluated the use of a novel, water resistant, and breathable dialysis catheter dressing, Cath Dry.[figure1]

Methods: Participants were recruited from a dialysis center in Mission Hills, CA. The dressing was applied to enrolled participants (n=45) via sterile technique by dialysis nurses. Participants were instructed to not remove the dressing and advised to shower without restriction. All participants completed a quality of life survey before and after the study. Data on infections were collected during the study period.

Results: Participants were enrolled for 3 months, for a collective study period of 139 catheter-months. The expected infection rate for our population was approximately 3 episodes (based on National Healthcare Safety Network (NHSN) 2014 data of 2.16 infections per 100 catheter-months). During the study, we observed ***no*** catheter related infections. We compared our rate of zero infections to the 2014 NHSN infection rate using a one-sided exact test based on the binomial distribution. Our infection rate was significantly less than the NHSN rate (p = 0.0449). Quality of life survey results showed 78% of patients felt their catheter was not clean/protected prior to the study whereas 100% of patients felt their catheters were clean/protected during the study. Similarly, 68% of participants felt their inability to shower adversely affected their quality of life. At the end of the study 100% of participants felt that Cath Dry improved their dialysis experience.

Conclusions: Cath Dry, a water resistant and breathable dialysis catheter dressing significantly reduced infections in our participants when compared to 2014 NHSN infection rates. Use of Cath Dry contributed positively to the quality of life, dialysis experience and hygiene of our participants.

Funding: Pharmaceutical Company Support - CathDry, Inc.

SA-PO1056

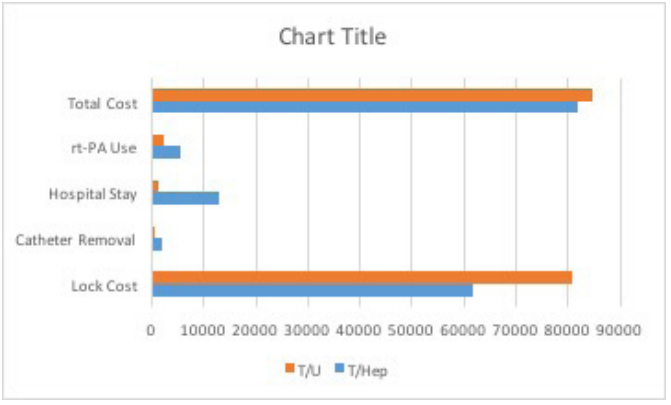
Randomized Controlled Trial of Taurolidine Citrate versus Taurolidine Urokinase Lock to Prevent Tunneled Catheter Thrombosis in Hemodialysis Patients: Cost Analysis and Effectiveness Study Abdullah Hamad, Rania Abdelaziz Ibrahim, Ashraf A.F. Ibrahim, Fadwa S. Al-Ali. *Nephrology, Hamad General Hospital, Doha, Qatar.*

Background: Catheter malfunction is a frequent complication and responsible for most of catheter removals. In a recent trial, we found benefit of using Taurolidine citrate with Urokinase (T/U) versus Taurolidine Citrate with Heparin (T/Hep) in decreasing catheter thrombosis and infection. We are presenting a cost effectiveness analysis of the trial.

Methods: In a prospective randomized controlled trial in Qatar. HD patients received T/Hep or T/U catheter locks and followed for 6 months. We analyzed incremental cost. Cost was calculated based on actual purchasing price for our hospital for T/Hep, T/U and rt-PA. Hospitalization and procedure costs estimated from hospital billing department.

Results: There were 93 patients in T/Hep and 84 in the T/U. Total 7 catheters were removed in T/Hep versus 1 only in T/U. Rt-PA use was lower in T/U than T/Hep. Cost for T/U lock was significantly higher than T/Hep (80800 US$ versus 61700 US$ pValue < 0.05). Cost difference was eliminated when adding additional costs of hospitalizations, catheter removal procedure and rt-PA (total cost was 82000 US$ in T/Hep versus 84720 US$ in T/U, p Value 0.9 NS). Detailed cost analysis shown in Table 1/Figure 1.

	Taurolock/Hep (#unit)	Cost (US dollars)	Taurolock/U (#unit)	Cost (US dollars)
catheter lock	4491	61700	4386	80800
catheter removal	7	2000	1	300
hospital length of stay	47 days	13000	5 days	1370
rt-PA use	118 times	5300	50 times	2250
Total	N/A	82000	N/A	84720



Conclusions: In a comparison trial where we found clinical benefit for T/U with less need for rt-PA and catheter removal compared to T/Hep, cost analysis confirmed cost effectiveness in T/U (although it is higher cost) after adding the saving of less hospitalization, less rt-PA use and catheter removal cost.

Funding: Government Support - Non-U.S.

SA-PO1057

Use of Taurolidine Citrate with Urokinase Lock for Dialysis Catheter Malfunction: A Prospective Pilot Study Mohamed Yahya Mohamed, Abdullah Hamad, Hicham Bouanane, Hoda Tolba, Ramshad Netoth Kuniyil, Mohammed Ezzat Mohammed, Aisha Abdulla, Fadwa S. Al-Ali. *Nephrology, Hamad General Hospital, Doha, Qatar.*

Background: Thrombolytics are used to treat hemodialysis (HD) catheter malfunction. Blood flow rate (BFR) during dialysis is a surrogate outcome and an established marker of catheter malfunction. We are presenting a prospective pilot study to introduce Taurolidine-urokinase-U25.000 (T/U) catheter lock in regard to improving catheter malfunction.

Methods: All HD patients in the 2 largest outpatient facilities in Qatar (460 patients) were evaluated. Patients were included if they have permanent dialysis catheter with poor BFR (mean of less than 250 ml/min for 6 weeks prior to inclusion in study) (phase 0). We have 2 phases. Phase 0 was observation for 6 weeks with our current practice followed by phase 1 where patients were started on T/U catheter lock every session for 6 weeks. BFR in HD sessions and need for recombinant tissue plasminogen activator (rt-PA) treatment for acute nonfunctioning catheters were monitored in both phases.

Results: 25 HD patients included in the study (14 Males and 11 females). Baseline catheter locks (phase 0) were heparin 5000 unit/mL (11 patients), heparin 5000 unit/mL with rt-PA lock on weekend session (10 patients) and 4 patients on Taurolodine with Heparine 500 units. Mean BFR was significantly higher in phase (1) with T/U (252+/-36 ml/min) compared to phase (0) lock solutions (198+/-23) (pValue 0.0001 95% CI of this difference: From -65 to -40). Rt-PA treatment needed for acute catheter malfunction was significantly less in T/U (phase1) versus other locks (phase 0) (0.7 +/- 1.4 versus 3.2+/-3.1 pValue 0.0007, 95% CI 1.12 to 3.92). Sixteen patients (64%) achieved BFR > 250 ml/min after applying T/U while 3 patients only (12%) showed no improvement in BFR. One patient expired due to congestive heart failure complications 3 weeks into the study. No adverse events reported during study period. Cost analysis comparison was 12700 (T/U) versus 6900 US dollars (baseline locks).

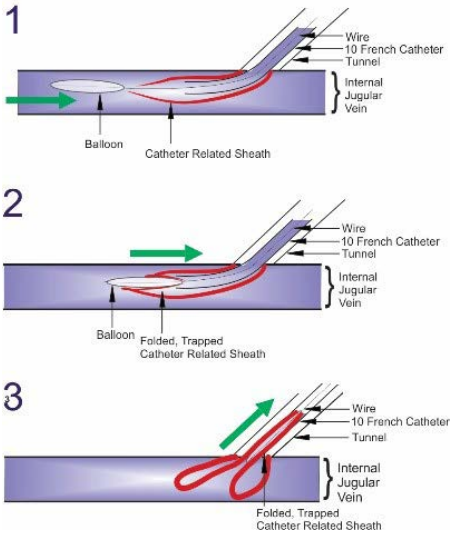
Conclusions: In a pilot study to introduce T/U catheter lock, we found significant improvement in BFR, decrease in need for rt-PA and most patients achieved BFR above 250 ml/min but with 84% increase in cost.

SA-PO1058

A Novel Technique for Catheter-Related Sheath Removal Grant Meltzer,[1,2] Adam S. Przebinda,[1,2] Zahid Bashir Ahmad.[1,2] *[1]Dept of Nephrology, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK; [2]Dept of Nephrology, Veterans Affairs Hospital, Oklahoma City, OK.*

Background: Catheter-related sheaths (CRS) are sock-like structures composed of inflammatory cells and connective tissues which form on the outside of indwelling central venous catheters (CVC), as a thrombogenic response. CRS, also known as fibrin sheaths or sleeves can inhibit tunneled dialysis catheter function through obstruction of the side ports or catheter tip.

Methods:



Step 1: Angiogram estimates terminal position of CRS. Balloon is deployed beyond this point and partially retracted

Step 2: CRS is folded and trapped against the 10 French catheter

Step 3: Balloon and sheath are withdrawn.

Results: Current techniques to salvage affected catheters include thrombolytic agents and/or stripping procedures. However, standard care at most centers is catheter exchange with balloon disruption of the CRS. Disruption of the CRS, though generally well tolerated, raises concern for potential complications, notably pulmonary embolism of CRS fragments.

Conclusions: We report a new technique which retrieves the CRS, thereby eliminating the risk for pulmonary embolism.

Funding: VA Support

SA-PO1059

Outcomes after Stent Graft Placement for Cephalic Arch Stenosis – Effect of Access Flows and Cephalic Arch Angle Florian E. Toegel,[1] Patrick McGlynn,[1] Prakrati C. Acharya,[2] Adina Simona Voiculescu,[1] Dirk M. Hentschel.[1] *[1]Nephrology, Brigham and Women's Hospital, Boston, MA; [2]Medicine, Mount Auburn Hospital, Cambridge.*

Background: Cephalic arch stenosis (CAS) is a common complication of brachial-cephalic autogenous accesses and limits access survival. Treatment with angioplasty (PTA) is complicated by high recurrence rates. Covered stent placement is widely practiced but outcomes data are limited. We report the long-term outcome after CAS stent graft placement in relation to access flows and cephalic arch angle.

Methods: Retrospective chart review of patients undergoing PTA and stent graft placement between 2008-2013.

Results: 50 patients underwent placement of stent grafts for CAS after failure of PTA due to recoil and clinical symptoms < 90 days, or rupture during any PTA. Time from fistula creation to first procedure in the cephalic arch averaged 564 days. Progression from first angioplasty for CAS to stent graft placement averaged 342 days (range 23-1369) and follow up after stent graft placement was on average 2.7 years (1001 days). An average number of 1.5 stents was placed per cephalic arch. The acuteness of the cephalic arch angle was neither associated with time to first intervention nor with recurrence of stenosis after initial angioplasty, but a more acute angle was associated with a higher number of procedures after stent placement. Time between interventions before stent graft progressively declined from 131 days to 85 days and decline was faster with higher access flows. After stent placement time between procedures significantly increased to 379 days, 187 days and 307 days (1st, 2nd and 3rd procedure) and procedure frequency significantly declined to an average of 0.97 procedures per year. Higher flow accesses had a longer intervention-free interval after stent placement (440 days flow >1400 ml/min, 247 days flow 800-1400ml/min, 174 days flow < 800 ml/min).

Conclusions: Stent graft placement extents the procedure free interval, extending access life. Higher flow accesses benefited proportionally more from stent graft placement compared to lower flow accesses. The acuteness of the cephalic arch angle is associated with a higher number of procedures after stent graft placement.

SA-PO1060

Blood Flow Velocity Predicts Cephalic Arch Stenosis in Patients with Brachiocephalic Fistula Access Mary S. Hammes, Sydeaka Watson, Alkesh A. Amin, Brian Funaki. *Univ of Chicago.*

Background: The lower arm radiocephalic fistula (RCF) is the first access recommended for patients with ESRD on hemodialysis; however, there is a high failure rate compared to other arteriovenous fistula (AVF) configurations. An upper arm brachiocephalic fistula (BCF) is the next recommended access to be placed, but these most commonly fail owing to cephalic arch stenosis (CAS). Patients with BCF are 37 times more likely to develop

CAS than those with RCF. Our hypothesis is that the high incidence of CAS in patients with BCF is due to an unphysiologic high flow state that worsens over time after AVF placement. The aim of the current study was to examine the relationship between time to CAS (from surgical creation) and blood flow velocity (BFV) measured over time. A secondary aim was to examine the relationship between demographic variables that may predict CAS.

Methods: Thirty-seven patients with a primary BCF were included in the analysis. A venogram of the cephalic arch and venous Doppler was done at time of BCF maturation, and annually up to the time of CAS or 36 months. BFV was measured 10 cm proximal to the cephalic arch over several heart cycles and the average calculated. A joint model for longitudinal and survival data was used to determine variables associated with BFV trends or time to CAS. A bivariate analysis was performed to determine the association between variables and BFV trends or time to CAS.

Results: Using a joint longitudinal and survival model, BFV was predictive of CAS when adjusted for BMI, coronary artery disease (CAD), diabetes, and gender ($p < 0.001$). Using a longitudinal model fit for each variable (gender, age, ethnicity, BMI, CAD or diabetes), CAD was the only significant predictor of high BFV ($p = 0.008$).

Conclusions: There is a relationship between BVF and the development of CAS over time.As an AVF ages, increased flow within the artery and vein induces dilatation resulting in gradual reduction in resistance. The high flow circuit in BCF leads to altered hemodynamics causing pathological accelerated access growth including aneurisms, cardiac overload and as we have shown in this analysis, CAS. Efforts to decrease high flow in an AVF are needed to prevent these adverse complications.

Funding: NIDDK Support, Other NIH Support - National Institute of Diabetes and Digestive Diseases (NIDDK) and the National Institutes of Health (NIH) under award number RO1DK090769

SA-PO1061

Impact of Banding Procedure and Factors Associated with Cephalic Arch Stenosis in Brachiocephalic Fistulae Yaeni Kim, Ji Hyun Yu, Byung Ha Chung, Bumsoon Choi, Cheol Whee Park, Chul Woo Yang, Yong-Soo Kim. *Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Republic of Korea.*

Background: Cephalic arch stenosis (CAS) is the most common stenosis in brachiocephalic fistula (BCF). Recurrent stenosis and unacceptable primary patency rate after percutaneous transluminal angioplasty (PTA) often occur in CAS. We aimed to evaluate the patency rate of CAS in dysfunctional BCF and to identify factors that may affect their patency rate and the impact of banding procedure.

Methods: Out of 374 angiography in 178 patients with dysfunctional BCF from 2010 to 2015 in our center, 234 angiography in 86 patients revealed CAS. PTA was the first choice of management. Cutting balloon angioplasty was performed when resistant to high pressure PTA. Endovascular banding (MILLER) was done in cases of recurrent CAS (>3 times) with high access flow (>1.5 L/min). Kaplan–Meier method was employed to evaluate patency rates.

Results: Primary, primary assisted, and secondary patency rates of CAS were 60.9%, 96.3%, and 94.1% at 3 months and were 52.1%, 95%, and 91.3% at 6 month and were 33.4%, 86.9%, and 88% at 1 year, respectively. Number of PTAs less than or equal to 1.65 per access-year showed favorable primary and secondary patencies when compared to those with more than 1.65 PTAs per year. Maximal diameter of distal cephalic vein to cephalic arch (CV_CA) ratios showed a significant difference between dysfunctional BCF with CAS and without CAS. ROC curve drawn to predict the value of CV_CA ratio in the development of CAS revealed that ratio of 1.61 had 86% sensitivity and 100% specificity in predicting the development of CAS. Proximal 1/3 lesion in CAS was associated with poorer primary patency rate than those with distal lesion. MILLER procedures were performed in 15 patients. The number of PTA prior to MILLER was 4.26 per access-year, whereas it reduced to 1.16 following the procedures.

Conclusions: Size discrepancy between CV_CA during fistula maturation might be a risk factor for developing CAS. MILLER procedure could improve the outcome of recurrent CAS. We need further studies to determine the indications for the banding in dysfunctional BCF with CAS.

SA-PO1062

Survival and Central Vein Stenosis in Catheter-Only Dialysis Patients Sarah Hildebrand, Neill D. Duncan, Damien Ashby. *Imperial Renal and Transplant Centre, London, United Kingdom.*

Background: Compared to other forms of access, arteriovenous fistulae are associated with improved survival in haemodialysis patients, and are widely believed to be superior. In a recent meta-analysis, compared to fistula access, catheters were found to carry an increased risk for mortality with hazard ratio 1.5, though the substantial potential for bias was noted. Centre level data avoids some of this bias, so the outcome in centres with unusual practice patterns can be informative.

Methods: This retrospective study examined survival after 90 days, in a cohort of patients who never had non-catheter access. A subgroup were assessed for the presence of central venous stenosis.

Results: Between March 2006 and November 2014, 1514 patients (mean age 61.4, range 16–91, 60.2% male) started dialysis via tunneled catheter, reached at least 90 days, and remained on this type of access throughout the observation period. Over a follow-up period covering 4758 patient-years, there were 608 deaths (40.2%) and unadjusted median survival was 60.3 months. One year (after 90 days) survival was 89.0%, with survival constant over at least the first three years, at 87.8%. Over the same period, average survival in UK prevalent dialysis patients was 89.0% (standardized to age 60). Adjusting for national fistula prevalence, this suggests that compared to dialysis by fistula, dialysis by catheter access carries a modestly increased risk for mortality with hazard ratio 1.2. From a randomly selected subgroup of 110 patients, central venous stenosis was present in 12 (10.9%). Compared to those unaffected, patients with central vein stenosis did not have a significantly longer haemodialysis vintage (64.8 vs 55.3 months), but did have a significantly greater number of previous catheter insertions (3.4 vs 2.0, p=0.02).

Conclusions: The disadvantage of catheter dialysis appears to be diminished in catheter-only patients. This could be because catheter outcomes are improved in centres where they are more frequently used, or because the advantages of fistula access are over-estimated, as a result of selection bias. The risk of central venous stenosis more closely associates with number of procedures, than the duration of line use.

SA-PO1063

Superior Vena Cava Stenosis in Hemodialysis Patients with a Tunneled Cuffed Catheter: Prevalence and Risk Factors Benjamin Seront,[1] Michel Y. Jadoul,[1] Ralph Crott,[2] Laura Labriola.[1] *[1]Nephrology, Cliniques Univ Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; [2]Public Health, Cliniques Univ Saint-Luc, Belgium.*

Background: Central vein stenosis (i.e. subclavian/internal jugular/superior vena cava) is a major cause of vascular access (VA) failure and morbidity in hemodialysis (HD) patients. However the actual prevalence and risk factors of superior vena cava stenosis (SVCS) are unknown.

Methods: In this monocentric retrospective observational study, all in-center HD patients with a tunnelled cuffed catheter (TCC) between Jan 1st 2008 and Dec 31st 2012 were included (n=117, 65.9 + 15 y, 43.5% diabetics). SVCS was defined as >50% reduction of vein diameter on phlebography or injected CT (and/or need of angioplasty). Imaging was triggered by clinical SVCS syndrome or VA dysfunction. We recorded demographics and medical history (including port, pace-maker, defibrillator), as well as medications potentially influencing catheter permeability, and obtained a detailed VA history, i.e. *n* of previous arteriovenous fistulas (AVF), and last or "culprit" (in use at time of stenosis detection) TCC details (location, brand, diameter and length).

Results: Among the 117 patients [214 TCC carried for 697 (range 44-4,246) days, total 80,911 catheter-days, median HD vintage 1,202 (60-6,126 days)], 11 had a SVCS (9.4%, 0.136/1,000 catheter days). Only 2 presented with clinically obvious SVCS, with complete occlusion in one. *N* of TCC per patient was 1.8 (range 1-7): 2.64 + 1.8 in SVCS group *vs* 1.75 + 0.94 in negative group (*p* 0.13). On multivariate analysis (Poisson), diabetes [IRR 4.63 (1.2-17.8) *p* 0.03] and total duration of TCC carriage [IRR 1.47 (1.2-1.7) per year; *p* 0.0001] (but not HD vintage, *n* of previous AVF, *n* of TCC, site or length of TCC) were associated with SVCS. Limitations: As not all patients underwent imaging, the prevalence of SVCS may be higher than detected.

Conclusions: Superior vena cava stenosis is all except a rare condition, mostly asymptomatic, strongly associated with diabetes, and promoted by long-term TCC carriage. Thus, as the prevalence of TCC is growing worldwide, the morbidity associated with SVCS may be expected to grow in the future.

SA-PO1064

A Novel Method to Visualize the Position of Hemodialysis Central Venous Catheter: Dynamic Sonographic Visualization of Microbubbles Rogerio Passos, Zilma Regia de Sousa Barreto, Roseanne Ferreira de Freitas Euzebio, Paulo Benigno Pena Batista. *General Intensive Care Unit I, São Rafael Hospital, Salvador, Brazil.*

Background: The insertion of hemodialysis catheter is an integral part of the management of critically ill patients requiring continuous renal replacement therapy (CRRT). Doppler ultrasound imaging guidance for the insertion compared with anatomic landmarks has benefits regarding clinical outcomes and its use is strongly recommended. Traditionally, a postprocedural chest radiography (CXR) is performed for catheter confirmation; however obtaining one can take up to several hours, delaying catheters use in patients requiring emergent dialysis initiation. The primary goal of this study was to determine if sonography microbubble protocol after central venous access was accurate to identify catheters tip correct position compared to CXR and mean time of each procedure.

Methods: This study included a convenience sample of critically ill patients requiring CRRT with supradiaphragmatic hemodialysis catheters and a CXR for confirmation. Ultrasound was used for confirmation by visualizing microbubble artifact in the right atrium after injection of saline through the distal port. Blinded chart review was performed to assess CXR timing and catheter position. Sensitivity, specificity, negative predictive value, positive predictive value and time difference between the procedures relative to the standard reference, the CXR, were analyzed.

Results: 97 patients were enrolled. The microbubble test was 87,5% sensitive (95% CI= 0.42-1.00) and 97,6% specific (95% CI= 0.92-1.00) in confirming catheter placement, with 75% PPV, 98,8% NPV. Concordance between the tests was 97%, with an expected agreement of 59%. The mean time required to perform microbubble protocol was 10.55±3.89 minutes vs 133.51±44.75 minutes for CXR. The interrater reliability was strong: k=0.78 (95% CI= 0.54-1.02) for all images ($p<0.001$).

Conclusions: The rapid appearance of prominent turbulence in the right atrium on chest ultrasound after CVC saline flush serves as a precise bedside screening test of optimal hemodialysis catheter position and was significantly faster than CXR in our population of critically ill patients requiring CRRT.

SA-PO1065

Effect of Argatroban for the Prevention of Hemodialysis Tunneled-Cuffed Catheters Thrombosis Hua Liu, Hongli Jiang, Kehui Shi, Quan He. *Blood Purification, The First Affiliated Hospital of Medical College of Xi'an Jiaotong Univ, Xi'an, Shaanxi, China.*

Background: Thrombosis-related malfunction of tunneled-cuffed central venous catheters (TCCs) for hemodialysis (HD) currently leads to a high rate of untimely catheter removal. To examine argatroban in the prevention of thrombosis of TCCs, and investigate further the efficacy and safety of argatroban in preventing thrombosis.

Methods: To compare the effect of preventing thrombosis between using urokinase group (UK group) and argatroban group (AT group), the 42 patients of TCCs were collected since Jan. 2013 to Jan. 2014, including 23 patients using UK, 19 patients using AT, and drugs were taken monthly, a total of 12 months. The adverse events and interventions of pre-dialysis, blood flow, transmembrane pressure and venous pressure of dialysis were observed in two groups. The changes of C-reactiveprotein (CRP) were observed in two groups after treatments.

Results: The intervention rates of the two groups after treatments were 4.8% vs. 10.3% (AT vs. UK, $P < 0.05$). In the two groups, the blood flow were all increased after treatments, and transmembrane pressure and venous pressure were all reduced ($P < 0.05$). Before and after each preventive therapy, there was significant difference in activated partial thromboplastin time (APTT) in the two groups (UK vs. AT, P<0.05). In AT group, the CRP gradually reduced during 12 months of treatment ($P < 0.05$).

Conclusions: Argatroban or urokinase could prevent the thrombosis of TCCs, by dripping at regular periods, and the blood flow of dialysis was increased. Argatroban group had higher safety, less thrombosis incidence and inflammatory reaction than urokinase group, which may predict that the long-time argatroban application could reduce inflammatory in maintenance hemodialysis patients .

SA-PO1066

Tunneled Hemodialysis Catheter (TDC) Survival with Use of Tissue Plasminogen Activator (tPA) Instillation Seyed-Ali Sadjadi, Sreesh G. Iyengar, Navin Jaipaul. *Nephrology, Loma Linda VA Medical Center, Loma Linda, CA.*

Background: In the United States up to 80% of patients start dialysis by way of TDCs despite attempts to reduce this. Besides carrying a higher risk of infection, TDC's may cause formation of blood clots, impairing blood flow and thus adequate dialysis, causing increased morbidity and mortality. Prior studies have shown that tPA is effective in maintaining patency of TDCs, especially short term and in the setting of catheter dysfunction. In our study we attempt to establish evidence for long-term patency with use of thrombolytics.

Methods: This is a retrospective cohort study with 169 study subjects. The Nephrology dialysis unit database was searched to identify all hemodialysis patients with TDC's placed. The electronic medical record was reviewed to see if subjects had or had not received tPA. The data was analyzed to compare "early" (30 days), "late" (90 days) and "very late" (180 days) TDC survival with and without tPA. Secondarily we also determined average number of tPA doses used.

Results: With regards to "early" catheter survival at 30 days, there was no significant difference in survival between catheters that did and did not receive tPA (p value 0.591). There was no significant difference in "late" catheter survival at 90 days either (p value 0.497). With regards to "very late" catheter survival at 180 days, the difference was not significant (p value 0.252). The number of tPA doses averaged 4.9 doses with a wide standard deviation of 8.8. With regard to catheter survival, catheters treated with tPA survived 80 days versus 77 days in those catheters not treated with tPA (p value 0.124). With regards to TDC location, left versus right sided, there was no significant difference in survival (p value 0.392).

Conclusions: If one considers the "gold standard" for a TDC as one that remains functional without the need for tPA until removal. In our study, the overall catheter survival in days was improved with the use of tPA by 3 days, neither statistically or clinically significant. TDCs treated with tPA survived the same length of time as the "gold standard" catheters, thus leading to our conclusion that use of tPA in TDC's is non inferior to the "gold standard."

SA-PO1067

Expanded Indications of Occluded Arteriovenoius Graft Puncturing with Ultrasound Guide Akashi Togawa. *Dept of Nephrology, Shizuoka Saiseikai General Hospital, Shizuoka, Japan.*

Background: We have tried placing a regular needle catheter through the occluded arteriovenoius graft (AVG) to the brachial artery as a temporary vascular access ("occluded AVG puncturing"). We previously reported that the occluded AVG puncturing is useful as a back-up hemodialysis vascular access (Togawa 2012 J Vasc. Accsess). After the first report, we tried to expand the indication of occluded AVG puncturing with ultrasound-guided puncturing technique.

Methods: Occluded AVG puncturing was performed approximately 15-30 mm from the site of anastomosis between the artery and graft. The body of the catheter passes through the coagulated blood in the graft and the tip of the catheter is placed in the artery. We used 50mm needle for occluded AVG puncturing. The subcutaneous veins or deep veins were used for the return circuit of hemodialysis. In some patients, ultrasound guided puncturing was performed for catheter insertion of veins.

Results: From June 2011 to May 2016, we performed 143 punctures of 12 patients. Puncture was performed in patients with difficulty of immediate intervention or re-surgery. In the patients undergoing the longest period, we performed 75 occluded AVG puncturing for 6 months. Even if there was a bend in the anastomotic site in some degree, it was possible to place the tip of the catheter in the artery under ultrasound guide. Sufficient blood flow was able to obtain in all patients. None of the patients experienced complications such as hematoma formation, injury of the artery, arterial occlusion or puncture-related infection. With the occluded AVG puncture, the patients were able to avoid hospitalization with catheter insertion and urgent VA repair. In addition, with the occluded AVG puncturing, some patients were able to continue hemodialysis as an outpatient for long-time.

Conclusions: Occluded AVG puncturing with ultrasound guide might be safe for long-term use. Occluded AVG puncturing might be considered in patients who have difficulty in AVG re-creation because of low cardiac function or vulnerability of the skin.

SA-PO1068

Shall We Abandon Frequently Thrombosed Accesses? Janet Yanqing Mei,[1] Zubin Irani,[2] Jie Cui.[3] *[1]Harvard School of Public Health; [2]Interventional Radiology Div, Massachusetts General Hospital; [3]Renal Div, Massachusetts General Hospital.*

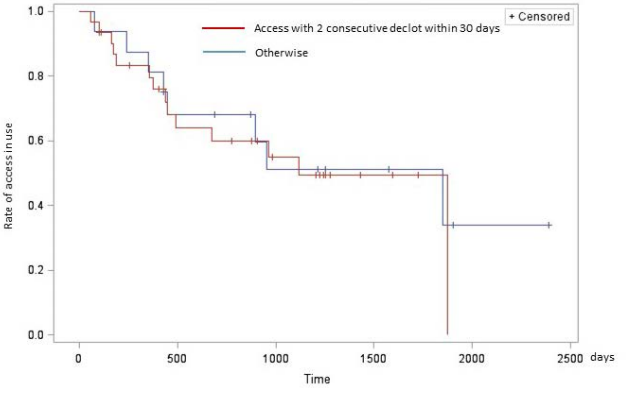
Background: Whether and when a frequent thrombosed access should be abandoned is unclear. In this study, we had a 5 year follow up of those accesses, which defined as having 2 thrombectomies within 30 days.

Methods: This is a retrospective cohort study. Patients received thrombectomy/declotting procedures in 2012 in interventional radiology division at Massachusetts General Hospital were included. Information regarding all arteriovenous accesses those patients have had until April, 2016 were collected. Kaplan-Meier estimator was used to evaluate the rate of access-in-use.

Results:

	Patients(n=43)
Age at 1st access	58.8±15.0
Men	60.5%
No. of access per patient	2±1
Access type	
Fistula	30
Graft	68
Hypertention	81.4%
Diabetes	60.5%
CHF	53.5%

Sixty-eight accesses had at least one clotting event and 48 (70.6%) had subsequent events. Thirty-three accesses had at least three events; three cases showed decreasing intervals between each event. There were 31 accesses with two declots within 30 days; 5 had new accesses within approximately 3 months (range: 21 to 98 days); 65.2% had a following declot within 30 days. Frequently thrombosed group had similar rate of access-in-use across time compared to access group that did not need frequent declot.



Conclusions: In this study, the intervals between clotting events generally do not hold a decreasing pattern. For frequently clotted accesses, they have a moderate risk of a following declot within 30 days. Their longevity is similar to that of their counterparts. We conclude that frequent-thrombosed accesses should not be abandoned quickly.

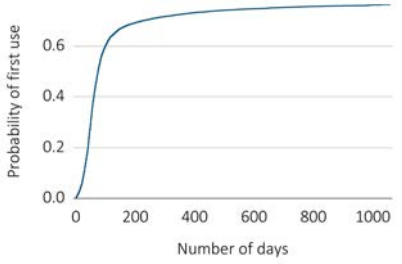
SA-PO1069

Successful Arteriovenous Graft Placements in Hemodialysis Patients: Results from the USRDS Kenneth J. Woodside,[1] Sai Hurrish Dharmarajan,[1] Brett W. Plattner,[1] Douglas E. Schaubel,[1] Purna Mukhopadhyay,[2] Kaitlyn Ratkowiak,[2] Ronald L. Pisoni,[2] Rajiv Saran.[1] *[1]Univ of Michigan; [2]Arbor Research Collaborative for Health.*

Background: While an arteriovenous fistula (AVF) is the vascular access of choice for hemodialysis (HD), some patients cannot support an AVF, and an arteriovenous graft (AVG) is placed. We previously described AVF maturation in prevalent HD patients. Herein, we describe predictors of successful AVG placement.

Methods: We assessed the relationship between patient characteristics and time to first AVG use by Cox regression in HD patients with AVG placements in 2013 or 2014 using ESRD Medicare claims data and CROWNWeb in the USRDS, with follow-up through 12/31/15.

Results: There were 24,222 AVGs placed in 22,634 prevalent HD patients. Of these AVG, 18,229 (75.3%) were successfully utilized (Figure). Of successful AVG, 52.8% were used by 2 months and 85.2% by 4 months (median 57 days [IQR 39-87 days]). Patients 22-44 years were less likely (HR 0.94 [95%CI 0.89, 0.99]), and those ≥75 years were more likely (HR 1.11 [95%CI 1.07, 1.16]), to successfully use the new AVG, compared to the 45-64 year reference group. Successful AVG use was more likely in black vs white HD patients (HR 1.05 [95%CI 1.02, 1.09]). There were no significant differences by sex or comorbidities. HD vintage interval ≥2 years were associated with successful AVG use. Those with AVG at HD initiation were more likely (HR 1.33 [95%CI 1.22, 1.44]), and those with AVF at HD initiation were less likely (HR 0.95 [95%CI 0.89, 1.01]), to have subsequent successful AVG, compared to patients who initiated HD by catheter only. There was wide variation in successful AVG placement by ESRD Network.



Conclusions: We have characterized AVG maturation in a national US sample and identified important associations with multiple patient and regional factors. National time to AVG first use was longer than expected and requires further study .

Funding: NIDDK Support

SA-PO1070

An Innovative Vascular Access for Chronic Hemodialysis: Subcutaneous Polytetrafluoroethylene (PTFE) from Internal Iliac Artery to Left Renal Vein

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Background: The longer hemodialysis (HD) patients survive, the longer vascular access becomes a problem. This may reach life-threatening proportions and eventually lead to the need of innovative solutions.

Methods: We report a case of a 44-yr. old woman with unknown etiology stage 5 CKD on HD for 14 years, during which she had thrombosed fistulas on both upper and lower extremities and also failed peritoneal dialysis (PD) and a kidney transplantation (KT). A second KT was discarded by the transplant team. HD became temporarily possible due to extreme vascular accesses: two arterio-arterial PTFE grafts (bilateral axillary-axillary artery bypass) and a translumbar inferior vena cava tunneled catheter, successful for only a short period. Considering the exhaustion of options, we placed a double-lumen catheter (DLC) into right femoral artery as an emergency access, until a whole-body CT angiography revealed occlusion of all main venous trunks - jugular, subclavian, and iliacs) and infrarenal vena cava – with the exception of the left renal vein and suprarenal vena cava. We then decided to construct an unconventional long term vascular access for HD, using an abdominal 6 mm subcutaneous tunneling PTFE linking the internal iliac artery (end-to-side) to the left renal vein (after nephrectomy).

Results: As venogram demonstrated a patent anastomosis, this innovative access was used 11 days from the surgery (July 3rd, 2014) and remains patent 23 months thereafter. So far, no infectious or thrombotic complications were detected.

Conclusions: Placement of a PTFE arteriovenous graft from internal iliac artery to left renal vein is a viable option for HD patients excluded from PD or KT with exhaustion of vascular access.

SA-PO1071

Role of CTGF in Peritoneal Fibrosis in Mice

Naohiro Toda,[1] Masato Kasahara,[2] Kiyoshi Mori,[3] Masashi Mukoyama,[4] Motoko Yanagita,[1] Hideki Yokoi.[1] *[1]Dept of Nephrology, Kyoto Univ Graduate School of Medicine, Kyoto, Japan; [2]Inst for Advancement of Clinical and Translational Science, Nara Medical Univ, Nara, Japan; [3]School of Pharmaceutical Sciences, Univ of Shizuoka, Shizuoka, Japan; [4]Dept of Nephrology, Kumamoto Univ Graduate School of Medical Sciences, Kumamoto, Japan.*

Background: Connective tissue growth factor (CTGF/CCN2) regulates signaling of other growth factors and promotes fibrosis. CTGF is shown to be an aggravating factor in thickening peritoneum and peritoneal function. Inhibition of CTGF using knockout mouse has not been examined in peritoneal fibrosis because of its perinatal death.

Methods: To study the role of CTGF in peritoneal fibrosis of adult mice, we generated CTGF floxed mice, and these mice were crossed with RosaCreER^{T2} mice. We administered tamoxifen (TAM) to 3, 6-week old mice to delete CTGF gene throughout the body in Rosa-CTGF cKO mice. We evoked peritoneal fibrosis by intraperitoneal injection of chlorhexidine-gluconate (CG) in wild-type and Rosa-CTGF cKO miceand examined peritoneal injury by Masson's trichrome staining, immunohistochemistry, mRNA expression of peritoneum and peritoneal equilibration test.

Results: After induction of peritoneal fibrosis in wild-type mice, mice showed increased CTGF expression and severe thickening of peritoneum.In contrast, CG-treated Rosa-CTGF cKO mice exhibited reduced thickening of peritoneum by 30%on day 28. Peritoneal CTGF mRNA expression was decreased by 80% in Rosa-CTGF cKO mice in peritoneal fibrosis. Peritoneal equilibration test also revealed that increase of peritoneal permeability in CG-treated wild-type mice was normalized in CG-treated Rosa-CTGF cKO mice. Immunohistochemical study revealed that CG-treated Rosa-CTGF cKO mice showed number of αSMA- and CD31-positive cells in peritoneum. Analyses of peritoneal mRNA showed that CG-treated Rosa-CTGF cKO mice exhibited reduced expression of αSMA, CD31 and VEGF.

Conclusions: These results indicate that the deficiency of CTGF can reduce peritoneal thickening and maintain peritonealfunction by reducing angiogenesis and fibrosis in peritoneal fibrosis model, suggesting that CTGF plays an important role in the progression of peritoneal fibrosis.

SA-PO1072

Blocked Heat Shock Factor 1 as Novel Pathomechanism Caused by Relevant Stressors in Peritoneal Dialysis Fluid

Rebecca Herzog,[1,2,3] Klaus Kratochwill,[1,3] Christoph Aufricht.[3] *[1]Christian Doppler Laboratory for Molecular Stress Research in Peritoneal Dialysis, Medical Univ of Vienna, Austria; [2]Zytoprotec GmbH, Vienna, Austria; [3]Pediatric Nephrology, Medical Univ of Vienna, Austria.*

Background: PD-fluids (PDF) cause injury of mesothelial cells but also induce cytoprotective mechanisms. Recent studies, however, suggest that PDF blocks the heat shock response, one of the evolutionary most important stress responses. The resultant increased vulnerability of the mesothelial cells could lead to progressing fibrosis of the peritoneal membrane. The aim was to identify the molecular mechanisms leading to the PDF-induced inadequate stress response.

Methods: The induction of the stress response in mesothelial cells was analyzed using combined *in-vitro* and *in-vivo* models of PDF exposure and heat stress as the gold standard. In addition single cytotoxic components of PDF, like glucose degradations products (GDP) and acidosis as well as the impact of cytoprotective additives were investigated. The status of heat shock factor 1 (HSF1) activation, Hsp72 expression, the stress-proteome and viability of the mesothelial cells were analyzed.

Results: Compared to heat, PDF leads to increased lethality but decreased Hsp72 expression. A concurrent blockage of the nuclear shift, phosphorylation and DNA-binding of HSF1 with reduced activity of the promotor was found. The inadequate HSF1 activation could be unblocked by a neutral pH, filter-sterilized PDF (without GDPs) or addition of alanyl-glutamine. The HSF1 blocking caused by the acidosis was associated with activation of GSK-3β, while the GDPs directly interfered with HSF1 promotor activity.

Conclusions: The PDF-mediated inadequate induction of the cellular stress response represents a new pathomechanism in PD. Our results demonstrate that the cytotoxic factors such as acidosis and GDPs of PDF lead to a HSF1 block via different molecular mechanisms and post-translational modifications resulting in decreased stress response and increased vulnerability of mesothelial cells exposed to PDF which could be restored by addition of alanyl-glutamine.

Funding: Pharmaceutical Company Support - Zytoprotec GmbH

SA-PO1073

The Role of WNT Signalling in Peritoneal Membrane Injury

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Background: Patients on peritoneal dialysis are at risk of developing peritoneal fibrosis and angiogenesis which can lead to a decline in peritoneal membrane function. Transforming growth factor beta (TGFB) is the primary cytokine involved in inducing epithelial to mesenchymal transition (EMT) and fibrosis. The WNT/b-catenin (canonical) signalling pathway has been shown to interact with the TGFB pathway to promote fibrogenesis. In contrast, non-canonical WNT signalling may have protective effects. Therefore, we investigated the role of WNT signalling in peritoneal membrane injury.

Methods: Using adenovirus mediated gene transfer of TGFB, we induced fibrosis and EMT in the mouse peritoneum. Using an adenovirus, we concurrently overexpressed the WNT inhibitor DKK1, or the non-canonical WNT5a, and evaluated EMT, fibrosis, and angiogenesis.

Results: The addition of AdDKK1 to AdTGFB mediated injury resulted in attenuation of angiogenesis in the mouse peritoneum. This also resulted in a decrease in EMT and an increase in the expression of the epithelial marker E-cadherin. This demonstrates that the WNT/b-catenin pathway is involved in peritoneal membrane angiogenesis. The treatment of mouse peritoneum with AdTGFB and AdWNT5a also resulted in a decrease in angiogenesis and reduction in vascular growth factor expression. Furthermore, addition of WNT5a inhibited glycogen synthase kinase 3 phosphorylation suggesting WNT5a may antagonize the canonical WNT pathway.

Conclusions: The WNT/b-catenin pathway is involved in epithelial cell transition and angiogenesis. WNT5a may be protective against peritoneal membrane injury by antagonizing β-catenin dependent WNT signalling.

Funding: Private Foundation Support

SA-PO1074

The Effect of Protein Transduction Domain Recombinant Bone Morphogenetic Protein-7 on Epithelial-Mesenchymal Transition in Peritoneal Mesothelial Cells Ji Min Park,[2,3] Seonghun Kim,[1] Youn Kyung Kee,[2] Hyoungnae Kim,[2] Min-Uk Cha,[2] Tae-Hyun Yoo.[1,2] *[1]Dept of Internal Medicine, College of Medicine, Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ, Seoul, Korea; [2]Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea; [3]Dept of Internal Medicine, Severance Biomedical Science Inst, Brain, Korea.*

Background: We investigated the effect of Protein transduction domain (PTD)-mediated bone morphogenetic protein-7 (tissue-regeneration polypeptide 2, TRP2) on TGF-β1-induced epithelial-mesenchymal transition (EMT) in cultured human peritoneal mesothelial cells (HPMCs). In addition, we investigated how to deliver the drugs to peritoneum in vivo models.

Methods: In vitro, HPMCs were cultured in normal glucose + TGF-β1 with or without TRP2. In vivo, saline (control group, n=3), 4.25% PD solution (PD group, n=3), or 4.25% PD solution + TRP2 (PD + TRP2 group, n=5) were infused for 4 weeks in 11 Sprague-Dawley rats, then sacrificed after 4 weeks. E-cadherin, ZO-1, α-SMA, snail, vimentin, type I collagen, and fibronectin were estimated. PF was assessed by Masson's trichrome (MT) staining.

Results: In vitro, protein expression of E-cadherin and ZO-1 (epithelial marker) were significantly decreased, while α-SMA, snail, vimentin (mesenchymal marker), type I collagen and fibronectin were significantly increased in TGF-β1-stimulated HPMCs compared to control group, and these changes were significantly improved by TRP2 treatment. In vivo, peritoneal EMT and PF were significantly increased in PD rats compared to control rats. The thickness of mesothelial layer and the intensity of MT staining in the peritoneum of PD rats were also significantly higher compared to control rats. These changes of the peritoneum in PD rats were significantly ameliorated by the administration of TRP2.

Conclusions: This study suggests that TRP2 directly inhibits the process of TGF-β1-induced PF via peritoneal EMT in HPMCs. In addition, TRP2 mitigates PF in PD rats. The effect of PTD-mediated recombinant protein delivery system may be a potential therapeutic strategy for prevention of PF in PD patients.

SA-PO1075

MicroRNA-200c Inhibits TGF-β1-Induced Epithelial-to-Mesenchymal Transition and Fibrogenesis in Peritoneal Mesothelial Cells Susan Yung, Jessica Y.S. Chu, Mel Chau, Mandy K.M. Kam, Daniel Tak Mao Chan. *Dept of Medicine, The Univ of Hong Kong, Hong Kong.*

Background: Progressive peritoneal fibrosis is a common complication that limits the effectiveness of long-term peritoneal dialysis (PD). Epithelial-to-mesenchymal transition (EMT) of mesothelial cells is a salient feature in peritoneal fibrosis but how this is triggered remains obscure. This study investigated the role of microRNA-200c (miRNA-200c) in EMT and fibrogenesis in a murine PD model and cultured peritoneal mesothelial cell.

Methods: Male C57BL/6N mice were administered PBS or glucose-based PD fluid twice daily by intra-peritoneal injection for up to 30 days. Parietal peritoneum was obtained and miRNA-200c expression examined using locked nucleic acid in-situ hybridization. Cultured human peritoneal mesothelial cells were stimulated with exogenous TGF-β1 and the expression of miRNA-200c and EMT markers was investigated. The effect of miRNA-200c overexpression on fibrogenesis was investigated in separate experiments.

Results: PD fluid, but not PBS, reduced peritoneal miRNA-200c expression in C57BL/6N mice. This effect was observed after 3 days and was sustained for 1 month, and was associated with mesothelial cell denudation and increased submesothelial collagen deposition. TGF-β1 decreased miRNA-200c and E-cadherin expression in mesothelial cells in a dose-dependent manner, and this was accompanied by increased SNAIL, fibronectin and collagen I synthesis. Over-expression of miRNA-200c suppressed the pro-fibrotic effect of TGF-β1 in mesothelial cells.

Conclusions: Our data demonstrate that miRNA-200c regulates EMT and fibrogenesis in mesothelial cells, and reduced peritoneal miRNA-200c expression is associated with peritoneal fibrosis in PD.

Funding: Government Support - Non-U.S.

SA-PO1076

High Glucose and Mannitol Concentrations Differentially Influence the Adhesive and Proliferative Properties of Mesothelial Cells Vassilios Liakopoulos,[1] Vasiliki Peppa,[2] Michail Daniilidis,[1] Konstantinos I. Gourgoulianis,[2] Chrissi Hatzoglou,[2] Sotirios G. Zarogiannis.[2] *[1]Dialysis Unit, 1st Dept of Medicine, Medical School, Aristotle Univ of Thessaloniki, Thessaloniki, Greece; [2]Dept of Physiology, Medical School, Univ of Thessaly, Larissa, Greece.*

Background: Peritoneal mesothelial cells in the case of peritoneal dialysis are exposed to hyperosmotic conditions that result in chronic inflammation and consequently fibrosis of the peritoneal membrane. Hyperosmotic stress is an established fibrotic inducer as seen in several *in vitro* studies. However, the *in vitro* models used until now focused on acute hyperosmotic effects on mesothelial cells. The aim of our study was to investigate the chronic in vitro hyperosmotic stress, on cell adhesion and proliferation of mesothelial cells.

Methods: Mesothelial cells (MeT-5A) were constantly exposed to high glucose (100mM) or high mannitol (100mM) concentrations and adhesion and proliferation assays were performed on the first and second passage after the first application of hyperosmotic stress.

Results: Chronic exposure to mannitol increased the adhesion rate of MeT-5A cells, while the opposite effect was observed when cells were chronically exposed to glucose (1st passage: $OD_{isosmotic}$=0.13±0.03, $OD_{Mannitol}$=0.18±0.02, p<0.05; $OD_{Glucose}$=0.08±0.01, p=ns, 2nd passage: $OD_{isosmotic}$=0.19±0.01, $OD_{Mannitol}$=0.27±0.01,p<0.001; $OD_{Glucose}$=0.06±0.01, p<0.01). The proliferation rate was significantly reduced only in the presence of glucose-rich solution (p<0.001) and was not affected by chronic exposure to mannitol-rich solution.

Conclusions: The results of our study indicate that chronic exposure to osmotic stress affects mesothelial cell adhesion and proliferation depending on the osmotic agent used. High concentration of mannitol caused a significantly milder effect than high concentration of glucose. Our results implicate that the model that we employed for the mimicking of chronic stress may prove beneficial for studying peritoneal membrane changes with possible clinical relevance.

SA-PO1077

The Role and Mechanism of β-Catenin Signaling Pathway of High Glucose Induced Peritoneal Fibrosis in C57BL/6 Mice Hao Deng,[1] Jia Shen,[1] Xiuxiu Li,[1] Yan Jiang,[1] Jingyi Zhou,[1] Jianghua Chen.[1] *[1]Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China; [2]Dept of Nephrology, The People's Hospital of Zhejiang Province, Hangzhou, Zhejiang, China.*

Background: Long-term exposure to bio-incompatible high glucose peritoneal dialysate leads to peritoneal fibrosis and thus decrease dialysis efficiency. This study explored the possible role of β-catenin in high glucose dialysate induced peritoneal fibrosis.

Methods: C57BL/6 mice received daily intraperitoneal injection with 10% body weight of saline, 4.25% glucose peritoneal dialysis fluid (PDF), or PDF combined with 5 mg/kg ICG-001 for 30 days. Mouse peritoneal epithelial cells (mPEC) were cultured in 4.25% glucose or combined with 10 μM ICG-001 for 48 h.

Results: The greater thickness of parietal peritoneum, lower expression of E-cadherin, and higher expressions of Vimentin, β-catenin and Snail were demonstrated in the PDF treated mice, and Vimentin, GSK-3β, Snail expression as well as β-catenin activation were increased in HG treated mPEC, which were all modulated by treatment with ICG-001 combination treatment.

Conclusions: The activation of β-catenin signaling participated in the process of high glucose induced peritoneal fibrosis, and the epithelial-to-mesenchymal transition (EMT) of PECs is one of underlying mechanisms of this pathological change.

Funding: Government Support - Non-U.S.

SA-PO1078

Tight Junction Protein Expressions from Peritoneal Dialysis Effluent: The Role of Claudin-15 Gheun-Ho Kim, Jong Wook Choi, Sua Kim, Eun Young Choi. *Internal Medicine, Hanyang Univ College of Medicine, Seoul, Republic of Korea.*

Background: We hypothesized that tight junction (TJ) proteins may have roles in paracellular transport of solute and water in peritoneal dialysis (PD) patients. Previous studies on TJ proteins in PD patients were only from cultured human peritoneal mesothelial cells. Here, we explored expression of TJ proteins directly from PD effluent and investigated their relationship with functional parameters in performing PD.

Methods: PD effluents were collected for the previous 24 hours from 20 patients when they visited outpatient clinic for the scheduled peritoneal equilibration test (PET) using a 4.25% glucose solution over 4 hours. Different molecular sizes (3 kDa, 30 kDa, and 100 kDa) of Amicon Ultra-15 Centrifugal Filter Units were used to concentrate proteins in PD effluents before immunoblot analyses for occludin, ZO-1, claudin-1, and claudin-15 were carried out. We also collected clinical data including patient demographic characteristics, fundamental laboratory findings, residual renal function, peritoneal clearance, and results of PET.

Results: Immunoblotting from PD effluents revealed discrete bands of occludin (~65 kDa), ZO-1 (~215 kD), claudin-1 (~22 kDa), and claudin-15 (~22kDa) in all 20 patients. Peritoneal KT/V urea, peritoneal creatinine clearance, and ultrafiltration volume did not significantly correlate with the individual TJ protein expression. According to the transport characteristics in PET, patients were grouped into those with low (L, n=3), low-average (LA, n=11), and high-average (HA, n=6). The claudin-15 expression was significantly decreased in HA (68 + 26%, P<0.05) compared with L (102 + 44%) and LA (117 + 34%) whereas the expression of occludin, ZO-1, and claudin-1 were not significantly different between groups. Notably, claudin-15 expression significantly correlated with the decrease in dialysate sodium concentration at 1 h during PET (r=0.47, P<0.05).

Conclusions: In this pilot study, we could detect significant levels of TJ proteins from the PD effluent and suggest the possibility of new peritoneal functional biomarkers. In particular, the roles of peritoneal claudin-15 in PD patients need to be investigated by further studies.

Funding: Pharmaceutical Company Support - Fresenius Medical Care

SA-PO1079

The Effect of Periostin on the Progression of Peritoneal Fibrosis Jae Yoon Park,[1] Jin Ho Hwang,[2] Seung Hee Yang,[3] Kook-Hwan Oh,[4] Yon Su Kim,[4] Jung Pyo Lee.[5] *[1]Dept of Internal Medicine, Dongguk Univ Ilsan Hospital; [2]Dept of Internal Medicine, Chung-Ang Univ Hospital; [3]Kidney Research Inst, Seoul National Univ Hospital; [4]Dept of Internal Medicine, Seoul National Univ College of Medicine; [5]Dept of Internal Medicine, Seoul National Univ Boramae Medical Center.*

Background: Peritoneal fibrosis limits long-term peritoneal dialysis(PD). Periostin,a matricellular protein,was initially identified in osteoblasts as an adhesion molecule during bone formation. Recently,the role periostin has been reported in diverse processes and pathologies in tissue remodeling through the promotion of adhesion,cell survival,cellular dedifferentiation and fibrogenesis. However,its role in peritoneal fibrosis is not known well.

Methods: We investigated expression of periostin in overnight PD effluents using the enzyme linked immunosorbent assays from 127 PD patients and *in vivo* in C57BL/6 mice with peritoneal fibrosis model that was induced by intraperitoneal injection of 0.1% chlorhexidine solution.

Results: Mean periostin protein concentration was 6,543pg/mL in first overnight effluents(1 month after start of PD) and 7,404pg/mL in 1 year effluents of the patients. Peritoneal transport type and equilibration ratios between dialysate and plasma for creatinine were significantly related with the periostin level of the 1 year effluents of the patients. Periostin expression was strongly induced in peritoneal fibrosis model. Periostin was expressed predominantly in submesothelium and in lesser abundance in upper margin of abdominal muscle layer of mice with peritoneal fibrosis. Periostin messenger RNA was increased in peritoneal fibrosis model compared to the control. Messenger RNA expression of monocyte chemotactic protein-1,α-smooth muscle actin,fibronectin and collagen 1 was also increased in peritoneal fibrosis model.

Conclusions: Periostin expression becomes higher in the peritoneal cavity of PD patients and its level can differentiate the peritoneal permeability after 1 year from the start of PD. In addition, periostin expression is related in peritoneal fibrosis in C57BL/6 mice. Thus, our study implicate periostin signaling in the mediation of peritoneal fibrosis as a consequence of PD.

SA-PO1080

Periostin-Binding DNA Aptamer Ameliorates Peritoneal Dialysis-Induced Peritoneal Fibrosis Boyoung Nam,[1] Youn Kyung Kee,[2] Hae-Ryong Yun,[1] Changhwan Seo,[1] Tae-Hyun Yoo.[1,2] *[1]Dept of Internal Medicine, College of Medicine, Severance Biomedical Science Inst, Brain Korea 21 PLUS, Yonsei Univ, Seoul, Korea; [2]Dept of Internal Medicine, Yonsei Univ College of Medicine, Seoul, Korea.*

Background: Peritoneal fibrosis (PF) is a major complication, leading to ultrafiltration failure in patients on peritoneal dialysis (PD). In PD-related PF, the protein expressions of various extracellular matrix including periostin are increased via the transforming growth factor-β1 (TGF-β1) pathway. This study was undertaken to evaluate the impact of periostin inhibition by novel aptamer-based inhibitor on TGF-β1-induced epithelial-mesenchymal transition (EMT) in human peritoneal mesothelial cells (HPMCs) and in an animal model.

Methods: In vitro, HPMCs were exposed to TGF-β1 (2ng/ml) to induce EMT and fibrosis with or without periostin siRNA (100nM) or periostin-binding DNA aptamer (200nM). In vivo, PD catheters were inserted into 48 C57BL/6 mice, and saline (C group, N=24) or 4.25% PD solution (PD group, N=24) was infused for 4 weeks. Twelve mice from each group were treated with periostin-binding DNA aptamer (500μg/kg/d) (PA). mRNA and protein expressions of periostin, fibronectin, α-smooth muscle actin (α-SMA), snail, and E-cadherin in HPMCs and mouse peritoneum were evaluated by real-time PCR and western blot analysis. PF was also assessed by Masson's trichrome (MT) staining.

Results: In vitro, TGF-β1 treatment up-regulated periostin, fibronectin, α-SMA, and snail expressions, while E-cadherin expression was decreased by TGF-β1 in cultured HPMCs ($P<0.01$). Not only periostin siRNA but also periostin-binding DNA aptamer attenuated TGF-β1-induced periostin, fibronectin, α-SMA, and snail expressions and restored E-cadherin expression in HPMCs ($P<0.05$). In vivo, the expressions of periostin, fibronectin, α-SMA, and snail were increased, whereas E-cadherin expression was decreased in the peritoneum of PD mice ($P<0.05$). The thickness of the submesothelial layer and the intensity of MT staining in the peritoneum were higher in PD mice compared to C mice ($P<0.05$).

Conclusions: These findings suggest that PA can be a potential therapeutic strategy for PF in PD patients.

SA-PO1081

Protein Kinase C-β Deficiency Increases Glucose-Mediated Peritoneal Damage in a Mouse Model of Peritoneal Dialysis via Up-Regulation of Protein Kinase C-α Michael S. Balzer,[1] Wang Le,[2] Song Rong,[1] Sibylle Von Vietinghoff,[1] Barbara Hertel,[1] Hermann G. Haller,[1] Nelli Shushakova.[1] *[1]Dept of Nephrology and Hypertension, Hannover Medical School, Hannover, Germany; [2]Dept of Nephrology, Tongji Medical College, Wuhan, China.*

Background: Peritoneal membrane (PM) damage during peritoneal dialysis (PD) is mediated largely by high glucose-induced pro-inflammatory and neoangiogenetic processes, finally resulting in PM fibrosis and ultrafiltration (UF) failure. We have previously shown that classical protein kinase C (PKC)-alpha exerts glucose-mediated pro-inflammatory properties in a PD mouse model. In other organ systems, PKC-beta similarly exerts glucotoxic effects. In this study we evaluate the role of PKC-beta in glucose-mediated PM damage.

Methods: SV129 WT and PKC-beta$^{-/-}$ mice on SV129 background were subjected to a PM damage model comprising catheter-delivered once-daily treatment with high glucose (4.25%) PD fluid (PDF) for 5 weeks. We performed UF capacity testing, PM histology and immunofluorescence. Peritoneal cellular and cytokine response was analyzed by FACS and ELISA. We further analyzed LPS and PDF-induced inflammatory responses in WT, PKC-alpha$^{-/-}$ and PKC-beta$^{-/-}$ immortalized mouse peritoneal mesothelial cells (MPMC) in vitro.

Results: When compared to WT mice, in PKC-beta$^{-/-}$ mice PDF treatment resulted in disproportionate PM fibrosis and UF failure, marked PM leukocyte recruitment with a high proportion of infiltrating neutrophils and highly significant up-regulation of pro-inflammatory cytokines (MCP1, CXCL2, TNF-alpha, IL-6), TGF-β, and VEGF. In vitro LPS and PDF-stimulated immortalized PKC-beta$^{-/-}$ MPMC demonstrated an increased inflammatory response compared to WT cells, which could be abrogated by additional pharmacological PKC-alpha blockade. This was corroborated by significant mesothelial in vivo and in vitro up-regulation of PKC-alpha in PKC-beta deficiency.

Conclusions: At the PM, PKC-beta exerts anti-inflammatory properties in a glucose-mediated, catheter-based in vivo PD mouse model via regulation of PKC-alpha expression in mesothelium and is essential for adequate inhibition of pro-inflammatory cytokine production and cell influx into the peritoneal cavity in response to PDF treatment.

Funding: Private Foundation Support

SA-PO1082

Inhibition of the H3K9 Methyltransferase G9a Ameliorates Methylglyoxal-Induced Peritoneal Fibrosis Kazuya Maeda, Shigehiro Doi, Toshinori Ueno, Takao Masaki. *Dept of Nephrology, Hiroshima Univ Hospital, Hiroshima, Japan.*

Background: According to reports, H3K9 histone methyltransferase G9a activity is induced by transforming growth factor-β1 (TGF-β1) and plays an important role in the progression of cancer and fibrosis. In peritoneal dialysis (PD) patients, long-term exposure to PD fluid causes peritoneal fibrosis through induction of TGF-β1. In this study, we investigated whether inhibition of G9a-mediated H3K9 methylation attenuates peritoneal fibrosis in a mouse model of peritoneal fibrosis and human peritoneal mesothelial cells (HPMCs).

Methods: Peritoneal fibrosis was induced by peritoneal injection of methylglyoxal (MGO) in male C57/B6 mice for 3 weeks. BIX01294 was administered by subcutaneous injection at the same time. In an *in vitro* study, HPMCs were pre-incubated with 2 μmol/l BIX01294 1 hour before stimulation with 5 ng/ml of TGF-β1. In peritoneal dialysis patients, HPMCs were isolated from human peritoneal dialysis effluent.

Results: G9a was upregulated in the peritoneum of MGO-injected mice, TGF-β1-stimulated HPMCs and human PD effluent. Subcutaneous injection of BIX01294, a G9a inhibitor, significantly suppressed submesothelial zone thickness and cell density in MGO-injected mice. Immunohistochemical staining revealed that BIX01294 treatment not only decreases mono-methylation of H3K9 (H3K9me1), but also decreases the number of mesenchymal cells, the accumulation of collagen and the infiltration of monocytes. In addition to pathological change, BIX01294 also inhibited expression of TGF-β1 in peritoneal fluid and improved peritoneal function. Furthermore, BIX01294 treatment inhibited TGF-β1-induced epithelial-mesenchymal transition by suppressing H3K9me1 in HPMCs.

Conclusions: These results suggest that BIX01294 is a candidate drug for reducing peritoneal fibrosis through the suppression of G9a-mediated H3K9 methylation.

SA-PO1083

Angiotensin Blockade Limits Peritoneal Inflammation Caused by Short-Term Peritoneal Dialysate and Catheter Effects in Rats Tiane Dai,[1] Pei Zhang,[1] Qiaoyuan Wu,[1] Sharon G. Adler,[1] Cynthia C. Nast.[2] *[1]Nephrology, Los Angeles Biomedical Research Inst at Harbor-UCLA Medical Center, Torrance, CA; [2]Pathology, Cedars-Sinai Medical Center, Los Angeles, CA.*

Background: Angiotensin blockade is advocated for peritoneal dialysis (PD) patients to preserve residual renal function (RRF). We tested whether losartan, an angiotensin II blocker (ARB) attenuates peritoneal inflammation.

Methods: PD was performed using 4.25% Dianeal (n=6) or 4.25% Dianeal + Losartan (n=6) BID x 10 days in a non-uremic rat model as described (Dai et al, KI 86:1197, 2014). PD fluid was collected for MCP-1, IP10 (aka CXCL10 and mob-1), and VEGF cytokine measurements, and parietal peritoneum was harvested for morphometric analysis of peritoneal membrane thickness. Cytokine measures were log-transformed for normalization and analyzed by 2-tailed t-test. Morphometric data were analyzed similarly without log-transformation.

Results: Morphometric measurements of mean peritoneal membrane width, reflecting peritoneal edema, inflammation, early fibrosis and reactive mesothelium, was higher in rats receiving Dianeal alone (107.5 + 32.5 (SD)) vs Dianeal+Losartan (66.2 + 19.7)($p=0.02$). In PD fluid, there were higher levels of IP10 ($P<0.01$) and VEGF ($P<0.05$), but not MCP-1, in rats with Dianeal+Losartan vs Dianeal alone. Weak correlations were observed between morphometrically measured peritoneal thickness and IP10 ($r = -0.42$) and between peritoneal width and VEGF ($r = -0.38$). In this experimental model, at least in the short-term, losartan limited edema, inflammation, fibrosis, and mesothelial hypercellularity in the peritoneum caused by combined catheter and dialysate exposure.

Conclusions: Apart from their known beneficial impact on RRF, ARBs may also preserve peritoneal integrity by limiting peritoneal injury.

Funding: Other NIH Support - UCLA CTSI

SA-PO1084

Tamoxifen Attenuates High Glucose-Induced Peritoneal Fibrosis by Reducing β-Catenin Activation In Vivo and In Vitro Pengpeng Yan,[1] Jia Shen,[1] Xuelin He,[1] Hongfeng Huang,[1] Xiang Zhao,[2] Jianghua Chen.[1] *[1]Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China; [2]Dept of Nephrology, The People's Hospital of Zhejiang Province, Hangzhou, Zhejiang, China.*

Background: Peritoneal fibrosis is a severe complication of long-term peritoneal dialysis, which has been successfully attenuated by Tamoxifen in clinic treatment; however, the definite mechanism remains obscure.

Methods: C57BL/6 mice received daily intraperitoneal injection of saline, 4.25% high glucose PDF or PDF combined with Tamoxifen for 30 days, and mouse peritoneal epithelial cells (mPECs) were cultured in 4.25% glucose or combined with Tamoxifen for 48h.

Results: Tamoxifen alleviated thickening of peritoneum, and reversed the expression of E-cadherin, Vimentin and β-catenin induced by PDF in mice model. Furthemore, Tamoxifen diminished epithelial-to-mesenchymal transition, as well as the phosphorylation of GSK3β, nuclear β-catenin and Snail in mPECs after high glucose exposure.

Conclusions: Tamoxifen significantly attenuates EMT progression of peritoneal epithelial in fibrosis pathology partly via suppressing β-catenin signal activation.

Funding: Government Support - Non-U.S.

SA-PO1085

Biocompatibility of a New Bicarbonate Containing PD Solution, Reguneal - Measured as In Vitro Proliferation of Fibroblasts Bart Dioos,[1] Goedele Paternot,[1] Rose-Marie Jenvert,[4] Annick Duponchelle,[1] Mark R. Marshall,[2] Souzana S. Deenitchina,[3] Anders Per Wieslander.[4] *[1]Europe R&D, Baxter International Inc, Braine-l'Alleud, Belgium; [2]Therapeutic Area, Baxter Healthcare (Asia) Pte Ltd, Singapore, Singapore; [3]Medical Affairs, Baxter Japan Ltd, Tokyo, Japan; [4]Europe R&D, Baxter International Inc, Lund, Sweden.*

Background: Long term exposure to conventional peritoneal dialysis fluids (PDFs) often leads to peritoneal membrane remodeling and failure. Such fluids typically have suboptimal pH and supraphysiologic concentrations of lactate, and high concentrations of glucose degradation products (GDPs) mainly formed during heat sterilization. Many GDPs are highly reactive carbonyl compounds that are cytotoxic and promoters of advanced glycation end products. To improve biocompatibility, a new bicarbonate-based PDF for Japan has been developed (Reguneal™, Baxter), manufactured in a two-compartment bag and optimized on pH and GDPs. This study investigates biocompatibility of Reguneal™ using a well-established in-vitro fibroblast proliferation assay with neutral red uptake.

Methods: PDFs were diluted 1+1 with tissue cultures media plus 10% serum before 72 h exposure for cytotoxicity testing. Reguneal™ and other enhanced-biocompatibility two-compartment PDFs available in Japan were compared to a lab-made sterile filtered control.

Results: Data are presented as % inhibition of proliferation (mean±SD), from 2 assays / bag in 2 bags of each PDF. The results demonstrate that the Reguneal™ is comparable to the sterile filtered control (i.e. causing no harm for the cells, thus without any cytotoxic effects) and significantly different from other PDFs (P<0.05).

2L PDF Products (% dextrose)	% Inhibition of Proliferation
Baxter Reguneal (2.5%)	4±3
JMS Perisate NL (2.5%)	11±4
Terumo Midpelliq L (2.75%)	19±7
Fresenius Staysafe Balance (2.5%)	17±4
Baxter Dianeal-N (2.5%)	14±3

Conclusions: Recently, others have shown that Reguneal™ improves markers of peritoneal membrane failure in effluent dialysate, compared to conventional PDFs (Taro Hoshino 2016). Using in-vitro biological analysis, we now show that Reguneal™ is a highly biocompatible PDF. Such fluids might help to reduce PDF-induced peritoneal membrane remodeling and failure.

Funding: Pharmaceutical Company Support - Baxter International Inc

SA-PO1086

Effects of a Bicarbonate/Lactate-Buffered Neutral Peritoneal Dialysis Fluid on Angiogenesis-Related Proteins in Patients Undergoing Peritoneal Dialysis Hiromichi Ueno, Tetsu Miyamoto, Yumi Furuno, Kenichiro Bando, Junichi Nakamata, Yoko Fujimoto, Yutaka Otsuji, Masahito Tamura. *2nd Dept of Internal Medicine, UOEH, Kitakyushu, Japan.*

Background: Continuous exposure to peritoneal dialysis fluid (PDF) drives pathological responses including peritoneal angiogenesis, resulting in a high peritoneal solute transport rate. Experimental evidence supports the view that high lactate content in PDF is a non-physiological factor that results in the development of peritoneal membrane failure. This study used the antibody array method to evaluate the effects of a newly available bicarbonate/lactate-buffered neutral PDF on the profile of angiogenesis-related proteins in drained dialysate of patients undergoing peritoneal dialysis (PD).

Methods: This was an 8-week crossover trial of 10 PD patients. Five patients each completed 4 weeks of PD using bicarbonate/lactate-buffered neutral PDF (Reguneal-LCa®) or lactate-buffered neutralPDF (Dianeal N PD-4®) and crossed over to the other treatment arm with no change of glucose concentration in the PDF. The concentrations of 19 angiogenesis-related proteins in the dialysate after each treatment were semi-quantitatively determined using the RayBio® C-Series Human Angiogenesis Antibody Array, and were compared between the two treatments.

Results: In the 19 angiogenesis-related proteins investigated, the expression of CXCL1/2/3, which belongs to the CXC chemokine family, significantly decreased after use of the bicarbonate/lactate-buffered PDF compared to the lactate-buffered PDF (P=0.04). The bicarbonate/lactate-buffered PDF tended to lower PDGF-BB and VEGF-D levels in dialysate (P=0.08 and 0.05 respectively). Patients with shorter dialysis period tended to have lower levels of angiogenesis-related protein levels when using the bicarbonate/lactate-buffered PDF. Antibody array-derived values were validated by the enzyme-linked immunosorbent assay.

Conclusions: The bicarbonate/lactate-buffered neutral PDF may modulate the profile of angiogenesis-related proteins, including CXC chemokines, in the effluent of PD patients, suggesting that bicarbonate/lactate-buffered PDF is more biocompatible than lactate-buffered PDF.

SA-PO1087

Neutral Peritoneal Dialysis Solutions Prevent Morphological Changes in the Peritoneal Membrane Mitsuhiro Tawada,[1] Yasuhiko Ito,[1] Chieko Hamada,[2] Masashi Mizuno,[1] Yasuhiro Suzuki,[1] Fumiko Sakata,[1] Shoichi Maruyama.[1] *[1]Dept of Nephrology and Renal Replacement Therapy, Nagoya Univ, Nagoya, Aichi, Japan; [2]Dept of Nephrology, Juntendo Univ, Tokyo, Japan.*

Background: The morphological changes induced by bioincompatible peritoneal dialysis solutions are well known. However, the morphological damage induced by long-term peritoneal dialysis neutral solutions has not been reported in detail. The aim of this study was to investigate the effects of pH neutral solutions on the peritoneal membrane.

Methods: This study used pathological and immunopathological techniques to assess peritoneal membrane biopsy samples from peritoneal dialysis patients treated with acidic solutions or neutral solutions.

Results: The morphological changes were compared between the acidic solution group (n=52) and neutral solution group (n=45). According to the analyses, the ratio of lumen diameter to vessel diameter (L/V ratio) was significantly smaller (p<0.01), peritoneal membrane was thicker (p<0.01) and accumulation of advanced glycation end-products (AGEs) was higher (p<0.01) in the acidic solution group than in the neutral solution group. In addition, the L/V ratio in the acidic solution group significantly decreased over time (p<0.01), although no such change was seen in the neutral solution group. There was no significant difference in the number of CD31 positive vessels between the two groups. Furthermore, we compared biopsy samples from subjects in the acidic solution group (n=33) with samples from subjects in the neutral solution group (n=22) who were treated for 4 to 10 years. In this cohort, PD duration was matched between the two groups. Further, while the L/V ratio (p<0.01) and AGEs (p<0.01) were significantly different, there was no significant difference in peritoneal thickness and number of CD31 positive vessels between the two groups.

Conclusions: These findings suggest that neutral peritoneal dialysis solutions prevent morphological changes after long term PD treatment, particularly in terms of vasculopathy.

SA-PO1088

Histopathological Characteristics of Visceral Peritoneal Injury in Patients Treated with Neutral pH Peritoneal Dialysis Solution Maiko Furuya, Yudo Tanno, Yu Honda, Nanae Matsuo, Yukio Maruyama, Ichiro Ohkido, Masato Ikeda, Keitaro Yokoyama, Takashi Yokoo. *Dep of Nephrology and Hypertension, Jikei Univ School of Medicine, Tokyo, Japan.*

Background: Encapsulating peritoneal sclerosis (EPS) develops when intestinal peristalsis is inhibited by inflammatory adhesions of encapsulating membrane to visceral peritoneum. Since it is difficult to obtain samples of visceral peritoneum, it could be histopathologically evaluated only at the timing of enterolysis with severe EPS.For that reason, little has been known about characteristics of visceral peritoneal injury in early stage or newly formed membrane-like structure (neomembrane) resulting in encapsulation. We previously reported laparoscopic approach for evaluation of EPS (KI 2012). In this study, we would report macroscopic findings of visceral peritoneum in patients treated with neutral pH solution alone for 4 years or more by laparoscopy, and histopathological investigation of the neomembrane.

Methods: 23 patients underwent laparoscopy at the time of PD catheter removal. Duration of PD in these patients was 66±17 months. Clinically, none of these patients had developed EPS by the time of the investigation. Macroscopic findings of visceral peritoneum were categorized according to color changes, presence of neovasucularizations, neomembranes, and adhesions. Subsequently, neomembranes were pathologically studied.

Results: As compared with laparoscopic findings in patients treated with acidic solution, the degrees of color changes, presence of neovascularizations, and adhesions were all mild. Neomembranes identified in 5 patients were all soft and elastic. None of them had severe adhesions to the visceral peritoneum, and intestinal peristalsis under the neomembrane was maintained. In pathological findings, the neomembrane showed no mesothelial cells, presented with discontinuous and undeveloped elastic fibers different from the existing biomembranes, and had no inflammatory cellular infiltration or fibrin deposition.

Conclusions: Unlike encapsulating membrane in EPS, neomembrane observed in patients receiving neutral pH PD solution had no inflammatory adhesions to the visceral peritoneum, suggesting its lower effect on intestinal peristalsis.

SA-PO1089

Ferric Pyrophosphate Citrate (Triferic) Delivery via Peritoneal Dialysate for Iron Supplementation in Rats Ajay Gupta, John E. Dillberger, Raymond D. Pratt. *Rockwell Medical Inc., Wixom, MI.*

Background: Iron deficiency is commonly present in peritoneal dialysis (PD) patients. Intraperitoneal (IP) route is convenient and merits investigation for iron delivery. In previous animal studies IP iron dextran was found ineffective in delivering iron in CKD-PD patients (Moniem et al, 2007), while causing iron deposition, inflammation, and fibrosis in peritoneal membrane. Soluble $FeCl_3$ by IP administration also failed to increase serum iron levels in an animal study (Suzuki et al, 1994). Administration of ferric pyrophosphate citrate (FPC, Triferic®) via hemodialysate is safe and effective in maintainin iron balance and hemoglobin in CKD-HD patients (Fishbane et al, 2015). We have examined toxicity (T) and toxicokinetics (TK) of intraperitoneal FPC in iron-replete rats.

Methods: Rats with chronic implanted catheters were administered intraperitoneally 10 mL/kg of either vehicle (Dianeal 1.5%) or FPC (50, 150, or 450 µg iron/kg with 1.5%Dianeal) over ~1 minute, 3 times/week for 4 weeks (T animals, n=30 each group). Using similar procedure, another group of animals were administered vehicle (n=6) or FPC (n=18/dose group) according to the same schedule for determination of serum iron parameters (TK animals). Animals were euthanized at the end of the dosing period or after a 3-week recovery period.

Results: FPC did not cause any significant histologic changes in peritoneal membrane and abdominal organs including liver. There was a dose dependent increse in total serum iron and transferrin saturation (TSAT) with each dose of Triferic.

FPC induced increase in serum iron lvels and peak TSAT achieved in TK animals

Dose (µg FPC iron/kg body weight)	Increase in serum iron above baseline (µg/dL)	Peak TSAT
50	91	55%
150	124	64.5%
450	278	88%

There was no histologic evidence of systemic iron accumulation.

Conclusions: IP infusion of Triferic is effective in increasing circulating serum iron levels and TSAT in iron-replete rats with no significant local toxicity. Delivery of Triferic via perioneal dialysis merits further investigation in CKD-PD patients.

Funding: Pharmaceutical Company Support - Rockwell Medical Inc.

SA-PO1090

Matrine Prevents Escherichia Coli Biofilm Formation Through Blockade of Outer Membrane Protein A Expression Yun-Hua Ma, Yunhua Liao, Xi Peng. *Renal Div, Dept of Medicine, First Affiliated Hospital of Guangxi Medical Univ, Nanning, Guangxi Zhuang Autonomous Region, China.*

Background: Escherichia coli (E.coli) is the common pathogenic bacteria causing peritoneal dialysis (PD)-associated peritonitis. In our previous studies we found that sophora flavescens had the interventional effect of E.coli biofilm (BF) formation. However, the precise mechanism is largely unknown. The present study is to investigate the relationship between matrine and OmpA expression.

Methods: We established a model of matrine interfere with E.coli biofilms in vitro. We observe the effect of effective of E.coli BF formation using the crystal violet staining. Detecting the expression of OmpA mRNA in different stages of BF formation by real-time fluorescence quantitative PCR.

Results: The minimum inhibitory concentration (MIC)for E.coli of Matrine and levofloxacin were 4096µg/ml and 0.015625 µg/ml, respectively. In presence of 1/2MIC matrine at 1,3 and 7days, the E.coli viable counts was significantly increased from111.3±12.9 ×104 CFU/ml 155.4±18.6×104 CFU/ml, 163.9±8.0 ×104 CFU/ml to 71.0 ±5.7 ×104 CFU/ml in the buffer control , to 89.0±11.1 ×104 CFU/ml, 69.1±5.7 ×104 CFU/ml in 1/2MIC matrine group(P<0.001), respectively. There was no significant difference between 1/2MIC levofloxacin group and 1/2MIC matrine group (P>0.05). Consistently, the biofilm formation capacity of each strain was estimated using the crystal violet staining. Compare with the buffer control, the OD_{570} values was significantly decreased from 0.956±0.118, 1040±0.335, 1.119±0.245 to 0.694±0.184, 0.689±0.098, 0.504±0.133(P<0.001) in different stages of BF formation, respectively.The aforementioned effect was significantly attenuated in OmpA mRNA expression(P<0.001).

Conclusions: Matrine prevents E.coli biofilm formation through blockade of OmpA mRNA expression in vitro.

Funding: NIDDK Support

SA-PO1091

Pig Trial of Automated Wearable Artificial Kidneys Based on Peritoneal Dialysis Martin Roberts, Christian G. Bluchel, Jezreel S. Zaragosa. *Nephrology, VA Sepulveda, UCLA Geffin, AWAK Technologies, Los Angeles, Burbank, CA; Biomedical Engineering Research Centre, Temasek Polytechnic, Singapore, Singapore; AWAK Technologies LTD, Singapore, Singapore.*

Background: We have developed an automated wearable artificial kidney (AWAK PD) using Tidal PD. To test the safety and efficacy of the AWAK PD we needed a pig PD model. There are no reports in the literature of pigs maintained on PD other than our recently published abstracts on CAPD and APD. Our objective was to maintaining pigs on the AWAK PD for 1 week.

Methods: The pigs were received in 2 groups. Group 1 consisted of 2 pigs, average weight 20.5 kg and group 2 of 4 pigs, average weight of 40 kg. The pigs were 5/6 nephectomized by removing 2/3 of the left kidney and the whole right kidney. A Tenckhoff catheter and central venous line was installed. CAPD with 2.5% Dianeal was performed during which the fill volume was increased from 0.5 to 1 L. Afterwards the pigs were maintained on APD. PD was conducted through a tether system linking the tether-end plate in the jacket worn by the pig and a swivel arrangement. The system provided the pig with unrestrained movement within the cage while protecting the integrity of the catheter line and the exit-site. Blood and dialysate samples were assayed for urea, creatinine and phosphorus and the volume of the drained dialysates measured.

Results: Both pigs in group 1 developed hernias which were partially restrained with bandages. In addition, 1 pig was excluded because of puncture of the peritoneal catheter. One pig in group 2 was excluded because of peritonitis during APD. Ninety 7hr dialyses were averaged to give clearances and standard deviations of urea,12.3 ±1.6, creatinine 5.8 ±1.1, and phosphorus 10 ±2.8. Average weekly Kt/V/SD of urea was 5.2 ±2. Daily ultrafiltration in group 1 was negative due to the hernia and in group 2 was 1275 ±349. All the pigs continued to have urine output.

Conclusions: Four pigs were successfully maintained for 1 week on the AWAK PD. The AWAK PD was safe and effective. Kt/V was adequate to maintain a 5/6 nephrectomized pig. Ultrafiltration was negative in the first group because of hernia leakage. The second group had adequate UF.

Funding: VA Support

SA-PO1092

The Dialysate Losses of Vitamin D-Binding Protein Do Not Predict Their Impaired Physiological Function Thalita Moura Santos Braga, Erica Adelina Guimarães, Rodrigo Souza Adao, Wagner Dominguez, Fabiana Graciolli, Hugo Abensur, Rosilene M. Elias, Rosa M.A. Moyses. *Nephrology, Faculty of Medicine, Univ of São Paulo, São Paulo, Brazil.*

Background: Vitamin D-binding protein (VDBP) transports and prolongs the serum half-life of 25-hydroxyvitamin D (25OHD). Patients on peritoneal dialysis (PD) lose VDBP to the dialysate, which aggravates as the therapy extends. However, whether VDBP loss in patients on PD has any clinical importance and compromises its biological role is not known.

Methods: Dialysate and serum VDBP levels were measured in 13 adults on automatic peritoneal dialysis (APD). Concentrations of serum free (FDBP), bioavailable (Bio-DBP), and VDBP-bound 25(OH)D (VDBP-D) were calculated, as well as the amount of total dialysate lost in 24-hour. The patients were submitted to peritoneal equilibrium test and nutritional status evaluation by subject global assessment (SGA) and bioimpedance analysis. 25OHD, alkaline phosphatase (AP), lipid profile, 24-hour total protein and albumin lost were also assessed.

Results: Patients aged 43±15 years (69.2% women), on APD for 23 months. Nine patients (69.2%) were classified as well nourished/mild nutritional risk (WN/MNR) and 61.5% had high/high average transport (H/HA) characteristics. Serum FDBP correlated with AP (r=-0.621, p=0,024) and LDL (r=0.616, p=0.025). Bio-DBP correlated with 25OHD (r=-0.600, p=0.039); VDBP-D correlated with total (r=-0.567, p=0.043) and LDL cholesterol (r=-0.737, p=0.004). The dialysate VDBP concentration correlated with HDL (r=0.634, p=0.049) and SGA (r=0.758, p=0.029). The 24-hour loss of VDBP correlated with the 24-hour loss of albumin (r=0.806, p=0.005), muscle mass (r=0.857, p=0.007) and bone mass (r=0.738, p=0.037). The serum Bio-DBP was higher among WN/MNR patients than in those with mild/moderate malnourished (5.6±2.9 *vs.* 2.0±0.0 mcg, p=0.030). VDBP did not differ between H/HA and low/low average transporters.

Conclusions: The loss of VDBP through the dialysate occurs in parallel with albumin loss and depends on nutritional status and muscle reserves, but not peritoneal permeability. High total and LDL cholesterol may result in reduced biological function of VDBP in patients on APD.

Funding: Government Support - Non-U.S.

SA-PO1093

The Effect of Low-Calcium Peritoneal Dialysis Solution in Transperitoneal Calcium Balance in Peritoneal Dialysis Patients Sandra Beltrán, Belen Vizcaino, Pablo Molina, Mercedes Gonzalez, Luis M. Pallardo. *H. Univ Dr. Peset; H. Univ Dr. Peset; H. Univ Dr. Peset.*

Background: Despite that guidelines recommend the use of low-calcium peritoneal dialysis solution, its use is not very extended in the current practice.

The objective of the study was to analyse the effect of low-calcium peritoneal dialysis solution on the mineral metabolism and the transperitoneal balance of calcium on a cohort of patients that started Peritoneal Dialysis (PD).

Methods: Prospective observational study of 44 patients starting PD between May 2013 to September 2015. We compared data after one year of treatment with low-calcium peritoneal dialysis solution. The transperitoneal calcium balance was calculated on the 24 hours peritoneal effluent collection according to the formula for peritoneal mass transfer as: (Concentration of Calcium x Drained volume)-(Concentration of Calcium x Infused volume).

Results: Mean follow up period was 14±8 months. Serum calcium remained stable (9.3±0.6 to 9.2±0.5 mg/dL, p=<0.39), no episodes of hipocalcemia were reported. PTH-i increased not significantly (254±148 to 282±162 pg/mL, p=0.28), serum phosphorous slightly increased (4.5±1.2 to 4.9±1.61 mg/dL, p=0.04). Residual Renal Function decreased significantly after one year of follow up (7.8±3.5 to 6.09±4.0 ml/min /1.73 mm^2, p=0.005). Nine patients with (PTH-i< 150 pg/mL), significantly increased their level of PTH-i (94.2±38.7 to 221±145 pg/mL, p=0.020). Nineteen patients had hipercalcemia (Serum Ca >9.5 mg/dL) at the start of PD, and except one, all of them normalized their calcium levels

after treatment. (9.8±0.26 to 9.5±0.23 mg/dL, p=0.001). The transperitoneal calcium balance was negative (-37 mg/dl/day. IC 95% -54 to -237). We did not find significant differences on the transperitoneal balance of calcium depending on the peritoneal membrane transport.

Conclusions: The use of low calcium peritoneal dialysis solution is safe, and is associated to a slight negative calcium balance with a good control of PTH-i levels. Moreover, patients with low PTH-i levels could improve with this strategy. Our results support guidelines recommendations of using low-calcium peritoneal dialysis solution in our PD patients.

SA-PO1094

Restored Stress Responses and Immune Competence in Clinical Peritoneal Dialysis Effluents Explored by a High Performance Multi-Omics Approach

Klaus Kratochwill,[1,2] Rebecca Herzog,[1,2] Seth L. Alper,[3] Andreas Vychytil,[4] Christoph Aufricht.[4] *[1]Christian Doppler Laboratory for Molecular Stress Research in Peritoneal Dialysis, Medical Univ of Vienna, Austria; [2]Zytoprotec GmbH, Austria; [3]Beth Israel Deaconess Med Ctr, Harvard Medical School, Boston, MA; [4]Medical Univ of Vienna, Austria.*

Background: Although PD effluent (PDE) represents a rich source of protein biomarkers for monitoring disease and therapy, the presence of high-abundance plasma proteins in PDE has limited proteomics analysis of its constituents. Here we report a search for PDE biomarkers following patient treatment with a novel PD fluid, using highly sensitive proteomics analysis of enriched low-abundance proteins, combined with metabolome and transcriptome analyses.

Methods: In 2 randomized cross-over trials, PD patients (n=26) received either standard PD fluid or PD-protec™ (same fluid with 8 mM alanyl-glutamine). PDE supernatants were directly used for metabolomics or were depleted of high-abundance plasma proteins, and resulting enriched low-abundance proteins were subjected to TMT-labeling and filter-aided sample preparation liquid chromatography coupled to mass spectrometry (FASP-LC-MS). Cellular fractions were analyzed by microarrays and RNA sequencing.

Results: Using this workflow, PDE proteome coverage was increased 18-fold as compared to combined existing literature. The proteins identified in PDE include representatives of biological processes and pathways previously undetected in PDE proteomes. Proteins linked to membrane remodeling and fibrosis were overrepresented in standard PDE compared to plasma, whereas underrepresented proteins indicate decreased immune competence. PDE from patients treated with PD-protec™ exhibited restoration of proteomic and transcriptomic indicators of important immune processes.

Conclusions: Our data suggests feasibility of a novel proteomics technique to investigate cell-derived biomarkers for PD pathomechanisms. Treatment with PD-protec™ was associated with restoration of immunorelevant biomarkers. These results indicate that PDE biomarkers may serve as surrogates for evaluation of novel interventions in PD, providing novel tools for monitoring PD therapy.

Funding: Pharmaceutical Company Support - Zytoprotec GmbH

SA-PO1095

Low Dentin Matrix Protein 1 Is Associated with Incident Cardiovascular Events in Peritoneal Dialysis Patients

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Background: Recent reports demonstrated that dentin matrix protein 1 (DMP1) acts as an inhibitor of vascular calcification (VC). We investigated the prognostic value of DMP1 on cardiovascular outcomes in prevalent peritoneal dialysis (PD) patients.

Methods: We recruited 223 prevalent PD patients and measured DMP1 levels. Lateral lumbar spine radiographs were used for measurement of VC. Major cardiovascular events were compared between the two groups. In vitro, osteocytes were cultured in media containing indoxyl sulfate (IS), then the expressions of DMP1 were examined.

Results: The mean age was 52.1±11.8 years, and 116 (52.0%) patients were male. The median value of log DMP1 was 0.91 (0.32–2.81 ng/ml). The multiple logistic regression analysis indicated that DMP1 levels were independently associated with the presence of VC after adjustment for multiple confounding factors (P=0.005). In IS-stimulated osteocytes, transcript and protein expression levels of DMP1 were significantly decreased compared to control osteocytes. During a mean follow-up duration of 34.6 months, incident cardiovascular events were observed in 41 (18.4%) patients. A Kaplan-Meier plot showed that the low DMP1 group had a significantly higher rate of incident cardiovascular events compared with the high DMP1 group (log-rank test, P=0.026). In addition, multiple Cox proportional hazard analysis showed that low DMP1 was significantly associated with incident cardiovascular events (P=0.029) after adjustment for multiple confounding factors.

Conclusions: DMP1 might be considered the novel factor that contributing the pathophysiology of cardiovascular disease in dialysis patients.

SA-PO1096

The Effects of Peritoneal Effluent Mitochondrial DNA on Intraperitoneal Inflammation and Peritoneal Solute Transport Rate in Peritoneal Dialysis

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Background: Local chronic intraperitoneal inflammatory status commonly affects peritoneal dialysis (PD) patients. Mitochondrial DNA (mtDNA) released into extracellular subsequent to cell injury and death can promote inflammation in patients and animal models. However, the effects of peritoneal effluent mtDNA on intraperitoneal inflammation and peritoneal solute transport rate (PSTR) in PD patients remain unclear. We aimed to examine the peritoneal effluent mtDNA and elucidate their relationship with intraperitoneal inflammation and PSTR.

Methods: We select the incident patients who began PD therapy at the First Affiliated Hospital of Zhejiang University between January 1, 2009, and December 30, 2010. Peritoneal dialysis effluent was collected at the time of peritoneal equilibration test. The peritoneal effluent mtDNA was detected by quantitative real-time PCR assay, the concentrations of dialysate IL-6, IL-17A, TNF-α and IFN-γ were quantitated by ELISA assay. The results were compared with PSTR, patient survival and technique survival.

Results: One hundred and eighty-nine patients were included in the study. The average age was 47.1 ± 13.5 years, 55.6% of the patients were males. The median follow-up period was 41.9 months. The average PSTR was 0.66 ± 0.12, the median mtDNA level was 4325 copies/ul. The median concentrations of IL-6, IL-17A, TNF-α and IFN-γ were 25.9, 10.8, 25.8 and 17.9 pg/ml, respectively. We found that peritoneal effluent mtDNA was significantly correlated with PSTR (r =0.461, P < 0.001), IL-6 (r = 0.568, P < 0.001), TNF-α (r = 0.454, P < 0.001) and IFN-γ (r = 0.203, P = 0.005). After adjustment for multiple covariates, peritoneal effluent mtDNA was independently correlated with IL-6 and PSTR. Peritoneal effluent mtDNA was not associated with patient and technique survival.

Conclusions: We found that theperitoneal effluent mtDNA level correlated with the degree of intraperitoneal inflammatory status in PD patients. Peritoneal effluent mtDNA was an independent determinant of PSTR but did not affect patient and technique survival.

SA-PO1097

Irisin Levels and Adequate Dialysis in Nondiabetic Peritoneal Dialysis Patients

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Background: Irisin is a recently discovered hormone thought to be involved in energy regulation. However, only a single study has focused on irisin levels in peritoneal dialysis patients, but that study did not control for multiple factors. Therefore, it remains unclear whether irisin is affected by dialysis adequacy or whether irisin is associated with protein-energy wasting and insulin resistance in chronic kidney disease.

Methods: Atotal of 59 nondiabetic peritoneal dialysis (PD) patients and 52 healthy controls were enrolled in this cross-sectional study. Case histories and blood, urine, and dialysate samples were analyzed. Serum irisin levels were measured by ELISA and compared between the two groups.

Results: Serum irisin levels were lower in nondiabetic PD patients (median (interquartile range): 17.02 (11.27-20.09) ng/ml) compared with age- and sex-matched healthy controls (22.17 (17.00-26.57) ng/ml). Multivariate regression analysis revealed that fasting glucose levels were inversely correlated with serum irisin levels in PD patients. No association of serum irisin levels with homeostatic model assessment of insulin resistance was observed, nor was there an association between the Geriatric nutritional risk index and serum irisin levels. Conversely, peritoneal Kt/Vurea (β=4.933; 95% CI, 0.536-9.331; P =0.029) and peritoneal C_{Cr} (β= 0.259; 95% CI, 0.053-0.465; P=0.015) were positively associated with serum irisin levels among PD patients.

Conclusions: Serum irisin levels in non-diabetic PD patients were lower than those in healthy controls, and peritoneal Kt/V and creatinine clearance were positively correlated with serum irisin levels. Thus, adequate dialysis may improve irisin secretion.

Funding: Government Support - Non-U.S.

SA-PO1098

Peritoneal Dialysis Removes More Serum Sclerostin Than Hemodialysis in Uremic Patients

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Background: It's not known whether PD could remove serum sclerostin in uremic patients or not. This study observed the removal of sclerostin by PD and compared the difference of the removal of it between PD and HD.

Methods: Subjects in four groups were from Jiangxi Provincial People's Hospital. Control: 56 healthy volunteers; CKD5: 24 cases in stage 5 CKD but not on dialysis; HD: 42 cases on HD; PD: 100 cases on PD (only 81 serum samples). Sclerostin was determined with ELISA kit.

Results: (1) Compared with control, serum sclerostin in CKD5 and HD groups was increased, with it was higher in CKD5 than in HD, the differences among all groups were statistically significant (P < 0.05); on the other hand, sclerostin in serum and PD fluid in PD group was close to that in control.

Table1-1. Sclerostin in each group (Mean±SD)					
	Control	CKD5	HD	PD(serum)	PD(Fluid)
Sclerostin(pg/ml)	6.59±2.30	10.79±3.25	8.76±3.50	6.25±4.96	5.13±1.42
Table1-2. Sclerostin in PD group patients stratified by age					
	Number	Mean	SD	P	
1(≤45yrs, serum)	41	5.89	5.577		
2(>45yrs, serum)	40	6.06	3.271	0.868	
1(PD fluid, PD fluid)	48	5.10	1.470		
2(PD fluid, PD fluid)	52	5.16	1.326	0.836	
Table1-3. Sclerostin in PD group patients stratified by PD time					
1(≤12mos, serum)	58	5.27	3.810		
2(>12mos, serum)	23	7.74	5.778	0.068	
1(≤12mos, PD fluid)	72	5.1	1.344		
2(>12mos, PD fluid)	28	5.2	1.527	0.76	

(2) Patients in PD group were stratified according to age (45yrs or older) or PD time (on PD for 12 months or longer). For resulting groups, the differences in serum or PD fluid sclerostin were all not statistically significant (P>0.05) (Table1-2, 1-3).

Conclusions: Serum sclerostin was increased in CKD5 patients than in normal individuals. HD and PD both could remove serum sclerostin while PD removed more. Patient's age and time in PD had no effects on the removal of it in PD group. The findings could provide insights for CKD-MBD pathogenesis in CKD patients and the basis for choosing dialysis modes.

Funding: Government Support - Non-U.S.

SA-PO1099

Relationship between Glucose Spike and Cardiovascular Risk Factors in Diabetic Patients with Peritoneal Dialysis: A Cross-Sectional Study

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Background: Several reports have reported that glucose spike (GS), postprandial increase in blood glucose, may be a risk factor for mortality and CVD incidence in patients with diabetes. We investigated relationship between glucose spike and cardiovascular risk factors in diabetic PD patients.

Methods: We measured diurnal variation in blood glucose for 7 days using continuous glucose monitoring (CGM, *ipro2: Medtronic, Northridge, CA, USA*). GS was defined as mean amplitude of glycemic excursion (MAGE), which calculated as an average value of times exceed over 1SD of average blood glucose. We evaluated relationships between MAGE and cardiovascular risk factors, including HbA1c, GA, blood pressure (BP), peritoneal function, echocardiographic findings, pulse wave velocity (PWV).

Results: Overall, 22 diabetic PD patients were included (mean age; 65.7 year old, male/female; 16/6, average PD vintage; 31 months). Median value of MAGE was 60±22.85. We deviated participants into two groups; Low MAGE (<60) group and high MAGE (≥60) group. Low MAGE group was older, longer PD vintage and lower PWV levels. There was no difference in HbA1c, ejection fraction, BP, peritoneal function, past history of CVD, and smoking between two groups. In the multiple regression analysis, higher level of MAGE was an independent predictor for worsening PWV (P=0.0045).

Conclusions: Higher MAGE was strongly correlated with high level of PWV. Even after adjusting by cardiovascular risk factors, higher level of MAGE was an independent predictor for PWV. These results suggest that GS might be involved in atherosclerosis progression in diabetic PD patients.

SA-PO1100

Adequacy of a Single Daily Icodextrin Exchange as Initial Therapy for Incident End-Stage Renal Disease Patients with Residual Kidney Function: Predictions from the Three-Pore Model

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Background: Incremental dialysis is the treatment of ESRD patients with gradually increasing dialysis doses in response to declines in their residual kidney function. Incremental PD may impose fewer restrictions on patients' lifestyle, help attenuate lifetime peritoneal and systemic exposure to glucose and its degradation products, and minimize connections that could compromise the sterile fluid path. In this study, we utilized a three-pore kinetic model to assess fluid and solute removal for single daily icodextrin regimens for patients with varying glomerular filtration rates (GFR).

Methods: Single icodextrin exchanges of 8 to 16 hours using 2 and 2.5 L bag volumes were simulated for different patient transport types (i.e. high to low) to predict daily peritoneal ultrafiltration (UF), daily peritoneal sodium removal, and weekly total (peritoneal + residual kidney) Kt/V (Kt/V_{Total}) for patients with GFRs ranging from 0 to 15 mL/min/1.73m^2. Adequacy of treatments was assessed based on weekly $Kt/V_{Total} \geq 1.7$.

Results: Daily peritoneal UF varied from 359 to 607 mL and daily peritoneal Na removal varied from 52 to 87 mEq depending on length of icodextrin exchange and bag volume. Both were effectively independent of patient transport type. GFR needed to achieve adequate dialysis varied between 5 and 10 mL/min/1.73m^2 depending on patients' total body water (TBW) and bag volume.

Single Daily Icodextrin	GFR needed to achieve weekly $Kt/V_{Total} \geq 1.7$			
	TBW: 30L (55 kg)	TBW: 40L (73 kg)	TBW: 50L (91 kg)	TBW: 60L (109 kg)
2L	6	8	9	10
2.5L	5	7	9	10

Conclusions: A single daily icodextrin exchange can be tailored to provide adequate UF and Na removal in incident ESRD patients with sufficient RKF. UF and Na removal are relatively independent of patient transport, but achieving an adequate Kt/V_{Total} is highly dependent upon TBW/BSA. Smaller patients (i.e. 55 kg) may achieve adequate dialysis (weekly $Kt/V_{Total} \geq 1.7$) with GFR as low as 6 mL/min/1.73m^2. A solitary icodextrin exchange may therefore be reasonable initial therapy for some incident ESRD patients. Potential lifestyle and clinical benefits need to be evaluated.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

SA-PO1101

The Role of Inflammation in the Effect of BMI on Patient Survival in Peritoneal Dialysis Patients: Results from the GLOBAL Cohort Study

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Background: A higher body mass index (BMI) is known to predict better survival in haemodialysis, with a recent report demonstrating that this is primarily in patients with high levels of systemic inflammatory markers. Studies of patients on peritoneal dialysis (PD) have not shown a consistent relationship between BMI and survival but the reasons for this are unclear. We hypothesised that the reason for the lack of association in previous studies was due to lower levels of systemic inflammation in PD patients.

Methods: We used incident (measures within 3 months of starting) and prevalent PD patients from the Global Fluid Study, a cohort study of 10 centres from Korea, Canada and the UK. Plasma samples were assayed for IL-6 and a contemporaneous BMI was measured. The primary analysis was Cox regression stratified by centre testing the effect of BMI in a univariable model on patients with plasma IL-6 above median, with sensitivity analyses including using plasma IL-6 levels above the 75th centile, testing plasma IL-6 and BMI for an interaction, using patients with albumin levels <35g/l and <30g/l and testing for an effect of dialysate glucose load and restricting the analysis to 1 year follow up.

Results: Of the 559 incident and 376 prevalent patients, 241 and 186 respectively died during follow up. The median and 75th centile for plasma IL-6 levels were 1.49 and 2.83 in incident patients and 1.26 and 2.46 in prevalent patients respectively. There was no benefit of BMI in the inflamed group in either incident (HR 1.03, 95% CI 0.99-1.07) or prevalent (HR 0.98, 95% CI 0.95-1.02) patients. This pattern was replicated in patients with plasma IL-6 levels >75th centile and there was no interaction between IL-6 and BMI in either incident or prevalent patients. There was no benefit in patients with albumin levels <35g/l or <30g/l, nor any interaction or effect of dialysate glucose load.

Conclusions: The protective effect of BMI for inflamed haemodialysis patients is absent in inflamed peritoneal dialysis patients. This might be due to the extra caloric loading in PD but it is not affected by the amount of dialysate glucose prescribed.

SA-PO1102

Association between Diuretic Use and Residual Kidney Function in Peritoneal Dialysis Patients: International Comparison from the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS)

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Background: Preservation of residual kidney function (RKF), as determined by urine volume or mean urea and creatinine clearances (GFR_r), is strongly associated with better survival on dialysis. Modest sized trials have demonstrated that diuretics can maintain urine volume and that renin angiotensin system inhibitors (RASi) might preserve RKF in PD patients.

Methods: The PDOPPS is a prospective cohort study of PD treatment and outcomes in Australia, Canada, Japan, New Zealand, Thailand, the United Kingdom and the United States (US). Based on an initial cross-section of 1,655 patients in Australia, Canada, Japan and US, linear models were used to estimate the associations of diuretic, ACEi/ARB use with 24-hour urine volume and GFR_r.

Results: Among patients with RKF,diuretic use was highest in Japan (74%) and lowest (39%) in Australia. ACEi and/or ARB use was highest in Japan. In adjusted models, greater urine volume and higher GFR_r were associated with shorter PD vintage and diuretic use, but not with ACEi or ARB use.

Table 1a) Patient characteristics by country

	Australia	Canada	Japan	US
Number of patients	198	402	522	533
24-hour urine volume measurement in 8 months	70%	76%	58%	94%
Prior HD	27%	27%	26%	38%
Anuric	6%	12%	5%	20%
24-hour urine volume (L), median [IQR]	0.98 [0.48,1.49]	0.75 [0.32,1.29]	0.73 [0.30,1.21]	0.55 [0.10,1.15]
Weight (Kg) , mean (std)	79.6(18.8)	76.7(19.3)	59.5(12.4)	81.2(21.8)
GFR, (mL/min/1.73m^2) , median [IQR]	4.0 [1.5,6.4]	4.0 [1.6,6.2]	0.7 [0.3,3.5]	2.9 [0.5,6.6]
Diuretic use for patients with urine output	39%	60%	74%	51%
ACEi	27%	29%	7%	20%
ARB	22%	27%	62%	24%
PD vintage (years), mean (std)	1.9(1.8)	2.4(2.7)	3.1(3.0)	2.1(2.0)

Table 1b) Effect estimates with 95% CI for PD vintage, Diuretic, ACEi, and ARB in two models*

	Model Outcomes	
	log(24-hour Urine Volume+1)/Weight*100	log(GFR,+1)
PD vintage	-0.06(-0.07,-0.04)	-0.12(-0.15,-0.09)
Diuretic	0.14(0.06,0.21)	0.16(0.02,0.29)
ACEi	0.04(-0.06,0.13)	0.10(-0.07,0.26)
ARB	-0.03(-0.11,0.05)	-0.02(-0.17,0.13)

*Models adjusted for PD vintage, patient age, black race, gender, and diabetes, accounting for facility clustering.

Conclusions: Diuretic use is strongly associated with urine volume in this early cross-sectional analysis. As the study accrues follow-up time, PDOPPS will provide important longitudinal data on practice variation and outcomes to evaluate the role that diuretics may play in preserving residual kidney function among PD patients.

SA-PO1103

Substantial Decrease in Renal Function and Quality of Life in Peritoneal Dialysis Patients with Diabetes Mellitus after Discontinuation of Vasopressin-2-Receptor Antagonist, Tolvaptan Takeyuki Hiramatsu, Yuko Asano, Masatsuna Mabuchi, Akiko Ozeki, Hideaki Ishikawa, Shinji Furuta. *Dept of Nephrology, Konan Kosei Hospital, Konan, Aichi, Japan.*

Background: Last year we reported that tolvaptan preserved residual renal function in peritoneal dialysis (PD) patients. Here, we followed the patients after tolvaptan discontinuation.

Methods: Twenty four incident PD patients with congestive heart failure were followed for 24 months. Patients were divided into two groups, group A (n=15) and group B (n=9). In group A, patients received 15 mg/day of tolvaptan from the initiation of PD, and in group B, tolvaptan was administered when urine volume lowered below 500 ml/day. We evaluated the medical costs, urine volumes, urine Kt/V, quality of life (QOL) assessed with Short – Form Health Survey (SF-36), and comorbidities which occurred during 12 months after tolvaptan discontinuation.

Results: In group A, urine volume, urine Kt/V, and QOL scores were substantially decreased after tolvaptan discontinuation(* : p<0.05 vs at baseline).

		before 6 months	at baseline	after 6 months	after 12 months
Residual renal function	urinary volume (mL/day)	1080.0 ± 465.7	984.0± 490.0	650.0 ± 484.2	552.0 ± 414.1*
	urine Kt/V	0.862 ± 0.362	0.831 ± 0.452	0.455 ± 0.359*	0.306 ± 0.256*
SF - 36	summary of physical components	38.6 ± 13.8	37.8 ± 13.4	28.3 ± 13.2*	25.1 ± 10.6*
	summary of mental components	51.2 ± 9.0	49.6 ± 9.4	48.4 ± 11.3	40.6 ± 9.2

Hospitalization was seen in total 9 patients (6 for heart failure, 1 for myocardial infarction, 2 for severe infection), 2 patients died, and 2 patients were switched to hemodialysis (HD). Eleven patients continued on PD. In group B, all patients showed that urine volume was not increased by tolvaptan use, however decreased to 0 mL within 6 months after tolvaptan discontinuation. Moreover 3 patients died, 6 were switched to HD in group B. The medical costs were also increased in group B.

Conclusions: After discontinuation of tolvaptan, renal function and QOL were substantially decreased in PD patients. Residual renal function was thought to be important for the survival and QOL in PD patients.

SA-PO1104

Association of Plasma Brain Natriuretic Peptide Concentration with Loss of Residual Renal Function in Peritoneal Dialysis Patients Yasuhiro Kawai,[1] Shigeru Tanaka,[2] Masatoshi Hara,[1] Hiroaki Tsujikawa,[1] Hisako Yoshida,[3] Kazuhiko Tsuruya,[1,4] Takanari Kitazono.[1] *[1]Dept of Medicine and Clinical Science, Kyushu Univ, Fukuoka City, Fukuoka Prefecture, Japan; [2]Div of Internal Medicine, Fukuoka Dental College, Fukuoka City, Fukuoka Prefecture, Japan; [3]Dept of Clinical Research Center, Saga Univ, Saga City, Saga Prefecture, Japan; [4]Dept of Integrated Therapy for Chronic Kidney Disease, Kyushu Univ, Fukuoka City, Fukuoka Prefecture, Japan.*

Background: Plasma brain natriuretic peptide (BNP) concentration is widely accepted as a marker of fluid status in patients with chronic kidney disease (CKD) including dialysis. We have reported that BNP is independently associated with kidney function decline in predialysis CKD patients (Yoshitomi R, et al. J Hypertens, 2016). However, the relationship between BNP and residual renal function (RRF) in peritoneal dialysis (PD) patients remains unclear. The aim of this study was to elucidate the relationship between BNP and loss of RRF in PD patients.

Methods: We followed retrospectively 104 PD patients who started PD in our hospital between June 2006 and May 2016. Five patients were excluded because of missing data. We divided the remaining 99 subjects into two groups with high and low BNP by a median of plasma BNP concentration (95.7 pg/mL). We estimated the association between BNP and loss of RRF (daily urine volume <100 mL) using a Kaplan-Meier method and Cox proportional hazards model.

Results: During a median range follow-up period of 24 (12-36) months, 31 patients had lost RRF. The event-free RRF survival in the high BNP group was significantly lower than in the low BNP group by the Kaplan-Meier method (p = 0.004). After adjusting for potential confounders such as age, sex, diabetic nephropathy, systolic blood pressure, urinary protein/creatinine ratio, and renal Kt/V, high plasma BNP concentration was independently associated with loss of RRF (hazard ratio for high BNP group vs. low BNP group, 3.34; 95% confidence interval, 1.29 to 9.17; p = 0.012).

Conclusions: Plasma BNP concentration at PD initiation could be an independent predictor of loss of RRF in PD patients.

SA-PO1105

Association of Serum Total Bilirubin with Loss of Residual Renal Function in Peritoneal Dialysis Patients Hiroaki Tsujikawa,[1] Shigeru Tanaka,[2] Masatoshi Hara,[1] Yasuhiro Kawai,[1] Yuta Matsukuma,[1] Hisako Yoshida,[3,4] Kazuhiko Tsuruya,[1,4] Takanari Kitazono.[1] *[1]Dept of Medicine and Clinical Science, Kyushu Univ, Fukuoka, Japan; [2]Div of Internal Medicine, Fukuoka Dental College, Fukuoka, Japan; [3]Dept of Clinical Research Center, Saga Univ, Saga, Japan; [4]Dept of Integrated Therapy for Chronic Kidney Disease, Kyushu Univ, Fukuoka, Japan.*

Background: Bilirubin has been recognized as a novel endogenous antioxidant. Low serum bilirubin has been reported to be associated with the progression of kidney disease in patients with chronic kidney disease. However, it is unclear whether a relationship exists between low serum bilirubin and loss of residual renal function (RRF) in peritoneal dialysis (PD) patients. The aim of this study was to investigate the relationship between serum total bilirubin concentration and loss of RRF within 3 years after starting PD.

Methods: We followed retrospectively 104 PD patients who started peritoneal dialysis in our hospital between June 2006 and May 2016. Ten patients who had chronic liver disease or cirrhosis were excluded and the remaining 94 patients were included in the present study. Patients were divided into three groups based on tertile of serum total bilirubin concentration: Tertile 1 (T1) <0.3; T2 = 0.3; T3 ≥0.4. We estimated the relationship between serum bilirubin and loss of RRF (defined as daily urine volume <100 mL) within 3 years after starting PD using a Cox proportional hazards model.

Results: During the 3-year observation period, 22 patients had lost RRF. The incidence rate of loss of RRF increased linearly with the decrease in serum total bilirubin levels (*P* for trend <0.05). After adjusting for confounding factors, low serum total bilirubin level was an independent predictor of loss of RRF (hazard ratio [HR] for every 0.1 mg/dL decrease, 1.50; 95% confidence interval [CI], 1.01 to 2.51; HR (95%CI) for T2 and T1 [vs. T3] 2.03 (0.65-7.88) and 3.70 (1.00-15.9), respectively.

Conclusions: This result suggests that lower serum total bilirubin level is associated with loss of RRF in PD patients.

SA-PO1106

Statin Treatment Strongly Prevents Residual Renal Function in Peritoneal Dialysis Patients Using Contrast Medium Administration Saeko Miura, Fumiko Kuwahara, Kenji Harada, Hidetoshi Kanai. *Dept of Nephrology, Kokura Memorial Hospital, Kitakyushu City, Japan.*

Background: Recently, prospective studies have demonstrated that statins have a protective effect in preventing contrast-induced nephropathy (CIN), but there has been no study that statins have prevent residual renal function (RRF) in peritoneal dialysis (PD) patients. Here, we investigated whether or not statins prevent RRF and decrease the rate of transferred to hemodialysis (HD) in PD patients undergoing iodinated contrast medium administration (ICMA).

Methods: This study was based on a single center retrospective registry that consisted of 116 patients initiated PD between January 2010 and December 2012. We allocated 85 patients who underwent ICMA. The patients were divided into two groups according to

use of statin at the time of ICMA, as follows: statin-treated group (Group A, n=41), and statin-naive group (Group B, n=44). RRF was determined based on the mean 24-hour urine volume and estimated glomerular filtration rate (eGFR). These measures of RRF were determined on the day before ICMA (baseline), and 48 hours, 2 weeks, and 4 weeks after ICMA. The primary endpoint was defined as the rate of decline in RRF. Secondary endpoints were defined as the rate of transfer to HD. The 3-year event rates were estimated by Kaplan Meier analysis with P values from log-rank tests.

Results: Group A had higher BMIs, and higher baseline eGFR than Group B. There were significant differences between Group A and Group B with respect to the decline in urine volume 2 weeks after ICMA (192±205 vs. 335±329 mL : P=0.018). Between the two groups, there were no significant differences in the rate of declined eGFR. After 3 years, the rate of transferred to HD of Group A was significantly lower than that of Group B (P <0.001, log-rank test). In multivariate Cox proportional hazard model, we demonstrated that statin treated group was a significant lower risk for the transferred to HD (HR 0.280, 95% CI 0.114-0.686, P=0.005) after ICMA.

Conclusions: Pre-procedure statin treatment is associated with preservation of the RRF and transfer to HD among PD patients undergoing ICMA.

SA-PO1107

Comparison of Advanced Image-Guided Percutaneous (AIP) versus Advanced Laparoscopic Surgical (ALS) Technique for the Placement of Peritoneal Dialysis (PD) Catheters

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Background: PD offers more advantages to patients with ESRD.Timely placement of a functional PD catheter with minimal complications is crucial to ensure patient acceptance and long term PD success. AIP and ALS techniques both represent best practice catheter placement options as taught by the PD University. We conducted a retrospective cohort study to compare access time to procedure, complications, and overall catheter survival between placement techniques.

Methods: Patient charts for a subpopulation of KPNC members who had either an ALS or AIP PD catheter placed between 1/1/2011 and 12/31/2013 were reviewed by two nephrologists and two Interventional Radiologists. Wilcoxon two-sample tests were employed to compare access times. Occurrence of complications was compared using chi-square tests. Modified least squares regression was used to compare adjusted one-year catheter survival.

Results: We identified 191 PD catheters placed via AIP and 238 via ALS technique. Adjusted one year PD catheter survival was 80% by AIP vs. 91% by ALS. Major complications were rare in either group (<1%). Minor complications occurred in 45.6% of AIP and 38.7% of ALS cases. Median access time to procedure was 12 and 33 days for AIP and ALS patients, respectively.

	AIP (n=191)	ALS (n=238)	p-value
Adjusted One year catheter survival (Proportion (95% CI)	0.80 (0.74-0.87)	0.91 (0.87-0.96)	0.009
Access time, days, (Median IQR)	12.0 (6.0, 19.0)	33.0 (13.0, 57.0)	<0.0001
Major Complications (n, %)			0.49
None	190 (99.5)	237 (99.6)	
Any	1 (0.5)	1 (0.4)	
Minor Complications (n, %)			0.17
None	104 (54.4)	146 (61.3)	
Any	87 (45.6)	92 (38.7)	

Conclusions: Both AIP and ALS techniques have excellent one year survival with very low major complication rates. Though a slightly lower one year catheter survival rate was demonstrated among AIP cases, these patients had a much shorter access time. The techniques complement each other; therefore either may be used based upon local resources and expertise to increase the adoption of PD.

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SA-PO1108

Fluoroscopic and Ultrasound Guided Placement versus Laparoscopic Placement of Peritoneal Dialysis Catheters: A Single Center Experience

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Background: A variety of peritoneal dialysis catheter (PDC) placement techniques are available including laparoscopic placement by surgeons, and percutaneous placement by interventional radiologists. The aim of this study was to compare the one-year outcomes of both techniques.

Methods: We retrospectively reviewed the medical records of 240 patients who had their first PDC placed between January 2005 and December 2015. We compared the outcomes of the catheters placed using fluoroscopic and ultrasound guidance (IR group, n=50), with the catheters placed using laparoscopic technique (LAP group, n=190). The primary endpoint was complication-free catheter survival at 365 days. Secondary endpoints were complication-free catheter survival at 90 days, overall catheter survival at 365 days, median days-to-first complication and median days-to-catheter removal. Between-group differences were assessed using Chi square, Mann-Whitney U tests and Kaplan Meier methods.

Results: The study included 240 patients, 134 females (56%), median age was 54.7 years (IQR=41.3-64.3), and median BMI was 28.3 (IQR=24.1-34.5). There was no significant difference in the baseline characteristics of both groups. In the IR group, the complication-free catheter survival at 90 and 365 days were 64% and 48%, compared to 70.5% (p=0.37) and 53.4% (p=0.49) respectively, in the LAP group. Catheter malfunction was significantly higher in the LAP group (30%) compared to the IR group (16%, p=0.05). Catheter leak was significantly higher in the IR group (10%) compared to the LAP group (3.2%, p=0.05). There was no statistically significant difference in the overall catheter survival at 365 days between the two groups.

Conclusions: The fluoroscopic and ultrasound guided placement of PDC offers a clinically effective alternative to laparoscopic placement with similar survival rates. The rate of catheter malfunction was higher in the LAP group, while the rate of catheter leak was higher in the IR group.

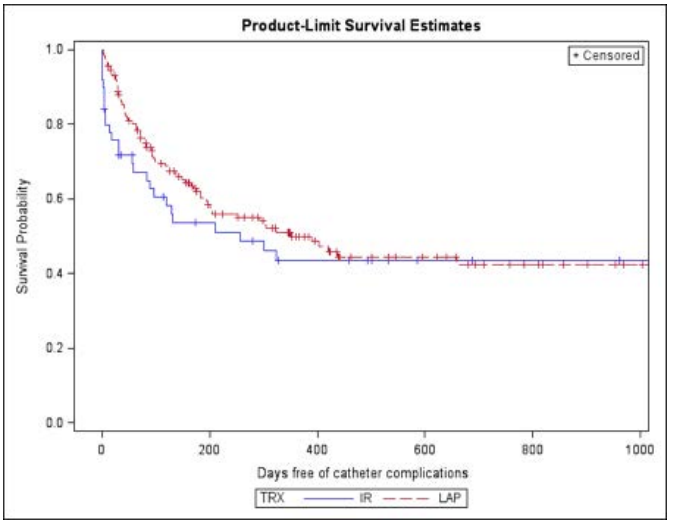

Figure 1: Complication-free catheter survival for the two groups

Table1: Demographic characteristics of patients in each group.

	Overall		IR		Laparoscopic		
Characteristics	**n=240**	**%**	**n=50**	**%**	**n=190**	**%**	**P-value**
Age (median, IQR)	54.7	(41.3, 64.3)	56.4	(47.2, 66.4)	54.34	(40.3, 63.41)	0.1023
Gender Female	134	55.83	21	42	113	59.47	0.0268
Male	106	44.17	29	58	77	40.53	
BMI (median, IQR)	28.3	(24.1, 34.5)	27.9	(25.7, 31.7)	28.5	(23.7, 34.6)	0.9157
Diabetes	115	47.92	25	50.00	90	47.37	0.7403
Hypertension	222	92.5	44	88.00	178	93.68	0.2232
Coronary Artery Disease	59	24.58	17	34.00	42	22.11	0.0822
Congestive Heart Failure	57	23.75	14	28.00	43	22.63	0.4274
Peripheral Vascular Disease	29	12.08	8	16.00	21	11.05	0.3396
Cerebrovascular Disease	14	5.83	3	6.00	11	5.79	0.9999
Urgent Start	29	12.08	18	36.00	11	5.79	<0.0001
Elective	211	87.92	32	64.00	179	94.21	

SA-PO1109

Laparoscopic versus Radiologic Peritoneal Catheter Outcomes in Urgent and Elective Dialysis Starts

Ammar Almehmi,[1] Bradford Jackson,[2] Ahmed Kamel Abdel Aal.[3] *[1]Nephrology and Radiology, UAB; [2]Preventive Medicine, UAB; [3]Radiology, UAB.*

Background: Urgent unplanned dialysis starts are commonly seen in clinical practice, responsible for about one third of the incident dialysis cases. Both radiologic (IR) and laparoscopic (LAP) placement of peritoneal catheters (PDC) have been utilized in both urgent and elective dialysis starts. The aim of our study is to compare PDC outcomes between urgent dialysis start and elective dialysis start in both LAP and IR groups.

Methods: We retrospectively reviewed the medical records of 240 patients who underwent de novo PDC placement. The study cohort was divided based on dialysis start and placement technique as shown in Table 1. Medians and interquartile ranges (IQR) were calculated for continuous variables, and frequencies and percentages for categorical variables. Between group differences were compared using Fisher's Exact test and Kruskal-one way analysis of variance. Complication free survival and overall catheter survival curves were estimated using the Kaplan Meier approach, and Log-Rank tests were used to assess homogeneity across strata.

Results: In the urgent start cohort, the complication-free catheter survival at 90 and 365 days were 61% and 39%, respectively, in the IR group, as compared to 73% (p=0.69) and 73% (p=0.07), respectively, in the LAP group. Further, in the elective start cohort, the

complication-free catheter survival at 90 and 365 days were 66% and 53%, respectively, in the IR group, as compared to 70% (p=0.59) and 52% (p=0.92), respectively, in the LAP group. Overall survival at 365 days among urgent start cases was 33% in both IR and LAP groups (p=0.99). Similarly, in the elective start cohort, the overall survival at 365 days was 64% and 49% (p=0.15) in the IR and LAP groups, respectively.

Conclusions: Peritoneal catheters placed radiologically or laparoscopically had comparable outcomes in urgent and elective dialysis starts.

Study Cohort (n= 240)			
Laparoscopic (LAP) group (n= 190)		Radiologic (IR) group (n=50)	
Urgent dialysis start	Elective dialysis start	Urgent dialysis start	Elective dialysis start
n= 11	n= 179	n= 18	n = 32

SA-PO1110

Modified Simple Peritoneal Wall Anchor Technique in Peritoneal Dialysis Hideaki Oka,[1] Shunsuke Yamada,[2] Taro Kamimura,[1] Yutaro Hirashima,[1] Tomoya Shukuri,[1] Seishi Aihara,[1] Atsumi Harada,[1] Kazuhiko Tsuruya.[2,3] *[1]Div of Kidney Center, Matsuyama Red Cross Hospital, Matsuyama, Japan; [2]Dept of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan; [3]Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.*

Background: Outflow obstruction, a common complication in patients with peritoneal dialysis (PD), usually results in unnecessary catheter removal or replacement. This studydescribes a modified, simple method of anchoring a PD catheter on the anterior peritoneal wall without using a laparoscopic system (peritoneal wall anchor technique, PWAT).

Methods: We performed a retrospective cohort study of consecutive PD catheter insertions, and compared the catheter survival rate between the traditional method and the modified, simple PWAT. The traditional method was used in 54 cases and the modified, simple PWAT was used in 17 cases. The primary endpoint was the occurrence of surgical catheter repair because of outflow obstruction by day 365. The secondary endpoint was the occurrence of catheter migration with obstruction requiring any interventions, including the alpha-replacement method by day 365. Catheter survival was analyzed by Kaplan-Meier survival curves.

Results: Migration-free catheter survival was significantly (P=0.02) higher in the PWAT group (100%, 17/17) than in the traditional group (72.2%, 39/54). Catheter survival without surgical repair or cessation of PD was also significantly (P=0.04) higher in the PWAT group (100%, 17/17) than in the traditional group (77.8%, 42/54). Similarly, migration-free and surgery-free catheter survival rates in cases with a straight-type catheter in the PWAT group were significantly higher than those in cases with a straight-type catheter in the traditional group.

Conclusions: Our results suggest that the modified, simple PWAT provides a better catheter survival rate than the traditional method by preventing catheter migration with obstruction in PD.

SA-PO1111

A Modified Seldinger's Percutaneous Peritoneal Dialysis Catheter Implantation Method; Viable Option for Patients Requiring Unplanned Urgent-Start Peritoneal Dialysis Il Young Kim, Jong Man Park, Harin Rhee, Sang Heon Song, Eun Young Seong, Dong Won Lee, Soo Bong Lee, Ihm Soo Kwak. *Dept of Internal Medicine, Pusan National Univ School of Medicine, Yangsan, Republic of Korea.*

Background: Urgent-start peritoneal dialysis (UPD) is applied to patients who need PD in less than 2 weeks, but are able to wait for more than 48 hours before starting the PD. A modified Seldinger's percutaneous PD catheter implantation method with no break-in time performed by nephrologists has been used for more than 10 years in our institution. To evaluate the usefulness and safety of this method in patients undergoing UPD, we reviewed the clinical outcomes of the two (percutaneous and surgical) PD catheter implantation methods in our university hospital.

Methods: This study included 172 patients who underwent UPD. Based on the PD catheter implantation method, the patients were divided into a percutaneous group (n = 104) and a surgical group (n = 68). PD catheters for percutaneous group were placed using a modified Seldinger's percutaneous implantation method with tapered dilators.

Results: The percutaneous group showed higher BUN, higher serum creatinine, lower hemoglobin, and lower serum albumin levels compared with the surgical group. The percutaneous group showed significantly shorter break-in time after catheter implantation (0.6±2.5 vs. 6.4±3.9 days, p<0.05). There were no significant differences in 90-day infectious complications (peritonitis, exit site infection, and tunnel infection), and also 90-day mechanical complications (pericatheter leakage, catheter migration, diminished outflow, hemorrhage, bowel perforation, hernia and catheter reinsertion) between the two groups. One-year catheter survival was 96.2% in percutaneous group, and 97.1% in surgical group with no significant difference.

Conclusions: The percutaneous group showed more advanced kidney dysfunction, but was able to start PD successfully with shorter break-in time. Moreover, no significant differences of 90-day infectious/mechanical complications and 1-year catheter survival rates were seen between both groups. A modified Seldinger's percutaneous catheter implantation method by nephrologists can be a safe and effective option for unplanned UPD.

SA-PO1112

Tailoring the Peritoneal Catheter Access: One Size Does Not Fit All Mercedes Gonzalez, Sandra Beltrán, Antonio Vazqueez, Belen Vizcaino, Pablo Molina, Luis M. Pallardo. *Nephrology, H. Univ Dr. Peset; Nephrology, H. Univ Dr. Peset; General and Digestive Surgery, H. Univ Dr. Peset; Nephrology, H. Univ Dr. Peset; Nephrology, H. Univ Dr. Peset; Nephrology, H. Univ Dr. Peset.*

Background: Tenckhoff catheter remains the first choice in the treatment of peritoneal dialysis (PD). The selection of the catheter length is not usually done increasing the risk of catheter dysfunction. The objective of the study was to analyse the correlation between patient's height and intraperitoneal length (IP-L), measured from the peritoneal entry (at the level of the deep cuff) to the Pouch of Douglas during catheter insertion procedure.

Methods: A protected rigid guide was introduced in the peritoneal cavity during catheter insertion and when the Pouch of Douglas was reached, the protected guide was removed and length measured with a sterile ruler. If IP-L was less than 19 cm, a 16.3 cm of IP-L self-locating PD-catheter was placed (short catheter), and if it was higher than 19 cm, a 21.5 cm of IP-L self-locating PD-catheter (long-catheter) was used. Test of correlation were made with patient's height and with navel-pubic symphysis length. Mechanical complications were recorded.

Results: 64 catheters were placed. The mean follow-up was 14.6±7.6 months. The patient's height was positively correlated with IP-L, R^2=0.136, p=0.03. Mean patients' height with long-catheter was 171.63±7.45 cm vs 166.18±8.45 cm for patients with short-catheters (p=0.009). Patients' height was divided in three groups: > 170 cm, between 171 to 168 cm and < 168 cm. A significantly higher percentage of differences between IP-L and height were observed in the 171 to 168 cm group (35%, 91% and 38%, respectively, p=0.008). There was no significant correlation of IP-L measured with this procedure with navel-pubic symphysis length (R^2=0.69,p=0.08). During all the follow-up period, only five patients (3%) had an omental wrapping that required surgical repair.

Conclusions: Measuring IP-L during the catheter insertion procedure is an easy way of improving the election of the best catheter length. Patients of height from 168 to 171cm could benefit from this new measurement.

SA-PO1113

Mortality and Hospitalizations in Intensive Dialysis: A Systematic Review and Meta-Analysis Anna Mathew,[1] Jody-Ann McLeggon,[1] Nirav R. Mehta,[1] Sam Leung,[1] Valerie Suzanne Barta,[1] Thomas Mcginn,[1] Gihad E. Nesrallah.[2] *[1]Hofstra Northwell School of Medicine, Northwell Health, NY; [2]Dept of Nephrology, Humber River Hospital, Canada.*

Background: Most ESRD patients are treated with 3 times/week hemodialysis (HD), but some receive intensive HD as short or nocturnal regimens. Existing data on mortality and hospitalization in intensive compared to conventional HD is conflicting. The objective of this study was to review the available evidence on intensive compared to conventional HD to evaluate outcomes of mortality and hospitalization.

Methods: We searched Cochrane Central Register, MEDLINE, EMBASE and Web of Science until March 15, 2016. We included observational studies and RCTs comparing intensive HD (>4 HD/week or >5.5 hrs/HD) with conventional HD (≤4 HD/week and ≤5.5 hrs/HD) that reported mortality and/or hospitalization. We evaluated risk of bias using standard tools. We conducted meta-analyses using random effects models. When reported, we analyzed home vs. in-center, and nocturnal vs. short daily HD separately to reduce heterogeneity.

Results: Twenty-three studies (2 RCTs and 21 observational) with 48,018 reported patients (38,300 on conventional HD and 9,718 on intensive HD) were included in the systematic review. Due to incomplete data reporting, 8 studies were included in the meta-analysis. Compared with conventional HD, home nocturnal [HR 0.45; 95% CI 0.32, 0.63; I^2=31%], home short daily [HR 0.86; 95% CI 0.78, 0.96; I^2=0%] and in-center nocturnal [HR 0.73; 95% CI 0.60, 0.90; I^2=57%] HD had significantly lower mortality. Compared to conventional HD, hospitalization rate/year [mean difference -0.25; 95% CI -0.41, -0.08; I^2=7%] and hospitalization days [mean difference -1.97; 95% CI -2.32, -1.61;I^2=2%] were significantly lower in nocturnal HD. Selection bias, lack of data, and limited number of RCTs precluded some data pooling and comparisons between important subgroups.

Conclusions: Intensive HD may be associated with reduced mortality and hospitalization compared to conventional HD. Confounding by indication and the lack of multiple randomized controlled trials limits the preferential use of intensive HD. Focus is needed on identifying specific patient groups who benefit from intensive HD.

SA-PO1114

Meta-Analysis of Cardiovascular and Quality of Life Outcomes in Randomized Clinical Trials of Intensive Hemodialysis Eric D. Weinhandl,[1,2] Fredric O. Finkelstein,[3] Allan J. Collins.[2] *[1]NxStage Medical, Inc., Lawrence, MA; [2]Univ of Minnesota, Minneapolis, MN; [3]Yale Univ, New Haven, CT.*

Background: There have been 3 parallel-group randomized clinical trials of intensive versus conventional hemodialysis: a trial of frequent nocturnal hemodialysis in Canada (*JAMA*, 298:1291-1299), the Frequent Hemodialysis Network (FHN) Daily Trial (*N Engl J Med*, 363:2287-2300), and the FHN Nocturnal Trial (*Kidney Int*, 80:1080-1091). We conducted a meta-analysis of individual treatment effects on cardiovascular and quality of life outcomes that were reported in all of these trials.

Methods: We abstracted end-of-study treatment effects in the aforementioned trials for each of the following outcomes: left ventricular mass, pre-dialysis systolic blood pressure

(SBP) and diastolic blood pressure (DBP), serum phosphorus, and physical component summary (PCS) and mental component summary (MCS) scores from 36-Item Short Form Survey (SF-36). Each summary treatment effect was estimated by a random effects model.

Results: Sample sizes of the trials were 51, 245, and 87. The duration of the Canadian trial was 6 months, whereas the duration of each FHN trial was 12 months. Summary treatment effects for intensive versus conventional hemodialysis are shown in the table. Summary treatment effects on left ventricular mass, pre-dialysis SBP and DBP, serum phosphorus, and SF-36 PCS and MCS were statistically significant ($P < 0.01$) and all favored intensive hemodialysis. Individual treatment effects on serum phosphorus were heterogeneous ($P = 0.02$), due to a smaller effect size in the FHN Daily Trial.

	Summary Treatment Effect	95% Confidence Interval	P-value
Left ventricular mass (g)	-13.4	(-19.5, -7.3)	<0.001
Pre-dialysis SBP (mmHg)	-9.6	(-12.8, -6.3)	<0.001
Pre-dialysis DBP (mmHg)	-4.9	(-6.8, -3.0)	<0.001
Serum phosphorus (mg/dL)	-1.0	(-1.6, -0.3)	0.005
SF-36 PCS	2.4	(0.7, 4.1)	0.007
SF-36 MCS	3.4	(1.4, 5.4)	0.001

Conclusions: In meta-analysis of 3 randomized clinical trials that collectively included 383 patients, intensive versus conventional hemodialysis had significant, beneficial effects on left ventricular hypertrophy, blood pressure, phosphorus balance, and health-related quality of life.

SA-PO1115

Cumulative Incidence of Kidney Transplant and Death in Incident ESRD Patients on Intensive Home Hemodialysis

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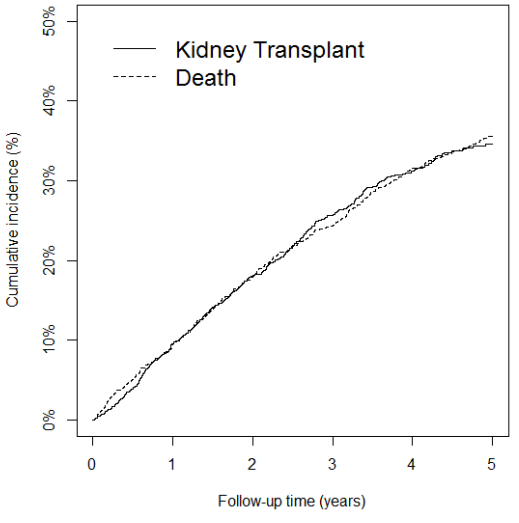
Background: Intensive home hemodialysis (HHD) has been primarily prescribed as a reactive therapy for patients who have accumulated years on dialysis. Clinical outcomes in incident ESRD patients on intensive HHD have not been described. We analyzed incidence of kidney transplant and death in incident ESRD patients on intensive HHD with the NxStage System One cycler (NxStage Medical, Inc., Lawrence, Massachusetts).

Methods: HHD patients were ascertained from NxStage records. We identified patients who initiated HHD between January 1, 2006, and December 31, 2012, and within 3 months after the date of ESRD onset. Comparator cohorts of incident ESRD patients on conventional hemodialysis (CHD) or peritoneal dialysis (PD) were ascertained from United States Renal Data System (USRDS) records. We followed patients from dialytic modality initiation to the earliest of transplant, death, or December 31, 2013, but for a maximum of 5 years. For HHD, we estimated cumulative incidence of transplant and death. For each modality, we estimated transplant and death rates, standardized by age, race, and sex with HHD.

Results: The HHD cohort comprised 1898 patients. Mean age was 56.6 years, 70.4% were male, and 81.6% were white. At 5 years, cumulative incidence of transplant and death were 34.5% and 35.6%, respectively.



With HHD, 5-year rates of transplant and death were 11.6 and 11.6 events per 100 patient-years (PY), respectively. In incident ESRD patients on CHD, standardized rates of transplant and death were 3.7 and 17.7 events per 100 PY, respectively; on PD, corresponding rates were 8.4 and 13.1 events per 100 PY.

Conclusions: Prescription of intensive HHD in incident ESRD patients is associated with equal 5-year probabilities of transplant and death. More studies are needed to assess benefits and risks of intensive hemodialysis as a first prescription, relative to both CHD and PD.

SA-PO1116

Hemodialysis Adequacy and Biochemical Outcomes in the FREEDOM Study of Daily Home Hemodialysis

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Background: Questions regarding hemodialysis adequacy and biochemical control with low dialysate volume persist. We analyzed dialysis dose and biochemical parameters in Following Rehabilitation, Economics and Everyday-Dialysis Outcomes Measurements (FREEDOM), a prospective cohort study of daily home hemodialysis on the NxStage System One cycler (NxStage Medical, Inc., Lawrence, Massachusetts).

Methods: We identified FREEDOM participants who completed 12 months of follow-up on daily home hemodialysis. Urea clearance and ultrafiltration volume were was assessed once per month; standardized Kt/V was estimated according to Leypoldt *et al* (*Hemo Int*, 8:193-197). Biochemical parameters were ascertained from monthly and quarterly blood tests. Adjusted mean differences between month 12 and baseline were estimated by mixed models.

Results: The cohort comprised 247 patients. Mean age was 51.4 years, 65% were male, and 63% were white. Mean standardized Kt/V was 2.28 at baseline and between 2.29 and 2.38 during the follow-up months. Mean biochemical parameters at baseline and month 12 and adjusted mean differences between month 12 and baseline are shown in the table.

	Baseline	Month 12	Adjusted Mean Difference	P-value
Blood urea nitrogen (mg/dL)	59.6	58.4	-1.7	0.27
Creatinine (mg/dL)	9.5	9.1	-0.3	0.24
Bicarbonate (mmol/L)	23.1	23.9	0.9	0.008
Potassium (mmol/L)	4.8	4.5	-0.3	<0.001
Sodium (mmol/L)	137.9	136.6	-1.2	<0.001
Albumin (g/dL)	3.9	4.0	0.1	0.001
Hemoglobin (g/dL)	11.8	11.1	-0.7	<0.001
Ferritin (ng/mL)	573.7	599.9	-57.0	0.16
Transferrin saturation (%)	31.4	28.4	-2.5	0.12
Alkaline phosphatase (IU/L)	107.3	108.3	0.0	>0.99
Calcium (mg/dL)	8.9	9.0	0.1	0.14
Parathyroid hormone (pg/mL)	434.4	512.3	54.8	0.23
Phosphorus (mg/dL)	5.6	5.3	-0.3	0.03

Conclusions: Daily home hemodialysis with low volume dialysate delivered an adequate dialysis dose in patients that completed FREEDOM. Treatment for 12 months was associated with statistically significant increases in bicarbonate and albumin and significant decreases in potassium, sodium, hemoglobin, and phosphorus.

SA-PO1117

Incidence of Therapy Cessation among Home Hemodialysis Patients in the United States

Eric D. Weinhandl,[1,2] Allan J. Collins.[2] *[1]NxStage Medical, Inc., Lawrence, MA; [2]Univ of Minnesota, Minneapolis, MN.*

Background: Therapy cessation is a headwind to home hemodialysis (HHD) program growth and maintenance. Assumptions about the magnitude of incidence of cessation are diverse. We assessed incidence of cessation in a national population of HHD patients.

Methods: We identified patients who initiated HHD training on the NxStage System One cycler (NxStage Medical, Inc., Lawrence, Massachusetts) between January 1, 2010, and December 31, 2014, according to NxStage records. We followed patients from training initiation to the earlier of therapy cessation or March 31, 2016. We estimated cumulative incidence (CI) of cessation due to technique failure (TF), death, transplant, and composites thereof. We also estimated interval rates of cause-specific cessation.

Results: The cohort comprised 15,108 patients. Mean (standard deviation) duration of successful HHD training was 32 (23) days. CI of therapy cessation is shown in the table. After training, 60-month CI was 38.6% for technique failure 32.4% for death and transplant.

	Cumulative Incidence (%)					Relative Rate (=1.00 during First Year at Home)	
	Technique Failure	Death	Transplant	Death + Transplant	Total	Technique Failure	Death + Transplant
Training	15.5	0.7	0.3	1.0	16.6	5.18	0.63
0-1 mo	17.5	1.2	0.5	1.7	19.2	0.98	0.60
1-2 mo	19.6	1.9	0.6	2.5	22.1	1.07	0.81
2-3 mo	21.9	2.5	1.0	3.5	25.4	1.21	0.91
3-6 mo	27.4	4.3	2.1	6.4	33.8	1.06	1.04
6-9 mo	31.8	5.7	3.6	9.2	41.0	0.95	1.13
9-12 mo	35.3	7.0	4.7	11.8	47.1	0.86	1.14
12-24 mo	44.2	11.5	8.9	20.4	64.6	0.69	1.22
24-36 mo	49.3	14.6	11.5	26.1	75.4	0.58	1.21
36-48 mo	52.1	17.0	13.6	30.6	82.7	0.46	1.36
48-60 mo	54.1	18.5	14.9	33.4	87.6	0.47	1.16

Relative to rates of cause-specific cessation during the first year at home, TF was more likely during training and the first 6 months at home. Death and transplant were more likely after the first 6 months at home.

Conclusions: Most patients who initiate HHD training transition to home. In the long run, roughly half of therapy cessation at home is due to TF. Studies are needed to assess whether TF during training can be reduced and to identify predictors of TF at home.

SA-PO1118

Association between Daily Hemodialysis, Access to Renal Transplantation and Patients' Survival in France Adelaide Pladys,[1] Sahar Bayat,[1] Cécile Couchoud,[2] Cecile M. Vigneau.[3] *[1]METIS, Ecole des Hautes Etudes en Sante Publique, Rennes, France; [2]Registre REIN, Agence de la Biomedecine, La Plaine Saint Denis, France; [3]Service de Nephrologie, CHU Pontchaillou, Rennes, France.*

Background: Daily Hemodialysis (DHD) has been developed to enhance patients' quality of life and blood purification. But its association with survival remains controversial and the association between DHD and the access to renal transplantation has never been evaluated.

Methods: All incident patients ≥18 years starting DHD between 2003 and 2012 for a period ≥30 days in France were extracted from REIN (Renal Epidemiology and Information Network). Using a propensity score, we matched each patient on DHD to three patients on hemodialysis (HD) 3x/week. Survival was studied using the Cox model and access to renal transplantation using the Fine and Gray model.

Results: Were included 575 patients on DHD and 1696 on HD 3x/week. Survival: At the endpoint (31/12/2013), 48% patients on DHD and 32.5% patients on HD 3x/week were dead. After adjustment, DHD was associated with an increased risk of death (HR=1.58 95%CI: 1.4-1.8). The risk of death 2 years after dialysis initiation was 20% in DHD patients and 10% in HD 3x/week ones. Placement on the renal transplant waiting list:Patients older than 80 years were excluded (n=232). By the end of 2013, 176/516 (34.1%) patients on DHD and 598/1523 (39.3%) on HD 3x/week were waitlisted. In the adjusted model, DHD was not significantly associated with the probability of being waitlisted. Access to renal transplantation after waitlisting: Patients on DHD had a reduced access to renal transplantation (SHR=0.72 95%CI: 0.56-0.91). The probability of transplantation 2 years after placement on the waiting list was 51.5% in DHD patients and 60.3% in HD 3x/week ones.

Conclusions: In France, DHD is associated with a lower chance of renal transplantation after being waitlisted and with a higher risk of death. DHD is addressed to various profiles: young patients who access to renal transplantation and old ones in bad clinical conditions. DHD indications in France might be different from other countries. However, the development of new low-flux machines might modify the nephrologists' indications for DHD.

SA-PO1119

Cognitive Impairment in Patients with ESRD and Impact on Dialysis Modality Choice Anuradha Jayanti,[1] Philip Foden,[3] Alison J. Wearden,[2] Sandip Mitra.[1] *[1]Nephrology, Central Manchester Foundation Trust, Manchester, United Kingdom; [2]School of Psychological Sciences, Univ of Manchester, Manchester, United Kingdom; [3]Biostatistics, Univ of Manchesterl, Manchester, United Kingdom.*

Background: Kidney disease is associated with significant cognitive dysfunction.We investigate the association between objective and subjective cognitive function in predialysis patients and investigate if either, can predict dialysis modality choice.

Methods: Two hundred and twenty predialysis patients' data were used to ascertain the demographics, clinical, laboratory and neuropsychometric variables. The latter includes trail making tests A and B- executive function; 3MS- global cognitive function and metacognition questionnaire for subjective assessment of one's cognitive ability. The outcome variable was hospital and self-care modality choice.

Results: Within the study cohort, 90 patients chose fully-assisted haemodialysis and 114 patients chose self-care dialysis. The median 3MS, TMT-A and B scores were greater for assisted vs self-care group. Metamemory was not significantly different between groups but metaconcentration score was significantly worse in the 'assisted-dialysis' group. Univariate analysis showed that variables significantly ($p<0.05$) associated with self-care modality choice include lower TMT A and B scores and higher metaconcentration scores amongst others. Hierarchical regression showed highly significant association between perceived concentration and self-care modality choice ($p<0.01$). Adjusted and unadjusted analyses showed a significant association between perceived concentration and TMT-B scores ($p<0.01$). With every 1.6-minute increase in TMT-B there was a one-unit reduction in metaconcentration score and this was associated with 20% lower odds of choosing self-care over fully-assisted dialysis modality.

Conclusions: Patient's own perception of their cognitive ability is a significant predictor of self-care dialysis modality choice. Subjective report of 'metaconcentration' is strongly associated with poorer outcome on trails making test B, a test of executive brain function.

Funding: Pharmaceutical Company Support - Baxter Extramural Grant

SA-PO1120

Home Hemodialysis in a Large U.S. Dialysis Organization Suzanne Laplante, Angelito A. Bernardo, J. Ken Leypoldt, Gregory C. Cherkowski, Amin Torabkhani, Dilip Makhija. *Baxter Healthcare Corporation, Deerfield, IL.*

Background: The number of home hemodialysis (home HD) patients is growing in the USA. However, little is known of their disease and dialysis characteristics. This study was undertaken to describe the home HD patient population of a large dialysis organization (LDO) in the USA.

Methods: Stable (same modality for last 60 days of first 90 days on dialysis) incident home HD patients were identified from 2012-2015 US LDO anonymized records. Patient demographics and disease characteristics were compared to in-center population (ICHD) using Student t-tests or Chi-Square tests. Home HD treatment characteristics were summarized with descriptive statistics.

Results: 447/673 (66.4%) stable incident home HD patients were men (ICHD: 56.2% of 94,645; $p<0.0001$). Patients were on average 58.2±14.2 years old at dialysis initiation (ICHD: 63.2±14.8; $p<0.0001$) with a body mass index of 31.6±8.6 (ICHD: 29.5±10.3 kg/m^2; $p<0.0001$). 74.3% were Caucasians (ICHD: 44.6%; $p<0.0001$). 26.2% had a Charlson comorbidity index of ≤3 (ICHD: 16.8%; $p<0.0001$). The primary cause of ESRD was: diabetes (34.3%; ICHD: 43.1%), hypertension (23.3%; ICHD: 29.0%), glomerulonephritis (9.1%; ICHD: 4.6%), cystic disease (8.2%; ICHD: 1.4%) ($p<0.0001$). Baseline serum albumin was 3.7±0.5 (ICHD: 3.4±0.5 g/dL; $p<0.0001$). Most patients (n=512/549; 93.3%) performed at least 3 sessions per week and 498 (90.7%) regularly (i.e., ≥ 70% of the time) avoided a 2-day gap. Treatment duration was available for ≥10% of dialysis sessions in 362 patients (65.9%); most patients (n=544; 99.1%) dialyzed for ≥2 hours. Four (4) patients used a nocturnal regimen. Weekly standard Kt/V was ≥ 2.1 in 412/524 patients (78.6%).

Conclusions: Patients on home HD are generally overweight Caucasian males with less comorbidity compared with ICHD patients. In addition, glomerulonephritis and cystic disease are more frequent primary causes of ESRD in home HD patients. Most patients avoid a 2-day gap without dialysis, but 21.4% do not reach the minimal weekly standard Kt/V of 2.1. Better recording of the dialysis parameters, for example through remote connectivity, could ensure optimal treatment monitoring and clinical outcomes.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

SA-PO1121

Usage of High-Dose Hemodialysis at Home in a Large U.S. Dialysis Organization Suzanne Laplante, Angelito A. Bernardo, J. Ken Leypoldt, Gregory C. Cherkowski, Amin Torabkhani, Dilip Makhija. *Baxter Healthcare Corporation, Deerfield, IL.*

Background: To date, technological advances in hemodialysis (HD) have not resulted in significant survival improvement. The 2-day weekly gap in the conventional hemodialysis (CHD) 3 days-a-week regimen (weekly standard Kt/V=2.1) has been associated with increased mortality. Several large observational studies have shown an association between a high-dose regimen (i.e., more frequent and longer HD with weekly standard Kt/V ≥3.0) and 30-45% superior survival. Home is the best place to perform high-dose HD. There is a growing population of home HD patients in the USA, but the number of patients using a high-dose HD regimen is unknown. This study aimed at identifying the proportion of patients on high-dose home HD.

Methods: Stable (same modality for last 60 days of first 90 days on dialysis) incident home HD patients were identified from 2012-2015 anonymized records of a large US dialysis organization (LDO). Patients were categorized as using a CHD regimen or high-dose HD regimen (no 2-day gaps without dialysis; if short-daily: ≥5 sessions of ≥2 hours per week, if nocturnal: ≥3.5 sessions of ≥6 hours per week; standard Kt/V ≥3.0). Patient demographics as well as disease and treatment characteristics were to be compared using Student t-tests and Chi-square tests.

Results: 673 stable incident home HD patients were identified with information on the dialysis regimen available for 549. Most home HD patients (n=498; 90.7%) avoided the 2-day gap ≥70% of the time. Only 34 patients (6.5%) reported a standard weekly Kt/V ≥3.0 in ≥70% of the time and only 2 patients (0.4%) had a regimen corresponding to high dose. Hence, no statistical comparison between the high dose HD and CHD cohort was performed.

Conclusions: Despite the wealth of evidence supporting high-dose HD, only 0.4% of home HD patients of a large US LDO have been using this regimen. While patients regularly avoid the 2-day gap; the session durations and/or dialyzer clearance are likely insufficient to reach a high-dose regimen. This may be due to lack of awareness on the benefits of high dose or unfavorable dialysis provider economics in the US single bundle payment environment.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

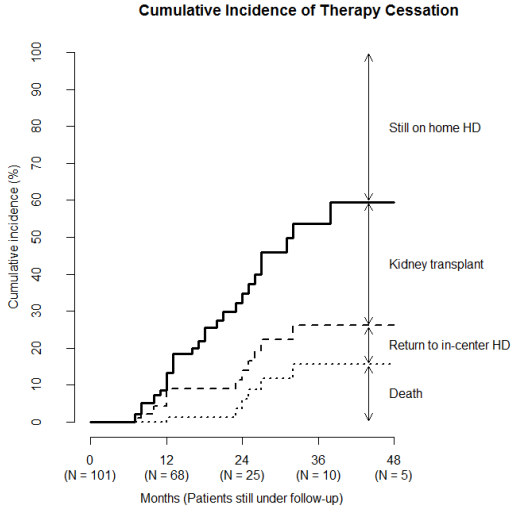
SA-PO1122

Rapid Training, High Long-Term Retention, and Good Clinical Outcomes in a European Cohort of Home Hemodialysis Patients Using the NxStage System One Maria Fernanda Slon,[1] Natalie L. Borman,[2] Maxence Ficheux,[3] Hafedh Fessi,[4] Giacomo Colussi,[5] Roberto Corciulo,[6] Maria A. Bajo.[7] *[1]Hospital de Navarra, Spain; [2]Queen Alexandra Hospital, United Kingdom; [3]CHR Clémenceau, France; [4]Hôpital Tenon, France; [5]Niguarda Hospital, Italy; [6]Policlinic Univ, Italy; [7]Hospital Univ La Paz, Spain.*

Background: Home hemodialysis (HHD) facilitates more flexible and frequent treatment, which may improve clinical outcome and quality of life. We assessed training intensity, therapy cessation, and clinical outcomes in a European cohort of HHD patients using the NxStage System One.

Methods: We collected baseline and follow-up data about 127 home hemodialysis patients on the NxStage System One at 7 centers in France, Italy, Spain, and the United Kingdom. We followed patients from HHD initiation until the earliest of death, return to in-center HD, kidney transplant, or October 31, 2015. We analyzed the subset of patients with complete baseline data and >6 months on HHD.

Results: The study cohort comprised 101 patients. Mean age was 49.7 years, 66% were male, and mean lifetime dialysis duration was 3.2 years. Most patients (95%) were prescribed 5 or 6 sessions per week and mean treatment duration was 15.1 hours per week. Mean training duration was 3.8 weeks and 7% required >6 weeks; mean number of training sessions was 16.7 and 9% required >30 sessions. Cumulative incidence of therapy cessation is shown in the figure. After 2 years, 6% had died, 7% had returned to in-center HD, and 21% had received a transplant. After 4 years, 79% of those still on dialysis remained on HHD. During all 162.6 follow-up years, rates of death and transplant were 3.7 and 10.5 events per 100 patient-years, respectively.



Conclusions: Home hemodialysis with the NxStage System One in 4 European countries was associated with rapid training, high long-term therapy retention, and good clinical outcomes, including high incidence of transplant and low risk of death.

SA-PO1123

Tablet-Based Training for In-Center Self-Care Dialysis – A Pilot Study

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Background: Educating dialysis patients about their therapy options, kidney function and health maintenance is a goal for everyone caring for this complex patient population. It is thought that educated patients may make better choices and will be more adherent with their therapy. However, training today is labor intensive and time consuming for staff and has been noted as a burden and barrier to patients in selecting a self-care modality.

Methods: A new tablet-based patient training app has been developed as part of the Tablo™ Hemodialysis System. It is designed as a self-guided educational tool to reduce training time for the patient and minimize clinic staff time burden in providing training. Patients (n=16) from 4 dialysis units agreed to complete the app which has 10 modules with comprehension quizzes. Each quiz must be successfully completed prior to moving on to the next module. The time spent completing each module was recorded into the app's proprietary algorithm and analyzed. Patients also completed a survey on their experience.

Results: Of the 16 surveys collected, 94% (n=15) agreed that the app was easy to understand and 75% (n=12) believed that the app provided information that would increase their interest in becoming more involved in their dialysis therapy. The format and content was considered easy to follow (88%) and 81% reported that they were surprised at how much they learned. The average time spent on the app to complete the training was 3 hours and 19 minutes.

Conclusions: A new tablet-based app developed for the Tablo™ Hemodialysis System provides approachable patient education that may increase patient interest in self-care and reduce the amount of training time required to reach competency needed for self-care whether at home or in-center.

Funding: Pharmaceutical Company Support - Outset Medical, Inc.

SA-PO1124

More Intensive Dialysis in the FHN Daily Trial Provided Limited Reduction in Uremic Solute Levels

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Background: The Frequent Hemodialysis Network (FHN) Daily Trial compared conventional 3 times weekly hemodialysis to more frequent treatment with a longer weekly treatment time. Evaluation at 1 year showed modest or no effects on physical or cognitive performance.

Methods: This study compared concentrations of uremic solutes in pre-treatment samples at 1 year from 53 FHN subjects who received hemodialysis 3 times weekly for 10.9 ± 1.3 hours/week and 30 subjects who received hemodialysis 6 times weekly for 14.6 ± 1.7 hours/week. Relative concentrations of solutes identified as uremic in previous studies were assessed by metabolomic analysis and concentrations of selected solutes were further quantified by liquid chromatography/tandem mass spectrometry with isotopic dilution.

Results: Metabolomic analysis showed that the FHN's combined increase in frequency and weekly time reduced the levels of 107 uremic solutes by an average of only 15%. Quantitative analysis confirmed limited reduction in the concentrations of selected protein-bound uremic solutes:

	3x weekly	6x weekly	% Difference (mean; 95% CI)
p-cresol sulfate (mg/dl)	3.2 ± 1.4	3.3 ± 1.6	4 (-18, 26)
indoxyl sulfate (mg/dl)	2.9 ± 1.1	2.5 ± 1.0	-13 (-30, 4)
hippurate (mg/dl)	5.7 ± 4.0	4.8 ± 3.3	-17 (-45, 12)

Kinetic modeling suggested that our ability to lower solute concentrations by increasing hemodialysis frequency and weekly time may be limited by the presence of non-dialytic solute clearances and/or changes in solute production.

Conclusions: The failure to achieve larger reductions in uremic solute levels may account in part for the limited improvement in physical and cognitive performance observed with increasing frequency and weekly treatment time in FHN Daily Trial subjects.

Funding: NIDDK Support, VA Support

SA-PO1125

Does the Extracorporeal Blood Flow Affect Solute Removal on Short Daily Hemodialysis with Low Dialysate Flow Rate?

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Background: Short daily home hemodialysis (SDHD) with low dialysate flow rate (Qd) confers advantages, especially improved quality of life. The blood pump flow rate (Qb) is an important part of the dialysis prescription, but its effect on solute clearance during a short treatment with low Qd has not been described. We conducted a prospective study to assess the impact of changes in Qb on dialysis dose and solute removal.

Methods: We studied 17 patients starting SDHD. Each patient was observed for 3 consecutive HD sessions, across which only Qb was altered (300, 400 and 450 mL/min). For all sessions, Qd was 180 mL/min and session duration was 2 hours. Urea, Beta-2-microglobulin (β2m), and phosphorus were measured in the blood before and after each dialysis session.

Results: Mean (standard deviation) age and dialysis vintage were 42.9 (13.7) and 5.4 (7.8) years, respectively; 53% were male; 62.5% had residual renal function;and 94,1% had an arterio-veinous fistula . Mean (standard deviation) single pool Kt/V (spKt/V), B2m reduction ratio (B2mRR), and phosphorus reduction ratio (PRR) are displayed in the table 1.

Qb(ml/min)	spKt/V	β2m RR	PRR
300	0.54(0.1)	0.40(0.07)	0.46(0.10)
400	0.58(0.08)	0.45(0.06)	0.48(0.08)
450	0.61(0.09)	0.48(0.06)	0.49(0.07)

In bivariate analysis with accounting for repeated observations, increasing Qb resulted in a significant increase in spKt/V (0.048 [95% confidence interval, 0.03-0.06] increase in spKt/V per 100 mL/min increment in Qb [$p < 0.05$]) and a significant increase in β2mRR (5-point [95% confidence interval, 3-7] increase in β2mRR per 100 mL/min increment in Qb [$p < 0.05$]). Increasing Qb had no significant effect on PRR.

Conclusions: Increasing Qb on SDHD improves the removal of urea and beta-2-microglobulin, but with potentially limited clinical impact. Patients with a vascular access that does not permit use of a high blood pump flow rate can still benefit from this dialytic modality.

SA-PO1126

Weekly Standard Kt/V and Clinical Outcomes in Home and In-Center Hemodialysis Matthew B. Rivara,[1] Vanessa A. Ravel,[2] Elani Streja,[2] Yoshitsugu Obi,[2] Scott V. Adams,[1] Alfred K. Cheung,[3] Kamyar Kalantar-Zadeh,[2] Rajnish Mehrotra.[1] *[1]Kidney Research Inst, Seattle, WA; [2]UC Irvine, Irvine, CA; [3]Univ of Utah, Salt Lake City, UT.*

Background: Patients undergoing hemodialysis (HD) with a frequency other than thrice-weekly are not included in clinical performance metrics for dialysis adequacy. Weekly standard Kt/V (stdKt/V) is comparable across treatment frequencies and location (in-center or home), but there is a paucity of data on its association with clinical outcomes.

Methods: We examined data from incident dialysis patients treated with in-center (N = 109,273) or home HD (N = 2,373). We used multivariable linear regression to examine the association of baseline stdKt/V with blood pressure and metabolic control (serum potassium, calcium, bicarbonate, and phosphorus) stratified by dialysis modality. We used Cox regression to examine the association of stdKt/V with mortality, first hospitalization, and for home HD, transfer to in-center HD.

Results: There were no clinically significant associations between baseline stdKt/V and markers of metabolic control, irrespective of dialysis modality. Patients with stdKt/V >2.3 had lower adjusted blood pressures compared to patients with stdKt/V <2.1, and this difference was greater for home HD relative to in-center HD. There was no association between stdKt/V and adjusted risk for mortality, hospitalization, or transfer to in-center HD among patients undergoing home HD (Table). Among patients undergoing in-center HD, stdKt/V ≥ 2.3 was associated with a 4% lower risk (95% CI: 2% to 7% lower) for death compared to stdKt/V 2.1 to < 2.3.

Conclusions: Differences in in achieved stdKt/V are associated with few clinically meaningful differences in blood pressure or metabolic complications. Additionally, current targets for stdKt/V have limited utility in identifying individuals at increased risk for adverse clinical outcomes among those undergoing home HD.

Table:

	StdKt/V	Mortality		Hospitalization		Transfer to In-Center HD	
		HR	95% CI	HR	95% CI	HR	95% CI
In-Center HD	<2.1	1.14	1.11, 1.18	1.13	1.10, 1.15	-	-
	2.1 to <2.3	Ref	Ref	Ref	Ref	-	-
	≥ 2.3	0.96	0.93, 0.98	0.99	0.98, 1.01	-	-
Home HD	<2.1	1.17	0.79, 1.74	1.11	0.95, 1.30	1.20	0.91, 1.60
	2.1-<2.3	Ref	Ref	Ref	Ref	Ref	Ref
	≥2.3	1.17	0.77, 1.79	1.03	0.87, 1.23	1.16	0.84, 1.58

Funding: NIDDK Support

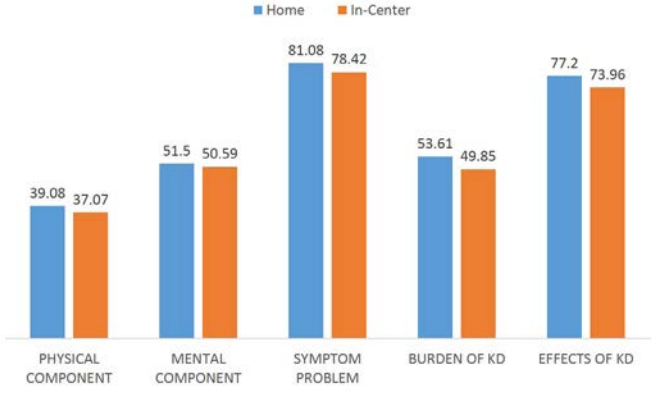
SA-PO1127

Profiles of Quality of Life in Home and In-Center Dialysis Patients in a Large National Population Nwamaka Denise Eneanya,[1] Sophia Rosen,[2] Marta Reviriego-Mendoza,[2] Dugan Maddux,[2] Stephanie Johnstone,[2] John W. Larkin,[2] Len A. Usvyat,[2] Franklin W. Maddux.[2] *[1]Div of Nephrology, Massachusetts General Hospital; [2]Fresenius Medical Care North America.*

Background: Although profiles of quality of life (QOL) are well-characterized for the in-center hemodialysis (HD) population, there is limited data investigating QOL in home dialysis patients (Pts). We aimed to determine the profiles of, and differences in, Kidney Disease QOL (KDQOL) survey scores in dialysis Pts treated at home versus in-center within a large national population.

Methods: We analyzed data from 3,434 home peritoneal and HD dialysis Pts who completed the KDQOL survey during 120 to 365 days after the first date of dialysis (FDD) between Jan 2013 to Dec 2015. The Pt's modality was determined using the active record of modality 120 days from FDD. Clinically similar in-center Pts during the same time frame were identified using 1:1 nearest neighbor matching on logit of propensity score for: age at FDD, race, and sex, as well as, body mass index and albumin during the first 120 days of dialysis. KDQOL scores were compared between groups.

Results: We observed home dialysis Pts had on average 2.0 and 0.91 points higher physical and mental component scores respectively than in-center dialysis Pts (both p<0.001; Figure 1). Home Pts also exhibited on average 2.7, 3.8 and 3.2 points lower dialysis-related symptoms & problems, burden of kidney disease (KD), and effects of KD on daily life scores respectively (all p<0.001; Figure 1).



Conclusions: Pts treated by home dialysis modalities appear to have slightly better QOL outcomes, compared to their in-center HD counterparts. Albeit significant, differences in KDQOL scores between groups are small and further studies are needed to determine clinical relevance. This study was limited to a partial population of home Pts secondary to poor documentation of clinical parameters used for matching.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

SA-PO1128

Home Hemodialysis Using NXTStage System One Improves Blood Pressure Control and Reduces Risk of Intra Dialytic Hypotension Nicholas Sangala, Katey Atkins, Venkat Gangaram, Natalie L. Borman. *Wessex Kidney Centre, Queen Alexandra Hospital, Portsmouth, Hampshire, United Kingdom.*

Background: Chronic hypervolaemia and hypertension are significant contributors to cardiac mortality in patients with end stage renal disease on maintenance haemodialysis. Dry weight reduction can achieve better blood pressure control but is associated with an increased risk of intra dialytic hypotension (IDH), which is itself an independent risk factor for cardiac death. Home dialysis is associated with better blood pressure control but its impact on IDH is unknown.

Methods: We reviewed the records of 33 patients receiving home haemodialysis using NXTstage System One between June 2014 and March 2016. For each patient observations from 21 consecutive haemodialysis sessions including pre and post dialysis blood pressure & weight, dialysis length and ultrafiltration volume were recorded along with patient co-morbidities, antihypertensive medication, and episodes of IDH. We collected the same data from in-centre haemodialysis patients matched for age and co-morbidities who had received 21 consecutive sessions of haemodialysis at their usual centre to use as a comparator.

Results: Home haemodialysis patients had a lower systolic blood pressure (131mmHg vs 139mmHg p=0.052) and a lower drop in their systolic blood pressure (0.84% vs 7.2% p=0.0013) than in-centre patients. Ultrafiltratiion volume (1.16L vs 1.85L p=0.0001) and rate (4.46ml/kg/hr vs 6.33mls/kg/hr p=0.0001) were also lower. In-centre patents were more likely to experience IDH than those dialysing at home (RR=2.48 p=0.019). IDH complicated more in-centre sessions than home haemodialysis sessions (RR=6.47 p<0.0001). Antihypertensive use was similar in both groups.

	Home HD	In Centre HD (Matched)	*p* value
Total Patients	33	91	
Age	54.4	56.8	NS
Symptomatic Patients	6	41	0.019
Episodes of IDH	6	107	<0.0001
Pre Dialysis Systolic (mmHg)	131	139	0.052
Ultrafiltration Rate (ml/kg/hr)	4.46	6.33	0.0013
Ultrafiltration Volume (L)	1.16	1.85	0.0001

Conclusions: Home haemodialysis is associated with better blood pressure control and less IDH than in-centre haemodialysis.

SA-PO1129

Improved Long-Term Clinical Parameters in Nocturnal Hemodialysis Thijs Thomas Jansz,[1] Akin Ozyilmaz,[2] Tiny Hoekstra,[1] Brigit C. van Jaarsveld.[1] *[1]Nephrology, VU Univ Medical Center, Amsterdam, Netherlands; [2]Dialysis Centers Groningen, Groningen, Netherlands.*

Background: Nocturnal hemodialysis (NHD), characterized by 8hr dialysis sessions at least thrice weekly, has been shown to improve clinical parameters in HD patients. However, it is not yet known to what extent these improvements last in the long run. We aimed to study long-term clinical parameters in NHD.

Methods: A longitudinal historical cohort was created by collecting data from medical records of 159 in-center and home-treated NHD patients from two centers in the Netherlands, from switch from conventional HD to NHD (any time after April 2004) until discontinuation of NHD. We followed patients until February 1, 2016. Data were collected on phosphate and hypertension control, nutritional status and anemia control at 0, 3, 6, 12, 18, 24 months of NHD treatment, and yearly thereafter. We compared data between baseline and 12 months, and also used generalized linear mixed models for a 6 year longitudinal analysis, adjusting for patient demographics and clinical parameters.

Results: At baseline, mean age was 52.0 ±1.2 years, 32.1% of patients were female, and median duration of end-stage renal disease was 41 (IQR 12-101.5) months. Patients underwent NHD 8 hrs 3-5 times weekly. Median follow-up duration was 18.4 (IQR 7.5-35.4, range 0.4-129.6) months. Phosphate levels and number of phosphate binding pills were lower at 12 months (p<0.01), decreasing predominantly in the first 3 months and remaining stable afterwards. Diastolic blood pressure decreased -1.2 ±0.4 mmHg annually (p<0,01), and number of types of antihypertensive agents was lower at 12 months (p<0.01), again with a major decrease in the first 6 months. CRP decreased -0.08 ±0.04 mg/l annually (p=0,03), while albumin increased 0.22 ±0.07 g/l annually (p<0,01). Post-dialysis weight remained stable over the years. Erythropoiesis-stimulating agent (ESA) resistance index decreased significantly over time (p<0.01), with a 43% reduction in median weekly ESA dose (p<0.01) and a stable hemoglobin.

Conclusions: After switching to NHD, patients develop a considerably lower need for phosphate binding pills, antihypertensive agents and ESA, while clinical parameters remain stable or improve during a 6-year follow-up.

SA-PO1130

Pregnancy Outcomes in Women on Intensive Hemodialysis Compared to Renal Transplant Recipients Arrti A. Bhasin, Anny V. Gonzalez, Nusrat Zaffar, Sarah Mullin, Dini Hui, Rohan D'Souza, Christopher T. Chan, Michelle A. Hladunewich. *Medicine, Obstetrics and Gynecology, Univ of Toronto, Toronto, ON, Canada.*

Background: Data from the US and Italy suggest that patients with a functional renal graft typically have more successful pregnancy outcomes than those with end-stage renal disease (ESRD) on dialysis. As a result, pregnancy counselling often encourages women to wait until after transplantation to conceive. However, reported pregnancy outcomes to date have included women on conventional hemodialysis (HD), while comparisons to women on intensive HD regimens (>36 hours of HD per week) have yet to be made. As such, we sought to compare pregnancy outcomes in renal transplant recipients to women with ESRD on intensive HD.

Methods: In this retrospective cohort study that spanned 2000-2016, pregnancy outcomes of 19 women with ESRD on intensive HD were compared to 45 pregnancies amongst women conceiving post renal transplantation. The primary outcome was the live birth rate, with secondary outcomes including gestational age, birth weight and pregnancy-associated complications.

Results: The two cohorts were comparable with respect to age and cause of ESRD with the average age being 32 in both cohorts. There was no significant difference in the live birth rate at 89 vs 86% in the HD patients and the transplant recipients, respectively (p= 0.71). Similarly, there was no significant difference in gestational age (33.9±7 vs 31.5±11 weeks). However, babies born to women on intensive HD were significantly smaller (2264±727 g) compared to those born to transplant recipients (2935±477 g; p=0.001). With respect to pregnancy complications, significantly more transplant recipients were delivered by caesarean section than dialysis patients (47 vs 17%, p=0.03), and fewer pregnancies were without complications (26 vs 53%, p=0.04) with the most frequent complications in transplant recipients being hypertension, preeclampsia and cholestasis while the intensively dialyzed HD population most frequently developed cervical incompetence.

Conclusions: Pregnancy outcomes in intensively dialyzed HD patients are similar to renal transplant recipients. As such, pregnancy on intensive HD can be considered a viable reproductive option.

SA-PO1131

Association between Bioimpedance, Overhydration and Inflammation Biomarkers in a Spanish Home Dialysis Unit Loreto Fernandez,[1] Maria Fernanda Slon,[1] Carmen Sayon-Orea,[2] Jesus Arteaga.[1] *[1]Nephrology, Complejo Hospitalario de Navarra (CHN), Spain; [2]Preventive Medicine, CHN, Pamplona, Spain.*

Background: Peritoneal dialysis (PD) and in-center hemodialysis patients are at increased risk of overhydration thus leading to cardiovascular events and mortality. Bioimpedance is a useful tool to assess body composition. However, there is scarce data of this tool in frequent home hemodialysis (HHD). The aim of this work is to compare hydration status in two Home-dialysis groups (PD versus HHD) measured by means of bioimpedance and BNP (Brain Natriuretic Peptide). Interestingly, we analysed their correlation and also with some inflammation markers (PCR, Il-6).

Methods: This is a cross- sectional study of 53 Spanish home- dialysis patients: 37 on PD and 16 on HHD. Demographics, dialysis adequacy and cardiovascular risk (presence of heart disease and/or LVH measured by echocardiogram) data were collected from their medical records. Hydration status biomarker (Brain Natriuretic Peptide, BNP), inflammation (CRP, IL-6) and nutritional (albumin, cholesterol) parameters were collected from blood tests. Also a bioimpedance was conducted. We took as overhydration (OH) parameter the OH%ECW (extracellular water), and for nutrition: LTI (lean tissue index), FTI (fatty tissue index).

Results: We found no differences among DP and HHD groups in terms of demographics and cardiovascular characteristics. The OH%ECW was >10% only in 30% of patients with no differences among groups. Moderate and positive association was observed between OH (% ECW) and BNP levels(r = 0.4; p = 0.002); however among groups only held significance in PD (r = 0.4 and p 0,01). Cholesterol was positively associated with FTI (r = 0.29 and p = 0.03), while albumin did with LTI (r 0.28, P = 0.03). IL-6 and CRP were positively associated (r 0.42, p = 0.002) and this association was stronger among the HHD group (r 0.75, p = 0, 0019). No relationship between inflammatory markers and hydration status, LVH or time on dialysis was observed.

Conclusions: BNP levels may be a good marker of overhydration in home dialysis patients, especially in those on PD. HHD patients have better control of dry weight, nevertheless they could be more inflamed than PD patients.

SA-PO1132

The Relationship of Hydration Status to Macro and Microcirculation in Conventional and High Dose Hemodialysis Nicos Mitsides,[1] Tom Cornelis,[2] Nanda Diederen,[3] Natascha Broers,[3] Jeroen Kooman,[3] Sandip Mitra.[1] *[1]Manchester Academic Health Science Centre, United Kingdom; [2]Jessa Hospital, Hasselt, Belgium; [3]Univ Hospital Maastricht, Netherlands.*

Background: Fluid management presents one of the greatest challenges in hemodialysis(HD). Overhydration(OH) has been linked to adverse cardiovascular outcomes but the link between circulation and fluid compartments remains poorly defined.

Methods: We report the baseline findings of a 2yr multicentre, longitudinal study investigating compartmental fluid distribution with macro- and micro-circulation parameters in conventional (CHD) and high dose HD (HDHD). We assessed Fluid compartments with Multifrequency bioimpedance, macrocirculation with pulse-wave velocity(PWV) and mean arterial pressure (MAP) measurements and microcirculation with sublingual dark-field capillaroscopy.

Results: 72 participants, were equally split between CHD and HDHD (>12hrs/wk). Visit MAP correlated with OH index (p=0.02), Total Body Water (TBW)(p=0.01), Extracellular Water (ECW)(p=0.01) and Intracellular Water (ICW)(p=0.02) in a linear regression model adjusting for age, cardiovascular disease(CVD), diabetes(DM), BMI and dialysis modality. 24hr MAP was also linked to TBW (p=0.02), ECW (0.03) and ICW (p=0.03). Although PWV correlated with MAP (p=0.01), it was not associated with fluid indices. Microvascular luminal diameter (dynamic % Cell filling) was correlated with ECW ($p<0.05$) but the positive relationship of injury to the Perfused Boundary Region of endothelial glycocalyx to ECW/ICW ratio (p=0.04) was explained by loss of ICW (p=0.01). MAP was not associated with microcirculation parameters but high PWV did and correlated well with dynamic Red Cell width (p=0.02).

Conclusions: MAP shows strong association with all fluid indices but PWV is predominantly linked to microcirculatory parameters across all haemodialysis modalities.

Funding: Clinical Revenue Support

SA-PO1133

Dalteparin for Circuit Anticoagulation in Patients Undergoing Daily Hemodialysis Karen Qi,[1] Norman Muirhead,[1,2] Seadna Ledger,[1] Nicole Seymour,[1] Jarrin D. Penny,[1] Shih-Han S. Huang.[1,2] *[1]London Health Sciences Centre, London, ON, Canada; [2]Dept of Medicine, Nephrology, Western Univ, London, ON, Canada.*

Background: Dalteparin, a low molecular weight heparin, has been shown to be effective and safe for hemodialysis (HD) circuit anticoagulation and has advantages over unfractionated heparin (UFN). However, there is limited evidence for its use in frequent HD. We had conducted an observational study in our in-centre short-hour daily HD program to assess the effectiveness, the dosage and the bleeding risk of dalteparin in this specific population.

Methods: We recruited 7 patients who were part of the in-centre short-hour daily HD program at the London Health Sciences Centre. All patients were switched from UFN to dalteparin at a starting dose of 2500 units(u) every 48 h. The dosage was titrated based on the circuit clotting score and the bleeding risk. All patients were followed from May 2015 to May 2016. We used descriptive analysis to report the mean (+/- standard deviation) UFN and dalteparin doses, number of bleeding episodes and mean clotting scores.

Results: Of the 7 patients (57% male, age 52 ± 6 y, dialysis vintage 11 ± 6 y, receiving median 12 hours over 6 HD treatments/week), the mean UFH dose during HD treatments was 1142± 351 u/h and the clotting score was <2 over 99% of the treatments. Within the first 4 weeks of switching, the mean dalteparin dose was 1687 ± 602 u/ treatment and 9% of the treatments had clotting score > 2. One patient required dose increase. All anti-Xa levels were <0.4. After 1 year, one patient passed away due to sepsis, one discontinued due to new diagnosis of diabetic retinopathy and another was dialyzing well without anticoagulation. Three patients remained on starting dose. During the 1 year period, no patient experienced significant bleeding events requiring hospitalization or interventions. No fistula clamping/compression times were increased.

Conclusions: This small but important pilot study has demonstrated the effectiveness and safety of dalteparin in short-hour HD. This should be further assessed in a larger and perhaps home HD population, which is being conducted at this point.

SA-PO1134

Comprehensive Dialysis Transportation: The Way to Sustain a Long-Term In-Center Short Daily Hemodialysis Program Felipe Pascoal, Adolfo Simon, Kelia Xavier, Vilber Bello, Juliane Lauar, Istenio Pascoal. *Centro Brasiliense de Nefrologia, Brasília, DF, Brazil.*

Background: There is a rising demand for dialysis treatment among senior population. Dialysis physical toll prevents many patients arriving at the dialysis clinic via traditional transit from safely returning home the same way. While in-center short daily hemodialysis has been consistently associated with better outcomes, the availability of convenient transportation may be its most important limiting factor. Therefore, we examined the impact of a comprehensive transportation program on in-center daily hemodialysis compliance, vintage and survival.

Methods: We assessed the prevalence of absences from hemodialysis sessions (no shows), the length of time on dialysis and the actuarial survival rate of 145 privately insured patients (93M/52F; mean age 56.1±19.3 yrs, range 8-95) receiving in-center short daily hemodialysis treatments (6-7 times/week; lasting 118±18.7 min, range 90-180; ultrapure dialysate and single-use highflux dialyzer). Round-trip free of charge shared passenger-transportation has been provided by a dedicated fleet of 10 midsize vans and 10 full time trained drivers, running about 1200 km throughout the day to timely attend 5 dialysis shifts, from 7am to 9pm, 7 days a week.

Results: From June 2006 to May 2016, 74% (108/145) of our short daily hemodialysis patients were transported to and from the clinic by an exclusive transportation service and the remaining 26% (37 patients) used their private transportation (self-driven or brought by a family member or caregiver). No patients relied on public transport. Over the 10-year study period, average missed treatment rate was 1.4% or 4.4 days per patient-year. There was no patient dropout, allowing a dialysis vintage of 42.1±33.6 mo (3-120). In parallel,

the 5-year cumulative patient survival rates were 97%, 92%, 84%, 71% and 63% at 12, 24, 36, 48 and 60 mo, respectively. Institutional transport costs have been offset by combining low missed treatment rate with high patient retention rate.

Conclusions: Providing reliable transportation options for all patients helped us overcome compliance challenges on the way to establishing and sustaining an active in-center short daily hemodialysis program.

SA-PO1135

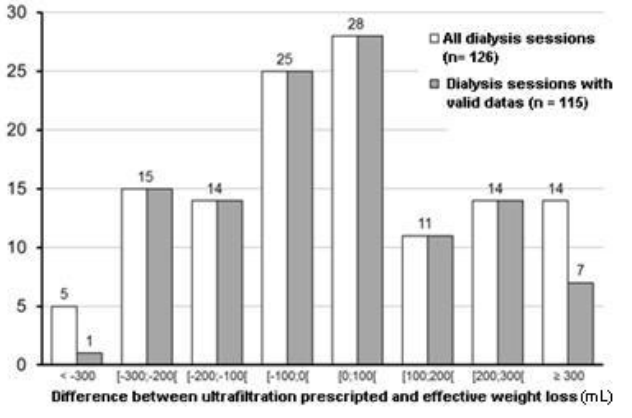
Short Daily Hemodialysis Is Feasible and Safe with Physidia S3 Monitor

Louis De Laforcade,[1] Roula Galland,[3] Walid Arkouche,[4] Maxence Ficheux,[5] Patrick Henri,[5] Francois Babinet,[7] Maurice Laville.[1,2] *[1]Dpt of Nephrology, Hospices Civils de Lyon, Pierre Bénite, France; [2]Unit 1060 CarMeN, Univ Lyon I Claude Bernard, Oullins, France; [3]Calydial, Vénissieux, France; [4]AURAL, Lyon, France; [5]Nephrology Hemodialysis, CHU Caen, Caen, France; [6]Nephrology Hemodialysis, CH Cherbourg, Cherbourg, France; [7]ECHO Association, Le Mans, France.*

Background: Short daily hemodialysis (SDH) improves hemodynamic tolerance, life quality and cardiac outcomes. Physidia S3 is a low flow dialysis machine designed for SDH.

Methods: We designed a multicentric, prospective, observational study. Main inclusion criterias were: patients treated with hemodialysis since 3 months or more, clinically stable, who were 18 years old or more, stable vascular access (No catheters). Inclued patients underwent SDH (5 or 6 times a week) on Physidia S3machine with bicarbonate buffer, during 2 weeks. Primary outcome was the ability to deliver a conform dialysis session (session duration with a ±15% tolerance and weight loss with a tolerance of ±300g in accordance with medical prescriptions).

Results: 11 patients (6 men) were inclued. Median age was 53 years, median dry weight was 60 kg, median BMI was 24.4 kg/m2. 126 sessions were analysed, dialysis duration was respected in 96% of them, and weight loss in 85%. 82% of the dialysis respected both duration and weight loss criteria. After excluding human errors in weighting or result reporting, 90% of the dialysis sessions were conform.



SDH on Physidia S3 provided an adequate quality of dialysis: median eKt/V was 0.54 per session and median stKt/V 2.45 per week. Median blood urea was reduced by 44% during a dialysis session, median plasma potassium was reduced from 4.8 mmol/l to 3.8 mmol/l, median phosphatemia was reduced from 1.70 mmol/l to 0.84 mmol/l.

Conclusions: SDH with Physidia S3 provides a good conformity with medical prescriptions, and a good adequation of dialysis.

SA-PO1136

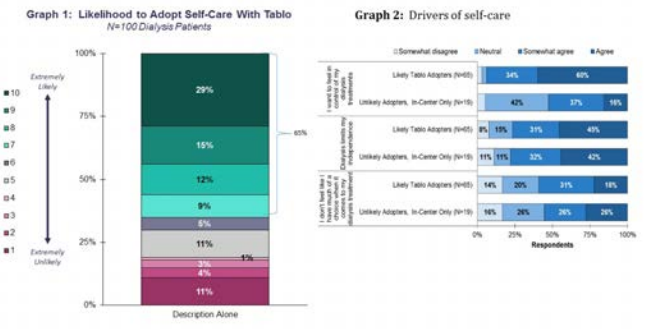
An Analysis of Patient Interest in In-Center Self-Care Hemodialysis with a Novel Hemodialysis System

Sarah S. Prichard,[1] Luis Alvarez,[2] Glenn Matthew Chertow.[3] *[1]Independent Consultant, North Palm Beach, FL; [2]Div of Nephrology, Dept of Medicine and Nephrology, Palo Alto Medical Foundation, Palo Alto, CA; [3]Div of Nephrology, Dept of Medicine and Nephrology, Stanford Univ School of Medicine, Stanford, CA.*

Background: Approximately 90% of dialysis patients are on in-center hemodialysis (ICHD), 9% on peritoneal dialysis (PD) and the remainder on HHD. Studies indicate a significant percent of patients are interested in in-center self-care hemodialysis (ICSCHD). Potential advantages for patients who select ICSCHD, include greater independence, flexibility, and control over their care. Barriers to adoption have been attributed to complexity of technology, training burden and the inability to be independent. We report on factors associated with patient selection of ICSCHD with the Tablo™ Hemodialysis System, designed to make ICSCHD easier and more accessible.

Methods: Patients (n=100) from a panel of dialysis patients across the US who had agreed to participate in survey research. Distribution of age range, sex, and race/ethnicity were pre-specified to ensure adequate representation of the overall US dialysis population. Participating patients reviewed the steps that they would perform independently during ICSCHD along with an image of the Tablo™ System. They completed a questionnaire on the likelihood of choosing ICSCHD using Tablo™, their attraction to the modality and reasons behind their selection.

Results: The patient population had an average age of 51 years (range 18 to 70) and included 56 women and 35 non-whites. Half the patients were on dialysis for 2 years or more. Graph 1 shows 65% of would likely adopt ICSCHD with Tablo™ while Graph 2 shows drivers behind their selection.



Conclusions: A high percentage of patients across broad demographic lines indicate interest in performing ICSCHD with the Tablo™ Hemodialysis System.

Funding: Pharmaceutical Company Support - Outset Medical, Inc.

SA-PO1137

Initial Experience of In-Center Self-Care Patients with the Tablo™ Hemodialysis System

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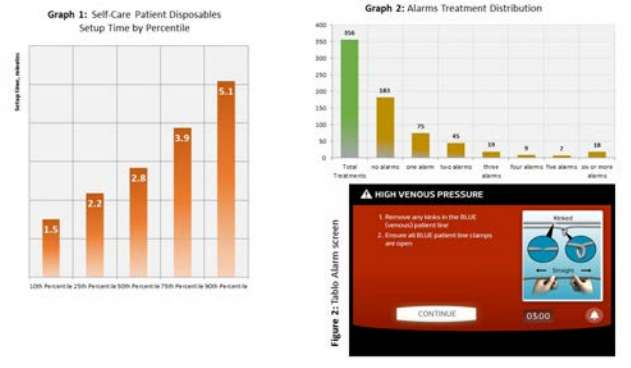
Background: Patients on hemodialysis (~70%) are interested in performing in-center self-care hemodialysis (ICSCHD) because it provides flexibility and control relative to in-center hemodialysis (ICHD). Yet, only ~8% of patients are on self-care in the US. Lack of adoption has been attributed to complexity of technology, and fear of self-cannulation. ICSCHD combines the clinical benefits of self-care with the security of a clinic setting. We assess the capability of patients performing ICSCHD with the Tablo™ Hemodialysis System.

Methods: We evaluated a subset of patients (n=20) who transferred to ICSCHD using the Tablo™ System. Using internal log file data that can be transmitted wirelessly after treatment, we measured the time required to set up, and the number and type of alarms that occurred. After each set-up step is completed or an alarm occurs a flag is logged in the data. The timing between flags was measured to determine set-up and alarm resolution times.

Results: System data files for 356 treatments were analyzed. Patients did not have dexterity or visual deficiencies, age ranged from 28-69 and there were 11 females. In 90% of treatments patients were able to set-up Tablo™ in 5 minutes.



There were 472 alarms, or 1.32 alarms per treatment, with a weighted average of 22.4 seconds to resolve an alarm, using the Tablo™ touchscreen. In 183 (51%) treatments there were no alarms.

Conclusions: Patients performing ICSCHD can quickly set-up and successfully manage their treatments using the Tablo™ Hemodialysis System.

Funding: Pharmaceutical Company Support - Outset Medical, Inc.

SA-PO1138

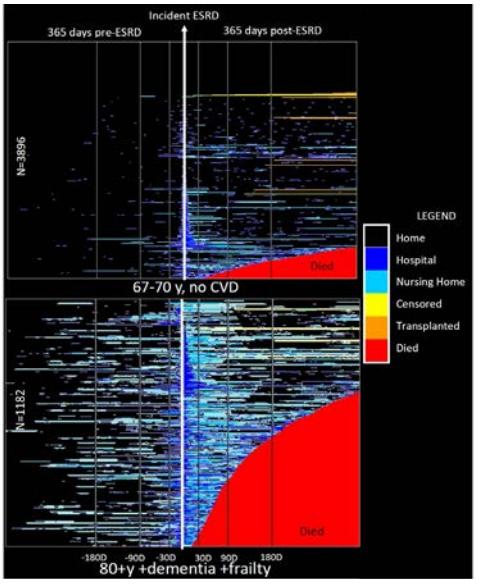
Institutionalization before and after the Transition from CKD to ESRD on Dialysis

Maria E. Montez-Rath,[1] Yuanchao Zheng,[1] Manjula Kurella Tamura,[1] Vanessa Grubbs,[2] Wolfgang C. Winkelmayer,[3] Tara I. Chang.[1] *[1]Stanford; [2]UCSF; [3]Baylor.*

Background: The transition from CKD to ESRD can be particularly unstable. We sought to examine the frequency of days spent institutionalized (hospital or nursing home) during the 1-year prior to and after dialysis initiation in older patients.

Methods: We used the USRDS to identify patients aged ≥67y at the time of incident ESRD with Medicare A+B. We created "heat maps" by color-coding each day in the 365 days pre- and post-ESRD; each patient is represented by a single horizontal row with dark/light blue indicating institutionalized days. We used zero-inflated negative binomial models that accounted for number of days alive to quantify the mean number of institutionalized days in the 1st year post-ESRD, adjusting for baseline characteristics.

Results: The top heat map (Figure) depicts 67-70 year-olds without cardiovascular disease (CVD). The larger amount of black vs. blue reflects the larger proportion of time spent at home vs. in an institution. The bottom heat map depicts 80+ year-olds with dementia+frailty, and shows a relatively large proportion of institutionalization and death.



The adjusted average number of institutionalized days differs widely depending on the subgroup (Table).

Table: Adjusted average number of institutionalized days in the first 365 days post-ESRD

	Age Category (y)			
	67-70	**71-74**	**75-79**	**80+**
Overall	49	55	63	75
CVD+	53	59	67	79
CVD-	33	37	42	54
Dementia+	75	85	88	103
Dementia-	47	53	61	72
Frail+	86	93	96	105
Frail-	41	47	54	66
Dementia+Frail+	108	113	113	120
Dementia-Frail-	42	46	52	59

Conclusions: Older patients who initiate dialysis spend a substantial proportion of time institutionalized, particularly octogenarians and patients with dementia, frailty and CVD. Continued efforts to improve shared decision-making about dialysis initiation in high-risk subgroups are needed.

Funding: NIDDK Support

SA-PO1139

Generalisability of SPRINT to Community Dwelling Individuals over the Age of 75: Informing Estimation of Baseline Adverse Event Risk

Donal J. Sexton,[1,2,3] Mark Canney,[1,2] Mark Alan Little,[2] Conall M. O'Seaghdha,[3] Rose Anne M. Kenny.[1] *[1]The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin, Dublin, Ireland; [2]Trinity Health Kidney Centre, Trinity College Dublin, Dublin, Ireland; [3]Dept of Renal Medicine, Beaumont Hospital, Dublin, Ireland.*

Background: With the publication of the ≥ 75 yrs subgroup analysis of the SPRINT trial, the generalizability of this study merits evaluation. SPRINT found reduced cardiovascular events and all-cause mortality in those randomized to a systolic BP target of < 120 mmHg.

Methods: Data from the 1st (2009-2011) and 3rd wave (2015) of The Irish Longitudinal Study on Ageing, a prospective cohort study of community dwelling older adults in Ireland (N=5390). We applied the inclusion/exclusion criteria for SPRINT.

Results: Mean follow up was 3.42 yrs. For those ≥ 75 yrs meeting final inclusion criteria we compared characteristics and outcomes of those with CKD: 37.8%(45,566 in the population) to those without CKD: 62.2%(74,933). Frailty (by Fried Index) was more common at baseline in CKD: 12.6% Robust (15,121), 19.4% Pre-frail (23,200) and 5.9% Frail (7,100) compared to 23.8% (28,703) Robust, 35.2% Pre-frail (42,450) and 3.2% Frail without CKD (3,805) P = 0.02. Those reporting difficulties climbing one flight of stairs was more common in CKD (28.8% No, 9% yes) than without CKD (53.4% no and 8.8% yes), P=0.04. A history of having previously fractured a hip, was more common in CKD (33.1% No, 4.8% Yes) than without CKD (59% No and 3.2% Yes) P=0.03. Reporting a fear of falling was also more common at baseline in CKD (29.8% No, 8% Yes) than without CKD (56.7% No and 5.5% Yes), P=0.003. Outcome rates over follow up in this study per 100 person years (95%CI) were: Syncope 1.4(0.5-3.6) in CKD and 1.2(0.5,2.7) without CKD, Injurious falls 14.8(8.6,25.5) in CKD vs 11(6.3, 19.4) without CKD, fractures (hip/wrist/spine) due to falls 0.7(0.2,2.7) in CKD vs 0.6 (0.2, 1.8) without CKD.

Conclusions: Community dwelling individuals ≥ 75 yrs meeting eligibility for SPRINT are a heterogeneous group. Given the observation of higher baseline frailty in those with CKD than without in this study, the balance of risk:benefit when implementing the results of SPRINT may be influenced by the presence of CKD.

SA-PO1140

A Delphi Study on Frailty in Adults with End Stage Renal Disease

Sarah Rasmussen, Dorry L. Segev, Mara McAdams-DeMarco. *JHU.*

Background: End stage renal disease (ESRD) patients are at higher risk of frailty, a loss of physiologic reserve that is associated with poorer outcomes. However, some components of the frailty phenotype may not accurately characterize frailty in ESRD patients.

Methods: In a two-round Delphi study we distributed 2 anonymous surveys to nephrologists, geriatricians and transplant surgeons at JHU (round 1 n=41; round 2 n=36). Consensus and moderate consensus were defined as >80% and 60-80% agreement, respectively. Fisher's exact test was used to examine differences by specialty.

Results: The response rate for both rounds was 87%. 98% of clinicians said ESRD patients are more likely to be frail than healthy adults. There was consensus that 4 of the 5 Fried frailty components should not be removed from the definition of frailty in ESRD patients, but only moderate consensus that weight loss should not be removed (71%). Nephrologists were less likely to want to remove weight loss (p=.03). 10 new ESRD-specific components were identified (9 included in round 2). There was moderate consensus that history of falls and physical decline should be added. Nephrologists were more likely to want to add history of falls (p=.01); gerontologists were less likely to want to add cognition (p=.03).

1st round: components identified	2nd round: % wanting to add component	% wanting to add component by specialty			
		Nephrology	Gerontology	Transplant Surgery	P-value
History of falls	64	83	38	100	**.01**
Physical decline	64	67	50	100	.46
Cognition	39	50	19	100	**.03**
Nutrition, diet	36	44	25	50	.38
Albumin	17	28	6	0	.24
Health care utilization	11	11	12	0	1.0
Metabolic bone disease	6	11	0	0	.54
Excess fluid	3	6	0	0	1.0
Ultrafiltration	3	6	0	0	1.0

There was consensus that prehabilitation could make transplant patients less frail (97%) and that patients will be interested in prehabilitation (97%). There was moderate consensus that using foot peddlers during dialysis would make patients less frail (80%) and that patients would be interested in foot peddlers (69%).

Conclusions: There is consensus that frailty is common in ESRD patients and that interventions could improve frailty in this population. However, some clinicians suggest a need for an ESRD-specific measure of frailty.

Funding: Other NIH Support - NIA, Private Foundation Support

SA-PO1141

Kidney Function and Objective Markers of Frailty in Community-Dwelling Older Adults

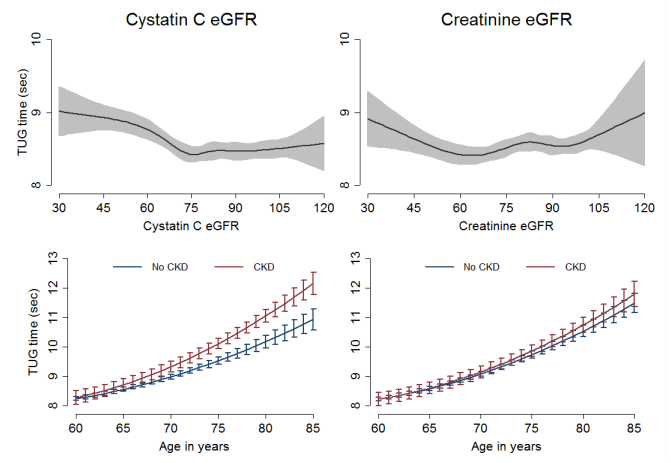
Mark Canney,[1,2] Donal J. Sexton,[1,2] Matthew D.l. O'Connell,[1] Neil O'Leary,[1] Rose Anne M. Kenny,[1] Mark Alan Little,[2] Conall M. O'Seaghdha.[3] *[1]The Irish Longitudinal Study on Ageing, Trinity College Dublin; [2]Trinity Health Kidney Centre, Trinity College Dublin; [3]Nephrology Dept, Beaumont Hospital, Dublin.*

Background: Frailty is a means of risk-stratification in advanced chronic kidney disease (CKD). We sought to determine the association between objective physical performance tests and kidney function across the spectrum of estimated glomerular filtration rate (eGFR) in older adults.

Methods: Cross-sectional analysis of 4562 participants from The Irish Longitudinal Study on Ageing, a representative national cohort of community-dwelling adults aged

≥50yrs. We categorized eGFR (mL/min/1.73m²) from cystatin C ($eGFR_{cys}$) and creatinine ($eGFR_{cr}$) as follows: ≥90(ref);75-89;60-74;45-59;<45. We used multivariable linear regression to examine the association between eGFR groups and gait speed, timed-up-and-go (TUG) and grip strength. Restricted cubic splines of continuous eGFR were modeled to further examine the relationship with TUG. We examined effect modification by CKD (eGFR<60) in the relationship between age and TUG.

Results: Mean(sd) age was 61.8(8.3)yrs, 54% were female and mean(sd) $eGFR_{cys}$ was 81(17.7)mL/min/1.73m². Participants with $eGFR_{cys}$<45 had slower gait speed (-3.6cm/s [95%CI, -6.9, -0.3]), longer TUG (0.4s [0.1, 0.7]) and weaker grip (-1.3kg [-2.4, -0.1]) vs the reference group. Associations between $eGFR_{cr}$ groups and outcomes were not significant. An $eGFR_{cys}$<75 represented a turning point for slower TUG; the relationship between $eGFR_{cr}$ and TUG was U-shaped. CKD defined by $eGFR_{cys}$, but not $eGFR_{cr}$, modified the relationship between age and TUG.



Conclusions: We observed a relationship between $eGFR_{cys}$ and objective frailty markers in older community-dwelling adults, evident at early eGFR declines. CKD defined by $eGFR_{cys}$, but not $eGFR_{cr}$, modified the relationship between age and physical performance.

SA-PO1142

Distribution of Cystatin C and Creatinine with Advancing Age

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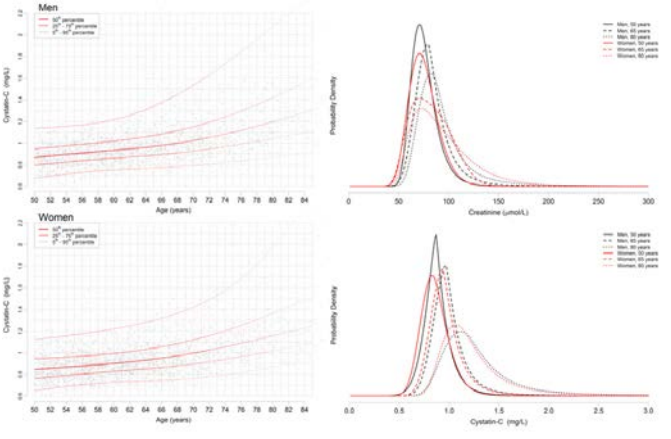
Background: Little is known about filtration marker distribution as we age. We modelled creatinine and cystatin C distributions across the age spectrum in the general population of older adults.

Methods: Cross-sectional analysis of 5387 participants from The Irish Longitudinal Study on Ageing, a representative national cohort of community-dwelling adults aged ≥50 years. Creatinine and cystatin C were measured simultaneously using standardised assays. Using generalized additive models we flexibly modelled the distribution of each biomarker from four parameters of the Box-Cox Power Exponential distribution: location, dispersion, skewness and kurtosis. The best fitting model for each parameter was sought using 3 to 5 cubic splines with age, sex and an age-sex interaction term as covariates. All models incorporated an inverse probability weight for study participation.

Results: Mean(sd) age was 63.9(9.2) years and 53% were female. We observed a strong non-linear relationship between cystatin C and age, with an upstroke at age 65 beyond which cystatin C levels rose sharply. The shape of the cystatin C distribution differed by age in both genders. As well as having higher median values, older individuals demonstrated greater variability in cystatin C compared to younger participants. The trajectory of creatinine with age was comparatively flat. Creatinine distribution also varied with age but to a lesser extent.



Conclusions: The relationship between cystatin C and age is complex and non-linear. Older adults demonstrate progressively greater variability in filtration marker distribution with advancing age, particularly for cystatin C. Such variability may contribute to the uncertainty of estimation of kidney function in the ageing population.

SA-PO1143

Low Body Mass Index as Risk Factor for Mortality in Older Adults

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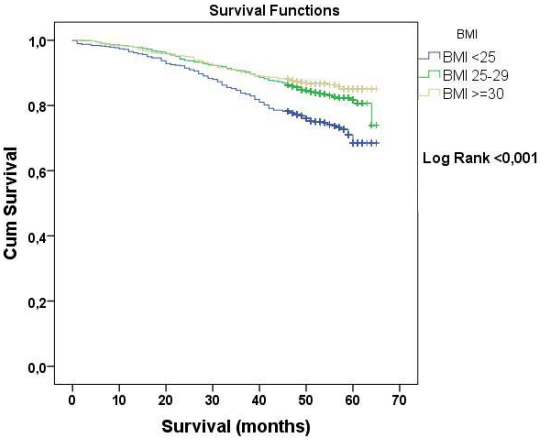
Background: High body mass index (BMI) is a known risk factor for cardiovascular events and mortality in middle aged adults. Its relationship in older age is less clear.

Methods: We used baseline and follow-up data from the Berlin Initiative Study (BIS), a population-based cohort that examines kidney function over time in subjects who are 70 years and older. Kaplan Meier analysis and Cox proportional hazard models were applied to assess the predictive value of BMI (3 categories: ≥30, 25-29, <25) with regard to overall mortality. Analyses were done for BMI only and adjusted for age, gender and additional known risk factors. Median follow-up were 54 months.

Results: 2068 BIS participants with a mean age of 80 years were followed. 52.6 % were female, 26.1 % had diabetes, 14 % had suffered from myocardial infarction (MI), 8.7 % from stroke, 78.8 % had antihypertensive medication, 53 % had a GFR_{BIS2} <60 ml/min/1.73m². Mean albumin was 39.9 g/L. After 4.5 years 385 had died. Survival was worst for subjects with a BMI <25 compared to subjects with a BMI >30 (log rank <0.001).



After multivariable adjustment for age, gender, albumin, diabetes, smoking, MI, stroke, hypertension, and decreased kidney function (GFR <60 ml/min/1.73m²) the relationship was less strong but still statistically significant.

	univariate			multivariate		
	p-value	HR	95% CI	p-value	HR	95% CI
BMI ≥30 (reference)	<0.001			0.003		
BMI 25-29	0.14	1.23	0.93-1.62	0.79	0.96	0.73-1.28
BMI <25	<0.001	2.03	1.54-2.67	0.02	1.43	1.06-1.92

Hazard ratios were attenuated by albumin, stroke, smoking and hypertension (not shown). Decreased GFR did not influence the results.

Conclusions: Lower BMI was associated with higher mortality in older adults.

Funding: Private Foundation Support

SA-PO1144

Prevalence of Frailty in Chronic Dialysis Patients in Japan

Hidemi Takeuchi,[1] Haruhito A. Uchida,[1] Yuki Kakio,[1] Yuka Okuyama,[1] Ryoko Umebayashi,[1] Michihiro Okuyama,[2] Taro Sugimoto,[1] Hitoshi Sugiyama,[1] Jun Wada.[1] *[1]Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama Univ, Okayama, Japan; [2]Cardiovascular Surgery, Okayama Univ, Okayama, Japan.*

Background: Recently, frailty has raised as the problematic expression of the elderly population, especially dialysis patients. Since potential causative factors of frailty present in the patients with CKD and ESRD, they are prone to develop frailty. The prevalence of frailty has reported 14 % of CKD patients and 42 % of dialysis patients in Western studies. However, that in dialysis patients in Japan remains unknown. The aim of this study was to examine the prevalence and the predictors of frailty in Japanese hemodialysis patients.

Methods: This study was a multicenter, cross-sectional and observational investigation, which was conducted at 6 institutions including 5 general hospitals and 1 clinic. The subjects were all chronic hemodialysis patients who regularly visited the institutions and were recruited from October 2015 to January 2016. To evaluate frailty status, we used the modified Fried's frailty phenotype definition modified for Japanese as the self-report questionnaire.

Results: Of 542 patients visiting each institution, 388 patients were enrolled in this study. Participants were 67 ± 12 years old, with more male gender (62.4 %). In total, 21.4 % of participants were categorized as frailty, 52.6 % as pre-frailty and 26.0 % as normal.

The prevalence of frailty increased steadily with age, was more prevalent in female and polypharmacy. Next, we performed multivariate logistic regression analysis for the predictors of frailty. The factors independently associated with frailty were determined as follows: female (OR = 3.864, 95 % C.I. 1.595-9.361), 75 years and over (OR = 5.375, 95 % C.I. 1.932-14.953), the number of medications (OR = 1.335, 95 % C.I. 1.156-1.541), DM (OR = 2.885, 95 % C.I. 1.181-7.048) and MNA-SF score ≤ 11 (OR = 8.550, 95 % C.I. 3.300-22.149).

Conclusions: The prevalence of frailty in Japanese dialysis patients was relatively lower than that of previous studies in Western countries. The patients of 75 years old and over, female, DM, polypharmacy and MNA-SF were closely associated with frailty.

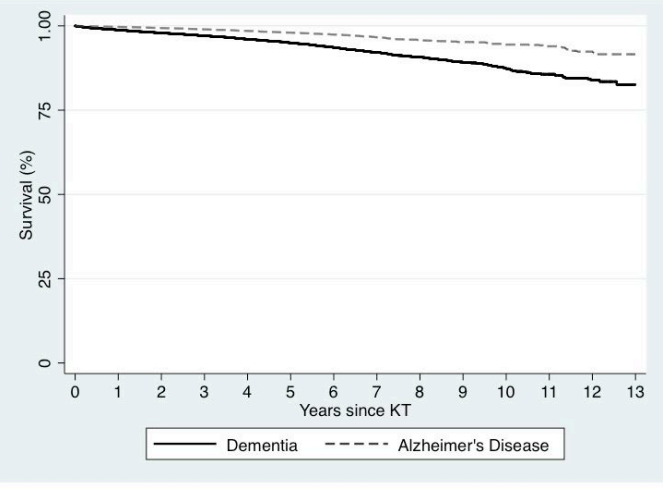
SA-PO1145

Dementia and Alzheimer's Disease among Older Kidney Transplant Recipients Mara McAdams-DeMarco, Sunjae Bae, Dorry L. Segev. *Johns Hopkins.*

Background: End stage renal disease and cognitive impairment share a common pathogenesis and dialysis increases the risk of cognitive impairment. KT is a growing treatment option for older adults yet, older recipients may develop dementia and Alzheimer's disease (AD) as the result of both their long standing kidney disease and the lifelong dependence on immunosuppressants, which are known to be neurotoxic.

Methods: We studied 43,606 older (aged >=55) KT recipients who were Medicare Primary (between 1/1/99-12/31/11) using SRTR data linked to Medicare claims. We estimated the cumulative incidence of dementia and AD (based on claims) using the Kaplan-Meier method. We developed a prediction model based on recipient, transplant, and donor factors known prior to KT for the post-KT incidence of dementia and AD (separately) using an AIC-based selection method for the Cox proportional hazards model.

Results: We estimated the post-KT cumulative incidence of dementia and AD to be 5.0% and 2.0% at 5 years and 12.7% and 5.6% at 10 years, respectively.



The prediction dementia model included recipient (age, race, education, BMI, history of diabetes, and time on dialysis), transplant (year of KT, previous KT, ABO incompatible, and peak PRA), and donor factors (race, hypertension, diabetes, and HCV) (C-statistic=0.66). The AD prediction model included recipient (age, education, BMI, history of diabetes, and time on dialysis), transplant (year of KT and previous KT), and donor factors (race and HCV) (C-statistic=0.70). The strongest predictors for both dementia and AD were recipient age (5y increase in age: dementia HR=1.49, 95%CI:1.43-1.56; AD HR=1.68, 95%CI:1.57-1.80) and history of diabetes (dementia HR=1.81, 95%CI: 1.43-1.56; AD HR=1.48, 95%CI:1.25-1.75).

Conclusions: Older KT recipients are at risk of dementia and AD. Recipient, donor, and transplant factors obtained prior to KT can be used to predict which older recipients are at risk of post-KT dementia and AD.

Funding: Other NIH Support - NIA, Private Foundation Support

SA-PO1146

Comparison of Geriatric and Medical Multi-Morbidity on Physical Function in Older Adults with Chronic Kidney Disease Christine Liu,[1,2] Eamon F. Fleming,[2] Jamie Giffuni,[3] Kieran Reid,[2] Sushrut S. Waikar,[4] Stephen L. Seliger,[3] Daniel E. Weiner.[2] *[1]Boston Univ, Boston, MA; [2]Tufts Univ, Boston, MA; [3]Univ of Maryland, Baltimore, MD; [4]Harvard Medical School, Boston, MA.*

Background: Geriatric conditions are combinations of signs and symptoms not linked to a disease, such as fatigue. Medical conditions relate to specific diseases. Geriatric multi-morbidity (2+ geriatric conditions) and medical multi-morbidity are common in older CKD patients and may impact physical function. We compared the impact of geriatric and medical multi-morbidity on physical function in older CKD patients.

Methods: The Aerobics, Weights, and Renal Disease Study is an ongoing randomized trial of exercise in adults 55+ years with CKD stage 3b-4. Data are from baseline. Persons were defined with 1) fatigue if ≥"good bit of time" to feeling worn out on Short Form-36 (SF-36); 2) chronic pain if ≥"moderate" pain on SF-36; 3) cognitive impairment if Montreal Cognitive Assessment <26; 4) poor appetite as reported on Memorial Symptom Assessment Scale (MSAS); and 5) dizziness as reported on MSAS. Hypertension, diabetes, CAD, cancer, and COPD were defined by self-report or record review. Physical function was assessed with the Short Physical Performance Battery (SPPB) and the SF-36 physical function domains. Linear regression was used, adjusting for age, sex, study site, BMI, and eGFR.

Results: Of 93 persons (27% female, mean age 68.2±8.3 years, mean eGFR 33.0±9.2 ml/min/1.73m^2), 46 (50%) had geriatric multi-morbidity and 70 (75%) had medical multi-morbidity. Geriatric multi-morbidity was associated with lower SPPB and SF-36 scores, but not medical multi-morbidity (Table).

Conclusions: In older adults with CKD, geriatric multi-morbidity likely has a stronger association with physical function than medical multi-morbidity.

Table: Least square means of associations of geriatric and medical multi-morbidity with physical function (N=93)

Outcomes	Multi-morbidity	Yes	No	Adjusted p value
SPPB	Geriatric	8.7	9.8	**0.05**
	Medical	9.1	9.3	0.72
SF-36 Physical function	Geriatric	53.8	75.3	**0.0001**
	Medical	61.0	68.1	0.19
SF-36 Role limitations-physical function	Geriatric	26.9	79.1	**<0.0001**
	Medical	49.3	56.6	0.37

Funding: NIDDK Support, VA Support, Private Foundation Support

SA-PO1147

Symptom Burden in Geriatric Hospitalized End Stage Renal Disease Patients: Quantifying Symptoms to Increase Nephrologist Awareness and Use of Palliative Care Consultation Areeba Jawed,[1] Sharon M. Moe,[1] Ranjani N. Moorthi,[1] Alexia Torke,[2] Michael T. Eadon.[1] *[1]Div of Nephrology, Dept of Medicine, Indiana Univ School of Medicine, Indianapolis, IN; [2]Internal Medicine, Indiana Univ School of Medicine, Indianapolis, IN.*

Background: End Stage Renal Disease (ESRD) patients have significant symptom burden. Reduced provider awareness of symptoms contributes to underutilization of symptom management resources. We hypothesized that improved nephrologist awareness of symptoms leads to symptom improvement.

Methods: In this prospective, multicenter intervention study, 51 geriatric ESRD inpatients underwent symptom assessment using the modified Edmonton Symptom Assessment System (ESAS) at admission and 1 week post-discharge. Enrollees were sequentially randomized into 2 groups. The nephrologist of each individual was provided baseline symptom assessment in group 1, but was unaware in group 2. Severity ratings were compared between in-hospital and post discharge scores and between groups.

Results: 50 patients completed the study; 1 died. Baseline characteristics were compared. For 70% of the total cohort physicians reported not being surprised if their patient died within a year. There was no difference in baseline scores between groups. Total ESAS scores improved more in group 1 (13.3) than group 2 (9.5) (p=0.04). Among individual symptoms, there was greater improvement in pain control (p=0.01), and itching (p=0.05) in Group 1 as compared to Group 2. There were three palliative care consults.

Conclusions: Our findings reinforce the high symptom burden prevalent in geriatric ESRD patients. The improvement in total scores, and individual symptoms of pain and itching in group 1 indicates better symptom control when physician awareness is increased and simple pharmacological interventions are available. Residual symptoms post hospitalization and low utilization of palliative care resources is suggestive of a missed opportunity by nephrologists to address the high symptom burden at the inpatient encounter which is selective for sicker patients and/or inadequacy of dialysis to control these symptoms.

Funding: Private Foundation Support

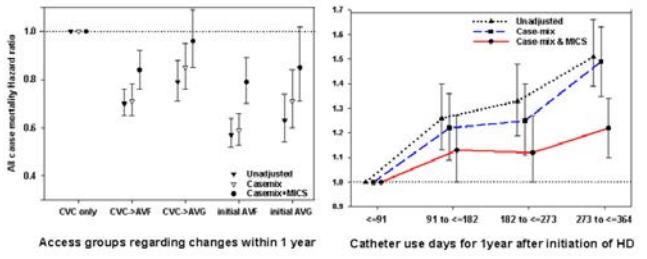
SA-PO1148

Use of Arteriovenous Fistula within 1 Year of Hemodialysis Initiation Was Associated with Better Survival in Comparison with Catheter Use among Patients Older Than 80 Gang Jee Ko,[1] Connie Rhee,[1] Tae Ik Chang,[1] Yoshitsugu Obi,[1] Melissa Soohoo,[1] Tae Woo Kim,[1] Rieko Eriguchi,[1] Hamid Moradi,[1] Vanessa A. Ravel,[1] Csaba P. Kovesdy,[2] Elani Streja,[1] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Univ of Tenn.*

Background: While arteriovenous fistulas (AVFs) are recommended as the preferred vascular access type in most hemodialysis (HD) patients, this remains widely debated in very old HD patients given their lower rates of AVF maturation and limited life expectancy.

Methods: We examined the conversion of access types within 1 year after HD initiation, and evaluated the association of dialysis access with mortality using Cox regression with adjustment for case-mix (demographics, comorbidities) and markers of malnutrition and inflammation (MICS) in 8,326 incident HD patients age 80 years, who survived the first year of HD from a large dialysis organization during 2007-2011.

Results: During the first year of HD, 27% of elderly patients exclusively used a central venous catheter (CVC). Ever use of AVF (CVC-to-AVF or initial AVF) within the first year of HD was associated with better survival compared to the CVC-only use. In fully adjusted models, no significant differences were noted between ever-use of AV graft in the first year of HD, compared to CVC-only. Longer use (total number of days in the first year of HD) of CVC following HD initiation was associated with incrementally worse survival (right panel).



Conclusions: It is suggested to consider converting access type to AVF from CVC and decreasing the periods time using CVC even in very old HD patients. Initiation of dialysis with a CVC catheter could be an acceptable option in elderly patients, as long as it is converted to an AVF as soon as possible.

Funding: NIDDK Support

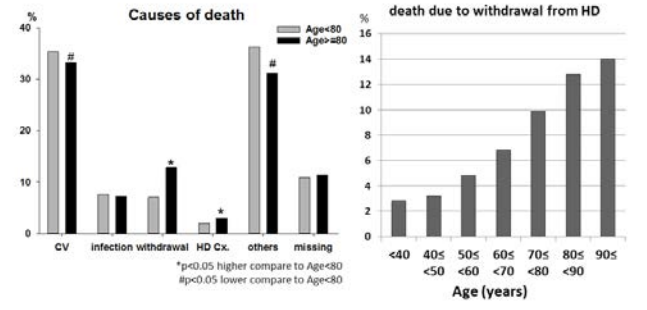
SA-PO1149

Death due to Dialysis Withdrawal among Elderly Incident Hemodialysis Patients Gang Jee Ko,[1] Tae Ik Chang,[1] Connie Rhee,[1] Tae Woo Kim,[1] Yoshitsugu Obi,[1] Rieko Eriguchi,[1] Melissa Soohoo,[1] Daniel L. Gillen,[1] Vanessa A. Ravel,[1] Csaba P. Kovesdy,[2] Elani Streja,[1] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine; [2]Univ of Tenn.*

Background: The population of elderly patients is rapidly growing among ESRD patients initiating dialysis. However, it is not clear whether death due to withdrawal from dialysis differs across age and which pattern it has, in particular among octogenarian and nonagenarian patients.

Methods: We compared causes of death, including withdrawal from dialysis, within the first year of dialysis among incident hemodialysis (HD) patients aged ≥80 years (N=17,296) vs. those <80 years of age (N=115,866) from a large national dialysis organization over a 5 year period (2007-2011). Comparisons were modeled using reported frequencies and logistic regression.

Results: Compared to patients <80 years of age, octogenarian and nonagenarian were more likely to be female (45.8 *vs.* 43.0%) and non-Hispanic White (67.7 *vs.* 43.7%), and were less likely to have diabetes (45.6 *vs.* 57.0%). Loss to follow-up during the 1st year of HD was more frequent in octogenarian and nonagenarian, and a greater proportion of these events was due to dialysis withdrawal as compared with younger patients (7.2 *vs.* 2.9%) besides death. Among octogenarian and nonagenarian, death due to dialysis withdrawal was the second most common cause of death (left panel), and we observed higher rates of dialysis withdrawal among death with increasingly older age (right panel). Octogenarian and nonagenarian showed a higher likelihood of death due to dialysis withdrawal compared to younger patients even after adjustment for demographics and comorbidities: adjusted OR 1.61 (95% CI: 1.47-1.77).



Conclusions: Withdrawal from dialysis is a major cause of loss to follow-up and death among elderly incident HD patients. Further studies are needed to determine the reasons underlying the differential causes of death across age groups.

Funding: NIDDK Support

SA-PO1150

Survival and Outcomes in Advanced Age with Renal Insufficiency (SOAAR) Hui Xue,[1] Shayna L. Henry,[2] Qiaoling Chen,[2] Mi Chang,[1] Nichole Mihara,[1] Mark P. Rutkowski.[1] *[1]Nephrology, Kaiser Permanente Southern California, CA; [2]Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA.*

Background: While the elderly are the fastest growing segment of individuals with End Stage Renal Disease (ESRD), there is limited evidence for an overall survival or quality adjusted life advantages of Renal Replacement Therapy (RRT) compared to conservative approaches in this group. This study aims to illuminate the outcomes and survival of elderly patients with advanced renal failure with respect to RRT choice, and to identify factors associated with disease progression and worse outcomes.

Methods: From 2003 to 2008, 2,062 adults, mean age 81.1±4.7yrs (range 75-99), 49.5% female, who initiated RRT or maintained eGFR ≤ 20 for at least 3 consecutive months were followed for 5 years with censoring at December 31, 2013. Subjects who did not initiate RRT were observed until death or censor date. Risk of transition to ESRD vs death was stratified into 5 year age groups. Healthcare utilization was also assessed based on RRT use.

Results: The risk of progression to ESRD is higher than death upto age 90, p<0.001. Median survival was 33 (95% CI 30, 36) and 20 (17, 22) months for RRT and non-RRT groups, respectively (p<0.001). Quality-adjusted survival was 21 (19, 23) and 14 (12, 15) months for RRT and no RRT groups, respectively (p<0.001). Peritoneal dialysis offered greatest survival benefit compared to hemodialysis or no RRT (p<0.001). Initial results suggest that age is a better predictor of death than baseline eGFR, with age and survival inversely related, and those patients initiating RRT at the oldest ages (90+ years) experiencing the most limited survival (logrank p<.001). However, RRT was associated with greater healthcare utilization, including more hospitalizations and ER visits, greater SNF use, and lower hospice referral (p<0.001).

Conclusions: RRT appears to afford older adults with ESRD a survival advantage over conservative, non-RRT approaches, but decrements in quality of life may still limit its utility among the elderly. The potential for these findings to provide decision support for initiating or forgoing RRT in elderly patients will be discussed.

Funding: Private Foundation Support

SA-PO1151

Impact of Race and Socioeconomic Factors on Mortality among Nursing Home Patients on Maintenance Dialysis Robert Nee,[1] Lawrence Agodoa,[2] Kevin C. Abbott.[2] *[1]Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; [2]NIDDK, National Insts of Health, Bethesda, MD.*

Background: The impact of race and socioeconomic factors on survival rates of nursing home (NH) patients with treated end-stage renal disease is unknown. We evaluated race/ethnicity, health insurance and ZIP code-level median household income (MHI) as predictors of mortality of NH patients on dialysis.

Methods: In this retrospective cohort study using the United States Renal Data System database, we identified 56,194 nursing home patients initiated on maintenance dialysis from January 1, 2007 through December 31, 2013, followed until 31 May 2014. Covariates include demographic and clinical characteristics and other co-morbid conditions from the Medical Evidence Form 2728. ZIP code-level MHI data was obtained from the 2010 United States Census. We conducted adjusted Cox regression analyses with all-cause mortality as the outcome variable.

Results: Within this NH cohort, 50.5% were female, 26.7% were African-Americans (AA), 8.9% were Hispanic, and the mean age was 71.1 ± 12.1 years. Adjusted Cox analysis showed significantly lower risk of death among AA vs non-AA NH patients (adjusted hazard ratio [AHR] 0.89; 95% confidence interval [CI] 0.87-0.91) and Hispanic vs non-Hispanic NH patients (AHR 0.87; 95% CI 0.84-0.91). Employer group health insurance (AHR 0.94; 95% CI 0.91-0.97) and dual-eligibility for both Medicare and Medicaid (AHR 0.75; 95% CI 0.73-0.77) were significantly associated with lower risk of death. However, Medicare (AHR 1.12, 95% CI 1.09-1.15) and Medicaid (AHR 1.13; 95% CI 1.10-1.16) alone were significantly associated with higher risk of death. Compared to those in higher area-level MHI quintile levels, NH patients in the lowest quintile were significantly associated with higher risk of death (AHR 1.10; 95% CI 1.07-1.13).

Conclusions: AA and Hispanic NH patients on dialysis had an apparent survival advantage. The type of health insurance coverage and area-level income were also independent predictors for survival.

SA-PO1152

Association of Dietary Sodium Intake with Change in Cognitive Function and Brain Magnetic Resonance Imaging Indices Kristen L. Nowak,[1] Linda F. Fried,[2,3] Anna Jeanette Jovanovich,[1,4] Joachim H. Ix,[5] Anne B. Newman,[2] Zhiying You,[1] Suzanne Satterfield,[6] Michel Chonchol.[1] *[1]Univ of Colorado Anschutz Medical Campus; [2]Univ of Pittsburgh; [3]VA Pittsburgh Healthcare System; [4]Denver VA Medical Center; [5]Univ of California San Diego; [6]Univ of Tennessee Health Science Center.*

Background: Dietary sodium may influence cognitive function via its influence on cerebrovascular function and cerebral blood flow. We hypothesized that high dietary sodium intake is associated with a decline in cognitive function over time. We further hypothesized that sodium intake is associated with micro- and macro-structural brain magnetic resonance imaging (MRI) indices.

Methods: 1,216 participants in the Health ABC study with measurement of dietary sodium intake and change in the modified mini mental state exam (3MS) were included. Multivariable logistic regression was used to examine the association between baseline dietary sodium intake (food frequency questionnaire) and odds of a clinically significant decline in 3MS score after 7 years (>5 points or to <80 points). In a sub-group who participated in the Healthy Brain substudy (n=257), multiple linear regression models were used to assess the association of sodium intake with micro- and macro-structural brain MRI indices.

Results: Participants were 74±3 years with a mean dietary sodium intake of 2,645±1098 mg/day. During follow-up, 340 (28%) had a clinically significant decline in 3MS score (i.e. cognitive impairment). Dietary sodium intake was not associated with increased odds of cognitive impairment in either the unadjusted model (OR: 1.15, 95% CI: 0.93-1.41 per doubling of sodium intake) or model adjusted for demographics, education, co-morbid conditions, smoking, alcohol, body-mass index, blood pressure, estimated glomerular filtration rate, total kcals, and potassium intake, (OR: 1.36, 95% CI: 0.90-2.07 per doubling of sodium). Similarly, sodium intake was not associated with micro- or macro-structural brain MRI indices in unadjusted and adjusted models.

Conclusions: In the Health ABC study, higher sodium intake was not associated with a decline in cognitive function over time or with micro- and macro-structural brain MRI indices.

Funding: Other NIH Support - NIA

SA-PO1153

Chronic Hyponatremia and Association with Bone Frailty Associated Falls and Fractures Simran K. Bhandari,[1] Annette Adams,[1] Bonnie H. Li,[1] Shirin Sundar,[2] Holly Krasa,[2] Siddhesh Kamat,[2] John J. Sim.[1] *[1]Dept of Nephrology and Hypertension, Kaiser Permanente Southern California; [2]Otsuka Pharmaceuticals.*

Background: Chronic hyponatremia is known to cause cognitive impairment and contribute to osteoporosis, both of which may lead to greater risk of serious falls/fractures (FX) among the elderly. We sought to evaluate whether chronic hyponatremia was associated with increased risk for FX based on serial sodium (Na) measurements among a large diverse population.

Methods: A cohort study was performed within Kaiser Permanente Southern California between 1/1/98 – 12/31/14 among individuals ≥ 55 years with ≥ 2 Na measurements and with dual x-ray absorptiometry (DXA) result. Time weighted (TW) and arithmetic mean Na values were used to define chronic hyponatremia as Na <135 mEq/L. FX were determined from combinations of ICD-9 diagnosis codes, procedure codes, and E codes. Multivariable logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for FX.

Results: 385,778 subjects were identified for the study (68% women and mean age 63). Osteoporosis (DXA T-score < -2.5) was found in 43.7%. Chronic hyponatremia was identified in 12% (n = 46,444) and 2.8 % were found to have TW mean Na of < 135 mEq/L. A total of 49,840 (13%) subjects had a FX. Hyponatremia was present in 24.1% with FX compared to 10.3% without a FX. Individuals who had FX were more likely female and had greater rates of osteoporosis and cardiovascular disease. Compared to Na ≥ 135, chronic hyponatremia was associated with an increased risk of FX (OR 1.41 (1.38, 1.45)). A 5mEq/L increase in TW mean Na was associated with a decreased risk of FX (OR 0.89 (0.84, 0.93)).

Figure 1. Unadjusted and adjusted estimates of the association between hyponatremia and falls/fractures.

Model	Na<135mg/L OR (95% CI)	TW Na, 5 unit increase OR (95% CI)
Unadjusted	2.32 (2.28, 2.36)	0.83 (0.78, 0.88)
Adjust for demographics[1]	1.89 (1.86, 1.93)	0.88 (0.84, 0.94)
Adjust further for comorbidities[2]	1.87 (1.84, 1.91)	0.88 (0.84, 0.94)
Adjust further for labs[3]	1.57 (1.54, 1.61)	0.85 (0.81, 0.90)
Adjust further for pharmacologic exposures[4]	1.41 (1.38, 1.45)	0.89 (0.84, 0.93)

[1]Age, sex, race/ethnicity
[2]Diabetes, cardiovascular disease, peripheral vascular disease, hypertension, hypothyroidism, and prior fracture
[3]Potassium, carbon dioxide, chloride, BUN, creatinine, calcium, hemoglobin, TSH, alkaline phosphatase, HgbA1C, albumin
[4]Bisphosphonates, other osteoporosis druges, anti-hypertensives, anti-arrythmics, anti-coagulants, anti-seizure medications, endocrine and hormonal therapies, corticosteroids, thiazide diuretics, benzodiazepines, anti-depressants, proton-pump inhibitors

Conclusions: Among a large population with DXA measurements, we found chronic hyponatremia was associated with higher risk for having FX. There was a dose dependent protective association with higher TW mean Na values and FX.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceuticals

SA-PO1154

Medicare Advantage Plan Star Rating and Voluntary Disenrollment of Incident Dialysis Patients Qijuan Li,[1] Amal Trivedi,[1] Omar Galarraga,[1] Daniel E. Weiner,[2] Vincent Mor.[1] *[1]Health Services, Policy and Practice, Brown Univ; [2]Tufts Medical Center.*

Background: There has been limited focus on Medicare Advantage (MA) plan quality ratings and beneficiaries' decisions to disenroll, particularly among high-cost populations with intensive health care needs. Accordingly, we assessed the association between publicly reported MA plan quality ratings and voluntary disenrollment by incident dialysis patients.

Methods: Data on 50,391 incident dialysis patients were assembled from four national administrative databases spanning 2007 and 2013. We used conditional logit regression, controlling for patient and plan characteristics, to examine the association between MA plan star ratings at the time of initiating dialysis and disenrollment rates from MA plans to Traditional Medicare in the following year.

Results: Disenrollment rates for incident dialysis patients ranged from 8.8% among plans rated with 2.5 or fewer stars to 22.7% among plans rated with 4 or more stars. Compared to MA plans with star ratings of 4 or above, adjusted disenrollment rates were 3.9 (95% CI 2.4 to 5.5), 5.0 (95% CI 3.5 to 6.5), and 12.1 percentage points (95% CI 10.0 to 14.3) higher among MA plans with star ratings of 3.5, 3 and 2.5 or less, respectively. The disenrollment rate from MA plans to Traditional Medicare among incident dialysis patients was significantly higher than among all MA beneficiaries (14.9% vs 12.0%; p<0.01). Among MA plans with 2.5 or fewer stars, the adjusted disenrollment rate of incident dialysis patients was about 5.8 percentage points (95% CI 1.4 to 10.1) higher than that of all MA beneficiaries.

Conclusions: MA plans with worse star ratings had higher rates of disenrollment by incident dialysis patients in the following year. The association between star ratings and disenrollment was stronger among incident dialysis patients than among all MA beneficiaries, especially in low-quality plans. These findings suggest that the rate of voluntary disenrollment among high-cost, high need patients may be an important measure of MA plan quality. Low plan quality may lead to increased expenditures in Traditional Medicare by shifting this high-cost population from MA plans to Traditional Medicare.

Funding: Other NIH Support - R36 AHRQ Dissertation Grant

SA-PO1155

Serum 25-Hydroxyvitamin D Status, Body Composition, and Muscle Strength in Ambulatory Patients on Hemodialysis Dong Ho Yang,[1] So-Young Lee.[1] *[1]Internal Medicine, CHA Bundang Medical Center, Seongnam, Gyeonggi-do, Republic of Korea; [2]Internal Medicine, Seoul Bukbu Geriatic Hospital, Seoul, Republic of Korea.*

Background: Sarcopenia and muscle weakness are prevalent in patients with end stage renal disease, and vitamin D has various actions in skeletal muscle. We investigated the relationship between serum 25-hydroxyvitamin D [25(OH)D] status and skeletal muscle mass and muscle strength in ambulatory hemodialysis patients.

Methods: The current study involved 122 ambulatory hemodialysis patients. We evaluated serum 25(OH)D, body composition including skeletal muscle mass as measured by bioimpedance, muscle strength as measured by dynamometer (handgrip strength), and 4-meter walking speed in these participants. Alow muscle mass was defined by the SMM index (SMI: SMM [kg] / height [m2] > 7.0kg for men, > 5.7kg for women). Sarcopenia was defined if the patients having a low hand grip or walking speed (thresholds defined on the basis of the lowest sex-specific quintiles among general population) were identified as having a low muscle mass.

Results: The participants' average age was 60.6±1.2 years old, 54.1% were male, 57.4% had diabetes mellitus, and their mean duration of dialysis was 44.7±49.6 months. The mean 25(OH)D serum level was 16.2±0.9 ng/ml. Sarcopenia was identified in 16.4% of the participants. An analysis using the Pearson's correlation coefficient revealed a positive correlation between serum 25(OH)D levels and skeletal muscle mass (Pearson = 0.455, p < 0.001). Patients having a higher serum 25(OH)D level had a better hand grip strength (Pearson = 0.351, p< 0.001). Binary logistic regression analysis showed that ambulatory hemodialysis patients with above-median serum 25(OH)D levels had significantly more skeletal muscle mass (odd ratio [OR] 1.34; 95% Confidence interval [CI]: 1.20-1.51, p <0.001) and better hand grip strength (OR 1.06; 95% CI: 1.02-1.10, p=0.03).

Conclusions: In this study, serum 25(OH)D level was significantly associated with handgrip strength as well as skeletal muscle mass among ambulatory hemodialysis patients.

SA-PO1156

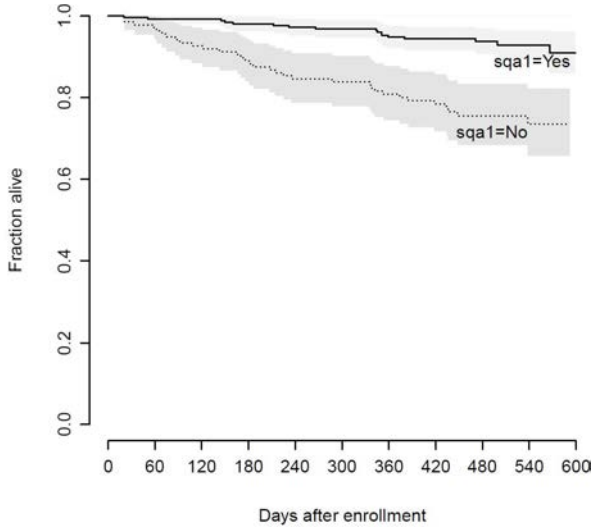
The Utility and Reliability of a Provider-Based Subjective Health Measure in Older Adults with CKD Stage 4-5 Andrei Javier,[1] Rocio Figueroa,[2] Huzaifah Salat,[1] Cesar Y. Cardona,[3] Jennifer Morse,[1] Thomas G. Stewart,[1] Manisha Jhamb,[4] Edward D. Siew,[1] Talat Alp Ikizler,[1] Khaled Abdel-Kader.[1] *[1]Vanderbilt Univ; [2]Univ of New Mexico; [3]Meharry Medical College; [4]Univ of Pittsburgh.*

Background: Nephrologists report prognostic uncertainty as a key barrier to advance care planning. We hypothesized the surprise question (SQ) would demonstrate acceptable test-retest and inter-rater reliability (until now uncharacterized) and be an effective predictor of mortality in older adults with CKD 4-5.

Methods: We enrolled 388 patients at a nephrology clinic from June 2014 to January 2015. Eligibility criteria were age > 60 years and CKD stage 4-5. Exclusion criteria were ESRD or kidney transplant prior to enrollment or eGFR > 60 within 12 months. Baseline characteristics were obtained from the health record. We collected SQ responses from attendings and fellows in a blinded fashion immediately after each visit.

Results:

	Total N=388 (%)	SQ 'Y' N=251 (65%)	SQ 'N' N=137 (35)	P
Age, median (IQR)	71 (65-77)	69 (65-74)	74 (68-80)	<.001
Female	195 (50)	127 (51)	68 (50)	0.9
Race				0.7
White	321 (83)	209 (84)	112 (82)	
Black	58 (15)	36 (14)	22 (16)	
DM with microvascular dsz	196 (51)	117 (47)	79 (58)	0.04
HTN	381 (98)	247 (98)	134 (98)	0.9
CAD	151 (39)	86 (34)	65 (47)	0.01
CHF (reduced EF)	34 (9)	10 (4)	24 (18)	<.001
Arrhythmia	97 (25)	49 (20)	48 (35)	<.001
Cerebrovascular dsz	88 (23)	49 (20)	39 (28)	0.04
PVD	78 (20)	48 (19)	30 (22)	0.5
eGFR	23 (16-28)	24 (18-29)	20 (15-25)	<.001



The SQ demonstrated good inter-rater (Kappa 0.60, 95% CI 0.48-0.68) and test-retest reliability (Kappa=0.64, 95% CI 0.55-0.74), and associated with mortality (P<0.001).

Conclusions: The SQ can be a helpful tool to identify CKD 4-5 patients at higher risk for short term mortality, but will likely require use in conjunction with other patient characteristics.

Funding: NIDDK Support, Private Foundation Support

SA-PO1157

The Pattern of Renal Histopathology in Elderly Korean with Renal Diseases: A 12-Year Review of a Single-Centre Renal Biopsy Database Yong Un Kang, Ha Yeon Kim, Chang Seong Kim, Eun Hui Bae, Seong Kwon Ma, Soo Wan Kim. *Chonnam National Univ Medical School.*

Background: Studies on biopsy-proven renal disease in the elderly are extremely limited in Korea. This study aimed to investigate the spectrum of renal histopathology and their clinical manifestations in elderly patients undergoing renal biopsy.

Methods: All native renal biopsies (n=99) performed in patients aged ≥65 years from January 2004 to December 2015 were retrospectively analyzed.The results were compared with a control group of 1,045 patients aged <65 years receiving renal biopsy during the same period.

Results: The number of the elderly was 99 patients with an age of 69.78±4.11 (range 65–81) years at the time of biopsy (men, 55 patients; women, 44 patients). The most common indication for renal biopsy was nephrotic syndrome (NS) (44.5%), followed by acute kidney injury (AKI) and NS (16.2%) and AKI (14.1%). Idiopathic membranous nephropathy (iMN, 16.2%) was the most frequent diagnosis, followed by minimal change disease (14.1%), diabetic nephropathy (DN, 12.1%), focal sclerosing glomerulonephritis (6.1%), IgA nephropathy (IgAN, 6.1%), lupus nephritis (LN, 6.1%) and vasculitis (5.1%) and amyloidosis (4%). In patients with NS and AKI, iMN (25.0%) and vasculitis (20.0%) was the leading cause. Comparison with the control group showed iMN (P=0.004), DN (P=0.005), vasculitis (P<0.001) and amyloidosis (P<0.001) to be more frequent and IgAN (P<0.001) and LN (P=0.014) less frequent in the elderly.

Conclusions: These datas indicate that their clinical manifestations and histopathology differ between elderly and non-elderly Korean with renal diseases. Our data are an important contribution to the epidemiology of renal disease in elderly Korean.

Funding: Government Support - Non-U.S.

SA-PO1158

10 Years Follow-Up of Renal Function in Elderly with Chronic Kidney Disease Manuel M. Heras,[1] Maria Teresa Guerrero,[2] Maria Jose Fernandez Reyes,[1] Angelica Muñoz,[2] Alvaro Molina,[1] Maria Astrid Rodriguez Gomez,[1] Ramiro Callejas,[1] Leonardo Calle,[1] Carmen Rita Martin Varas.[1] *[1]Nephrology, General Hospital Segovia, Segovia, Spain; [2]Geriatrics, General Hospital Segovia, Segovia, Spain.*

Background: Chronic Kidney Disease (CKD) is a global public health problem. Prevalence of low estimated glomerular filtration (eGFR) increases with age. We followed-up for 10 years the renal function (RF) of elderly with CKD.

Methods: 80 clinically stable patients, with a median age of 83 years; women: 68,8%; diabetics: 35%; alleatory recruited in the Departments of Geriatric and Nephrology, within January-April 2006, were followed-up for 10 years. We separated them in two groups based in their serum creatinine (sCr) baseline: Group 1: 38 patients with sCr≤1,1 mg/dl (range:0,7–1,1); and Group 2: 42 patients with sCr>1,1 mg/dl (range: 1,2–3,0). We measured creatinine, urea in serum; and estimated GFR baseline and 10 years, using abreviated MDRD. Statistical comparisons using repeated measures, SPSS 15.0 program.

Results: After 10 years of follow-up, 61 patients died (Group 1=23, Group 2=38, P=0,003) and 19 patients (including 2 males) with a mean age of 86,47±6 years (range: 79-97) remained in the study. Overall data regarding changes in RF (baseline/10 years) in surviving patients were as follows: sCr (mg/dl): 1,02±0,20/ 1,14±0,91 (not significant [ns]); urea (mg/dl): 43,08±12,0/ 66,16±57,0 (ns); MDRD (ml/min/1.73m2): 60,21±12,0/ 63,33±20,0 (ns). No significant differences in changes in RF by groups. Deterioration of sCr (mg/dl) was higher in those with/without proteinuria baseline: 1,25±0,35/ 2,80±2,68 vs 0,99±0,18/ 0,93±0,32, P=0,002. Three patients (Group 2) progressed to end-stage renal disease (ESRD), only one is alive at 10 years.

Conclusions: Elderly patients with worse baseline RF, the risk ESRD is attenuated when an excess of mortality is taken into account. Only proteinuria determinated worse follow-up of RF. Therefore allow us an optimist message for elderly with low eGFR without proteinuria.

SA-PO1159

One Year Mortality after Dialysis Initiation in a Portuguese Elderly Cohort:Development of a Predictive Mortality Risk Score Andreia Campos, Josefina Lascasas, Jorge Malheiro, Sofia Correia, Sofia Santos, António Cabrita. *CHP, Nephrology Dept.*

Background: In the last years, Portuguese elderly(≥65 years old,y)population has grown significantly. Because early mortality after dialysis(D)initiation is common, we aimed to analyze 1y mortality in elderly starting D and to establish a predictive risk scoring model(SM).

Methods: We selected a cohort of 208 patients(P) who initiated D between 2012-2015. A scoring system was constructed in which points(Ps) were assigned to each risk factor by using the b-coefficients(B) from the final Cox regression. A risk score was made by adding points for each risk factor(RF). We compared SM with others previously described.

Results: The overall 1y mortality was 20,2%. In a univariate analysis of demographics, clinical and social variables, the significant predictors of mortality were: nephrology follow up<1y(Fup), age>75y, ischemic nephropathy, congestive heart failure(CHF), hemiplegia, past malignancy history(M), chronic lung disease, lower albumin level(A), need of urgent D and beginning by catheter. These variables were included in a multivariate analysis: independent predictors of mortality were identified and points were assigned to each RF for the SM.

RF	B	HR IC95%	*P*	Ps
Fup<1y	0.8	2.2(1,0-4,6)	0.038	1
>75y	0.8	2.3(1,1-4,6)	0.028	1
M	0.9	2.6(1,1-6,3)	0.035	1
CHF	0.8	2.1(1,0-4,4)	0.046	1
A(mg/dl)			0.025	
<3	2.0	7.7(1,6-35,7)		2
3-3,5	2.1	8.0(1,7-38,1)		2
3,5-4	1.4	4.0(0,8-19,4)		1

Mortality rates ranged from 0% to 61.5% according to SM.

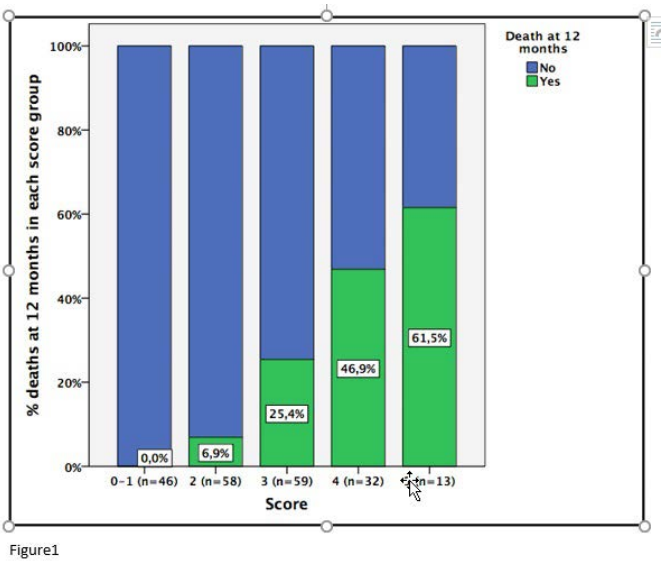


Figure1

AUC in SM, Couchoud and Cohen scores are 0.82, 0.77 and 0.85 respectively. There is no difference between them(p>0,05).

Conclusions: This simple prediction tool based on readily available clinical and laboratory data can assist in predicting short-term prognosis among elderly patients starting D. It may be useful in counseling patients and guiding clinical decision making.

SA-PO1160

Detecting the Minimum Recommendation of Physical Activity Level in Hemodialysis Patients: A 7-Year Retrospective Cohort Study

Ryota Matsuzawa,[1] Takahiro Shimoda,[2] Noritaka Mamorita,[2] Kei Yoneki,[2] Manae Harada,[2] Takaaki Watanabe,[2] Mika Matsumoto,[2] Atsushi Yoshida,[3] Yasuo Takeuchi,[2] Atsuhiko Matsunaga.[2] *[1]Kitasato Univ Hospital, Sagamihara, Japan; [2]Kitasato Univ, Sagamihara, Japan; [3]Sagami Circulatory Organ Clinic, Sagamihara, Japan.*

Background: Sedentary lifestyle is a well-known indicator of poor prognosis in hemodialysis patients. However, because the minimum recommendations for physical activity level are unknown in these patients, we retrospectively investigated the association between physical activity level and mortality risk.

Methods: A total of 282 outpatients (age, 64.8 ± 10.6 years; hemodialysis duration, 7.0 ± 7.8 years) who required hemodialysis 3 times a week were followed up for up to 7 years. Physical activity levels and patient characteristics, including age, sex, body mass index, hemodialysis duration, comorbid conditions, and nutritional status, were obtained at baseline. Physical activity was objectively evaluated using an accelerometer as the number of steps taken on a non-dialysis day based on the data of 4 consecutive non-dialysis days. A Cox proportional hazard regression model with smoothed plot for hazard ratios of all-cause mortality according to physical activity levels was used to detect the minimum recommendation.

Results: Fifty-six patients died during follow-up. In a Cox proportional hazard regression model adjusted for patient characteristics, the hazard ratio in the group with lower physical activity level was 2.18 (95% confidence interval = 1.16 - 4.09) compared with that in the group with higher level. Based on the smoothed plot for hazard ratios, we detected 2500 steps per non-dialysis day as a cut-off point of physical activity for poor prognosis (Fig. 1).

Conclusions: Lower physical activity level is associated with higher mortality risk. We recommend that hemodialysis patients take at least 2500 steps per non-dialysis day to avoid the worst possible outcome.

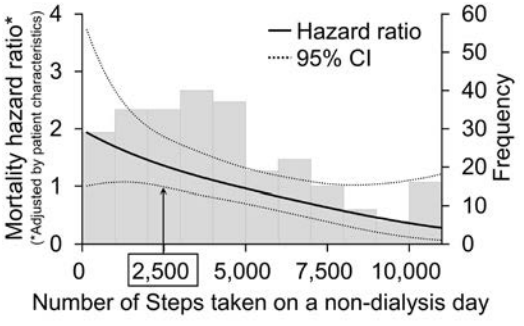


Fig 1. Smoothed plot for hazard ratios of the all-cause mortality according to physical activity.

Funding: Government Support - Non-U.S.

SA-PO1161

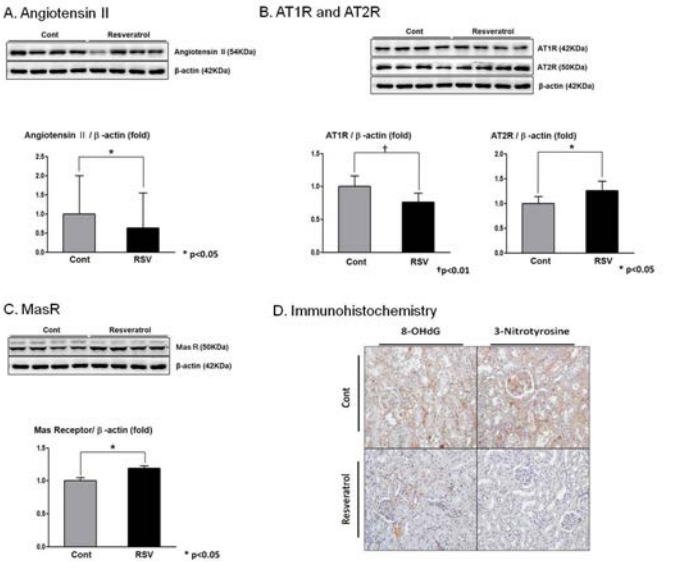
Effects of Resveratrol on Renin-Angiotensin System in the Aging Kidney

In-Ae Jang, Eun Nim Kim, Tae Hyun Ban, Hye Eun Yoon, Cheol Whee Park, Bumsoon Choi. *Div of Nephrology, Dept of Internal Medicine, College of Medicine, The Catholic Univ of Korea, Seoul, Korea.*

Background: The renin-angiotensin system, especially angiotensin II (ANGII) / angiotensin II type 1 receptors (AT1R) axis plays an important role in aging process of kidney through progressively increased oxidative stress. In the present study, we aimed to evaluate the effect of resveratrol, a naturally found polyphenol with antioxidant activities, in modulation of renin-angiotensin system in aging kidney of mice and to identify the putative underlying signaling pathways.

Methods: 18-month-old male C57BL/6 mice were divided into two groups and received either normal mice chow or underwent resveratrol treatment for 6 months. Intrarenal expression of renin-angiotensin system molecules, as well as pro- and antioxidant enzymes were measured, and mice kidney was isolated for histological analysis.

Results: Resveratrol-treated group showed significant improvement in renal function; serum creatinine decreased (0.25±0.05 mg/dL vs. 0.67±0.34 mg/dL; p <0.03 vs. control group), creatinine clearance increased (0.28±0.07 ml/min vs. 0.10±0.04 ml/min; p <0.001) and albuminuria decreased (29.47±14.32 μg/24hr vs. 67.69±22.79 μg/24hr; p <0.03) compared with control group. There were decreases in mesangial volume and tubulointerstitial fibrosis in resveratrol-treated mice. The expressions of ANGII, ACE and AT1R significantly decreased in resveratrol group, whereas those of ACE2, AT2R and MasR increased. Resveratrol increased the expression of phosphorylated eNOS and SOD2 significantly while the expressions of Nox4, fibronectin and collagen IV decreased. Immunohistochemistry revealed that 8-OHdG-positive area and 3-nitrotyrosin-positive area decreased in resveratrol group.



Conclusions: Resveratrol exerts renoprotective effects on aging kidney, associated with reduction of oxidative stress and inflammation through AT2R and MasR activation.

PUB001

Effects of High Dietary Sodium on Renal Tissue Sodium Content, Renal Heparan Sulfate Proteoglycans and Tubulo-Interstitial Remodeling Ryanne S. Hijmans, Pragyi Shrestha, Saleh Yazdani, Gerjan Navis, Jacob van den Born. *Nephrology, Univ Medical Center Groningen, Groningen, Netherlands.*

Background: High sodium intake is associated with hypertension and renal damage. Studies suggest that sodium-induced blood pressure-independent pathways can also cause renal damage. Heparan sulfate proteoglycans act as co-receptors for growth factors and chemokines and orchestrate tubulo-interstitial (TI) remodeling. Our aim is to investigate blood pressure-(in)dependent effects of high sodium intake on TI remodeling associated with structure and function of renal proteoglycans.

Methods: Wistar rats (N=5/group) received a normal chow diet for 4 weeks (C) or 8% NaCl chow diet (High Salt: HS) for 2 or 4 weeks. Blood pressure (BP) was monitored, and plasma, urine and tissue collected. Cortex homogenates were dissolved in nitric acid and sodium was measured by flame spectroscopy (expressed per dryweight or nitrogen content). Stainings were done for podoplanin+ lymphvessels, α-SMA+ myofibroblasts, collagen III, CD3+ T-cells, ED1+ macrophages (Mφ), heparan sulfate domains JM403, 10E4 and functional domains for MCP-1 and L-selectin binding. Statistical differences and correlations were tested by Kruskall Wallis and Spearman Rank correlation.

Results: HS rats showed a BP increase of ~10-15 mmHg at week 1 ($p<0.05$), which returned to C values later on. At week 4 cortical sodium increased ~0,1 mmol/mg in HS rats vs. week 2 ($p<0.05$), accompanied by partial loss of JM403 and 10E4, and increased MCP-1 and L-selectin binding to heparan sulfate. HS rats showed renal lymphangiogenesis, inflammation and profibrotic changes (all $p<0.05$ vs C). Cortical sodium correlated with L-selectin binding (r=0,668, p=0,007) and T-cells influx (r=0.554, p=0.03). Reduced (peri-) glomerular 10E4 and JM403 correlated with increase of myofibroblasts (r=-0.579, p=0.02) and Mφ (r=-0.644, p=0.01). Reduced JM403 correlated with increased lymphangiogenesis (r=-0.549, p=0.03) and L-selectin binding (r=-0.595, p=0.02).

Conclusions: These data suggest that increased cortical sodium by HS diet changes heparan sulfate structure and contributes to pro-fibrotic and pro-inflammatory tissue responses. Whether this is BP-independent is not clear yet.

PUB002

Abstract Withdrawn

PUB003

Protective Effects of Epigallocatechin Gallate and Dipeptidyl Peptidase IV Inhibitor Gemigliptin on Tacrolimus-Induced Nephrotoxicity in Mice Hyun Lee Kim,[2] Hyun Ho Ryu,[1] Byung Chul Shin.[2] *[1]Emergency Medicine, Chonnam National Univ Hospital, Gwangju, Republic of Korea; [2]Internal Medicine, Chosun Univ, Gwangju, Republic of Korea.*

Background: It has been reported that the proteinuria is an early predictive marker in detection of tacrolimus (TAC) nephrotoxicity. The aim of this study was to investigatethe renoprotective effects of eipgallocatechin gallate (EGCG) and dipeptidyl peptidase IV (DPP IV) inhibitor gemigliptin on TAC-induced acute nephrotoxicity in mice.

Methods: The mice (n=20) were divided into 5 groups (n=5/group); control group wereintraperitoneally (IP) injected 0.9% saline, TAC group were IP injected TAC2 mg/kg, DPP IV inhibitor group were given inaddition gemigliptin 20 mg/kg (G20) by oral gavage. TAC-EGCG group were given TAC by IP injection and EGCG 100 mg/kg by subcutaneous injection. TAC-EGCG-G20 group were given with same dosages.

Results: The 24 hours urine protein amounts were significantly increased in TAC group (46.1 ± 10.9mg/day) compared to control group (11.3 ± 4.4mg/day) and significantly decreasedin TAC-EGCG-G20 group (13.1 ± 5.9mg/day, $P<0.01$) compared to TAC group. The nitric oxide production by TAC was significantly suppressed by EGCG and gemiglipin management. Renal tissue malondialdehyde level was significantly increased in TAC group compared to control group andsignificantly decreased in TAC-EGCG-G20 group compared than that of TAC group. The renal function and antioxidant enzyme activities were significantly suppressed in TAC group compared with control group and restored in EGCG and gemiglipin treatment group.

Conclusions: EGCG and gemigliptin treatment has beneficial antiproteinuric and renoprotective effects onTAC-inducedacute renal injury in mice.

PUB004

The Role of Calpain and Caspase System in Fractalkine Regulation in Lipopolysaccharide-Treated Endothelial Cells Hye Min Choi, Young Eun Kwon, Dong-Jin Oh. *Dept of Internal Medicine, Myongji Hospital, Seonam Univ College of Medicine, Goyang, Korea.*

Background: Chemokines and adhesion molecules expressed by vascular endothelial cells are essential for endothelial cell-leukocyte interactions. Fractalkine (CX3CL1) is a chemokine with a unique CX3C motif, and is produced by endothelial cells stimulated with tumor necrosis factor (TNF)-α, interleukin (IL)-1, lipopolysaccharide (LPS) and interferon (IFN)-γ. There have been several reports that the caspase/calpain proteases are activated in endotoxemia that leads to acute inflammatory process, and we aimed to determine the role of caspases/calpain in regulating fractalkine levels in LPS-treated endothelial cells.

Methods: Human umbilical vein endothelial cells (HUVECs) were exposed to LPS. The changes of CX3CL1 expression were compared in control, LPS-(0.1 μg/ml), IL-1α-(50 μM), IL-1β-(50 μM), LPS+IL-1α-, LPS+IL-1β-, and LPS+IL-1α+IL-1β-treated HUVECs. The changes of CX3CL1 expression was compared with 50 μM inhibitor of caspase-1, caspase-3, caspase-9, and calpain, and a pancaspase inhibitor in LPS-treated HUVECs.

Results: It was observed that 1) there was a dose-dependent increase in CX3CL1 expression in LPS-treated HUVECs. 2) the expression of CX3CL1 was highest in IL-1β-treated HUVECs compared to control, LPS-, IL-1α-, LPS+IL-1α-, LPS+IL-1β-, LPS+IL-1α+IL-1β-treated cells. In addition, 3) the expression of CX3CL1 was highly inhibited with calpain inhibitors, and significantly decreased with the individual inhibitors of caspase-1, caspase-3, and caspase-9. On the contrary, CX3CL1 expression was significantly augmented with a pancaspase inhibitor.

Conclusions: It is concluded that the caspase and calpain system are important modulators of CX3CL1 levels in LPS-treated endothelial cells.

PUB005

Protective Effects of Celastrol in a Mouse Model of Acute Tubular Injury Zhechi He, Jia Shen, Jingyi Zhou, Yan Jiang, Rending Wang, Jianghua Chen. *The Kidney Disease Center, The First Affiliated Hospital of Zhejiang Univ, Hangzhou, Zhejiang, China.*

Background: Celastrol, extracted from a Chinese traditional herb Tripterygium wilfordii, as a potent immunosuppressive and anti-inflammatory agent, while the effects on acute tubular injury(ATI) is little known.

Methods: Kidney ischemic-reperfusion (KIR) model was induced in C57BL/6 mice by clamping the right renal artery for 45 minutes, and saline orcelastrol (5mg/kg) was given by intraperitoneal injection daily after reperfusion.Oxygen-glucose deprivation (OGD) mimicks ischemia injury on HK2 cells, and celastrol (10 ng/ml) was administrated the cells with re-oxygenation. Tissue sections was revealed by hematoxylin-eosin and Masson's stainings. The inflammation cytokines (IL-6,IL-10,TNF,IFN-γ) in serum and kidney tissues were measured by a cytometric bead array.An intracellular signaling array was used to screen the activation of signaling nodes *in vivo* and *in vitro* models. The expressions of p-Akt, total Akt,p-p53, and total p53was measured further to confirm the array assay.

Results: The tubular injury, and the levels of inflammation cytokines were significantly decreased by celastrol administration. The activation levels of Akt and p53 were reduced by celastrol *in vivo* and *in vitro*.

Conclusions: Celastrol is a potential drug candidate to alleviate the ATI, and the protective effect partly through the reduction of Akt and p53 activation and inflammation.

PUB006

Reproduction of Aristolochic Acid-Induced Nephropathy by Prescribed Herbal Medicine in Experimental Mouse Model Long Jin, Jian Jin, Chul Woo Yang. *Convergent Research Consortium for Immunologic Disease, Seoul St. Mary's Hospital, The Catholic Univ of Korea, Seoul, Korea.*

Background: The Chinese medicine (CM) in the slimming preparations contained aristolochic acid (AA), and AA extracted from CM is now considered to induce the nephropathy, such as interstitial fibrosis and tubular atrophy. To demonstrate the exact effect of this renal disease, we studied mouse treated with AA and CM on the renal injury.

Methods: C57BL/6 mice were divided into control, vehicle, AA and herbal medicine groups, and each group comprised five mice. The Same dose of AA and herbal medicine (5 mg/kg) was given to mice intraperitoneally for five days. The AA dose was chosen based on the previous study that 5 mg/kg of AA produces characteristic AA nephropathy in mice. We observed survival rate for each group, and measured body weights and serum creatinine. As a marker of oxidative stress, we measured serum 8-hydroxy-2'-deoxyguanosine (8-OHDG) levels.

Results: After five days, the survival rate was significantly decreased in the mice treated with AA and herbal medicine compared with the control and vehicle groups. There was marked body weight in both of AA and herbal medicine groups compared to the control and vehicle groups. Serum creatinine levels were significantly increased in both of AA and herbal medicine groups compared with control and vehicle groups ($P<0.05$, respectively) and there was no significant difference between AA and herbal medicine groups. Serum 8-OHDG levels were significantly increased in the AA and herbal medicine groups compared with control or vehicle groups ($P<0.05$, respectively) and there was no significant difference between AA and herbal medicine groups.

Conclusions: Intake of medications containing AA will induce renal injury and there is a strong relation between renal disease and the consumption of Chinese medicine, which is containing AA.

Funding: Clinical Revenue Support

PUB007

Sulodexide Protects Contrast-Induced Nephropathy in Sprague-Dawley Rats Feng Wang, Jianyong Yin, Zeyuan Lu, Nian-Song Wang. *Nephrology, Shanghai Jiao Tong Univ Affiliated Sixth People's Hospital, Shanghai, China.*

Background: Sulodexide is a powerful atithrombin agent, nevertheless, its effect on contrast-Induced Nephropathy (CIN) remains unknown. In current study, we evaluated the therapeutic effects of sulodexide on CIN and investigate underlying mechanisms.

Methods: CIN model was induced by intravenous injection of indomethacin, followed by Ioversol and L-NAME in Sprague-Dawley rats. Sulodexide or an equivalent volume of vehicle was intravenously delivered 30 min before induction of CIN. The animals were sacrificed at 24h after CIN and tissues were harvested to evaluate renal injury, kidney

oxidative stress and apoptosis levels. Plasma Antithrombin (ATIII) activities were also measured. For in vitro studies, HK2 cells were exposed to Ioversol or H2O2, respectively and the cyto-protective effects of sulodexide were also determined.

Results: Compared to untreated CIN group, improved renal function, reduced tubular injury, decreased levels of oxidative stress and apoptosis and were observed in CIN rats receiving sulodexide injection. In addition, our results also showed that ATIII activity was significantly higher in sulodexide-administered group than that in vehicle-injection CIN rats. Our in vitro experiments demonstrated that sulodexide pretreatment protected HK2 cells against the cytotoxicity of Ioversol via inhibiting caspase-3 activity, and preincubation with sulodexide could also attenuate H2O2-induced increases in ROS, apoptosis and caspase-3 levels.

Conclusions: Sulodexide could protect against CIN through activating ATIII, and inhibiting oxidative stress and apoptosis.

Funding: Government Support - Non-U.S.

PUB008

Sulodexide Protect against Renal Ischemia-Reperfusion Injury by Activation of Antithrombin III Feng Wang, Jianyong Yin, Zeyuan Lu, Nian-Song Wang. *Nephrology, Shanghai Jiao Tong Univ Affiliated Sixth People's Hospital, Shanghai, China.*

Background: Sulodexide is a potent atithrombin agent, however, its effect on renal ischemia-reperfusion injury (IRI) is unknown. In present study, we assessed the therapeutic effects of sulodexide for renal IRI and tried to investigate the potential mechanism.

Methods: One dose of sulodexide were injected intravenously in rats immediately after unilateral kidney ischemia for 45 min. The animals were sacrificed at 3h and 24h respectively. Renal function and tubular injury were assessed. TUNEL staining and caspase-3 expression were utilized to assess cell apoptosis. SOD concentration and Antithrombin III (ATIII) activity were also assayed. For in vitro study, hypoxia injury model for HK2 cells were carried out. Apoptosis and ROS level were evaluated after sulodexide pretreatment.

Results: Sulodexide pretreatment improved renal dysfunction and alleviated tubular pathological injury at 24h after reperfusion. Meanwhile, the levels of oxidative stress and cell apoptosis were also remarkably reduced by sulodexide administration. In addition, our results also showed that ATIII was activated at 3h after reperfusion, which preceded alleviation of renal injury. It was also observed that sulodexide pretreatment could reduce apoptosis and ROS level in HK2 cells under hypoxia injury.

Conclusions: Injection intravenously of sulodexide could protect against renal IRI. The therapeutic effects might be attributed to its activation for AT-III.

Funding: Government Support - Non-U.S.

PUB009

MicroRNA-375 Is Induced via p53 and NF-κB to Repress Hnf-1β in Cisplatin Nephrotoxicity Jielu Hao,[1,2] Qiang Lou,[1,3] Qingqing Wei,[1,2] Shuqin Mei,[1,2] Lin Li,[1,2] Changlin Mei,[1,2] Zheng Dong.[1,2] *[1]Nephrology, Shanghai Changzheng Hospital, Shanghai, China; [2]Cellular Biology and Anatomy, Augusta Univ, Augusta, GA; [3]Henan Univ, Kaifeng, Henan, China.*

Background: Nephrotoxicity is a major limiting factor for cisplatin-mediated chemotherapy in cancer patients. The pathogenesis of cisplatin-induced nephrotoxicity remains largely unclear and effective kidney protective approaches are currently lacking.

Methods: We tested the PT-Dicer$^{-/-}$ mouse model where Dicer (a key enzyme for microRNA production) was specifically ablated from kidney proximal tubule cells resulting in the depletion of the majority of microRNAs. To identify the specific microRNAs involved in cisplatin nephrotoxicity, we profiled microRNA expression changes by microarray analysis.

Results: We show that cisplatin nephrotoxicity was not affected by overall depletion of microRNAs from kidney proximal tubular cells in conditional Dicer-knockout mice. MiR-375 was identified by microarray and further verified in cisplatin-treated renal tubular cells. Inhibition of miR-375 led to a significant decrease of tubular cell apoptosis during cisplatin treatment, suggesting that miR-375 is injurious or pro-apoptotic.Blockade of p53 or NF-κB led to the attenuation of miR-375 induction during cisplatin treatment, supporting the involvement of p53 and NF-κB in miR-375. At the downstream of miR-375, hepatocyte nuclear factor 1 homeobox B (Hnf-1β) was identified as a key target of this microRNA. Notably, Hnf-1β was shown to cytoprotective in renal tubular cells.

Conclusions: Together, these results suggest that upon cisplatin exposure, p53 and NF-κB may work collaboratively to induce miR-375, which represses the cytoprotective gene Hnf-1β, resulting in renal tubular cell apoptosis.

PUB010

Correlation between Atherosclerosis and Markers of Kidney Injury in Brazilian Afrodescendants Natalino Salgado Filho, Dyego José Araujo Brito, Joyce S. Lages, Gyl Barros-Silva, Bernardete Jorge Leal Salgado, Elton Jonh Freitas Santos, Alcione Santos. *Federal Univ of Maranhão.*

Background: Atherosclerotic lesions are highly prevalent among afrodescendants leading to increased morbidity and mortality from cardiovascular events. Thus, the aim of this study was to investigate the association between atherosclerosis and markers of kidney injury in hypertensive afrodescendants from quilombo remnants communities in northern of Maranhão State/Brazil.

Methods: Cross-sectional study that assessed hypertensive afrodescendants from PREVRENAL cohort underwent two different imaging methods for diagnosis of atherosclerosis disease: 1- Carotid doppler ultrasonography (doppler US) to assess the intima-media thickness (cIMT) and/or 2- Coronary computed tomography for determination calcium score (CCS). The markers of kidney injury evaluated were 1- estimated glomerular filtration rate (eGFR) and; 2- albuminuria. Information about clinical, laboratory and imaging data were collected in PREVRENAL study database. To evaluate factors associated with the occurrence of coronary and carotid atherosclerosis was adjusted Poisson model with robust variance.

Results: Two hundred-six patients (mean age 61.32±12.44 years and 61.65% women) underwent carotid doppler US and 155 patients (mean age 61.42±12.42 years and 62.58% women) underwent coronary CT were included in the study. cIMT presented high in 59.22% individuals evaluated and 41.94% of patients had CCS> 0. In the multivariate regression model, age> 60 years (PR 1.23, p-value = 0.001), ACR> 30mg/g (PR 1.18, p-value = 0.040) and eGFR/CKD-EPI using cystatin C (PR 1.25, p-value = 0.045) were independently associated with carotid atherosclerosis. The model for coronary calcification were associated with CCS: male gender (PR 1.53, p-value = 0.010), age ≥ 60 years (PR 1.78, p-value = 0.001), use of ASA (PR 1.67, p-value = 0.018) and smoking (PR 1.51, p-value = 0.011).

Conclusions: The occurrence of atherosclerotic lesions was high in this group. Markers of kidney injury were associated only with carotid lesions, whereas traditional factors for atherosclerotic disease were associated with coronary lesions.

PUB011

Ischemic Postconditioning Inhibits Ischemia-Induced AKI-to-CKD Progression via Akt/GSK3β Pathway Jia Shen,[1,2,3] Hao Deng,[1,2,3] Yan Jiang,[1,2,3] Hongfeng Huang,[1,2,3] Jianghua Chen.[1,2,3] *[1]Kidney Disease Center, The First Affiliated Hospital Zhejiang Univ, Hangzhou, Zhejiang, China; [2]Kidney Disease Immunology Laboratory, The Third Grade Laboratory, State Administration of Traditional Chinese Medicine of the People's Republic of China, China; [3]Key Laboratory of Zhejiang Province, China.*

Background: Ischemia-reperfusion (IR) injury, a relevant factor of acute kidney injury (AKI), will induce renal fibrosis, and then chronic kidney disease(CKD). Postconditioning can minimize the effect of IRI, while its function and related mechanism in the transition of AKI to CKD remains unknown. It has been reported previously that type II epithelial-to-mesenchymal transition (EMT) in tubular epithelial cells plays a vital role in the pathogenesis of renal fibrosis. This study aims to investigate the underlying molecular mechanism.

Methods: We established a single renal IR model in C57BL/6 mice. All mice with IR injury were divided into 2 groups, which are with (IR group) or without (PC group) additional ischemic interruption reperfusion before permanent perfusion. Renal function, fibrosis and EMT-related makers were detected and measured. A protein array was used to evaluate the expression and activation levels of signal node proteins in kidneys.

Results: PC group was associated with reduced BUN of 54.0 ± 5.7 mg/dl and Cr of 0.420 ± 0.033 mg/dl ($p<0.05$) as well as amelioration in acute tubular necrosis from 2 weeks to 8 weeks compared with I/R group. Immunohistochemistry and western blotting at both 4 weeks and 8 weeks indicated lower expressions of Snail and EMT-related protein makers (α-SMA, fibronectin and S1004A) in PC group. The protein chip showed down regulation of phosphorylation levels of Akt (Ser473), Akt (Thr308), and GSK3β (Ser9), and verified by *in vivo* Immunohistochemistry and western blotting.

Conclusions: Postconditioning suppressed the EMT of tubular epithelial cells caused by IRI, and it related with a down regulation of Akt/GSK3β signal pathway, and this could be a therapeutic procedure to kidney IR injury and reduce the pathological progress of AKI to CKD.

Funding: Government Support - Non-U.S.

PUB012

A New, Human In Vitro Model for Renal Ischemia Reperfusion Injury Marc J. Weidenbusch, Johannes Bauernschmitt, Hans J. Anders. *Nephrologisches Zentrum, Klinikum der Univ München, München, Bavaria, Germany.*

Background: During transplantation long-lasting damage is done to the graft by ischemia reperfusion injury (IRI), which to a large extent are not well characterized until today. Therefore, good models are needed to further investigate diagnostic and therapeutic options for IRI. Mouse models allow complex investigations, but results often cannot be transferred to humans. There is intriguing new evidence for an important involvement of the Krebs cycle and the accumulation of intracellular succinate in the formation of IRI**.** Therefore, our goal was to establish a new IRI model incorporating new pathophysiological insights in a human cell culture system.

Methods: HK-2 cells were treated with different substances to mimic IRI. Therefore, besides from hydrogen peroxide (H2O2) we used the inhibitors of the respiratory chain Antimycin A and Oligomycin as well as the citric cycle metabolites succinate and malonate. Subsequently, the cell toxicity was assessed by the established LDH release assay and the results were additionally validated using the AO/PI assay. All experiments were repeated at least twice and results were examined for statistical significance using two-sided student's t-tests.

Results: All substances were able to induce cell death. Because IRI in vivo leads to massive cell death within a short period of time, we concentrated especially on those substances that were able to induce significant cell death in less than two hours. While H2O2 doesn't cause any significant cell death at that time point, the combination of Antimycin A and succinate showed to be very effective (more than 60% cell death) and started to kill cells already after 30 minutes of incubation. Importantly, Antimycin A and succinate

elicited cell death also in a dose-dependent manner. Cell death in our model involves reverse electron flow through the respiratory chain, since the effect could be completely suppressed by complex II inhibition using malonate.

Conclusions: Significant cell death in human tubular epithelial cells can be induced by IRI typical reversal of electron flow in the respiratory chain. Therefore the combination of Antimycin A and succinate appears to be an appropriate model for renal IRI.

Funding: Government Support - Non-U.S.

PUB013

The Role of Glycosphingolipids in Cisplatin-Induced Acute Kidney Injury

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Background: Acute kidney injury (AKI), resulting from chemotherapeutic agents such as cisplatin, remains an obstacle in the treatment of cancer. Cisplatin-induced AKI involves apoptotic and necrotic cell death, pathways regulated by sphingolipids such as ceramide. Data indicate that C57BL6 mice treated with cisplatin had elevated ceramide synthase and acid sphingomyelinase activities as well as increased ceramide levels in the renal cortex 72 h following cisplatin treatment. We hypothesized that inhibition of ceramide synthesis would protect mice from cisplatin-induced AKI. Pre-treatment of mice with inhibitors of acid sphingomyelinase and *de novo* ceramide synthesis (amitriptyline and myriocin, respectively) protected from cisplatin-induced AKI. Data indicate that ceramides are also metabolized into glucosylceramides (GluCers) in the renal cortex following cisplatin treatment. GluCers play a role in kidney aging, diabetic nephropathy, and lupus nephritis. Thus, we determined whether ceramide and/ or its metabolism to GluCers plays a causative role in cisplatin-induced AKI.

Methods: To determine which lipid species is contributing to kidney injury, we treated mice with a potent and highly specific inhibitor of glucosylceramide synthase, the enzyme responsible for catalyzing the glycosylation of ceramide to form GluCers.

Results: Inhibition of glucosylceramide synthase exacerbated cisplatin-induced AKI according to markers of kidney injury, inflammation, cell stress, apoptosis, and mitochondrial homeostasis.

Conclusions: Taken together, data suggest that ceramides play a role in kidney injury in response to cisplatin, whereas the metabolism of ceramides to GluCers is renoprotective.

Funding: NIDDK Support

PUB014

Repeated, Low-Dose Administration of Cisplatin Leads to Long-Term, Irreversible Fibrosis

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Background: Cisplatin is a potent chemotherapeutic used in the treatment of many solid tumor cancers. The dose-limiting toxicity of cisplatin is nephrotoxicity, which can lead to acute kidney injury (AKI). Thirty percent of patients treated with a cisplatin will develop AKI. The long-term effects of AKI are an increased mortality rate and an increased likelihood of developing chronic kidney disease (CKD). CKD in itself is a progressive, irreversible disease characterized by a permanent loss of kidney function that often culminates in fibrosis. Currently, there are no therapeutic interventions to stop the progression of AKI to CKD. One potential reason for this is that there are no animal models that can be used to study the transition from AKI to CKD. In the standard model of AKI, mice receive a high dose of cisplatin (15-30 mg/kg) that leads to moribund status 72 hours after injection, and thus long-term studies are not feasible. We have previously developed a repeated, low-dose cisplatin regimen that allows for long-term studies of kidney function. With this model we found that repeated, low dosing of cisplatin induces fibrosis after 24 days.

Methods: To determine whether the fibrosis induced by this model is irreversible and progressive, we treated 8 wk old FVB mice with our repeated dosing regimen and followed treatment with a 6 month age out.

Results: We found that fibrosis was still present after this 6 month period as evidenced by increased Pai-1 mRNA expression levels, positive staining for α-SMA indicative of myofibroblasts, and elevated levels of overall collagen deposition. Furthermore, BUN remained elevated compared to baseline levels even though injury as measured by NGAL was no longer detectable.

Conclusions: These data indicate that fibrosis is a permanent pathological outcome following repeated injury from low-dose cisplatin, suggesting that targeting mediators of the fibrotic pathway might be beneficial for the development of therapeutic agents to prevent cisplatin-induced AKI to CKD progression.

Funding: NIDDK Support

PUB015

Src Inhibition Protects against Ischemic Acute Kidney Injury in Mice

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Background: Activation of Src has been associated with the development of renal fibrosis and diabetic nephropathy. However, its role in acute kidney injury (AKI) is still poorly understood.

Methods: In this study, we examined the effects of Src inhibition in a murine model of ischemia-reperfusion (I/R)-induced AKI using PP1, a highly selective inhibitor of Src family kinases.

Results: At 48 h after I/R, mice developed renal dysfunction and renal tubular damage, which was accompanied by elevated expression and phosphorylation of Src. Administration of PP1 immediately after the onset of reperfusion protected against renal dysfunction and attenuated kidney damage. The protective actions of PP1 were associated with inhibition of renal tubule injury and cell death and suppression of l expression of multiple proteins involved in the assembly of cell-cell adhesion and tight junction such as E-cadherin, ZO-1, claudin-1/4. Similarly, PP1 treatment inhibited expression of these proteins in vitro cultured renal tubular cells following oxidant injury. Moreover, I/R injury led to an increase in phosphorylation (activation) of STAT3 and NF-kappa B in the kidney; treatment with PP1 diminished this response.

Conclusions: Collectively, these results indicate that Src inhibition is effective against renal tubule injury through maintaining epithelial cellular attachment and integrityand suppressing proinflammatory responses after I/R injury. Thus targeting Src may be a promising therapeutic strategy for treatment of AKI.

Funding: NIDDK Support

PUB016

Contribution of DNases to Kidney Cell Death after Acute Injury In Vitro or In Vivo

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Background: Our previous studies showed that genetic inactivation of two kidney apoptotic endonucleases, DNase I and EndoG, was partially protective against tubular epithelial cell death induced by cisplatin. Recent discovery of endonuclease inhibitors provides a unique opportunity to determine the contribution of individual endonuclease to kidney cell death.

Methods: This study was aimed to determine if the two new endonuclease inhibitors recently identified by us, IG-17 for DNase I and PNR-3-82 for EndoG, could ameliorate cisplatin toxicity to kidney tubular epithelial cells *in vitro* and *in vivo*.

Results: *In vitro* experiments using NRK-52E cells showed that the compounds are able to suppress endonuclease activity inside the cells, provide partial protection against cisplatin toxicity measured using LDH release assay and TUNEL. *In vivo* experiments were done in mice, which received cisplatin (20 mg/kg, IP) after SC injections of the inhibitors (5 mg/kg). Kidney failure was measured by serum creatinine and BUN. Structural kidney damage was assessed by acute tubular necrosis. The results from both *in vitro* and *in vivo* experiments showed that TUNEL was inhibited the most, followed by structural protection, and followed by kidney function (*in vivo*).

Conclusions: This observation suggests that enzymatic DNA fragmentation only partially is responsible for mechanism leading to cell death or spreading of cell death (necrosis). The other part of endonuclease activity, may, in fact, act in an opposite direction by protecting against kidney cell death.

Funding: NIDDK Support, Other U.S. Government Support, VA Support

PUB017

Intra-Arterial Continuous Infusion Is Less Harmful Than Bolus Infusion of Contrast Dye in CI-AKI Rodent Model showing Hyperacute Rise in Serum NGAL and L-FABP

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Background: Contrast induced acute kidney injury (CI-AKI) is the second common cause of in-hospital AKI, leads to higher morbidities and mortalities. Despite in vitro studies revealed dose proportional toxicity of contrast media, there is yet no data on whether the method of contrast medium administration will alter the risk of CI-AKI. In this preliminary study, we aimed to prove that continuous intra-arterial infusion of contrast media would cause less CI-AKI than bolus infusion, even under the same amount.

Methods: Female SD rats were sedated with urethane and catheterized at left carotid artery. Urografin, high osmolarity contrast media, was given intra-arterially via the carotid artery catheter for the same total amount (20ml/kg, LD50 dose). Bolus group received four boluses within 20 minutes, and continuous group received continuous infusion for 20 minutes. Serum and urine samples were taken at baseline and at 5 hours after completion of infusion. After 5 hours, rats were sacrificed, and we further examined survival rates, and measured kidney tissue, serum and urine creatinine and AKI biomarkers (NGAL, KIM-1, L-FABP, Cystatin C) by ELISA.

Results: Bolus group had higher mortality (3/10 rats vs. 1/12 rats), and higher CI-AKI rate (9/10 rats vs. 8/12 rats) than continuous group at 5 hours. There is a trend of higher serum creatinine in bolus group (0.69 +/- 0.32 mg/dL) than in continuous group (0.46 +/- 0.23 mg/dL). Notably, there is an early rise of serum NGAL and L-FABP in bolus group (serum NGAL 5hr/baseline ratio: 25.75 vs. 3.62, p=0.017, serum L-FABP 5hr/baseline ratio: 55.52 vs. 3.09, p=0.012). Histological examinations demonstrated tubular vacuolization in both bolus and continuous groups, implying cellular stress to contrast toxicity.

Conclusions: Our preliminary data suggested a novel method to ameliorate CI-AKI by continuous infusion to kidneys, in association with a less hyperacute rise in serum AKI biomarkers of NGAL and L-FABP.

PUB018

Human Peripheral Blood Mononuclear Cells Incubated by Quality and Quantity-Control Culture System Dramatically Improve Ischemia/Reperfusion Acute Kidney Injury in Mice Takayasu Ohtake,[1] Maki Sumida,[2] Daisuke Katagiri,[2] Ryo Matsuura,[2] Eisei Noiri,[2] Shuzo Kobayashi.[1] *[1]Nephrology, Immunology, and Vascular Medicine, Shonan Kamakura General Hospital, Kamakura, Kanagawa, Japan; [2]Nephrology and Endocrinology, The Univ of Tokyo, Bunkyo-ku, Tokyo, Japan.*

Background: There is currently no established treatment that promotes kidney repair after acute kidney injury (AKI). We examined the capacity of human peripheral blood mononuclear cells (MNCs), which was incubated using quality and quantity control (QQc) culture system (Masuda H. et al: Stem cells Translational Research 2012), on ischemia/reperfusion (IR) AKI in mice.

Methods: IR was induced in male NOD/SCID mice. Human peripheral blood MNCs were incubated for 1 week in QQc culture media. A hundred μL saline containing 10^6 human post-QQc MNCs was infused via tail vein at 24 hours after IR induction (post-QQc group). 10^6 human pre-QQc MNCs group (direct MNCs injection without QQc culture: pre-QQc group) and vehicle group were used as control. Blood urea nitrogen (BUN), serum creatinine (sCr), tubular damage scores, peritubular capillary (PTC) loss, and interstitial fibrosis were evaluated.

Results: QQc-culture significantly increased the number of CD34+ cells and endothelial progenitor cell (EPC) colonies compared with pre-QQc human MNCs. Human post-QQc MNCs administered 24 hours after IR AKI dramatically improved kidney function at 48 hours after cell infusion compared with vehicle control group (vehicle control vs. post-QQc: BUN; 99.5±39.4 vs. 36.1±4.3 mg/dl, $p<0.05$, Cr; 0.89±0.19 vs. 0.25±0.06 mg/dl, $p<0.05$, N=13 in each group, mean±SE). Tubular damages significantly improved in post-QQc group compared with vehicle control group. PTC loss at 48 hours after cell injection was also significantly improved in post-QQc group (vehicle: post-QQc: 50.2±1.5 vs. 27.2±2.0 %, $p<0.01$). Furthermore, interstitial fibrosis area (%) 2 weeks after AKI was also significantly improved in post-QQc group (vehicle vs. post-QQc: 45.2±1.8 vs. 21.9±1.4 %, $p<0.01$). These beneficial effects were not found in pre-QQc MNCs group.

Conclusions: Human post-QQc MNCs dramatically improved kidney function, tubular and microvasculature damage, and interstitial fibrosis in mice IR AKI.

Funding: Private Foundation Support

PUB019

Mild Intracellular Acidification by Dexamethasone Attenuates Mitochondrial Dysfunction in a Human Inflammatory Proximal Tubule Epithelial Cell Model Jitske Jansen,[1] Tom Schirris,[2,3] Milos Mihajlovic,[1] Lambertus P.W.J. Van den Heuvel,[4] Frans G. Russel,[2,3] Rosalinde Masereeuw.[1] *[1]Pharmacology, Utrecht Inst for Pharmaceutical Sciences, Utrecht, Netherlands; [2]Pharmacology & Toxicology, Radboudumc, Nijmegen, Gelderland, Netherlands; [3]Center for Systems Biology and Bioenergetics, Radboud Center for Mitochondrial Medicine, Radboudumc, Nijmegen, Gelderland, Netherlands; [4]Pediatrics, Radboudumc, Nijmegen, Gelderland, Netherlands.*

Background: Mitochondria are assumed to be important targets to improve renal function during acute kidney injury (AKI) and glucocorticoids may exert beneficial effects on these organelles. Here, we investigated the effect of dexamethasone in an experimental inflammatory renal cell model to unravel its mitochondrial target.

Methods: Matured conditionally immortalized proximal tubule epithelial cells (ciPTEC) were treated with the endotoxin lipopolysaccharide (LPS; 10 μg/ml) for 24 hours, with or without co-treatment of dexamethasone (10 μM) for 4 hours, 37°C, 5% (v/v) CO_2. A panel of mitochondrial parameters and intracellular pH was investigated in the presence or absence of dexamethasone.

Results: LPS treatment of cells led to increased generation of reactive oxygen species (ROS) (122 ± 6 % of control; $p< 0.001$), which was attenuated by dexamethasone. In addition, the membrane potential was reduced in LPS challenged cells (85 ± 4 % of control; $p< 0.05$), which was counteracted by dexamethasone (124 ± 5 %; $p< 0.001$). The mitochondrial oxygen consumption was decreased in LPS treated cells (17.6 ± 7.5 *vs.* 55.5 ± 4.7 pmol×s^{-1}×10^6 cells in control; $p< 0.001$) and again this was improved towards control levels upon dexamethasone co-treatment (43.1 ± 7.5 pmol×s^{-1}×10^6 cells). Finally, we demonstrated that dexamethasone acidified the intracellular milieu (87 ± 2 % of control; $p< 0.05$) and reversed the LPS-induced alkalization.

Conclusions: Dexamethasone restored mitochondrial function under inflammatory conditions by decreasing cellular pH. This supports the hypothesis that mitochondria are key modulators in renal inflammation and interesting targets for the treatment of septic-AKI.

Funding: Government Support - Non-U.S.

PUB020

Contrast Medium Induced Autophagy and Apoptosis in Kidney Proximal Tubular Cells Jasmine Fuller, Zheng Dong. *Cellular Biology and Anatomy, Augusta Univ, Augusta, GA.*

Background: Contrast medium-induced acute kidney injury (CM-AKI) is one of the leading causes of acute kidney failure during hospitalization. It has been defined as the occurrence of acute renal impairment within 2-7 days after administration of iodinated contrast medium in medical imaging. The mechanism of CM-AKI is not completely understood and there is no effective treatment for this disease. Autophagy is a cellular process of "self-eating," wherein various cytoplasmic constituents are broken down and recycled through the lysosomal degradation pathway. Autophagy has been shown to play a protective role in acute kidney injury models such as cisplatin treatment and ischemia-reperfusion.

Methods: To study the role of autophagy in CM-AKI, we administered 150 mgI/mL of contrast medium to renal proximal tubule cells (RPTC) for 24 hours.

Results: Contrast medium induced apoptosis at 24 hours as shown by cell morphology and the cleavage of caspase-3 into active forms. Contrast medium also induced autophagy at 6 hours as shown by increased LC3II protein signal. During contrast medium treatment, inhibition of autophagy by chloroquine (CQ) enhanced apoptosis in RPTC, while activation of autophagy by rapamycin (Rap) diminished apoptosis, further supporting a protective role of autophagy.

Conclusions: These results reveal autophagy induction and its protective role during contrast medium treatment of kidney tubular cells.

Funding: NIDDK Support

PUB021

Nephropreventing Effect of Hypoxia-Inducible Factor 1α in a Rat Model of Ischemic Acute Kidney Injury Nanmei Liu. *Dept of Nephrology, Jiming Hospital of Shanghai, China.*

Background: Characterized with acute renal dysfunctions, acute kidney injury (AKI) is often found in 5% hospitalized patients and 50% in patient with sepsis. Until now, no safe and effective therapy has been found to treat or prevent AKI specifically. Hypoxia condition was shown to influence renal injuries and function.

Methods: As HIF-1 α is the main regulator of cell response to hypoxia, in this study we investigated the potential protective effect of HIF-1 α in a rat AKI model. We found that HIF-1 α injection increased survival of rat with AKI, and the function of kidney was also protected in terms of Cr and BUN. A HE and PAS staining assay was used to assess the structural damages of kidney in different groups.

Results: Our data showed that ischemic injury induced damages to kidney tubules and nephrocytes, and in HIF1-α treated group, AKI caused less damage obviously. HIF1-α also inhibited AKI induced cell apoptosis, and retained cell proliferation in kidney tissues. We also found the downstream factors EPOR, VEGF, PHD3 was also regulated by HIF1-α in response to AKI damage. Finally, it was observed that HIF1-α also increased the percentage of adult resident progenitor cells (ARPC), which was found very low in AKI rats. The survival of ARPC isolated from AKI rat was also increased by HIF1-α.

Conclusions: HIF1-α plays a protective role in ischemic AKI model, which was related with the protection of ARPC, indicating a novel potential therapy for AKI.

PUB022

Effect of Adipose-Derived Stem Cells Incubated with Astragaloside IV on the Model of Acute Renal Injury in Mice Nanmei Liu. *Jiming Hospital of Shanghai.*

Background: To evaluate the effect of biological behaviour on human adipose-derived mesenchymal stem cells (hADSCs) incubated with Astragaloside IV(Ast). hADSCs were labeled with PKH26, and then incubated with Ast. The effect and mechanism of Ast-hADSC transfected on the model of acute renal injury (ARI) were investigated.

Methods: We used P3-P5 cells labeled with PKH26, and observed cell morphology under light microscope and fluorescence microscope. Cellular proliferation was determined by Cell-Counting Kit-8 (CCK8). The experimental model was established 24hrs later, hADSC or Ast-hADSC suspension containing 1105 were injected into tail vein. The AKI mice were injected with 100μl normal saline as the controls. After all the mice were sacrificed, the renals were dyed by H&E and TUNEL. The protein level of Caspase-3, Bcl-2, and Bax in renal tubules was detected by Western blot. The level of TNF, IL-6, RANTES in renal tissue homogenate was detected by ELISA. The hADSC and Ast- hADSC desposition in kidney was observed by fluorescence histochemistry.

Results: Absorbanee values of cultured cells were significantly increased at different time points but absorbanee values was the most obvious change at 72hrs. Renal tubular structure were impaired in AKI group after cisplatin administration, the HE staining tubular necrosis count were lower in hADSC and Ast-hADSC group than those in model group. The levels of TNF-,IL-6,RANTES in AKI group's renal tissue homogenate were increased significantly, while hADSC and Ast-hADSC group intervention changed these cytokines levels to the opposite direction. Contrasted with those in the model group, the level of Caspase-3, Bax in hADSC and Ast-hADSC group decreased notably, while the level of Bcl-2 increased siginificantly. A small quantity of red fluorescent protein from hADSC and Ast-hADSC was presented in renal tissue, but transformatation to the renal tubular epithelial cells was not observed.

Conclusions: Implantation of hADSC and Ast-hADSC could provide advanced benefits in protection against renal tubular injury by improving microcirculation, regulation apoptosis protein expression and proliferation in vitro and hADSC incubated with Ast can better improve the effect of the repair of damaged kidney tissue.

PUB023

The Role of Toll-Like Receptors in Myeloma Light Chain Toxicity on Renal Proximal Tubule Cells M-Altaf Khan,[1] Vecihi Batuman.[1,2] *[1]Medicine, Nephrology & Hypertension, Tulane Univ, School of Medicine; [2]VA, SLVHCS, New Orleans, LA.*

Background: The role of innate immunity mediated by Toll-like receptors (TLRs) in multiple myeloma (MM) nephropathy and their potential use as therapeutic target have not been investigated previously. We evaluated the effect of (S,R)-3-phenyl-4,5-dihydro-

5-isoxasole acetic acid (GIT27), an active immuno-modulatory agent which suppresses TLR2/6- and TLR4-mediated signaling, on kappa light chains (K-LC) toxicity on renal proximal tubule epithelial cells (RPTECs).

Methods: Urinary monoclonal free K-LC were isolated from a MM patient. Confluent human RPTECs were treated with or without GIT27 (25 μM - 300 μM) 1 hr prior exposure to 25 μM of K-LC for 24 hr.

Results: K-LC significantly injured RPTECs, arrested cell growth and induced significant release of inflammatory cytokines (IL-6, TNF-α, and MCP-1). GIT27 significantly inhibited secretion of TNF-α in a dose-dependent manner with an effective optimum dose of 150 μM (Untreated = 15.6 ± 1.4 vs K-LC = 143.7 ± 19.4 vs GIT27 + K-LC = 20.6 ± 1.2 SE, pg/ml). The mRNA expression of kidney injury biomarkers (KIB) NGAL was significantly increased by 424 fold and KIM-1 by 3.2 fold in RPTECs exposed to K-LC compared to untreated RPTECs. After exposure to K-LC, the mRNA expression of kidney injury-prominent TLRs (TLR2, TLR3, TLR4, TLR6 and TLR9) was significantly upregulated in RPTECs. TLR6 showed the highest increase (5.7 fold) followed by TLR2 (3.5 fold). In this study, TLRs followed both MyD88- and TRIF-dependent pathways as mRNA expression of both adaptor proteins was significantly upregulated. TLRs activation resulted in increased expression of pro-inflammatory cytokines (IL-6, 35.7 fold; TNF- α, 21.5 fold and IL-18, 0.21 fold), chemokines (MCP-1, 23.3 fold), pro-fibrotic (TGF-β1, 1.5 fold). The pro-apoptotic genes (P53, 0.17 fold and Bcl2, 1.3 fold) were also significantly upregulated by K-LC in RPTECs.

Conclusions: K-LC is highly nephrotoxic and NGAL could be a diagnostic KIB for MM. Innate immunity mediated by TLR2, TLR4 and TLR6 play a major pathogenic role in LC toxicity on kidney and could prove to be promising drug targets. The TLRs suppressor GIT27 may be a potential therapeutic to ameliorate K-LC-induced kidney injury in MM.

Funding: Private Foundation Support

PUB024

Improving Long-Term Outcome of AKI by eEPC Pharmacological Preconditioning

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Background: Exogenously administered early Endothelial Progenitor Cells (eEPCs) significantly protect mice from acute kidney injury (AKI). AKI may increase long-term mobidity since it has been identified as risk factor for chronic kidney disease. Aim of this study was to analyze long-term alterations of kidney function in mice after systemic eEPC treatment with versus without pharmacological cell preconditioning. Our additional interest focused on the analysis of different markers of renal excretory dysfunction / damage.

Methods: 8-12 weeks old male C57/Bl6N mice were subjected to bilateral renal pedicle clamping for 45 minutes. Donor-derived syngeneic eEPCs (0.5×1.000.000) were i.v. injected at the end of ischemia. Cells were either administered natively or after preincubation with established eEPC agonists (Angiopoietin-1 - Ang-2 and Bone Morphogenetic Protein-5 - BMP-5). Analyses were performed 6 weeks later. The following parameters were evaluated and compared: serum creatinine, serum cystatin C, and serum and urinary KIM-1.

Results: Ischemia induced a significant and persistent increase in serum creatinine at week 6. Administration of native eEPCs did not protect from renal excretory dysfunction if evaluated by creatinine levels. Ang-2 failed to further stimulate renoprotective competence of the cells while BMP-5 preconditioning significantly improved serum creatinine. Cystatin C was more sensitive than creatinine since serum levels were lower even after the injection of native cells. There were no differences in serum or urinary KIM-1 concentrations between any of the respective groups.

Conclusions: (I) BMP-5 potentiates AKI-protective competence of eEPCs in the long-term. (II) cystatin C is more sensitive for detecting alterations in renal excretory function than serum creatinine, even after several weeks. (III) In mice, KIM-1 is not useful for diagnosing kidney damage late after ischemia.

PUB025

Characters of Exosome Secretion under Three In Vitro Models of AKI

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Background: Exosomes are cell-produced vesicles of 50-100nm in diameter that contains proteins, RNAs, and DNAs. Recent work has implicated exosomes as important ways of intercellular communication. The production, regulation and function of exosomes in kidneys and kidney cells remain largely unclear. In this study, we characterized exosome production during stress or injury of renal tubular cells.

Methods: Mouse proximal tubular BUMPT cells and were treated with or without Hypoxia (in chamber with 1% oxygen for 8h, 16h, 24h) or Cisplatin (40 nM for 8h, 16h, 24h) or ATP-depletion (10 mM Azide for 1.5h or 3h ATP-depletion, then recovery in fresh media without FBS for 6h,12h, 24h). The media were collected for exosome isolation by a commercial kit (Invitrogen, Total Exosome Isolation) or by standard ultracentrifugation. Transmission electron microscopy was used to verify the morphology of the isolated exosome. Nanoparticle Tracking Analyzer (NTA,Zeta View) was used to measure the concentration and size of the samples. Immunoblot analysis of exosome markers CD63 and TSG101 was conducted to confirm the quality and quantity of exosome.

Results: Both Invitrogen kit and ultracentrifugation were able to isolate exosomes from cell culture media. The average size of exosome secreted by BUMPT cells in all 3 injury models was 113.18±14.3 nm by the NTA measurement which was comparable to that from normal control cells(111.42±12.6nm, $P < 0.05$). Hypoxia significantly increased exosome production in a time dependent manner ($P < 0.05$); 1.5h ATP-depletion with azide followed by recovery could slightly inhibit exosome release ($P > 0.05$), while 3h ATP-depletion with azide significantly increased exosome production during 12h recovery($P < 0.05$). Cisplatin might also induce exosome production, but thei increase was not statistically significant ($P > 0.05$).

Conclusions: Renal tubular cells may produce more exosomes in response to hypoxia and ATP-depletion with recovery, but cell injury or stress does not have significant effect on the size of exosome released by the cells.

PUB026

Acutely Injured Kidneys Release Proteins into the Serum That Cause Oxidative Stress and Are Partially Inhibited by Catalase, N-Acetyl Cysteine, or Rotenone

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Background: The uremic state that is induced by Acute Kidney Injury (AKI) adversely affects multiple organ systems by mechanisms that are still poorly characterized. To study the consequences of the AKI environment on therapeutically employed Mesenchymal Stem Cells (MSC) and renal tubular cells, we developed a novel in vitro assay of exposing MSCs or cultured rat proximal tubular cells (NRK) to serum from animals that had AKI, Nephrectomy (NPHX), or SHAM surgeries.

Methods: Serum was obtained from rats 24 hrs post ischemia/reperfusion-AKI (50 min bilateral pedicle clamp, AKI serum, SCr ~4.9 mg/dL), and control serum was obtained following SHAM surgery (SHAM serum), or bilateral nephrectomy (NPHX serum, SCr ~4.8 mg/dL). Serum samples were evaluated for ROS activity with the Amplex Red H_2O_2 assay.

Results: Culturing normal rat kidney cells (NRK, proximal tubular) or rat MSCs in 10% AKI serum (compared to SHAM or NPHX serum) for 48 hrs resulted in increased oxidative stress, including increased anti-oxidant gene expression, increased GSH levels, and increased cellular ROS activity. Compared to SHAM or NPHX serum, serum from rats with AKI had increased Amplex Red activity, which identifies the injured kidney as the source of potentially multiple pro-oxidant factors. The ROS generating properties of AKI serum were completely eliminated with heat inactivation (65°C for 35 min), which is suggestive of a protein mediator. Catalase, N-Acetyl Cysteine (NAC), or rotenone partially reduced—but did not eliminate-- the ROS activity of AKI serum in a dose-dependent manner.

Conclusions: These results suggest that the injured kidney releases heat-sensitive factors into the blood stream (likely proteins) that generate ROS and may adversely affect both renal tissue and distant organs. The AKI serum ROS activity is only partially reduced by catalase, NAC, or rotenone treatment. The exact nature of the pro-oxidant principle that is released by the injured kidney remains to be determined.

Funding: VA Support

PUB027

Neferine Modulates Cisplatin- Induced Acute Kidney Injury via Activating Autophagy

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Background: Extensive studies have shown that apoptosis and autophagy are involved in the pathogenesis of cisplatin-induced AKI. Neferine is not only a strong inducer of autophage, but also has antiapoptosis properties. The objective of this study is to determine the effect of Neferine in cisplatin-induced AKI.

Methods: In vivo,Neferine with different concentration was used to pretreat the cisplatin induced acute kidney injury (AKI) in BALB/c mice. The pathological changes were observed by HE staining. The apoptosis was detected by TUNEL assay and cleaved-caspase3 expression level. The autophage was determined by LC3 expression detection and transmission electron microscope observation. In vitro, changes of apoptosis and autophage were further clarified in NRK-52E cells treated with cisplatin and different concentrations of Neferine. Autophage inhibitor Chloroquine and AMPK inhibitor Compound C were used to indentify the possible mechanism modulating the protective role of Neferine in cisplatin-induced AKI.

Results: Both in vivo and in vitro, Cisplatin induced extensive renal tubular damage, increased cleaved-caspase3 expression obviously but increased the expression of LC3 slightly. Neferine pretreatment ameliorated the cisplatin-induced pathological changes and apoptosis, increased the expression of LC3 significantly and decreased cleaved-caspase3 expression obviously. The transmission electron microscope confirmed the observations. Further study found that Neferine pretreatment couldn't ameliorate the apoptosis induced by Cisplatin in NRK-52E cells while autophage was inbibited by Chloroquine. Stimulation of NRK-52E cells with cisplatin resulted in a significant decrease of the expressions of p-AMPK and increased the expression of p-mTOR in the NRK-52E cells compared with the control. More interesting, while AMPK/mTOR pathway was inbibited by Compound C, Neferine pretreatment couldn't attenuate the damage induced by Cisplatin in NRK-52E cells.

Conclusions: Neferine plays a protective effect on cisplatin induced AKI possibly through promoting autophagy by AMPK/mTOR signaling pathway. Neferine may serve as a potential treatment strategy to suppress cisplatin-induced AKI.

Funding: Government Support - Non-U.S.

PUB028

Inhibition of Histone H3 K27 Demethylase Aggravates Rhabdomyolysis Induced Acute Kidney Injury Na Liu, Shougang Zhuang. *Dept of Nephrology, Shanghai East Hospital, Shanghai, China.*

Background: Accumulating data reveal epigenetic change regulates chronic kidney diseases and acute kidney damage. However, role and exact mechanisms of protein methylation mediated acute kidney injury (AKI) are still obscure.

Methods: In this study, we establish a glycerol-induced murine rhabdomyolysis model. Following glycerol (GL) injection intramuscular, the mice developed severe acute tubular injury as indicated by worsening renal dysfunction, increased NGAL and KIM1 expression and enhanced tubular cell apoptosis. GSK J4, a special JMJD3 inhibitor, treatment significantly enhanced serum creatinine and BUN as well as severe renal pathologic damage in GL injured kidneys.GSK J4 also increased expression of NGAL and KIM-1compared with GL treated alone group. To detect cell apoptosis change with or without GSK J4 in GL injured kidney, we further proceed TUNEL staining and cleaved caspase-3 immunoflurescence. JMJD3 inhibition prodominantly upregulated TUNEL and cleaved caspase-3 positive cells in GL treated kidney.

Results: To discuss the underlying mechanisms of GSK J4 on AKI process, we investigate GSK J4 role on histone methylation as well as tubular epithelial cell dedifferation and proliferation which play pivotal role in AKI regeneration. After Rhabdomyolysis-induced AKI, the kidney displayed a remarkable regenerative capacity by evidence of increased expression of Pax-2 and vimentin,and upregulation of PCNA. GSK J4 administration predominantly downregualated expression of Pax-2 and vimentin as well as PCNA. Further mechanism studies revealed that the injured kidney after AKI underwent hypermethylation indicated by increased level of di-methyl-histone H3 K27 and tri-methyl-histone H3 K27. JMJD3 inhibition further upregulated methyl-histone H3 K27 after acute kidney injury.

Conclusions: In summary, we have demonstrated that inhibition of Histone H3 K27 demethylation aggravates Rhabdomyolysis induced acute kidney injury. This effect was associated with upregulation of methyl-histone H3 K27 as well as downregualtion of tublular epithelial cell dedifferation and proliferation. As such, methylation inhibition may hold a therapeutic potential for treatment of Rhabdomyolysis induced acute kidney injury.

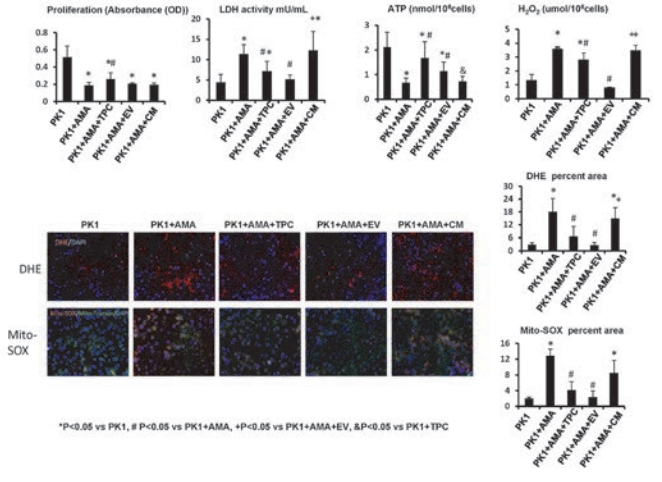
PUB029

Renal Tubular Progenitor Cells Protect Tubular Epithelial Cells by Shuttling Extracellular Vesicles Xiang-Yang Zhu, Xiangyu Zou, Soon Hyo Kwon, Alfonso Eirin, Amir Lerman, Lilach O. Lerman. *Divs of Nephrology & Hypertension and Cardiovascular Diseases, Mayo Clinic, Rochester, MN.*

Background: In situ tubule-committed progenitor cells (TPC) contribute to the turnover and repair of the kidney tubule, but their mode of communication is unknown. Extracellular vesicles (EVs) are important mediators of intercellular communication, but the role of TPC-derived EVs in kidney tubular protection is unclear. We hypothesized that TPC may ameliorate kidney tubular cell injury through their EV progeny.

Methods: TPCs (CD133+/CD24+) were isolated from normal pig kidneys, and EVs from the culture medium. Antimycin A (AMA, 1μmol/L) was used to induce mitochondrial and cellular injury in porcine tubular epithelial cells (PK1), which were then co-cultured for 3d with TPCs (transwell), TPCs-derived EVs, or EV-depleted conditioned medium (CM) alone. MTT and LDH activity assays were used to evaluate PK1 proliferation and injury. PK1 energy production was measured by ATP levels, cellular oxidative stress by hydrogen peroxide assay and Dihydroethidium (DHE), and mitochondrial oxidative stress with Mito-SOX staining.

Results: AMA impaired PK1 proliferation, increased LDH release, decreased ATP production, and increased cellular and mitochondrial oxidative stress. Co-culture with TPC without cell contact improved all these injury indices. TPC-derived EVs showed similar beneficial effects, except for cellular proliferation. Contrarily, these protective effects were abolished using EV-depleted CM.



Conclusions: TPCs alleviated AMA-induced tubular cell injury by releasing EVs that restored energy production and decreased oxidative stress. These findings underscore the endogenous repair capacity of renal tubular cells, and the role of EVs as vectors of the protective effects and intercellular communications of TPCs.

Funding: NIDDK Support

PUB030

Autophagy Protects against Contrast Induced Tubular Epithelial Injury Moo Yong Park, Seung Duk Hwang, Byung Chul Yu. *Dept of Internal Medicine, Soonchunhyang Univ Bucheon Hospital, Bucheon, Republic of Korea.*

Background: Radiocontrast-induced nephropathy (RCN) is common cause of acute kidney injury in hospital. However, preventing and treating strategies against developing RCN were very limited. The role of autophagy in the pathogenesis of RCN remains undetermined, therefore we investigated its role in RCN.

Methods: We examined the expression of autophagic and apoptotic proteins during progression of contrast (idoxanol) induced injury to renal tubular epithelial cells (RTEC). For determine protective role of autophagy against contrast injury, we inhibit autophagy with small interference RNA (siRNA) for ULK1, and measured the changes of cell viability and induction of apoptotic and autophagy protein for 48hr.

Results: Following contrast exposure to RTEC, cell viability was reduced for 3hr, but it was increased at 24hr and 48hr. Apoptosis was detected as early as 1hr after contrast exposure as indicated by induction of caspase 3 and 8 and they were increased for 48hr. Otherwise autophagy, indicated by LC3 and autophagy-related gene protein 7 (ATG7), was detected at 3hr after contrast exposure, and induction of LC3 and ATG7 were further increased up to 48hr. After inhibiting autophagy by ULK1 siRNA, survived RTEC was not increased at 24 and 48hr after contrast exposure.

Conclusions: Autophagy plays cytoprotective role in contrast induced RTEC injury and it may occur independently of apoptosis.

PUB031

Activation of 5-Hydroxytrptamine Receptor 1F Mediates Mitochondrial Biogenesis through AKT/eNOS and ERK/FOXO3a Pathways in the Kidney Whitney Sharee Gibbs, Craig Cano Beeson, Rick G. Schnellmann. *Dept of Drug Discovery and Biomedical Sciences, Medical Univ of South Carolina, Charleston, SC.*

Background: We recently made the novel observation that LY344864 (LY), a selective 5-HT_{1F} receptor agonist, induces renal mitochondrial biogenesis (MB) and accelerates recovery of renal function following I/R-induced acute kidney injury in mice. The mechanism of 5-HT_{1F} receptor mediated MB is unknown. It has been proposed that ERK1/2 is a negative regulator of MB and eNOS activation induces MB through cGMP generation. Therefore, we investigated the role of ERK1/2 and eNOS in 5-HT_{1F} receptor induced MB.

Methods: Mitochondrial respiration (FCCP-OCR, a marker of MB) was measured in renal proximal tubule cells using a Seahorse instrument. Signaling pathways were explored using pharmacological inhibitors and immunoblot analysis. cGMP levels were measured using an ELISA.

Results: LY increased p-Akt at 15-30 min and was attenuated by the Gβγ inhibitor gallein. eNOS, a downstream target of Akt, was measured following LY in the presence and absence of gallein or the Akt inhibitor GDC-0068 (GDC). LY increased p-eNOS at 1 hr, that was attenuated by gallein or GDC. cGMP was also increased at 1 hr. Pretreatment with gallien, GDC, the nitric oxide synthase inhibitor L-NAME or the guanylate cyclase inhibitor ODQ attenuated LY-induced increases in FCCP-OCR.

In parallel to the Akt/eNOS/cGMP pathway, p-ERK1/2 was decreased at 1 hr following LY exposure and gallein and GDC blocked this reduction, indicating that both Gβγ and Akt mediate LY reduction of p-ERK1/2. c-Raf phosphorylation by Akt is known to reduce MEK/ERK signaling. A 30 min exposure to LY elevated p-c-raf and GDC blocked this increase. The inactive form p-FOXO3a, a downstream phosphorylation target of ERK1/2 and transcription factor involved in MB, was decreased following LY at 2 hr. Akt phosphorylation of c-raf decreased p-ERK1/2, reducing p-FOXO3a and increasing PGC-1α.

Conclusions: This study reports the novel finding that Gβγ heterodimer initiates renal MB by increasing Akt/eNOS/cGMP and decreasing ERK/FOXO3a pathways. Thus, 5-HT_{1F} receptor agonists are potent and efficacious inducers of MB and potential therapeutics for renal injury.

Funding: Other NIH Support - NIGMS GM084147, VA Support

PUB032

Abstract Withdrawn

PUB033

Acute Kidney Injury in Patients with Severe Sepsis or Septic Shock: A Comparison between the Risk, Injury, Failure, Loss of Kidney Function, End-Stage Kidney Disease (RIFLE), Acute Kidney Injury Network (AKIN) and Kidney Disease Improving Global Outcomes (KDIGO) Classifications

Iolanda Nunes Godinho,[1] Marta Pereira,[1] Natacha Rodrigues,[1] Joana Gameiro,[1] Marta R.A. Neves,[1] Joao Gouveia,[2] Zelia Costa-e-Silva,[2] António Gomes da Costa,[1] Jose António Lopes.[1] *[1]Div of Nephrology and Renal Transplantation, Dept of Medicine, Hospital de Santa Maria, Lisbon, Portugal; [2]Div of Intensive Medicine, Dept of Medicine, Hospital de Santa Maria, Lisbon, Portugal.*

Background: Using the RIFLE, AKIN and KDIGO systems, the incidence of acute kidney injury (AKI) and their ability in predicting in-hospital mortality in severe sepsis or septic shock was compared.

Methods: Retrospective analysis of 457 critically ill patients with severe sepsis or septic shock hospitalized between January 2008 and December 2014. Multivariate logistic regression was employed to evaluate the association between RIFLE, AKIN and KDIGO with in-hospital mortality. Model fit was assessed by the goodness of-fit test, and discrimination by the area under the receiver operator characteristic (AuROC) curve. Statistical significance was defined at a P <0.05.

Results: RIFLE (84.2%) and KDIGO (87.5%) identified more patients with AKI than AKIN (72.8%) (P<0.001, respectively). AKI defined by AKIN and KDIGO was associated with in-hospital mortality (AKIN - adjusted OR 2.3, 95%CI 1.3-4, P=0.006; KDIGO - adjusted OR 2.7, 95%CI 1.2-6.2, P=0.021) while AKI defined by RIFLE was not (adjusted OR 2.0, 95%CI 1-4, P=0.063). The AuROC curve for in-hospital mortality was similar between the three classifications (RIFLE 0.652, P<0.001; AKIN 0.686, P<0.001; KDIGO 0.658, P<0.001).

Conclusions: RIFLE and KDIGO diagnosed more patients with AKI than AKIN however the prediction ability for in-hospital mortality was similar between the three systems.

PUB034

Non-Critical Care Hospital-Acquired Acute Kidney Injury: Risk Factors and Clinical Outcomes

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Background: Non-critical care Hospital-Acquired Acute Kidney Injury (Non ICU HA-AKI) is a common complication associated with worse clinical outcomes. We analysed the risk factors and outcomes in this condition.

Methods: Paired case-control 1:2 study was carried out from April-December 2014 at a University Hospital in Bogotá, Colombia. Non ICU HA-AKI was defined by creatinine KDIGO criteria after 24 hours of hospitalization. Controls was paired by date and type of attention. We analysed outcomes and performed univariate and multivariate analysis of risk factors.

Results: Of 16368 admissions, 101 patients fulfill criteria. Mean length of hospitalization to AKI was 7.9±8.8 days, 44.2% fulfilled KDIGO1 criteria and 32.7% KDIGO2, 4.9% requiered dialysis. Hospital length of stay was longer in patients with AKI (p<0.01) 13 vs 6 days, ICU admission was higher in cases OR 2.43 [95%CI 1.2-4.7 p=0.004] as well as mortality OR 26.2 [95%CI 8.8-104 p<0.01]. In multivariate analysis, sepsis OR 3.6 [95%CI 1.3-10.1 p=0.01], dehydration OR 14,4 [95% CI 4.5-46.2 p=0.0001], baseline eGFR OR 0.96 [95% CI 0.94-0.98 p=0.0001], contrast OR 4.33 [95% CI, 1.60-11.66 p=0.004], recently NSAIDs use OR 3.23 [95% CI 1.22-8.52 p=0.017] and Charlson comorbidity index OR 1.23 [95% CI 1.05-1.43 p=0.007] were independent risk factors.

	Cases (101) %	Controls (202) %	All (303) %
Diabetes	13.8	17.3	16.1
Hypertension	48.5	42.5	44.5
Cardiac failure	26.7	18.3	21.1
CKD	21.7	6.9	11.8
COPD	22.7	11.8	15.5
Neoplasm	41.5	29.7	33.6
NSAIDs use	37.6	15.8	23.1
ACEi/ARBs	47.5	48.5	48.2
Sepsis	52.5	16.3	28.4
Dehydration	56.4	6.4	23.1
Diuretics	39.6	18.3	25.4
Contrast	48.5	32.2	37.6
eGFR	73.5±30.4	91.4±22.4	85.4±26.7
Charlson index	5.2±2.3	3.2±2.9	3.8±3.1

Conclusions: Non-ICU HA-AKI is associated with a longer hospital stay, ICU requirement and high mortality rate. The majority of risk factors are potentially preventable.

PUB035

Incidence and Characteristics of Acute Kidney Injury in Children and Adolescents with Diabetic Ketoacidosis

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Background: Diabetic ketoacidosis (DKA) is a potentially lifethreatening acute complication of type 1 diabetes mellitus (T1DM). DKA is also associated with numerous acidbase, hydration and electrolytes derangements. Acute kidney injury (AKI) is a known complication of DKA, mainly resulting from hypovolemia due to glucoseinduced osmotic polyuria. However, there is paucity of knowledge about acute kidney injury in children with DKA.

Methods: Retrospective chart review of 21 children (with median age of 12 years) hospitalized consecutively with DKA over a oneyear period at Northwest Texas pediatric hospital was done after IRB approval. Patients were classified as per the pRIFLE classification into Risk of AKI, AKI and acute kidney failure. Pearson correlation was used to correlate clinical and laboratory parameters in these populations.

Results: Among the 21 children hospitalized with DKA, 4 children (19%) were at risk of AKI, 7 (33.33%) had AKI, 7 (33.33%) had acute renal failure (ARF). No patients required renal replacement therapy or dialysis. Only 2 of 21 patients had an admission diagnosis of AKI. Twentyeight percent of patients with either AKI or acute kidney failure had severe DKA. Median time of resolution for AKI was 11 days. Admission eGFR was negatively correlated with age (r = 0.35; p=0.12). No correlation was found between admission eGFR and blood glucose on admission or severity of DKA.

Conclusions: For the first time we showed that there is a high incidence of AKI in pediatric DKA population. AKI is a frequently associated, but underdiagnosed condition in children with DKA. Older age may be a risk factor for AKI. However, it is usually transient and resolves by fluid replacement as per DKA management.

PUB036

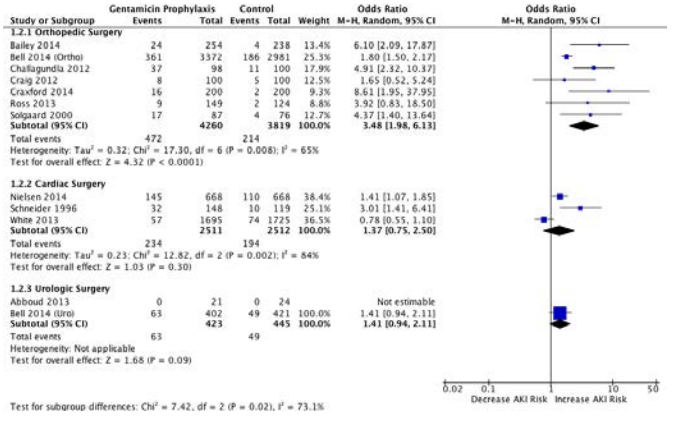
Surgical Prophylaxis with Gentamicin and Acute Kidney Injury

Weeraporn Srisung,[1] Jirapat Teerakanok,[1] Pakpoom Tantrachoti,[1] Amputch Karukote,[2] Kenneth Nugent.[1] *[1]Internal Medicine, TTUHSC; [2]Mahidol Univ.*

Background: Gentamicin has been increasingly used instead of cephalosporins for surgical prophylaxis in an attempt to reduce the rate of "Clostridium difficile" infection. There are limited data regarding nephrotoxicity related to gentamicin in these patients.

Methods: We have conducted a meta-analysis to evaluate the risk of acute kidney injury (AKI) in gentamicin-containing surgical prophylactic regimens, compared to regimens without gentamicin, in several types of surgery. Electronic searches were performed using PubMed and Embase. Statistical analysis was then performed using a random-effect model; heterogeneity (I^2) was calculated.

Results: Eleven studies with fifteen cohorts with 18,354 patients are included in the analysis. Subgroup analysis was performed according to surgery type. We have found that antibiotic prophylaxis with gentamicin containing regimen has significant risk for developing postoperative AKI in orthopedic surgery (OR [95%CI] = 3.48 [1.98,6.13]). The results were inconclusive in other types of surgery .



Conclusions: Therefore, physicians should consider risks and benefits of using this regimen in individual patients.

PUB037

Factors Associated with Renal Recovery from Acute Kidney Injury Requiring Renal Replacement Therapy

Katsuhito Ihara, Madoka Kimura, Yukiko Tanaka, Atsuki Ohashi, Hitomi Tanaka, Seiji Inoshita. *Internal Medicine, Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan.*

Background: Recovery of renal function after an episode of acute kidney injury (AKI) is an important clinical measure of morbidity, but factors associated with the renal recovery are currently not clear.

Methods: In this single center retrospective cohort study, we studied AKI patients who were admitted to the ICU or general wards, and required renal replacement therapy (RRT) during 1 January 2010 and 31 December 2013. Patients were excluded if they underwent RRT prior to the admission including those on chronic RRT, or they were cardiopulmonary arrest on admission. Demographic data, co-morbidities, clinical history, cause of AKI, and laboratory data were collected at the time of RRT initiation, and patients were followed until death or discharge. The primary outcome was RRT withdrawal, which was defined as being free from RRT. A priori determined covariates of age, gender, vasopressor use, mechanical ventilation, oliguria (urine output <0.5 mL/kg/h), cardiovascular disease, diabetes mellitus, surgery, sepsis, contrast agent, and pre-existing CKD (eGFR <60 mL/min/1.73 m^2) were included in Cox hazard models to estimate hazard ratio (HR) of RRT withdrawal.

Results: A total of 337 patients were enrolled. The mean age was 66 years, 28.8 % were female, and 46.3 % had sepsis. During follow-up (median 6 days, IQR 2-22 days), 159 patients achieved RRT withdrawal, and 146 died. In multivariable Cox analysis, significant factors associated with RRT withdrawal were pre-existing CKD (HR 0.52 [95 % confidential interval {CI} 0.33-0.82]), male (HR 0.68 [95 % CI 0.47-0.99]), mechanical ventilation (HR 0.57 [95 % CI 0.35-0.93]), and oliguria (HR 0.60 [95 % CI 0.41-0.86]).

	HR [95% CI]
Age (+ 1 year)	0.99 [0.98-1.01]
Male	0.68 [0.47-0.99]
Use of vasopressor	1.77 [1.04-3.01]
Mechanical Ventilation	0.57 [0.35-0.93]
Oliguria	0.60 [0.41-0.86]
CVD	0.99 [0.65-1.51]
CKD	0.52 [0.33-0.82]
Diabetes	1.23 [0.81-1.88]
Use of contrast agent	1.14 [0.76-1.69]

Conclusions: Among individuals with AKI requiring RRT, male gender, pre-existing CKD, mechanical ventilation, and oliguria were negatively associated with RRT withdrawal.

PUB038

Improvements in Recognizing and Managing Medications in Patients with AKI, Better Long-Term Management and Follow-Up Needed

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Background: Care bundles, education programs, and electronic alert systems have all been cited as possible ways to improve care. However, it is still unclear just how much impact these interventions have in a real life clinical setting, or in which areas valuable resources should be focused on in order to improve outcomes.

Methods: Our hospital has implemented an electronic altering system for patients with AKI along with a structured education program for clinicians. To assess the effectiveness of these inventions we audited medication and IV fluid prescriptions in patients with AKI over a period of 3 months.

Results: We identified 397 patients with AKI stage 2/3 from August to October 2015. 40% of AKI was identified on admission units, 38% on medical wards. The number of patients prescribed a diuretic, Angiotensin converting enzyme inhibitor(ACE)/ Angiotensin receptor blocker(ARB), Non-steroid anti-inflammatory drugs (NSADS), or given Intravenous fluids pre-admission, 24 hrs post admission, and at point of discharge are shown in Figure 1.

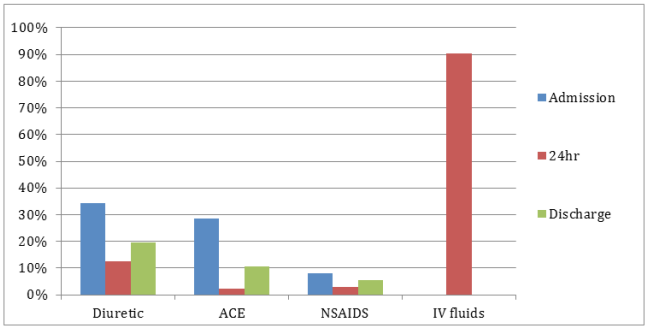


Figure 1: Changes in Medication and intravenous fluid prescription for patients with AKI.

For patients who survived to discharge, 17% had a repeat blood tests carried out in a non-hospital setting with-in 4 weeks of discharge, 59% if patients did not have any repeat blood test with-in 4 weeks of discharge.

Conclusions: The majority of patients with AKI and on potentially nephrotoxic medications pre-admission had their medications altered with-in 24hr of admission and was given intravenous fluid. The percentage of patients with AKI identified on the medical wards is higher than reported in the literature, suggesting changes in practice regarding investigating AKI in our hospital. The vast majority of patients who suffered AKI are not been followed up in secondary or primary care with follow up blood tests. More resources and research is needed to focus on improving AKI follow up care.

PUB039

Comparison of Tziakas Risk Score versus Mehran Risk Stratification in Predicting Contrast-Induced Acute Kidney Injury among Patients Undergoing Coronary Angiography and/or Percutaneous Coronary Intervention

Frederick Elises Ogbac, Michelle Jane Aguirre Buaron, Russel Redoblado Semeniano, Oscar D. Naidas. *St. Luke's Medical Center - Quezon City, Quezon City, Philippines.*

Background: Contrast-induced acute kidney injury (CI-AKI) is a form of acute kidney injury (AKI) that occurs after the administration of contrast media. In patients who underwent percutaneous coronary intervention (PCI), there was a 3.3% to 19% incidence of CI-AKI. Among these patients, dialysis was needed in 0.3% to 3%. Furthermore, they have a higher mortality rate of 7.1% to 81.2%. It is therefore necessary to measure the patient's risk to develop CI-AKI in order to prepare them for the procedure.

Methods: This was a cross-sectional analytic study conducted at St. Luke's Medical Center - Quezon City. Patients aging >18 yrs old who underwent coronary angiography or PCI were included in the study. The following patients were excluded: incomplete data, already on renal replacement therapy, and underwent multiple procedures. Included patients were stratified using both tools. The study outcomes were the occurrence of CI-AKI or need to do dialysis. CI-AKI was defined as an increase in serum creatinine >0.5mg/dL or >25% from baseline.

Results: A total of 414 patients were included. 55 patients (13.28%) developed CI-AKI. Comparing the accuracy indices, Tziakas Risk Score (84.5 {81.1-88.0}) has a higher over-all accuracy than Mehran Risk Stratification (81.6 {77.9-85.4}). Sub-group analysis of patients who underwent coronary angiography showed no statistical difference (*p*-value=0.51) between the Area Under the Curve (AUC) of the 2 stratification tools. But the sub-group analysis of patients who underwent PCI showed a statistically higher (*p*-value=0.03) AUC for Tziakas Risk Score (AUC-0.79;SE-0.5) than Mehran Risk Stratification (AUC-0.71;SE-0.06).

Conclusions: In conclusion, Tziakas Risk Score or Mehran Risk Stratification can be used to stratify patients who will undergo coronary angiography. For patients who will undergo PCI, Tziakas Risk Score has a better predictive value compared to Mehran Risk Stratification. In clinical practice, we recommend Tziakas Risk Score as the risk stratification tool.

PUB040

Cytokine Clearance in Continuous Venovenous Hemofiltration and Continuous Venovenous Hemodialysis

Ling- Xin Chen,[1] Sevag Demirjian,[2] Suneel M. Udani,[1] Sharon A. Trevino,[1] Jay L. Koyner.[1] *[1]Nephrology, Univ of Chicago Hospitals, Chicago, IL; [2]Nephrology and Hypertension, Cleveland Clinic, Cleveland, OH.*

Background: In the past, it was believed that Continuous Venovenous Hemofiltration (CVVH) provided improved middle molecule and cytokine clearance compared to Continuous Venovenous Hemodialysis (CVVH).

Methods: We conducted a multicenter prospective unblinded randomized trial of patients with severe acute kidney injury. Patients were randomized to CVVH or CVVHD. Blood, urine and effluent were collected at 0, 4, 24 and 48 hours after initiation of CVVH or CVVHD with collections stopping at the time of the first circuit change. Levels of electrolytes and cytokines were tested in both groups of patients and compared. Clearances of each cytokine was calculated and compared between groups and across time-points.

Results: We enrolled 21 patients with 11 patients receiving CVVH and 9 receiving CVVHD. There was no difference in baseline demographics, baseline renal function or ICU type across the 2 groups. The mean(SE) time to first filter change for the cohort was 30.4(6.7) hours. No significant differences were found between the two modalities in terms of cytokine concentrations at enrollment, 4 and 24 hours. We had sufficient samples to calculate 4 hour cytokine clearances in 19 patients and found no difference in 4 hour cytokine clearances.

	Mean 4 hour dialysis clearances (mL/min)		
	CVVHD (n=8)	CVVH (n=11)	p
IL-1 beta	38728.6 (108357.1)	28781.95 (65434.52)	0.82
IL-1 RA	30.22 (48.25)	8.81 (4.30)	0.25
IL-6	11.50 (9.41)	18.79 (13.75)	0.19
IL-10	72.20 (55.88)	38.14 (28.22)	0.15
TNF-alpha	58.21 (34.76)	54.01 (26.22)	0.78
Creatinine	61.58 (25.43)	51.39 (21.14)	0.37
BUN	138.08 (54.42)	93.65 (26.20)	0.06

Conclusions: In our randomized multicenter study, there was no significant difference in cytokine clearance between CVVH and CVVHD.

Funding: Pharmaceutical Company Support - NxStage

PUB041

Poor Nutritional Status Is Associated with the Incidence of Acute Kidney Injury in the Treatment of Head and Neck Cancers with Concurrent Chemoradiotherapy Using High-Dose Cisplatin Akihiko Kato,[1] Takayuki Tsuji,[2] Naro Ohashi,[2] Hideo Yasuda.[2] *[1]Blood Purification Unit, Hamamatsu Univ Hospital, Hamamatsu, Shizuoka, Japan; [2]Internal Medicine 1, Div of Nephrology, Hamamatsu Univ School of Medicine, Hamamatsu, Shizuoka, Japan.*

Background: Identifying potential risk factors is critically important for reducing the burden of acute kidney injury (AKI) in cancer patients receiving cisplatin (CDDP) treatment. We aimed this study to explore the risk factors for CDDP-induced AKI in head and neck cancer patients with concurrent chemoradiotherapy.

Methods: We retrospectively reviewed medical records for 40 head and neck cancer patients who underwent chemoradiotherapy including 66-70 Gy with CDDP 80 mg/m^2 on Days 1, 22 and 43 (age: 60±10 years old, male/female=38/2). We also evaluated the association of nutritional parameters with CDDP-induced nephrotoxicity in the first-line setting of CDDP.

Results: CDDP-induced AKI developed in 11 out of 40 (27.5%) patients in the first course, 6 out of 35 (17.1%) patients in the second, and 2 out of 34 (5.9%) patients in the third. Serum creatinine levels were increased from 0.76±0.16 in the first to 0.92±0.23 mg/dL in the last administration. No difference was found in basal creatinine clearance (79.5±21.0 vs. 87.3±26.7 ml/min) and CDDP dosage (120±19 vs. 132±32 mg) between patients with AKI development and those without. Dairy dietary food intake and anthropometric parameters were also identical between the two groups. However, there was a significantly lower level of serum albumin (3.5±0.6 vs. 3.9±0.5 g/dL, p<0.01), cholinesterase (237±49 vs. 299±85 IU/L, p<0.03) and hemoglobin (11.8±1.3 vs. 12.9±1.5 g/dL, p<0.05) in patients with AKI than those without. The Geriatric Nutritional Risk Index (GNRI) was also significantly lower in AKI patients (86±9 vs. 96±10, p<0.01). In patients having high nutritional risk (GNRI<92), the incidence of CDDP-induced AKI was significantly higher than those not having (47.1 vs. 13.0%, p<0.02).

Conclusions: These findings suggest that poor nutritional status just before chemoradiotherapy was associated with CDDP-induced AKI in advanced head and neck cancer patients. GNRI less than 92 may be useful in predicting the risk of AKI in these patients.

PUB042

Acute Kidney Injury after Laparoscopic Abdominal Surgery Nattachai Suwachittanont, Thaksa-On Wirotwan, Passisd Laoveeravat, Nattachai Srisawat. *Excellence Center for Critical Care Nephrology, Faculty of Medicine, Chulalongkorn Univ and King Chulalongkorn Memorial Hospital, Bangkok, Thailand.*

Background: Laparoscopic abdominal surgery can induce many physiologic changes including renal function. Many studies demonstrating the relationships of pneumoperitoneum and renal function disturbance were conducted in animal models and showed controversial conclusions. Therefore our objectives were (1) to describe incidence of acute kidney injury (AKI) in patients underwent laparoscopic abdominal surgery and (2) to identify risk factors associated with development of AKI in these circumstances.

Methods: In this prospective cohort study, the medical records of patients who underwent laparoscopic abdominal surgery at King Chulalongkorn Memorial Hospital, Thailand from June 2012 to December 2013 were reviewed. Demographic data (gender and age), preoperative clinical characteristics (body weight, height, heart rate, blood pressure, serum creatinine, estimated glomerular filtration rate and co-morbidities including hypertension, diabetes mellitus and hyperlipidemia) and intraoperative data (operative time, inflation time, mean intra-abdominal pressure and duration of intraoperative hypotension) were collected. We used AKIN criteria to diagnose AKI. Therefore, we collected blood samples, urine samples and we also monitored daily urine output of all patients.

Results: A total of 62 patients were included in this study. Twelve patients (19%) developed AKI. Patients with postoperative AKI had more body weight (p=0.04), more height (p=0.002), more inflation time during surgery (p=0.035) and more exposure index defined as the product of operation time and intra-abdominal pressure (p=0.03). In addition, we found that duration of intraoperative hypotension (mean arterial pressure < 65 mmHg) was independently associated with AKI (adjusted OR=1.19, 95%CI= 1.02-1.37, p=0.022).

Conclusions: Our incidence of AKI was 19% which higher than reported in previous studies. Intraoperative hypotension was the independent factor of AKI associated laparoscopic surgery. Therefore, awareness of physician about intraoperative hypotension should be considered in order to reduce the risk of AKI.

PUB043

Prompt Reversal of Acute Renal Failure (ARF) by Large-Volume Diuresis in 36 Consecutive Patients with Anasarca: Evidence for Congestive Kidney Failure as Suggested by Animal Data Showing Impaired Function by Renal Vein Hypertension/Congestion Grant Meltzer,[1,2] Kai Lau.[1,2] *[1]Dept of Nephrology, Univ of Oklahoma Health Sciences Center, Oklahoma City, OK; [2]Medical Service, VA Medical Center, Oklahoma City, OK.*

Background: Fluid overload in ICU patients is known to link to greater ventilator dependency, longer hospital stay, worse mortality & more ARF. But a causal relationship is not proven. Animal studies showed renal vein hypertension with or without saline loading impairs function. In patients with anasarca & unexplained ARF, we tested the hypothesis that fluid overload was causative & diuresis curative.

Methods: We studied 36 consecutive patients with acute gain of >3 kg weight or ≥3 L fluid, ≥50% acute drop in creatinine clearance (CrCl) or ≥2 x rise in serum creatinine (Scre) without known or identifiable causes. They got IV furosemide at rates without causing hypotension or unstable hemodynamics. All relevant data like weights, fluid balance, volume markers & renal responses were noted, reviewed & statistically analyzed.

Results: Primary etiologies of fluid overload were heart failure (40%), liver failure (22%), CKD (16%), proteinuria (9%) & iatrogenic causes (10%). In the evolution of ARF, weight rose by 12.5 kg in 14 d. Scre rose from 1.3 to 4.4 mg%. CrCl fell from 76 to 25 ml/min. The falls in CrCl correlated with weight gains (p<0.02). Furosemide caused 15.2 kg diuresis in 12 d, dropped Scre to 1.45 mg% & raised CrCl to 67 ml/min. ARF fully resolved in 33 patients. In 3, Scre was stable despite >4 kg diuresis. Gains in CrCl correlated with diuresis volume (p<0.04). At a diuretic rate of 1.5 kg/d, no adverse events occurred.

Conclusions: Our data support the entity of Congestive Kidney Failure (CKF) as induced by acute & major salt retention or fluid overload but resolved by diuresis. 2. CKF is likely mediated by reduced cardiac output, systemic or renal venous congestion, renal interstitial edema &/or intra-abdominal hypertension. 3. It can alone induce or aggravate ARF by other causes. 4. Likely under-recognized, CKF is preventable & treatable. 5. Diuresis in cohorts at rates & monitored as ours should be safe & effective.

Funding: NIDDK Support, Private Foundation Support

PUB044

The Relationship between Cancer and Acute Tubular Necrosis in Patients with Chronic Kidney Disease Gregory John Wilson,[1,2] Andrew John Mallett,[1,2,3] Adrian Lawrence Kark,[1,2] Ken-Soon Tan,[2,4] Rajitha Asanga Abeysekera,[1,2] Zaimin Wang,[2,3] Helen G. Healy,[1,2] Wendy E. Hoy.[2,3] *[1]Dept of Renal Medicine, Royal Brisbane and Women's Hospital, Brisbane, Australia; [2]CKD.QLD & NHMRC CKD.CRE, Univ of Queensland, Brisbane, Australia; [3]Centre for Chronic Disease, Univ of Queensland, Brisbane, Australia; [4]Dept of Renal Medicine, Logan Hospital, Brisbane, Australia.*

Background: Acute tubular necrosis (ATN) occurs commonly in patients with cancer, yet it is not known how these conditions and other comorbidities influence the development and progression of chronic kidney disease (CKD).

Methods: Patients enrolled (with informed consent) in the RBWH and Logan CKD.QLD registries (n=2,367) were assessed for a diagnosis of an acute kidney injury (AKI) as either the primary cause of their CKD or an acute on chronic kidney injury. From this group, patients with ATN as either the primary cause of CKD (primary ATN) or as an acute on chronic kidney injury (ATN on CKD) were selected, and compared with CKD patients without AKI (CKD only).Changes in estimated glomerular filtration rates (eGFR) at one and two years after consent, where available, were calculated.

Results: 823 patients (35%) had a diagnosis of AKI and among them 97 patients (4% overall) had a diagnosis of ATN. 31 patients had a diagnosis of primary ATN (mean age 59; 61% male), and 66 had ATN on CKD (mean age 66; 55% male). 1544 patients had CKD only (mean age 67; 50% male). 19% of CKD only patients had cancer: rates were higher in those with primary ATN (42%, OR 3.03, p= 0.002), and marginally higher in those with ATN on CKD (29%, OR 1.7, p=0.06). Diabetes (DM) and hypertension (HTN) were recorded in 52% and 80% of CKD-only patients: rates were significantly lower for patients with primary ATN (DM 19%, p<0.001 and HTN 55%, p=0.001), but were not for patients with ATN on CKD (DM 41%, p=0.1, and HTN 74% p= 0.3. The mean rate of eGFR decline (ml/min/1.73m^2/yr) in patients with cancer and CKD only was 0.91 (SD=5.12), for patients with primary ATN and cancer was 3.63 (SD=4.90) and for ATN on CKD and cancer was 0.88 (SD=5.56).

Conclusions: These findings suggest that ATN in patients with cancer may be an independent risk factor for developing CKD. However an effect on progression is not yet clear.

PUB045

Increased Levels of uPAR Correlate with Disease Severity in Hantavirus-Induced Acute Renal Failure Stefan Hägele,[1] David Changli Wei,[2] Jochen Reiser,[2] Martin G. Zeier,[1] Ellen Krautkrämer.[1] *[1]Dept of Nephrology, Univ Hospital Heidelberg, Heidelberg, Germany; [2]Dept of Medicine, Rush Univ, Chicago, IL.*

Background: Hantavirus disease caused by Puumala and Dobrava-Belgrade virus is characterized by acute kidney injury (AKI) with often massive proteinuria. The underlying mechanisms for renal failure are not completely understood. Recently, serum soluble urokinase-type plasminogen activator receptor (uPAR) has been identified as one of the key factors for proteinuria in focal segmental glomerulosclerosis (FSGS) by impairing podocyte function.

Methods: We analyzed levels of uPAR and its ligand urokinase-type plasminogen activator (uPA) in serum samples of patients with acute hantavirus disease and of healthy control persons. Serum uPAR levels were correlated with hantaviral clinical parameters.

Results: Serum uPAR levels were significantly higher in hantavirus-infected patients. In contrast, levels of the ligand uPA were not elevated. The concentration of serum uPAR correlated with clinical parameters and highest uPAR levels were observed in patients with severe AKI.

Conclusions: The correlation between increased serum uPAR levels and laboratory parameters indicates a possible role of uPAR in the severity of hantavirus-induced AKI. Elevated levels of soluble uPAR may contribute to podocyte dysfunction and may be relevant in the pathogenesis of proteinuria induced by hantavirus infection.

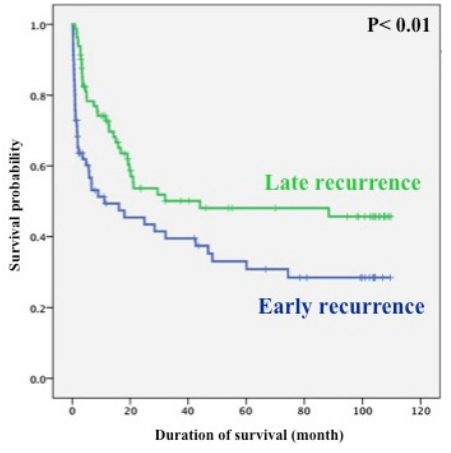
PUB046

Patients with Early Recurrence of Acute Kidney Injury Are Poor Prognosis
Keisuke Sako, Kengo Furuichi, Yasunori Iwata, Norihiko Sakai, Takashi Wada.
Nephrology, Kanazawa Univ Hospital, Kanazawa, Ishikawa, Japan.

Background: Preventing recurrent AKI would improve kidney dysfunction and mortality. However, it is still unclear how long should we follow the AKI cases after the kidney injury. In this study, we evaluate interval of recurrent AKI and prognosis of these cases.

Methods: This study was observational cohort study. An entry criterion of this study is all cases admitted and visited to Kanazawa University Hospital from November 1st, 2006 to October 31st, 2007. A total of 21,939 cases were evaluated retrospectively from November 1st, 2006 to December 31st, 2015. Primary end point was death. Observation time after index AKI were two years for short-outcome and ten years for long-outcomes. Recurrent AKI was defined as re-increase of serum creatinine after index AKI.

Results: One hundred fifty one cases occurred recurrent AKI within two years. Cases recurred AKI within 28 days were defined as the early recurrence group (n=70), and others were defined as the late recurrence group (n=81). Their clinical factors were almost no difference between two groups. However, rates of all-cause mortality were higher in the early recurrence group (p<0.01; Log-rank test). Multiple cox regression analysis revealed that AKI stage III in first AKI showed high HR for death in early recurrence group (HR 3.269; p<0.05), and AKI Stage III in recurrent AKI showed high HR for death in late recurrence group (HR 5.600; p<0.01).



Conclusions: Patients with recurrent AKI within 28 days after index AKI showed poor prognosis. Careful follow-up for at least 28 days after AKI would be required to detect recurrence of AKI and predict prognosis after AKI.

PUB047

Metformin Associated Lactic Acidosis with Acute Kidney Injury: Results of a French Observational Multicenter Study Carried Out in 2015
Alain Wynckel,[1] Anthony Corchia,[1] Zoubir Djerada,[2] Thiery Trenque,[3] Philippe Rieu.[1] *[1]Nephrology, CHU, Reims, France; [2]Pharmacology, CHU, Reims, France; [3]Pharmacovigilance, CHU, Reims, France.*

Background: Metformin associated lactic acidosis (MALA) remains a controversial issue in the literature.

Methods: Our observational multicenter study focused on MALA (pH <7.35, blood lactate > 2 mmol/L) associated with acute kidney injury (AKI), occurring from January to December 2015. The same questionnaire was sent to 67 nephrology departments (ND) and 17 intensive care units (ICU). Clinical characteristics, baseline chronic treatment, precipitating factors, need for vasoactive drugs, extrarenal support, renal recovery, mortality and the worst biological values were recorded for all the patients. Plasma metformin levels were collected if available.

Results: 42 ND did not observe MALA. 158 MALA were collected. Mean age was 70 ± 12 years. Preexistent eGFR was less than 60ml/min per 1.73m^2 in 38 patients and was unknown in 20 patients. The mean pH was 7.13 ± 0.20. Mean serum creatinine and blood arterial lactate were 604 ± 360 µmol/L and 10.2 ± 8.1 mmol/L respectively. A septic or cardiogenic shock was documented in 34 patients. Gastro intestinal disorders or acute cardiac dysfunction were observed in 79 of the 97 patients who did not need vasoactive drugs. Plasma metformin level was positively correlated with blood lactate level and negatively correlated with pH. Need for vasoactive drugs, baseline mean pH and lactate concentration did not differ significantly between survivors (n=137) and non survivors (n=21). Death was related to septic or cardiogenic shock in 12 patients. Hemodialysis was performed in 119 patients. The correction of lactic acidosis was obtained in 48 hours in 109 patients. Complete renal recovery was observed in 91% of the patients with a previous eGFR > 60ml/min per 1.73m^2.

Conclusions: MALA occurred mainly in patients without preexistent renal failure. Septic shock was not the predominant triggering factor. The majority of patients with MALA survived when hemodialysis was performed early despite a mean pH that is usually thought to be fatal. Temporary metformine withdrawal is recommended in dehydrated patient.

PUB048

Abstract Withdrawn

PUB049

Can We Blame Vitamin D for Contrast Induced Nephropathy? A Prospective Single Center Study
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Background: Contrast induced nephropathy (CIN) is one of the major causes of acute kidney injury (AKI) for hospitalized patients, few mechanisms were suggested to cause CIN, one of which is the anti-oxident, anti-inflammatroy effect of vitamin D on the kidney. Our study is to evaluate the factors associated with CIN including vitamin D deficiency.

Methods: in a tertiary referral hospital, we prospectively collected data, blood and urine samples for all patients admitted to our cardiology unit, and signed the consent form to participate in our study. all consented patients were asked to have a creatinine level withdrawn 48-72 hours after the procedure. CIN was defined as increase in serum creatinine by 25% from the baseline within 48-72 hours after the contrast administration. we excluded patients with advanced CKD (stage 4,5), patients with recent contrast administration.

Results: between June 1.2015 - January 10. 2016, we approached 1810 patients, 327 patients agreed and signed the consent to participate in the study, 123 patients did not come back for follow up creatinine,for baseline characteristics see table 1, the contrast media used was low osmolality for all patients, the average contrast used was 99.8 ml (SD 68.7) for the CIN group and 99.2 ml (SD 65.7) for the other group. mean creatinine for CIN group was 73.3 mmol/l vs. 87.6 mmol/l for the other group,78.2% of all patients were vitamin D defificent (mean 13.6 ng/ml). in our study only 10.4% received pre procedure hydration, the incidence of CIN was 14.9%, admission creatinine (P=0.001) and the use of diuretics (P=0.047) were associated with CIN, vitamin D was not associated with increase incidence of CIN in our study (P=0.097).

Conclusions: incidence of CIN is high among hospitalized patients, in many cases its a preventable complication of contrast media if adhered to general recommendation of adequate pre contrast hydration.

PUB050

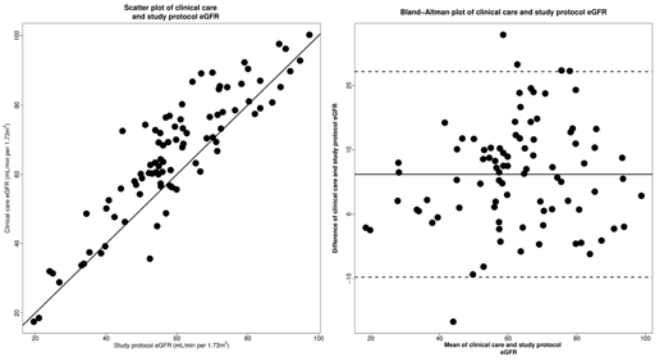
Study Protocol Renal Function Measurements Are Comparable to Clinical Care Measurements in a Cardiac Surgery Cohort
Eric McArthur,[1] Amit X. Garg,[1] Steven G. Coca,[2] Chirag R. Parikh,[3] Heather Thiessen Philbrook.[3]
[1]Inst for Clinical Evaluative Sciences, ON, Canada; [2]Icahn School of Medicine at Mount Sinai, NY; [3]Yale Univ, CT.

Background: In the era of electronic medical records, it is appealing to utilize measurements available from routine clinical care instead of laborious and expensive study protocol visits. However, clinically obtained lab values are prone to ascertainment bias. It is not known if renal function measured during clinical care is comparable to protocol-based visits.

Methods: The TRIBE-AKI cohort is comprised of adults undergoing cardiac surgery. We examined a subset of the cohort in Ontario, Canada who had estimated glomerular filtration rate (eGFR) measured in follow-up as per study protocol, with a clinical care eGFR collected from an outpatient laboratory within one year of the study protocol visit (using CKD-EPI equation). Comparability of the eGFRs was assessed using Pearson's correlation, concordance correlation, and a Bland-Altman plot.

Results: Overall, 224 adults had a study protocol visit a median 3.0 years (IQR 2.9-3.2) after surgery, of which 88 (39%) had their eGFR measured in clinical care. The mean eGFR in clinical care was 66 mL/min/1.73m^2 (SD 18) and was 59 mL/min/1.73m^2 (SD 17) at protocol visits. A correlation of 0.90 (95% CI 0.85, 0.93) and concordance of 0.84 (95% CI 0.77, 0.89) indicated strong correlation and moderate concordance. The Bland-Altman plot showed, among those with mild or no chronic kidney disease, clinical care may slightly overestimate eGFR relative to protocol-based eGFR.

Conclusions: Clinical care eGFR may be marginally higher compared to study protocol eGFR, but the values were largely comparable in follow-up after cardiac surgery. Supplementing research studies with eGFR collected from electronic medical records may help minimize costs and loss to follow-up, but further research should confirm these findings.



Funding: Other NIH Support - NIH grant RO1HL085757

PUB051

Analysis of Kidney Injury Markers in Children with Cancer Marcelo Rodrigues Bacci, Marina M. Sonnenfeld, Carolina Y. Tamashiro, Fernando Luiz Affonso Fonseca. *General Practice, ABC Medical School, Santo Andre, São Paulo, Brazil.*

Background: Children are subjected to develop acute kidney injury(AKI) when in a chemotherapy(CT) routine basis. Still, when the AKI is not present the pattern of glomerular biomarkers of renal dysfunction is not known. The association between its levels before the initiation of CT could predict the occurrence of AKI later on.The aim of the study is to evaluate AKI in pediatric oncology patients in current CT.

Methods: It is a cross-sectional study. Individuals from 2 to 18 years-old with a confirmed diagnosis of acute lymphoblastic leukemia, acute myeloid leukemia and any solid tumors receiving CT were included. Exclusion criteria involved patients with end stage renal disease or in dialysis and with an eGFR less than 60 mL/min/1.73m^2 and also with any other immunodeficiency. Individuals with prior organ transplants were excluded as well. Blood samples were collected in order to analyze the following variables before and after CT : serum creatinine,C cystatin, NGAL, interleukin-6, TNF-alpha, C-reactive protein and homocysteine.

Results: A total of 26 children were included. About 17 had acute lymphoblastic leukemia, 2 had acute myeloid leukemia, 3 with neuroblastoma, 1 with testicle neoplasia, 1 with adrenaloma, 1 with osteosarcoma and 1 with rabdomiosarcoma. About 61.5% were male and the mean age was 9,48 years. NGAL and C cystatin in blood were measured with the following median results in the sample:0.3 and 6.6. Serum creatinine median was 0.6 mg/dL. Spearman correlation test analysed the correlation between C cystatin and inflammatory and renal dysfunction biomarkers. The correlation was not significant between NGAL and creatinine (p=0.213) and between C cystatin and creatinine (p=0.113). The correlation between C cystatin and NGAL was also not significant with a p=0.464. The performance in the receiver operating characteristics analysis the area under the curve for NGAL in detecting acute kidney injury was 0.280. The performance of C cystatin had the value of 0.565 .

Conclusions: This model could not predict AKI in patients receiving CT. NGAL and C cystatin were not correlated with the development with AKI in children receiving CT.

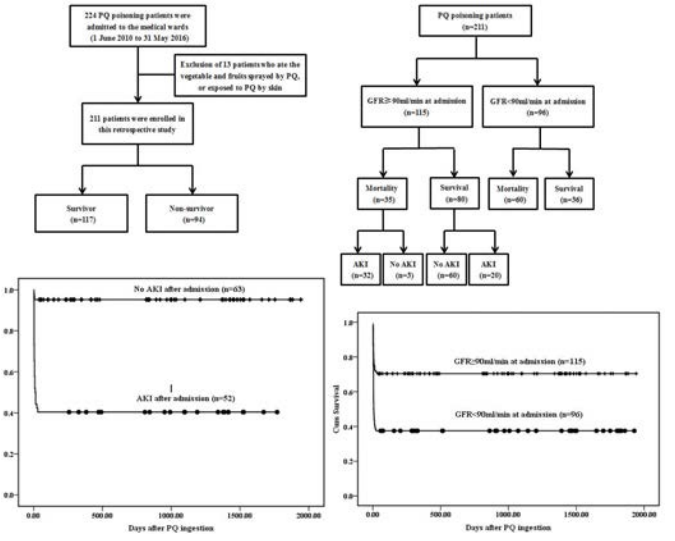
PUB052

Analysis of Prognostic Factors in Patients with Paraquat Poisoning for Optimal Therapy Regimen Ying Xu, Jingyun Le, Jianghua Chen. *The Kidney Disease Center, The First Affiliated Hospital, School of Medicine, Zhejiang Univ, Hangzhou, Zhejiang, China.*

Background: Paraquat (PQ) is an effective quaternary nitrogen herbicide which is highly toxic to human. The purpose of this study was to identify prognostic factors after PQ poisoning and discuss the efficacy of current therapy regimen.

Methods: In this retrospective study, 211 cases admitted to our hospital between 1 June 2010 and 30 April 2016 were enrolled. The demographic characteristics, medical records of clinical features, laboratory parameters, therapy regimen and the prognosis were retrospectively analyzed.

Results: The overall survival rate was 55.45%. The mean age was 35.85 years with 55.45% being female. The average amount of PQ ingestion was 30.79 ml. Twelve Patients who ingested PQ combined with alcohol had a higher survival rate. The patients in survival group ingested less amount of PQ, presented with lower serum creatinine level and higher glomerular infiltration rate at admission, developed lower incidence of acute kidney injury and pulmonary CT deterioration. As to the therapy regimen, the survivors were treated with higher dosage of methylprednisolone, daily dose of aspirin, daily dose of rapamycin and lower daily dose of vitamin C. The frequency of hemoperfusion was much more in the survival group. The Cox regression analysis demonstrated that larger amount of PQ ingested (HR 1.006, *P*=0.003), abnormal renal function at admission (HR 12.540, *P*=0.001) or developed AKI after admission (HR 21.327, *P*<0.001) were the independent risk factor. Higher dose of methylprednisolone (HR 0.577, *P*<0.001) and aspirin (HR 0.998, *P*=0.027) were independent protective prognostic factor .



Conclusions: The non-survivor characteristics are larger amount of PQ ingestion, manifestation of abnormal renal function at admission or developed AKI after admission, whereas the survivor characteristics are higher dose of methylprednisolone and aspirin.

PUB053

Ionomic Profile as a Biomarker for Acute Kidney Injury after Cardiac Surgery Ziyan Shen,[1,2,3] Xiaoyan Zhang,[1,2,3] Jie Teng,[1,2,3] Xiaoqiang Ding.[1,2,3] *[1]Dept of Nephrology, Zhongshan Hospital, Shanghai Medical College, Fudan Univ, Shanghai, China; [2]Kidney and Dialysis Inst of Shanghai, Shanghai, China; [3]Kidney and Blood Purification Laboratory of Shanghai, Shanghai, China.*

Background: Ion transportation, one of the fundamental renal tubular functions, is veiled during acute kidney injury (AKI). This study is aimed to map the urinary ionomic profile of patients with AKI after cardiac surgery in order to screen out representative ions and set up an ionomic model to early diagnose AKI after cardiac surgery.

Methods: A total of 261 patients undergoing cardiac surgery were recruited. Urine samples of pre-operation and 2h, 12h, 24h and 48h after operation were collected. Urinary concentration of 18 ions were measured by inductively coupled plasma spectroscopy (ICP-MS) and adjusted by urinary creatinine. AKI was diagnosed according to KDIGO guideline.

Results: Urinary concentration of 18 ions changed dynamically during perioperative period of cardiac surgery, especially at 2h after operation. The urinary concentrations of Cu, Pb, Al, Zn, Cd, Co, Tl, Ba, V, Ga, Se, W, U at 2h after operation were significantly higher than those of pre-operation, whereas B, As, Sr, Pd at 2h after operation were significantly lower than pre-operation. At 48h after operation, urinary ionic concentration gradually recovered to preoperative levels. There was remarkable difference in urinary ionomic profile between AKI and non-AKI groups during the perioperative period. Urinary Ion Index (UII) model to early diagnose AKI was established by bioinformatic method. Prediction equation is as following: 0.21× lg(urinary Fe at 2h after operation) + 0.32×lg(urinary Cd at 2h after operation). The cutoff value of UII was 1.85 and AUC was 0.76±0.11, while the sensitivity, specificity and accuracy were 0.61±0.17, 0.97±0.09 and 0.82±0.08, respectively.

Conclusions: Urinary ionic concentrations change dynamically during perioperative period of cardiac surgery. There is remarkable difference in urinary ionomic profile between AKI and non-AKI groups. Urinary Fe and Cd at 2h after operation can be used efficiently to construct the early diagnosis model for AKI after cardiac surgery with considerable accuracy.

PUB054

A Case of Atypical Hemolytic Uremic Syndrome Presenting as Dermatomyositis and Complicated with Viral Infections I-Ru Chen,[1] Han-Mou Tsai,[2] Hsin Hung Lin,[1] Chiu-Ching Huang.[1] *[1]Kidney Inst and Div of Nephrology, Dept of Internal Medicine, China Medical Univ Hospital, Taichung City, Taiwan; [2]MAH Hematology Associates, New Hyde Park, New York.*

Background: Atypical hemolytic uremic syndrome (aHUS) usually presents with the triad of acute renal failure, thrombocytopenia and microangiopathic hemolytic anemia (MAHA). It is unusual to present with features of dermatomyositis without the triad.

Methods: A 41 years old woman was admitted for fever, polyarthralgia, proximal limb weakness, erythematous rashes, heliotrope rashes, periungual erythema and Gottron's papules. Her LDH, ALT, CPK, amylase, lipase and CRP were elevated but her platelet count and serum Cr were not. Serology testing failed to detect any autoantibodies. Four days later she lost her left visual acuity, platelet count decreased to 53x10^9/L, Cr increased to 1.64 mg/dL and LDH increased to 1659 from 537 IU/L. Despite daily plasma exchange her platelet count further decreased. Hemodialysis was started for oliguria and pulmonary edema. She then developed seizure, altered mental status and respiratory failure that required endotracheal intubation. Eculizumab was given on day 20, her general status improved and her leukocytosis resolved. Yet her fever persisted and her platelet count, after increasing

to a maximum of $58x10^9$/L, failed to normalize after two weekly doses of eculizumab. Extensive microbiological investigation revealed by PCR herpes simplex virus type 1 and CMV viremias. Neither was detected in a saved blood sample of day 14.

Results: Four days after adding acyclovir, before ganciclovir was instituted, her platelet count normalized. Fever resolved after 3 weeks of anti-CMV therapy. Her skin rashes subsided and her Cr normalized after 8 doses of eculizumab therapy. Kidney and skin biopsies showed thrombotic microangiopathy. Gene sequence analysis detected a CFH miss-sense mutation (G936A).

Conclusions: aHUS may present with features mimicking dermatomyositis. Our case is also unusual in that its course was complicated with viremia of HSV and CMV. In a case of aHUS, lack of expected responses to anticomplement therapy should prompt rigorous searches for concurrent illnesses.

PUB055

Phenotype of Proton Pump Inhibitor Associated Drug Induced Kidney Disease (DIKD): Results from the DIRECT Study Linda Awdishu,[1] Rajasekara Chakravarthi Madarasu,[2] Stuart Goldstein,[3] Ashita J. Tolwani,[4] Melanie S. Joy,[5] Etienne Macedo,[1] Dinna Cruz,[1] Jorge Cerda,[6] David T. Selewski,[7] Michael Zappitelli,[8] Andrew J.P. Lewington,[9] Maria Ostermann,[10] Vivekanand Jha,[11] Ravindra L. Mehta.[1,12] *[1]Univ of California, San Diego; [2]Star Kidney Centers; [3]Cincinnati Children's Medical Center; [4]Univ of Alabama at Birmingham; [5]Univ of Colorado, Denver; [6]Albany Medical College; [7]Univ of Michigan; [8]McGill Univ Health Centre; [9]Leeds Teaching Hospital; [10]Guy's and St. Thomas' Hospital; [11]Postgraduate Inst of Medical Education and Research; [12]On Behalf of the DIRECT Investigators.*

Background: Proton pump inhibitors (PPIs) have strong evidence for efficacy and a favorable side effect profile. However, there are concerns given overprescription and recent association of chronic kidney disease with PPI use.

Methods: DIRECT is an international multi-center study which enrolled 634 patients with DIKD to identify drug-related polymorphisms by GWAS studies that were associated with standardized phenotypes. Each presumed PPI case was adjudicated by 2 nephrologists.

Results: PPI associated DIKD cases (N=28) were confirmed by adjudication (21 adult and 7 pediatric patients). Implicated PPI's were omeprazole (N=9,22.2±6.7mg), esomeprazole (N=3,20 mg), lansoprazole (N=5,27±6.7mg) and pantoprazole (N=10,38±6.3mg). Patients were 43% male with mean age of 51.6±20 years in adults and 12.6±3.3 years in pediatrics. Subjects were 79% white, 11% black and 11% asian. Co-morbidities included hypertension, diabetes and cancer in adults and hypertension, cancer and liver disease in pediatrics. The mean Scr increased from 0.99±0.47 to 3.76±2.22mg/dL in adults and 0.34±0.22 to 1.14±0.46 mg/dL in pediatrics. Median (IQR) time to onset was 6 (3-14) days. Common risk factors were hyperglycemia and additional nephrotoxic exposures. Biopsies were performed in 29% demonstrating interstitial nephritis in 75% of cases. However, blood eosinophils were within normal range (2.0±1.5%). Dialysis was required for 14.3% of cases. Mortality was 3.7% and 13.6% at hospital discharge and 90 days.

Conclusions: PPIs may cause interstitial nephritis in susceptible caucasian patients at standard doses.

Funding: Private Foundation Support

PUB056

Biomarkers Utilization to Detect Subclinical Kidney Injury in Acute Stroke: Organ Cross-Talk Begoña Campos, Anthony C. Leonard, Charuhas V. Thakar. *Nephrology, Univ of Cincinnati, Cincinnati, OH.*

Background: Acute kidney injury (AKI) affects 25% of patients admitted with stroke, predicts high mortality. Recent study shows that 10% of stroke patients have unrecognized chronic renal insufficiency, which predicts poor outcomes. Neutrophil gelatinase associated lipocalin (NGAL) has been used as a reliable kidney injury biomarker, which predicts both AKI and clinical outcomes. Animal studies show that this protein is expressed early and highly induced in the kidney after ischaemic or nephrotoxic AKI. In this study we evaluate if NGAL could be used to detect subclinical Kidney injury in patients suffering from other vital organ ischemia; acute stroke.

Methods: Based on the established knowledge of NGAL, we studied the occurrence of subclinical kidney injury. In a prospectively collected biological repository of eligible acute stroke subjects (2013-14), there were 38 cases of stroke (14 Ischemic; 24 hemorrhagic). Demographic, comorbid and laboratory variables were collected at the time of admission with stroke, along with de-identified plasma samples for biomarker assays. We assayed the samples for NGAL based on established methods.

Results: Based on literature, we chose 150 ng/ml as the upper limit of normal baseline NGAL in plasma. As shown in Table 1 of the 31 patients with baseline creatinine of < 1.2 at the time of stroke, 4 (12%) already had positive biomarker levels (range 151 to 248 ng/ml) indicating subclinical kidney injury. 1/4 patients with subclinical injury went on to develop clinically apparent AKI. Median NGAL levels were significantly different across stroke patients with baseline creatinine of < or >/= 1.2 mg/dl (71.2 vs 154.5, p = 0.01).

	Biomarker -ve (NGAL < 150 ng/ml)	Biomarker +ve (NGAL >/= 150 ng/ml)	N
Creatinine <1.2	27	4 (subclinical Injury)	31
Creatinine >1.2	3	4	7
TOTAL	30	8	38

Conclusions: NGAL levels at the time of acute stroke may indicate subclinical kidney injury and suggest vital organ cross talk. Biomarker utilization can discriminate those patients with subclinical kidney injury. Larger studies with longitudinal follow up are needed to examine the biomarker-based risk stratification in vital organ ischemia.

PUB057

Acute Kidney Injury Result from Rhabdomyolysis and Continuous Renal Replacement Therapy Meng Wang, Hongli Jiang, Hua Liu, Quan He. *Blood Purification, The First Affiliated Hospital of Xi'an Jiaotong Univ, Xi'an, Shaanxi, China.*

Background: Rhabdomyolysis(RM) can lead to acute kidney injury(AKI) as a life-threatening complication. Whether to use continuous renal replacement therapy(CRRT) or not for RM is still controversial. We aim to assess risk factors for AKI and evaluate further if the CRRT is effective.

Methods: 57 cases of RM were selected from our hospital (August 2013 - May 2016). Logistic regression analyses were performed to determine risk factors for AKI by collecting the medical records. All patients received etiological and rehydration therapy. Meanwhile, 32 patients received more than 24 hours of CRRT. Laboratory datas such as concentrations of myoglobin (MB), creatine kinase (CK), creatine kinase isoenzyme-MB (CK-MB), lactic dehydrogenase (LDH), aspartate aminotransferase (AST), lanine transaminase (ALT) in blood and CRRT effluents were collected.

Results: The incidence of AKI was 40%. Logistic regression analysis showed hypoalbuminemia, hypocalcemia, urine protein test positive were independently associated with AKI (p<0.05). Duration of CRRT and hospital stay were significantly higher among patients with AKI, compared with patients without AKI (p<0.05). After 24 hours of treatment, comparing with the conventional treatment patients, the concentrations of serum MB, CK, CK-MB, LDH, AST, were significantly decreased in the CRRT intervention patients (p<0.05), but there was no statistically significance in ALT level. Concentrated CRRT effluents were detected that the concentrations of the CK, CK-MB, LDH, AST, and ALT were trace amounts.

Conclusions: Prevention of AKI is important for RM patients, especially for patients with hypoalbuminemia, hypocalcemia and urine protein test positive, for whom CRRT could be a benefical intervention. CRRT could remove MB out of blood circulation directly, while the macromolecular metabolism products such as CK, CK-MB, LDH, AST, couldn't remove directly, but their serum levels were significantly decreased in CRRT intervention patients. It was suspected associating with retarding progression and helping improving metabolic function of body. Further studies and more datas are required to confirm the mechanism.

PUB058

The Impact of Elevated Preoperative Serum Creatinine on Acute Kidney Injury following Cardiac Surgery and the Protective Role of Dopamine Xuxia Gao,[1] Xinbao Yao.[2] *[1]Internal Medicine, Beijing Anzhen Hospital, Capital Medical Univ, Beijing Inst of Heart, Lung and Blood Vessel Diseases, Beijing, China; [2]Pharmacy, Beijing Anzhen Hospital, Capital Medical Univ, Beijing Inst of Heart, Lung and Blood Vessel Diseases, Beijing, China.*

Background: Preoperative renal function is an independent risk factor for Acute kidney injury (AKI) following cardiac surgery. The objective of this study is to investigate the impact of elevated preoperative serum creatinine (Scr) on AKI, and the protective effect of dopamine.

Methods: 1700 patients undergoing cardiac surgery in Beijing Anzhen Hospital from March 2008 to October 2008 were analyzed retrospectively. AKI was defined as a ≥ 50% or 26.5μmol/L increase in Scr from the preoperative value. The AKI patients (n=264) were divided into normal (n=191) and elevated Scr group (n=73) according to preoperative Scr; 124 patients with elevated Scr and complete clinical records were divided into Control (n=18) and Dopamine group (n=106, dopamine was administered postoperatively in 10 to 15mg/h for 1 to 5 days). The prevalence, the recovery of AKI, and the length of stay in the intensive care unit (ICU) were compared by chi-square test or student t-test; Risk factors were determined by multivariable logistic regression analysis.

Results: 264 of 1700 cases (15.5%) suffered from AKI. Compared to the normal Scr group, the prevalence of AKI increased (44.2% vs 12.4% , P<0.05), and the recovery rate of AKI (postoperative Scr went down to the preoperative level in 7 days)decreased (30% vs 68.8%, P<0.05) significantly in the elevated Scr group. Multivariable analysis revealed that elevated Scr (OR: 1.39, 95% CI: 1.22, 1.57)and older age (OR: 1.08, 95% CI: 1.00, 1.16) were risk factors for this difference. Between Dopamine and Control groups, pre- and intra-operative variables were comparable. Compared to Control, the prevalence of AKI decreased (36.8% vs 66.7%, P<0.05), and the length of stay in ICU was shortened (33±3.6h vs 74±45.5h, P<0.05) significantly in Dopamine group.

Conclusions: Elevated preoperative Scr increases the prevalence of AKI and make AKI more difficult to recover. Lower dose of dopamine may have protective role on AKI in patients with elevated preoperative Scr.

Funding: Government Support - Non-U.S.

PUB059

Prevalence and Severity of Depression among Patients with Pregnancy Related AKI Presenting to a Tertiary Care Hospital of a Developing Country
Syed Rizwan A. Bokhari,[1] Zumar Sardar,[1] Sidra Saleem,[1] Khalid Tahir,[1] Abeera Mansur.[2] *[1]Nephrology, Allama Iqbal Medical College/ Jinnah Hospital, Pakistan; [2]Nephrology, Doctors Hospital and Medical Center, Pakistan.*

Background: Acute kidney injury (AKI) in pregnant women is commonly seen in developing countries. It is associated with significant morbidity, social and personal implications. We conducted a study to assess the prevalence and severity of depression in patients with pregnancy related AKI (PRAKI) in a tertiary care center.

Methods: Patients with PRAKI admitted from 1-16 to 6-16 under Nephrology service, Jinnah Hospital, Lahore, Pakistan were included in this cross sectional study. The Hamilton Rating Scale for Depression (HAM-D) version translated and adapted in Urdu, was used to assess the study population. These patients were interviewed with the (HAM-D) questionnaire on their first encounter with Nephrology. Previous history of psychiatric illness was excluded. The diagnosis of AKI was based on the classification of the Acute Kidney Injury Network group.

Results: The mean age of the patients was 24±5 years. Seventeen (57%) patients were multipara and 13(43%) were prim gravida. Of the 30 patients with AKI, 8 (27%) presented before 28-weeks and 22 (63%) patients after 28-weeks of gestation. The cause of AKI included postpartum hemorrhage in 9 (30%), sepsis in 8 (27%), preeclampsia/eclampsia in 6(20%), shock in 4(13%) and coagulopathy in 3(10%) of patients. Alive and heathy fetus was found in only 15 (50%) of patients. Twenty-one (70%) patients received average of 5-8 hemodialysis sessions during their hospital stay. Twenty-three (76 %) had no depression (0-7 score), 2 (7%) had mild (8-13 score), 3 (10%) had moderate (14-18 score) and 2 (7%) had severe (19-22 score) depression according to HAM-D score.

Conclusions: Our study depicted considerable depression of varying degrees in women with PRAKI. Increased awareness and effective monitoring for depression should be integrated into regular maternal care to decrease morbidity associated with it.

PUB060

Incidence of Chronic Renal Replacement Therapy after Acute Kidney Injury at a University Hospital in Northeastern Mexico
Mara Cecilia Olivo, Lilia Maria Rizo Topete, Jesus Cruz Valdez. *Nephrology, Hospital Univ Dr. Jose Eleuterio Gonzalez, Monterrey, Nuevo Leon, Mexico.*

Background: Acute kidney injury (AKI) is a condition that affects 1 in 7 patients admitted to hospital and it can be prevented. AKI can occur in any clinical condition, increasing mortality and hospital costs.

Methods: Prospective, cross-sectional, descriptive study. Hospitalized patients who requires interconsultation by the Nephrology Department from March 2015 to March 2016 were included.

Results: 942 patients were included, 387(41%) developed AKI or AKI over Chronic Kidney Disease (CKD),56% were male, mean age 52.1 years (SD 17.5). The most frequently comorbidities: Diabetes Mellitus 39%, Hypertension 38.2% and obesity 13.9%. The main causes of AKI: 32% pre-renal, 27% infectious and 17% heart disease. Mortality in critical ill patients with AKI was 63%. 198 patients developed AKI, 46.5% required acute renal replacement therapy (RRT), 43.4% died, 30.4% of them recovered renal function without RRT and 26% requiring chronic RRT. 189 patients developed AKI over CKD, 46.5% of them required acute RRT, 28.5% died, 31.8% recovered renal function without RRT required with an average creatinine of 2.5(SD 1.22) at discharge and 39.7% developed ESRD requiring chronic RRT.

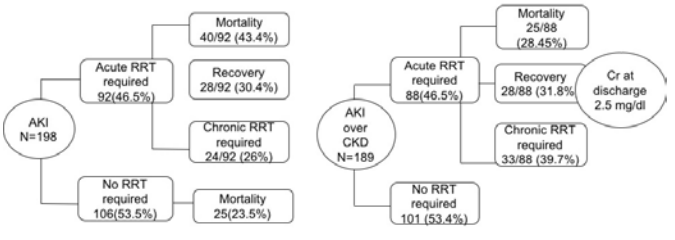


Figure 1. Renal Replacement Therapy in patients with AKI

Chi square was used to find the difference between the need of RRT among patients with AKI vs AKI over CKD (p=0.15). The global mortality associated with AKI was higher (32.8%) than in patients with AKI over CKD (13.3%) (p=0.001).

Conclusions: No difference between group AKI and AKI over CKD to continue in chronic RRT, however in relation to mortality there is a significant difference between AKI against AKI over CKD, beeing higher in the fist one. This relates in our hospital with the critically ill patient, and can be compared with other international statics.

PUB061

Rituximab Is Effective Treatment for Small Vessel Vasculitis in Absence of Circulating ANCA
Leanne A. Ogden, Ajay Prabhakar Dhaygude. *Renal Unit, Royal Preston Hospital, Preston, United Kingdom.*

Background: The antibody depleting monoclonal antibody Rituximab has been shown to be effective in ANCA associated vasculitis, as shown by the RAVE and RITUXVAS studies. Rituximab, apart from B cell depletion, facilitates B cell/T cell interaction. B cells are also known to be present in tissue infiltrate without being detected peripherally. Literature suggests ANCAs are absent in up to 10% of cases and the efficacy of Rituximab in these patients is a rarely studied group.

Methods: This retrospective, single centre study reviewed the case notes of all patients with vasculitis who were treated with rituximab and were ANCA negative at the time of treatment.

Results: 10 patients were identified, all Caucasian. Results shown in table

ANCA status at presentation (%)	Anti-PR3 (50) Anti-MPO (10) ANCA negative (40)
Organ Involvement (%)	Renal (60) Multisystem (70)
Dialysis Required (% of those with renal involvement) - at presentation	50
Mean eGFR at treatment commencement (renal involvement, dialysis independent) (mls/min)	28
Mean eGFR at follow up (renal involvement, dialysis independent) (mls/min)	32

Indications for rituximab were cyclophosphamide resistance in 9(90%). 1(10%) patient had suspected urothelial malignancy. Mean age at presentation was 60 (range 35-77 years). 1g of Rituximab was given fortnightly, with a mean cumulative dose of 4.5g of rituximab. 7 (70%) patients achieved remission following rituximab treatment. 2 (20%) patients achieved partial remission (1 had destructive ENT granulomatous disease and 1 developed AA amyloid secondary to vasculitis). 1 (10%) died whilst receiving rituximab treatment as a result of a perforated bowel.

Conclusions: This retrospective study supports the use of rituximab in the absence of circulating autoantibodies and has shown:70% complete remission; 20% partial remission; 10% mortality. Of those with renal involvement 1(16%) has remained dialysis dependent. The treatment was tolerated well with no infections requiring hospital admission. To the best of our knowledge this is the largest published series in use of rituximab in ANCA negative patients.

PUB062

The Relationship between the Hourly Urine Output and the Clinical Outcome in Nontraumatic Exertional Rhabdomyolysis
Won Jae Shin, Young-Il Jo. *Div of Nephrology, Dept of Internal Medicine, Konkuk Univ Medical Center, Seoul, Republic of Korea.*

Background: Early and aggressive fluid resuscitation is required for the prevention of acute kidney injury (AKI) in rhabdomyolysis. However, the optimal fluid and rate of repletion are unclear. The purpose of this study is to evaluate the relationship between the degree of diuresis and the clinical outcomes in nontraumatic exertional rhabdomyolysis.

Methods: We reviewed the medical records of patients who were diagnosed with nontraumatic exertional rhabdomyolysis from January 2011 to December 2015 in Konkuk university medical center. Total 40 cases were analyzed.

Results: Patients were categorized according to the hourly urine output during initial 48 hours; the low urine output (< 200 mL/hr) and the high urine output (>200 mL/hr) group. No significant differences were noted between two groups in initial levels of CPK, serum myoglobin, and creatinine. The hourly urine output was significantly high in the high urine output group (143.7±36.71 vs 291.0±79.08, p<0.001). The clinical outcomes including maximal level of CPK, incidence of AKI and mean hospital stay showed no significant differences between two groups.

Table 1. Group comparison

	The low urine output group(< 200ml/hr)	The high urine output group(> 200ml/hr)	P-value
Number	13	27	
Hourly urine output (ml/hr)	143.74 (121.56-165.92)	291.07 (259.79-322.36)	0.000
Amount of initial hydration (ml/kg/hr)	2.51 ± 0.73	4.62 ±1.58	0.000
CPK, initial (U/L)	45097.00 ± 44495.17	59969.78 ± 41900.85	0.309
CPK, maximum (U/L)	46853.15 ± 44439.95	56263.85 ± 38803.11	0.497
Creatinine, initial (mg/dL)	1.25 ± 1.32	1.04 ± 0.96	0.566
AKI, initial (number [%])	2 (15.38)	2 (7.41)	0.584
AKI, developed (number [%])	1 (7.69)	0 (0.00)	0.325
Use of bicarbonate for treatment (number [%])	3 (23.08)	10 (37.04)	0.484
Mean hospital stay (day)	8.38 ± 8.04	7.07 ± 2.87	0.451

Conclusions: Our results indicated that we should not effort to maintain the desired diuresis of approximately 200 to 300 mL/hour for prevention of AKI in nontrumatic exertional rhabdomyolysis.

PUB063

Kidney Function in Patients with Acquired Thrombotic Thrombocytopenic Purpura: Initial Presentation and Long-Term Outcomes Dustin J. Little,[1] Evaren E. Page,[2] Lauren M. Mathias,[2] Sara Vesely,[2] James George.[2] *[1]Walter Reed National Military Medical Center, Bethesda, MD; [2]Univ of Oklahoma Health Sciences Center, Oklahoma City, OK.*

Background: Little is known about the incidence, severity, and significance of AKI among TTP patients. In 2003, we used a simple SCr- and RRT-based OK AKI criteria to report low rates of AKI among TTP patients in the Oklahoma TTP registry. A recent report of high rates of severe AKI among TTP patients may be limited by referral bias as all subjects were admitted to the ICU of a single tertiary care medical center. Additionally, long-term renal and health outcomes following TTP complicated by AKI have not been reported. We analyzed kidney function of patients enrolled in the OK TTP registry, using both the OK and KDIGO criteria for AKI diagnosis and staging, and investigated for associations between AKI and subsequent CKD.

Methods: Acquired autoimmune TTP was diagnosed among patients referred to the Oklahoma Blood Institute, by identifying severe (<10%) ADAMTS 13 deficiency with the presence of an inhibitor or increased ADAMTS13 activity to >10% during remission. AKI was diagnosed and staged via the previously published OK and KDIGO criteria. eGFR was calculated using the CKD-EPI equation.

Results: The diagnosis of TTP was confirmed in 75 patients enrolled in the registry from 1995-2014. Rates of overall and severe AKI were 59% and 9% by KDIGO and 50% and 7% by OK criteria, respectively. Compared to subjects without AKI, initial mortality rates were significantly increased in OK (8/40 vs. 1/35; p=0.03) but not KDIGO AKI patients. eGFR of <60 mL/min/1.73m^2 at follow-up was more common among survivors with AKI by OK criteria (6/32 vs. 0/32 without AKI; p=0.02), but not by KDIGO criteria.

Conclusions: AKI is common among TTP patients, but severe AKI is rare. A simple, SCr-based OK criteria better identified patients at risk for early mortality and decreased eGFR at follow-up, when compared to KDIGO. Our study provides the most complete and comprehensive description of AKI and long-term renal outcomes in TTP patients, and provides clinicians with important information to facilitate prognostic discussions and inform monitoring strategies in patients with a history of TTP.

PUB064

Incidence and Risk Factors of Acute Kidney Injury after Femur Fracture Surgery Young Ju Na, Sang-Kyung Jo, Won-Yong Cho, Myung-Gyu Kim, Sung Yoon Lim, Jihyun Yang. *Nephrology, Korea Univ Anam Hospital, Seoul, Korea.*

Background: As the aging population increases, the number of patients with femur fractures caused by falling and traffic accidents is also increasing. It is known that mortality is high as well as the clinical course and prognosis are not good when acute kidney injury(AKI) is shown in the femur fracture patients. Nevertheless, there are not enough studies about AKI from the femur fracture patients. In this study, we want to show the correlation between the incidence and risk factors of AKI in patients with femoral fracture.

Methods: We retrospectively evaluated the medical records of 311 patients who were operated on for femoral fracture at Korea University Anam Hospital between January 2012 and October 2015. We evaluated the Incidence and Risk factors of AKI after Femur Fracture surgery and compared between AKI and normal kidney function (NKF) groups.

Results: The overall incidence of AKI was 9.2%. When compared to the normal kidney function (NKF) groups, the AKI group had a higher incidence of anemia (86.4% vs 51.6%, p = 0.001), hyponatremia (31.8% vs 13.4%, p = 0.021), ESR (45.5% vs 10.6%, p = 0.000), use of contrast agent (27.3% vs 6.9%, p = 0.001).

In logistic regression analysis of risk factors, age (p = 0.049), lower estimated glomerular filtration rate levels (p = 0.05), contrast use(p = 0.04), diabetes mellitus (p = 0.002), heart failure (p = 0.012) were statistically significantly correlated with the development of AKI.

Conclusions: AKIafter femur fracture was associated with longer hospitalization, morbidity and mortality. It is recommended that close evaluation and monitoring is needed for patients who have the risk factor of AKI after operation for femur fracture to reduce the possibility of AKI. In the future, We need prospective studies including biomarkers.

Funding: Private Foundation Support

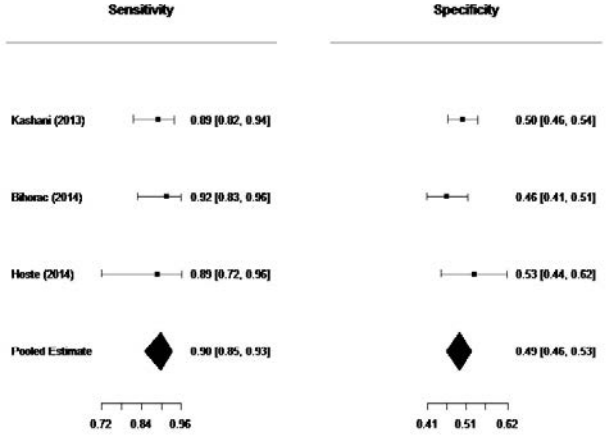
PUB065

Diagnostic Accuracy of the NephroCheck for Acute Kidney Injury in Critical Care: Systematic Review and Meta-Analysis Andrew J.P. Lewington,[1,2] Elizabeth D. Mitchell,[3] Judy M. Wright,[3] David Allan Cairns,[3] Michelle Hutchinson,[3] Michael P. Messenger,[2,3] Claire Louise Corps,[1] David M. Meads,[3] Alison F. Smith,[2,3] Rebecca L. Kift,[1,2] Linda Sharples,[3] Patrick Hamilton,[4] Aleksandra Sobota,[3] Peter S. Hall.[2,5] *[1]Leeds Teaching Hospitals NHS Trust, United Kingdom; [2]NIHR Diagnostic Evidence Cooperative Leeds, United Kingdom; [3]Uni of Leeds, United Kingdom; [4]Uni of Manchester, United Kingdom; [5]Uni of Edinburgh, United Kingdom.*

Background: New diagnostics for early diagnosis of acute kidney injury (AKI) are needed. The Nephrocheck® test (ASTUTE Medical, San Diego, CA) combines two urine biomarkers metalloproteinase inhibitor 2 and Insulin-like growth factor-binding protein 7. Independent analysis is needed for evidence-based clinical adoption policy. We therefore conducted a systematic review and meta-analysis of clinical validity, efficacy, utility, and cost-effectiveness in critical care.

Methods: The search looked at 12 databases and 2 trials registers in Nov 2015 with pre-defined eligibility criteria and quality assessment (QUADAS-2) by 2 reviewers. Meta-analysis used Bayesian hierarchical regression to estimate joint pooled sensitivity and specificity for AKI KDIGO stages 2–3 within 12 hours. Prospectively registered on PROSPERO ref. CRD42014013919.

Results: The search identified 122 original articles of which 29 were subject to full text review. Ten studies were included in the review; and 3 in the meta-analysis. The mean participant median age was 64 years and 58% were male. Using the high sensitivity cut-off (0.3), pooled sensitivity was estimated as 0.90 (95% CI 0. 85-0.93) and pooled specificity as 0.49 (95% CI 0.46-0.53) (Figure 1). No clinical efficacy, clinical utility or cost-effectiveness studies were identified.



Conclusions: Nephrocheck has high sensitivity and moderate specificity for AKI in adult critical care settings. Further research to estimate clinical utility and cost-effectiveness is worthwhile.

Funding: Government Support - Non-U.S.

PUB066

The Lifespan of CRRT Dialyzer Is Proportional to Bleeding Diathesis in DIC Jae Seok Kim,[1] Byoung Geun Han,[1] Seung-Ok Choi,[1] Min Keun Kim,[1] Minseob Eom,[2] Jae Won Yang.[1] *[1]Internal Medicine, Yonsei Univ Wonju College of Medicine, Wonju, Republic of Korea; [2]Pathology, Yonsei Univ Wonju College of Medicine, Wonju, Republic of Korea.*

Background: CRRT needs continuous systemic anticoagulation to maintain extracorporeal circuit. But, frequent dialyzer clotting reduces the efficiency of CRRT. Therefore, we aim to investigate which conditions contribute to frequent dialyzer clotting and dialyzer lifespan.

Methods: We investigated retrospectively the medical records of thirty patients who had been received CRRT. Heparin was used primarily for circuit anticoagulation in 4 patients, and nafamostat mesilate was used alternatively in 26 patients. We investigated clinical situations, CRRT prescriptions and basic blood tests including DIC profile. Dialyzer lifespan was calculated as: CRRT maintenance time (hours) divided by the frequency of dialyzer membrane clotting. In addition, we estimated DIC severity by ISTH DIC scoring system.

Results: The results showed that D-dimer and FDP had significant positive correlations with dialyzer lifespan respectively (r=0.38, p=0.048 / r=0.40, p=0.041), while hemoglobin concentration, platelet count, PT and activated PTT did not show the relationships with diaylzer lifespan. Transfusion of packed RBC, fresh frozen plasma and platelet concentrate did not show the relationships with dialyzer lifespan, and clinical severity including initial mean blood pressure, urinary amount and APACHE score also had no relationships. CRRT prescription including CRRT dose, blood flow and type of anticoagulation had no correlations with diaylzer lifespan. When compared with non-DIC group (n=20), DIC group (n=10) had longer dialyzer lifespan, but did not quite achieve statistical significance (DIC vs. non-DIC, 48.0±19.5 vs. 33.4±18.3 hours, p=0.052). When compared with non-sepsis group (n=11), sepsis group (n=19) had shorter dialyzer lifespan significantly (sepsis vs. non-sepsis, 32.2±16.1 vs. 48.8±21.3 hours, p=0.022).

Conclusions: Our study indicates that the more DIC gets worse, the less dialyzer clotting is frequent in CRRT. We believe that local predisposition to bleeding in DIC may play a role in preventing dialyzer clotting although PT and activated PTT had no significant relationships with it.

PUB067

Clinical Case with Interstitial Nephritis Induced by Mycophenolate Mofetil Valentin Ch. Ikonomov, Miroslava Stancheva Benkova, Aleksandar Aleksandrov Petrov, Iliana Georgieva Teodorova, Petar Petrov. *Clinic of Nephrology Acute and Peritoneal Dialysis with Apheresis and Transplantation, Univ Hospital "St. Marina" , Medical Univ Varna, Varna, Bulgaria.*

Background: Acute interstitial nephritis (AIN) is an inflammatory disease, characterized with generalized or local infiltration of the renal interstitium with T-lymphocytes, macrophages, eosinophilia and plasmic cells. The most common causes

of AIN are: drug-induced nephropathy, infections, autoimmunology diseases, cancer, and idiopathic interstitial nephritis. The cell-mediated response is more important than the humoral induced acute interstitial nephritis. For the definite diagnosis, a kidney biopsy is indicated. Microscopic linear or granular deposition of immunoglobulins and complement in the interstitium and/or on the tubule basal membrane is characteristically linked to AIN. Key in the treatment is to identify the agent/drug, causing the disease and apply low-dose steroid therapy for 4 to 6 weeks. Alternative to corticosteroids is MMF.

Methods: Here we introduce the clinical case of a 45-years old woman with previously proven chronic membranous nephropathy, treated with Mycophenolate mofetil for 3 months. The patient worsened her renal function (urea 22,5 mmol/l, creatinine 909 µmol/l), which led to additional acute morphological examination. The renal biopsy has shown focal lymphocyte infiltration in the interstitium and tubular atrophy, without immunofluorescent deposition of globulins.

Conclusions: Discontinuation of the treatment with Mycophenolate mofetil, corticosteroid infusion and dialysis improved the renal function, reaching the normal levels for the patient – creatinine 200 µmol/l.

PUB068

Epidemiology of Acute Kidney Injury in an American Inner City Population

Justin Lee Loy,[1] Gayatri Lessey,[1] Osezua J. Olear,[1] Michael A. Fischman,[1] Bhupinder K. Prajapati,[1] Muner Mohamed,[1] Asana Anderson,[1] Alan D. Weinberg,[2] Jonathan M. Barasch,[3] Subodh J. Saggi.[1] *[1]Nephrology, SUNY Downstate Medical Center, Brooklyn, NY; [2]Biostatistics, Mount Sinai School of Medicine, New York, NY; [3]Nephrology, Columbia Univ, New York, NY.*

Background: Data on incidence of AKI in hospitalized patients can be extracted based on ICD codes. While these databases give insight into distributions of AKI across different populations, age groups, gender and race during different time periods, they are limited in being retrospective with fragmented information on patient details. We prospectively conducted a study on hospitalized patients with specific details over a 3 year period to define our population phenotype to validate roles of biomarkers in AKI. We report the epidemiological characteristics of our predominantly African American (AA) inner city population who developed AKI.

Methods: Patients had their initial plasma, serum and urine stored for bio-banking. We gathered data on age, gender, race, BMI, DM, HTN, CKD, CHF, length of stay and medications given. Analysis was done by SAS 9.3, Chi square analysis and student "t" test.

Results: Mean age was 59±18 years, male:female ratio 1.4:1, 93% were AA, mean BMI 28±7.4, 33% DM, 69% HTN, 17% CHF and 25% CKD (eGFR <60 ml/min/1.73^2 BSA). AKI was identified in 8.82%, was associated with DM p=0.05, HTN p=0.005 and polypharmacy p= 0.0003. Average number of medications in patients with AKI was 12. CKD and DM were strongly associated p=0.012 but CKD with new AKI was not p=0.15. Incidence rate ratio of AKI was 25% at baseline, 30.4% on admission, 32% on Day 3.

Conclusions: There was a higher rate of AKI on admission in our population (~2%) and a 2% increase in incidence rate ratio by Day 3. An association was found between being diabetic and hypertensive. Preexisting CKD was not associated with AKI perhaps due to the inability to detect AKI by traditional methods at baseline or by day 3 using AKIN criteria. This suggest the value of using biomarkers to capture this population. It seems that patients on more than 8 medications and with hospital stays beyond 3 days are specifically vulnerable to AKI, the latter due to excess pharmacological exposure.

PUB069

Incidence of Hypocalcemia in Pediatric Patients Receiving Continuous Renal Replacement Therapy and Tandem Therapeutic Plasma Exchange

Tara Haworth,[1] Ji Yeon Lee,[1] Jennifer L. Morris,[1] Katharine Sigler,[1] Ayse Akcan Arikan,[1,2] Poyyapakkam Srivaths.[1,2] *[1]Texas Children's Hospital, Houston, TX; [2]Baylor College of Medicine, Houston, TX.*

Background: Therapeutic plasma exchange (TPE) is often performed in tandem with dialytic therapy in pediatric patients as vascular access and need for continuous dialysis would limit separate procedures. There is dearth of data regarding the incidence of hypocalcemia with tandem procedures.

Methods: Retrospective review to evaluate the incidence of hypocalcemia during continuous renal replacement (CRRT) and tandem TPE performed at our institution from January 2012 through December 2014.

Results: Twenty-three patients underwent 115 procedures; median of 4 tandem sessions (IQR 2.5-5.5) were instituted per patient. Demographics: Median age 2.5 yrs [IQR 0.96-9.50], 35% male, wt 14.7 kg [IQR 10.0-36.2], and BSA 0.56 m^2 [IQR 0.45-1.14]. Liver failure with coagulopathy was the most common indication (64.5%). Continuous venovenous hemodialfiltration and centrifugal based TPE was performed in all patients. The median CRRT flow rate was 2,163 ml/1.73 m^2/hr [IQR 1,985-3,364] and apheresis duration 50 minutes [IQR 30.5-102.5]. Fresh frozen plasma (FFP) was the most common replacement fluid (96.5%); median FFP replacement volume 700 mL [IQR 500-2350]. Regional anticoagulation with 3% citrate solution (ACD-A) was used to provide anticoagulation for both CRRT and TPE. Median ACD-A rate was 90 ml/hr [IQR 70-165]; intravenous (IV) calcium chloride infusion rate (2.16 mg/mL of elemental calcium) 60 ml/hr [IQR 40-100]; inlet flow rate 38.5 ml/min [IQR 26.3-50.0]; ratio 1.8 [IQR 1.2-2.3]. During tandem therapy, median ionized calcium (iCa) was 1.12 mmol/L [IQR 0.96-1.19]; hypocalcemia (iCa <1.0 mmol/L) occurred in 52 procedures (45%). Calcium boluses were given during 40 procedures (35%). Hypocalcemia was not affected by diagnosis, age, or inlet flow. Earlier institution data had shown only 3% hypocalcemia with non-tandem TPE.

Conclusions: Hypocalcemia occurred in nearly half of TPE procedures in tandem with CRRT even with IV calcium replacement at 1.8 x inlet flow. Exogenous calcium supplementation should be increased in patients undergoing tandem therapy to prevent hypocalcemia.

PUB070

AKI in Heart Failure Admissions and Impact of Non-Specialist Care

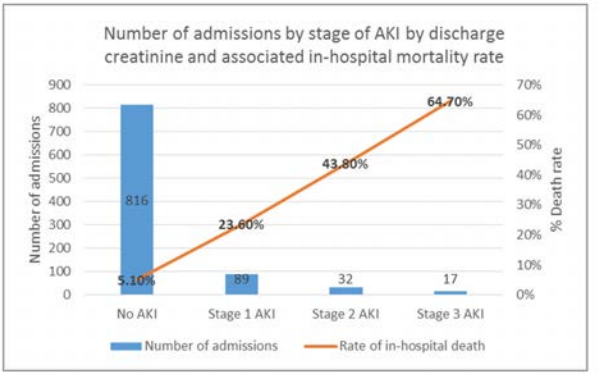
Rebeka E. Jenkins, Saraniga Gugathas, Juan Carlos Kaski, Lisa J. Anderson, Debasish Banerjee. *St. George's Hospital.*

Background: Persistent AKI in heart failure (HF) can be associated with poor outcome, but the effect of specialist care is not clear. We investigated the impact of persistent AKI and specialist care on mortality, length of stay (LOS) in a inner-city UK hospital.

Methods: Data were analysed for all HF admissions between 1/3/2013-31/3/2015. Discharge creatinine[crt] and crt>3months prior to admission determined persistent AKI using KDIGO criteria.

Results: Data on baseline crt were available in 953 out of 1056 admissions with acute HF. 138 [10%] of the 953 admissions were associated with AKI; 89-stage 1, 32-stage 2, 11-stage3. Patients with AKI were similar compared to non-AKI in age [77±10 vs 77±13 years; p=0.961], diabetes [42% vs 40%; p=0.393], presence of systolic dysfunction [65% vs 57%; p=0.122], pre-existing stage 4/5 CKD [10% vs 12%, p=0.404], haemoglobin [11±2 vs 12±2 g/L; p=0.453]. AKI admissions had higher potassium (K) [4.7±0.9 vs 4.3±0.6 mmol/L; p=0.000], higher BNP, longer (LOS) [13±12 vs 10±12 days; p=0.002], less ACEi/ARB therapy [46% vs 59%; p=0.006], higher in-patient mortality [33% vs 5%; p=0.000]. Mortality increased with worsening AKI Stage 1-24%, stage 2-43%, stage 3-64% [see figure]. In logistic regression age, AKI, CKD 4/5 were independent predictors of in-hospital mortality adjusted for each other, diabetes, systolic dysfunction and specialist care. AKI-HF admissions under the non-specialist care were older than those under specialist cardiology care [79±10 vs. 73±10 years; p=0.002], with less systolic dysfunction [59% vs 79%; p=0.023], similar diabetes, higher K [4.8±1 vs 4.5±1; p=0.030]; with no significant increase in LOS or in-hospital mortality [39% vs 24%; p=0.068].

Conclusions: Persistent AKI during acute HF admissions was a strong independent predictor of mortality, which worsened with severe AKI, with longer admission, which was not significantly affected by non-specialist care.



PUB071

Fatal Milk Acid

Tokameh Entezari. *Internal Medicine, 1, Reno, NV.*

Background: Metformin associated lactic acidosis has been described but delayed presentation of this condition has not been recognized. We present a case of severe lactic acidosis in a patient with acute renal failure 24hrs after admission.

Methods: A 65 year old diabetic woman on metformin was admitted due to abnormal renal function on routine labs and inability to urinate for 48hrs. Creatinine was 7.72, bicarbonate 17 and anion gap 16. She was hemodynamically stable, but decompensated 24 hrs after admission with acute respiratory distress and severe metabolic acidosis. Arterial ph was 6.88, bicarbonate of 3 and lactate of 14mmoles. She was intubated for and received 200mmoles of intravenous bicarb push. An emergent hemodialysis was performed with normalization of blood pH and reduction of lactate to 5mmoles.

Results: Acidosis and lactate normalized with repeat dialysis. Throughout her hospital course, her blood pressure was normal to high and did not require any vasopressors. Her renal function eventually improved and dialysis was discontinued. Renal biopsy showed ATN, nephrosclerosis with features of focal global glomerulosclerosis. Metformin is actively excreted, un-metabolized, via transporters in the proximal tubules of the kidneys with an estimated half-life of 5hrs. In renal failure, metformin accumulates and leads to lactic acidosis by enhancing anaerobic metabolism and inhibiting pyruvate dehydrogenase. Also renal failure further leads to reduced excretion of lactic acid. This patient is unusual given her development of lactic acidosis almost 24 hrs after admission to hospital. She had no other concurrent reason for developing lactic acidosis. This case highlights the importance of carefully monitoring and recognizing delayed development of lactic acidosis in patients taking metformin and acute renal failure. Appropriate treatment could be lifesaving in these patients.

Conclusions: Delayed development of life-threatening lactic acidosis is uncommon complication in diabetic patients who stopped metformin with acute severe renal failure.

PUB072

Application of Cardiothoracic Bioimpedance Hemodynamics and Volemic Parameters in Acute Kidney Injury Francisco Javier Lavilla, Nuria Garcia-Fernandez, Maria Jose Molina Higueras, Pelayo Moiron Fdez-Felechosa, Christian Israel Alfaro Sanchez, Paloma L. Martin Moreno, Pedro Errasti. *Nephrology, Clínica Univ de Navarra, Pamplona, Navarra, Spain.*

Background: Evaluate appplication of cardiothoracic bioimpedance (CTBIA) hemodynamics and volemic parameters in Acute Kidney Injury (AKI).

Methods: Cohort 50 patients (mean age 71.2 years SD 1.6, 79.6% males) with AKI. Evaluate hemodynamic parameters (cardiac output –CO-, cardiac output index –COI- and systemic vascular resistance index –SVRI-), thoracic volemic parameters (Thoracic fluid volumen TFV-, Thoracic fluid volumen index –TFVI-) and impedance (Z),analytical (c-reactive protein –CRP-, brain natriuretic factor -BNF-) and clinical parameters (hypotension, respiratory failure, renal replacements requeriments and Karnofsky index –K-).

Results: Patients with lower vascular resistance and higher cardiac work, are associated with hypotension (¿inflammatory state, hipovolemia?). Patients with higher BNF have low cardiac output with high vascular resistences (¿heart failure?). Lower cardiac output are associated with hypoalbuminemia. Patients with higher thoracic volumen have higher risk of respiratoy failure and higher renal replacement therapy requeriments (¿hyperexpansion?). Thoracic hypervolemia are associated with poor impedance (TFV r=-0.931 p= 0.001; TFVI r=-0.885 p=0.001) and poor chronic health status.

	CO l/min	COI l/min/m2	TFV l/kOhm	TFVI l/kOhm/m2	SVRI dyn s cm-5 m2	Z Ohm
CRP r p	ns	ns	-0.310 0.046	-0.353 0,022	ns	ns
BNF r p	-0.303 0.054	ns	ns	ns	0.462 0.002	ns
ALB r p	-ns	-0.426 0.034	ns	ns	ns	ns
Karnofsky	ns	ns	ns	ns	ns	0.426 0.035
Hypo. p NO/YES	0.092 4.5/5.7	0.072 2.4/5.5	ns	ns	0.004 2982/1980	ns
Vent. Asis. R. p NO/YES	ns	ns	0.049 38.3/50	0.105 20.7/25.8	ns	ns
RRT. p. NO/YES	ns	ns	0.005 37/49.2	0.037 20.2/25.1	ns	ns

Conclusions: CTBIA can be used to evaluate clinical evolution and theraphy in AKI, as a patients with vasoplegic state (inflammatory origen and higher multiorgan failure risk) or thoracic hypervolemia (higher respiratoy failure and intubation risk).

PUB073

Role of TIMP-2 and IGFPB7 in Predicting Outcomes of Post-Hospitalization Dialysis-Dependent AKI (PHD-AKI) Emaad M. Abdel-Rahman, Jitendra K. Gautam. *Nephrology, Univ of Virginia, Charlottesville, VA.*

Background: Predicting outcomes of patients with PHD-AKI is important to ensure adequate medical management. This is becoming more crucial with CMS reversing their clarification, allowing AKI patients to be dialyzed at outpatient ESRD facilities. Tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7(IGFBP7) are expressed in renal tubular cells during cellular stress and injury. Studies showed these biomarkers as being superior to exisiting markers in predicting AKI .We hypothesize that a decrease in these biomarkers in PHD-AKI will signal less renal epithelium stress and possible renal recovery. We aim to evaluate the value of TIMP-2, and IGFBP7 as predictors of renal recovery of PHD-AKI within 90 days post hospital discharge (PHD).

Methods: In this pilot study, 10 patients with PHD-AKI were studied. Within the 90 days PHD, 5 remained dialysis dependent (group 1) and 5 recovered their kidney function (group 2). Blood and urine were obtained from each patient on their first hemodialysis session PHD. TIMP-2 and IGFBP7 in plasma and urine were determined using the R & D Systems (Minneapolis, MN, USA) sandwich ELISA as per manufacturer's recommendations. Frozen samples were thawed and brought to room temperature, appropriate dilutions were tested for the biomarkers along with known standard. Final absorbance at 450 nm was read using Synergy2 from Biotek Corp (Winooski, VT, USA). Microsoft Excel and OriginPro 7.5 from Origin Labs (Northampton, MA, USA) were used for graph plotting and statistical analysis.

Results: The mean plasma level of plasma TIMP-2 x IGFBP7 were 26.5 $(ng/ml)^2/1000$ and 10.6 $(ng/ml)^2/1000$ for groups 1 and 2 respectively. The mean urine TIMP-2 x IGFBP7 were 138.2 $(ng/ml)^2/1000$ and 8.4 $(ng/ml)^2/1000$ for groups 1 and 2 respectively.

Conclusions: Biomarkers TIMP-2 and IGFBP7 may have a role in predicting recovery in patients with PHD-AKI. Further data is needed to elicit the role, if any, for these biomarkers as predictors of renal recovery. Currently, we continue to recruit more patients, obtaining plasma and urine samples twice/week from patients along with recording patients' demographics and comorbidity data.

PUB074

Acute Kidney Injury. Unicentric Observational Prospective Study. Identification Parameters to Reduce Mortality and Hospitalization Francisco Javier Lavilla, Nuria Garcia-Fernandez, Maria Jose Molina Higueras, Pelayo Moiron Fdez-Felechosa, Christian Israel Alfaro Sanchez, Paloma L. Martin Moreno, Pedro Errasti. *Nephrology, Clínica Univ de Navarra, Pamplona, Navarra, Spain.*

Background: Evaluate prognosis in acute kidney injury (AKI). Identificate parameters to reduce mortality and hospitalization.

Methods: In a cohort of 2714 patients (62 years-old SD 0.3, 71.6 % male) with a diagnosis of ARF (creatinine increase > 20%). Inclusion period: 3/1996 to 3/2016. We evaluate individual severity (ISI), multiple organ failure index (MFO), Karnofsky, ECOG, analytical parameters, and renal replacement therapy requirement (RRTR).

Results: The death rate was 17.1%. ISI and MOFI are associated with mortality risk, ROC curve analysis showed high sensitivity and specificity: ISI (0.838, SD: 0.011, 95% CI:0.816-0.860), MOFI (0.868, SD: 0.009, 95% CI:0.850-0.886).Multivariate logistic regression analysis showed that variables included in ISI: oliguria (OR 6.241, 95% CI4.894-7.96) and coma (OR 8.218, 95% CI6.04-11.1) influenced independently. Evaluating MOFI, the respiratory failure showed, as well, an independent correlation (OR 4.378, 95% CI 3.822-5.016). Karnofsky (69.6 SD 0.3 vs 62.2 SD 0.6) and ECOG (1.86 SD 0.02 vs 2.77 SD 0.07) was higher in death patients (p<0.001). Analytical parameters observed differences.

	Initial creatinine	Peak creatinine	Creatine increment	Lower Albumin	Lower hemoglobin	Lower Platelets	Basal C reactive protein	Peak Brain Natriuretic Factor
No exitus	1.73	2.12	1.30	2571	9.1	120.802	9.1	7129
Exitus	1.92	2.23	1.55	2407	8.0	83127	13.2	12673
p	0.007	<0.001	0.005	0.058	0.032	>0.001	<0.001	<0.001

Treatment: Exitus rate was higher in replacement therapy (no requeriment: 8.5%, IHD 30.6%, CRRT 45%, and IHD with CRRT 40.6%) (p<0.001).

Conclusions: ISI and MOFI are good prognostic predictors of outcome. Oliguria and respiratory failure correlates to mortality. Prognostic depends on health state prior to injury and evolution of creatinine, hematological, protein, inflammatory and cardiac congestion status. Use of renal replacement therapy predicts a worst prognosis.

PUB075

Intradialytic Hypotension in Acute Kidney Injury: A Systematic Review Adrianna Douvris,[1] Swapnil Hiremath,[2,3] Edward George Clark.[2,3] *[1]Dept of Medicine, Univ of Ottawa; [2]Kidney Research Centre, Ottawa Hospital Research Inst; [3]Div of Nephrology, The Ottawa Hospital.*

Background: Intradialytic hypotension (IDH) is a frequent complication of hemodialysis in end-stage kidney disease. Most studies on current interventions have focused on this chronic population. IDH is also an important concern for critically ill ICU patients with acute kidney injury (AKI) requiring renal replacement therapy (RRT), complicating an estimated 30% of treatments. We undertook a systematic review to synthesize the evidence surrounding dialysis-related interventions used to minimize IDH in critically ill patients with RRT-requiring AKI. Our outcomes included the incidence of IDH, RRT-related complications, in-hospital mortality and renal recovery.

Methods: We searched MEDLINE, EMBASE and CENTRAL databases using a comprehensive search strategy. We had performed an initial search of these databases and Prospero, which yielded no prior or ongoing systematic reviews on this topic. Study quality was assessed using the Newcastle Ottawa Scale and ROBINS-I tool for observational studies and the Cochrane Collaboration's Tool for assessing risk of bias for RCTs.

Results: A total of 14 studies were identified for qualitative synthesis: 7 randomized controlled trials (RCTs) and 7 observational studies. Our search identified only 1 to 2 studies per dialysis-related intervention, which included sodium modeling, ultrafiltration profiling, blood volume and temperature control, blood volume monitoring, extended duration of dialysis, CRRT pump speeds at initiation, dialysate solutions, and dialyzer membranes. Some strategies were employed in combination. Variable definitions of IDH were employed. We were unable to do a formal meta-analysis due to the heterogeneity of interventions, dialysis modalities, and outcomes assessed. Study quality was generally low.

Conclusions: Little high-quality evidence exists with respect to interventions for reducing IDH in RRT-requiring AKI. Standardization of the definition of IDH in this context could help facilitate future studies that seek to minimize the persistently high rates of mortality and dialysis-dependence after RRT-requiring AKI through a reduction in IDH.

PUB076

Fractional Excretion of Sodium (FeNa) <1 Is Sensitive but Not Specific for Hepatorenal Syndrome (HRS) Diagnosis in Cirrhotic Patients Hani Wadei, Ali Alsaad.[2] *[1]Transplantation, Mayo Clinic, Jacksonville, FL; [2]Medicine, Div of Nephrology and Hypertension, Mayo Clinic, Jacksonville, FL.*

Background: FeNa<1 favors HRS diagnosis in cirrhotic patients with renal dysfunction however FeNa<1 has not been previously correlated with renal histology . **Aim:** correlate FeNa<1 with histological findings on renal biopsy and determine the accuracy of FeNa in diagnosing HRS.

Methods: 88 liver transplant candidates with renal dysfunction and/or proteinuria underwent percutaneous kidney biopsy, iothalamate GFR, 24-hr urine collection for urinary Na and protein excretions and random urine Na and creatinine. FeNa was calculated using the equation [(urine sodium x serum creatinine)/(serum sodium x urine creatinine)] x 100. Patients on renal replacement therapy were excluded.

Results: Table 1 represents patients' characteristics

Age	60 ± 7
Male gender	57 (65)
HCV infection	40 (45)
History of diabetes	35 (40)
History of hypertension	40 (45)
Iothalamate GFR ml/min	28 ± 14
Serum creatinine (mg/dl)	1.9 ± 0.9
Serum Na (mEq/dl)	137 ± 5
24-hr urinary protein excretion (mg/d)	87 (0-13625)
FeNa<1	**77 (87)**
Hematuria	40 (45)
Diuretic use	64 (72)
Kidney Biopsy	
HRS	10 (11)
ATN	12 (14)
MPGN	13 (15)
Minimal histology	15 (17)
≥30-40% IF/GS	38 (43)

77 (87%) had FeNa<1. FeNa<1 was present in 10/10, 10/12, 11/13, 12/15 and 34/38 in patients with HRS, ATN, MPGN, minimal histological findings and advanced (≥30-40%) interstitial fibrosis (IF) and/or glomerulosclerosis (GS), respectively (P=0.6). FeNa<1 was 100% sensitive and 14% specific in diagnosing HRS. ROC confirmed that FeNa <1 performs poorly in diagnosing HRS, AUC=0.58.

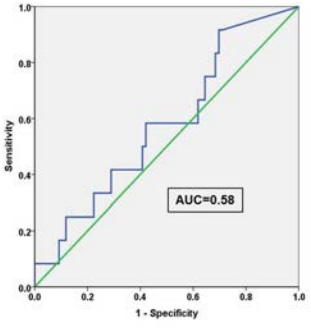


Figure 1: ROC curve demonstrates the poor diagnostic performance of FENA<1 in diagnosing HRS. AUC= 0.58

Conclusions: FeNa<1 is common in cirrhotic patients with renal dysfunction and does not differentiate between HRS and other causes of renal dysfunction.

PUB077

The Recognition of Acute Kidney Injury and Referral to a Nephrology Unit Influence the Outcomes of Hospital-Acquired Acute Kidney Injury

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[1]Internal Medicine 1, Hamamatsu Univ School of Medicine, Hamamatsu, Shizuoka, Japan; [2]Blood Purification Unit, Hamamatsu Univ Hospital, Hamamatsu, Shizuoka, Japan.

Background: Several studies have shown an increasing incidence and high mortality of hospital-acquired acute kidney injury (HA-AKI). Although AKI criteria of KDIGO has been widely used to detect AKI events early and avoid development of AKI in hospitalized patients, it is not unclear where and how often HA-AKI events are recognized and whether the recognition and referral to a nephrology unit influence their outcomes.

Methods: We searched retrospectively the incidence of AKI events from electronic database of Hamamatsu University Hospital (Shizuoka, Japan) that provides all major medical and surgical specialities, and reviewed medical records of the patients. AKI was defined as more than 1.5 times increasing from baseline of serum creatinine within 7 days based on KDIGO AKI criteria. The study population consisted of 5,591 adult patients who were admitted to the hospital from April to September 2015. All HA-AKI events were analysed.

Results: 135 HA-AKI episodes (128 patients, 2.41%) were detected during the study period. 84 episodes (62.2%) as stage 1, 30 episodes (22.2%) as stage 2, 21 episodes (15.6%) as stage 3 were classified, respectively. 43.7% of the HA-AKI patients suffered from cancer. All hospital mortality was 33.6% (43 patients). 86 episodes (63.7%) of the HA-AKI were recognized by the attending doctors. Only 15 episodes (17.4%) of the recognized cases were referred to nephrology. Whereas the referred cases had more severe AKI compared to non-referred cases, these referred cases were significantly less short-term of hospital mortality compared to the non-referred cases (0 vs. 25.4%, p<0.05). Nephrologist contributed to discriminate between intrinsic and pre-renal AKI, and induce renal replacement therapy properly.

Conclusions: AKI was common in hospitalized cancer patients and associated with high mortality. Recognition of AKI and referral to a nephrology unit might improve hospital mortality after HA-AKI.

PUB078

Dapsone Induced Methemoglobinemia: A Case Series

Sohail Abdul Salim, Iasmina Craici, Swetha Rani Kanduri, Yougandhar Akula. *Nephrology, Univ of Mississippi Medical Center, Jackson, MS.*

Background: Dapsone, a sulfone antibiotic, has been used in renal transplant recipients for prophylaxis of Pneumocystis Carinii Pneumonia in patients with documented sulfa allergy. Acquired Methemoglobinemia caused by dapsone is not uncommon in transplant patients with normal G6PD levels. Discrepancy between pulse oximetry (PO) and arterial oxygen saturation (SpO**2**) readings, a phenomenon known as "saturation gap" is noted.

Methods: None

Results: Case 1:72 Male with Deceased Donor Renal Transplant (DDRT) with sob for 2-3 weeks on mild to moderate exertion, found to have Pulse oximetry saturation of 82% and arterial Po2 of 100 with methemoglobin level of 21.3%Case2: 24 female with lupus nephritis and hemolytic anemia. Few weeks prior she was switched from Bactrim to dapsone. Pt methemoglobin level was 4.6% and came down to normal levels as soon as dapsone was stopped. Case 3: 52 y/o Female DDRT admitted for worsening SOB and dyspnea on exertion with methemoglobin level of 7.2%.

Conclusions: Dapsone might be reasonable alternative in TMP/SMX intolerance, but clinicians should have a higher suspicion of Methemoglobinemia. Symptoms can occur at Methemoglobin levels ranging from 1.9% to 26.8%, mostly at the 100 mg dose and could be worse in patients with preexisting coronary and chronic lung disease. Adequate level of suspicion with appropriate labs could lead to early recognition, which is key to effective management.

PUB079

The Activation of Notch3 in Endothelial Cell Aggravate Renal Fibrosis in Obstructive Nephropathy

Hui Xu, Jin Zhang, Ting Ding. *Nephrology Dept, Xiangya Hospital, Central South Univ, Changsha, Hunan, China.*

Background: Notch3 has been showed to be protective in generating functional arteries. But the role of notch3 activation in chronic kidney injury (CKD) is controversial. Angitensin II (AngII) plays a key role in arteries function and the progression of kidney diseases. This study was to assess the expression of notch3 in obstructive nephropathy.

Methods: The expression of Notch3 in injured kidney of obstructive nephropathy patients was analyzed by immunohistochemistry. The expression of Notch3 and (AngII) was detected in 3, 7, 14 and 21 unilateral ureteral occlusion (UUO) rats by western blot or realtime PCR. After the stimulation of AngII, the expression of notch3 in proximal tubular or endothelial cell lines was assessed by western blot or realtime PCR.

Results: The expression of notch3 is upregulated in the renal cortex of obstructive nephropathy patients. Consistently, the expression of notch3 and AngII increased time-dependently in the renal cortex of UUO rats. Moreover, after the stimulation of AngII, the expression of notch3 was up-regulated in endothelial cells but not the proximal tubular epithelial cells.

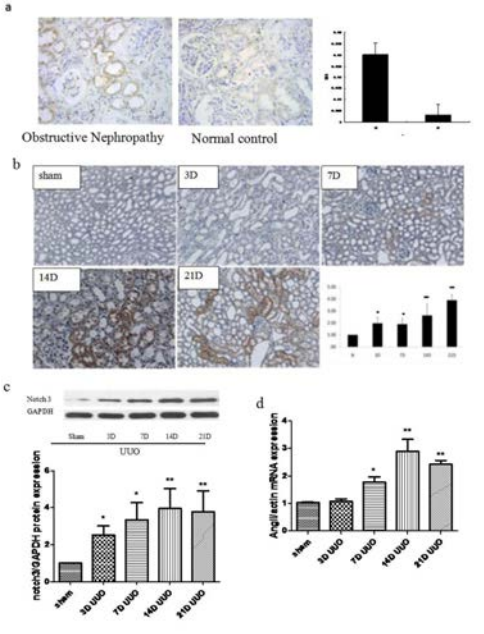


Figure1 a. Notch3 in the renal cortex of obstructive nephropathy patients and normal control by immunohistochemistry; b. Notch3 in the renal cortex of UUO rats by immunohistochemistry; c. Notch3 in the renal cortex of UUO rats by western blot; d. AngII in the renal cortex of UUO rats by realtime PCR.

Conclusions: The activation of notch3 plays a role in obstructive nephropathy and renal fibrosis. AngII is an important physiological factor in triggering the expression of notch3 expression. Blocking the expression of notch3 may be a potential therapeutics for renal fibrosis.

Funding: Government Support - Non-U.S.

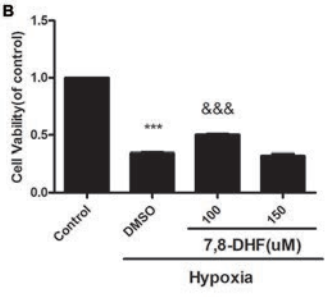
PUB080

7,8-DHF Treatment Induces Cyr61 Expression to Suppress Hypoxia Induced ER Stress in HK-2 Cells Yan Xu, Rui Ma. *Dept of Nephrology, Affiliated Hospital of Qingdao Univ, Qingdao, Shandong, China.*

Background: Hypoxia is the leading cause to AKI and the proximal renal tubular cells are the most damaged part in kidney. In this study we explored function of 7,8-DHF in protecting human proximal tubular cell line HK-2 from hypoxia insults.

Methods: The cultured HK-2 cells were pretreated with 7,8-DHF and exposed to 12 h hypoxia. Then the cytotoxicity of 7,8-DHF and cell viability were determined. The protein expression of the possible downstream biomarker as cysteine-rich protein 61 (Cyr61) and endoplasmic reticulum (ER) stress marker as CCAAT/enhancer-binding protein homologous protein (CHOP) were identified by western blot analysis. Real-time PCR was selected to test the mRNA expression of ER stress associated signaling pathway, such as protein kinase-like ER kinase(PERK),Glucose-regulated protein 78(GRP78),splicing X-box–binding protein-1(xbp1s),activating transcription factor 6(ATF6). In study of overexpression of Cyr61, apoptotic rate, mRNA and protein levels of ER stress markers and apoptotic parameter as cleaved Caspase-3 were detected.

Results: In hypoxia induced HK-2 cells, 7,8-DHF improved cell viability.



Mechanistically, 7,8-DHF could elevate the expression of cysteine-rich protein 61 (Cyr61), a protective immediate early gene in AKI. In addition, treatment of 7,8-DHF decreased CCAAT/enhancer-binding protein homologous protein (CHOP) expression, which is a mark protein during endoplasmic reticulum (ER) stress activation. Intriguingly, overexpression of Cyr61 significantly reduced CHOP expression.

Conclusions: 7,8-DHF could protect HK-2 cells from hypoxia insult by activating Cyr61 signaling and suppressing ER stress and have potential clinical implications for the treatment of AKI.

Funding: Government Support - Non-U.S.

PUB081

Activation Inhibits but Deactivation of the Renin Angiotensin System Accelerates Differentiation of Human Podocytes Vinita Vishnoi, Abheepsa Mishra, Ashwani Malhotra, Pravin C. Singhal. *Medicine and Immunology, Feinstein Inst for Medical Research and Hofstra North Well Medical School, Great Neck, NY.*

Background: Activation of renin angiotensin system (RAS) has been shown to play a role in the development of focal glomerulosclerosis (FSGS). Loss of critical number of podocytes has been incriminated for the development of FSGS. Usually, a subset of parietal epithelial cells (PECs) or cells of renin lineage serve as progenitors cells and are differentiated into podocytes to repopulate the glomerular basement membrane. We asked whether activation of the RAS in adverse milieus such as high glucose would prevent but inhibition of the RAS would accelerate differentiation of podocytes.

Methods: Immortalized proliferating human podocytes (HPs) which proliferate at 33˚C but differentiate at 37˚C (differentiation complete on 10th day). HPs were incubated at 37˚C either for 3 days (short duration, SD) or for 8 days (long duration, LD). HPs were reincubated in media containing either buffer or high glucose (HG, 30 mM) for the next 48 hours. HPs were treated under similar conditions with variable concentrations of HG (5, 10, 15, 25, 30 mM). Protein blots and cDNAs of SD/HPs were probed for podocalyxin. Protein blots and cDNAs of LD/HPs were probed for nephrin. To evaluate the role of RAS, SD/HPs and LD/HPs were incubated in media containing either buffer, losartan (an Ang II blocker, 10^{-7}M)/aliskiren (renin inhibitor, 10^{-6}M)/ captopril (an angiotensin converting enzyme inhibitor (10^{-6}M), or losartan/aliskiren/captopril with or without HG (30 mM) for 48 hours. Protein blots and cDNAs were probed for podocalyxin and nephrin.

Results: HG down regulated podocalyxin in SD/HPs in a dose dependent manner. Similarly, HG down regulated nephrin in LD/HPs in a dose dependent manner. Losartan, captopril, and aliskiren up regulated expression of podocalyxin as well as of nephrin both at basal and HG-stimulated states.

Conclusions: Activation of the RAS in high glucose milieu prevents whereas inhibition of RAS accelerates differentiation of podocytes.

Funding: NIDDK Support

PUB082

How Many Podocyte Autophagosomes in Two Kinds of Nephropathy: IgAN and IMN? Shikai Liang. *Zhejiang Provincial People's Hospital, Dept of Nephrology, Hangzhou, China.*

Background: The aim of this study was to investigate the number of autophagosomes in podocyte from kidney tissue of immunoglobulin A nephropathy (IgAN) and idiopathic membranous nephropathy (IMN).

Methods: The changes of kidney tissue pathology were detected after hematoxylin and eosin (HE), periodic acid-Schiff (PAS), Masson's trichrome and immunofluorescence (IF). The autophagosomes of podocyte were analysed by transmission electron microscopy (EM). Clinical data, including age, gender, edema, serum creatinine, estimated glomerular filtrating rate (eGFR), hematuria, urine protein excretion and serum albumin, were collected from inpatient medical record.

Results: It was found that the number of autophagosomes in podocyte of nephropathy group were lower when compared with the control group. At the same time we did not find the difference of the parameter between these two kinds of nephropathy. Further study showed that the index was affected by two factors: eGFR and gender.The cases with worse eGFR (eGFR<60 ml/min) and male patients presented more autophagosomes. Furthermore, each nephropathy had its own character. The phenomena of reduced autophagosomes was found in IMN cases, did not change from male to female, and further aggravated from pathological stage I to II. By contrast, IgAN cases with less eGFR exhibited more autophagsomes.

Conclusions: Therefore, the results of the present study indicate that autophagy participates in podocyte injury and the progression of IgAN and IMN.

PUB083

Mechanisms of Graphene Toxicity to Kidney Tubular Epithelial Cells Tariq Fahmi,[1] Alena Savenka,[1] Alexei G. Basnakian.[1,2] *[1]Dept of Pharmacology and Toxicology, Univ of Arkansas for Medical Sciences, Little Rock, AR; [2]Central Arkansas Veterans Healthcare System, Little Rock, AR.*

Background: Graphene is a new nanomaterial that is extremely light, flexible and strong. It is expected to be commonly applied in the future due to its versatility. However, since it is a carbon-based nanomaterial, its potential toxicity is a health and environmental concern. Kidney is one of the primary organs for the assessment of nanomaterial toxicity.

Methods: By using a near infrared fluorescence (NIRF) DNase activity probe, we have established that graphene induces nephrotoxicity that occurs mainly through DNA destruction. A non-modified graphene (50 μg/ml) exposed with cultured rat kidney tubular epithelial NRK-52E cells induced an LDH release and a TUNEL-type DNA fragmentation usually associated with cytotoxicity.

Results: Dark-field and phase-contrast microscopy showed that TUNEL-positive cells have significantly higher graphene content than TUNEL-negative cells. DNase activity quantified in live cells using the oligonucleotide-based NIRF probe was increased in the presence of graphene in parallel with the TUNEL. Cell death DNases, such as caspase-activated DNase (CAD), endonuclease G (EndoG), and DNase I, and the marker of oxidative stress, heme oxygenase-1 (HO-1) were shown to be elevated. We then applied specific chemical inhibitors to determine whether the DNase and oxidative pathways are mechanistically involved in the graphene toxicity.

Conclusions: The hypothesis was confirmed by the fact that all of the inhibitors abolished the graphene toxicity. In summary, the measuring of DNase activity by using NIRF probe in combination with TUNEL assay and are appropriate tools for the assessment of graphene toxicity, and oxidative injury and DNases are the mechanisms of the latter.

Funding: NIDDK Support, Other U.S. Government Support, VA Support

PUB084

Calcitriol Mitigates Advanced Glycation End Product (AGE)-Elicited Imbalance between Th17 and Treg Cells via VDR-State3- RORγt/Foxp3 Pathway in Diabetic Nephropathy Ao Cheng, Yanlin Zhang. *Dept of Nephrology, The First Affiliated Hospital of Xiamen Univ, Xiamen, Fujian, China.*

Background: Our previous studies have found AGE-HSA can induce the initial T CD4+cells to generate Th17 cells by RAGE- RORgt signaling. In addition to regulate calcium and phosphorus metabolism, Calcitriol has immunomodulatory effects. The main purpose of this experiment is to explore whether calcitriol could regulate advanced glycation end products elicited Imbalance between Th17 and Treg Cells.

Methods: (1) Recruitment of 20 healthy adults and 50 diabetic nephropathy patients and detection activited Vitamin D content and ratio of Th17 cells / Treg cells to verify the correlation. (2) Prepared AGE-HSA in vitro and isolated and cultured the initial CD4+T cells from healthy volunteers peripheral blood: a) AGE-HSA stimulated initial CD4+T cells, or pretreatment with calcitriol, and to detect the ratio of Th17 cell and Treg cells and determine the expression mRNA and protein of RORgt, Foxp3, STAT3 and HIF-1α; b) Pretreatment initial CD4+T cells with VDR siRNA, AGE-HSA and or not calcitriol stimulated initial CD4+T cells to detect the ratio of Th17 cell and Treg cells and the expression of RORgt, Foxp3, STAT3 and HIF-1α.

Results: (1)In patients with diabetic nephropathy, there is lower of vitamin D and increasing of Th17 cells and the reduction of Treg cells. The ratio of Th17 cells and Treg cell is imbalance (increase in the proportion). There was a negative correlation between the concentration of vitamin D and ratio of Th17 cells and Treg cells; (2) the AGE-HSA induced the initial CD4+ T cells to differentiate Th17 cells, and calcitriol could migitated effects of AGE-HSA; (3) After the suppression VDR, it can reduce the effects of Calcitriol.

(4) AGE-HSA up-regulated expression RORγ. With pretreatment of calcitriol, there was reduced the expression of RORγt, HIF-1α and STAT3 induced by AGEs and increased expression of Foxp3.

Conclusions: In patients with diabetic nephropathy, there was negatively correlated between the content of vitamin D and the proportion of Th17 cells and Treg cells, and calcitriol mitigates AGE-HSA elicited imbalance between Th17 and Treg Cells via VDR-State3- RORγt/Foxp3 Pathway.

Funding: Government Support - Non-U.S.

PUB085

Enrichment of Collecting Duct Cells by FACS Sorting from Whole Kidney Using L1-CAM

Yasunobu Ishikawa,[1] Sorin V. Fedeles,[2] Chao Zhang,[2] Saori Nishio,[1] Stefan Somlo.[2] *[1]Medicine II, Hokkaido Univ, Sapporo, Hokkaido, Japan; [2]Internal Medicine, Yale Univ School of Medicine, New Haven, CT.*

Background: The sensitivity for discovering *in vivo* biological effects of gene mutations in whole kidney tissue is compromised by the complexity resulting from cell type heterogeneity in tissue. For example, inactivation of *SEC63*, one of genes that causes human autosomal dominant polycystic liver disease, is known to result in increased spliced XBP1 (XBP1s), a transcription factor involved in the unfolded protein response. However, when using whole kidney protein and RNA (ASN, 2015 TH-OR066), this response was undetectable in whole kidney tissue following inactivation of *Sec63* only in collecting ducts (CD). We therefore investigated cell type specific enrichment of CD from whole kidney by FACS sorting.

Methods: WT (wild type), SKO (*Sec63$^{fl/fl}$; Pkhd1-cre*), DKO (*Sec63$^{fl/fl}$; Xbp1$^{fl/fl}$; Pkhd1-cre*) kidneys at postnatal day 35 were harvested and a single cell suspension was made. L1-CAM, a transmembrane glycoprotein belonging to the Ig superfamily of cell adhesion molecules, was conjugated to Alexa Fluor 647. Cells were stained with L1-CAM-647 (L1) and LTL-FITC (LTL) (a proximal tubule maker) prior to analysis using MoFlo cell sorters.

Results: IF showed that L1-CAM co-localized with THP positive and AQP2 positive tubules, indicating L1-CAM is expressed in murine thick ascending limb of loop of Henle and CD. L1^{+}/LTL^{-} and L1^{-}/LTL^{+} cells were separated by FACS. In whole kidney mRNA, expression of megalin (proximal tubule) is ~3-4 fold higher than AQP2 and ENaC (CD). L1^{+}/LTL^{-} cells showed ~3 fold higher expression of AQP2 and ENaC relative to megalin, indicating a ~10-fold enrichment of CD cells relative to proximal tubules. qRT-PCR analysis of whole kidney from WT, SKO and DKO showed no difference in gene expression of ERdj4 which is transcriptional target gene of Xbp1s whereas expression of ERdj4 in L1^{+}/LTL^{-} cells from SKO kidneys was increased 1.4-fold compared with WT and DKO.

Conclusions: FACS sorting by L1-CAM and LTL achieves ~10-fold enrichment of collecting duct cells relative to proximal tubules, enabling detection of modest cell type specific changes in gene transcription.

PUB086

Up-Regulation of Liver Hnf1α Gene Expression-a Possible Cause of Elevated CRP Biosynthesis Accompanied Inflammation in Experimental Chronic Renal Failure

Elzbieta Sucajtys-Szulc, Marek Szolkiewicz, Boleslaw Rutkowski, Alicja Debska-Slizien. *Dept of Nephrology, Transplantology and Internal Medicine, Medical Univ of Gdansk, Gdansk, Poland.*

Background: High sensitivity C-reactive protein (hsCRP), a marker of inflammation and predictor of cardiovascular risk is usually elevated in CKD patients. Regarding that HNF1α activates *Crp* gene expression through binding to specific site present in promoter of this gene, we examined HNF1α and CRP mRNA levels in the liver and serum CRP concentration in rats with experimentally induced chronic renal failure (CRF).

Methods: Rats underwent 5/6 nephrectomy or a sham surgery. Liver expressions of *Crp, Hnf1α* genes were quantified by qPCR. Serum CRP concentration were estimated with an immunoassay.

Results: Experimental CRF was associated with significant increase of liver HNF1α mRNA (approx. 2-fold greater that in controls (CON) and pair-fed (PF) rats). The pattern of changes in liver HNF1α mRNA levels strictly resembles the pattern of changes in liver CRP mRNA. These differences in liver CRP mRNA levels were paralleled by differences in serum CRP concentration (179±19 μg/ml in CON; 219±41 μg/ml in PF; 392±42 μg/ml in CRF respectively). We found positive correlations between the liver levels of HNF1*α* mRNA and: the liver levels of CRP mRNA ($r=0.78$, $p<0.01$) and serum CRP concentration($r=0.83$, $p<0.01$). Moreover, strong positive correlation between the liver levels of CRP mRNA and serum CRP concentrations ($r=0.85$, $p<0.01$) was found.

Conclusions: The results presented hereby indicate that up-regulation of *Hnf1α* gene expression was associated with significant increase of liver CRP mRNA and serum CRP concentrations in rats with CRF. Considering the above discused data, it is likely that HNF1α plays an important role in controlling CRP biosynthesis in CRF. Our finding provide a new information about coordinated up-regulation of *Hnf1α and Crp* genes in liver and association of this events with inflammation in chronic renal failure.

PUB087

The Explorative Analysis for Characteristics and Classification According to C4d Staining in Glomerulonephritis

Na Kyoung Hwang, Jong Man Park, Harin Rhee, Il Young Kim, Eun Young Seong, Dong Won Lee, Soo Bong Lee, Ihm Soo Kwak, Sang Heon Song. *Internal Medicine, Pusan National Univ School of Medicine, Busan, Korea.*

Background: The C4d is widely used as a footprint of the complement activation by classic or lectin pathway. It has mainly applied to antibody mediated rejection in kidney transplantation. A few studies have suggested that the C4d would have an important role in glomerulonephritis. This study aimed to analyze the C4d staining status at the time of renal biopsy and its association with clinical characteristics in glomerulonephritis.

Methods: This retrospective study included 392 patients who underwent renal biopsy between 2009 and 2016. We categorized the patients according to the C4d deposit and compared the baseline characteristics.

Results: The C4d deposits were detected in 29.1% (69/237) with IgA nephropathy (IgAN), 67.1% (47/70) with membranous nephropathy (MN), 39.5% (17/43) with minimal change disease (MCD), 57.1% (8/14) with membranoproliferative glomerulonephritis (MPGN), and 71.4% (20/28) with lupus nephritis (LN). It deposits mainly in the mesangium (IgAN, MCD, LN) and the glomerular capillary wall (MN, MPGN, LN). Clinically, the group having mesangial C4d deposit had higher proteinuria level compared with C4d-negative group in IgAN ($p=0.045$). However, there was no significant difference with baseline clinical characteristics in other glomerulonephritis. Interestingly, IgM was co-localized with C4d in IgAN (43.5% vs. 30.4%; $p=0.053$), MN (38.3% vs. 14.3%; $p=0.048$), MCD (40.0% vs. 7.1%; $p=0.008$), and LN (61.5% vs. 13.3%; $p=0.008$) compared with C4d-negative groups. The C4d-positive group has lower frequency of C3 staining and higher frequency of C4 staining in IgAN. There was no relationship between IF staining and serum level of Immunoglobulin or complements.

Conclusions: The C4d positively deposited with high frequency in glomerulonephritis and the C4d-positive area was so variable according to the type of glomerulonephritis. Additionally, IgM was co-localized with the C4d and the further evaluation for the role of IgM is necessary. In the future, extended study is needed for the prognostic role of the C4d through long-term follow-up.

PUB088

Podocyte Adhesion to Collagen-Coated Surface Is Affected after Exposure to Serum of Patients with Preeclampsia

M. Lourdes Gonzalez Suarez,[1] Allan W. Ackerman,[1] Sonu Kashyap,[1] Muthuvel Jayachandran,[1] Natasa Milic,[2] Wendy White,[1] Joseph P. Grande,[1] Vesna D. Garovic.[1] *[1]Mayo Clinic, Rochester, MN; [2]Medical Faculty Univ of Belgrade.*

Background: Podocyte proteins, such as nephrin, podocin, and synaptopodin maintain the structure and function of the slit diaphragm. Injury to this structure causes proteinuria and foot process effacement. Podocyturia has been described in preeclampsia. It remains unclear the mechanism of injury that causes podocytes detachment from the glomerular basement membrane in preeclampsia.

Methods: We conducted cell adhesion assays on collagen-coated plates, using an immortalized human podocyte cell line after 3-4 weeks of differentiation. Podocytes were exposed to serum of patients with preeclampsia (n=7) and normotensive pregnancy (n=10) at delivery. Fetal bovine serum (FBS) was used as control. Non-attached living podocytes were detected by flow cytometry. For Western blots, lysates of podocytes were incubated with antibodies against nephrin, podocin, synaptopodin, and integrin β1. Experiments were done in triplicates. Statistical analysis was done using paired t- test and Wilcoxonsign-rank.

Results: There was a significant increase ($p=0.03$) in number of living podocytes that were not able to adhere to the surface after incubation with preeclamptic versus normotensive sera. Expression of podocin in suspended cells was decreased after incubation with preeclamptic versus normotensive sera. Integrin β1 expression was increased, and expressions of nephrin and synaptopodin were decreased in suspended compared to attached cells in all three conditions.

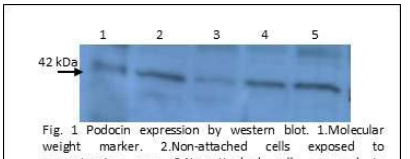


Fig. 1 Podocin expression by western blot. 1.Molecular weight marker. 2.Non-attached cells exposed to normotensive sera. 3.Non-attached cells exposed to preeclamptic sera. 4.Attached cells exposed to normotensive sera. 5.Attached cells exposed to preeclamptic sera

Conclusions: Podocin expression is decreased in non-attached cells after exposure of preeclamptic serum and may represent a disease-specific mechanism for podocyte detachment that may contribute to podocyte dysregulation in preeclampsia.

Funding: Private Foundation Support

PUB089

Renoprotective Effect of the Xanthine Oxidoreductase Inhibitor, Topiroxostat, in Addition to Inactivation of RAS, on Adenine-Induced Renal Injury Atsuko Ikemori,[1,2] Takeshi Sugaya,[2] Mikako Hisamichi,[2] Kenjiro Kimura,[3] Yugo Shibagaki.[2] *[1]Anatomy, St. Marianna Univ School of Medicine; [2]Div of Nephrology and Hypertension, Dept of Internal Medicine, St. Marianna Univ School of Medicine; [3]Tokyo Takanawa Hospital.*

Background: The aim of this study is to reveal the effect of a xanthine oxidoreductase inhibitor, Topiroxostat (Top), compared to Febuxostat (Feb), in addition to inactivation of RAS on an adenine-induced renal injury model.

Methods: Angiotensin II type 1a receptor (AT1a) hetero deficient and human L-FABP chromosomal transgenic mice (L-FABP$^{+/-}$AT1a$^{+/-}$) mice, and urinary liver type fatty acid binding protein (L-FABP), a biomarker of tubulointerstitial damage, were used. These male mice (n=48) were fed a 0.2% w/w adenine-containing diet. Four weeks after starting this diet, renal dysfunction was confirmed and the mice were divided into six groups: the adenine group was given the diet containing adenine and the control group was given only the diet. The Febuxostat-high (Feb-H) or low (Feb-L) groups and Topiroxostat-high (Top-H) or low (Top-L) groups were given diets containing Feb-H (3mg/kg), Feb-L (1mg/kg), Top-H (3mg/kg), and Top-L (1mg/kg) in addition to adenine for another 4 weeks.

Results: Serum creatinine levels, urinary L-FABP, urinary 15-F2t-isoprostane levels and urinary angiotensinogen were significantly lower in the Feb-H and Top-H groups compared to the adenine group. The degree of macrophage infiltration, tubular damage, renal fibrosis, and renal xanthine oxidoreductase (XOR) activity were significantly attenuated in the Feb-L, Feb-H, Top-L and Top-H groups compared to the adenine group. The tubular damage, urinary angiotensinogen, and the renal xanthine oxidoreductase activity (XOR) in the Top-H group, were significantly lower than those in the Feb-L group. Because the dosages of high-dose Top group are equivalent to dosages of the low-dose Feb group, Top with stronger XOR inhibitory potency might prevent the progression of CKD more than Feb.

Conclusions: Top may be useful as add-on therapy to the RAS inhibitors for preventing the progression of CKD.

Funding: Pharmaceutical Company Support - Sanwa Kagaku Kenkyusho Company

PUB090

Role of Nuclear 1 Factor Related Factor 2 (Nrf2) Activator, Bardoxolone Methyl, in Hypertensive Renal Injury Mikako Hisamichi,[1] Atsuko Ikemori,[1,2] Takeshi Sugaya,[1] Kenjiro Kimura,[3] Yugo Shibagaki.[1] *[1]Div of Nephrology and Hypertension, Dept of Internal Medicine, St. Marianna Univ School of Medicine, Kawasaki, Japan; [2]Dept of Anatomy, St. Marianna Univ School of Medicine, Kawasaki, Japan; [3]JCHO Tokyo Takanawa Hospital, Tokyo, Japan.*

Background: Nuclear 1 factor related factor 2 (Nrf2) activators have an anti-oxidant effect and might be a new treatment strategy for chronic kidney disease. Aldosterone (Ald) causes renal damage via generation of oxidative stress in hypertensive renal injury. The aim of this study is to reveal the renoprotective effect of the Nrf2 activator in a systemic Aldo infusion model.

Methods: To evaluate the degree of tubulointerstitial damage using the urinary liver type fatty acid binding protein (L-FABP), known as a biomarker of tubulointerstitial damage, we used human L-FABP chromosomal transgenic (L-FABP$^{+/-}$) mice because L-FABP is not expressed in the kidneys of wild-type mice. Male L-FABP$^{+/-}$ mice were divided into three groups: the Ald group received systemic aldosterone infusions via an osmotic minipump and were given 1% NaCl water for 35 days. The Ald-Nrf2 group was given Bardoxolone Methyl intraperitoneally in addition to an injection of aldosterone and salt. The dose of the Nrf2 activator was gradually increased every 7 days, reaching 10mg/kg/daily and continued for 14 days. The control group was given only a vehicle.

Results: The gene expressions of MCP-1, RANTES, and collagen typeIand type III, as well as the degree of macrophage infiltration, and collagen type Iand type III-positive areas were significantly greater in the kidneys of the Ald group compared to those in the control. In the Ald-Nrf2 group, such renal inflammatory reaction and renal fibrosis were significantly attenuated. Although the degree of renal human L-FABP gene expression and urinary human L-FABP levels significantly increased in the Ald group compared to the control, such an increase was suppressed in the Ald-Nrf2 group. The same trend can be observed in urinary albumin levels.

Conclusions: The Nrf2 activator, Bardoxolone Methyl, ameliorated the degree of hypertensive renal disease, and thus may be an effective treatment for hypertensive renal disease.

PUB091

Antiphospholipase A2 Receptor Antibody Titer Is Associated with Idiopathic Membranous Nephropathy Disease Activity Regardless of Pathological Grading Juan Jin. *Zhejiang Provincial People's Hospital, Dept of Nephrology, Hangzhou, China.*

Background: Membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults, and anti-M-type phospholipase A2 receptor (anti-PLA2R) antibodies are found in the majority of patients with idiopathic MN (IMN). We investigated the assocation of anti-PLA2R antibody titer with IMN disease activity and pathological grading.

Methods: A total of 131 patients with biopsy-proven IMN who had not received immunosuppressive treatment at the time of renal biopsy and serum sample collection were included in the study. Forty-two patients had IMN, 9 patients had secondary MN (sMN) and 223 had other glomerulonephritis.Circulating anti-PLA2R antibodies were analyzed by ELISA analysis.

Results: Anti-PLA2R antibodies were detected in 69.0% (29/42) of patients with IMN, 3.0% (1/33) of patients with mesangial proliferative glomerulonephritis, and 0% (0/223) of patients that had other glomerulonephritis. The prevalence of anti-PLA2R antibodies was higher in patients with (91.2%) compared to patients without (42.1%) nephrotic syndrome. Urinary protein was significantlylower ($p = 0.002$), while total protein and albumin were significantly higher ($p < 0.001$ and $p = 0.002$, respectively) in patients with anti-PLA2R antibodies.The sensitivity, specificty, positive predictive value and negative predictive value were 71.4%, 99.6%, 96.7% and 94.7%, respectively.

Conclusions: Our results indicate that anti-PLA2R titersreflect MN disease activity and can therefore be used as a specific marker of IMN. However, we did not identify any relationship between anti-PLA2R antibody titer and MN pathological stage.

PUB092

The Study of Syndrome Differentiation Based on Renal Biopsy Pathology of Diabetic Kidney Disease Maosheng Chen. *Zhejiang Provincial People's Hospital, Dept of Nephrology, Hangzhou, China.*

Background: Research the distribution of syndrome differentiation in Traditional Chinese Medicine(TCM) on diabetic kidney disease (DKD) and its relationship with pathological stage of DKD.

Methods: Bring into the DKD patients through pathological diagnosis which have more than one year disease course, to classify by the Tervaet criterion of pathological stage of DKD, to differentiate the syndrome differentiation in TCM by collecting clinical data, and have a statistical processing at last.

Results: We collected 353 DKD patients meeting the criterion in total, classified by the pathological stage criterion of DKD, among them there were 52 patients with phase I, 90 patients with phase IIa, 29 patients with phase IIb,141 patients with phase III, 41 patients with phase IV. About syndrome differentiation, there were 13 patients with Yin-Xu-Zao-Re type, there were 151 patients with Qi-Yin-Liang-Xu type, there were 140 patients with Pi-Shen-Qi-Xu type, there were 49 patients with Yin-Yang-Liang-Xu type, there were 19 patients with Han-Shi type, there were 68 patients with Shi-Re type, there were 212 patients with Yu-Xue type, there were 54 patients with Tan-Yu type. In the patients with Yin-Xu-Zao-Re type, the renal interstitial inflammation was more serious than other typs. In the patients with Pi-Shen-Qi-Xu type,the glomerular segmental sclerosis, nodular changes, and fibrinoid exudation were more serious than other groups. In the patients with Yu-Xue syndrome differentiation, interstitial fibrosis and tubular atrophy (IFTA), interstitial inflammation, hyaline degeneration, angiosclerosis,and fibrinoid exudation were more serious than other types significantly. Multivariate COX analysis showed that syndrome differentiation were independent risk factors for renal prognosis.

Conclusions: Among the syndrome differentiation of DKD, Qi-Yin-Liang-Xu type and Yu-Xue type were more frequently than other tyes. The result showed that syndrome differentiation was correlated significantly with pathological stage of DKD, Yin-Yang-Liang-Xu type and Tan-Yu type were independent risk factors for renal prognosis in DKD.

PUB093

ZNF268 Mediates Podocyte Response to PAN through Interaction with NF-κB Pathway Khaldoun Al-Romaih,[1] Khalood Aldosari,[1,2] Zakia M. Anwar Shinwari,[1] Basma Mohammed Alahideb,[1] Maram Alwahebi,[1] Rabab Hassan Allam,[1] Ayodele Alaiya.[1] *[1]Stem Cell and Tissue Re-Generation Program, King Faisal Specialist Hospital and Research Centre; [2]College of Medicine, Alfaisal Univ, Riyadh, Saudi Arabia.*

Background: Nephrotic Syndrome (NS) is a progressive kidney disease that is characterized by protein leakage into the urine. In vivo induced nephrosis by puromycine aminonucleoside (PAN) leads to the onset of proteinuria. The glomerular visceral epithelial cells (podocytes) and their injury are central to the development of proteinuria. Nuclear factor κB (NF-κB) has been implicated in the podocyte injury and onset of proteinuria. Observation, in systems other than podocytes, suggested the involvement of transcription regulation of zinc finger protein ZNF268 in mediating NF-κB pathway.

Methods: ZNF268 protein expression was analyzed in differentiated human podocyte cells. The interaction between ZNF268 and NF-kB and family members in the context of podocyte response to sub-lethal doses of PAN treatment was also studied.

Results: Expression of different isoforms of ZNF268 was seen by Immunoblotting in differentiated podocytes including ZNF268a, and ZNF268b. ZNF268 showed diffused cytoplasmic localization and focal nucleus localization. Sub-lethal doses of PAN treatment (5, 10, and 20 ug/ml) caused accumulation of ZNF268 and NF-kB-p65 in the nucleus. Also an interaction between ZNF268 and NF-kB -p65 was seen in the PAN-treated differentiated podocytes.

Conclusions: These observations highlight the potential role of ZNF268 as a mediator of response to PAN treatment in human cultured differentiated podocytes.

Funding: Government Support - Non-U.S.

PUB094

Chemical Induction of Proteinuria in Larval Zebrafish Using Puromycin
Philipp Niggemann,[1] Patricia Ann Schroder,[2] Heiko Joachim Schenk,[1] Hermann G. Haller,[1] Mario Schiffer.[1] *[1]Hanover Medical School; [2]MDI Biological Laboratory.*

Background: Zebrafish have become a widely used model organism in glomerular kidney research. Developing a method that produces a standardized glomerular proteinuria phenotype in zebrafish through treatment via the fishwater would be an asset to high throughput testing of potential beneficial drugs. Thus far such a method does not exist.

Methods: We induced glomerular proteinuria phenotypes in zebrafish of different genetic backgrounds by treating the zebrafish embryos with Puromycin Aminonucleoside (PAN) in the fishwater at varying timepoints. Treatment with PAN was conducted at timepoints from 44hpf to 50hpf. Different crosses of Tg(l-fabp:DBP-EGFP) zebrafish backcrossed onto AB or *nacre* background were examined.

GFP fluorescence content was measured in 96hpf embryos' eyes as a readout of their proteinuria phenotype.

Results: Embryos homozygous for the *nacre* mutation were more susceptible to PAN treatment compared to embryos with an AB background. Moreover, we noted that a treatment at 46hpf reliably yields consistent phenotypes. Treatments at later timepoints were less effective in proteinuria induction. This specific line crossing is a good starting point for testing of drugs potentially beneficial for the treatment of proteinuria.

Conclusions: The basis of *nacre* is a mutation in the *Mitf* transcription factor regulating the formin-homology protein Dia1. Further studies are on the way to examine the relation between the *Mitf* mutation and a higher susceptibility for a disruption of the filtration barrier.

Funding: Other NIH Support - under grant numbers P20GM0103423 and P20GM104318

PUB095

Peroxisome Proliferator-Activated Receptor α-Dependent Renoprotection of Murine Kidney by Irbesartan
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Background: Activation of renal peroxisome proliferator-activated receptor α (PPARα) is renoprotective, but there is no safe PPARα activator for patients with chronic kidney disease (CKD). Studies have reported that irbesartan (Irbe), an angiotensin II receptor blocker (ARB) widely prescribed for CKD, activates hepatic PPARα. However,Irbe's renal PPARα-activating effects and the role of PPARα signaling in the renoprotective effects of Irbe are unknown.

Methods: Herein, these aspects were investigated in kidneys of wild-type (WT) and *Ppara*-null (KO) mice and in the murine protein-overload-nephropathy (PON) model, respectively. The results were compared with those of losartan (Los), another ARB that does not activate PPARα.

Results: PPARα and its target gene expression were significantly increased only in the kidneys of Irbe-treated WT mice and not in KO or Los-treated mice, suggesting that the renal PPARα-activating effect was Irbe-specific. Irbe-treated-PON-WT mice exhibited decreased urine protein excretion, tubular injury, oxidative stress, and pro-inflammatory and apoptosis-stimulating responses, and they exhibited maintenance of fatty acid metabolism. Furthermore, the expression of PPARα and that of its target mRNAs encoding proteins involved in oxidative stress, pro-inflammatory responses, apoptosis, and fatty acid metabolism was maintained upon Irbe treatment. These renoprotective effects of Irbe were reversed by the PPARα antagonist MK886 and were not detected in Irbe-treated-PON-KO mice.

Conclusions: These results suggest that Irbe activates renal PPARα and that the resultant increased PPARα signaling mediates its renoprotective effects.

PUB096

Drug Treatment Response in Patients Diagnosed with Membranoproliferative Glomerulonephritis in a Fourth-Level Hospital at the City of Barranquilla-Colombia
Gustavo Aroca Martinez,[1,2] Andres A. Cadena,[1,2] Alex A. Domínguez,[2] Diana Carolina Silva,[2] Jossie E. Fontalvo,[2] Henry J. Gonzalez Torres.[2] *[1]Clinica de la Costa, Barranquilla, Colombia; [2]Univ Simón Bolívar, Barranquilla, Colombia.*

Background: The Membranoproliferative Glomerulonephritis (MPGN) is the third of fourth leading cause of End-stage renal disease among the glomerulonephritides. However, the benefits of immunosuppression treatment and the prognosis in patients with MPGN are often unknown due to a lack of controlled clinical trials.

Methods: The retrospective study was conducted in a fourth-level hospital at Barranquilla and included medical records of patients with MPGN who underwent renal biopsies from 2007 to 2014. Patients were classified according to the type of Treatment response in Responders and Non-responders. The Responders were those with Partial remission (Improvement of at least 50% of the 24hrs proteinuria and active urinary sediment) and Complete remission (24hrs proteinuria <0.5g and inactive urinary sediment). Non-responders were those who had no change in the 24hrs proteinuria or increase of 25% from the same, End-stage kidney disease and active urinary sediment. The immunosuppressive treatment included Mycophenolate and Cyclophosphamide alone and/or conjugated steroids. The treatment response was evaluated at 6 and 12 month.

Results: Of the 58 patients, 30 (52%) were females and 28 (48%) were males, with an overall mean age of 35 ± 13 years. The Nephrotic syndrome was the most common clinical presentation (70%) and 63% of the patients developed CKD at year to be evaluated. Serum Creatinine and 24hrs proteinuria did not change significantly over 6 months of treatment both males and females. 15 (25.8%) patients achieved remission (22.4% partial and 3.4% complete) and 43 (74.1%) failed to enter remission. 39.6% of females and 37.9% of males failed to achieve remission at 6 months. At 12 months, only 5 Patients (8.6%) achieved response (partial or complete) compared to 13 Patients (22.4%) of the previous semester.

Conclusions: MPGN is a major cause of CKD among the study population. Immunosuppressive drug therapy revealed no statistically significant benefits in remission of the impaired renal function at 6 and 12 months.

PUB097

An Enzyme-Linked Immunosorbent Assay (ELISA) for the Quantification of Mouse Endostatin as a Marker of Decreased Kidney Function in ETV6/RUNX1 and BCL2 Transgenic Mice
Jacqueline Wallwitz,[1] Dagmar Stoiber.[2] *[1]The Antibody Lab GmbH, Vienna; [2]Ludwig Boltzmann Inst of Cancer Research, Vienna.*

Background: Endostatin is a protein with approximately 20 kDa produced by proteolytic cleavage of collagen XVIII. It is one of the most potent endothelial cell-specific inhibitors of angiogenesis with influence on proliferation, migration and apoptosis. In order to investigate the biological functions of Endostatin in more depth this work presents the development and validation of a specific, high-quality ELISA for detecting mouse Endostatin.

Methods: We developed an immunoassay which is based on a sandwich type format with an immobilized polyclonal antibody used to capture mouse Endostatin which is subsequently detected with a horseradish peroxidase labelled polyclonal anti-Endostatin antibody. To investigate the importance of Endostatin as a potential biomarker for impaired kidney function we determined serum concentration of Endostatin in ETV6/RUNX1 and BCL2 transgenic mice.

Results: The novel sample-saving Endostatin ELISA is optimized for mouse serum and plasma. Assay characteristics such as precision, dilution linearity and spike-recovery as well as sample stability meet high quality standards. In this study we demonstrate that the glomerulonephritis phenotype of ETV6/RUNX1 and BCL2 transgenic mice is also accompanied with higher Endostatin serum concentration.

Conclusions: In conclusion, this high-quality ELISA provides a reliable and accurate tool for the quantitative determination of mouse Endostatin in serum and plasma samples.

PUB098

Deficiency of Purinergic P2X7 Receptor Protects against Progression of Chronic Renal Injury
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Background: Chronic kidney disease (CKD) is defined as progressive loss of renal functional. The ionotropic ATP-gated receptors the P2X7-receptor (P2X7R) is detected on immune cells like lymphocytes, macrophages and dendritic cells. P2X7R mediates Ca2+ and Na+-influx and mediates the release of pro-inflammatory cytokines (IL1β and IL18). Here, we test whether P2X7-receptor deficiency prevents progression of CKD after subtotal nephrectomy (SNX).

Methods: SNX was performed in wild type (control) and P2X7R knock out (KO) mice and assessment was performed at different time points for 35 days. Kidneys were removed on day 35 for further assessment (quantitative PCR (qPCR), Western Blot (WB), histology).

Results: On day 35, remnant-kidney-mass was significantly lower in P2X7R-KO mice. In P2X7R-KO mice urine urea level was significantly higher on day 5 and day 35, urine creatinine level was higher throughout day 5 to 35 and albumin-creatinine ratio was lower throughout day 10 to 35 compared to controls. Systolic blood pressure was significantly lower in P2X7R-KO mice. qPCR analysis showed reduced expression of collagen1, MCP-1 and NFκB in P2X7R-KO mice. WB showed a significantly lower levels collagen1 in P2X7R-KO mice. There was a significantly reduced number of sclerosed glomeruli in P2X7R-KO mice compared to controls.

Conclusions: These data indicate reduced compensatory hypertrophy in P2X7R-KO kidneys. Urine samples suggest a preserved tubulo-interstitial function in P2X7R-KO mice. Despite small difference in systolic blood pressure, heart weight showed no difference, indicating blood pressure independent effects on organ injury. Reduced collagen1-expression in qPCR and WB indicate lower fibrosis, possibly contributing to reduced hypertrophy. The reduced number in sclerosed glomeruli and reduced proteinuria indicate a preserved glomerular function. Reduced inflammatory response indicated by lower MCP-1 and NFκB expression are likely the underlying cause for the attenuated progression of renal injury in this model. Therefore, P2X7 deficiency protects against progression of chronic renal injury.

Funding: Clinical Revenue Support

PUB099

PEDF Protein as a Potential Therapeutic Candidate for Diabetic Nephropathy: Bioinformatic Analysis of Transcriptional and Posttranscriptional Elements Associated with Personalized Gene Expression
Mohammed A. Al-Obaide, Tetyana L. Vasylyeva. *Pediatric, Texas Tech Univ Health Sciences Center, Amarillo, TX.*

Background: Pigment epithelium-derived factor (PEDF) protein is encoded by SERPINF1 gene. PEDF is a multifunctional 50 kDa glycoprotein that belongs to the non-inhibitory Serine Protease Inhibitor (SERPIN) subfamily. It has renoprotective, neuroprotective, anti-angiogenic, anti-inflammatory and anti-apoptotic properties. We hypothesized that PEDF might be a potential therapeutic target for diabetic nephropathy (DN).

Methods: PubMed and publicly available databases, NCBI-GenBank, UCSC Genome Bioinformatics, Ensembl, ENCODE, FANTOM5, DBTSS, EPD, and MpromDB were systematically utilized for search and bioinformatic analysis of PEDF regulatory sequences. The structural features of PEDF regulatory sequences were analyzed using DNALive tool. Algorithm Fold of "RNA structure" Webservers software was used to predict the secondary structure and stem-loops for the SERPINF1 mRNA transcript. Identification of un-reported mature sequences of miRNA was performed by using miRBase BLASTN search tool.

Results: We identified twenty three tissue specific transcription starting sites (TSS) and several specific enhancers for SERPINF1 gene, which showed variable expression patterns in Kidney.SERPINF1 genomic space also contains promoter flanking, enhancers and CTCF regions. Many SNPs were identified within promoter flanking and enhancer regulatory sequences. Analysis of sequence-dependent physical properties of the SERPINF1 promoters' DNA sequences showed specific correlation with the high and low expressed TSS. Stem-loops in the SERPINF1 mRNA secondary structure were also identified that are likely candidates for posttranscriptional regulation by miRNA.

Conclusions: This study provides further insight into the regulatory features that govern PEDF expression and reveals novel regulatory sequences associated with transcription process in kidney and might play a role in pathogenesis of DN. The SERPINF1 regulatory elements could be exploited in targeted therapy.

PUB100

Identifying Late-Onset Nephropathic Cystinosis Cases Using Electronic Health Records (CystEHR)
Robert M. Haws,[1] Elizabeth Mcpherson,[1] Krishna Reddy Polu,[2] Gregg C. Checani,[2] Nils F. Confer,[2] Jeremy Pomeroy,[1] Burney Kieke,[1] Robert Steiner,[3] Jeffrey J. Vanwormer.[1] *[1]Marshfield Clinic Research Foundation; [2]Raptor Pharmaceuticals Inc; [3]Univ of Wisconsin.*

Background: Nephropathic cystinosis (NC), a rare autosomal recessive disorder, typically presents with Fanconi syndrome by 1 year of age. Caused by lysosomal cystine accumulation, NC contributes to 5% of pediatric renal failures and affects multiple organs. The estimated 15 cases diagnosed annually in the US are believed to represent half of actual cases, as less severe atypical variants presenting in adolescence and young adulthood may be missed. The frequency of late onset cystinosis (LOC) cases is unknown and clinical recognition/treatment is likely suboptimal.

Methods: Reusable logic is being developed to identify LOC cases using electronic health records (EHR) from Marshfield Clinic Health System (MCHS). Stage 1 involves retrospective EHR screening to identify suspected NC cases from patients 1-30 years of age. Renal and extra-renal features indicative of NC were ascertained via clinical experience, literature search, and chart review of existing cystinosis cases within MCHS. Patients with NC clinical features were extracted from EHR based on diagnostic codes, lab values, and natural language processing. This algorithm will be validated using data from Stage 2, where suspected NC cases will be confirmed using prospectively collected leukocyte cysteine levels, genetic analysis, and ocular examination.

Results: Approximately 600,000 patients were screened for cystinosis clinical features. An initial EHR screen identified 950 patients with ≥1 renal plus ≥1 extra-renal feature. The screening algorithm, based on chart review of these cases, is being refined to determine the precise combinations of clinical features, including number and severity, and to identify potential LOC patients for Stage 2. Results of Stage 1 will be available at the time of presentation.

Conclusions: CystEHR is the first known study to develop an EHR-based algorithm for cystinosis identification, which will help determine the degree to which LOC is missed. Once validated, this algorithm could be used in other large EHR systems to update cystinosis incidence and improve clinical recognition.

Funding: Pharmaceutical Company Support - Raptor Pharmaceuticals Inc

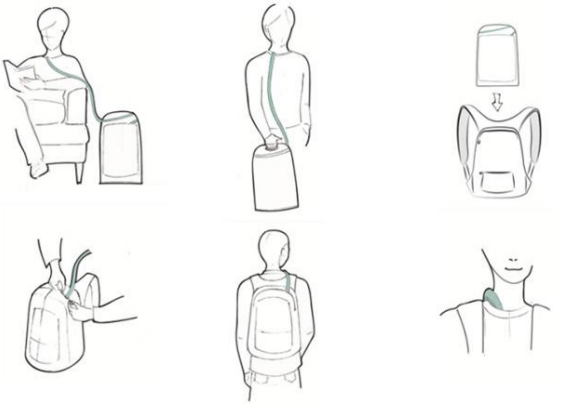
PUB101

A Backpack Design Is the Best Solution for a Conceptual Design of a Wearable Artificial Kidney
Mauro Neri, Alessia Buffagni, Francesco Garzotto, Marta Zaccaria, Fiorenza Ferrari, Alessandra Brendolan, Federico Nalesso, Claudio Ronco, Anna Lorenzin. *Nephrology, Dialysis and Transplantation, International Renal Research Inst of Vicenza (IRRIV), S.Bortolo Hospital, Vicenza, Italy.*

Background: For hemodialysis patients, a miniaturized wearable artificial kidney (WAK) would allow for more freedom of movement and maintenance of a higher quality of life. In order to be truly wearable (and not only portable), not only single components, but even the device as a whole has to be designed in a convenient layout. The aim of this abstract is to propose a new concept of layout for wearable artificial kidney and to compare it with previous proposals.

Methods: The WAK general layout has to be designed providing ergonomics and low-weight, respecting the consequential phases of blood ultrafiltration process. Furthermore, the patient should not be hindered while performing daily activities and should not feel embarrassed wearing the device. Assuming a vascular access placed in jugular vein, four main proposals of layout have been considered, also based on previous proposals from literature: Belt-like device (horizontal arrangement); Jacket device (frontal arrangement); Sling shape device (frontal and vertical arrangement); Backpack device (rear and vertical arrangement).

Results: The last option seems to meet the requirements better than the others. A backpack design (commonly used in everyday life) would offer more space for the components and cause less discomfort for the patient. A schematic preliminary draw of the device is represented in Fig.1 .



Conclusions: With a backpack design, hemodialysis patients would use their own personal device only, in which all the disposable components could be replaced as a unique cartridge, designed to be extremely easy to fit and dispose. Furthermore, the backpack shape can be re-arranged into a "sleep station" to perform night treatments as well.

PUB102

A Novel Electronic Device for Measuring Urine Flow Rate
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Background: Most vital signs in the ICU are electronically monitored. However, clinical practice for urine output (UO) measurements still requires manual recording of data subject to human errors. UO is an underutilized biomarker for monitoring kidney function, fluid balance and hemodynamic status. Diuretics must be administered with caution and when appropriate. The use of a medical device that provides accurate data of UO in real-time can aid in defining kidney function, patient fluid status, and response to diuretic treatments.

Methods: RenalSense has developed the *Clarity RMS™ sterile sensor kit* for electronic UO monitoring. The sensor, incorporated within a standard sterile urinary catheter drainage tube, monitors urine flow in real-time as it exits the foley catheter. The sensor, connected by a cable to a laptop computer, uses software designed by RenalSense (Clarity RMS™ monitor). The drainage bag was placed on a scientific scale (gold standard) to validate the sensor measurements. For comparison of sensor data to the manual records, a standard urinometer was incorporated into the RenalSense drainage bag for the nursing staff to record UO as per standard practice. Sensor measurements and nurses' records of UO were compared to the scale data. 1635 hours of UO data from 40 patients were collected.

Results: The *Clarity RMS™* device identified 40% more of cases of acute kidney injury (AKI), as defined by the AKIN (Acute Kidney Injury Network) criteria for UO, than nursing staff records. Common human errors with regard to the UO information included missing hours of data, imprecise records of hourly output, and an incomplete picture of patient fluid balance. Graphical presentation of electronic data showed real-time response to repeated diuretic administration, as well as response to fluid bolus.

Conclusions: An electronic device for recording UO has been shown to be crucial for identifying AKI. Automated urine monitoring documented diuretic response in real-time with continuous graphic monitoring of UO; highlighting possible applications of this tool for future decisions as to timely diuretic administration, furosemide stress tests, and dose response.

Funding: Pharmaceutical Company Support - RenalSense

PUB103

Remote Monitoring of Home Dialysis Patients: Leveraging Policies for Other Chronic Diseases in U.S. and Europe
Katherine Rojahn, Suzanne Laplante, James A. Sloand. *Baxter Healthcare Corporation, Deerfield, IL.*

Background: Remote monitoring (RM) has shown to be useful in managing chronic disease patients. RM may represent an opportunity to better manage end-stage renal disease (ESRD) patients treated by home dialysis. Research was conducted to identify public policies of RM in the US and 4 European countries (Germany, Italy, Spain, UK), which potentially could be leveraged for ESRD.

Methods: Medical literature, internet, and targeted Ministry of Health websites were searched to identify RM policies for ESRD and chronic diseases such as diabetes,

heart failure, chronic pulmonary obstructive disease, and hypertension. RM was defined as patients' clinical data collection and transmittal to a hospital or physician's office, for monitoring and clinical action. Original searches were conducted Q1-2014 and complemented by 1-hour interviews with 4-5 payers/policymakers per country. Searches were updated Q4-2015/Q2-2016. Selection criteria included: policies focusing on telehealth or related terms. Data extracted consisted of: date of issue, disease areas covered, geographic scope, type of policy, and details. Each was rated according to criteria of successful public health policy including: targeted scope, identified criteria for decision-making framework, and evidence collection.

Results: Overall, more than 43 policies were identified: US=10, Italy=11, Germany=5, Spain=9, UK=8. 20 policies were nationally funded and 23 were regional. Most policies included funding for research (22) and financial incentives (13). 4 countries had policies to invest in health IT infrastructure (4) and RM guidelines (6). 24 policies were identified that may be leveraged for ESRD, of which 6 ranked the highest (US=3, Italy=1, Spain=2) for being an ongoing initiative involving data tracking, and/or established financial incentive for healthcare professionals. 10 were identified as potential long term opportunities, which included hospital or research programs (US=2, Italy=2, Germany=2, Spain=2, UK=2).

Conclusions: Our research identified policies that may be leveraged for ESRD population. Short term and long term opportunities will help to generate evidence of the benefit of RM for home dialysis.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

PUB104

In Vitro Characterization of Qidni-X1, an Implantable Renal Replacement Therapy (Artificial Kidney) Device with Animal Blood Morteza Ahmadi. *Qidni Labs Inc., San Francisco, CA.*

Background: There are over 650,000 patients with End Stage Renal Disease in US. More than 100,000 patients are in the waiting list for kidney transplant and only 25,000 kidney transplants are performed each year. Qidni-X1 is an implantable renal replacement therapy under development for patients with end stage renal disease. We report on in vitro characterization of Qidni-X1 for hemodialysis and hemofiltration of animal blood.

Methods: Blood was pumped into Qidni-X1 under normal blood pressure and the hemofiltrate was collected. For hemodialysis, dialysate was pumped into the device. The composition of blood was measured using VetScan VS-2 chemistry analyzer.

Results: 75 ml of fluid was removed in each hour of hemofiltration. In hemodialysis, reduction in urea and creatinine was recorded while no significant change in the level of albumin was observed.

Conclusions: In in vitro experiments with animal blood, Qidni-X1 has been effective in removing fluids during hemofiltration and reduction of urea and creatinine without significant change in albumin level in hemodialysis.

Funding: Pharmaceutical Company Support - Qidni Labs Inc., Government Support - Non-U.S.

PUB105

Podocyte-Specific Deletion of the Vitamin D Receptor Gene Did Not Increased Albuminuria Excretion under Physiologic Condition in a Short Time Li Ni, Xinxin Jiang, Jing Chen. *Nephrology, Huashan Hospital, Fudan Univ, Shanghai, China.*

Background: Vitamin D and its analogues possess important beneficial activity in podocytes. To understand the role of vitamin D in regulating podocytes structure and function, the vitamin D receptor (VDR) gene was selectively deleted in podocytes using the Cre-LoxP system.

Methods: Exon 3 in the VDR gene was the target sequence. The recombinant VDR allele with the loxP bordered exon 3 was maintained in the C57/BL6J background.Mice harboring the recombinant allele (VDR loxP/loxP) were bred with EIIa-Cre to verify the efficiency of VDR knockout. Then, a podocyte-specific VDR knockout mice were generated by mating VDR-floxed mice with Nestin-CreER^{T2} mice. Urine albumin excretion rate(UACR) was measured and the kidneys were obtained for immunofluorescence staining and HE staining.

Results: VDR-KO mice were generated by mating VDR-floxed with EIIa-Cre mice. Intestinal DNA from VDR-KOmice was extracted and an transcript in the 830bp band was detected by PCR. After sequencing and comparing with VDR gene, the transcript was confirmed a null allele of exon 3. Immunofluorescence, Western blot and RT-PCR all confirmed the absence of VDR expression in the intestine of VDR^{KO} mice. These results suggested that the deletion of exon3 in VDR gene caused the loss of VDR expression. Double-transgenic VDR $^{fl/fl}$/nestin-CreER^{T2} mice were treated with tamoxifen. After tamoxifen induction, expression of VDR in glomerlus of VDR$^{fl/fl}$/nestin-Cre^{+} mice was decreased significantly. Before tamoxifen induction, UACR was in VDR$^{fl/fl}$/nestin-Cre^{+} mice and wide-type mice was 77.79±42.39mg/g and 37.15±27.25mg/g, respectively, without statistical significance(p=0.08). After tamoxifen induction, UACR of VDR$^{fl/fl}$/nestin-Cre^{+} mice was increaseed but did not reach statistical significance. Serum BUN, creatinine, calcium and phosphate levels were normal and had no difference in these groups. The histology of the kidney by HE staining did not observed abnormality.

Conclusions: The model of VDR gene knockout in podocyte was successfully generated. Under physilogic condition, podocyte VDR knockout had no obvious effect on proteinuria in a short time. The long-term effect required further observation.

Funding: Government Support - Non-U.S.

PUB106

A New View on Glomerular Filtration Wilhelm Kriz,[1] Kevin V. Lemley.[2] *[1]Neuroanatomy, Medical Faculty Mannheim, Univ of Heidelberg, Mannheim, Germany; [2]Div of Nephrology, Children's Hospital Los Angeles, Los Angeles, CA.*

Background: The glomerular filtrate flow represents the highest extravascular fluid flow in the body. It consists of the outflow from glomerular capillaries, through the GBM and into Bowman's space. This latter step creates a problem: in contrast to its exit from capillaries, its entry tends to separate the podocytes from the GBM. This problem has become clear since we learned that podocytes are lost by detachment from the GBM as viable cells. This also disproved the idea that foot processes (FPs), like pericyte processes, counteract the pressure driven expansion of the GBM. Their interdigitating pattern provides the channels (filtration slits), through which the filtrate enters Bowman's space. They are bridged by the slit diaphragm (SD), a unique adherens junction. So far no satisfying hypothesis has been proposed that would explain the complexity of this structure.

Methods: Traditional view The pattern of FPs and filtration slits bridged by the SD is considered to restrict the passage of plasma proteins. It is a sensitive structure that is lost early in pathological situations leading to FP-effacement, consistently associated with the loss of permselective function. Supporting the high filtrate flow has never been considered as a function of the SD.

Results: New view The slits between FPs channel the flow of filtrate into Bowman's space. A filtrate flow of 25 nl/min (rat) creates a shear stress on the FPs as high as 8 Pa (Endlich and Endlich, Sem Nephrol 2012). Much lower values of shear stress (0.5 Pa) on podocytes in culture lead to their detachment. The SD, mechanically connecting opposite FPs, "utilizes" the shear stress on one FP to balance the shear stress on the opposite FP. This is supported by the observation that loss of the SD-connection between adjacent FPs represents the earliest failure starting detachment of a podocytes.

Conclusions: Consequence The elastic GBM continually adapts in area to capillary pressure fluctuations. In consequence, the FPs steadily change in area, shown by us in the isolated perfused rat kidney. This ensures that the flow rate per unit area of SD, the source of local shear stress, does not change with varying filtration pressure.

Funding: Private Foundation Support

PUB107

Angiotensin Receptor Blockers Prevent Kidney Injury by Preserving Podocytes Katherine Mikovna Scovner, Minglei Lu, Lance D. Dworkin, Rujun Gong. *Nephrology, Rhode Island Hospital, Brown Univ, Providence, RI.*

Background: Angiotensin receptor blockers (ARB) prevent chronic kidney disease. We assess blood pressure (BP) and proteinuria (UprotV) in spontaneously hypertensive rats (SHR) given variable doses of ARB therapy. To further assess glomerular injury, podocyte number is also evaluated.

Methods: SHR were untreated (C) or given 3 doses of candesartan daily (standard 5 mg/kg (T5), high 25 mg/kg (T25), and very high 75 mg/kg (T75)). Tail-cuff BP and 24-hour urine protein excretion were measured monthly for 14 months after which time the rats were sacrificed. Podocyte number was then measured by quantifying cells positive for WT-1 in each glomerulus based on immunohistochemistry staining.

Results: BP was very high in C but normal and not different in all treatment groups. UprotV was reduced in T5 and completely prevented in T25 and T75. Podocyte number was greatest in T75, fell with decreasing doses of ARB, and was least in C (means for T75: 18.2; T25: 15.0; T5: 12.9; C: 11.3. P value < 0.0001).

Conclusions: BPs are controlled in all doses of ARB therapy administered to SHR. However, high and very high doses of ARBs completely prevent UprotV. Increasing doses of ARB therapy are also associated with better preservation of podocytes. The reduced destruction of podocytes may be the reason for decreased UprotV seen at higher doses of ARB therapy. Loss of podocytes leads to uncovering of the basement membrane and increased protein filtration ultimately causing glomerulosclerosis. ARB therapy may thus be renal protective for its protection of the podocytes. BP is normal in all treated groups, but there is decreased UprotV and increased podocytes seen at the higher doses compared to standard dose of ARB therapy. Therefore, the mechanism of protection of podocytes and decreased UprotV may be independent of hemodynamic changes. It may instead be related to the therapy's suppression of inflammation as has previously been theorized.

PUB108

Sirtuin 3 Deficiency Mediates Mitochondrial Dysfunction of Podocytes in Diabetic Mice Zengchun Ye, Ming Li, Wenbo Zhao, Meijun Si, Cheng Wang, Tan-Qi Lou. *Dept of Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China.*

Background: Mitochondria play essential roles in many aspects of biology, and their dysfunction has been linked to podocytes injury in diabetic nephropathy. Sirtuin 3 (SIRT3) is a nicotinamide adenine dinucleotide (NAD+)-dependent deacetylase, which mediates the deacetylation of various metabolic and antioxidant enzymes, in turn controlling energy metabolism and mitochondrial function. This study is to investigate the roles of Sirt3 in mitochondrial dysfunction of podocytes in diabetic mice.

Methods: To assessthe expression of Sirt3 and mitochondrial complex activity, mitochondria were isolated from podocytes of16-week-old diabetic (*db/db*) and non-diabetic (*db/m*) mice. Moreover, diabetes was induced in Sirt3-knockout mice by streptozotocin (STZ) injection. The expression of Sirt3 was measured by western blotting. Mitochondrial complex I activity was detected by microplate assay kit purchased from Abcam.

Results: We found that Sirt3 was decreased significantly in podocytes of db/db mice when compared to db/m mice. Furthermore, Sirt3-deficient diabetic mice induced by STZ experienced more severe mitochondrial dysfunction in podocytes, including reduced complex I activity and decreased level of mitochondrial DNA. And *in vitro* studies, we also found that high glucose could reduce the expression of Sirt3 in podocytes and lead to decrease of mitochondrial complex I activity. Overexpression of Sirt3 in cultured podocytes can restore the activity of mitochondrial complex I.

Conclusions: Collectively, these data suggest that Sirt3 plays an important role in regulating the mitochondrial function in podocytes. Decrease of Sirt3 expression in podocytes lead to reducing mitochondrial complex I activity in diabetic mice. Our study uncovers a previously unrecognized role of Sirt3 in the pathogenesis of diabetic nephropathy, thus implicating Sirt3 as a new potential therapeutic target to treat diabetic nephropathy.

Funding: Government Support - Non-U.S.

PUB109

Fibrinogen A α Type Amyloid: A Rare Entity Ankita Tandon,[1] William F. Glass,[1] Ala Abudayyeh.[2] *[1]Renal Diseases and Hypertension, The Univ of Texas Medical School at Houston; [2]Div of Internal Medicine, Section of Nephrology, The Univ of Texas MD Anderson Cancer Center.*

Background: With the help of laser micro dissection and mass spectrometry, patients that were initially misdiagnosed with AL amyloid can now be found to have sporadic hereditary amyloidosis. We describe a case of a patient who was initially diagnosed with AL amyloid and later found to have fibrinogen A alpha type amyloid.

Methods: 77 year old man with atrial fibrillation was referred by his urologist for proteinuria. Lab work indicated IgG 921 mg/dL, IgM 43 mg/dL and IgA 475 mg/dL. Serum and urine protein electrophoresis was negative for an M protein. Kappa light chain was 26.1 mg/L, lambda light chain was 12.9 mg/L with a kappa to lambda light chain ratio of 1.72 (normal 0.26 - 1.65). Bone marrow biopsy showed normal trilineage hematopoiesis with no evidence of plasma cell dyscrasia. It was also negative for amyloid deposition by congo red staining. Fat pad biopsy was also negative for amyloid. Bone survey showed no evidence of lytic lesions. The patient continued to have 8 g of proteinuria during this time. Due to the unclear etiology of the amyloidosis, repeat renal biopsy was performed for laser microdissection and mass spectrometry to identify the amyloid protein. Mass spectrometry demonstrated fibrinogen A alpha type amyloid.

Conclusions: A high index of awareness is necessary for the diagnosis of hereditary sporadic amyloidosis. It can be misdiagnosed as AL amyloidosis, which carries significant implications for the patient, as he is now being treated for a condition he doesn't have, and for family members, who then remain unaware that a hereditary amyloidosis runs in their family.

PUB110

Ischemia Leads to Increases in Tight Junction Mobility following FRAP In Vivo Alexander Louis Kolb,[1] Josephine Axis,[3] Robert L. Bacallao,[2] Kurt Amsler.[3] *[1]Biology, Indiana Univ Purdue Univ Indianapolis, Indianapolis, IN; [2]Nephrology, Indiana Univ School of Medicine, Indianapolis, IN; [3]Biomedical Scienes, New York Inst of Technology College of Osteopathic Medicine, Old Westbury, NY.*

Background: After an injury to a cells tight junction it is hypothesized that these junctions become immobile and have a slow turnover rate contributing to leak and polarity changes leading to cell death. However, our in vivo data indicates ischemia increases the rate of tight junction turnover compared to pre ischemic tight junctions.

Methods: In vivo- Adenoviral GFP occludin was hydrodynamically delivered through the renal vein. Four days later the kidney was exposed and labeled tight junctions were selected for FRAP. FRAP was conducted on both pre and post ischemic tight junctions and on non-tight junction regions. In vitro-GFP occludin transduced MDCK cells were serum starved overnight. Cells were treated with 0 μM H_2O_2, 55 μM H_2O_2 or 110 μM H_2O_2 for 2 hours at 37° C before FRAP.The tight junction region or a non-tight junction region of the apical membrane was selected for FRAP.

Results: In vivo- The immobility of pre ischemic tight junctions is 93% (SD 9%). The immobility of ischemic tight junctions is 34% (SD 24%). The average half-life for recovery of ischemic tight junctions is 23.13 seconds (SD 1.07). The pre ischemic tight junctions show minimal recovery at 180 seconds post FRAP. In vitro: Control cells treated with 0 μM H_2O_2 have an immobility of 43% (SD 14%;) with a half-life of 68.2 seconds (SD 17.3 seconds). Cells treated with 55 μM H_2O_2 have an immobility of 32% (SD 16%) with a half-life of 88.5 seconds (SD 23.7 seconds). Cells treated with 110 μM H_2O_2 have an immobility of 37% (SD 15%) with a half-life of 82.3 seconds (SD 21.03 seconds). Results are statistically significant, p value <0.05.

Conclusions: In vitro tight junction turnover following FRAP occurs much faster in wild type cells then it does in injured cells. This data indicates that injury actually slows down tight junction turnover compared to control cells. However, these results are contradictory to the in vivo data that indicates ischemic injury increases tight junction turnover.

Funding: NIDDK Support

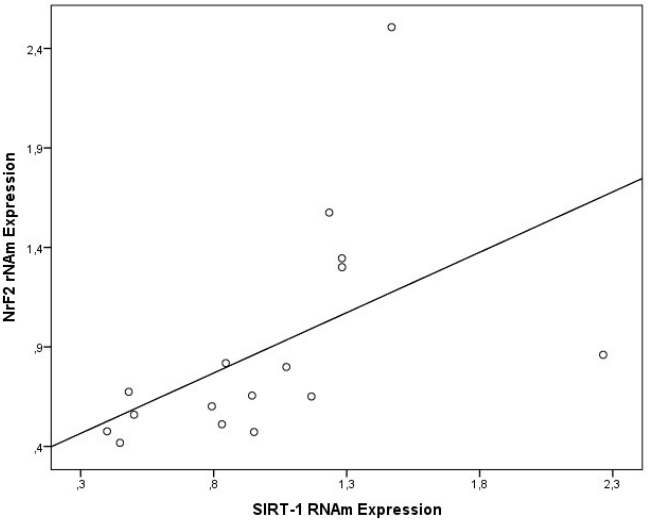
PUB111

Sirtuin-1 (Sirt-1) and Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) Interplay in Nondialysis CKD Patients Denise Mafra,[1] Juliana Saldanha,[1] Felipe Rizzetto Santos,[2] Viviane Oliveira Leal,[4] Alex Sandro Duarte Albuquerque.[3] *[1]Federal Fluminense Univ; [2]Federal Hospital of Lagoa; [3]Federal Univ of Rio de Janeiro; [4]Univ of the State of Rio de Janeiro.*

Background: The transcription factor nuclear factor-erythroid 2-related factor 2 (Nrf2) is responsible for the expression of antioxidant response element-regulated genes and is recognized to be a major cellular defense mechanism. The high Nrf2 expression might be mediate by Sirt1 activation. Sirtuins (SIRTs), a family of NAD-dependent histone deacetylases, regulate DNA repair and recombination, chromosomal stability, and gene transcription. In particular, SIRT-1 activation is associated with longevity and attenuation of metabolic disorders. There is no report about association between SIRT-1 and Nrf2 gene expression in CKD patients. The aim of this study was to verify the possible association between SIRT-1 and nuclear factor erythroid 2-related factor 2 (Nrf2) expression in nondialysis CKD patients.

Methods: Sixteen nondialysis CKD patients (65 ± years old, 11 women, estimated glomerular filtration rate (eGFR) of 33.1 ± 13.7mL/min/1.73m^2, and body mass index (BMI) of 28.5 ± 7.5kg/m^2) were studied. The peripheral blood mononuclear cells were isolated and processed for the evaluation of expression of Nrf2 and SIRT-1 by quantitative real-time polymerase chain reaction.

Results: Nrf2 and SIRT-1 mRNA expression was 0.65 (1.01) and 0.91 ± 0.39, respectively. SIRT-1 mRNA expression was negatively correlated with age (r= -0.53; p = 0.03); however, it was positively correlated with Nrf2 mRNA expression (r= 0.77; p = <0.001).



The linear regression analysis showed that age was an independent predictor for SIRT-1 expression after adjustment of gender, BMI, and eGFR(B = -0.54, p = 0.04).

Conclusions: Gene expression of SIRT-1 and Nrf2 are directly associated and age may be negatively related to antioxidant protection in nondialysis CKD patients.

PUB112

Effects of a Medical Food (ErgoD2) on the Progression of Chronic Kidney Disease Marvin Stanley Hausman,[1] Michael Herman Hermelijn,[2] Alvaro Mercado,[3] Kyle H. Ambert,[4] Bruno Michel Jedynak,[5] Hector J. Rodriguez.[6] *[1]Entia Biosciences, Portland, OR; [2]Bonaire Medical Clinic, Kralendijk, Bonaire, Netherlands Antilles; [3]Savia Salud, Medellin, Colombia; [4]Intel Corporation, Life Sciences, Hillsboro, OR; [5]Portland State Univ, Portland, OR; [6]Cedars-Sinai Medical Center, Los Angeles, CA.*

Background: Current standard of care overlooks the fact that Chronic Kidney Disease (CKD) is a multisystem functional disorder involving free radicals, inflammatory molecules, as well as catalytic metals, such as iron, that promote free radical production. This study proposes a novel non-pharmacologic approach to reno-protection through the use of a natural mushroom-based medical food, ErgoD2, which contains two potent antioxidants not produced by humans, L-Ergothioneine and vitamin D2. Two previously completed pilot studies in patients with type 1 and 2 diabetes and stage 5 CKD, treated with ErgoD2, revealed a significant decrease in plus 3 free radical iron.

Methods: 60 stage 3 and 4 CKD patients are under evaluation and following 2 stable values for eGFR, HbA1C and blood pressure receive two-500 mg capsules of ErgoD2 twice daily for 12 months. Patients are re-evaluated every 3 months with repeat physical and blood biomarker measurements standard in these disease stages, as well as Kidney Disease Quality of Life (KDQOL) questionnaires.

Results: To date, 24 patients are receiving ErgoD2 and 11 patients have completed three months of therapy. Three-month treatment results in the initial small group of patients showed eGFR improvement in 8 patients, stabilization in 1 patient and decline in 2 patients (see table below).

		eGFR	eGFR	%
Patient	Sex	Baseline	Treated	Change
1	F	54	66	22.2
2	F	15	15	0.0
3	F	17	19	11.8
4	F	45	47	4.4
5	M	50	46	-8.0
6	M	38	40	5.3
7	M	43	59	37.2
8	F	44	48	9.1
9	M	48	50	4.2
10	M	56	50	-10.7
11	F	40	45	12.5

Conclusions: The medical food, ErgoD2, represents a novel, non-pharmacologic approach to reno-protection. Continuation of the current open clinical trial is warranted and further data will be presented.

Funding: Pharmaceutical Company Support - Entia Biosciences, Inc.

PUB113

Treatment of Metabolic Acidosis in CKD Yields Better Overall Outcomes and at Lower Per Patient Cost when Done with Fruits and Vegetables Than $NaHCO_3$

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Background: Both $NaHCO_3$ and base-producing fruits and vegetables (F+V) improve metabolic acidosis (MA) in CKD and provide kidney protection but whether they differ in overall outcomes and management costs is unknown.

Methods: We randomized 108 subjects with CKD stage 3 eGFR (30-59 ml/min/1.73 m^2) and MA with plasma TCO_2 >22 but <24 mM as follows: F+V (n=36) to reduce dietary potential renal acid load (PRAL) 50% in the patient but was given to all household members, oral $NaHCO_3$ (HCO_3, n=36) to reduce PRAL 50%, or no alkali (Usual Care n=36). All were treated with antihypertensive and cholesterol-lowering drugs and followed 5 years with twice-yearly assessments of deaths, myocardial infarction (MI), cerebrovascular accident (CVA), and management costs. We used retail F+V cost although they were given free of charge, pharmacy drug costs, and Diagnosis Related Group costs for hospitalizations.

Results: There were 3 deaths in Usual Care, 1 in HCO_3 (all from MIs), and none in F+V. There were 6 MIs in 5 patients in Usual Care, 2 MIs in 2 patients in HCO_3, none in F+V, and one CVA in Usual Care but none in HCO_3 or F+V. Five-year cost per household was higher for F+V ($385,809) than HCO_3 ($231,981) and Usual Care ($263,634) but 5-year per patient cost was lower in F+V ($198,124) than the remaining groups. Lower per patient costs for F+V than HCO_3 and Usual Care was due to offsetting lower costs for hospitalizations ($0 vs. $50,074 vs. $95,360) and management of hypertension ($79,760 vs. $155,372 vs. $152,305) and serum cholesterol ($8,477 vs. $16,447 vs. $16,169).

Conclusions: Treating metabolic acidosis in this CKD population with F+V yielded fewer deaths, fewer cardiovascular events, and lower overall per patient management costs compared to HCO_3 and Usual Care over 5 years.

PUB114

An Open-Label Pilot Study of New Spherical Carbon Adsorbent Renamezin: Efficacy in Reducing Indoxyl Sulfate in Chronic Kidney Disease

Seung Kyu Kim,[1] Seok-Hyung Kim,[1] Hoon Young Choi,[1] Sang-Ho Lee,[2] So-Young Lee,[3] Dong Ho Yang,[3] Joo-Hark Yi,[4] Sang-Woong Han,[4] Young-Il Jo,[5] Hyeong Cheon Park.[1] *[1]Gangnam Severance Hospital, Yonsei Univ College of Medicine, Republic of Korea; [2]College of Medicine, Kyunghee Univ, Republic of Korea; [3]CHA Bundang Medical Center, CHA Univ, Republic of Korea; [4]Hanyang Univ Guri Hospital, Republic of Korea; [5]Konkuk Univ Hospital, Republic of Korea.*

Background: Reduced renal function in chronic kidney disease(CKD) causes systemic accumulation of indoxyl sulfate (IS), which has been shown to promote CKD progression. Renamezin® (Daewon Pharmaceutical Co., Korea) is a newly developed oral spherical carbon adsorbent with modified micropores that has high specificity for adsorbing indoles in the gastrointestinal (GI) tract. Aim of the study was to investigate whether oral administration of Renamezin® would reduce serum IS levels in CKD patients.

Methods: A total of 35 stable pre-dialysis CKD patients [mean age: 62 years, 82.9% male, serum creatinine (SCr) 1.5 ~ 5.0 mg/dL] were enrolled in this open-label pilot study. Renamezin® (7 capsules, t.i.d., 6 grams/day) was administered for 4 weeks. Serum IS as well as other parameters were measured at baseline and after 4 weeks. Wilcoxon Rank test was used to assess differences in IS before and after Renamezin® treatment.

Results: The mean SCr and estimated glomerular filtration rate (eGFR) was 2.58±0.98 mg/dL and 29.5±12.8 ml/min per 1.73 m^2, respectively. Serum IS negatively correlated with renal function(r=-0.478, p=0.003). Four weeks of Renamezin® treatment significantly reduced serum IS from baseline of 0.369±0.243 mg/dL to 0.322 ± 0.303 mg/dL (mean reduction of 14.6%, p=0.02) that was independent of baseline renal function. During the 4-week treatment period, Renamezin® did not adversely affect other renal parameters (SCr and eGFR) and was well tolerated (mean drug compliance: 92.1%). No severe side effects were reported except for GI symptoms (vomiting and diarrhea) in 4 patients (11.6%) and skin rashes in 1 patient (2.9%).

Conclusions: Our results suggest that newly developed carbon adsorbent Renamezin® significantly reduces serum indoxyl sulfate levels in moderate to severe pre-dialysis CKD patients.

Funding: Pharmaceutical Company Support - Daewon Pharmaceutical Co., Korea

PUB115

Abstract Withdrawn

PUB116

Safety, Tolerability and Pharmacokinetics of KBP-5074 in Patients with Mild-to-Moderate Chronic Kidney Disease: A Randomized, Open-Label Study

Bin Zhang,[1] Paul W. Crawford,[2] William B. Smith,[3] Kenneth Lasseter,[4] Fred Yang,[1] Xiaojuan Tan,[1] Peter Pelka.[1] *[1]KBP Biosciences USA Inc; [2]Research by Design Inc.; [3]New Orleans Center for Clinical Research; [4]Clinical Pharmacology of Miami, Inc.*

Background: Chronic kidney disease (CKD) is one of the leading causes of morbidity and mortality in the United States. Albuminuria and hypertension are two key risk factors for the development of end-stage renal disease. Effective therapy to combat these risk factors in CKD patients remains elusive. KBP-5074 is a novel, non-steroidal, highly selective mineralocorticoid receptor antagonist being developed for CKD.

Methods: In this randomized, open-label study, 14 patients with mild-to-moderate CKD (estimated glomerular filtration rate [eGFR] ≥30 and ≤89 mL/min/1.73 m^2, using the modification of diet in renal disease formula), albuminuria (urine albumin to creatinine ratio [UACR] ≥30 mg/g and ≤3,000 mg/g), and normal serum potassium (≤4.8 mmol/L at baseline) were randomized to either KBP-5074 0.5 mg (n = 8) or 2.5 mg (n=6) once daily and treated for 8 weeks. Safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) measures were assessed throughout this study.

Results: The mean age of the participants was 64 years; 35.7% were male. Baseline eGFR, blood pressure, and UACR values were similar in the 2 arms. Dose-dependent PK measures were observed, which was similar to healthy adults who received the same dose of KBP-5074. Compared to baseline, UACR was reduced by 58.9% in the KBP-5074 0.5 mg group and by 50.7% in the 2.5 mg group by Week 8. PK/PD analysis showed a trend toward a decrease in both systolic and diastolic blood pressures. Adverse events related to KBP-5074 were mild and infrequent. 2 subjects in the 2.5 mg group developed hyperkalemia (serum potassium >5.5 mmol/L); 1 subject in the 0.5 mg group with baseline serum potassium 5.0 mmol/L also developed hyperkalemia on study. These three subjects continued in the study. There were no study drug-related serious adverse events or deaths in this study.

Conclusions: This study demonstrated that KBP-5074 at a dose of 0.5 mg QD was safe and showed potential to reduce UACR and blood pressure in patients with mild-to-moderate CKD.

Funding: Pharmaceutical Company Support - KBP Biosciences USA Inc

PUB117

Influence of Depression, Anxiety and Stress on Dialysis Decision-Making

Cicero Italo Leite Bezerra, Bruno C. Silva, Glauce Rejane dos Santos, Keisy Lima Rizzetto, Rosilene M. Elias. *Nephrology, Univ de Sao Paulo, Sao Paulo, SP, Brazil.*

Background: The choice of renal replacement therapy (RRT) modality and the sharing-decision making is a situation that often involves anxiety and stress, which could influence on the modality choice. Depression is another factor highly prevalent among these patients that could also influence on this decision. However, only few studies have addressed the impact of these factors on the modality choice, which was the main objective of this current prospective study.

Methods: Patients were approached while attending the structured Pre-Dialysis Multidisciplinary Education Programme, with information session to help on the RRT modality decision-making. Scales of anxiety, depression and stress (Hospital anxiety and depression scale and perceived stress scale, respectively) were applied after the mentioned session and repeated later on when patients were already on peritoneal dialysis-PD or hemodialysis-HD. Demographic, clinical, biochemical and personal characteristics were also assessed.

Results: Sixty-three patients were enrolled (age 53 ± 15 years, 56% men, 59% Caucasian, 56% married, and 41% diabetic). Demographic, clinical and biochemical characteristics did not distinguish patients who choose PD or HD as their initial RRT modality. Women presented higher scores of depression (p=0.039), stress (p=0.050) and had a tendency toward to present higher scores of anxiety (p=0.064) than men. Scores of depression, anxiety and stress did not have any impact on the RRT modality. A small sample of the study population who already initiated dialysis was re-evaluated showing significant reduction of anxiety, depression and stress scores (p=0.004, p=0.012 and p=0.0016, respectively). Family support was the main determinant of PD choice.

Conclusions: Although women have presented high scores of depression, anxiety and stress, none of these factors have affected the decision-making process between PD and HD. Despite high levels of depression, anxiety and stress while on the process of RRT decision-making, these factors may be alleviated after the dialysis initiation.

PUB118

Mild Cognitive Impairment Is Highly Prevalent and Strongly Associated with Physical Function in Elderly Patients with Pre-Dialysis Chronic Kidney Disease Yuhei Otobe,[1] Koji Hiraki,[1] Chiharu Hotta,[1] Yasuhiro Taki,[2] Naohiko Imai,[2] Tsutomu Sakurada,[2] Yugo Shibagaki.[2] *[1]Dept of Rehabilitation Medicine, St. Marianna Univ School of Medicine Hospital, Kawasaki, Japan; [2]Div of Nephrology and Hypertension, Dept of Medicine, St. Marianna Univ School of Medicine, Kawasaki, Japan.*

Background: Chronic kidney disease (CKD) has been reported to be a risk factor for cognitive decline. However, the prevalence of mild cognitive impairment (MCI), a prodrome of dementia, and its risk factors remain to be determined. The purpose of this study is to clarify the prevalence and to elucidate the risk factors of MCI in elderly patients with pre-dialysis CKD.

Methods: The subjects were 122 elderly (≥ 65 years old) pre-dialysis CKD patients of our outpatient nephrology clinic (average age 77.7 years old with 96 males). Mini Mental State Examination (MMSE) and Japanese version of Montreal Cognitive Assessment (MoCA-J) was used as cognitive function tests. Patients with MMSE>23 and MoCA-J≥26 were diagnosed as normal, those with MMSE>23 and MoCA-J<26 were diagnosed as having MCI, and those with MMSE≤23 diagnosed as having dementia. Grip strength, knee extension strength, 4m comfortable walking speed, one leg stance time, the skeletal muscle index were measured as physical function. We investigated the presence of diabetes, history of smoking/drinking, and blood biochemical test as patients' characteristics.

Results: 47 cases were identified as normal, 71 cases MCI, and 4 cases dementia, thus, 58.2 % of the elderly pre-dialysis CKD patients had MCI, and this prevalence was much higher than the prevalence of 18.8 % in community dwelling elderly Japanese. Characteristics of Normal group and MCI group were compared. Age was 74.9 vs 78.9 years ($p < 0.01$), hemoglobin was 12.4 vs 11.6 g/dL ($p < 0.01$), walking speed was 124.5 vs 103.6 cm/sec ($p < 0.01$), one leg stance time was 28.9 vs 12.7 sec ($p = 0.01$). By logistic regression analysis, age and walking speed were significantly associated with MCI ($p < 0.01$).

Conclusions: Mild cognitive impairment is highly prevalent (58.2%) and strongly associated with physical function in elderly patients with pre-dialysis chronic kidney disease.

PUB119

Disease Awareness Significantly Impacts the Quality of Life in CKD Patients Colin A. Hinkamp,[1] Emma Rebecca Segal,[1] Xuerong Wen,[1] Ashutosh M. Shukla.[2,1] *[1]Medicine, Univ of Florida, Gainesville, FL; [2]NF/SG VHS, Gainesville, FL.*

Background: Despite established value in the management of many chronic conditions, there is limited data correlating disease awareness to quality of life (QoL) in CKD patients.

Methods: We conducted a cross sectional study of patients attending a university nephrology practice with the aim of assessing the effect of demographic, socioeconomic, literacy and disease awareness states on QoL. All consenting subjects were administered a set of surveys aimed to gather demographics, Charlson Comorbidity Index (CCI), REALM-SF, KDQoL-36, and a novel CKD disease awareness questionnaire.

Results: Initial findings of an ongoing study with the first 108 enrollees is presented. We found high health literacy and mildly elevated comorbidity indices across the spectrum of CKD. Despite these, average CKD patients displayed poor CKD awareness (19.6 ± 9.2, out of 45) and average physical (39.6 ± 11.7) and mental (49.5 ± 10.4) QoL. Univariate analysis showed that physical QoL had the strongest positive correlation with CKD awareness ($R=0.27$; $p=0.009$) and strongest negative correlation with comorbidities indices ($R=-0.45$; $p<0.001$). Multivariate analysis, adjusting for age, gender, health literacy, economic affluence and renal function, showed that amongst the factors affecting mental QoL, male gender, African American race, and economic affluence had the strongest positive impact. Multiple comorbidities and poor CKD awareness had the strongest negative impact on physical QoL. Duration of renal care was found to be insignificant after adjusting for other risk factors.

	Significant Risk Factors	Estimates ± SE	p
KDQoL Physical Score	CKD Awareness	0.36 ± 0.12	0.003
	Length of Renal Care	0.27 ± 0.17	0.12
	CCI score	-2.43 ± 0.44	<0.0001
	R^2	0.32	
KDQoL Mental Score	Household Income	6.01 ± 2.27	0.01
	Race	7.61 ± 2.66	0.005
	Gender	5.27 ± 2.33	0.03
	R^2	0.17	

Conclusions: Our results show that disease awareness and not just the nephrology care is a significant modifiable risk-factor affecting CKD patients' QoL. It provides rationale for elucidating the viability of improving outcomes by adding an educational component to standard treatment.

PUB120

Quality of Life of Non-Dialysis Chronic Kidney Disease Patients: Comparative Reports of Nephrologists and Patients According to the First Results of MAEVA Gilbert Deray,[1] Jean-Philippe Bertocchio,[2] Myriam Rouchon Isnard,[3] Philippe Zaoui,[4] Thierry Baranger.[5] *[1]SITEGPR Nephrology, La Pitié-Salpêtrière Hospital, Paris, France; [2]Renal and Metabolic Diseases Unit, European Georges-Pompidou Hospital - Paris Descartes Univ, Paris, France; [3]Dialysis Unit, AURA Auvergne, Chamalières, France; [4]Nephrology, Grenoble Univ Hospital, La Tronche, France; [5]Nephrology-Dialysis, Bordeaux Nord Aquitaine Polyclinic, Bordeaux, France.*

Background: The quality of life (QoL) of non-dialysis chronic kidney disease (CKD) patients is impaired, but very little has been specifically published. The French study MAEVA aimed to evaluate this clinical aspect and to compare the opinion of nephrologists and patients on the comprehensive management of CKD patients in France.

Methods: A self-completion questionnaire was sent by mail to 1,282 French nephrologists. A "mirror" self-completion questionnaire was given to CKD patients (stages 3, 4 and 5) by nephrologists. Data were collected prospectively and anonymously.

Results: Between February and August 2015, 261 nephrologists and 172 patients completed the questionnaires. Responding patients (22%) stated their renal condition had a major impact on QoL. CKD affected energy (77%), physical capacity (75%), mood (64%), sleep (55%), sexuality (45%), and appetite (33%). However, nephrologists did not systematically investigate QoL impairment: only 51% of respondents questioned their patients on QoL, and approximately one third probed them on sleep disorders, depression or anxiety (39%, 38% and 30%, respectively). Sexuality was rarely discussed by nephrologists, with only 16% stating that they investigated possible sexual disorders. This figure was confirmed by patients, of whom 17% only mentioned that they have been questioned on this issue during follow-up. However, 59% of patients felt comfortable with discussing such topic with their nephrologist.

Conclusions: Regarding QoL, communication between non-dialysis CKD patients and nephrologists could be improved by the use of tools, such as an adapted questionnaire completed by patients before visit.

Funding: Pharmaceutical Company Support - Roche

PUB121

Magnetic Resonance Spectroscopy and Psychological Status in CKD Stage 4-5 Patients Chun Zhang, Ying Chen, Shan Chen, Cheng Wan, Hua Su. *Nephrology, Union Hospital, Tongji Medical College, Huazhong Univ of Science and Technology, Wuhan, Hubei, China.*

Background: The study aimed to explore magnetic resonance spectroscopy (MRS) and psychological status in CKD stage 4-5 patients.

Methods: This study enrolled 35 patients with stage 4-5 CKD, including 10 pre-dialysis patients, 15 hemodialysis (HD) patients and 10 peritoneal dialysis (PD) patients. Dialysis duration, dialysis sufficiency, hemoglobin (Hb), and parathyroid (PTH) were recorded as baseline data. All the patients accepted psychological assessment by SDS, SAS, SCL-90 and MRS for bilateral amygdalae, hippocampi and anterior cingulate cortices (ACC).

Results: The positive rates of SDS and SAS were 20%, while that of SCL-90 was 34.29% in CKD stage 4-5 patients. SDS score, F1 somatization, F7 terror were negatively correlated with N-acetyl Aspartate (NAA)/Creatinine (Cr) in right amygdala. F9 psychosis was negatively correlated with Myo-inositol (MI)/Cr in left hippocampus, and Glutamate complex (Glx)/Cr in ACC. Compared to HD patients, pre-dialysis patients got higher scores in SCL-90, F2 force, F3 relationship, F5 anxiety, F8 paranoid, and F9 psychosis. In addition, the pre-dialysis patients graded higher in F9 psychosis than the PD patients. The HD patients had a lower NAA/Cr in left amygdale and a higher Glx/Cr in ACC than pre-dialysis patients. Among all patients, the HD patients had the highest Choline-containing compounds (Cho)/Cr and MI/Cr in ACC. Moreover, the HD patients' Cho/Cr in left amygdala was higher than PD patients'. PTH was negatively correlated with F9 psychosis, while dialysis duration, Cho/Cr, MI/Cr, and Glx/Cr in left amygdala were positively correlated. Dcr4/Pcr was negatively associated with MI/Cr in left amygdala. Hemoglobin level showed a negative correlation with NAA/Cr in left amygdala and a positive correlation with MI/Cr in left hippocampus.

Conclusions: CKD stage 4-5 patients are inclined to suffer from many psychological problems, especially the pre-dialysis patients. HD patients present the most obvious alterations in MRS. PTH might influence F9 psychosis, while dialysis duration, dialysis sufficiency, and Hb level have certain effects on MRS.

Funding: Government Support - Non-U.S.

PUB122

Kidney Disease in Type 2 Diabetes Is an Independent Risk Factor for Peripheral Artery Disease: A Cross-Sectional Analysis Niraj Desai, Nivetha Subramanian, Krishna H. Patel, Jennifer W. Xu, Michael S. Simonson. *Nephrology, Case Western Reserve Univ School of Medicine, Cleveland, OH.*

Background: Diabetic kidney disease (DKD) affects more than 7 million adults in the United States, is the most common cause of end stage renal disease, and doubles the risk of coronary artery disease and death. Patients with DKD also suffer from disproportionately high rates of critical limb ischemia and amputation. We asked whether DKD is a risk factor for peripheral artery disease (PAD).

Methods: We conducted a cross-sectional analysis of patients with type 2 diabetes and glomerular filtration rate (eGFR) ranging from 7-146 ml/min/1.73 m2. PAD was diagnosed

by standardized physical examination and history. eGFR was calculated from the serum creatinine-based MDRD equation. Potential confounders of the relationship between eGFR and PAD were assessed by multivariable logistic regression.

Results: Of 96 participants (median age 58 (range 30 - 84); median eGFR 72.4 ± 33.0 ml/min/1.73 m2), 43 % had PAD. Duration of diabetes (7.0 ± 7.2 years) and HbA1c (7.7 ± 1.8 %) were similar in patients with and without PAD (P = 0.901 and 0.196, respectively). eGFR < 60 ml/min/1.73 m2 was associated with increased risk of PAD (odds ratio ± SE) 2.7 ± 1.3, P = 0.034. Association of low eGFR with PAD was stronger (3.7 ± 2.1, P = 0.023) after adjustment for PAD risk factors in the general population: systolic blood pressure, smoking, duration of diabetes and HbA1c. PAD was not associated with albuminuria defined as albumin/creatinine ratio (1.0 ± 0.001, P = 0.425).

Conclusions: Our results suggest that kidney disease in type 2 diabetics is a risk factor for PAD. For timely diagnosis and risk factor modification, patients with DKD should be screened for PAD.

Funding: Other NIH Support - NIH R01DK096549 and the Rosenberg Foundation for Kidney Research

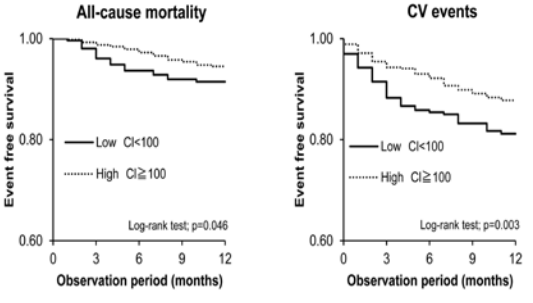
PUB123

Serum Chloride Levels Predict Cardiovascular Morbidity and Mortality in Patients on Incident Dialysis Yosuke Saka,[1] Tomohiko Naruse,[1] Daijo Inaguma.[2] *[1]Internal Medicine, Kasugai Municipal Hospital, Kasugai, Aichi, Japan; [2]Nephrology, Nagoya Daini Red Cross Hospital, Nagoya, Aichi, Japan.*

Background: Patients with advanced chronic kidney disease (CKD) have an electrolyte imbalance due to impaired kidney function. Several studies have associated increased morbidity and mortality with abnormalities in serum sodium, potassium and phosphate among patients with CKD. However, whether serum chloride levels are associated with morbidity and mortality in such patients, especially those on incident dialysis, remains obscure. We investigated whether serum chloride levels can predict morbidity and mortality after starting dialysis in the AICOPP study (Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis).

Methods: Among 1,525 patients who started dialysis between October 2011 and September 2013 and were enrolled in the retrospective, multicenter cohort AICOPP study, 278 were excluded from analysis due to incomplete data. We followed up the remaining participants for 12 months after enrollment. The primary and secondary endpoints were all-cause mortality and cardiovascular (CV) events, respectively. Serum chloride levels were categorized as low or high (Cl < 100 and ≥ 100 mEq/L, respectively) and data were analyzed using the Kaplan-Meier method and Cox hazards models.

Results: The mean serum chloride level was 103.9 mEq/L. Approximately 20% of the patients had low serum chloride levels that were significantly associated with all-cause mortality and CV events.



Multivariate Cox hazards models selected low serum chloride as an independent risk factor for CV events (adjusted hazard ratio [HR], 1.68; 95% confidence interval [CI], 1.08 – 2.59, p < 0.05).

Conclusions: Serum chloride levels might serve as a practical biomarker to predict morbidity and mortality, especially CV events, in patients on incident dialysis.

PUB124

Effect of Methoxy Polyethylene Glycol – Epoetin β (Mircera) on Plasma Levels of sE-selectin, sICAM-1, sVCAM-1, NT-proBNP and Left Ventricle Structure and Function in Patients with Chronic Kidney Disease Jacek Rysz,[1] Ewa Majewska,[2] Beata Franczyk,[1] Zbigniew Baj,[2] Piotr Bartnicki.[1] *[1]Dept of Nephrology, Hypertension and Family Medicine, Medical Univ of Lodz, Lodz, Poland; [2]Dept of Pathophysiology and Immunology, Medical Univ of Lodz, Lodz, Poland.*

Background: Anemia and endothelial dysfunction may be involved in pathogenesis of atherosclerosis, disadvantageous changes in left ventricle structure and function and cardiovascular complications in CKD patients. In this study we aimed to determine effect of Mircera on chosen plasma and echocardiographic parameters in CKD.

Methods: 28 patients with stage IV of CKD and anemia, treated with Mircera, were enrolled to the study. Control group included 15 volunteers. Plasma levels of sE-selectin, sICAM-1, sVCAM-1 were measured with ELISA kits. Echocardiographic examination was performed (EF – ejection fraction, LVM – left ventricle mass, LVESd – left ventricle end systolic diameter, LVEDd - left ventricle end diastolic diameter).

Results:

	CKD before treatment	CKD after treatment	Control group
Hb [g/dl]	9.5 (9.0 – 10.1)*	11.5 (11.0 – 12.1)* •	14.5 (13.3 – 14.9)
NT-proBNP [pg/ml]	355.6 (282.3 - 432.7) *	302 (182.1 – 401.3)* •	75 (49 – 101)
sE-selectin [ng/ml]	33.1 (25.6 – 36.4) *	29.3 (24.8 – 33.9)* •	16.1 (11.9 – 22.2)
sICAM-1 [ng/ml]	460.1 (352 – 519.2)*	409.1 (371.3 – 501)* •	245 (232 – 281)
sVCAM-1 [ng/ml]	2640 (1790 – 4052)*	2340 (1450 – 2945)* •	890 (680 – 1340)
EF [%]	34 (29 – 40)*	41 (36 – 49)* •	58 (50 – 64)
LVM [g]	286.4 (218.3 – 359)*	278.1 (186 – 352.1)*	208.2 (165 – 249)
LVESd [mm]	41.2 (35.1 – 47.4)*	39.2 (33.1 – 45.2) * •	36.1 (30.2 – 40.9)
LVEDd [mm]	49.1 (41.3 – 54.9)*	46.9 (40.1 – 51.9)* •	40.6 (32.9 – 47)

*p < 0.05 to control group, •p < 0.05 to CKD before treatment.

Conclusions: Evaluated plasma and echocardiographic parameters were significantly increased but EF was significantly decreased in CKD patients compared to controls. Anemia treatment with Mircera may diminish endothelial dysfunction as well as improve left ventricle structure and function in these patients.

PUB125

The Association between Insulin Resistance and Atrial Fibrillation: A Cross-Sectional Analysis from the Systolic Blood Pressure Intervention Trial Monique E. Cho,[1] Timothy Craven,[2] Alfred K. Cheung,[1] Stephen P. Glasser,[3] Mahboob Rahman,[4] Elsayed Z. Soliman,[2] R. Stafford,[5] Karen C. Johnson,[6] Jeffrey T. Bates,[7] Anna Marie Burgner,[8] Addison A. Taylor,[7] Leonardo Tamariz,[9] Rocky Tang,[10] Srini Beddhu.[1] *[1]Univ of Utah; [2]Wake Forest School of Medicine; [3]Univ of Alabama at Birmingham; [4]Case Western Reserve Univ; [5]Stanford Prevention Research Center; [6]Univ of Tennessee Health Science Center; [7]Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine; [8]Vanderbilt Univ; [9]Univ of Miami; [10]Columbia Univ.*

Background: Observational studies conducted in the general population have suggested that metabolic syndrome (MetS), which is closely linked to insulin resistance (IR), is associated with atrial fibrillation (AF). It is less clear, however, if IR is associated with AF in an older population with greater cardiovascular (CV) risk, including chronic kidney disease (CKD). We thus investigated the association between MetS and IR with AF in the participants of the Systolic Blood Pressure Intervention Trial (SPRINT).

Methods: We limited our analyses to 8263 SPRINT participants with all available covariates for analyses. We defined IR as fasting glucose ≥100 mg/dL and increased serum triglycerides-to-HDL-cholesterol ratio levels ≥ 3.0 for whites and Hispanics and ≥2.0 for non-Hispanic blacks. MetS was defined based on the Modified Third National Cholesterol Education Program. We used body mass index >30 kg/m^2 as a substitute for waist circumference, which was not collected. CKD was defined as MDRD eGFR <60 ml/min/1.73m^2. Multivariable logistic regression models were used to examine the strength of association between the risk factors and AF.

Results: The baseline prevalence rates for IR and MetS were 60% and 55%, respectively, while 8.2% of the participants had AF. In multivariate regression analyses, only age, white race, history of CV disease, decreased serum triglyceride level, and albuminuria remained significantly associated with AF risk. AF was not associated with IR or presence of MetS in CKD or non-CKD subgroups.

Conclusions: In contrast to the general population, IR and MetS were not associated with AF in the older population with increased CV risk studied in SPRINT.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIA, and NINDS, VA Support

PUB126

Serum Free Light Chains Predict All-Cause Mortality in Chronic Kidney Disease: A Systematic Seview and Meta-Analysis Simon D.S. Fraser,[1] Anthony Fenton,[2] Scott Harris,[1] Anne Burmeister,[5] Adam Shardlow,[4] Sophie Liabeuf,[6] Ziad Massy,[7] Martin J. Landray,[8] Jonathan R. Emberson,[8] Philip A. Kalra,[3] Paul Cockwell,[2] Maarten W. Taal.[4] *[1]Southampton Univ; [2]Univ Hospitals Birmingham; [3]Manchester Univ; [4]Nottingham Univ; [5]Binding Site; [6]Amiens Univ Hospital; [7]Ambroise Paré Univ Hospital & Inserm; [8]Oxford Univ.*

Background: Serum immunoglobulin (Ig) free light chain (FLC) assays are used in identifying and monitoring clonal FLC (kappa (κ) or lambda (λ) in paraproteinaemia. In the absence of a paraprotein, high serum levels of polyclonal combined (c)FLC (κ and λ) have been associated with increased mortality in CKD. The study aimed to synthesise current evidence for cFLC as a mortality risk predictor in CKD.

Methods: Four databases (Medline, Embase, CINAHL, PubMed) were searched using terms for CKD and Ig light chains. Inclusion criteria: quantitative CKD studies, FLCs measured, mortality as outcome. Excluded: paraproteinaemia and dialysis associated terms. Two reviewers independently assessed study inclusion and quality. Individual patient data obtained from all included studies were combined for common variables and Cox regression models used to explore the relationship between cFLC>43.3mg/L (95th percentile normal range) and all-cause mortality using fixed effect for study ID.

Results: 5 cohort studies were included (combined n=3688). All had used the Freelite™ assay. Studies were moderate to high quality. Mean age was 67 (SD 14) years, 1842 (50%) were male, 810 (22%) had diabetes and 1229 (33%) had cardiovascular disease (CVD).

Mean eGFR was 41.8 ml/min/1.73m2 (SD 17.4). On multivariable analysis adjusted for age, sex, diabetes, CVD, MDRDeGFR, albumin, calcium and renin angiotensin system inhibitors, elevated serum cFLC was independently associated with all-cause mortality.

	HR	95% CI	p
Age(years)	1.06	1.05-1.06	<0.001
Male(y/n)	1.28	1.10-1.51	0.002
Diabetes(y/n)	1.31	1.12-1.53	0.001
CVD(y/n)	1.59	1.36-1.85	<0.001
eGFR (ml/min/1.73m2)	0.98	0.97-0.98	<0.001
Albumin (g/L)	0.95	0.94-0.97	<0.001

Conclusions: In this first meta-analysis of patient-level data cFLCs predicted all-cause mortality across the full spectrum of CKD and may be useful for risk-stratification.

PUB127

HDL and LDL Cholesterol Subfractions in Chronic Kidney Disease Patients

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Background: Chronic kidney disease (CKD) is a worldwide public health problem which is associated with increased cardiovascular risk. Recent studies indicate that the level of individual LDL and HDL subfractions may be more important that their total concentration. Moreover, some points that in pathological conditions HDL may lose its protective functions.

Methods: The study group consisted of a total of 115 patients with CKD (25 with stage II, 25 - stage III, 25 – stage IV, 40 – stage V), and control group consisted of 25 healthy volunteers. Complete medical history was obtained from all subjects. Subfractions of LDL (7) and HDL (10) cholesterol were analysed with the use of Lipoprint™ system (Quantimetrix Corp.) according to the manufacturer's instructions.

Results: Differences in nearly all LDL and HDL subfractions distribution were observed between CKD stages and between CKD patients and controls. HDL1-HDL4 and large HDL subfractions were significantly more abundant in patients with end-stage renal disease, while their amount was lower in controls (HDL1 - P<0.0001; HDL2- p=0.013; HDL3 – p=0.003; HDL4 – p=0.004). The highest concentration of HDL7- HDL10 and small HDL subfractions were found in control group, and it gradually decreased along with worsening kidney function (HDL7 – P=0.001; HDL8- P<0.0001; HDL9 – P<0.0001; HDL10 – P<0.0001). Moreover, the concentration of IDL-C, IDL-B and IDL-A were higher in patients with CKD V, while LDL2 and LDL3 concentration were higher in control group (IDL-C – P=0.010; IDL-B- p=0.001; IDL-A – p<0.0001; LDL2 – P<0.0001; LDL3 – P=0.007).

Conclusions: This study indicated higher prevalence of large HDL subfractions in CKD V patients. Predomination of larger HDL particles in patients with coronary artery disease was observed in other studies. Despite the fact that role of individual HDL subfractions remains unknown, it can be hypothesized that the abundance of large HDL or decreased concentration of small HDLs may participate in increased cardiovascular risk observed in CKD.

PUB128

The Association between Creatinine versus Cystatin C-Based eGFR and Cardiovascular Risk Using PDAY Risk Score in Children with Chronic Kidney Disease

Sheena Sharma, Michelle Denburg, Susan L. Furth. *Nephrology, Children's Hospital of Philadelphia, Philadelphia, PA.*

Background: Children with CKD have a high prevalence of cardiovascular disease (CVD) risk factors. Among adults with CKD, cystatin C-based eGFR demonstrate a stronger predictive value for cardiovascular events compared to creatinine-based eGFR. The PDAY (Pathobiological Determinants of Atherosclerosis in Youth) risk score is a validated tool used to estimate the probability of atherosclerotic lesions within coronary arteries in adults. The objective was to assess the association between cystatin C- vs creatinine-based eGFR and cardiovascular risk using modified PDAY risk score as a proxy for CVD in children and young adults.

Methods: We used cross-sectional data from 71 CKD subjects (15.5 yrs, (13, 17), eGFR creatinine 50mL/min/1.73m^2 (27, 74), eGFR cystatin C 53mL/min/1.73m^2 (32, 74)), and 33 controls (15.1 yrs (13, 17), eGFR creatinine 112mL/min/1.73m^2 (85, 128), eGFR cystatin C 114mL/min/1.73m^2 (87, 135)). eGFR was calculated using age-appropriate creatinine and cystatin C-based formulas. PDAY risk scores (include sex, age, serum lipoprotein, obesity; modified by smoking, hypertension, hyperglycemia) were used to determine probability of coronary artery atherosclerosis. Spearman's correlation, chi-square, and ordinal logistic regression were used.

Results: PDAY scores ranged from -2 to 16 (higher score equals greater risk). The correlation between eGFR creatinine and eGFR cystatin C with coronary PDAY scores were -0.26 (p<0.007) and -0.27 (p<0.005), respectively. Ordinal logistic regression showed similar association between higher eGFR creatinine and eGFR cystatin C and lower PDAY scores. Chi-square between CKD severity (stage 1-4) and PDAY categories (low 0,-1; moderate 1-5; high risk ≥5) was not significant for eGFR creatinine (p=0.09) but was significant for eGFR cystatin C (p=0.03).

Conclusions: The correlation between eGFR by cystatin C or creatinine with PDAY risk score was similar. A slightly stronger association between CKD stage and PDAY score was seen with eGFR cystatin C when assessed by chi-square. Further studies should explore the association between cystatin C and cardiovascular risk in children with CKD.

PUB129

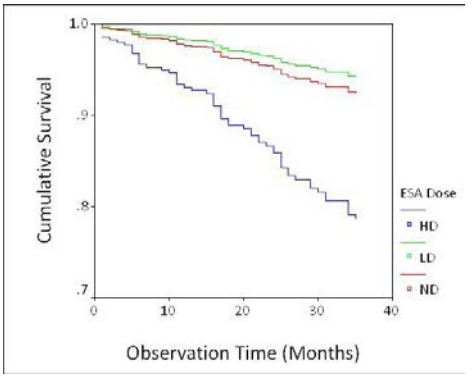
Higher-Dose Erythropoiesis-Stimulating Agents (ESA) to Maintain Higher Target Hemoglobin Is Associated with Higher Risk of Mortality and Cardiovascular Event Risk in Patients with Chronic Kidney Disease (CKD): The CKD-ROUTE Study

Seiko Ishikawa,[1] Soichiro Iimori,[2] Shotaro Naito,[2] Eisei Sohara,[2] Tomokazu Okado,[2] Sei Sasaki,[2] Tatemitsu Rai,[2] Shinichi Uchida.[2] *[1]Nephrology, Tokyo Kyosai Hospital, Japan; [2]Nephrology, Tokyo Medical and Dental Univ, Japan.*

Background: Recent studies showed that the use of ESA for treatment of renal anemia to achieve high hemoglobin (Hb) levels was associated with an increased risk of adverse events in CKD patients. We evaluated the relationships among ESA doses, mortality, and risk of CV events.

Methods: This prospective cohort study was comprised of 776 pre-dialysis patients with CKD G2-G5 enrolled from 2010 to 2011. Patients were followed up until ESRD, death, transfer, or the end of 3-years follow-up. The outcome was a composite of all-cause mortality or CV events. We categorized patients into 3 groups according to ESA doses : no dose group (ND) ; lower dose group (LD) (<3111 IU/month) ; higher dose group(HD) (≥3111 IU/month). Three groups were compared using the log-rank test and the adjusted hazard ratio (aHR) was estimated using multivariate cox hazards model.

Results: During a median follow-up of 36 months, 64 CV events occurred, 40 patients died, and 97 patients reached the outcome. HD was associated with greater mortality and risk of CV events than both LD and ND (HD vs LD: aHR 2.05 [95% confidence interval (CI) 1.04-4.06], HD vs ND: aHR 1.94 [95%CI 1.00-3.75]). When patients were further stratified according to their achieved Hb levels, ESA dose did not affect the outcome in patients with Hb < 10 g/dl. However, in patients with Hb ≥ 10 g/dl, higher ESA dose increased mortality and CV event risk (HD vs LD: aHR4.01 [95%CI 1.28-12.6], HD vs ND: aHR 3.03 [95%CI 1.32-6.99]).



Conclusions: Use of higher-dose ESA to achieve higher target Hb levels in CKD patients was associated with greater risk of mortality and CV events.

PUB130

Undiagnosed and Uncontrolled Hypertension in Primary Care: The Role of Awareness of the Renal Risk

Marco Sartori,[1] Luca Valerio,[2] Silvia De Rosa,[1] Faeq Husain-Syed,[1] Stefano Cattin,[1] Mirella Zancato,[3] Claudio Ronco.[1] *[1]Nephrology, St. Bortolo Hospital, Italy; [2]Medicine, Univ of Amsterdam, Netherlands; [3]Pharmacy, Univ of Padua, Italy.*

Background: To assess the distribution and features of pts with undiagnosed and uncontrolled arterial hypertension(AHT)in the community setting,we have conducted a cross-sectional survey of the general population through community pharmacies in the North-Eastern area of Italy.In addition,we assessed awareness among pts of the role of AHT as a risk factor for chronic kidney disease(CKD).

Methods: The survey was carried out between Oct-2014 and Feb-2015.Participants were selected among the pts of 35 pharmacies.All participants were interviewed by using a structured questionnaire(18-items),and their blood pressure(BP)was measured.The survey included previous diagnosis of AHT,risk factors for CKD,and knowledge of AHT as risk factor for CKD.We identified factors associated with awareness of the renal risk associated with AHT.

Results: The sample included 2036 subjects aged ≥18 yrs(39.2% male;24% below age 45;31.4% older than 65;44.6% between age 45 and age 65).40.1% of subjects was in treatment for AHT;awareness of the renal risk associated with AHT was reported by 48.4% of the participants.Non-white ethnicity,smoking,higher BMI were all associated with lower awareness of the hypertensive renal risk.In contrast, diagnosis of AHT,family history of AHT,and family history of renal disease were all associated with higher awareness of the hypertensive renal risk,with family of history of renal disease displaying the strongest association(OR 2.32[1.70-3.15];p<0.05).All associations were statistically significant for p<0.05.Of 1219(59.9%)participants without diagnosis of AHT 29.0% were found to have AHT upon BP mesurement.In this group awareness of the hypertensive renal risk has a protective effect against undiagnosed AHT(OR 0.69[0.52-0.92];p<0.05).In contrast, awareness of the hypertensive renal risk has not protective effect against uncontrolled AHT among hypertensive pts.The rate of uncontrolled AHT was 58.0% of hypertensive pts.

Conclusions: The rate of awareness of the renal risk associated with AHT demands more attention in the primary care setting due to its potential benefit on undiagnosed AHT.

Funding: Private Foundation Support

PUB131

Hypertriglyceridemia and Inflammatory Markers as Predictors of Survival in Cohort of Patients with Chronic Kidney Disease Maristela Bohlke,[1] Gabriela Araujo Duarte,[1] Alexia Schuch,[1,2] Jamile Gardin Dos Santos,[1] Luiza Morrone Gastaud,[1] Mateus De Mamann Vargas,[1] Annelise Reges,[1] Franklin Correa Barcellos.[1,2] *[1]Medicine School, Univ Catolic of Pelotas, Pelotas, Brazil; [2]Medicine Faculty, Univ Federal of Pelotas, Pelotas, Brazil.*

Background: Systemic inflammation, dyslipidemia and other metabolic disorders has been associated with increased cardiovascular mortality. Exercise is a non-drug intervention with positive effects on metabolic profile and inflammation in individuals with chronic diseases and the general population. Objective is correlate inflammatory and metabolic markers with the long-term prognosis of a cohort of patients with chronic kidney disease (CKD) who suffered an intervention with exercise.

Methods: Hypertension and nondiabetic patients with GFR ≤60 mL/min/1.73m2 were included in a randomized clinical trial (RCT) that evaluated effects of an exercise program on cardiovascular disease markers. demographic factors and clinical (blood glucose, lipid profile, C-reactive protein (CRP), body mass index (BMI), ankle brachial index (ABI) at baseline and after 4,8 and 16 weeks of exercise. At the end of the intervention patients were followed-up to investigate the exercise long-term effects and identify quality predictors of life and mortality.

Results: A total of 150 patients allocated to the RCT, 65 patients had CKD. The long-term follow-up lasted for an average of 2.75 (1:06 to 4:29) years. Predictors of mortality were elevated CRP levels (OR 1.16 95% CI 1:00 to 1:34) and triglycerides (OR 1.1 95% CI 1:00 to 1:01). Other markers such as LDL cholesterol, BMI and blood glucose showed no detectable impact on mortality, as well as intervention with physical exercise. The ITB tended (OR 0 .027 0 95% CI .00 to 2.44) to be associated with mortality. Among the 65 patients with CKD were recorded 10 deaths during the follow-up period.

Conclusions: Larger studies with adequate samples are needed to confirm the prognostic impact of hypertriglyceridemia and elevated CRP for patients with pre-dialysis CKD, as well as the tendency of association between peripheral arterial disease as with ABI and mortality in this population increase.

PUB132

Change in Albuminuria and Incident Cardiovascular Events among Diabetic Patients: Results from the Kailuan Study in China Jinwei Wang,[1] Shouling Wu,[2] Luxia Zhang.[1] *[1]Renal Div, Dept of Medicine, Peking Univ First Hospital, Beijing, China; [2]Dept of Cardiology, Kailuan Hospital, Tangshan, Hebei, China.*

Background: Albuminuria is one of the biomarkers to define chronic kidney disease. However, there are few studies concerning pattern of albuminuria change in relation to adverse outcomes.

Methods: Our study is based on a cohort study among 101510 employees of Kailuan group in Tangshan of China. Diabetic patients without a history of cardiovascular disease(CVD) at baseline(2006-2007) and also available at the second circle of examination(2008-2009) were included(n=5002). Definition of diabetes was based on glucose concentration or self-reported diagnosis. Albuminuria was measured by dipstick test from morning spot urine. CVD was a composite of myocardial infarction and stroke and followed-up until December 31, 2010. A total of 4954 participants were included in the final analysis after excluding 48 CVD events occurred baseline through the second circle of examination. Latent mixture modeling was used to identify albuminuria trajectories. Multivariate Cox proportional hazards regression model was fit to assess the association of albuminuria trajectories with CVD. The covariates included age, gender, education, smoking, body mass index, mean arterial pressure, and estimated glomerular filtration rate.

Results: The mean age of the study participants was 52.5±9.5 years with 78.16% of males. Three discrete trajectory groups of albuminuria were identified: persistent negative(74.2%[95% confidence interval[CI] 72.8-75.6], n=3799), positive to negative(8.6%[95%CI 7. 6-9.7], n=363) and persistent positive(17.2% [95%CI 16.1-18.4], n=792). With a median of 1.95 years (0.08-2.56 years) of follow-up, 63 composite CVD were recorded with 39, 5 and 19 events in the three groups, respectively. Using the persistent negative group as reference, persistent positive group showed an increased risk of CVD with the multivariate adjusted hazard ratio(HR) of 2.2(95%CI 1.3-3.9), while positive to negative group did not show an association with CVD(HR=1.2 [95%CI 0.5-3.0]).

Conclusions: Persistent albuminuria was found as a risk factor for CVD, while transient albuminuria shows no risk among diabetic patients.

Funding: Government Support - Non-U.S.

PUB133

Echocardiographic Evaluation of Left Atrial Volume Index in Patients with Chronic Kidney Disease Syed Rizwan A. Bokhari,[1] Muhammad Zaman Khan Assir,[2] Shahbaz Sarwar,[3] Afshan Ittifaq,[1] Zumar Sardar,[2] Abeera Mansur.[1] *[1]Nephrology, DHMC, Pakistan; [2]Medicine, AIMC/JHL, Pakistan; [3]Cardiology, DHMC, Pakistan.*

Background: Chronic kidney disease (CKD) patients are at high risk of developing cardiovascular disease (CVD) predominantly ischemic heart disease (IHD) and cardiomyopathy. Left atrial volume index (LAVi) is an indicator of left ventricular diastolic dysfunction independent of volume status. A high LAVi is an independent poor prognostic factor in patients with CVD. We conducted this study to find out correlation of LAVi and other echocardiographic parameters with eGFR.

Methods: We prospectively enrolled 153 subjects, 72 (47%)patients with and 81 (53%) control subjects without CKD. Demographic, clinical and Echocardiographic parameters including systolic and diastolic volumes, Left atrial volume, left atrial volume index (LAVI), Ejection fraction (EF), Pulmonary artery systolic pressure (PASP) and E/e ratio were measured in all participants.

Results: From the total of 153 individuals, males with and without CKD were 42 (58.3%) Vs 54(66.7%) (p.value 0.318), Females with CKD were 30 (41.7%) Vs 27 (33.3%) without CKD (p-value 0.287). Median age of patients with CKD was 67 (range 27-90years), and 35 (range 17-90) years in control group. Hypertension was seen in 38 (52.8%) with CKD Vs 10(12.3%) in control group p-value <0.001, Diabetes Mellitus (DM) was found in 35 (48.6%) with CKD vs 8 (9.9%) without CKD (p-value <0.001) and Coronary artery disease (CAD) was present in 26 (36.1%) as compared to 8 (9.9%) patients in control group (p-value <0.001). Patients with CKD had significantly higher median LAVi (31.5 [range 9-69] vs 22 [range 10-31]; p value <0.01), higher median E/e ratio (10 [range 4-16] vs 7 [range 4-15]; p value <0.01), higher median PASP (40 [range 27-82] vs 26.5 [range 20-55]; p value < 0.01) and lower EF (60 [range 15-72] vs 65 [range 32-70], p value of 0.01). There was a significant negative correlation of eGFR with LAVi (r=-0.577; p value< 0.001), PASP (r=-0.466; p value <0.001) and E/e ratio (r=- 0.383; p vale <0.001).

Conclusions: Patients with CKD have higher LAVi, PASP and E/e ratio and lower EF as compared to those without CKD. There is significant negative correlation between eGFR and LAVi.

PUB134

Interleukin-18 May Predict Cardiovascular Mortality in Chronic Kidney Disease among Non-Diabetic Post-Myocardial Infarction Patients in 2-Year Follow-Up Maria Wanic-Kossowska,[1] Dorota Formanowicz,[2] Elzbieta Pawliczak,[1] Krzysztof Schwermer.[1] *[1]Dept of Nephrology, Transplantology and Internal Medicine, Poznan Univ of Medical Sciences, Poznan, Poland; [2]Dept of Clinical Biochemistry and Laboratory Medicine, Poznan Univ of Medical Sciences, Poznan, Poland.*

Background: The incidence and severity of cardiovascular (CV) complications in patients with chronic kidney disease (CKD) is disproportionate compared to well-known traditional atherosclerosis risk factors profile. The aim of our study was to investigate whether and how non-traditional risk factors, such as interleukin-18 (IL-18), due to its pleiotropic properties, is prospectively associated with CV deaths in patients with CKD in the 2-year follow-up.

Methods: The study was carried out in a group of 200 non-diabetic patients, aged 45-80 years, with different stages of CKD and the history of myocardial infarction in the past. They have been followed for 2-years for having CV-related deaths. At the beginning of this study hsCRP, NT-proBNP, GFR, albumins, ferritin, and IL-18 in the serum have been measured. Additionally, all patients had an assessment of carotid intima media thickness. Moreover, a formal model of the involvement of IL-18 in the atherosclerotic plaque formation, expressed in the language of Petri nets theory, has been built and analyzed.

Results: In our study we found that an increase in serum concentration of IL-18 above the cut-off point (1584.5 pg/ml) was characterized by 20.63-fold higher risk of CV deaths among studied patients. IL-18 serum concentration was found to be superior to the studied well-known CV risk parameters.

Conclusions: IL-18 seems to be important indicator and predictor of cardiovascular death in two-year study among non-diabetic patients with different stages of CKD. The importance of IL-18 in the process of atherosclerotic plaque formation has been confirmed by systems analysis based on a formal model.

Funding: Government Support - Non-U.S.

PUB135

End-Stage Renal Disease versus Death in a Portuguese Cohort of Elderly Patients: An Approach Using Competing Event Analysis Josefina Lascasas,[1] Isabel Fonseca,[1] Jorge Malheiro,[1] Idalina Beirão,[1] Sofia Correia,[1] Andreia Campos,[1] Pedro Oliveira,[2] Luisa Lobato,[1] António Cabrita.[1] *[1]Nephrology Dept, CHP, Porto, Portugal; [2]Inst Ciências Biomédicas Abel Salazar, Univ Porto, Porto, Portugal.*

Background: Portugal is facing an increasingly ageing, and has the highest incidence of end stage renal disease(ESRD)among European countries. Chronic kidney disease(CKD) prevalence is higher in elderly, but mortality outweighs the risk of progression to ESRD, which makes it a challenge to determine each patient's risk for requiring renal replacement therapy(RRT) in relation to the competing risk of death.

Methods: Longitudinal cohort study, with consecutive CKD patients aged≥ 65 years(yrs) referred to outpatient clinic during 2012, followed until the time of the first event(RRT or death) or until April 30, 2016. A competing risk analysis using STATA statistical software was performed between those two mutually exclusive endpoints.

Results: Among 416 patients,age 76±8 yrs(36%≥80 yrs), 52% male, mean eGFR EPI 32ml/min, 49.7% had diabetes, and 71% cardiovascular disease. Median follow-up was 3.6 yrs(min-max:0.02-4.3), during which 36 patients progressed to ESRD(8.7%) and 103 died(24.8%). The rate(per 100 person-yrs) was 2.7 for ESRD and 7.8 for death. The independent predictors for RRT with competing risk of death were:lower age(sHR=0.97; P=0.029),creatinine>2mg/dl(sHR=2.48, P=0.012),and peripheral vascular disease(sHR=2.50, P=0.011) at baseline;and having one or more hospitalizations during the follow-up (sHR=4.07, P=0.002). The independent predictors for patient death with competing risk of RRT were: age>80 yrs(sHR=2.22; P<0.001), creatinine>1.6 mg/dl(sHR=2.59, P=0.003)and having one or more hospitalizations during the follow-up(sHR=4.55, P<0.001).

Conclusions: During a median follow-up of 3.6 yrs, older CKD are near 3-fold more likely to die from any cause than progress to ESRD. Age,late nephrology referral(higher creatinine at the first observation) and hospitalizations are the most important predictors of the competing events ESRD and death. A greater burden of vascular disease, present in our cohort, as a predictor for RRT, highlights the importance of strategic targeting vascular risk reduction in these patients.

PUB136

P2Y12 Antagonists for Acute Coronary Syndrome in Chronic Kidney Disease: A Meta-Analysis of Randomised Controlled Trials Peter J. Gallacher. *Centre for Cardiovascular Sciences, Univ of Edinburgh, Edinburgh, United Kingdom.*

Background: Chronic kidney disease (CKD) patients are under-represented in cardiovascular trials and less likely to receive secondary prevention. Dual antiplatelet therapy with aspirin and $P2Y_{12}$ antagonists (e.g. clopidogrel) is standard treatment following acute coronary syndrome. We aimed to determine how reduced eGFR influences major adverse cardiovascular events (MACE) and bleeding risk in patients treated with these agents for acute coronary syndrome.

Methods: Central, Embase, and Medline databases were searched from 1946 through to June 2016 for randomised controlled trials (RCTs) comparing $P2Y_{12}$ antagonists with another antiplatelet agent, standard care or placebo in adults with acute coronary syndrome in the presence or absence of CKD, defined as an eGFR of $\leq$60mL/min/1.73m^2. Two assessors independently screened relevant studies. The primary outcome was MACE; a composite of cardiovascular death, myocardial infarction (MI) or stroke. The secondary outcome was TIMI major bleeding. Publication bias was determined using Eggers regression test and heterogeneity was calculated using the I_2 test. Summary effects of relative risk (RR) ratios were collated using a random-effects model.

Results: Of 4,382 studies, five international, multi-centre, double-blinded RCTs with low risk of bias studies were included in the analysis. From 57,611 patients, eGFR data were available for 88.6% (n=51,031). CKD patients comprised 21.2% of the population (n=10,480), of whom 1.1% (n=560) had an eGFR <30mL/min/1.73m^2. Treatment reduced MACE in both those with CKD (n=10,840; RR 0.89 [CI 0.69-1.18]) and those without (n=40,191; RR 0.79 [CI 0.63-1.00]). TIMI major bleeding risk was increased in both those with (n=9,350; RR 1.04 [CI 0.63-1.72]) and those without CKD (n=28,301; RR 1.39 [0.94-2.07]).

Conclusions: $P2Y_{12}$ antagonists after acute coronary syndrome confer benefit to CKD patients, although to a lesser degree than in those with normal renal function. They are associated with a lower risk of major bleeding in CKD; this may reflect premature mortality due to other causes. Those with severe CKD, and so the greatest cardiovascular risk, are vastly under-represented in cardiovascular trials.

PUB137

The Clinical Characteristics and Therapy in Aortic Dissection Patients with Chronic Kidney Disease Zhen Su. *Nephrology, The First Affiliated Hospital of Wenzhou Medical Univ, Wenzhou, Zhejiang, China.*

Background: Chronic kidney disease (CKD) is a common condition that elevates the risk of adverse outcomes including cardiovascular disease. Aortic dissection (AD) is one of the most frequent life-threatening cardiovascular diseases. AD in CKD is rarely reported. This study aimed to evaluate the features and therapy in AD with CKD.

Methods: A retrospective analysis of 412 AD patients who admitted to our hospital during January 2005 to June 2015. 40 patients (34 males; mean age, 60.47± 16.05 years) were identified as CKD. We collected their baseline data as well as clinical features and followed up their outcomes. We compared them with 372 AD patients without CKD (268 males; mean age, 55.73±14.71 years). All patients underwent contrast-enhanced computerized tomography (CT) (nonionics and low-osmolarity contrast were used) to confirm the diagnose of AD.

Results: The most common etiologies of these CKD patients were glomerulonephritis, benign hypertensive nephrosclerosis and gouty nephropathy. 21 patients were medically treated, 13 received endovascular repair and 6 were surgically treated. During the median follow-up of 20 months (range, 1-124 months), 5 patients developed Acute renal failure on CKD after surgical treatment, and all of them required CRRT. Those who received endovascular therapy seemed to have a more favorable outcome than who maintained conservative medical therapy, though without significance (1-year survival 88% vs 68.6%, respectively; log-rank test p = 0.07). We classify dissections that involve the ascending aorta as type A and all other dissections as type B. In type B AD patients with CKD, endovascular treatment patients significantly had a favorable survival (1-year survival 100% vs 60% medically treated, respectively, log-rank test p = 0.011). Compared with those without CKD, AD cases with CKD had more hypertension (P <0.001), less likely to present with abrupt onset pain (p = 0.001), more often diagnosed incidentally (p =0.002) and more patients prone to medical treated (p=0.005).

Conclusions: endovascular treatment has acceptable outcomes in CKD patients when they suffered AD and such patients had their atypical features which need the physicians pay more attention.

PUB138

The Impact of Admission Serum Creatinine on Major Adverse Clinical Events in ST-Segment Elevation Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention Mohamed Khayata, Mohit Gupta, Shyam Bhakta, Rupesh Raina. *Internal Medicine, Akron General Medical Center, Akron, OH.*

Background: Impaired renal function has been shown in previous studies to be an independent predictor of cardiovascular adverse events amongst patients admitted for percutaneous coronary intervention (PCI). We will investigate the impact of admission serum creatinine on major cardiovascular outcomes among STEMI patients undergoing PCI.

Methods: A Retrospective Institutional Review Board approved study of patients admitted for STEMI was conducted using the National Cardiovascular Database Action Registry (NCDR) at Cleveland Clinic Akron General (CCAG) Hospital. The primary outcome was a composite of major clinical events (cardiogenic shock, atrial fibrillation, ventricular tachycardia/fibrillation, heart failure, bleeding, mechanical ventilation). Creatinine was an independent and continuous variable. Statistical analysis was performed via the Mann Whitney U test.

Results: 1452 subjects who were admitted to CCAG hospital between January 2011 and September 2015, with the diagnosis of STEMI were included. The cohort consisted of primarily older Caucasian males with creatinine levels from 0.83 mg/dL to 1.2 mg/dL. Higher levels of creatinine on admission was associated with an increased incidence of the composite clinical outcome (p<0.001), atrial fibrillation (p=0.021), cardiogenic shock (p=0.002), bleeding (p<0.001), and heart failure (p<0.001).

Characteristics	N=1452	Major Adverse Event During Hospital Stay	p Value
Age (Mean +/- SD)	64 +/- 14	Atrial Fibrillation	0.021
Gender (Male%)	64	Ventricular Tachycardia / Ventricular Fibrillation	0.884
Race (Caucasian%)	85	Dialysis	0.713
Hypertension	72	Mechanical Ventilation	0.731
Diabetes Mellitus	29	Cardiogenic Shock	0.002
History of Heart Failure	13	Heart Failure	0.000
Current Smoker	40	Bleeding	0.000
Creatinine (Median (IQR))	1(0.83-1.2)	Composite Event	0.000

Conclusions: In the setting of STEMI, elevated creatinine was associated with an increased risk of developing major clinical events including cardiogenic shock, atrial fibrillation, bleeding and heart failure.

PUB139

The Error of Estimated GFR in Patients with Acute Heart Failure: The Cardiologist in the Mist Sergio Luis Lima,[1] Pablo Jorge,[1] Martin L. Garcia,[1] Ana Aldea Perona,[1] Natalia Negrín,[1] Federico J. Gonzalez-Rinne,[1] Esteban Porrini.[2] [1]*Hospital Univ de Canarias, La Laguna, Spain;* [2]*Univ de La Laguna.*

Background: In diverse populations, estimated GFR (eGFR) showed a wide error in predicting real renal function. This error has never been tested in patients with acute heart failure (AHF).

Methods: We analyzed 30 patients (12 women) with AHF in whom GFR was measured by iohexol plasma clearance (mGFR) and estimated with 52 formulas (creatinine and cystatin-based) 48 hours after admission in a condition of clinical stability. The agreement between mGFR and eGFR was assessed by the Total Deviation Index (TDI), Concordance Correlation Coefficient (CCC) and coverage probability (cp).

Results: Age 63±12 yr; DM 55%; HTA 74%; dyslipidemia 78%; previous ischemic disease 44%; new-onset AHF 59%; creatinine 1.36±0.69mg/dl; NT-proBNP 6048±4915pg/ml; troponin-I 0.05ng/ml (median). 58% received high doses of furosemide (>125mg) in the first 24 hours. 44.4% had left ventricular ejection fraction<35%. Formulas showed poor agreement with mGFR: CCC~0.70; TDI from 106,8% to 49,6% (~62%), indicating that 90% of eGFR showed an error of ±62%. No formula included 90% of eGFR within a cp of ±10% Table 1 shows a sub-group of formulas.

	CCC (95%CI)	TDI (95%CI)	CP (95%CI)	N
Creatinine based formulas				
aMDRD	0.70 (0.51)	69 (94)	22 (18)	30
CKD_EPI	0.72 (0.55)	70 (95)	22 (17)	30
RuleMC	0.61 (0.43)	107 (145)	15 (11)	30
Effersoe	0.63 (0.42)	80 (108)	20 (16)	30
Cystatin-C based formulas				
Hoek	0.73 (0.54)	50 (67)	29 (22)	30
RuleCisc	0.75 (0.56)	52 (70)	28 (22)	30
CKD_EPI_cisc	0.75 (0.57)	54 (74)	27 (21)	30
Creatinine and cystatin-C based formulas				
Stevens	0.73 (0.53)	55 (75)	27 (21)	30
Ma	0.63 (0.43)	72 (98)	21 (15)	30
CKD_EPI_crecisc	0.75 (0.57)	56 (76)	26 (20)	30

Errors in CKD classification were observed: one in three patients with eGFR>60 ml/min (stage 1-2) had mGFR<60 ml/min (stage 3).

Conclusions: Formulas do not accurately reflect the GFR in patients with AHF. The clinical consequences of this error must be evaluated in prospective studies.

Funding: Government Support - Non-U.S.

PUB140

Serum 1,25 Dihydroxyvitamin D Is Independently Associated with Left Ventricular Hypertrophy and Diastolic Dysfunction in Patients with Chronic Kidney Disease Il Young Kim, Jong Man Park, Harin Rhee, Sang Heon Song, Eun Young Seong, Dong Won Lee, Soo Bong Lee, Ihm Soo Kwak. *Dept of Internal Medicine, Pusan National Univ School of Medicine, Yangsan, Republic of Korea.*

Background: Cardiovascular disease is the leading cause of death in chronic kidney disease (CKD) patients. Increased left ventricular mass and diastolic dysfunction is known for the predictors of the cardiovascular complications in these patients. This study investigated the association between serum 1,25 dihydroxyvitamin D [$1,25(OH)_2D$] and left ventricular mass/diastolic dysfunction in pre-dialysis CKD patients.

Methods: This study included 246 patients with pre-dialysis CKD [glomerular filtration rate (GFR) < 60 ml/min/1.73m^2]. Two-dimensional echocardiography was performed to measure the left ventricular mass index (LVMI). Tissue Doppler imaging was used to measure the early mitral inflow velocity (E) and the peak early mitral annular velocity (E'). Diastolic dysfunction was estimated by the ratio of E to E' (E/E').

Results: In univariate analysis, LVMI was significantly correlated with the presence of hypertension, GFR, $1,25(OH)_2D$, and parathyroid hormone (PTH). E/E' was significantly associated with the presence of hypertension, $1,25(OH)_2D$, and PTH. In multivariate analysis, LVMI was independently associated with the presence of hypertension (β = 0.175, P = 0.003), $1,25(OH)_2D$ (β = -0.140, P = 0.025), and PTH (β = 0.351, P < 0.001). PTH (β = 0.160, P = 0.016) and $1,25(OH)_2D$ (β = -0.135, P = 0.039) were independent predictors of E/E'.

Conclusions: This study shows that $1,25(OH)_2D$ is independently associated with left ventricular hypertrophy and diastolic dysfunction in pre-dialysis CKD patients. Further studies are needed to determine whether the therapy with vitamin D supplement prevents these cardiac changes in them.

PUB141

Non-Dipping Status in 24-H Ambulatory Blood Pressure Monitoring Is Associated with Left Ventricular Hypertrophy in Patients with Non-Dialysis Chronic Kidney Disease Patrick Saudan,[1] David Antoine Jaques,[2] Hajo Mueller,[3] Sophie M. De Seigneux,[1] Pierre-Yves F. Martin,[1] Belen Ponte.[1] *[1]Div of Nephrology, Geneva Univ Hospitals, Geneva, Switzerland; [2]Div of General Internal Medicine, Geneva Univ Hospitals, Geneva, Switzerland; [3]Div of Cardiology, Geneva Univ Hospitals, Geneva, Switzerland.*

Background: Few studies have assessed the role of 24-h ambulatory blood pressure monitoring (ABPM) in non-dialysis CKD adults. We conducted a study to examine the association of ABPM dipping status with the development of left ventricular hypertrophy (LVH) in this population.

Methods: Within a prospective cohort of 242 patients with stage IIIb-IV CKD, 72 had both ABPM and transthoracic echocardiography performed simultaneously in addition to usual renal function tests. Dipping status ≥10% was considered normal.

Results: Mean age and eGFR were 69 yrs and 36ml/min/1.73m respectively in this cohort. There were 67% male, 49% diabetics and 42% presented LVH. Median left ventricular mass index was119 (109-136) vs 82 (63-91) g/m^2 in patients with and without LVH respectively. Mean ABPM systolic and diastolic BP did not differ between patients with and without LVH (132/78 vs 133/75 mm Hg). Normal systolic and mean BP dippings were present in 57 and 62% in patients without LVH and 23 and 33% in patients with LVH. Multivariate logistic regression analysis showed that systolic and mean dipping status remained associated with LVH: OR 0.21 (p<0.01) and OR 0.26 (p=0.014). Diastolic dipping was not associated with LVH (OR 0.71, p 0.52). No other variable was associated with LVH in this model adjusted for GFR, anti-hypertensive medication, smoking, hemoglobin, PTH and diabetic status.

Conclusions: These data confirm the high incidence of LVH amongst CKD patients. Systolic and mean BP non-dipping status are associated with LVH in patients suffering from non-dialysis CKD.

PUB142

Impact of Anticoagulation and Antiagregation on the Anemia and Hemorrhagic Events in Patients with Chronic Kidney Disease Stage 3 and 4 Ana M. Garcia Prieto, Marian Goicoechea, Tania Linares, Ursula Verdalles, Eduardo Verde, Maria Soledad Garcia de Vinuesa, Jose Luno. *Nephrology, Gregorio Marañón Hospital, Madrid, Spain.*

Background: There is controversy about the risk/benefit of anticoagulation/antiagregation in chronic kidney disease (CKD) patients not in dialysis. We analyze the impact of anticoagulation/antiagregation on the anemia and bleeding risk in CKD patients.

Methods: 232 CKD patients stage 3 and 4 were followed in the outpatient clinic of Nephrology with a mean follow-up of 36.7 +/- 11.6 months. 81 patients did not receive anticoagulation or antiagregation, 91 received acenocumarol and 60 patients received antiagregation. Hemorrhagic and cardiovascular events were collected.

Results: There were no differences between groups regarding age, renal function or inflammatory parameters (CRP and fibrinogen). Hemoglobin and ferritine levels were significantly higher in patients who did not receive anticoagulation or antiagregation. During follow up 36 hemorrhagic events occurred: 4 in the control group, 17 in the anticoagulation group and 7 in the antiagregation group (log Rank: 9,010, p=0,011). In a Cox model adjusted by age, renal function and hemoglobin levels, the anticoagulation increased the risk of bleeding almost four times (HR 3,7(1,6-8,5), p=0,002) and antiagregation almost three times (HR 2,6 (1,1-5,9), p=0,025). 64 cardiovascular events were registered, 21 were classified as atherosclerotic events: 10 in the antiagregation group, 8 in the control group and 2 in the anticoagulation group (log rank: 8.351; p=0.015). In a Cox model adjusted by age, renal function and previous cardiovascular events, the anticoagulation reduced the risk of atherosclerotic events in 86% (HR 0.136 (0.033.0.551), p=0.005).

Conclusions: Anticoagulation and antiagregation increase the hemorrhagic risk in patients with CKD and worsen the anemia, fact that must be taken on account to optimize treatment and valuate the risk/benefit in the prescription of these drugs. Anticoagulation reduces the atherosclerotic events in more than 85%. Antiagregation does not prevent atherosclerotic events and increases the risk of bleeding, thus it should not be a first election treatment neither in primary nor secondary prevention.

PUB143

Association of Vascular Disease with Mortality and Development of End Stage Renal Disease in Patients with Chronic Kidney Disease Olufemi B. Aina, Candace D. Grant, Farah Daccueil, Nobuyuki (Bill) Miyawaki, Shayan Shirazian, Joseph Mattana. *Medicine, Winthrop-Univ Hospital, Mineola, NY.*

Background: Patients with chronic kidney disease (CKD) are disproportionately affected by atherosclerotic vascular disease (AVD). AVD can plausibly contribute to progression of CKD to end stage renal disease (ESRD) but AVD also predisposes to cardiovascular mortality and may therefore reduce the risk of ESRD via the competing risk of death. In this study we evaluated the relationship between AVD, the development of ESRD, and mortality in patients with CKD.

Methods: We conducted a prospective observational study of 623 patients with stage 3 and 4 CKD. Demographic, clinical and laboratory variables were recorded and patients divided into two groups based on the presence or absence of AVD, defined as having a diagnosis of coronary artery disease, myocardial infarction and/or peripheral vascular disease. Development of ESRD and death without ESRD were recorded over 2 years of follow up.

Results: Out of 623 patients with CKD 285 had AVD. Patients with AVD were older than those without (75.8 ±10.0 vs 65.6 ±15.0 y, p<0.001) and had lower eGFR (33.8 ±11.5 vs 36.4 ±11.7 mL/min/1.73 m2, p<0.01). Mortality was higher in patients with AVD (16.8 vs. 5.3%, p<0.0001) and increased with age. There was a trend toward higher ESRD incidence in AVD patients but in contrast with mortality, ESRD incidence decreased with age though remained higher in AVD patients. ESRD incidence in AVD patients <65 was 17.1 vs 9.5% in those without and for AVD patients ≥65 the incidence was 6.6 vs 3.3% though these differences did not reach statistical significance.

Conclusions: Our findings suggest that despite significantly higher mortality rates in patients with CKD who have AVD, they may also experience an increased risk of development of ESRD. This effect may be especially pronounced in younger patients with CKD and AVD where the competing risk of death is lower. This observation may be helpful in decision making such as planning for renal replacement therapy in patients with CKD and AVD and suggests shared pathophysiological mechanisms contributing to both cardiovascular death and progression of CKD to ESRD.

PUB144

Fracture Risk Assessment (FRAX) in Chronic Kidney Disease (2-5ND) Sarcopenia's Role Secundino Cigarran,[1] Ana Maria Sanjurjo Amado,[1] Mª Milagros López Hernández,[1] Juan Latorre,[1] Jesus Calvino.[2] *[1]Nephrology, Hospital Da Costa, Burela, Lugo, Spain; [2]Nephrology, Hospital Lucus Augusti, Lugo, Spain.*

Background: A higher risk fractures has been well recognized among patients with chronic kidney disease (CKD).FRAX is a well-accepted tool for fracture risk assessment in the general population.In CKD many pts are frail and prone to falling which predisposes to suffer a fracture.Bone changes in CKD are over impose to normal aging evolution, as sarcopenia.The aim of this cross-sectional study is to assess the relationship of body composition and sarcopenia in CKD (2-5ND) pts with FRAX.

Methods: 411 pts >70 yo were enrolled, (mean age 75 yo, 40% diabetic status, 44.4% female) from our CKD unit. (Stage 2 19%; Stage 3A 39%; Stage 3B 73%; Stage 4 25% and Stage 5ND 2%). Spanish FRAX was use to calculate the 10-year probability of a major osteoporotic fracture. Vertebral score was >10% at 10 yr and hip fractures risk score >3% as at risk.Body composition assessment was performed with vectorial bioelectrical impedance (EFG, Akern Fl. ITA and multifrequency Bioscan 920, Maltron,London UK). Handgrip strength in both arms was performed with (Handgrip Akern. FL. Ita).Biochemical markers of CKD-MB, nutrition,renal function (CKD-EPI & ACR),inflammation and CV risk were performed.

Results: 170 pts (39.8%) were in risk of hip & vertebral fractures and 256 pts (61%) in risk of hip fracture alone.In bivariate analysis female (p<0.001) and older (p<0.001) evidenced high risk of fractures.

Variable	No Fracture risk	Fracture (vertebral/hip) risk	P
Muscle Mass (%)	40.2±7.34	36.31±6.64	.000
TBW (%)	51.27±5.89	46.8±6.37	.000
ECW(%)	48.78± 5.46	50.25±4.97	.006
ICW (%)	51.28 ± 5.44	49.74±4.98	.006
Interstitial Fluid (L)	13.06± 2.55	11.13±2.68	.001
Plasma volume (L)	3.72±0.73	3.18±0.77	.001
Fat Mass (%)	35.42± 7.55	41.24±8.05	.001
Phase Angle (°)	5.48±1.14	5.19±0.94	.007

No other significances were met.HGS was lower in the fracture risk group (29.2 ± 8.7 Kg vs 20.4± 7.0 kg; p<0.001).

Conclusions: FRAx is a useful tool to predict fracture risk in CKD pts.Our study reflects bone-muscle cross talk.Importance of physical exercise should not be underestimated.

Funding: Other NIH Support - SERGAS

PUB145

Muscle-Kidney Crosstalk through microRNA-29a in Mice with Chronic Kidney Disease Aiqing Zhang, Haidong Wang, Bin Wang, Faten Hasounah, Xiaonan H. Wang. *Renal Div, Emory Univ, Atlanta, GA.*

Background: Kidney fibrosis is a progressive process that ultimately leads to end-stage renal failure. Muscle wasting is a serious complication of chronic kidney disease (CKD) and contributes substantially to the morbidity and mortality of patients. Exosomes, natural carriers of many signaling molecules including microRNA (miR), mediate organ to organ communication. Our studies have suggested that MiR-29 could be a therapeutic target to treat muscle wasting but it also has anti-fibrotic activities. We hypothesized that miR-29 could benefit both unilateral ureteral obstruction (UUO)-induced muscle wasting and kidney fibrosis through exosome-mediated muscle-kidney crosstalk.

Methods: UUO was induced by left ureteral ligation. A NanoSight instrument was used to quantify exosomes. A miR deep sequencing assay and qPCR were used to identify microRNA. We used Adeno-Associated Virus (AAV) for miR overexpression. Immunohistochemistry (Mason Trichrome) identified renal fibrosis.

Results: We found that serum-derived exosomes from UUO mice are larger than control exosomes. MiRNAdeep sequencing showed that miR-29a-5p was significantly increased in serum exosomes but decreased in skeletal muscle and kidney tissue of UUO vs controls. Uremic serum enhanced exosome/miR29a secretion by cultured skeletal muscle cells. When we overexpressed miR-29a by injecting AAV into tibialis anterior muscle, the cross-sectional area increased and UUO-induced up-regulation of muscle atrogin-1 and MuRF1 decreased. Interestingly, kidney fibrosis was also partially depressed in these mice, confirmed with decreased α-smooth muscle actin (αSMA), vimentin, fibronectin and collagen1α. Exosomes containing miR-29a secreted by cultured skeletal muscle cells were able to transfer miR-29a to human kidney cells and attenuate uremic serum-induced up-regulation of αSMA, providing indirect evidence of muscle-kidney crosstalk.

Conclusions: Overexpression of miR29a in muscle not only attenuated skeletal muscle atrophy but also ameliorated UUO-induced renal fibrosis through exosome-mediated muscle-kidney crosstalk.

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PUB146

Childhood IgA Nephropathy Presenting Acute Nephritic Syndrome at Onset Yuko Shima,[1] Koichi Nakanishi,[1] Taketsugu Hama,[1] Masashi Sato,[1] Hironobu Mukaiyama,[1] Hiroko Togawa,[1] Hiroshi Kaito,[2] Kandai Nozu,[2] Ryojiro Tanaka,[3] Kazumoto Iijima,[2] Hiroyuki Suzuki,[1] Norishige Yoshikawa.[4] *[1]Pediatrics, Wakayama Medical Univ, Wakayama, Japan; [2]Pediatrics, Kobe Univ, Kobe, Japan; [3]Pediatric Nephrology, Kobe Children's Hospital, Kobe, Japan; [4]Clinical Research Center, Wakayama Medical Univ, Wakayama, Japan.*

Background: Acute nephritic syndrome (ANS) is a rare manifestation of IgA nephropathy (IgAN). Clinical characteristics and long-term outcomes of childhood IgAN presenting ANS (ANS-IgAN) at onset are not clear.

Methods: Retrospective analysis of 538 consecutive biopsy-proven IgAN children from July 1976 to June 2013 to compare clinical and pathological findings between ANS-IgAN and others.

Results: Nine ANS-IgAN (1.7%) at onset, all were due to edema. Clinical findings showed significant differences (ANS vs. non-ANS) in mean blood pressure (91 vs. 75 mmHg; p=0.03), proteinuria (2.1 vs. 0.5 g/day/m^2; p=0.0005), and duration from onset to renal biopsy (2.0 vs. 8.0 months; p=0.016). There were no significant differences in MEST score or patient/glomerular ratios showing crescent and global sclerosis, but there were significant differences in patient ratios showing diffuse mesangial proliferation. Logistic analysis suggested a significant independent relationship between proteinuria and tubular atrophy/interstitial fibrosis area and ANS-IgAN. Kaplan-Meier analysis suggested that patients with ANS-IgAN had significantly lower renal survival rates than the others (p<0.001). ANS-IgAN at 5 years was 64.8% (95% CI: 33.8–88.4). Prognostic factors for renal survival were proteinuria disappearance (p<0.001) and ANS at onset (p=0.002). Among nine ANS-IgAN patients, four were treated with combination therapy (PSL and immunosuppressants), three had no medication (from before the early 1980s), and two were unknown. Three patients (33.3%) reached CKD III–V (eGFR <60) during the observation period (6.8 ± 2.9 years). Two patients demonstrated heavy proteinuria even after 2-year combination therapy. One patient showed remarkably deteriorated renal function with severe tubular atrophy at diagnosis.

Conclusions: Patients with ANS-IgAN showing evident chronic lesion at onset have a poor prognosis as a consequence of refractoriness to treatment.

PUB147

A "Mini-Epidemic" of Anti-GBM Disease: Epidemiological, Clinical and Immunological Study Umesha Lingaraj. *Dept of Nephrology, Inst of Nephrourology, Bangalore, Karnataka, India.*

Background: Acute glomerulonephritis due to anti-GBM antibody disease is rare, estimated to occur in fewer than one case per million population & accounts for less than 20% of RPGN. It accounts for fewer than 3 percent of all kidney biopsies done with crescentic glomerulonephritis. Cases of Anti-GBM disease occurring in cluster have rarely been reported.

Methods: A Cross-sectional Observational study. All biopsy proven anti-GBM disease cases were collected from January-2015 to March-2015 at our Institute. All cases were analysed for demographic & clinical profile, pathological findings, treatment received and special search for any common environmental antigenic source.

Results: Total of 11 new biopsy proven anti-GBM cases were collected. Age group varied from 17-80years. 7 were males & 4 were females. All were dialysis dependant at presentation. Seven had active cellular crescents and three had fibrocellular. Only one patient was a smoker and none had history of exposure to any forms of hydrocarbons. The peak was seen from January 2015 to March 2015, which does not correlate with any of the infections seasonal occurrence in southern India. Though there was clustering of cases to southern territories of Karnataka state, no common etiological agents could be identified. No patient had any previous urological surgeries. All patients received Methylprednisone with Plasmapharesis 5-7 sessions and Cyclophosphamide. All 11 patients were dialysis dependant at the end of 3 months.

Conclusions: Anti-GBM disease cannot be regarded as a rare cause of renal failure and lung hemorrhage. With the occurrence of such epidemics within a short period of time, suggest a possible unidentified environmental factor like infection or occupational agents as inciting agents. Identification of possible inciting agents could help us in instituting appropriate preventing measures.

PUB148

Are We Slowing the Rate of CKD Progression in Children? A Single Center Study Isabel Roberti, Shefali Vyas. *BarnabasHealth Children's Kidney Center, Barnabas Health Medical System, West Orange, NJ.*

Background: CKD progresses to ESRD with a variable decline in eGFR from 1.3 to 4.2 ml/min/1.73 m^2/yr depending on etiology, proteinuria and HTN.

Methods: Retrospective study of all children with CKD (eGFR: 20 to 70 ml/min/1.73m^2)* diagnosed by age 10 yrs and followed for ≥3 yrs. Etiology of CKD, eGFR at presentation, clinical data, meds used and rate of eGFR decline were reviewed. Children with AKI at presentation were included if CKD was diagnosed and eGFR reached >20*. All children received ACEis and rigorous control of acidosis, nutrition, growth, anemia, iPTH, HTN and proteinuria was done as per center protocol.

Results: 37 children had CKD, diagnosed from birth (N=7) to age 10 yrs (5.8±3 yr). 26 males, 15 C, 11 AA, 8 H, 3 other. **Mean eGFR at presentation:** 46.2 *(SD=2.99). Ten (27%) had eGFR ≤29 *. **Etiology**: 31 CAKUT (6 dysplasia), 2 aHUS, 1 twin transfusion, 1 GN, 2 tubular diseases. **AKI at presentation** =10 (27%); 4 required PD. **Follow-up time**: 3 to 18 yrs (8.7±3.9yrs). **eGFR change:** 10 increased, 2 unchanged, 25 deteriorated (rate of eGFR decline/yr =1.31±0.88*). **Children with initial eGFR ≤ 29*** (N=10) 4 either improved or were stable at last f/u; 3 progressed to ESRD (after mean f/u of 13 yrs) and received pre-emptive txp (8% of all children). No decrease >50% from baseline eGFR or progression to ESRD was seen in others - p=0.03. **Meds/therapies used**: GH =12, erythropoeitin =7, GT feeds =12. **Co-morbidities**: HTN =5, obesity =7, hyperlipidemia =5, malnutrition =1, CIC =7, VP shunt =2, UTIs =10, other congenital malformations = 11, single kidney =9, neurodev. delay = 2; Uprot/Cr≥1 =7; UAc>7.5 =12. **No single factor including AKI, single kidney, prematurity, CKD stage or age at presentation predicted eGFR changes overtime.**

Conclusions: 30% of our children with CKD had increase or stable eGFR* (including 40% of those with initial eGFR<29). Progression to ERSD was only seen in 3 (all had initial eGFR<29*). We report a lower than expected rate of eGFR decline and attribute it to rigorous control of nutrition, underlying condition and co-morbidities. Prediction of eGFR change can't be made at time of CKD diagnosis except for children with eGFR ≤29% who are at a significantly higher risk for ESRD.

PUB149

The Evaluation of the Associations between Measures of Kidney Dysfunction and Oral Health Status Jun-Beom Park,[1] Hye Min Choi.[2] *[1]Periodontics, The Catholic Univ of Korea, Seoul, Republic of Korea; [2]Internal Medicine, Seonam Univ Myongji Hospital, Goyang, Republic of Korea.*

Background: Urinalysis was considered an important part of the physician's diagnosis. Urinary sodium was considered an indicator of dietary sodium intake.The purpose of the present study was to investigate the association between urinary sodium, urinary sodium/creatinine, and urinary sodium/urine specific gravity and oral health behavior using nationally representative data.

Methods: Data from the Korea National Health and Nutrition Examination Survey conducted between 2008 and 2010 were used; the sample analyzed in this study consisted a total of 15,013 respondents over 19 years old who had no missing values for the urinalysis or outcome variables.

Results: Urinary sodium level was significantly lower in females ($P<0.05$). The rate of hypertension and diabetes was significantly lower in females ($P<0.05$). Adjusted odds ratios of urinary sodium and their 95% confidence intervals in relation to the frequency of tooth brushing (≤1, 2, and ≥3 times per day, respectively) were 1, 0.963 (0.794, 1.168), and 0.897 (0.741, 1.086) for males ($P>0.05$) and 1, 0.898 (0.704, 1.145), and 0.734 (0.573, 0.939) for females ($P<0.05$). Adjusted odds ratios and their 95% confidence intervals of urinary sodium regarding the number of secondary oral hygiene products used per day (0, 1 and ≥2, respectively) were 1, 0.986 (0.839, 1.158), and 0.766 (0.542, 1.081)for males ($P>0.05$) and 1, 0.851 (0.735, 0.985), and 0.798 (0.63, 1.01) for females ($P<0.05$).

Conclusions: Poor oral hygiene behavior was associated with higher sodium consumption in females. This association between sodium uptake and oral health behavior was independent of various potential confounding factors such as age, body mass index, smoking, drinking, exercise, diabetes, hypertension, and metabolic syndrome. Oral hygiene behavior may be considered an independent risk indicator for high urinary sodium level in Korean females.

PUB150

A Tale of Two Endpoints: Pre-Dialysis Education and Beyond
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Background: Renal Replacement Therapy (RRT) planning in CKD patients should ideally happen 3 to 6 months prior to anticipated start of RRT to enable dialysis access and pre-emptive transplant work up to be done in time for start of dialysis through a permanent access. Our study aims were to analyse trends and timelines in referral to our Pre-dialysis education service, the subsequent patient choice of RRT, access creation, transplantation and RRT start.

Methods: 76 patients were referred following clinician review for pre-dialysis education given by the CKD nursing team between July 2014 and June 2015 where both modalities of dialysis, transplantation and conservative care was discussed. Data collection from clinic letters for timelines and the hospital IT system for results was performed in January 2016, therefore individual follow up varied from 6 to 18 months. Analysis was done using EPI-INFO 7.

Results: 45(59%) were males. Mean age was 68. 68(88%) were white. 24 patients had hypertension, 18 had Diabetes.

Timelines & Trends	Mean ± SD	Median	Range
eGFR at referral for education (ml/min)	15.5 ± 5.37	16	5 to 49
Time to access referral in months *n=42/61(69%)[Choice HD:31;PD:30]*	4.1 ± 3.68	3.5	0 to 15
eGFR decline/change at access referral (ml/min)	2.3 ± 3.13	2	+4 to -13
Time to access creation after access referral in months *n=29(48%)*	2.6 ± 3.18	1	0 to 14
Time to start of dialysis after education in months *n=19(25%) [10:PD;9:HD]*	5.8 ± 4.83	4	-2 to 16
eGFR at dialysis start (ml/min)	7.1 ± 3.58	6	3 to 19

6 patients started HD with a line. For a cut off eGFR for referral towards education at >=15ml/min, we derived a non-significant p value of 0.36 for an odds ratio of 3.0 for starting HD via line with referrals to education at a lower eGFR.

Conclusions: Due to variable rate of decline in renal function in varied age groups and with multiple comorbidities, a timely referral for pre-dialysis education and access creation would have to depend on individual assessment and clinical judgement. Even with early education, there may be a small risk of rapid decline in a group of patients and other factors influencing RRT start via alternative access or modality.

PUB151

Risk of Developing CKD at Any Given Blood Pressure Is Higher in Patients with Antihypertensive Medication Than in Those without in the Japanese General Population: An Analysis from Large Database of National Health Check-Up
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Background: Higher systolic blood pressure (SBP) may increase the risk of developing chronic kidney disease (CKD) in the general population, but it remains unknown how different the risks conferred are in those with antihypertensive medication (med+) and in those without (med-).

Methods: Using national health check-up database from 2008 to 2011 in the general Japanese population aged 39 to 74 years, we evaluated the association of SBP with incidence of CKD 2 years later in 128,005 participants without CKD (proteinuria and/or eGFR <60, ml/min/1.73m2). SBP was categorized by every 10mmHg from the lowest (<100mmHg) to the highest category (>180mmHg), with further stratification into med+/-. We calculated odds ratio (OR) for estimating adjusted risk of developing CKD using logistic regression model.

Results: Participants including 62% of female and 25.9% of med+ had mean age of 63 years. Two years later, 12,379 (9.7%) developed CKD. Multivariate analysis showed the risk of developing CKD increased as SBP rose up in both med- and med+ (P for trend 0.001, <0.001), having the highest risk in each of the highest category (OR 1.75, 2.01) as compared with med- with SBP 100 to 109mmHg. Estimated risk in med+ with any SBP were higher than those in med- within the same SBP category, especially showing statistically significance in med+ with SBP ranging 110 to 160mmHg.

Conclusions: In the general population, the risk of CKD conferred by any given SBP was higher in those with antihypertensive medication than in those without. This result indicates that risk stratification by SBP requires to take use of antihypertensive medication into consideration.

PUB152

Low Serum Uric Acid Level Is a Risk Factor for 5-Year Mortality in Incident Hemodialysis Patients
Yoshiko Nishizawa,[1] Sonoo Mizuiri,[1] Mariko Asai,[1] Kyoka Ono,[1] Kazuomi Yamashita,[1] Kenichiro Shigemoto,[1] Takao Masaki.[2] *[1]Div of Nephrology, Ichiyokai Harada Hospital, Hiroshima, Saeki-ku, Japan; [2]Nephrology, Hiroshima Univ Hospital, Hiroshima, Minami-ku, Japan.*

Background: 'J-shaped' association between uric acid and mortality has been controversial in maintenance hemodialysis patients. However, low serum uric acid (UA) level at the initiation of dialysis has not been fully clarified as a risk factor for mortality.

Methods: A retrospective study was conducted on 252 consecutive incident hemodialysis (HD) patients who started HD between 2005 and 2010. Data collection was terminated either at the 5-year observation of the study or at the time of death. Age, sex, presence of diabetes mellitus (DM), hemoglobin (Hb), serum uric acid (UA), creatinine (Cr), blood urea nitrogen (BUN),C-reactive protein (CRP), albumin (Alb),phosphate(P),albumin-adjusted calcium (Ca), phosphate,and geriatric nutritional risk index (GNRI) at the initiation of dialysis were recorded.The cumulative 5-year survival rate was estimated in the each UA quartile group. The hazard of survival rate between the each group was also evaluated by Cox regression analysis. For 5-year all-cause mortality and the lowest UA quartile (Q1≤5.9 mg/dl), risk factors including age, sex, DM, Hb, UA, Cr, BUN, CRP, Alb, Ca, P and GNRIwere assessed by univariate and multivariate logistic regression analysis.

Results: The cumulative 5-year survival rate of the patients in Q1 (45.5%) was significantly lower than those of the patients in Q2 (5.9-7.2 mg/dl, 68.3%), Q3 (7.2-8.3 mg/dl, 68.7%), and Q4 (≥8.3 mg/dl, 67.8%). Comparing with UAin Q4 as a reference group, the hazard ratio of patients with UA in Q1 was 2.3 ($p<0.01$). Age ($p<0.05$), BUN ($p<0.001$), UA ($p<0.01$), Cr ($p<0.01$) and Alb ($p<0.05$) were associated with 5-year all-cause mortality. The lowest UA quartile(QI) was significantly associated with age($P<0.01$), sex($P<0.05$), Cr ($P<0.01$), BUN ($p<0.01$), P ($P<0.01$), and GNRI ($P<0.05$) in univariate logistic regression analysis. In the multivariate model, Cr ($P<0.05$) was detected.

Conclusions: Low serum uric acid (≤5.9 mg/dl) level at the time of initiation of dialysis is a risk factor for 5-year mortality.

PUB153

Median Nerve Thickness Related to Renal Impairment in Inflammatory Arthritis
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Background: Autoimmune processes, contribute to the burden of kidney disease. The reported kidney disease prevalence in patients with rheumatoid arthritis (RA) is 5-15%. Subclinical decreased kidney function has been identified as an independent risk factor for CV events with increase mortality in RA. On the other hand, both RA and renal impairment associated with increase prevalence of carpal tunnel syndrome. This study aims to establish the the relation of the to the median nerve thickness to the renal function in RA.

Methods: 120 RA patients recruited through a specialized rheumatology clinic. 8–16 MHz linear array transducer probe was used. The median nerve was examined at the entrance of the carpal tunnel, between the pisiform bone and the tubercle of the scaphoid bone, where the distal volar crease is an external pisiform landmark. The cross-sectional area of the median nerve was calculated directly by the software of the US equipment. Each median nerve was measured three times, and the mean value was used for further analyses. GFR calculated used DMARD formula. The average median nerve thickness was used when exploring bivariate correlations to the renal variables (Pearson's correlation coefficients). All statistics were performed using STATA program.

Results: The mean (SD) age of participants was 49 (13) years and female were 82%. The average median nerve thickness was 9.79 ±2.6 mm2 (Range 1.5 -22.25). The average GFR was 122 ± 20 ml/min(59.6-286). Thickness of the median nerve was positively associated with the age of the participants (p=0.03, CI:0 .00, 0.08), body mass index (p=0.04, CI: 0.00, 0.21), uric acid level (p= 0.033, CI:0.00, 0 .01), & urine microalbumin (p=0.04, CI 0.00, 0.01). GFR showed no significant relation to the median nerve thickness.

Conclusions: RA patients without symptoms or clinical signs have a median nerve thickness that is positively correlated to the level of microalbumin and uric acid. Whether sosnographic examination of the median nerve would be helpful in anticipating who is going to have a deteriorated renal function need to be explored in a larger study.

Funding: Government Support - Non-U.S.

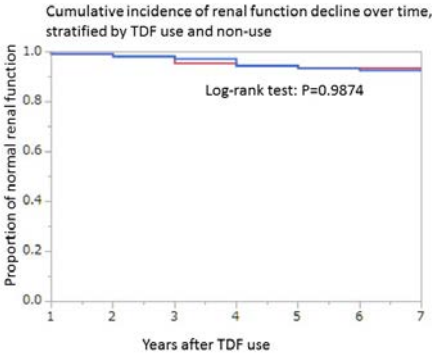
PUB154

Long-Term Exposure to Tenofovir Is Not Linked with Increased Risk of Renal Dysfunction: A Propensity Score-Matched Analysis Minoru Ando,[1,2] Kumiko Momoki,[2,3] Ken Tsuchiya,[2] Kosaku Nitta.[2] *[1]Dept of Medicine, Fu-chu Medical and Welfare Center, Tokyo, Japan; [2]Dept IV of Internal Medicine, Tokyo Women's Medical Univ, Tokyo, Japan; [3]Dept of Nephrology, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan.*

Background: Tenofovir disoproxil fumarate (TDF) has nephrotoxicity; however, it has not been validated in the clinical setting for HIV care. A retrospective cohort study with a propensity score (PS)-matched analysis is considered comparable to randomized control trials.

Methods: A retrospective cohort study was performed in 661 HIV-infected patients receiving antiretroviral therapy from 2008 to 2014. PS matching using a multivariate logistic regression model was performed to match each TDF user with TDF non-user in a 1-to-1 fashion, and 214 patients (107 in each) were eligible for analysis. Baseline covariates that would relate significantly to the decision to use or not to use TDF were chosen in the PS scoring. A decline in eGFR was defined as an eGFR decline ≥30% from baseline. The difference in proportion of eGFR decline between the PS-matched groups was analyzed by McNemar test. A multivariate Cox proportional hazards model was constructed to calculate hazard ratio (HR) with its 95% confidence interval (CI) of TDF use for eGFR decline. Cumulative incidence of eGFR decline over time was drawn by Kaplan-Meier method.

Results: eGFR decline developed in 8 and 7 in the TDF users and the non-users, respectively; moreover, the proportions were not significantly different between the groups (7.48% versus 6.54%; p = 0.7889). The Kaplan-Meier estimates were not different between the groups .



The HR (95% CI) of TDF use was not statistically significant (HR, 0.88 [95%CI, 0.31-2.46], p = 0.8112).

Model	HR (95% CI)	P value
Unadjusted	0.87 (0.31-2.45)	0.8039
Adjusted for PS	0.88 (0.31-2.46)	0.8112

Conclusions: Long-term exposure to TDF is less likely to develop renal dysfunction.

PUB155

Dialysis Therapy and Conservative Management of Advanced Chronic Kidney Disease: A Meta-Analysis Paweena Susantitaphong,[1] Supakanya Wongrakpanich,[2] Wikrom Chaiwatcharayut,[2] Suramath Isaranuwatchai,[1] Jirat Chenbhanich,[1] Natanong Thamcharoen,[3] Kearkiat Praditpornsilpa,[1] Somchai Eiam-Ong,[1] Bertrand L. Jaber.[4] *[1]Div of Nephrology, Dept of Medicine, Chulalongkorn Univ, Thailand; [2]Einstein Medical Center, Philadelphia; [3]Dept of Medicine, Bassett Medical Center, Cooperstown; [4]Dept of Medicine, St. Elizabeth's Medical Center, Boston.*

Background: Dialysis in the elderly with advanced chronic kidney disease (CKD) and multiple co-morbidities may not be associated with improved life expectancy compared to conservative non-dialytic management.To inform clinical practice,we performed a quantitative meta-analysis of all available studies examining this question.

Methods: A systematic literature search was conducted in MEDLINE,Scopus,Cochrane,and ClinicalTrials.gov to identify cohort studies examining the association of dialysis vs.conservative management of stage5 CKD with clinical outcomes. Random-effect models were used to compute the pooled adjusted hazard ratio (HR) for all-cause mortality, and the weighted mean difference (WMD) for continuous variables.

Results: In the 11 cohort studies (11,120 patients) that were identified,patients initiating dialysis were significantly younger by approximately 7 years compared to conservative management.The mean GFR of patients initiating dialysis was 10.4 mL/min/1.73m2 (95%CI 8.4 to 12.4),which was significantly lower than those receiving conservative management (WMD-1.04 mL/min/1.73m2;95%CI-1.94 to-0.13). By meta-analysis, while dialysis was associated with a significantly lower age-adjusted risk of death compared to conservative management (age-adjusted pooled HR 0.65;95%CI 0.46 to 0.91;P=0.01), after adjustment for co-morbidities,dialysis was marginally associated with improved survival (adjusted pooled HR 0.54;95%CI 0.29 to 0.99;P=0.05).

Conclusions: Initiation of dialysis therapy in older patients with co-morbidities might not be associated with a lower adjusted mortality risk compared to conservative management. We were unable to compare the two strategies in terms of patient centered quality of life measures. Efforts must focus on promoting patient values and preferences, shared decision-making, and symptom burden alleviation.

PUB156

Prevalence of Proteinuria in Patients Requiring Hyperbaric Oxygen Therapy (HBOT) Melissa L. Swee, Douglas L. Somers. *Nephrology, Univ of Iowa Hospitals and Clinics, Iowa City, IA.*

Background: Hyperbaric Oxygen Therapy is a medical treatment using high levels of pressurized oxygen (100%) in order to treat a variety of conditions, including decompression sickness, poorly healing skin ulcers, radiation cystitis, and carbon monoxide poisoning. Despite gaining popularity in recent decades, there is little data about the effects of hyperbaric oxygen therapy on the kidneys.

Methods: Approval by the Institutional Review Board was obtained. This is a retrospective chart review investigating the degree of proteinuria on urine dipstick on all patients undergoing hyperbaric oxygen therapy at the University of Iowa from January 2010 to May 2015. Other variables that were investigated included serum creatinine, age, sex, and co-morbid medical conditions. Descriptive statistics were utilized in order to calculate the prevalence of proteinuria among these populations.

Results: The records of 326 patients were examined. In this population, 201 did not have urine dipstick performed and therefore were excluded from analysis. Among those examined, proteinuria (1+ or higher) was found in 7 of 33 patients with carbon monoxide poisoning (21%), 31 of 67 patients with non-healing soft tissue infection or osteomyelitis (46%), 9 of 33 patients with a history of cancer of the head and neck (27%), and 8 of 11 patients with radiation cystitis (73%).

Conclusions: To our knowledge, this is the largest study to date examining proteinuria in patients who are undergoing hyperbaric oxygen therapy. Our results indicate that there is a higher than expected rate of proteinuria in these patients, particularly in those with carbon monoxide poisoning and history of cancer of the head and neck. The reasons for this are unclear and require further research. A prospective study measuring proteinuria prior to and after sessions of hyperbaric oxygen therapy has been approved by the IRB at the University of Iowa and is forthcoming.

PUB157

Glomerular Filtration in Patients with Advanced Chronic Kidney Disease by Berlin Study Initiative Equation Marisol Poma Tapia,[1] Fernando Tornero,[1] Jose A. Herrero,[1] Jose Maria Bautista,[1] Amir Shabaka,[1] Marta Calvo,[1] Virginia López de la Manzanara Pérez,[1] Fabio Procaccini,[1] Mauricio Alejandro Miranda Cam.[1] *[1]Nephology, Hospital Clínico San Carlos, Madrid, Spain; [2]Nephology, Hospital Clínico San Carlos, Madrid, Spain; [3]Nephology, Hospital Clínico San Carlos, Madrid, Spain.*

Background: We estimate the glomerular filtration rate (eGFR) using formula based on serum creatinine (Cockroft-Gault, MDRD and CKD-EPI). These equations are poorly developed in the elderly population. Recently described new equations specifically designed in this population as the Berlin Initiative Study (BIS 1). Our goal is to assess the difference in measured GFR by CKD-EPI and BIS1 in patients in advanced chronic kidney disease (CKD).

Methods: We studied 182 patients, 117 over 70 years old and 65 under of the advanced chronic kidney disease program with eGFR <20 ml / min according CKD-EPI equation. We compare the difference between CKD-EPI and BIS 1 equations.

Results: The mean age of patients over 70 years was 80.88 +/- 5.98 (66 males, 51 females) and under 70 was 58.84 +/- 5 (39 men, 26 women). The eGFR measured by CKD-EPI was similar in both groups (15.92 + 0.5 ml / min in patients over 70 years VS 16.2 + 0.8 ml / min in younger, p NS). However, when we use the BIS1 equation older patients have a significantly lower GFR that younger (19.6 + 0.4 ml / min vs 24.16 + 1.0 ml / min; p <0.001). When equate both equations CKD-EPI gives lower values of eGFR in 96.5% of patients with lower levels (16.03 + 0.45 ml / min vs 21.3 + 0.50 ml / min; p <0.001). If we analyze the difference between the two equations by the age we note that CKD-EPI gives lower values in patients under 70 years, being the difference between the two equations of -7.94 + 0.45 ml / min for under 70 years and -3.67 + 0.16 ml / min for over 70 years (p <0.011).

Conclusions: The eGFR by BIS1 equations in patients over 70 years old gives higher than estimated by CKD-EPI equations, although it is more correlated than younger patients. patients under 70 years, being the difference between the two equations of -7.94 + 0.45 ml / min for under 70 years and -3.67 + 0.16 ml / min for over 70 years (p <0.011).

Funding: Clinical Revenue Support

PUB158

A Randomized Controlled Trial Comparing In-Person and Wiki-Inspired Nominal Group Techniques for Engaging Stakeholders in Chronic Kidney Disease Research Prioritization Meghan J. Elliott,[1] Sharon Straus,[1] Neesh I. Pannu,[2] Sofia B. Ahmed,[3] Helen Tam-Tham,[3] Maoliosa Donald,[3] Erin Lillie,[1] Braden J. Manns,[3] Brenda Hemmelgarn.[3] *[1]Univ of Toronto; [2]Univ of Alberta; [3]Univ of Calgary.*

Background: Few studies have evaluated stakeholder engagement in chronic kidney disease (CKD) research prioritization. In this randomized controlled trial, we sought to compare an in-person nominal group technique (NGT) approach with an online wiki-inspired alternative to determining the top 10 CKD research priorities.

Methods: Participants included adults ≥18 years with access to a computer and Internet, high health literacy, and from one of the following stakeholder groups: patients with non-dialysis CKD, their caregivers, CKD health care providers, or CKD health policymakers. 56 participants were randomized to a wiki-inspired modified NGT that occurred over 3 weeks *vs.* a one-day in-person NGT workshop, informed by James Lind Alliance methodology, to determine the top 10 CKD-related research priorities. The primary outcome was the pairwise agreement between the two groups' final top 10 ranked priorities, evaluated using Spearman's correlation coefficient. Secondary outcomes were participant engagement and satisfaction and wiki tool usability.

Results: Spearman's rho for correlation between the two lists was 0.139 (95% CI -0.543 to 0.703, p=0.71), suggesting low correlation between the top 10 lists across the two groups. Both groups ranked the same item as the top research priority, with 5 of the top 10 priorities ranked by the wiki group within the top 10 for the in-person group. In comparison to the in-person group, participants from the wiki group were less likely to report: satisfaction with the format (73.7% vs.100%, p=0.011); ability to express their views (57.9% vs 96.0%, p=0.0003); and perception of meaningful contribution (68.4% vs 84.0%, p=0.004).

Conclusions: A CKD research prioritization approach using an online wiki-like tool identified low correlation in rankings compared with an in-person approach, with less satisfaction and perceptions of engagement. Modifications to the wiki tool are required before it can be considered an alternative to an in-person workshop for engaging patients in research prioritization.

PUB159

Clinical Predictors of Maternal and Fetal Outcomes in Pregnancy of Chronic Glomerulonephritis Patients Yuehong Li, Jiaxuan Lv. *Nephrology, Beijing Tsinghua Changgung Hospital, Medical Center of Tsinghua Univ, Beijing, China.*

Background: Analysing the predictors of maternal and fetal outcomes in pregnancy of chronic glomerulonephritis (CGN) patients is helpful to acknowledge the effects of pregnancy on chronic kidney diseases. Decreased kidney function, uncontrolled hypertension and serious proteinuria are unfavorable pregnancy outcomes observed in some cohorts, but not enough studies on outcomes of pregnancies in CGN patients. The aim of the study was to define the predictors of adverse maternal and fetal outcomes in CGN patients.

Methods: Maternal and fetal outcomes in 60 pregnancies of CGN patients from Jan. 2006 to Jan. 2016 were retrospectively analyzed. Clinical manifestations, laboratory data, medication and outcomes before and during pregnancies of these patients were analyzed by univariate and logistic regression.

Results: 1. CGN patients were associated with more adverse pregnancy outcomes. The gestational ages were shorter, the incidents of preeclampsia and gestational hypertension were increased. The rates of premature delivery and low birth weights were higher. 2. Prenatal proteinuria (1.8±2.1 g/d vs 0.6±0.8 g/d, *P*=0.032) and blood pressure (11.7% vs 3.3%, *P*=0.001) significantly increased compared with pre-pregnancy stage. 3. Proteinuria ≥1.0 g/d (OR 12.22, 95%*CI* 3.16~47.32, *P*=0.001) was the predictor of adverse maternal outcomes. Blood pressure ≥140/90 mmHg (OR 8.97, 95%*CI* 1.69~47.53, *P*=0.010) and uric acid ≥363 umol/l (OR 7.35, 95%*CI* 1.88~28.76, *P*=0.004) were the predictors of adverse fetal outcomes. 4. Proteinuria of 6-months after delivery are slightly increased.

Items	Pre-pregnancy	Post-6months delivery	*P*
Proteinuria (g/d)	0.6±0.8	0.8±0.6	0.032
Plasma albumin (g/l)	36.5±4.0	37.0±4.2	0.531
Creatinine (umol/l)	67.0±7.5	70.2±7.9	0.296
Uric acid (umol/l)	313.0±86.3	316.4±89.3	0.585

Conclusions: Maternal-fetal risks are increased in pregnancies of CGN patients. Proteinuria ≥1.0 g/d is the predictor of adverse maternal outcomes. Blood pressure ≥140/90 mmHg and uric acid ≥363 umol/l are the predictors of adverse fetal outcomes.

PUB160

Specialists' Perspectives on the Management of Patients with Systemic Lupus Erythematosus: A Mixed-Methods Study David J. Tunnicliffe,[1,2] Davinder Singh-Grewal,[1] Jonathan C. Craig,[1,2] Shilpa Jesudason,[4] Daniel Sumpton,[1,2] Allison Tong.[1,2] *[1]Univ of Sydney; [2]Centre for Kidney Research, Children's Hospital at Westmead; [3]Central and Northern Adelaide Renal and Transplantation Service, Royal Adelaide Hospital.*

Background: Different specialists are involved in the management of patients with systemic lupus erythematosus (SLE) but unwarranted variation in practice remains unexplored. We aimed to describe specialists' attitudes and perspectives on the management of SLE.

Methods: Immunologists, nephrologists and rheumatologists (n=43) caring for adult patients with SLE in Australia completed a face-to-face semi-structured interview and seven clinical vignettes on the management of lupus nephritis. Descriptive statistics were calculated for responses to vignettes and qualitative data were analyzed thematically.

Results: Nephrologists were less likely to report the use of mycophenolate mofetil in the management of class II lupus nephritis, while there was no difference in the use of hydroxychloroquine. Five themes underpinned management of SLE: safeguarding patient priorities (emphasizing patient goals, protecting fertility, preventing cosmetic side-effects, maximizing adherence); persisting through ambiguity (uncertainty in etiology, inapplicable evidence, comprehending information dispersion); fundamental instincts and habits (learnt familiarity, empathy for the vulnerable); defining responsibility (core educator role, retaining disease control, avoiding severe outcomes, maintaining versatility of skills, protecting specialists' interests); and optimizing nuances of the health system (capitalizing on multi-disciplinary care, accessing effective therapies, improving specialists decisional-confidence).

Conclusions: Clinicians aim to achieve optimal outcomes for patients with SLE, but specialists often felt constrained by an unclear understanding of SLE, poor-quality evidence, and competing priorities to standardize practice. In order to help guide decisions and help eliminate unwarranted variation in practice, we recommend that future collaborative multidisciplinary efforts be undertaken to ensure improved models of shared care across specialties, and a clear direction for future research.

PUB161

Healthcare and Research Priorities of Adolescents and Young Adults with Systemic Lupus Erythematosus - A Mixed-Methods Study David J. Tunnicliffe,[1,2] Davinder Singh-Grewal,[1,3,4] Jonathan C. Craig,[1,2] Martin Howell,[1,2] Ming-Wei Lin,[5] Angelique F. Ralph,[1,2] Allison Tong.[1,2] *[1]Univ of Sydney; [2]Centre for Kidney Research, Children's Hospital at Westmead; [3]Dept of Rheumatology, Sydney Children's Hospital Network; [4]Faculty of Medicine, Univ of New South Wales; [5]Dept of Immunology, Westmead Hospital.*

Background: The care of adolescents and young adults with systemic lupus erythematosus (SLE) is particularly challenging. The disease may be severe, adolescent patients have complex medical and psycho-social needs, and they must navigate the transition to adult services. To inform patient-centered care, we aimed to identify the healthcare and research priorities of adolescents and young adults with SLE and describe the reasons underpinning their priorities.

Methods: Face-to-face, semi-structured interviews and focus groups were conducted with patients with SLE, aged from 14 to 30 years, from five centers in Australia. In five allocation exercises, participants allocated ten tokens (i.e. votes) to 1) research topics (medical management, prevention and diagnosis, lifestyle and psychosocial), 2-4) research questions associated with research topics, and 5) healthcare specialties, and discussed the reasons for their choices. Descriptive statistics were calculated for votes and qualitative data was analyzed thematically.

Results: From the 26 participants, there was an undifferentiated allocation of votes to research topics and associated research questions. They allocated their votes towards medical and mental health specialties in the management of SLE, whilst fewer votes were given to allied health. Seven themes underpinned participants' priorities: improving service shortfalls, strengthening well-being, ensuring cost efficiency, minimizing family/community burden, severity of comorbidity or complications, reducing lifestyle disruption, and fulfilling future goals.

Conclusions: Young patients with SLE value comprehensive care, in particular rheumatology, nephrology, and mental health. Research on improving psychological health and self-management of symptoms may improve treatment satisfaction and health outcomes for adolescents and young adults with SLE.

PUB162

Impact of an On-Line Course for Primary Health Care Physicians on Patients at Risk for Chronic Kidney Disease (CKD) Maria Alejandra Guzman,[1,2] Alfonso M. Cueto-Manzano,[1] Cristina Chavez,[3] Hector Martinez Ramirez,[1] Jorge Lopez-Leal,[1] Roxana Marquez-Herrera,[1] Norma Palacios,[3] Enrique Rojas-Campos.[1] *[1]Unidad Investigación Médica en Enfermedades Renales, HE-CMNO IMSS, Guadalajara, Mexico; [2]ISN-Fellowship Program, ISN; [3]Coordinación Nacional de Educación en Salud, IMSS, DF, Mexico.*

Background: On-site education increases clinical competence of family physicians (FP) and preserves renal function of early CKD patients; on-line learning might have higher impact, however, this has not been probed. Aim: to assess the impact of an on-line course for FP on patients at risk for CKD.

Methods: Fifty FP from 2 Family Medicine Units were registered in an on-line course implemented during Aug-Oct/2015. One-hundred forty-seven patients attended by those FP registered, with diagnosis of diabetes mellitus and/or hypertension, were retrospectively studied (from medical charts). Patients were divided in 2 groups: those whose physician approved the course (G1), and those whose physician did not approve (G2).

Results: Main results are shown in Table.

	G1(n60)		G2(n87)	
Variable	**Baseline**	**Final**	**Baseline**	**Final**
FP Advice to improve				
Diet(%)	37	58*	58**	68
Physical activity(%)	32	52*	41	49
Emotion management(%)	8	33*	20	21
Referral to dietitian(%)	10	17	7	18*
Referral to self-help group(%)	3	10	7	16
Creatinine request(%)	50	60	37	31**
GFR estimation(%)	27	40	11	11**
Urinalysis request(%)	33	35	10	24**
Clinical-Biochemical				
Systolic blood pressure(mmHg)	126±13	123±12*	123±13	122±11
Diastolic blood pressure(mmHg)	76±8	75±8	77±8	76±7
Creatinine(mg/dL)	0.9(0.7-1)	0.8 (0.7-1)*	0.9(0.7-1)	0.8(0.7-1)
Glucose(mg/dL)	130±40	120±41*	124±44	123±61
eTFG(mL/min/m^2)	79(68-95)	74(62-91)*	82(75-97)	86(63-107)
*p<0.05 vs baseline same group;**p<0.05 vs group 1 same evaluation				

Conclusions: FP who successfully completed the on-line course significantly increased advice to patients to improve diet, physical activity, emotional management, levels of systolic blood pressure and glucose. Although kidney function remained clinically stable in both groups, FP who successfully completed the course tended to request serum creatinine and estimate GFR more frequently than the others.

PUB163

Impact of an On-Line Course about Prevention, Diagnosis and Tratment of Early Chronic Kidney Disease (CKD) in the Primary Health-Care
Maria Alejandra Guzman,[1,2] Alfonso M. Cueto-Manzano,[1] Cristina Chavez,[3] Hector Martinez Ramirez,[1] Jorge Lopez-Leal,[1] Roxana Marquez-Herrera,[1] Norma Palacios,[3] Enrique Rojas-Campos.[1] *[1]Unidad Investigación Médica en Enfermedades Renales, HE-CMNO IMSS, Guadalajara, Mexico; [2]ISN Felloship Program, ISN; [3]Coordinación Nacional de Educación en Salud, IMSS, DF, Mexico.*

Background: The Mexican Institute of Social Security (IMSS) is the major health care provider. On-site education increases clinical competence of family physicians (FP) and preserves better renal function of early CKD patients; on-line learning might have higher impact, however, this has not been probed. Aim: to report the experience in implementing an on-line course on early CKD in primary health care.

Methods: An on-line course was developed in collaboration with IMSS Educational Experts. It was focused on early CKD, containing 5 units: General Aspects, Prevention, Diagnosis, Treatment, and Follow-up/Referral to Nephrologist. Each unit contained relevant information, clinical cases, homework, summary, and final test; all the latter, together with a final course evaluation, had to be approved to obtain credits. The course was implemented in Aug-Oct/2015.

Results: One-hundred eight FP from 3 Family Medicine Units (FMU No. 53, 78, and 171) of Guadalajara city, were initially registered; roughly, one third of physicians belonged to each FMU. Forty-four FP never started (terminal efficiency 58%), half of them were male, and their age was 45±9 yrs. At the end of Unit 1, 14 FP dropped out (70%), 2 (10%) at the end of Unit 2, 3 (15%) at Unit 3, and 1 (5%) at Unit 5; 43% were male and age was 45±8 yrs. Forty-four FP completed the course, and all of them finally approved it (modified terminal efficiency 100%); these latter subjects were younger 43±8 yrs (p=0.008), and tended (NS) to have more men (68%) in the group than those who did not approved.

Conclusions: An on-line course about early CKD was successfully developed and applied in FP of the primary health-care. A significant proportion of physicians dropped out before starting; however, those physicians who remained finally approved the course. Terminal efficiency was adequate; however, it is needed to implement strategies to increase it in order to improve tools against kidney disease.

PUB164

CKD.QLD: Management of Chronic Kidney Disease through Tele-Health in Queensland, Australia
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Background: In some areas of Australia, access to specialists is limited by geographical location and resources. We explored a Tele-heath program for management of chronic kidney disease (CKD) patients in rural, regional and remote Queensland.

Methods: Patients were among those attending renal clinics in Toowoomba Hospital, but living at some distance. Their first review was at Toowoomba Hospital to ascertain their clinical profile and to discuss the process. Tele-health clinics in Kingaroy & Cherbourg were coordinated by the renal nurse practitioner. Other hospital locations were managed by local nursing personal. At each clinic the patients' health records and relevant investigations are assembled in advance. Consultations are conducted through Queensland Health (QH) facilities.

Results: 151 patients were seen between November 2011 and May 2016, with over 400 consultations. Total distance traveled by all patients to specialist clinics at Toowoomba for their first consultation was 55,619 kilometers (range 63.5 to 672). Mean age was 64.0 (SD13.9) years, median 67 yr, and 48.3% were males. A quarter (27.8%) were Aboriginal. Major risk factors include hypertension (94%), smoking (current or former) (64.2%), diabetes (58.2%) and obesity (58.2%). Diabetic nephropathy (40.7%) was the dominant cause for CKD followed by renovascular (18.5%) and glomerular disease (9.9%) There were 4 transplant patients. Co-morbidities included coronary artery disease (30.4%), chronic lung disease (19.2%), cerebrovascular (15.8%) and peripheral vascular disease (9.9%). On follow up 21 (13.9%) have died without dialysis and 4 (2.6%) started planned RRT. About half of patients who died were identified for conservative therapy.

Conclusions: CKD patients from regional and remote areas have multiple risk factors and co-morbidities. They can be managed successfully by Tele-health with significant savings in distance traveled and resources utilized.

PUB165

Knowledge, Attitude and Practices of Immediate Blood Relatives/ Spouse(s) of Patients with End Stage Renal Disease Toward Organ Donation
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Background: A strong relationship between knowledge and organ donation has already been established. Despite the various available options of Renal Replacement Therapy (RRT), majority of the patients with End Stage Renal Disease (ESRD) do not receive any RRT.In the absence of a well-organized deceased donor program, living donors constitute the major donor source.With this premise, a cross sectional study was done to assess the knowledge, attitude and practices (KAP) in immediate blood relatives and spouse(s) of ESRD patients and to assess the factors influencing KAP.

Methods: 379 subjects from attendants of 238 ESRD patients were administered a pre-tested questionnaire. All consenting attendants (aged 18 years and above) of CKD stage 5 ESRD patients were included. Assessment of factors influencing the KAP was done using Pearson Chi-Square test.

Results: 91.8% attendants had heard about organ donation. 67.5% had knowledge about organ donation which was significantly associated with the relationship with patient [spouse (p=.001), son (p=.005)], education status [graduates and above (p=.001)] and higher socioeconomic status (p=.004). 50.6% had positive attitude towards organ donation which was significantly associated with gender [females (p=.002)], relationship with the patient [mother (p=.0254), spouse (p=.001), son (p=0.02)] and the number of dependants [6-8 (p=.04)]. 41.2% subjects had positive attitude towards practicing organ donation which was significantly associated with marital status [Single (p=.04)-more motivated], education status [graduates and above (p=.001)].

Conclusions: More knowledge about organ transplantation can be transformed into better attitude which can lead to increased number of organ donations. More and more people should be educated and made aware of the importance of organ donation.

PUB166

Patient Partnership as the Core of a National Patient-Oriented Kidney Research Network: Can-SOLVE CKD
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Background: Patient-oriented research (POR) focuses on priorities that matter to patients, seeking to engage them throughout the research process, and to generate results that can rapidly advance improvements in health and care. The Canadians Seeking Solutions and Innovations to Overcome (Can-SOLVE) CKD Initiative embraces a national partnership strategy with patients across Canada to transform kidney research and care.

Methods: The James Lind Alliance method was adopted to discern top research priorities with patients and families with CKD. Patient partners, researchers and policy-makers developed in workshops research proposals and various components in Can-SOLVE CKD. A national Patient Council was formed to lead all aspects of Can-SOLVE CKD. The extent and impact of patient engagement is continually assessed with surveys and testimonials.

Results: The priority-setting workshops identified research questions for early and advanced CKD, resulting in a 3-themed research program in Can-SOLVE CKD (early identification, access to novel therapies, and models of care). A diversely representative Patient Council of >30 members is a key strength, secured federal funding support and has become the core driver of the research agenda. Quantitative and qualitative survey results demonstrated that the patient partners are highly engaged and appreciative of having a voice in research, along with concrete insights on needs for training and other supports for effective partnership in research. In their qualitative feedback, patient partners expressed that they were empowered in their involvement, while allowing peer support and giving back.

Conclusions: Patients are making a unique and important contribution to Can-SOLVE CKD. They are critical partners in kidney research, and feel a sense of hope in the partnership in transforming kidney care and therapy. Meaningful engagement with patients enables a new era in kidney research to co-create better kidney health and care with researchers and policy-makers across Canada.

Funding: Government Support - Non-U.S.

PUB167

Development of an Automated CKD Risk Management System
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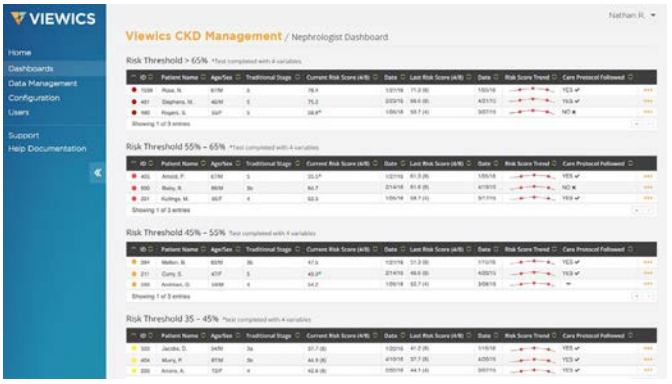
Background: CKD is managed according to eGFR based stages rather than risk of progression, resulting in variable and suboptimal care. Here we describe the development of an automated system that actualizes the highly accurate Kidney Failure Risk Equation (KFRE) via a practical, automated clinical solution.

Methods: We defined a four-step protocol based on the KFRE that recommends referral to nephrologist, multidisciplinary care enrollment, dialysis discussion and education and fistula placement at specific risk thresholds. Utilizing the Viewics platform (Figure 1), we automated the input of patient's lab results and demographic information and calculation of the KFRE algorithm. A series of dashboards was created to enable primary care and nephrologist clinicians, as well as program managers to track patient

results, protocol recommendations, and required actions. Finally, custom patient education reports were automatically created, which detail individual risk of renal failure and care recommendations, designed to reduce anxiety and better engage patients in their care.



Results: Our solution is a cloud-based, HIPAA compliant, end-to-end program which readies the risk score prediction for clinical adoption and improved CKD management. It comprises a lab and EMR integration platform, personalized risk prediction for renal failure, automated and integrated care management recommendations for primary care physicians and nephrologists, and customized patient education reports.

Conclusions: This program accurately predicts the risk of progression from CKD to ESRD for at least five years, and its integration into practice allows for more appropriate care and improved outcomes. Total annual cost savings to an ACO with a population of 25,000 covered lives was estimated at $2 million as a result of delaying stage 3 progression, reclassifying stage 4s, and providing earlier nephrologist care for patients with a high risk of progression.

Funding: Pharmaceutical Company Support - Viewics Inc.

PUB168

Incidence of Cisplatin-Induced Nephrotoxicity among Patients Using Saline Hydration, Potassium Chloride, Magnesium Sulfate and Mannitol

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Background: Cisplatin is the standard drug for treating solid-organ malignancy however, can cause tubular toxicity, decrease in GFR, and increase creatinine causing AKI, interstitial injury and probably CKD. To prevent nephrotoxicity that can lead to CKD, maintenance of adequate hydration and replacement of electrolytes are necessary but no standardized hydration protocols available. Determination of the incidence of cisplatin-induced nephrotoxicity using isotonic saline, KCl, $MgSO_4$ and mannitol can help improve the hydration regimen for the prevention of nephrotoxicity.

Methods: A retrospective study evaluating the incidence of nephrotoxicity among patients using cisplatin-based chemotherapy hydrated with isotonic saline, KCl, $MgSO_4$, and mannitol from January 2011-2015. Estimated GFR was calculated using CKD-EPI. Nephrotoxicity is defined as lower GFR, higher creatinine, and reduced magnesium and potassium levels. Descriptive statistics were done. Any associated p-values <0.05 will be considered statistically significant.

Results: Total of 53 patients were analyzed which showed an increasing trend in creatinine and decreasing trend in eGFR until 3 months after chemotherapy. The baseline creatinine, eGFR, and serum electrolytes compared with the results 3 months post-chemotherapy were found to be significantly different.

	Chemotherapy Cycle (n=53)		
	Baseline	3 months post	p-Value
Creatinine (mg/dl)	0.9 (0.57-1.54)	1.07 (0.55-1.78)	**0.0000***
Sodium (mmol/L)	136 (127-143)	135 (114-142)	**0.0000***
Potassium (mmol/L)	4 (2.8-5.1)	3.80 (2.9-4.8)	**0.0008***
Magnesium (mg/dL)	2.1 (1.4-2.5)	1.7 (1.1-2.4)	**0.0000***
Ionized Calcium (mg/dL)	1.19 (0.95-1.37)	1.15 (0.89-1.39)	**0.0076***

The incidence of decreased renal function after 3 months from the last chemotherapeutic cycle was 33% (n=18).

Conclusions: Despite judicious hydration, Cisplatin therapy may induce permanent nephrotoxicity with an incidence of 33% three months after 3 chemotherapeutic cycles. Cisplatin induces nephrotoxicity as evidenced by electrolyte imbalance, increased mean serum creatinine and decreased estimated GFR.

PUB169

Urinary Procollagen Type-III Amino Terminal Propeptide (PIIINP) Predicts End Stage Kidney Disease (ESKD) and All-Cause Death in Non-Dialysis CKD Patients

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Background: Tubulointerstitial fibrosis is the final common pathway to ESKD. Since urinary PIIINP is correlated significantly with the severity of fibrosis in renal biopsy, it could be a marker of progressive kidney diseases. Recent cross-sectional study demonstrated that the urinary PIIINP was correlated with the progression of CKD in the community based population. In this prospective study, we investigated whether urinary PIIINP was associated with renal outcome and mortality in pre-dialysis advanced CKD patients.

Methods: A total of 132 CKD patients were recruited from January 2011 to December 2014. Patients with liver disease, lung fibrosis, and malignancies were excluded. Urinary PIIINP was measured using the radioimmunoassay at baseline. Multivariate Cox regression analysis and log-rank test were adopted using urinary PIIINP/Cr as the explanatory variable and initiation of RRT and all-cause death as the primary composite endpoint.

Results: The study population included 71, 51, and 10 patients with CKD stage 3, 4, and 5, respectively. The mean age of the overall patients were 68 years and 70.5% were male sex. Forty-four patients (33.3%) had diabetes. A total of 14 patients (11%) started RRT and 8 patients died during the follow-up period (mean, 40.1 months) The patients were stratified into two groups based on the cut-off value of urinary PIIINP/Cr determined by the ROC analysis. The Kaplan-Meier survival curves showed that the patients' group with higher urinary PIIINP had significantly poorer outcomes ($p = 0.000$). Furthermore, multivariate Cox regression analysis revealed that higher urinary PIIINP wassignificantly associated with increased risk of RRT and all-cause death adjusted for the age, gender, the etiology of diabetes, blood pressure, eGFR, and urinary protein. (HR; 3.177, 95%CI; 1.018–9.915, $p = 0.046$).

Conclusions: Urinary PIIINP in pre-dialysis and anvanced CKD patients might be a novel prognostic marker for ESKD and all-cause death.

PUB170

Neck Circumference Predicts Renal Function Decline in Overweight Men and Women: A Community-Based Prospective Cohort Study

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Background: Upper body subcutaneous fat, commonly estimated by neck circumference (NC), has recently been noticed as the main determinant of systemic free fatty acid concentrations in overweight patients. Therefore, the association between upper body subcutaneous fat, represented by NC, and incident chronic kidney disease (CKD) was explored.

Methods: The data was retrieved from the Korean Genome and Epidemiology Study (KoGES) cohort. Overweight was defined as body mass index ≥ 23 kg/m^2, and subjects were followed at a 2-year interval from 2003 to 2012. Incident CKD was defined as the composites of estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 or development of proteinuria. A total of 35,709 cohort subjects were screened. After exclusion, 2,268 overweight subjects were eligible for final analysis.

Results: The mean age was 36.3±3.0 years, and 1,285 patients (56.7%) were male. The subjects were divided into two groups according to the median value of NC in male and female subjects, respectively. High NC showed significantly high prevalence of hypertension (male, P<0.001; female, P=0.009) and diabetes (male, P=0.002; female, P<0.001), while eGFR was significantly low only in male subjects with high NC (male, P<0.001; female, P=0.167). In multiple Cox analysis, higher NC values were independently associated with incident CKD development in female subject after adjusting for multiple confounding factors [NC, 1 cm increase, male; hazard ratio (95% confidence interval)=0.989 (0.89-1.10), P=0.841, female; 1.159 (1.02-1.31), P=0.019]. However, a significant relationship was not found in male subjects.

Conclusions: NC is independently associated with the incidence of CKD in overweight female subjects. Upper body subcutaneous fat, chiefly represented by NC, could be considered as a practical risk factor for CKD.

PUB171

Early Emergence of Proteinuria Portends Subsequenct Development of Kidney Function Decline or Nephrotic Syndrome after Stem Cell Transplantation

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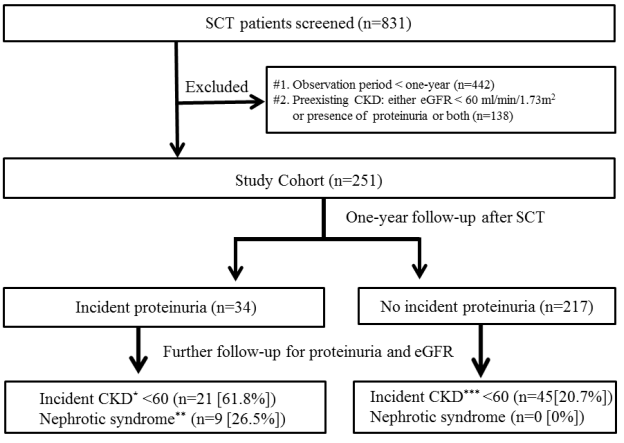
Background: Stem cell transplantation (SCT) places a heavy burden on the kidneys. New proteinuria after SCT may portend the subsequent development of kidney insults.

Methods: A total of 831 patients who received allogeneic SCT between August 2004 and July 2015 were surveyed. Excluding those with prior kidney disease and those who were not followed over one year, 251 were eligible for the study. A historical cohort study was

performed. Dipstick proteinuria ≥1+ within one year after SCT with persistence at least for 3 months was defined as 'incident proteinuria', and subsequent persistence of an eGFR of < 60 mL/min/1.73m^2 for 3 months or longer was defined as 'incident CKD'. Additionally, kidney-biopsied tissue was investigated in all patients who developed nephrotic syndrome.

Results: The mean duration of follow-up was 3.4 (1.7-5.7) years [median (interquartile range)], and 34 patients (13.5%) developed incident proteinuria. Sixty-six of 251 (26.3%) developed incident CKD, and 9 (3.6%) developed nephrotic syndrome due to membranous nephropathy in 8 (89%) or minimal change disease in one (11%). The incidence of such kidney disease was extremely greater in patients with incident proteinuria than those without (61.8% vs 20.7% in incident CKD, and 26.5% vs 0% in nephrotic syndrome).



Figure

Conclusions: SCT patients who manifest incident proteinuria are more predisposed to incident CKD or nephrotic syndrome thereafter. Dipstick urinary protein test is a simple measure to predict the ensuing emergence of kidney disease that should be treated by nephrologists.

PUB172

Accumulation of Proatherogenic Metabolite Trimethylamine-N-Oxide and Gut Microbiome in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease Tetyana L. Vasylyeva, Ruchi Singh, Palika Datta, Kathleen A. Rewers-Felkins, Mohammed A. Al-Obaide. *Pediatrics, Texas Tech Univ Health Sciences Center, Amarillo, TX.*

Background: Increased trimethylamine N-oxide (TMAO) levels have been causally linked with chronic kidney disease (CDK) progression and cardio-vascular disease development. TMAO is produced in liver from gut microbial product trimethylamine (TMA). Our previous data showed significant gut microbial dysbiosis in patients with T2DM and advance CKD (stages 4-5) secondary to diabetic nephropathy. We hypothesized that TMAO levels in patients with T2DM and CKD are influenced by gut microbiome and FMO3 gene expression.

Methods: Twenty T2DM CKD 4-5 (not on dialysis) patients and 20 healthy adults with no significant medical issues and normal renal function were recruited. Age, gender, and dietary habits were recorded. High throughput sequencing method (the bacterial 16S rRNA) was used to study gut microbiome. TMAO concentrations were quantified by MS and analyzed by the two-samples t-test. FMO3 transcript expressions were extracted from FANTOM 5 database.

Results: The ratio of the phyla Firmicutes to Bacteroidetes were significantly increased in the CKD group compared to the healthy group ($p < 0.001$). Firmicutes represented by abundance of TMAO producing bacteria and Bacteroidetes were inversely associated with TMA and TMAO levels. TMAO level in T2DM patients was 2.7 ±1.46 µg/ml compared to 0.43± 0.20 µg/ml in healthy subjects ($p < 0.001$). FANTOM 5 database showed one of FMO3 promoters is most active in liver, whereas other promoters showed low activity or were inactive.

Conclusions: The elevated level of TMAO in T2DM CKD patients is associated with increased number of TMA producing bacteria in addition to poor renal clearance. Restoration of normal gut microbiome and control of FMO3 expression could significantly modulate thisproatherogenic metabolite.

PUB173

Risk Factors for Sleep-Disordered Breathing in Chronic Kidney Disease Mari Okada, Takahiro Masuda, Atsushi Miki, Takuya Miki, Erika Hishida, Marina Kohara, Takuya Murakami, Tomoyuki Yamazaki, Taro Sugase, Yuko Watanabe, Takahisa Kobayashi, Tetsu Akimoto, Shigeaki Muto, Daisuke Nagata. *Div of Nephrology, Dept of Medicine, Jichi Medical Univ, Shimotsuke, Tochigi, Japan.*

Background: Sleep-disordered breathing (SDB) in chronic kidney disease (CKD) predicts the progression of CKD, cardiovascular events and mortality (Sakaguchi et al. CJASN 2013; Masuda et al. NDT 2011). However, the risk factors associated with SDB in CKD patients remains unclear.

Methods: Fifty CKD patients who have not yet received dialysis were enrolled in this study. Overnight pulse oximetry was performed to diagnose SDB. Patients were divided into two groups according to 3% oxygen desaturation index (3%ODI) by pulse oximetry: normal (3%ODI<5 events/h) and SDB (5 events/h≤3%ODI). We examined predictors of SDB using multivariable logistic regression analysis.

Results: Average age was 49.8±16.5 years, male was 46.0%, body mass index (BMI) was 25.4±5.9kg/m^2 and estimated glomerular filtration rate (eGFR) was 55.9±4.8 mL/min/1.73m^2. Average 3%ODI was 12.2±16.2 events/h and twenty-nine patients (5≤3%ODI<15 events/h, 15 patients; 15 events/h≤3%ODI, 14 patients) were diagnosed as SDB. Age (normal 41.5±15.2 vs SDB 55.7±14.9* years, *P<0.05), BMI (22.3±3.9 vs 27.7±6.1* kg/m^2), systolic blood pressure (122±4 vs 135±4* mmHg) and urine protein (1.2±1.2 vs 2.8±3.4* g/day) were higher, and eGFR (72.3±6.9 vs 49.4±5.7* mL/min/1.73m^2), serum albumin (3.6±0.7 vs 3.1±0.9* g/dL), serum calcium (Ca) (9.2±0.4 vs 8.8±0.8* g/dL) and urine Ca (81±62 vs 49±45* mg/day) were lower in the SDB group than those in the normal group. Multivariate logistic regression analysis including age, gender, BMI, systolic blood pressure, eGFR, serum albumin, serum Ca, urine protein and urine Ca showed that BMI (odd ratio [OR] 1.85: 95% confidence interval [CI]: 1.20–3.69, P=0.003) and systolic blood pressure (OR 1.11: 95% CI: 1.02–1.28, P=0.009) are independently associated with SDB.

Conclusions: These results suggest that high blood pressure and BMI are risk factors for SDB in CKD.

PUB174

Blockade of P2X7 Receptor Is Protective in the Adriamycin Model of Chronic Kidney Disease Yuan Min Wang,[1] Geoff Yu Zhang,[1] Andrew Sawyer,[1] Jianheng Zhou,[1] Min Hu,[2] Guoping Zheng,[2] Qi Cao,[2] Yiping Wang,[2] Simon C. Robson,[3] David C. Harris,[2] Stephen I. Alexander.[1] *[1]Centre for Kidney Research, The Children's Hospital at Westmead; The Univ of Sydney, Sydney, NSW, Australia; [2]Centre for Transplantation and Renal Research, Univ of Sydney, Westmead Inst of Medical Research, Sydney, NSW, Australia; [3]Transplant Inst, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.*

Background: Extracellular purines have both protective and damaging effects on the immune system and on the kidney. ATP is released from injured tissues through its major receptor P2X7 (P2X7R) to induce inflammation and release pro-inflammatory cytokines, such as interleukin-1β. Extracellular ATP and P2X7 appear to be involved in early stages of damage in nephritis. A804598 (A8) is a potent competitive P2X7R antagonist. Blockade of P2X7 by A8 could potentially limit kidney injury. The aim of the study is to evaluate the role of extracellular ATP and P2X7R in Adriamycin Nephropathy (AN, a toxin-induced model of proteinuric kidney disease) by increasing extracellular ATP or blockade of P2X7R.

Methods: AN was induced with Adriamycin (ADR) in three groups: ADR, ADR+A8, ADR+ATP and a normal control group. ATP or A8 was injected prior to and 24 hours after ADR injection, followed by a further 4 weekly injections. Four weeks after AN induction, renal function and histology were assessed. Serum cytokines were measured using Cytometric Bead Array (CBA) and apoptosis was assessed by TUNEL assay in primary tubular cells.

Results: Mice receiving P2X7R antagonist A8 had significantly less kidney injury with reduced proteinuria and serum creatinine, less glomerulosclerosis and tubular damage than mice receiving ATP or ADR alone. *In vitro* TUNEL assay showed direct pro-apoptotic effects of ATP on renal tubular cells with apoptosis peaking at 2 hours with 3mM ATP. There was significantly less apoptosis in tubular cells exposed to P2X7R antagonist A8 after ATP treatment.

Conclusions: P2X7R blockade protects against kidney injury through inhibition of tubular cell damage by ATP in Adriamycin Nephropathy.

PUB175

High-Intensity Exercise Did Not Adversely Affect the Renal Function or Proteinuria in Stable Patients with IgA Nephropathy after the Initial Treatment Tatsuyuki Inoue, Hitoshi Sugiyama, Masashi Kitagawa, Jun Wada. *Dept of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama Univ, Okayama, Japan.*

Background: IgA nephropathy (IgAN) often occurs in young adults. In IgAN, proteinuria and hypertension are the main risk factors for end-stage kidney disease and can be caused by lifestyle-related diseases. Although patients with stable IgAN are generally young or middle-aged with a high level of daily activities, the actual lifestyle of these patients has not been explored, particularly with respect to their exercise regimen.

Methods: We surveyed the outpatients with IgAN at Okayama University Hospital via a questionnaire about their lifestyle. The degree of exercise was evaluated using the method of the Washington University and divided into five categories. We also investigated the kind of each exercise and further analyzed the relationships between the subjects' lifestyle and data extracted from the medical record. The severity of IgAN was determined by the Japanese clinical and histological grading system.

Results: We obtained valid responses from 81 patients, including 57 with stable IgAN who were not taking corticosteroids. Males accounted for 46% if the subjects, the mean age was 43.7 years old, the mean estimated glomerular filtration rate (eGFR) was 68.7 ml/min/1.73 m^2, and the mean daily protein excretion was 0.28 g/gCr. 91% practiced some form of diet therapy, usually salt restriction (79%). Most (54%) engaged in moderate exercise (category 4). A significantly positive correlation was noted between daily proteinuria at diagnosis and exercise intensity ($r^2 = 0.18$, $p = 0.01$). However, this correlation had disappeared at the final observation. We did not observe any relationships

between exercise intensity and daily proteinuria, change in the protein excretion, or the eGFR at the final observation. Some (34%) felt that their quality of life had been increased by the improvement in their diet after the diagnosis.

Conclusions: This study showed that stable IgAN patients are conscious of their risk of developing lifestyle-related diseases. High-intensity exercise during the period when initial treatments for IgAN are essential did not appear to affect patients with stable IgAN adversely.

Funding: Government Support - Non-U.S.

PUB176

Apparent Disparity between Renal Cortical Blood Flow and Oxygenation in Diabetic Nephropathy as Evaluated by Magnetic Resonance Imaging

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Background: A role for hypoxia in the progression of chronic kidney disease (CKD) has gained attention mostly based on pre-clinical data [PMID: 9551436]. Translation to humans has been challenging due to the lack of accepted markers of hypoxia in humans. Blood oxygenation level dependent (BOLD) MRI is the only known non-invasive method currently available to evaluate relative oxygenation status of the kidney. Chronic hypoxia theory also suggests the cause for the increased hypoxia is due to loss of peri-tubular capillaries. Arterial spin labeling (ASL) based renal perfusion MRI has shown reduced blood flow in CKD [PMID: 23447145].

Methods: A group of subjects with diabetes and stage 3 CKD (n=32; eGFR=50.9 ml/min/1.73 m^2) participated. Subjects were instructed not to take NSAIDs for 3 days and ACEi/ARB 1 day prior to MRI. For reference, similar data was acquired in a group of healthy subjects (n=29; eGFR=99.3 ml/min/1.73 m^2). Both groups were instructed to fast after midnight on the day of the MRI and take half the dose of insulin if applicable. BOLD and ASL perfusion MRI data was acquired on 3.0 T scanner. Reduced blood oxygenation should result in increased R2*.

Results: While cortical blood flow showed significant reduction in CKD compared to control (115.0±36.2 *vs.* 206.3±44.0, $p<0.0001$) and a significant correlation with eGFR ($\rho=0.68$, $p<0.0001$), cortical R2* did not change (18.9±2.4 vs. 18.0±1.6, $p=0.09$; $\rho=-0.26$, $p=0.05$). Since age was significantly correlated with eGFR ($\rho=-0.60$, $p<0.0001$), we performed multiple linear regression to rule out age as a confounder.

Conclusions: The reason for the apparent discrepancy between the reduced cortical blood flow and preserved oxygenation may be due to the corresponding reduction in both GFR and solute load reabsorption, resulting in reduced oxgyen consumption. Further, if blood flow reduction is primarily due to reduction in blood volume (loss of vasculature), that may also support a reduction in R2* compensating any increase due to reduced blood oxygenation. Future studies are needed to better understand this apparent disparity.

Funding: NIDDK Support

PUB177

Characterization of the Novel Kidney Function Markers C-Mannosyltryptophan and Pseudouridine

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Background: C-Mannosyltryptophan (CMT) and pseudouridine (PU) were previously identified as novel kidney function markers using an untargeted mass-spectrometry based metabolomics approach that provided semi-quantitative measurements. We here aimed to obtain absolute concentrations of these markers to provide reference values in blood and urine and to evaluate the agreement of their semi-quantitative and targeted measurements.

Methods: Paired samples (blood, urine) were obtained in 2012 from control participants in the Qatar Metabolomics Study on Diabetes. CMT, PU and creatinine (CREA) were measured using targeted liquid chromatography tandem mass-spectrometry based assays with stable isotope-labeled standards and semi-quantitatively on the Metabolon metabolomics platform version 3. Concentrations were evaluated in both biosamples separately and as their fractional excretion (FE).

Results: Absolute concentrations were available for 111 participants (41% male, mean age 38.3, mean BMI 28.3). The table shows the median and interquartile range of the two markers in blood and urine.

median (interquartile range)	Blood (µmol/l)	Urine (µmol/mmol creatinine)	FE (%)
CMT	0.25 (0.22-0.29)	3.4 (2.7-3.9)	70.8 (65.6-77.8)
PU	2.9 (2.5-3.2)	39.7 (35.1-43.2)	76.0 (68.6-82.4)

The FE of both PU and CMT supports their net reabsorption. Among 77 participants with both absolute and semi-quantitative measurements, both measurement types showed a good correlation for CMT, PU and CREA in blood and urine (Spearman correlation range 0.67-0.89).

Conclusions: We provide reference values for novel markers of kidney function in blood and urine for use in future studies. Semi-quantitative and absolute concentrations show good agreement in blood and urine. A comparison of FE across methods and marker characterization in CKD patients is currently ongoing and will be ready at the time of the conference.

PUB178

An Association between Remodeling of Large Arteries and Arteriosclerosis of Small Renal Arteries in Chronic Kidney Disease

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Background: Remodeling of large arteries may promote organ damage by leading to arteriosclerosis of small arteries. In the present study, we examined the association between arteriosclerosis of small renal arteries and remodeling of large arteries in patients with chronic kidney disease (CKD).

Methods: A total of 174 consecutive patients who underwent renal biopsy at our department between 2010 and 2013 were considered for the study. We excluded patients with vasculitis etc., leaving us with 102 patients. Using pathological specimens, the intimal thickening of the renal small arteries (RSA-IT) was semiquantitatively evaluated. Remodeling of large arteries and endothelial function were assessed by brachial–ankle pulse wave velocity (ba-PWV) and percentage flow-mediated dilatation (%FMD) of the brachial artery.

Results: The mean values for age, blood pressure, and estimated glomerular filtration rate (eGFR) were 40 years, 124 /74 mm Hg, and 72 ml/min/1.73 m^2, respectively. There was a positive correlation between the Log RSA-IT score and Log ba-PWV and a negative correlation between %FMD and both Log RSA-IT and ba-PWV. Patients with high ba-PWV, which was defined as a ba-PWV score equal to or more than the median value, were characterized by older age, higher incidence of comorbidities such as hypertension and diabetes mellitus, higher high-sensitive C-reactive protein (hs-CRP), lower %FMD, and higher RSA-IT score. We conducted multivariate logistic analysis for high RSA-IT, which was defined as a score equal to or more than the median value. High ba-PWV was significantly associated with high RSA-IT independent of age, sex, eGFR, and comorbidities such as hypertension. However, its significance disappeared upon additional adjustment with hs-CRP. Subgroup analysis revealed that patients with a combination of high RSA-IT and ba-PWV had relatively high urine protein.

Conclusions: Remodeling of large arteries may lead to the development of CKD because arteriosclerosis of the small renal arteries is promoted in association with inflammation.

PUB179

Monocyte Count and the Risk of Incident Chronic Kidney Disease and Progression to End Stage Renal Disease

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Background: Experimental evidence suggests a role for monocytes in the biology of kidney disease progression; however, whether monocyte count is associated with risk of incident CKD, CKD progression, and ESRD has not been examined in large epidemiologic studies.

Methods: We built a cohort of 1,594,700 United States Veterans and used survival models to examine the association between monocyte count and risk of incident CKD and risk of CKD progression (defined as doubling of serum creatinine, eGFR decline ≥ 30%, or the composite outcome of ESRD, dialysis or renal transplantation). Monocyte count was categorized into quartiles (Q): Q1 >0.00 to ≤0.40, Q2 >0.40 to ≤0.55, Q3 >0.55 to ≤0.70, and Q4 >0.70 k/cmm.

Results: Over a median follow up of 9.16 years (IQR: 8.26-9.42); in adjusted models, there was a graded association between monocyte counts and risk of renal outcomes. Compared to Q1, Q4 was associated with increased risk of incident eGFR<60 ml/min/1.73m^2 (HR=1.13; CI:1.12-1.14) and risk of incident CKD (HR=1.15 ; CI:1.13, 1.16). Q4 was associated with increased risk of doubling of serum creatinine (HR=1.22; CI:1.20-1.24), ≥30% eGFR decline (HR=1.18; CI:1.17-1.19), and the composite renal endpoint (HR=1.19; CI:1.16-1.22). Cubic spline analyses of the relationship between monocyte count levels and renal outcomes showed a linear relationship where risk was increased with higher monocyte count.

Conclusions: Our results demonstrate a significant association between high monocyte count and risks of incident CKD and CKD progression.

Funding: VA Support

PUB180

Toll Like Receptors, Cytokines, and Cathelecidin as a Complex Inflammatory Mechanism in HD and PD Patients

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Background: It has been reported that Toll-like receptors (TLR) expression on neutrophils and monocytes are associated with increase cytokines synthesis and may result in more inflammation. However, the TLRs expression, cytokines and Catelecidin on PMN

and PBMC from chronic kidney disease patients is unclear. **Objective**: To evaluate TLR-2, TLR-4, TNF-α, IL-6,IL-10,MCP-1 and Catelecidin on expression in neutrophils (PMN) and monocytes (MN) from HD and PD patients.

Methods: Blood samples from 43 HD patients, 46 PD with creatinine clearance between 15 a 60 mL/min/1,73 mm^2 and 71 age-and gender-matched healthy volunteers (CONT). TLR2 and TLR4 were analyzed by Flow cytometry. The TNF-α, IL-6, IL-10 MCP-1 and Cathelecidin were analyzed by ELISA.

Results: The expression of TLR2 and TLR4 on neutrophils from HD patients was higher than PD and CONT patients ($p<0.001$). In monocytes, TLR-2 expression was higher in HD patients compared to others groups ($p<0.001$) and TLR4 expression was higher inPD patients compared to the CONT and HD patients ($p<0.001$). Regarding to cytokines, we observed that HD and PD patients showed an increase of TNF, IL-6 , IL-10 and MCP-1 levels compared to CONT. In relation to Cathelecidin levels observed in HD patients that had higher levels compared to CONT and PD groups,We also observed a significant correlation between TLR4 and IL-10, MCP-1 and cathelecidin on neutrophils. In monocytes, observed a significant correlation only between TLR4 and MCP-1.

Conclusions: It is possible that the high expression ofTLR2 and TLR4 on neutrophils and monocytes caused by the effect by uremic toxins and the dialysis procedures. Besides, the high expression of TLR2 and TLR4 in these cells resulted in an increase of TNF-α,IL-6, IL-10, MCP-1 and cathelecidin levels, suggesting that TLRs are associated with inflammatory mechanisms in uremic patients. So, these results suggest that TLRs could be a novel target to therapeutic strategic to reduce the inflammation .

Funding: Private Foundation Support

PUB181

Hydration Status Assessment and Phase Angle Estimation by Multi-Frequency Bioimpedance in Patients with Chronic Kidney Disease

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Background: Body composition assessment has the potential to improve the care of patients with chronic kidney disease (CKD). Bioimpedance (BIA) is the most widespread method for estimating body composition due to its safety, ease of use, low cost and portability. The aims of this study were to determine the hydration status and the phase angle at 50KHz (PA) by BIA in patients with CKD, and to analyse the association between them and common biochemical characteristics.

Methods: The study group consisted of 32 patients (70±13 years, 16 males) with eGFR in between 6-68 mls/min, no one yet on dialysis. Body composition and PA at 50kHz were assessed by BIA (In Body S10). The following parameters of body composition were collected for the study with the help of BIA: total body water , intracellular water, extracellular water, ratio of extracellular water/total body water, body fat mass, soft lean mass, fat free mass, skeletal muscle mass and body mass index . Parameters such as urea, creatinine, albumin, sodium, potassium, ferritin, parathormone, calcium, phosphorus, urine protein and e GFR (MDRD-formula) were collected.

Results: 16 (50%) of our patients had diabetes. 18/32 (56%) were taken diuretics. Patients with oedemas or uncontrolled arterial hypertension showed mean estimate fluid overload significantly higher than that of the other study patients. PA was positively associated with albumin (r=0,465), e GFR (r=0,462) and negatively correlated with creatinine (r=-0,311) and urea (r=-0,500). Ratio extracellular water/total body water was positively correlated with body mass index (r=0,276), age (r=0,543) and negatively correlated with ferritin (r=-0,352) and urea (r=-0,511).

Conclusions: Estimating body composition, hydration status and PA by BIA provides useful information for treating patients with CKD.The 50kHz phase angle seems to represents an overview of nutritional, inflammatory and metabolic status of the patient with CKD.

PUB182

Renal Impairment: Global Prevalence and Risk Factors. Control Participants from the INTERSTROKE Study

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Background: Chronic kidney disease is increasingly prevalent and well described in some regions of the world. However, it is likely that there are significant differences in prevalence and risk factors between regions. In these analyses, we explore the prevalence of renal impairment (an indicator of CKD) and risk factors in an international population.

Methods: INTERSTROKE is a case-control study (of acute first stroke) in 32 countries in Asia, America, Europe and Africa. In these analyses, we include only the controls (without a history of stroke) with available serum creatinine measurement. The CKD-EPI formula was used to estimate GFR and renal impairment (RI) was defined as eGFR<60ml/min/1.73m^2. Multivariable-adjusted logistic regression was used to explore risk factors for RI.

Results: Of 10,517 included participants, mean age was 61.9 (13.3) years and 58.8% (n=6,181) were male. Mean eGFR was 81.6 (22.2) ml/min/1.73m^2 and 17.3% (n=1,819) had RI. There were significant variations in age-adjusted RI prevalence between regions: Western Europe & North America 8.4%, Eastern & Central Europe 11.9%, Africa 11.8%, South Asia 23.2%, China 24.1%, South East Asia 19.9% and South America 15.4%. After multivariable adjustment, factors that were associated with increased odds of RI included age (OR 1.08 [1.08-1.09]), female gender (OR 1.33 [1.18-1.49]), hypertension (OR 1.39 [1.19-1.63]), diabetes (OR 1.63 [1.40-1.90]) and cardiovascular disease (OR 1.44 [1.18-1.77]). There were regional differences in the association between RI and risk factors: (i) age was significant in all regions; (ii) female gender was significant only in Africa, South Asia and China; (iii) hypertension was significant only in South East Asia and South America; (iv) diabetes was significant in Western Europe / North America, Eastern & Central Europe / Middle East, South Asia, China and South East Asia.

Conclusions: We report an overall RI prevalence rate consistent with previous studies, but significant regional variations in prevalence and risk factors.

PUB183

Predictors of Rapid Progression in Women with X-linked Alport Syndrome

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Background: Females with X-linked Alport syndrome (AS) have a wide variability in disease course. Predictors of rapid kidney disease progression in this population are unknown.

Methods: ATHENA (NCT02136862) is a non-interventional, global, multicenter study enrolling patients with CKD due to AS. Urine and plasma biomarkers and estimated GFR (eGFR) were assessed at baseline and every 12 weeks thereafter. P-values for categorical variables were calculated based on Fisher's Exact test. P-values for continuous variables were based on t-tests.

Results: We analyzed 28 women with X-linked AS enrolled to date with at least 3 eGFR values. Women were categorized as a slow progressor if eGFR slope declined <5ml/min/1.73m2 per year and a rapid progressor if eGFR declined ≥5ml/min/1.73 per year. Proteinuria, genotype, urine biomarkers, blood biomarkers, hearing loss, or hypertension were not predictive of rapid progression.

Baseline	Slow progressor (N=20)	Rapid progressor (N=8)	P-value
Age (mean, SD)	49.6 (14.9)	50.0 (11.3)	0.95
$eGFR_{CKD-EPI}$ (ml/min/1.73m^2; mean, SD)	60.3 (22.1)	71.3 (20.1)	0.26
Proteinuria >1gm/24 hours	6 (31.6%)	3 (42.9%)	0.66
Genotype			0.22
Missense	9 (45%)	6 (75%)	
Other	11 (55%)	2 (25%)	
Urine biomarkers (mean, SD)			
KIM-1 (pg/mL)	899 (760)	1223 (1180)	0.42
B2-microglobulin (ng/mL)	157 (244)	158 (139)	0.99
Clusterin (ng/mL)	304 (187)	641 (648)	0.05
NGAL (ng/mL)	16 (13)	19 (11)	0.65
Blood biomarkers (mean, SD)			
TGF-β1 (pg/mL)	10132 (3121)	10506 (3052)	0.78
NGAL (ng/mL)	141 (47)	130 (45)	0.57

Conclusions: In this small cohort of women with X-linked AS we have thus far been unable to identify traditional clinical or novel biomarker predictors of rapid decline in GFR.

Funding: Pharmaceutical Company Support - Regulus Therapeutics, Inc

PUB184

Hormone Therapy and Urine Protein Excretion: A Systematic Review and Meta-Analysis

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Background: Animal models suggest estrogen has a renoprotective effect, but human studies have had variable results.

Methods: We performed a systematic review and meta-analysis of observational studies and randomized controlled trials (RCTs) that evaluated the association of hormone therapy (HT) and urine protein excretion (albuminuria/proteinuria) in post-menopausal women. We searched Medline, Embase, Cochrane Register of Controlled Trials and Scopus. Two reviewers screened all abstracts/texts and assessed quality. Dichotomous (odds ratios (ORs)) and continuous measures (mean differences) of the association between HT and urine protein excretion were converted to standardized mean differences (SMDs).

Results: We identified 1088 abstracts - 143 full texts were reviewed and 12 studies were included. The quality of studies was low to moderate. The SMD of the effect of HT on urine protein excretion was -0.11 (95% CI -0.27-0.05, p=0.16). Pooling adjusted ORs, the odds of having elevated albuminuria in HT users was 0.84 (95% CI 0.60-1.18, p=0.31) as compared to non-users. Pooling continuous measures, urine protein excretion was lower in HT users as compared to non-users (SMD -0.25, 95% CI -0.31- -0.19, $p<0.001$). There were no differences in pre-defined subgroups.

Subgroup	# of studies	I^2(%)	Standardized Mean Difference (95% CI)	p-value for interaction
Study Design				
Randomized Controlled Trials	3	0	0.02 (-0.29 – 0.33)	0.38
Observational Studies	9	81	-0.14 (-0.31 – 0.04)	
Women with Diabetes				
Includes	7	70	-0.02 (-0.22 – 0.17)	0.18
Excludes	5	81	-0.30 (-0.64 – 0.05)	
Quality				
High/Moderate	8	78	-0.06 (-0.36 – 0.25)	0.25
Low/Very Low	4	44	-0.25 (-0.36 - -0.13)	

In a post-hoc analysis, the OR for HT use and elevated albuminuria was 1.13 (95% CI 0.76-1.68) in population-based and 0.63 (95% CI 0.53-0.75) in non-population-based cohorts (p=0.007 for interaction).

Conclusions: HT is associated with decreased urine protein excretion, but the observed benefit may be due to study design, reported outcomes and unmeasured confounders.

Funding: Other NIH Support - UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS)

PUB185

Differential Diagnosis of Thrombotic Microangiopathy: Survey Results from 16 Countries Hermann G. Haller,[1] T. Sakari Jokiranta,[11] Oguz Soylemezoglu,[2] Jack F. Wetzels,[3] Michel Tsimaratos,[4] Saleh Ali Al Shurafa,[5] Mohan Shenoy,[6] Ondrej Viklicky,[7] Manuel Macia,[8] Tatiana Pankratenko,[10] Rosanna Coppo.[9] *[1]Medical School Hannover, Germany; [2]Baskent Univ, Turkey; [3]Radboud Univ Medical Centre, Netherlands; [4]Hôpital Necker-Enfants Malades, France; [5]Hospital Qatif Central Hospital, Saudi Arabia; [6]Royal Manchester Children's Hospital, United Kingdom; [7]Inst for Clinical and Experimental Medicine, Czech Republic; [8]Hospital Virgen de la Candelaria, Spain; [9]Fondazione Ricerca Molinette, Ospedale Regina Margherita, Italy; [10]M.F. Vladimirskiy Moscow Regional Research and Clinical Inst, Russian Federation; [11]Univ of Helsinki, Finland.*

Background: The differential diagnosis of thrombotic microangiopathy (TMA) is complex but important to inform treatment decisions. A survey was devised with the objective of understanding current practices across Europe.

Methods: Over 450 clinicians, from 16 European countries were invited to complete an online survey.

Results: Of 254 respondents, 82% were nephrologists, 69% had >10 years' experience in their specialty, and 89% had diagnosed a patient with TMA. Results show a differential diagnosis of TMA is usually made within 1-2 (53%) or 3-4 days (26%) of presentation. Similarly, therapy is usually initiated within 1-2 (44%) or 3-4 days (30%), however 13% report treatment initiation >1 week post-presentation. Thrombocytopenia, hemolytic anemia and acute renal failure are the main diagnostic criteria used. Extrarenal symptoms and a panoply of other conditions are considered when assessing the differential diagnosis. 70% and 78% of respondents stated they always request complement protein levels and ADAMTS13 activity. However, only 65% agree that an ADAMTS13 activity >10% rules out thrombotic thrombocytopenic purpura. For the diagnosis of atypical hemolytic uremic syndrome, 93% request ADAMTS13 activity and 83% request complement protein levels. Variability in available guidelines and extent of family history taken was evident.

Conclusions: This survey highlights the variability of current practices of European physicians in differentially diagnosing TMA and the need to increase awareness of diagnostic tests and international guidelines available.

Acknowledgements: The authors wish to thank the survey participants.

Funding: Pharmaceutical Company Support - Alexion Pharma GmbH

PUB186

Nutritional and Inflammatory Parameters during Transition from Pre-Dialysis Chronic Kidney Disease to End Stage Renal Disease Dugan Maddux,[1] Frank van der Sande,[2] Jeroen Kooman,[2] Jochen G. Raimann,[3] Jennifer A. Vosburgh,[1] Marta Reviriego-Mendoza,[1] John W. Larkin,[1] Terry L. Ketchersid,[1] Len A. Usvyat,[1] Peter Kotanko,[3,4] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Maastricht Univ Medical Center, Maastricht, Netherlands; [3]Renal Research Inst, New York, NY; [4]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Malnutrition and inflammation during transition from chronic kidney disease (CKD) to end stage renal disease (ESRD) has not been characterized. We investigated longitudinal trajectories of albumin levels (Alb) and white blood cell counts (WBC) in patients (Pts) during their transition from CKD to ESRD.

Methods: We analyzed data from the Fresenius Medical Care CKD Data Registry on 14,095 Pts who transitioned to ESRD treated by dialysis between 2008 and 2016. Mean Alb and WBC were captured during 12 months before and after transition to ESRD. We analyzed Alb and WBC in Pts who survived, or died during the first year of dialysis.

Results: We observed mean Alb declined at transition to and 1 month after starting dialysis; thereafter Alb gradually rebounded (Figure 1A). Pts who died during the first year of dialysis generally had lower Alb 3 months before and 1 month after transition to dialysis, compared to survivors (Figure 1B). In survivors, mean WBC increased slightly in pre-dialysis months and decreased after dialysis start (Figure 1C). In those who did not survive, WBC tended to be higher than survivors during the year before, and more notably after starting dialysis (Figure 1D).

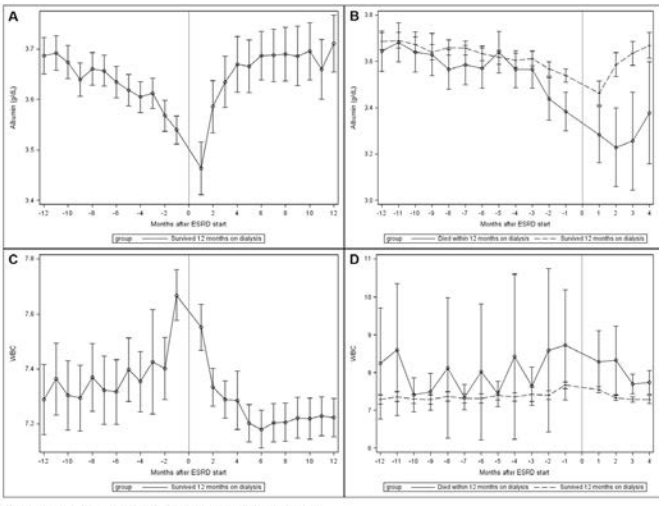


Figure 1. Error bars represent the 95% confidence intervals.

Conclusions: These results suggest the emergence of a pro-inflammatory phenotype in the months before dialysis initiation. These changes were more pronounced in Pts who died in the first year on dialysis, while in contrast Alb and WBC counts improved in survivors. Factors underlying the pre-ESRD pro-inflammatory surge deserve further research.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB187

Potential Association of Hyperhomocysteinemia with Target-Organ Damage in Patients with Primary Glomerulonephritis Zengchun Ye, Wenbo Zhao, Meijun Si, Ming Li, Cheng Wang, Tan-Qi Lou. *Div of Nephrology, Dept of Medicine, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, China.*

Background: Hyperhomocysteinemia (HHcy) leads to increased oxidative stress and decreased antioxidant capacities in vascular endothelial cells, which are related to increased cardiovascular risk. This study is to investigate the prevalence of hyperhomocysteinemia in patients with primary glomerulonephritis and its relationship with target-organ damage.

Methods: This study included 601 patients with primary glomerulonephritis who were enrolled in the Third Affiliated Hospital of Sun Yat-sen University from May 2010 to March 2015. Demographic and laboratory data were collected. Plasma homocysteine was detected and estimated glomerular filtration rate (eGFR) was calculated. Doppler ultrasound was used to evaluate the changes of cardiac structure and function. Multiple linear regression analyses were used to evaluate the correlation between plasma homocysteine and target-organ damage.

Results: The prevalence of hyperhomocysteinemia was 45.92% (276/601) in patients with primary glomerulonephritis. And the incidence of hyperhomocysteinemia in CKD stage 1, stage 2, stage 3, stage 4, and stage5 was 10.34%, 24.53%, 57.58%, 72.55% and 89.53%, respectively. With the deterioration of renal function, the incidence of hyperhomocysteinemia increased significantly. eGFR in patients with hyperhomocysteinemia was significantly lower than those of normal homocysteine, and the left ventricular mass index and carotid artery intima media thickness were significantly increased. Multiple linear regression analysis shown that homocysteine was associated with impaired renal function. Plasma homocysteine concentration is related to eGFR, calcium×phosphorus, serum uric acid, LDL-C, gender and hemoglobin.

Conclusions: The prevalence of hyperhomocysteinemia in patients with primary glomerulonephritis was 45.92%. Hyperhomocysteinemia was associated with impaired renal function in these patients. Further prospective randomized clinical trials are needed to clarify whether lowering homocysteine treatment has a beneficial effect in attenuating the progression of renal failure in primary glomerulonephritis patients.

Funding: Government Support - Non-U.S.

PUB188

A Prospective Study of Cutaneous Manifestations in Patients of Advanced Chronic Kidney Disease in a Tertiary Care Centre in Eastern India Pinaki Mukhopadhyay. *Dept of Nephrology, NRS Medical College, Kolkata, India.*

Background: A wide variety of skin diseases occur in patients with chronic kidney diseases(CKD). Dermatological manifestations vary from age, region, race , severity of CKD and also basic disease or etiology. There is no such detail study regarding cutaneous manifestations in advanced CKD patients in Eastern India.We aim to evaluate the spectrum and frequency of dermatological manifestations in CKD patients, and also to compare cutaneous manifestations in CKD, between patients on dialysis and not on dialysis.

Methods: All patients with CKD stage 3 and beyond including patients in hemodialysis having dermatological manifestations were included. Detailed epidemiological, clinical and biochemical parameters were recorded. All patients were followed up three years. Patients with renal transplant, cutaneous diseases prior to CKD and , patients below the age of 12 years were excluded.

Results: A total of 225 patients were included in this study in which 64% were male and 36% were females, showing high male predominance. Their age ranged from 12 to 68 with mean age being 46.8 years. Majority of patients belonged to the age group of 50-70 years(60%).The means of hemoglobin, blood urea, serum cretinine were 8.9 gm% (S.D±2.05gm%), 98.07 mg/dl (S.D ±63.2 gm/dl) and 5.03 gm/dl (S.D±3.77 gm/dl) respectively. The most common skin manifestations observed were pruritus (52%) , followed by infections (36%) , xerosis (16%), acquired perforating dermatosis (16%) and others like vesicobullous diseases, adenoma sebaceum (8%).Bacterial infection(20%) is more prevalent than fungal(8%) and viral (8%) infection among study population. No significant differences in frequency and type of skin manifestations have been found between hemodialysis and without hemodialysis group. Severity of pruritus increases with duration of chronic kidney disease. Cutaneous manifestations increases with severity of kidney disease ($p<0.01$).

Conclusions: CKD is associated with a complex array of cutaneous manifestations and there distribution and frequency is closely related to the duration and fall in glomerular filtration rate.

PUB189

CKD and Prevalence of Strongyloidiasis in a Community-Based Hospital in Okinawa, Japan Takayuki Adachi,[1] Kunitoshi Iseki.[2] *[1]Internal Medicine, Tomishiro Central Hospital, Tomigusuku, Okinawa, Japan; [2]Clinical Research Center, Tomishiro Central Hospital, Tomigusuku, Okinawa, Japan.*

Background: Strongyloides stercoralis (strongyloidiasis, S) is an intestinal helminth that infects humans when they come in contact with soil containing the larvae. In advanced stages ofchronic kidney disease(CKD), patients often are associated with decreased cell-mediated immunity, under-nutrition, and anemia. The prevalence of S has been reported to be 6.3% among the Ryukyu University hospital patients in Okinawa from 1991 to 2004. However, the current prevalence is not known nor the effect of CKD;estimated glomerular filtration rate <60 mL/min/1.73 m^2.

Methods: We analyzed hospitalized patients who had undergone a stool test between September 2005 and June 2015 in Tomishiro Central Hospital, Okinawa, Japan. Also, background data such as renal function, proteinuria, anemia, nutritional status, and comorbid conditions were collected. Anemia was defined as hemoglobin level <13 g/dL in men and <12 g/dL in women.

Results: A total of 2,184 patients (median age, 74.0 [61.0-81.0] years; male ‘ 52.8%) were tested and 8% of them (median age, 75.0 [71.0-80.8] years; male ‘ 66.1%) were positive for S. In patients with S, 31.8% had CKD, 32.2% diabetes, 59.8% hypertension, 63.3% anemia, 65.4% eosinophilia, and 32.5% proteinuria. The mortality rate of S patients was 27.6% and the median survival period was 20.5 [1.0-42.3] months.

Conclusions: Large doses of steroids and/or immunosuppressants are usually indicated for nephrotic syndrome, rapidly progressive glomerulonephritis, renal transplants, and so on. CKD is often associated with protein energy wasting and immunodeficiency. In such cases, work-ups, such as stool tests to rule out S, are mandatory. Results suggest that S is still prevalent and common in elderly men who have CKD in Okinawa.

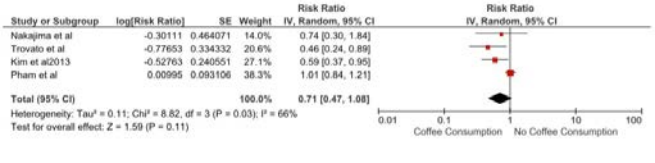
PUB190

Association of Coffee Consumption and Chronic Kidney Disease: A Meta-Analysis Natanong Thamcharoen,[1] Karn Wijarnpreecha,[1] Panadeekarn Panjawatanan,[3] Wisit Cheungpasitporn,[2] Charat Thongprayoon.[1] *[1]Dept of Medicine, Bassett Medical Center, Cooperstown, NY; [2]Dept of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [3]Dept of Biochemistry, Faculty of Medicine, Chiang Mai Univ, Chiang Mai, Thailand.*

Background: The risk of chronic kidney disease (CKD) in patients who regularly drink coffee is controversial. The aim of this meta-analysis was to evaluate the association between coffee consumption and CKD.

Methods: A literature search was performed using MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews from inception until 30 April 2016. Studies that reported odd ratios or hazard ratios comparing the risk of CKD in patients consuming significant amount of coffee versus those who did not consume coffee were included. Pooled risk ratios (RR) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method.

Results: Four observatioal studies with 14,898 individuals were included in our analysis to assess the association between coffee consumption and CKD. Coffee consumption was defined as 1 cup of coffee per day or greater. The pooled RR of CKD in patients consuming coffee was 0.71 (95% CI, 0.47-1.08).



The subgroup analysis showed the pooled RRs of CKD of 1.10 (95% CI, 0.94-1.29) in males and 0.81 (95% CI, 0.58-1.13) in females, respectively.

Conclusions: Our study demonstrates no significant association betweern coffee consumption and CKD in males. However, future studies are required to assess a potential inverse association between coffee consumption and risk for developing CKD in females.

PUB191

Plasma Convertase Subtilisin/Kexin Type9(PCSK9) Concentration in Elderly Patients with Chronic Kidney Disease Hoichi Amano,[1] Takashi Yokoo.[1] *[1]Div of Nephrology and Hypertension, The Jikei Univ Hospital, Hospital, Tokyo, Japan; [2]Div of Internal Medicine, Kanagawa Prefectural Shiomidai Hospital, Hospital, Kanagawa, Japan; [3]Dialysis center Fukushima Medical Univ, Hospital, Fukushima, Japan.*

Background: The elderly patients with chronic kidney disease (CKD) are at high risk for cardiovascular events in spite of lower level of low density lipoprotein cholesterol (LDL-C). The reason why plasma LDL-C concentration is relatively lower is not fully explained. As PCSK9 plays an important role in regulating plasma LDL-C by the mechanism which secreted PCSK9 binds to the LDL receptors (LDLR) and promotes LDLR degradation. Thus, we investigated the relationship between the magnitude of renal impairment and plasma PCSK9 levels.

Method: Concentrations of fasting serum PCSK9, lipids, creatinine and cystatin-C were measured in 219 Japanese elderly outpatients with CKD including patients receiving peritoneal dialysis (PD) or hemodialysis (HD).

Result: Plasma PCSK9 concentrations (215±76ng/mL ng/ml [SD]) did not correlate with baseline eGFR in the study population. Mean plasma PCSK9 levels in PD patients (344 ± 145 ng/ml) were significantly higher than other CKD stages ($p< 0.001$, ANOVA). Those in HD patients (165 ± 56 ng/ml) were significantly lower than other CKD stages ($p< 0.001$, ANOVA).

Conclusion: Plasma PCSK9 levels did not correlate with kidney function. PD is associated with higher plasma PCSK9 concentration and HD is lower.

PUB192

Patients Transitioning into Dialysis without Pre-Dialysis Nephrology Care Tend to Have Lower Comorbidity Index Sheetal Chaudhuri, Len A. Usvyat, John W. Larkin, Marta Reviriego-Mendoza, Chris Churchill, Lisa Dombro, Franklin W. Maddux. *Fresenius Medical Care North America, Waltham, MA.*

Background: More than 50% of patients who start dialysis do not have prior nephrology care; those patients are also reported to have poorer outcomes. We aimed to understand whether patients who start hemodialysis (HD) without prior nephrology care also have a higher comorbidity index prior to dialysis initiation.

Methods: We analyzed data from 142 patients' ≥65 years of age who transitioned to dialysis and received HD for at ≥3 months at FMCNA facilities within a selected Universal American ACO. Comorbidities were captured for the patients during the first 3 months of HD, and we calculated the non-ESRD hierarchical condition category (HCC) score to estimate the patients' comorbidity index. Patients were stratified based on whether they received pre-HD nephrology care.

Results: Of the 142 patients studied, 49 had pre-HD nephrology care. We found that patients with pre-HD nephrology care had a mean HCC score of 4.1, which was higher than the mean HCC score of patients with no pre-HD nephrology care who had a HCC score of 2.9 (Table 1).

Table 1	Number of Patients	Mean HCC Score
No Pre-ESRD Encounters	93	2.9
With Pre-ESRD Care	49	4.1

Conclusions: Given that patients with no pre-HD nephrology care have poorer outcomes, we would have expected that they would also have a higher disease complexity based on their comorbidities; this analysis suggests the opposite. Further studies are needed to investigate if outcomes differ in patients with and without pre-ESRD nephrology care controlled for their comorbidity index at the dialysis initiation.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB193

Self-Reported Medication Non-Adherence Association with End-Stage Renal Disease and All-Cause Mortality in Adults with Chronic Kidney Disease Esteban A. Cedillo-Couvert, Ana C. Ricardo, Jinsong Chen, Michael J. Fischer, Marie Krousel-Wood, John W. Kusek, Swati Lederer, Eva Lustigova, Akinlolu O. Ojo, Anna C. Porter, Lisa Sharp, James H. Sondheimer, Clarissa Jonas Diamantidis, James P. Lash. *The Chronic Renal Insufficiency Cohort (CRIC) Study Group.*

Background: In the general population, medication non-adherence contributes to poorer clinical outcomes. However, little is known about medication non-adherence among adults with chronic kidney disease (CKD). We evaluated the association of self-reported medication non-adherence with incident end-stage renal disease (ESRD) and all-cause mortality among adults with CKD.

Methods: Prospective observational study of 3428 adults with CKD enrolled in the CRIC Study at seven clinical centers in the U.S. Baseline self-reported medication adherence was based on responses to questions assessing unintentional (forgetting) and intentional (purposely missing or adding a pill) nonadherence in the past week. We performed Cox proportional hazard regression analyses (adjusted for clinical center, socio-demographic characteristics, clinical factors, use of cardiovascular medications and depressive symptoms) to relate type of non-adherence with incident ESRD and all-cause mortality.

Results: At baseline,mean age was 60 years, 45% were women, mean eGFR was 43.4 ml/min/1.73 m^2, and participants were on a mean of 9.3 medications/day. One-quarter of

participants reported unintentional and 15% intentional (10% purposefully missing a pill, 5% added a pill) non-adherence. Over a median follow-up of 6 years, 823 individuals experienced ESRD and 675 died. Hazard ratios are shown in the following table:

Adjusted Hazard Ratio (95% CI)			
Outcome	Forgetting a Pill	Purposely Missing a Pill	Purposely Adding a Pill
ESRD	1.09(0.92,1.29)	1.34(1.08,1.67)	1.07(0.79,1.46)
All-cause mortality	1.10(0.90,1.33)	1.32(1.04,1.68)	1.26(0.92,1.74)

Conclusions: Baseline self-reported intentional non-adherence characterized by missing a pill, but not purposefully adding a pill or forgetting a pill, was associated with an increased risk for ESRD and all-cause mortality in CRIC Study participants. Future work is needed to better understand reasons for this association.

Funding: NIDDK Support

PUB194

Analysis of Autonomic Nervous Dysfunction Characteristic in Chronic Kidney Disease Patients with Acute Ischemic Stroke Wenbo Zhao, Zengchun Ye, Ming Li, Meijun Si, Hui-Qun Li, Tan-Qi Lou. *Dept of Nephrology, The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China.*

Background: Autonomic nerve function damage is a common symptom of stroke, but there is little about its effects on stroke patients with renal insufficiency. This study explored the association between autonomic function and renal impairment in patients with acute stroke.

Methods: etrospective analysis of 232 cases (67.22 years old, male, 57.8%.) , Autonomic function evaluated by heart rate variability using 24 hours dynamic electrocardiogram. Renal impairment evaluated by glomerular filtration rate (EPI - eGFR). The national institute of health stroke scale (NIHSS) scores to measure the severity of the stroke.

Results: SDANNindex VLF value, LF and LF/HF significantly reduced ($P < 0.05$) in moderate eGFR group. Autonomic function lower significantly ($P < 0.05$) in severe stoke patients compared with mild-to-moderate groups .Multiple linear regression analysis found that the NIHSS score, history of diabetes associated with SDANN index and LF. Gender, NIHSS score, history of diabetes associated with VLF. But eGFR was not included in the regression model.

Conclusions: eGFR associated with autonomic nerve dysfunction in acute stoke patients, but not the main factors that influence the effect of autonomic nerve dysfunction; History of diabetes, NIHSS score, gender differences are the main influencing factors of autonomic nerve dysfunction in patients with acute ischemic stroke accompany renal insufficiency.

PUB195

Early Pre-Operative, and Prolonged Post-Operative Nephrological Consultation Might Prevent the Worsening of Renal Impairment in Renal Cancer Patients Candidates to Nephrectomy Laura Cosmai,[1] Wanda Liguigli,[2] Camillo Porta,[3] Maurizio Gallieni,[4] Marina Foramitti,[1] Fabio Malberti.[1] *[1]Nephrology, Istituti Ospitalieri, Cremona, Italy; [2]Oncology, Istituti Ospitalieri, Cremona, Italy; [3]Oncology, IRCCS San Matteo Univ Hospital Foundation, Pavia, Italy; [4]Nephrology, San Carlo Borromeo Hospital, Milan, Italy; [5]Nephrology, Istituti Ospitalieri, Cremona, Italy; [6]Nephrology, Istituti Ospitalieri, Cremona, Italy.*

Background: Partial nephrectomy (PN) is recommended as the preferred surgical option in organ confined renal tumours measuring up to 7 cm, whilst radical nephrectomy (RN) is the preferred option for tumors of more than 7 cm; RN is also recommended if PN is not technically feasible. RN in particular may affect renal function, expecially in patients (pts) with pre-existing chronic kindey disease (CKD).

Methods: From December 2012 to January 2015, 97 pts candidates to RN were referred to our Ambulatory of Onco-Nephrology; of these pts, 21 had a pre-existing stage III to V CKD. Nephrological consultation was performed before surgery, immediately post surgery, and then every 3 months for the first 3 years post-RN. Primary endpoint of this single-arm, prospective, pilot study was the percentage of pts who developed some worsening of kidney function over the 3-years follow-up. Interventions during Nephrological consultations included management of co-morbidities and risk factors (e.g. hypertension, diabetes …), prevention of further renal damage from potentially nephrotoxic drugs (e.g. NSAIDs) and protocols of hydration before contrast medium administration for routine Oncological follow-up.

Results: Immediately post-RN, 46 pts presented a reduction in eGFR (9 within the group with pre-existing CKD, and 37 in the group without known renal impairment). Of these 46 pts, at a 3-months post-RN 30 recovered to their pre-nephrectomy renal function, while the remaining 16 did not show any further decrease in eGFR. Only 5 pts (out of 97) were lost at follow-up during the 3 years subsequent to RN. Of the 92 pts who reached the 3 year post-RN mark, just 2 showed a decline in eGFR.

Conclusions: An early and prolonged Nephrological consultation in cancer pts candidates to RN might prevent kidney impairment.

PUB196

Quality of Perceived Physician-Patient Interaction and Risk of End-Stage Renal Disease and Hospitalization in Hispanics with Chronic Kidney Disease Esteban A. Cedillo-Couvert, Jesse Yenchih Hsu, Ana C. Ricardo, Michael J. Fischer, Ben Gerber, Edward J. Horwitz, John W. Kusek, Eva Lustigova, Amada Renteria, Sylvia E. Rosas, Milda Renne Saunders, Daohang Sha, Anne M. Slaven, James P. Lash. *Chronic Renal Insufficiency Cohort (CRIC) Study Group.*

Background: Quality of physician patient interaction influences health outcomes in the general population but little is known about this in chronic kidney disease (CKD). We evaluated the association of perceived quality of physician-patient interaction with risk of end stage renal disease (ESRD) and all-cause hospitalization in Hispanics with CKD.

Methods: We studied Hispanics with CKD enrolled in the prospective observational Hispanic CRIC Study**.** Quality of interaction with primary care providers was ascertained using the Ambulatory Care Experiences Survey sub-scales (range of score 0-100 with higher score indicating better performance) of communication quality, health promotion, interpersonal treatment, and patient trust. Outcome measures were incident ESRD and all-cause hospitalization.

Results: The mean age of the 289 participants was 56 yrs, 38% were women, 70% had health insurance, and the mean eGFR was 38.4 ml/min/1.73 m^2. Baseline subscale scores and hazard ratios are shown below:

Association of High vs Low* Physician-Patient Interaction Scores with Incident ESRD and Hospitalization			
ACES Sub-scale	**Median (IQR)**	**ESRD Hazard Ratio† (95% CI)**	**Hospitalization Rate Ratio‡ (95% CI)**
Communication Quality	100 (80-100)	0.63 (0.37-1.08)	0.62 (0.50, 0.76)
Health Promotion	80 (60-100)	0.83 (0.50-1.39)	0.77(0.63, 0.94)
Interpersonal Treatment	100 (80-100)	0.87(0.52-1.47)	0.65 (0.52, 0.79)
Patient Trust	93.3 (73.3-100)	0.76 (0.45-1.30)	0.79 (0.64, 0.97)
*100 vs < 100 due to highly skewed score distribution †Cox models ‡Poisson regression Adjusted for socio-demographic characteristics, hypertension, diabetes, cardiovascular disease, kidney function, quality of life, and depression			

Conclusions: Among HCRIC participants, higher perceived quality of physician-patient interaction was associated with a lower rate of hospitalization but not ESRD. How these interactions influence this outcome requires further study.

Funding: NIDDK Support

PUB197

Parental Health Literacy and Progression of Chronic Kidney Disease in Children Ana C. Ricardo, Vivien H. Goh, Adam S. Hamidi, Lynn N. Pereira, Aisha Betoko, Bradley Warady, Marva M. Moxey-Mims, Susan L. Furth, James P. Lash. *On Behalf of the Chronic Kidney Disease in Children (CKiD) Cohort Investigators.*

Background: Although health literacy has been associated with adverse outcomes in children, this association has not been evaluated in the setting of chronic kidney disease (CKD).

Methods: We conducted a parental health literacy assessment of 367 children enrolled in the prospective multicenter observational Chronic Kidney Disease in Children (CKiD) cohort study. Using parametric failure-time models, we evaluated the association between parental health literacy and CKD progression, defined as time to the composite event of renal replacement therapy (RRT, dialysis or kidney transplant) or 50% decline in estimated glomerular filtration rate (eGFR). Parental health literacy was measured once using the Short Test of Functional Health Literacy (STOFHLA) that included 2 reading passages and 4 numeracy items (possible range from 0 to 100). Clinical and demographic characteristics of the cohort were measured at baseline. Literacy levels were assumed to remain relatively stable over time.

Results: Median patient age was 9.5 years, 63% were male, and 59% non-Hispanic white. A glomerular diagnosis was present in 32% of participants. Median eGFR at baseline was 63 ml/min/1.73m^2, and median urine protein-to-creatinine ratio was 0.22. The median (IQR) STOFHLA score was 98 (93-100). Over a median follow-up of 5.9 years, the overall composite rate of RRT or 50% eGFR decline was 2.8 per 100 person-years. Results of multivariable models are presented in the table.

Relative time (95% CI) to CKD progression per 1 SD increase in STOFHLA score	
Model 1[a]	1.25 (1.11, 1.41)
Model 2[b]	1.29 (1.13, 1.48)
Model 3[c]	1.30 (1.08, 1.56)
[a]Adjusted for clinical center, baseline age, gender and race. [b]Variables in model 1 plus baseline GFR, proteinuria, glomerular diagnosis, age at CKD onset, bmi z-score, small for gestational age, albumin and dyslipidemia. [c]Variables in model 2 plus baseline maternal education, income and health insurance.	

Conclusions: In this cohort of children with CKD, high parental health literacy was associated with 30% longer time to the composite CKD progression outcome.

Funding: NIDDK Support

PUB198

Application of Urinary Albumin: Creatinine Ratio to Predict Renal Replacement Therapy and All-Cause Mortality in a CKD Cohort
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Background: This study aims to examine the association of albuminuria with RRT and mortality in CKD patients.

Methods: Subjects were patients with CKD and not on kidney replacement therapy enrolled in renal clinics in Queensland, Australia. Informed consenting of patients began in 2011. The categories of albuminuria were defined by gender-specific ACR values recommended by Australasian Proteinuria Consensus Working Groups. Events of RRT and death without RRT were recorded until end of 2015. Cox regression analyses were applied.

Results: A total of 1,615 patients were eligible, with 788 (49%) females. They were followed for a total of 3,397 person years. Age at consent ranged from 18 to 96 years, mean of 65 years (SD: 15 years). The percentages of patients with CKD stage 1, 2, 3A, 3B, 4 and 5 at consent were 6.6%, 12.5%, 20.8%, 30.8%, 25.6% and 3.7%, respectively. The prevalence of microalbuminuria and macroalbuminuria at consent was 32.1% and 34.7%, respectively. 69 patients started RRT and 111 patients died without RRT.After adjusted age, gender and CKD stage, the hazard ratio (HRs) (95% CI) of macroalbuminura for RRT (combined non-albuminuria and microalbuminuria as reference group) was 10.5 (4.2-26.6). The HRs (95% CI) of microalbuminuria and macroalbuminura for death were 2.1 (1.1-3.7) and 3.4 (1.9-6.0) (non-albuminuria as reference group), respectively.

Conclusions: In this cohort,macroalbuminuria was a significant predictor of future RRT whilst both micro- and macroalbuminuria increased mortality risk.

Funding: Government Support - Non-U.S.

PUB199

Novel ELISA for the Measurement of Human Periostin in Patients with Impaired Kidney Function
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Background: Periostin (osteoblast-specific factor OSF-2) is a soluble extracellular matrix protein that is associated in kidney development and kidney injury. Periostin consists of a conserved N-terminus and a C-terminal region which is affected by different splicing variants. Currently, at least seven splicing isoforms of human Periostin have been identified.

Methods: We developed a sandwich ELISA, which also enables the detection of all known human circulating Periostin isoforms. Our novel assay utilizes monoclonal and purified polyclonal antibodies and recognizes epitopes that are conserved between human and animal species e.g. mouse, rat, cynomolgus macaque, dog, and cat Periostin.

Results: The novel Periostin ELISA assay is optimized for human serum and plasma (citrate, heparin, EDTA) and covers a wide calibration range between 125 to 4,000 pmol/l. Assay characteristics such as precision, dilution linearity and spike-recovery as well as sample stability meet the standards of acceptance. Periostin serum and plasma concentration in apparently healthy individuals, show mean values of 864 +/- 269 pmol/l (n=24) and 817 +/- 170 pmol/l (n=20), respectively. Patients with impaired kidney function show an increase of Periostin compared to healthy individuals, suggesting that Periostin is a mediator in CKD and perhaps a promising biomarker for kidney injury in clinical renal disease.

Conclusions: In conclusion, this high-quality ELISA provides a reliable and accurate tool for the quantitative determination of Periostin in human healthy and diseased samples.

PUB200

Mexican Chronic Renal Insufficiency Cohort (MCRIC) Study: Baseline Characteristics
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Background: Chronic kidney disease (CKD) represents a major public health problem in Mexico. Despite the magnitude of this problem, little is known about risk factors for progression of kidney disease for individuals with CKD living in Mexico. The objective of this study is to describe the baseline characteristics of MCRIC Study participants, and to compare these characteristics with Mexican-American and non-Hispanic white individuals enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study.

Methods: We conducted a cross-sectional analysis of 249 adults with CKD (entry estimated glomerular filtration rate [eGFR] 20-60 ml/min/1.73 m²) enrolled in MCRIC. We compared demographic and clinical characteristics of MCRIC participants with all Mexican-Americans in CRIC and Hispanic CRIC (HCRIC), and with 249 non-Hispanic (NH) white CRIC participants matched for age, gender, diabetes status, and eGFR.

Results: Results are summarized in the table.

Variable	Mexican CRIC N=249	HCRIC/CRIC Mexican-Americans N=341	CRIC NH-Whites[a] N=249
Age, years (mean)	56	56	56
Female (%)	29	43 [b]	28
< High School Education (%)	59	69 [b]	4 [b]
Current Smoker (%)	10.8	6 [b]	13
Diabetes (%)	54.2	70 [b]	55
Systolic Blood Pressure, mmHg (mean)	123	139 [b]	122
Diastolic Blood Pressure mmHg (mean)	74	73	69 [b]
Blood Pressure < 140/90 mmHg (%)	78	54 [b]	81
Body Mass Index≥30 kg/m2 (%)	30	55 [b]	56 [b]
eGFR, ml/min/1-73m2 (mean)	40	38 [b]	40 [b]
Urine to Protein ratio g/g (median)	0.63	0.95	0.22

[a] Age, gender, diabetes and eGFR matched to MCRIC
[b] p<0.05 (MCRIC is the reference group for all comparisons)

Conclusions: Compared with Mexican-Americans with CKD, Mexicans with CKD living in Mexico are less likely to be obese and have better blood pressure control. Longitudinal follow-up is ongoing and will provide insights into differences in risk for CKD progression.

Funding: Other NIH Support - Fogarty Award

PUB201

The Impact of Diabetes on the Progression of Renal Disease in the Elderly
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Background: Elderly and diabetes are risk factors for chronic kidney disease (CKD). Diabetics patients have a faster decline of renal function. There are few data regarding the progression of CKD in elderly especially those with diabetes. The aim of this study was to compare progression of renal disease in diabetic and non-diabetic elderly CKD patients.

Methods: A retrospective observational study that evaluated elderly CKD stage 2-5 non-dialysis patients followed in a CKD Unit Care from April 2011 to April 2015. Renal disease progression was evaluated by the change in eGFR using BIS formula, divided per years of follow-up (mL/min/year), stratified in rapid progressors (≥ 5 mL/min/year); slow progressors (≥ 1 mL/min/year to < 5 mL/min/year), stable (≥ 0 and <1 mL/min/year) and improved function (< 0 mL/min/year). Proteinuria was measured in a spot urine sample.

Results: A total of 340 patients [73 (69-79) years, 56% male, 65 % white, 41% diabetics] were evaluated. In comparison to non-diabetics, diabetic patients had a higher proteinuria at baseline. There were no differences in age, blood pressure, kidney function between the two groups at baseline. The change of eGFR during the follow up was higher in the diabetic group [1.10 (-1.53 – 3.46) vs. 0.57 (-1.54 – 2.51) mL/min/year, p = 0.09], without statistical significance but with a trend p. Proportion of rapid progressors and dialysis initiation was significantly higher in diabetic group (15 vs 8%, p = 0.04; and 10 vs 3%, p=0.03; respectively).

Conclusions: There was no statistical significance in renal progression between the groups, but there is a tendency (p trend) to a faster progression in the diabetics group. The presence of diabetes affected the need for dialysis and the number of rapid progressors.

PUB202

Double-Hit of Advanced Age and Lung Cancer Leads to Increased Fibrosis and Decreased Overall Survival in a Repeated Low-Dose Regimen of Cisplatin Nephrotoxicity
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Background: Cisplatin-induced acute kidney injury (AKI) has a high mortality rate and poor long-term prognoses, including a 30x greater risk of developing chronic kidney disease (CKD). Understanding processes involved in the cisplatin-induced AKI to CKD transition is essential for developing novel therapeutics. We have developed a repeated, low-dose cisplatin model that allows for long-term survival of mice, and better recapitulates the type of dosing regimen humans receive. In this model, fibrosis is the main pathology associated with repeated, low-dose administration of cisplatin, and thus the transition from AKI to CKD can be studied. While this model better recapitulates the dosing regimen humans receive, it does not take into account comorbidities present in patients receiving cisplatin, namely advanced age and cancer, which is important as only individuals with cancer receive cisplatin and the majority of cancer patients are diagnosed at 60 years of age or older. It is believed that renal function declines and with normal aging and that processes of maladaptive repair also occur during aging.

Methods: Here, we determined the impact of age and cancer on the cisplatin-induced AKI to CKD transition. We compared saline and cisplatin-treated 8 wk old and 40 wk old FVB mice and found that fibrosis and renal function were not affected by aging alone. However, aged mice with mutant Kras driven lung cancer had decreased overall survival and significantly increased kidney fibrosis as compared to age matched control mice.

Results: Preliminary data suggest this the exacerbated kidney fibrosis in aged mice with lung cancer may be mediated by activation of EGFR signaling pathways in the kidney cortex.

Conclusions: Thus, understanding the mechanisms by which the comorbidities of aging and cancer impact the cisplatin-induced AKI to CKD transition may uncover novel therapeutic targets for improving long-term outcome and quality of life.

Funding: NIDDK Support

PUB203

Rehydration with Fructose Worsens Dehydration-Induced Renal Damage

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Background: We reported that recurrent heat stress and dehydration induces chronic kidney disease due to polyol-induced fructose generation with metabolism by fructokinase. Here we test if there is a significant difference for kidney injury in mice between two different rehydration methods:pure water and fructose water.

Methods: We used two groups of mice.Mice were recurrently exposed to heat(39.5 C^0 for 30 min/h 5x/d for 5 wks).After mice became dehydration condition,we gave these mice rehydration with pure water(n=9, W) or 10% fructose water(n=9, F)consisting of 6 ml each night.Furthermore we made a control group (C),which did not have dehydration. We compared kidney function among three groups.

Results: Dehydration conditions was similar between W and F group[serum osmolality(sOsm)of W:344mOsm/kg; F:340 mOsm/kg].sOsm was significantly different between dehydration groups and control group(307 mOsm/kg)(P<0.001).Urine osmolality (uOsm) had also significant differences between dehydration groups(W: 3095,F: 2825 mOsm/kg) and control group(1976 mOsm/kg)(P<0.001).Serum copeptin level(vasopressin marker)in F group(22 pg/ml)was significantly higher than W(16 pg/nl) and C(12.5pg/ml) groups(P<0.001).Urine NGAL(ng/mg creat)in F group (156)was significantly higher than W (141) and C(47)groups(P<0.01).Interstitial fibrosis area in glomeruliin F group(0.53%) was significantly larger than W(0.43%) and C(0.33%)groups(P<0.001).Macrophage (F4/80) infiltration area in gromerulus in F(0.22%)was significantly larger than W(0.080%) and C(0.048%) groups(P<0.001).Kidney MCP-1 level in F group(28.4 pg/mg) was significantly higher than that in C group(24.8pg/mg).(P=0.031).MCP-1 level had no significant difference between F and W group(26.1 pg/mg).

Conclusions: Rehydration with fructose in heat stressed,dehydrated mice caused renal damage,likely due to higher vasopressin levels.This result suggests rehydration with soft drinks in the setting of heat stress and dehydration may not be good for the kidney.

Funding: Private Foundation Support

PUB204

Impact of Direct Acting Antiviral Agents on Kidney Function in Hepatitis C Virus Infected Patients

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Background: Hepatitis C virus (HCV) infection is a public health issue with approximately 170 million individuals infected worldwide. The prevalence of HCV infection is higher in patients with chronic kidney disease (CKD) and data suggests that it is a risk factor for CKD progression. The new direct acting antivirals (DAA) have transformed the treatment of HCV with high (>90%) sustained virologic response (SVR) rates achieved. The objective of this study is to evaluate the relationship of DAAs treatment and kidney function.

Methods: We used a retrospective and descriptive design. Consecutive patients with HCV and on DAA's were identified at the Miami VAMC from 2015 to 2016 (n=397). The following DAA agents were used: ledipasvir, sofosbuvir, simeprivir, ribavirin and daclastavir. Serum creatinine with estimated glomerular filtration rate calculations (eGFR/MDRD formula) were obtained. The following data was obtained: gender, age, creatinine (Cr) and eGFR before and at 12 weeks following completion of therapy were obtained. Blood pressure (BP) measurements before starting and after therapy were also analyzed.

Results: 397 patients were identified, 380 males and 17 were females. The mean age was 63 years old (range 36-84). Most of the patients were treated with a combination of drugs: sofosbuvir (390/396:98.5%), ribavirin (201/396:50.8%), ledipasvir (195/396:49.2%), simeprivir (155/396:39.1%) or daclastavir (8/396:2%). The mean Cr before therapy was 1.4 mg/dl and eGFR was 53 ml/min, after DAA therapy the mean Cr was 1.2 mg/dl and eGFR was 64 ml/min (p=0.001), the mean systolic BP before therapy was 130 mmHg and 134 mmHg after, the diastolic BP before and after therapy was 80 mmmHg.

Conclusions: The use of DAA agents to treat HCV was associated with a statistically significant improvement in eGFR. No significant changes were seen in systolic or diastolic BP at the end of treatment. Prospective long-term studies are needed to establish a clear relationship between renal function and treatment of HCV-positive patients with DAA.

PUB205

The Association of Dietary Phosphate to Protein Ratio with Metabolic Syndrome: Analysis of KNHANES Data

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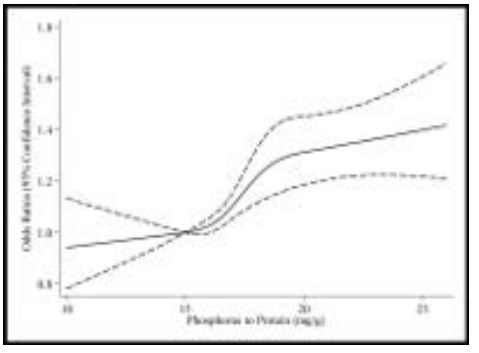
Background: To keep adequate phosphate to protein ratio of dietary intake is important for the control of hyperphosphatemia among hemodialysis patients. However, whether dietary phosphate to protein ratio (p/prot) is also important in general population was unknown. We investigated the association of p/prot with metabolic syndrome.

Methods: We used The Korean National Health and Nutrition Examination survey (KNHANES) 2005 – 2014 data (n = 45,648). Metabolic syndrome was defined by fulfilling 3 or more criteria of the modified National Cholesterol Education Program Adult Treatment Panel III. Data available for estimated GFR, nutritional survey, metabolic syndrome were used. (n = 16,576).

Results: Dietary p/prot were divided by quartiles: mean dietary p/prot were 13.4 ± 1.5 mg/g, 16.2 ± 0.6 mg/g, 18.4 ± 0.7 mg/g, 21.9 ± 2.3 mg/g, respectively. Age was showed linear association with p/prot (β=0.058, p<0.001). Protein intake was inversely associated with increased p/prot (β=-0.041, p<0.001). A sigmoidal association of p/prot with metabolic syndrome was found.



P/prot higher than 18mg/g had odds ratio (OR) of 1.280 to metabolic syndrome [95% confidence interval (C.I.) 1.192 – 1.374]. Adjusted with sex, body mass index, low educational status, number of moderate-vigorous activities per week and smoking, p/prot showed adjusted OR of 1.262 to metabolic syndrome [95% C.I. 1.163 – 1.370]. However, when age was added in the model, the impact of high p/prot was reduced. [Adjusted OR, 1.084, 95% C.I 0.997 – 1.179].

Conclusions: In KNHANES population, ingestion of food with high p/prot was associated with metabolic syndrome. High p/prot was associated with low protein intake, which requires further dietary pattern analysis. Impact of p/prot could be different in different age group.

PUB206

Correlation Analysis of Renal Ultrasound Elastography and Clinical and Pathological Changes in Patients with Chronic Kidney Disease

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Background: To analyze the correlations with the Estimates of tissue Young's modulus (YM) of renal cortex, medulla and clinical biochemical indicators and pathological changes in patients with chronic kidney disease (CKD).

Methods: A total of 113 cases of CKD patients were enrolled in this study. Pearson's correlation analysis was used for the Young's modulus values and various related factors. In the correlation analysis, the variables showing significant correlation with the Young's modulus were introduced into the regression equation for multivariate linear regression analysis.

Results: The YM of CKD patients was significantly higher than that of the control group; and with the progression of CKD, the YM of the renal cortex and medulla gradually increased.The Young's modulus of the renal cortex was positively correlated with serum creatinine, urea nitrogen, cystatin C, serum phosphorus, calcium and phosphorus product, iPTH and uric acid levels and was negatively correlated with urinary MA, urinary NAG, eGFR, and hemoglobin levels. The YM of the renal medulla was positively correlated with SBP, serum creatinine, BUN, iPTH, and UA and was negatively correlated with urinary MA, urinary NAG, eGFR, and hemoglobin levels. Serum cystatin C, uric acid, and iPTH levels were independently correlated with the YM of the renal cortex. Serum creatinine, uric acid levels and smoking were independently correlated with the YM of the renal medulla. The YM of the renal cortex in the patients with phases IV and V based on the Lee grading system of IgA nephropathy were significantly higher than phases II and III. According the Oxford classification , the YM of the renal cortex and medulla in the T1 and T2 patients were significantly higher than those of the T0 patients. The YM of renal medulla in focal segmental glomerulosclerosis was significantly higher than that in minimal change nephropathy.

Conclusions: Renal ultrasound elastography is expected to provide a new indicator for determining CKD progression and the extent of kidney fibrosis and to distinguish between focal segmental glomerulosclerosis and minimal change nephropathy.

PUB207

Left Atrial Function: A Cardiac Computed Tomography Study of Patients with Chronic Kidney Disease Laust Dupont,[1] Simon Winther,[2] Hanne Skou Joergensen,[1] My Svensson,[3] Per R. Ivarsen.[1] *[1]Dept of Nephrology, Aarhus Univ Hospital, Aarhus N, Denmark; [2]Dept of Cardiology, Aarhus Univ Hospital, Aarhus N, Denmark; [3]Dept of Nephrology, Oslo Univ Hospital, Akershus Univ Hospital, Oslo, Norway.*

Background: Previous studies using 2-dimensional-echocardiography show that left trial end-diastolic volume (LaEDV) is predictive for CV outcomes and mortality in CKD patients. Cardiac computed tomography (CCT) angiography measure LaEDV more precise than echocardiography.

Hypothesis: LaEDV and left atrial ejection fraction (LaEF) measured by CCT is predictive of major adverse cardiac events (MACE), and is positively correlated to functional metrics of left ventricular (Lv) function and plasma-pro-brain natriuretic peptide (pro-BNP) in CKD.

Methods: 167 kidney transplant candidates from 9 regional centres underwent CCT angiography prior to kidney transplantation. La and Lv volume and function were determined using CCT. MACE and mortality data were extracted from Western Denmark Heart Registry, review of patient records and patient interviews.

Results: LaEDV was significantly associated with pro-BNP ($p<0.05$, $r=3.98$), Lv end-diastolic volume ($p<0.05$, $r=0.14$) and mass ($p<0.05$, $r=0.05$). LaEF was significantly associated with age ($p<0.05$, $r=-0.003$) and pro-BNP ($p<0.05$, $r=-0.03$). During a median follow-up of 3.3 years (*range:* 0.3-5.1), 22 (15.0%) patients suffered MACE and 24 (16.4%) died. MACE and survival analysis showed no relation to LaEDV (*survival*: HR=0.99, p=0.53 – *MACE*: SDHR=1.00, p=0.92) and LAEF (*survival*: HR=0.50, p=0.74) – *MACE:* SDHR=0.16, p=0.45), whereas Lv ejection fraction was solely associated to increased MACE risk and not mortality (*survival:* HR=0.98, p=0.46– *MACE:* SDHR=0.94, p<0.05).

Conclusions: Using CCT, LaEDV correlates to functional parameters of Lv in CKD. The association does not apply to LVEF. We failed to detect any association between LaEDV, MACE and mortality in this cohort of kidney transplant candidates. Similar results were found for LaEF. Lv ejection fraction was solely associated to MACE.

Funding: Private Foundation Support

PUB208

Timing and Pregnancy in ESRD Patients: When Is Conception Better? Amelia Rita Bernasconi,[1] Liliana Susana Voto,[2] Alicia M. Lapidus,[2] Rosa Alejandra Waisman,[2] Ricardo M. Heguilen.[1] *[1]Medicine, Hospital J.A. Fernández, Caba, Buenos Aires, Argentina; [2]Materno-Fetal, Hospital J.A. Fernández, Caba, Buenos Aires, Argentina.*

Background: Pregnancy (P) in women with renal disease (CKD) implies significant risk for adverse maternal and fetal outcomes. Although advances in antenatal and neonatal care continue to improve them, risks remain proportionate to the degree of underlying renal dysfunction.There is evidence to suggest that pt with 1-2 CKD, normal bp, and no urinary protein, P is safe. Trying to stablish better timing of pregnancy in further ESRD pt is still controversial.

Methods: we compared the outcome of Pt in 3 different CKD groups. Group A:(10 ESRD 4-5 p pt); Group B: 10 P in HD (pt in dialysis between 1-10 years); Group C: 10 P in renal transplant women (4 w/related donor).

Results: All groups mean age was similar, no DBT, no SLE. Folic acid, rHuEpo and IS maintained stable mothers H^{to} (28%) and HB (8.7 g/dl) in all groups. Aimed at improving fetal lung maturity, intramuscular betamethasone was administered at 32 weeks. Methylprednisone pulse was given peripartum to avoid intra and postpartum stress in Group C. Amlodipine and or labetalol were used when necessary in the three groups. GA: pt entered in an intensified HD schedule (> 20 h/w) when SCR increased to 3,5 mg/dl. GB: intensified dose was prescribed. GC: all pt received appropriate medication for P. Main data are shown in table one.

	GA (n: 10)	GB (n: 10)	GC (n: 10)	p
Age, *y*	25.5 ± 5.6	31.4 ± 4.6	26.2 ± 6.7	NS
Gestational age, *w*	31.8 ± 4.3	32.0 ± 3.9	36.6 ± 1.6	0.03
Weight at birth, *g*	1495 ± 744	1418 ± 436	2714 ± 545	0.001

Conclusions: better timing for conception maybe during transplantation according to our data. In preconception counselling patients should be advised of the high risk of fetal demise and early Hd start in ESRD 4-5, intensified Hd schedule in those previously in RRT, and graft loss in declining renal function pt, and adverse pregnancy outcome in. According to our study the administration of human recombinant erythropoietin has a beneficial effect in pregnancy without side effects. Preterm delivery, IUGR and low birth weight are common in this population.

PUB209

Comparison of Different Definitions of Progression of Chronic Kidney Disease and Predisposing Factors in a Public Renal Practice: Queensland, Australia Rajitha Asanga Abeysekera,[1,3] Zaimin Wang,[1,2] Jianzhen Zhang,[1,2] Helen G. Healy,[1,3] Anne Cameron (Salisbury),[1,2,3] Wendy E. Hoy.[1,2] *[1]NHMRC CKD.CRE and CKD.QLD, 1, Brisbane, Queensland, Australia; [2]School of Medicine, Univ of Queensland, 2, Brisbane, Queensland, Australia; [3]Kidney Health Service (RBWH); Metro North Hospital and Health Service, 3, Brisbane, Queensland, Australia.*

Background: We compared different definitions of CKD progression and assessed factors associated with progression.

Methods: Annual data ofCKD patients in the public renal practice of the RBWH, who were enrolled in the CKD.QLD registry were analysed from consent until 31st July 2015. 905 and 682 patients were studied at 1 and 2 years follow up. Six definitions of progression were evaluated- Definition **i:** loss of EGFR of >2ml/min/1.73m^2/year, **ii**: loss of >5ml/min/1.73m^2/year, **iii**: change of CKD stage, **iv**: combination of CKD stage change & 25% eGFR reduction, **v**: 20% eGFR reduction, and **vi**: start of renal replacement therapy. Age, gender, renal diagnosis, AKI, presence of diabetes, and number of comorbidities were evaluated as potential predictors over the first year.

Results: Proportions defined as progressing at one year, in descending order, were: Definition **i** 42.8%, **ii** 26.7%, **iii** 18.5%, **iv** 14.7%, **v** 7.9% and **vi** 3.3%. At two years, the proportions were 38%, 15.5%, 23.2%, 21.9% and 12% and 2.2% respectively, representing a similar rank order, except for the lesser frequency of Definition **ii.** Among the four major groups of renal diagnoses, proportions who progressed, regardless of definition, were, in descending order, diabetic nephropathy, renovascular disease, genetic renal disease, and glomerulonephritis. More patients with >8 comorbidities progressed, versus those with <4 comorbidities. Compared to stage 1, 2 and 3A, more patients in CKD stage 3B, 4 and 5 progressed. More patients with any diagnosis of AKI progressed compared to patients without AKI ($p<0.005$). Patients <40 years old had the lowest rates of progression. Males tended to more often be progressors, although this was not significant.

Conclusions: There is some consistency of the different definitions of progression. The choice of a particular expression should be context specific. These data give valuable insights into progression of CKD.

PUB210

The Effects of Pazopanib versus Sunitinib on Renal Outcome in Metastatic Renal Cell Carcinoma Eun Jeong Lee, Subin Hwang, Hye Ryoun Jang, Wooseong Huh, Dae Joong Kim, Yoon-Goo Kim, Ha Young Oh, Jung Eun Lee. *Nephrology Div; Dept of Medicine, Samsung Medical Center, Sungkyunkwan Univ School of Medicine, Seoul, Korea.*

Background: Pazopanib and sunitinib are used as the first-line treatment of metastatic renal cell carcinoma (RCC). Several studies have reported similar efficacy with a favorable safety profile of pazopanib. The aim of this study was to examine the renal outcome after pazopanib versus sunitinib treatment in patients with metastatic RCC.

Methods: We reviewed medical records of 304 patients with metastatic renal cell carcinoma who received pazopanib (n=103) or sunitinib (n=201) therapy from 2007 to 2016. The primary outcome was chronic kidney disease (CKD) progression, defined as a drop in glomerular filtration rate (GFR) category accompanied by a 25% or greater drop in GFR from baseline, during treatment. Secondary outcome was disease progression-free survival.

Results: Overall, 47% of subjects had CKD stage 3 or 4 at baseline. Distributions of CKD stage were similar between two treatment groups. Treatment durations were 363 (129 ~ 504) days in pazopanib group and 360 (91 ~ 510) days in sunitinib group. Incidence of CKD progression was 19% in pazopanib group 17% in sunitinib group at 1 year after treatment ($p = 0.083$ by log rank test). Lower serum albumin levels and older age were independent risk factors of CKD progression. Progression-free survival was higher in pazopanib group than in sunitinib group ($p = 0.04$ by log rank test, 53% vs 42% at 1 year after treatment). In sunitinib group, dose reduction was conducted more often than in pazopanib group during treatment (68% vs 40%, p=0.032).

Conclusions: The effects of pazopanib versus sunitinib treatment on CKD progression were similar in real-world practice. However, higher percentage of pazopanib group continued the regular dosage of drugs and more favorable cancer outcome was observed in pazopanib group.

PUB211

Urinary N-Acetyl Cysteine and Kidney Disease Progression in HIV-Infected Patients: A Prospective Study Clara Dias,[1] Lucília N. Diogo,[1] Pedro Pereira Campos, Ana R. Lemos,[1] Emília C. Monteiro,[1] Karina Soto,[1,2] Sofia Pereira.[1] *[1]CEDOC, NOVA Medical School/Faculdade de Ciências Médicas, Lisbon, Portugal; [2]Nephrology, Hospital Fernando Fonseca, Lisbon, Portugal.*

Background: Chronic kidney disease has emerged as a major health concern in HIV-patients, its early diagnosis is paramount to prevent progression. Screening and searching for new non-invasive pathophysiologic markers are a key challenge. *N*-acetyl cysteine-disulfides conjugates are products of *N*-acetyltransferase 8, an enzyme mainly expressed in proximal tubular cells that has been pointed out as a candidate for renal regulation and nephrotoxic response. *N*-acetyl-cysteine conjugates were identified in urine open the possibility of using as surrogate of *N*-acetyl cysteine-disulfides conjugates. The aim of the present study was to determine if urinary *N*-acetyl-cysteine (uNAC) can be uses as biomarker of kidney disease progression.

Methods: As a part of an ongoing prospective study of HIV+ population, a 1-year analysis was performed in a cohort of patients under combined antiretroviral therapy, with visits at 0 (M0), 6 (M6) and 12 (M12) months. Glomerular filtration rate (eGFR) was estimated by CKD-EPI equation, expressed in mL/min/1.73m^2. Patients were divided in 2 groups according their eGFR evolution: Group1, stable eGFR; Group2, decline in eGFR≥10% at M12.uNAC was quantified by HPLC with fluorescence detection. Data are presented as percentage relative to M0.

Results: A total of 24 HIV-infected patients were included (67% men, 33% Black, 54 [IQR47-62] years old at M0). Patients with eGFR≥90 had higher uNAC at M0 than patients with kidney disease (*Unpaired t*-test, p=0.005). Among patients with stable eGFR, the levels of uNAC remained unchanged after 12 months in opposite to patients with a declined eGFR (*Two-way RM ANOVA* with *Bonferroni* post-test, p<0.05). Ten patients had a pronounced declined eGFR (83±SD7%), at M12 (*Paired t*-test, p=0.010). Correlated with a significant decrease in uNAC (60±40%) (*Wilcoxon signed rank* test, p=0.006).

Conclusions: Kidney disease progression was associated with a significant decline in uNAC. The present results suggest that uNAC has a role as a newly non-invasive indicator of kidney disease progression in HIV.

Funding: Government Support - Non-U.S.

PUB212

Risk Factors Involving CKD Progression – Brazilian Perspective

Paula Ferreira Orlandi,[1] Naohiko Fujii,[1] Roberto Zatz,[2] Harold I. Feldman.[1] *[1]Center for Epidemiology and Biostatistics, Univ of Pennsylvania, Philadelphia, PA; [2]Nephrology Div, Univ de São Paulo, São Paulo, São Paulo, Brazil.*

Background: Few data are available about CKD progression in the Brazilian population . This study evaluates the association between established risk factors for CKD progression and the development of ESRD in a retrospective cohort of individuals followed in an outpatient CKD Unit in São Paulo, Brazil.

Methods: A total of 2290 individuals with mean age of 63±15 yrs were followed by a median of 4 years. All had at least 2 consecutive eGFR measurements <=60 ml/min/1.73m2 in an interval >=3 months. Clinical and laboratorial assessments included standardized serum creatinine and urinary protein to creatinine ratio (PCR), obtained from electronic medical records. Main outcome was ESRD, defined as initiation of dialysis, transplantation or eGFR<10ml/min/1.73m2. We performed survival analyses with the Cox proportional hazards model. Creatinine based CKD-EPI equation was used to estimate eGFR.

Results: Participants were predominantly white (79%), with history of hypertension in 88.6% and diabetes in 39.9%. Incidence rate of ESRD was 3.2 per 100 persons-year. Among the most significant factors associated with ESRD were: baseline eGFR (HR 2.27 [95%CI 1.14, 4.55] for eGFR 30-45 and 4.7 [2.3, 9.3] for eGFR<30; Ref: eGFR 45-60; P<0.001); PCR (HR 2.7 [1.17, 6.27] for PCR 30-300 mg/gCr and 8.3 [3.8, 18.2] for PCR>300; Ref: PCR<30; P<0.001); age (HR 0.57 [0.43, 0.76] for age 55-75 and 0.19 [0.10, 0.35] for age>75; Ref: age<55; P<0.001); systolic blood pressure (sBP) (HR 1.67 [1.15, 2.43] for sBP 120-140 mmHg and 2.28 [1.57, 3.31] for sBP≥140; Ref: sbp<120, P=0.001); and serum albumin (Alb) (HR 0.63 [0.43, 0.91], 0.49 [0.34, 0.70], and 0.47 [0.30, 0.74] for Alb 4.1-4.4 g/dL, 4.4-4.6, and ≥4.6, respectively; Ref: Alb<4.1, P=0.0002).

Conclusions: This is one of the first studies analyzing renal outcomes in a cohort of Brazilian patients. A significant association of risk factors such as ethnicity, diabetes and BMI with ESRD was not observed, whereas older age, sbp, and albumin were significantly associated with ESRD.

PUB213

A Fascinating Case of Anti Glomerular Basement Membrane (GBM) Disease with Coeexisting Anti Neutrophil Cytoplasmic Antibody (ANCA) following Aortic Dissection

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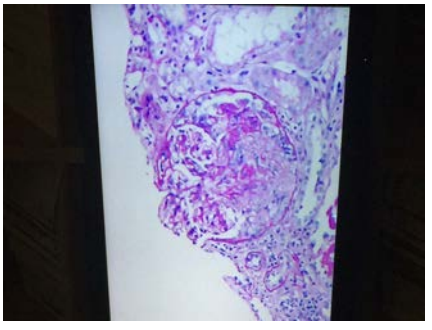
Background: About 30% of patients with anti-GBM disease have co existing ANCA positivity. The occurrence of this disease after aortic dissection has not been reported in literature. We describe this case of a "double positive serology" presenting with Rapidly Progressive Glomerulonephritis & diffuse alveloar hemorrhage (DAH) after an aortic dissection.

Methods: 45yrs woman with controlled hypertension presented with sudden chest & back pain. **Exam** found tachypnic, even on oxygen. **CT** confirmed type A aortic dissection extending to the upper pole of left kidney. After repair, she was **discharged**. She **represented** 2 weeks later with hemoptysis & dyspnea. **Creatinine** rose to 2.2, & urine had dysmorphic RBCs. **Bronchoscopy** confirmed DAH. **Renal biopsy** found 75% glomeruli with cellular crescents in the same stage.



Immunofluorescence stain revealed 2+ linear GBM staining. Anti GBM & p-ANCA **titers** were elevated. Patient was **treated** with plasma exchanges, steroids & IV Cyclophosphamide over 3 months that lead to resolution of hemoptysis and significant improvement of renal function.

Conclusions: Our patient presentation & renal biopsy findings support more an Anti GBM disease with co existing p- ANCA positivity. Anti GBM disease & ANCA associated vasculitis are diseases characterized by circulating antibodies. The principal target for the anti-GBM antibodies is the alpha-3 chain of type IV collagen. Type IV collagen is also in subintimal membrane of aorta . We postulate that the aortic dissection exposed the hidden antigenic domain of type IV collagen resulting in antibody formation that resulted in this anti GBM disease few weeks later. **CONCLUSION:** Aortic dissection could be a risk factor for developing anti GBM disease in future.

PUB214

Twenty-Six Cases Treated by Short Term Steroid Regimen for Adult Steroid Sensitive Nephrotic Syndrome

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Background: The appropriate treatment duration for adult steroid sensitive nephrotic syndrome (SSNS) is not clear. In pediatric field, recent trials revealed that 2 months short term steroid regimen for SSNS children is not inferior than extended course of steroid in the occuerence of frequent relapse or steroid dependent disease. This is the case series of 26 adult steroid sensitive nephrotic syndrome patients treated by 2 months short term steroid regimen.

Methods: Among the biopsy-proven adult MCNS or FSGS cases in Nagoya university affiliated hospitals during Feb. 2015 to Jan. 2016, patients satisfied the following criteria: over 20 years old, first time episode of nephrotic syndrome, acieved remission within 4 weeks and concent of the patient was obrained. Treatment plan of short term steroid regimen is as below; (1) prednisolone 0.8-1.0 mg/kg/day as initial dose and continued for 4-6 weeks. (2) prednisolone reduced to 0.5-0.6 mg/kg/alternative day and continued for 4 weeks. We compared the patients with histrical control from our retrospective cohort (140 cases).

Results: There were 26 cases (male: 13, median age: 50.0). The initial steroid dose was 50 mg/day in the midian. All the patients except 1 was finished steroid administration without relapse. Throughout the observation period (median: 204.5 days), 14 cases (53.9%) experienced relapse and 1 patinet (3.8%) developed to frequent relapse. The adverse events were observed in 2 cases (3 incidents). None had an episode of adrenal insufficiency. Compared with the histrical cintol, patients treated by short term regimen relapsed earlier from the baseline (131 vs 357 days, p<0.001), but the cumulative steroid dose at 3, 6 and 9 months from the baseline were significantly lesser in short term regimen patients (1822 vs 2855 mg, 2160 vs 4095 mg and 1781 vs 4887 mg respectively).

Conclusions: Although the timing of relapse in short term regimen is earlier than conventional one, short term steroid regimen may detect the frequent relapse or steroid dependent cases in SSNS earlier and lesser steroid exposure. For further comparison, it is necessary to analyze by extending observation period.

PUB215

Monotypic Atypical Anti-GBM Nephritis in a 9/11 First Responder

Neeraj Sharma,[1] Hone S. Kaw,[1] Hiba M. Ahmed,[1] Mandeep Samra,[1] Farah Piracha,[1] Ananea Adamidis,[2] Jennine Michaud,[1] Michael Yudd.[1] *[1]Renal Section, Dept of Veterans Affairs NJ Healthcare System, East Orange, NJ; [2]Renal Medicine Associates, Teaneck, NJ.*

Background: Atypical anti-GBM nephritis (AAGN) is rare, and is characterized by bright linear anti-GBM immunoglobulin staining in the absence of circulating anti-GBM antibodies. As opposed to typical anti-GBM, the clinical course of AAGN is frequently renal-limited and indolent. Nasr et al described 20 patients with this – we add another.

Methods: 44 year old white man, a first responder at the World Trade Center in 9/11, developed gross hematuria in 2007. Urologic work up was negative. In 2010, labwork showed creatinine 1.4 mg/dL, urinalysis 2+ protein and large blood, urine protein/creatinine ratio 0.8, with the following negative or normal studies: ANCA, anti-GBM, SPEP, κ/λ ratio, complements, hepatitis B/C and HIV. First renal biopsy, in 2010, showed mild endocapillary proliferation with linear IgG1λ deposits and no electron dense deposits. He was started on steroids, but could not tolerate them and stopped. Ace inhibitor was started. Six years later, labwork showed moderate worsening: creatinine 1.7mg/dL, urine protein 2.9 g/day, urinalysis 2+ protein, large blood. Repeat biopsy in 2016 showed similar findings: mesangial proliferative GN with MPGN features, the same monotypic-restricted bright linear deposits on IF, and no electron dense deposits, with mild increase in chronicity. Bone marrow biopsy showed no monoclonality.

Conclusions: Our patient had an indolent renal-limited course over at least 9 years. Biopsies showed mild proliferative changes and diffuse linear GBM staining with a monotypic IgG1λ, and no electron-dense deposits. Monoclonal gammopathy was not present. Environmental factors may trigger anti-GBM disease, particularly hydrocarbon exposure . Whether toxic exposure at 9/11 could have played a role is not known. The cause of the linear Ig accumulation in the GBM is uncertain. Potential mechanisms include: antibodies reactive to a GBM antigen, likely different from the conventional 3NC1 of anti-GBM nephritis; physicochemical properties of the Ig chains independent of antigen, similar to MIDD findings; abnormalities of the GBM.

PUB216

Glomerular Diseases Associated with Malignancies: Clinical Presentation, Histopathology and Outcome Sophia Lionaki,[1] Konstantinos Panagiotellis,[1] Joan Vlahadami,[2] Ioanna Tsoubou,[1] Chrisovalantis Vergadis,[3] George Liapis,[4] Petros P. Sfikakis,[5] Athanasios Tzioufas,[2] John Boletis.[1] *[1]Nephrology, Laiko Hospital, National & Kapodistrian Univ, Athens, Greece; [2]Pathophysiology, National & Kapodistrian Univ, Athens, Greece; [3]Radiolody, Laiko Hospital, Athens, Greece; [4]Pathology, Laiko Hospital, Athens, Greece; [5]Propeudeutic and Internal Medicine, National & Kapodistrian Univ, Athens, Greece.*

Background: To study the glomerular diseases, associated with malignancies (GDAM), with respect to clinical characteristics and histopathological findings.

Methods: We retrospectively studied the medical charts of all patients with GDAM, diagnosed in our hospital between 2008-2015 and recorded demographic, clinical, laboratory and histopathological findings, as well as the type of malignancy and the outcomes at end of follow up.

Results: Twenty nine biopsy proven cases with GDAM were identified, with a mean age of 62.4(±12.0) years at kidney biopsy. Renal histopathology revealed: membranous nephropathy in 9 cases (31.0%), membranoproliferative glomerulonephritis in 5(17.2%), lupus-like nephritis in 4(13.8), minimal change disease in 4(13.8%), pauci-immune glomerulonephritis in 3(10.3%), IgA nephropathy with crescents in 1(3.4%), amyloidosis in 1(3.4%) and interstitial nephritis in 2(6.9%). 13(44.8%) patients presented with acute nephritic syndrome and 4(30.8%) with rapidly progressive glomerulonephritis. 12(41.4%) patients developed acute renal injury within 2.85(±2.83) months from kidney biopsy and 5(17.2%) required dialysis. 14(48.3%) cases had a solid tumor and 15(52.7%) a hematologic malignancy.

Characteristic	Median (range) or (mean±sd) or N (%)
24h proteinuria (g/day)	4.2 (0.12-16.9)
Hematuria	19 (65.5)
Ser creatinine (mg/dl)	1.2 (0.8-9.6)
Immunosuppressive therapy	14 (48.3)
GDAM outcome Remission Treatment resistance ESRD Death	 13(44.8) 8(27.6) 4(13.8) 7(24.1)
Follow up time (months)	30 (±26.05)

Conclusions: Patients with GDAM may present with various clinical pictures, combined with diverse histopathological patterns. Prompt and accurate diagnosis, recognition of the specific characteristics of each patient and individualized management are critical for renal and patient outcome.

PUB217

Improving Administration Rate of Pneumococcal Polysaccharide Vaccine (PPSV23) in Children > 2 Years with Nephrotic Syndrome: A Single Center Experience Siddharth A. Shah. *Pediatric Nephrology, Univ of Louisville, Louisville, KY.*

Background: Pneumococcal infections are major cause of morbidity and mortality in children with nephrotic syndrome. Apart from pneumococcal vaccines, other strategies have not shown to decrease the risk of pneumococcal infections. Previous study showed high serological response to pneumococcal vaccine in nephrotic children even at disease onset on high-dose prednisone therapy. IgM is less likely to be lost in urine in active disease state given its high molecular weight compared to IgG. The challenges to improve coverage with PPSV23 vaccine include vaccine availability, compliance to clinic visits and patient education.

Methods: A standard protocol was established to administer PCV13 and PPSV23 vaccine as per ACIP guidelines. All patients with clinical diagnosis of nephrotic syndrome and age range between 2 and 18 years were included in the study. Two strategies were implemented including: 1) Inpatient administration of PPSV23 vaccine at time of initial diagnosis of nephrotic syndrome or during hospital admission for relapse or infection 2) Outpatient administration of PPSV23 vaccine. Letters were mailed to family. PPSV23 documentation and alerts were added to Clinical Notes to help improve patient education.

Results: Overall, 58 children and adolescents with clinical diagnosis of nephrotic syndrome were included in the study. The PPSV23 immunization rate had improved to 80% after 2 years compared to 32% at beginning of study. Hospital administration of PPSV23 vaccine helped achieve better immunization rates. The PPSV23 vaccine administration rate was only 60% in children who received vaccines at outpatient basis even with patient letter and clinic visit reminders.

Conclusions: PPSV23 (Pneumovax) is readily available across major hospitals in United States in contrast to local pediatrician offices. PPSV23 vaccine should be administered as early as possible in children>2 years of age with nephrotic syndrome. PPSV23 administration at time of initial hospital admission for nephrotic syndrome or hospital admission for relapse may be an effective strategy to help improve immunization coverage in children with nephrotic syndrome.

PUB218

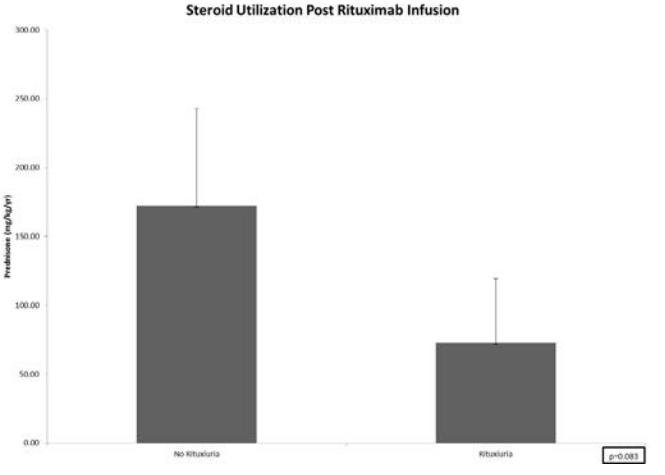
Study of Urinary Excretion of Rituximab in Pediatric Nephrotic Syndrome Jason Peter Thomas,[1] Teri L. Crumb,[2] Tracy J. Koehler,[3] Alejandro Quiroga.[2] *[1]Pediatric Residency, Grand Rapids Medical Education Partners, Grand Rapids, MI; [2]Pediatric Nephrology, Helen DeVos Children's Hospital, Grand Rapids, MI; [3]Research Dept, Grand Rapids Medical Education Partners, Grand Rapids, MI.*

Background: Rituximab (RTX) is a monoclonal antibody used in patients with steroid dependent nephrotic syndrome as an alternative to cyclophosphamide. As a protein, it is susceptible to excretion in the urine of patients with nephrotic range proteinuria.

Methods: This is a pilot pediatric clinical research trial (n=7) which enrolled patients prior to their clinically indicated RTX infusion. Serial urine samples were obtained pre/post-infusion to evaluate for RTX via ELISA. Patients received 2 doses of RTX (375 mg/m^2) 2 weeks apart.

Results: Rituximab was found in 3/7 patient's serial samples. There is a non-statistically significant increased likelihood of rituxiuria in patients with higher levels of proteinuria. Two weeks after infusion, 85% of the patients had no proteinuria. Two of three patients that excreted RTX in the urine were able to wean off steroids. Patients with rituxiuria required a lower cumulative dose of prednisone/kg/year post infusion (p=0.083).

Subject	Pre-Infusion (ug/mL)	1-3hr (ug/mL)	Infusion Completion (ug/mL)	24hr Post Infusion (ug/mL)
1	Not Detected	Not Detected	Not Detected	Not Detected
2	Not Detected	Not Detected	Not Detected	Not Detected
3	Not Detected	Not Detected	Not Detected	Not Detected
4	Not Detected	Not Detected	Not Detected	Not Detected
5	Not Detected	0.34	0.37	0.21
6	Not Detected	Not Detected	0.19	Not Detected
7	Not Detected	Not Detected	31.67	2.20



Conclusions: Patients with nephrotic range proteinuria receiving RTX developed rituxiuria in 42% of the cases. There is an increased likelihood of response to RTX as measured by cumulative steroid dose 1 year after therapy in patients with rituxiuria.

Funding: Private Foundation Support

PUB219

IgA Nephropathy (IgAN) in Patients over 64 Years Old: A Devastating Disease with No Effective Treatment Angel M. Sevillano, Eduardo Gutierrez-Martinez, Manuel Praga. *On Behalf of Glosen, Grupo de Estudio de las Enfermedades Glomerulares de la Sociedad Española de Nefrología (G.L.O.S.E.N.), Spain.*

Background: Recent data from the Spanish Registry of Glomerulonephritis show that the incidence of IgAN is increasing among elderly subjects. Limited information about clinical characteristics, response to treatments and outcomes of elderly IgAN has been published.

Methods: Retrospective cohort study performed in 21 nephrology departments that collected data from patients over 64 years with biopsy-proven IgAN who were identified at each participating center in the period 1990-2015. This time interval was divided into five consecutive five-year periods. 142 patients with a mean follow-up of 48±52 months were included in the study.

Results: The incidence of IgAN in patients over 64 years increased in the last years, from 6 cases in 1990-1995 to 56 in 2011-2015 (p=0.00). Patients were divided according to the type of clinical presentation: 1) asymptomatic proteinuria and hematuria (n = 80, 56%) 2) Hematuria-induced AKI (n = 48, 34%) 3) Crescentic IgAN (> 50% crescents) (n = 7, 5%) and 4) nephrotic syndrome (n = 7, 5%). When comparing the two most common types of presentations (1 and 2), patients with hematuria-induced AKI were older, had higher serum creatinine at baseline, a higher number of cases with gross hematuria and more patients receiving oral anticoagulants (all significant). For the whole group of patients, renal and

patient survival at 1,3 and 5 years were 85%, 80% and 66%, and 95%, 84% and 75.7% respectively. At 5 years 49% of patients had died or reached ESRD. Most patients (83%) received RAAS blockade and 45% were treated with corticosteroids alone or accompanied by other immunosuppressive drugs. Among patients with hematuria-induced AKI, 56% received immunosuppressive treatments. There were no differences in the outcomes of treated and untreated patients.

Conclusions: Prevalence of IgAN is increasing among subjects over 64 years. Hematuria-induced AKI is a frequent type of presentation and oral anticoagulants may play a triggering role. Renal and patient survival is poor and immunosuppression does not improve prognosis.

PUB220

Significance of M2 Macrophage in Tubulointerstitial Disease Secondary to Primary Sjogren's Disease Jun Li,[1] Ya-Fen Yu,[1] Chang-Hua Liu.[2] *[1]Dept of Nephrology, The Affiliated Hospital of Jiangnan Univ, Wuxi, Jiangsu, China; [2]Dept of Nephrology, Clinical Medical College, Yangzhou Univ, Yangzhou, Jiangsu, China.*

Background: The study aims to observe the clinicopathologic significance of M2 macrophage in tubulointerstitial injury secondary to primary sjogren's disease.

Methods: Renal tissue samples from patients with tubulointerstitial disease secondary to primary sjogren's disease (SS, n =8), chronic tubulointerstitial nephritissecondary to drug (CIN, n =8), normal control kidneys (n =3) were included in this study. The expression of CD163 and CD68 was detected by immunohistochemistry or immunofluorescence.

Results: (1) Renal involvement was the first manifestation in six of eight (6/8) patients with pSS, including proteinuria, renal dysfunction, renal tubular acidosis and multiple renal stone; and one patient had intractable hypokalemia. (2)In the normal kidneys samples, CD163 and CD68 were occasionally expressed in tubulointerstitial tissue. (3) There were more CD163 and CD68 positive cells infiltration in tubulointerstitial injury of pSS, especially in patients with hypokalemia. CD68 positive cells were expressed around chronic tubulointerstitial injury and proteinuria casts. There was a negative correlation between the number of CD68-positive cells in tubulointerstitial lesions and estimated glomerular filtration rate(r=-0.700, p=0.004).CD163 positive cells were mainly expressed in acute tubulointerstitial injury of pSS, which positively correlated to N-acetyl-β-D-glucosaminidase(NAG, r=0.627, p=0.012)and beta2-microglobulin(r=0.602, p=0.018) separately. (4)Compared with CIN, patients with pSS had higher serum globulin level, ESR and lower urinary osmotic pressure. During follow-up of one year, four patients with pSS and acute tubular injury acquired improved renal function on therapy of middle dose of steroid and total glucosides of paeony. The remaining four patients with pSS had stable renal function.

Conclusions: M2 macrophage are involved in acute tubular injury in patients with primary sjogren's disease. Early intervention can improve renal function of tubulointerstitial injury secondary to primary sjogren's disease.

PUB221

Regional Incidence and Outcomes of Anti-GBM Disease Andrew Nixon, Ajay Prabhakar Dhaygude. *Renal Medicine Dept, Royal Preston Hospital, Preston, Lancashire, United Kingdom.*

Background: Anti-GBM disease is a rare autoimmune disorder characterised by rapidly progressive glomerulonephritis.[1] The estimated incidence is 1 case/million.[1] Renal survival is poor in those that present with severe acute kidney injury.[2]

Methods: Clinical records of all patients diagnosed with anti-GBM disease between 1/1/2010 and 11/1/2015 were reviewed.

Results: Eighteen patients were diagnosed giving a regional annual incidence of 3.4/million. The median age was 65yrs (M:F::1:1). The majority (16) were Caucasian. Five patients were also ANCA positive. Pulmonary haemorrhage was present in 3. A renal biopsy was performed in 7. The average percentage of crescents on biopsy was 94%. Steroids, cyclophosphamide and plasma exchange were administered to 12. Table 1 demonstrates 1yr patient and renal survival.

	Patients N (%)	1-Year Patient Survival N (%)	1-Year Renal Survival N (%)
Creat <500µmol/L	4 (22)	3 (75)	1 (25)
Creat >500µmol/L	14 (78)	11 (79)	2 (14)
-Dialysis first 72hrs	8 (57)	7 (88)	1 (13)
-No dialysis first 72 hrs	6 (43)	4 (66)	1 (17)
Total	18	14 (78)	3 (17)

There was no significant difference in 1yr renal (P>0.999) or patient survival (P>0.999) for those presenting with a creat<500µmol/L and those presenting with a creat>500µmol/L. There was also no significant difference in 1yr renal (P>0.999) or patient survival (P=0.539) for patients with a creat>500µmol/L that required dialysis within 72hrs and patients with a creat>500µmol/L that did not require dialysis within 72hrs.

Conclusions: This single centre study shows that the incidence of anti-GBM disease is over three-fold higher in the North West of England than reported elsewhere in the literature.[1] Furthermore, this study demonstrates that 1yr renal survival remains poor irrespective of presenting creatinine or initial dialysis requirement. **References:** 1. Pusey CD. Anti-glomerular basement membrane disease. Kidney Int. 2003 Oct;64(4):1535-50. 2. Levy JB et al. Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. Ann Intern Med. 2001 Jun 5;134(11):1033-42.

PUB222

Twelve Hints and Tips for the Management of STEC-HUS Outbreaks Gianluigi Ardissino,[1] Francesca Tel,[1] Damiano Picicco,[1] Laura Daprai,[1] Valentina Bianchini,[2] Antonella Dodaro,[1] Milena Arghittu,[1] Mario Vittorio Luini.[2] *[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano; [2]IZLER, Sezione di Lodi, Italy.*

Background: Shigatoxin-producing Escherichia Coli(S)Hemolytic Uremic Syndrome(HUS)is an endemo-epidemic thrombotic microangiopathy (TMA)and the management of outbreaks(O)is very challenging for both clinicians and public health(PH) professionals as shown in Germany in 2011. In SO, health care providers should be guided by clear and integrated(clinical/PH, hospital/community, human/veterinary/environmental) indications on priorities and most appropriate actions to protect individuals and the community.

Methods: Based on the experience gained in the management of 2 S-HUS O, which took place in Northern Italy in 2013 and 2015 (8 S-HUS, 41 infected), new recommendations were developed and tested; theese may worth being shared with the nephrology scientific community, the front line in S-HUS O.

Results: In case of proven or supected SO(2 or more S infections or S-HUS temporally/spatially related):1.The event must be immediately reported to the relevant health authority (HA);2.HA must promptly inform physicians operating in the involved area in order to have patients(pts)with diarrhea(bloody or watery)tested for a.hemoglobinuria(uHb)with urine dipstick to actively identify pts with ongoing TMA and b.for the presence of Shigatoxin(Stx) in the stools with PCR; 3.Pts with positive dipstick will be immediately addressed to blood testing to rule in/out the signs of TMA(platelet consumption, hemolysis, renal damage);4.If stools are Stx+ or HUS is confirmed, a stool sample must be sent to the appropriate lab for S isolation and serotyping; 5.Stx+Pts must continue daily testing for uHb to early detect TMA onset;6.Family members of Stx+Pts should be tested for Stx regardless of symptoms;7.A sample collecting point should be identified for easy access of pts to tests;8-12 continues.

Conclusions: This relatively novel approach to the management of a S-HUS O provides the best opportunity for early identification of S-HUS during an O and for protecting both the individuals and the community from the possibly devastating effect of infection spreading while enhancing the likelihood of identifying the source of the infection.

PUB223

Clinical Investigation of Preeclampsia in Patients with IgA Nephropathy Miho Karube, Shinya Kaname, Hideki Shimizu, Yoshinori Komagata, Yoshihiro Arimura. *The First Dept of Internal Medicine, Kyorin Univ School of Medicine, Mitaka, Tokyo, Japan.*

Background: To evaluate the effect of preeclampsia on the renal prognosis in patients with IgA nephropathy.

Methods: In 15 patients with IgA nephropathy that experienced childbirth in the past 5 years in our hospital, 5 patients developed preeclampsia (PE) or superimposed preeclampsia (SPE), thus the 5 patients (IgAN group)were retrospectively analyzed for clinical features including onset time of PE, the child weight and childbirth weeks, blood pressure, renal function, degree of proteinuria, and uric acid levels, and were compared with 20 patients that had no known renal disease before pregnancy and were complicated by PE or SPE (non-IgAN group).

Results: No significant differences were observed in childbirth ages (35 years), blood pressure levels, delivery weeks and body weight of children between both groups. The primipara rate was higher in the non-IgAN group, although the premature infants were seen in both groups. However, the onset of hypertension was earlier in IgAN group than in non-IgAN group (22 vs. 27 weeks). Although proteinuria, serum Cr and uric acid levels were transiently worsened after delivery in both groups, the recovery was delayed in patients of IgAN group. Moreover, in 60% of the patients of IgAN group, renal function progressively worsened one year after delivery.

Conclusions: These results shows that although proteinuria may increase in IgAN and non-IgA groups, proteinuria may appear earlier and may be sustained longer, resulting in worsening renal function in IgAN. patients with PE or SPE.

PUB224

Effect and Security of Azathioprine in Maintenance Therapy for Refractory Nephropathy Mengjun Liang, Yajuan Huang, Xing Zhang, Jiafan Zhou, Rui Zhang, Jiang Zongpei. *Dept of Nephrology, The Six Affiliated Hospital, Sun Yat-sen Univ, Guangzhou, China.*

Background: Refractory nephropathy relates to steroid resistant or frequently relapsing nephritis. Maintenance therapy has been called for lupus nephritis(LN). Effect and security of azathioprine in maintenance therapy are still controversial.

Methods: We conducted a retrospective study enrolling patients treated with azathioprine(50mg/d) and low-dose prednisone as nephritic maintenance therapy in our center from 2013.01 to 2016.01.

Results: Forty-four patients were enrolled, with 10 minimal-change disease(MCD), 9 idiopathic membranous nephropathy(IMN), 12 IgA nephropathy(IgAN), 3 focal segmental glomerulosclerosis(FSGS), 1 ANCA glomerulonephritis(ANCA-GN) and 9 LN. Relapse frequency of MCD patients was 3.5(Min-Max, 1-8). Eight IMN patients(88.9%) were treated with steroid plus cyclosporine as initial therapy with remission duration of 6.7±2.4months. Cellular crescent scale in IgAN patients was 11.4(5.0-72.4)%. Among them, 39 patients(88.6%) had persistent remission with efficiency of 80%, 88.9%, 100%, 33.3%, 100% and 100% in MCD, IMN, IgAN, FSGS, ANCA-GN and LN, respectively(p=0.030). The maintenance remission duration was 13(1-36)months. Relapse occured in 5

patients(11.4%) with 1 due to self-withdrawal. Nine patients(20.5%) met side effects with 2 dyshepatia, 2 leukocytopenia, 3 upper respiratory infection, 1 dermapostasis and 1 paramenia that were cured readily, and 5 patients dropped out of azathioprine therapy.

Conclusions: Our research indicates that azathioprine plus low-dose prednisone will do good to maintenance therapy for refractory nephropathy. The low dose of azathioprine, 50mg/d, may be effective and secure for Chinese patients.

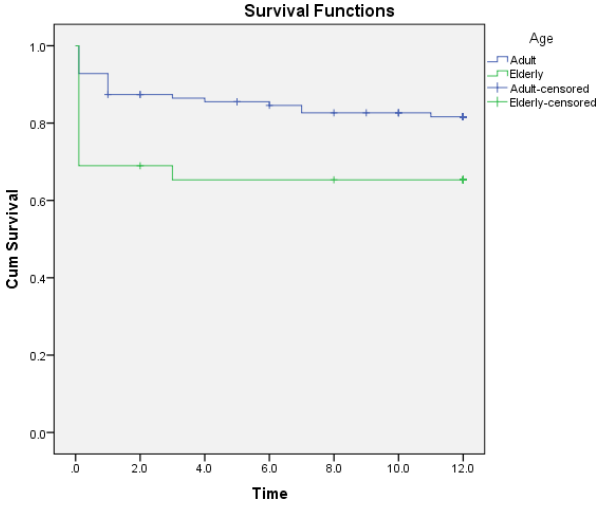
PUB225

IgA Vasculitis: Renal Outcomes in the Elderly James Stanway,[1] Patrick Hamilton,[2] Els Van de Perre,[4] James Tollitt,[5] Edmond O'Riordan,[5] Matthew David Morgan,[3] David R.W. Jayne,[4] Michael Venning,[2] Alan D. Salama.[1] *[1]UCL; [2]Manchester Royal Infirmary; [3]Univ of Birmingham; [4]Univ of Cambridge; [5]Salford Royal NHS Trust.*

Background: IgAV in adults has a poorer renal outcome compared with children. There are no data on renal prognosis in the elderly, in whom other forms of small vessel vasculitis fare worse. We investigated the renal outcomes in IgAV patients categorized according to age in a UK population.

Methods: We retrospectively analysed renal outcomes in patients from 5 UK sites with biopsy proven IgAV, defined as IgA GN on renal biopsy and evidence of vasculitis, including vasculitic lesions on renal or skin biopsy or purpuric rash. Primary outcome was progression to ESRD at 1 year, defined as doubling of serum creatinine from biopsy or use of renal replacement therapy. Secondary outcome was progression to ESRD at 5 years and eGFR at 1 year.

Results: We identified 111 18-65 year olds and 29 over 65s. Renal survival was 71.4% overall, 73.9% in the <65s and 61.7% in the 18-65s, p=0.21. Log-rank test showed significantly poorer 1 year survival in the >65s, p=0.035, but similar outcomes at 5 years. All >65s progressing to ESRD did so in the first year, 82% presented at ESRD compared to 28% of 18-65s. Mean eGFR at biopsy was 80mls/min and 56mls/min in 18-65 and >65 groups respectively p=0.014. An eGFR at biopsy below 30mls/min was associated with poorer 1 and 5 year survival; HR 9.8 (p<0.001) and 6.7(p<0.001) respectively. In those not reaching ESRD, there was a small increase in eGFR over the first year, no significant difference between age groups. Timing of biopsy with regard to eGFR and treatment given varied between sites.



Conclusions: In the short term, renal outcome is worse in patients aged over 65 years. An eGFR less than 30mls/min at biopsy is an important predictor for renal survival. Earlier biopsy and diagnosis may improve renal outcome in older subjects.

PUB226

Proliferative Glomerulonephritis with Monoclonal Ig Deposits: A 21 Cases Report Marc Ulrich,[1] Viviane Gnemmi,[2] Francois Glowacki,[1] Arnaud Lionet,[1] Cécile Lemoine,[1] Cyrille Vandenbussche,[1] Laurence Vrigneaud,[3] Christian Noel,[1] Celine Lebas.[1] *[1]Néphrologie et Transplantation, CHRU Lille, Lille, Nord, France; [2]Anatomopathologie et Cytopathologie, CHRU Lille, Lille, Nord, France; [3]Néphrologie, Dialyse et Médecine Interne, CH Valenciennes, Valenciennes, Nord, France.*

Background: Proliferative glomerulonephritis with monoclonal Ig deposits (PGNMID) was described by Nasr in 2004 with limited information on prognosis and treatment.

Methods: We retrospectively identified patients with histological PGNMID (strictly glomerular monoclonal immune deposits without organization on electronic microscopy (EM)) without cryoglobulinemia.

Results: We included 21 cases of PGNMID with 1 recurrence and 3 de novo occurrence on allograft. Mean age was 54,6 years. At diagnosis, mean creatininemia was 3,1 mg/dL, mean proteinuria 3,7 g/24h and haematuria was present in 90,5%. Eight patients had monoclonal spike. Main pathological presentation was membrano-proliferative glomerulonephritis (n=16) with IgG3 Kappa immune deposits in 62%. EM revealed non organized deposits, mostly sub-endothelial. Fourteen patients received chemotherapy 16,6 months after diagnosis meanly, 10 before end stage renal disease (ESRD). ESRD occurred in a mean time of 27,5 months in 4 of 7 non-treated patients and 6 of 14 treated patients. One patient experienced partial response (proteinuria 0,5g/24h and creatininemia 1,7 mg/dL versus 2,3 mg/dL, without histologic features of PGNMID at 6 months) without chemotherapy. Five patients deceased (mean time from diagnosis 44 months), one of them, transplanted, died of infectious complications.

Conclusions: This cohort confirms published data. PGNMID outcome is variable with nearly 50% of patients progressing to ESRD. A spontaneous partial response raises the matter of multiple diseases under PGNMID term. Nevertheless, nothing differentiated this case from the others. Even if early chemotherapy treatment may be valuable, there was no renal survey difference between chemotherapy and abstention group in this series, maybe because of the small sample size. Chemotherapy in transplanted patients may lead to infectious complications and Rituximab could be an alternative for them.

PUB227

Kidney Biopsy in aHUS May Be Misleading as to Final Renal Outcome Gianluigi Ardissino, Donata Cresseri, Francesca Tel, Michela Perrone, Stefania Salardi, Martina Sgarbanti, Silvana Tedeschi, Piergiorgio Messa. *Fondazione IRCCS Ca' Granda Osp. Maggiore Policlinico, Milano, Italy.*

Background: Kidney biopsy (KB) is an important tool for diagnosis, staging and defining disease prognosis but in thrombotic microangiopathies (TMA) but in many centers (particularly in pediatrics) the diagnostic process relies upon lab findings, only.

Methods: Herein we describe 2 patients (pt) with aHUS in which KB was performed and the results, as to opportunity of renal recovery, were strikingly different compared to the ultimate (favorable) outcome obtained.

Results: A 42 yo woman was diagnosed aHUS 58 days (d) after delivery. Firstly addressed to plasmaexchange (PEX) the pt started Eculizumab (E) while on dialysis 18 d after diagnosis. TMA promptly improved and 3 mutation were detected on complement regulatory genes (CFH,CFI,THBD). KB performed for the persisting anuria on d 28 showed:diffuse thickening and reduplication of capillary walls, severely ischemic glomerular tuft and marked vascular intimal thickening. Nevertheless, E was continued, the pt was exposed to last dialysis on d 35, sCr peaked to 9.1 mg/dL, reached the nadir of 1.4 mg/dL 11 months later and so far it remains stable after 5 years of observation. A 28 yo girl was diagnosed aHUS following few weeks of generalized malaise. The pt was first addressed to PEX but the disease rapidly progressed to a peak sCr of 9.4 mg/dL. E was started on d 8 and KB was performed for the persistent anuria, on day 17 with the following findings: diffuse ischemic and segmental sclerotic glomerular lesions associated with vascular intimal fibrosis and lumen reduction. No mutation, nor AntiCFHAb, were detected. Renal function slowly improved and the patient remained dialysis dependent for 6.5 months, the nadir of sCr (1.3) was reached 3.1 yrs later and now has a stable renal function (sCr 1.3) after 3.6 yrs.

Conclusions: The presented observations rise the issue that KB in TMAs may not be informative and sometimes is frankly misleading for the decision making process on whether to address/continue complement inhibition. In our experience E is worth being tried anyhow as long as TMA is ongoing.

PUB228

Unique Case of Renal Amyloidosis: Leukocyte Chemotactic Factor 2 (Lect2) Deepti D. Torri, James J. Wheeler. *Park Nicollet Health System, St. Louis Park, MN.*

Background: The LECT2 associated renal amyloidosis is a recently recognized and unique clinical entity that primarily involves the kidneys, liver, spleen and adrenal gland. The most clinically significant feature is the slow progressive renal failure with an ethnic predominance in Mexican Americans or Middle Easterns.

Methods: A 68-year-old Mexican female presented to urgent care with throbbing headaches for the past two weeks. Her exam was significant for lower extremity pitting edema and hypertensive urgency, BP of 182/112. Her laboratory data revealed serum creatinine (Scr) of 4.2, with no prior baseline serum creatinine available for comparison. She was then seen in the nephrology clinic for evaluation of renal failure, volume overload and uncontrolled hypertension. Her additional laboratory testing,showed a spot urine total protein to creatinine ratio (TP/CR) of 8 gm. Serological workup was negative. She then underwent kidney biopsy that showed renal amyloidosis with marked diffuse involvement of glomeruli, interstitium and vessels. Liquid chromatography tandem mass spectrometry was done, which detected peptide profile consistent with LECT2. Her ultrasound of abdomen showed no splenomegaly or hepatomegaly and her echocardiography showed normal ejection fraction of 60%. She had no other organ involvement. Given her uremic symptoms and volume overload status she was initiated on dialysis.

Conclusions: LECT-2 associated renal amyloidosis represents a unique and perhaps not uncommon disease, especially in Mexican Americans.The pathogenesis and prognosis remain to be determined.The primary involvement is the kidneys. It typically does not involve the heart or the bone marrow. Liver involvement is typically isolated and, thus, does not likely occur in conjunction with kidney involvement. There is no treatment per se for renal LECT2 amyloidosis. The management is a kidney transplant or initiation of dialysis if they develop end stage renal failure.

PUB229

Efficacy of Steroid Monotherapy for Pure Membranous Lupus Nephritis Frank Ward, Mohammad Saad Alkhowaiter, Joanne M. Bargman. *Nephrology, United Health Network, Toronto, ON, Canada.*

Background: The benefit of combination immunosuppressive therapy over steroid monotherapy in pure membranous lupus nephritis (MLN) is unclear. Steroid monotherapy could reduce unnecessary exposure to additional immunosuppressive agents. We reviewed patient characteristics and outcomes in pure MLN at our institute in those treated with steroid monotherapy or combination therapy.

Methods: In a retrospective, observational cohort study we identified all patients with biopsy-proven pure MLN (ISN/RPS class V) treated since 1990. Inclusion criteria were 17 years or older, baseline proteinuria of at least 2g/day and minimum follow-up of 2 years. Combination therapy consisted of corticosteroids and at least one other agent. Outcomes were complete remission (CR), partial remission (PR) or no response based on serial proteinuria measurement. Categorical data were analysed by Fisher's Exact test and continuous data by Student's t-test.

Results: Steroid monotherapy and combination therapy groups were similar in terms of gender, age, duration of SLE, initial serum albumin and proteinuria levels, proportion of sub-nephrotic patients, estimated GFR, C3/C4/dsDNA titres, use of renin-angiotensin blockade and initial prednisone dosing. Combination therapy patients were more likely to have had extra-renal manifestations (100% vs. 40%, p=0.02). CR or PR was achieved in all steroid monotherapy patients and 88% of combination therapy patients. Time to remission (CR or PR) was significantly shorter in the steroid monotherapy group (6.4 months vs. 27.7 months, p=0.007). There was a non-significant trend towards a higher relapse rate in steroid monotherapy treated patients (60% vs 25%, p=0.26). Follow-up duration was similar between groups (mean 79.4 months vs. 60.7 months, p=0.44) and estimated GFR did not differ at latest follow-up (111ml/min/1.73m^2 vs. 112ml/min/1.73m^2, p=0.92).

Conclusions: Steroid monotherapy appears to be efficacious in pure MLN, and may be an appropriate first-line treatment in renal-limited disease. The relapse rate may be higher than that observed with combination therapy. Although limited by study design and sample size, these findings warrant further investigation by a larger, prospective, randomized clinic trial.

PUB230

Risk Factors for Renal Scarring in Children with Myelomeningocele Fatma Lale Sever, Yesim Kucukkagnici, Nur Canpolat, Salim Caliskan. *Pediatric Nephrology, Istanbul Univ, Cerrahpasa Medical Faculty, Istanbul, Turkey.*

Background: Most of children with myelomeningocele have neurogenic bladder. Bladder dysfunction predisposes patients to urinary tract infections, renal scarring and renal failure. We aimed to evaluate risk factors for renal scarring in these patients.

Methods: This single center study involves 53 children with neurogenic bladder due to myelomeningocele (28 male; mean presentation age 18±19 months; current age 7.0±3.6 years), followed-up at least for one year after urodynamic testing. Anthropometric indices, spinal lesion levels, shunt status, ambulatory ability, urinary tract infection (UTI), ultrasound and urodynamic parameters, eGFR and serum cystatin-C levels were recorded. 47 patients (89%) were performing clean intermittent catheterization (CIC). Patients applying at least >75% of CIC suggestions were defined as "compliant". Low bladder capacity was defined as<65% of expected volume by urodynamic test. Renal scarring was diagnosed by current DMSA scans.

Results: The mean follow-up period was 66±34 months. 24 patients (45%) had VP shunt. Spinal lesion levels were as follows: lumbosacral region in 28, lumbar in 13, sacral in 7 and thoracolumbar in 5. DMSA scintigraphy revealed renal scarring in 9 (17%) patients, which was not associated with gender, presentation, CIC initiation and current age, level of spinal lesion, ambulatory disability or none of urodynamic parameters except low bladder capacity. Significant risk factors for renal scarring are shown in Table 1.There was no difference between eGFR values of the patients with or without scarring, whereas serum cystatin C levels differ significantly (0.80±0.2 vs 0.63±0.09 mg/dL, p=0.03).

	All patients n=53	Scarring (+) n=9	Scarring (-) n=44	p
No. of UTI between 0-2 years	0.9±1.4	3.0±1.9	0.6±1.0	0.007
UTI >3, n(%)	8 (15%)	4 (44%)	4 (9%)	0.008
VUR (+), n(%)	9 (17%)	5 (56%)	4 (9%)	0.001
CIC compliance, n(%)	38 (71%)	4 (44%)	34 (90%)	0.002
Low bladder capacity	10 (19%)	5 (56%)	5 (11%)	0.002

Conclusions: CIC compliance and avoidance of UTI may prevent renal scarring in patients with myelomeningocele.

PUB231

Unusal Cause for Headache in Lupus Nephritis Patient Viswanathan S. Iyer. *Nephrology, Pinnacle Health, Harrisburg, PA.*

Background: Therapy with mycophenolate is the norm in the care of lupus nephritis. Here we report an unusual complication of treatment with this drug.

Methods: Known lupus nephritis with class 4 disease-had worsening of renal functions and proteinuria after being stable for 3 years when mycophenolate mofetil was omitted for a month. Repeat kidney biopsy showed collapsing lesions and focal glomerulosclerosis consistent with a podocytopathy. Mycophenolate was restarted at her tolerated dose of 750 mg twice a day along with full dose of steroids. Up to six months into the therapy patient complained severe headache and a MRI done showed multiple bilateral brain masses with surrounding vasogenic edema, most extensive in the right temporal lobe (Fig 1). CSF was not obtained due to mass effects and uncal herniation on the right side. Neurosurgeon did an open brain biopsy that showed multiple organisms largely tachyzoites seen in H&E and immunohistochemistry for toxoplasma. HIV test was negative but her CD4 count was low at 175/cumm at that time. She was started on hemodialysis waiting for her PD catheter to mature. Anti-toxoplasmosis regimen chosen was sulfadiazine 1g four times a day,Dara prim 50 mg daily and leucovorin 20 mg daily. A repeat MRI was performed 2 weeks later as patient had persistent headache despite an initial improvement,showed a right posterior temporal mass and associated vasogenic edema worsened since the initial study when most other lesions seen initially had progressively decreased in size(Fig 2). Regimen was changed to Clindamycin 600 mg four times a day along with atovaquone 750 mg bid ,Dara prim and leucovorin. Repeat MRI after 4 weeks showed marked interim improvement in lesion in the right temporal lobe with minimal sequela of toxoplasmosis in other areas. A repeat CD4 was at 512 /cumm by then. She is now on atovaquone prophylaxis due to Bactrim allergy.

Conclusions: Non HIV toxoplasmosis itself is rare so also this infectious complication in the treatment of lupus with mycophenolate. Reactivation of dormant toxoplasmosis is a possibility and consideration need to be give for checking CD4 counts while on therapy with mycophenolate mofetil so that appropriate prophylaxis can be initiated.

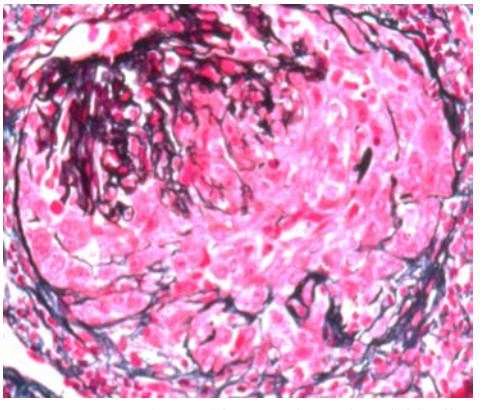
PUB232

Pauci Immune Glomerulonephritis a Case Series Giovanna Y. Arteaga Muller, Lilia Maria Rizo Topete, Allina Primavera Flores Mendoza, Elisa Maria Guerrero Gonzalez, Concepcion Sanchez Martinez, Jesus Cruz Valdez. *Nephrology, Univ Hospital José E. González of the Autonomous Univ of Nuevo León, Monterrey, Mexico.*

Background: ANCA associated vasculitis affects kidneys frequently more than half of the cases progress to ESRD with renal replacement therapy.

Methods: A retrospective observational study was made to describe pauci-immune glomerulonephritis diagnosed by kidney biopsy, from 2008 to 2015. Medical records were used to obtain demographic variables, clinical and paraclinical features of the patients.

Results: Ten patients were identified with crescent formation pauci-immune deposit glomerulonephritis,50% male with a median age of 35.5 years, 100% of patients presented malaise, microscopic hematuria and proteinuria, only 30% of proteinuria in nephrotic range,70% presented nephritic syndrome, 50% fever, 90% anemia, 40% leucocytosis, 30% alveolar hemorrhage, of histopathologic findings 80% crescent formation in more than 50% of glomeruli (Figure 1) all of then with progression to CKD.In regard to clinical diagnosis; the mean time of disease development at the time of histopathologic diagnosis was 5 months, 8 patients met criteria por microscopic polyangiitis of which 62.5% were male, 87.5% required chronic HD,75% nephritic syndrome,2 patients adenocarcinoma,2 cases overlap rheumatoid arthritis and systemic sclerosis, of the 10 patients only 1 was ANCA negative. Of the patients with polyangiitis with granulomatosis diagnosis 100% presented leucocytosis and proteinuria in nephrotic range, only 50% nephritic syndrome.



Conclusions: In our case series pauci-immune glomerulonephritis affected males and females equally, a larger number of males was affected with microscopic polyangiitis. It is relevant to identifyy clinical features of this disease to achieve early diagnosis. In our series kidney survival was only modified if the number of crescent formations were less than 50% in kidney biopsy.

PUB233

Determinants of Urinary Soluble CD163 over Time in an Intensive Care Cohort Donal J. Sexton,[1] Mark Canney,[1] Eoin Joseph Cotter,[3] Peter P. Doran,[2] Patrick T. Murray,[2] Mark Alan Little.[1] *[1]Trinity Health Kidney Centre, Trinity College Dublin, Dublin, Ireland; [2]Dept of Medicine, Univ College Dublin, Dublin, Ireland; [3]Royal College of Surgeons, Dublin, Ireland.*

Background: Urinary soluble CD163 (UsCD163) holds promise in the management of patients with ANCA associated vasculitis and possibly other forms of glomerulonephritis. Little is known about the determinants of urinary UsCD163 in a critical care setting.

Methods: A consecutive sample of intensive care patients (N=438), investigating UsCD163 on repeated testing and its association with clinical parameters. Analysis was

performed using generalised linear mixed-effects models. Individual trajectories were drawn to map discernible longitudinal clusters, which identified 5(Fig 1). Cluster A was the largest. Univariate associations between time-invariant and time-varying covariates with UsCD163 were explored. 44 clinical parameters were investigated. Time-varying covariates: serum creatinine, sepsis and urinary albumin excretion.

Results: Mean (sd) age 61.9(16)yrs, 66% were male and 222 (38%) had AKI by KDIGO criteria. Median UsCD163 level was 0.06 ng/mmol (IQR 0.02-0.13, cutoff 0.3, Fig 2). Clusters A (N=224) and B (N=30) were characterised by a consistently low UsCD163 value throughout the observation period. Although a number of clinical covariates were associated with cluster membership on univariate analysis, with multiple comparison adjustment only one association remained: RRT appeared more likely in cluster C vs. A. In the mixed effects models (cluster A & B), UsCD163 levels were not associated with any of the clinical parameters studied.

Conclusions: In the setting of critical illness, UsCD163 is generally low with sporadic high values that fall into several patterns. These do not associate with any specific clinical parameters, in particular sepsis or AKI, and may be a reflection of unquantified parameters such as macroscopic haematuria.

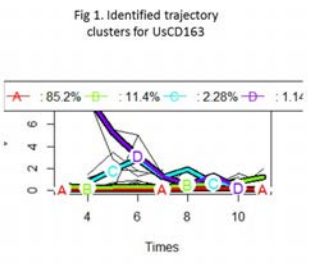


Fig 1. Identified trajectory clusters for UsCD163

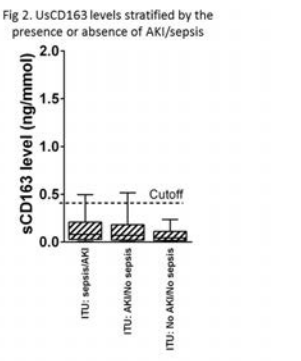


Fig 2. UsCD163 levels stratified by the presence or absence of AKI/sepsis

PUB234

Complications of Percutaneous Kidney Biopsies in Patients with or without Renal Failure: A Single Center Experience Andrea Guarnieri, Serena Bainotti, Ariaudo Claudia, Elisabetta Moggia, Carlo Ferrando, Paola Inguaggiato, Alfonso Pacitti. *Nephrology and Dialysis, S. Croce-Carle Hospital, Cuneo, Italy.*

Background: Percutaneous renal biopsy (PRB) of native kidneys is an essential tool in the diagnosis and management of renal diseases. Reduced GFR is one of the leading risk factors for complications. Aim of the study is to compare the incidence of complications in two groups of patients with different GFR.

Methods: PRB of native kidneys were performed in 188 adult patients from january 2010 through dicember 2015 in our unit. Renal biopsies were performed by two nephrologists usign real-time ultrasound with a 18-gauge automated biopsy needle. We compared 95 patients with eGFR > 60 mL/min (Group 1) with 93 patients with eGFR < 30 mL/min (Group 2).

eGFR (CKD-EPI) (mL/min/1.73mq)	Group 1 > 60	Group 2 < 30	p (t-test)
Number of patients	95	93	
Age, years	47 ± 16	64 ± 13	< 0,000
eGFR, mL/min/1.73mq	94,8 ± 21,95	15 ± 6,92	< 0,000
SCr, mg/dL	0,87 ± 0,22	4,2 ± 1,89	< 0,000
BP Systolic, mmHg	129 ± 16,2	136 ± 16,9	< 0,05
Pre-PRB Hb, g/dL	12,8 ± 1,9	10,1 ± 1,4	< 0,000
Bleeding Time, min	4,4 ± 1,7	4,8 ± 1,9	> 0,05
Kidney Length, mm	110 ± 14	107 ± 15	> 0,05
Number of glomeruli	19 ± 12	15 ± 11	> 0,05

We evaluated: 1. Minor complications: gross ematuria with rapid resolution, hemoglobin drop 1-2 g/dL, perinephric hematoma but spontaneously resolving. 2. Major complications: persistent gross hematuria, hemoglobin drop > 2 g/dL, hematoma requiring blood transfusion, loss of kidney, death.

Results: Adequate material for diagnosis was obtained in 98,9% of biopsies. Minor complications were observed in 34 patients of Group 1 (36%) and in 25 patients of Group 2 (27%). Most prevalent complication was a small symptomless hematoma assessed by ultrasound. Major complications were 2 in Group 1 (2 Hb drop > 2 g/dL) and 4 in Group 2 (3 Hb drop > 2 g/dL with one requiring blood transfusion and one loss of kidney). No statistical difference between groups was observed (Chi-square test).

Conclusions: Percutaneous renal biopsy is a low-risk procedure. In our experience reduced eGFR in not associated with an increased risk of minor and major complications.

Funding: Government Support - Non-U.S.

PUB235

Thrombotic Microangiopathy, the Broad Clinical Spectrum of the Same Lesion Lida Maria Rodas Marin,[1] Jessica Ugalde-Altamirano,[1] Luis F. Quintana,[1] Manel Sole,[2] Adriana Garcia,[2] Esteban Poch,[1] Josep Miquel Blasco Pelicano.[1] *[1]Nephrology and Renal Transplant, Hospital Clinic, Barcelona, Spain; [2]Pathology, Hospital Clinic, Barcelona, Spain.*

Background: Thrombotic microangiopathy (TMA) is a common histological lesion to multiple clinical diseases, which is characterized by the presence of endothelial cell injury and microvascular thrombi.TMA should be suspected in front the presence of hemolytic microangiopathic anemia(HMA), thrombocytopenia and kidney injury.After a clinical suspicion or histological confirmation, a broad differential diagnosis is required.

Methods: We reviewed all the renal biopsies performed in Hospital Clínic of Barcelona, in the period 2005-2015.We present the analysis of demographic, clinical and histological data of cases of TMA was identified.

Results: TMA was detected in 87 renal biopsies of 71 patients during a 10 year period: 24 patients with TMA in native kidneys,13 women and 11 men with a mean age of 46.79±15.56 years. At the onset of the disease all the patients presented signs HMA (Hb:92.08±25.61 g/L;LDH:959±709U/L) and 62% with thrombocytopenia (Platelets 128±65 10^9/L).Renal manifestations AKIN3 (Creatinine 7.33±5.57mg/dL) and proteinuria (2643±2120mg/g) in all the patients.Histological lesions included vascular involvement in 95.83% and glomerular changes in 87.5%.Transplanted kidneys:47 patients that presented histological TMA with 63 biopsies:16 women and 31 men, with a mean age of 43.66+15years.The main causes of ESRD were: 25% congenital diseases, 16% aHUS, 10% IgAnephropathy and 10% diabetic nephropathy. The onset of the disease was detected after a graft biopsy due to AKI. At that point, despite 60% of the patients manifested anemia (Hb<12 g/L),21% of the patients showed signs of hemolysis and 19% thrombocytopenia. All the biopsies demonstrated acute vascular and glomerular TMA changes (only 48% with chronic changes).

Conclusions: In our series we demonstrate the variability of clinical entities associated with TMA, especially in renal transplant patients were the renal biopsy is necessary to ensure a correct etiological diagnosis. We also observed that TMA over kidney grafts manifested with HMA and thrombocytopenia in less than 21% of the patients, complicating the clinical suspicion.

PUB236

miRNAs as Biomarkers of Kidney Damage in Patients with Systemic Lupus Erythematosus Gustavo Aroca Martinez,[1,2,3] Elkin Navarro,[1] Lisandro Pacheco,[1] Lisneth Almendrales,[2] Andres A. Cadena,[1,2] Antonio Iglesias Gamarra.[4] *[1]Nephrology, Univ Simon Bolivar, Barranquilla, Atlantico, Colombia; [2]Nephrology, Clin de la Costa, Atlantico, Colombia; [3]Nephrology, Uninorte, Barranquilla, Atlantico, Colombia; [4]Rheumatology, Univ Nacional, Bogota, Cundinamarca, Colombia.*

Background: Renal involvement is a severe manifestations of systemic lupus erythematosus (SLE). Is priority the development of diagnostic tests for kidney disease in patients with SLE through non-invasive methods, due to the date this is done by kidney biopsy, it presents complications. The microRNA's (miRNA's) are found in tissues with variable expression, and changes in expression are related to pathological processes of various diseases. The aim of this study was to identify differentially expressed miRNAs in patients with lupus nephritis (LN) potentially allow the diagnosis of renal damage in patients with SLE.

Methods: A case-control and cross-sectional study, in which we characterized the differential expression profiles of miRNAs among 14 patients with LN Class II: 4 patients, LN class III: 4 patients, LN IV: 6 patients) compared with 8 patients with LES without nephritis or with 8 healthy control individuals, by sequencing by Illumina. We validated by qPCR diagnosis by renal biopsy in 180 samples using a group of miRNAs as biomarkers.

Results: We found 89 serum miRNAs that showed statistically significant changes in the proportion of their expression, comparing patients with LN individuals with healthy controls. We find the contrast with the results of the diagnosis by renal biopsy miRNAs miR-221-5p, miR-380-3p, miR-556-5p, miR-758-3p and miR-3074-3p sensitivity averaged 97% , specificity 70.3%, positive predictive value 82.5%, negative predictive value 96% and 87.9% efficiency diagnosed.

Conclusions: Whereupon we propose that these microRNAs are potential molecular biomarkers of kidney damage in patients with SLE and request the patenting of the potential usefulness of these microRNAs diagnosed. The miR-221-5p microRNAs, miR-380-3p, miR-556-5p, miR-758-3p and miR-3074-3p are potential diagnostic biomarkers of LN in patients with systemic SLE and the differential expression pattern of microRNAs have significant implications for the pathophysiology of renal damage in LN patients.

Funding: Other NIH Support - COLCIENCIAS

PUB237

Primary versus Secondary Recurrent Membranous Glomerulonephritis in Simultaneous Liver-Kidney Transplantation after MRSA Infection: A Diagnostic Challenge Ekamol Tantisattamo, Dilip Samarapungavan, Ping L. Zhang. *Oakland Univ William Beaumont School of Medicine, William Beaumont Hospital, MI.*

Background: Anti-PLA2R Ab and IgG4 are still useful tools in differentiating primary from secondary membranous glomerulonephritis(MGN) in kidney transplantation.

Methods: A 50-year-old man with primary MGN 7 years earlier. Urinary protein/creatinine ratio(UPCR) was 10.2 g/g of Cr. He developed ESRD. He was then diagnosed with HBV infection. Tenofovir was initiated. Despite viral load became undetectable; he had ESLD from HBV cirrhosis. He underwent SLK 6 months later. He had delayed renal allograft function. Biopsy performed 3 weeks post-transplant revealed borderline changes for acute cellular rejection. He had MRSA bacteremia concomitant with proteinuria of 8 g from 24-h urine collection. After the bacteremia resolved, the second biopsy was performed and revealed stage II MGN without features of secondary MGN. HBV viral load was undetectable. Serum anti-PLA2R Ab was undetectable. Serum IgG3 and %IgG3, but not IgG4 were elevated. Recurrent secondary MGN was diagnosed. UPCR spontaneously decreased to 1.1 g/g of Cr without intensified immunosuppression or ACEI/ARB(Figure 1).

Results: Our patient recovered from bacteremia before the biopsy was performed. Infection could trigger secondary MGN, and its resolution lead to decreased proteinuria. This is quite similar to the pathogenesis of *de novo* primary MGN which is not related to anti-PLA2R Ab or co-localized IgG4.

Conclusions: Differentiating primary from secondary MGN particularly in patients with underlying diseases commonly associated with secondary MGN(HBV) is challenging. Further studies should elucidate diagnostic and prognostic utilities of anti-PLA2R Ab and IgG4 subclass in differentiating primary vs. secondary MGN in transplantation with co-existing conditions and infection associated with secondary MGN.

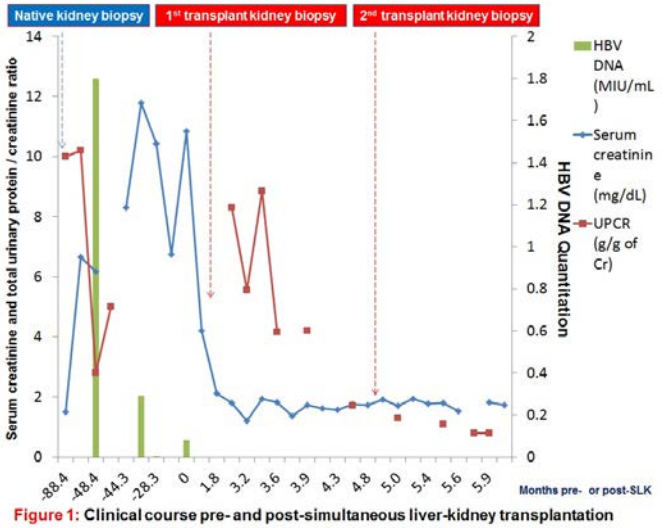


Figure 1: Clinical course pre- and post-simultaneous liver-kidney transplantation

PUB238

Urinary Findings Does Not Reflect Kidney Status in Chronic Glomerulonephritis after Steroid Therapy Byoung-Soo Cho,[1] Hyaejin Yun,[1] Sung Min Jung,[2] Hyun Soon Lee.[3] *[1]MIRAE ING Kidney center, Seoul, Korea; [2]EWha Women's Medical College, Seoul, Korea; [3]Korea Pathology Lab, Seoul.*

Background: Routine urinalysis, especially hematuria and proteinuria, has long been used as the most important laboratory tools in the diagnosis of glomerulonephritis and also widely adopted as a screening tool for kidney problems at school screening or health checking program. Recently other newly developed markers for kidney injury, such as cystatin-c, KIM-1, L-FABP, NGAL etc., were developed but not routinely used because lack of accumulated convincing data as yet.

Methods: We performed follow up kidney biopsy who showed normal urinalysis and serum cystatin-c for more than 3 months after steroid therapy to check the kidney status in 20 patients with chronic GN. Of the 20 patients, ten were IgAN and others were 2 allergic purpura nephritis, 2 FSGS, 2 MGN, 2 diffuse mesangial proliferative GN, nonspecific glomerulonephritis, and membranoproliferative GN. All 20 patients took long term steroid therapy more than 6 months. Mean age was 30.7 years old. Mean follow up biopsy interval was 13.6 months. All kidney biopsy were performed at the OPD level without admission. We used ACE-Cut disposable biopsy needle under the ultrasound guide(LOGIQ E9).

Results: All 20 cases showed abnormal urinalysis such as persistent hematuria, persistent proteinuria or associated with hematuria and proteinuria at initial kidney biopsy, and showed persistent normal urinalysis findings include hematuria and proteinuria more than 3 months at the time of follow up renal biopsy. However only 3 cases showed normal renal pathologies at the time of follow up biopsy. Seventeen cases showed persistent original diseases although slight to moderate degree pathological improvement. Three pathologically improved cases were 2 MGN and one focal nonspecific glomerulonephritis. These 3 cases did not show any sclerotic lesions at the initial renal biopsy, and age were 1, 23 and 28 years old.

Conclusions: Any one who showed segmental or global sclerosis, when associated with moderate to severe tubular atrophy and interstitial fibrosis at initial kidney biopsy, follow up kidney biopsy is mandatory even showed persistent normal urinalysis and lab findings before finishing steroid therapy.

PUB239

Clinical and Histological Features of Patients with Membranoproliferative Glomerulonephritis Classified by Immunofluorescence Findings Cristiane B. Dias,[1] Lectícia Jorge,[1] Leonardo Abreu Testagrossa,[2] Denise M. Malheiros,[2] Viktoria Woronik.[1] *[1]Nefrologia, Hospital das Clínicas de São Paulo, São Paulo, São Paulo, Brazil; [2]Patologia, Hospital das Clínicas de São Paulo, São Paulo, São Paulo, Brazil.*

Background: A new classification system for membranoproliferative glomerulonephritis (MPGN) according to immunofluorescence (IF) has been proposed. The aim of this study was to evaluate the clinical and biochemical characteristics of patients with MPGN grouped by IF analysis.

Methods: This was a retrospective study of patients with renal biopsy-proven MPGN unrelated to systemic lupus erythematosus (SLE), diagnosed between 1999 and 2014.

Results: We evaluated 92 patients, which were divided into three groups determined by immunofluorescence: immunoglobulin positive; C3 positive only; and negative IF. Data on diagnosis are in table 1.

Parameter	Immunoglobulin positive (n = 73)	C3 positive (n = 9)	IF negative (n =10)	P-value
Age (years)	44.9 ± 14.6	44.6 ± 20.0	43.8 ± 15.0	ns
Male gender, n (%)	45 (61.6)	6 (66.6)	7 (70.0)	ns
Creatinine (mg/dL)	1.8 (1.1–3.6)	1.8 (1.3–5.4)	2.1 (1.6–5.1)	ns
GFR (mL/min/1.73m^2)	41.0 (20.0–65.0)	42.0 (15.5–50.0)	39.5 (11.2–53.5)	ns
Proteinuria (g/day)	6.3 ± 3.4	6.0 ± 3.0	5.5 ± 3.5	ns
Serum albumin (g/dL)	2.5 ± 0.6	2.5 ± 0.3	2.7 ± 0.5	ns
Low C3, n (%)	35 (52.2)	4 (44.4)	5 (50.0)	ns
Low C4, n (%)	23 (34.3)	2 (22.2)	4 (40.0)	ns
Low C3 and C4, n (%)	18 (26.8)	2 (22.2)	3 (30.0)	ns
Arterial hypertension, n (%)	41 (56.0)	2 (22.2)	3 (30.0)	ns
Hematuria, n (%)	51 (70.0)	5 (55.5)	10 (100.0)	ns

Infection was the most common in the three groups. Hepatitis C virus (14 patients) and schistosomiasis (7 patients) located mainly in immunoglobulin positive groups. Eleven patients, despite having been diagnosed with infectious disease, autoimmune disease, or monoclonal gammopathy, showed no immunoglobulin deposition on immunofluorescence.

Conclusions: The new classification enlightens a systematic approach to evaluation of secondary causes.

PUB240

Surgical and Oncologic Outcomes of Small Renal Tumors Treated with Nephron-Sparing Surgeries - Correlation with Pathology of the Tumor-Parenchymal Interface and Status of the Surgical Margin Maria M. Picken,[1] Gopal N. Gupta.[2] *[1]Pathology, Loyola Univ Chicago, Maywood, IL; [2]Urology, Loyola Univ Chicago, Maywood, IL.*

Background: Approaches to nephron-sparing surgeries (NSS) of renal lesions include partial nephrectomy (PN) and tumor enucleation (TE). Our objective was to examine the pathology of the pseudocapsule and status of the surgical margin in small renal masses treated by NSS, and to correlate these findings with the surgical and oncological outcomes.

Methods: All consecutive renal TE and PN cases obtained between Jan 2012-Dec 2014, that also had available clinical follow-up, were included; pathologic features and clinical data were reviewed and analyzed.

Results: A total of 117 NSS specimens (59 EN, 58 PN) were reviewed. Clear cell renal cell carcinomas and paraganglioma had the thickest pseudocapsules (0.36 mm), while angiomyolipomas lacked a well-defined pseudocapsule. Other tumors were intermediate in their characteristics. The positive margin rate for TE and PN was 17.2% and 0%, respectively. Compared to PN, TE involved a significantly shorter procedure time, less blood loss and fewer post-op complications.

	TE	PN	p-value
# of patients	59	58	
mean age (range)	57 yrs (31-80)	62 (24-83)	0.781
M:F (ratio)	35:24 (1.5:1)	29:29 (1:1)	0.356
# of NSS without hilar clamp (%)	31 (52.5%)	0(0%)	<0.001
average clamping time	25 min	25 min	1
Procedure time	181 min	241 min	<0.001
Blood loss during NSS	180 ml	280 ml	<0.001
Average hospital stay	1.71 days	2.67 days	<0.001
Patients with post-op complications (%)	7/59 (12%)	15/58 (26%)	0.062
Patients re-admission within 1 month (%)	0 (0%)	7 (12.1%)	0.006
Median follow up - months (range)	22 (11-40)	19 (8-42)	
Tumor recurrence	0	0	

None of the patients from either group was found to have a local recurrence after follow-up imaging.

Conclusions: Although positive surgical margins were encountered in some TEs, local tumor recurrence was comparable to PN. Thus, TE with maximal nephron sparing, is a reasonable choice for pT1 renal tumors, especially for those without a prominent infiltrative growth pattern.

Funding: Clinical Revenue Support

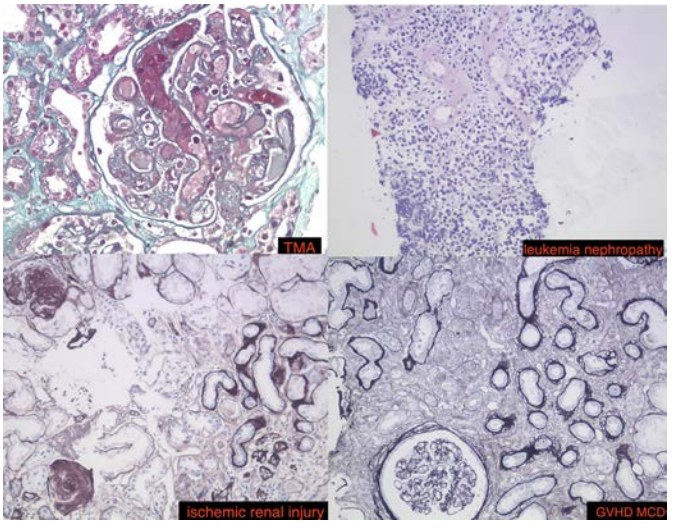
PUB241

Analysis the Clinical and Pathology of Renal Injury in Patients Received Hematopoietic Stem Cell Transplantation Jiaxuan Lv. *Beijing Tsinghua Changgung Hospital, Medical Center, Tsinghua Univ, Beijing, China.*

Background: The rate of acute and chronic renal injury is very high in patients received hematopoietic stem cell transplantation(HSCT),but not enough studies about it.Analyzing the reason of renal injury in these patients can improve the renal damage and improve the prospects of survival.

Methods: Clinical, laboratory data, treatment issue and renal pathology results of eight patients with renal injury after HSCT from July.2015 to May.2016 were retrospectively analyzed.

Results: The clinical manifestation of renal injury after HSCT showed as proteinuria, hypertension and renal function damage. The pathological damages involved in glomerulus, renal tubular interstitial and vessel, which is related with bone marrow graft versus host disease, drug damage and thrombotic microangiopathy (TMA).



Conclusions: Renal injury after HSCT varied in different kinds, renal biopsy is important for diagnosis and treatment. According to the renal pathology, early intervention can relieve kidney injury.

PUB242

Clinical and Pathological Features Analysis of Collagen Type III Glomerualopathy Shao Min Gong, Hong Liu, Weili Luo, Xiaoqiang Ding. *Nephrology, Zhongshan Hospital,Fudan Univ, Shanghai, China.*

Background: Collagen type III glomerualopathy, characterized with collagen Type III deposits in mesangial and subendothelia area, is a kind of relatively rare autosomal recessive glomerular disease with few reports of sporadic cases. The specific treatment remains unknown due to the mechanism of this disease has not been elucidated. We reported four sporadic cases in adult without extra-renal organ involvement.

Methods: We searched the database of patients receiving renal biopsy during Jan.2007 to Aug.2015 in Zhongshan Hospital,Fudan University. The clinical and pathological characteristics of 4 cases who were proven as collagen type III glomerualopathy were analyzed.

Results: Four cases comprise of 2 males and 2 females aging 45.5±10.7 years old, none of the cases were reported to have any familial history of kidney diseases. 3 cases complicated with hypertension and none of the cases was found to have extra-renal organ involvement. The quantitative of 24-hour proteinuria was 3.8±3.6g(ranging from 0.32 to 7.56g), the eGFR was 27.1±39.2ml/min/1.73m^2(ranging from 10.3-81.3 ml/min/1.73m^2, calculated by MDRD formula). The light microscopy results of each case were membranoproliferative glomerulonephritis, focal segmental proliferative and sclerosis glomerulonephritis, IgA nephropathy, nodular glomerulosclerosis, respectively. Collagen type III was detected by immunohistochemical test in four case. One case with minor declined eGFR and mild proteinuria remained stable after recieving conservative therapy. 2 cases had improvement in renal function and partial remission of proteinuria after recieving glucocorticoids and immunosuppressive agents while 1 case with severe renal impairment onset developed into end stage renal disease and received hemodialysis.

Conclusions: The sporadic cases of collagen type III glomerualopathy in adults may be underestimated. The majority of cases presented with porteinuria and multiple light microscope pathological type. Immunohistochemical analysis and electronic microscope examination are essential to confirm the diagnosis, which should not be neglected to avoid missing diagnosis this rare disease.

Funding: Government Support - Non-U.S.

PUB243

The Significance of Cryoglobulin Deposition Discovered by Renal Biopsy in Patients with Lupus Nephritis Companying Cryoglobulinaemia Wen Wen, Yuehong Li. *Nephrology, Beijing Tsinghua Changgung Hospital, Beijing, China.*

Background: To investigate the relationship between cryoglobulin deposition and manifestations of patients diagnosed as lupus nephritis and cryoglobulinaemia.

Methods: Retrospectively collected the clinical materials of patients diagnosed as lupus nephritis companying cryoglobulinaemia with or without cryoglobulin deposition from October 2012 to May 2014. Their clinical data, renal pathological features and ultrastructural morphology were analysed. Statistical analyses were performed using SPSS software (version 17.0). The Mann-Whitney U test was used for the comparison of continuous variables; the Fisher exact tests were used for the comparison of proportions. A value of $P < 0.05$ indicated statistical significance.

Results: There were 12 patients suffering from lupus nephritis and cryoglobulinaemia. Eight were female, and 4 were male. Their mean age at the time of renal biopsy was 37.1±10.6 years old. The classification of lupus nephritis of them ranged from III to V. Seven of them had depositions of cryoglobulin in renal biopsy. The occurrence of acute kidney injury (AKI), IgA and complement C4 were higher in patients with cryoglobulin deposition than those without. The improvements of parameters of renal damage were fewer in patients with cryoglobulin deposition after 3 and 6 months.

Conclusions: In patients with lupus nephritis and cryoglobulinaemia, cryoglobulin deposition in kidney may increase the risk of AKI and impede the patients from recovery.

Funding: Private Foundation Support

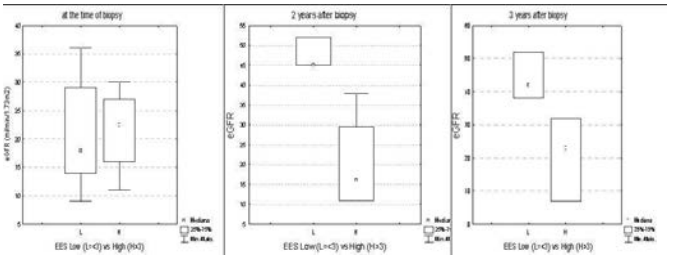
PUB244

ETAR Expression in Kidney Biopsies of Patients with ANCA-Associated Glomerulonephritis Predicts GFR Decline: Preliminary Results Olumide Olatubosun Rowaiye,[1] Piotr Donizy,[2] Mariusz Kusztal,[1] Miroslaw Banasik,[1] Magdalena Krajewska,[1] Agnieszka Halon,[2] Marian Klinger.[1] *[1]Nephrology and Transplantation Medicine, Wroclaw Medical Univ, Wroclaw, Poland; [2]Pathomorphology, Wroclaw Medical Univ, Wroclaw, Poland.*

Background: ANCA-associated glomerulonephritis (AAGN) is often characterized by a decline in renal function. Endothelin has been implicated in renal cell injury, inflammation and fibrosis. We hypothesized that degree of endothelin-1 type A receptor (ETAR) expression in renal specimen can predict decline in eGFR in AAGN patients.

Methods: Immunohistochemical (IH) evaluation for ETAR expression was performed on the renal biopsies of AAGN using anti-ETAR antibody (rabbit polyclonal, ABCAM, USA). Control reactions were performed on 5 normal kidneys. A composite ETAR expression score [EES] was calculated for each biopsy based on the intensity of expression (0 for negative, 3 for high) using the formula: g (0-3) + v (0-3) + t (0-3) + i (0-3).

Results: Cohort consisted of 5 patients with PR3-ANCA, 5 with MPO-ANCA and 1 ANCA-negative (7M, 4F). Histopathological class: 3 crescentic, 7 mixed, 1 sclerotic. Tubular epithelium revealed diffuse cytoplasmic pattern of ETAR expression in all analyzed patients. Renal vessels were negative for ETAR. In 3 patients immunoreativity of ETAR was observed only in glomerular crescents. Composite EES was in range 1-6 for all patients. In general patients with higher composite EES (>3) showed a decline in eGFR when compared to lower EES (≤3) after 24 (20 vs 47ml/min; p<0.05) and 36 months (20 vs 44ml/min;p<0.05) irrespective of histopathological class.



Conclusions: ETAR expression in renal biopsy seems to be useful in predicting decline in renal function in AAGN, irrespective of histopathological class, in long term. Further studies will elucidate relevance of ETAR expression and its antibody presence in patients with AAGN.

Funding: Government Support - Non-U.S.

PUB245

Glomerulopathies Secondary to *Schistosoma mansoni*: Revisiting a Forgotten Enemy Precil Diego Miranda de Menezes Neves,[1] Ramaiane Aparecida Bridi,[1] Bernardo V. Reichert,[1] Lectícia Jorge,[1] Luis Yu,[1] Viktoria Woronik,[1] Leonardo Abreu Testagrossa,[2] Denise M. Malheiros,[2] Cristiane B. Dias.[1] *[1]Nephrology Service, Univ of Sao Paulo School of Medicine, São Paulo, Brazil; [2]Pathology Div, Univ of Sao Paulo School of Medicine, São Paulo, Brazil.*

Background: Schistosomiasis mansoni is a parasitic disease caused by Schitosoma mansoni (SM). This is an endemic disease in some regions of Brazil. The kidney may be impaired, particularly in the form of glomerulopathies. We aim to make clinical and epidemiological characterization of patients with glomerulopathies secondary to SM.

Methods: Identification of cases of glomerulopathies secondary to SM in the period of 1992-2015. We revised their clinical, epidemiological and renal biopsy data.

Results: Of an initial casuistic of 21 patients, two of them were excluded due to neoplasia at the time of renal biopsy. Patients were predominantly male (79%), white (52%),mean-age 38.8±7,8 y.o. The diagnosis of SM was made through fecal analysis (94%), 64.7% had hepatosplenic disease. The most common clinical presentation was nephrotic syndrome (48%), hypertension was evidenced in 66% and 74% had hematuria. The mean of serum creatinine was 1.43±0,5mg/dL (CKD-EPI: 67.5±30ml/min/1,73m^2), mean 24h proteinuria: 6.9±3g, serum albumin: 2.1±0,7g/dL and low serum complement C3 and/or C4 in 48% of cases. The histological presentation more frequent was Membranoproliferative Glomerulonephritis (MPGN) 69%, followed by Focal Segmental Glomerulosclerosis (21%), Membranous Nephropathy (5%) and Focal Proliferative Glomerulonephritis (5%). In 60% of cases antimicrobial treatment wasn't effective to induce remission than immunossupressive therapy was required. Of these ones, 70% with diagnosis of MPGN. The follow-up was 70 (14-124) months, and at that time 26,3% of patients undergone dialysis and mortality rate was 10,5% due to non-related nephropathy causes.

Conclusions: The histological presentation as MPGN was associated with worst response to antimicrobial treatment, need for immunosuppressive treatment, higher rate of progression to end-stage renal disease/dialysis and higher mortality compared to other subtypes of glomerulopathies.

PUB246

Cohort of Native Kidney Percutaneous Biopsies in an Urban Center with a Majority of African American Patients Ravi K. Thimmisetty, Nashat Burhan Imran, Muhammad Omar Azam, Yahya M. Osman Malik. *Internal Medicine/Nephrology, Wayne State Univ, Detroit, MI.*

Background: The percutaneous biopsy of native kidneys can aid in: confirming a suspected diagnosis, anticipating recurrence post-transplant, prognosticating the kidney disease, or even deterring clinicians from committing to therapy in cases of advanced fibrosis. kidney biopsy may even alter the pre-biopsy proposed management. Indications for biopsy depends on the treating nephrologists but include: nephrotic syndrome, acute nephritic syndrome, and unexplained acute kidney injury. We are reporting our 5-year experience in an urban center with majority African American patients.

Methods: Epidemiological retrospective analysis, single-center, urban medical center with a predominant demographic of African Americans. Cohort: all non-cancer and non-transplant native kidney biopsies from February, 1st 2011 till June, 6th 2016. All biopsies were done in one center and under ultrasound guidance by either the nephrology service or interventional radiology.

Results: There was total of 561 biopsies in this time period. All transplant biopsies and onco-surgical biopsies were excluded. The final 143 biopsies were analyzed with the following findings: average age at the time of biopsy was 43.6 years (18-86), 49% male, 76.2% African Americans, average proteinuria 4.8 g/g, hypertension 76.2%. Unexplained acute kidney injury was the most common indication for biopsy (34%) followed by nephrotic syndrome (31%). Accurate pre-biopsy clinical diagnosis was accurate in 49% of the time. Focal segemental glomerulosclerosis (FSGS) and lupus nephritis classes were equally the most common diagnosis. Among African Americans, FSGS was incorrectly presumed in 53% of the cases and was not suspected in 65% of patients with histological evidence of FSGS.

Conclusions: Percutaneous native kidney biopsy in our urban center showed FSGS and lupus nephritis as the most common diagnosis. Presumption that African American patient would have FSGS was incorrect in more than half of the time and was not even suspected in 65% of the cases.

PUB247

Evaluation of microRNA Profiles in Patients with Autosomal Dominant Polycystic Kidney Disease Ismail Kocyigit,[1] Serpil Taheri,[2] Elif Funda Sener,[2] Eray Eroglu,[1] Fahir Ozturk,[1] Aydin Unal,[1] Gokmen Zararsiz,[3] Murat H. Sipahioglu,[1] Yusuf Ozkul,[2] Bulent Tokgoz,[1] Oktay Oymak,[1] Tevfik Ecder.[4] *[1]Nephrology, Erciyes Univ Medical Faculty, Kayseri, Turkey; [2]Medical Biology, Erciyes Univ Medical Faculty, Kayseri, Turkey; [3]Bioistatistics, Erciyes Univ Medical Faculty, Kayseri, Turkey; [4]Nephrology, Bilim Univ, Istanbul, Turkey.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is one of the progressive hereditary disorders. Biomarkers are needed to predict clinical course of the disease. In this study, we aimed to investigate the association of microRNAs (miRNAs) with the clinical course of ADPKD and to test the availability of miRNAs as a biomarker in ADPKD patients.

Methods: Eighty ADPKD patients (52 hypertensive, 28 normotensive) and 50 healthy subjects were enrolled to the study. Ambulatory blood pressure monitoring was performed. The expressions of miRNAs were determined by Biomark Real Time PCR system in the serum samples obtained from all study participants. oRNAs (miRNAs) with the clinical course of ADPKD and to test the availability of miRNAs as a biomarker in ADPKD patients.

Results: The mean age was 44.6±12.7 in the patient group, while it was 45.4±12.7 in the control group. Altered expression in 15 miRNAs was observed in the ADPKD patients with hypertension compared to those of the healthy controls. When hypertensive ADPKD patients were compared with normotensive ADPKD patients, we determined altered expressions in 4 miRNAs. One of these was upregulated (miR-3907), while the others were down-regulated (miR-4687-5p, let-7c-5p, let-7d-3p). Also, miR-1587, miR-3907, miR-92a-3p and miR-3911 showed dynamic changes which correlated with chronic kidney disease stages in ADPKD patients.

Conclusions: We found an association of upregulation of miR-3907 and clinical course of ADPKD. We plan to assess prognostic potential of this miRNA in a follow-up analysis.

PUB248

Positive Predictive Values of International Classification of Diseases, 10th Revision Coding Algorithms to Identify Patients with Autosomal Dominant Polycystic Kidney Disease Vinusha Kalatharan,[1] York P. Pei,[4] Kristin Clemens,[1] Rebecca K. Mctavish,[1] Stephanie Dixon,[1,3] Matthew Rochon,[5] Danielle Marie Nash,[3] Arsh Jain,[2] Sisira Sarma,[1] Andrew Zaleski,[5] Andrea Lum,[5] Amit X. Garg.[1,2,3] *[1]Epidemiology & Biostatistics, Western Univ, London, ON, Canada; [2]Div of Nephrology, Dept of Medicine, Western Univ, London, ON, Canada; [3]Inst for Clinical Evaluative Sciences, London, ON, Canada; [4]Div of Nephrology, Univ Health Network, Univ of Toronto, Toronto, ON, Canada; [5]Dept of Radiology, Western Univ, London, ON, Canada.*

Background: International Classification of Disease, 10th revision (ICD-10) codes for autosomal dominant polycystic kidney disease (ADPKD) exist within several administrative databases. It is unknown whether these codes identify patients who meet strict clinical criteria for ADPKD.

Methods: We obtained a list of emergency room visits and hospital admissions in London, Canada between April 1st, 2002 and March 31st, 2014 for adults where either ICD-10 codes Q61.2 (polycystic kidney disease, autosomal dominant) or Q61.3 (polycystic kidney disease, unspecified) were assigned to a hospital encounter. From this list, we manually reviewed a random sample of patient medical charts, and determined whether ADPKD was present or not according to strict clinical criteria. We calculated the positive predictive value (95% confidence interval) for 9 different coding algorithms. We also used province wide databases to assess the number of patients in Ontario identified with different code sets.

Results: The presence of either ICD-10 code Q61.2 or Q61.3 in a hospital encounter had a positive predictive value of 85% (95% CI: 79% to 89%) for the identification of ADPKD, and identified 2981 adults in Ontario (0.02% of the general population). The presence of ICD-10 code Q61.2 in a hospital encounter had a positive predictive value of 97% (95% CI: 86% to 100%) for the identification of ADPKD, and identified 394 adults in Ontario (0.003% of the general population).

Conclusions: Most patients with ICD-10 administrative codes Q61.2 or Q61.3 assigned during their hospital encounters have ADPKD according to strict clinical criteria. These codes can be used to assemble and study cohorts of adult patients with ADPKD and hospital encounters.

Funding: Private Foundation Support

PUB249

Low Serum Levels of 1,25-Dihydroxyvitamin D, Not 25-Hydroxyvitamin D, Are Associated with Greater Total Kidney Volume (TKV) in Patients with Early Autosomal Dominant Polycystic Kidney Disease (ADPKD) Kristen L. Nowak,[1] Zhiying You,[1] Myles S. Wolf,[2] Michel Chonchol,[1] Berenice Y. Gitomer.[1] *[1]Univ of Colorado Anschutz Medical Campus; [2]Northwestern Univ.*

Background: The association of circulating vitamin D with kidney growth in patients with ADPKD is currently unknown. We sought to determine whether serum vitamin D levels are related to risk of TKV progression in patients with early ADPKD and estimated glomerular filtration rate (eGFR) > 60 ml/min/1.73m^2.

Methods: 25-hydroxyvitamin D (25(OH)D) and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) were measured in 462 hypertensive ADPKD patients who participated in the HALT-PKD trial study A. Participants were randomized to standard or low blood pressure control and to either lisinopril plus telmisartan or lisinopril plus placebo, with evaluation of height-corrected TKV (HtTKV) at baseline, 24, 48, and 60 months. The study population was divided into tertiles of 25(OH)D and $1,25(OH)_2D$ levels. We used mixed effect models to examine the associations across tertiles of 25(OH)D and $1,25(OH)_2D$ with repeated measures of HtTKV during the course of the study.

Results: At baseline, participants had a mean age of 37 ± 8 years, mean CKD-EPI eGFR of 91.4 ± 17.4 mL/min/1.73m^2, and median (IQR) 25(OH)D, $1,25(OH)_2D$ and HtTKV of 31.5 (24.1 – 38.2) ng/mL, 36.6 (30.0-44.7) pg/mL and 589 (406-860) mL/m, respectively. After adjustment for age, gender, race, randomization group, body-mass index, systolic blood pressure, eGFR, urine albumin excretion, serum calcium, phosphate and parathyroid hormone level, the lowest $1,25(OH)_2D$ tertile was associated with greater HtTKV (ß=123.05, [95% CI 44.74, 201.36]; $p < 0.0001$ compared with the highest $1,25(OH)_2D$ tertile). Similarly, when evaluated as a continuous variable, higher levels of

1,25(OH)$_2$D were associated with a lower HtTKV (ß= -167.23, [95% CI -86.81, -247.65]; p=0.002 per natural log unit increase). In contrast, there was no association between 25(OH) D levels and HtTKV (p=0.50).

Conclusions: Low serum 1,25(OH)$_2$D level, but not 25(OH)D level, is independently associated with a higher HtTKV over time in patients with early ADPKD.

Funding: NIDDK Support

PUB250

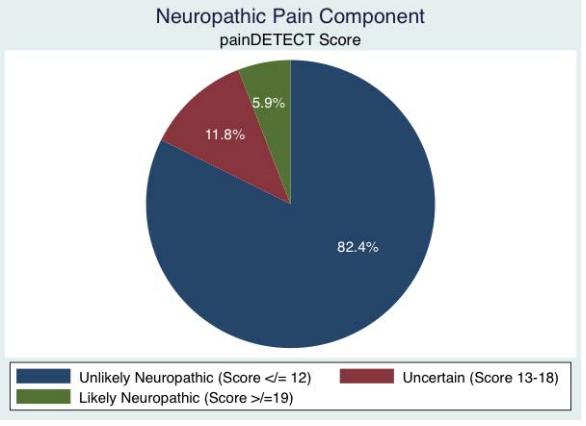
Improving Our Understanding of Pain in Autosomal Dominant Polycystic Kidney Disease Ragada El- Damanawi,[1] Tess Harris,[2] Thomas F. Hiemstra,[1] Michael C. Lee.[3] *[1]Dept of Renal Medicine, Cambridge Univ NHS Trust, Cambridge, United Kingdom; [2]Polycystic Kidney Disease (PKD) Charity, London, United Kingdom; [3]Div of Anaesthesia, Cambridge Univ NHS Trust, Cambridge, United Kingdom.*

Background: In Autosomal Dominant Polycystic Kidney Disease (ADPKD) pain is an early prominent feature affecting 60%. Multiple mechanisms result in pain, the severity of which correlates poorly with renal size. We conducted a survey to get a better understanding of patients experience of pain.

Methods: We used the painDETECT questionnaire, which was distributed to patients attending an ADPKD information day in Birmingham. 34 attendees completed the questionnaire.

Results: Participants were asked about how strong on average their pain was over the last 4 weeks using a scale 0= none to 10=maximum, 20.6% (7/34) had no pain, the majority 55.9% (19/34) scored pain between 1-5, and 23.5% (8/34) scored pain between 6-10. Of those that did experience pain (n=27), the pain quality is shown in table 1. 11.8% (4/34) said they had persistent pain with slight fluctuations, 8.8% (3/34) had persistent pain with pain attacks, most commonly 44% (15/34) had pain attacks without pain in between, and 20.6% (7/34) had pain attacks with pain between them. 82.4% (28/34) had a painDETECT score of ≤12 indicating the pain was not neuropathic-figure 1.

Pain Quality	Experienced Moderately-Very Strongly
Burning	22.2% (6/27)
Tingling or prickling	14.8% (4/27)
Light touch triggers pain	22.2% (6/27)
Sudden, electric shocks	**51.9% (14/27)**
Hot or cold painful	3.7% (1/27)
Numbness	3.7% (1/27)
Slight pressure triggers pain	**48.1%(13/27)**



Conclusions: In patients with ADPKD pain was episodic and nociceptive in quality, with not much of a neuropathic component. Our management should focus on intermittent therapy, and less on anti-neuropathic medications. There may be a role for renal denervation.

PUB251

Performance of Equations to Estimate Glomerular Filtration Rate in a Longitudinal Study of Autosomal Dominant Polycystic Kidney Disease Chengli Shen,[1] Doug Landsittel,[1] Maria V. Irazabal,[2] Alan S.L. Yu,[3] Arlene B. Chapman,[4] Michal Mrug,[5] Jared J. Grantham,[3] Kyongtae Ty Bae,[1] William M. Bennett,[6] Michael F. Flessner,[7] Vicente E. Torres,[2] The Crisp Investigators.[1] *[1]U of Pittsburgh, Pittsburgh, PA; [2]Mayo Clinic College of Medicine, Rochester, MN; [3]Kansas U, Kansas City, KS; [4]U of Chicago, Chicago, IL; [5]U of Alabama, Birmingham, AL; [6]Legacy Good Samaritan Hospital, Portland, OR; [7]National Inst of Diabetes, Digestive and Kidney Diseases, Bethesda, MD.*

Background: The reliability of estimated glomerular filtration rate (GFR) to reflect actual GFR values in clinical trials for ADPKD is controversial. Since 2001 the Consortium for Radiologic Studies of Polycystic Kidney Disease (CRISP) has followed 241 ADPKD patients (entry creatinine clearance >70 ml/min) with measurements of iothalamate clearance and serum creatinine yearly during four years and every other year afterwards. CRISP has shown a strong association of baseline height adjusted total kidney volume (HtTKV) and change in HtTKV with the rate of decline in iothalamate clearance.

Methods: We have evaluated the performance of GFR estimations by the MDRD and CKD-EPI equations relative to measured GFR using iothalamate clearance by mean bias, precision, accuracy, and strength of association with baseline HtTKV and change in HtTKV.

Results: Mean biases of MDRD GFR and CKD-EPI GFR values were large and positive (but highly variable) when measured GFR was ≥70 (10.1±26.9 and 6.2±22.6) and small and negative when it was <70 ml/min/1.73 m^2 (-1.9±9.5 and -5.0±9.9). Precision was higher when measured GFR was <70 ml/min/1.73 m^2.Measured and estimated GFR slopes and overall declines were not different. All were equally capable to detect the effect of baseline HtTKV and of change in HtTKV on the rate of GFR decline during 4, 8 or 12 years of follow-up. Beta coefficients were modestly higher with measured than with estimated GFR, but this advantage was offset by larger standard errors.

Conclusions: Determinations of estimated GFR using the MDRD or CKD-EPI equations are adequate to detect changes in kidney function over time in longitudinal studies and clinical trials of ADPKD.

Funding: NIDDK Support, Other NIH Support - CRISP

PUB252

Online Survey Exploring Opinions of European Caregivers about Testing for Autosomal Dominant Polycystic Kidney Disease Stephanie Le De Rechter,[1] Djalila Mekahli,[1] Jonathan A. Kringen,[2] Elena N. Levtchenko,[1] Peter Janssens,[1] Max Liebau,[5] Carsten Bergmann,[3] Bert Bammens,[1] Pascal Borry,[1] Franz S. Schaefer.[4] *[1]Univof Leuven; [2]Univ of New Haven; [3]Bioscientia Center for Human Genetics, Ingelheim; [4]Univ of Heidelberg; [5]Univ Hospital of Cologne.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is considered an adult disease. Whether minor offspring of ADPKD patients should have diagnostic testing remains controversial. However, the attitudes of caregivers have never been studied.

Methods: We used an online questionnaire aimed for pediatric and adult nephrologists, and an adapted version for geneticists.

Results: A total of 410 caregivers responded: 151 adult nephrologists, 216 pediatric nephrologists, and 43 geneticists. All three specialities similarly agreed that it was appropriate to encourage clinical testing in adults (group mean = 5.31, sd = 1.16). While all supported that clinical testing in minors should be encouraged (group mean = 4.76, sd = 1.50), pediatric nephrologists demonstrated significantly stronger agreement (t =3.60, p < .001) than geneticists. Regarding ethical concerns, although all specialities exhibited some disagreement with the statement that "prenatal genetic diagnosis is ethically justified" (group mean = 3.08, sd = 1.76), adult and pediatric nephrologists exhibited significantly higher levels of disagreement compared to geneticists (tadult = -2.10, p < .05; tpediatric = -3.19, p < .01). Similarly, all groups disagree on the statement "termination of pregnancy for ADPKD is ethically justified" (group mean = 2.78, sd = 1.67). Finally, geneticists exhibited agreement with the statement that "pre-implantation genetic diagnosis is ethically justified" (geneticist mean = 4.48, sd = 1.63). This position was significantly different that of adult and pediatric nephrologists who exhibited disagreement (tadult = -2.51, p < .05; tpediatric = -4.43, p < .001).

Conclusions: Our survey demonstrated that most of the caregivers will support clinical testing of the offsprings of ADPKD families, however, there is no consensus on the value of genetic testing neither on the ethical issues of the family planning.

Funding: Government Support - Non-U.S.

PUB253

CRISPR-Cas9 Mediated Knockout of Ciliary Genes to Study PKD in Zebrafish Stephanie Jerman, Zhaoxia Sun. *Genetics, Yale Univ School of Medicine, New Haven, CT.*

Background: Polycystic Kidney Disease (ADPKD) is one of the most commonly occurring genetic disorders in the world with limited treatment modalities, resulting in many PKD patients progressing to end-stage renal disease. Thus, to understand the fundamental biology of PKD is an important area of research. Several recent studies suggest a critical role of the primary cilium, a signaling organelle with various sensory functions, in the development and manifestation of cysts in ADPKD. Notably, polycystin-2, one of the two proteins known to be mutant in Autosomal Dominant PKD, encodes a cation channel targeted to cilia. Many other ciliary proteins, including Arl13b and IFT57, when mutant lead to cyst formation. The earliest stages of vertebrate embryonic development rely on maternally supplied gene products. In zebrafish, these maternal contributions can have a protective effect on offspring, masking the true null mutant phenotype. For example, *Pkd2* homozygous mouse mutants develop kidney cyst similar to what is observed in patients with Autosomal Dominant PKD; however, *Pkd2*$^{-/-}$ zebrafish do have body curvature and left-right defects indicative of ciliary defects but do not display kidney cysts unless subjected to morpholino knockdown of *Pkd2*, which eliminates the maternal contribution. However, toxicity and off-target effect of morpholino knockdown is a concern. To address this issue and reveal the true null phonotype of ciliary mutants, this study focused on understanding the role of polycystin-2, Arl13b, and IFT57 within the primary cilium using maternal zygotic zebrafish to eliminate maternally contributed mRNA in mutant offspring. Maternal zygotic mutants were generated using CRISPR sgRNAs specific to the ciliary genes of interest and Cas9-nanos, which is preferentially expressed in the germline. These results provide novel insight into the function of *PKD2, Arl13b, and IFT57* within cilia and the role of the primary cilium in PKD and other cystic disorders.

Funding: Other NIH Support - 2T32DK007356-36

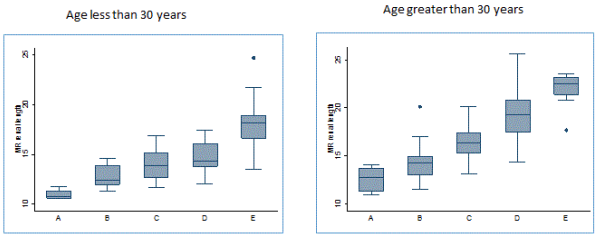
PUB254

Kidney Length Identifies Risk Categories of Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) Bharathi V. Reddy,[1] Doug Landsittel,[2] Chengli Shen,[2] Kyongtae Ty Bae,[2] Alan S.L. Yu,[3] Vicente E. Torres,[4] Maria V. Irazabal,[4] Frederic F. Rahbari-Oskoui,[5] Michal Mrug,[6] Arlene B. Chapman.[1] *[1]U Chicago; [2]U Pittsburg; [3]U Kansas; [4]Mayo Clinic; [5]Emory U; [6]UAB Birmingham.*

Background: Recently, a classification system establishing low and high risk ADPKD patients for progression to ESRD has been developed using height corrected total kidney volume (htTKV), age and serum creatinine (1A-1E, Irazabal, JASN. 2015 Jan;26(1):160-72). The Consortium for Radiologic Studies in Polycystic Kidney disease (CRISP) has demonstrated that kidney length (KL) performs as well as htTKV in predicting future Stages 3-5 CKD. Therefore we determined the corresponding MR based KL measures in participants in Classes IA-IE in CRISP.

Methods: Baseline coronal MRI maximum KL in 231 CRISP Class 1A-1E participants were assessed in those < 30 and >30 years of age.

Results: 145 participants were > and 84 patients < 30 years of age. In those < 30 years, 5, 17,29,18 and 32% of patients were in class 1A, 1B, 1C, 1D and 1E. In those >30 years, 7, 30, 30, 26 and 8% were in class 1A, 1B, 1C,1D and 1E. KL is less in all risk categories in young vs. old patients. The maximum KL observed in younger patients was 11.77, 14.58, 16.85, 17.43 and 24.66 in class 1A, 1B, 1C, 1D and 1E. In those >30 years, the maximum KL was 14.12, 20.15, 20.17, 25.65 and 23.55 in class 1A, 1B, 1C, 1D and 1E. Mean KL is < threshold to predict future stage III CKD in groups 1A-1D and 1A-1C in younger and older patients.



Conclusions: KL, which can be easily obtained by MRI and other imaging modalities show incremental change throughout the Irazabal classification of disease severity, highlighting which groups will progress to CKD.

PUB255

The Intrarenal Renin-Angiotensin System in Polycystic Kidney Disease: A Cross-Sectional Study Mahdi Salih,[1] Ron T. Gansevoort,[2] Stephan J.L. Bakker,[2] Robert Zietse,[1] Alexander H. Danser,[1] Ewout J. Hoorn.[1] *[1]Erasmus Medical Center; [2]Univ Medical Center Groningen.*

Background: Renin-angiotensin system (RAS) inhibitors are the preferred drugs for hypertension in autosomal dominant polycystic kidney disease (ADPKD). However, the relative role of the systemic and intrarenal RAS in hypertensive patients with ADPKD remains unresolved. Tubulocystic epithelium can synthesize functional renin, possibly in response to local hypoperfusion, but urinary renin has not been measured in patients with ADPKD. Therefore, we tested the hypothesis that ADPKD activates the intrarenal RAS resulting in higher urinary renin.

Methods: Patients with ADPKD (DIPAK cohort) were matched to patients with CKD (PREVEND cohort) based on gender, eGFR (CKD 3), RAS-inhibitor use, and blood pressure. Angiotensinogen (AGT), renin, and aldosterone were measured in plasma and 24h urine. Urinary renin was measured with a sensitive enzyme-kinetic assay.

Results: 69 patients with ADPKD were matched to 58 patients with CKD (43% male, 78% RAS-inhibitor use, eGFR 46 ml/min, blood pressure 131/77 mmHg). Patients with ADPKD were younger (47 vs. 69 years) and had more albuminuria (40 vs. 27 mg/day). While plasma levels of AGT, renin, and aldosterone were similar between groups, urinary AGT and renin excretion were 4.8 and 6-fold higher in ADPKD (P<0.01). These differences persisted in the subset of patients without RAS-inhibitors. A subanalysis in patients with similar age and albuminuria (31 ADPKD vs. 9 CKD patients) still showed higher urinary AGT (3.5-fold) and renin (8.7-fold) excretion in ADPKD. In a multivariable analysis, ADPKD, plasma renin, and albuminuria were identified as independent predictors for urinary renin. Urinary renin did not correlate with blood pressure or total kidney volume. In three patients with available plasma, cyst fluid, and urine, analysis of the concentration ratios indicated that relatively more renin than albumin was excreted in urine, suggesting local renin release from cysts.

Conclusions: In addition to plasma-derived urinary renin, the consistently higher urinary renin excretions in patients with ADPKD also supports the possibility of activation of the intra-renal RAS.

PUB256

Patient Survey of Current Water Intake Practices in Autosomal Dominant Polycystic Kidney Disease: The WIPP Survey Ragada El-Damanawi,[1] Tess Harris,[2] Thomas F. Hiemstra.[1] *[1]Dept of Renal Medicine, Cambridge Univ NHS Trust, Cambridge, Cambridge, United Kingdom; [2]Polycystic Kidney Disease (PKD) Charity, London, United Kingdom.*

Background: Vasopressin drives cyst growth in Autosomal Dominant Polycystic Kidney Disease (ADPKD). It can be suppressed through high water intake, although the effects of this approach on renal outcomes are unproven. We conducted a survey of ADPKD patients to determine current fluid intake practices and willingness to participate in a randomised water intake trial.

Methods: In collaboration with the PKD Charity, we developed and distributed an online patient questionnaire. Participants were arbitrarily divided into those reporting a high water intake (>2 litres/day) and those reporting a lower intake. Responses were compared between groups.

Results: 89 ADPKD patients responded [65 female (73%); 84 caucasian (94%); 80 British (93%)]. The median age range was 45-49 years. One third (30/89, 33.7%) received a diagnosis of ADPKD during the 4th decade of life. More patients in the high water intake group (47 of 54, 87%) reported regularly drinking beyond thirst compared to the low water intake group (18 of 35, 32%, p=0.001). Reports of nocturia were not different between groups (p=0.663) and both groups equally believed high water intake was beneficial - table1.

	Low Intake ≤ 2 Litres/ day (N= 35)	High Intake > 2 Litres/day (N=54)	p value
Intake Beyond Thirst	52% (18/35)	87% (47/54)	0.001
Nocturia	63% (22/35)	57% (31/54)	0.663
Believe high water intake beneficial	49% (17/35)	52% (28/54)	0.099

Despite only 15 (17%) living with affected family members, the majority (70 of 89, 79%) regularly discussed management with their relatives. Most patients (80 of 89, 90%) indicated willingness to participate in a randomised trial of high versus *ad lib* water intake.

Conclusions: Current water intake practices vary widely among UK patients with ADPKD. A trial of high versus standard water intake in ADPKD is urgently needed and likely to be supported by patients. Many patients regularly discuss their condition with affected family members, suggesting that contamination between trial arms is possible and may require cluster randomisation.

PUB257

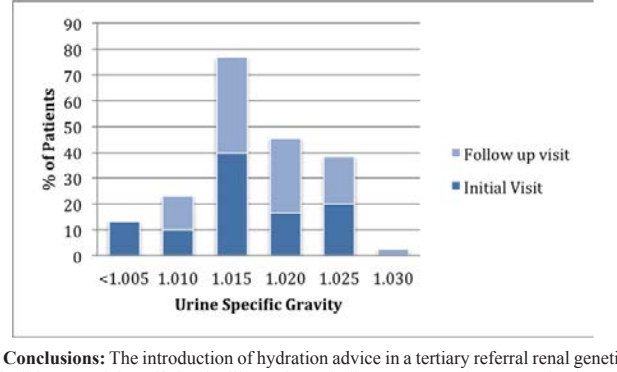
Influencing Urine Specific Gravity in the Management of Autosomal Dominant Polycystic Kidney Disease Ragada El-Damanawi, Richard N. Sandford, Fiona E. Karet, Thomas F. Hiemstra. *Dept of Renal Medicine, Cambridge Univ NHS Trust, Cambridge, United Kingdom.*

Background: Vasopressin receptor blockade slows cyst growth in Autosomal Dominant Polycystic Kidney Disease (ADPKD). High water intake readily suppresses vasopressin release, and may be an alternative to Vasopressin antagonists. Patients are often advised to drink beyond thirst. However, the effect of this advice is unknown. As vasopressin suppression results in water diuresis with a urine specific gravity (uSG)<1.010, uSG provides a surrogate for vasopressin suppression. We assessed uSG in a cohort of ADPKD patients to establish prevalent hydration status.

Methods: High water intake advice for ADPKD was introduced in our centre in 2013. In this single-centre retrospective cohort study, we determined adherence to hydration advice by assessing uSG. Data were extracted from patient case records.

Results: Data were available for 77 patients [41(53%) male; 56 (73%) Caucasian; 5 (6%) PKD2 mutation]. The mean (SD) age at diagnosis was 29±14 years, and at referral 40±14 years. 59 patients (77%) had a family history of ADPKD. At baseline 40 (52%) has CKD1 or 2; 13 (17%) CKD3 and 3 (4%) CKD4. CKD5 patients were referred to Low Clearance services and thus not included.

Baseline median uSG was 1.015 (IQR 1.015-1.020), 41 patients (53%) demonstrating uSG>1.010. Serial uSG data was available for 48 patients. There was no difference (p=0.1154) in mean uSG at first visit [1.016±0.006(SD)] and follow-up visit [1.018±0.005], despite hydration advice (figure 1). Renal function did not differ (p=0.1053) between initial visit [eGFR 75.5ml/min±23.5 (SD)] and follow up [72.2ml/min±26.7].



Conclusions: The introduction of hydration advice in a tertiary referral renal genetics clinic did not result in sufficiently dilute urine to indicate vasopressin suppression in many patients. Further studies assessing strategies to promote hydration are warranted.

PUB258

Autosomal Dominant Polycystic Kidney Disease in the Southwest of Ireland Michael Keyes, Dearbhla Kelly, Edward Philip Mcmonagle, Liam F. Casserly. *Dept of Nephrology, Univ Hospital Limerick, Limerick, Ireland.*

Background: Autosomal dominant polycystic kidney (ADPKD) is the most common genetic cause of chronic kidney disease (CKD). In a recent cross-sectional survey, it accounted for 7.3% of patients with CKD in the Republic of Ireland. ADPKD is caused by mutations of either PKD1 (which encodes polycystin-1), on chromosome 16, or PKD2 (which encodes polycystin-2), on chromosome 4.

Methods: This was an observational study of all patients with ADPKD who attended the Nephrology services in University Hospital Limerick from January 2000-June 2016. Patients were identified by interrogation of the departmental database. Retrospective chart review enabled documentation of demographic and clinical characteristics along with treatment course and outcome. Water intake and access to genetic counseling were also recorded.

Results: 99 patients with ADPKD were identified. The mean age of the population was 58.7 years (SD ± 13.9, range 29-88 years). 56.7% were female. 13 patients (13.1%) had no family history of ADPKD but only 1 patient had genetic testing for PKD1 and PKD2 genes performed. 76.8% of patients developed hypertension and 51.5% of patients were treated with renin-angiotensin system [RAS] inhibitors. The mean delta glomerular filtration rate (GFR) was -1.2ml/min (SD ± 2.8). 28.3% were dialysis-dependent and 21.2% of patients received a renal transplant. No patient was counseled regarding increased water intake and no patient was in receipt of a vasopressin receptor antagonist. 37.4% were screened for cerebral aneurysms with only 2 positive cases.

Conclusions: Genetic testing for patients with ADPKD without a family history should be performed to ensure that other hereditary or acquired ciliopathies are not misdiagnosed. Only half the population in this study received a RAS inhibitor but the rate of progression of kidney disease was slow. Vasopressin receptor antagonists are not yet in widespread use in Irish patients. Patients with APDKD should receive counseling regarding increased water intake in order to adequately suppress anti-diuretic hormone levels to inhibit cyst growth. There was a low incidence of cerebral aneurysms in this population.

PUB259

Renal Angiomyolipoma: Outcomes of Selective Arterial Embolization on Glomerular Filtration Rate Ammar Almehmi,[1] Alian Albalas,[3] Ahmed Kamel Abdel Aal.[2] *[1]Nephrology and Radiology, Univ of Alabama at Birmingham, Birmingham, AL; [2]Radiology, Univ of Alabama at Birmingham, Birmingham, AL; [3]Nephrology, Univ of Alabama at Birmingham.*

Background: Selective arterial embolization (SAE) is a surgery-sparing treatment for renal angiomyolipoma (AML). However, limited data are available on the effects of SAE on glomerular filtration rate (GFR). Further, the outcomes of contrast exposure on GFR during SAE procedure remain unknown. The aim of this study was to evaluate the change in serum creatinine and GFR in patients with AML who underwent SAE.

Methods: This is a retrospective review of AML cases that were treated with SAE procedure at our center from 2004 to 2015. Data collected from medical records included demographics, tumor side and size, and other laboratory parameters. Serum creatinine and calculated GFR were collected immediately prior and 3 months after SAE procedure.

Results: This study included 42 patients who underwent SAE. Indications for SAE included back pain, hematuria and retroperitoneal hemorrhage. Baseline characteristics were: age (median +/- 25^{th}-75^{th} interquartile) 42 (32-64) year; 81% females; 66% whites. Hypertension and tuberous sclerosis were present in 33% and 42.9% of patients, respectively. Tumor size (median +/- 25^{th}-75^{th} interquartile) was 5.9 (4.7-8.5) cm. Two episodes of acute kidney injury occurred post SAE with complete renal recovery. Although mean serum creatinine increased from 0.98 mg/dl to 1.15 after SAE procedure, no statistically significant difference was noted in post SAE GFR (60 vs 70 ml/min; p=0.125).

Conclusions: Selective arterial embolization is a safe, surgery-sparing treatment for renal AML. Despite contrast exposure and partial parenchymal loss, renal function (i.e. GFR) remained well preserved after SAE procedure.

PUB260

Genome Editing-Based Cell Culture Models for Studying ADPKD Alexis Hofherr, Tilman Busch, Andreas Nold, Albert Bohn, Amandine Viau, Frank Bienaime, E. Wolfgang Kuehn, Michael Kottgen. *Renal Div, Dept of Medicine, Faculty of Medicine, Univ of Freiburg, Freiburg im Breisgau, Baden-Wuerttemberg, Germany.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic cause of end-stage renal disease. Mutations in two genes, *Polycystic Kidney Disease 1* (*PKD1*) and *PKD2*, cause ADPKD. Data from humans and animal models show that both genes are part of a morphogenetic program to maintain kidney structure. However, the molecular functions of the respective proteins, Polycystin-1 (PC1) and transient receptor potential Polycystin-2 (TRPP2), have remained elusive.

Methods: Analyses of polycystin-dependent events driving cystogenesis *in situ* are complicated by a complex interplay of endogenous and environmental factors. *In vitro*, wild-type renal cell lines, including Madin-Darby Canine Kidney (MDCK) and mouse Inner Medullary Collecting Duct 3 (mIMCD3) cells, have been well-characterized. But a lack of differentiated ADPKD mutant cell lines has confounded molecular studies of polycystin function: the majority of isolated primary cells are heterogenous and have a finite replicative capacity; the generation of immortalized differentiated renal epithelial cells from ADPKD patients or mouse models has proven difficult; murine embryonic fibroblasts (MEFs) from genetically modified ADPKD mice lack the epithelial characteristics of renal tubular cells; and the physiological relevance of heterologous expression systems has been questioned. We therefore hypothesized that the manipulation of native proteins in differentiated renal epithelial cell lines may accelerate novel insights into polycystin function.

Results: Here we present ADPKD-specifc *in vitro* models of varying complexity. Based on MDCK and mIMCD3 cells we generate ADPKD models with: 1) deletion of PKD genes; 2) rescue of polycystin expression; 3) introduction of highly antigenic epitope-tags into the *Pkd1* genomic locus; and 4) combination of multiple alleles.

Conclusions: We hope that our genome-edited cell culture models may help to clarify the function of polycystin proteins in renal epithelial cells.

Funding: Government Support - Non-U.S.

PUB261

Efficient Genome Editing of Differentiated Renal Epithelial Cells Alexis Hofherr,[1] Tilman Busch,[1] Nora Marie Huber,[2] Sebastian Arnold,[2] Michael Kottgen.[1] *[1]Renal Div, Dept of Medicine, Faculty of Medicine, Univ of Freiburg, Freiburg im Breisgau, Baden-Wuerttemberg, Germany; [2]Experimentelle und Klinische Pharmakologie und Toxikologie, Faculty of Medicine, Univ of Freiburg, Freiburg im Breisgau, Baden-Wuerttemberg, Germany.*

Background: The recent advent of highly efficient genome editing technologies has enabled a new paradigm in which genomes can be precisely manipulated. This includes the targeted introduction, alteration, and/or removal of genomic sequences. However, respective methods have been described mainly in haploid or non-differentiated cells. The application in well-differentiated renal epithelial cells has been hampered by a range of technological issues, including optimal design, efficient expression of multiple genome editing constructs, attainable mutation rates, and best screening strategies.

Methods: Here we show how to overcome these challenges to rapidly generate heterozygous and homozygous genomic sequence alterations in renal cells using transcription activator-like effector nucleases (TALENs) and the clustered regularly-interspaced short palindromic repeat (CRISPR) system.

Results: The cell lines most widely used to study renal epithelial biology are Madin-Darby Canine Kidney (MDCK) cells and mouse Inner Medullary Collecting Duct 3 (mIMCD3) cells. Both cell lines retain core epithelial characteristics, are phenotypically stable, and develop clear apico-basolateral polarity. We therefore developed a genome editing-based framework to efficiently expand on the genetics of wild-type MDCK and mIMCD3 cells. Applications include, but are not limited to, large genomic deletions, loss-of-function mutations, and knock-ins by homologous recombination. Furthermore, we describe how to translate these genetic alterations into complementary mouse models. Notable features of genome edited cell lines are, a high degree of differentiation, phenotypic and genetic stability, experimental tractability, and suitability for small and high throughput screening.

Conclusions: We anticipate that the developed genome editing workflow may help to clarify gene functionality in differentiated renal epithelial cells in health and disease.

Funding: Government Support - Non-U.S.

PUB262

Serum from Diabetic-End Stage Renal Disease (DM-ESRD) Patients Affects Endothelial Reparative Ability María Marques Vidas,[1] Estefanya Garcia Menendez,[1] Matilde Alique,[3] Elena Corchete,[2] Jeanette Nora Fernandez C.,[1] Patricia De Sequera,[2] Rafael Perez-Garcia,[2] Rafael Ramirez,[3] Jose M. Portoles.[1] *[1]Nephrology, H U Puerta de Hierro Majadahonda, Majadahonda, Madrid, Spain; [2]Nephrology, HU Infanta Leonor Vallecas, Madrid, Spain; [3]Physiology Lab, U Alcalá de Henares, Alcalá de Henares, Madrid, Spain.*

Background: Chronic renal disease and diabetes mellitus are associated with higher rates of cardiovascular disease. Circulating micoparticles (MPs) are intercellular communication mediators that module mechanisms of vascular endothelium lesion and reparation. The aim of this study was to evaluate the effect of the MPs from DM-ESRD patients on the vascular endothelium.

Methods: We used pooled serum obtained from DM-ESRD patients stage 4 (n=5), on peritoneal dialysis (PD, n=5), on haemodialysis pre-session (pre-HD, n=5) and post-session (post-HD, n =5), and healthy volunteers (n=5). MPs were isolated, and HUVEC were incubated with and without the addition of MPs. We analysed proliferation and apoptosis averages and ICAM and VCAM expression.

Results: The serum from DM-ESRD patients on any stage induced an increase on the expression of both ICAM and VCAM on HUVEC ($p< 0.001$*). Treatment with HD or PD did not modify this effect with respect to VCAM; however, the pre-HD serum pool induced a higher expression of ICAM ($p< 0.01$**). The presence of MPs decreased ICAM up-expression on all study groups (p ns). DM-ESRD serum was less effective on inducing cellular proliferation than control serum, especially on HD groups when tested without MPs. Finally, DM-ESRD serum induced a significant increase on apoptosis rate, especially on HD groups. The presence of MPs seemed to increase apoptosis rate in every study group but PD (p ns).

Conclusions: We conclude that the serum from DM-ESRD patients induces inflammatory changes and modification of the endothelial proliferative and apoptosis rates. The uraemia correction with the different types of renal substitutive therapy did not restore this effect and HD even seemed to exacerbate it. The presence of MPs protects the endothelial reparative ability even though they induced an increase on the apoptosis average on HUVEC, probably pointing towards a dual effect on endothelial reparative mechanisms.

PUB263

SGLT2 Inhibitor Ipragliflozin Increases Fluid and Food Intake to Maintain Body Fluid Volume and Weight Takahiro Masuda,[1] Yuko Watanabe,[1] Minami Watanabe,[1] Keiko Fukuda,[1] Akira Onishi,[2] Volker Vallon,[2] Daisuke Nagata.[1] *[1]Div of Nephrology, Dept of Medicine, Jichi Medical Univ, Shimotsuke, Tochigi, Japan; [2]Univ of California San Diego & VA San Diego Healthcare System, San Diego, CA.*

Background: We previously reported that sodium-glucose cotransporter (SGLT) 2 inhibitor Ipragliflozin increases urine volume (UV) and Na excretion, whereas body fluid volume is maintained possibly due to an increase in fluid and food intake (ASN Kidney Week 2015). We therefore evaluated whether preventing the increase in fluid and food intake during SGLT2 inhibition induces body fluid reduction.

Methods: Male Sprague-Dawley rats (average 20.5±0.5 weeks of age) were treated with vehicle (Veh), 0.01% (in diet) Ipragliflozin (Ipra) and 0.01% Ipra by pair-feeding and drinking with Veh (Pair-Ipra) (n=8) for 7 days. Rats were placed in metabolic cages to measure UV and food and fluid intake. Bioimpedance spectroscopy (ImpediVet) was used to assess body water on day 0 and day 7.

Results: Compared with Veh, Ipra increased food and fluid intake; Pair-Ipra prevented the increase (food intake: 20.3±0.9, 29.2±1.2*, 21.9±0.6# g/day, fluid intake: 41.1±3.6, 78.4±7.9*, 43.7±1.4# ml/day, *P<0.05 vs Veh, #P<0.05 vs Ipra). Pair-Ipra decreased body weight (BW) vs Veh and Ipra (ΔBW: Veh -5.4±0.5, Ipra-4.1±0.6, Pair-Ipra -11.2±0.5*# %). Serum glucose was similar among groups (210±16, 176±13, 178±3mg/dl, P=0.11). Ipra and to a lesser extent Pair-Ipra increased UV (19.3±1.9, 53.7±3.6*, 31.6±1.8*# ml/day), Na excretion (2.2±0.1, 3.5±0.1*, 2.6±0.1*# mEq/day), Cl excretion (2.9±0.1, 4.7±0.2*, 3.6±0.1*# mEq/day) and K excretion (4.1±0.1, 5.5±0.2*, 5.0±0.2*mEq/day). Pair-Ipra decreased fluid balance (fluid intake - UV) (Δfluid balance: -2.2±10.0, 27.3±16.0, -42.8±6.5*# %). Pair-Ipra decreased total body water (-9.8±1.6%¶, ¶P<0.05 day 0 vs day 7), extracellular water (-11.5±1.7%¶) and intracellular water (-8.6±2.6%¶), while Ipra or Veh had no significant effect.

Conclusions: SGLT2 inhibitor Ipragliflozin increases fluid and food intake in euglycemic rats. Preventing the increase in fluid and food intake causes body fluid and weight reduction. Thus, SGLT2 inhibition increases fluid and food intake to maintain body fluid volume and weight.

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

PUB264

Protective Effect of ApoAI/ABCA1 on Kidney inflammation of STZ Induced Diabetic Nephropathy Rats Tong Li,[1] Ricong Xu,[2] Huanfang Yang.[3] *[1]Shenzhen No.2 People's Hospital, Shenzhen; [2]Shenzhen No.2 People's Hospital, Shenzhen; [3]Shenzhen No.2 People's Hospital, Shenzhen.*

Background: To discuss the protective effect of ApoAI/ABCA1 pathway on kidney inflammation of STZ-induced diabetic nephropathy rats.

Methods: Forty Sprague-Dawley male rats were randomly divided into 4 groups: Normal group,DN group(diabetic nephropathy),DN+GFP group and DN+ApoA-I group. The DN rats model were injected by abdominal streptozotocin(STZ) (65 mg /kg). The successful models were defined as FBG> 16.7 mmol/L, UGLU >3+ . DN+GFP group and DN+ApoA-I group were injected with AdV-GFP or AdV-AI (1×1011v.p./mice/d) by tail vein . After 4 weeks, kill the rats and get out the kidneys, and then test the expression of ABCA1 mRNA and TTP protein in the kidney by RT-PCR and Western blot; Collect blood in postcava, and then test the content of TNF-α and MCP-1in serum respectively by ELISA.

Results: Compared with the control group, the expression of ABCA1 mRNA and TTP protein in the kidney were reduced in the DN group($P < 0.05$);There were no differences of ABCA1 mRNA and TTP protein in the kidney between the DN group and DN+GFP group; However, Compared with DN+GFP group, the contents of serum TNF-α and MCP-1 were reduced ,what's more, the expression of ABCA1 mRNA and TTP protein in the kidney were increased in the DN+ApoA-I group($P < 0.05$).

Conclusions: Activation of ApoA-I / ABCA1 pathway could protect STZ-induced diabetic nephropathy rats from inflammatory injure , This effect may be through down regulation of TNF-α,MCP-1 and over xpression of ABCA1 mRNA ,TTP protein in the kidney.

Funding: Government Support - Non-U.S.

PUB265

The Protect Effect of Ouabain in Diabetic Nephropathy Dong Li,[1] Xiaowei Wang.[2] *[1]Pediatric Dept, Dalian Municipal Women and Children's Medical Center, Dalian, Liaoning, China; [2]Basic Medicine Dept, Dalian Medical Univ, Dalian, Liaoning, China.*

Background: Diabetic nephropathy is the main cause of kidney injury. As a plant-derived cardioglycoside, ouabain was well-established inhibitor of Na-K-ATPase activity. Recent investigations demonstrate at nanomolar concentrations, ouabain increases Na-K-ATPase activity, and increase cell proliferation. We aim to study the potential protect effect of Ouabain in diabetic nephropathy.

Methods: Primary tubular cells of rats were cultured and treated with glucose (5mM, 10mM, 15mM and 25mM) to perform the diabetic nephropathy model, meanwhile 5nM ouabain was added and incubated together for 8hrs, 18hrs and 24hrs separately. Cells were observed under imaging, Apoptosis data was performed with TUNEL method.

Results: With the 10mM glucose incubation for 8hrs, 18hrs and 24hrs separately, the PTCs were damaged under imaging, and 18hrs was the top point, TUNEL showed the mean index of apoptosis was 2.9%±0.3%(control)and for 18hrs treatment apoptotic index was increased to 21.2%±4.1% (P<0.01). In the co-incubated with ouabain 5nM for 18hrs group, Ouabain significantly alleviated the apoptosis, apoptosis index was 6.5%±1.3%.

Conclusions: Apoptosis play a role in Diabetic Nephropathy, Ouabain may perform as an anti-apoptotic factor and play a protect effect on it.

Funding: Government Support - Non-U.S.

PUB266

Renoprotective Effect of Uremic Clearance Granules in Streptozotocin-Induced Diabetic Nephropathy Hua Jin, Shang Guo Piao, Ji Zhe Jin, Long Ye Zhang, Can Li. *Nephrology, YanBian Univ Hospital, YanJi, JiLin, China.*

Background: Uremic Clearance Granules (UCG), a compounded Chinese patent medicine, has been shown to exert beneficial effects on chronic renal failure. However, its role in diabetic nephropathy (DN) has not to be illustrated. The present study investigated the renoprotection of UCG in a rat model of streptozotocin (STZ)-induced DN.

Methods: Diabetes was induced with STZ (65 mg/kg) by intraperitoneal injection in male Wistar rats. Two weeks after STZ injection, diabetic rats were treated daily for 12 weeks with UCG (5g/kg). Basic parameters (body weight, fasting blood glucose level, 24h urinary protein excretion, and renal function), histopathology, inflammatory (ED-1 and Toll-like receptor-2 [TLR-2]) and glomerulosclerotic factors (Transforming growth factor-beta inducible gene-h3 [βig-h3] and connective tissue growth factor [CTGF]), and oxidative stress (8-hydroxy-2¢-deoxyguanosine, 8-OHdG) were studied at 4, 8, 10, and 12 weeks.

Results: UCG treatment significantly improved body weight loss, 24h urinary protein excretion, and renal dysfunction induced by diabetes in a time-dependent manner (all p<0.05). These changes were accompanied by a significant attenuation of glomerulosclerosis. Increased expression of inflammatory (ED-1 and TLR-2) mediators and glomerulosclerotic (βig-h3 and CTGF) factors in diabetic rat kidney wasmarkedly reduced by treatment with UCG (all p<0.01). Moreover, increased urinary 8-OHdG excretion in diabetic rats was decreased by treating UCG. There was no significant between-groupdifference in blood glucose level.

Conclusions: UCGtreatment may confer renoprotection by anti-inflammatory and anti-fibrotic actions in STZ-induced DN.

Funding: Other NIH Support - National Natural Science Foundation of China, Other U.S. Government Support

PUB267

High Fat Diet Given with Low Doses of Streptozotocin Induces Type 2 Diabetic Nephropathy in Endothelial Nitric Oxide Synthase Knockout Mice M-Altaf Khan,[1,2] Federico Jose Teran,[1,2] Kathleen S. Hering-Smith,[1,2,3] Molly Fisher,[4] Dewan S. Majid,[2] L. Gabriel Navar,[2] Vecihi Batuman.[1,2,3] *[1]Medicine, Nephrology & Hypertension, Tulane Univ, School of Medicine; [2]Physiology/THRCE, Tulane Univ, School of Medicine; [3]VA, SLVHCS, New Orleans, LA; [4]Medicine/Nephrology, Albert Einstein College of Medicine, Bronx, NY.*

Background: Wild type (WT) mice are usually resistant to the development of diabetic nephropathy (DN). We hypothesized that aged eNOS$^{-/-}$ mice fed a high fat diet (HFD) are more susceptible to streptozotocin (STZ) induced DN than mice fed a regular diet (RD) or HFD only.

Methods: Male eNOS$^{-/-}$mice were fed a HFD (52% fat Kcal) for 9 - 12 weeks to develop β-cell resistance and low doses of STZ (50 mg/kg b.w., ip) were administered for 3 days to induce diabetes. Control eNOS$^{-/-}$ or WT (C57Bl6/J) mice were fed a RD and all mice were sacrificed at 16 - 20 weeks of age.

Results: All eNOS$^{-/-}$ mice on HFD, after the 3rd STZ injection, developed diabetes with non-fasting blood glucose levels > 300 mg/dl that continued to increase with age. The diabetic (DB) eNOS$^{-/-}$ mice had significantly higher blood hemoglobin A1C levels (9.21 ± 0.18% SE) compared to non-diabetic (ND) eNOS$^{-/-}$ mice on RD (4.4 ± 0.4%) or on HFD alone (5.4 ± o.4%), and WT mice on RD (4.7 ± 0.05%) only. Aged DB eNOS$^{-/-}$ mice developed significant polyuria, glucosuria, albuminuria and proteinuria compared to ND eNOS$^{-/-}$ mice. Diabetic eNOS$^{-/-}$ mice showed higher systolic blood pressure and significantly higher pulse rate, and a significant increase in serum creatinine (ND = 0.11 ± 0.1 vs DB = 0.252 ± 0.05 mg/dl). These mice showed a significant increase in urinary angiotensinogen (AGT) (DB = 275.2 ± 44.5 vs ND = 29.8 ± 8.2 or ND WT = 12.04 ± 2.5 ng/day) reflecting augmentation of the intrarenal renin-angiotensin system (RAS). Urinary kidney injury biomarkers (NGAL and KIM-1) were significantly increased in association with glomerulosclerosis. Aged DB eNOS$^{-/-}$ mice also showed metabolic acidosis with significantly lower blood HCO_3 and urinary pH values.

Conclusions: Aged eNOS$^{-/-}$ mice on HFD and STZ develop diabetes and nephropathy with increased serum creatinine, albuminuria, urinary AGT and metabolic acidosis. These mice can be used as a model of type 2 DN with hypertension.

Funding: Other NIH Support - NIH Renal COBRE (P30GM103337)

PUB268

Effect of CS-3150, a Non-Steroidal Selective Mineralocorticoid Receptor Antagonist, on Blood Pressure and Renal Injury in High Salt-Treated Type 2 Diabetic Mice Akira Nishiyama, Hirofumi Hitomi, Daisuke Nakano. *Dept of Pharamacology, Kagawa Univ Medical School, Japan.*

Background: The aim of the study was to examine the effect of CS-3150, a non-steroidal selective mineralocorticoid receptor (MR) antagonist, on blood pressure and renal injury in high salt diet-treated type 2 diabetic KKAy mice, and compare the effects with spironolactone, a steroidal MR antagonist.

Methods: Male 11-week-old KKAy mice were treated with normal salt diet (NS: 0.3% NaCl, n = 5), high salt diet (HS: 4% NaCl, n = 8), HS + CS-3150 (1 mg/kg/day, p.o., n = 8), or HS + spironolactone (20 mg/kg/day, p.o., n = 7) for 8 weeks. Renal oxidative stress was evaluated by dihydroethidium florescence intensity assay.

Results: As compared with NS-treated KKAy mice, HS-treated diabetic KKAy mice demonstrated hypertension, albuminuria, glomerular injury (glomerular PAS staining-positive area) and tubulointerstitial fibrosis (Azan staining-positive area) with increased oxidative stress at 19 weeks of age. Treatment with CS-3150 and spironolactone decreased blood pressure to a similar extent in HS-treated KKAy mice. In contrast, CS-3150 caused greater attenuation of albuminuria, glomerular injury and tubulointerstitial fibrosis as compared with spironolactone.

Conclusions: These data indicate that CS-3150 elicits antihypertensive and renal protective effects in HS-treated type 2 diabetic mice.

Funding: Government Support - Non-U.S.

PUB269

L-Carnitine Protects against Streptozotocin-Induced Diabetic Nephropathy Ji Zhe Jin, Long Ye Zhang, Shang Guo Piao, Can Li. *Nephrology, YanBian Univ Hospital, YanJi, JiLin, China.*

Background: We have recently demonstrated that L-carnitine confers renoprotective effect on cyclosporine-induced nephropathy in the rats. The present study investigated whether L-carnitine protects against streptozotocin (STZ)-induced diabetic nephropathy (DN).

Methods: Diabetes was induced with STZ (65 mg/kg) by intraperitoneal injection in male Sprague-Dawley rats. Two weeks after STZ injection, diabetic rats were treated daily for 10 weeks with vehicle or L-carnitine (50 or 200mg/kg). The renoprotective effects of L-carnitine were studied by evaluating the expression of fibrotic cytokine-transforming growth factor-beta1 (TGF-β1) inducible gene-h3 (βig-h3), of apoptosis or autophagy-related gene-active caspase-3 or LC3, and the concentration of oxidative stress. In addition, renal function, fasting blood glucose level, and 24h urinary protein excretion were also compared for different groups.

Results: L-carnitine induced dose-dependent decreases in the expression of βig-h3, caspase-3, and LC3, and in the concentration of urine 8-OHdGCG. These were accompanied by a significant attenuation of glomerulosclerosis.Renal function and 24h urinary protein excretion significantly improved with administration of L-carnitine at different time points, although fasting blood glucose level was unaffected.

Conclusions: L-carnitinetreatment protects against STZ-induced DN.

Funding: Other NIH Support - China National Foundation, Other U.S. Government Support, Government Support - Non-U.S.

PUB270

The Effect of miR-29c on Inflammation through Tristetraprolin in Diabetic Nephropathy Jing Li,[1,2] Jing Zhao,[1,2] Jia Guo,[1,2] Zhanzheng Zhao.[1,2] *[1]The Nephrology Center of the First Affiliated Hospital of Zhengzhou Univ, Zhengzhou, Henan, China; [2]Zhengzhou Univ Inst of Nephrology, Zhengzhou, Henan, China.*

Background: Inflammation is a key factor of diabetic nephropathy (DN). Emerging evidence has demonstrated that miRNAs play a mediatory role in the inflammation of diabetic nephropathy. Tristetraprolin(TTP) could modulate the mRNA expression of inflammatory cytokines. In this study, we investigated the repertoire of miRNAs in the blood plasma, urinary sediment and kidney tissues of patients with DN and their potential regulatory role in inflammation invloved in DN.

Methods: The miRNA expression profiling of the blood plasma, urinary sediment and renal biopsy samples was performed by a microarray analysis, which showed that miR-29c was significantly differential expression. Mice podocytes were cultured under different conditions, and the protein expressions were examined by western blot or ELISA. The real-time PCR was used to detect the miR-29c or mRNA expressions. Dual luciferase reporter assay kit was used to detect the interaction between TTP 3'UTR and miR-29c.

Results: 1. The expression of miR-29c was significantly increased in the blood plasma, wherease, decreased in the urinary sediment and kidney tissues of the DN patients compared with the controls. The miR-29c expression in blood plasma was closely negatively correlated with the TTP level ($R = -0.9$, $P < 0.05$) and positively with the inflammatory cytokine IL-6 level ($R = 0.879$, $P < 0.05$). 2. The expressions of miR-29c and inflammatory cytokines IL-6 and TNF-α were up-regulated under high glucose in mice podocytes, with the decreased expression of TTP. 3. Up-regulation of miR-29c by mimics led to the increased expressions of inflammatory cytokines IL-6 and TNF-α and a decreased expression of TTP. However, inhibition of miR-29c by inhibitor exerted the opposite effect. 4. The dual-luciferase reporter assay showed that miR-29c directly targeted the TTP 3'UTR. 5. The expression of TTP could be increased wherease inflammatory cytokines IL-6 and TNF-α decreased after miR-29c inhibitor transfected in high glucose-treated podocytes.

Conclusions: These findings suggested that miR-29c accelerated high glucose-induced inflammation through directly down-regulating TTP.

Funding: Government Support - Non-U.S.

PUB271

Carbamylation of Albumin Reduces Binding to FcRn and Cubilin Mark C. Wagner,[1] Jered Myslinski,[1] Shiv Pratap Singh Yadav,[3] Silvia B. Campos-Bilderback,[1] Sudhanshu Kumar,[1,2] George Rhodes,[1] Ruben M. Sandoval,[1] Sarah E. Wean,[1] Fnu Ashish,[3] Bruce A. Molitoris.[1,2,4] *[1]Medicine, Indiana Univ School of Medicine, Indianapolis, IN; [2]Cellular & Integrative Physiology, Indiana Univ School of Medicine, Indianapolis, IN; [3]CSIR-Inst of Microbial Technology, Chandigarh, India.*

Background: Elevated urea levels in CKD patients leads to carbamylation, a chemical modification of lysines within proteins. This irreversible non-enymatic posttranslational modification results in formation of e-amino-carbamoyl-lysine (homocitrulline) a hallmark of aging as evidenced by carbamylation of skin and matrix proteins. Elevated serum urea also promotes albumin carbamylation, a known risk factor for mortality in CKD patients, and was recently found to be associated with heart failure and mortality in diabetic patients with ESRD.

Methods: Since cubilin/megalin and FcRn interact to mediate PT transcytosis of albumin we investigated if carbamylated albumin would be handled differently by the kidney by quantifying binding to both FcRn and cubilin.

Results: Independent binding (K_D) to either FcRn or cubilin was measured using Microscale Thermophoresis and found to be markedly reduced, $p<0.0001$ (FcRn 2.0 ±0.5 to 37.0 ±1.7 mM, Cubilin 0.16 ± 0.007 to 2.4 ± 0.14 mM). Since the isoelectric point of carbamylated albumin was more anionic than unmodified albumin we also determined how other charge modifications impacted binding. Alterations in albumin charge are likely to occur when different drugs such as antibiotics and other molecules interact with albumin. Binding analysis showed similar binding for cationic albumin to both FcRn (1.2 mM) and cubilin (0.12 mM) while anionic albumin had weaker binding to cubilin (5.4 mM, $p<0.0001$) and FcRn (>100 mM, $p<0.0001$).

Conclusions: To further understand the molecular cubilin-albumin interaction we performed molecular docking of cubilin 7, 8 domains with albumin. This revealed a lysine residue in albumin likely to be carbamylated that could contribute to the weaker binding observed. Studies are presently underway to quantify serum clearance and *in vivo* handling of these albumins in order to better understand their physiological processing.

Funding: NIDDK Support, VA Support

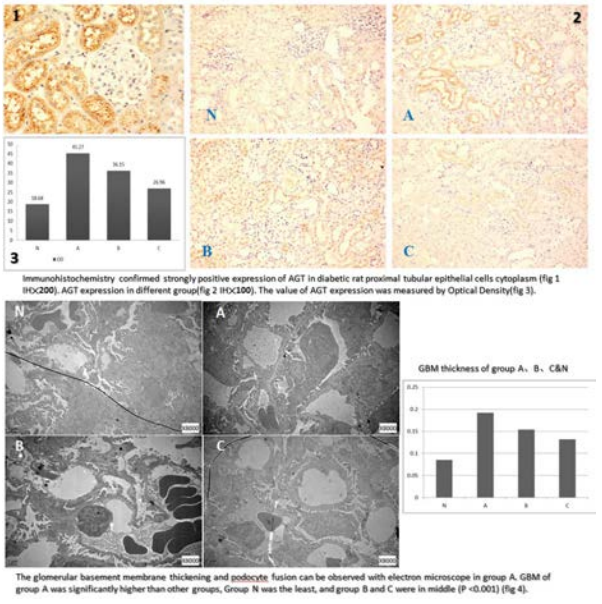
PUB272

Urinary Angiotensinogen Is a New Biomarker of Early Renal Pathological Change in Diabetic Rats Zhuang Zhen, Jiaxuan Lv. *Nephrology, Beijing Tsinghua Changgung Hospital, Beijing, China.*

Background: Urinary angiotensinogen might be a marker for activation of renin-RAS of DN. The purpose of this study was to investigate the relationship between AGT in blood, urine and renal tissue with renal function, renal pathological changes in diabetes animal models with the intervention of ARB drugs, to explore the functional roles of UAGT changes in the pathogenesis of DN and possible mechanisms.

Methods: 41 rats,4 groups, diabetic group and healy controll,the other two diabetic groups were treated with different doses of losartan.In a 12-week investigation, we detected the changes of AGT in all rats' blood and urine and the association between RAS activation and urinary proteins were analyzed in this study. After 12 weeks, we made renal tissue specimens, and stained observe pathological changes. By immunohistochemistry we detected the expression of AGT.

Results: The serum AGT had no significant differences. The urinary AGT of the diabetic rats was significantly different from the control group, the UAGT of the diabetic rats under different treatments was also obviously different. The level of UAGT was positively associated with urinary protein ($r=0.493$, $P<0.01$) and negatively correlated with CCr ($r=-0.474$, $P=0.007$). Further immunohistochemistry confirmed strongly positive expression of AGTin diabetic rat proximal tubular epithelial cells cytoplasm. The value of AGT expression was measured by Optical Density. Group A was significantly higher than other groups, group B and C expression decreased gradually($P<0.001$). The GBM thickening and podocyte fusion can be observed with electron microscope in group A. GBM of group A was significantly thicker than other groups ($P<0.001$).



Conclusions: In the early stage of DN, rising UAGT reflects renal local RAS activation and is associated with proteinuria, and damaged renal function. UAGT is a new biomarker of early pathological changes in diabetic rats.

PUB273

Meprin β-Associated Changes in Serum and Urine Metabolite Profiles of Mice with Streptozotocin (STZ) Induced Type 1 Diabetes
Jessica Gooding,[2] Jean-Marie V. Niyitegeka,[1] Susan Mcritchie,[2] Susan Sumner,[2] Elimelda Moige Ongeri,[1] Courtney Whitaker.[2] *[1]Biology, North Carolina A&T State Univ, Greensboro, NC; [2]NCTraCS Metabolomics Core, RTI International, Research Triangle Park, NC.*

Background: The pathophysiology of diabetic nephropathy (DN) is not fully understood. Meprin metalloproteinases are the most abundantly expressed proteins in the brush border membranes of proximal kidney tubules. Meprin ß has been implicated in the pathophysiology of DN in humans and mice. Single nucleotide polymorphisms (SNPs) in the meprin ß gene were associated with human DN in the Pima Indians, a US ethnic group with extremely high rates of diabetes and DN. The mechanism(s) by which meprins modulate the progression of DN are not known.

Methods: Low dose STZ was used to induce type 1 diabetes in 8 week old male wild-type (WT) and meprin ß knockout (ßKO) mice. Control mice were injected with sodium citrate buffer. Urine and blood samples were collected at 4 and 8 weeks post-STZ injection. Enzyme-linked immunosorbent assays (ELISA) were used to determine the levels of creatinine and two protein-based kidney injury markers, neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1). For metabolomics analysis, plasma and urine samples were loaded onto a UPLC-QTOF system for separation by HILIC chromatography and detection in MS^E mode.

Results: Diabetic meprin ßKO mice had significantly higher levels of plasma NGAL at 4 weeks but not at 8 weeks post STZ injection. The levels of urinary KIM-1 were significantly higher in meprin ßKO mice at both 4 weeks and 8 weeks when compared to their WT counterparts. Multivariate data analysis (OPLS-DA) showed urine metabolites important to differentiating meprin ßKO mice and WT, including four metabolites that have previously been shown to be indicators of kidney injury (*Hippuric acid, Methyladenosine, L-Carnitine, and Nicotinic acid).*

Conclusions: Meprin ß partially protects mice from the tubular kidney injury associated with diabetes. Meprin β expression and/or activity impacts the levels of plasma and urine metabolites in DN. The identities of these metabolites will advance understanding of the metabolic pathways impacted by meprins in DN.

Funding: Other NIH Support - NIH/NIGMS # SC3GM102049; NIH Center Grant # U24DK097193 NIH/NCATS award # UL1TR001111; and NIGMS # K01GM109320

PUB274

Carbamylation Is a Potent Competitor of Glycation for Protein Modifications In Vitro Et In Vivo
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Background: Chronic kidney disease (CKD) and diabetes mellitus accelerate protein aging through nonenzymatic post-translational modifications like glycation (addition of sugars) and carbamylation(addition of isocyanic acid, mainly generated from urea dissociation) occurring on the same binding sites. Our objective was to evaluate their potential competitive effect.

Methods: *In vitro*, albumin was incubated for three weeks with glucose, urea or cyanate. *In vivo*, carbamylation was amplified by subtotal-nephrectomy or oral cyanate consumption for 6 weeks in diabetic (*db/db*) or non-diabetic mice. LC-MS/MS was used for measuring carbamylation (homocitrulline, carbamylated hemoglobin) and glycation (furosine) markers. Fructosamine and HbA1c were measured by colorimetry and immunoassay, respectively.

Results: A reciprocal inhibition of 30% between glycation and carbamylation was evidenced *in vitro*. *In vivo*, after 5 weeks of CKD, plasma HCit concentrations were indifferently increased in diabetic or control mice. On the contrary, fructosamine and HbA1c were decreased in CKD-diabetic compared to diabetic mice. These decreases, (-16% and -35% respectively, $p<0.05$) were confirmed, in cyanate vs water drinking diabetic mice.

Conclusions: *In vitro* glycation and carbamylation inhibit reciprocically. However, *in vivo*, carbamylation gets the upper hand. Thus, classical markers of diabetes metabolic control should be interpreted with caution in diabetic patients with CKD because of this competitive effect.

PUB275

Association between Body Mass Index, Abdominal Circumference and Blood Pressure, Fasting Blood Sugar, HbA1c in Retired People of a Japanese Company
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Background: Body mass index(BMI) and abdominal circumference(AC) is associated with blood pressure(BP),fasting blood sugar(FBS),and HbA1c. However, reference values of BMI,AC as risk factors to BP,FBS,HbA1c remain controversial in Japanese. We analyzed results of medical check up in retired people of a Japanese company to disclose association between BMI,AC and BP,FBS,HbA1c.

Methods: We recruited total 24781 person retired of a Japanese company who are 50-74years old between 2004 and2014 and analyzed their results of medical check up to check the correlations between BMI,AC and BP,FBS,HbA1c.We used linear mixed model. BMI was divided into 5 subgroups:A;<18.5,B;18.5≤BMI<22,C;22≤BMI<25,D;25≤BMI<30 ,E;≥30kg/m^2. AC was divided into 4 subgroups:F<80,G;80≤AC<85,H;85≤AC<90,I;≥90cm.

Results: BMI and systolic BP became linear relation.(CvsA ,estimated value[;EV];-5.65mmHg, P<0.0001.CvsB,EV-2.63, P<0.0001. CvsD,EV3.00,P<0.0001. CvsE,EV7.87,P<0.0001.)After correct by BMI,AC and systolic BPbecame linear relation. (FvsG,EV1.12mmHg,P<0.0001.FvsH,EV2.21,P<0.0001.FvsI,EV3.35,P<0.0001.) BMI and FBS became linear relation.(CvsA ,EV-1.87mg/dl, P<0.0001.CvsB,EV-1.12, P<0.0001. CvsD,EV1.97,P<0.0001.CvsE,EV7.84,P<0.0001.)BMI and HbA1c became linear relation.(CvsA ,EV-0.04%, P<0.0001.CvsB,EV-0.03,P<0.0001. CvsD,EV0.06,P<0.0001. CvsE,EV0.28,P<0.0001.)After correct by BMI,AC and FBS became linear relation. (FvsG,EV0.94mg/dl,P<0.0001.FvsH,EV2.04,P<0.0001.FvsI,EV3.15,P<0.0001.) After correct by BMI,AC and HbA1c became linear relation.(FvsG,EV0.02%,P<0.0001. FvsH,EV0.05,P<0.0001.FvsI,EV0.09,P<0.0001).

Conclusions: The elevation of SBP,FBS andHbA1c was observed for a AC of 80cm and up,and a BMI of 25 kg/m2 and up in middle-aged and elderly Japanese.

Funding: Government Support - Non-U.S.

PUB276

Renal Biopsy Findings in Patients with Diabetes: Experience in our Centre
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Background: The prevalence of renal disease unrelated to diabetes(NDRD)in patients with diabetes mellitus(DM)is variable.To be able todistinguish between both categories is an important issue given their prognostic and therapeutic implications.The sudden onset of nephrotic syndrome(NS),late age at diagnosis of the disease,the short duration of DM,the absence of retinopathy or hematuria and acute kidney injury(AKI)are considered as predictors of NND.The aim of our study is to assess renal biopsies performed in diabetic patients and correlate histological findings with clinical and laboratory parameters,in order to know which variables are associated with NND.

Methods: We retrospectively reviewed the medical records of patients who underwent kidney biopsy from January 2008 toDecember 2015.The indications of renal biopsy included:AKI,chronic kidney disease(CKD)and NS.Based on the biopsy findings the patients were categorized as:isolated diabetic nephropathy(DN,group 1);NDRD superimposed on DN(DNNDRD,group 2);isolated NDRD(group 3).

Results: A total of 54 patients underwent renal biopsy.Indications for kidney bio psy:AKI(64.4%),NS(20.3%),CKD(13.4) and nephrotic proteinuria(1.9%).In 72% of cases we found histological lesions different to DN.Glomerulonephritis(GN,27.5%),ac ute interstitial nephritis(AIN,18.5%),acute tubular necrosis(ATN,18.5%),hypertensive nephrosclerosis(5.5%) and myeloma cast nephropathy(1.8%).Proteinuria was significantly higher in patients with DN alone when compared to patients with NDRD or DNNDRD. Longer duration of DM and presence of retinopathy was more prevalent in groups 1 and 2 compared to group 3.Hematuria and leukocyturia was more common in patients with NDRD or DNNDRD.GN,AIN and ATN were the most common findings seen in all NDRD.

Conclusions: 70% of biopsies in diabetic patients revealed NDRD,most of them would alter treatment decisions.Tubulointerstitial lesions were a common biopsy finding with higher incidence of ATN and AIN.The shorter duration of DM and no previous CKD were the main predictors of NDRD.An active urinary sediment and the absence of diabetic retinopathy suggests a different lesion to DN.

PUB277

Cortical Distribution Pattern of Renal Histopathological Lesions in Type 2 Diabetes Takaya Sasaki, Kentaro Koike, Nobuo Tsuboi, Go Kanzaki, Kotaro Haruhara, Yusuke Okabayashi, Tetsuya Kawamura, Yoichi Miyazaki, Makoto Ogura, Takashi Yokoo. *Div of Kidney and Hypertension, The Jikei Univ School of Medicine, Minato-ku, Tokyo, Japan.*

Background: The renal histopathological findings in diabetic nephropathy show some variation in severity within the same kidney specimen of each individual. However, the potential mechanisms involved in such variation remain largely unknown. We previously reported the zonal distribution patterns of renal lesions in non-diabetic kidneys (2015 ASN). The aim of this study was to examine whether or not the distribution of diabetic renal lesions is related to the renal anatomical organization.

Methods: We examined both the juxtamedullary (JM) and superficial (SF) cortices of autopsied kidneys with a history of type 2 diabetes. The renal histopathological findings closely related to diabetes were evaluated in 50 glomeruli per cortex. The cortical distribution index (CDI) was defined as follows to quantify the distribution pattern: CDI = (SF - JM) / (mean value of SF and JM).

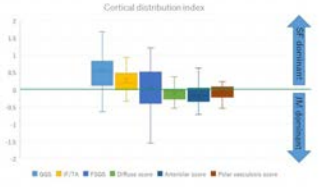
Results: A total 42 autopsy kidneys were analyzed. The average values were age of 74 years and estimated glomerular filtration rate (eGFR) of 71 ml/min/1.73 m^2. Some diabetes-specific lesions showed significant zonal differences, while other lesions did not (Table). The scores for diffuse lesion, arteriolar hyalinosis and polar vasculosis were significantly higher in the JM cortex than in the SF cortex (Figure). Neither age nor eGFR nor hypertension were found to be independent factors associated with the CDI of each lesion in multivariate analyses.

Table

Variables	Value		
	SF cortex	JM cortex	p-value*
Global glomerulosclerosis (%)	22.1±11.1	14.8±10.6	<0.001
Interstitial fibrosis/tubular atrophy (%)	24.6±14.9	20.1±14.3	<0.001
Segmental glomerulosclerosis	5.05±3.90	4.88±3.78	NS (0.426)
Diffuse score	1.05±0.71	1.15±0.71	0.002
Arteriolar hyalinosis score	1.22±0.55	1.40±0.59	0.020
Polar vasculosis	0.522±0.179	0.563±0.200	0.050
Nodular lesion	2.60±6.15	2.88±7.00	NS (0.186)
Duplication	14.7±10.1	16.0±8.8	NS (0.051)
Mesangiolysis	2.28±3.20	3.05±4.85	NS (0.240)
Exudative lesion	1.55±2.03	1.83±2.42	NS (0.409)

*: Wilcoxon signed-rank test

Figure



Conclusions: These results suggest that the glomeruli in the JM cortex may be more susceptible to specific renal histopathological lesions in diabetes than those in the SF cortex. The structural and/or functional differences, which are independent of age, renal function, and blood pressure, may have marked influence on the development of such lesions.

PUB278

Dialysis in Vancomycin Toxicity Jason M. Kidd, Andinet Gizaw, Todd W. Gehr. *Internal Medicine, Div of Nephrology, Virginia Commonwealth Univ Medical Center, Richmond, VA.*

Background: Vancomycin is a glycopeptide antibiotic used to treat gram positive infections including MRSA. Therapeutic monitoring of serum levels is widely performed by clinicians with the expectation this will lead to improvement in treatment as well as minimize toxicity.Known adverse effects of include infusion related reactions as well as nephrotoxicity. Nephrotoxicity is more common in patients receiving other nephrotoxins or who have altered hemodynamics. The molecular weight of vancomycin is 1450 Da and it is 10-50% protein bound. We present a case utilizing high efficiency dialysis to remove vancomycin in a patient with oliguric renal failure due to vancomycin nephrotoxicity.

Methods: A 58 year old female with myelodysplastic syndrome was admitted with neutropenic fever. She was empirically treated with intravenous vancomycin 1 g every 12 hours for 4 days. Dose was then increased to 1250 mg every 8 hours for the next 5 days based on initial clearance data. The patient's serum creatinine was 0.4 mg/dl on the day of admission. On day 11, her serum creatinine had increased to 0.8 mg/dl. A vancomycing level was checked and was found to be 400 mg/l. She was oliguric. She had no eosiniophilia and urine sediment was bland. In the setting of her renal failure and toxic vancomycin level, dialysis was initiated.

Results: The patient was initially treated with high flux, F-180 dialyzer for an 8 hour treatment after which her vancomycin level decreased to 113 mg/l. The following day, she was dialyzed again for 4 hours and level was 61 mg/l. The next morning, her vancomycin level had increased to 81 mg/l, likely related to tissue rebound. Dialysis was repeated on this day for a 6 hour treatment and level the next morning was 42 mg/l. Her urine output subsequently increased and vancomycin level slowly decreased over the next several days without further dialysis sessions.

Conclusions: Hemodialysis with a high flux dialyzer removes significant amounts of vancomycin. Nephrotoxicity from vancomycin is generally self limited. This case illustrates a potential use of high flux hemodialysis in patients with severe toxicity.

PUB279

Safety and Efficacy of Citrate Anticoagulation for Continuous Renal Replacement Therapy for Acute Kidney Injury following Liver Transplantation: A Single Centre Experience Nicoletta Pertica, Paolo Ria, Gianluigi Zaza, Antonio Lupo. *Nephrology, AOUI, Verona, Italy; Nephrology, AOUI, Verona, Italy; Nephrology, AOUI, Verona, Italy; Nephrology, AOUI, Verona, Italy.*

Background: Acute kidney injury (AKI) following liver transplantation (LTx) is a frequent and serious complication with an high incidence of requiring continuous renal replacement therapy (CRRT). KDIGO guidelines indicate the use of citrate as loco-regional anticoagulant drug for CRRT regardless patient's hemorrhagic risk, however, the use of citrate is still under debate in patients with liver failure and/or LTx because of the potential risk of plasmatic citrate accumulation due to reduced liver clearance. Aim of the study wash to evaluate the safety and efficacy of citrate as locoregional anticoagulation drug in CRRT for AKI following LTx.

Methods: A retrospective analysis was performed in 5 patients with AKI post Ltd who were tremate in out transplant centre with CRRT using citrate as local anticoagulant. No patients with very high liver enzimes after LTx (more than double the normal range) were included. All the patients were treated with CVVHDF, using Trisodiumcitrate solution with a concentration of 18 mmol/l each bags.

Results: All the patients developed AKI during the early peri-operative corse. The main indication to CRRT was fluidi overload. No patients showed complications related to citrate accumulation. 4 patients were treated at the beginning with heparine as anticoagulant and then shifted to citrate caused by circuits coagulazione. Treatments with citrate was interrupted where it was no longer needed or when other examinations had to be made. None were stopped due to circuit coagulation.

HEPARIN						
	Total number of dialysis sessions	Sessions number	Heparin dose (U/h)	Protamine	Average time (Hours)	Number of session interrupted for clotting
Patient 1	7	3	750	YES	7	3
Patient 2	2	NO SESSIONS WITH HEPARINE				
Patient 3	22	16	500	YES	20,5	16
Patient 4	4	1	750	NO	22	1
Patient 5	3	4	750	YES	9,75	3
Median Value			550		14,8	

CITRATE						
	Total number of dialysis sessions	Sessions number	Citrate dose (U/h)	Metabolic complications	Average time (Hours)	Number of session interrupted for clotting
Patient 1	7	4	2,4	NO	24,5	0
Patient 2	2	2	2,4	NO	72	0
Patient 3	22	6	2,5	NO	55,3	0
Patient 4	4	4	2,5	NO	42,25	0
Patient 5	3	1	3	NO	48	0
Median Value			2,56		48.4	

Tab 2: CRRT data

Conclusions: Our result, even if in a small series of patents, evidence that CRRT with citrate can be a safe and promising treatment for AKI after Ltx.

PUB280

Administration of Iron Sucrose and Ferric Carboxymaltose during Hemodialysis (HD) Does Not Accelerate Lipid Peroxidation Jaromir Eiselt,[1] Daniel Rajdl,[2] Lukas Kielberger.[1] *[1]Internal Dept 1, Charles Univ, Plzen, Czech Republic; [2]Dept of Biochemistry, Charles Univ, Plzen, Czech Republic.*

Background: Intravenous iron (Fe_{iv}) may induce oxidative stress. Isoprostanes, specifically 8-iso-Prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$), represent a reliable biomarker of *in vivo* lipid peroxidation. We sought to determine whether administration of two Fe_{iv} formulations and a sham comparator affect the level of 8-iso-$PGF_{2\alpha}$ in HD patients.

Methods: A total of ten maintenance HD patients received intravenous infusion of a) 200 mg of iron sucrose in 100 mL of normal saline, b) 200 mg of ferric carboxymaltose in 100 mL of normal saline, c) 100 mL of normal saline without iron (sham comparator) from minute 60 to 90 of HD. Plasma levels of 8-iso-$PGF_{2\alpha}$ were assessed before infusion (minute 60 of HD), after infusion (min. 90), 1 hour after infusion, at the end of HD and before the next HD session using enzyme immunoassay.

Results: We did not detect significant changes in the level of 8-iso-$PGF_{2\alpha}$ after administration of two different Fe_{iv} agents. Moderate decrease of 8-iso-$PGF_{2\alpha}$ documented after infusion of the sham comparator could reflect an imbalance between elimination of the free fraction of 8-iso-$PGF_{2\alpha}$ without concomitant formation of this substance in the absence of Fe_{iv}. Results are presented in table 1.

Plasma 8-iso-prostaglandine $F_{2\alpha}$ (pg/L) before and after iron infusion during hemodialysis					
	Before Fe_{iv} infusion (min. 60 of HD)	End of Fe_{iv} infusion (min. 90 of HD)	1 h after Fe_{iv} (min. 150 of HD)	2.5 h after Fe_{iv} (min. 240 of HD)	46 h after Fe_{iv} (before next HD)
Iron sucrrose	27 (24-30)	33 (26-35)	31 (29-33)	24(23-27)	35 (24-38)
Ferric carboxymaltose	20 (17-28)	21 (18-25)	19 (18-22)	20 (18-23)	23 (20-25)
Isotonic saline (sham comparator)	22 (18-31)	18 (16-25) [a]	24 (17-30)	25 (19-31)	26 (21-29)
Data are expressed as median (interquartile range); Friedman test; [a] $p<0.05$ *vs.* min. 60, min. 240 and before next HD					

Conclusions: The study did not prove any acute effect of tested iron preparations on oxidative stress. Single infusion of iron sucrose or ferric carboxymaltose administered during hemodialysis does not cause measurable elevation of 8-iso-$PGF_{2\alpha}$.

Funding: Government Support - Non-U.S.

PUB281

Impact of Comorbidities on Hemoglobin Stability in CKD Patients on Hemodialysis, Treated with C.E.R.A. in Current Practice: Is the Comorbidity Scoring Still Useful? The MIRIADE Study

Luc Frimat,[1] Philippe Zaoui,[2] Jean-Paul Jaulin,[3] Mustapha Amirou,[4] Gilles Sinnasse-Raymond,[5] David Pau,[5] Guy Rostoker.[6] *[1]Nephrology, Nancy Univ Hospital, Vandoeuvre, France; [2]Nephrology, A Michallon Hospital, Grenoble, France; [3]Nephrology, Les Oudairies Hospital, La Roche sur Yon, France; [4]Nephrology, Jacques Puel Hospital, Rodez, France; [5]Medical Dept, Roche, Boulogne Billancourt, France; [6]Claude Galien Private Hospital, Quincy sous Sénart, France.*

Background: The MIRIADE study assesses the real-life impact of comorbidities on hemoglobin (Hb) stability in patients (pts) with chronic kidney disease on hemodialysis (HD), treated with C.E.R.A., its use, and safety.

Methods: In this French prospective and multicenter cohort, a 6-month data collection was performed from C.E.R.A. initiation following erythropoietin stimulating agent (ESA) treatment, in HD pts with Hb level between 10 and 12 g/dL. Comorbidities were defined by the Charlson Index (CCI adjusted on age) and Hb stability as a variation of +/- 1g/dL after the 6-month treatment period.

Results: From the 585 pts included in efficacy analysis in 2014, 58% were men. The CCI distribution was as follows: CCI ≤3 (12% of pts), 4 ≤ CCI ≤5 (17%), 6 ≤ CCI ≤7 (31%) and CCI ≥8 (40%). At C.E.R.A. start, its median monthly dose was always under the theoretical conversion dose defined according to the previous ESA, and with a 100 µg/monthly dose over follow-up (little variation according to the CCI). Hb level was stable in 56% of pts (67% if CCI ≤3). Pts with stable Hb were more numerous to have Hb level between 10 and 12 g/dL at M6 (85% vs. 46% if non-stable Hb). Pts with inflammatory syndrome (CRP >5 mg/L, p=0.04), those having received more than 200 mg of IV iron (p=0.03), or those transfused prior to C.E.R.A. start (p=0.03) were less likely to reach stable Hb under C.E.R.A. at M6. Among the 644 C.E.R.A.-treated pts, 4 pts had one serious adverse event related to treatment.

Conclusions: In HD pts, a stable Hb level within the therapeutic target was observed in current practice with a lower C.E.R.A. dose, regardless of comorbidities scores.

Funding: Pharmaceutical Company Support - Roche

PUB282

Factors That Condition the Response to Erythropoietin in Patients on Hemodialysis

Natalino Salgado Filho,[1] Elton Jonh Freitas Santos,[2] Joyce S. Lages,[1] Gyl Barros-Silva,[1] Dyego José Araujo Brito,[1] Bernardete Jorge Leal Salgado,[1] Alcione Santos.[1] *[1]Federal Univ of Maranhão, São Luis, Brazil; [2]EBSERH - HUUFMA, São Luis, Brazil.*

Background: Anemia is an inevitable complication of hemodialysis patients, the main cause is erythropoietin deficiency. Several erythropoiesis-stimulating agents (ESAs) are available for treating anemia. However, part of the patients on hemodialysis remains anemic even using ESAs. This study was aimed at determining clinical-laboratorial factors associated with maintenance of hemoglobin levels < 10 g/dL in hemodialysis patients treated with recombinant human erythropoietin (EPO).

Methods: This was a prospective longitudinal analytical study that spread over a period of six months. Anemia was characterized as a hemoglobin level < 10 g/dL. A longitudinal logistic regression model with random effects was used to analyze the relationship clinical-laboratorial parameters with the anemia. To evaluate the dose-response effect of EPO therapy, we used the erythropoietin resistance index (ERI), calculated as the weekly weight-adjusted dose of EPO divided by the hemoglobin level.

Results: The prevalence of anemia in the study period ranged from 23.91% to 43.80%, in the adjusted analysis. The increase in the probability of anemia was negatively associated with age (**-0.016; p=0.039**) and the body mass index (**-0.057; p=0.032**). Positively with: the presence of hypertension (**1.040; p=0.019**), the ferritin (**0.318; p=0.005**), the erythropoietin resistance index (**0.184;p<0,001**) and the C-reactive protein (**0.270; p=0.002**).

Conclusions: We observed a high anemia prevalence and the factors associated were: age, nutritional status, hypertension, inflammation and recombinant human erythropoietin resistance.

PUB283

Utilization of Darbepoetin Alfa as an Erythropoiesis Stimulating Agent in Patients Receiving In-Center Hemodialysis

Mahmoud T. El-Khatib,[1,2] Heather Duncan,[1] Kotagal Shashi Kant.[1,2] *[1]Internal Medicine, Nephrology & Hypertension, Univ Cincinnati Coll Med, Cincinnati, OH; [2]Dialysis Clinic, Inc, Cincinnati, OH.*

Background: Previous studies have compared Epoetin alfa with Darbepoetin alfa and demonstrated equivalence in safety and efficacy for the treatment of anemia in chronic kidney disease. Other studies indicate that the cost of using Darbepoetin alfa is higher than Epoetin alfa. These studies have compared the two Erythropoiesis Stimulating Agents (ESAs) with intravenous (IV) administration of both drugs, but no subcutaneous (SC) route comparison is available. This study compares differences in hemoglobin and ESA dose, as well as IV iron dose and resulting iron stores after switching the entire dialysis unit from Epoetin alfa given SC to Darbepoetin alfa given IV.

Methods: Records for 78 patients who dialyzed in the same unit between January to April 2015 (Epoetin) as well as January to April 2016 (Darbepoetin) were reviewed for labs and medication administrations. To compare doses of these two drugs, a conversion of 3000 units of Epoetin to 10 mcg Darbepoetin was used to create ESA equivalent doses in mcg. Patients served as their own controls so that Paired t-tests could be used to analyze the differences.

Results: A statistically higher hemoglobin was found in the Darbepoetin period compared to the Epoetin period. Ferritin was lower in the Darbepoetin period, while T-sat and albumin were equivalent. ESA equivalent doses were lower with Darbepoetin, but more iron was used. While controlled by DCI algorithms, the number of ESA dose changes in the four month period was lower in the Darbepoetin period.

all data are the mean of 4 months	Hemoglobin (g/dL)	Ferritin (ng/mL)	T-Sat (%)	Albumin (g/dL)	IV Iron use (mg/month)	ESA dose (mcg/month)	total dose changes in 4 months
2015-Epoetin	11.20	1202.6	28.5	3.94	103.5	89.1	4.8
2016-Darbepoetin	11.39	1075.6	29.2	3.96	142.8	76.5	3.7
p	**0.02**	**0.015**	0.42	0.28	**0.005**	**0.03**	**.008**

Conclusions: Hemoglobin was higher and dose changes were less frequent when Darbepoetin was used and less ESA was needed to maintain hemoglobin levels. More iron was given with Darbepoetin, yet ferritin was lower.

PUB284

Differential Oxidative Stress and Endothelial Dysfunction Induction by Brand and Generic Sodium Ferric Gluconate Formulations

Amy Barton Pai,[1] Paul H. Neumann,[2] Teresa Marie Regis.[2] *[1]Univ of Michigan College of Pharmacy, Ann Arbor, MI; [2]Albany College of Pharmacy and Health Sciences, Albany, NY.*

Background: Intravenous iron products are colloidal nanoparticle suspensions making formulation of bioequivalent generics challenging. Differences in oxidative stress induction with generic iron sucrose outside the US compared to the reference listed drug (RLD) have been shown. There are no data comparing oxidative stress by the RLD Ferrlecit® and the only FDA approved generic, sodium ferric gluconate complex (SFGC).

Methods: Human umbilical vein endothelial cells were incubated with Ferrlecit® and SFGC in dose response (0 to 200 mcg/mL for 24 h) and time (0 to 24 h) studies. Induction of the transcription factor nuclear factor erythroid-2-related factor 2 (Nrf2), a master regulator of detoxification and heme-oxygenase 1 (HO-1) a Nrf2-regulated enzyme were determined in lysate by immunochemistry. Intracellular labile iron (ILI) was determined the Phen Green SK fluorescent probe. Endothelial cell monolayers were treated with each product at 50 µg/ml for 24 h and permeability was measured by the clearance rate of labeled albumin between the luminal and abluminal compartments.

Results: ILI significantly increased dose dependently with both formulations. Ferrlecit® treated cells had higher ILI at all studied doses except 50 µg/ml ($p<0.01$). Induction/stabilization of Nrf2 by Ferrlecit® was greater than SFGC at all doses, significancant at the 100 mcg/mL dose ($p<0.05$). Similarly, Ferrlecit®-induced upregulation of HO-1 was greater than SFGC at all doses, significantly at the 100 and 200µg/mL doses ($p<0.001$). At 50µg/ml, both compounds induced significant stabilization of Nrf2 by 3 to 6 hours ($p<.0001$). HO-1 increased with SFGC at 24 hours ($p<0.0001$) but was lower than Ferrlecit® ($p<0.0004$). Both IV iron formulations increased endothelial barrier permeability, which was significant for Ferrlecit® ($p<0.05$), compared to untreated controls.

Conclusions: The generic SFGC was associated with a lower oxidative stress response and endothelial permeability despite being a "bioequivalent" product. These differences may be due, in part, to different labile iron release profiles and requires further study.

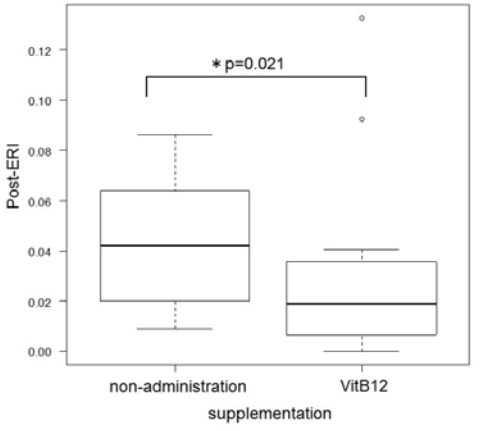
PUB285

Vitamin B12 Can Reduce Dose of Erythropoietin Even in Elderly Hemodialysis Patients Suspected for Potential Vitamin B12 Deficiency Shunichi Shibazaki, Katsuji Tuda, Kohei Miura, Makoto Araki. *Nephrology, Suwa Central Hospital, Chino, Nagano, Japan.*

Background: Potential vitamin B12 deficiency is often overlooked, even though it is a common nutritional deficiency in elderly hemodialysis patients because aging itself is a risk factor and dialysis removes vitamin B12. We attempted to evaluate whether a vitamin B12 supplement can reduce a dose of erythropoietin even with suspected potential vitamin B12 deficiency, which is diagnosed with homocystine and Vitamin B12 values.

Methods: A cohort study was conducted by collecting data from September 2015 to March 2016 at Suwa Central Hospital. Inclusion criteria were: outpatients in maintenance hemodialysis, over 65 years old, suspected potential vitamin B12; vitamin B12 < 400 pg per milliliter (lower limit of normal range), and homocysteine > 13.5 nmol per milliliter. We divided participants into two groups: a vitamin B12 supplementation group (injections of more than 500 µg per week) and a non-supplementation group. We evaluated the erythropoietin resistance index (ERI) between the two groups at the start and three months later. ERI was determined as the weekly weight-adjusted dose of darbepoetin (µg/kg/week) divided by hemoglobin concentration (g/dL).

Results: 24 patients were included. There was no difference in hemoglobin concentration, vitamin B12 concentration and frequency of iron deficiency at the start. There was also no difference in ERI; both groups were 0.04. Vitamin B12 concentration became higher in the supplementation group (> 1,500 pg per milliliter) than in the non-supplementation group (297 pg per milliliter) after three months. ERI improved in the supplementation group (0.02), but deteriorated in the non-supplementation group (0.05, p = 0.021) .



Conclusions: Vitamin B12 supplement can improve ERI and reduce dose of erythropoietin even in elderly hemodialysis patients with suspected potential vitamin B12 deficiency.

PUB286

Algorithm Based Erythropoiesis Stimulating Agents Dosing to Improve Anemia Management in a Pediatric Hemodialysis Population Shagun Berry,[1] Beth A. Vogt,[2] Robert J. Cunningham,[2] Tamar Y. Springel.[2] *[1]Dept of Biology, Case Western Reserve Univ, Cleveland, OH; [2]Dept of Pediatric Nephrology, Rainbow Babies Children's Hospital at Univ Hospitals, Cleveland, OH.*

Background: Dialysis providers attempt to maintain hemoglobin (Hgb) levels within a goal range. We set out to improve the number of patients meeting the Hgb target, which we set at 10-12 g/dL, with a computer-based algorithm for dosing of erythropoiesis stimulating agents (ESA) in a pediatric hemodialysis (HD) population.

Methods: Population: Chronic HD patients at our institution from 2013 until 2015. Algorithm: We utilized a Microsoft Excel based program that recommended an ESA dose based on the current and previous month's Hgb levels. Outcome: Our primary outcome was Hgb divided into three categories: <10, 10-12, and >12. Our secondary outcome was ESA dose in u/kg. Explanatory variables: We included race, age, Kt/V urea, intact PTH (iPTH), nPCR, percent iron saturation, and albumin. Statistic: Pre- and post-algorithm periods were compared. The association of the algorithm with Hgb category and ESA dose was tested by multinomial logistic regression and linear regression respectively. We adjusted for the explanatory variables.

Results: We had 17 patients, 7 pre- and 10 post-algorithm, with 55 Hgb values pre- and 94 post-algorithm. There were significant differences in age, iPTH, and albumin, however not in Hgb or ESA dose. The algorithm was associated with an increased risk of Hgb >12 (RRR=1.03, p=0.03).

Conclusions: This algorithm was not associated with improvement in Hgb 10-12 and was associated with an increased risk of Hgb >12. The increased risk was not associated with higher doses of ESA or higher iron saturation, which may indicate a more efficient ESA utilization. The retrospective nature and small size limit this study, however more at goal patients may result from adjustment of the algorithm.

PUB287

Intermittent Low Dose of Iron Supplementation Improves Erythropoietic Resistance Index and Reduces Hemoglobin Cycling in Chronic Hemodialysis Patients Tatsuo Tsukamoto, Motoko Yanagita. *Nephrology, Graduate School of Medicine, Kyoto Univ, Kyoto, Japan.*

Background: We have measured iron loss by iron contents of residual blood in the blood tubing set and dialyzer, and estimated that 500mg of iron would be lost by routine hemodialysis procedure in Japan (Am J Nephrol 2016,43,32-38). In this study, we show here the stable iron status as well as hemoglobin (Hb) level by an intermittent low dose of iron supplementation. Moreover, we demonstrate the improvement of erythropoietic resistance index (ERI) and the reduction of Hb cycling by the iron supplementary protocol in chronic hemodialysis patients.

Methods: 156 patients of Otowa Memorial Hospital were enrolled after informed consent. Men were consisted in 64.7%, and the mean age was 69.2±13.5 (m±SD). 40.4% was diabetic. 40mg of iron (saccharated ferric oxide) was administered once a month or every four weeks after hemodialysis session. Hb, TSAT (transferrin saturation), and ferritin were monitored every month before and after the intermittent iron supplementation. Erythropoiesis-stimulating agents (ESAs) used in this study were human recombinant erythropoietin (rHuEPO), darbepoetin-α (DA), and continuous erythropoietin receptor activator (CERA). DA was converted to 200U, and CERA was 240U of rHuEPO, respectively. ERI was calculated with rHuEPO dose in a month divided by Hb and body weight (dry weight). The dose of ESA was determined by an attending physician along the Japanese guideline for renal anemia in chronic kidney disease 2008.

Results: Hb levels kept from 11.2±1.0g/dL at the beginning to 10.9±1.0g/dL after 12 months. TSAT and ferritin did not change from 26.3±12.2% and 88.9±86ng/mL to 25.7±9.9% and 77.6±94.6ng/mL, respectively. ERI significantly reduced from 36.8±36.8 to 30.3±21.1. Hb cycling reduced from 123 times per 6 months before the supplement to 103 times after 6 months and 68 times after 1 year.

Conclusions: Intermittent iron supplementation (total 500mg a year) could improveERI and reduces Hb cycling with stable iron status in chronic hemodialysis patients.

Funding: Clinical Revenue Support

PUB288

Similar Anemic Control between Chronic Kidney Diseases Patients with and without Transplantation on Entry to Dialysis Ken Sakai,[1] Yasushi Ohashi,[3] Masaki Muramatsu,[1] Yoshihiro Itabashi,[1] Hiroki Hase,[2] Seiichirou Shishido.[1] *[1]Nephrology, Toho Unversity Ohmori Hospital, Tokyo, Japan; [2]Nephrology, Toho Unversity Ohashi Hospital, Tokyo, Japan; [3]Nephrology, Toho Unversity Sakura Hospital, Chiba, Japan.*

Background: Transplant recipients are supposed to be more anemic at re-entering hemodialysis due to chronic rejection. This study aimed to clarify how transplant recipients can re-enter dialysis safely by focusing on anemic control.

Methods: From 2012 to 2014, a total of 29 transplant recipients entered hemodialysis again by chronic rejection (Chronic Kidney Disease with Transplant: CKDT). At the same time, in 2014, a total of 30 CKD patients without transplantation entered dialysis as control group (CKD). CKDT recipients (age41.9±11.8yrs , m:f=18:10, diabetic 10%, duration of graft survival 12.5±4.3y) were younger and less diabetic compare to CKD (age53.2±10.5yrs , m:f=21:9, diabetic 36%). We analyzed both patient characteristics at entering dialysis by retrospective chart review.

Results: At entering dialysis, there was no significant differences for the dose of darbepoetin (DA:µg/month), Hb (g/dl), albumin(g/dl), CRP (mg/dl), CTR (%), eGFR (ml/min/1.73m^2), BUN (mg/dl), Cr (mg/dl) and initial ultrafiltration (UF: L/session) between CKD and CKDT. The only difference between groups was mean body weight (BW) at entry to dialysis (CKDT group, 58.5±15.1 kg; CKD group, 67.1±14.8 kg; P=0.03). However, DA dose per kilogram of BW did not differ between groups (CKDT, 2.28±2.03 µg/kg; CKD, 2.12±1.6 µg/kg; P=0.95) in the final month before entry to dialysis.

Conclusions: Safely re-initiation of dialysis is also important for recipients survival. Anemia was supposed to be higher in transplant recipients by immunosuppression, this single center analysis did not show any difference of anemia compare to CKD with well using ESA.

PUB289

MicroRNA 499 Gene Expression in Patients on Hemodialysis with Cardiovascular Complications Magdy M. Elsharkawy, Amr Mohab, Haitham Ezzat, Hesham Elsayed. *Nephrology Dept, Ain Shams Univ, Cairo, Egypt.*

Background: MicroRNA 499 is an evolutionarily conserved muscle-specific microRNA that is encoded by an intron of the myh7 gene and is likely to play a role in myosin gene regulation. It has been shown to be involved in inhibiting apoptosis and myocardial infarction. It is unknown whether levels of microRNAs are affected in patients undergoing hemodialysis.

Methods: The aim of this study was to assess circulating levels of microRNA 499 in hemodialysis patients and whether the levels are affected by dialyzer membranes (high flux vs low flux). The studied population consisted of 32 ESRD patients (22 males and 10 females) with an age ranged from 38-75 years on regular hemodialysis (4 hours, 3 times weekly) for at least one year duration with cardiovascular events in the last 6 months and 32 healthy controls (20 males and 12 females) with an age range from 54-60 years. Patients

were involved into a two-stage sequential study; high flux hemodialysis stage (stage I), then low flux hemodialysis stage (stage II). Expressed levels of plasma microRNA 499 have been measured by Real Time-PCR.

Results: Statistically significant higher levels of circulating microRNA 499 were observed in all the studied patients compared to the levels found in healthy controls ($p<0.0001$). MicroRNA 499 was found to be a dialyzable marker. A significant decrease in plasma levels of microRNA 499 was obtained after either high flux or low flux dialysis compared to plasma levels of microRNA 499 found before dialysis ($p<0.0001$). On comparing both types of hemodialysis membranes with respect to microRNA 499 clearance, we found that low flux membrane showed better clearance for microRNA 499 than high flux membrane with a statistically significant difference between them ($p<0.001$).

Conclusions: In conclusion microRNA 499 levels are elevated in patients with ESRD with cardiovascular complications. High flux membrane seems to be less efficient in microRNA 499 clearance in cardiac patients on hemodialysis.

PUB290

Lower Limb Vascular Disease in Patients on Chronic Hemodialysis Treatment Lene Boesby,[1] Julie Broesen,[1] Pernille Moerk Hansen.[2] *[1]Dept of Cardiology-Nephrology-Endocrinology, Hilleroed Hospital, Hilleroed, Denmark; [2]Dept of Nephrology, Herlev Hospital, Herlev, Denmark.*

Background: Patiens receiving chronic hemodialysis (HD) treatment have an elevated risk of developing vascular disease. The primary aim of this study was to evaluate the cause and frequency of lower limb arteriel ischaemia leading to surgical interventions, in a well characterized center-HD population. The secondary aim was to evaluate whether having diabetes mellitus (DM) influenced the result.

Methods: This is a single center retrospective study covering a 4-year period from 6.1.2008 - 6.1.2012. Combining registration codes for lower extremity amputation (digital, metatarsal, crus and femoral amputation (LEA)) and HD, patients were indentified and included in the study. Further data were registered from electronic patient files. Patients were excluded from the study if HD treatment was started < 3 months prior to LEA.

Results: We registered 180 HD-patients per year. 18 patients had ≥1 LEA during the investigation period, 8 (44%) of these patients had DM. There were no significant differences between gender, age, systolic or diastolic blood pressure, previous cardiovascular events, HD vintage or mineral metabolic control comparing LEA-patients with or without diabetes. In the group af patients with DM one was smoking at the time of LEA compared to four in the non-DM group. The number of re-amputations and patients who died within six months after LEA was higher in non-DM patients. Of the non-DM patients 63% had no previous record of consultations with chiropodist, orthopedic or vascular surgeon prior to LEA, whereas all of the DM patients had.

	non-DM (n=10)	DM (n=8)
Profylactic intervention	3	8
Re-LEA	4	2
Death < 6 months after LEA	8	5

Conclusions: In our population more than half of the patients who underwent LEA did not have DM. Only 37% of these patients have had an evaluation by chiropodist, orthopedic or vascular cunsultation prior to LEA, despite long HD vintage. To further explore these results a nationwide study is planned.

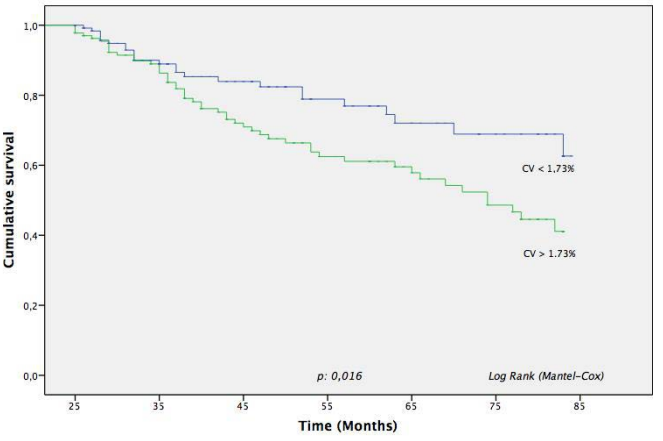
PUB291

Sodium Variability and Survival in Hemodialysis Patients Eduardo Baamonde, Nicanor Vega-Diaz, Elena Oliva-Damaso, Patricia Pérez Borges, Jose C. Rodriguez-Perez. *Nephrology, Hospital General Univ de Gran Canaria Dr. Negrin, Las Palmas, Spain.*

Background: The concentration of serum sodium (SNa^{+}) prehemodialisis (pre-HD) not always responds to the classic "set point" pattern. Recent evidence has shown that, variability of key laboratory parameters such as hemoglobin are also associated with important outcomes such as survival in HD patients Aims: we investigate the relationship between SNa^{+} preHD variability and survival in a population of HD patients.

Methods: Retrospective analysis of 261 prevalent HD patients (60.9% male; 51.7% diabetics; mean age 60.04 ± 14.09 years, time in HD: 69.64 ± 50.53 months; follow-up time: 48.78 ± 19.09 months). SNa^{+} concentration was corrected for glucose concentration. The first 24 SNa^{+} monthly measures were used for the study. SNa^{+} variability was calculated by the SD and coefficient of variation (CV).Crude mortality rates were computed. Kaplan-Meier, Log rank test and Cox regression were used to analyze the survival rate.

Results: 6221 determinations of SNa+ were analyzed. The average concentration of SNa^{+} was: 138,26 mEq/L (range: 151,65-120,86 mEq/L).The median of SNa^{+} SD and CV was 2,37 mEq/L and 1,73% respectively. The survival rate in the low CV group was significantly higher than in the other group.



Sodium variability low (blue) vs high (green)

This finding was corroborated in the adjusted Cox regression.

	Hazard Ratio	95% CI	p value
Age (years)	1,03	1,01 to 1,05	,020
KT/V	0,10	0,01 to 0,33	,000
IDGW (%)	0,43	0,24 to 0,76	,004
Albumin (g/dL)	0,11	0,01 to 0,31	,000
SNa^{+}CV (%)	0,57	0,35 to 0,94	,028
UF rate (ml/Kg/mn)	1,20	1,01 to 1,43	,044
Gender	0,67	0,39 to 1,12	,129
Diabetes	0,65	0,39 to 1,09	,103

Conclusions: Patiens with highest SNa^{+} variability show reduced survival compared with those with SNa^{+}lower variability. The relationship persisted after adjustment for potential confounders.

PUB292

Aldosterone Levels Elevated in Dialysis Patients: Are We Underused Blockers Renin Angiotensin-Aldosterone System? Ramiro Callejas,[1] Manuel M. Heras,[1] Carmen Rita Martin Varas,[1] Leonardo Calle,[1] Alvaro Molina,[1] Maria Astrid Rodriguez Gomez,[1] Olaia Rodriguez Fraga,[2] Vanesa Lopes-Martin,[1] Maria Jose Fernandez Reyes.[1] *[1]Dept of Nephrology, General Hospital Segovia, Segovia, Castilla y Leon, Spain; [2]Dept of Clinical Analysis, Univ Hospital La Paz, Madrid, Spain.*

Background: Serum aldosterone system (AS) is a marker of cardiovascular (CV) risk in the general population. **Objective:** To analyze AS levels in dialysis patients and its relationship with characteristics of dialysis; comorbidity ; blood pressure and use of blocking the renin angiotensin aldosterone system (BSRAA).

Methods: We determined AS in 102 patients (81 hemodialysis and 21 peritoneal dialysis); mean age 71.4 ± 12 years; 54.9% male; 29.4% diabetics; time on dialysis 59.3 ± 67meses. In 44 hemodialysis patients plasma renin (RP) was measured.

Results: The mean was 72.6 ± AS 114.9 ng / dl (vn 1.17-23.6 ng / dl). 57.8% of patients had levels above normal which were not related to dialysis characteristics or comorbidity. Twenty five treated with BSRAA had significantly lower levels of AS. Only 21% of patients with heart failure and and 19.2% with ischemic heart disease used BSRAA. There is an inverse correlation between AS and systolic blood pressure (BP) and direct with RP. The logistic regression analysis to see associated factors with AS levels above the median, systolic BP was the only independent risk variable in the overall population (OR 0.97; p = 0.022); in the 44 patients in whom RP was determined this was the only independent risk factor (OR 2.24; p = 0.012).

Conclusions: A high percentage of dialysis patients have elevated levels of AS that are not related to characteristics of dialysis and if with decreased systolic and activation of the RAAS. In patients with a history of heart disease the BSRAA are underused.

PUB293

Dual Control of Blood Pressure and Hemodynamics in Hemodialysis Patients Dan Sapoznikov, Michal Dranitzki Elhalel, Dvora Rubinger. *Nephrology and Hypertension Services, Hadassah Univ Medical Center, Jerusalem, Israel.*

Background: Systolic blood pressure (SBP) is dually controlled by baroreflex (BARO) and non-baroreflex (NON-BARO) sympathetically mediated central mechanisms.

Methods: To assess the relative contribution of these mechanisms during hemodialysis (HD), beat-to-beat SBP and interbeat interval (IBI) monitoring using Finometer device was performed during a 4 hr regular stable HD session in 49 non-diabetic patients (Pt), age 52±15 y. Cardiac output (CO), stroke volume (SV) and total peripheral resistance (TPR)

were calculated using the Modelflow simulation method. BARO and NON-BARO activity episodes were evaluated by two regression coefficients: 1. Calculation of the slope of the regression line between IBI and SBP in 1 min sequences; a positive regression coefficient was considered to be representative of BARO activity, and 2. A positive correlation between power spectrum of SBP in the low frequency range and SBP was considered to represent NON-BARO sympathetic activity. LFα coefficient, a measure of BARO function was calculated as the square root of the ratio between average IBI power and average SBP power in the low frequency band (0.04-0.15 Hz).

Results: The averaged variables for the 1st and the 4th HD hr (median and interquartile range) are shown in Table 1.

	HD 1st hr	HD 4th hr	p
SBP (mmHg)	132 (27)	132 (31)	NS
IBI (ms)	811 (170)	800 (190)	NS
% BARO episodes	35 (31)	43 (48)	0.006
% NON-BARO episodes	47 (60)	41 (50)	NS
CO (L/min)	6.94 (2.13)	5.68 (2.21)	0.001
SV(ml)	89 (26)	76 (36)	0.001
TPR (mmHg.s/ml)	0.863 (0.936)	0.998 (0.410)	0.001

During HD LFα increased from 3.73 (2.24) in the 1st to 3.98 (2.90) the last hr (p=0.013).

Conclusions: Our data show :1.During a stable HD session, the maintenance of constant SBP is achieved by a transition from centrally mediated sympathetic activity to activation of the baroreflex. 2.The decrease in CO and SV during ultafiltration is compensated by an increase in TPR.The interaction between BARO and NON-BARO mechanisms seems to be critical for intradialytic hemodynamic stability and prevention of hypotensive episodes.

PUB294

Percutaneous Perfusion Monitoring Provides Accurate and Timely Detection of Hemodialysis Induced Multi-Organ Injury

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Background: The safe delivery of hemodialysis (HD) faces dual challenges: (1) the accurate detection of systemic circulatory stress producing cardiovascular (CV) injury and (2) doing so within a time frame sufficient to enable effective proactive intervention. Non-invasive, real-time monitoring of CV stability is now available. We performed a pilot study to directly examine the capability of such technology to detect deleterious effects of HD upon two crucial vulnerable vascular beds (heart, kidney), using advanced multi-modal imaging.

Methods: 8 patients were repeatedly evaluated during HD with cardiac (echocardiography) and renal perfusion imaging (256-slice CT). Continuous CV physiologic monitoring was performed throughout using oximeter-based pulse waveform analysis [CVInsight® Monitoring System (CVI), Intelomed]. Longitudinal strain (LS) values for 12 left ventricular segments were generated using speckle-tracking software [EchoPac, GE], to assess the presence of HD-induced myocardial stunning. Renal perfusion was evaluated for the entire kidney.

Results: A reduction in pulse strength (PS) of >40% detected by CVI was associated with renal and cardiac ischemic challenge. This reduction occurred in 6/8 patients, all of whom exhibited myocardial stunning and a significant reduction in renal perfusion (p=0.04). The remaining 2 patients tolerated HD with maintained renal perfusion, no evidence of myocardial stunning or reduction in PS. The decrease in PS began early during HD (median 12 min, range 2-23 min). Earlier onset was associated with increased evidence of HD-induced multi-organ injury, with respect to both the degree of myocardial stunning (r=0.80, p=0.02) and fall in renal perfusion (r=0.78, p=0.04).

Conclusions: CVInsight® appears useful to identify patients vulnerable to circulatory stress during HD. Detection of the propensity for organ injury occurs early in HD and may potentially enable timely and pre-emptive intervention to prevent previously undetected recurrent insults to both residual renal function and the heart.

Funding: Pharmaceutical Company Support - Intelomed. Inc

PUB295

Erythrocyte Sodium Sensitivity (ESS) Is Significantly Elevated in Hemodialysis Patients

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Background: Hemodialysis (HD) patients exhibit elevated vascular dysfunction compared to the general population. Disturbances in the endothelial glycocalyx, which selectively buffers sodium, can damage the erythrocyte glycocalyx and lead to elevated ESS. ESS, which can be estimated by a novel "salt blood test" (SBT), reflects glycocalyx damage of both the vascular wall and the erythrocyte (RBC) surface. In parallel, senescent and damaged RBCs lose membrane asymmetry with exposure of phosphatidylserine (PS) on the outer surface, which is an early sign of suicidal erythrocyte death (eryptosis) and is related to RBC life span. We explored the distribution of ESS and levels of eryptosis in HD patients compared to healthy subjects (HS).

Methods: Blood samples were collected from chronic HD patients before mid-week treatment and from HS. ESS was measured by SBT [Oberleithner and Wilhelmi, Pflugers Arch 2013] in triplicates. Percentage of reticulocytes and eryptotic RBC with elevated PS exposure were assessed by BD FACSCalibur™ with RETIC-Count™ (BD Biosciences, USA) and Annexin-V-Fluos (ROCHE, Germany) respectively, and used for calculation of absolute eryptotic RBC (A-ERYPTO-RBC) and absolute reticulocyte count (A-RETIC) from absolute RBC count.Two-tailed homoscedastic TTEST was used to explore associations between parameters (P<0.05). Data is presented as M±SD.

Results: We analyzed data from 20 HD patients (age 28-76 years, 11 males, 11 white, 10 diabetic) and 11 HS (age 30-71 years, 5 males, 9 white). SBT was significantly higher in HD compared to HS group (3.93±1.5 vs 1.95±0.51). While A-RETIC was significantly lower in HD group (4.95±1.76 vs 7.06±1.59 $x10^4$ cells/µL), there was no difference in A-ERYPTO-RBC between HD and HS (2.26±1.58 vs 2.35±1.38 $x10^4$ cells/µL).

Conclusions: Higher levels of ESS in HD patients reflect disturbed endothelial glycocalyx and might be related to increased vascular damage in this population. Difference between the groups in absolute reticulocyte count but not in eryptotic RBCs likely indicates higher turnover of RBC in HD population.

Funding: Pharmaceutical Company Support - Renal Research Institute

PUB296

Brain Natriuretic Peptide as a Sensitive Cardiac Biomarker for Hypervolemia in Hemodialysis Patients

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Background: Evaluation of volume status is sometimes a clinical dilemma in hemodialysis (HD) patients. BNP is an important biomarker in patients with CKD.

Methods: We enrolled 40 ESRD patients older than 20 years, on regular HD 3 times weekly with duration of HD more than 12 months. Inclusion criteria for patients: 1) Ejection fraction> 55%, LV end systolic (2-4 cm) and diastolic (3.7-5.5 cm) internal dimensions on ECHO. 2) Patients with mild LVH; intraventricular wall thickness in diastole < 1.3 cm. 3) Hypertensive patients with or without antihypertensive medications. Exclusion criteria: Patients with volume or pressure overload due to other causes than fluid overload (ex. anemia, heart failure, valvular lesions). In addition to full history taking and thorough clinical and cardiac examination, lab. investigations were done including CBC, renal and liver functions, with serum BNP samples collected post dialysis. Radiological studies done included: Echo, IVC collapsibility index for assessment of volume status.

Results: Our results showed no statistical substantial differences between hyper and normovolemic patients concerning patients' characteristics as gender, smoking, and presence of DM or hypertension. Moreover, no significant association was existing between BNP levels and patients' characteristics (ex: age and sex) or lab results (ex: creatinine, Ca, HgB), however, there was an inverse relationship between BNP and IVC collapsibility index (mean was 29.248 %). In addition, patients with hypervolemia had significantly higher BNP levels, as compared to euvolemic ones, with a significant difference (p value = 0.011) and the most pertinent level of BNP was (17.650 pg/ml) to discriminate hyper/normovolemic patients, with a sensitivity of 71%, and a specificity of 77.8%.

Conclusions: our study would appear to provide an evidence that plasma BNP levels were correlated to the degree of fluid retention in HD patients indicating that elevated levels may possibly be regarded as a marker of volume overload in absence of other causes and even before being clinically evident.

PUB297

The Study of Death Risk Factor and Survival among Maintenance Hemodialysis Patients

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Background: To identify the cause and the risk factors associated with death and evaluate the survival among maintenance hemodialysis(MHD) patients.

Methods: All of the patients undergoing maintenance hemodialysis in the dialysis center of the 3rdAffiliated Hospital of Sun Yat-sen University for at least 3 months from Jan 1st, 2013 to Dec 31st, 2015 were analyzed. The baseline variables and laboratory results were collected,death and survival were recorded. Logistic regression and multivariate COX regression were used to detect the relative factors.

Results: A total of 183 patients were included in the study.The mean age was 58.21±16.45.Male 113,female 70. Death were recorded in 36 cases after average 32months followed.The main cause of death were cardiovascular disease (33.3%), infectious disease(25%), cerebro-vasculardisease(13.9%),potassemia(11.1%), tumor(5.6%). Logistic regression showed that age (HR=1.068,95%CI:1.026-1.113), HBP(HR=3.660, 95%CI:1.187-11.286),hypoproteinemia (HR=0.886, 95% CI:0.788-0.994), acidosis (HR=0.816, 95% CI: 0.687-0.969) , hyperuricemia(HR=0.996, 95% CI: 0.992-0.999) were risk factors for death. The average survival time in death cases were 47.8months after hemodialysis.Cox proportional hazards regression model showed that age(HR=1.033, 95%CI:1.000-1.066), acidosis (HR=0.863, 95% CI:0.760-0.979), hyperuricemia(HR=0.997, 95% CI: 0.994-1.000)were risk factors for death.

Conclusions: To maintenance hemodialysis patients,the main cause of death were cardiovascular or cerebrovascular disease and infection.Age, hypoproteinemia, acidosis, hyperuricemia are risk factors for death.

PUB298

Serum Nitric Oxide and Natriuretic Peptides Have a Relationship with Whole Blood Viscosity in End-Stage Renal Disease Undergoing Hemodialysis

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Background: A change of whole blood viscosity (WBV) may increase risk of major atherosclerotic events. NO regulates the renal function through the modulation of the vascular tone. WBV related with vascular shear stress may be linked to production of NO. WBV is also associated with volume status during hemodialysis. Atrial natriuretic peptide (ANP) and B type natriuretic peptide (BNP) may be linked to WBV because they can be indicators of blood volume. This study was planned to investigate correlation between WBV at several shear rates during hemodialysis and serum levels of NO, ANP, and BNP in ESRD patients.

Methods: This study included 31 end-stage renal disease patients who were enrolled. We measured WBV using a scanning capillary tube viscometer pre- and post- dialysis to quantify viscosity. Serum NO, ANP, and BNP level before hemodialysis was assayed using an ELISA method.

Results: The mean WBV variations at shear rates of 1, 5 and 300 s^{-1} for pre-dialysis were 168.5±62.5, 76.9±20.6, and 33.3±3.8 mP, respectively. The mean values of post-dialysis WBV obtained at a shear rate of 1, 5 and 300 s^{-1} were 240.4±84.4, 100.8±28.0, and 38.5±6.4 mP, respectively. Mean serum levels of NO, ANP, and BNP were 13.97±10.34 µg, 198.85± 61.56 pg/mL, and 1233.32± 280.81 pg/mL. Serum NO levels was positively correlated with WBV at a shear rate of 1, 5 and 300 s^{-1} at pre-dialysis. (p=0.09, p=0.015, and p=0.010, respectively). There was also statistical significance at post-dialysis. Serum ANP levels were negatively correlated with WBV at a shear rate of 1, 5 and 300 s^{-1} at only pre-dialysis (p=0.014, p=0.008, and p=0.009, respectively). However, BNP levels did not show any correlation with WBV.

Conclusions: Correlation between serum NO, ANP levels and WBV may indicate an important role of endothelial dysfunction in ESRD patients. However, whether monitoring of ANP, BNP, and NO has a relationship with WBV requires further controlled study.

PUB299

Reactive Hyperemia Index and Its Clinical Correlates in Dialysis Patients

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Background: Reactive hyperemia index (RHI), as a reflection of endothelial function, has been suggested to be an independent predictor of adverse outcome both in the general population and patients with chronic kidney disease. However, its value in risk stratification in patients on maintenance hemodialysis remains inexplicit.

Methods: This is a cross-sectional analysis of midterm baseline data from a cohort study. Two-hundred and fifty six dialysis patients from four tertiary hospitals in East China were recruited.Reactive hyperemia index was measured by peripheral arterial tonometry (EndoPAT 2000) on a midweek nondialysis day. Blood pressure level was determined by ambulatory blood pressure monitoring. Demographic and clinical information, as well as routine laboratory results were also recorded. Stepwise linear regression analysis was used to determine independent clinical correlators with natural logarithm of RHI (LnRHI).

Results: Among the 258 patients, peripheral arterial tonometry results were available for 218 patients. Average value of LnRHI was 0.57±0.31. In univariate correlation analysis, systolic blood pressure, diastolic blood pressure and heart rate were positively correlated with LnRHI, while age and body mass index (BMI) were inversely related to LnRHI. Stepwise linear regression analysis results demonstrated that systolic blood pressure (ß=0.004, $p<0.001$) and age (ß=-0.004, $p=0.015$) were independently correlates of LnRHI.

Conclusions: Our results indicate that reactive hyperemia index was affected by blood pressure and age in patients on maintenance hemodialysis. The prognostic value of RHI remains to be explored by follow up of this study population.

Funding: Government Support - Non-U.S.

PUB300

Do Patients in Chronic Hemodialysis Have Another Atherogenic Phenotype

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Background: High cardiovascular morbidity and mortality is observed in patients (PTS) with end-stage renal disease (ESRD). Dialysis patients revealed nearly 20 times higher the risk of dying from cardiovascular disease in comparison with the general population. There is growing evidence that dysregulation of lipid metabolism is connected with CKD. The research is now focused on the lipoprotein classes and subclasses and on the possible role of small dense LDL and small HDL particles in the atherogenesis. The aim of our study was to examine differences in individual lipoprotein classes and subclasses between chronic high volume hemodiafiltration (HD HDF) PTS and healthy volunteers (CON).

Methods: 60 PTS on HD HDF for at least 12 months and 60 CON were included into the study. PTS and CON were age-matched. Individual lipoprotein classes and subclasses (resp.) were analysed by Quantimetrix Lipoprint (TM) System using Lipoprint LDL and HDL subfractions Kit and Lipoware software.

Results: PTS differed from CON by decreased levels of total-, LDL-, and HDL-cholesterol (all P<0.001) that was connected with increased triacylglycerol concentration (P<0.001). Decreased HDL-C level in PTS were connected with fall of intermediate and small HDL levels (both P<0.001). PTS had increased VLDL levels (P<0.01) that was associated with opposite changes in concentration of large (P<0.001) as well as small dense LDL (P< 0.05).

Conclusions: The results of the study showed different atherogenic phenotype of HD HDF PTS and implicated delayed VLDL/LDL catabolism and remodelling connected with changes in HDL homeostasis that warrant further research. *The study was supported by research from the Ministry of Health of the Czech Republic (project RVO-VFN64165/2012), and the Ministry of Education, Youth and Sports of the Czech Republic (research project PRVOUK-P25/LF1/2 of Charles University in Prague, the 1st Faculty of Medicine).*

PUB301

Comparison of 3D Echocardiographic and Cardiac MRI Measurements of Left Ventricular Structure and Function in Hemodialysis Patients

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Background: This study compared left ventricular (LV) end diastolic volume (LVEDV), LV end systolic volume (LVESV), LV diastolic mass (LVDM) and ejection fraction (EF) in hemodialysis (HD) patients using transthoracic 3D echocardiography (3DE) and cardiac MRI (CMR).

Methods: 3DE and CMR (3 Tesla) scans were performed on 25 prevalent HD patients. CMR LV volumetric and mass analysis was undertaken using the software package CMR[42]. 3DE apical four chamber full volume 3DE images (iE33, Philips) were obtained and analysed with vendor specific software. Dependent sample t-tests were performed to compare LV volumes, mass and EF by 3DE and CMR. Pearson's correlation coefficient was performed to assess correlations between variables (LVEDV, LVESV, LVDM and EF) from 3DE and CMR. Statistical significance was accepted at $P < 0.05$ level.

Results: Eight patients were excluded from the analysis due to poor image quality from the 3DE. LVEDV (189.58 mL ± 60.88 mL versus 91.42 mL ± 25.86 mL, $P<0.001$) and LVESV (94.37 mL ± 39.60 mL versus 39.50 mL ± 12.93 mL, $P<0.001$) were significantly higher for CMR compared to 3DE. There was no significant correlation between LVEDV (r=0.479, $P=0.052$) for CMR and 3DE. There was a significant correlation between LVESV (r=0.743, $P=0.001$) for CMR and 3DE. LVDM (108.05 g ± 35.31 g versus 163.48 g ± 35.32 g, $P<0.001$) and EF (51.30% ± 6.72% versus 56.45% ± 8.63%, $P=0.011$) were significantly lower for CMR compared to 3DE. Both LVDM (r=0.735, $P=0.001$), and EF (r=0.559, $P=0.020$) significantly correlated between CMR and 3DE.

Conclusions: This study suggests 3DE underestimates LVEDV and LVESV compared to CMR. While LVDM is overestimated by 3DE compared to CMR. EF was comparable when measured by both imaging tools.

PUB302

Coronary Artery Calcification Score (CACS) and Cardiovascular Events in Maintenance Hemodialysis Patients

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Background: Coronary artery calcification is known as a frequent complication in patients with chronic renal failure and contributes to their excess death with cardiovascular events. We examined the relationship between the coronary artery calcification score (CACS) and cardiovascular events in maintenance hemodialysis patients .

Methods: A retrospective study was conducted on 322 patients who received maintenance hemodialysis within 5 years between2011 and 2015. The Agatoston's CACS>400, age, sex, dialysis vintage, presence of diabetes mellitus (DM), history of smoking, hemoglobin, serum creatinine(Cr), uric acid, phosphate, intact parathyroid hormone(iPTH), total cholesterol (T-CHO), CRP, β2-microglobulin (β2MG), albumin-adjusted serum calcium (Ca), geriatric nutritional risk index (GNRI) and PCR were used as independent variable. Risk factors related to cardiovascular events were assessed by univariate and multivariate logistic regression analysis using the above variables. Risk factors related to CACS >400H and serum β2MG >30mg/l were also evaluated.

Results: CACS(2378±2228 vs 1307±1938H, P<0.01), DM (77 vs 69%, P<0.01), β2MG(28±9 vs 25±8mg/l, P<0.05) were significantly higher in patients who had cardiovascular events than patients who did not, While iPTH and CRP were significantly lower (P<0.01). DM (OR 0.34, 95% CI 0.15-0.72, P<0.01), CACS >400 (OR 0.32, 95% CI 0.12-0.72, P<0.05), and β2MG (OR 0.96, 95% CI 0.92-1.00, P<0.05) were detected as cardiovascular events-associated factors. Age (OR 0.95, 95% CI 0.92-0.97, P<0.01), DM (OR 0.30, 95% CI 0.18-0.50, P<0.01) were detected as CACS >400 -associated

factors. Dialysis vintage (OR 0.97, 95% CI 0.96-0.99, P<0.01), Cr(OR 0.80, 95% CI 0.73-0.88, P<0.01) and iPTH (OR 1.00, 95% CI 1.00-1.01, P<0.01) were related to serum β2MG>30mg/l.

Conclusions: DM, CACS >400, and high β2MG levels were risk factors for cardiovascular events in the patients who received maintenance hemodialysis within 5 years.

PUB303

The Relationship between Arterial Stiffness and Brain Small Vessel Disease in Dialysis Patients Ke Zheng,[1] Xuemei Li.[2] *[1]Dept of Nephrology, Peking Union Medical College Hospital, Beijing, China; [2]Dept of Nephrology, Peking Union Medical College Hospital, Beijing, China.*

Background: Dialysis patients have high prevalence of cardiac and cerebral vascular diseases .Our previous study showed the prevalence of brain small vessel diseases (SVDs) increased significantly. The mechanisms of this phenomenon was still unknown. Arterial stiffness has close relationship with cardiac vascular diseases. PWV can reflect the degree of arterial stiffness, and it was considered to be a prediction index of cardiac events. Whether abnormal PWV will have impact on brain SVDs? By now, there is no data about this.

Methods: (1) Subjects:427 convenient subjects who were on chronic hemodialysis and/or peritoneal dialysis in PUMCH dialysis center were screened. (2)Arterial stiffness assessment: PWV was assessed by SphygmoCor® on femoral-carotid artery .(3) Brain SVDs were evaluatied by 3T-magnetic resonance imaging.

Results: (1)202 subjects entered this study, male47.6%, average age56.3yrs, average dialysis vintage 59.9 moths, HD61.4%.(2)Average BP136.9/78.4mmHg, Hgb 112.0g/L, Alb38.0g/L,Calcium and phosphamid product 3.87±1.08mmol^2/L^2.(3) Average PWV10.6±2.3 m/s. 47.2% participants could be diagnosed as arterial stiffness (PWV>10 m/s). (4) By MRI, the prevalence of microbleeds was 42%, lacuna infarct was 39.5% and abnormal white matter lesions 51.5%. (5) Compared to patients with normal PWV, patients with abnormal PWV had more lesions in all kinds of SVDs (P<0.05). (6) PWV was relative with WML scores (r=0.410), lacunar infarct (r=0.281)and weakly relative with microbleed (r=0.164, P=0.029). Age was also relative with PWV,WML and lacunar infarction. By multiple linear regression analysis, after adjusted for dialysis vintage, calcium and phosphamid product and hsCRP, PWV still was an independent risk factor of WML but no longer risk factor of lacuna infarct. After adjusted age on above model, PWV was no longer risk factor of WML.

Conclusions: In our dialysis patients, there were a high prevalence of arterial stiffness. Patients with arterial stiffness had more severe SVDs. PWV was relative to WML and lacunar infact. Intervention of arterial stiffness maybe can be an alternative method to alleviate dialysis patients' brain SVDs.

PUB304

Patient Survival on Peritoneal Dialysis Compared with Hemodialysis Jwa-Kyung Kim,[1] Sun Ryoung Choi,[2] Sung Gyun Kim.[1] *[1]Internal Medicine, Kidney Research Inst, Hallym Univ Sacred Heart Hospital, Anyang, Korea; [2]Internal Medicine, Sahmyook Medical Center, Seoul, Korea.*

Background: It was recently reported that the overall mortality rate of incident peritoneal dialysis (PD) patients was constantly higher compared to hemodialysis (HD) patients in Korea. We aimed to investigate whether the overall survival of patients with PD is still inferior among patients who were cared at university hospitals in Korea.

Methods: We included all patients who had started dialysis between January 1, 2006 and October 31, 2013 at 5 general hospitals of Hallym University Medical Center (Gangnam, Gangdong, Chunchun, Hangang, Hallym Sacred Heart Hospital) in South Korea. Patients were followed up until October 31, 2014.

Results: We analyzed eligible 846 patients (461 HD patients and 385 PD patients). Median follow-up time was 46.1 months (range, 3.0-106 months). The crude incidence rates of all-cause mortality in PD and HD patients were 86.1 and 82.8 per 1000 patient-years, respectively. The overall survival rate of PD patients was similar with that of HD patients (Fig 1, $P = 0.960$). The 2-year and 5-year survival rates were 87.8% and 65.1% in patients with PD, and 86.5% and 64.3% in patients of HD. At the time of dialysis start, PD patients showed lower age, lower systolic blood pressure, lower Charlson comorbidity index (CCI), lower hemoglobin levels, lower serum creatinine levels, and lower blood glucose levels than HD patients. In multivariate Cox analysis, adjusting age, sex, body mass index, blood pressure, primary renal disease, CCI, hemoglobin levels, albumin levels, and serum creatinine levels, hazard ratio of peritoneal dialysis on all-cause mortality was 1.509 (95% CI, 1.160-1.962, $P = 0.002$). Among female patients or patients without diabetes mellitus, hazard ratio of peritoneal dialysis was not significantly increased [1.114 (0.703-1.767) and 1.785 (0.965-3.302), respectively].

Conclusions: The overall survival of patients with PD might be inferior compared to the survival of HD. Among female patients or the patients without diabetes mellitus, the survival rate of PD might be similar to those of HD.

PUB305

The Study of Cardiac Valve Calcification in Maintenance Hemodialysis Patients and Its Related Risk Factors Ming Li,[1] Huiqing Chen,[2] Zengchun Ye,[1] Wenbo Zhao,[1] Tan-Qi Lou.[1] *[1]Div of Nephrology, The Third Affiliated Hospital of Sun Yat-sun Univ, Guangzhou, Guangdong, China; [2]Div of Paediatrics, The First Affiliated Hospital of Sun Yat-sun Univ, Guangzhou, Guangdong, China.*

Background: To explore the cardiac valve calcification(VC) in maintenance hemodialysis(MHD) patients and to analyze the risk factors.

Methods: Patients with MHD aged>14 years without history of heart valve disease and heart surgery were enrolled in the study. The color doppler uhrasonography was performed on 181 MHD patients to detect the cardiac VC.The patients were divided into two groups:VC group and no VC group.General clinical information, blood biochemical results were collected for analyzation among different groups.

Results: Of all the patients, male 112, female 69, the average age were 57.9+16.3 years. VC was found in 72 patients(39.8%),60(33.1%) with aortic valve calcification,30(16.5%) with mitral valve calcification,and 18(9.9%) with both. Compared with patients with no VC, patients with VC were older, more obesity,had longer hemdialysis duration, higher proportion of patients with hypertension and DM, higher plasma phosphate and serum uric acid, serum triglyceride.Multivariate Logistic regression showed that age(β=1.109,*P*=0.000), hemdialysis duration(β=1.390,*P*=0.001),BMI (β=1.187,*P*=0.008) were independently correlated with VC.VC also was founded positive correlation to pulmonary artery hypertension(PAH)(*P*=0.006).

Conclusions: cardiac valve calcification(VC) is common phenomenon in MHD patients,and aortic valve calcification is more common than mitral valve calcification.The major risk factors for cardiac VC are age, hemdialysis duration and BMI. VC is positive correlation with PAH.

PUB306

Cyclophilin A and Sclerostin as Markers of Atherosclerosis in Dialysis Patients Yoo Jin Lee, Yang Wook Kim, Sihyung Park, Bongsoo Park. *Internal Medicine, Haeundae Paik Hospital, Busan, Republic of Korea.*

Background: Systemic inflammation and oxidative stress caused by endothelial dysfunction are related to atherosclerosis, which is one of major cause of death in dialysis patients. In addition, vascular calcification is an additional important factor of atherosclerosis in dialysis patients. Cyclophilin A (CyPA) is secreted by vascular smooth muscle cells in response to oxidative stress, which makes vascular inflammation and calcification by Wnt pathway. Sclerostin is known to as an antagonist of the Wnt pathway in bone modeling and vascular calcification.

Methods: Sixty patients (control n=20, hemodialysis n=20, peritoneal dialysis n=20) were enrolled in this cross sectional and single-center study.Serum CyPA, sclerostin were analyzed by ELISA. Ankle-brachial index (ABI) and carotid intima-media thickness (carotid IMT) were performed to measure atherosclerosis of peripheral and carotid arteries. Presence of atherosclerosis was defined as ABI ≤ 0.9 and carotid IMT ≥ 0.754 mm.

Results: Four patients (ABI ≤ 0.9 and carotid IMT ≥ 0.754 mm) had atherosclerosis and 35 patients did not have atherosclerosis (ABI > 0.9 and carotid IMT < 0.754 mm). The level of CyPA was higher in atherosclerosis group (42.8 ± 17.4 ng/mL vs. 32.21 ± 13.5 ng/mL, $p = 0.21$). The level of sclerostin was also higher in atherosclerosis group (3.98 ± 1.51 pg/mL vs. 3.45 pg/mL ± 3.1, $p = 0.33$). In subgroup analysis with non-atherosclerosis group, CyPA was highest in hemodialysis (control 30.23 ± 11.6 ng/mL; hemodialysis: 41.7 ± 16.4 ng/mL; peritoneal dialysis: 27.0 ± 10.2, $p = 0.57$). Sclerostin was higher in dialysis group than control (control: 0.91 ± 0.2 pg/mL; hemodialysis group: 5.99 ± 3.18 pg/mL; peritoneal dialysis group: 4.83 ± 2.98, $p = 0.01$).

Conclusions: This study did not prove the clinical usefulness of CyPA and sclerostin on prediction of atherosclerosis in dialysis patients because of small sample size. However, CyPA and sclerostin would be good biochemical parameters for assessing atherosclerosis in dialysis patients.

PUB307

A Validation Study of the Quick Sequential Organ Failure Assessment (qSOFA) for Japanese Patients Undergoing Hemodialysis Hiroki Nishiwaki, Sho Sasaki, Takaya Ozeki, Hiroo Kawarazaki, Shun Minatoguchi, Masahide Furusho, Masahiko Yazawa, Daisuke Uchida, Kenichiro Koitabashi, Takeshi Hasegawa. *JOINT-KD Group, Japan.*

Background: Hemodialysis (HD) patients are high risk population for bloodstream infection, due to daily punctures to vascular access. As the previous study, qSOFA had predictive validity (AUROC = 0.81; 95%CI, 0.80-0.82) among non-ICU encounters without hemodialysis. This study aim is to examine the performance of qSOFA proposed as an easy-to-use score which rapidly identify sepsis in general population for patients undergoing HD.

Methods: This was a multi-center retrospective observational study of patients undergoing HD. The study subjects were maintenance HD patients over 18 years old suspected with bloodstream infection who had blood cultures drawn in outpatient setting or within 2 days after admission from August 2011 to July 2013 in 11 Japanese tertiary care centers in JOINT-KD group. We did complete data analysis in this study. Main outcome measure was in-hospital mortality. As the previous study, qSOFA was defined as the score range was 0-3 points, with 1 point each for systolic hypotension [100mmHg], tachypnea [22/min], or altered mentation [GCS<13]. The cutoff point defined as 2 and more. The performances of qSOFA were evaluated using the areas under the receiver operating characteristics curves (AUROC) for discrimination, and Hosmer–Lemeshow test for calibration.

Results: Data from 220 consecutive patients were analyzed for qSOFA evaluation. The in-hospital mortality was 14.6%. AUROC of qSOFA was 0.648 (95% CI 0.57 to 0.73). The sensitivity and specificity were 36.8% and 92.9%, respectively. The logistic regression analysis showed that the pseudo R2 was 0.100. The Hosmer-Lemeshow test showed $p<0.01$.

Conclusions: qSOFA may not be useful in identifying sepsis in Japanese HD patients compared to that in the general population.

PUB308

Recurrent Peritonitis in Peritoneal Dialysis in Qatar, an 8-Year Epidemiologic Study

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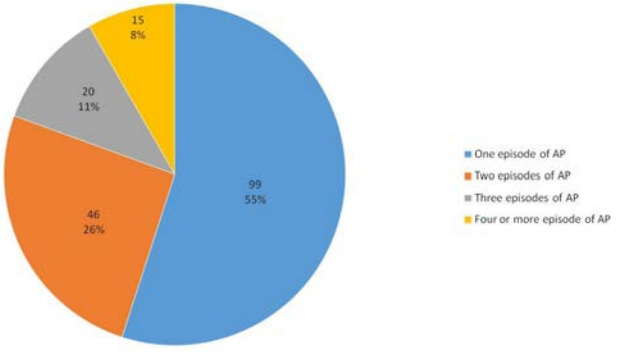
Background: Acute peritonitis (AP) is a common and devastating complication in end stage renal disease patients on Peritoneal Dialysis (PD). We are reporting an epidemiologic study of recurrent AP in PD patients in Qatar over 8 years follow up.

Methods: We retrospectively reviewed the medical records of all PD patients in the biggest dialysis center in Qatar from 2007 to 2014. The analysis was conducted to repot the epidemiology, outcome and associated risk factors of recurrent AP.

Results: We had a total of 318 AP episodes in 180 patients between 2007 and 2014. 99 (55%) patients had single AP while 81 (45%) had 2 episodes or more (recurrent AP) .



Patients on automated PD carried a higher risk of developing recurrent AP (OR= 1.46, 95% CI:1.01-1.71). First episode of AP caused by gram positive (G+) cocci carried a significant risk of recurrent AP (OR= 4.3, 95 % CI: 2.2-8.2). Multivariate logistic regression model including both Gram + infection and automated PD as predictors of recurrent AP revealed the same predictive value of the G+ cocci infection to have at least another AP episode (OR = 3.9, 95% CI: 2.0-7.7). Additionally, negative-culture AP carried a significant protective role from a repeated AP (OR= 0.35, 95% CI: 0.19 – 0.66). Most deaths occurred with the first episode of peritonitis (4 out of six). Gram negative- associated AP carried the highest risk of death while no deaths was reported in association with G+ AP.

Conclusions: In this 8 year follow up epidemiologic study, recurrent AP was prevalent (45%) among all AP cases. and its risk increases with G+ cocci infections. However, G- infections were associated with increased mortality risk. Our results signify the importance of implementing more efficient care bundles to prevent recurrent AP.

PUB309

Factors Associated with Foot Ulceration and Lower Extremity Amputation in Adults with End-Stage Renal Disease on Dialysis: A Cross-Sectional Observational Study

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Background: Dialysis patients are at increased risk for foot ulceration, which often precedes more serious lower limb complications. Limited data exist regarding the prevalence and factors associated with foot disease in this patient group. The aim of this study was to investigate factors associated with foot ulceration and amputation in the dialysis population.

Methods: This multi-centre cross-sectional observational study recruited 450 adults on dialysis from satellite and home-therapy dialysis units in Melbourne, Australia. Data collection involved a participant interview, medical record review, a health-status questionnaire and a foot examination. Logistic regression analyses were conducted to evaluate associations between screened risk factors and the primary and secondary outcomes.

Results: Mean age was 67.5 ± 13.2 years, 64.7% were male, 94% were on haemodialysis, the median dialysis duration was 36.9 (IQR, 16.6 to 70.1) months, and 50.2% had diabetes. There was a high prevalence of previous ulceration and amputation (21.6% and 10.2%), and 10% had current ulceration. Foot examination identified 50% with neuropathy and/or peripheral arterial disease. Factors significantly associated with foot ulceration were previous amputation (OR, 10.19), peripheral arterial disease (OR, 6.16) and serum albumin (OR, 0.87). For amputation, previous and current ulceration (OR, 167.24 and 7.49) and foot deformity (OR, 15.28) were significant factors.

Conclusions: Dialysis patients have a high burden of lower limb complications. Those with markedly higher risks of foot ulceration and/or amputation include those with lower serum albumin, previous/current ulceration or amputation, peripheral arterial disease, and foot deformity.

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PUB310

Description of Kuwait Dialysis Population - 2015

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Background: Dialysis population is growing, but basic data is lacking.

Methods: Brief data on dialysis patients presented.

Results: Population Health: Population in 2015 was 4.3 million, 30% Kuwaitis. Population is young (29.5 median age) plagued with risk factors for chronic kidney disease (CKD) development; diabetes (17.9% prevalence), hypertension (20% prevalence), obesity (42% obese), and smoking (20% of adults smoke). **Dialysis Services:** Ministry of health (MoH) centers provide dialysis freely for Kuwaitis, children of Kuwaiti women married to non-Kuwaiti men and residents from other Gulf states. Bedoons (Stateless people) get dialysis for a fee per hemodialysis (HD) session. Other expatriates leave as chronic dialysis is not provided in MoH units even when cost is covered, but some may access peritoneal dialysis (PD) for a fee. Military hospital has a small HD unit for defense ministry personnel and their families. One private center provides HD for $250 per session not including medications, which they get from MoH hospitals. **Dialysis Population:** Number increased by 4%from 1650 in 2014 to 1720 in 2015. Patients starting dialysis in 2015 were 410 (85% Kuwaitis). Non-Kuwaiti are 70% of the population, but 70% of dialysis patients are Kuwaitis as expatriates access to dialysis is minimal. So, incidence is 95 PMP and prevalence is 405 PMP for total population, and prevalence is 930 PMP and incidence is 275 PMP for Kuwaitis only (1.3 Million Kuwaitis, 1200 Kuwaitis on dialysis and 355 Kuwaitis started dialysis in 2015). More than 45% on dialysis due to DM. Mortality increased from 11.5% in 2014 to 13.5% in 2015. Hepatitis C found in 7%, and hepatitis B found in 2% of patients. Access was arteriovenous fistula in 42%, arteriovenous graft in 7.5%, and tunneled catheters in 50%. Low flux HD used in 32%, and high flux HD in 20%, and hemodialfiltration in 48% of patients. PD usage increased from 9.5% in 2013, to 10.5% in 2014, and to 12% in 2015, with automated PD used in 56% of cases.

Conclusions: Young society plagued with CKD risk factors. Incidence and prevalence rates are high, and PC use is high. Hepatitis C is a problem. Mortality is reasonable.

PUB311

Longer Haemodialysis Sessions Improved Clinical and Biochemical Markers Compared to Conventional Sessions: A Non-Randomised Trial

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Background: Data suggest extended haemodialysis (HD) provides significant physical and psychological benefits, including reduced mortality. Home HD patients have more opportunity than those in-centre to undergo extended treatments. Additionally, increasing HD incidence is resulting in an increased demand for HD. In-centre nocturnal HD (INHD) delivers extended HD sessions in addition to daytime slots, but is not routinely provided.

Methods: This non-randomised controlled trial enrolled 10 patients who elected to begin INHD (3x5-8hours) and 12 control patients receiving standard therapy (3x4hours) matched for age, gender and dialysis vintage. Clinical parameters relating to dialysis quality —such as ultrafiltration volumes (UFvol; Litres) absolute (absUFrate; mL/hour) and relative (relUFrate; mL/hour/Kg) UF rates, volumes cleared (mL) and urea reduction ratios (%) – were collected at baseline and following six months of treatment. Phosphate and haemoglobin levels were also compared. A mixed 2-way ANOVA was used to analyse main effects of time, treatment group and interaction.

Results: Our analysis showed significant time effects of volume cleared (p=0.005), AbsUFrate (p=0.001), relUFrate (p=0.001), phosphate (p=0.009) and haemoglobin (p=0.035). We found UFvol to have a significant group*time interaction (p=0.024) and URR to have both significant interaction and time effects ($p\leq0.001$). Post hoc analysis revealed no significant changes to any parameters in the control group, however the INHD group showed significant increases in volume cleared, UF volume, URR and haemoglobin over the study ($p\leq0.048$); and significant reductions in absUFrate, relUFrate and phosphate over the same period ($p\leq0.008$).

Conclusions: Over 6 months of INHD, patients show significant improvements in all clinical and biochemical parameters reported. Although patients were less strict with fluid restrictions, rates of fluid removal were still significantly reduced, clearance higher and biochemistry improved.

Funding: Private Foundation Support

PUB312

Incidence of Hepatitis C Virus Infection in a Large Cohort of Dialysis Patients in the United States Pablo E. Pergola, Rebecca Vincent Rokosky, Navid Saigal. *Renal Associates PA, San Antonio, TX.*

Background: Rates of Hepatitis C Virus (HCV) chronic infection in dialysis patients are unknown. Published data are based only on HCV antibody (Ab) testing. Until the recent approval of direct acting antiviral agents (DAAs) with high efficacy and limited toxicity, no effective therapies were available for dialysis patients. Routine testing for HCV Ab and PCR is not standard of care on all dialysis facilities. Studies testing for HCV Ab and PCR are needed to determine the true incidence of chronic HCV infection in the dialysis population.

Methods: Observational, population-based cohort of prevalent dialysis patients, from 8 dialysis centers belonging to a large dialysis organization. All patients were tested as part of routine care between Sept 2015 and May 2016 for Hepatitis C Ab and if positive, a HCV PCR was performed.

Results: 687 patients were tested (626 in-center HD, 54 PD, 7 home HD), 48 were found to be HCV Ab+ (6.7%); 34 of the HCV Ab+ patients were PCR+ (66% or 4.7% of the total). None of the HCV PCR+ patients were co-infected with either Hep B or HIV. Only 10/48 patients were aware of the HCV Ab+ diagnosis. Mean age 61 (range 30-92), Male 33 (70%), Hispanic 32 (70%), Black 5 (10%). Of the HCV PCR+ patients, by zip code analysis, mean income was $43,116, high school graduation 75.2%, and poverty rate 23.8%. At the time of this report, only 5 patients were actively being treated (14% of HCV PCR+; genotypes 1A and 1B). Since this observation began, of the HCV PCR+ patients, 1 died from metastatic hepatocellular carcinoma (HCC), 1 was diagnosed with HCC and 1 with renal cell carcinoma (8.8% of HCV PCR+ had malignancies detected so far).

Conclusions: Rates of HCV infection in dialysis patients appear significantly higher than the general population (0.7/100,000 per CDC, 1.0% per NHANES 2003-2010). All dialysis patients should be tested for HCV Ab with reflex PCR, at dialysis initiation and every 6 months (CDC). All infected patients without contraindications should be offered treatment with approved therapies. All should have abdominal imaging due to long HX of untreated infection (until now no treatment offered or possible) and overall higher rates of malignancy in dialysis patients.

Funding: Clinical Revenue Support

PUB313

Association of Potassium Gradient with Near-Term Clinical Outcomes in Hemodialysis Patients Steven M. Brunelli,[1] Nina Oestreicher,[2,3] Charles Du Mond,[2] David M. Spiegel,[2] Csaba P. Kovesdy.[4] *[1]DaVita Clinical Research, Minneapolis, MN; [2]Relypsa Inc, Redwood City, CA; [3]Univ of California San Francisco, San Francisco, CA; [4]Univ of Tennessee Health Science Center, Memphis, TN.*

Background: A high serum to dialysate potassium (K) gradient leads to rapid lowering of K during dialysis and may confer a greater risk of adverse events. Here, we examined the near-term association of K gradient with key clinical outcomes.

Methods: This retrospective (2010-2011) study considered 830,741 patient-intervals, each defined by a measurement of serum K made among adult Medicare Parts A & B enrollees who received in-center hemodialysis on a Monday/Wednesday/Friday schedule at a large US dialysis organization. K gradient was considered based on the difference in K concentration (serum - dialysate) on the date of measurement; analyses account for multiple observations per patient. Outcomes considered over the day of the qualifying gradient and the next day were: hospital admissions (all-cause and cardiovascular [CV]), emergency department (ED) visits, and deaths.

Results: Higher K gradient was associated with younger age, greater fistula use, lower comorbidity scores, and better nutritional indices. Adjusting for patient differences, higher K gradient was associated with greater risk of all-cause hospitalization and ED visit. A similar but non-significant trend was seen for CV hospitalization. No associations were observed with mortality, possibly due to the low number of events. Results were similar when the outcome window was limited to the date of measurement only.

	Potassium Gradient Category (mEq/L)						
	<0	0 - <1	1 - <2	2 - <3	3 - <4	4 - <5	≥5
Intervals	1251	25,119	139,631	327,906	238,739	80,286	17,809
Hosp (n)	11	313	1399	2734	1865	688	191
Adjusted OR (95% CI)	0.34 (0.16, 0.74)	0.98 (0.86, 1.12)	0.96 (0.90, 1.03)	1 (ref)	1.08 (1.01, 1.15)	1.26 (1.14, 1.38)	1.59 (1.36, 1.87)
CV Hosp (n)	1	49	240	490	351	103	30
Adjusted OR (95% CI)	N/E *	1.02 (0.75, 1.41)	1.01 (0.86, 1.19)	1 (ref)	1.11 (0.96, 1.28)	1.03 (0.83, 1.28)	1.37 (0.94, 2.00)
ED Visits (n)	18	459	2459	5129	3535	1255	372
Adjusted OR (95% CI)	0.34 (0.19, 0.63)	0.85 (0.76, 0.94)	0.96 (0.91, 1.01)	1 (ref)	1.06 (1.01, 1.11)	1.17 (1.08, 1.25)	1.54 (1.36, 1.74)
Deaths (n)	0	16	65	99	62	24	3
Adjusted OR (95% CI)	N/E *	1.05 (0.59, 1.88)	1.11 (0.79, 1.57)	1 (ref)	1.15 (0.82, 1.61)	1.47 (0.90, 2.39)	0.94 (0.29, 3.03)

* Non-estimable due to a paucity of outcome events

Abbreviations: CI, confidence interval; CV, cardiovascular; ED, emergency department; Hosp, hospitalization; N/E, non-estimable; OR, odds ratio;

Conclusions: Higher K gradient is independently associated with greater risk of all-cause hospitalization and ED visit. Further work is needed to determine whether directed intervention ameliorates this risk.

Funding: Pharmaceutical Company Support - Relypsa Inc

PUB314

Validation of an Anthropometric Model to Predict Brain Mass: Relevance for the Assessment of Brain Oxygen Demand Natasha Sharda,[1] Hanjie Zhang,[2] Israel Campos,[2] Stephan Thijssen,[2] Peter Kotanko.[2] *[1]Western Univ, London, ON, Canada; [2]Renal Research Inst of New York, NY.*

Background: Evidence indicates that HD patients suffer from structural brain damage. While the exact basis of these pathologies is unknown, poor oxygen delivery relative to brain oxygen demand may be a contributing factor. Brain oxygen demand depends critically on oxygen consumption which can be estimated if mass is reliably known. To that end we computed brain mass using published anthropometric formulae and compared the results to that actually measured in a large cohort of U.S subjects.

Methods: A Pubmed literature search revealed two papers of interest to our research question. Mehrpour reported a regression model utilizing age, gender, and height to predict brain mass determined from autopsies of non-pathological specimens in an Iranian population (Mehrpour, *J Forensic Leg Med*. 2010). We validated that model in a U.S population for both genders, aged 18-84 yrs with heights ranging from 140-190cm (Dekaban, *Ann Neurol*. 1978). The mean data points in the Dekaban paper were used as predictors in the Mehrpour model.

Results: The Mehrpour model consistently underestimated average brain mass in males (mean difference 78g) and overestimated it in females (mean difference 40g). The maximum absolute difference between estimated and measured brain mass was 100g for both sexes.

Figure 1. Difference between estimated and measure brain mass as a function of age and gender.

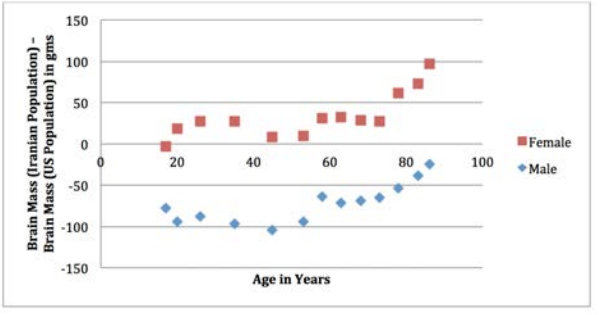


Figure 1 shows the average differences as a function of age and gender. When data is restricted to an age range of 55-74 yrs representing 90% of the U.S HD population, a further reduction in variation is noted.

Conclusions: The Mehrpour regression model provides a fair estimate of brain mass within a U.S population. Given an average brain mass of 1,311g in males and 1,285g in females, the average difference is 5.9% and 3.1%, respectively. Further studies are needed to validate the Mehrpour model in HD patients.

PUB315

Associations between Sleep Quality/Depressive Symptoms and Albumin/Phosphate Level Nien-Chen Li, Stephanie Johnstone, Joy R. Lutz-Mizar, Felicia N. Speed, Marta Reviriego-Mendoza, John W. Larkin, Norma J. Ofsthun, Franklin W. Maddux. *Fresenius Medical Care North America, Waltham, MA.*

Background: Patients (pts) undergoing hemodialysis (HD) often complain about poor sleep quality (SQ) and are known to be at an increased risk for experiencing depressive symptoms. As a function of a Fresenius Medical Care North America Social Worker (SW) Quality Improvement Program, we investigated whether profiles of SQ and depressive symptoms are associated with alterations in levels of albumin (Alb) and phosphate (PO4).

Methods: We investigated 1,244 HD pts enrolled in the 8-week SW program from 7/1/13 and 2/28/14. SQ was assessed upon enrollment to the SW program. The SQ survey included 5 items, which were reduced to 3 by factor analysis that included: difficulty sleeping, difficulty awakening, and restless legs during sleep. Each item was scored on a scale from 1-10, with 10 indicating the worst score. For depressive symptoms, the Center for Epidemiologic Studies Depression Scale-10 (CESD-10) questionnaire was utilized. Means of Alb and PO4 were calculated over 30 days before the SW program. Correlations between SQ factors/CESD and albumin/PO4 mean levels were calculated.

Results: Pts had a mean age of 55.3 ± 13.9 years, 52.4% were males, 68.7% were white, 57.6% with diabetes, 19.8% with coronary artery disease, and 37.5% with congestive heart failure. The mean levels of Alb and PO4 were 3.9±0.4 and 5.9±1.6, respectively. Mean scores of CESD, difficulty sleeping, difficulty awakening and restless legs during sleep were 9.7±6.6, 4.4±2.8, 2.3±2.4, 3.2±3.1, respectively. We found that Alb was negatively correlated with CESD (r=-0.06, p=0.045) as well as restless legs during sleep (r=-0.07, p=0.02); however, PO4 was positively correlated with restless legs during sleep (r=0.06, p=0.03).

Conclusions: This study indicates that low levels of Alb are associated with worse depressive symptoms and restless leg syndrome in HD patients, while high PO4 levels are associated with restless leg syndrome. Social work interventions that can improve SQ and depressive symptoms may have the potential to improve HD pts outcomes.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB316

Body Temperature and Systolic Blood Pressure Patterns before Vancomycin Treatment in Hemodialysis Patients Sophia Rosen,[1] Yue Jiao,[1] Sheetal Chaudhuri,[1] Hao Han,[1] Marta Reviriego-Mendoza,[1] John W. Larkin,[1] Len A. Usvyat,[1] Ravi I. Thadhani,[2] Peter Kotanko,[3,4] Jeffrey L. Hymes,[1] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Massachusetts General Hospital Div of Nephrology, Boston, MA; [3]Renal Research Inst, New York, NY; [4]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Infection is the second leading cause of death for dialysis patients (pts). Predicting infection before occurrence of apparent clinical markers would be desirable. We examined patterns of body temperature (BT) and systolic blood pressure (SBP) in hemodialysis (HD) pts before vancomycin treatment for an infection.

Methods: The analysis included 3,510 HD pts from the Fresenius Medical Care Data Warehouse from Jan 2010 to Sep 2015 who were treated with vancomycin for about 2 weeks. Data for predialysis BT and SBP measurements was collected 1 month before and after the vancomycin course. We compared several combinations of time points prior to vancomycin treatment using a repeated measures analysis of variance.

Results: We observed slight, but significant increases in average BTs during the time points 6-4, 3-1, and the mean of 6-1 days before starting vancomycin, as compared to the mean or any individual time point 30-7 days prior to pts receiving vancomycin (all $p<0.01$; Figure 1A). This change coincides with a subtle decrease in SBP one week before starting vancomycin as compared to earlier period ($p<0.001$; Figure 1B). Albeit significant increases were observed in BT before starting vancomycin, the mean BTs rose to a maximum of clinically normal levels of 97.5°F.

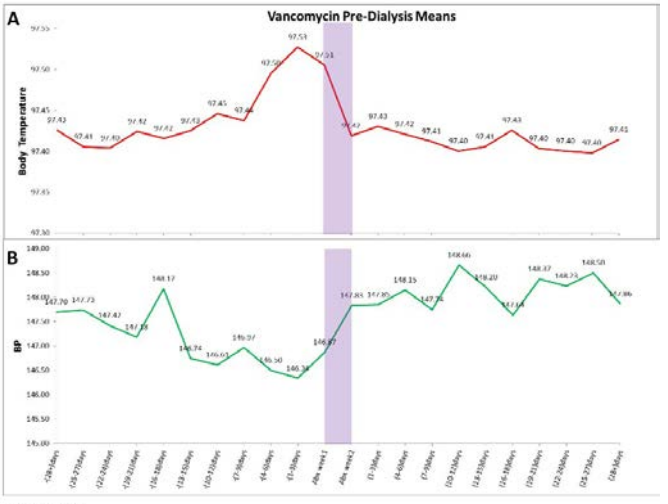


Figure 1

Conclusions: Small but measurable increases in BT and decreases in SBP prior to vancomycin treatment in HD patients likely antedate clinical infection.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB317

Bilateral Breast Pyoderma Gangrenosum in an Hemodialyzed Patient Cured by Corticosteroids with Wound Care Achour Laradi, Francois Babinet, Stephanie Lanoiselee. *Nephrologie Dialyse, ECHO-DIALYSE CMCM, Le Mans, France.*

Background: Pyoderma Gangrenosum(PG) is a rare neutrophilic but destructive and painful cutaneous disease with progressive ulcerations and necrosis of the skin.The typical lesions appear generally on the extremities.PG is associated with with specific diseases such as inflammatory bowel and myeloproliferative diseases .There are rare reports on Hemodialyzed Patients (HD).

Methods: A 62 -year -old female HD since 13 years with a medical history of a monoclonal gammapathy Ig G Lambda (2007) and Multiple Myeloma treated in 2016 , parathyroidectomy and adnexectomy.She was taken Cinacalcet, Sevelamer and Vitamin D.She presented in April 2015 with multiple bilateral breast painful cutaneous large ulcerations with elevated borders that gradually expanded surrounded by indurated violaceous plaques.The causes of cutaneous ulcerations were ruled out such as adverse drug effects, ,mycobacteries infection ,calciphylaxis,vasculitis and arteriosclerotic ulcers. Mammography was normal.Histological lesions showed a diffuse neutrophilic infiltration consistent with PG surinfected with Escherichia Coli and Streptococcus Agalactiae. Systemic corticosteroids were started (1 mg/kg) combined with antibiotics and advanced wound care with negative-pressure wound dressing.

Results: A positive response to therapy on the left breast was obtained within 3 months with a wound recovery with the wound depth decreasing from 5 cm to 2 cm and the diameter from 4 cm to 1 cm after 4 months.The right lesions are almost cleared after 8 months of .This is in accordance with previous reports showing that the majority of patients cleared witn the first six months of treatment and 95 % of patients attained remisssion within 3 years.Plastic surgery was not performed.

Conclusions: PG warrants attention in HD patients who accumulate multiple comorbidities and underlying conditions such myeloma and are at higher risk of PG which could be an overreactive inflammatory response linked to a neutrophil dysfunction with an overexpression of interleukin-8 and 18 .Diagnosis is based on clinical feature .Corticosteroid therapy needs a mean period of 11.5 months to achieve remission.Surgical approaches should be excluded.

PUB318

Effects of Dialysis Modalities on Markers of Mineral and Bone Disorders in ESRD Patients Melissa Soohoo,[1] Matthew B. Rivara,[2] Elani Streja,[1] Scott V. Adams,[2] Vanessa A. Ravel,[1] Onyebuchi A. Arah,[3] Kamyar Kalantar-Zadeh,[1] Rajnish Mehrotra.[2] *[1]UC Irvine, Irvine, CA; [2]Kidney Research Inst, Seattle, WA; [3]UCLA, Los Angeles, CA.*

Background: Mineral and bone disorders (MBD) are highly prevalent in patients undergoing maintenance dialysis, and are associated with adverse clinical outcomes. There are limited data on the effects of implementation in clinical practice of hemodialysis with either longer treatment time or higher frequency on markers of MBD.

Methods: This cohort study used data from 132,523 incident dialysis patients treated with any of the following modalities: conventional thrice-weekly in-center hemodialysis (HD), nocturnal in-center HD (NICHD), home HD (HHD), or peritoneal dialysis (PD). We analyzed the data using marginal structural models fitted with inverse probability weights to adjust for confounding due to fixed and time-varying covariates. We estimated the effects of treatment with different dialysis modalities on time-varying serum concentrations of four markers of MBD: calcium, phosphorus, parathyroid hormone (PTH) and alkaline phosphatase.

Results: Compared to conventional HD patients, patients treated with NICHD had lower mean PTH (21 pg/mL [95% CI 6 to 37] lower), whereas PD and HHD patients had higher mean PTH (44 pg/mL [95% CI 36 to 51] higher and 52 pg/mL [95% CI 34 to 69] higher, respectively). Compared to conventional HD patients, serum phosphorus was lower for patients treated with NICHD (0.45 mg/dL [95% CI 0.38 to 0.53] lower), PD (0.15 mg/dL [95% CI 0.12 to 0.18] lower) or HHD (0.33 mg/dL [95% CI 0.27 to 0.40] lower). There were no clinically significant associations between dialysis modality and concentrations of calcium or alkaline phosphatase (Table).

Conclusions: Among incident dialysis patients, treatment with dialysis modalities with longer treatment times or higher frequency was associated with altered patterns of serum phosphorus and PTH compared to conventional HD.

Table:

Phosphorus					Parathyroid Hormone				
Modality	Estimate	LCL	UCL	p-value	Modality	Estimate	LCL	UCL	p-value
HD	5.62	5.56	5.68	<.001	HD	373	352	394	<.001
NICHD	-0.45	-0.53	-0.38	<.001	NICHD	-21	-37	-6	0.01
PD	-0.15	-0.18	-0.12	<.001	PD	44	36	51	<.001
HHD	-0.33	-0.40	-0.27	<.001	HHD	52	34	69	<.001
Calcium					**Alkaline Phosphatase**				
Modality	Estimate	LCL	UCL	p-value	Modality	Estimate	LCL	UCL	p-value
HD	9.15	9.12	9.18	<.001	HD	122.6	119.3	125.9	<.001
NICHD	0.04	0.01	0.08	0.02	NICHD	-1.4	-4.4	1.6	0.36
PD	-0.06	-0.07	-0.05	<.001	PD	-6	-8.2	-3.7	<.001
HHD	0.00	-0.03	0.03	0.86	HHD	-8.3	-11.6	-5.0	<.001

Funding: NIDDK Support

PUB319

Abstract Withdrawn

PUB320

Prognostic Significance of the Interval Change of Plasma Neutrophil Gelatinase-Associated Lipocalin Level during the First 48 Hours in Patients Starting Continuous Renal Replacement Therapy Ha Yeon Kim, Tae Ryom Oh, Eun Hui Bae, Soo Wan Kim, Seong Kwon Ma. *Dept of Internal Medicine, Chonnam National Univ Medical School, Gwangju, Korea.*

Background: The present study investigated the clinical significance of the interval change of plasma neutrophil gelatinase-associated lipocalin (pNGAL) during the first 48 hr in acute kidney injury (AKI) patients starting continuous renal replacement therapy (CRRT).

Methods: This retrospective observational study included 404 AKI patients treated with CRRT. The patients were divided into two groups; renal recovery (n=120, 29.7%) vs. renal non-recovery (n=284, 70.3%) or survivor (n=193, 47.8%) vs. non-survivor group (n=211, 52.2%). The cut-off value of pNGAL was 200 ng/mL, and that of serum cystatin C (sCysC) was 1.0 mg/L. The estimated glomerular filtration rate (eGFR) was calculated by CKD-EPI equation. Exclusion criteria was a patient less than 18 years old, death with 24 hr after CRRT starting or a patient with maintenance renal replacement therapy.

Results: The volume of hourly urine output during the first 48 hr was significantly higher in the renal recovery group compared with the renal non-recovery group, and in the survivor group compared with the non-survivor group. The level of pNGAL at baseline or at 48 hr did not differ between renal recovery group and non-recovery group, and survivor group and non-survivor group. However, the value of ΔpNGAL was significantly higher in the renal recovery group compared with the renal non-recovery group (90.6 ± 82.9 vs. 33.8 ± 53.7, p<0.001), and in the survivor group compared with the non-survivor group (129.8 ± 182.4 vs. -98.5 ± 162.6, p<0.001). The level of sCysC at baseline, at 48 hr or ΔsCysC did not differ between the both groups. That of sCr at baseline, at 48 hr or ΔsCr also did not differ.

Conclusions: The interval change of pNGAL during the first 48 hr may predict renal outcome and survival of AKI patients undergoing CRRT although the value of pNGAL per se has a limitation on the prediction of outcomes. Urine output is also a robust prognostic biomarker in these patients.

PUB321

An Effect That Parameters Using Body Composition Monitor Have on Hemodialysis Patients: A Systematic Review and Meta-Analysis of Observational Studies Seon Deok Hwang,[1] Jin Ho Lee,[3] Woo Yeong Park,[2] Moon-Jae Kim,[3] Seoung Woo Lee.[4] *[1]Inha Univ College of Medicine; [2]Keimyung Univ Kidney Inst; [3]Bongseng Memorial Hospital; [4]Inha Univ College of Medicine; [5]Inha Univ College of Medicine.*

Background: It is reported that, with regard to assessment of patients' nutritional status, the interest in sarcopenia has recently risen, and an effect is produced on mortality as well, and overhydration in dialysis patient has an effect not only patient's cardiovascular mortality but also prognosis. The purpose of this study is to examine what effect is produced on dialysis patient by the measurement of tissue index and overhydration degree, using body composition monitor. .

Methods: A systematic review and meta-analysis using a random-effects model was performedWe searched the Cochrane Central Register, OVID MEDLINE, EMBASE, and Pubmed until March 15, 2016. We reviewed the reference lists of relevant reviews, registered trials, and relevant conference proceedings. Definition of overhydration group >15% and low LTI group <10% compare with reference group.

Results: Six trials were included, consisting of a total of 39615 patients In the pooled analysis, In overhydration group, The pooled hazard ratio (HR) for overall survival of overhydration vs.non overhydration was 2.01 ([95% confidence interval (CI): 1.397-2.890, P[thinsp]=[thinsp]0.001). HR for mortality in Low LTI Group was 1.53 (95% CI), 1.407 to 1.670]; P=0.001) in a random-effects model respectively. In the sensitivity analysis, the result from the most recent study showed the most heterogeneity.

Conclusions: Being diagnosed with low lean tissue index and determining whether to be overhydrated by using BCM may become a factor in increasing mortality in dialysis patients.

PUB322

Treatment Outcomes for Calcific Uraemic Arteriolopathy: One Centre's Experience Andrew Nixon, Annabel Roberts, Ajay Prabhakar Dhaygude. *Renal Medicine Dept, Royal Preston Hospital, Preston, Lancashire, United Kingdom.*

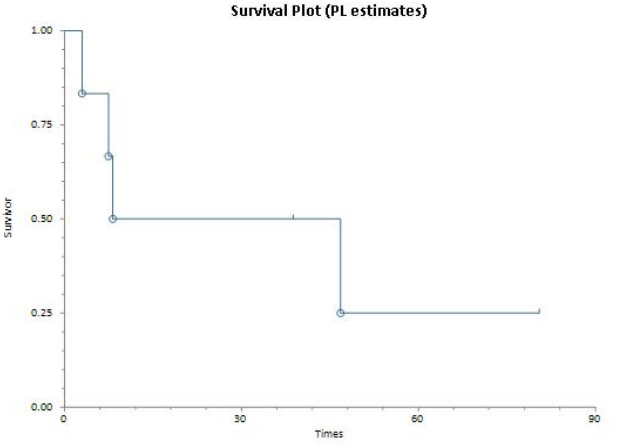
Background: Calcific Uraemic Arteriolopathy (CUA), also known as calciphylaxis, is a rare disorder that primarily affects patients with dialysis-dependent end-stage renal disease.[1] It is characterised histologically by medial calcification of arterioles.[1] It is associated with severe pain, skin ulceration and a significantly increased mortality risk.[1]

Methods: Clinical records were reviewed for all patients diagnosed with CUA between 2009 and 2015.

Results: Six patients were diagnosed. Table 1 demonstrates patient demographics and clinical characteristics.

Demographics and Clinical Characteristics	
Median Age	61
M:F	1:1
Dialysis	5
Median Dialysis Vintage (range)	39 months (12-109)
Previous Renal Transplant	4
Diabetes Mellitus	2
Warfarin	3
Mean Calcium Phosphate Product	3.8 $mmol^2/L^2$
PTH Above KDOQI Targets	4
Lower Limb Lesion(s)	6

Treatment included: increasing dialysis dose(6), IV sodium thiosulphate(6), dietary/ pharmacological hyperphosphataemia management(6), cinacalcet if uncontrolled hyperparathyroidism(3), stopping contributory medications(3) and regular wound care(6). Wound debridement was performed for 3 patients. Amputation was required for 1 patient. Lesions resolved in 4 patients. One-year survival rate was 50% with a median survival of 8.2 months. No deaths were directly due to CUA. Figure 1 demonstrates survival analysis (months).



Conclusions: This single centre study reports a median survival over three-fold greater than that published previously in the literature.[2] Thus, providing support for a multi-modal, multi-disciplinary approach to the management of CUA. **References:** 1. Nigwekar SU et al. Calciphylaxis: risk factors, diagnosis, and treatment. Am J Kidney Dis. 2015 Jul;66(1):133-46. 2. Weenig RH et al. Calciphylaxis: natural history, risk factor analysis, and outcome. J Am Acad Dermatol. 2007 Apr;56(4):569-79.

PUB323

Hemodialysis and Hemodiafiltration Affect VAP-1 and Endocan Levels in Regards to Type of Anticoagulant Jolanta Malyszko,[1] Ewa Koc-Zorawska,[1] Jacek S. Malyszko.[2] *[1]2nd Dept Nephrology, Medical Univ, Bialystok, Poland; [2]1st Dept Nephrology, Medical Univ, Bialystok, Poland.*

Background: Traditional anticoagulants used in hemodialysis-HD are heparin and low molecular weight heparins-LMWHs. Repeated and prolonged exposure to UFH and/ or LMWHs may further disturb hemostasis in uremic patients. VAP-1 (vascular adhesion protein) is secreted by vascular smooth muscle cells, adipocytes, and endothelial cells with functional monoamine oxidase activity and is elevated in atherosclerosis, diabetes mellitus and obesity. Endocan is a novel soluble dermatan sulfate proteoglycan derived from endothelium. Its elevated level is connected with endothelial activation, inflammation or carcinogenesis In this cross-sectional study we aimed to assess the effects of UFH and LMWHs on VAP-1and endocan in 80 hemodialyzed patients and 17 patients treated by means of hemodiafiltration-HDF. We also assessed the effects on single HD session on VAP-1 land endocan evels in regard to the type of anticoagulant.

Methods: Patients were selected from the group of hemodialyzed subjects who had been receiving enoxaparine (n=42), dalteparine (n=10), nadroparine (n=6) or unfractionated heparin –UFH (n=20) as an anticoagulant during their HD sessions. VAP-1 was assessed using kits from BioVendor, Modrice, Czech Republic. Endocan was assessed using commercially available kits from Lunginov, France.

Results: Diabetic patients had higher serum VAP-1 and endocan than non-diabetic. Patients on HDF had significantly lower VAP-1snd endocan when compared with HD patients. We found that VAP-1 and endocan concentration in patients dialyzed by using LMWH or UFH were similar. HD session was associated with a significant increase in endocan level (p<0.001), however, there was no effect on HD session on VAP-1 concentration.

Conclusions: HDF is associated with lower VAP-1and endocan levels indicating less pronounced endothelial cell injury and more favorable effect of this type of treatment. Dialysis session affect endothelial function reflecting by a significant rise in endocan levels. Type of heparin seem to have no effect on VAP-1 and endocan levels in hemodialyzed patients. However, the cross-sectional but not prospective design is a limitation of this study.

Funding: Government Support - Non-U.S.

PUB324

Comprehensive Analysis of Support Interventions on Quality of Life in Patients with End Stage Renal Disease on Hemodialysis May Christine Zeta,[1] Jennie Z. Ma,[2] Uta Erdbruegger,[1] Emaad M. Abdel-Rahman.[1] *[1]Nephrology, Univ of Virginia, Charlottesville, VA; [2]Public Health Sciences, Univ of Virginia, Charlottesville, VA.*

Background: Decreased health-related quality of life (HRQOL) is common in chronic hemodialysis (HD) patients and is associated with mortality, complications and reduced compliance with treatment. Interestingly, achievement of widely accepted clinical performance targets is not related to HRQOL of hemodialysis patients. The effectiveness of a multidisciplinary team approach in support interventions targeting adult patients with ESRD has not been systematically assessed. The aim of this study was to comprehensively describe these interventions and QOL measures from a pilot study with intensified HRQOL testing.

Methods: This is a pilot study of 8 adult patients on hemodialysis who consented to perform the Kidney Disease and Quality of Life questionnaire (KDQOL™36) on an intensified schedule (months 0, 3, 6, 9, and 12). Interventions normally given as standard

of care were documented for each time period (T1=0-3 months, T2=4-6, T3=7-9, T4=10-12). Five intervention categories were determined—nutrition, education/counselling, psychosocial, medical management/treatments, and rewards/gifts.

Results: 40 KDQOL questionnaires completed by 8 patients during the 1-yr study period were analyzed. The average KDQOL scores were: Physical=35.6, Mental=49.6, Burden of Disease=51.6, Symptoms/Problems=80, and Effects of Kidney Disease=65. During the study the mean scores over the 1-yr study period did not change markedly. The average number of interventions for each time period was 7, most of which were related to nutrition, followed by medical management. Overall no change in number of interventions were observed over time.

Conclusions: The HRQOL scores and number of interventions did not change markedly during the study period. Interestingly, most interventions were related to nutrition counseling. More patients are needed to assess the effectiveness of these support interventions on patient's quality of life and to determine the optimal frequency of its testing.

PUB325

Impaction Factors for Mortality of Maintain Hemodialysis Patients Chang Wang, Yuan Yang, Fang Yuan, An Zhou, Youming Peng, Xing Chen, Hong Liu. *2nd Xiangya Hospital, Central South Univ.*

Background: The mortality of hemodialysis in the five-yearon hemodialysis is still high, despite progression of hemodialysistechnological and applicationof different dialysis techniques. The study of the long time survival outcome and risk factors for maintain hemodialysis (MHD) of Chinese mainland patient are currently lacking.

Methods: A retrospective cohort study of 91 death MHD patients wascarried out, and data was collected by the 2nd Xiangya hospital hemodialysis center from 2011 to 2015. The Kaplan-Merier test was used to analyze risk factors associated with 48m survival. Multivariate Cox regression was used to analyze independent risk factors of all-cause death.

Results: Results revealed the median survival time of 91 maintenance dialysis patient (25 female and 66 male) is 46 months. The Kaplan-Merier analysis showed the age of initiation dialysis >70y, diabetic nephropathy, cerebrovascular comorbility, eGFR<7 ml/min/1.73m^2 or > 10 ml/min / 1.73 m^2 at the initiation of dialysis were risk factors of mortality. While the serum albumin≥30g/l, or with haemoglobin≥100g/l at the initiation of dialysis, using high-flux dialyzer, AVF, HDF+HD dialysis model, Kt/V ≥1.2, dialysis frequency>2/w, or haemoglobin ≥110g/l, or iPTH ≥300 pg/ul, or prescript β-receptor blocker treatment had significantly longer survival time. Further, multivariate analyses showed baseline eGFR<7 ml/min/1.73m^2,diabetes, cerebrovascular disease, age of initiation dialysis >70y , baseline eGFR>10 ml/min/1.73m^2 were significant independent risk factors of higher all cause death in MHD patients; and using AVF vascular access, pre-dialysis hemoglobin≥100g/l, using high-flux dialyzer, and dialysis frequency>2 times/week were independent factors of reducing all-cause death in MHD patients.

Conclusions: In this study, old age, diabetes and CVD co-morbidity lead to an increased risk of death in MHD patients. Low hemoglobin and too high or low eGFR at the commencement of dialysis are associated with the poor survival time. Fortunately, dialysis frequency>2/w, fistula access and high-flux dialyzer are associated with better survival outcome.

PUB326

Increased Prevalence and Morbidity of *Clostridium difficile* Infection in Patients with End-Stage Renal Disease on Hemodialysis Hong Joo Lee. *Dept of Nephrology, Seoul Red Cross Hospital, Seoul, Republic of Korea.*

Background: Patients with end-stage renal disease(ESRD) on hemodialysis have impaired host defense mechanisms and frequently require antibiotics for various infective complications. Despite increasing efforts to prevent infection, the prevalence of hospital-associated *Clostridium difficile* infections (CDI) is increasing. Heightened awareness prompted this study of the prevalence and morbidity associated with CDI in ESRD patients on hemodialysis.

Methods: This was a single-center, retrospective case-control study. A total of 85 patients with CDI were identified based on a retrospective review of *Clostridiumdifficile* toxin assay or histology recordsat Seoul Red Cross Hospital from January 2011 to January 2015. CDI was diagnosed by enzyme immunoassay for toxins and, more recently, polymerase chain reaction (PCR) testing.In 85 patients with CDI, 15 patients with end-stage renal disease on hemodialysis included as cases and 60 patients without hemodialysis were used as controls. We compared the baseline characteristics and identified independent risk factors that could predict the development or prognosis of CDI. Hospital outcomes and survival were also compared between cases and controls.

Results: Independent risk factors for occurance of CDI included age, duration of antibiotics and ESRD on hemodialysis. Hemodialysis patients with CDI had more baseline comorbidities and received more blood products than non-hemodialysis patients with CDI. All were treated with metronidazole or vancomycin. Patients on hemodialysis with CDI showed poorer responses to the initial metronidazole therapy. Hemodilalysis patients with CDI had more septicemia, longer hospital stay, and lower 3-year survival than non-hemodialysis patients with CDI.

Conclusions: The prevalence of CDI is increasing, contributing importantly to morbidity and mortality in ESRD patients on hemodialysis.

PUB327

The Increase of Serum Myostatin Level Was Suppressed by Intra-Dialytic Exercise in Hemodialysis Patients Shigeichi Shoji,[1] Hisayo Yokoyama,[2] Kiyonori Takai,[1] Senji Okuno,[1] Tomoyuki Yamakawa,[1] Eiji Ishimura,[3] Yoshiki Nishizawa,[4] Masaaki Inaba.[4] *[1]Internal Medicine, Shirasagi Hospital, Osaka, Japan; [2]Dept of Environmental Physiology for Exercise; [3]Dept of Nephrology; [4]Dept of Metabolism, and Molecular Medicine, Osaka City Univ Graduate School of Medicine, Osaka, Japan.*

Background: Myostatin is a TGF-β family member that act as a negative regulator of skeletal muscle mass. In healthy people, aerobic exercise and resistance training decreased the level of serum myostatin. (Hittel DS, et al, Med Sci Sports Exerc, 2010). But there was no reports of the effects of intra-dialytic exercise on muscle and bone metabolism with the change of the serum myostatin levels.

Methods: This study is a non-randomized controlled trials; 12 exercised group and 10 no exercised group. Pre and after exercise, body composition were measured by DXA (QDR-4500; Hologic Inc, Waltham,MA), exercise capacity was measured by cardio pulmonary exercise test, and the serum levels of myostatin (time-averaged concentration: TAC) were measured.

Results: After 12 weeks intra-dialytic, aerobic and resistance exercise, serum myotatin levels increased in both groups. But the statistically significant suppression of serum myosttin levels by exercise was found by two-way (group x intervention) ANOVA with repeated measurements.

	Control(pre)	C(post)	Exercise G(pre)	E(post)	group effect	Inter-vention effect	Inter-action
Myostatin ng/mL	10.5 ±4.0	22.9 ±2.5#	17.4 ±4.5*	23.8 ±6.9#	0.077	<0.001	0.007
P1NP ug/L	323 ±155	406 ±258	267 ±125	250 ±87	0.135	0.175	0.047
TRACP-5b mU/dL	470 ±274	584 ±392	503 ±292	477 ±236	0.779	0.294	0.108
FGF-23 pg/mL	4416 ±3860	3770 ±3448	2937 ±2793	2490 ±1978	0.307	0.134	0.778
Sclerostin pmol/L	249 ±151	198 ±123#	184 ±77	157 ±55#	0.278	<0.001	0.146

Exercise has significant interventional effect on handgrip strength and PINP. 10m gait speed, peak VO2 and heart rate recovery has significantly improved in only exercise group. Body composition, bone mineral density, and muscle mass and muscle strength (knee extension strength) have no change after exercise.

Conclusions: In hemodialysis patients, intra-dialytic exercise suppress the increase of serum myostatin level.

PUB328

Can We Use Cellulose Triacetate Membrane for Postdilution Online-Hemodiafiltration? Marta Albalate,[1] Patricia Martínez-Miguel,[4] Lourdes Bohorquez,[2] Patricia De Sequera,[1] Rafael Ramirez,[2] Hanane Bouarich,[4] Guillermina Barril,[3] Rafael Perez-Garcia.[1] *[1]Nephrology, Infanta Leonor Hospital, Madrid, Spain; [2]Physiology, Alcalá de Henares Univ, Alcalá de Henares, Madrid, Spain; [3]Nephrology, La Princesa Hospital, Madrid, Madrid, Spain; [4]Nephrology, Principe de Asturias Hospital, Alcalá de Henares, Madrid, Spain.*

Background: Synthetic membranes have been the only used in the postdilution online-HDF. We have a new asymmetric cellulose triacetate (ACT) (Solacea®, Nipro) suitable for this technique (Kuf 76/ml/h/mmHg). The aim is to describe ACT performance and behaviour to identify: purifying efficiency, use in clinical practice, biocompatibility and inflammatory effect.

Methods: Prospective observational multicentre study. Twelve patients (9 men, 65 (41-85)years) were included. Each patient was treated with ACT for a month without changing their previous schedule. 127 full sessions were collected. Effective time (EfT), Qb, Qd, ultrafiltrate volume (UF), infusion volume (IV), Kt, maximum PTM and technical or coagulation problems during treatment were collected. At the first treatment, blood samples were taken before and after dialysis to determine RR of urea, creatinine, β2microglobulin, myoglobin and retinol binding protein (PTR). At 30' one second blood was removed. Monocyte subpopulations were measured before the start of the first and the last dialysis session.

Results: 1) Efficiency: EfT 248.9(10.3)', effective Qb 371(28.2) ml/min, UF 2.6(0.6) l, IV 26.7(2.8) l, Kt 57.3(4.3) l, maximum PTM 83(22.6) mmHg, RRurea 81(5.2), Cr 74.7(4.6), mioglobin 71(6.8), β2m 76.5(4.8) and PTR 18.6(7.6)% 2) Clinical use: There were no complications or alarms or need to change dosage of heparin. 3) Biocompatibility: Leukocyte and platelet initial vs. 30' didn't change 4) Inflammation: After ACT percentage of CD14+CD16++ was lower (33.8(13) vs. 26.4(13.1), p<0.04) (%), no differences were found in other subpopulations.

Conclusions: ACT achieved adequate Kt, IV and RRs without technical problems, making it a potential treatment for post-HDF and a solution to allergic patients to synthetic membranes. Also, our preliminary results show that ACT seems to be a biocompatible membrane that selectively decreases the percentage of pro-inflammatory monocytes.

PUB329

Factors Associated with Dialysis Withdrawal Billie Axley, Michael R. O'Connell, Dugan Maddux, John W. Larkin, Marta Reviriego-Mendoza, Stephanie Johnstone, Michelle L. Gilliland, Rebecca L. Wingard, Tammy C. Green, Franklin W. Maddux. *Fresenius Medical Care North America, Waltham, MA.*

Background: Little is known about the factors that may influence discussions with patients about withdrawal from hemodialysis (HD). To explore this we surveyed a group of HD staff including nephrology nurses, social workers, and dietitians.

Methods: A voluntary, electronic survey was offered to staff at 20 Fresenius Medical Care North America HD clinics during February of 2016. The survey questions identified: 1) most common reasons for a patient/family to initiate a conversation about HD withdrawal, 2) when a patient/family request(s) for HD withdrawal is most often made, and 3) describe process(s) in place to support the patient/family when a decision is made to withdraw from HD. Responses from 28 HD staff were analyzed.

Results: We found that clinic staff reported decreased quality of life and failure to thrive as the most common reasons for a patient/family member to initiate a conversation about withdrawal from HD (89% & 79%, respectively) (Figure 1A). Withdrawal requests by the patient/family were mostly made during hospitalization, followed by requests being made during HD (57% & 21%, respectively) (Figure 1B). Most common processes in place supporting patients requesting dialysis withdrawal were hospice referral (68%), and home care arrangements via social workers and clinic managers (43%); 14% reported there was not a specific process in place (Figure 1C).

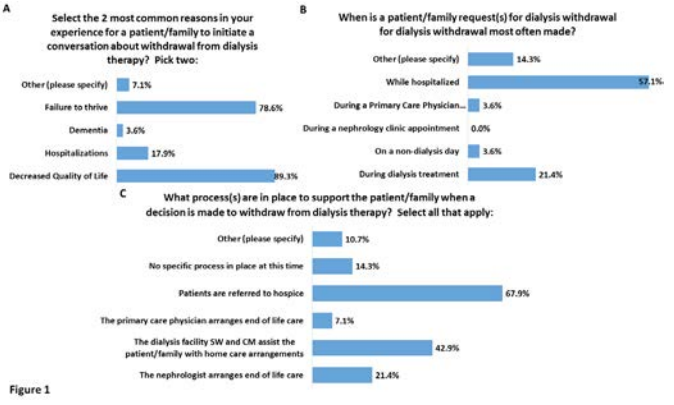


Figure 1

Conclusions: Survey results from a multidisciplinary group of dialysis clinic staff suggest that the most common reasons for patients and families to request dialysis withdrawal were decreased quality of life and failure to thrive, and these requests were commonly made while patients were hospitalized. These findings support the need for strategies that focus on the patients' values and wishes.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

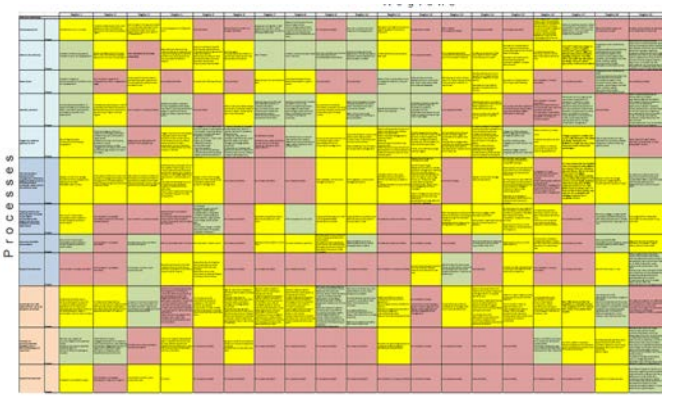
PUB330

Provincial Initiatives to Implement a Palliative Approach to Renal Care across Ontario Sarbjit Vanita Jassal,[1,3] Marnie MacKinnon,[3] Sharon Gradin,[3] Tea Palamarevic,[3] Peter G. Blake.[2,3] *[1]Div of Nephrology, Faculty of Medicine, Univ Health Network, Toronto, ON, Canada; [2]Div of Nephrology, Univ of Western Ontario, London, ON, Canada; [3]Ontario Renal Network, Toronto, ON, Canada.*

Background: The Ontario Renal Network (ORN) provides policy, financial, and governance oversight to individuals receiving renal care in the Province of Ontario. Through their planning work with patients and family members, the ORN identified palliative and end of life care as a priority. We present the provincial strategy used to develop an integrated process for the early identification and provision of a palliative approach to renal care.

Methods: Information about current practices was collected from all renal centres across the province through a process mapping exercise. Process maps were collated and synthesized using aggregate gap analysis. Clinician understanding of palliative care was evaluated by questionnaire.

Results: The current state mapping process showed a number of clinical initiatives had been initiated across a number of centres, suggesting heightened clinical awareness of the need for a palliative approach to renal care.



Processes were, however, often inconsistently delivered, and at risk due to poorly coordinated community engagement. Informal survey results suggest practicing clinicians are aware of the need to include a palliative care approach to renal care, but they do not feel enabled or sufficiently trained.

Conclusions: Key opportunities to effectively roll out provincial-level initiatives can be identified from the process maps. A provincial level initiative can facilitate clinician driven initiatives to improve the provision of renal services to patients.

PUB331

Development of a Medical Writing Elective for Nephrology Fellows Amir Kazory, Abhilash Koratala, Maryam Sattari. *Univ of Florida.*

Background: While half of the American medical schools provide formal training in writing history and physicals, less than 15% offer any type of formal medical writing courses designed to teach the skills needed to write grant proposals and peer-reviewed journal articles. Similarly, although faculty development in the "effective writing of grants and manuscripts" continues to be a perceived need for academic physicians, there has been minimal documented progress in improving the availability of formal writing education in the recent years. To address this gap, a "medical writing elective" (MWE) was designed at the University of Florida specifically for nephrology fellows.

Methods: Based on the published literature and our own experience with development and directorship of MWE for medical students and internal medicine residents, we constructed an interactive multimodality curriculum for nephrology fellows. The goals of this renewable 2-week MWE are to (1) provide fellows with knowledge and experience about various aspects of medical writing (e.g. case reports, clinical vignettes, and poster/oral presentations in scientific meetings), (2) enhance their education by advancing their medical writing skills and editing abilities, and (3) increase and enrich their scholarly output in order to improve their future career opportunities. Teaching methodology of the MWE includes (1) didactic lectures, (2) writing assignments, and (3) small group sessions with the faculty. Fellows are also assigned a writing project for the elective, for which they prepare a clinical vignette abstract and/or a case report.Examples of planned topics include introduction to writing various types of manuscripts, plagiarism/self-plagiarism, patient privacy, journal rankings, and submission/revision requirements.

Conclusions: This multimodality MWE is meant to address the need for dedicated educational resources to teach trainees the fundamental principles of medical writing. We plan to pilot-test the acceptance and effectiveness of this curriculum in a small sample of nephrology fellows using a pre- and post-test format of knowledge assessment and pre- and post-elective scholarly productivity. If successful, it can be customized for use in other disciplines and specialties.

PUB332

An Innovative Collaboration between Patients and an Industry-Supported Rare-Disease Registry Len Woodward,[1] Gema Ariceta,[2] Christoph Gasteyger,[3] Sally A. Johnson,[4] Johan Vande Walle,[5] Christoph Licht.[6] *[1]aHUS Alliance; [2]Univ Hospital Vall d'Hebron; [3]Alexion Pharma GmbH; [4]Great North Children's Hospital; [5]Ghent Univ Hospital; [6]The Hospital for Sick Children.*

Background: Partnership between patient (pt) organizations and clinical researchers can promote innovation and support pt-focussed research. Few reports on such activities exist; we describe a collaboration between a group of pt organizations and a pt registry.

Methods: The global atypical Haemolytic Uraemic Syndrome (aHUS) Registry (NCT01522183) is an observational, multicentre registry of pts with aHUS which will assess long-term outcomes. The aHUS Alliance comprises 12 pt organizations worldwide that aim to work with international clinical research networks. The aHUS Registry Scientific Advisory Board (SAB) invited the aHUS Alliance to submit research ideas important to pts with aHUS. Such ideas were subsequently generated independently of the SAB by pts and the aHUS Alliance.

Results: In November 2015, 24 identified research ideas were presented to the SAB. The majority related to three topics: understanding causes of thrombotic microangiopathy, the clinical and psychological/social impact of living with aHUS, and comparing regional disease characteristics. The top five research priorities are shown (Table). The proposals have led to an ongoing analysis of data on pts with kidney transplants enrolled in the registry and a proposal to analyse annual immune cycles is in development that includes three aHUS Alliance members as investigators.

Table. Key research priorities for pts with aHUS

1. What are transplant outcomes without eculizumab and what non-kidney damage is likely from any resulting aHUS onset?
2. What are the barriers to diagnosis, and how can they be overcome?
3. Can a blood test be developed to allow pts in remission to monitor themselves?
4. Is there a "golden period" for diagnosis which predicts more favourable outcomes for pts with aHUS?
5. Do annual immune activity cycles predict a time of year when aHUS onset is more likely?

Conclusions: Research priorities for pts include understanding barriers to rapid diagnosis, avoiding irreversible organ damage and kidney transplantation outcomes. Analyses of the aHUS Registry will include topics proposed by the Alliance as a priority. It is key that the collaboration continues in the long-term. **Acknowledgments:** We thank the patients and the aHUS patient organisations involved.

Funding: Pharmaceutical Company Support - Alexion Pharmaceuticals, Inc.

PUB333

What Can Social Media Tell Us about Patient Experiences of Living with IgA Nephropathy? Jonathan Barratt,[1] Karen Molyneux,[1] Lydia Yijian Chen.[2] *[1]Infection, Immunity & Inflammation, Univ of Leicester, Leicester, United Kingdom; [2]DataTellsLife, DataIntelligence, Co. Ltd, Hong Kong.*

Background: The use of social media around the world has exploded in recent years and is changing the way medicine is practiced and healthcare is delivered. Social media is increasingly used to share experiences of living with chronic disease, the impact of treatments for these diseases and the quality of interactions with health providers. It is often the first port of call for people living with chronic disease who are searching for advice and guidance on managing their condition. IgA nephropathy is a disease that more frequently affects young adults, a population that is immersed in the social media revolution.

Methods: To understand the key issues impacting on the lives of people with IgAN and to identify areas of unmet need, particularly in terms of education about IgAN we undertook a systematic social media text mining and thematic analysis examining both twitter and instagram feeds between 27/07/2015 and 31/05/2016.

Results: Between 27/07/2015 and 27/07/2015 there were 3575 posts including the keyword IgA nephropathy (96.3% twitter, 3.97% instagram). 14% of posts contained public geographic location information and of these 22.5% Europe, 65.56% North America, 9.20% Asia, 1.57% Oceania, 0.78% Africa, 0.39% South America. When analysing posts by content the commonest topics discussed were how to diagnose IgAN, what treatments are available and how to prevent kidney failure. Informal peer support networks were identified and these focused on providing advice and support around several key areas: coping with disease symptoms and side effects of treatments (particularly steroids), diet, feedback on recent blood and urine tests and how to slow progression of IgAN.

Conclusions: Patients with IgAN commonly use social media to share experiences and look for advice on managing their disease. Analysis of social media data provides a rich seam of real life patient experience, highlights common areas of poor knowledge and misconception that can prompt nephrologists to raise these issues during outpatient reviews.

Funding: Pharmaceutical Company Support - 2DataTellsLife, DataIntelligence, Co. Ltd

PUB334

Effect of Online Educational Interventions in Hyperkalemia among Nephrologists Edward L. Jackson, Don Blatherwick, Karen Badal. *Medscape Education, LLC.*

Background: Chronic hyperkalemia is a poorly understood condition that has been associated with the use of renin-angiotensin aldosterone system (RAAS) inhibitor therapies in patients that would otherwise benefit from them. A study was conducted to determine whether a curriculum of online educational interventions could address underlying educational needs among nephrologists in the area of evaluation and management of chronic hyperkalemia.

Methods: Educational interventions covered a range of topics related to hyperkalemia and included a text-based introductory primer, a video lecture, and three video discussion-based interventions, which were launched between September 25, 2016 and January 6, 2016. Data were collected between September 25, 2015 and April 5, 2016. Educational impact for each intervention was assessed by comparing each participant's responses to 4 matched, content-related knowledge questions asked both pre- and post-education. Statistical analysis for each question included a paired 2-tailed t-test, McNemar's $\chi 2$ statistic and probability (P values) to determine significance level, with a $P < .05$ as meeting statistical significance.

Results: For nephrologists who participated in at least one of the online interventions and completed all pre- and post-assessment questions, a comparison of responses demonstrated a high level of baseline knowledge of hyperkalemia. Significantly improved learners were observed in several specific topic areas including: Site of drug action of emerging potassium binders (95% versus 80%, n=111); Initiation of potassium binder therapy prior to initiating a RAAS inhibitor (84% versus 66%, n=155); Evidence from clinical trials for maximizing RAAS inhibitor therapy in patients with heart failure (76% versus 43%, n=129); Evidence from clinical trials of novel potassium binders (94% versus 74%, n=124).

Conclusions: As a result of participation in a curriculum of clinically relevant educational interventions in text and video formats designed to address identified gaps, significant improvement in knowledge of hyperkalemia was demonstrated in several areas including knowledge of novel potassium binder therapies, and clinical trials of RAAS inhibitor therapies.

Funding: Pharmaceutical Company Support - Relypsa

PUB335

Single Tertiary Center Experience with Therapeutic Plasma Exchange Tahir Zaman, Christine K. Raj, Alfred K. Cheung, Josephine Abraham. *Univ of Utah, Univ of Utah, Salt Lake City, UT.*

Background: The field of nephrology has acquired the role of performing therapeutic plasma exchange (TPE) in the U.S. Since November??, 2014 at the University of Utah, the Division of Nephrology has assumed the responsibility of supervision and conduct of TPE . The University of Utah is a tertiary referral center for the Intermountain west, including the states of Utah, Idaho, Montana, Wyoming and Nevada. Herein we report our one-year experience with TPE.

Methods: A retrospective review was performed for TPE procedures provided by our apheresis center from January 2015 to December 2015. We largely followed the guidelines provided by the American Society for Apheresis (ASFA) for indications under 4 categories. Indications at the time of consultation and the numbers of apheresis procedures were recorded.

Results: A total number of 504 TPE procedures were performed, with 64%, 28% and 8% in ASFA Category 1, Category 2 and category 3 indications, respectively. A significant portion of the cases was related to kidney transplants and other renal indications (38%), which was quite similar to that for neurological conditions (42%). Hematology conditions comprised of 10%, while miscellaneous conditions accounted for the remaining 9%. Several indications for TPE are for treatment of renal related pathology. In renal transplantation TPE has been used for pre-transplant desensitization, used in treatment of recurrent FSGS and acute antibody mediated rejection. In general nephrology TPE has been used for treatment of granulomatosis with polyangiitis, thrombotic microangiopathy, cryoglobinemia and for anti-GBM related disease.

Conclusions: Overall the field of nephrology stands to benefit from performing TPE. Though initially there were some start-up struggles including setting up our electronic medical records for ease of usage and teaching both the faculty and nursing how to perform the procedure, ultimately we believe that TPE can be used to enhance the attraction of the field of nephrology.

PUB336

Intensive Lifestyle Program in Chronic Kidney Disease Sahil Bawa,[1] Michael J. Germain,[2] Sam A. Headley.[3] *[1]Nephrology, RTANE, Springfield, MA; [2]Nephrology, Baystate Medical Center, Springfield, MA; [3]Exercise Science, Springfield College, Springfield, MA.*

Background: Cardiorespiratory fitness(CRF) level and Physical Activity(PA) levels are low in Chronic Kidney Disease(CKD) which contribute to increased mortality in these patients(Pt's).There is relatively little research to determine the impact of the lifestyle intervention on the quality of life in CKD Pt's.

Methods: Forty Five,Stage3-4(i.e.GFR 59-15ml/min),CKD Pt's between the ages of 18-75 not currently enrolled in a regular exercise training program(3 days/week for last 6 months) and who do not suffer from severe bowel obstruction,impaction or Pt's without postoperative motility disorders will be enrolled.Pt's will be randomly assigned to intervention or control group,and will be allowed to participate only if their nephrologist gives them the permission to do so following which they will be asked to complete a 3 day diet log and Exercise Benefits/Barrier Scale at the start of the study and also be asked to wear a 7 day activity monitor.An assessment will be done at the start of study which will include evaluation of blood pressure,medications and state of the blood vessels.Other indices of physical function(Functional Movement Screen,hand grip strength,6 minute walk,sit to stand test,short physical performance battery,leg strength and power) will be done.Pt's will be re-evaluated with blood work and physical examination at months1,3 and 6 months.It is expected that all Pt's will be on ACE/ARB,if they are not then also they can participate.Serum Potassium levels will be monitored regularly and if it goes >5.2mEq/L Veltessa(VEL) will be prescribed to the intervention group.

Results: To determine the effect of a 6 month comprehensive,integrated and individualised lifestyle intervention(CIILI) program on SPPB and other indices of physical function,Pt's with ACE/ARB prescribed VEL compared to those not on VEL and CRF levels in patients with stage 3-4 CD.

Conclusions: We hypothesize that a CIILI program will lead to enhanced physical function primarily assessed by SPPB and patients prescribed VEL will better tolerate the ACE/ARB prescription that not on VEL and better CRF levels in the intervention group.

PUB337

Electronic Cigarettes Induce Renal Fibrosis: A Novel MiR-29b-3p Mediated Mechanism Christopher A. Drummond,[1] Laura E. Crotty Alexander,[2,3] Jiang Tian.[1] *[1]Medicine, Univ of Toledo, Toledo, OH; [2]Pulmonary Critical Care Section, Veterans Affairs San Diego Healthcare System, San Diego, CA; [3]Div of Pulmonary, Critical Care and Sleep Medicine, Univ of California San Diego Health Sciences, San Diego, CA.*

Background: Clinical studies indicate that combustible cigarette smoke increases renal and cardiac tissue injury progression and functional decline in the setting of chronic kidney disease (CKD). Novel nicotine delivery devices like electronic (e)-cigarettes are used by over 10% of the population and produce vapor which may also induce renal injury. We undertook these studies to estimate the effects of e-cigarettes and to investigate mechanisms by which renal tissue injury occurs.

Methods: Our current study induced 8 week-old female CD-1 mice to inhale e-cigarette vapor containing 24mg/mL of nicotine suspended in a solution of 50% propylene glycol and 50% vegetable glycerin for 1- and 6-months.

Results: Following e-cigarette exposure, assessment of renal fibrosis and expression of the antifibrotic microRNA miR-29b-3p were evaluated. Mice exposed to e-cigarette vapor suffered a 31% decline in renal tissue expression of miR-29b-3p vs air-exposed controls ($p<0.05$). Additionally, mRNA targets of miR-29b-3p that regulate fibrosis formation or are part of fibrosis were also significantly increased in the kidneys of e-cigarette exposed mice versus air controls, i.e., Collagen 1A1 (increased 98%; $p<0.05$); Collagen 3A1 (129% increase; $p<0.05$); Collagen 4a1 (72% increase; $p<0.05$); Integrin beta 1 (58% increase; $p<0.05$); and Fibrillin 1 (100% increase; $p<0.05$). Lastly, we observed a significant increase in renal fibrosis as assessed by Trichrome staining in these animals.

Conclusions: These data are the first to indicate that e-cigarettes induce renal fibrosis. More importantly, these data provide a novel miR-29b-3p mediated mechanism linking e-cigarette vapor exposure and renal injury.

Funding: NIDDK Support, Other NIH Support - NHLBI, VA Support, Private Foundation Support

PUB338

Protection Mechanisms of Ferulaic Acid for Podocyte in Adriamycin-Induce Nephropathy Rats Minggang Wei.[1] [1]*The First Affiliated Hospital of Soochow Univ, Suzhou, China;* [2]*Jiangsu Province Hospital of TCM, Nanjing, China.*

Background: Chronic renal failure (CKD) is one of the importment public health problem. Renal fibrosis is the main reason for the progressing of CKD. Ferulaic acid is one of the main active material which extracted from some chinese herbs such as Radix Angelicae Sinensis et al. The podocyte is the main component of glomerular filtration membrane, and it's damage or apoptosis directly related to renal fibrosis. In this study, we verified that ferulaic acid could delay renal fibrosis through protecting the intact structure of podocyte and regulating the level of cell factors such as TGF-β_1 and Smads et al.

Methods: In this study, we established the adriamycin-induce nephropathy rat modle characterized by podocyte damage and renal fibrosis. We can find that the expression of TGF-β_1, Smad2/3, and extracellular matrix (ECM) such as collagen and fibrotion were significantly increase in renal tissure. Meanwhile, the expression of podocyte remarks protein of nephrin significantly decrease in renal tissure. Using ferulaic acid obviously attenuate the level of collagenI, collagenIV, fibrotion and TGF-β_1. In the vitro, ferulaic acid up-regulate the level of nephrin and podocine for TGF-β_1-induce podocyte. Furthermore, the expression of collagenI, collagenIV, fibrotion, samd2/3 and ILK decrease significantly after add ferulaic acid in the well. If up-regulaing the respond of samd2/3, we can see the cell factors and ECM have the same manifestation as the adriamycin-induce nephropathy rat modle. If inhibiting the respond of samd2/3, we can see the opposite phenomenon.

Results: whether the podocyte is integrity or not has intimate relation with renal fibrosis. Ferulaic acid can relieve the damage of podocyte and the level of ECM both in vivo and in vitro.

Conclusions: Ferulaic acid maybe one of the utility traditional medicine which can delay renal fibrosis.

Funding: Government Support - Non-U.S.

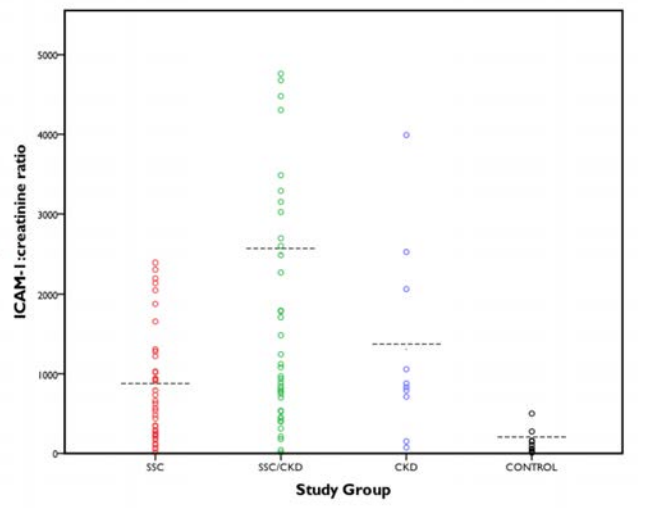
PUB339

Urinary Cell Adhesion Molecules as Markers of Renal Involvement in Systemic Sclerosis Edward Stern,[1] Aine Burns,[2] Robert J. Unwin,[2] Christopher Paul Denton.[1] [1]*Centre for Rheumatology and Connective Tissue Diseases, UCL, London, United Kingdom;* [2]*Centre for Nephrology, UCL, London, United Kingdom.*

Background: Renal involvement in systemic sclerosis (SSc) includes scleroderma renal crisis as well as progressive organ fibrosis. Detection and management of these disease complications is challenging and there is a clinical need for biomarkers that reflect renal involvement. The immunoglobulin superfamily adhesion molecules ICAM-1 and VCAM-1 are upregulated in affected tissues in SSc and other connective tissue diseases. Serum levels of ICAM-1 and VCAM-1 have been elevated in previous studies, but this may reflect the multi-organ burden of disease and organ-specific analysis may be more robust.

Methods: We collected urine and serum from 80 SSc patients, with or without renal disease, and compared them with patients with CKD of other causes (n=10) and healthy controls (n=12). We used bead-based multiplex analysis to measure cell adhesion molecule concentrations. Results were compared among groups by Kruskal-Wallis test.

Results: 40 SSc patients had CKD defined by eGFR. Risk factors for renal involvement (SSc-CKD) included diffuse skin involvement and anti-RNA polymerase III antibodies. Serum concentrations of ICAM-1 or VCAM-1 did not differ significantly between SSc-CKD and the three control groups. Urine VCAM-1 concentrations were increased in SSc patients with renal involvement (mean VCAM-1:creatinine ratio 922, SD 953 versus 654, SD 708 for those without renal involvement) but this did not reach significance. Urine ICAM-1 was significantly upregulated in SSc-CKD (mean ICAM-1:creatinine ratio 1601, SD 1394 versus 806, SD 701 for SSc without renal involvement and 1307, SD 1211 for CKD of other causes, $p<0.001$).



Conclusions: This is the first study to examine urinary cell adhesion molecule concentrations in SSc. Our results confirm the potential utility of urine sICAM-1 as a marker of renal involvement in SSc.

Funding: Government Support - Non-U.S.

PUB340

Urinary and Serum Trefoil Factor 3 Is Significantly Associated with Renal Tissue Fibrosis in Patients with Tubulointerstitial Nephritis Keiko Tanaka, Hitoshi Sugiyama, Toshio Yamanari, Ayu Akiyama, Akifumi Onishi, Masashi Kitagawa, Tatsuyuki Inoue, Jun Wada. *Dept of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama Univ Graduate School, Okayama, Japan.*

Background: Trefoil factor 3 (TFF3) is a small peptide involved in mucosal protection. TFF3 is widely expressed in multiple tissues including kidney. Previous studies have suggested that serum and urinary TFF3 significantly increase in patients with chronic kidney disease and that urinary TFF3 decreases in rats with acute kidney injury. However, it is unclear whether serum or urinary TFF3 is associated with human renal tissue injury. The aim of this study is to elucidate the relationship between the serum and urinary levels of TFF3 and the degree of renal tubulointerstitial injury.

Methods: The total study population included 112 patients (tubulointerstitial nephritis [TIN], n=34; IgA nephropathy [IgAN], n=57, and patients with minor glomerular abnormalities and thin basement membrane disease as controls, n=21) who underwent renal biopsy. The serum and urinary TFF3 concentrations were determined by a specific ELISA. The degrees of tubulointerstitial cell infiltration and fibrosis in biopsy specimens were semiquantitatively graded and defined by the inflammation score and the fibrosis score, respectively.

Results: The median serum and urinary levels of TFF3, and the mean fibrosis score and inflammation scores of the TIN group were significantly higher than those of the other groups ($p<0.0005$). A statistically significant positive correlation was observed between both the urinary and serum levels of TFF3 and the renal fibrosis score in the TIN group. A similar but non-significant tendency was observed in the IgAN group. There was no correlation between either the serum or urinary level of TFF3 and the renal inflammation score in the control and TIN groups.

Conclusions: The data indicate that the serum and urinary levels of TFF3 are significantly increased and they could reflect renal tissue fibrosis in patients, especially those with tubulointerstitial nephritis. Further studies are required to elucidate the precise distribution of renal TFF3 protein and mRNA, and the mechanism underlying the contribution of TFF3 to renal fibrosis.

PUB341

Icariin Plays a Protective Role in Angiotensin II-Induced Renal Fibrosis Independent of Estrogen Receptor Signaling Pathway Yi Wang, Hongli Zhang, Min Chen, Xiangchen Gu. *Dept of Nephrology, Yueyang Hospital of Traditional Chinese and Western Medicine, affiliated to Shanghai Univ of T.C.M.*

Background: Ang II plays a crucial role in the development and progression of renal fibrosis. Previous studies have demonstrated that estradiol could attenuate AngII induced renal fibrosis. Icariin, an active ingredient extracted from Chinese herb Epimedium, has been proved to have the same effect as estradiol on many animal disease models. In this study, we tried to ascertain the effect of icariin on the Ang II-induced renal fibrosis rodent model.

Methods: Ovariectomized SD rats were randomized into 4 groups, treated with Icariin after implantation of Ang II osmotic mini pumps at the rate of 1000ng/kg/min. The rats were sacrificed after 4 weeks of treatement. The serum estrogen level, pro-fibrotic factors, renal function, renal morphology and ER (estrogen receptor) α and β expression levels

were assessed. NRK-49F cell lines with ER knockdown and empty vector were generated using siRNA. The cell lines were stimulated with Ang II after pretreatment of Icariin. The profibrotic markers were measured as well.

Results: In contrast to AngII model group, rats treated with Icariin exhibited a significant decrease in the mRNA levels of TGF-β1, CTGF, Cola1, ColIV and Fibronectin by qPCR method. Masson Trichrome staining also demonstrated less Collagen depositions in this group. Renal functions of the treatment group were improved as well, compared to that of AngII model group. However, ER α and β expressions remained the same in all groups. In vitro study demonstrated that pretreatment of Icariin significantly decreased the expressions of profibrotic factors induced by AngII in NRK49F cell lines with both ER knockdown and empty vector.

Conclusions: Icariin can attenuate AngII induced renal fibrosis. But it might not be related to the estrogen receptors signaling pathway.

PUB342

Long-Term Lithium Treatment Causes Renal Interstitial Fibrosis in Mice

Mohammad Alsady,[1] Theun de Groot,[1] Leunie Van der Tholen,[1] Toin Van Kuppevelt,[2] Johan Van der Vlag,[3] Peter M.T. Deen.[1] *[1]Dept of Physiology, Radboud Univ Medical Center, Nijmegen, Netherlands; [2]Dept of Biochemistry, Radboud Univ Medical Center, Nijmegen, Netherlands; [3]Dept of Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands.*

Background: Lithium is the main treatment of bipolar disorder, but prolonged lithium treatment results in the development of renal interstitial fibrosis in 20% of the patients. Renal fibrosis is a hallmark and common outcome in the development of chronic kidney disease (CKD). To fully understand the development of lithium-induced CKD, the use of animal models is essential. Rats have been instrumental in this and long-term lithium treatment has been shown to induce renal interstitial fibrosis. However, considering the broad knowledge of the renal physiology, the versatility and availability of gene knockout strains, mice are the preferential mammalian model to study lithium-induced CKD, but proper model have never been reported. Therefore, we investigated whether mice could be used as a model to study Li-induced CKD development.

Methods: 10 weeks old male C57Bl/6 mice were fed a normal rodent diet or a diet with 40 mmol/kg food of lithium chloride for 40 weeks. One kidney was used to collect cortex and medulla for RT-qPCR and immunoblot analysis. The other kidney was fixed and stored for immunohistological analysis.

Results: Chromotrop-Anilinblue (CAB) trichrome staining of the kidneys revealed development of interstitial fibrosis in the cortico-medullary region, dilated tubuli, tubular atrophy and decreased glomerular size. Moreover, lithium treatment increased αSMA staining in renal cortex and outer medulla of mice indicating an increase in myofibroblasts in the interstitial compartments. Although EW3D10 staining showed that the endothelium around collecting ducts was pro-inflammatory, no increase was observed for inflammatory markers in RT-qPCR analysis.

Conclusions: We show that 40 weeks lithium treatment results in the development of renal interstitial fibrosis and that mice can be used as a model to study Li-induced CKD development. In line with data in rats, no increase was observed for inflammatory markers.

Funding: Government Support - Non-U.S.

PUB343

Acute Phase Serum Creatinine Correlates with Subsequent Tubulointerstitial Damage and Predicts AKI to CKD Transition in Rats with Ischemia-Reperfusion Injury

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Background: A strong correlation is reported between AKI episodes and the long term development of CKD. Failed redifferentiation and growth arrest of injured tubules are key processes. Thus, the severity and duration of the initial tubular insult likely predict subsequent development of CKD, which requires experimental proof.

Methods: Male SD rats were subjected to bilateral ischemia-reperfusion injury (IRI, 40 to 50min). Serum creatinine (sCre) and proteinuria were measured at 24, 48 h and day 28. At day 28, the positional relationship of damaged tubules and active fibroblasts was investigated by double immunostaining of γH2AX, vimentin and αSMA. Correlations between acute phase sCre and subsequent sCre, proteinuria and interstitial fibrosis were plotted with each individual IRI rat. As an accelerated model of AKI to CKD transition, rats were subjected to IRI 2 weeks after 75% renal mass reduction, which were followed for 28 days.

Results: sCre reached 1.95±0.207 mg/dL at 24 h, ($P<0.05$ vs sham), which returned to baseline at day 28. Non-significant proteinuria developed at day 28, which had no significant correlation with sCre in the acute phase. Histologically, various degrees of tubular damage and interstitial fibrosis were evident; γH2AX- positive, damaged tubules were observed in a patchy manner, which were surrounded by vimentin- and αSMA- positive active fibroblasts. These fibrotic areas were clearly separated by sharply demarcated normal parenchyma. Percent fibrotic areas positively correlated with acute phase sCre, in both cortex and medulla (cortex: $R^2=0.4033$, $P< 0.01$, medulla: $R^2=0.473$, $P< 0.001$ at 24h). This correlation was retained in kidneys subjected to various severity of ischemia, ranging from 40 to 50 min of cross-clamp, and in kidneys superimposed on renal mass reduction.

Conclusions: These findings emphasize a need to develop more sensitive biochemical markers to detect AKI to CKD transition, and render support to the prevalent view that mitigating initial tubular damage has a key role in preventing subsequent CKD development.

PUB344

Role of Smad3 Linker Region Phosphorylation in Nocantharidin Inhibiting Renal Interstitial Fibrosis

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Background: Our previous study showed that Nocantharidin(NCTD) could inhibit renal interstitial fibrosis and also promote Smad3 linker region phosphorylation. Based on the above results, this study will investigate: 1) effect of Smad3 linker region phosphorylation on renal interstitial fibrosis; 2) role of Smad3 linker region phosphorylation in NCTD inhibiting renal interstitial fibrosis.

Methods: 1.Human proximal tubular cell line (HK-2 cells) separately transfected with Smad3 linker region phosphorylation site mutant viruses (TGF-β1+S3-LM group) or wild type viruses (TGF-β1+S3-WT group) and HK-2 cells without any transfection (TGF-β1 group) were stimulated by 5 ng/ml TGF-β1 for 24h. The expressions of fibronectin (FN) and collagen I (Col-I) mRNA and protein in each group were detected by real-time PCR and western blot. 2. HK-2 cells separately transfected with Smad3 linker region phosphorylation site mutant viruses (NCTD+TGF-β1+S3-LM group) or wild type viruses (NCTD+TGF-β1+S3-WTgroup) were simultaneously treated with 5ng/ml TGF-β1 and 2.5μg/ml NCTD for 24h. The expressions of FN and Col-I mRNA and protein in each group were detected by real-time PCR and western blot.

Results: 1. Compared to blank control group, the expressions of FN and Col-I mRNA and protein were increased in TGF-β1 group. And their expressions were higher in TGF-β1+S3-LM group than in TGF-β1 group and TGF-β1+S3-WT group($P<0.05$). 2. Expressions of FN and Col-I mRNA and protein were decreased in NCTD+TGF-β1+S3-LM group compared to TGF-β1+S3-LM group ($P<0.05$). Similarly, their expressions were also lower in NCTD+TGF-β1+S3-WT group than in TGF-β1+S3-WT group ($P<0.05$). But expressions of FN and Col-1 were higher in NCTD+TGF-β1+S3-LM group compared to NCTD+TGF-β1+S3-WT group($P<0.05$).

Conclusions: 1. Smad3 linker region phosphorylation could block TGF-β1 signaling pathway in HK-2 cells and thus inhibit renal interstitial fibrosis; 2.NCTD's anti-renal interstitial fibrotic effect was not fully dependent on its promotion of Smad3 linker region phosphorylation.

Funding: Government Support - Non-U.S.

PUB345

A Monoclonal Antibody Neutralizing Transforming Growth Factor Beta Delays the Progressive Decline of Glomerular Filtration Rate in Hyperoxaluria-Related CKD

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Background: Hyperoxaluria can lead to progressive chronic kidney disease (CKD), e.g. in primary hyperoxaluria, a process that is associated with massive intrarenal crystal deposition, nephron loss and tubulointerstitial fibrosis. There is little evidence that fibrosis is a cause rather than a consequence of nephron loss, hence, we hypothesized that blocking fibrogenesis would not affect CKD progression.

Methods: We used a model of progressive oxalate nephropathy by feeding mice a sodium oxalate-rich, calcium-free diet for 14 days. Mice were randomized to injections with either a neutralizing TGFβ or control IgG antibody until the end of the study.

Results: As expected anti-TGFβ antibody treatment decreased interstitial fibrosis, which was associated with less tubular atrophy and RNA expression levels of kidney injury and fibrosis, and decreased the number of profibrotic macrophages. Most importantly, this antifibrotic effect significantly improved renal excretory function as demonstrated by a significant increase in the glomerular filtration rate from 20μl/min to 100μl/min ($P<0.01$), and reduced serum creatinine (1.7mg/dl to 1.0mg/dl, $P<0.01$) and BUN (78.9mg/dl to 38.2mg/dl, $P<0.05$) levels.

Conclusions: These results support the concept that TGFβ-mediated renal fibrosis contributes to nephron loss. A monoclonal antibody against TGFβ may retard CKD progression in primary hyperoxaluria and potentially other forms of CKD.

PUB346

The Expression of WNT1-Inducible Signaling Pathway Protein-1 Correlates with Renal Fibrosis

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Background: WNT1-inducible signaling pathway protein-1 (WISP-1) plays a pathological role in pulmonary fibrosis, but the role of WISP-1 in renal fibrosis is unknown. In this study, we explored the expression of WISP-1 in renal fibrosis in patients and in TGF-b-treated tubular epithelial cells (TECs) and in the obstructive nephropathy mouse model.

Methods: The serum and kidney tissues from renal biopsy-proved renal fibrosis patients including IgA nephropathy (IgAN), diabetic nephropathy (DN), primary focal segment glomerular sclerosis (FSGS) was collected to examine the levels of WISP-1 by ELISA and Immunohistochemistry staining, respectively, and the minimal change disease (MCD) and the healthy as controls. The expression of WISP-1 was also examined in TGF-b-induced renal fibrosis in tubular epithelial cells (TECs) and in the fibrotic kidneys of obstructive nephropathy model by Realtime PCR and Western blotting.

Results: Immunohistochemical analysis showed that WISP-1 was highly expressed in tubulointerstitial area in renal fibrosis patients of IgAN, DN and FSGS, but not in the expression of WISP-1 in MCD and the healthy. The WISP-1 expression in serum of renal biopsy-proved renal fibrosis patients by ELISA was significantly increased compared with

the control groups (P<0.05). More importantly, the WISP-1 expression was positively correlated with renal fibrosis (r^2=0.228, P=7.36×10^{-7}) and serum creatinine (Scr) (r^2=0.046, P=0.023), while negatively with estimated glomerular filtration rate (eGFR) (r^2=0.051, P=0.017). In accordance with these results, when the fibrotic indexes including Col I, a-SMA, fibronectin were increased both in TGF-b-induced renal fibrosis in TECs and in UUO mouse model, the expression of WISP-1 was also significantly elevated (P<0.05).

Conclusions: We explored the WISP-1 was highly expressed not only in biopsy-proved renal fibrosis patients, but also in TGF-b-induced renal fibrosis in TECs and in the fibrotic kidneys of obstructive nephropathy model. And the WISP-1 expression level in serum correlated with the fibrosis in renal tissue, and also correlated with the renal function.

PUB347

A Challenging Case of Poorly Controlled Hypertension in a Patient with a Solitary Kidney

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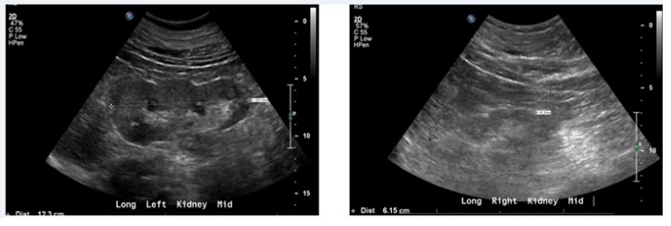
Introduction: Patients with a solitary kidney secondary to unilateral renal atrophy often have poorly controlled hypertension (HTN). Elevated renin levels and subsequent activation of the renin angiotensin aldosterone system (RAAS) are expected due to reduced renal perfusion to the atrophic kidney. Since the pathophysiology of HTN in patients with an atrophic kidney is similar to patients with renal artery stenosis, treatment with RAAS blockade seems appropriate.

Case Description: JD is a 36 year old male who was referred to nephrology for evaluation of his poorly controlled HTN and CKD. Prior to his initial visit a renal ultrasound showed an atrophic right kidney (Figure 1). He was treated with losartan and metoprolol. However his HTN remained poorly controlled, and he had worsening azotemia (Table 1). Since he had progressive renal dysfunction and uncontrolled HTN, there were ongoing discussions with the patient of stenting his right renal artery. While he was considering this intervention, amlodipine was added. Subsequently, he had significant improvement in his blood pressures and proteinuria.



Date	Blood Pressure Reading	Medications and Dose	Spot urine TP/Cr (g/day)	Serum Cr (mg/dl)	eGFR (ml/min/1.73m2)	Changes
12/03/2015	197/110	Losartan 50mg daily, Metoprolol XL 50mg daily	3.16	1.84	46	Losartan increased
12/07/2015	197/123	Losartan 75mg daily, Labetalol 400mg BID	Not Checked	1.87	45	Losartan increased
1/21/2016	180/105	Losartan 100mg daily, Labetalol 400mg BID	1.76	2.06	40	Amlodipine started
3/17/2016	142/82	Losartan 100mg daily, Amlodipine 10mg daily, Labetalol 400mg BID	0.89	1.87	45	None

Discussion: Combination therapy with RAAS blockade and amlodipine may reduce the potential need for renal artery stenting in patients with poorly controlled HTN and progressive renal disease in the setting of a solitary kidney.

PUB348

Breast Nodules: An Unusual Metabolic Complication in a Dialysis Patient

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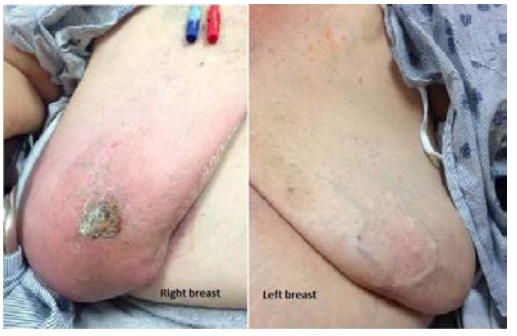
Introduction: Calcific uremic arteriolopathy (CUA) or Calciphylaxis affects 1-4% of the population with End Stage Renal Disease (ESRD) and associated with high mortality. About 90% lesions occur on the lower extremities followed by lower abdomen. We report a case of CUA of the breast, which is an uncommon location.

Case Description: A 54 year old Caucasian woman on hemodialysis secondary to diabetic nephropathy for a year was admitted for management of breast lesions. Other past medical history includes hypertension, atrial fibrillation on Warfarin and morbid obesity. She noted a tender nodule under the skin on the lower right breast 3 months ago which progressed to open wound with surrounding redness and intense pain. Also developed similar nodule in the left breast a month ago.



Labs showed creatinine of 5.6mg/dl, phosphate 6.2 mg/dl, Parathyroid hormone (PTH) 340 pg/ml, serum albumin 2.8 g/dl and alkaline phosphatase 186 U/l. Blood cultures negative. Punch biopsy of the lesion showed skin and subcutaneous tissue with mild acute and chronic inflammation, fibrosis and focal necrosis. Focal calcium deposition was seen within a small blood vessel. No malignancy. A diagnosis of CUA was made and she was started on Sodium thiosulfate (STS) with dialysis along with supportive care and Warfarin was discontinued. Lesions showed some improvement during 1 month follow up.

Discussion: Clinicians should consider atypical presentations of CUA and be aware of its risk factors in patients with advanced kidney disease to ensure prompt treatment and avoid unnecessary workup. High Calcium-Phosphate product and PTH, hypoalbuminemia, diabetes, obesity,warfarin use, female sex, protein C or S deficiency are some of the reported risk factors. Also, there are reports of CUA being associated with metastatic malignancy which needs to be ruled out. Early treatment has led to decreases in mortality of this once uniformly fatal disease.

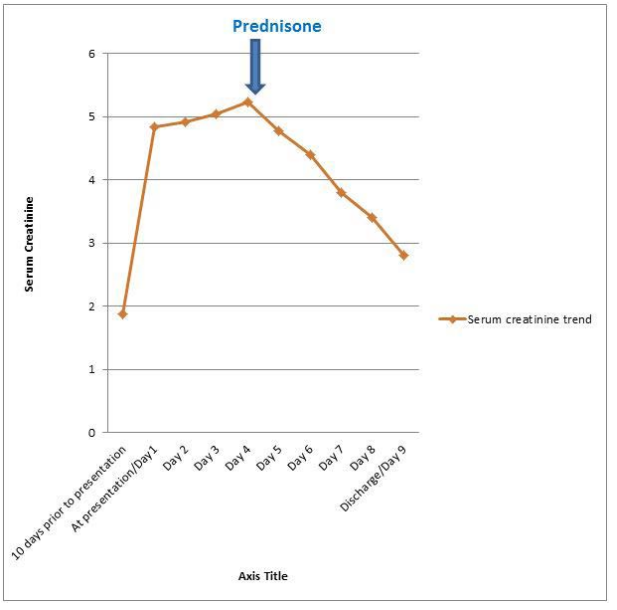
PUB349

Cefepime Induced Encephalopathy and Acute Interstitial Nephritis

Abhilash Koratala, S. Irfan Qadri, Rupam Ruchi. *Univ of Florida.*

Introduction: Cefepime (CP) is an extended-spectrum, 4th generation cephalosporin that has been implicated in encephalopathy especially in patients with renal impairment. Rarely, it can also lead to acute interstitial nephritis (AIN). We report the case of a patient who presented with both these entities.

Case Description: 58 year old Caucasian male with history of Chronic kidney disease stage 3a, Hypertension, Diabetes mellitus was admitted for altered mental status (MS). He was discharged 10 days prior to presentation on IV CP for the treatment of Thoraco-lumbar osteodiscitis, started 2 weeks ago at 2g every 12 hours. CT head was negative. He was completely disoriented and exhibited myoclonic jerks. EEG revealed frequent generalized rhythmic delta activity with triphasic morphology without overt seizure suggestive of possible CP induced encephalopathy. He also had Acute Kidney injury at presentation with serum creatinine (Cr) of 4.84 mg/dL (baseline 1.9). He also had anion gap metabolic acidosis with serum bicarbonate of 16 mmol/L and normal lactate, osmolar gap and toxicology. Urinalysis showed 47 white blood cells per hpf with positive urine eosinophils. No significant proteinuria or evidence of proliferative glomerulonephritis. No skin rash. We suspected CP induced AIN and the drug was discontinued on day 2 of hospital admission. CP level 48 hours after the last dose was 94 mcg/ml (elevated) and Cr stayed high. So, we chose to treat him with oral steroid therapy for AIN (Prednisone approx. 0.8mg/kg/day) and creatinine showed downward trend with improvement in MS.



Discussion: CP is usually considered to be a safe antibiotic and is widely prescribed with few adverse reactions reported. We did the literature search which revealed only

one published case of CP induced AIN (Mac et al. 2015).Clinicians should be aware of its potential nephrotoxic and neurotoxic effects and promptly discontinue the drug with consideration of Steroids if AIN is suspected.

PUB350

Aloe Vera Juice Induced, Biopsy Proven, Acute Tubular Necrosis

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Introduction: *Aloe vera* juice is sold over-the-counter as a natural remedy for constipation and arthritis. Numerous compounds contained in the *Aloe vera* plant have been shown to inhibit cyclooxygenase-2 (COX-2). We present a case of *Aloe vera* juice-induced, biopsy proven, acute tubular necrosis (ATN).

Case Description: A 50 year old woman with a past medical history of CKD3, diabetes mellitus, and hypertension presented with increasing dyspnea on exertion, orthopnea, and bilateral leg edema over the past 2 weeks. She denied taking any known nephrotoxins. One month prior, she started drinking *Aloe vera* juice daily for joint pain. Physical exam was remarkable for bibasilar crackles on lung auscultation and 4+ bilateral leg edema. Labs revealed K 5.5 mEq/L, HCO_3 19 mEq/L, BUN 88 mg/dL, Cr 7.14 mg/dL, albumin 2.0 g/dL. Ten months prior to presentation, serum Cr was 1.3 mg/dL. UA showed >1000 protein, 11-25 RBC, 5-10 WBC, FENa 3.7%, and urinary protein excretion was 11.67 g/24hr. Further testing revealed normal C3/C4, A1c 11.3%, negative for HIV, HBV, HCV, anti-GBM ab, normal ANA titer, ASO titer, SPEP and UPEP. Renal US showed normal sized diffusely echogenic kidneys without hydronephrosis or calculi. She remained hypervolemic despite high dose diuretics and hemodialysis was initiated. Renal biopsy revealed ATN with nodular diabetic glomerulosclerosis, moderate arterial sclerosis, and mild parenchymal scarring.

Discussion: *Aloe vera* contains compounds including aloesin, aloeresin A, aloe-emodin, and isorabaichromone, which have demonstrated *in vitro and in vivo* activity against COX-2, NO synthase, and prostaglandin E2 production. Additionally, *Aloe vera* extract can induce ATN in rats. Frequent ingestion of these biologically active substances could therefore induce afferent vasoconstriction in patients who are prostaglandin-dependent to maintain GFR and we hypothesize this prolonged renal hypoperfusion to be the mechanism by which *Aloe vera* can induce ATN. Our case represents a potentially severe side effect of *Aloe vera* juice and nephrologists should be aware of this underrecognized nephrotoxin.

PUB351

An Unusual Case of Atypical Hemolytic Uremic Syndrome

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Introduction: Hemolytic uremic syndrome (HUS) is characterized by a microangiopathic hemolytic anemia (MHA) and acute kidney injury (AKI). The most common cause of HUS is the classic form associated with a Shiga toxin-producing strain of *E coli*. The combination of MHA and AKI can also be caused by atypical HUS (aHUS), which involves deficiency of complement factors regulating the alternative complement pathway. The incidence of aHUS is far lower than that of than classic HUS.

Case Description: A 19 year old female presented with abdominal pain, bloody diarrhea and oliguria. On admission she was alert and oriented. Vital signs, examination of the heart, lungs and abdomen were normal. Laboratory data: WBC 22 k/uL, Hgb 6.1 g/dL, platelets 290 k/ul, blood urea nitrogen 77 mg/dL, creatinine 7.23 mg/dL, serum LDH 1042 IU/L, haptoglobin undetectable. Coomb's test was negative. Blood smears revealed many schistocytes. A diagnosis of aHUS was made after excluding classic HUS (negative Shiga toxin test) and TTP (ADAMTS13 activity 77%). Blood tests were sent to look for abnormalities in complement factors known to be associated with aHUS. The patient was started on prednisone and plasma exchange. Renal function slowly improved and creatinine eventually fell to 1.5mg/dl. However, the MHA persisted and plasma exchange was continued. The patient then developed nephrotic range proteinuria. A renal biopsy was done which showed features of vascular microangiopathy consistent with aHUS. Complement profiles demonstrated the presence of autoantibodies to complement factor H (CFH) as well as a heterozygous deletion of genes encoding *CFHR1 and CFHR3*. The patient was started on once weekly doses of eculizumab, after which the MHA resolved completely. Plasma exchange and prednisone were discontinued.

Discussion: Atypical HUS can be caused by a genetic defect (caused a *CFH* gene conversion or by a deletion of the genes encoding *CFHR1* and *CFHR3*) or by the presence of autoantibodies to CFH. While most patients have either genomic defect or autoantibodies, this patient has the combination of autoantibodies to CFH as well as a heterozygous deletion of *CFHR1/CFHR3*. The mechanisms responsible, and the clinical implications of this combined abnormality remains to be elucidated.

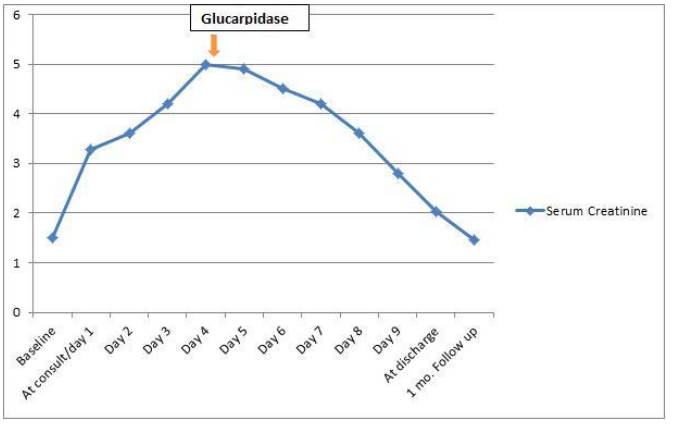
PUB352

Methotrexate Nephrotoxicity Treated with Glucarpidase

Abhilash Koratala, S. Irfan Qadri, Lalitkumar Jaykrishan Mundhra, Rupam Ruchi. *Nephrology, Univ of Florida.*

Introduction: Methotrexate (MTX) is an antimetabolite used in the treatment of malignancies and rheumatologic conditions. High-dose MTX (HDMTX), defined as doses > 500 mg/m,^{2} is implicated in renal toxicity. We report a case of MTX nephrotoxicity successfully treated with Glucarpidase (GP), a recombinant enzyme that inactivates MTX.

Case Description: 67 year old Caucasian male with history of Heart transplant (on Cyclosporine), Hypertension, Chronic Kidney Disease stage 3a likely secondary to calcineurin (CNI) toxicity was admitted for new-onset seizure. He was diagnosed with Post-transplant lymphoproliferative disorder and started on high-dose MTX (8200 mg/day) and rituximab 2 days prior to Nephrology consult for Acute Kidney Injury (AKI). His baseline serum creatinine (Cr) was ~ 1.5 mg/dL. No IV contrast exposure, diarrhea, vomiting, or urinary symptoms. IV sodium bicarbonate & Leucovorin were given with MTX. When we were consulted, Cr was 3.27 mg/dL & urine Ph was 6. The next day, Cr increased to 3.6 & 24-hour MTX level was 26 mcmol/L (markedly elevated). MTX was held and IV hydration was given. Cr continued to rise to 4.2mg/dL (day 3). Decision was made to administer GP on day 4 due to worsening renal function. MTX level on day 5 was 0.69 mcmol/L. His Cr plateaued and trended down to 2 mg/dL at discharge and was 1.47 at 1 month follow up. No renal replacement therapy was needed. Cr trend shown below.



Discussion: HDMTX causes AKI by tubular crystal precipitation, exacerbated by acidic urine & volume depletion. It can also cause transient decline in GFR which may be prolonged in the presence of concomitant nephrotoxins (our patient was on CNI). Even with fluids & urine alkalinization, the risk of HDMTX nephrotoxicity is ~ 2%. Awareness of the utility of GP (FDA-approved) may mitigate the need for dialysis in selected cases of HDMTX renal injury. The drawback of GP is its cost and availability.

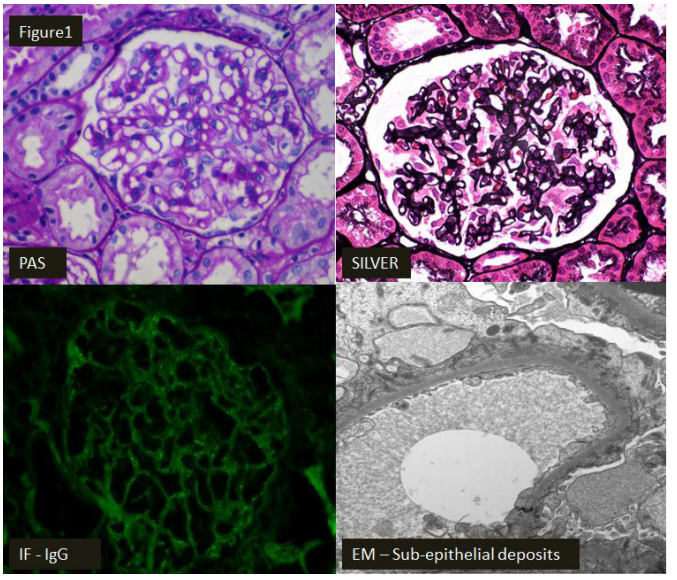
PUB353

Course of Membranous Nephropathy during Multiple Gestations: A Case Report

Abhilash Koratala,[1] Kawther Farouk Alquadan,[1] Dara N. Wakefield,[2] A. Ahsan Ejaz.[1] [1]*Nephrology, Hypertension and Renal Transplantation, Univ of Florida;* [2]*Pathology, Immunology and Laboratory Medicine, Univ of Florida.*

Introduction: Physiological adaptations in Pregnancy (PG) can unmask underlying occult proteinuric renal disease. However, the effect of multiple pregnancies on the course of the disease is unknown. We report the clinical course of a case of idiopathic membranous nephropathy (MN) through multiple pregnancies.

Case Description: 25 year-old Hispanic female was referred for 21gm of proteinuria at 35 weeks gestation during her 3rd pregnancy. She was previously seen at our institution five years ago during her 1st pregnancy when 13gm of proteinuria was recorded at 25 weeks of gestation. At that time, she was treated with oral steroids and delivery was induced at 35 weeks due to intra-uterine growth restriction. Placental biopsy revealed focal, tightly adherent blood clot, consistent with possible abruption. Renal biopsy performed in the postpartum period was consistent with MN.



She was treated with ACEI and at 3-month follow-up she was asymptomatic, without edema and urine protein-creatinine ratio (UPCR) had decreased to 7g/g. She was lost to follow-up for 5 years until this recent admission. In the interim, she apparently had a second successful pregnancy but no data was available. Placental biopsy after the current pregnancy

showed the placenta was critically small for gestational age and had focal intervillous fibrin deposition. At one month post-partum, UPCR was 1.8 g/g, without any treatment. Patient unfortunately was again lost to follow-up.

Discussion: We conclude that spontaneous remission of MN can occur despite physiological changes associated with pregnancy and the natural course of MN probably follows that of non-pregnant individuals. We also provide histological data that these patients may be at increased risk for placento-maternal complications.

PUB354

Not a Malignant or a Granulomatous Process, It's a Lurking Infection: Hypercalcemia with *Pneumocystis jirovecii* Pneumonia

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Introduction: 1-25 dihydroxy vitamin D mediated hypercalcemia is observed in granulomatous diseases and many immunocompromised patients are affected. Pneumocystis jirovecii pneumonia (PCP) in HIV patients is rarely implicated as a cause of hypercalcemia through this mechanism.

Case Description: A 74-year-old male presented to us with generalized weakness. He had a calcium level of 13.4 mg/dl, with appropriately suppressed parathyroid hormone (PTH) level (18) and normal PTH-related peptide. Elevation of 1-25 Dihydroxy Vitamin D (155) with a decrease in 25-OH vitamin D (24) was detected. Serum and urine electrophoresis were normal. A bone scan revealed a lesion on the right 7th rib. This was biopsied and found to be negative for malignant cells as well as mycobacterial, fungal, granulomatous and lymphoproliferative disease. His respiratory status declined and he developed acute hypoxic respiratory failure. CT scan thorax revealed bilateral 'ground-glass' opacities and pulmonary nodules. Subsequent bronchoscopy showed organizing pneumonitis with 'cotton-candy' intra-alveolar exudates. Silver stain was positive for PCP. HIV was positive by western blot assay, viral load was 123388 and his CD4 count was 12. No evidence of cytomegalovirus was seen on biopsied specimens. The patient was started on Trimethoprim/sulfamethoxazole and steroids and his Calcium level gradually normalized.

Discussion: Hypercalcemia in HIV patients occurs in the setting of extra renal production of 1-25 dihydroxy vitamin D from granulomatous infection mediated release of cytokines and activation of macrophages. A case report described PCP infection causing hypercalcemia in a renal transplant patient and attributed it to a similar mechanism. Though PCP infection is common in HIV, there have been no reported cases of hypercalcemia in these patients. Exhaustive work up to delineate the cause of elevated calcium led to the discovery of PCP and then HIV in our patient. This case highlights the fact that 1-25 dihydroxy vitamin D mediated hypercalcemia in HIV hosts should raise suspicion for an indolent PCP infection.

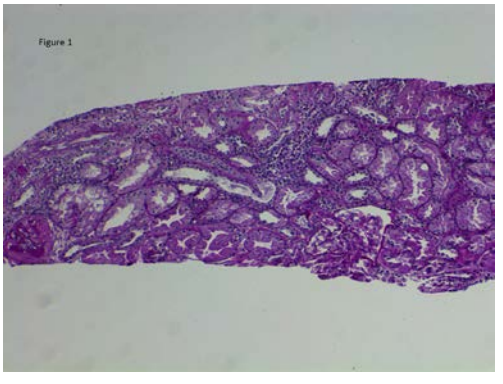
PUB355

Mycophenolate Mofetil for Tubulo-Interstitial Nephritis in Sjogren's Syndrome: A Case Report

Abhilash Koratala, Westley Reeves, Mark S. Segal. *Univ of Florida.*

Introduction: Treatment of renal manifestations of Sjogren's syndrome (SS) is largely based on extrapolations from treatment of other inflammatory conditions and small open-label studies. We report a case of Tubulo-interstitial nephritis (TIN) from SS that remained stable on Mycophenolate mofetil (MMF) for the past 14 years.

Case Description: In 2002, a 25 year old Caucasian woman presented to our clinic for elevated serum creatinine (Scr) for few months and a renal biopsy demonstrating TIN that did not respond to 1 month course of prednisone 60mg/day. In 2000, she was diagnosed of SS. Labs showed Scr of 1.5 mg/dL, non-gap acidosis, potassium 3.4 mmol/L, urine pH 7.5, positive ANA, anti-SSA, anti-SSB and rheumatoid factor. We started MMF 500mg bid along with alkali therapy for RTA. Her Scr remained stable for 2 years & MMF tapered off in early 2004. In late 2004, she was started back on MMF 500mg bid as her Scr increased to 2 mg/dL and her MMF was eventually increased to 1000mg bid. In early 2005, she unilaterally stopped MMF and her Scr increased to 2.7 mg/dL. A repeat renal biopsy showed significant TIN, mesangial expansion without glomerular deposits.



We pulsed her with solumedrol and started back on MMF 1000mg bid. Her Scr stabilized at ~1.8mg/dL. MMF was later tapered to 500mg bid in 2009. She was maintained on MMF of 500mg bid and when we saw her back in 2016, her Scr was 1.9 mg/dL.

Discussion: When our patient was started on MMF in 2002, there was not much experience with it in SS induced TIN and the data favored steroid monotherapy. We chose MMF as a steroid-alternative agent with a better side-effect profile. Though she required prolonged therapy, she did well with stable renal function. Our case supports the use of MMF for SS induced TIN,in line with currently emerging evidence. 14 year follow-up establishes the long term safety of this medication, though results are not necessarily generalizable to all patients.

PUB356

The Use of Calcineurin Inhibitors for Lupus Flare in Pregnancy

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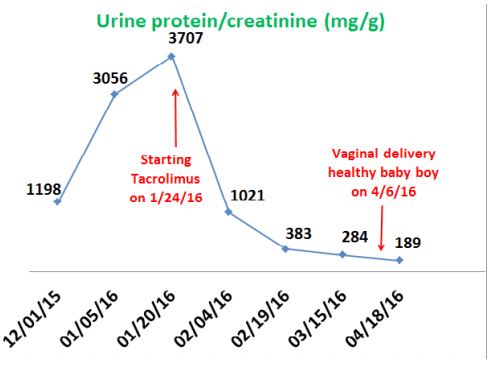
Introduction: When lupus nephritis flares during pregnancy, it becomes challenging to preserve renal function, save the life of the fetus, and avoid teratogenicity. The following case describes a strategy that resolved this dilemma.

Case Description: A 24-year-old woman with biopsy-proven lupus nephritis (class IV) was admitted during her last trimester after deteriorating renal function was discovered on routine blood test. Lupus nephritis was diagnosed in '14 when she presented with skin rash and hematuria. She was treated with Prednisone and Mycophenolate. Renal function improved, but in Mar'15, Mycophenolate was replaced with Azathioprine 200mg BiD because she was not using contraception reliably. In Aug'15, kidney function was stable and Azathioprine was reduced to 150mg BiD with Prednisone 2.5mg daily. Later that month, she became pregnant. For the first 2 trimesters, her creatinine was 0.6mg/dL, but, in early Jan'16, creatinine increased to 1.2mg/dL and she was admitted for 3 days of intravenous steroids. Azathioprine was increased to 200mg BiD and Hydroxychloroquine 400mg daily was added with 60mg Prednisone daily. Her creatinine increased to 1.7mg/dL and urine protein/creatinine ratio increased from 1198 to 3707mg/g. Tacrolimus was chosen for greater immunosuppression with a better safety profile than Mycophenolate or Cyclophosphamide. Within 1 week of starting Tacrolimus, creatinine stabilized at 1.0mg/dL and urine protein/creatinine ratio decreased to 1021mg/g. Her pregnancy went to full-term and a healthy boy was delivered.



Discussion: The heightened risk of lupus nephritis flare during pregnancy is well recognized and Steroids and Azathioprine remain the treatments of choice. In more complicated cases like ours; the use of Tacrolimus can be lifesaving to the mother and the fetus.

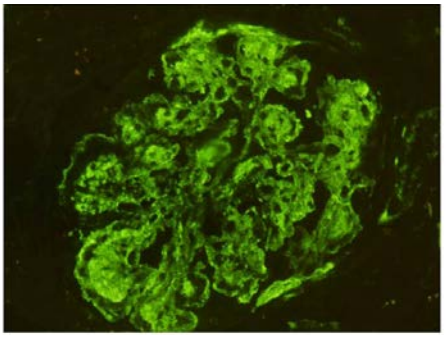
PUB357

C3 Glomerulonephritis [C3GN]Associated with Septic Shock

Hezekiah O. Sobamowo, Elmoutaz T. Mousa. *Nephrology, Texas Tech Univ, Lubbock, TX.*

Introduction: C3GN is characterized by predominant C3 deposits and the absence of immune deposits on immunofluorescence microscopy as well as absence of electron dense deposits on the mesangial and or subendothelial areas. We report a case of C3 glomerulonephritis with associated septic shock.

Case Description: 24y old Hispanic male with past medical history of unknown renal disease. Prior Kidney biopsy in 2009 showed Post infectious glomerulonephritis and possible MPGN type 1. He presented with 3 weeks history of unproductive cough, runny nose, low grade fever, chills, night sweats, SOB/DOE, nausea, vomiting and profuse watery diarrhea with worsening fatigue. He developed severe hypotension requiring pressor support. Urinalysis showed: protein>500, RBC 6, WBC 9,prerenal urinelytes, UPCR 10G, 24Hr urine Protein of 34G with CrCl of 13 and M-Spike on SPEP of unknown significance. Respiratory Viral culture was positive for Influenza Type B. ANA, ANCA, Anti GBM, ASO and HIV serologies were all negative. Low C3 and Normal C4 were noted. Renal Ultrasounds revealed Echogenic small size kidneys. He required hemodialysis twice during the course of the admission. Kidney biopsy revealed obsolescent glomeruli with moderate increase of mesangial matrix and splitting of the glomerular basement membrane. There is moderate tubular loss and atrophy and interstitial fibrosis. Immunofluorescent study revealed 3(+) C3 with diffuse effacement of foot processes.



C5b-9 [MAC] level was elevated while factor H, factor B and C3 nephritic factor were all within normal limits. He was managed with Lisinopril while currently undergoing screening tests to initiate eculizumab.

Discussion: C3 glomerulonephritis, [previously mis diagnosed as Post Infectious GN due to the GBM deposits] is related to dysregulation of alternative pathway of complement. The cause remains relatively unknown.

PUB358

Can Cocaine Cause Lupus Nephritis? Dunia Diaz, Ileana Farrada, Rute C. Paixao. *Cleveland Clinic Florida, Weston, FL.*

Introduction: Cocaine, especially if adulterated with Levamisole, has been associated with several forms of vasculitis. Even though, pauci-immune crescentic glomerulonephritis in association with antineutrophil cytoplasmic antibodies has been the only nephritis described, other forms may soon emerge.

Case Description: A 48 year old Caucasian man with chronic sinusitis was noted to have acute kidney injury (AKI) (creatinine of 2.7mg/dL from baseline of 1.2mg/dL) after having routine lab work. At that time, he was admitted for intravenous hydration. Renal function improved with the intervention, but creatinine did not return to baseline. Work up in the hospital revealed leukopenia WBC 2.9 x 10^9/L, anemia Hb 11.8 g/dL, 2+ protein and 3+ blood on urinalysis, positive ANA of 1:160, positive MPO- and PR3-ANCA, and low C3 88 mg/dL and C4 14 mg/dL levels. Anti-dsDNA and anti-Sm antibodies were negative. On follow up, he only complained of nonspecific arthralgia. Vital signs and physical exam were normal. Urine microscopy showed many RBCs/hpf but no casts. On further questioning, he admitted to chronic cocaine use leading to severe intranasal inflammatory erosion and septal perforation. He then underwent a kidney biopsy, which revealed immune complex mediated membranous glomerulonephritis with focal proliferation. No necrosis, crescents, or thrombi. Immunofluorescence studies showed diffuse membranous and mesangial staining for IgG, IgM, C3, C4, Kappa, and Lambda consistent with lupus nephritis. Further serological work up was negative except for positive anti-chromatin and anticardiolipin IgM antibodies. HIV and hepatitis were negative.

Discussion: In this peculiar case, it is difficult to distinguish with certainty between idiopathic vs drug induced lupus nephritis. Even though cocaine/Levamisole induced lupus nephritis has not been described, there has been case reports that it can lead to cytopenias, low complements, and positive ANA +/- Anti-dsDNA antibody. This patient's presentation of AKI, non-specific arthralgia, cocaine induced septal perforation/severe intranasal inflammatory erosion together with Caucasian ethnicity, no family history of autoimmune disease, and mixed serology makes us wonder if this is more than just idiopathic lupus nephritis.

PUB359

The Saga of Mis-Folded Proteins Ahmed H. Alaini, Saeed Kamran Shaffi. *Nephrology, UNM, Albuquerque, NM.*

Introduction: Amyloid light chain (AL) amyloidosis is a disorder that is characterized by a clone of plasma cells that produce an abnormal protein which deposit on organs. We describe a case of AL amyloidosis with renal involvement, but no bone marrow abnormality.

Case Description: A 74-year-old previously healthy female presented to the hospital with malaise, and swelling of the lower extremities. Physical examination was significant for pallor, normal vitals, a 2/6 ejection systolic murmur and 2+ lower limb edema. Pertinent laboratory data are shown in Figure 1.

Figure 1: Diagnostic data	
Hemoglobin level (gm/dl)	6.7
Creatinine (mg/dl)	2.99
BUN (mg/dl)	31
Serum Albumin (g/dl)	1.2
Serum calcium (mg/dl)	7.7
Urinalysis	Protein +++
Urine protein creatinine ratio (g/g)	15
Urine microscopy	Bland
Serum protein electrophoresis	IgA lambda M-Component of 0.24 mg/dl
Free light chain ratio	1.01 (Kappa 5.61↑, Lambda 5.56↑)

Kidney biopsy showed extensive renal glomerular involvement with amyloidosis. Immunofluorescence and liquid chromatography tandem mass spectrometry showed peptide profile consistent with AL amyloidosis. Bone marrow biopsy was normocellular without plasma cell abnormalities. Fat pad biopsy was negative. Echocardiography was normal. She was started on bortezomib and dexamethasone chemotherapy and is being followed in the nephrology clinic for her progression of kidney disease.

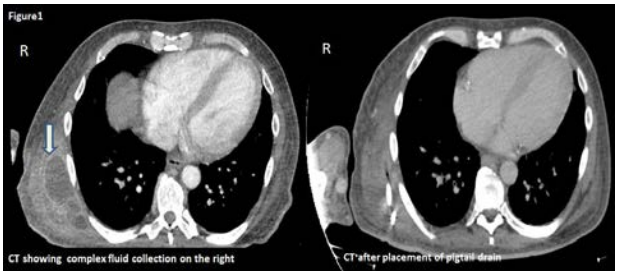
Discussion: Light chain amyloidosis is caused by a small clone of plasma cells which secrete a protein that has a propensity to mis-fold and deposit on organs as beta pleated sheets which stain Congo red on light microscopy. The bone marrow biopsy might be normal because of the paucity of the abnormal cells. This is different from immunoglobulin deposition disease where a large clone of abnormal plasma cells secretes light and/or heavy chains that deposit on renal parenchyma, but do not mis-fold and form beta pleated sheets; thus doesn't stain with congo red. Bone marrow biopsy shows abnormal plasma cells. Plasma cells can also secrete freely filtered light chains that bind to Tam-Horsfall protein and form proteinaceous casts resulting in cast nephropathy. It is imperative to elucidate signs of end organ damage when plasma cell dyscrasias are suspected as the bone marrow biopsy might not reveal plasma cell abnormality.

PUB360

Subscapular Abscess Associated with Buttonhole Cannulation Technique of AV Fistula Abhilash Koratala, S. Irfan Qadri, Volodymyr Chornyy, Kawther Farouk Alquadan, A. Ahsan Ejaz. *Nephrology, Hypertension and Renal Transplantation, Univ of Florida.*

Introduction: Infectious complications of the vascular access are an important cause of morbidity and mortality among HD patients. Type of vascular access and cannulation techniques are risk factors for these complications. Herein, we report an unusual case of subscapular abscess associated with buttonhole cannulation technique (BHCT) of AVF for HD access.

Case Description: 51 y.o. Caucasian male with ESRD secondary to diabetes, on HD using BHCT of RUE AVF for 6 months, presented with a 2 day history of right shoulder pain. Contrast CT demonstrated a complex abscess beneath right scapula without scapular osteomyelitis. Blood cultures were positive for MRSA and appropriate antibiotics were administered. Subsequently, a CT-guided pigtail catheter was inserted to drain the abscess. Culture of the abscess aspirate was also positive for MRSA.TEE was negative for valvular vegetations and US of AVF negative for localized infection. Eventually, symptoms subsided and cultures turned negative. Pre and post-procedure CT images are shown.



In the absence of other etiologies, we suspect that BHCT was the likely source of blood stream infection (BSI) that culminated in subscapular abscess.

Discussion: AVF is the most preferred long term HD access due to lower associated complications. BHCT is gaining popularity due to less pain, aneurysm formation and disfigurement. However, it may pose an additional risk factor for development of infectious complications. In fact, recent evidence suggests a higher rate of local infection and bacteremia associated with BHCT, which is an important concern for immunocompromised dialysis patients. Nephrologists should be aware of these potential risks while recommending BHCT to their patients and have a high index of suspicion for BSI-related complications while evaluating HD patients presenting with unusual symptoms.

PUB361

Acute Kidney Injury with Acute Interstitial Nephritis Nonreversible, Requiring Hemodialysis, Unmasking Primary Amyloidosis Himabindu Valluru, Rahul Valluru, Muner Mohamed, Moro O. Salifu, Mary C. Mallappallil. *Nephrology, SUNY Down State, Brooklyn, NY.*

Introduction: Primary systemic amyloidosis is a monoclonal plasma cell characterized by deposition of extracellular immunoglobulin light chain fibril in various organs. It is a rare disease with broad range of manifestations. Signs and symptoms may not be experienced until the condition is advanced. We report a case of acute interstitial nephritis to an antibiotic which did not resolve despite steroid treatment that unmasked primary amyloid on kidney biopsy.

Case Description: A 64 year-old man with hypertension, presented with confusion, progressive bilateral lower extremity edema and was found to have acute ischemic stroke on CT head. In addition he was also noted to have new onset of systolic heart failure (sCHF). Both CVA and sCHF symptoms were improving but he had a fever with suspected peripheral intravenous line infection for which he was started on prophylactic vancomycin and zosyn. Subsequently, he was noted to have an acute rise in serum BUN and creatinine levels. Acute interstitial nephritis was suspected, antibiotics were discontinued with no improvement in renal function despite being started on prednisone. Hemodialysis was started and a kidney biopsy was obtained which revealed acute interstitial nephritis with interstitial fibrosis/inflammation, tubular atrophy and AL type/lambda light chain restricted amyloidosis. Bone marrow biopsy consistent with lambda restricted plasma cell neoplasm. Echocardiogram revealed cardiac amyloidosis. He progressed to become dialysis dependent while chemotherapy was planned.

Discussion: Upon review of literature, patients with AL amyloidosis presented with symptoms of specific organ involvement at the onset. This is a rare case of a patient who presented with normal renal function and developed acute kidney injury due to acute interstitial nephritis which unmasked an underlying primary systemic amyloidosis with renal and cardiac involvement.

PUB362

Pazopanib Induced Hypertension and Proteinuria: A Case Report

Vikrampal Bhatti, Abhilash Koratala. *Univ of Florida.*

Introduction: Pazopanib (PZ), an oral anti-angiogenic Tyrosine kinase inhibitor targeting vascular endothelial growth factor (VEGF) receptor is one of the first line treatment options for advanced renal cell carcinoma (RCC). Proteinuria (PTN) and uncontrolled hypertension (HTN) from Bevacizumab (a VEGF inhibitor) is well established but there is paucity of such data with the use of PZ. We report a case of PZ induced nephrotic-range PTN and HTN.

Case Description: 68 year old Caucasian male with history of HTN, Coronary artery disease and hypothyroidism presented to our institution with HTN emergency, with a BP of 220/120 and troponinemia from demand ischemia. 5 months prior to presentation, he was diagnosed with metastatic right RCC for which he underwent radical right nephrectomy and started on PZ therapy. His baseline creatinine (Cr) was 1.1 mg/dL, which stabilized at ~1.3 mg/dL after nephrectomy. At presentation, his Cr was 2.3 mg/dL with Urine protein-creatinine (Upc) ratio of ~5.5 g/g. His HTN was well controlled before starting PZ. He was given IV Labetalol without much response and so transitioned to Nitroglycerin drip after which BP improved. His 24-hour urine protein was 4.9 g and serum albumin 3.4 g. His BP improved over the next few days and Cr trended down to 1.7 mg/dL. We diagnosed these as complications of PZ therapy and discontinued the drug. We chose to monitor expectantly without renal biopsy. At 1 month follow up, his serum Cr was 1.6 mg/dL and Upc was ~2.5 g/g.

Discussion: There has been conflicting evidence on whether HTN can be used as a biomarker for efficacy of VEGF inhibitor therapy. However, there is no evidence to say that treatment of HTN in these patients would compromise outcome. Clinicians must monitor all patients treated with VEGF inhibitors for the development of HTN and PTN. Choice of anti-hypertensive depends on patients' co-morbidities. However, it's reasonable to treat with vasodilatory drugs such as ACEIs, Calcium channel blockers & nitrates based on the mechanism of VEGF inhibitors causing decrease in production of Nitric oxide and Prostacyclin in Vascular endothelial cells leading to vasoconstriction. PTN caused by these agents is usually non-nephrotic (unlike our patient) and rarely warrants discontinuation of therapy.

PUB363

Unusual Presentation of an Uncommon Disorder: Type 1 Distal Renal Tubular Acidosis

Joseph H. Zeidan, Gaurav K. Sharma, Luis A. Lopez. *Internal Medicine, Mercy Hospital and Medical Center, Chicago, IL.*

Introduction: Renal Tubular Acidosis (RTA) is an uncommon disorder that rarely occur in adults. Each type of RTA has a different etiology along with a different mode of presentation. As this case will show, following a step-wise approach to acidosis will ultimately lead to a diagnosis.

Case Description: A 33-year old woman presented with abdominal pain and diarrhea for 3 days. On exam, she had tenderness in the RLQ without guarding or rigidity. Labs showed a serum bicarbonate of 14 mmol/L, a normal anion gap of 16, potassium 4.0 mmol/L, urine pH of 6.0. Arterial blood gas was obtained to evaluate the acidosis with a pH 7.32, HCO3 10 and pCO2 19.5. The acidosis worsened to a level of 10 to which the working diagnosis was a RTA. To confirm a urine anion gap was calculated and equaled a positive 32. A continuous bicarbonate infusion was initiated and the level rose to 20. To differentiate the type of RTA a fractional excretion sodium bicarbonate (FeHCO3) was obtained and an undetectable level of bicarb in the urine was found confirming the diagnosis of RTA type 1. The patient was ultimately discharged and followed for further evaluation and treatment of RTA.

Discussion: RTA is defined by a preserved glomerular filtration rate with the inability of the tubules to conduct normal function. The acid-base balance cannot be maintained leading to a metabolic acidosis with a normal anion gap. Type 1 differs from the others by the inability to excrete acid leading to increasing levels of hydrogen ion in the serum. Type 2 is characterized by the kidney's inability to reabsorb bicarbonate. Initial evaluation of a normal anion gap metabolic acidosis involves distinguishing RTA from GI related disorders. History usually provides sufficient information but this case was not clear. Her diarrhea had resolved prior to admission becoming the red-herring of the case. By following step-wise approach toward acidosis confusion was avoided. Using the urine anion gap to differentiate RTA from GI cause, then FeHCO3 to separate type 1 from type 2 led to the diagnosis of type 1 RTA. This case provides insight regarding step-wise approach specifically when history, physical and labs don't formally coincide.

PUB364

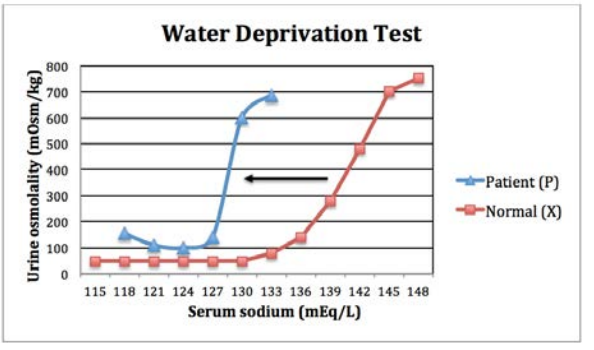
Reset Osmostat after Withdrawal of Chronic Desmopressin

Daniel Christopher Andreoli, William Luke Whittier. *Nephrology, Rush Univ Medical Center, Chicago, IL.*

Introduction: A reset osmostat as a cause of hyponatremia can be found in a variety of clinical settings, including pulmonary and neurological disease, as well as in physiologic circumstances such as pregnancy. We present a case of a 72-y/o Caucasian man with a longstanding history of self-medicating with desmopressin who presented to the hospital with profound hyponatremia. On discontinuation of desmopressin, he was found to have a reset osmostat. We theorize that his reset osmostat may have developed secondary to longstanding use of desmopressin.

Case Description: A 72 y/o male physician presented with symptomatic atrial fibrillation and a serum sodium concentration (SNa^+) of 115 mEq/L. His past medical history was notable for ten years of "polyuria" for which he self-prescribed oral desmopressin, in spite of not having formal urinary measurements or testing. Prior to these practices, his SNa^+ was 140 mEq/L. His oral desmopressin was discontinued on admission and D5W infusion was started to blunt the expected brisk risk in SNa^+. On day 1 of admission, his SNa^+ and urine osmolality (Uosm) were 121 mEq/L and 110 mOsm/kg. By day 2 of admission, his SNa^+ and Uosm were 127 mEq/L and 142 mOsm/kg. A twelve-hour water deprivation test was performed.

Upon water deprivation, his daily urine output decreased from five liters to one, with an increase in his urine osmolality to 685 mOsm/kg while his SNa^+ stayed constant at 130 mEq/L. His SNa^+ remained between 129-132 mEq/L for the rest of the hospitalization and on follow-up (See Figure).



Discussion: A reset osmostat was diagnosed by demonstrating normal urinary dilution at a SNa^+ of 110-127 mEq/L but with urinary concentration at a SNa^+ of 130 mEq/L. We hypothesize that this patient's reset osmostat may have developed secondary to prolonged exposure to exogenous desmopressin.

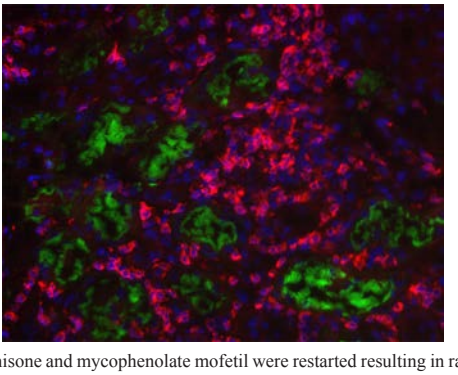
PUB365

Urinary Excretion of a1 Microglobulin Is Not an Accurate Marker of Tubulointerstitial Nephritis

Anneke Bech,[1] Michiel W.P. Bleeker,[3] Meyke Hermsen,[2] Bart Smeets,[2] Jack F. Wetzels.[1] *[1]Nephrology, Radboud Univ Medical Center; [2]Pathology, Radboud Univ Medical Center; [3]Nephrology, Bernhoven Hospital.*

Introduction: Tubulointerstitial nephritis (TIN) is a frequent cause of kidney injury. Kidney biopsy is considered the golden standard for diagnosis, however cannot be used for guiding treatment and diagnosing relapse. Serum creatinine is being used but is neither sensitive nor specific. Urinary excretion of alpha1microglobulin (a1m) reflects tubular inflammation and may be a promising tool. Median urinary a1m excretion in 13 patients with suspected TIN indeed was elevated (147 mg/10 mmol creatinine, IQR 98-201). The following case however questions its use in patients with TIN.

A 66 year old lady was evaluated for a rise in serum creatinine. She did not have complaints and did not use any drugs. Her medical history revealed Sjogren's syndrome with two episodes of TIN. The first episode of biopsy proven TIN was in May 2010 for which she was succesfully treated with oral prednisone for 18 months. In October 2012 she developed a relapse with a rise in serum creatinine up to 141 µmol/l. She received oral prednisone and mycophenolate mofetil until June 2015. Since then serum creatinine started to rise from 105 µmol/l to 155 µmol/l. A TIN relapse was considered less likely in view of an a1m excretion of only 47 mg/10 mmol creatinine. A kidney biopsy was performed, which showed an active TIN with multiple infiltrating lymphocytes in proximal tubules. The proximal tubules had normal brush borders and revealed normal staining for megalin (not shown). **Figure legend:** Kidney biopsy with staining for CD3 (lymphocytes) and lectin (brush border) showing active inflammation in the cortex.



Oral prednisone and mycophenolate mofetil were restarted resulting in rapid decrease of serum creatinine.

Discussion: This case shows that a (near) normal urinary excretion of a1m does not rule out active TIN.

PUB366

An Unusual and Fatal Case of Cryptococcal Infection in a Renal Transplant Recipient Yorg Al Azzi, Ibadete Sulejmani, Geoffrey K. Dube. *Medicine, Columbia Univ, New York, NY.*

Introduction: Disseminated cryptococcal infections are a known complication of immunosuppression. However, the presentation can be atypical and can lead in some cases to fatal outcomes. We present here a case of a renal transplant patient who initially presented for evaluation of abdominal pain, was suspected to have military TB but succumbed to splenic rupture in the setting of disseminated cryptococcal infection with lung, liver and renal allograft involvement.

Case Description: 58yo M ESRD 2/2 to type 2 DM,s/p LRRT from his daughter in 11/14(Campath induction, maintained on tacrolimus and mycophenolic acid). Seven months post transplant, he experienced epigastric pain with occasional dry heaves for 1 wk, and noted that this pain was persistent and more intense than his usual reflux. On presentation,CT of the abdomen was unremarkable except for military lesions at the lung base suspicious for TB. His review of systems was positive for night sweats. He worked at a prison and had never had a positive PPD. CT chest and abdomen showed miliary nodules throughout the lungs, two cavitary lesions on the peripheral lung and splenomegaly with nonspecific patchy hyperdense foci likely due to blood products. Sputum cultures were negative for AFB. He was started empirically on anti-TB therapy. One day later, he developed hypotension associated with an acute drop in his hemoglobin from 11 to 8.5. He had a PEA arrest and expired. The next day,his serum cryptococcal antigen was reported to be positive with a titer of >1:1024. His blood and sputum cultures remained negative for AFB. Autopsy showed diffluent spleen with hemorrhagic infarcts and splenic rupture, necrotizing cryptococcal pneumonia with miliary lesions through the parenchyma and pleura, necrotizing cryptococcal hepatitis, cryptococcal myocarditis, and infiltration of the renal allograft with Cryptococcus, consistent with disseminated Cryptococcal infection.

Discussion: To our knowledge, this is the first case of disseminated cryptococcal infection in a renal transplant recipient causing death by splenic rupture. This case highlights the need to be aware of atypical presentations of cryptococcal infection in immunosuppressed patients, especially renal transplant recipients.

PUB367

Is It All in the Head? - An Interesting Presentation of Hyponatremia John Sy, Mitchell R. Lunn. *Div of Nephrology, Dept of Medicine, UCSF, San Francisco, CA.*

Introduction: Inpatient-onset hyponatremia can present an interesting diagnostic and management challenge. We present a case of rapid-onset hyponatremia caused by trimethoprim and review reports of this uncommon occurrence.

Case Description: A 32F was admitted for altered mental status and diagnosed with anti-NMDA receptor encephalitis. A culprit teratoma was excised on hospital day 15. On day 19, she was transferred to our hospital due to limited response to treatment with immunoglobulin and high-dose steroids. On day 23, she was started on a steroid taper, lansoprazole, trimethoprim/sulfamethoxazole, fluconazole, calcium/vitamin D, and tenofovir (to prevent latent hepatitis B reactivation). On day 27, her serum sodium fell to 117 from 133 the day prior, she seized, and nephrology was consulted. Vitals were notable for a BP 113/69, HR 82, temperature 36.8°C, and SpO_2 100% on ambient air. She was obtunded, non-responsive, but euvolemic. Laboratory tests revealed creatinine 0.46, potassium 3.6, bicarbonate 23, glucose 105, magnesium 1.7, urine sodium 159, and urine osmolality 532. TSH was 1.19 and AM cortisol was 17. Aldosterone and renin were 5 and 0.59, respectively. CT head and chest were unremarkable. She was started on hypertonic saline and all medications except steroids were discontinued. On day 28, the patient developed hypotension requiring vasopressor support and continued on hypertonic saline. On day 29, she was weaned off of vasopressors, and serum sodium normalized to 141. She was discharged on day 33 without need for salt supplementation or fluid restriction to a nursing facility.

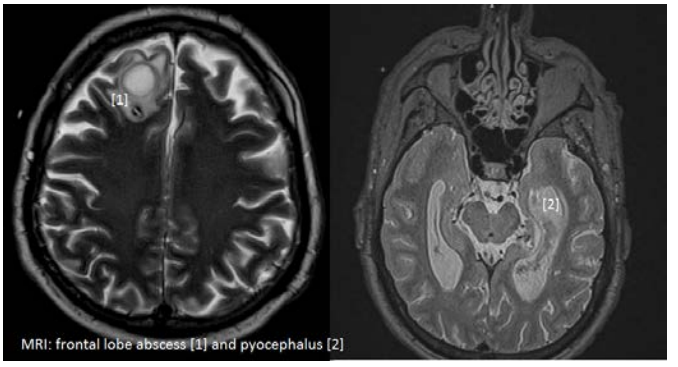
Discussion: Although this presentation was suggestive of SIADH and she was managed accordingly, her hypotension suggested a salt-wasting disorder. Resolution of her hyponatremia after stopping of medications suggested an iatrogenic etiology, and literature review identified trimethoprim as the likely culprit. This case highlights that SIADH remains a diagnosis of exclusion; alternative etiologies should be sought if clinical findings are inconsistent with the presumed diagnosis.

PUB368

Pauci-Immune Glomerulonephritis in the Very Elderly: To Treat or Not to Treat? Volodymyr Chornyy, Abhilash Koratala, S. Irfan Qadri, Rupam Ruchi. *Nephrology, Univ of Florida, Gainesville.*

Introduction: Anti-Neutrophil cytoplasmic antibody (ANCA) positive renal vasculitis constitutes ~ 20% of biopsied acute kidney injury (AKI) cases in the very elderly. Treatment strategies in this population are not well defined. Herein, we report a case of disseminated Nocardial brain abscess as a complication of immunosuppression (IS).

Case Description: An 80 year old Caucasian man with CKD stage 3b due to hypertension & biopsy proven cANCA associated glomerulonephritis (GN), presented with new-onset seizures, altered mental status, AKI & non-nephrotic range proteinuria. Four months prior to presentation, he was diagnosed with ANCA-GN & received 2 monthly doses of IV Cyclophosphamide (~1g/dose). Additional doses were held due to poor tolerance. Prednisone 40mg/day was continued & SCr improved from 3 mg/dl at initial presentation to ~ 2 mg/dL. CT/MRI of the brain revealed multiple intracranial axial lesions suggestive of abscesses with extension of the temporal lobe lesion into the ventricular system causing secondary pyocephalus.



Cultures obtained from brain biopsy were positive for Nocardia. Unfortunately, his mental status and overall condition deteriorated and the patient succumbed to infectious complications.

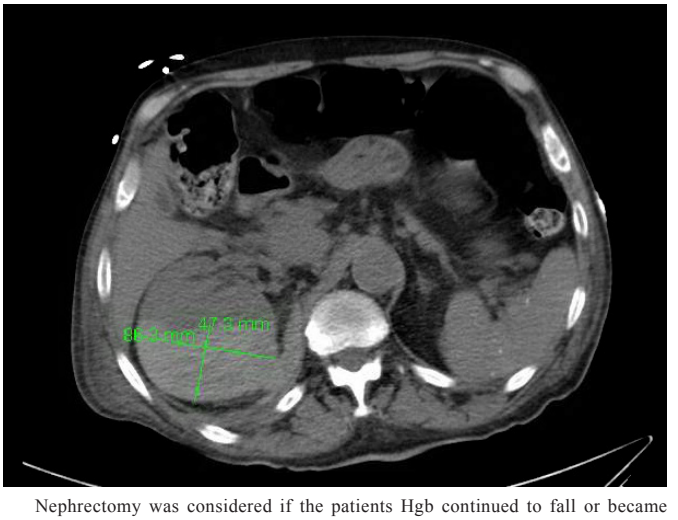
Discussion: Response to therapy in elderly patients with ANCA-GN is variable and there exists a substantial risk of mortality due to the disease state and/or treatment related complications. Current data regarding ANCA vasculitis shows up to 90% of untreated patients will become dialysis dependent or die within the 1st year after diagnosis. Infectious complications are reported in up to 40% of those who are treated with IS resulting in impaired quality of life & an increase in the cost of healthcare. Clinicians should carefully weigh the risks and help guide decision-making regarding the use of IS in this age group.

PUB369

An Unusual and Spontaneous Reason for Anemia and Kidney Failure Joseph H. Zeidan, Gaurav K. Sharma, Lana Akkari. *Internal Medicine, Mercy Hospital and Medical Center, Chicago, IL.*

Introduction: Often anemia and acute kidney injury are common findings in hospitalized patients. Etiology are usually mutually exclusive and then have tailored treatment. During the evaluation of this case an interesting and rare prospective is shown when these two conditions coincide.

Case Description: A 74 year-old man was admitted and treated for pneumonia, but his hospitalization was marred by complications that began with a hemoglobin drop from 13.1 gm/dL to 10.7 by day 2. He denied melanotic stool or other signs of bleeding, two sets of FOBT were negative and the LDH and haptoglobin were normal and Coombs negative. Reticulocyte count showed a proper bone marrow response and physical exam was benign. By Day 5 the Hgb fell to 6.8 gm/dL, so was transfused a unit of packed RBC making it 7.5 but subsequently fell to 6.7. Simultaneously, the creatinine increased from 0.8 mg/dL to 2.1 over the same days despite no offending agent. Suspecting kidney pathology, evaluation with an abdominal CT scan revealed a subcapsular right renal hematoma measuring 8.6cm x 4.7 x 13.4 with mass effect on parenchyma.



Nephrectomy was considered if the patients Hgb continued to fall or became hemodynamically unstable, however neither were the case. The patients hemoglobin eventually stabilized and creatinine would return to baseline.

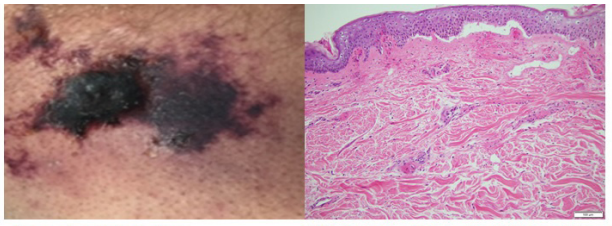
Discussion: Spontaneous renal hematomas are rare and difficult to diagnose. A meta-analysis, by Zhang *et al,* showed that renal hematomas are normally associated with an underlying tumor, vascular disease or infection, but only 6.7% were idiopathic. In this patient, he did not possess any underlying disorder making a diagnosis as this difficult to suspect. Understanding the laboratory findings of this case, the positive and negative, ultimately led to suspicious pathology involving the kidney. The end result was using a modality of 100% sensitivity to diagnoses a spontaneous renal hematoma.

PUB370

The Utility of Skin Biopsy in Dialysis Patients with Necrotic Skin Lesions David Levy, Fatima Khalid, Sai Subhodhini Reddy, Scott E. Liebman. *Medicine - Div of Nephrology, Univ of Rochester Medical Center, Rochester, NY.*

Introduction: Calciphylaxis is a rare but devastating condition that mainly affects patients with end stage renal disease (ESRD). Clinically, diagnosing calciphylaxis can be challenging as it may present similarly to peripheral vascular disease, also common in dialysis patients.

Case Description: A 39 year old male with a history of ESRD due to type 1 diabetes on thrice weekly hemodialysis (Kt/V of 0.7 in the setting of many missed sessions), hypertension and severe peripheral vascular disease complicated by a left lower extremity amputation, presented with necrotizing penile lesions, which ultimately required partial penectomy. Pathology was consistent with ischemia. He was also noted to have a pericardial rub which was managed by daily dialysis to partial effect. Several months later, he presented once again with painful, necrotic thigh lesions. He was noted to have bilateral thigh lesions (see figure) in the setting of inadequate dialysis (Kt/V of 1.1 and many missed sessions), and a recurrent pericardial rub. Due to concern for calciphylaxis a skin biopsy was performed. The biopsy showed pandermal necrosis and intravascular thrombi; findings consistent with calciphylaxis rather than ischemia. His PTH was noted to be 181pg/ml, serum calcium of 7.6mg/dl and phosphate was 7mg/dl which improved to 4.8 after increasing his dose of Sevelamer. He was started on sodium thiosulfate and a pain regimen.



Necrotic thigh lesion

Skin biopsy: Necrosis of the epidermis and upper dermis. A blood vessel also shows a small thrombus

Discussion: Our case demonstrates the potential benefits of obtaining a skin biopsy of dialysis patients presenting with necrotic skin lesions. Since most patients with ESRD have complex medical histories including vascular disease, it can be challenging to clinically differentiate between calciphylaxis and ischemic disease.

PUB371

A Case of Epstein-Barr Virus Associated Post-Transplant Lymphoproliferative Disorder Appearing in Cervix Hafiz Ali Sroya, Rawan T. Al-Odat, Eduardo A. Alas, Antonia Harford, Pooja Singh. *UNM School of Medicine.*

Introduction: PTLD is the most common malignancy complicating solid organ transplantation (excluding non melanomatous skin cancer and in situ cervical cancer). Recent reports suggest that PTLD is increasing in frequency. Manifestations include involvement of the GI tract, lungs, skin, liver, CNS and the allograft itself. PTLD involving the cervix in a renal transplant recipient has not been reported previously, to our knowledge.

Case Description: A 48 YO female with ESRD due to IgA nephropathy underwent DDKT 13 years ago with thymo induction and subsequent maintenance immunosuppression with Tacrolimus & MMF and had excellent graft functions. Two years post-transplant, renal allograft biopsy performed for evaluation of proteinuria, hematuria and worsening renal function revealed recurrence of IgA. Patient was managed conservatively and graft functions returned to baseline. Eleven years post transplantation, during routine healthcare maintenance, she was found to have an abnormal Pap smear leading to colposcopy and cervical conization that showed cervical leiomyomata & residual high-grade CIN. So MMF was stopped and Tacrolimus was switched to Sirolimus (dose 0.5mg daily). Follow-up Pap smear was normal at 6 months; however at one-year was again abnormal with positive high-risk HPV. A cervical cone biopsy showed polymorphic EBV-associated PTLD, rich in B & T cells. She was treated with further reduction in her immunosuppression with Sirolimus dose decreased by 50% to 0.5mg every other day. A repeat biopsy of the cervix after 3 months showed resolution of PTLD.

Discussion: PTLD can involve atypical organs such as the cervix as in our case. Mostly it occurs in the first year post-transplant but in our case PTLD occurred 13 years post-transplant. Although Tacrolimus carries a significantly higher risk of PTLD, in our case, PTLD developed while on Sirolimus. Risk stratifications and optimal treatment strategies specific to kidney transplantation are lacking but immunosuppression reduction is the most accepted treatment and may result in resolution of the disease process as in our case. This case demonstrates the importance of continued cancer surveillance throughout the post renal transplant course.

PUB372

Chloride and Acid-Base Status as a Hint to Diagnose Parathyroid Adenoma Min Zhuo, Jiahua Li. *Internal Medicine, John H Stroger Jr. Hospital of Cook County, Chicago, IL.*

Introduction: PTH level is the first branching point in approaching hypercalcemia. When PTH level is equivocal, a detail medical history could be very helpful. However, medication history could also mislead us to a premature diagnosis. This case we used chloride and acid-base status to correct a misdiagnosis of Milk-Alkali syndrome and found a subtle parathyroid adenoma.

Case Description: A 66-year-old woman presented with a 3-day history of nausea, fatigue, and frequent urination. She denied dysuria, vomiting, abdominal pain, or fevers. She reported taking 6 to 20 tabs of "Tums" (calcium carbonate) daily for the past four months. Her vitals were within normal limit except for heart rate of 110 bpm. The thyroid gland was normal size, and no neck nodules were palpable. Rest of the cardiopulmonary and abdomen exams were unremarkable. Her metabolic panel was remarkable for Na 141 mEq/dl, K 3.2 mEq/dl, Cl 111 mEq/dl, $HCO3^-$ of 19 mmol/dl, anion gap 11, BUN 26 mg/dl and creatinine 1.1 mg/dl, Ca^{2+} of 14.8 mg/dl, Mg^{2+} of 0.7 mg/dl, and Phos 1.2 mg/dl. PTH was 7 pg/ml. Urine pH was 5.5. Urine electrolytes panel was UNa 77 mEq/dl, UCl 85 mEq/dl, UK 17 mEq/dl, yielding a UAG of +9. 24-hr urine calcium was 208 mg. Her calcium normalized to 8.2 mg/dl and bicarbonate normalized to 23 mEq/dl concomitantly with 4-day intravenous hydration. Potassium, phosphorus, and magnesium were replaced. Her OTC multivitamins and calcium carbonate were discontinued, but her repeat BMP remained hypercalcemic in the post-hospital clinic visit. Finally, a sestamibi parathyroid scan revealed a small parathyroid adenoma.

Discussion: PTH was low normal which limited its use for differentiating causes of hypercalcemia. At a glance, patient's history suggested Milk-Alkali syndrome, which was described as excessive calcium and alkali intake and impaired calcium excretion by alkalosis, as the cause of the hypercalcemia. However, patient's hypercalciuria and metabolic acidosis went against Milk-Alkali syndrome. PTH can inhibit Na-H exchange in distal tubule causing increased bicarbonate wasting, hyperchloremia and type 1 RTA. Hyperchloremic metabolic acidosis led to an investigation of PTH-dependent mechanism and the discovery of a subtle parathyroid adenoma.

PUB373

A Case of Wilson's Disease Presenting with Acute Renal Failure Requiring Continuous Veno Venous Hemofiltration Nick D. Youssefi. *Dept of Nephrology, Dartmouth Hitchcock, Lebanon, NH.*

Introduction: Wilson's disease is due to a genetic abnormality inherited in an autosomal recessive manner that disrupts cellular copper transport. Impaired biliary copper excretion leads to accumulation of copper in several organs most commonly the liver, brain, and cornea. Renal failure associated with Wilson's disease has been reported but is very rare.

Case Description: We present a case of a 47 year-old-man who presented to the hospital with chronic progressive abdominal pain for the past 4 months. Patient had a liver biopsy 1 month prior suggestive of Wilson's disease. The patient endorsed 3 weeks of progressive lower extremity swelling. Patient had associated lightheadedness, fatigue, and decreased appetite. Vital signs on admission: BP 100/60mmHg HR 77 T 97.7F 98%RA. Physical exam notable for jaundice, ascites, 2+ edema. No Kayser-Fleischer rings noted. Within 48 hours, the patient developed respiratory failure requiring intubation and hypotension requiring vasopressor support. CXR revealed pulmonary edema. CT abdomen revealed a stable renal cyst, no hydronephrosis. Blood, urine, sputum, ascites fluid cultures were all negative. Serum ceruloplasmin level was 29.9 mg/dL, serum copper 0.96 mcg/mL, 24 hour urine copper excretion 561 mcg/spec. Serum creatinine 3.96mg/dL with baseline 1.24mg/dL. Urine microscopy revealed few granular casts and renal tubular epithelial cells. No renal biopsy was performed. Patient developed oligoanuric renal failure requiring continuous veno-venous hemofiltration (CVVH) support. Patient received plasmapheresis in conjunction with CVVH. No penicillamine given. Patient was transferred to an outside hospital for liver transplant evaluation. On transfer, patient was still intubated, on vasopressors, and oliguric.

Discussion: The association of renal failure and Wilson's disease has been reported in only a few case reports worldwide. Renal involvement in Wilson's disease frequently causes damage to the proximal tubule, acidification defects, and decreases in filtration rate or effective renal blood flow. Our patient developed oligoanuric renal failure requiring CVVH and plasmapheresis.

PUB374

Acidotic Hypercapnia: A Case Series of Acidosis Driven Respiratory Muscle Dysfunction Catherine King, Rahul Mukherjee. *Respiratory Medicine, Birmingham Heartlands Hospital, Birmingham, West Midlands, United Kingdom.*

Introduction: It is commonly assumed that respiratory acidosis follows the development of acute hypercapnia. This case series describes 4 patients with hypercapnia secondary to metabolic acidosis demonstrated through serial arterial blood gases (ABG) treated with Non-invasive Ventilation (NIV).

Case Description: Case 1: A 64 year-old with diabetes on metformin and chronic obstructive pulmonary disease (COPD) with pneumonia and non ST-elevation myocardial infarction. Initial ABG - metabolic acidosis which deteriorated despite standardised treatment, with onset of hypercapnia and NIV requirement. Case 2: A 75 year-old with COPD admitted with breathlessness secondary to congestive cardiac failure required NIV to treat acidotic hypercapnia. Applying the Henderson-Hasselbach equation to his ABG, predicts bicarbonate 29mmol/L not 17.9, confirming metabolic acidosis. Case 3: A 78

year-old with severe COPD and shortness of breath/cough, treated for acute exacerbation COPD. Initial ABG - metabolic acidosis but later developed progressive hypercapnia requiring NIV. Case 4: A 60 year-old obese lady with drowsiness/agitation, treated for sepsis. ABG - mixed respiratory/metabolic acidosis due to combination of obstructive sleep apnoea and non-steroidal anti-inflammatory drug-induced acute on chronic renal failure. NIV was later commenced for worsening hypercapnia.

Case	Initial ABG	Pre-NIV ABG	Post-NIV ABG
1	pH 7.336, PaO2 11.2, PaCO2 5.56, HCO3 20.8, lactate 1.4	pH 7.143, PaCO2 11.8, PaO2 8.76, HCO3 22.8, lactate 2.7	pH 7.462, PaCO2 5.7, PaO2 7.91, HCO3 29.8 lactate 0.9
2	pH 7.06, PaCO2 12.0, PaO2 8.55, HCO3 17.9		pH 7.43, PaCO2 5.10, PaO2 8.11, HCO3 25.4
3	pH 7.30, PaCO2 6.06, PaO2 8.73, HCO3 20.8	pH 7.066, PaCO2 12.3, PaO2 8.52, HCO3 18.2	pH 7.458, PaCO2 6.12, PaO2 7.48, HCO3 31.1
4	pH 7.224, PaCO2 5.93, PaO2 11.5, HCO3 17.2	pH 7.26, PaCO2 8.0, PaO2 10.3, HCO3 23.6	pH 7.464, PaCO2 4.75, PaO2 9.43, HCO3 21.8

Discussion: Acidotic hypercapnia is an under-recognised subtype of respiratory failure; in all 4 cases this acidosis reversed completely with NIV and optimal medical management. Acidosis is a known cause of muscular dysfunction and may contribute to respiratory muscle fatigue. We postulate a similar causation of respiratory failure described previously due to circulatory shock (Type 4 respiratory failure) which resolves when shock is corrected. Further trials are required to decide the best management of acidotic hypercapnia.

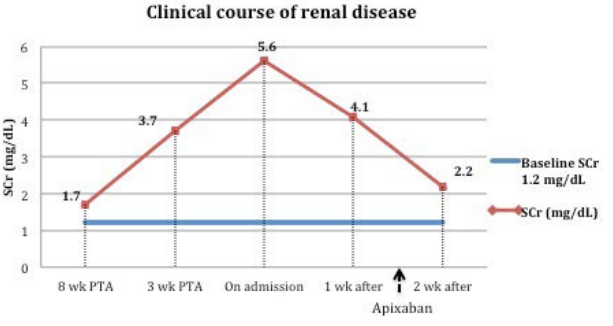
PUB375

Steroid May Be an Effective Treatment for Warfarin Related Nephropathy

Natanong Thamcharoen,[1] Ridhmi P. Rajapakse,[1] Raquel M. Rosen,[1] Vivette D. D'Agati.[2] *[1]Medicine, Bassett Medical Center, Cooperstown, NY; [2]Pathology and Cell Biology, Columbia Univ College of Physicians and Surgeons, New York, NY.*

Introduction: Warfarin-related nephropathy (WRN) manifests as acute kidney injury (AKI) from over-anticoagulation, mostly INR > 3, causing glomerular hemorrhage and tubular obstruction by red blood cell (RBC) casts and oxidative stress damage to tubules. We report a case of a patient with biopsy-proven WRN and therapeutic INR.

Case Description: An 83-year-old man with CKD stage 3A, coronary artery disease, atrial fibrillation, admitted for AKI with creatinine (Cr) of 5.6mg/dL, tea-colored urine. He had several hospitalizations over the past 6 months and was exposed to multiple antibiotics. Last antibiotic use was a month ago. He had gastric bleeding (GIB) 4 months ago from INR of 6 resulting in hypotension and AKI with renal recovery to baseline (1.2 mg/dL). Lab showed rapidly rising Cr over several weeks.



INR was within therapeutic range after the GIB. Urinalysis showed RBC presented since 4 months ago. Urine protein creatinine ratio was 1.8 g/g. Urine sediment showed dysmorphic RBC and RBC casts. Serologic tests and complement levels were all normal. He received steroids for presumed vasculitis related nephropathy. Renal biopsy later showed diffuse acute tubular injury and numerous RBC casts, suggestive of WRN without evidence of glomerulonephritis or allergic interstitial nephritis. Cr improved with steroid therapy which was gradually tapered. Later, warfarin was switched to apixaban.

Discussion: When other causes have been excluded, WRN should be considered as a cause of AKI despite therapeutic INR. The standard treatment includes reversal of coagulopathy and supportive care. Interestingly, prednisone was proven to be effective in our patient, however its role should be further evaluated.

PUB376

Hypernatremia after Bariatric Surgery: A Case of NDI with Unknown Etiology

Jiandong Zhang,[1] Itunu O. Owoyemi,[1] Reginald Ifeanyi Obi,[2] Hsiao Ling Lai.[2] *[1]General Internal Medicine, Vidant Medical Center, Brody School of Medicine, East Carolina Univ, Greenville, NC; [2]Div of Nephrology and Hypertension, Vidant Medical Center, Brody School of Medicine, East Carolina Univ, Greenville, NC.*

Introduction: Hypernatremia is a common electrolyte disorder with incidence of about 0.3-5.5% in hospitalized patient, bearing 30-80% mortality in ICU. Thus, appropriate recognition of underlying etiology is vital to the appropriate treatment of this disorder.

Case Description: Here we report 56 yo CM with Hx of T2DM, morbid obesity, who was referred to nephrology consult for hypernatremia (day 45 of admission). He was initially present for gastric bypass operation, and complicated for EJ tube leakage which require multiple OR visits for drainage manipulation. His lab revealed a serum sodium in the range of 140-150 prior to this episode of 160-165. Serum osmolality as 320-330 mOsm, Uosm 100-200 mOsm on multiple occasions, UA revealed a UNa+ of 20s mmol/L, UCr 18.18 mg/dL. Negative for protein or glycosuria. His free water deficit was calculated as 11L, D5W was initiated to replace free water. Shortly after, patient then developed massive volume of urinary output > 4L per day. DDAVP was administered without improvement in UOP or osmolality, suggesting that nephrogenic diabetes insipidus is likely to attribute to this case. Thereafter, HCTZ and amiloride was started and polyuria-polydipsia was gradually controlled in a period of about 3 weeks course. Pt was educated to have a good management of osmotic load and water intake, and discharged with HCTZ 12.5mg bid.

Discussion: DI is a rare cause of hypernatremia, but inherits with unique interventions. In adult settings, most of DIs are acquired form secondary to medications or electrolyte abnormalities. Here, we ruled out lithium use, hypokalemia or hypercalciuria. Genetic test for possible mutations in patient and his family was discussed. Nephrogenic diabetes insipidus (NDI) is a rare kidney disorder that may be inherited or acquired, caused by impaired ability of kidney collecting duct tubules to concentrate urine. Management for NDI paradoxically involves diuretics beyond correction of modifiable secondary contributing components.

PUB377

A Case of Tenofovir-Induced Acute Kidney Injury (AKI) with Fanconi Syndrome

Michael J. Rogers,[1] Allison Bigeh,[2] Elise J. Barney.[3] *[1]Internal Medicine, Banner Univ Medical Center, Phoenix, AZ; [2]Clinical Medicine, AT Still Univ, Kirksville, MO; [3]Nephrology, Phoenix VA Healthcare System, Phoenix, AZ.*

Introduction: Tenofovir disoproxil fumarate (TDF) is a nucleotide-reverse transcriptase inhibitor used in HAART therapy for HIV. TDF is filtered by the glomerulus and secreted by proximal tubular epithelial cells. Nephrotoxicity, although rare, is well described, specifically causing proximal renal tubular acidosis or rarely Fanconi Syndrome (FS). The suspected mechanism is via inhibition of tubular mitochondrial DNA polymerase. Here we report a case of TDF-induced FS in an HIV+ patient with acute renal failure.

Case Description: A 65 year-old non-diabetic male with history of hypertension and HIV on HAART therapy presented with acute hallucinations, 2 months of oliguria and admitted with AKI. Labs showed BUN 66, creatinine 6.79, total CO2 16, anion gap 15, and normal potassium, phosphorous, and lactate. Urinalysis showed glycosuria and proteinuria; urine protein/creatinine ratio was 829 mg/g. Serologies and workup, including urine microscopy were negative. HgA1c was normal. HIV RNA was 55 copies/mL. Renal ultrasound was unremarkable. TDF was held; however the patient became anuric and required hemodialysis. Two months later, he is non-oliguric but remains dialysis-dependent. Recent urinalysis showed persistent glycosuria and 24-hour urine confirmed proteinuria of 815 mg. Renal biopsy showed acute tubular injury with diffuse early fibrosis. Chart review revealed 7 years of glycosuria, subnephrotic proteinuria with chronic renal dysfunction over the last 2 years (creatinine 1.24-1.39), and recent hypophosphatemia. The consistent factor was TDF therapy for many years.

Discussion: There are limited data regarding TDF-induced FS and its course, although it is thought to be reversible after drug cessation. Chronic kidney disease due to TDF has been debated. As TDF is a cornerstone of HAART, early recognition of FS is crucial. This case highlights the importance of monitoring kidney function closely, as proximal tubule dysfunction may present indolently and could be permanent if diagnosis is delayed.

PUB378

Echocardiographic Evidence of Dialysis-Related Amyloidosis Presenting as New-Onset Ascites and Liver Failure

Carsten R. Hamann,[1] Nicole Syed,[2] Nicole Kristine Shah-Ghassemzadeh,[1] Seyed-Ali Sadjadi.[1] *[1]Dept of Internal Medicine, Loma Linda Univ Medical Center, Loma Linda, CA; [2]Dept of Family Medicine, Univ of California: Riverside, Morreno Valley, CA.*

Introduction: Dialysis-associated amyloidosis(DRA) is a common but infrequently reported complication of long term hemodialysis(HD) and peritoneal dialysis, caused by deposition of beta-2-microglobulin(B2M) amyloid fibrils in articular and visceral tissue. B2M is a ~12,000 dalton glycosylated polypeptide, inefficiently filtered by traditional HD filters, notably low-flux filters. DRA most commonly presents with articular involvement, notably carpal tunnel syndrome and scapulohumeral periarthritis. Visceral involvement of DRA is rarely reported.

Case Description: We present the case of a 33 year old female with end stage renal disease(ESRD) secondary to hemolytic uremic syndrome on HD, hypertension(HTN), pulmonary HTN, and recently diagnosed diastolic heart dysfunction who presented to our university-based medical center with a 1 month history of worsening abdominal distention and pain. Abdominal ultrasound showed hepatic cirrhosis with ascites. Peritoneal fluid analysis was consistent with cardiogenic ascities with a serum-ascites albumin gradient of 1.2. Echocardiogram showed hyperdynamic left ventricular function, an ejection fraction of >70%, right ventricular systolic pressure ~45 mmHg, severe dilation of all four chambers, and a speckled appearance of left ventricular walls suggestive of amyloidoisis. Serum B2M was elevated to 64.8 mg/dl.

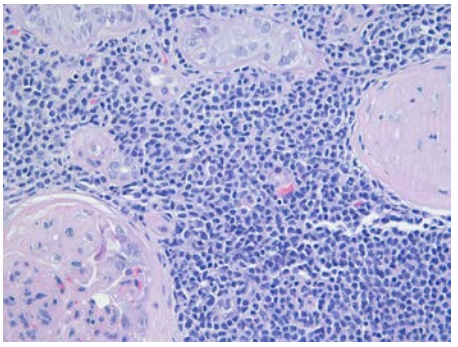
Discussion: We believe this case exemplifies a rare presentation of visceral DRA with cardiac involvement. Clinicians taking care of patients with ESRD who have been on long term hemodialysis or peritoneal dialysis must be cognizant of the myriad ways DRA can present. Visceral DRA, in particular DRA with cardiac involvement, is rare but should be on the differential for any patient with ESRD who presents with signs of infiltrative heart disease, including congestive liver failure, cirrhosis and ascites.

PUB379

Renal Failure due to Direct Infiltration of Chronic Lymphocytic Leukemia Bartlomiej Posnik, Nina Undevia Yedavalli. *Internal Medicine, West Suburban Medical Center, Oak Park, IL.*

Introduction: Chronic lymphocytic leukemia (CLL) is a cancer due to uncontrolled growth and accumulation of mature B lymphocytes. Asymptomatic kidney involvement of is fairly common with up to 90% of patients having interstitial infiltration on autopsy. Less than twenty cases of acute renal failure due to direct CLL infiltration have been reported in the literature.

Case Description: An 86 year-old African American female was diagnosed with stage IV CLL when she presented with extensive lymphadenopathy. Treatment with bendamustine and chlorambucil was discontinued due to poor compliance, creatinine of 1.95 mg/dL, and disease progression. Creatinine was later found to be 4.2 mg/dL with renal ultrasound consistent with medical renal disease. Protein electrophoresis with immunofixation of urine and serum was normal. Creatinine reached a maximum value of 5.7 mg/dL. Renal biopsy demonstrated dense infiltration of small lymphoid cells consistent with low grade B cell lymphoma as well as some focal segmental glomerulosclerosis.



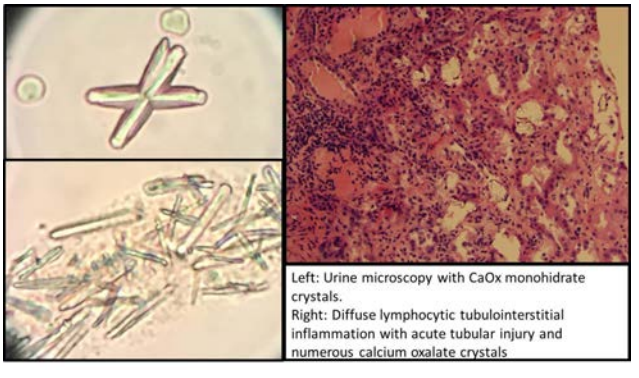
Discussion: Renal insufficiency is not uncommon in CLL patients as it can be seen in 7.5% of patients at the time of initial diagnosis and another 16.2% at some later time. The mechanism of renal failure in patients with direct CLL infiltration is thought to be due to compression of the renal tubules and microvasculature leading to obstruction and ischemia. The most common pattern seen on kidney biopsy is dense interstitial infiltration in the cortex with some degree of glomerular fibrosis/sclerosis. Most important is the absence of immune complexes. There is no agreed upon standard of care for treatment, it should be individualized. Regardless of the treatment modality, there seems to be a high recurrence rate. Recognition of this rare phenomenon is crucial as prompt recognition and intervention may reverse renal damage and recover function.

PUB380

Acute Oxalate Nephropathy- The Answer Is in the Urine Mahrukh Rizvi, Rebeca D. Monk. *Nephrology, Univ of Rochester School of Medicine, Rochester, NY.*

Introduction: Prompt recognition and rapid institution of therapy is crucial to preserve renal function in AKI. An easy but underutilized test is urine microscopy. We highlight the importance of urine microscopy in this case of suspected ethylene glycol (EG) ingestion. Ultimately a renal biopsy confirmed the diagnosis.

Case Description: A 59 y/o male presented with ~ 10 hrs of odd behavior. He was disoriented, afebrile, and hypertensive (225/120) with labs notable for pH 7.2, HCO3 7.8, PCO_2 8.4, anion gap (AG) 26, albumin 4.1, lactate 8.4, BUN 19, Cr 1.9 (0.7 one year ago). A drug screen and toxic alcohols were negative. On transfer to our hospital, ~ 30 hrs after initial symptomatology, an OG was obtained and negative. Urine microscopy revealed sheets of needle shaped calcium oxalate monohydrate crystals. EG ingestion was suspected and he was started on a Na-Bicarb drip to prevent tissue deposition of EG metabolites, however, patient refusal, lack of OG and EG levels continued to lead away from a final diagnosis of EG toxicity and early dialysis. His renal function quickly deteriorated over the next 48 hrs ultimately necessitating dialysis. A renal biopsy was obtained which revealed diffuse lymphocytic tubulointerstitial inflammation, acute tubular injury and numerous calcium oxalate crystals.



Left: Urine microscopy with CaOx monohidrate crystals.
Right: Diffuse lymphocytic tubulointerstitial inflammation with acute tubular injury and numerous calcium oxalate crystals

Discussion: EG is metabolized in the liver with a half life of 2.5-8.4 hrs. A lack of OG, presence of AG and Calcium Oxalate crystals suggest a late presentation when a negative OG and EG level is not unusual. This case highlights the utility of early urine microscopy and the importance of understanding the toxicokinetics of EG and other toxic alcohols to allow prompt diagnosis of ingestion despite significant laboratory gaps and lack of exposure history particularly in high risk patients with severe depression. Our patient ultimately admitted to EG ingestion and currently remains on dialysis.

PUB381

AA Amyloidosis in an IV Drug User – A Cautionary Tale Mahrukh Rizvi, Rebeca D. Monk. *Nephrology, Univ of Rochester Medical Center, Rochester, NY.*

Introduction: Most common reports of renal disease in IV drug users are related to HIV, HBV, and HCV infections. This has led to harm reduction initiatives nationwide aiming to decrease disease transmission via needles. A relatively rare but catastrophic form of renal disease in IV drug users is systemic amyloidosis, first reported in the 70's. Given grave outcomes, it deserves the spot light, especially to encourage early wound care into harm reduction initiatives in this population.

Case Description: A 38 year old Hispanic female with IV heroin and cocaine abuse with chronic lower extremity (LE) ulcers at injection sites presented with pain. Her exam was notable for a BP of 176/105, HR 75, Temp 97.3. Skin exam revealed superficial erosions on bilateral forearms, large wound bed in the left LE and ulceration with tender areas of eschar in the right LE. Admission labs revealed a creatinine of 2.4 mg/dL, albumin of 1.4 g/dL, CRP 70 mg/L, antibodies to Hepatitis C, 18 g of protein in the urine, oval fat bodies in the urine sediment with no red blood cells. A renal biopsy revealed AA amyloidosis with severe tubular atrophy and loss and interstitial fibrosis.

Discussion: In a case series, >50% of patients with AA amyloidosis from IV drug use required dialysis within one month. Median survival is reported to be 25 months, which compares unfavorably with median survival of 52 months for all patients with AA amyloidosis on dialysis. Providing dialysis is challenging in these patients due to difficulty obtaining permanent vascular access, tunneled lines being used for drug injection, poor hygiene, and infectious complications. This case underscores a grave, albeit rare complication of IV drug use resulting from chronic soft tissue infection. Whether street contaminants contribute to development of AA amyloidosis remains unknown. We bring this case to the spotlight to encourage early attention to skin complications in IV drug users. Isolated programs for easily accessible, cost-effective medical and wound care for IV drug users with soft tissue infections have been established. This has resulted in significant reductions in ED visits, hospital admissions, and costs in those areas. Perhaps, similar efforts should be initiated nationally.

PUB382

A Case of Membranoproliferative Glomerulonephritis Secondary to Sjogren's Syndrome Rafael Franjul. *Nephrology Fellowship, Newark Beth Israel Medical Center, Newark, NJ.*

Introduction: This case represents an overview of an atypical acute presentation of a chronic disease that manifested with Nephrotic Syndrome in a 70 years old female needing acute renal replacement therapy and the investigative effort where and autoimmune disease was found and treated in hopes of renal recovery.

Case Description: 70 years old Female from the Philippines presented complaining of dyspnea on exertion and lower extremity edema for 3 weeks prior to presentation. Was started on diuretics to manage symptoms, but there was no improvement and symptoms progressed. An echocardiogram performed revealed pericardial effusion and patient was admitted to the hospital for pericardial window. Developed respiratory distress requiring ventilator support via endotracheal tube. Was started on furosemide drip, but renal function worsened. On admission patient with Scr of 3.17 mg/dL, unknown baseline, no history of kidney disease. Her past medical history was significant for long standing hypertension and patient was deaf and mute since childhood with unknown etiology, family history was noncontributory. Her medications consisted in carvedilol 12.5mg every 12 hours; isosorbide mononitrate 30 mg daily; hydralazine 50 mg every 12 hours; losartan 100 mg daily. No history of tobacco, alcohol or recreational drugs. On Review of systems she admitted to dry eyes for several years as well as joint pain. Her vital signs were stable, and physical exam demonstrated distant heart sounds, diffuse crackles and lower extremity pitting edema of +2 bilateral; no focal neurological deficit and no joint deformities appreciated. Her initial laboratory work up revealed a normocytic anemia; Serum Sodium level 148 mEq/L; Potassium 4.7 mEq/L; CO2 22 mEq/L; Calcium 7.9 mg/dL; Phosphorus 5.8 mg/dL; Albumin 2.5 g/L; BUN 66 mg/dL and creatinine 3.27 mg/dL. Urinalysis was significant for proteinuria +4. Spot urine protein/creatinine ratio of 4.7 g/mg. Further investigation for evaluation of renal failure showed significantly positive SS-A IgG. Kidney biopsy showed a membranoproliferative pattern. A trial of cyclophosphamide was initiated and patient remained on RRT while awaiting progression or recovery of her renal funcion.

PUB383

An Unusual Case of Light Chain (AL) Amyloid Nephropathy Amtul Aala, Basma Omar Merhi. *Nephrology, Alpert Medical School of Brown Univ, Providence, RI.*

Introduction: Light chain (AL) amyloidosis is usually associated with plasma cell dyscrasia but not as common with Lymphoma. Here, we report an unusual case of AL amyloid nephropathy as a renal manifestation of an otherwise quisescent B-cell lymphoproliferative disorder (BCLPD).

Case Description: An 85 year old female with history of breast cancer treated with lumpectomy and radiation therapy, diet controlled diabetes mellitus and hypertension was diagnosed with lambda light chain restricted B-cell lymphoproliferative disorder by bone marrow biopsy (immunophenotypically consistent with Marginal zone lymphoma) five years prior to presentation and managed conservatively. She recently presented with lower extremity edema, dyspnea and 10 lb weight gain and diagnosed with nephrotic range proteinuria with urine protein/ creatinine ratio 5.5 g/g and acute kidney injury with serum creatinine of 1.3mg/dl from baseline 0.6mg/dl. Serologies for hepatitis B & C, HIV, ANA, anti-ds DNA and complement levels (C3 and C4) were negative. SPEP showed high kappa and lambda light chain with normal ratio of 0.9 with negative urine immune-fixation for para-proteins. Age-appropriate cancer screening was negative but no prior colonoscopy reported. CT scan abdomen and pelvis showed stable splenomegaly, and scattered retroperitoneal and right common iliac lymph nodes, the largest measuring 1.1 cm. Kidney biopsy was performed with findings of AL amyloid nephropathy [light chain type (lambda-restricted)], with deposition in the glomeruli and arterioles, mild interstitial fibrosis and tubular atrophy, and moderate arteriosclerosis. As her AL amyloid nephropathy was likely secondary to BCLPD, the plan was to initiate chemotherapy. Due to poor performance status and limited cognitive function, chemotherapy was withheld. Her condition declined and sadly she passed away.

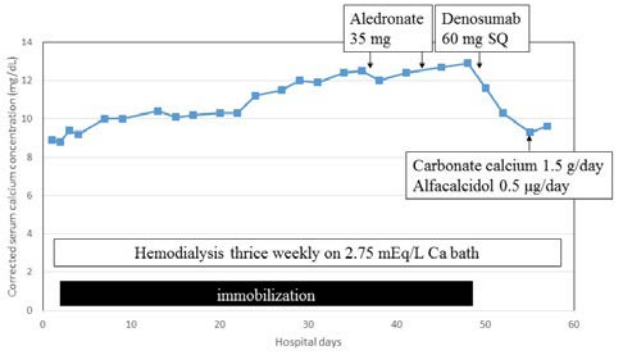
Discussion: AL amyloidosis is a rare manifestation of BCLPD with only limited case reports published. This condition is more common in elderly female patients with multi-systemic involvement upon presentation. Aggressive therapy with high-dose melphalan and stem cell transplantation may improve patient survival. AL amyloidosis should be in the differential diagnosis of proteinuria in patients with BCLPD.

PUB384

Denosumab for Treatment of Immobilization-Related Hypercalcemia in a Patient with End-Stage Renal Disease Atsuko Uehara, Masahiko Yazawa, Yugo Shibagaki. *Div of Nephrology and Hypertension, St. Marianna Univ Hospital.*

Introduction: The effectiveness and safety of denosumab for the treatment of immobilization-related hypercalcemia in end-stage renal disease (ESRD) remain uncertain. Here, we describe a case of immobilization-related hypercalcemia successfully treated with denosumab in a patient undergoing hemodialysis.

Case Description: A 79-year-old man with diabetic nephropathy was diagnosed with gastric cancer and gastric resection was recommended five months prior to admission. However, he developed acute kidney injury due to contrast-induced nephropathy. He admitted and initiated hemodialysis, but he experienced acute myocardial infarction and acute heart failure, for which he became bedridden, and operation was cancelled. Afterwards, his serum calcium gradually elevated from 8.8 to 12.9 mg/dl, and general fatigue developed. Immobilization-related hypercalcemia was diagnosed after excluding other possibilities. Alendronate was given for two weeks, without any improvement. He was then administered 60 mg of denosumab subcutaneously with calcium supplement and alfacalcidol and his serum calcium decreased to 9.3 mg/dl one week later, and was controlled within the 9.0-10.0 mg/dl range.



Discussion: Immobilization-related hypercalcemia in patients undergoing maintenance dialysis is not rare. The report on the effectiveness and safety of denosumab for immobilization-related hypercalcemia in patients with ESRD has been scarce. Our case indicated that denosumab can be a vial for intractable immobilization-related hypercalcemia in patients with ESRD.

PUB385

A Dying Kidney's Last Stand: Removal of Renin-Secreting Atrophic Kidney Improves Blood Pressure Control Robin Shah, Jason Prosek. *Div of Nephrology, The Ohio State Univ Wexner Medical Center, Columbus, OH.*

Introduction: About 20 to 30 percent of cases of hypertension are considered resistant and are often driven by secondary processes. A subset of secondary hypertension features elevated renin levels as its characteristic attribute. A measurable rise in renin could be secondary to decreased arterial blood flow to the kidney. We present a case in which a patient with resistant hypertension is found to have asymmetric renin secretion, prompting nephrectomy which led to improvement in both renin levels and blood pressure control.

Case Description: A 58 year old male with a history of abdominal aortic aneurysm (AAA), hypertension, and chronic kidney disease with a baseline serum creatinine (SCr) of 1.3 mg/dL was referred to the nephrology clinic for resistant hypertension. Five years prior to evaluation, he had an AAA repair with stent which was felt to be obstructing flow to the right renal artery. Despite subsequent angioplasty and stenting, blood flow to the right kidney progressively worsened, confirmed via CT angiogram which revealed severe, diffuse narrowing of the renal artery and an atrophied right kidney. He also continued to have symptoms of headache, flushing, and blood pressure readings of 200/100 mmHg despite 4 antihypertensives including an angiotensin receptor blocker and diuretic. Plasma renin level was 45 ng/mL/hr (normal less than 3.95 ng/mL/hr). Renal vein sampling revealed asymmetric renin release, with right renal vein level at 247 ng/mL/hr and left renal vein level at 65.55 ng/mL/hr (central renin level was 63 ng/mL/hr). The patient was referred for right nephrectomy. Two months after nephrectomy, his blood pressure improved to 130/80 on fewer antihypertensives, and his symptoms improved. Repeat renin level was 1.0 ng/mL/hr. His kidney function has remained stable with a SCr of 1.3 mg/dL.

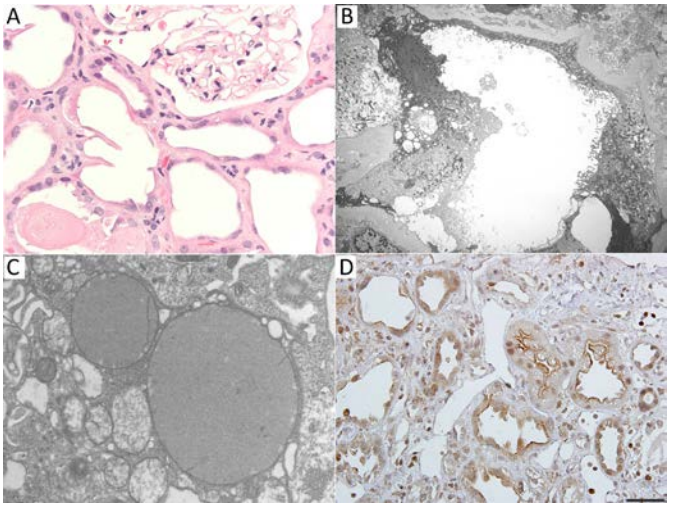
Discussion: This case demonstrates that excessive renin production in an atrophied kidney can cause resistant hypertension. Thus, recognizing this is important as some patients may benefit from nephrectomy that may ultimately improve blood pressure with a measurable decrease in renin secretion and preserve the other kidney's function.

PUB386

Literal ATN: Tenofovir Toxicity, Regeneration and Oxidative Stress Kenneth M. Ralto,[1] Melanie P. Hoenig,[1] Zsuzsanna Zsengeller,[2] Seymour Rosen.[2] *[1]Nephrology, Beth Israel Deaconess Medical Center, Boston, MA; [2]Pathology, Beth Israel Deaconess Medical Center, Boston, MA.*

Introduction: In most cases of acute tubular necrosis (ATN) there is limited epithelial injury (Rosen et al, JASN 2008) but in a few situations widespread tubular destruction occurs. Tenofovir disoproxil fumarate (TDF) is a nucleoside reverse transcriptase inhibitor, widely used for prevention and treatment of human immunodeficiency virus infection. TDF is excreted by the kidney via glomerular filtration and active proximal tubular secretion. It has been shown that TDF inhibits mitochondrial DNA polymerase-γ, leading to mitochondrial DNA depletion and cell injury apparently due to the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in rats (Abraham et al, J Biomed Sci 2013).

Case Description: A 54-year-old man with HIV on emtricitabine/rilpivirine/TDF presented with fatigue and nausea. Laboratory studies showed a creatinine of 14.8 mg/dL, bicarbonate of 11 mEq/L, glycosuria and proteinuria. Urine sediment was notable for muddy brown casts. TDF was withheld and a renal biopsy was performed. The biopsy showed regenerative changes with simplified, attenuated epithelium in the proximal tubules on H&E staining (A) and by EM (B). Megamitochondria with markedly diminished cristae, typical of TDF toxicity, were seen (C). Lastly, nitrotyrosine immunostaining highlighted areas of oxidative and nitrosative stress in the proximal tubules (D). The patient required hemodialysis, but subsequently, his renal function improved sufficiently to discontinue hemodialysis and his creatinine decreased over several months.



Discussion: The renal biopsy showed severe proximal tubular damage, megamitochondria and evidence of oxidative/nitrosative stress, features consistent with TDF nephrotoxicity. These findings support the idea that TDF leads to proximal tubular damage through mitochondrial injury and generation of ROS/RNS.

PUB387

MUCIN-1 Kidney Disease in the Family Samuel Mon-Wei Yu,[1] Anthony J. Bleyer,[2] Kisra Anis,[1] Belinda Jim.[1] *[1]Medicine, Jacobi Medical Center, Bronx, NY; [2]Nephrology, Wake Forest School of Medicine, Winston-Salem, NC.*

Introduction: Mucin-1 kidney disease (MKD) is a rare hereditary kidney disease. It is one of several diseases now termed autosomal dominant tubulointerstitial kidney disease (ADTKD), as proposed by a KDIGO consensus report in 2014. Although the pathophysiology of MKD is still under investigation, genetic testing has been developed to detect the most common mutation, a single cytosine insertion into a string of seven cytosines in the variable number of tandem repeat (VNTR) region of the MUC1 gene.

With this diagnostic tool, nephrologists can offer genetic counseling to affected families and closely follow up progression of disease. Here we report a patient with strong family history of chronic kidney disease (CKD) who tested positive for the MUC1 mutation.

Case Description: A 41-year-old Hispanic female with a history of gestational diabetes and hypertension was referred to renal clinic for newly-diagnosed CKD stage 3. Her mother passed away at age of 42 and was on hemodialysis (HD). One brother presented at age 33 with uremic encephalopathy and bilateral atrophic kidneys, which required HD followed by renal transplant. A second brother presented at the age of 32 for evaluation of CKD stage 3 and was found to have tubulointerstitial kidney disease by renal biopsy. A third brother apparently was diagnosed with leukemia the age of 4, developed ESRD due to medications, required HD for 4 years, and died at the age of 19. Our patient had a renal biopsy which revealed chronic tubulointerstitial nephropathy. Given the family history, she was referred for genetic testing and found to have a MUC1 mutation.

Discussion: Unlike ADTKD due to UMOD or REN mutation, MKD does not have associated findings such as hyperuricemia or anemia in childhood. Renal ultrasound usually is normal or shows occasional cysts, and urinalysis is bland without proteinuria. The age of onset of end-stage kidney disease can vary significantly within families, suggesting other genetic variants may affect outcome. To diagnose MKD, it is extremely important for nephrologists to collect a comprehensive family history and refer for genetic testing in order to make a diagnosis and begin counseling.

PUB388

Unconventional Treatment of IgA-Dominant *Staphylococcus* Infection-Associated Glomerulonephritis Abbas Raza,[1] Satyam Arora.[2] *[1]Internal Medicine, St. Luke's Univ Hospital, Bethlehem, PA; [2]Nephrology Associates, St. Luke's Univ Hospital, Bethlehem, PA.*

Introduction: IgA-dominant *Staphylococcus* infection-associated glomerulonephritis is a rare but increasingly diagnosed condition. About 20% of cases are Methicillin-Sensitive *Staphylococcus aureus* (MSSA) associated. Antibiotic treatment is linked with renal recovery in ~60% cases. Duration of antibiotic therapy and use of steroids remain controversial. We report a case of MSSA associated IgA-dominant glomerulonephritis where renal function significantly recovered within 12 months of antibiotics and without steroid therapy.

Case Description: A 67-year-old male with history of diabetes and multiple comorbidities, presented with a right hand cellulitis. He was found to have MSSA sepsis, aortic valve vegetation, L3-L4 discitis, epidural abscess, and osteomyelitis. Patient was started on IV Cefazolin. His recovery was complicated by worsening renal function. Creatinine (Cr) increased from baseline 0.7 mg/dL to 2.8 mg/dL. Workup showed urine protein-to-creatinine ratio (UPC) of 8.2, normal C3 and C4, no monoclonal gammopathy, negative ANA, negative anti-DS DNA, negative ANCA, negative GBM antibody, and high ASO titers. Renal biopsy showed acute glomerulonephritis with mesangial IgA deposition and diabetic glomerulosclerosis. Patient was diagnosed with IgA-dominant *Staphylococcus* infection-associated glomerulonephritis. Along with RAS blockade agents, patient was treated with 12 months of antibiotics. Follow up blood work showed Cr and UPC improved to 1.21 mg/dL and 3.8, respectively.

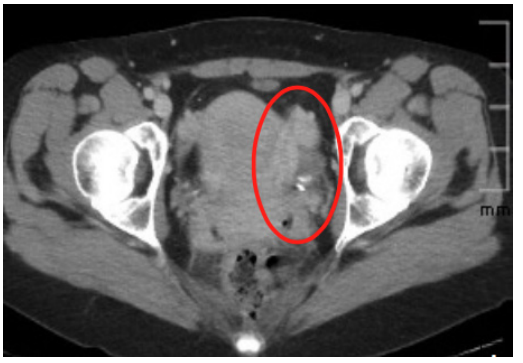
Discussion: Although patients with IgA-dominant *Staphylococcus* infection-associated glomerulonephritis are increasingly recognized, the management has not been well studied. Typically, up to 6 weeks of antibiotics is prescribed. The use of steroids is unclear. Our patient was treated with an unconventionally long duration of antibiotics and without steroids with significant improvement in renal function. Our case illustrates that longer duration of antibiotics may be employed for worsening renal function. Further studies will be needed to focus on the length of an antibiotic course in IgA-dominant *Staphylococcus* infection-associated glomerulonephritis.

PUB389

Three Cases of Uncommon Renal Diseases in Pregnancy Amtul Aala, Basma Omar Merhi. *Nephrology, Alpert Medical School of Brown Univ, Providence, RI.*

Introduction: Renal disorders during pregnancy should be managed by a multidisciplinary team to avoid dangerous clinical consequences to the mother and fetus. Here, we present three uncommon renal disorders in pregnancy: Von-Hippel Lindau disease (VHL), Gitelman syndrome (GS) and Nutcracker syndrome (NS), with successful maternal and fetal outcome in all 3 cases.

Case Description: Case 1: A 30 year-old G4P1 with VHL diagnosed at age 12 presented at 22 weeks gestation. She had a history of successfully resected pheochromocytoma, multiple renal cell carcinomas (RCC) and retinal tumor. After first pregnancy, she stopped annual screening for VHL. Renal ultrasound during this pregnancy revealed bilateral solid masses highly suspicious for RCC confirmed by MRI. She delivered a healthy baby on term. She started the contraceptive vaginal ring and had a follow-up surgical consultation. **Case 2:** 33 year-old G2P1 with GS presented at 10 weeks gestation. She has eight-year history of muscle cramps, palpitations, and intermittent hypokalemia that responded to oral potassium supplement. At 24 weeks gestation, potassium level stayed normal with oral potassium supplement. She was induced by artificial rupture of membranes due to pregnancy-induced hypertension and delivered a healthy baby. **Case 3:** A 31-year-old G2P1 presented at 13 weeks gestation. She denied flank pain; her blood pressure and kidney function were normal. Abdomen and pelvis CT scan showed dilated left gonadal vein consistent with left renal vein compression suggestive of NS. With conservative management, she had an uncomplicated pregnancy and delivered a healthy baby.



Discussion: Experienced specialists, maternal-fetal obstetrics working with nephrologist should care for these patients with intensified surveillance, appropriate treatment plans and mode of delivery to avoid dangerous and preventable clinical consequences, as these renal diseases may affect pregnancy outcome.

PUB390

Carfilzomib-Induced Thrombotic Microangiopathy after Drug Re-Exposure Leading to Acute Renal Failure Emily Lu,[1] Sunil Rangarajan,[2] Steven Salvatore,[1] Sheron Latcha.[3] *[1]Weill Cornell Medicine/New York-Presbyterian Hospital; [2]Univ of Alabama at Birmingham; [3]Memorial Sloan Kettering Cancer Center.*

Introduction: Drug-induced thrombotic microangiopathy (DITMA) has been reported with the 1st generation proteasome inhibitor (PI) bortezomib. There are only a few reported cases of DITMA following treatment with the 2nd generation PI carfilzomib. This is the first report of a case of renal TMA following re-exposure to carfilzomib previously used as maintenance therapy in a patient with Multiple Myeloma (MM).

Case Description: A 56 year old male with MM which was previously treated with bortezomib and carfilzomib underwent autologous stem cell transplant (ASCT) with carfilzomib conditioning. While in serologic partial remission, he received carfilzomib maintenance therapy. One week later, he presented with fever, non-bloody diarrhea, and anuric acute renal failure unresponsive to aggressive volume repletion. Influenza A serology was positive. Vital signs and exam were notable for persistent hypertension and edema. Initial labs showed: Serum creatinine 15mg/dL (0.9 mg/dl one week prior), blood urea nitrogen 115mg/dL, anion gap 17, lactic acid 1.6mmol/L, hemoglobin 8g/dL (baseline 11-12g/dL), platelet 90,000/uL (baseline 300,000/uL); with normal values for C3, C4, ANCAs (MPO, PR3), SPEP/UPEP, hepatitis B and C panels, ADAMTS13, and an atypical HUS panel. Lactate dehydrogenase was >1800 IU/L, haptoglobin 75mg/dL, and the peripheral smear showed 3+ schistocytes. Further workup for infections was negative. Renal ultrasound showed no hydronephrosis. Hemodialysis was started and a renal biopsy was performed. Pathology showed 41 glomeruli, severe acute TMA involving glomeruli and small vessels, global glomerulosclerosis (5 of 41 glomeruli), with no glomerular crescents or immune complex deposits.

Discussion: This is the first case report of biopsy proven TMA from carfilzomib used in a patient who was previously treated with carfilzomib. The patient may have been sensitized to TMA from prior exposure to the drug or from the ASCT.

PUB391

C3 Glomerulopathy with Atypical Hemolytic Uremic Syndrome Misdiagnosed as Primary Membranoproliferative Glomerulonephritis and Malignant Hypertension Robert Schoepe, Keith R. Superdock. *Lankenau Medical Center, Wynnewood, PA.*

Introduction: Atypical hemolytic uremic syndrome (aHUS) is caused by dysregulation of the complement system. A genetic defect causes uninhibited activation of the alternative pathway causing thrombotic microangiopathic hemolytic anemia (MAHA) and renal disease. A treatment now exists for aHUS in eculizumab, a monoclonal antibody for C5, a key in complement activation.

Case Description: Ms. S is a 25 year old who presented three years prior with uncontrolled hypertension, severe anemia, renal failure of unknown duration, and nephrotic-range proteinuria. A biopsy revealed membranoproliferative glomerulonephritis (MPGN) in late crescentic stage with severe intrarenal arteriosclerosis. Immunofluorescence showed widespread C3, some C1Q, kappa and lamda chains along the glomerular basement membrane (GBM) and 4+ IgM along the GBM and in the mesangium. It was determined to be "probably type I MPGN", with immunofluorescence not completely typical of a primary MPGN. Work up revealed a low C3 level and a normal C4 level. She was determined to have end stage renal disease (ESRD) and started on hemodialysis. Her course was complicated by persistent anemia and eight admissions for hypertensive emergencies. Review of her records for renal transplantation evaluation revealed low platelet and haptoglobin levels and elevated LDH levels. She again had a low C3 level and a normal C4 level. Her initial biopsy was then re-evaluated revealing dense deposit disease, a C3 glomerulopathy, consistent with aHUS. She was started on eculizumab and has since only had one admission for hypertensive emergency and her hemoglobin, platelet, LDH, and haptoglobin levels have improved.

Discussion: She was misdiagnosed as primary MPGN despite evidence of MAHA attributed to malignant hypertension. No further investigation of her disease process

occurred given the irreversible ESRD. She had systemic manifestations of her disease for years and would have had recurrence in a transplanted allograft. Patients who present with advanced renal disease due to glomerulonephritis and malignant hypertension with MAHA should be evaluated for aHUS as treatment can manage systemic manifestations and prevent recurrence in allografts.

PUB392

Anti-Neutrophil Cytoplasmic Antibody Negative Granulomatosis with Polyangiitis Associated with Crescentic IgA Nephropathy - A Clinical Conundrum Shirin Sharma, Eric J. Bloom, Rasib Raja. *Nephrology, Einstein Medical Center, Philadelphia, PA.*

Introduction: GPA could present as ANCA negative in 40%of the patients. Chen et al reported 32.9% patients who were ANCA negative had fewer extrarenal symptoms than patients who tested positive.Interestingly,there have been several case reports of ANCA vasculitis associated with crescentic IgAN.Since the majority of the patients were ANCA positive,not much is known about the treatment of ANCA negative GPA with Crescentic IgAN.

Case Description: We present the case of a 52 year old gentleman who presented with palpable purpura,epistaxis,polyarthritis,hematuria,proteinuria and chronic sinusitis. A left thigh punch biopsy showed intense perivascular and interstitial infiltrate and leukocytoclasis. He tested negative for hepatitis,ANA,MPO and PR3. He was started on MTX and Prednisone 60 mg daily.CT chest was negative for granulomas.Subsequently,the patient developed right foot drop secondary to mononeuritis multiplex and digital ischemia of bilateral fourth toes,hearing loss and blurry vision. Given the progression of his symptoms he was switched to Rituximab 850 mg every 4 weeks.A kidney biopsy was done given the hematuria and proteinuria which was consistent with IgA nephropathy (MEST score 0).His S.Cr remained normal for 1 year and the U Pr/Cr improved.However the patient stopped MTX on his own.His S.Cr increased to 1.32 and proteinuria worsened. A repeat kidney biopsy showed advanced IgA nepropathy with crescents(M2E1S0T1). Repeat ANCA testing was negative. He was started on pulse steroids and IV Cyclophosphamide and now his S.Cr is 1.37 mg/dL with persistent proteinuria.

Discussion: Due to lack of prospective clinical trials for ANCA negative vasculitis, the treatment is tailored to the patients clinical response and the side effect profile. Rituximab appears to effective for ANCA negative GPA,but steroids and cyclophosphamide have been shown to be more beneficial for Crescentic IgAN.(5yr renal survival 28%).The association between ANCA negative GPA and crescentic IgAN is rare and the interest in an adequate treatment strategy remains high.

PUB393

ANCA Associated Cescentic Glomerulonephritis in a HIV Positive Patient with Disseminated Kaposi Sarcoma Tanu Duggal,[1] Manoj Das,[1] Nilang G. Patel,[2] Pradeep Arora.[2] *[1]Medicine, VCU, Richmond, VA; [2]Medicine, VAMC, Richmond, VA.*

Introduction: A 53 year old male was admitted with serum creatinine of 5.6 mg/dl. He had HIV infection since 1997 **accepting HAART therapy sporadically**, hypertension, drug abuse and hepatitis C Physical examination revealed: T 101 °F, BP 130/80 mmHg, and 1+ lower extremity edema. Laboratory data included: UA with 30 mg/dl protein, 20 RBCs and 30 WBCs; 24 hour urine protein excretion of 6.4 g; HIV PCR viral load of 7400; CD4 count of 300; normal C3 and C4, P-ANCA positive at 1:640. Biopsy of the tongue and a lesion on the shoulder revealed Kaposi tumor. Kidney biopsy showed crescentic glomerulonephritis. Patient was treated with HD + steroid + plasmapheresis without improving kidney function. After re-initiating HARRT therapy, his creatinine improved to his baseline and remained stable for the next 4 years.

Discussion: HSP, PAN, AAV have been reported with HIV. To best of our knowledge this is first case of biopsy proven AAV related to HIV who recovered with HAART therapy.

Presentation + labs	Kidney Biopsy	Management	Outcome
56 Y M, Microscopic hematuria, CR 0.8 mg/dl, skin biopsy - HSP	-	HAART	R
38 Y M - Skin + Joint, M/E Hematuria, Skin Biopsy HSP	-	HAART	R
51 F, Joint + Ocular, Anti MPO +, Cr 2.4 mg/dl	AASV	S + Rituxamab	R
46 F, Skin, ANCA + , Cr 4.7 mg/dl	AASV	S+ HAART	I
60 M, Skin + abdominal, M/E hematuria, Skin Biopsy HSP	-	S+ HAART + D + P	Death
25 M AKI, hemoptysis, Diffuse alveolar haem, ANCA +	AASV	CYC + S + P + HAART	I
35 M Skin + abdominal, Proteinuria 12 Gm, Cr 2 mg/dl, ANCA +	HSP	CYC + HAART	I
33M Skin + Joint, RBC cast	-	HARRT	I
26 Y male, Skin, Nephrotic , M/E Hematuria, HSP	HSP	S + P + HARRT	I
29 M, Muscular, serum Creatinine 1.7 mg/dl, RBC +	Polyarteritis nodosa	S + zidovudine	Death
54 M, M/E hematuria, CR 2.5 mg/dl	Pauci immune Vasculitis	D	Death

S=Steroid, P=Plasmapheresis, D=Dialysis, AASV= ANCA Associated Systemic Vasculitis, CYC=Cyclophosphamide, HSP= Henoch-schonlein purpura, R=Remission, I=Improved

PUB394

TMA in the Setting of CMV Reactivation Jordan Gabriela Nestor, Hilda E. Fernandez. *Dept of Medicine, Div of Nephrology, Columbia Univ Medical Center, New York, NY.*

Introduction: Renal disease due to abnormalities in the complement alternative pathway (AP) includes C3 glomerulopathies and atypical HUS. AP disorders result from loss of surface or fluid-phase complement control caused by acquired or genetic defects. TMA diagnosis is often clinically challenging in the setting of multi-organ involvement.

Case Description: 30yo AA F p/w 3/5 strength all extremities. Admitted w/ initial labs notable for Cr 1.0 mg/dL, CPK 22000 iU/L, LDH 2500 IU/L, +SMA Ab, and muscle biopsy c/w necrotizing myopathy. Treated with 7 day steroid pulse w/o improvement. On HD#17, had two witnessed GTCs on HD#17. CT head w/ hypodensities c/f infarcts. MRI with multiple FLAIR hyperintensities. MRA/MRV unremarkable. ICU transfer on HD#19. CBC showed platelet count 49K/mL with repeat count of 6K/mL. Also had low haptoglobin, normal coagulation factors/fibrinogen, elevated bilirubin, transaminitis, and schistocytes on peripheral smear in setting of rising creatinine. SLE/APLS Abs were negative. PLEX initiated HD#19 due to c/f TTP. ADAMTS13 prior to PLEX was 41% (low normal), GI PCR panel negative for STEC. LP bland. Concern for Macrophage Activating Syndrome, started anakinra for elevated ferritin/CRP. BM Bx w/o evidence of malignancy. Developed anuric AKI, initiated CRRT. New CMV viremia HD#23 detected (6K copies/mL), initiated ganciclovir for CMV reactivation. aHUS genetic panel sent to lab. Platelets improved on PLEX. Renal biopsy HD#36 c/w thrombotic microangiopathy . Held Anakinra, received 1st dose of eculizumab on HD#38. HD#60, platelets remain stable, LDH improved, though mental status and renal function have not yet recovered.

Discussion: A genetic susceptibility to de novo TMA in patients with complement gene abnormalities may have played a role in this case, where an initial insult by ischemia–reperfusion enhanced by viral infections, immunosuppressive drugs, or dysregulated complement activation resulted in TMA. Reactivation CMV viremia following pulse steroids may have served as the trigger of TMA.

PUB395

Cardiac Arrest as a Consequence of Tenofovir Induced Hypokalemia Abhilash Koratala, Volodymyr Chornyy, S. Irfan Qadri, Rupam Ruchi. *Nephrology, Hypertension & Renal Transplantation, Univ of Florida.*

Introduction: Tenofovir is a nucleotide reverse transcriptase inhibitor used for the treatment of HIV infection and is a key component of the commonly used anti-retroviral drug, Truvada®. Tenofovir induced proximal tubulopathy and dyselectrolytemia with or without Fanconi syndrome has been documented in the literature. We report a case of severe hypokalemia and renal tubular acidosis (RTA) that lead to cardiac arrest in a HIV patient.

Case Description: 59 year old Caucasian female presented to our institution for weakness, failure to thrive and hypokalemia. She has history of HIV for ~8 years, well controlled on tenofovir containing HAART. 4 months prior to presentation, she suffered a sudden cardiac arrest after a diarrheal episode and required ICU stay at an outside facility where she was told that her serum potassium at admission was 'close to zero'. Cardiac catheterization did not reveal any ischemic etiology. She was discharged with oral potassium supplementation 40mEq twice a day. However, she was feeling sick with weakness, nausea, intermittent vomiting & weight loss and thus came to us. At presentation, her serum potassium was 2.5 mmol/L, magnesium 1.9 mg/dL, phosphate 1.6 mg/dL and bicarbonate 13 mmol/L with anion gap of 14. Her renal function was preserved and had mild proteinuria of ~0.5 g/g. Initial work up was negative for malignancy. We noted that she had glycosuria with normal serum glucose and had a potassium-creatinine ratio of 250 mmol/g and fractional excretion of phosphate 65%. We diagnosed her with Tenofovir induced proximal RTA with Fanconi syndrome.Her HAART was changed to non-tenofovir based regimen and at 1 month follow up, her serum potassium was stable at 3.8 mmol/L on 40mEq/day oral potassium supplementation.

Discussion: Patients on Tenofovir therapy are prone to developing severe hypokalemia in the setting of RTA especially when combined with gastro-intestinal losses and/or poor eating. These patients should be frequently monitored with urinalysis and renal function panel while on therapy. Raising the awareness among clinicians with regard to this potential side effect is vital for early intervention and prevention of life-threatening complications.

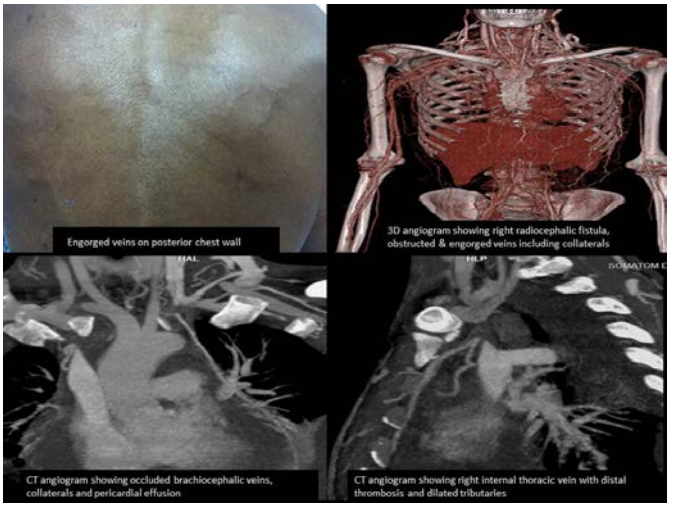
PUB396

Cardiac Tamponade in a Hemodialysis Patient: Delayed Complication of Central Venous Catheter Insertion Boju Sangeetha Lakshmi,[1] Hari Krishna Reddy Mogili,[1] Anil Kumar Cheni Venkata,[1] R. Ram,[1] V. Siva Kumar,[1] Abhilash Koratala.[2] *[1]Sri Venkateswara Inst of Medical Sciences, India; [2]Univ of Florida.*

Introduction: Case reports of pericardial tamponade after a central venous catheter insertion exist in the pediatric literature but generally due to direct mechanical trauma. Tamponade caused by Superior vena cava (SVC) obstruction has been documented in adult oncology patients from tumor compression or infiltration of SVC. We report a case of pericardial effusion (PEF) as a delayed complication of Internal Jugular (IJ) hemodialysis (HD) catheter insertion due to SVC obstruction and impairment of pericardial fluid drainage.

Case Description: A 41 y.o. Asian-Indian male with ESRD secondary to chronic glomerulonephritis, on HD for 7 years presented to our institution with progressive shortness of breath for a month. He has history of secondary failure of multiple AV fistulas in the past. Both IJ veins were cannulated twice each as a temporary access whenever an AVF had failed and catheter retained for ~ 8 weeks. Exam showed facial edema with engorged veins on the neck and chest. Pulsus paradoxus was noted and imaging revealed massive PEF with

tamponade. Pericardiocentesis was done with drainage of ~6L serous fluid and analysis was negative for infection or malignancy. His Kt/V was optimal and we dialyzed him daily for a week but he had recurrent PEF. CT showed thrombosis with total occlusion in left brachiocephalic vein, distal right brachiocephalic vein and proximal SVC with extension into distal part of bilateral internal thoracic veins. Collaterals were noted in abdominal and chest wall as shown in the CT angiogram.



He ultimately required pericardiectomy for management of recurrent PEF.

Discussion: Serious complications of SVC stenosis associated with CVC use is an under-recognized problem and should be considered HD patients with persistent or recurrent unexplained shortness of breath.

PUB397

A Case of Hyponatremia Associated with SGLT-2 inhibitor Empagliflozin

Lauren Paster,[1] Khurram Mehtabdin,[1] Kenar D. Jhaveri,[1] Alyson Myers,[2] Richard L. Barnett.[1] *[1]Div of Kidney Disease and Hypertension, Northwell Health, Great Neck, NY; [2]Div of Endocrinology, Northwell Health, Great Neck, NY.*

Introduction: Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are increasingly used to treat type 2 diabetes mellitus (T2DM). Volume depletion alone or with diuretics has been noted but hyponatremia has not been reported with these agents. We describe the first case of symptomatic hypovolemic hyponatremia in a patient treated with empagliflozin and hydrochlorothiazide (HCTZ).

Case Description: A 69 year old Caucasian female with history of T2DM and hypertension presented with dizziness. She had been initiated on empagliflozin 9 days prior, in addition to 6 month continuous use of HCTZ-lisinopril, diltiazem, atenolol and atorvastatin. At that time she was counseled to augment water intake to reduce risk of urinary tract infections. Labs from one month prior to empagliflozin initiation included Cr 1.3 mg/dL and Na 134 mmol/L. Physical exam was notable for orthostatic changes but negative for edema, confusion or seizure-like activity. Admission bloodwork included Na 112 mmol/L, Cr 1.7 mg/dL and glucose 207 mg/dL. Urine studies included: Na 27, Cl 24, K 20, Cr 58, glucose >1000 (all in mg/dL) and osmolality 261. Cortisol and thyroid studies were normal. Empagliflozin was held, along with HCTZ-lisinopril, diltiazem and atenolol. Sodium increased to 115 within the first 24 hours and further rose to 125 by the following day with the addition of 1.5% saline. After discontinuation of hypertonic saline, Na rose to 133 over the next 48 hours. Serum Cr, which had peaked at 2.22 declined to 1.4 1 week post-discharge. Throughout her hospitalization $U_{Na}>U_{Cl}$, FeCl < 1%, $U_{osm}>250$ and persistent glycosuria were noted, consistent with prolonged empagliflozin +/- HCTZ effect.

Discussion: A literature search revealed no associations between SGLT-2 inhibitors and hyponatremia. Adding empagliflozin to a patient on HCTZ who was advised to increase free water intake promoted her symptomatic hypovolemic hyponatremia. Given the increasing utility of SGLT-2 inhibitors in patients with T2DM and hypertension, caution should be used when combining these agents with thiazide diuretics.

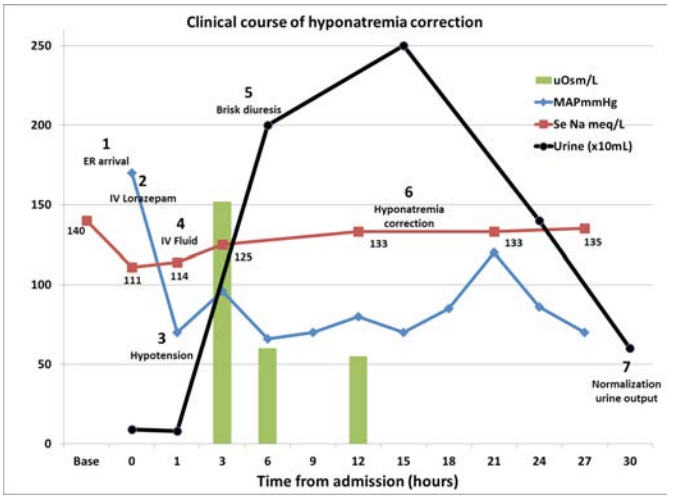
PUB398

Renal Response to Acute Hyponatremia during Alcohol Withdrawal

Vikrampal Bhatti, Volodymyr Chornyy, Kawther Farouk Alquadan, A. Ahsan Ejaz, Abhilash Koratala. *Nephrology, Hypertension and Renal Transplantation, Univ of Florida.*

Introduction: We present this case of hyponatremia to illustrate the renal physiology of sodium and water balance. Clinical presentation and laboratory data are depicted in the form of a graph.

Case Description: A 56 year old female with history of alcohol abuse and binge drinking 1) presented with agitation, tremors, mouth dryness and signs of alcohol withdrawal after abstinence for several days. No nausea, vomiting or pain. On exam, BP was 230/140mmHg with heart rate 120bpm, respiratory rate 22pm, chest clear to auscultation, abdomen non-tender, no organomegaly, no lower extremity edema, non-focal neurologic exam. Routine chemistries including alcohol level and drug screen ordered. 2) Given intra venous Lorazepam and agitation improved. 3) 1hour later, there was a precipitous drop in BP. Serum sodium at admission was 111meq/L. Baseline serum sodium was 140meq/L documented at clinic visit 2 weeks prior to ER visit. 4) 1 liter Normal saline bolus administration, additional Half liter Normal saline. 5) Brisk urine output noted. 6) Serial serum sodium with upward trend. Patient more coherent, intact neurological exam. Urine osmolar changes shown. 7) Urine volume decreased with improved serum sodium. Oral rehydration allowed. Patient discharged to rehabilitation facility after 72 hours with normal neurological, medical and laboratory status.



Discussion: Hyponatremia is a commonly encountered problem and treatment varies with the nature of onset - acute or chronic, severity and symptoms. In the above case of hypovolemic hyponatremia, intravascular volume repletion reduced ADH secretion (decreased UOsm) and the kidneys responded by producing dilute urine (brisk diuresis), excreting free water and subsequent correction of hyponatremia.

PUB399

Dialysis Disequilibrium Syndrome with Mild Azotemia due to Septic Encephalopathy

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Introduction: Dialysis Disequilibrium Syndrome (DDS) was initially described as a constellation of neurological symptoms of cerebral edema, occurring early during the first dialysis in patients with high BUN. We present a patient who continues to have DDS at low levels of BUN, two years after an episode of severe sepsis.

Case Description: A 24 year old woman presented in septic shock from Group A streptococci, two days after a vaginal delivery. She had DIC with distal gangrene in all four extremities. She also had AKI and has remained dialysis-dependent two years later. Since discharge, she has had persistent memory deficits, and periodic headache and vomiting. These symptoms worsen after 2 hours on dialysis. Pre and post-dialysis CT scans showed cerebral edema on the post-dialysis scan only. MRI of brain showed diffuse cerebral edema with bifrontal predminance. Lab tests done pre and post-dialysis showed changes in osmolality 291 to 289, BUN 17 to 9, CO2 29 to 31 and ADH 2 to 13. There were no signs of volume overload or orthostasis. Symptoms improved with reduction of dialysis time to 2 hrs on a small dialyzer without ultrafiltration, using 145 Na and 35 HCO3 concentration in the dialysate.

Discussion: DDS was first described in 1962, occurring early during first dialysis in patients with high BUN. Animal studies demonstrated that the major mechanism of DDS was the rapid lowering of blood urea by dialysis. Slower diffusion of urea from brain to blood created an osmotic gradient that induced movement of water from the blood to the brain. Classic DDS has now become uncommon, perhaps due to the wide-spread recognition of DDS and the earlier start of dialysis. Recent reports describe DDS occurring without high levels of BUN suggesting that additional mechanisms may be involved. In our patient, a severe episode of systemic sepsis has left her with a propensity for recurrent cerebral edema late in dialysis. We speculate that septic encephalopathy has caused persistent changes in the blood-brain/brain-CSF barriers or in neuronal transporters that make her more susceptible to DDS even with small osmotic shifts at low level azotemia. Disclaimer: None

Funding: VA Support, Clinical Revenue Support

PUB400

Late-Onset Warfarin-Induced Skin Necrosis Suspected to Be Calciphylaxis in a Patient with End-Stage Renal Disease on Hemodialysis Emily Lu,[1] Joanna Harp,[2] Jeffrey I. Silberzweig.[1] *[1]Nephrology & Hypertension, Weill Cornell Medicine/New York Presbyterian Hospital (WC/NYPH), New York, NY; [2]Dermatology, WC/NYPH.*

Introduction: Warfarin-Induced Skin Necrosis (WISN) is a rare complication almost always occurring <10 days after warfarin initiation; "late-onset WISN" develops beyond this time. It is characterized by cutaneous purpuric, necrotic lesions requiring prompt diagnosis and treatment due to high morbidity/mortality. We present a case of cutaneous purpura and necrosis in end-stage renal disease (ESRD) initially attributed to calciphylaxis.

Case Description: A 58-year-old woman with ESRD on hemodialysis (HD), peripheral vascular disease, and deep vein thromboses on chronic warfarin presented with extensive lower extremity cutaneous purpuric, necrotic lesions. She had calcium 8.9mg/dL, albumin 1.8g/dL, phosphorous 3.4mg/dL (8.5 in the past year); intact parathyroid hormone 99 pg/mL (1000 in the past year). Her INR was 4.0 but labile. Leg X-ray showed marked vascular calcification. Hypercoaguable workup (this admission and one year ago) was unrevealing; Proteins C and S (from warfarin use) and Factor X activity were decreased; but Factor V Leiden, Prothrombin gene mutation, Antithrombin III mutation, Cardiolipin IgG/IgA/IgM antibodies, Homocysteine, complement levels C3 and C4, cryoglobulins, SPEP and HIT antibody were negative/normal. A full APLS workup could not be performed due to warfarin use. Platelet count was normal. Infectious studies were negative. Based on these findings, her skin lesions were initially attributed to calciphylaxis. Two subsequent skin biopsies demonstrated pauci-inflammatory thrombogenic vasculopathy with no vascular calcium deposition (negative Von Kossa stain), suggesting a thrombotic or procoagulant etiology and effectively ruling out calciphylaxis. Given the dramatic presentation of skin lesions, labile INR, and exclusion of other compatible etiologies, we diagnosed late-onset WISN. The skin biopsy findings were pivotal in directing our treatment and led to improvement of skin lesions.

Discussion: This case highlights the diagnostic challenges and importance of skin biopsy in establishing the diagnosis of WISN, particularly in ESRD patients when calciphylaxis is suspected.

PUB401

Idiopathic Tubulointerstitial Nephritis and Uveitis Joana Gameiro, Sofia C.A. Jorge, Joana M. Dias, Jose António Lopes, António Gomes da Costa. *Service of Nephrology and Renal Transplantation, Centro Hospitalar Lisboa Norte, EPE, Lisbon, Portugal.*

Introduction: NIA is an uncommon cause of acute kidney injury, mostly related to infections, drugs or systemic diseases.

Case Description: We report the case of a an eighteen years old caucasian female who presented with vomiting, nausea, fever, weight loss and impaired renal function. She had neither urinary symptoms nor rash, arthralgias or recent infection. She took no regular medication and there was no prior use of antibiotics or non-steroidal agents. Physical examination was normal. Laboratory revealed hemoglobin 9 g/dL, creatininemia 2.9mg/dL and uremia 66mg/dL. Liver function tests and ionogram were normal. Urine examination revealed 24h-proteinuria 400mg and no eosinophiluria. Urine culture was sterile. Renal ultrasound was normal. Immunologic study was negative for antinuclear antibody, anti-neutrophil cytoplasmic antibody against myeloperoxidase and proteinase 3, anticardiolipin antibody, lupic anticoagulant antibody and anti-beta 2-glycoprotein antibody; TASO, rheumatoid factor and IGRA were negative. Serologic study was negative for HIV, HBV, HCV, Adenovirus, Parvovirus, Coxsackie, EBV, CMV, Herpes virus, Salmonella, brucella, borrelia burgdoferi, leptospira interrogans, Togavirus, coxiella burnetii, Legionella, Mycoplasma pneumoniae, Chlamydia pneumoniae and trachomatis. ACE levels and body CT scan were normal. A kidney biopsy was performed and revealed acute interstitial nephritis, with edema and inflammatory cell infiltration with multiple eosinophils. One-week later she was diagnosed with anterior uveitis. The diagnosis of idiopathic tubulointerstitial nephritis and uveitis (TINU syndrome) was then made and she started prednisolone 1mg/kg/day, tapered over 14 weeks, with complete renal function and ocular manifestations recovery.

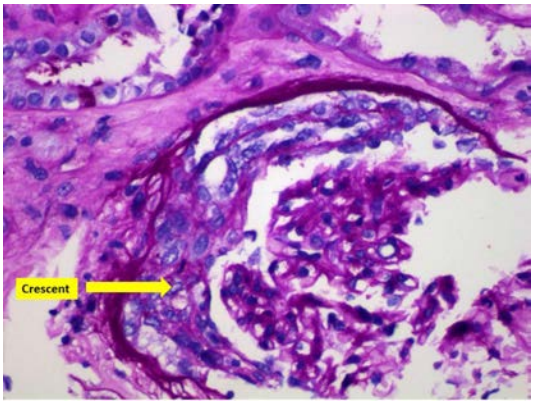
Discussion: TINU diagnosis can be especially difficult in some cases because manifestations may not occur at the same time as illustrated in this case. Still, TINU syndrome should be considered in the differential diagnosis of renal-ocular syndrome. The renal prognosis is excellent and nephritis is often self-limited. Symptoms respond well to corticosteroids, but uveitis often relapses even after a long term follow-up.

PUB402

MPO-C-ANCA-Associated Necrotizing and Crescentic Glomerulonephritis Abhilash Koratala, Dara N. Wakefield, Kawther Farouk Alquadan, A. Ahsan Ejaz. *Univ of Florida.*

Introduction: MPO and PR-3 are the major autoantigens in ANCA-associated vasculitis (AAV). 90% of patients with AAV have either MPO-(P)ANCA or PR-3-(C)ANCA. Generally, antibodies causing cytoplasmic (C) ANCA pattern are directed against PR-3 while those causing perinuclear (P) ANCA are directed against MPO. We present a case of necrotizing and crescentic glomerulonephritis where antibodies against MPO produced a cytoplasmic pattern.

Case Description: 73 y.o. white male, former smoker was admitted with progressive flu-like symptoms and SOB attributed to multifocal pneumonia and pulmonary fibrosis. He was started on antibiotics. Later, he developed ARDS needing mechanical ventilation with FiO2 55-60%. Bronchoscopy showed diffuse alveolar hemorrhage. C-ANCA and MPO positive, but PR-3 negative. Clinical course was complicated by hypotension and SCr worsened from 0.8mg/dL to 2.35mg/dL. However urine output remained at 2-2.7L/day. Renal US revealed 13.5cm right and 12.7cm left kidney. UA: 288 RBC/hpf, 2 WBC/hpf, 1 coarse granular cast and 1 RBC cast. Renal biopsy showed necrotizing and crescentic glomerulonephritis with 50% glomerular involvement with necrosis and/or crescents and arterial and arteriolar nephrosclerosis. IF was nonspecific. Treated with IV methylprednisolone, Cyclophosphamide and Plasma exchange. SCr improved to 1.58mg/dL and he was discharged. He did not require dialysis during hospital stay.



Discussion: False positive MPO-C-ANCA can occur in autoimmune entities whereby antibodies to epitopes on MPO can produce cytoplasmic pattern. Regardless of the staining pattern, it may be the induction of MPO (e.g., propylthiouracil) or anti-MPO antibodies that result in the necrotizing glomerulonephritis as illustrated above. Underlying lung disease, suspected recent flu and other environmental factors are also contributing stimuli for the development of MPO-antibodies. Our case supports the pathogenic role of MPO in AAV.

PUB403

An Obscure Cause of Recurrent Hyperphosphatemia Shameem Ahmad Beigh, David Levy, Sai Subhodhini Reddy. *Nephrology Div, Univ of Rochester Medical Center, Rochester, NY.*

Introduction: Dialysis patients often struggle with multiple dietary constraints imposed on them due to renal failure. Phosphate restriction is commonly stressed due to the known increased risk of mortality of patients with higher serum phosphate levels. The combination of a limited phosphate diet, prescription medication and residual renal function often limit the prevalence of significant hyperphosphatemia among peritoneal dialysis patients. We however, will present a case of a patient with recurrent hyperphosphatemia secondary to drinking water which was refractory to medical therapy.

Case Description: HS is a 51 year old male with ADPKD complicated by ESRD and started on peritoneal dialysis (CCPD, dwell volume of 2L, 4 exchanges with 1.5% glucose solution and manual day exchange with 2.5 L of 2.5% glucose) in November 2014. Since September 2014 he was noted to have high levels of serum phosphate which was initially treated with Sevelamer 2400mg three times daily with meals. In spite of this his serum phosphorous remained high (6.6-7.8 mg/dl) and Sevelamer 800mg with snacks was added. In January 2016 his serum phosphate was noted to be 7.5mg/dl and his Kt/V was 2.33. Velphoro 1000mg with meals was started. In March 2016 he switched from tap water to bottled water and his serum phosphate improved to 4.9 mg/dl. Further investigation was done by the patient and it was determined that phosphorous was being added to the water supply to prevent pipe corrosion.

Date	9/14/15	10/12/15	11/9/15	1/18/16	3/9/16	4/5/16
Serum calcium (mg/dl)	8.8	9.0	8.8	8.6	8.2	8.2
Serum Phosphorus (mg/dl)	6.6	7.8	7.2	7.5	5.8	4.9
PTH (pg/ml)	N/A	N/A	N/A	N/A	N/A	458
Current medications	Sevelamer 2400 mg	Sevelamer 2400 mg	Sevelamer 2400 mg and 800 mg with snacks	Sevelamer 2400 mg and 800 mg with snacks	Velphoro 1000mg	Velphoro 1000mg
Changes	None	Sevelamer 800 mg with snacks added	None	Velphoro 1000 mg satrted, Sevelamer stopped	Changed to bottled water from tap water	None

Discussion: Our case demonstrates the importance of investigating all potential sources (including drinking water) of exogenous phosphate intake.

PUB404

A Case Report Describing Therapy for Acute Urate Nephropathy in Spontaneous Tumor Lysis Syndrome from Chronic Myelomonocytic Leukemia Justin A. Chen,[1] Inderpreet S. Sekhon.[2] *[1]Nephrology, Univ of California, Davis School of Medicine, Sacramento, CA; [2]Nephrology, Veterans Affairs Medical Center, Sacramento, CA.*

Introduction: Tumor lysis syndrome (TLS) with release of intracellular potassium, phosphate and nucleic acids, occurs in certain cancers after chemotherapy, but may occur spontaneously in cancers with a high proliferative rate or large tumor burden. One type of kidney injury from TLS is caused by uric acid crystal precipitation within renal tubules.

Case Description: An 84 year old man with chronic myelomonocytic leukemia was seen in the emergency room for abdominal pain. Serum creatinine (Cr) was 2.56 mg/dL (baseline 1-1.3 mg/dL). A non-contrast CT abdomen/pelvis revealed moderate right hydronephrosis and hydroureter from a 7 mm stone at the ureterovesicular junction and other non-obstructing calculi. He was discharged home with urology follow up, but was admitted to the hospital two weeks later after repeat labs showed a serum creatinine (Cr) of 4.9 mg/dL. On return to the hospital, physical exam revealed normal vital signs and dry mucous membranes. Other findings included hypokalemia (3.1 mmol/L), hyperphosphatemia (5.2 mg/dL), hyperuricemia (22.3 mg/dL), and leukocytosis (100.1 K/mm^3). Urinalysis (UA) detected small blood, pH 5, and uric acid crystals which were confirmed with microscopy. The patient was administered rasburicase, IV fluids (3 amps of sodium bicarbonate per liter of D5 0.45% normal saline at 150 cc/hour), and IV furosemide. Urine output was 3-4 L/day. Repeat UA on hospital day #3 was notable for absence of uric acid crystals and pH 7. Cr was 2.18 mg/dL at discharge on hospital day #6. Repeat CT abdomen/pelvis showed resolution of hydronephrosis and disappearance of uric acid stones.

Discussion: Acute urate nephropathy therapy includes IV fluids and loop diuretics as well as medications aimed at reducing the uric acid burden. Urinary alkalinization is generally not recommended due to concern for calcium phosphate crystal precipitation. Our case illustrates that administration of IV sodium bicarbonate and loop diuretics in select cases may be effective in the treatment of acute urate nephropathy without the untoward consequences of alkali therapy.

PUB405

Unsuspected Protein S Deficiency Caused Vascular Thrombosis and Loss of Pancreas and Kidney Grafts Despite Initial Excellent Function and No Rejection Sushanta K. Goswami,[1,2] Kai Lau.[1,2] *[1]Dept of Nephrology, Univ of Oklahoma, Oklahoma City, OK; [2]Medical Service, VA Medical Center, Oklahoma City, OK.*

Introduction: Thrombophilia poses risks for venous thromboembolism & arterial occlusion causing strokes & MI. It rarely induces thrombosis of allograft without rejection, sepsis, DIC, microangiopathy, proteinuria, protein C or S deficiency. We here report the loss of pancreas & kidney grafts 10 d post-op due to unrecognized protein S deficiency in a 34-year-old non-pregnant type 1 diabetic woman.

Case Description: We reviewed clinical & lab data for hypercoagulable risk factors to define the role of protein S. Both kidney & pancreas functioned well from d 1 to 7. Nadir serum creatinine was 0.9 mg% & glucose normal off insulin. On d 9, she was readmitted for severe pancreas graft pain.

Doppler showed venous occlusion, no arterial diastolic & tiny systolic flow, normal pancreas morphology & iliac vascular flow. Resected pancreas confirmed infarction & no rejection. Doppler showed no flow in renal arcuate, interlobar & interlobular vessels despite good central hilum flow. Renal biopsy showed no rejection. Systemic heparin failed to prevent renal vascular occlusion & relentless failure, forcing graft resection. Parts of her small bowel were resected for ischemia. Detailed thrombophilia workup yielded negative/normal results in: blood & urine cultures, liver function, hepatitis, HIV, CMV, EBV, factors II, V, VII, VIII, XI, AT3, DIC, protein C activity, homocysteine, Leiden genotype, lupus anticoagulant by IgG & IgM vs. cardiolipin & beta 2 glycoprotein-1. Dilute Russell Viper Venom Test was prolonged. It remained so in mixing & confirmation studies. Total protein S level was 78%, but free level (58%) & activity (63%) were low (normal 65-150%), indicating type 3 deficiency.

Discussion: 1.To our knowledge, she is the first reported case of diffuse vascular thrombosis due to protein S deficiency that caused infarction of pancreas & kidney grafts and parts of her bowel. 2. Our experience supports a role for pre-op thrombophilia screening to identify those at increased risks for vascular thrombosis & prophylactic heparin.

Funding: NIDDK Support, Private Foundation Support

PUB406

An Unusal Cause of Relapse of Pseudomonas Peritonitis in a Peritoneal Dialysis Patient Avantika Chenna, Pradeep Reddy Thodima, Eric J. Bloom. *Nephrology, Albert Einstein, Philadelphia.*

Introduction: Per ISPD, peritonitis due to gram negative organisms should be adequately covered by third generation cephalosporin or aminoglycosides and in sometimes floroquinolone. E. Goffin etal in a multicenter study said that oral ciprofloxacin provides satisfactory results in gram-negative infections similar to intraperitoneal ceftazidime or aminoglycosides. We present a case of a 52 yo african american female who is legally blind, with ESRD on PD now diagnosed with relapse of pseudomonas peritonitis. She was taking ciprofloxacin along with her phosphate binder resulting in decreased bioavailability of ciprofloxacin. This is the first case of its kind per our literature review.

Case Description: 52 year old female with h/o ESRD on PD for 4 years and recent pseudomonas peritonitis s/p cathter removal admitted for abdominal pain, nausea and vomiting. Physical exam positive for abdominal tenderness. Vital signs were stable except blood pressure of 190/100 mmHg. Her home medications include sevelamer 2400 mg TID with meals, ciprofloxacin 500 mg qd, lisinopril 20 mg qd, nifedipine 60 mg qd, colicalciferol 50,000 q weekly. During the previous admission 8 days ago, patient was treated with cefepime and PD cathter was removed on the third day of treatment due to persistent, leukocytosis and effluent culture positive for pseudomonas aeruginosa. She was discharged on oral ciprofloxacin to complete antibiotic treatment for duration of 2 weeks after clinical improvement based on sensitivity report.On repeat admission, patient was treated intravenous cefepime and also discharged on intravenous antibiotics because repeat cultures were now resistant to flouroquinolones.

Discussion: Sevelamer is a phosphate-binding cationic polymer that is devoid of calcium which leads to decrease in relative oral bioavailability of ciprofloxacin when administered together.Concomitant administration of these drugs may decrease clinical efficacy of the drug and promote bacterial resistance to ciprofloxacin. It is very important to instruct CKD patients on sevelamer to take ciprofloxacin 2 hrs before or 6 hrs after sevelamer ingestion to avoid decreased bioavailability and to prevent the emergence of bacterial resistance .

PUB407

Case Series Describing Use of Tapentadol for Pain Management in Patients on Chronic Hemodialysis Nicole M. Wegrzyn, Jacqueline Helen Pratt, Mena Milad Raouf, Katie E. Cardone. *Dept of Pharmacy Practice, Albany College of Pharmacy, Albany, NY.*

Introduction: Approximately 50% of patients receiving hemodialysis report musculoskeletal and/or neuropathic pain types. Of those patients, 75% of hemodialysis (HD) patient report that their pain management was inadequate. Limited medication options exist for safe and effective pain management in End Stage Renal Disease (ESRD). Tapentadol is a mu-opioid agonist and also blocks reuptake of norepinephrine, the latter of which is particularly useful for the treatment of neuropathic pain. . Tapentadol is primarily metabolized via Phase 2 glucuronidation to tapentadol-O-glucuronide, which is renally excreted. Neither tapentadol-O-glucuronide nor other metabolites of tapentadol have been found to bind to opioid receptors or any other screened receptor or enzyme. Concerns of tapentadol-O-glucuronide accumulation limit the drug's use in patients on HD. Demonstration of significant HD removal of this major metabolite could justify the use of tapentadol for pain management in patients on dialysis.

Case Description: The main objective of this case series is to describe dialysis clearance of tapentadol and its primary metabolite, tapentadol-O-glucuronide, in patients on high-flux HD who are currently using tapentadol for chronic pain management. This preliminary study will justify the need for a more comprehensive pharmacokinetic study to help elucidate the safety of tapentadol in chronic HD. The study inclusion criteria are as follows: age $\geq$ 18 years, chronic hemodialysis prescription, and active tapentadol therapy. Each subject will provide four 5 mL blood samples for analysis at pre-determined time intervals. Blood samples will be collected and analyzed for concentrations of tapentadol, tapentadol glucuronide, tapentadol-O-sulfate, and N-desmethyltapentadol. Descriptive data analysis will be reported in addition to calculation of tapentadol clearance, metabolite clearance, intradialytic clearance and interdialytic clearance.

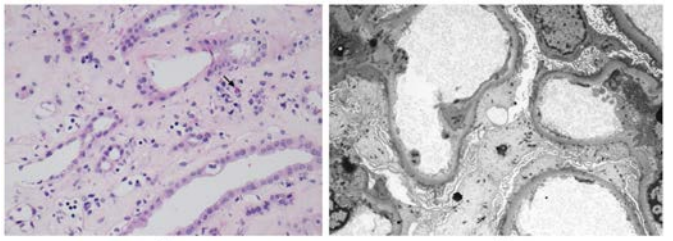
Discussion: This study will provide meaningful data regarding the pharmacokinetic profile of tapentadol and tapentadol metabolites in patients receiving chronic hemodialysis.

PUB408

NSAID Induced AIN and Minimal Change Disease with Complete Resolution George C. Bonifant, Purva D. Sharma, Ira S. Meisels. *Nephrology, Icahn School of Medicine at Mount Sinai and Mount Sinai St. Luke's Hospital, New York, NY.*

Introduction: NSAID use has been linked to Allergic Interstitial Nephritis and Nephrotic Syndrome. We report a case of AIN and Minimal Change Disease (MCD) in a patient with heavy exposure to NSAIDs who was dialysis dependent for a month before full recovery.

Case Description: 77 year old obese female with hypertension came in with cough, tachypnea and edema for 3 days. Reported use of naproxen (500 mg 1-2/day for 6 weeks) for chronic back pain. BP was 146/77, RR 16 and O2 saturation 96% on room air in the ER. Physical exam notable for wheezing with 3+ dependent edema. Labs revealed creatinine 10.47 mg/dL (1.2 ten months prior), CBC 32% Eosinophils, U/A 4+ Protein, MPO, PR3 and anti-GBM negative, Complements normal, polyclonal SPEP, +ve urine eosinophils. Urine Microscopy showed non-dysmorphic RBC's, fine granular casts and no cellular casts. UACR was 7020 mg/g. Initiated on dialysis hospital day 3 for oliguria. Biopsy revealed glomerulosclerosis of 7/17 glomeruli, moderate IFTA, hypersensitivity-type AIN and moderate Arteriosclerosis. EM showed diffuse podocytopathy consistent with MCD. Immunofluorescence was negative. Received Prednisone for 8 days, but chances of recovery were low due to IFTA so steroids were held on discharge. Continued on outpatient dialysis for 3 weeks. Urine output improved in week 4 with repeat creatinine 1.2 mg/dL, so dialysis was held. Last creatinine 1.0 mg/dL with protein-100 on U/A and bland urine sediment.



Renal biopsy during AKI. (a) Hematoxylin and eosin staining showing diffuse edema and focal interstitial inflammation including eosinophils involving the medulla (magnification x200). (b) Electromicroscopy showing diffuse effacement of foot processes with microvillous transformation of podocytes (magnification x1500).

Discussion: Our case shows important features of NSAID induced AIN and nephrotic syndrome. She presented with classic features of drug induced AIN, typically absent in NSAID induced AIN. There was complete recovery of renal function despite interstitial fibrosis. Lastly, complete recovery of kidney function occurred in 3 weeks with withdrawal of the drug without a substantial amount of steroid use.

PUB409

Calcium Kidney Stone Former with Hyponatremia Eman Mohammad Shaban, Jie Tang. *Nephrology, Univ Medicine, Brown Univ, Providecne, RI.*

Introduction: 45-year-old female presented with recurrent calcium phosphate kidney stone. Her past medical history was also significant for anxiety, depression, and hypothyroidism. She was on venlafaxine, alprazolam, buspirone, and synthroid. Her recent TSH was unremarkable. She felt well other than intermittent flank pain, and had been passing small stones once every 3-4 months with stable medullary nephrocalcinosis and stone burden per ultrasound. She underwent another lithotripsy for stone removal recently.

Case Description: Her physical examination was unremarkable. Her BMI was 26. Initial laboratory tests showed normal serum sodium at 137 meq/L, serum potassium at 4.5 meq/L, serum bicarbonate at 23 mg/dl with an anion gap of 10, and normal serum creatinine at 0.8 mg/dl. 24-hour urine showed a low volume at 0.93 liter, pH 7.4, and urine calcium at 100 mg. Her supersaturation of Calcium Oxalate and Brushite were both high (2.3, 3.4 respectively). She was instructed to increase her fluid intake targeting urine output of 2-2.5 liters/day, and restrict salt intake to maintain low urinary calcium excretion. Since then, patient followed the dietary instructions well with increased urine output. But at her 3-month follow-up, she complained of nonspecific weakness. She did not report any flank pain or new stone event. Repeat laboratory test showed acute hyponatremia with serum sodium down to 131 meq/L. The rest of basic metabolic panel were unremarkable, including a baseline serum creatinine and normal serum bicarbonate. Her repeat 24-hour urine showed a total volume of 2.97 liter which was significantly increased from her prior measurement, urine pH was 6.8, and urine calcium remained under control at 138 mg / day. Supersaturation of Calcium Oxalate and Brushite were normalized at 1.15 and 1.19 respectively. She was euvolemic by physical examination, and the rest of laboratory data were consistent with hyponatremia from SIADH.

Discussion: High fluid intake and salt restriction are standard measures for calcium kidney stone prevention. However, the same measures could lead to clinically significant hyponatremia in patients at risk for SIADH, like our patient with long history of mood disorder and taking psychotropic medications.

PUB410

Outbreak of Catheter-Related Bloodstream Infection by Elizabethkingia: Gram Negative Bacteria Poorly Known in Dialysis Center Luis Felipe Cintra, Maria C.C. Andreoli, Nadia Guimaraes- Souza, Thais Nemoto Matsui, Adriano Luiz Ammirati, Ana Karoline Nobrega Cavalcanti, Carlos Tadeu Bichini Guardia, Alessandra Correa Pereira, Marisa Petrucelli Doher, Fabiana Dias Carneiro, Bruna Gomes Barbeiro, Bento C. Santos. *Dialysis Center, Hospital Israelita Albert Einstein.*

Introduction: Multiresistant bacterias are becoming increasingly common in health care centers and today are the global focus due to increasing difficulty on infection´s treatment caused by these micro-organisms.

Case Description: From January to March 2016, were detected 4 cases of catheter-related bloodstream infections (CRBSI) by gram-negative bacteria Elizabethkingia in a dialysis center. This bacteria is associated with severe nosocomial's infections, high antimicrobial resistance, and sensitivity profile not yet well-known. Four patients presented bacteremia during hemodialysis session. Hemocultures collected in the catheter of dialysis (MALD-TOF method) and in peripheral blood culture had growth difference greater than 2 hours. In 3 cases Elisabethkingia miricola and in one case Elisabethkingia meningoseptica. In all cases, the antibiogram was sensitive only to Levolfoxacin and Sulfamethoxazole-trimethoprim, and resistance to all other antibiotics tested. Exchange of the central catheter associated to antibiotic therapy for 14 days in all patients were the treatment choice. The patient with E. menigoseptica and one case with E. miricola were treated with Levofloxacin. The others received sulfamethoxazole-trimethoprim once Levofloxacin minimum inhibitory concentration was higher in this cases. None of patients had complications and three patients were submitted to arteriovenous fistula confection.

Discussion: The early clinical recognition of infection, isolation in hemoculture and treatment based on antibiogram were fundamental to the treatment´s success.

PUB411

An Atypical Presentation of Atypical Hemolytic Uremic Syndrome Marilyn (Linh) M. Phung,[1] Christoph Licht,[2] Jocelyn S. Garland.[1] *[1]Nephrology, Kingston General Hospital, Kingston, ON, Canada; [2]Pediatric Nephrology, The Hospital for Sick Children, Toronto, ON, Canada.*

Introduction: Atypical hemolytic uremic syndrome (AHUS) is a systemic thrombotic microangiopathy (TMA) caused by dysregulation of the complement system that cause significant morbidity and mortality, most notably with renal involvement.

Case Description: A 21 year old previously healthy female presented to the emergency room with a 2 week history of epigastric pain and non-bloody diarrhea. She had been seen twice before with these symptoms but had been sent home after supportive care, with noted preserved renal function. On her third visit, she had developed vomiting, fever, severe bilateral flank pain and anuria. Her creatinine was found to be elevated and continued to worsen despite aggressive fluid resuscitation. Post-renal causes were excluded. Urine microscopy was non-contributory. Hemolytic work up showed worsening anemia and thrombocytopenia, elevated lactate dehydrogenase and bilirubin. Shistocytes were absent on blood smear and direct Coombs was negative. On history, she reported recent exposure to contaminated water from camping. Plasmapharesis was started, and an urgent renal biopsy was performed which later confirmed TMA. ADAMSTS13 activity returned as sufficient and Stool Shiga toxin was negative, suggesting against TTP or STEC-HUS. With complement low, the patient was diagnosed with AHUS. Unfortunately, LDH and creatinine remained high despite plasmapharesis, thus requiring dialysis; she was started on eculizumab after blood counts failed to improve. Her medical condition stabilized and she was discharged home to continue maintenance eculizumab infusions and hemodialysis as an outpatient. Unfortunately, she has not shown renal recovery and is undergoing assessment for transplant.

Discussion: This case highlights the importance of early recognition and treatment of TMA to mitigate the rapid development of end-organ damage. Evidence of a TMA process does not always require the presence of fragments on blood smear, or low haptoglobin levels. Subsequently, it is also important to distinguish between the etiologies of TMA as their management is notably different.

Funding: Government Support - Non-U.S.

PUB412

Acute Generalized Exanthematous Pustulosis Leading to Acute Kidney Injury through Glomerular Damage Larissa Kruger Gomes, Poorva Bindal, Ryan D. Stephenson. *Internal Medicine Dept, Univ of Connecticut, Farmington, CT.*

Introduction: Acute generalized exantematous pustulosis (AGEP) is a rare drug-mediated reaction leading to sterile pustule formation and systemic inflammation. The most common end-organ involvement in AGEP is acute kidney injury (AKI), happening in one third of cases. Nonetheless, the pattern of renal injury varies. We show a case of AKI mediated by AGEP in the setting of glomerular damage.

Case Description: 51-year-old female with past medical history of chronic obstructive pulmonary disease and morbid obesity presenting with a whole body pustular rash. Two weeks prior to admission the patient had an episode of cellulitis of the left foot for which she was being treated with vancomycin and cefepime. On day nine of treatment she developed a generalized exanthematous pustular rash, which got progressively worse and became associated with altered mental status. Furthermore, on admission she presented with a white blood cell count of 20.000 cells/mcL and a creatinine (Cr) of 2.4 mg/dL, from her baseline of 0.8mg/dL. The urinalysis (UA) showed dysmorphic red blood cells, 0.8 Protein/Cr ratio and a FeNa of 1.1%. Urine was negative for eosinophils or casts. After removing the antibiotics the patient's Cr returned to baseline after one week. No corticosteroids were used. A biopsy of the skin was able to confirm a pattern of involvement compatible with AGEP. No kidney biopsy was obtained.

Discussion: Normally, drug-mediated renal injury involves an acute interstitial nephritis or acute tubular necrosis pattern; nonetheless, in this case, the renal insult pattern was suggestive of a glomerular level damage given UA findings and FeNa. Recent research shows involvement of T-cell mediated response in AGEP that would explain glomerular damage mediated by IV hypersensitivity reaction. Further characterization of renal pattern of injury would be helpful to determine role of immunosuppression or apheresis methods in the management of this ailment. Renal injury by AGEP continues to be a rare form of AKI, however, further studies for characterization of pattern or renal insult are needed to establish beneficial interventions and proper prognostication.

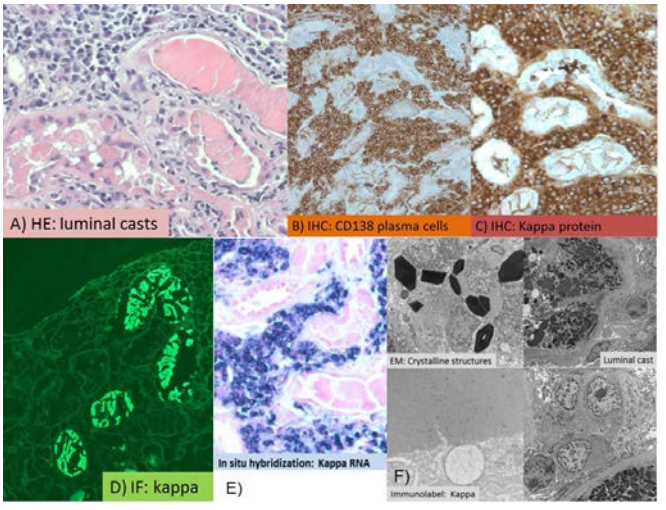
PUB413

Crystalline Light Chain Proximal Tubulopathy with Monoclonal Plasma Cell Infiltrate Abhilash Koratala, William L. Clapp, Dara N. Wakefield, A. Ahsan Ejaz. *Univ of Florida.*

Introduction: We present a rare case of crystalline Light chain proximal tubulopathy (LCPT) in a patient with Multiple myeloma.

Case Description: 69 year-old white male presented to the ER with fatigue and atypical chest pain. MI was ruled out but noted to have elevated SCr of 12.5mg/dL (14 months ago, 0.9mg/dL). On exam, vitals were stable, he was mildly lethargic and no pedal edema. Labs: Na 140meq/L, K 3.8meq/L, Cl 98meq/L, HCO3 19meq/L, BUN 112mg/dL, Ca 9.5mg/dL, Phos 10mg/dL, Hgb 6.2g/dL. UA: pH 6.0, protein 100mg/dL, RBC 1-2/hpf, WBC 2/hpf, no casts. Renal US: R 15.5cm, L 15cm, no hydronephrosis. He did not respond to iv fluids and developed pulmonary congestion and became more lethargic which prompted urgent initiation of hemodialysis. Renal biopsy showed A)Prominent tubulointerstitial injury associated with accumulation of PAS negative luminal casts which have eosinophilic, hard,

and irregular, fracture lines and focally appear broken with a crumbled appearance. Congo red negative. B) Extensive confluent sheet-like infiltrative pattern of kappa-immunoreactive plasma cells (CD138) with C) Intense cytoplasmic positive immunoreactivity for kappa LC. D) Luminal casts show intense staining for kappa LC (4+). E). Kappa RNA. F) Intracytoplasmic electron-dense crystalline cast fragments in tubule cells, plasma cells and the interstitium.



Bone marrow biopsy confirmed Multiple myeloma. Treated with Cyclophosphamide, Bortezomib and dexamethasone. Patient remains dialysis-dependent.

Discussion: Our case of LCPT is characterized by occurrence in an older patient, cytoplasmic inclusion of kappa-restricted monoclonal LC, crystals not detected by LM or IF but by EM and was associated with heavy-burden myeloma. IF-Frozen and IF-Peroxidase have low sensitivity for detection of LCPT, and pronase digestion for formalin-fixed sections maybe required to detect crystalline LCPT. Alternately, immuno-gold staining may be required.

PUB414

An Unusual Case of Nephrotic Syndrome Associated with Increased Bleeding Risk Arjun Sekar,[1] Taranpreet Kaur,[1] Jonathan J. Taliercio,[1] Leal C. Herlitz.[2] *[1]Dept of Nephrology & Hypertension, Cleveland Clinic Foundation, Cleveland, OH; [2]Dept of Pathology, Cleveland Clinic Foundation, Cleveland, OH.*

Introduction: We describe a case of suspected renal amyloidosis with workup revealing increased bleeding risk. We discuss the association of amyloidosis with increased bleeding & methods to prevent bleeding post kidney biopsy.

Case Description: A 75 year old female with IgM Kappa paraproteinemia was evaluated for nephrotic syndrome & CKD stage 3. Workup revealed Factor 10 deficiency, so kidney biopsy was deferred. Bone marrow biopsy suggested lymphoplasmacytic lymphoma and treatment was initiated with bortezomib & rituximab. However, renal function continued to worsen (protein creatinine ratio increased to 28.1 from 22, and creatinine 4.1 mg/dl from 1.8,) with associated fluid overload prompting hospitalization. PLA2R was negative. Abdominal fat pad biopsy was negative for amyloidosis. Serum Monoclonal testing was significant for serum kappa 2150 mg/dl (Normal; 534-1267) & kappa/lambda ratio 33. On admission she got factor 9 infusion (40 units/kg) and factor 10 level increased to 33% from 11%. Prior to kidney biopsy she received 4356 units of prothombin complex concentrate (PCC) & factor 8 inhibitor bypassing activity (FEIBA) & 2673 units post procedure. INR and APTT levels remained stable and she tolerated the procedure without major bleeding. Kidney biopsy revealed kappa light chain amyloidosis with extensive glomerular and tubulointerstitial involvement. Treatment with cyclophosphamide was initiated.

Discussion: Amyloidosis is an established, independent risk factor for bleeding per a prospective study. Proposed mechanisms are increased vessel fragility and impaired vasoconstriction from amyloid deposition in blood vessels. Per a study, 9% of patients with amyloid also had factor 10 deficiency. If kidney biopsy is indicated for suspected amyloidosis, testing for factor deficiency is essential. Ideally it should be avoided and abdominal fat pad biopsy (57-85% sensitivity) should be pursued. However, in our case, kidney biopsy was warranted due to worsening renal function. PCC-FEIBA complex administration can reduce the risk of bleeding in these cases.

PUB415

ANCA Vasculitis with IgA Deposits Tahir Zaman,[1] Divya Raghavan,[1] Josephine Abraham,[1] Monica Patricia Revelo Penafiel,[2] Laith Al-Rabadi.[1] *[1]Nephrology, Univ of Utah, Salt Lake City, UT; [2]Pathology, Univ of Utah, Salt Lake City, UT.*

Introduction: ANCA-associated vasculitis is known to present with rapidly progressive glomerulonephritis with morphologic features of segmental necrosis and crescents with negative immunofluorescence. The coexistence of IgA deposits has been reported in the literature. Presence of immune deposits should not exclude ANCA vasculitis as the main pathologic process.

Case Description: A 59-year-old man presented to the hospital with lower extremity swelling and a 2-month history of tea-colored urine associated with fevers and myalgia. Patient was found to have acute kidney injury with a serum creatinine of 8 mg/dl. Serum creatinine was 1 mg/dl 3 months ago. Urine analysis showed 3+ blood and 2+ protein. Urine microscopy revealed dysmorphic RBCs and RBC casts. His chest radiograph was unremarkable. Serologic workup was pending when the renal biopsy was performed. Light microscopy revealed diffuse necrotizing crescentic glomerulonephritis that raised suspicion for ANCA vasculitis despite the presence of IgA and C3 deposits by immunofluorescence. Serologic workup confirmed our suspicion and revealed a positive ANCA of 1:320 titer (perinuclear pattern) and elevated MPO at 287 AU/ml. Due to the severity of patient's renal failure and impending need for dialysis, he was treated aggressively for microscopic polyangiitis with oral cyclophosphamide, plasmapheresis and steroids. Renal function has improved significantly with Cr down to 2 mg /dl.

Discussion: ANCA vasculitis with IgA deposits is an uncommon entity. The diffuse necrotic and crescentic process in the absence of significant hypercellularity should prompt consideration of ANCA associated vasculitis despite the presence of immune deposits. Renal biopsy and serologic evaluation were critical to finding the unifying diagnosis and initiating the appropriate therapeutic interventions. The relevance of IgA deposits in the setting of ANCA vasculitis is still unclear and warrants further studies.

PUB416

Catastrophic Antiphospholipid Syndrome: A Role for Renal Biopsy in an Unusual Presentation Tahir Zaman,[1] T. S. Bjordahl,[1] Monica Patricia Revelo Penafiel,[2] Monique E. Cho.[1] *[1]Univ of Utah, Univ of Utah, Salt Lake City, UT; [2]Pathology, Univ of Utah, Salt Lake City, UT.*

Introduction: Catastrophic antiphospholipid syndrome (CAPS) is a rare but important cause of thrombotic microangiopathy.

Case Description: A 27 year-old woman with history of lupus, epilepsy, and deep vein thrombosis (DVT) on chronic anticoagulation presented with severe pleuritic chest and back pain and nausea. CT angiogram and transesophageal echocardiogram performed for a peak serum troponin level of 12 ng/ml excluded epicardial coronary thrombosis and aortic dissection. MRI of the heart revealed transmural enhancement of the lateral wall and apex, suggestive of myocardial injury but atypical for infarction. The patient was treated for presumed lupus myopericarditis with methylprednisolone, colchicine, and mycophenolate mofetil without any clinical improvement. Her course was further complicated by worsening thrombocytopenia and new upper extremity DVT. The patient's serum creatinine also increased to 1.3 mg/dL from a baseline value of 1.1 mg/dL with 1.14 g/d of proteinuria and rare urinary dysmorphic red cells. Because of the diagnostic uncertainty, a renal biopsy was performed, revealing thrombotic microangiopathy (TMA) and focal proliferative glomerulonephritis. Serologic tests showed profoundly elevated titers for anti-cardiolipin IgM (108 MPL) and anti-Beta-2 glycoprotein IgM (>150 SMU). Based on multiple sites of thrombosis (extremity, kidney, presumed myocardium), rapid onset, and the presence of antiphospholipid antibodies, CAPS became the unifying diagnosis. The patient was treated accordingly with heparin, pulse steroids, plasmapheresis, and rituximab therapy with marked clinical improvement subsequently.

Discussion: TMA due to CAPS is a rare but important cause of glomerular pathology. Because cardiac MRI cannot differentiate myocarditis from diffuse microvascular ischemia, renal biopsy was key to identifying the correct diagnosis and determining the course of therapy in our case, despite unimpressive renal presentation. A possible therapeutic role for rituximab in lupus patients with CAPS is discussed.

PUB417

Acute Hyponatremic Encephalopathy after Orthopedic Surgery: Should Thiazides Be Withheld Perioperatively? Di Pan,[1] Thalia Salinas,[1] Franco Vallejo,[1] Anip Bansal.[2] *[1]Medicine, Mount Sinai St. Luke's and West; [2]Nephrology, Mount Sinai St. Luke's and West.*

Introduction: Hyponatremia is a common occurrence in patients after orthopedic surgery. In patients who concurrently take thiazide diuretics perioperatively, profound hyponatremia can occur. We present 2 cases of severe symptomatic hyponatremia requiring intensive care after total shoulder arthroplasty (TSA).

Case Description: Patient 1: A 69-year-old female with a history of hypertension and osteoarthritis was found to have dizziness, vomiting, and dysarthria 36 hours after TSA. Laboratory testing revealed a serum sodium of 119 mmol/L that was significantly lower compared to 133 mmol/L at the time of her pre-operative evaluation 2 weeks prior to surgery. The patient did not receive any hypotonic fluids during and after her surgery, but had taken chlorthalidone 12.5mg the night before her operation. Patient 2: A 78-year-old female with a history of hypertension and osteoarthritis was found to have worsening confusion and urinary incontinence 48 hours after TSA. She had a decrease in her serum sodium from 141 mmol/L at the time of admission to 117 mmol/L at time of evaluation. The patient did not receive any hypotonic fluids during and after her surgery but reported increased fluid intake due to high ambient temperatures. She was maintained on her home-dose of hydrochlorothiazide 25mg perioperatively. Both patients received 3% NaCl boluses with prompt resolution of symptoms and improvement in hyponatremia.

Discussion: Hyponatremia is occasionally encountered after orthopedic procedures, and is a common side effect of thiazide diuretics. This can lead to adverse clinical outcomes such as longer hospital stays and significant morbidity, especially in the geriatric population. Post operative pain and nausea causing increased ADH secretion and decreased oral intake impairing free water excretion likely contribute to acute worsening of thiazide associated hyponatremia. As there is limited description of this in the literature, further studies should be done to evaluate the incidence and relative contribution of thiazides to post-operative hyponatremia. Clinicians should consider withholding these medications perioperatively to minimize the risk of this complication.

PUB418

The Efficacy of Eculizumab in Patients with Atypical Hemolytic Uremic Syndrome Daisuke Matsumura,[1] Eiichi Sato,[1] Hongmei Lu,[1] Mayumi Nomura,[1] Mayuko Amaha,[1] Shun Iida,[2] Akiko Fujii,[2] Yuko Ono,[2] Yoshihiko Ueda,[2] Tsukasa Nakamura.[1] *[1]Div of Nephrology, Dept of Internal Medicine, Shinmatsudo Central General Hospital, Matsudo, Chiba Prefecture, Japan; [2]Dept of Pathology, Dokkyo Medical Univ, Koshigaya Hospital, Koshigaya, Saitama Prefecture, Japan.*

Introduction: The effects of eculizumab for treatment of atypical hemolytic uremic syndrome (aHUS) vary by cases. We present three cases of aHUS who recovered from kidney damage, which initially required hemodialysis.

Case Description: Case 1: The patient was a 48 year-old female hospitalized for general fatigue. Blood tests revealed hemolytic anemia, kidney dysfunction,thrombocytopenia and red cell fragments in peripheral blood.She was diagnosed with aHUS. She underwent plasma exchange for one week without improvement in her thrombocytopenia and kidney function. She was thus started on eculizumab. The patient recovered her kidney function, and hemolytic anemia and thrombocytopenia resolved. Kidney biopsy revealed thrombotic microangiopathy (TMA), no evidence of glomerulosclerosis and tubulointerstitial change. Genetic examination showed an abnormality in C3. Case 2: A 67 year-old male was referred to our hospital with a diagnosis of aHUS. Despite receiving plasma exchange treatment, he required hemodialysis. After 2 weeks of hemodialysis, administration of eculizumab was started. The patient recovered kidney function and hemodialysis was stopped. Kidney biopsy revealed TMA, no evidence of glomerulosclerosis and tubulointerstitial change. Case 3: A 43 year-old male was found to have TMA by blood test. He was diagnosed with aHUS. Serum creatinine level was high (18.78 mg/dL) therefore he urgently required hemodialysis. Kidney biopsy revealed TMA, glomerulosclerosis and moderate tubulointerstitial change. Although eculizumab treatment was commenced 4 weeks after starting hemodialysis, his kidney function deteriorated and hemodialysis had to be maintained. Genetic examination showed an abnormality in CFH.

Discussion: We conclude that immediate administration of eculizumab may avoid progression to kidneydysfunction in aHUS. Furthermore, the efficacy of eculizumabmay correlate with the degree of glomerulosclerosis and the extent of tubulointerstitial lesions.

PUB419

Severe Hypercalcemia in a Young Man Who Loves Milk and Takes Vitamin Supplements Paul El Azoury, Alan Segal. *Nephrology, Univ of Vermont, Burlington, VT.*

Introduction: The most common causes of hypercalcemia are primary hyperparathyroidism, paraneoplastic syndromes, and variants of the so-called "milk-alkali" syndrome. Hypercalcemia is common in patients with cancer , mechanisms include : PTHrP ,osteolytic lesions and 1.25 (OH)2D3 production. Milk Alkali syndrome consists of the triad of Hypercalcemia ,metabolic Alkalosis and AKI .

here we report a case of a patient who presented with features and signs of Milk alkali syndrome due to consumption of high amounts of milk and supplements, found to have a Large B cell lymphoma .

Case Description: A 35 year old man with no medical history presented with generalized weakness and was found to have [calcium] 16.1 mg/dL, [tCO2] 40 mM, and Cr 1.7 mg/dL (baseline 0.8 mg/dL). Work-up showed suppression of PTH and no parathyroid hormone-related peptide (PTHrP), but 1,25-dihydroxyvitamin D3 was elevated at 169 pg/mL (nl 18-78). His dietary habits included drinking a gallon of raw whole milk daily and ingestion of multiple vitamin supplements including vitamin A and vitamin D (10,000 IU) daily. These data—along with the triad of hypercalcemia, metabolic alkalosis, and AKI in this young, healthy man—suggested the "milk-alkali" syndrome. However, the severity of the hypercalcemia was atypical, and careful physical examination revealed splenomegaly. Although laboratories rapidly normalized with IV saline, calcitonin, and pamidronate, a CT abdomen showed a large heterogeneous splenic mass and retroperitoneal lymphadenopathy. Biopsy of the splenic mass showed non-Hodgkin lymphoma, diffuse B cell type.

Discussion: The most common cause of lymphoma-associated hypercalcemia is PTHrP secretion by the tumor, but overproduction of 1,25-dihydroxyvitamin D3 also occurs, as in this case. In summary, we report a case of paraneoplastic hypercalcemia with an initial presentation mimicking "milk-alkali" syndrome. Our patient is responding well to chemotherapy.

PUB420

Rare Cause of Hypophosphatemia;Tumor Induced Osteomalacia Manini Vishwanath, Anirban Ganguli, Judith H. Veis. *Medicine/Nephrology, Washington Hospital Center, Washington, DC.*

Introduction: Tumor-induced osteomalacia(TIO) is a rare paraneoplastic syndrome causing severe hypophosphatemia. We present a rare case of metastatic prostate cancer with this condition.

Case Description: 65 year old male with past medical history of untreated Chronic Hepatitis C, HIV on HAART (never on tenofovir) and refractory prostate cancer with vertebral metastasis was admitted with failure to thrive and muscle cramps. Severe hypophosphatemia of 0.3mg/dl was noted(values were low normal 6 months prior, normal 6 years ago). He had hypocalcemia, with normal electrolytes, creatinine and blood gas profiles. Markedly elevated serum alkaline phosphatase, marginally low 25OH Vitamin-D, elevated PTH (290.1 pg/ml) and elevated fractional urinary phosphate excretion of 10% suggesting osteomalacia and renal phosphate wasting. Hypocalcemia resolved with oral calcium carbonate and calcitriol but hypophosphatemia improved only marginally with IV sodium phosphate and oral potassium phosphate. While generalized aminoaciduria was noted, there was no glycosuria suggesting that this could be either from partial Fanconi's syndrome or chronic liver disease as a cause. However markedly elevated FGF-23 levels (5950 RU/ml, normal <180) clinched the diagnosis of oncogenic osteomalacia. Despite maximal phosphate supplementation, moderate hypophosphatemia (1-1.5mg/dl) persisted over the following 2 weeks of observation.

Discussion: Severe and sustained hypophosphatemia of <1mg/dl is uncommon. Causes include renal phosphate wasting from genetic tubular defects causing hypophosphatemic rickets, drugs (cisplatin, ifosphamide, tenofovir), hyperparathyroidism (primary or secondary) or proximal tubular dysfunction (Fanconi's syndrome associated with renal tubular acidosis, aminoaciduria and renal glycosuria) all of which inhibit the specific Sodium-Phosphate cotransporter (NaPi 2a and 2c). Another rare cause is TIO, a paraneoplastic syndrome mostly reported in mesenchymal tumors but rarely in metastatic hormone-refractory prostate cancer with a dismal prognosis. Recently, Fibroblast Growth Factor(FGF-23), a specific phosphaturic hormone inhibiting the expression of NaPi2a and 2c, has been recognized as the primary mediator of this syndrome.

PUB421

Angiotensin Converting Enzyme Inhibitor Causing Seizures Sai Prasad Gadapa,[1] Siwadon Pitukweerakul,[2] Sree V. Pilla.[3] *[1]Internal Medicine, St. Francis Hospital, Evanston, IL; [2]Internal Medicine, St. Francis Hospital, Evanston, IL; [3]Internal Medicine, St. Francis Hospital, Evanston, IL.*

Introduction: This is a case report showing that Lisinopril can cause hyponatremia and when combine with thiazides can cause seizures secondary to hyponatremia.

Case Description: A 54 yo African American male with past medical history of schizophrenia and hypertension was brought to the ED with c/o vomiting since 2 days. H/o vomiting 2-3 episodes a day. Pt became less communicative over 2 days and as per the family member he goes into catatonic state when he becomes sick. He takes aripiprazole, lisinopril. On Examination BP 153/91, PR 94/min, T 98.5 F, RR 16/min, BMI 26.64 kg/m2, spo2 98%, stares blankly without interaction. BUN 12 mg/dL, creatinine 0.69 mg/dL, Na 107 mmol/L, K 4.4 mmol/L, Cl 74 mmol/L, co2 24 mmol/L, Ca 10.2 mg/dL, GFR MDRD Af Amer >60 ml/min/1.73 m, serum osm was 221 mOsm/kg, urine osmolality 734, urine sodium 105, urine creatinine 144, urine chloride 109, urine potassium 43. Patient was started on NS 0.9% 75 cc/hr, sodium improved to 109 mmol/L over 12 hours. Patient was switched to 3% Nacl at the rate of 10 cc/hr. Lisinopril was stopped. Patient was discharged on day 9 with serum sodium of 133 mmol/L and the patient was instructed to stop taking Lisinopril. After 7 months he was admitted with c/o seizures and his seizures were thought to be because of hyponatremia of 119. Review of his home medication showed that he was restarted on Lisinopril and hydrochlorothiazide.

Discussion: Initially patient was thought to have hyponatremia because of dehydration secondary to vomiting but his urine osmolality and urine sodium showed finding consistent with SIADH. Pt was on aripiprazole and Lisinopril. Aripiprazole wouldn't cause hyponatremia. There are few case reports saying that Lisinopril cause hyponatremia. Literature reports that ACE inhibitors are associated with high ADH levels. Other possible mechanism by which ACE inhibitor causing hyponatremia is failure to cross blood brain barrier and inhibit angiotensin converting enzyme therefore causing angiotensin II to stimulate release of Anti-Diuretic hormone.

PUB422

Female Patient with Membranous Nephropathy and Alport Disease: Case Report Mariana Pigozzi Veloso,[1] Precil Diego Miranda de Menezes Neves,[1] Francisco Zanotelli Mattedi,[1] Cristiane B. Dias,[1] Leonardo Abreu Testagrossa,[2] Lectícia Jorge,[1] Luis Yu,[1] Viktoria Woronik.[1] *[1]Nephrology, Univ of Sao Paulo, Sao Paulo, Brazil; [2]Pathology, Univ of Sao Paulo, Sao Paulo, Brazil.*

Introduction: The association of Hereditary Nephritis due to disorders of collagen IV like Alport Disease (AD) and immunocomplex nephropathies is uncommon.

Case Description: Women, 37 years old was referred to nephrology clinic due to anasarca, foamy urine and ten kg gain during the last two months. She denied any systemic symptoms or any exposure to nephrotoxic drugs. Obstetrical history showed seven pregnancies, eight living childbirths and no abortion. Pre eclampsia was developed in last pregnancy. Since then, she had hypertension and took medications for high blood pressure. Four of her sons had AD, one on dialysis. Two grandmother-sisters and three cousins developed end-stage kidney disease. Her parents were not blood relatives. Laboratory: BUN 10,28 mg/dL, serum creatinine 0.62 mg/dL, Estimated Glomerular Filtration Rate (CKD-EPI): 134ml/min/1,73m^2, albumine 1.3g/dL and 24h protein urine excretion of 5.5g. Urine sediment was unremarkable with 4 leucocytes and 9 red blood cells. Immunological investigation was negative. VDRL (Venereal Disease Research Laboratory test) was positive 1:1 and FTAbs (Fluorescent treponemal antibody-absorption test) was weakly positive (2.73 cut-off 0.216). Kidney Ultrasound: Right kidney 11,4 cm and left kidney 10,8 cm with normal ecogenicity. Kidney Biopsy Light Microscopy: Fourteen glomeruli with normal cellularity, capsule and Bowman space. Basal membrane with occasional spikes. Imunofluoroscence: IgG deposits 3+/3+, Kappa 2+/3+ and lambda 1+/3+ in glomerular capillaries, granular,global and diffuse pattern. Electron Microscopy: Capillary loops with epimembranous subepithelial electrondense deposits with spikes. Basal membrane irregularities characterized by thicked alternating with thinned areas and lamina dense delamination. Histopathologic Diagnosis: Membranous Glomerulonephritis (MGN) grade I and collagen IV genetic disease (AD).

Discussion: We report a double histopathological lesion – glomerular basement membrane lesion of hereditary nephritis and MGN, to our knowledge not described until now.

PUB423

Hypokalemia and Respiratory Alkalosis in Pregnancy Rudrick V. Ledesma,[1] Maureen E. Brogan.[2] *[1]Nephrology, Westchester Medical Center, Valhalla, NY; [2]Nephrology, Westchester Medical Center, Valhalla, NY.*

Introduction: Pregnancy causes physiologic changes in one's body. Cardiovascular, hormonal, renal, and respiratory changes occur. These are normal adaptations to accommodate the fetus and are imperative in an event of complications. We are presenting a case of a pregnant lady with respiratory alkalosis and severe hypokalemia.

Case Description: A 32 yo lady with pmh of hypokalemia exacerbated during pregnancy was seen in renal clinic for hypokalemia. She was 23 weeks with her 2nd pregnancy on her 1st renal visit. Her serum potassium levels were between 2.4 meq/L to 3.8 meq/L. It has been on the higher side after her potassium supplement was increased to 120 meqs per day. Symptoms include nausea and vomiting. Prior to the raising of her supplements, she was complaining of fatigue and leg cramps. No other subjective complaints. Laboratory studies showed glucose 85 meq/L, sodium 134 meq/L, potassium 3.3 meq/L, chloride 103 meq/L, bicarb 21 meq/L, BUN 0.52 mg/dl and creatinine 0.52 mg/dl. Urine pH 7.0 and sg 1.014. Urine lytes: UNa 67, UK 76, UCl 126, Uosm 499 and UCr 44.2 Thyroid function tests were within normal limits. Renin activity was 47 ng/ml/hr and Aldosterone 94 ng/dl. Cortisol level at 12:49 pm was 9.0 mcg/dl. ABG showed pH 7.46, PCO2 30, PO2 105, Bicarbonate 21.3.

Discussion: In pregnancy, there is an increase in total body K but a slight decrease in serum K. Serum renin activity and aldosterone level increase due to decreased systemic vascular resistance. The kaliuretic effect of aldosterone is countered by the potassium retention induced by elevated progesterone. Due to the physiologic changes in the lungs and increased progesterone, respiratory alkalosis is common. In normal pregnancy, serum potassium level is usually normal and serum bicarbonate level can be low. This is a unique case of a pregnant patient with severe hypokalemia and respiratory alkalosis. With her TTKG of 12, her hypokalemia is most likely from renal loss and less likely from intracellular shift caused by alkalosis. In her case, she may have an underlying condition causing hypokalemia that is exacerbated by pregnancy. The plan is to work her up for other causes of hypokalemia after her pregnancy.

PUB424

Unusual Etiology of Rapidly Progressive Glomerulonephritis Samir A. Brahmbhatt,[1] Jaime R. Jimenez Lopez,[1] Robert D. Zenenberg.[2] *[1]Internal Medicine, Morristown Medical Center, Morristown, NJ; [2]Nephrology, Morristown Medical Center, Morristown, NJ.*

Introduction: Between 10 to 40 percent of patients with anti-glomerular basement membrane (GBM) antibody disease are anti-neutrophil cytoplasmic antibody (ANCA) positive, and ANCA is usually directed against myeloperoxidase (MPO) rather than proteinase 3 (PR3). The following is a case of an elderly woman that presented with rapidly progressive glomerulonephritis (RPGN) found to be both PR3-ANCA and anti-GBM antibody positive with a linear pattern of IgG on immunofluorescence.

Case Description: A 60-year-old white woman with controlled hypertension, diabetes and obesity, presented with rash, eye pain, diplopia, and epistaxis that progressed over 6 months. During her hospitalization, she developed acute renal failure with proteinuria, hematuria and red blood cell casts. Her initial serologic workup revealed PR3 ANCA positivity. A subsequent renal biopsy revealed acute, severe and diffuse necrotizing crescentic glomerulonephritis, with linear staining for IgG; and a serum anti-GBM antibody was found to be positive as well. She had been initially treated with Rituximab, steroids and plasma exchange therapy. Because of worsening renal function, and the anti-GBM positivity, Rituximab was stopped, and started on Cyclophosphamide. Fortunately, she never required dialysis, and her creatinine stabilized at 1.4 mg/dL. Both serum PR3-ANCA and anti-GBM were found negative after treatment.

Discussion: To our knowledge, there is only a few reported cases of RPGN due to the coexistence of anti-GBM (proven by kidney biopsy and serology), with a positive PR3-ANCA. In patients with this coexistence, the relationship between the two antibodies is unknown. However, the production of ANCA appears to precede that of anti-GBM antibodies, at least in some patients. Coexistence of anti-GBM with MPO-ANCA is common, but typically associated with a worse prognosis. In this case, the association between anti-GBM disease and PR3-ANCA led to a better outcome.

PUB425

Gordon's Syndrome: A Rare Cause of Hypertension and Hyperkalemia Chinonye Chika Ogbonnaya-Odor. *Internal Medicine, Rutgers NJMS, Newark, NJ.*

Introduction: Gordon syndrome is a rare disorder characterized by hypertension, hyperkalemia, metabolic acidosis in the presence of normal GFR. It has been reported to be caused by genetic mutations that happen sporadically in the population, but can also be inherited in an autosomal pattern.

Case Description: A 23-year-old man with no reported past medical history, presented for evaluation, after referral from his primary provider, for lab abnormalities. The patient reported taking Theraflu for cold symptoms, two days prior to presentation. He denied any complaints except poor vision and headaches both chronic from childhood. He was afebrile, BP 146/78 mmHg, pulse 60 bpm, respiratory rate 16 breaths per minute, and oxygen saturation of 99% on room air. He was blind in the left eye but exam was otherwise benign. Pertinent laboratory studies were:, potassium 7.2 mEq/L, bicarbonate 18 mEq, creatinine 1.0 mg/dl and GFR >60 mL/min. Urinalysis: specific gravity 1.021, pH 5, negative for protein, glucose, ketones, blood, nitrite, and leukocyte esterase, RBC 3, and WBC 1. ECG showed sinus rhythm at 60 BPM with peaked T waves in most leads. He was treated with calcium, insulin and sodium polystyrene, twice within the next twelve hours, each time with improvement in hyperkalemia. His blood pressure was noted to be persistently elevated during hospitalization. Further studies to analyze etiology of hyperkalemia were done. Aldosterone level was slightly elevated but others including, renin level, cortisol stimulation test, TTKG, HIV, ANA, were normal. His blood pressure and hyperkalemia responded with 25 mg of hydrochlorothiazide. Given constellation of findings, patient history and blood pressure response to hydrochlorothiazide, the diagnosis of sporadic Gordon syndrome was made. At one month follow up he had self-discontinued hydrochlorothiazide, and metabolic acidosis and hyperkalemia recurred. Lifelong adherence to medication was stressed.

Discussion: Gordon syndrome is an important and easily treatable cause of hypertension and hyperkalemia that might be a frequently missed diagnosis due to its rarity. Recognition of this entity is important to ensure proper therapy.

PUB426

***Aspergillus niger* Peritonitis** Saad Mohammed Shariff, Eric L. Wallace. *Univ of Alabama, Birmingham, AL.*

Introduction: Fungal Peritonitis is a serious complication of peritoneal dialysis (PD) accounting for 3-10% of PD related peritonitis. Mold peritonitis, such as Aspergillus niger is a rare cause of peritonitis with a high mortality rate.

Case Description: A 70 year-old African American male with end stage kidney disease on PD presented with abdominal pain, chills, generalized weakness, diarrhea, nausea and vomiting for 5 days. Two weeks prior to admission patient noticed cloudy PD fluid and was treated for suspected bacterial peritonitis with Vancomycin and Ceftazidime.

Upon presentation, the patient was in septic shock. PD fluid analysis showed 1,879 WBC's, 82% neutrophils, 13% Macrophages, 3% Mesothelial cells, 2% Eosinophils and cultures were sent. Patient was continued on his original therapy with Vancomycin and Ceftazidime. Despite appropriate empiric antibiotics, repeat PD fluid analysis showed worsening of cell counts at 6994 WBC's with 78% neutrophil. Gram stain was negative. Linezolid and Micafungin were started and PD catheter was removed. Preliminary PD fluid cultures at three days showed mold and on day 7 this was identified as Aspergillus Niger. He was transitioned to Voriconazole. Repeat cultures done after 2 weeks showed no more fungal growth. A home visit by the PD nurse found out that there was mold growing under the PD machine.

Discussion: Aspergillus niger is a rare cause of fungal peritonitis in an immunocompetent patient on PD. Early antifungal therapy with removal of PD catheter is important. Based on our case report it is important for a home visit; especially after multiple episodes of peritonitis to identify and prevent fungal peritonitis; as in this case there was mold growing under the patient's cycler.

PUB427

Sirolimus Induced Pneumonitis Jin Han Lim, Won Kim, Kyung Pyo Kang, Sung Kwang Park, Sik Lee. *Internal Medicine, Chonbuk National Univ Medical School and Research Inst of Clinical Medicine, Jeonju, Korea.*

Introduction: Sirolimus is a potent immunosuppressive drug that has been successfully used with or without cyclosporine as an alternative to calcineurin inhibitors in patients who have undergone kidney transplantation. The major side effects of sirolimus are anemia, thrombocytopenia, and hyperlipidemia. Clinical adverse effects have also been reported with the increasing use of sirolimus. Of these, pulmonary toxicity is a rare but potentially serious complication. Herein, we report a case of sirolimus-induced pneumonitis in a renal transplant recipient 6 month after initiation of sirolimus treatment that was promptly resolved after the discontinuation of the drug.

Case Description: A 34-year-old male visited the emergency room for hemoptysis with dyspnea. He underwent renal transplantation 10 years ago and had switched the immunosuppressive drugs to sirolimus with tacrolimus 6 months ago. His basal serum creatinine level was 1.1 mg/dL. Physical examination revealed coarse crackling breath. Laboratory findings revealed a white blood cell count of 12600/mm^3, hemoglobin level of 13.1 g/dL, and platelet count of 306,000/mm^3. Arterial blood gas analysis showed arterial PO_2 of 55 mmHg. A chest CT scan showed extensive ground-glass opacity and consolidation in both lung fields. However, any definite signs of bacterial or fungal infection were not observed. We considered it as sirolimus-induced pneumonitis and promptly stopped sirolimus use. Treatment was continued with antibiotics and high- flow oxygen therapy. After discontinuation of sirolimus, radiological findings and clinical prognosis of the patient improved.

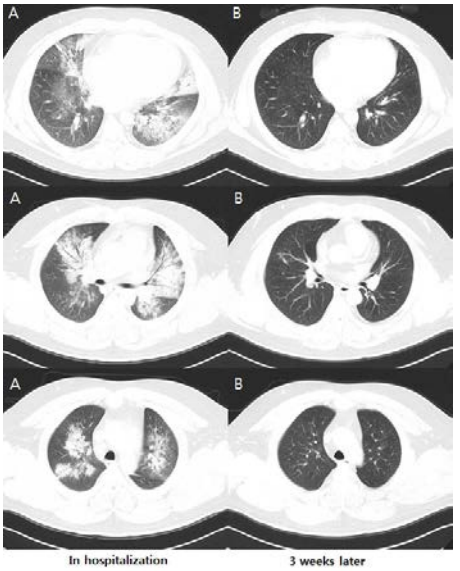


Figure 1. improvement of lung lesion after discontinuation of sirolimus

Discussion: Sirolimus-induced pneumonitis is a potentially fatal side effect. In patients with hemoptysis and being treated with sirolimus, this complication must be considered because early recognition along with drug discontinuation is essential to reverse the adverse effects.

PUB428

Two Cases of Lethal Disseminated *Varicella zoster* Infection with Lupus Nephritis during Remission Induction Therapy Masato Habuka, Michihiro Hosojima, Suguru Yamamoto, Takeshi Nakatsue, Yoko Wada, Junichiro James Kazama, Ichiei Narita. *Div of Clinical Nephrology and Rheumatology, Niigata Univ, Niigata, Japan.*

Introduction: Patients receiving glucocorticoids and immunosuppressants are at high rsik for severe infections, which can be a major cause of death during the disease course. Here we report two rare cases of disseminated varicella zoster virus (VZV) infection with lupus nephritis (LN) during remission induction therapy.

Case Description: Case1. A 46-year-old woman was admitted because of leukocytopenia, proteinuria, hypocomplementemia, and positivity for anti-nuclear antibody. By kidney biopsy, she was diagnosed as LN class III (A/C), and started on remission induction therapy with 45 mg of prednisolone and 3 mg of tacrolimus daily. Because of the kidney dysfunction, the tacrolimus was changed to mycophenolate mofetil (MMF), which led to gradual improvement. However, 52 days after the start of therapy, the patient developed abdominal pain and multiple skin blisters, which were diagnosed as disseminated VZV infection, and laboratory examinations demonstrated liver dysfunction and disseminated intravascular coagulation (DIC). Despite immediate administration of acyclovir and glucocorticoid pulse therapy, she died of hemorrhagic shock 7 days after the onset of abdominal pain. Case 2. A 26-year-old man was admitted because of weight gain, eyelid edema and proteinuria. By kidney biopsy, he was diagnosed as LN class IV (A) +V, and started on remission induction therapy with 60 mg of prednisolone and 500 mg of MMF daily, which was subsequently increased to 3000 mg. However, 76 days after the start of therapy, the patient developed back pain and multiple skin blisters, which were diagnosed as disseminated VZV infection, and laboratory examinations demonstrated liver dysfunction and DIC. Despite immediate administration of acyclovir,plasma exchange and hemodiafiltration, he died of septic shock 18 days after the onset of back pain.

Discussion: Since immunosuppressive agents are now used commonly in patients with autoimmune disorders, clinicians should bear in mind the possibility of disseminated VZV infection when patients suddenly develop abdominal or back pain with liver dysfunction and DIC.

PUB429

Thrombotic Microangiopathy in a Pregnant Kidney Transplant Recipient with De Novo Lupus-Like Nephritis Ryoko Mizuhara, Naoto Hamano, Masahiro Koizumi, Takehiko Wada, Masafumi Fukagawa. *Dept of Nephrology, Endocrinology and Metabolism, Tokai Univ School of Medicine, Isehara, Japan.*

Introduction: Pregnancy and various factors related to kidney transplantation can cause thrombotic microangiopathy (TMA), which can cause graft loss. However, TMA during pregnancy on the background of *de novo* lupus nephritis has not been reported.

Case Description: A 41-year-old Japanese kidney-transplant recipient was admitted to our hospital at a gestational age of 20 weeks due to hypertension, thrombocytopenia, and progressive renal dysfunction. She was initially on peritoneal dialysis for 8 months because of rapidly progressive glomerulonephritis due to anti-glomerular basement membrane syndrome. Four years before the admission, she received a living-donor kidney transplant from her father. Renal biopsy 2 years after transplantation revealed lupus-like nephritis with "full-house" pattern on immunofluorescence. However, her clinical course was stable without additional treatment. She achieved spontaneous pregnancy 4 years after transplantation. At prenatal checkup at 20 weeks of gestation, marked edema and hypertension (160/110 mmHg) along with thrombocytopenia were observed. Her serum creatinine level was elevated from 1.2 mg/dL to 2.1 mg/dL during 4 weeks. Her renal function continued to be deteriorated despite of immediate antihypertensive treatment. Renal pathology diagnosed TMA superimposed on the previous findings. Because of the intrauterine growth arrest, she underwent cesarean section at 25 weeks and delivered a baby weighing 530 grams. Her renal function and the platelet counts returned to the previous level during her uneventful postpartum period. The baby was discharged after the intensive care for 5 months.

Discussion: This case had several underling risks that cause TMA, such as lupus-like nephritis, pregnancy, and tacrolimus. Especially, *de novo* lupus nephritis in allograft is very rare. To determine the precise etiology and make a right decision on treatment strategy, renal biopsy can be a great tool even for pregnant recipients.

PUB430

Antibody-Negative Pauci-Immune Glomerulonephritis. A Case Report Josef Bautista, Nathaniel Nelson, Eric S. Kerns. *Section of Kidney Diseases and Hypertension, Brown Univ - Rhode Island Hospital, Providence, RI.*

Introduction: Pauci-immune crescentic glomerulonephritis is among the most common causes of rapidly progressive glomerulonephritis (RPGN) wherein ANCA antigens play a central role in the development of the disease. Very rarely however, there have been case reports of biopsy-proven pauci-immune glomerulonephritis wherein there is no or very low levels of ANCA antigens.

Case Description: We present a 66-year-old man with chronic obstructive pulmonary disease (COPD) who was brought in to the emergency department for shortness of breath and malaise. Physical exam was remarkable for breathing through pursed lips with diffuse wheezing. Initial blood work demonstrated a serum creatinine of 14.82 (baseline 1.3 measured less than five months prior) and severe metabolic acidosis. Urine studies showed nephrotic-range proteinuria and microscopic hematuria. Renal ultrasound revealed simple multiple cysts, but was otherwise unremarkable. Analysis of the urine sediment revealed numerous non-dysmorphic RBCs, but no cellular or granular casts. Subsequent work-up for his renal failure included negative p:ANCA, c-ANCA of 1:40, normal C3 and C4 levels, and negative MPO, PR3, ANA, dsDNA, HIV, anti-GBM, and hepatitis B and C. A renal biopsy showed numerous glomeruli with fibrocellular crescents but with negative immunofixation. Electron microscopy showed no deposits. He was started on pulse dose steroids and was put on plasmapheresis. He was also given Rituximab using the RAVE protocol and was eventually started on hemodialysis. He remains on hemodialysis up to the present time.

Discussion: ANCA-negative pauci-immune glomerulonephritis is a relatively underappreciated disease. The mechanism for this disease is unclear but neutrophils and possibly other antigens are thought to be involved. This syndrome may be underdiagnosed as ANCA serologies or other serum markers usually influence the decision to perform renal biopsies. This case illustrates the importance of maintaining high clinical suspicion for pauci-immune crescentic glomerulonephritis, particularly in patients with rapid deterioration in renal function, in spite of negative anti MPO or PR3 antigens.

PUB431

A Case of Recurrent Membranous Nephropathy in Transplant Presenting with Deep Vein Thrombosis Divya Raghavan,[1] Dylan V. Miller,[3] Monica Patricia Revelo Penafiel,[2] Josephine Abraham,[1] Faris A. Ahmed.[1] *[1]Dept of Nephrology, Univ of Utah, Salt Lake City, UT; [2]Dept of Pathology, Univ of Utah, Salt Lake City, UT; [3]Dept of Pathology, Intermountain Central Lab, Murray, UT.*

Introduction: Thromboembolism is a known complication of the nephrotic syndrome. We report a case of recurrent membranous nephropathy (MN) in the transplant kidney presenting with extensive deep vein thrombosis (DVT).

Case Description: A 58 year old man presented to clinic with bilateral leg pain (greater on the right). His history was significant for ESRD from MN status post living donor renal transplant a year ago. He was on mycophenolate sodium, prednisone and tacrolimus. Physical exam revealed mild tenderness below the allograft site and swelling of the right lower extremity from thigh to mid-calf. Labs showed a creatinine of 1.69 mg/dl (baseline 1.4-1.5 mg/dl) and urine protein-to-creatinine ratio (UPCR) of 9 g/g. Duplex ultrasound (US) showed DVT involving right common femoral vein and extending into right external iliac vein, along with DVT of left femoral, popliteal and posterior tibial veins. US of the transplant kidney showed a non-occlusive thrombus of the renal vein. He was admitted to the hospital and started on a heparin drip. He underwent catheter-directed thrombolysis of the right common femoral and right external iliac veins and was started on lisinopril for proteinuria and warfarin for anticoagulation. Biopsy was deferred because of anticoagulation. Donor-specific antibody testing was negative. CT chest, abdomen and pelvis to evaluate for secondary causes of MN was unremarkable. He was treated with rituximab 1 g for presumed recurrent MN and the dose was repeated in 2 weeks. His creatinine improved to 1.37 mg/dl and UPCR to 2.2 g/g about 2 months post-discharge.

Development of proteinuria in transplant patients with a history of MN should trigger prompt evaluation. MN can recur in the transplant kidney with a reported incidence between 10-40% in different studies. Patients with recurrence are at risk of graft loss and complications from the nephrotic syndrome. There is some data suggesting the efficacy of rituximab in these cases.

PUB432

Acute Kidney Injury with Use of Inhaled Tobramycin Silvi Shah,[1] Casey T. Weaver,[2] Gaurav Agarwal.[1] *[1]Nephrology, Univ of Alabama at Birmingham, Birmingham, AL; [2]Pathology, Univ of Alabama at Birmingham, Birmingham, AL.*

Introduction: Aminoglycosides nephrotoxicity is a well-known clinical entity. Nebulized aminoglycosides are used to reduce nephrotoxicity. We describe the clinical case of a 57-year-old woman who developed acute kidney injury after using inhaled tobramycin for prevention of pulmonary infections.

Case Description: A 57-year-old white woman with history of end stage renal disease due to unknown etiology and living unrelated kidney transplant seven years ago presented to the clinic for evaluation of acute kidney injury. She received induction immunosuppression with alemtuzumab, and was maintained on tacrolimus and mycophenolate mofetil. She had history of bronchiectasis and recurrent pulmonary infections with multidrug resistant Pseudomonas; and was on preventive therapy with tobramycin inhalation for the last 6 months. Physical examination was unremarkable except for bilateral wheezes on lung auscultation. Her baseline serum creatinine was 1.9 mg/dl. Blood work showed elevated serum creatinine of 2.5 mg/dl corresponding to estimated glomerular filtration rate of 24 ml/min/1.73 m^2. Urine microscopy did not show proteinuria or hematuria. Donor specific antibody and renal transplant ultrasound were unremarkable. Serum BK virus was not detectable. Tacrolimus trough level was therapeutic. Renal biopsy was performed for the evaluation of acute kidney injury. Light microscopy revealed acute tubular injury and acute tubular necrosis superimposed on chronic glomerulosclerosis and mild interstitial fibrosis/tubular atrophy. Electron microscopy showed presence of cytosegresomes and myeloid bodies in proximal tubular epithelial cells consistent with aminoglycoside toxicity. Inhaled tobramycin was discontinued and patient's renal function improved.

Discussion: There is minimal systemic absorption with inhaled aminoglycosides and renal toxicity has not been reported in randomized clinical trials. Acute kidney injury occurred in our patient due to use of inhaled tobramycin. Clinicians should be aware of this rare complication and patients on inhaled aminoglycosides should be monitored closely for worsening renal function.

PUB433

Cryoglobulin Mediated Renal Failure in the Setting of B Cell Lymphma Sudipta Mohanty,[1] Shuchi I. Vyas.[2] *[1]Dept of Medicine, Univ of Californa, Riverside, CA; [2]Nephrology Dept, Kaiser Permanente, Riverside, CA.*

Introduction: Cryoglobulinemia involves the deposition of specific insoluble immune complexes in the microvasculature. While most adults remain asymptomatic, there are a wide variety of potential clinical manifestations - renal failure, MPGN, proteinuria, hematuria, cutaneous lesions, arthralgia, neuropathy, etc. About 80% of cryoglobulinemia is associated with hepatitis C infection, and this concurrence is extensively reported in the literature [1]. However, many other less common etiologies and associations exist.

Case Description: An 84 year old male with history of essential hypertension presented with one year of hematuria and pruritic rash over his chest and lower extremities. He was found to a creatinine of 5.4 (GFR 9) in ER. The patient was admitted for work up and management of acute kidney injury. He developed worsening renal failure so was started on hemodialysis. A broad infectious, autoimmune, and myeloma work up revealed pANCA 1:1280 and qualitative serum cryoglobulin, prompting renal biopsy for suspicion of vasculitic glomerulonephritis. The biopsy revealed immune complex-mediated glomerulonephritis with cryoglobulin deposition and 10% crescents. Given lymphadenopathy noted on CT, a left groin lymph node biopsy was pursued at the same time and revealed atypical lymphoid proliferation nondiagnostic for malignancy. Plasmapheresis was initiated for cryoglobulinemia. The patient was also treated with corticosteroids. The results of the renal biopsy prompted a second left inguinal lymph node biopsy. This biopsy revealed low grade B-cell lymphoma. Oncology was consulted, but chemotherapy was deferred due to the patient's unstable clinical status. Hospital course was complicated by encephalopathy requiring endotracheal intubation for airway security and urobacteremic sepsis requiring broad spectrum antibiotics. The patient eventually stabilized with improvement in mental status, extubation, and resolution of infection. After 1.5 months of hemodialysis and 14 sessions of plasmapheresis, renal function recovered with a creatinine of 1.0 (GFR 69). The patient was discharged to a skilled nursing facility and remains dialysis free.

PUB434

Steadfast Renal Biopsies: Timely Diagnosis and Trigger for Treatment of Hidden AL Amyloidosis Adam Austin, Mauricio Monrroy, Llewellyn A. Foulke, Rafia I. Chaudhry. *Albany Medical College, Albany, NY.*

Introduction: Two cases highlight the crucial role of renal biopsy to establish systemic diseases for initiation of appropriate therapy.

Case Description: Case 1: 65 year-old female referred for microscopic hematuria for 1 year with PMHx of MGUS for 18 years, breast cancer s/p right mastectomy and severe peripheral neuropathy. Laboratory Data: Sr Cr elevation from 1.0 mg/dL to 1.3 mg/dL over 5 months, trace protein and moderate blood on UA with urine spot protein 53 mg/dL and urine Cr 143 mg/dL. No active sediment on urine microscopy was identified. Serum lambda and kappa light chains were not elevated. Serum electrophoresis: M-spike consistent with IgA lambda paraproteinemia. Urine protein electrophoresis was indeterminate, urine immunofixation confirmed Bence Jone protein (lambda type). Urine free light chains were elevated (kappa 139 mg/L, lambda 44 mg/L). This patient carried a diagnosis of "MGUS" without established organ involvement, monitored conservatively for 18 years. Renal Biopsy was diagnostic of Renal AL Amyloidosis, prompting initiation of systemic therapy. Case 2: 49 year-old male presented with 60 pound unintentional weight loss over 6 months, chronic diarrhea and peripheral edema with ascites. Pertinent laboratory Data: Hgb 12.3 g/L, serum Cr 1.3 mg/dL (remarkable considering the patient's high degree of protein and muscle wasting), serum albumin <1.5 gm/dL, calculated LDL 267 mg/dL. UA: +3 protein with urine sediment negative for casts; spot protein 307 g/dL, urine Cr 57.5 g/dL (ratio 5.3). With high degree of clinical suspicion for nephrotic syndrome secondary to systemic disease, renal biopsy was recognized as an important diagnostic component that could hasten treatment while other biochemical studies were pending results. Renal Biopsy confirmed AL Amyloidosis.

In both cases, the diagnosis of AL Amyloidosis associated with Monoclonal Gammopathies was established by renal biopsy prompting initiation of treatment that may have otherwise been delayed.

Discussion: It is crucial to consider renal biopsy early in the diagnostic workup of systemic illnesses, and subtle clues such as microscopic hematuria should prompt a clinical suspicion for renal involvement.

PUB435

Gender Differences in the Associations of Obstructive Sleep Apnea and Cardiovascular Outcomes in Patients with End Stage Renal Disease: A Systematic Review and Meta-Analysis Pulkit Gandhi,[1] Manoj Das,[2] Shweta Sharma.[3] *[1]Internal Medicine, Wright Ctr for Graduate Med Ed, Scranton, PA; [2]Nephrology, Virginia Commonwealth Univ, Scranton, PA; [3]Internal Medicine, Wright Ctr for Graduate Med Ed, Scranton, PA.*

Introduction: Obstructive sleep apnea (OSA) increases risk for cardiovascular events, especially stroke in the general population and in patients with ESRD. However, gender differences in these associations are unclear, as studies that assessed these differences reported conflicting results. We have attempted to systematically review the literature and pool all available evidence that has assessed the gender differences in the associations of OSA and cardiovascular outcomes in ESRD patients.

Case Description: Medline, Embase, Cochrane central library, and electronic databases were searched for relevant studies in all languages and without time restriction.

From a total of 2793 retrieved citations, 7 observational studies, representing 732 men and 550 women with ESRD and a diagnosis of OSA, were included in the review. In the pooled analysis, men were at lower odds for stroke (OR: 0.64, 95% CI: 0.44 – 0.92, P = 0.02, I^2: 78%, 6 included studies), but odds of CAD (OR: 0.86, 95% CI: 0.54 – 1.37, P = 0.51, I^2: 74%, 5 included studies) and cardiovascular mortality (OR: 0.95, 95% CI: 0.71 – 1.27, P = 0.71, I^2: 0%, 5 included studies) was similar in the two groups. When restricted to data from sleep clinic based studies the lower odds of stroke in men persisted (OR: 0.60, 95% CI: 0.37 – 0.98, P = 0.04, I^2: 81%, 6 included studies) but disappeared in population based studies (OR: 0.65, 95% CI: 0.29 – 1.46, P = 0.3, I^2: 84%, 3 included studies). Factors responsible for the high heterogeneity could not be assessed due to lack of availability of gender specific data.

Discussion: Lower odds of stroke among men with OSA may likely be due to selection bias as this was true only in the sleep clinic based studies and not in population based studies. More population based studies with gender specific details of OSA determinants like atrial fibrillation are needed to clearly elucidate this association in ESRD patients.

PUB436

Morton Lite Salt Induced Hyperkalemia Ryan A. Kunjal,[1] Adey Hasan,[2] Abdalagani Ahmed Abakar Baher,[2] Ciel Harris,[1] Andreea Poenariu.[2] *[1]Dept of Internal Medicine, Univ of Florida College of Medicine, Jacksonville, FL; [2]Dept of Nephrology, Univ of Florida College of Medicine, Jacksonville, FL.*

Introduction: We present a case of Morton Lite salt - induced hyperkalemia in a patient with stage 2 chronic kidney disease (CKD). There is increasing use of lower sodium content salt and salt substitutes as healthy alternatives for the control of hypertension. These typically contain high quantities of potassium chloride which can predispose patients with CKD to hyperkalemia.

Case Description: A 61-year-old male with Hypertension, Type 2 Diabetes, CKD and Schizoaffective disorder presented with potassium of 9.2mmol/L found on routine laboratory investigations. His medications included Aspirin, Glimepiride, Metoprolol and Quetiapine. He was asymptomatic on arrival with unremarkable vital signs and physical examination. The EKG demonstrated normal sinus rhythm with diffusely peaked T waves. Repeat serum potassium was consistent with the previous level in the absence of hemolysis. His creatinine was 0.83mg/dL and eGFR was 75ml/min. Serum renin and aldosterone were normal and spot urine potassium was mildly elevated at 154mmol/l. The renal sonogram was essentially normal. Calcium gluconate, insulin and oral sodium polystyrene sulfonate were successful in normalizing his potassium. The peaked T waves on EKG also resolved. Metoprolol was held due to its possible contribution to hyperkalemia. Nevertheless, the underlying cause remained elusive. Later, the patient admitted to daily use of 2 tsp. of Morton Lite Salt for bowel regularity over the past month. This was equivalent to 70mEq of K^+ /day which likely caused such severe hyperkalemia. He made a full recovery.

Discussion: Large potassium intake is a rare cause of severe hyperkalemia especially in the setting of normal or mildly impaired kidney function as in our patient and makes this case unique. However the patients to whom these products are targeted tend to also be those at highest risk for hyperkalemia due to concomitant renal impairment or use of medications such as ACE inhibitors. Greater awareness is needed of the potential dangers of these products and it is imperative that their labeling reflect such risks.

PUB437

ANCA-Positive Pauci-Immune Crescentic Glomerulonephritis and Bronchial Carcinoid: Accomplice or Innocent Bystander? Jason Christopher George,[1] Alicia Meadows,[2] Jamie Alton Green.[1] *[1]Nephrology, Geisinger Medical Center, Danville, PA; [2]Rheumatology, Geisinger Medical Center, Danville, PA.*

Introduction: Paraneoplastic glomerulonephritis (GN) is a well-known but rare phenomenon that can occur with various malignancies. Diagnosis is important to avoid potentially harmful therapy. We present a case of a patient who was concurrently diagnosed with anti-neutrophil cytoplasmic antibody (ANCA), pauci-immune crescentic glomerulonephritis and bronchial carcinoid.

Case Description: A 62-year-old woman with known history of hypertension presented with 7 months of fatigue, shortness of breath and persistent cough. She also had bilateral leg swelling and worsening hypertension. She denied joint pain or rash. Labs showed progressive renal dysfunction (creatinine 3.0 mg/dL from 2.2 mg/dL four months prior), serum albumin 3.5 mg/dL, microscopic hematuria (50+/HPF) and nephrotic-range proteinuria (protein/creatinine ratio 5.53). Serologies showed positive p-ANCA with confirmatory anti-myeloperoxidase antibody. CT scan showed a 2.3 cm lung mass and biopsy confirmed well-differentiated bronchial carcinoid. Renal biopsy showed pauci-immune crescentic glomerulonephritis with mild interstitial fibrosis and tubular atrophy. It was unclear if the GN was idiopathic or related to malignancy. Her primary tumor was resected and she was started on high-dose prednisone and rituximab for treatment of her GN with improvement in proteinuria.

Discussion: Paraneoplastic GN involves renal manifestations of malignancy not directly related to tumor burden. It is most commonly described with membranous nephropathy and minimal change disease. Malignancy-associated ANCA-positive glomerulonephritis has been described with renal cell carcinoma, adenocarcinoma of the lung, and gastric carcinoma. However, association with bronchial neuroendocrine malignancy has not been frequently reported. The pathophysiology is not completely understood but thought to be related to dysregulated T-cell and cytokine response. Treatment with immunosuppression in patients that have undergone complete tumor removal can result in partial or complete renal response. Early recognition and prompt treatment are critical to prevent irreversible renal damage.

PUB438

Dilemma of Choosing between Kidney Alone versus Simultaneous Liver Kidney Transplantation in Autosomal Dominant Polycystic Kidney Disease Patients with Advanced CKD and Significant Hepatic Cyst Burden Reddy Singasani, Hasenia Albanna, Mariella Ortigosa Goggins, K.K. Venkat, Anita K. Patel. *Nephrology, Henry Ford Hospital, Detroit, MI.*

Introduction: In autosomal dominant polycystic kidney disease (ADPKD), while renal cysts commonly cause ESRD requiring kidney transplantation, liver cysts are asymptomatic with preserved hepatic function in most patients.

Case Description: A 56-year-old white male with dialysis-dependent ESRD secondary to ADPKD presented with severe right upper quadrant abdominal pain. Pre-transplant testing revealed normal liver function. He was not qualified for simultaneous liver-kidney transplantation (SLK) as synthetic function of the liver was intact. He then received a kidney transplant following which he continued to feel extremely fatigued with abdominal distention, persistent severe right upper quadrant abdominal pain and marked ascites necessitating frequent paracentesis. Though his liver function tests were normal he received a liver transplant 9 months after kidney transplantation, which resolved his prior disabling symptoms.

Discussion: Organ Procurement and Transplantation Network (OPTN)/ United Network for Organ Sharing (UNOS) Policy 9.3: Score and Status Exceptions, states that "If a candidate's transplant program believes that a candidate's MELD or pediatric end-stage liver disease (PELD) score does not appropriately reflect the candidate's medical urgency, the transplant physician may apply to the Regional Review Board (RRB) for a MELD or PELD score exception." ADPKD may benefit from MELD score exception if they have markedly impaired quality of life and performance limitation (Mayo Modification type D or C).

PLD Classification – Mayo Modification

Types	A	B	C	D
Symptoms	0 - +	++/+++	++/+++	++/+++
Cyst Findings	Focal	Focal	Diffuse	Diffuse
Spared Remnant Volume	≤3	≤2	≤1	<1
PV/HV Occlusion	No	No	No	Yes

In retrospect, our patient may have qualified for simultaneous liver-kidney transplantation in the first place and the morbidity associated with undergoing two separate transplant operations may have been avoided.

PUB439

Catheter-Related Bacteremia and Epidural Abscess Caused by *Citrobacter koseri* in a Hemodialysis Patient Muner Mohamed, Himabindu Valluru, Rahul Valluru, Mary C. Mallappallil, Moro O. Salifu. *SUNY Downstate Medical Center; SUNY Downstate Medical Center; SUNY Downstate Medical Center; SUNY Downstate Medical Center; SUNY Downstate Medical Center.*

Introduction: Low virulent *Citrobacter koseri* is a gram negative bacillus which is a facultative anaerobe from the family of *Enterobacteriaceae* and is part of the flora of human digestive tracts. It may act as an opportunistic pathogen in immunosuppressed patients.*C. koseri* is known to be an uncommon but serious cause of both sporadic and epidemic septicemia and meningitis in neonates and young infants. However, the literature on *C. koseri* as a cause of spinal infection in adults is scant. Epidural abscess due to *C. koseri* is a rare condition. We report a remarkable case of dialysis catheter related *C. koseri* bacteremia complicated by epidural abscess in a patient who has successfully been treated in our hospital.

Case Description: A 77 year old man end stage renal disease on hemodialysis, hypertension, Coronary Artery Disease status post CABG, Heart Failure with Reduced Ejection Fraction and Abdominal Aortic Aneurysm presented to the emergency room with 4 days of constipation and left lower back pain and a white cell count of 22.91 k/ul, He was on hemodialysis (HD) at another facility for the past 23 months via a right internal jugular dual lumen cuffed catheter while his AVF was planned. Systemic blood cultures revealed *Citrobacter koseri* and blood cultures sent from the catheter revealed *Citrobacter koseri*. His cuffed hemodialysis (HD) catheter was removed. Due to his back pain he had an MRI without gadolinium that revealed an epidural abscess at the level of L4-S1.

He was treated with lumbosacral decompressive laminectomy and intravenous ceftriaxone for 2 weeks followed by oral ciprofloxacin for 4 weeks with resolution of the abscess on repeat imaging.

Discussion: We believe this is the first case described in the literature of a dialysis catheter related bacteremia and epidural abscess caused by *C. koseri* in an immunocompetent adult patient. This case emphasizes the need to minimize HD catheter time in patients to prevent complications that can occur even with usually low virulent organisms.

PUB440

Fibrongen A α-Chain Amyloidosis: Case Report Alessandra Correa Pereira,[1] Bento C. Santos,[1] Denise M. Malheiros,[2] Luis Felipe Cintra,[1] Ana Karoline Nobrega Cavalcanti,[1] Marisa Petrucelli Doher,[1] Carlos Tadeu Bichini Guardia,[1] Nadia Guimaraes- Souza,[1] Thais Nemoto Matsui,[1] Virgilio Gonçalves Pereira.[1] *[1]Hospital Israelita Albert Einstein, São Paulo, Brazil; [2]Univ de São Paulo.*

Introduction: Deposition of amyloid fibrils in organs and tissues characterizes one group of diseases known as amyloidosis. Mutations in the fibrinogen Aα-chain gene are the most common cause of hereditary renal amyloidosis in Europe, however it is uncommon in Brazil.Disease clinical course is poorly known, but coronary atherosclerosis appears to be linked. Diagnosis is made by renal biopsy showing amyloid deposit and genetic tests. Treatment options are limited. Hepatorenal transplantation is an alternative in patients with advanced disease.

Case Description: A 55 years old men, from São Paulo, dyslipidemic, presented persistent proteinuria in laboratory tests without clinical manifestation, with regula clinical examination.In 2012, after an increase of proteinuria without renal dysfunction, a renal biopsy was performed showing amyloid deposits. Clinical investigation found no evidence of cell dyscrasias or inflammatory disease that could suggested amyloidosis in other parts. During follow-up hypertension and coronary insufficiency emerged. In 2015, patient evaluated with ankle edema and nephrotic proteinuria (9,26g) with progressive renal impairment (glomerular filtration ratio: 50 mL/min /1.73m2). A second renal biopsy confirmed amyloid deposition. Liquid chromatography spectrometry prompted detected an abnormal sequence of amino acids in the light chain of the fibrinogen Aα (Glu545Val) confirming the diagnosis of hereditary renal amyloidosis. In the follow up patient kept proteinuria and stable renal function until now.

Discussion: Fibrinogen A alpha-chain amyloidosis is mainly a renal disease characterized by variable penetrance, distinct histological appearance, proteinuria, and progressive renal failure. In the presence of glomerular amyloid deposit without systemic amyloidosis should be investigated hereditary renal amyloidosis.

PUB441

A Case of Hypoaldosteronism in Disguise Susanne Francis Mclaughlin, Sreedhar A. Mandayam. *Nephrology, Baylor College of Medicine, Houston, TX.*

Case Description: A 41 year old man with mesothelioma was admitted to the hospital two weeks after his first cycle of Cisplatin for hyponatremia of 112. He was tachycardic, hypertensive, and mildly volume overloaded. There were no neurological deficits. Serum osmolality was 233. Urine osmolality was 697. Urine sodium was 84. TSH was normal. We suspected SIADH due to his lung disease, the Cisplatin, and nausea. He was fluid-restricted and given normal saline with furosemide to promote aquaresis. The following day, sodium was unchanged. We saw that he also had mild hyperkalemia in the preceding few weeks. He had received Fluconazole for a line infection. A diagnosis of adrenal insufficiency was entertained. However, a morning cortisol was 21.2, and he was not hypotensive. Doubting this diagnosis, we then tried two courses of 3% saline with furosemide, and a dose of Tolvaptan 15mg. This only raised his sodium to 113. An ACTH stimulation test was then performed. Cortisol increased from 21 to 22.5 to 23.2 after 30 and 60 minutes respectively. Although the morning cortisol was not low, we speculated that these results showed maximal stimulation of the patient's pituitary gland due to a relative mineralocorticoid

deficiency, and thus he was incapable of producing any more cortisol. We gave a trial of methylprednisolone 500mg. Sodium increased from 113 to 119 by the next morning. A second dose of methylprednisolone 500mg was given and sodium improved further to 127 the next day. Patient was then placed on scheduled fludrocortisone and sodium eventually normalized. We had hoped to more fully evaluate his pituitary-adrenal axis and establish a diagnosis of hypoaldosteronism, but unfortunately the patient succumbed to his illness.

Discussion: We present an interesting case of hyponatremia, initially felt to be SIADH, which did not respond to standard therapy. We then treated with steroids for suspected adrenal insufficiency despite a normal morning cortisol. Perhaps the fluconazole contributed to the hyponatremia, by reducing aldosterone secretion. We advocate for consideration of aldosterone deficiency, in the appropriate clinical scenario regardless of a normal morning cortisol.

PUB442

Anti-Glomerular Basement Membrane Negative Goodpasture Disease with Positive Serum Myeloperoxidase Ernest Daniel Moreno Dytiapco, Shubha Ananthakrishnan. *Dept of Nephrology, UC Davis Medical Center, Sacramento, CA.*

Introduction: In patients who present with rapidly-progressive glomerulonephritis, serologic testing is heavily relied upon in making a diagnosis. Presented here is a case of biopsy-proven anti-GBM disease (Goodpasture Disease) with negative anti-GBM IgG serology, but positive MPO serology.

Case Description: The patient is a 52-year-old woman with a history of Graves disease over 30 years prior, hypothyroidism, and eczema, who presented with 1 month of anorexia and hematuria. She denied hemoptysis, arthralgia, rash, fever, chills, NSAIDs, or herbal agents. Physical exam revealed a well-appearing, thin, white, middle-aged woman with trace peripheral edema. The rest of her exam was normal. Baseline serum creatinine (sCr) was 0.6 mg/dL. 4 weeks prior to presentation, sCr was 1.9 mg/dL, then steadily rose to a peak of 4.6 mg/dL upon presentation. Serum electrolytes and bicarbonate were normal. C3 and C4 were normal, ANA was negative, and MPO was 164 AU/mL (high). Anti-GBM IgG by indirect fluorescent antibody (IFA) and by multiplex bead assay were both negative. She then had a renal biopsy. Light microscopy showed necrosis and cellular to early-fibrocellular crescents involving greater than 50% of sampled glomeruli. Global glomerulosclerosis and segmental scarring/fibrous crescents were noted in 25% of glomeruli. She had mild early tubulointerstitial fibrosis. Immunofluorescence microscopy showed linear staining of glomerular basement membranes (GBM) for IgG, consistent with Goodpasture Disease. She was treated with methylprednisolone 750 mg IV for 3 days, then switched to prednisone and cyclophosphamide. Anti-GBM IgG testing by both IFA and multiplex bead assay were repeated and again, were negative. She received 7 sessions of plasmaphresis. After 3 months of steroids and cyclophosphamide, she was switched to maintenance azathioprine and low-dose prednisone. Her sCr at 3 months had improved to 1.3 mg/dL.

Discussion: This case underscores the importance of renal biopsy for definitive diagnosis of rapidly-progressive glomerulonephritis, as the serologic workup can be misleading. Renal biopsy in this case helped identify the true pathology and helped with therapeutic plan and prognosis.

PUB443

Renal Graft versus Host Disease with Focal Segmental Glomerulosclerosis Dominique Dorsainvil, William S. Asch. *Nephrology, Yale School of Medicine, New Haven, CT.*

Introduction: Graft Versus Host Disease (GVHD) is a feared, yet common complication of stem cell transplant (SCT). kidney involvement remains unusual contrary to the typical liver, skin and gastrointestinal manifestations. Main renal presentations pertain to nephrotic syndrome from either a membranous nephropathy in the majority of cases or minimal change disease. Rare cases related to focal segmental glomerulosclerosis (FSGS) have been described. We present a case of renal GVHD post STC with nephrotic syndrome from FSGS.

Case Description: 56 y/o man with ALL whom underwent chemotherapy prior to a matched unrelated donor allogenic stem cell transplant. He was preconditioned with whole body irradiation and pentostatin, engrafted on day 13 and was maintained on sirolimus and tacrolimus. His course was notable for a biopsy proven skin GVHD, severe sepsis complicated by idiopathic thrombotic purpura requiring pulse steroids, intra venous immunoglobulins and acute kidney injury secondary to acute tubular necrosis from which he recovered fairly rapidly. Sirolimus was stopped for concerns of lung toxicity. He was continued on tacrolimus and prednisone. During the same hospitalization, the former was discontinued for unclear reasons. No recurrent acute kidney injury or other side effects of tacrolimus were documented. Several weeks later, he represented to the hospital with nephrotic syndrome with up to 10g of proteinuria. He underwent a kidney biopsy which showed resolving TMA, enlarged glomeruli with collapsing capillary loops on light microscopy, complete foot process effacement on electron microscopy. Our renal pathologist concluded that these lesions were consistent with FSGS. He was restarted on tacrolimus for those findings along with persistent proteinuria. The proteinuria has since resolved.

Discussion: Case reports have associated cessation of immunosuppression with onset of renal GVHD, which was the case for our patient. What renders this case interesting is the histopathological findings of FSGS. A review by Troxel et al, mentioned that about 6% of published biopsy proven glomerulopathy in renal GVHD has similar findings. We also conclude that in this setting, those lesions respond well to immunosuppressive therapy.

PUB444

A Case of Undifferentiated Connective Tissue Disease with Membranous Glomerulonephritis in a Child Doaa Mohammed Youssef, Mohammed Abdelsalam. *Pediatrics, Zagazig Univ, Zagazig, Egypt.*

Introduction: The diagnosis of undifferentiated connective tissue disease (UDCTD) is used to those with features of autoimmune disease but not fulfilling the criteria of specific disorder**.** Membranous nephropathy (MN) is considered as a primary glomerular disease, also referred as idiopathic (Children have a higher frequency of secondary MN than adults); We described unusual case of coexistence of MN resulting in nephrotic syndrome (NS) with UDCTD in child.

Case Description: A 12 years old male presented to us with NS, proteinuria was 3 gm/day, creatinine normal. C3 was normal. he started steroid full dose for one month with remission. He relapsed after 2 months, there was edema, polymyositis, bilateral symmetrical gluteal and thigh induration with no tenderness, fingers swellings and scales. Dermatological consultation found localized scleroderma (morphea) like lesion, anti- Scl 70 , ANA, anti-double sDNA and pANCAs were negative. Skin biopsy was not done as the parents refused. EMG , nerve conduction velocity for gluteal and muscles of thigh and Doppler on renal arteries were normal. Patient was back on full dose corticosteroid for six weeks without remission. Renal biopsy showed diffuse MN with early secondary segmental sclerosis. We excluded secondary causes ofMN. The patient started cyclophosphamide orally on 2 mg/kg/day, with full dose oral steroids EOD. After 2 weeks of therapy, the patient was completely improved. The gluteal, thigh induration and proteinuria were disappeared. cyclophosphamide completed for 3 months with steroid withdrawal the patient is stable and in complete remission till now.

Discussion: Missing anti RNP excluded MCTD, presence of polymyositis and scleroderma with missing anti Scl 70 excluded the diagnosis of Overlap Syndrome; thus we proposed our case with UDCTD. MN with one of the mixed connective tissue diseases was reported previously in three cases one was 60 years old, one with renal cell carcinoma and one female child with MN for 5 years followed by developing scleroderma. We started cyclophosphamide with steroid as this combination was reported to be safer than using chlorambucil with steroid. Our case is considered one of few cases with this presentation of MN and UDCTD in children.

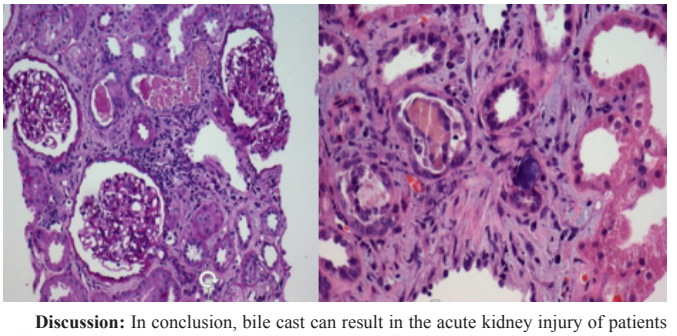
Funding: Private Foundation Support

PUB445

Bile Cast Nephropathy Associated with Acute Hepatitis A Jong-Hwan Jung, Seon-Ho Ahn. *Div of Nephrology, Dept of Internal Medicine, Wonkwang Univ College of Medicine, Iksan, Jeonlabukdo, Korea.*

Introduction: Acute kidney injury is well developed in advanced liver diseases, such as liver cirrhosis and acute hepatic failure. This acute renal dysfunction usually results from decrease of renal perfusion caused by hypovolemic condition. Severe jaundice may also contribute to the acute kidney injury caused by bile acid or bilirubin. Now, we present a interesting case, bile cast nephropathy complicated by acute hepatitis A.

Case Description: A 35-year-old male visited our emergent department with symptoms of nausea, abdominal discomfort, and oliguria. These symptoms and signs were developed abruptly recent several days ago, so he took a digestive medicine, however, these symptoms were aggravated more. He had no chronic diseases, such as diabetes, hypertension, and chronic hepatitis. His skin color was changed into yellowish on physical examination. His vital signs were stable on arrival. Serum total bilirubin, direct bilirubin, creatinine were 10.29 mg/dL, 7.95 mg/dL, and 14.30 mg/dL. Immunoglobulin M of hepatitis A was also positive. His uremic signs were aggravated although fluid therapy. His general condition was improved after hemodialysis, however, several clinical signs, such as generalized edema, hypertension, and hyperkalemia were still remained for four weeks. We performed renal biopsy. On the pathology, the renal tubular lumens frequently contain dark pigment casts with foreign body reaction and calcification, and interstitium focally exhibits mononuclear cell infiltration and fibrosis.



Discussion: In conclusion, bile cast can result in the acute kidney injury of patients with severe jaundice and hepatic failure. A direct bilirubin toxicity for renal tubules may contribute to this renal injury. We may carefully suggest that recovery of acute tubular necrosis can be delayed by the presence the tubular bile cast through this case.

PUB446

Intravitreal VEGF Inhibitors Causing Allergic Interstitial Nephritis
Debbie Valsan,[1] Saifullah Kazi,[1] Zia M. Umruddin.[2] *[1]Lankenau Medical Center; [2]Pottstown Memorial Hospital.*

Introduction: This case highlights the effect of intravitreal VEGF inhibitors in causing AIN.

Case Description: A 51 y/o male with a history of DM and HTN presents to his primary care office for nausea and vomiting in December 2010. His creatinine was 1.2 mg/dl in July 2010 and 1.9 mg/dl in October 2010 with repeat creatinine of 11mg/dl with a BUN of 106mg/dl. His medications include metformin, glyburide and Bevacizumab monthly intravitreal injections that he began on February 2010. Physical exam was unremarkable. Urine microscopy showed granular casts and eosinophils were negative. Ultrasound revealed normal sized kidneys with normal echotexture and no hydronephrosis. He was placed on pulse dose steroids given his rapid onset of renal failure with no clear etiology and pending serologic workup. Hemodialysis was initiated for uremic symptoms. Complete serologic panel was negative and complement levels were normal. Biopsy results showed AIN with ATN and early diabetic glomerulosclerosis. Bevacizumab was discontinued. He was placed on dialysis temporarily with oral steroids with improvement of creatinine to baseline. His creatinine was noted to slowly trend up at 1.72mg/dl in October 2015 and then at 2.4mg/dl a month later. Our patient was started on Ranibizumab intra ocular injections since August 2015 by a different ophthalmologist. Given his previous history, recommendations were made to stop the current therapy with Ranibizumab as no other etiology for this acute kidney injury was evident and his creatinine declined to 1.6 mg/dl.

Discussion: Histologic findings in patients who have been on VEGF inhibitors have included TMA, collapsing glomerulopathy, and isolated reports of cryoglobulinemic and immune complex GN. We report the first case of AIN in the setting of intravitreal Bevacizumab used for DME. Discontinuation of the potential causative agent is a mainstay of therapy. Drug-induced AIN is not dose dependent, and recurrence or exacerbation can occur with a second exposure to the same or a related drug. This was seen in our case with initiation of Ranibizumab. Regular monitoring of the renal function in these patients will help identify this problem and avoid significant morbidity associated with these new biologic agents.

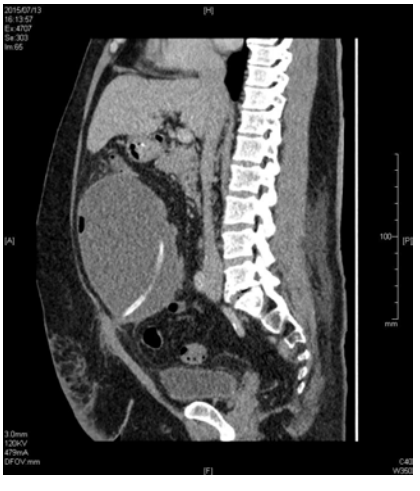
PUB447

"Extraperitoneal Dialysis" in Severe Obesity
Sawako Kobayashi, Takamasa Miyauchi, Hiroyuki Yamamoto, Fumika Taki, Masahiko Nagahama, Yasuhiro Komatsu. *Nephrology, St. Luke's International Hospital, Tokyo, Japan.*

Introduction: We report a case where a patient with misplaced Tenckoff catheter in extra-abdominal cavity underwent 5 months of "peritoneal dialysis".

Case Description: A 46 year old male started PD for ESRD secondary to hypertensive nephrosclerosis. He was extremely obese, weighing 158kg with BMI of 51.0kg/m^2. Four exchange of 2.5 L dialysate per day was successfully delivered without any infusion/drainage trouble. He was well despite of relatively low dialysis dose; a weekly Kt/V of 0.99 (peritoneal 0.84, renal 014), a total CCr of 46.0l/week (peritoneal 30.0, renal 15.9), ultrafiltration volume of 1500ml per day. Peritoneal equilibration test showed "low" category. Five months after initiation of PD, he was admitted to our hospital for PD peritonitis. A CT scan, taken with dialysate in the patient's abdomen, revealed a fluid collection approximately the size of 11cm x 19cm x 17cm in the abdominal wall, just between the rectus abdominis and peritoneum membrane. The tip of the catheter was detected outside of peritoneal cavity. Subsequently, he had his catheter surgically removed and switched to HD.

Discussion: Catheter misplacement can be easily detected because it would immediately result in difficulty in infusion and drainage; however, in this case, misplacement was not detected and "peritoneal dialysis" could be continued for a considerable amount of time. This is probably due to the patient's thick abdominal wall, which obscured the symptoms. This case shows that fluid and solute can be transported even when peritoneal dialysate is dwelled outside the abdominal cavity, between abdominal muscle and peritoneum. For obese patients, confirming the catheter position with additional measures such as lateral abdominal radiography is recommended, even without outflow failure at the time of catheter placement.



PUB448

Unusual Diffuse Proliferative Glomerulonephritis with Renal Parenchymal Involvement by CLL
Ana Belen Rivera de Rosales,[1] Duminda Siripala,[1] Agnes B. Fogo,[2] Ivo Lukitsch.[1] *[1]Nephrology, Ochsner Medical Center, New Orleans, LA; [2]Renal Pathology, Vanderbilt Univ.*

Introduction: Female patient with stage I CLL, subarachnoid hemorrhages and massive proteinuria. Biopsy shows an unusual cause.

Case Description: 49yo with stage 1 CLL and increasing WBC to 24K, not requiring therapy. Asymptomatic, without frequent infections. She had stable cervical nodes, mild dependent edema and history of subarachnoid hemorrhages. She again presented with headache, found to have subarachnoid hemorrhage and persistent hematuria and proteinuria of 20 grams that had been increasing over past two months with preserved renal function. Serologic evaluation revealed low C4. Urine sediment showed massive leukocyturia with RBC and WBC casts. Urine culture negative. Renal biopsy was done showing unusual diffuse proliferative glomerulonephritis with endocapillary proliferation and crescents without fibrinoid necrosis. IM was positive for mesangial and arteriolar granular C3 staining only without any deposits by EM. Positive staining for CD20, CD5 and CD23 confirmed renal parenchymal involvement by CLL. Despite initial steroid pulse she continued to have massive proteinuria. Because of the progressing GN and CNS bleed she received chemotherapy with Rituximab 375mg/m2 and cyclophosphamide 750 mg/m2 with high dose dexamethasone monthly times 3. Two weeks after first dose of chemotherapy proteinuria had decreased to 2 grams. On two month follow up her proteinuria reduced to one gram with resolution of leukocyturia.

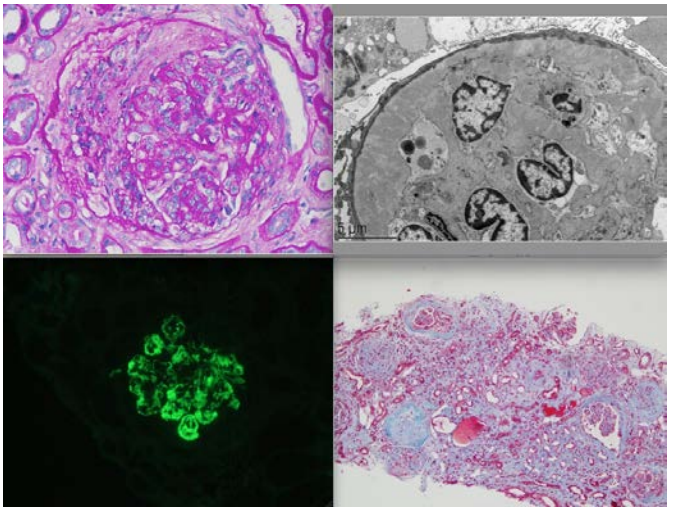
Discussion: Paraneoplastic etiology, not related to immune complex deposition is proposed as the cause for the proliferative glomerulonephritis. A paraneoplastic effect on the CNS vasculature may also be contributing. Treatment with chemotherapy led to resolution of proteinuria and leukocyturia with preserved renal function. To our knowledge has not been previously described.

PUB449

A Mid-Life Renal Crisis of Proteinuria and AKI
Monica Lona Reynolds,[1] Eddie R. Fuller,[1] Volker Nickeleit.[2] *[1]Nephrology, Univ of North Carolina, Chapel Hill, NC; [2]Nephropathology, Univ of North Carolina, Chapel Hill, NC.*

Introduction: Proliferative glomerulonephritis with monoclonal deposits is due to a single clone immunoglobulin that aggregates to form electron dense deposits in the glomeruli. It is common in older Caucasian women and treatment is variable. This 45-year-old previously healthy man presented with AKI, nephrotic proteinuria and active urine sediment.

Case Description: The patient presented to his PCP with fatigue and severe hypertension to 205/125. Labs revealed creatinine of 15.5mg/dl and he was admitted. The patient was well appearing with 1+ pitting edema in lower extremities. ANCA, ANA, HIV and Hepatitis were negative. C3 was 69. His urine protein to creatinine ratio was 13.9g. Urine sediment had dysmorphic RBC's and RBC casts. Biopsy (Figure 1) showed sclerosing MPGN with 30% crescents associated with IgG1 Kappa light chain restricted immune complex deposits. 50-60% of glomeruli were sclerosed. His SPEP/immunofixation revealed monoclonal IgG kappa. K/L free light ratio was 5.60. Myeloma bone survey was without lytic lesions and bone marrow biopsy was normocellular. The patient received three doses of IV methylprednisolone followed by prednisone and seven sessions of therapeutic plasma exchange. After Oncology consult, he received Cyclophosphamide, Bortezomib and Dexamethasone for 4 cycles. Cr is now 6.9mg/dl with persistent proteinuria. His K/L ratio decreased and he is pursuing transplant.



Discussion: In contrast to most patients with a proliferative GN and monoclonal IgG electron dense deposits, this patient presented with features worrisome of an underlying lymphoproliferative disorder/ plasmacytoma. Little data exists regarding treatment for these patients. Prognosis is grim with more than a third of patients with persistent dysfunction. Although he had sclerosis in half of glomeruli, our patient was treated aggressively.

PUB450

An Unexpected Diagnosis when Expecting: Scleroderma in a Patient with Class III Lupus Nephritis Meera Subash,[1] Amber P. Sanchez.[2] *[1]Dept of Medicine, Univ of California, San Diego, San Diego, CA; [2]Dept of Medicine, Div of Nephrology, Univ of California, San Diego, San Diego, CA.*

Introduction: We present an interesting case of a 39 year-old woman who was previously diagnosed with cutaneous lupus with +ANA with low C4, which initially responded to topical treatments. She continued with topical treatments until her third pregnancy. At the beginning of her pregnancy, she was diagnosed with systemic sclerosis when her fetus was unable to be visualized on abdominal ultrasound due to severe skin thickening that rapidly progressed during the pregnancy. She delivered successfully, and continued with steroid-sparing therapy for her cutaneous lupus until her scleroderma symptoms worsened in the setting of lupus nephritis.

Case Description: Her systemic sclerosis became complicated with diffuse skin thickening with calcinosis, chronic skin infections, Raynaud's phenomenon, pulmonary hypertension, and esophageal dysmotility. Her creatinine began to rise from a normal range with the eventual development of non-nephrotic, persistent proteinuria. A biopsy was performed, revealing a low-grade immune complex-mediated glomerulonephritis, most consistent with focal sclerosing lupus nephritis (Class III). She began treatment with rituximab with an increase in serum albumin and decrease in urine protein. Mycophenolate mofteil was slowly uptitrated as a steroid sparing therapy aligning with the Imperial Lupus Trial. Her urine protein levels stabilized and the patient is stable currently.

Discussion: Her case highlights the importance of screening patients who have been previously diagnosed with a single autoimmune disease entity for other autoimmune disorders as these syndromes often cluster and exacerbate renal dysfunction. The initial physical finding of thickened abdominal skin during a first trimester ultrasound that led to her diagnosis of systemic sclerosis is a fascinating component to this case. It can be surmised from the current scleroderma literature that females with scleroderma are encouraged to avoid pregnancy within the first 3 years of diagnosis because disease complications, specifically hypertension and renal function that can complicate pregnancy.

PUB451

Slowly Progressive Light Chain Cast Nephropathy with Proximal Tubulopathy Yuka Kawasaki, Yuhei Kirita, Itaru Nakamura, Yayoi Shiotsu, Tetsuro Kusaba, Keiichi Tamagaki. *Nephrology, Kyoto Prefectural Univ of Medicine, Kyoto, Japan.*

Introduction: Monoclonal gammopathy manifests as various forms of renal diseases. Light chain cast nephropathy (LCCN) is a common cause of acute kidney injury with multiple myeloma. Light chain proximal tubulopathy (LCPT) is an increasingly recognized, yet uncommon renal complication of monoclonal gammopathy. LCPT, particularly with crystals, usually presents as Fanconi syndrome. We report a case of slowly progressive renal insufficiency due to LCCN with LCPT.

Case Description: A 55-year-old man with a medium build presented with a gradual increase in the serum creatinine (Cr) level from 1.2 to 1.6 mg/dL in a year. His estimated GFR-creatinine (eGFRcr) and -cystatin C (eGFRcys) were 35.4 and 59.2 mL/min/1.73 m^2, respectively, with a difference between the values. Laboratory data showed mild proteinuria of 0.21 g/gCr, with no evidence of glycosuria, water-electrolyte imbalance, acidemia, or hypoalbuminemia. Urinary immunofixation showed the presence of free kappa light chains. The levels of serum free kappa and lambda light chains were 1,020 and 13.3 mg/dL, respectively. However, bone marrow-biopsy specimen revealed less than 10% of plasma cells. Renal biopsy showed crystalline variants of LCCN and LCPT. We diagnosed monoclonal gammopathy of renal significance and started chemotherapy along the guidelines for multiple myeloma.

Discussion: This case highlights the fact that LCCN can present an indolent course and LCPT with crystals does not always occur with Fanconi syndrome; thus, a diagnosis of slowly progressive renal insufficiency without any symptoms or abnormalities in laboratory evaluations should be made carefully. This case showed a difference between eGFRcr and eGFRcys, which may be useful for detecting LCPT. Cystatin C is freely filtered by the glomerulus, whereas Cr is not only filtered by the glomerulus but also secreted by the proximal tubule to some extent. Tubular injury induced by LCPT may elevate serum Cr than serum cystatin C, and make a difference between the eGFRcr and eGFRcys.

PUB452

Mycobacterium Genavense in a Kidney Transplant Patient Felix Nadrowitz,[1] Philip Kirschner,[2] Jan Menne.[1] *[1]Dept of Nephrology and Hypertension, Hannover Medical School, Germany; [2]Inst for Medical Microbiology and Hospital Epidemiology, Hannover Medical School, Germany.*

Introduction: Transplant recipients are highly susceptible for atypical infections as a consequence of their immunocompromised state. We report an exceptional case of a disseminated *Mycobacterium genavense* infection in a kidney transplant patient.

Case Description: The 26 years old Caucasian women received a kidney transplant from her father in 2010. In January 2016 she was admitted to our hospital with fever and diarrhea. Her immunosuppressive therapy consisted of tacrolimus, sirolimus and prednisolone. On admission inflammation markers were increased (CRP 23mg/l). Elevated serum creatinine (max. 198 µmol/L) indicated acute kidney injury. Differential blood count revealed pancytopenia and in particular distinct lymphocytopenia with 300/µl. Blood cultures and stool samples were repetitively negative. An Interferon-γ release assay was negative, as well. A kidney biopsy proved polyomavirus nephropathy, which is rare six years after transplantation. Thus, immunosuppression was reduced. Moreover, a colonoscopy and supplemental biopsies showed CMV-Colitis. Treatment with intravenous ganciclovir terminated diarrhea. However, fever persisted and inflammation parameters further increased, despite of additive broad-spectrum antibiotics. A chest CT scan detected bilateral ground glass infiltrates, in particular in the upper left lobe. Bronchoscopy was inconspicuous. 16S rRNA gene sequencing identified *Mycobacterium genavense* in blood cultures and the bronchoalveaolar lavage after six weeks, proving a disseminated infection. Antimycobacterial therapy was started with Clarithromycin, Rifampicin, Moxifloxacin and Ethambutol, adjusted to the impaired kidney function. However, patient's inflammatory parameters and fever episodes did not resolve after 12 weeks of therapy.

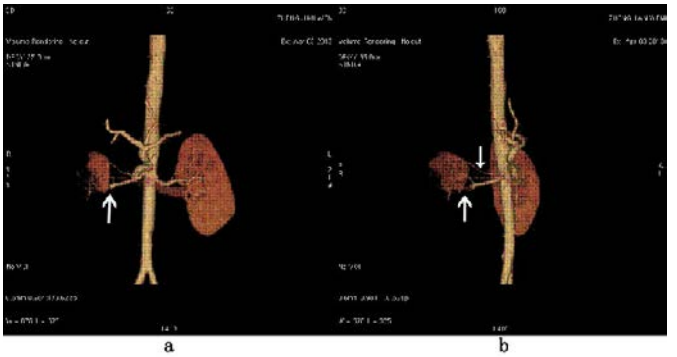
Discussion: This exceptional case illustrates rare infectious complications in a patient six years after kidney transplantion. The identification of *Mycobacterium genavense* is challenging due to the unspecific symptoms and its slow growth.

PUB453

Clinical Manifestations of Nephrotic Syndrome Complicated by Renal Artery Thrombosis: A Case Report Lihua Wang,[1,2] Xi Qiao.[1,2] *[1]Nephrology, Second Hospital of Shanxi Medical Univ, Taiyuan, China; [2]Shanxi Kidney Disease Inst, Taiyuan, China.*

Introduction: Although thrombotic complications in the venous system are common in patients with nephrotic syndrome, arterial thromboses associated with nephrotic syndrome are much less common. The main renal artery thromboses are extremely rarely observed. We report a case of nephrotic syndrome complicated by main renal artery thrombosis.

Case Description: The clinical data of a patient, who suffered from nephrotic syndrome complicated by right main renal artery thrombosis, were analyzed. The patient was a 38-year-old man, who presented with features of main renal artery thrombosis, when the nephrotic syndrome relapses after 1 year complete remission. The clinical manifestations were the appearance of severe lumbago suddenly, fever, percussion pain of ipsilateral kidney area, increase of the total number of white blood cells, white nucleus left, massive proteinuria, and aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), hydroxybutyrate dehydrogenase (HBDH) was increased obviously, hypertension did not occur. Renal artery thrombosis was diagnosed by echo Doppler and confirmed by computed tomography angiography (CTA).



Intravenous thrombolysis therapy was effective. CTA showed complete lysis of renal thrombus; clinically there was a regression of flank pain.

Discussion: Nephrotic syndrome with main renal artery thrombosis is rare, and the clinical manifestations are acute renal infarction. Renal Doppler and CTA should be carried out in these patients. When the disease is diagnosed at an early stage, an intravenous thrombolysis can be attempted. Timely diagnosis and properly treatment are important for improving the prognosis of patients.

PUB454

C-ANCA+ RPGN following Anti-TNF Use in Autoimmunity Anne S. Yu, Susan E. Quaggin, Jennifer A. Tuazon. *Nephrology, Northwestern Univ, Chicago, IL.*

Introduction: Rapidly progressive glomerulonephritis (RPGN) is characterized by rapid loss of renal function and glomerular crescent formation. In patients with rheumatoid arthritis (RA), there have been 3 case reports of acute renal failure due to pauci-immune necrotizing crescentic GN in the setting of anti-tumor necrosis factor-alpha (anti-TNFα) use. We present a case of a patient with RA who developed RPGN following treatment with etanercept.

Case Description: A 43-year-old woman with history of long standing RA (treated with steroids intermittently for 9 years and etanercept for 5 months), hypothyroidism, and recent pulmonary embolism, presented with headache, nausea, epigastric pain, and malaise. On admission, she was found to have acute renal failure (Cr 5.8 mg/dl from baseline 0.8 six weeks prior) with hematuria (>100 RBCs and RBC casts on urinalysis), sub-nephrotic range proteinuria (1.2 g/g Cr), and anemia (Hb 7.8). On exam, she was not hypertensive, with clear lungs, no leg edema, and no rashes. A renal biopsy was performed which revealed severe pauci-immune necrotizing crescentic GN with significant tubulointerstitial inflammation and minimal scarring. She had a positive C-ANCA (titer 1:1280) and anti-PR3 (158). She received pulse steroids and cyclophosphamide, with downtrend in Cr from peak of 6.5 to 4.6 by day of discharge and never required renal replacement therapy. Renal function continued to improve with Cr down to 1.2 after extended steroid taper and maintenance of cyclophosphamide over 3 months, with plan for a 6 month total treatment course.

Discussion: Treatment of RA with anti-TNFα agents has been associated with development of vasculitis and rarely pauci-immune GN. While anti-TNFα agents may stimulate formation of autoantibodies, mechanisms are unclear. The temporal relation of anti-TNFα use and new-onset renal disease suggests a pathogenic role of TNFα antagonists in development of GN. RPGN should be considered in patients with underlying autoimmunity and exposure to anti-TNFα who develop renal failure, as early diagnosis and initiation of therapy are essential to prevent irreversible loss of renal function.

PUB455

Crescentic IgA Nephropathy in a Patient with Active Pulmonary Tuberculosis Afsaneh Haftbaradaran,[1] Golriz Jafari,[1] Ruchika Bhasin,[1] Phuong-Thu T. Pham,[2] Phuong-Chi T. Pham.[1] *[1]Olive View-UCLA Med Ctr; [2]UCLA.*

Introduction: The presence of crescents in IgA nephropathy (IgAN) may be associated with a 1.5-fold increased risk of kidney failure. Concurrent diffuse mesangial proliferation may lead to a 50% risk of reaching end stage renal disease within 5 years. Given its worse prognosis compared with non-crescentic IgAN, the addition of cyclophosphamide to glucocorticoid has been suggested.

Case Description: 79-year old male with chronic obstructive pulmonary disease and alcoholism presented with anorexia and generalized weakness. Full evaluation revealed active pulmonary tuberculosis (TB). Patient received rifampin, isoniazid, pyridoxine, and ethambutol (RIPE) therapy when he began to develop new onset rapid kidney injury (creatinine [Cr] increase from 0.9 to 6.5 mg/dL within 2 weeks), proteinuria (none to protein/creatinine ratio 2.0 g/g), hematuria, and red blood cell casts. Kidney biopsy revealed active glomerular crescents approximated at 20%, with necrotizing lesions and acute tubular necrosis. Given the concurrent active pulmonary TB, patient was only given minimal glucocorticoids (solumedrol 300 mg IV daily for 3 days followed by a rapid prednisone taper to off within 2 1/2 months). Both kidney injury and proteinuria resolved within 3 months. At 6 month-follow up, patient had a Cr of 1.3 mg/dL and no proteinuria.

Discussion: Active TB has been reported to be associated with IgAN, mesangial proliferative, crescentic, membranous glomerulonephropathies, among others. Of interest, rifampin has also linked to crescentic GN. In the current case, patient received continuing full dose RIPE and a short course of glucocorticoids with complete resolution of proteinuria, hematuria, and marked improvement of Cr within 3 months. Given the acute onset of kidney injury following the diagnosis of active TB and the rapid resolution of kidney injury with RIPE, we suspect that the crescentic IgAN was associated with active pulmonary TB and less likely, rifampin or others. The association is important to recognize because unlike other underlying etiologies of crescentic IgAN where aggressive immunosuppressive may be indicated, it is contraindicated and unnecessary in patients with active pulmonary TB.

PUB456

Hyponatremia in an Unexpected Case of Extrapulmonary Tuberculosis Sayena Sajadi, Reginald Ifeanyi Obi. *Nephrology and Hypertension, East Carolina Univ, Greenville, NC.*

Introduction: Accurate diagnosis of hyponatremia is pivotal to optimum management. Discovery of the cause of hyponatremia is not always straightforward and requires thorough investigation and attention to detail. We describe a case of subacute hypoosmolar hyponatremia in a patient with multiple risk factors for various etiologies of hyponatremia.

Case Description: 51 year old male with history of HIV and subdural hematoma was admitted with concern for septic shock secondary to pneumonia. His exam was pertinent for BP 84/50 mmHg and Pulse 108. He was cachectic, tachycardic, with clear lungs, and irritable. Labs were pertinent for sodium 124 mEq/L, potassium 5.9 mEq/L, serum osmolality 260 mOsm/kg, urine osmolality 681 mOsm/kg, urine sodium 84 mEq/L, and morning cortisol 5.6 ug/dL. His PPD and Quantiferon Gold test were positive. He was started on broad-spectrum antibiotics as well as Haldol for agitation. Pulmonary TB was ruled out. A differential of SIADH and Cerebral Salt Wasting (CSW) was considered. CSW was ruled out after hydration led to further drop in sodium. A suspicion for adrenal insufficiency was entertained because of hyperkalemia in the setting of low normal cortisol. Evaluation with a cosyntropin stimulation test was performed and confirmed primary adrenal insufficiency likely due to infection of the adrenal glands with TB. The patient received appropriate therapy leading to resolution of hyponatremia.

Discussion: In the setting of various potential etiologies for hyponatremia, thorough workup is critical. Based on this patient's history of pneumonia, HIV, antipsychotic medication use, drop in sodium after receiving isotonic fluids, and urine and plasma sodium studies, SIADH may be suspected. However, detailed diagnostics review revealed primary adrenal insufficiency likely secondary to extrapulmonary TB and led to initiation of appropriate therapies. Hyponatremia is the most common electrolyte abnormality in extrapulmonary TB. Infectious adrenalitis secondary to TB can lead to hypocortisolism and relative hypersecretion of antidiuretic hormone, which leads to hyponatremia. Understanding the primary cause and mechanism of hyponatremia in this case led to appropriate therapy and resolution of hyponatremia.

PUB457

A Case of Atypical PostInfectious Glomerulonephritis in an Elderly Male Patient with Liver Cirrhosis Marika Manolopoulou,[1] Mark Lusco,[2] Leslie S. Gewin.[1,3] *[1]Div of Nephrology and Hypertension, Vanderbilt Univ Medical Center; [2]Dept of Pathology, Microbiology and Immunology, Vanderbilt Univ Medical Center; [3]Div of Nephrology and Hypertension, Veterans Affairs Medical Center, Nashville, TN.*

Introduction: Postinfectious Glomerulonephritis (PIGN) is usually a childhood disease that occurs after an upper respiratory tract infection or impetigo and follows a benign course. We present a case of an elderly male patient with liver cirrhosis with clinical evidence of RPGN and pathologic features of PIGN on biopsy.

Case Description: A 60 year old male patient with CKD 3, DM2, HCV cirrhosis (viral load undetectable on Harvoni therapy) presented with shortness of breath, edema, proteinuria (1.4 g), hematuria and serum creatinine 2.3. Hospital course was complicated by oliguria and peak serum creatinine of 5.3. Aside from low complements, he had negative workups both for causes of glomerular disease as well as active infections. Renal biopsy was performed and showed focal proliferative glomerulonephritis, mild diabetic nephropathy with a dominant C3 granular and chunky mesangial and segmental capillary loop staining in a "starry sky" pattern by IF. A late phase or resolving postinfectious etiology was suggested without evidence of subepithelial hump-type deposits. He was treated with a course of steroids, and on hospital day 10 his urine output and subsequently his renal function improved.

Discussion: PIGN follows a more aggressive course in elderly patients with multiple comorbidities. Even though there is no strong evidence that steroids help PIGN, our patient perhaps improved after steroid administration. Given pathologic evidence of PIGN with characteristic staining, this case illustrates the possibility that PIGN and C3 glomerulopathy might be diseases of the same disease spectrum.

PUB458

Bilateral Obstructing Ureter Calculi, the Cause of Stage 3 Acute Kidney Injury Sai Prasad Gadapa,[1] Siwadon Pitukweerakul,[2] Sree V. Pilla.[3] *[1]Internal Medicine, St. Francis Hospital, Evanston, IL; [2]Internal Medicine, St. Francis Hospital, Evanston, IL; [3]Internal Medicine, St. Francis Hospital, Evanston, IL.*

Introduction: Non-contrast CT abdomen and pelvis should be the imaging modality of choice in a patient with rapidly worsening kidney function.

Case Description: A 69-year-old man with altered mental status. His medical history included is alcoholic liver cirrhosis, schizoaffective disorder. His medications included the trazodone. He was admitted for elevated ammonia level and urinary tract infection secondary to E.coli and was getting treatment with antibiotic piperacillin-tazobactum, and lactulose. On hospital day 3 serum creatinine was 3.3 mg/dL, the creatinine the day prior was 1.2 mg/dL. He reported mild diffuse abdominal pain. On physical exam, the patient was afebrile; his HR was 85/min, BP 109/52 mm Hg, RR 20min, and oxygen saturation 94 % on 4 liters nasal cannula. The neurological examination was unremarkable. He did not make urine overnight. On hospital day 4 he made 300 ml of urine. Urine analysis revealed cloudy urine, Specific Gravity 1.002, pH 6, moderate blood, large leukocytes, rbc's 21-50/hpf. Urine sodium revealed 48 mmol/L, FENA 3.6%. The wbc was 21000/ccmm, with 17000 absolute neutrophils. The sodium was 130 mmol/L, K 4.5 mmol/L, cl level 103 mmol/L, HCO3 level 21 mmol/Lr, BUN level 43 mg/dL, creatinine level 5.0 mg/dLr, GFR MDRD 12 ml/min/1.73 m, and blood ammonia level 85 UMOL/L. Renal ultra-sonogram revealed no evidence of hydronephrosis. On hospital day 5 he had myoclonic jerks on neurologic examination. He underwent emergent hemodialysis. On hospital day 6 he had non-contrast CT abdomen and pelvis which revealed bilateral obstructing calculi within the mid distal ureters measuring approximately 8 mm respectively. Patient subsequently underwent bilateral ante-grade pyelogram and bilateral nephrostomy tube placement under ultrasound guidance.

Discussion: Renal ultrasound is the initial imaging of choice in renal failure; but lacks sensitivity to identify the cause of obstruction when obstruction is in the lower part of ureter. This case report give special importance to non-contrast CT abdomen and pelvis in management of rapidly worsening kidney function.

PUB459

A Case of Membranoproliferative Glomerulonephritis in Hyaline Variant Multicentric Castleman's Disease Sindhura Bobba, Davis Massey, Jason M. Kidd. *Depatment of Internal Medicine, Div of Nephrology, Virginia Commonwealth Univ Health system.*

Introduction: Membranoproliferative glomerulonephritis (MPGN) is a pattern of histologic injury characterized by endocapillary proliferation, mesangial hypercellularity, and capillary wall remodeling.MPGN is frequently immune complex mediated or due to complement dysregulation. Less commonly, MPGN can be seen without immunoglobulin or complement deposition. We present an uncommon cause of the MPGN pattern of injury related to Castleman's disease (CD).

Case Description: A 23 year old Caucasian man presented for evaluation of acute renal failure with progressive anasarca and mediastinal mass. At presentation, his serum creatinine was 1.8 mg/dl. Urinalysis was significant for monomorphic hematuria and proteinuria. A spot urine protein to creatinine ratio was 0.9 mg/mg. Hemoglobin was 9.3 g/dl. Contrasted tomography scan of his chest, abdomen and pelvis showed bilateral pleural effusions, anterior mediastinal mass and mediastinal lymphadenopathy.

A serologic work up was unremarkable including negative EBV IgM, CMV, HIV. Biopsy of the mediastinal mass was negative for malignancy. A bone marrow biopsy was unrevealing. Renal biopsy was performed. Light microscopy was significant for a

membranoproliferative pattern of injury. Immunofluorescence was unremarkable. No immune complexes were present on electron microscopy. He underwent axillary lymph node biopsy that showed multicentric Castelman's disease of hyaline vascular variant. He received 4 doses of etoposide and one dose of rituximab. Most recent serum creatinine was 0.72 mg/dl and he has lost 27 kg.

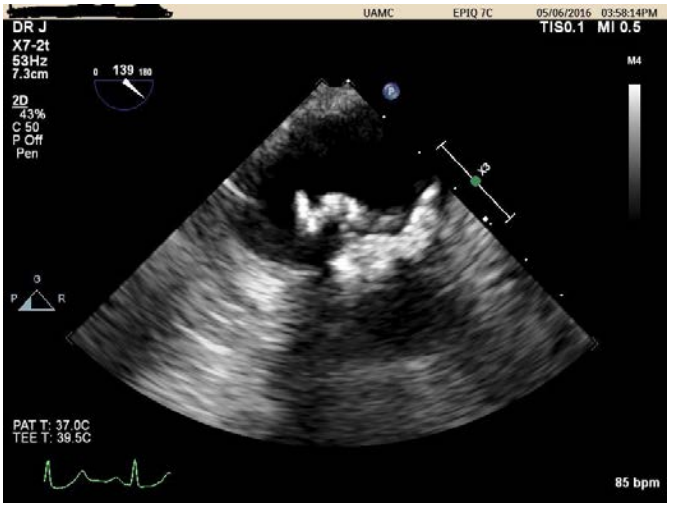
Discussion: A membranoproliferative pattern of injury is present in our patient without any immunune complexes, complement deposition or evidence of TMA. Increased production of IL6 and vascular endothelial growth factor(VEGF) have been implicated in the pathogenesis of CD. In mouse models, increased IL6 has been shown to induce podocyte apoptosis and podocyte specific overexpression of VEGF resulting in collapsing glomerulopathy [1]. It is unclear if either play a role in CD related renal manifestations. More study into the pathogenesis of renal disease in CD is needed. [1]Barlett, annurev-physiol 2016.

PUB460

Calcific Atrial Mass in End-Stage Renal Disease Mohamad Altriki, Prabir Roy-Chaudhury, Bijin Thajudeen. *Nephrology, Banner Univ of Arizona Medical Center, Tucson, AZ.*

Introduction: Metastatic cardiac calcification (MCC) has been widely reported in patients with ESRD promoted by elevated serum calcium-phosphate product, increased PTH,and reduction in body fluid inhibitors of calcification. Dystrophic cardiac calcification(DCC) is often associated with damaged tissue or systemic inflammation and when present, is usually extensive, often encompassing multiple cardiac chambers and valves. We present an unusual case of DCC as well as MCC involving left atrium(LA) in the setting of ESRD.

Case Description: A 55-year-old Caucasian male with h/o HTN, ESRD on HD, failure of previous renal transplant presented with symptoms of fever and chills. He was diagnosed with sepsis due to methicillin-resistant *Staphylococcus aureus* infection. A transesophageal echocardiogram done as part of the workup for MRSA bacteremia showed a large 2.2cm x 1.2cm calcified, highly mobile echo density attached to the Coumadin ridge within LA representing an old, calcified vegetation or a calcified thrombus.



Cardiac MRI confirmed the mobile calcified mass. Laboratory tests showed PTH of 670 pg/ml, corrected calcium of 8.9 mg/dl and phosphorus 6.2 mg/dl.

Discussion: In our patient, the calcification in the LA is a product of DCC promoted by MCC resulting from abnormal bone mineral metabolism disorder. Calcium deposition often involves the mitral valve, left ventricular free wall and septum as well as the LA appendage. It can lead to complicated valvular stenosis, cardiac arrhythmias, cardiac block and abnormal cardiac hemodynamics by effecting systolic and diastolic cardiac function. Over time LA pressure can increase due to decreased compliance of the LA wall and can be transmitted through pulmonary veins resulting in derangements in right heart hemodynamics. Awareness, early detection and treatment of the underlying cause, and resulting complications is the key to the patient outcome.

PUB461

Refractory Hyperkalemia with Calcineurin Inhibitor- Mechanism and Potential Treatment Option Abhisekh Sinha Ray,[1] Anjushree Kumar,[1] Sreeparna Ghosh,[2] Meenakshi Ghosh,[3] Priyeshkumar Patel,[1] Amna Ilahe.[1] *[1]Nephrology and Hypertension, Kansas Univ Medical Center, Kansas City, KS; [2]Internal Medicine, Interfaith Medical Center, Brooklyn, NY; [3]Pulmonary, SIU-SOM, Springfield, IL.*

Introduction: Calcineurin inhibitor (CNI), an important ammunition in immunosuppressive artillery in post-transplant setting, may cause recalcitrant hyperkalemia even with normal renal function. Although CNI can alter renal tubular potassium handling by multiple pathways but hyporeninemic hypoaldosteronism considered to be primary mechanism. Hence, fludrocortisone, a synthetic mineralocorticoid, may be useful in this scenario.

Case Description: A 30year-old female with alcoholic cirrhosis and hepatorenal syndrome received an orthotopic liver transplant (OLT). Post-OLT her renal function returned to normal with good urine output. Discharge medications included mycophenolate sodium, tacrolimus, prednisone and bactrim. For edema and hyperkalemia of 5.6meq/L, furosemide was started. She got readmitted on post-op day 20 with severe hyperkalemia of 7.8meq/L; managed conservatively with insulin-dextrose, sodium-bicarbonate and furosemide. She was discharged on furosemide, potassium (K) restricted diet and as needed Sodium Polystyrene Sulfonate(SPS). She continued to have hyperkalemia with normal serum creatinine and bicarbonate. Tacrolimus trough was maintained within 4-7ng/ml. Hydrochlorothiazide was added and bactrim was discontinued. However, K remained elevated around 6-7meq/L for next 8 weeks despite dual diuretic therapy and low K diet. She had to take SPS frequently and experienced severe abdominal cramping, diarrhea and weight loss. Trans-tubular potassium gradient was low with low plasma renin activity(3.1ng/ml/hour) and aldosterone level(<4ng/dl). CT scan showed bilateral normal adrenal glands. For presumed CNI induced hyperkalemia, fludrocortisone was initiated. Hyperkalemia dramatically improved in few days and remained in 3-4meq/L range over 18 months.

Discussion: Efficacy of Fludrocortisone therapy in CNI induced hyperkalemia is supported by very low level of evidence. However, to avoid the side effects with long term use of SPS or in case of refractory hyperkalemia, Fludrocortisone may be effective.

PUB462

Nivolumab Induced Renal Failure with Collapsing Focal Segmental Glomerulosclerosis (FSGS) - A Case Report Abhisekh Sinha Ray,[1] Sreeparna Ghosh,[2] Meenakshi Ghosh,[3] Sri G. Yarlagadda.[1] *[1]Nephrology and Hypertension, Kansas Univ Medical Center, Kansas City, KS; [2]Internal Medicine, Interfaith Medical Center, Brooklyn, NY; [3]Pulmonary, SIU-SOM, Springfield, IL.*

Introduction: Nivolumab, a monoclonal antibody against PD-1 (Programmed cell death protein 1) receptor, suppresses PD-1 pathway-mediated inhibition of anti-tumor immune response. This agent has been approved for metastatic melanoma, non-small cell lung cancer, advanced renal carcinoma, relapsing Hodgkin's lymphoma. Immune mediated nephritis of varying severity is reported in early literature and most had complete recovery with high dose steroid. However clinical experience is limited. We report a case of severe renal insufficiency with Nivolumab requiring long term renal replacement therapy.

Case Description: 42year-old male with stage IV adenocarcinoma of lung with disease progression despite chemo and radiation therapy received one dose of Nivolumab. Baseline creatinine(Cr) was 1.3mg/dl; urine analysis was negative for proteinuria. His 2nd dose of Nivolumab, scheduled after 2 weeks, was held due to elevated Cr(3.3mg/dl) and he was subsequently admitted. He developed progressive acute kidney injury without any response to conservative management with intravascular volume expansion. He had 30.8g/day proteinuria and was started on high dose intravenous steroid for suspected immune-mediated nephritis. His renal function and urine output worsened and renal biopsy was performed. Pathology showed collapsing focal segmental glomerulosclerosis (FSGS) involving 20 out of 46 glomeruli without any significant immune deposit. He continued to have heavy proteinuria, oliguria with Cr 8.2mg/dl on 12th day of hospitalization. He had to be started on hemodialysis for significant volume overload and severe azotemia. Steroid was slowly tapered off. Nivolumab therapy was never restarted, but even after 8months of the index event, he continued to be dialysis dependent.

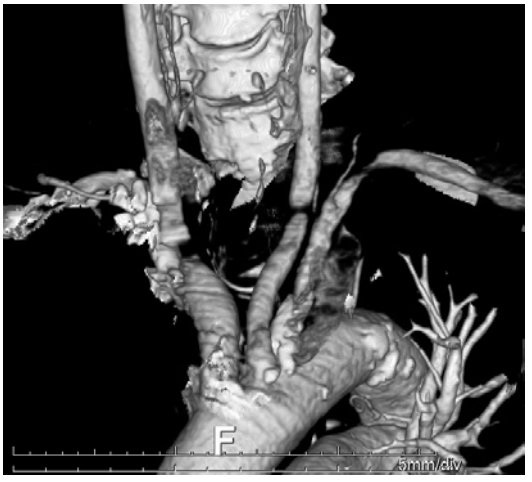
Discussion: Nivolumab is reported to cause steroid-responsive immune-mediated nephritis but our patient, who otherwise had mild non-proteinuric chronic kidney disease, developed end stage renal disease due to non-immune mediated collapsing FSGS after a single dose of Nivolumab.

PUB463

A Case of Subclavian Steal Syndrome Accompanied by Back-Flow of Vertebral Artery Detected after Arteriovenous Fistula Creation Makoto Sagasaki, Yukio Maruyama, Naoki Sugano, Izumi Yamamoto, Nanae Matsuo, Ichiro Ohkido, Keitaro Yokoyama, Takashi Yokoo. *Div of Nephrology and Hypertension, Dept of Internal Medicine, The Jikei Univ School of Medicine, Tokyo, Japan.*

Introduction: Subclavian steal syndrome (SSS) has a feature of a negative pressure gradient between the vertebral-subclavian artery junctions, resulting in altered vascular hemodynamics. SSS is relatively rare, but diabetes and atherosclerosis are strong risk factors. Especially, SSS becomes a major problem at the time of arteriovenous fistula (AVF) creation because of the diminished cerebral blood flow as a result of increased forearm blood flow.

A 71-year-old man was admitted for the initiation of hemodialysis (HD). He was already diagnosed as end-stage renal disease (ESRD) due to diabetic nephropathy, and got an operation of left forearm AVF creation just a month ago. He had no neurological symptoms including syncope and vertigo. There was no bilateral difference in blood pressure, and he did not complain numbness nor weakness in arm. Because carotid Doppler examination revealed back-flow of left vertebral artery, we considered the presence of SSS. Angiography revealed severe stenosis at the origin of left subclavian artery, and we performed percutaneous transcatheter angioplasty (PTA).



After PTA, stenosis of left subclavian artery disappear, the blood flow of left vertebral artery became normal, and he initiated HD using AVF in safety.

Discussion: In SSS, the proximal subclavian artery is stenosed, blood travels through ipsilateral vertebral artery to basilar artery and descends through contralateral vertebral artery to supply affected upper limb. Because AVF creation of affected forearm, theoretically, exacerbates the damage, we have to keep SSS in mind in the management of ESRD.

PUB464

Posterior Reversible Encephalopathy Syndrome in Chronic Kidney Disease Matthew Abramson,[1] Arun Kottarathara,[2] Yezina T. Nigatu,[2] Nand K. Wadhwa.[2] *[1]Dept of Medicine, Stony Brook Medicine, Stony Brook, NY; [2]Dept of Nephrology, Stony Brook Medicine, Stony Brook, NY.*

Introduction: Posterior Reversible Encephalopathy Syndrome (PRES) is a disorder of vascular dysautoregulation causing cerebral ischemia and edema, with vision loss, headaches, and/or seizures, and is often triggered by extreme fluctuations in blood pressure. We describe two cases of PRES, first in chronic peritoneal dialysis (CPD) and second in undiagnosed chronic kidney disease (CKD) stage 5. Both had vision loss with resolution of symptoms after control of hypertensive emergency.

Case Description: Case 1: A 48 year-old woman with ESRD of unknown etiology, on CPD for five years, who presented with one hour of bilateral vision loss and headaches. She was using frequently 4.25% dextrose PD solution and taking erythropoietin for anemia. BP was 267/120, creatinine 13.0, and hemoglobin 13.6. Head CT and MRI showed foci of edema in the parieto-occipital white matter. After two days of blood pressure control, her vision returned to normal. Repeat CT head 2 months later showed complete resolution. PRES here was likely due to hypertensive emergency in overly treated anemia and change to high solute transport in CPD. Case 2: A 29 year-old man with no medical history, presented with 2 weeks of severely blurred vision and headaches controlled with frequent NSAIDs. BP was 248/143 and serum Cr was 10.8. MRI brain revealed edema and ischemia in both occipital lobes and cerebellar vermis. Ophthalmology noted irreversible retinopathy and possibly permanent loss of vision. Complete recovery of vision occurred in 2 weeks with adequate control of BP.

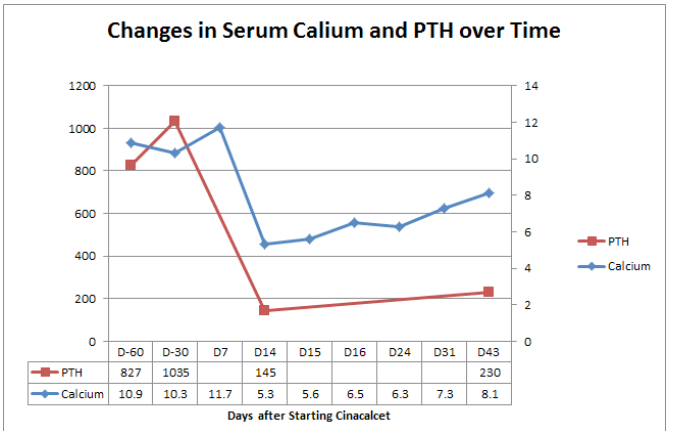
Discussion: First patient had been receiving CPD for 5 years resulted in loss of ultrafiltration, while the second patient with CKD stage 5 had no medical care in years. Both presented with vision loss and hypertensive emergency, and MRI showed edema of the occipital lobes, confirming PRES. Both patients improved with optimal blood pressure control, as well improvement of ultrafiltration in the second patient. Early recognition of PRES and adequate control of BP in CKD are warranted for possible full recovery.

PUB465

Severe Symptomatic and Prolonged Hypocalcemia Two Weeks after Starting Cinacalcet: A Call for Caution Sahar Koubar, Abd Assalam Qannus. *Nephrology, American Univ of Beirut, Beirut, Lebanon.*

Introduction: Cinacalcet hydrochloride, a calcimimetic allosteric modulator of the calcium-sensing receptor, is now widely prescribed for patients with secondary hyperparathyroidism not responding to activated forms of vitamin D. Mild hypocalcemia is a common complication; however it is rarely severe, abrupt and prolonged.

Case Description: A 55 year old male patient with ESRD presented to the emergency department with headache, nausea, and numbness of his extremities. His laboratory data revealed severe corrected hypocalcaemia of 5.7 mg/dl. He had secondary hyperparathyroidism (serum PTH 1035pg/dl) which was initially treated with activated vitamin D, however the latter was stopped because of significant elevation in serum calcium and phosphorus levels despite concomitant use of non-calcium based phosphate binders. Cinacalcet 30 mg has been started as an alternative two weeks prior to his current presentation. His PTH level was 145 pg/dl. He required a total of 12 g of IV calcium gluconate and 5g of oral calcium carbonate before he became asymptomatic with a serum calcium level above 6mg/dl. He was discharged home on maximum doses of oral calcium and activated vitamin D. His serum calcium level slowly improved over a period of 4 weeks. His PTH level was 230pg/dl by week 6.



	D-60	D-30	D7	D14	D15	D16	D24	D31	D43
PTH	827	1035		145					230
Calcium	10.9	10.3	11.7	5.3	5.6	6.5	6.3	7.3	8.1

Discussion: This dramatic effect of Cinacalcet mimics the effect of parathyroidectomy and consequent hungry bone syndrome, with profound and prolonged decrease in serum calcium levels. The underlying pathogenesis behind this effect is not known, but it could represent an upregulation of the calcium sensing receptor resulting in prolonged over suppression of PTH and hypocalcemia. Conclusion: Cinacalcet can cause acute, severe and symptomatic hypocalcaemia in susceptible patients, yet precipitating factors are not known. It is safer to check calcium level more frequently during the first month after initiating treatment.

PUB466

Spurious High Anion Gap Acidosis Associated with Monoclonal Gammopathy David Selzer, Joanna B. Eldredge, Satyam Patel, Joshua A. Schwimmer, Jordan L. Rosenstock. *Nephrology, Northwell Health - Lenox Hill Hospital, New York, NY.*

Introduction: We present a case in which the measured serum bicarbonate level was persistently 2 mmol/L, which proved to be spurious as blood gas analysis showed the pH and bicarbonate level were in the normal range.

Case Description: An 82-year-old female with chronic heart failure and diabetes mellitus, presented to the emergency department with dyspnea on exertion associated with lower extremity edema. Home medications included metoprolol, metformin, and furosemide. Physical exam and chest x-ray were consistent with an acute exacerbation of her congestive heart failure. Labs showed sodium 140 mmol/L, potassium 3.5mmol/L, chloride 103 mmol/L, bicarbonate 2 mmol/L, BUN 29 mg/dl, creatinine 1.1 mg/dl. Repeat labs confirmed a serum bicarbonate level of 2 mmol/L. Arterial blood gas drawn concomitantly revealed a pH of 7.49 and a PCO_2 33 mmHg, with a calculated bicarbonate of 24 mmol/L. Serum protein electrophoresis demonstrated monoclonal kappa light chains with a concentration of 13.2 mg/dL and both serum and urine immunofixation showed an IgA kappa monoclonal protein.

Discussion: Our case had extreme pseudohypobicarbonatemia on enzymatic assay with an anion gap of 35. However, a gas panel-derived plasma bicarbonate and arterial pH were within normal reference range. A similar case of pseudohypobicarbonatemia had been reported which noted interference in enzymatic assays secondary to paraproteins (IgM and IgG) in the blood with a mean bicarbonate level of 12.4.[i] Our case demonstrates a decrease in bicarbonate to 2 and was likely due to IgA paraprotein. Physicians should therefore consider monoclonal gammopathy when encountered by a significant discrepancy between enzymatic and gas panel derived bicarbonate levels. [i] Goldwasser,P. Pseudohypobicarbonatemia Caused by an Endogenous Assay Interferent: A New Entity *AJKD* 2011, 58 (4) 617-620.

PUB467

Cerebral-Salt-Wasting (CSW) Beyond a Reasonable Doubt Shaker Qaqish,[1] Ashvin Kamath,[1] Golriz Jafari,[1] Phuong-Thu T. Pham,[2] Phuong-Chi T. Pham.[1] *[1]OVMC; [2]UCLA.*

Introduction: CSW is an entity questioned by some experts. CSW-induced hyponatremia cases are often suggested to be misdiagnoses of syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

Case Description: A 26-year old male with no past medical history presented with 1 week of fevers, headaches, and lethargy. Full evaluation with brain CT revealed mild hydrocephalus, lumbar puncture with opening pressure of 55 cm H_2O, CSF consistent with viral vs. tuberculous meningoencephalitis. Patient received empirical ampicillin, acyclovir, and doxycycline. Hospital course was complicated by a rapid fall in serum sodium (SNa) [140 to 122 mEq/L within 41 hours]. This was initially attributed to the infusion of maintenance hypotonic 5% dextrose, 0.45 saline solution in a patient with presumed SIADH. Given evidence of increased intracranial pressure (ICP), plan was to correct hyponatremia by 5% with 600 mL of 3% saline within 6 hours followed by strict free H_2O intake restriction. Despite achieving the initial SNa goal of 125, patient continued to have high urine output (UO) reaching 300-500 mL/h with urine Na+K >200-280 mEq/L leading to a recurrent fall in SNa to 117 within hours of free H_2O restriction alone. Reinitiation of continuous 3% saline infusion was required at 200-400 mL/h to recorrect and maintain SNa to 130-135. Empirical administration of fludrocortisone at 0.2 mg bid did not seem to ameliorate

the condition. At this point, patient was transferred to an outside neurosurgery unit for a ventriculostomy placement. The receiving nephrology team assumed the misdiagnosis of SIADH as CSW and recommended discontinuation of 3% saline infusion. Within 5 hours, SNa dropped from 135 to 124 mEq/L. 3% saline infusion was restarted at high volume. Following a ventriculostomy placement, patient required lower volume of combination 0.9% (200mL/h) and 3% (50-100 mL/h) saline infusion. The etiology of meningoencephalitis is still under investigation. Initial endocrinologic findings: cortisol 25.8 mcg/dL, TSH 0.096 mIU/mL, free T4 0.90 ng/dL, T3 0.54 ng/mL, BNP 89.20 pg/mL.

Discussion: Whatever the contributing mechanisms, severe renal sodium wasting occurred in current patient with meningoencephalitis. Dismissing this condition lead to severe hyponatremia.

PUB468

Severe Acute Tubular Necrosis Associated with Tenofovir Alafenamide

Satyam Patel, Maria V. DeVita, Sandar Win, Michael F. Michelis. *Nephrology, Lenox Hill Hospital, New York, NY.*

Introduction: Tenofovir disoproxil fumarate (TDF) is a prodrug that is metabolized to tenofovir, which is subsequently converted intracellularly via phosphorylation to tenofovir-diphosphate, the active form of the drug responsible for antiviral properties. Elevated levels of tenofovir have been associated with nephrotoxicity. However, tenofovir alafenamide (TAF), a new prodrug of tenofovir, limits plasma exposure of tenofovir to 90% less than TDF, and hence, TAF has been associated with less nephrotoxicity. We describe a case in which TAF was associated with biopsy proven severe acute tubular necrosis (ATN).

Case Description: A 70 year old male with a medical history significant for HIV and chronic kidney disease [baseline creatinine (Cr) 2 mg/dL and Cr clearance > 40 mL/min] presented to the emergency department with complaint of shortness of breath for the past 2 weeks. He was recently switched from a single tablet drug consisting of efavirenz, emtricitabine, and TDF to a combination of elvitegravir, cobicistat, emtricitabine, and TAF 2.5 weeks prior to presentation. Physical exam was remarkable for moderate respiratory distress with use of accessory muscles, diffuse wheezing and rales in bilateral lung fields, and bilateral lower extremity edema. Laboratory values depicted severe anion gap acidosis (pH of 7.07) with serum bicarbonate level of 5 mmol/L, PCO2 of 16, blood urea nitrogen of 125 mg/dL, and Cr 10.5 mg/dL. Urine microscopy showed many red blood cells and white blood cells but no casts. Patient had 2.2 g/24 hrs of proteinuria. Urine output was less than 500 ml/day. Renal ultrasound was unremarkable. Subsequently, patient underwent hemodialysis for volume overload and severe metabolic acidosis. Renal biopsy showed diffuse and severe proximal tubular degenerative changes and mild foot process effacement consistent with acute tubular necrosis.

Discussion: Although TAF is approved for use in patients with mild to moderate kidney disease (Cr clearance of > 30 mL/min), our case depicts a patient who had ATN after being switched to a single tablet antiviral therapy which included TAF. Therefore, clinicians need to be cautious in using this new agent.

PUB469

Streptozocin Induced Acute Tubulo-Interstitial Nephritis

Irfan Ahmed Moinuddin, Sindhura Bobba, Anna K. Vinnikova, Davis Massey, Daniel E. Carl. *Nephrology, VCU Medical Center, Richmond, VA.*

Introduction: Drug induced acute tubulo-interstitial nephritis is an important cause of acute renal failure. Streptozocin has been used as an anti-cancer agent, its nephrotoxicity has been reported as reversible proteinuria, proximal tubular dysfunction; but tubulo-interstitial nephritis has been rarely reported.

Case Description: 65 year old female with adrenal carcinoma, initially on cisplatin based chemotherapy which was changed to streptozocin, presented with acute kidney injury. Her creatinine was <1 mg/dl and urinalysis was benign before streptozocin therapy. She developed fatigue, malaise, nausea/vomiting and decreased appetite within days after starting streptozocin and had a creatinine of 6.2 mg/dl three weeks after streptozocin administration. Urine microscopy showed many muddy brown casts and few non-dysmorphic RBCs. Hemoglobin was 7.5 and platelet count was as low as 11 with normal LDH, haptoglobin and total bilirubin and no schistocytes on peripheral smear. She had peripheral eosinophilia and also had urinary eosinophils. Ultrasound showed normal sized kidneys. She was started on prednisone for presumed interstitial nephritis as biopsy was deferred due to thrombocytopenia. Creatinine improved to 4 mg/dl, and was discharged on a 3 week prednisone taper. She was seen in the outpatient setting and her symptoms recurred after stopping the prednisone. She was re-admitted for worsening renal failure, with creatinine of 10 mg/dl (5 weeks after administration). Renal sonogram and urinalysis were unchanged. Urine eosinophils were negative and peripheral eosinophils were improved. Kidney biopsy was performed which showed severe ATN with interstitial lymphocytic infiltrate and the diagnosis was severe acute tubulo-interstitial nephritis. She was discharged with a creatinine of 9 mg/dl and most recent labs revealed a slight decrease to 8.5 mg/dl (9 weeks after administration). She was given another 4 weeks of prednisone after the biopsy results.

Discussion: Monitoring of renal function after starting streptozocin and early diagnosis of tubulo-interstitial nephritis is important as it is potentially reversible by removing the suspected agent and may respond to short course of steroids.

PUB470

Relapsing Calciphylaxis after Kidney Transplantation

Syed A. Ali, Jayme E. Locke, Song Ching Ong. *Univ of Alabama at Birmingham.*

Introduction: Calciphyaxis is a debilitating condition with calcification and thrombosis of cutaneous arterioles leading to ischemic necrosis. Risk factors include end stage kidney disease (ESRD), female sex, obesity, malignancy, chronic inflammation, hypercoagulable state, elevated calcium and phosphorus product and hyperparathyroidism. Available treatments include sodium thiosulphate, hyperbaric oxygen, parathyroidectomy, surgical resection and good wound care. Kidney transplantation may improve this condition through a reduction in systemic inflammation and restitution of normal calcium-phosphorus metabolism. We describe a kidney transplant patient with relapsing calciphylaxis.

Case Description: A 53-year old woman with ESRD due to lupus nephropathy complicated by antiphospholipid syndrome on hemodialysis for 15 years. The patient had calciphylaxis treated with intravenous sodium thiosulphate and parathyroidectomy 5 years pre-transplant. Lupus was quiescent and patient was on fondaparinux. The patient received a cadaveric kidney transplant with thymoglobulin induction and immunosuppression with tacrolimus, mycophenolate mofetil and prednisone. 4 months post-transplant the patient developed painful purpuric necrotic and indurated lesions on both thighs and forearms. Skin biopsy showed calcification of subcutaneous vessels with necrosis of dermis and epidermis consistent with calciphylaxis. Workup showed normal levels of aluminum, protein C and S and a negative antiphospholipid antibody level. Creatinine 0.9mg/dl. iPTH 38.2 pg/ml, Ca 9.5 mg/dl, Phosphorus 3.5 mg/dl, Alb 3.8 mg/dl. Tacrolimus levels 5-7 ng/dl. Patient received intravenous sodium thiosulphate , hyperbaric oxygen and specialized wound care. A per-cutaneous enteric feeding tube provoked further calciphylaxis lesions with extensive areas of skin and soft tissue necrosis. The patient developed sepsis and expired in spite of preserved kidney function.

Discussion: Kidney transplantation may not prevent recurrence of calciphylaxis. Calcineurin inhibitors decrease osteoprotegerin and increase receptor activator of nuclear factor k-B ligand (RANK-L) leading to increased extraosseous mineralization and vascular calcification and may have contributed to the patient's disease.

PUB471

Mucin-1 Kidney Disease: A Family History

Joana Gameiro, Sofia C.A. Jorge, Jose António Lopes, António Gomes da Costa. *Service of Nephrology and Renal Transplantation, Centro Hospitalar Lisboa Norte, EPE, Lisbon, Portugal.*

Introduction: Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD) refers to a group of diseases characterized by autosomal dominant inheritance, bland urinary sediment, absent-to-mild proteinuria, no severe hypertension, normal or small-sized kidneys on ultrasound, pathologic changes of tubular and interstitial fibrosis, and slowly progressive chronic kidney disease (CKD), resulting in the need for dialysis in the fourth through seventh decades of life. It is caused by mutations in the genes encoding uromodulin (UMOD), hepatocyte nuclear factor-1b (HNF1B), renin (REN), and mucin-1 (MUC1).

Case Description: We present the case of a 30 year-old caucasian female who was admitted to our department due to uremic syndrome. She had a chronic kidney disease of unknown etiology, with a previous creatinine of 2.7mg/dL when she was 27 years-old and had had no follow-up since then. She had a chronic hypocalemia and metabolic acidosis, a bland urinary sediment and normal sized kidneys on ultrasound. Imunologic, serologic and disproteinemic study was negative. She had a family history of chronic kidney disease without deafness or visual loss. Her grandmother died after 30 years of chronic kidney disease; her father had a history of gout and received a renal transplant at 37 years old; a cousin with chronic kidney disease in dialysis since he was 57 years old, with multiple kidney cysts, a kidney biopsy with tubulointerstitial nephritis, and negative study of the uromodulin gene; and also an uncle in dialysis since he was 60 years old. Genetic testing of the MUC1 gene was positive. She started peritoneal dialysis one month after being discharged and remains in this technique at a 2 year follow-up.

Discussion: Mucin-1 kidney disease formerly known as medullary cystic kidney disease type 1 is a familial progressive tubulointerstitial nephropathy belonging to the recently defined group of ADTKD. MUC1 gene encodes mucin-1, a protein expressed in many tissues, however no extrarenal manifestations have been described. Onset of end-stage renal disease is very variable between and within families as illustrated in our case.

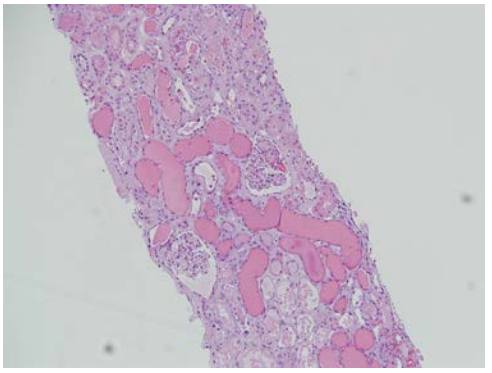
PUB472

Everoliums Associated Acute Tubular Injury with Proteinacious Casts

Zachary Freestone, Fuad S. Shihab, Faris A. Ahmed. *Nephrology, Univ of Utah, Salt Lake City, UT.*

Introduction: Mammalian target of rapamycin (mTOR) inhibitors are associated with marked proteinuria in patients with renal impairment and can lead to a unique form of cast nephropathy. Cast nephropathy with mTOR inhibitors has been associated with simultaneous use of calcineurin inhibitors. Many patients are placed on mTOR inhibitors for immunosuppressive therapy, but caution should be taken in the setting of tubular injury because of the risk associated with proteinuria and increased tubular damage.

Case Description: A 49 year old female with a history of type I DM received a simultaneous pancreas and kidney transplant. She had multiple admission to the hospital due to diarrhea and volume depletion associated with mycophenolate use. She was transitioned to everolimus in additon to tacrolimus due to the significant side effects related to mycophenolate. The patient was later admitted to the hospital with AKI after transition to everolimus and found to have 18 grams of proteinuria. Laboratory studies revealed an everolimus level of 9.2 ng/mL. Renal biopsy was performed and showed marked acute tubular injury and proteinaceous casts.



Everolimus was determined to be the cause of her proteinuria and contributed to her tubular injury. Proteinuria decreased to 3 grams upon cessation of everolimus. The patient had significant renal fibrosis upon recovery as evidenced by repeat renal biopsy 2 months after the insult.

Discussion: Our patient developed cast nephropathy with nephrotic range proteinuria as a result of everolimus use. Proteinuria improved significantly upon cessation of everolimus. Therapy with the use of mTOR inhibitors increases proteinuria and can lead to cast nephropathy. These medications can also delay recovery in the presence of tubular injury. Caution is to be used when using mTOR inhibitors in the setting of acute kidney injury with simultaneous use of calcineurin inhibitors.

PUB473

Anti-Neutrophil Cytoplasmic Antibodies Vasculitis after Influenza Vaccination Okechukwu Ebiem, Bharat Bajantri, Amandeep Singh, Kishore Kumar, Rabih Nasr. *Internal Medicine, Bronx Lebanon Hospital Center, Bronx, NY.*

Introduction: There are rare case reports of temporal association between influenza vaccination and anti-neutrophil cytoplasmic antibodies(ANCA)vasculitis. We describe a case of ANCA vascultis after receiving flu vaccine.

Case Description: A 67 year old man presented to emergency room with complaints of fever and myalgia for 3 weeks. His medical history includes diabetes, hypertension and congestive heart failure. Admission vitals and clinical examination were normal. He denied any systemic symptoms. Initial investigations revealed acute kidney injury with serum creatinine of 4.5, hyperkalemia of 6.1 and elevated ESR and CRP with microscopic hematuria. Autoimmune work up was significant for elevated myeloperoxidase-*anti-neutrophil cytoplasmic antibodies (*MPO-ANCA) titers. Kidney histopathology showed pauciimmune vasculitis with crescentic Glomerulonephritis. He had received flu vaccine 3 weeks prior to onset of symptoms. During hospitalization he was treated with steroids, cyclophosphamide and plasmapheresis that resulted in improvement in renal function.

Discussion: ANCA-vasculitis post influenza vaccination is speculated to be caused by auto-immunity. The mechanisms proposed for the induction of vasculitis by infectious agents include direct microbial invasion into endothelial cells, immune complex mediated vessel wall damage, and the activation of auto-reactive B and/ or T cells through molecular mimicry and superantigens. The latency period between vaccination and autoimmunity has been reported to be around 12 to 21 days and it is a diagnosis of exclusion. Similar vasculitic manifestations have also been reported with other vaccines like BCG and HPV. On review of literature, treatment modalities of influenza vaccine associated ANCA vasculitis includes steroids, cyclophosphamide, rituximab and plasmapheresis with some success. In our case, he received 7 sessions of plasmapheresis, oral cyclophosphamide and steroids with improvement in kidney function. It is important to recognize possible association between flu vaccine and ANCA vasculitis. Nephrologist should be vigilant for the possibility of developing renal vasculitis post flu vaccination.

PUB474

Case Series of Everolimus with Tacrolimus Causing Hemolytic Uremic Syndrome (HUS) within 3 Month Post Kidney Transplantation Sumeet Munjal, Aijaz A. Gundroo, Mareena Susan Zachariah, Shirley Shwu-Shiow Chang. *Div of Nephrology, Univ at Buffalo, NY.*

Introduction: Thrombotic microangiopathy (TMA) is a well recognized complication affecting 3-14% of renal allograft recipients who are on CNI based immunosuppressive regimen. TMA leads to thrombocytopenia, anemia, and acute renal failure. TMA with predominately renal feature is termed as HUS. We are reporting 2 cases of HUS with de novo use of everolimus & tacrolimus in living kidney recipients.

Case Description: Case 1: 31 yo WM S/P kidney transplant for ESRD sec to vesicoureteral reflux, thymoglobulin induction, maintained on prednisone, everolimus & tacrolimus presented with AKI 10 days post transplant with serum Cr 2 (baseline 1.6). He received steroids for presumed rejection. Transplant biopsy showed glomerular TMA with arterial fibrinoid necrosis, C4d 1+, DSA was -ve. PBS showed 1 schistocyte/HPF. Platelets were low, LDH 490, 3+ blood in urine, -ve lupus anticoagulant, ADAMTS13>100, and normal D-dimer and fibrinogen. Acute antibody mediated rejection was ruled out and diagnosis of drug induced TMA was made. CNIs were stopped, switched to Belatacept & MMF, received thymoglobulin and maintained on steroids. Plasmapheresis was initiated until hemolysis resolved. He responded to treatment and has stable allograft function. **Case 2**: 59 yo WM S/P kidney transplant for ESRD sec to DM2, simulect induction, on prednisone, everolimus and tacrolimus presented with AKI serum Cr 3 (baseline Cr 1), had DSA of 4300. Transplant biopsy showed Banff borderline cellular rejection, started on Steroids and IVIG. He presented with AKI Cr 9.2, nose bleed, thrombocytopenia, transaminitis, 2+ blood in urine and was started on dialysis, steroids, thymoglobulin, changed immunosuppression to MMF/tacrolimus. Repeat biopsy showed borderline cellular rejection, TMA, C4d 2. He was started on Plasmapheresis+IVIG. PBS showed no schistocytes, Cr dropped to 1.6 with DSA down to 2800.

Discussion: Our cases illustrate HUS secondary to everolimus/tacrolimus and TMA secondary to acute AMR. Post-transplant TMA should be identified early, differentials include AMR, TTP/HUS, and drugs (CNI/mTOR), with appropriate treatments can reverse AKI resulting in good renal outcome.

PUB475

Acute Renal Infarction as an Unusual Cause of Acute Abdomen and a Rare Complication of Cardiac Angiography Siwadon Pitukweerakul, Sai Prasad Gadapa, Sree V. Pilla, Pye Phyo Aung. *Medicine, Presence Saint Francis Hospital, Evanston, IL.*

Introduction: Renal infarction is a rare complication after coronary angiography. Other causes of renal infarction after coronary angiography are cholesterol emboli, paradoxical emboli via intra-cardiac shunt, extension of aortic dissection into renal arteries. This case demonstrates the case of renal infarction after cardiac angiography and radiographic finding of acute renal infarction.

Case Description: A 43 -year-old man presented with sudden onset of left flank pain and left lower back pain for four hours. Three days ago, he was admitted in the hospital for chest pain, underwent coronary angiography after an abnormal stress test which showed mild coronary artery disease and was subsequently discharged. Left flank pain was severe, stabbing, radiating to lower back. A physical examination was normal except costovertebral angle tenderness on the left side. Laboratory tests were within normal limits with serum creatinine of 0.9 mg/dLContrast computed tomography of abdomen and pelvis was shown in Figure 1 and 2. She was given with long term anticoagulation and pain medication.

Discussion: Acute Renal Infarction(ARI) is a very rare complication of coronary angiography. The most common symptoms of ARI are abdominal and/or flank pain, nausea, and vomiting. The most common cause of ARI is atrial fibrillation. Hypercoagulable disorders, bacterial endocarditis, hematologic disease, are less frequent but important causes of ARI. Contrast computed tomography is considered the gold standard for the diagnosis of ARI. Anticoagulation is the mainstay of the treatment of ARI. However, no definitive treatment strategy for ARI has yet been established due to the rarity of this disease.

PUB476

Non Hodgkin Lymphoma Presenting with Rapidly Progressive Glomeruolonephritis due to Membranoproliferative Glomerulonephritis with Concurrent Thrombotic Microangiopathy: Long Term Remission with Rituximab Suresh Balasubramony,[1] Tarek H. Saleh,[1] Barry M. Wall.[1,2] *[1]Univ of Tennessee Health Science Center, Memphis, TN; [2]VAMC.*

Introduction: Non-Hodgkin's lymphoma has been associated with a number of glomerular diseases.

Case Description: Case report: 73 yr old male with hypertension and diabetes mellitus with normal renal function, presented with an episode of gross hematuria with subsequent microscopic hematuria. Imaging studies of the abdomen and cystoscopy were negative. He subsequently developed anorexia and vomiting and acute renal failure: creatinine 7.2 mg/dl. Urinalysis was 4+ positive for blood and 24 hr urine protein excretion was 0.7 gm. Renal function initially improved with intravenous fluids, creatinine 3.1 mg/dl; however, proteinuria and microscopic hematuria persisted. He subsequently developed worsening anemia, dyspnea, and lower extremity edema. There was no hepatosplenomegaly or lymphadenopathy. Laboratory: hemoglobin 7.5 g/dL and platelets 156 K/uL . Studies for hepatitis B, C, HIV, antinuclear antibody, ASO titer, ANCA panel, ADAMTS13, and urine and blood cultures were normal or negative. C3 was low 75 (90-180 mg/dL) and C4 10 (10-40 mg/dL). Serum and urine electrophoresis did not identify any monoclonal proteins, however, serum free kappa /lambda ratio was elevated, 14.1. Cryoglobulins were trace positive with elevated rheumatoid factor. Kidney biopsy showed membranoproliferative GN with subendothelial immune complex deposition, basement membrane duplication, and concurrent thrombotic microangiopathy. Bone marrow biopsy showed scattered monoclonal lymphoid aggregates consistent with low grade B cell lymphoproliferative disorder. He was treated with 4 weekly doses of rituximab (700 mg). During 6 mos of follow-up, anemia, proteinuria, hematuria, dyspnea, and edema resolved with serum creatinine of 1.6 mg/dL.

Discussion: RPGN due to membranoproliferative glomerulonephritis with concurrent thrombotic microangiopathy is a rare complication of B cell Non Hodgkin lymphoma. Therapy with rituximab resulted in remission of both hematologic and renal manifestations.

PUB477

Acute Alcoholic Pancreatitis Induced aHUS: Role for Eculizumab Gitanjali Singh, Sarika S. Deshmukh, Satyarth Kulshrestha. *Nephrology, Univ of Iowa, Iowa City, IA.*

Introduction: Atypical Hemolytic Uremic Syndrome (aHUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury (AKI). Patients have dysregulated alternative complement pathway, majority have a mutation in complement factors H or I or membrane Cofactor Protein. Acute pancreatitis is reported

to be a trigger for TTP/HUS in literature. We report a rare case of aHUS triggered by acute alcoholic pancreatitis and successful use of Eculizumab in treating AKI/aHUS/ acute lung injury(ALI).

Case Description: A 44 yo Caucasian man, who has past history of hypertension, GERD, alcohol abuse and acute pancreatitis (idiopathic) presented with acute abdominal pain with nausea and dyspnea after binge drinking. On examination:normotensive non-obese man in respiratory distress. HEENT- icterus +; Pulmonary- bilateral diffuse crackles+; Abdomen- tender in periumbilical area with reduced bowel sounds. Laboratory data

	Day 0	Day 3 (Pre-Eculizumab)	Day 7	day 14
Lipase (U/ml)	894	258	37	69
Amylase (U/ml)	1351			
LDH		1453	829	460
T Bili/D bili	2.7/0.8	2.3/0.8	0.7/0.4	0.5
Hemoglobin (g/dL)	17	6.7	7.5	8.2
Platelets (1000/mm3)	211	16	264	494
Creatinine (mg/dL)	0.9	7.8	6.6	2.4
ADAMTS13 activity (%)		34		
Peripheral smear Schistocytes	3+	3+	2+	2+

ADAMTS13: 35%, C3 122, C4 20, Complement factor H 466 mcg/ml, Complement factor I 36 mcg/ml, INR 1. Urinalysis 3+ blood, UPC ratio 1.8. DIC screen negative. Clinical course: Renal function rapidly deteriorated, but stayed non-oliguric. By day 3, he had ALI, for which he was intubated. Eculizumab 900 mg single dose was given on day 4 after administering meningococcal vaccine on day 3. His lipase and amylase continued to trend down and AKI and ALI also started to resolve. He never required dialysis and was extubated 3 days after Eculizumab dose.

Discussion: Acute alcoholic pancreatitis triggered aHUS, a rare complication, reflects the presence of underlying complement dysregulation in our patient. In his case the aHUS continued though pancreatitis was resolving. He tested negative for common mutations and inhibitors. Single dose Eculizumab was effective in this case.

PUB478

Acute Kidney Injury due to Epstein-Barr Virus Faisal Anwar, Hafiz Ali Sroya, Rawan T. Al-Odat, Saeed Kamran Shaffi. *Nephrology, UNM, Albuquerque, NM.*

Introduction: EBV induced acute kidney injury is extremely rare in adults. We present a case of EBV induced acute interstitial nephritis (AIN).

Case Description: A 54 years old male with past medical history of hypertension presented to ED with a 3-week history of fever, distended abdomen, anorexia and skin rash. Physical examination showed epigastric tenderness, hepatomegaly, splenomegaly, and a maculopapular rash on the abdomen and legs. Diagnostic data are shown in Figure 1. During the course of hospitalization, his kidney function deteriorated and hemodialysis (HD) was initiated. Renal biopsy was performed that showed AIN as well as acute tubular necrosis. A diagnosis of EBV induced AIN was made. We started him on a steroid taper with gradual improvement of kidney function and discontinuation of HD.

Figure 1: Laboratory data

Variable	Results
BUN (mg/dL)	27 → Worsened to 161 during hospitalization
Creatinine (mg/dL)	1.58 → Worsened to 10.8 1.64 at the time of discharge
Urine microscopy	Muddy brown casts
HSV I&II and HIV	Non reactive
ANA, ANCA, Cryoglobulins, Hepatitis profile	Negative
EBV IgM	Positive
EBV IgG	Negative

Discussion: Infectious mononucleosis can cause acute interstitial nephritis albeit this is a rare occurrence in immunocompetent patients. Renal disease is self-limited with complete resolution of AKI in most cases. This disease entity should be considered in the patients with appropriate clinical history. Supportive care is the mainstay of treatment. Use of steroids in AIN is not supported by robust randomized trials; however, observational studies show some benefit if used early during the disease course. We used steroid in our patient with gradual improvement in renal function.

PUB479

Anti-Glomerular Basement Membrane Disease: A Case Report of an Uncommon Entity with Atypical Histological Findings Gerren Hobby,[1] Mohammed M. Siddiqui,[1] Shree G. Sharma,[2] Manisha Singh.[1] *[1]Div of Nephrology, Univ of Arkansas for Medical Sciences, Little Rock, AR; [2]Renal Pathology, Arkana Laboratories, Little Rock, AR.*

Introduction: Anti-glomerular basement membrane (anti-GBM) disease is an aggressive form of glomerulonephritis associated with a high mortality if not treated promptly. There has been recent increased awareness of atypical forms of anti-GBM disease which display a more indolent clinical course with varied pathological findings. We are reporting such a case.

Case Description: A 57-year-old Caucasian woman was admitted with 5 days of dyspnea and 1 day of hemoptysis. She carried no prior diagnosis of renal disease. Chest x-ray revealed diffuse bilateral opacities. Serum creatinine was 0.9 mg/dl on admission, but increased to 2.7 mg/dl over the course of 1 week. Urine sediment showed dysmorphic RBCs. Serologies were negative for ANA and ANCA. Complement levels were normal. Anti-GBM was positive at 31 units/ml (reference range 0-20 units/ml). Renal biopsy revealed linear IgG, kappa and lambda staining along the glomerular basement membrane but was notable for the absence of a diffuse crescentic picture, which is typically seen in anti-GBM glomerulonephritis. The biopsy also showed nodular glomerulosclerosis which is a very rare finding. After treatment with steroids, cyclophosphamide and plasmapheresis, hemoptysis resolved and serum creatinine improved to 1.8 mg/dl.

Discussion: In contrast to the classical presentation of anti-GBM disease, this patient presented with less severe renal failure in addition to having kidney biopsy findings which lacked an overt crescentic picture. Similar cases have recently been reported which importantly display poor renal survival when treated with conventional therapy despite a mild elevation in serum creatinine. Although this patient improved with standard treatment for anti-GBM disease, the subset of patients with atypical anti-GBM disease require special attention during diagnosis and treatment in order to achieve good outcomes.

PUB480

Complete Normalization of Serum Creatinine from Very High Levels due to Obstructive Uropathy Amar V. Patel, Muner Mohamed, Moro O. Salifu, Mary C. Mallappallil. *Div of Nephrology, SUNY Downstate Medical Center, Brooklyn, NY.*

Introduction: Acute renal failure is one of the commonest reasons for inpatient Nephrology consultation. Of these, 5-10% of cases are classified as being obstructive. The time to recovering renal function after the resolution of the obstruction determines the need for emergency dialysis. We report a case of a patient presenting with a serum creatinine of 35.9mg/dL and fully recovering renal function with relief of obstruction and without dialysis.

Case Description: A 66-year-old man with a past medical history of hypertension, presented to the emergency room (ER) with bilateral leg edema, distended abdomen, difficulty urinating and decreased appetite for 3 weeks duration. He was previously seen in the ER when he had a urinary tract infection and was treated with ciprofloxacin and hydrochlorothiazide. Significant finding on physical examination were BP 190/120mmHg, 1+ lower extremity edema, and a distended bladder. Initial laboratory data revealed Na 131mEq/L, K of 7.9mEq/L (non-hemolyzed), HCO3 of 8mEq/L, BUN 148mg/dL, and Cr 35.92mg/dL. Renal consultation requested for urgent dialysis. Foley bladder catheter was placed with approximately 4L of blood tinged urine. Later in the day there was an additional 5L or urine. Over the next 30 hours patient laboratory data improved dramatically.

	Na	K	HCO3	BUN	Cr
Admission	131	7.9	8	148	35.92
30 hours post urinary catheter	147	5.9	18	36	2.39

Patient was ultimately found to have obstructive uropathy secondary to prostatic cancer with a prostate specific antigen noted to be 61. His baseline creatinine 2 months later was 1mg/dL. He never had any hemodialysis.

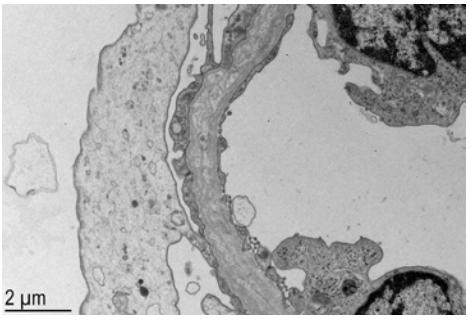
Discussion: Obstructive nephropathy requires advanced clinical decisions due to the multitude of factors potentially requiring a patient to undergo urgent dialysis. Our case exemplifies these points and the patient ultimately did not require hemodialysis with rapid recovery of renal function. The key factor was immediate urinary output after release of obstruction. This is the highest serum creatinine (35.9mg/dL) reported in the literature with complete recovery of renal function (serum creatinine 1mg/dL) after resolution of obstruction.

PUB481

Glomerular Basement Membranes under Stress - When a Big Organ Lands in a Small Body Francois Gougeon,[1] Alexei V. Mikhailov,[1] Keisha L. Gibson,[2] Harsharan Kaur Singh,[1] Volker Nickeleit.[1] *[1]Nephropathology, UNC-Chapel Hill, Chapel Hill, NC; [2]Nephrology, UNC-Chapel Hill, Chapel Hill, NC.*

Introduction: Donor/recipient body weight mismatch in kidney transplantation can be associated with decreased graft survival and increased proteinuria. These findings are reported in patients receiving kidneys too small for their body size. Glomerulomegaly, focal and segmental glomerulosclerosis, and rarely a peculiar form of glomerulopathy with basement membrane (GBM) remodeling have been observed. Glomerular alterations are attributed to non-immunological factors such as hyperfiltration and GBM "shear stress".

Case Description: We present a case of a 9 year old child with dwarfism (below 3rd percentile for age) who received an adult-sized kidney (11 cm in length) at age 5. She developed persistent nephrotic range proteinuria (urine protein to creatinine ratio of 8.1) within a year of transplantation. Serum creatinine levels were stable at 0.2-0.3 mg/dl. Hematuria and donor specific antibodies (DSA) were absent. Two biopsies performed to evaluate the cause of proteinuria (3 and 4 years post-grafting) revealed markedly remodeled GBM with splitting mimicking hereditary nephropathy (changes not seen in a remote native renal biopsy nor in the donor organ at time of transplant). There was no evidence of rejection, no interstitial fibrosis and C4d was not identified along peri-tubular capillaries. Diffuse C4d staining was however noted along the GBM. Graft function and proteinuria remained unchanged until end of follow-up 50 months post grafting.



Discussion: Here we show for the first time that a too large for body size mismatched graft is associated with injury to the GBM and a peculiar form of glomerulopathy. GBM remodeling is associated with GBM-C4d deposits in the absence of rejection and DSAs. Clinically, graft function was stable over 4.2 years with proteinuria as main symptom.

PUB482

Pauci-Immune Vasculitis with Hypocomplementemia: A Rare Presentation

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Introduction: Abnormal activation of the alternate complement pathway is increasingly being explored as a key pathogenic event in ANCA asscoiated vasculitis (AAV). While low C3 has been recently reported in AAV with histological signs of thrombotic microangiopathy, both C3 and C4 being low has rarely been described. We report a rare case of AAV where both complements were low on presentation.

Case Description: 60 yr old female presented with acute renal failure after being treated for pneumonia with various antibiotics over 2 months. Extensive infectious work up including pleural fluid analysis was repeatedly negative. She reported increasing fatigue and lower extremity swelling. She had bibasilar crackles, pedal edema and urine showed 2 + protein, large blood and many RBCs. Her labs on presentation are shown

Lab (reference range)	Day 1	Day 20	Day 80
Sodium (136-144mmol/L)	129	138	133
Potassium (3.5-5.1mmol/L)	5.8	4.6	4.4
Creatinine (mg/dL)	6.07	6.44 *on HD	3.85 **off HD
WBC (3.5-10.5 K/UL)	24.5	25.5	11.2
ANCA	POSITIVE	POSITIVE	Negative
ANA	>1:1280	1:640	1:640
Compliment 3 (69-152 mg/dL)	67	88	106
Compliment 4 (16-38 mg/dL)	9	18	25
Proteinase 3AB (<1.0 AI)	113.5	23.9	N/A

Emergent kidney biopsy showed severe cresenteric glomerulonephritis with no evidence of TMA. Additionally, she had leukocytosis as high as 38.5 K/UL and single large lesion on lung imaging suspicious for lung abscess. She was treated with plasmapheresis (3 sessions), pulse dose steroids and IV Cytoxan along with broad-spectrum antibiotics and started on hemodialysis. She responded dramatically with serological markers normalizing within a few weeks of treatment and eventually came off dialysis.

Discussion: While low C3 has been described previously, low C4 along with low C3 has rarely been described in AAV, In a case series of 46 patients with AAV where complement levels were analyzed, only one patient had both low C3 and C4. Here, we report another such a case.

PUB483

Acute Kidney Injury in the Postpartum Period: A Diagnostic Dilemma and Treatment Challenge

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Introduction: Atypical Hemolytic Uremic Syndrome (aHUS) is a rare disease. Etiology includes infection, drugs, transplant, pregnancy, autoimmune and metabolic disorders. Mutations of complement factor H and I, membrane cofactor protein and CD46 may be seen in some cases.

Case Description: A 23 year old Hispanic female presented 4 days after an elective C-section with nausea and vomiting. Periumbilical tenderness was found on exam. Her hemoglobin dropped from 12 g/dL to 5.7 g/dL and platelets decreased from 359,000 cells/nL to 141,000 cells/nL with a nadir of 58000 cells/nL. Serum creatinine increased from 0.6 mg/dL to 3 mg/dL. LDH and reticulocyte count were high and haptoglobin was low. Hepatic and coagulation profile were normal. Peripheral smear showed schistocytes. Abdominal imaging was unremarkable. Plasmapheresis was started for suspected TTP and she required dialysis for worsening renal function. Plasmapheresis was stopped when ADAMTS13 activity resulted at 75%. Eculizumab was started for probable aHUS. Renal biopsy revealed subacute/chronic thrombotic microangiopathy. Within 2 weeks of treatment, thrombocytopenia resolved and she was off dialysis.

Discussion: In our case, absence of preclampsia or significant transaminitis made HELLP unlikely. The ADAMTS13 level with failure of plasmapheresis made TTP unlikely. Diagnosis of aHUS was substantiated by microangiopathy on biopsy, negative shiga toxin, and improvement in thrombocytopenia and renal function with eculizumab. aHUS accounts for 8–18% of all TMA cases during pregnancy, most occurring postpartum. With complement gene abnormalities the likelihood of recurrence in future pregnancies is higher. aHUS mimics preeclampsia, HELLP and TTP. First episode has a 25% mortality with 50% requiring dialysis. Thus, consideration of early treatment for aHUS is imperative on clinical suspicion alone.

PUB484

Atypical Presentation of Vascular Calcification in a Chronic Haemodialysis Patient

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Introduction: Calciphylaxis (calcific uraemic arteriopathy) is a well described entity in patients with end stage kidney disease (ESKD). Though it presents primarily with skin lesions, atypical presentations have been reported. We report a case of calciphylaxis masquerading as giant cell arteritis, causing progressive visual loss in a haemodialysis patient.

Case Description: A 72-year gentleman with ESKD on hospital haemodialysis presented with headache and progressive visual loss in his single right eye. He was on oral anticoagulation for a prosthetic aortic valve and had recently undergone coronary artery bypass surgery, complicated by chronic ulcers at saphenous graft sites. Clinical examination revealed reduced visual acuity. Right eye fundoscopy revealed mild optic disc oedema and cotton wool spots. Investigations revealed an elevated ESR (89ml/hr) and normal calcium phosphate balance. The clinical presentation was suspicious for temporal giant cell arteritis. He received empiric treatment with pulse methyl prednisolone and underwent a temporal artery biopsy which revealed medial arterial calcification with no signs of vasculitis, suggestive of calciphylaxis. His visual loss did not improve and he was given a trial of hyperbaric oxygen therapy to improve retinal blood flow. Further imaging included a CT-angiogram of the brain and neck, which indicated significant calcified bilateral carotid stenosis; an MRI brain showing no acute ischaemia; and a cerebral perfusion scan showing diffuse perfusion abnormality. After a multi-disciplinary meeting, it was determined that his visual loss was irreversible and the benefits of carotid revascularisation were unclear. His dialysis program and medications were optimised to maintain a favourable haemodynamic and biochemical profile, and to retard progressive vascular calcification.

Discussion: This case report illustrates the challenges of managing the atypical presentation of an abstruse condition. There are few cases of calciphylaxis masquerading as giant cell arteritis described in literature. A high degree of suspicion is necessary for early diagnosis of calciphylaxis in a chronic haemodialysis patient on warfarin and assist in appropriate management.

PUB485

Successful PD Catheter Placement in a New ESRD Patient with Combined Antiphospholipid Syndrome and Factor XI Deficiency

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Introduction: Coagulopathies and bleeding disorders impact surgical morbidity and potential dialysis modalities for new ESRD patients. Our patient is a 68 year old female with a history of autoimmune hepatitis, antiphospholipid syndrome (APL), and factor XI deficiency. She is the first reported successful PD catheter placement in a patient with such combined bleeding and clotting disorders.

Case Description: She was diagnosed with APL after a workup for recurrent TIAs and a lacunar CVA, noted to have positive lupus anticoagulant, anticardiolipin, B2-glycoprotein, and antithrombin antibodies. She has a history of recurrent bleeding, for which a detailed evaluation uncovered a factor XI deficiency. Over the last 7 years she has had a gradual decline in eGFR, was referred to Nephrology and found to have nephrotic range proteinuria. A renal biopsy was considered but not done since the risk outweighed potential benefits; in the setting of APL the prolonged PTT could not be corrected despite multiple FFP infusions. When she reached ESRD the decision was made to pursue PD because of multiple risks associated with HD in the setting of her complex hematologic disorders, including bleeding with repetitive needle sticks vs. thrombosis of the AV fistula.

FFP and platelets were administered prior to placement of a temporary HD catheter. Hemodialysis was done before surgery to decrease uremic platelet dysfunction. The following day, additional FFP and platelets were infused followed by successful laparoscopic placement of a peritoneal dialysis catheter. DDAVP was not used due to its (rare) thrombosis side effect, as the patient has history of TIAs/CVA. An additional session of hemodialysis was done before the catheter was removed. Low volume recumbent exchanges were started one week later and her PD prescription has gradually been increased. For two months she has been doing well on PD.

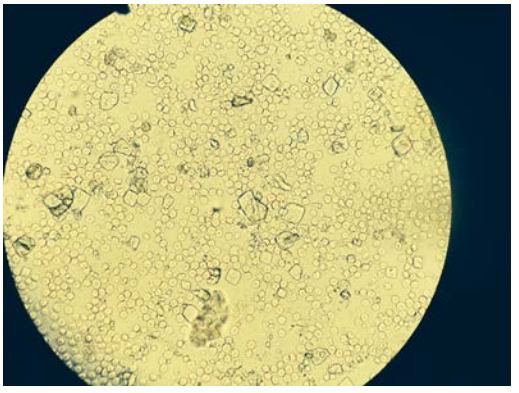
Discussion: To our knowledge, this is the first report of a successful PD catheter placement and initiation of PD in a patient with combined antiphospholipid syndrome and factor XI deficiency. Careful peri-operative planning can avoid adverse thrombotic or bleeding events.

PUB486

Rhabdomyolysis and Acute Uric Acid Nephropathy from Synthetic Bath Salt: (e)Uphoria to Uric Acid Nephropathy Ali Hasssan,[1] Paras Dedhia,[1] Charuhas V. Thakar.[1,2] *[1]Dept of Nephrology and Hypertension, Univ of Cincinnati, Cincinnati, OH; [2]Renal Section, Cincinnati VA, Cincinnati, OH.*

Introduction: Bath salts are synthetic cathinone derivatives of plant Catha edulis. "Flakka" is the street name for chemical compound α-Pyrrolidinopentiophenone (α-PVP). It is a stimulant of the monoamine cathinone class.

Case Description: A 37-year-old Caucasian male with no significant past history admitted to medical ICU after found down and unresponsive for unknown duration. He was intubated for airway protection. EMS noted that he was very combative and violent at the time of arrival. Physical examination was remarkable only for sinus tachycardia. Lab data was significant for anion gap metabolic acidosis (AG=15) with venous lactate of 30 mmol/l. Over next 24 hours, lactate decreased to 2.2 mmol/l with IV fluids. Hospital course was complicated by oliguric AKI with rapid worsening of creatinine from 1.1 mg/dl to peak creatinine of 9.9 mg/dl on hospital day7. Urine toxicology screen was negative. Urinalysis showed small blood with 3 RBCs. AKI work up was also significant for rise in creatine phosphokinase from 259 U/L to 11,28,00 U/L over next 24 hours. Uric acid on admission was 16.7 mg/dl and urine sediment showed rhomboid shaped uric acid crystals. His fractional excretion of uric acid was 148 % Due to hyperkalemia and oliguric AKI, he was started on dialysis and required six sessions of dialysis prior to recovery of renal functions. Follow up serum Cr at one month was 0.9 mg/dl. He confirmed injecting "Flakka" prior to hospital admission.



Discussion: Case studies have reported bath salts induced AKI from hemodynamic mediated ATN and rhabdomyolysis. This case highlights possibility of uric acid nephropathy as an additional mechanism.It also underscores importance of examining urinary sediment especially in cases where AKI pathogenesis is not well known.

PUB487

Binge Correction Guilherme Piovezani Ramos,[1] Larissa Kruger Gomes,[2] Kianoush Banaei-Kashani.[3] *[1]Internal Medicine, Mayo Clinic, Rochester, MN; [2]Internal Medicine, Univ of Connecticut, Farmington, CT; [3]Div of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.*

Introduction: Severe hyponatremia (HNa) is associated with high morbidity and mortality, which can be worsened by rapid corrections. Ethanol abuse can lead to HNa through different mechanisms. Identifying the primary process is crucial to correct sodium (Na) appropriately and prevent complications.

Case Description: A 40-year-old male presented with a week history of confusion and frequent falls. He had history of significant alcohol abuse. There were no deficits on neurologic exam. Laboratory evaluation: Na 103mmol/L, creatinine 6.5mg/dL and BUN 89mg/dL – unknown baseline. Urine showed osmolality 230mOsmol/L and Na 50mmol/L. Following admission to the ICU 0.9% NaCl was started with goal of correcting <10mmol/L/24hours. After 12-hours, Na was 115mmol/L and 0.45% NaCl started. Na continued to increase, peaking at 121mmol/L, after 18-hours when all infusions were stopped, and urine output was 12L. On day 3, he developed agitation refractory to alcohol withdrawal protocol. Examination on day 8 showed truncal ataxia, dysarthria and worsening cognition with a MRI-Brain confirming osmotic demyelination syndrome (ODS).

Discussion: Beer Potomania (BP) is an unusual cause of HNa, at high risk of ODS from rapid correction. Beer has minimal electrolytes and carbohydrate load suppresses urea production. As a result, daily solute excretion falls below 250mosmol/L, decreasing the capacity of free water excretion and this, in turn, results in HNa. Re-introduction of solute will lead to brisk diuresis and rapidly correct Na, despite free water replacement. Management of BP should include 1)ICU admission with q2h Na checks; 2)NPO for the first 24 hours with D5W for the caloric intake to promote solute diuresis; 3)intravenous fluids should be limited to symptomatic patients and given on small boluses with goal 2-3meq/L/hrx2-3hours. DDAVP should be utilized to increase free water retention in the case of brisk urination, to avoid rapid Na correction. By reporting an uncommon case of HNa complicated with ODS, we reinforce important aspects of the pathophysiology and Na corrections strategies in BP patients.

PUB488

Key Triggers and Interventions in Renal Cell Carcinoma and Pauci-Immune Crescentic Glomerulonephritis Natalia Plotskaya. *Internal Medicine Residency, Capital Health, Trenton, NJ.*

Introduction: Pauci-immune crescentic glomerulonephritis (PGN) has very high mortality rate and aggressive development. It occurs in association with ANCA positive systemic vasculitis and is recognized to be linked to renal cell carcinoma (RCC).

Case Description: A 59 yo male presented for evaluation of 4 weeks of dizziness, generalized weakness and unsteady gait. He did not have any past medical history and no family history of renal diseases. Physical examination revealed a non-specific unsteady gait. A CT scan discovered a 3.7 cm right renal mass, and after total nephrectomy histology revealed papillary RCC type 2. Non-neoplastic kidney tissue did not have signs of glomerular or tubular disease, nor amyloid deposition. Workup for metastatic disease was negative, however the patient's symptoms did not improve. Three months after nephrectomy, renal function declined and was refractory to intravenous fluids. Another metastatic work up was negative. Laboratory analysis shown proteinuria of 3.79 g/day, creatinine 3.78, BUN 41, ESR 120, CRP 8.7, C -ANCA titer of 1:40. Other serology, including complement levels, anti ds-DNA,ANA,cryoglobulin, anti-CCP antibodies, hepatitis B, C, HIV were all negative. The decision was made to proceed with biopsy of single left kidney as renal function deteriorated. Total of 6 glomeruli were sampled, one was globally sclerotic, 4 of 5 glomeruli were necrotizing with crescenting features. One focus of inflammation was admixed with smooth muscle cells raising the possibility of large vessel vasculitis. High dose steroids and cyclophosphamide was not successful in halting the decline in renal function, and hemodialysis was started.

Discussion: There is increasing evidence that RCC and ANCA associated PGN demonstrate a common underlying immunologic mechanisms of glomerular injury which are regulated by the podocytes Von Hippel Lindau gene. Our patient had severe systemic symptoms that did not improve after nephrectomy, suggesting that another process was active, however review of the surgical specimen confirmed no evidence of PGN at that time. Early ANCA screening could be beneficial in newly diagnosed RCC and further investigation of the role of chemokine specific therapy is warranted.

PUB489

Recurrence of ANCA Negative Pauci-Immune Crescentic Glomerulonephritis Post Kidney Transplantation Pradeep Vaitla,[1] Alton Brad Farris.[2] *[1]Transplant Nephrology, Emory Univ; [2]Renal Pathology, Emory Univ.*

Introduction: Pauci-immune glomerulonephritis is a relatively common cause of rapidly progressive renal failure. Frequency of ANCA negative pauci-immune glomerulonephritis is reported to be 20-30%. Recurrence of pauci immune glomerulonephritis is reported to be about 10-15% post kidney transplantation. However the recurrence of ANCA negative pauci immune glomerulonephritis post kidney transplantation is rarely reported. Very few case reports are available in the published literature.

Case Description: 49 year old caucasian female with no known medical problems presented with acute kidney failure in 2014. She was diagnosed with severe crescentic glomerulonephritis secondary to ANCA negative pauci-immune glomerulonephritis. She was treated with total plasma exchange and Rituximab but progressed to end stage renal failure. She received a living related renal transplantation in July 2015. Immunosuppression protocol: Basiliximab induction followed by maintenance with belatacept, tacrolimus, mycophenolate mofetil and prednisone. Per our institution protocol, tacrolimus was tapered off at 9 months post transplantation. After the taper of tacrolimus, she developed acute kidney injury with non nephrotic range proteinuria and microscopic hematuria. Kidney biopsy revealed severe crescentic glomerulonephritis. Immunofluorescence was negative, electron microscopy revealed no immune complex deposits or basement membrane thickening. Serology was negative for anti nuclear cytoplasmic antibody and anti glomerular basement antibody. She was started on high dose steroids and intravenous cyclophosphamide, response to treatment needs to be followed. Since no detectable circulating antibody was present, total plasma exchange was thought to be not helpful in this scenario.

Discussion: Recurrence of ANCA negative pauci-immune glomerulonephritis is rare. Reported data suggests, ANCA negative pauci-immune glomerulonephritis in native kidneys have poor renal prognosis and patients have less extra renal manifestations. It is important to consider recurrence as a possible etiology as the course of the disease is often rapid.

PUB490

Simultaneous Serious Infection of *Trichosporon asahii* and Multi Drug Resistant *Pseudomonas aeruginosa* in Kidney Transplant Patient Takamasa Miyauchi, Sawako Kobayashi, Hiroyuki Yamamoto, Takuya Fujimaru, Fumika Taki, Masahiko Nagahama, Yasuhiro Komatsu. *Nephrology, St. Luke's International Hospital, Chuo-ku akashi-cho, Tokyo-to, Japan.*

Introduction: *Trichosporon* species are increasingly recognized as a cause of systemic illness in immunocompromised patients. However such infection in kidney transplant patient is rare. We report a life-threating case of simultaneous infection of *Trichosporon asahii* and multi drug resistant pseudomonas aeruginosa (MDRP) in kidney transplant recipient.

Case Description: A 83-year-old Israeli male with ESKD due to ADPKD who received cadaveric kidney transplant six years ago, was admitted for a few days history of fever and right knee pain. His vital signs were a max body temperature of 40°C, heart rate(HR) 90 bpm, blood pressure(BP) 130/73 mmHg, and a pulse oximetry of 98% on room air. On physical exam, his right knee was erythematous and swollen with marked limitation of both active and passive ranges of motion. Blood and synovial fluid were sent for culture, and piperacillin/tazobactam was started empirically. Blood culture grew *trichosporon asahii*,

and synovial fluid grew multi drug resistant pseudomonas aeruginosa (MDRP). Therefore, antibiotics was switched to meropenem and aztreonam, and voriconazole was added. Ocular involvement was not detected. Since he had simultaneous serious infection of *trichosporon asahii* and MDRP, immunosuppressants, cyclosporine and mycophenolate mofetil were discontinued, and left prednisone alone. His medical course was complicated with C.difficile infection, but 6-week course of antibiotics were completed and he was fully recovered.

Discussion: ***Although*** *Trichosporon* infection is increasingly recognized as a cause of systemic illness in immunocompromised patients. Most cases are observed among hematologic malignancies while few cases are reported among transplant recipients. This case was successfully treated with triple antibiotics and discontinuation of immunosuppressants.

PUB491

HIV Associated Immune Complex Disease of the Kidney Rawan T. Al-Odat, Saeed Kamran Shaffi. *Nephrology, Univ of New Mexico, Albuquerque, NM.*

Introduction: HIV associated nephropathy (HIVAN) with histological features of focal segmental glomerulosclerosis (FSGS) has been well described in literature. However, in the era of highly effective anti-retroviral therapy (HAART), HIV immune complex disease of the kidney (HIVICK) is increasingly being recognized.

Case Description: A 43 years old male presented with malaise, fever, chills, night sweats and progressive swelling of the extremities. Physical examination was remarkable for a blood pressure of 170/100 mm/Hg, puffiness of face and trace edema of the upper and lower extremities. Pertinent diagnostic data are shown in Figure 1. Kidney biopsy showed collapsing FSGS as well as immune complex-mediated glomerulonephritis with a focal proliferative pattern of glomerular injury. He was started on HAART and losartan with improvement in kidney function.

Figure 1: Laboratory data

Variable	Results
Na (mmol/L)	134
HCO_3(mmol/L)	15
BUN (mg/dL)	90
Cr (mg/dL)	Admission 7.8 Baseline 1.0
Albumin (g/dL)	2.2
Complement (mg/dL)	Normal C3 and C4
ANA	1:80
Anti Double Stranded DNA	80 (Borderline)
SPEP	Normal
UPEP	Normal
Urine analysis	+3 protein, +2 blood
Urine microscopy	Fatty cast with few dysmorphic RBCs
UPCR (g/g)	7
HIV RNA PCR (copies/ml)	5789
CD4 count	109
Hepatitis panel	Non reactive
Renal U/S	Normal sized kidneys

Discussion: HIV can affect the kidneys in various ways. HIVAN – a condition which was identified in the pre-HAART era – is caused by direct viral infection of the podocytes resulting in collapsing FSGS. In HARRT naive patients, immune complex mediated proliferative pattern of injury is increasingly being recognized with membranous, membranoproliferative and IgA nephropathy phenotypes seen on kidney biopsy. HIVICK lesions are caused by an immune response to HIV antigens and thus require presence of HIV viremia. HIVICK is less likely to progress to end stage renal disease (ESRD) than HIVAN. HAART therapy dramatically improves outcomes of HIV associated renal disease irrespective of histological features.

PUB492

Alport Syndrome with Right-Hand Preaxial Polydactyly in Two Siblings Yuko Fujii,[1,2] Akira Ashida,[1] Hideki Matsumura,[1] Akihiko Shirasu,[1] Satoshi Yamazaki,[1] Hyogo Nakakura,[1] Kandai Nozu,[3] Kazumoto Iijima,[3] Motoshi Hattori,[4] Hiroshi Tamai.[1] *[1]Pediatrics, Osaka Medical College, Osaka, Japan; [2]Internal Medicine, Kanzaki Municipal General Hospital, Hyogo, Japan; [3]Pediatrics, Kobe Univ Graduate School of Medicine, Hyogo, Japan; [4]Pediatric Nephrology, Tokyo Women's Medical Univ, Tokyo, Japan.*

Introduction: Alport syndrome is one of the familial hereditary hemorrhagic nephritides leading to end-stage kidney disease. The genes responsible are *COL4A3, COL4A4* and *COL4A5*, which encode the α3, α4, α5 chains of collagen type IV, involved with the glomerular basement membrane. Polydactyly is characterized by supernumerary fingers or toes. Its etiology is not so apparent, but has been explained in terms of heredity, environmental factors, and other influences. Here we present the first report of two siblings with Alport syndrome and polydactyly.

Case Description: The patients were two siblings (a boy and a girl) with Alport syndrome. Their mother had also been diagnosed as having Alport syndrome, and the patients' grandmother and granduncle had requiring dialysis. Both the patients and their mother had hematuria, but had not developed any vision or hearing problems. Genetic analysis of the patients and their mother revealed a missense mutation (c.2822G>A) that can cause a change in the spatial structure of COL4A5. Therefore they were diagnosed as having X-linked Alport syndrome. Furthermore, although absent in other family members, the patients also had congenital preaxial polydactyly of the right hand. The polydactyly was not part of an anomaly syndrome, and no mental retardation was evident.

Discussion: To our knowledge there has been no previous report of patients with polydactyly in Alport syndrome. The present cases of polydactyly cannot be simply explained in terms of Mendel's law on the basis of the phenotypes. Some previous reports have indicated that preaxial polydactyly follows an autosomal dominant model, but this did not seem to be so in the present cases. Therefore, we intend to perform whole-genome sequencing to analyze the gene mutations in these patients. We believe that these two present cases will be useful for clarifying the pathogenesis of polydactyly associated with Alport syndrome.

PUB493

Childlike Spots in an Older Man: A Case of Malignancy-Associated Adult Henoch-Schonlein Purpura with Severe Multi-Organ Involvement Ana Claudia Onuchic,[1,2] Vivek Alaigh,[1,2] Catherine A. Zanoria,[1,2] Tanya L. Belle,[1,2] Sankar Narayan Niranjan,[2] Prashant Grover.[2] *[1]Univ of Connecticut, Farmington, CT; [2]St. Francis Hospital, Hartford, CT.*

Introduction: Henoch-Schönlein purpura (HSP) is a systemic small-vessel vasculitis associated with deposition of IgA immune complexes, typically manifested in childhood. Rare cases are described in adults, often more severe and disseminated, with malignancy as a predisposing factor.

Case Description: A 68 y/o male recently diagnosed with bladder cancer presented with a two-day history of abdominal pain, vomiting and back pain, associated with a persistent dark red rash of lower extremities and torso a few weeks prior. Outpatient skin biopsy had shown leukocytoclastic vasculitis but the rash recurred despite prednisone course. Initial inpatient workup showed acute kidney injury with serum creatinine (S_{Cr}) of 2.3mg/dL and urinalysis with leukocyturia, hematuria, 3+ protein and hyaline and white blood cell casts. Abdominal CT consistent with inflammation in the terminal ileum prompted exploratory laparotomy, revealing terminal ileum erythema/inflammation suggestive of vasculitis. Respiratory and renal deterioration, to S_{Cr} of 8.6mg/dL, required intubation and hemodialysis. Methylprednisolone 20mg IV q12hrs was started for presumed HSP. Skin biopsy was repeated to avoid the risk of renal biopsy, confirming leukocytoclastic vasculitis and IgA deposition by immunofluorescence. Serum IgA was high at 485mg/dL. New onset atrial flutter with episodes of wide complex tachycardia required prophylactic anticoagulation, complicated by intestinal bleed. Abdominal CTA showed contrast extravasation in the ileum, requiring embolization. Pulse-dose methylprednisolone and intravenous immunoglobulin were given; bleeding improved, but not renal function. Despite cardioversion and anti-arrhythmic agents, arrhythmia proved intractable and he expired.

Discussion: We present a case of adult HSP with renal, gastrointestinal, skin and likely cardiac involvement. This is one of few descriptions of HSP associated with bladder cancer in the literature. HSP is a rare but important cause of rapidly progressive glomerulonephritis and should be considered, especially in the setting of malignancy.

PUB494

Cutaneous Marginal Zone B-Cell Lymphoma in a Renal Transplant Recipient Yan Song, Jianghua Chen. *Kidney Disease Center, The First Affiliated Hosptial, Zhejiang Univ, Hangzhou, Zhejiang, China.*

Introduction: A 57-year-old Chinese female was presented with multiple cutaneous nodules and ulcers on the trunk and extremities for 1 month. The lesions first appeared as nodules and subsequently progressed to ulcer. The patient had no fever and fatigue. She had received a kidney from a living donor 11-year prior because of renal failure secondary to hypertension. The patient was maintained on oral prednisone (2.5 mg daily), mycophenolate mofetil (500mg daily), and cyclosporine (100mg daily) to anti-rejection. He had no history of previous opportunistic infections, including Epstein-Barr virus infection. On physical examination, her vital signs were normal. Cutaneous nodules and ulcerations were found on the legs and back.

Laboratory test results revealed a white blood cell count of 4.3* 109/L. Her serum creatinine was 387umol/L. A skin sample obtained from a nodule on the leg showed atypical lymphocytes infiltration. Immunohistochemistry revealed the atypical lymphoid cells were diffuse positive for CD20, CD79a, Bcl-2, and EBER. CD10, Bcl-6 and T cell markers were negative. No evidence of systemic involvement was found for the patient. A diagnosis of cutaneous marginal zone B-cell lymphoma was made. Her anti-rejection drug cyclosporine was changed to everolimus. After four months, the cutaneous nodules disappeared. Post-transplant lymphoproliferative disorders are a group of heterogeneous lymphoid complications, which range from indolent polyclonal proliferations to aggressive lymphomas. Generally, it is considered to be a consequence of intensive immunosuppressive drugs administered following solid organ or hematopoietic transplantation. The overall incidence of post-transplant lymphoproliferative disorders in adult kidney transplantation recipients was 1 - 3% worldwide. Treatment of post-transplant lymphoproliferative disorders includes immunosuppression reduction, chemotherapy, radiotherapy, and surgery.

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PUB495

Recurrent Malignant Hypertension in Lupus Nephritis Bogdan Marian Sorohan, Andreea Gamala, Andreea Andronesi, Marina Felicia Paraschiv, Roxana Adriana Jurubita, Bogdan Obrisca, Nicu Caceaune, Gener Ismail. *Nephrology and Internal Medicine, Carol Davila Univ of Medicine and Farmacy, Bucharest, Romania.*

Introduction: Systemic Lupus Erythematous (SLE) is a chronic autoimmune disease that frequently leads to kidney involvement. Hypertension in lupus nephritis (LN) is common, but malignant hypertension (MH) is a rare condition. MH in LN is associated with severe clinical manifestations and intrarenal vascular lesions, chronic inflammation being considered the central pathway.

Case Description: A 19-year-old woman with a history of SLE, class VI LN and MH presented with sudden drop in general status, confusion, diplopia, bradypsychia, bradilalia. Physical exam found cold extremities, cyanosis, high BP (260/100 mmHg) and tachycardia. Neurological exam showed impairment of the cerebelum, left central facial palsy and left sided hemiparesis. Lab work thrombocytopenia(105.000/mm3), hyperuricemia (11.2 mg/dl), hypoalbuminemia (2.8 g/dl) and an eGFR of 66.1 ml/min/1.73m^2. A cerebral CT showed no hemorrhagic lesions, but a diffuse hypodense edematous area in the pons, midbrain and bilateral thalamic nuclei. She was started on antihypertensives, Dexamethasone and Mannitol. After 5 days in ICU for neurological degradation (GSC=8), a brain MRA was performed and showed petechial hemorrhage and signal abnormalities suggestive for swelling lesions in deep thalamic regions, left internal capsule, pons, and midbrain. Nimodipine was added to the regimen. A work-up for JC virus and Listeria monocytogenes was negative.Evolution was favorable with complete remission of neurological symptoms. Repeated brain MRA confirmed regression of swelling and haemorrhagic lesions.

Discussion: This case describes the evolution of a young woman with lupus and recurrent MH, complicated with neurological manifestations.The diagnosis of hypertensive encephalopathy was sustained by improved clinical evolution under anti-edema measures, antihypertensives and by CT/MRI imaging. Differential diagnosis was made with central nervous system vasculitis and infections due to immunosuppressiontheraphy (tuberculosis, HIV, JC virus). MH is an important cause of neurological manifestations in SLE with LN, other than cerebral vasculitis and infections.

PUB496

Orlistat Induced Oxalate Nephropathy Leanne A. Ogden, Laurence R. Solomon, Beena Nair. *Renal Dept, Royal Preston Hospital, Preston, Lancashire, United Kingdom.*

Introduction: Orlistat is used for obesity when dietary and lifestyle changes are unsuccessful. It forms covalent bonds and inactivates gastrointestinal lipases. There are reports of kidney injury due to oxalate nephropathy. We describe 3 cases of Orlistat-induced oxalate nephropathy.

Case Description: 1:A 65-year old man was assessed for CKD. He had been prescribed Orlistat for ten months. Serum creatinine was 423 (106µmol/l a year earlier). Urinalysis showed +1 blood. Urinary oxalate-creatinine ratio was 160µmol/mmol (normal<33). Renal biopsy showed chronic interstitial inflammation with patchy fibrosis and tubular atrophy. Several tubules contained oxalate crystals. Serum creatinine fell to 316µmol/l and oxalate:creatinine ratio to 26µmol/mmol after stopping Orlistat. **2:**A 65-year old woman was prescribed Orlistat intermittently for 7 years. BMI was 36. Urinalysis was benign. Serum creatinine was 284µmol/l (normal 2 years earlier) and UACR<2 mg/mmol. Renal biopsy showed mild tubular atrophy, focal acute tubular necrosis and mild interstitial fibrosis. Many tubules contained oxalate crystals. Serum creatinine fell to 191µmol/l following cessation of Orlistat. **3:**A 74 year old man presented with AKI following a fall and required dialysis. He had pre-existing CKD (creatinine 150µmol/l). Orlistat was first prescribed in 2008 and intermittently until 2015. Renal function was slow to recover so biopsy was performed. This showed diabetic nephropathy and oxalate crystals in tubules. After two months he recovered independent kidney function with a creatinine of 383µmol/l.

Discussion: These cases demonstrate that Orlistat may cause kidney failure, which can be insidious. Two patients had no specific symptom. Urinalysis was benign. Cessation of Orlistat was followed by stabilisation or improvement of kidney function, but recovery was incomplete. Diagnosis required renal biopsy. Patients prescribed Orlistat are often at risk of kidney failure for other reasons such as pre-existing CKD, diabetes, hypertension and obesity. Many nephrologists do not biopsy such patients, the diagnosis is easily missed. Close monitoring of kidney function in patients taking Orlistat is warranted. Availability off-prescription should be reviewed.

PUB497

Successful Treatment with Rituximab for Refractory Steroid-Dependent Nephrotic Syndrome Complicated by Immune Thrombocytopenic Purpura: A Case Report Akihiko Shirasu,[1] Akira Ashida,[2] Hideki Matsumura,[2] Hyogo Nakakura,[2] Satoshi Yamazaki,[2] Yuko Fujii,[2] Motoshi Hattori,[3] Hiroshi Tamai.[2] *[1]Pediatrics, Hirakata City Hospital, Osaka, Japan; [2]Pediatrics, Osaka Medical College, Osaka, Japan; [3]Pediatric Nephrology, Tokyo Women's Medical Univ, Tokyo, Japan.*

Introduction: Rituximab is a chimeric anti-CD20 monoclonal antibody that inhibits CD20-mediated B-cell proliferation and differentiation. The use of rituximab for patients with refractory nephrotic syndrome (NS) was approved in Japan in 2014. Rituximab has also administered to patients with immune thrombocytopenic purpura (ITP) if there has no response to first-line therapy. Here, we report a case of refractory steroid-dependent NS complicated by ITP, which was treated successfully with rituximab.

Case Description: The patient was a 14-year-old boy with steroid-dependent NS complicated by severe and frequently relapsing ITP. He had developed NS at the age of 7 years. Histopathological examination by light microscopy showed minor glomerular abnormalities. Although immunofluorescence staining revealed granular IgG deposits along the capillary walls, electron microscopy demonstrated no electron-dense deposits. On the basis of these findings, we diagnosed him as having minimal-change NS, and he responded to a standard glucocorticoid regimen. However, 9 months after onset of NS, he developed ITP, and was treated with glucocorticoid and intravenous immunoglobulin. Although he achieved a temporary response, he was unable to attain permanent remission, and at the age of 9 years suffered a first relapse of NS. As relapses occurred thereafter, we tried additional immunosuppressive agents including cyclosporine and cyclophosphamide, but multiple relapses of both NS and ITP persisted. As he was still steroid-dependent for both NS and ITP at the age of 13 years, we administered rituximab once weekly for 4 weeks. Six months after the rituximab therapy,he has remained in remission of both ITP and NS and the dose of glucocorticoid have been reduced.

Discussion: Although this is a single case report based on short-term observation, we believe that rituximab therapy can be useful option for refractory NS and ITP, especially in adolescent patients who need to avoid the adverse effects of glucocorticoid.

PUB498

Kidney Transplantations with Both Recipients of Kidneys from the Same Deceased Donor with Diabetic Nephropathy Daigo Okada,[1] Masayoshi Okumi,[1] Kohei Unagami,[3] Ken-Ichiro Miura,[2] Hideki Ishida,[1] Motoshi Hattori,[2] Kazunari Tanabe.[1] *[1]Urology, Tokyo Women's Medical Univ, Tokyo, Japan; [2]Pediatric Nephrology, Tokyo Women's Medical Univ, Tokyo, Japan; [3]Nephrology, Tokyo Women's Medical Univ, Tokyo, Japan.*

Introduction: Few reports have been published on the transition of kidney function in kidney transplantation from a donor with diabetic nephropathy. To our knowledge, kidney transplantations with both recipients of kidneys from the same deceased donor with diabetic nephropathy have not been reported yet. We report the cases of two recipients of kidneys from an identical deceased donor who had diabetes. One recipient is a 58-year-old man, and the other is a 15-year-old girl. Both recipients received a kidney transplant from a 60-year-old woman with diabetes. A 0-hour biopsy revealed diabetic nephropathy with nodular sclerosis and polar vasculosis. The former recipient had a serum creatinine (S-Cr) level of 2.1–2.4 mg/dL. The results of the kidney biopsies performed 4 and 14 months after kidney transplantation showed no change as compared with the 0-hour biopsy result. The latter recipient had a S-Cr level of 1.6–1.8 mg/dL and proteinuria at discharge. Her S-Cr level increased gradually to 3.4 mg/dL at 7 months after kidney transplantation. Therefore, we performed an episode biopsy. Histological examination revealed an increment of tubular atrophy and fibrosis of cortical stroma due to diabetic nephropathy. We found no evidence of rejection and recurrence of focal glomerular sclerosis. This report suggests that graft function with diabetic nephropathy might worsen in spite of good glycemic control.

PUB499

Imatinib-Associated Acute Tubular Necrosis Nupur N. Uppal,[1] Valerie Suzanne Barta,[1] Rimda Wanchoo,[1] James M. Pullman,[2] Anna T. Levy,[3] Kenar D. Jhaveri.[1] *[1]Nephrology, Hofstra Northwell School of Medicine; [2]Pathology, Montefiore Medical Center; [3]Hematology/Oncology, Hofstra Northwell School of Medicine.*

Introduction: Imatinib(Gleevac) is an antineoplastic agent that acts by inhibiting tyrosine kinase enzyme and has been widely used for the treatment of various cancers. Acute kidney injury (AKI) is a rare adverse event of imatinib treatment. We report a case of biopsy proven acute tubular necrosis(ATN) with imatinib treatment.

Case Description: A 76-year-old female with history of hypertension, gastrointestinal stromal tumor (GIST) was initiated on imatinib after surgical resection for adjuvant therapy. A week later, serum creatinine (Scr) increased to 1.6mg/dl(baseline 1.03mg/dl). Patient denied use of any known nephrotoxic agents. There were no clinical or lab findings suggestive for prerenal AKI. Urinalysis revealed 100 milligrams of protein but no hematuria. AKI was thought to be related to imatinib treatment. Hence, dose of imatinib was reduced by 50%. Scr decreased to 1.3mg/dl six days after dose reduction. However, mutational analysis conferred imatinib resistance requiring resumption of previous higher dose of imatinib. Scr increased to 1.7mg/dl a week after increase in imatinib dose. A kidney biopsy was performed that confirmed toxic ATN with vacuolization with minimal interstitial fibrosis and tubular atrophy likely related to imatinib treatment. Patient was continued on imatinib therapy due to lack of availability of alternate chemotherapy with close monitoring of renal function. 3 months out, the Scr stabilized at 1.6mg/dl and the patient is disease free.

Discussion: This case describes fourth reported association of imatinib treatment with AKI. Out of three prior reported cases, two had ATN and one had tubular vacuolization on kidney biopsy. The injury appears to be dose related but only in the initial phase of the treatment. Although risk of nephrotoxicity is small with imatinib treatment, physicians should be aware of this potential adverse effect of this agent and renal function should be closely monitored during imatinib therapy.

PUB500

Recurrent Leg Cramps: An Unsuspected Presentation of Acute Arterial Thrombosis Leading to Amputation in a Child with Nephrotic Syndrome Amirtha Chinnadurai, Olivera Marsenic Couloures. *Pediatric Nephrology, Yale Univ School of Medicine, New Haven, CT.*

Introduction: Although Nephrotic Syndrome(NS) is known to cause hypercoagulability, thromboembolic complication is uncommon, with serious limb-threatening peripheral arterial thrombosis being extremely rare. We report a case of a child with leg cramps, progressing to cold pulseless right leg and amputation of the toes in his first relapse of Nephrotic syndrome.

Case Description: An 8-year-old African American boy with a new diagnosis of Nephrotic syndrome developed a relapse during the steroid wean. Over the next week, he presented twice to the ED with intermittent right leg cramps. Evaluation was unrevealing and he was discharged home after both visits. Subsequently, he developed intense right leg pain and limping. Physical examination revealed a cold, pale right lower leg with absent popliteal and dorsalis pedis pulses. US Doppler of the leg revealed a complete occlusion of the peroneal, anterior and posterior tibial arteries. Emergent surgical thrombectomy was

unsuccessful, thus catheter directed thrombolysis, systemic heparinization and antithrombin III (ATIII) infusion were initiated. Interval thombectomy was then performed together with a fasciotomy for compartment syndrome. The distal perfusion improved, despite this, all 5 digits of the right foot became gangrenous necessitating amputation. Investigation into the etiology of his thrombosis revealed low ATIII levels but normal levels of factors II, VII, IX, X and XIII. Genetic analysis for Prothrombin gene mutation, Plasminogen Activator Inhibitor Type I and Factor V Leiden mutation were negative. Complement levels were normal. Anti-DsDNA, ANCA and antiphospholipid antibodies were negative. Diagnosis of Focal Segmental Glomerulosclerosis (FSGS) was made by renal biopsy. After 7 weeks of hospitalization, the patient was able to ambulate with assistance and was discharged home.

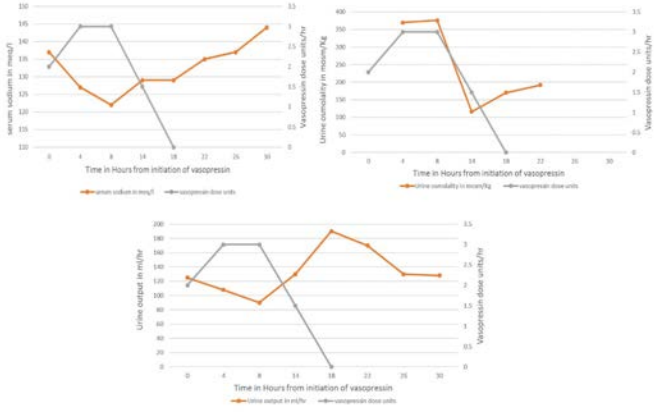
Discussion: Severe arterial thrombosis in our patient occurred during the relapse of NS (FSGS), without evidence of thrombophilia due to other primary or secondary cause. This case demonstrates a need for a high index of suspicion for arterial thromboembolic complications in Childhood Nephrotic syndrome.

PUB501

Pressor-Induced Hyponatremia Pradeep Chaganti, George C. Bonifant, Karim El Hachem, Steven D. Smith, Germaine Z. Chan, Anip Bansal. *Nephrology, Mount sinai St. Luke's and Mount Sinai West Hospital, New York, NY.*

Introduction: Vasopressin has vasoconstrictive effects through smooth muscle V1 receptors and also has antidiuretic activity via renal V2 receptors. Although rare, exogenous vasopressin administration in doses used for management of shock can be responsible for significant hyponatremia.

Case Description: A 39-year-old man with past medical history of Crohn's disease, ankylosing spondylitis, lung fibrosis and schizoaffective disorder was admitted for cavitary pneumonia with sputum positive for tuberculosis. Over the next few days he developed acute respiratory failure with septic shock requiring mechanical ventilation septic and vasopressor support with norepinephrine and vasopressin. His lab data on admission and prior to above decompensation revealed normal serum sodium and creatinine levels. Within hours of starting the vasopressin infusion, he developed significant hyponatremia with a nadir of 120 mEq/L. The patient was also started on IV Bactrim in D5W two days prior to this event for empiric Pneumocystis pneumonia treatment. He had normal cortisol and TSH levels. On switching vasopressin to another pressor, the serum sodium increased rapidly from 122 mEq/L to 135 mEq/L along with a relative increase in urine output and decrease in urine osmolality (see graphs below). Dextrose infusion was started to prevent overly rapid correction.



Discussion: Vasopressin does not usually result in hyponatremia when used in the management of shock. Possible explanations include lack of renal responsiveness secondary to renal hypoperfusion in setting of acute kidney injury, or lack of intake of hypotonic fluids. This rare side effect can happen due to concurrent factors like vasopressin support for shock, endotoxin induced vasopressin release in early septic shock, or relative cortisol deficiency in the setting of hypotonic solution administration.

PUB502

Post-Infectious Atypical Hemolytic Uremic Syndrome in an Adult Presenting without Schistocytes on Peripheral Blood Smear Dianne Victoria Vieja. *Internal Medicine, Section of Nephrology, Philippine General Hospital, Manila, Philippines.*

Introduction: Hemolytic Uremic Syndrome refers to the triad of hemolytic anemia, uremia and acute renal failure. Its hallmark feature is microangiopathic hemolytic anemia. However, there are patients who present with hemolysis and uremia that do not fit the typical criteria of HUS. These patients may be overlooked and hence important disease-modifying therapeutic intervention missed.

Case Description: A 38 year old man with presented with a 2 day history of watery diarrhea. On workup, he was had leucocytosis, hypokalemia, azotemia, hyperbilirubinemia, metabolic acidosis and high LDH. Proteinuria and hematuria were also noted. Stool, urine and blood cultures were negative. Antibiotics and electrolyte correction were started. Over the next days, patient remained oliguric and subsequent exam revealed anemia, thrombocytopenia and worsening azotemia. Further testing showed elevated reticulocyte count, negative Coomb's test but no schistocytes on peripheral blood smear. Renal replacement therapy was done and patient eventually discharged improved.

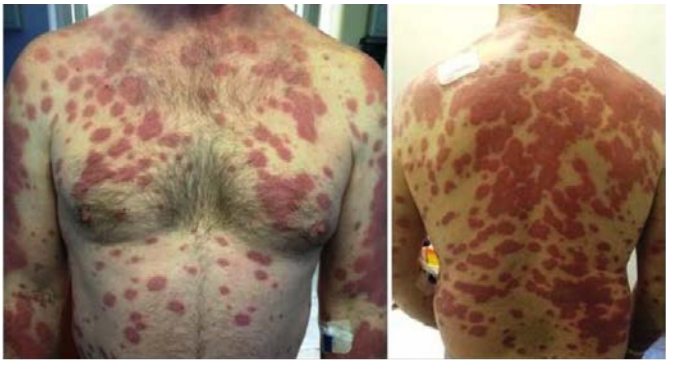
Discussion: HUS is a Thrombotic Microangiopathies resulting from an infection affecting children and elderly. It is due to Shigella or E.Coli with incidence rate of 90%. However, some cases are due to infections by viruses. Diagnosis rests on evidence of mechanical, non-immune hemolytic anemia (schistocytes), high LDH and renal injury. Clinical presentation may be mild and some may not present typically. Serres and Isenring in 2009 performed a retrospective study which showed that up to 44% of patients with biopsy-proven Thrombotic Microangiopathy HUS had normal platelet counts and no schistocytes. This is due to low level of hemolysis at the time of examination, as seen by the only mild thrombocytopenia in the patient. This case report emphasizes that HUS may be considered in the absence of the usual bacterial growth and also in the absence of schistocytes, both of which are textbook definitions of HUS.

PUB503

A Rare Case of Sweet Syndrome in Azathioprine Treated ANCA Vasculitis Mohamed Elsayed,[1,2] Ahmed Alghali,[1,2] Alaa M. Ali,[1,2] Arunkumar Aruna Udayakumar,[1,2] Muhammad Umair Sharif,[1,2] Austin G. Stack.[1,2,3] *[1]Nephrology Dept, Univ Hospital Limerick; [2]Graduate Entry Medical School, Univ of Limerick; [3]Health Research Inst, Univ of Limerick, Ireland.*

Introduction: ANCA associated vasculitis is frequently encountered in renal practice with immunosuppression being the main stay of management. Azathioprine (AZA) is commonly used and relatively safe for maintaining remission. AZA induced Sweet syndrome is a rare complication that was first reported in 2003.

Case Description: We describe a case of a 53-year-old male with MPO-ANCA vasculitis treated initially with pulse steroid therapy and rituximab achieving clinical remission although his MPO titre remained elevated. Azathioprine was commenced for maintenance therapy. Two weeks later, he presented with an acute onset of a generalized painful rash over the trunk and limbs. This was associated with fever and non-specific constitutional symptoms. Examination revealed conjunctivitis & painful erythematous papules/plaques.



Laboratory results showed 12.8x10^9/l leukocytosis with 87% neutrophilia , CRP of 237 mg/l , ESR of 60mm/hr and stable renal function with benign sediment. Infectious work up was negative. A skin biopsy showed acute neutrophillic dermatosis with no evidence of vasculitis confirming a diagnosis of Sweet syndrome. Work-up for occult malignancy was negative. A diagnosis of azathioprine-induced sweet syndrome was made based on temporality. Almost complete resolution was achieved with AZA discontinuation and a short pulse of oral steroids and colchicine therapy.

Discussion: Immunosuppressive therapy requires good surveillance for side effects and complications. Although rare, it is prudent to consider AZA induced sweet syndrome in patients presenting with fever and rash within weeks of initiating therapy after excluding infections, malignancy and acute vasculitis flare.

PUB504

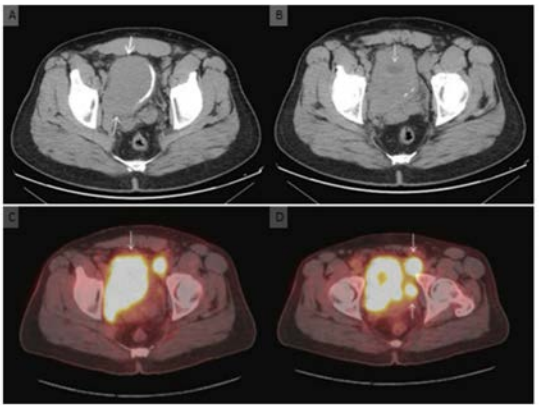
Pheochromocytoma(Paraganglioma) of the Urinary Bladder Causing Secondary Uncontrolled Hypertension Eyerusalem Engida Bayssa,[1,2] Amina Khan.[1,2] *[1]Nephrology, Kansas Univ Medical Center, Kansas City, KS; [2]Nephrology, Kansas City VA, Kansas City, KS.*

Introduction: Secondary hypertension due to a catecholamine secreting paraganglioma is extremely rare.

Case Description: A 56 year-old AAM presented with urinary urgency, frequency, dribbling and lower abdominal discomfort. Blood pressure was 162/110 mmHg on lisinopril 40mg, hydrochlorothiazide 25 mg daily and carvedilol 25 mg twice daily. Abdominal CT showed 9.4 X 6.9 cm right posterior bladder wall mass and enlarged bilateral pelvic lymph nodes. Urinalysis was significant for 11-15 RBCs/hpf. Pathology revealed paraganglioma. Free plasma metanephrine levels were elevated, 14690 pg/ml (normal <= 205). PET scan showed possible extension to the prostate and right lateral pelvic wall and left deep inguinal nodal enlargement. Radical cystoprostatectomy, bilateral lymph node dissection and urinary diversion by ileal conduit was done. Post op BP controlled with Propranolol 20mg every 6 hours, phenoxybenzamine 30mg TID, lisinopril 40mg, amlodipine 5mg

and hydrochlorothiazide 25mg daily. Intraoperative findings showed a bulky tumor that was unrespectable and large grossly positive lymph node. Oncology recommend radiation therapy in 3-4 weeks.

CT showing 9.4 x 6.9 cm right posterior lateral bladder mass(A). Necrotic center of bladder mass(B). PET showing intensely hypermetabolic bladder mass(C). Markedly enlarged left deep inguinal lymph nodes(D).



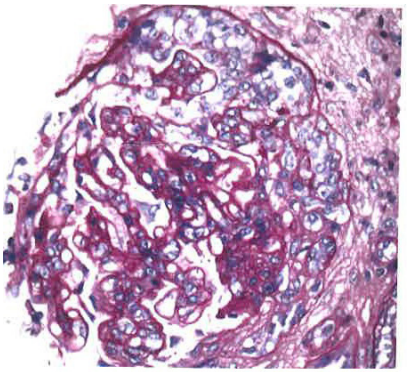
Discussion: Pheochromocytoma is a rare tumor occurs in less than 0.2% of patients with hypertension (1). One-third to one-half of extra adrenal pheochromocytoma associated with an inherited syndromes including MEN II, Neurofibromatosis type I, VHL and Carney-strataskis dyad(2). Plasma free metanephrine still the best biochemical test(3) . MRI and CT scan are useful to localize tumor. Perioperative preparation includes 3-4 weeks of α-adrenoreceptor blocked. Irradiation can be used for metastatic lesions. Chemotherapy plays a role in patients who exhibit symptoms from surgically inaccessible metastases tumors that cannot be controlled by α- and β-blocked.

PUB505

Acute Kidney Injury, Seizures and Thrombocytopenia in a Young Patient with Lupus Nephritis Hector Alvarado Verduzco,[1] Anjali Acharya.[2] *[1]Medicine, Jacobi Medical Center, Bronx, NY; [2]Nephrology, Jacobi Medical Center, Bronx, NY.*

Introduction: Posterior reversible encephalopathy syndrome (PRES) is a complex clinico-radiologic syndrome of varied etiologies, with neurological findings mainly suggestive of the posterior white matter involvement that frequently is reversible. Prompt recognition and treatment of underlying etiology is crucial.

Case Description: A 22 year-old patient with Systemic Lupus Erythematous (SLE) complicated with chronic kidney disease secondary to lupus nephritis class IV, presented with recurrent seizures and uncontrolled hypertension. She had acute kidney injury and thrombocytopenia. Repeat biopsy showed diffuse endocapillary and extracapillary proliferative with crescent (Figure 1) and membranous lupus nephritis (ISN-RPS class IV-G+V), new changes with endothelial swelling secondary to severe hypertension; but no thrombotic microangiopathy. Brain imaging showed left frontal and parietal infarct with improvement of lesions and symptoms after controlling blood pressure (BP), making PRES the diagnosis. She had recurrent episodes of seizures with brain edema on imaging.



Discussion: PRES is thought to be associated with disordered cerebral auto-regulation and endothelial dysfunction. Most cases present with systolic BP over 200 mm Hg or at least a 35% increase from baseline. Our case presents several unusual scenarios as described below. The most common abnormalities on MRI are punctuate or confluent areas of increased signal on T2-weighted images in the posterior fossa but in this patient, the MRI changes were in the frontal and parietal regions. Patient had recurrent seizures, which is unusual in PRES. Diagnosis can pose a challenge, as in our patient, when associated with SLE, as it can be confused with lupus vasculitis. In addition, treatment with cytotoxic agents if required can be an additional problem as these agents can contribute to PRES.

PUB506

Recurrent C3 Glomerulonephritis Treated with Eculizumab: A Case Report Trevor R. Smith, Mazdak A. Khalighi, Monica Patricia Revelo Penafiel, Josephine Abraham, Kalani L. Raphael. *Univ of Utah.*

Introduction: C3 glomerulonephritis (C3GN) is a rare cause of kidney disease that has a high recurrence rate (>50%) in the renal allograft. We present a case of recurrent C3GN in a renal allograft that was treated with and rapidly responded to eculizumab.

Case Description: A 70 year old male with membranoproliferative glomerulonephritis (MPGN) type I diagnosed in 2005 received a deceased donor renal transplant in 2013. Eighteen months later, he developed dysmorphic hematuria, sterile pyuria, and acute creatinine rise from 1.0 to 1.4 mg/dL; urine protein/creatinine was 200 mg/g. His immunosuppressive regimen included prednisone, mycophenolic acid, and tacrolimus. Renal biopsy demonstrated a focal exudative glomerulonephritis, C3-dominant immunofluorescence (IF), and mesangial, subendothelial, and intramembranous deposits by electron microscopy, consistent with C3GN. His original biopsy was re-evaluated, which was also consistent with C3GN. C3, C5 and Factor B levels were normal. However, complement Ba (1.9 mg/L), Bb (3.7 mg/L), and C5b-9 (0.49 mg/L) were elevated. C3 nephritic factor was negative, and no genetic variants were identified. The patient was monitored for 6 months, however, his creatinine increased to 1.7 mg/dL as did proteinuria. Eculizumab was initiated at 900 mg intravenously weekly for 4 weeks followed by 1200 mg every two weeks. After 1 month of therapy, the protein/creatinine ratio decreased from 1500 to 128 mg/g and hematuria and pyuria resolved. The most recent creatinine was 1.2 mg/dL, two months after starting eculizumab.

Discussion: There are few case reports regarding the use of eculizumab in C3GN and even fewer in kidney transplant patients, and the response to this therapy has been variable. This patient had a rapid response to eculizumab with resolution of proteinuria, hematuria, and pyuria and a near normalization of serum creatinine within two months. The sustainability of this response as well as the duration of treatment is uncertain. This case also highlights how the IF-based classification of MPGN, which is based on pathogenetic mechanisms, has impacted the diagnosis, evaluation, and treatment of MPGN.

PUB507

Multifactorial Hypertension - A Challenge to the Clinician Jyotsana Thakkar, Khurram Mehtabdin, Richard L. Barnett, Mala Sachdeva, Jamie S. Hirsch. *Div of Kidney Disease and Hypertension, Northwell Health, NY.*

Introduction: Incidentally discovered adrenal masses are common. About 15% of adrenal adenomas occur bilaterally and present challenges both in diagnosis and management. We describe a case of bilateral adrenal adenomas causing resistant hypertension (HTN).

Case Description: A 50 year old male with uncontrolled HTN for 25 years, chronic kidney disease stage III (baseline creatinine 1.6), and schizoaffective disorder was admitted to the hospital for hypertensive urgency with a blood pressure of 190/130. Patient's anti hypertensive regimen consisted of valsartan, amiloride, metoprolol and doxazosin. He was also taking potassium citrate supplements for hypokalemia and metabolic acidosis, which was attributed to topiramate. Other medications included monthly testosterone injections and over-the-counter caffeine supplements. Workup for secondary HTN was notable for elevated plasma aldosterone level (38.3 ng/dl), suppressed renin (<2.1 pg/dl), and normal metanephrines. Renal artery duplex showed no evidence of significant renal artery stenosis. CT scan and MRI of the abdomen revealed bilateral adrenal adenomas (1.4 x 1.5 cm on the left and 2.4 x 2.5 cm on the right). . Following readmission for AKI and hypertensive urgency (BP >200/110), adrenal venous sampling was undertaken for possible surgical intervention, and demonstrated the presence of an aldosterone producing adenomas with concentrations of 282 ng/dl and 22.9 ng/dl, on the left and right respectively. Surgical resection of the left adrenal mass was offered, but the patient declined and preferred therapy with a mineralocorticoid receptor antagonist. Initiation of spironolactone in conjunction with a thiazide diuretic was modestly helpful in reducing his blood pressure, to a current level of 150/90. He was advised to stop caffeine supplements and testosterone injections.

Discussion: While this patient had multiple reasons for uncontrolled hypertension, we believe that the primary driver was hyperaldosteronism, which may have been initially missed due to the presence of metabolic acidosis. This case emphasizes the importance of evaluating for secondary causes of HTN. Understanding the importance of the multifactorial nature of HTN can aide in the individualized treatment approach.

PUB508

Acute Generalized Exanthematous Pustulosis Associated Acute Interstitial Nephritis Jyotsana Thakkar, Bradley H. Goldberg, Mala Sachdeva. *Div of Kidney Diseases and Hypertension, Northwell Health, NY.*

Introduction: Acute generalized exanthematous pustulosis (AGEP) is characterized by the development of numerous nonfollicular sterile pustules associated with edematous erythema. Systemic organ involvement is uncommon. We present a case of AGEP with acute kidney injury (AKI).

Case Description: A 49 year old Caucasian female with recent bilateral breast reduction surgery ten days prior to admission presented with a diffuse body rash and severe odynophagia. She was started on cephalexin after the surgery. After three days on the antibiotic, she developed high fevers and a diffuse body rash. Due to suspicion of an allergy, antibiotic was discontinued and she was started on oral antihistamine and steroids. Subsequently, the rash worsened, she remained febrile, and developed severe odynophagia, prompting the ED visit on day ten. Initial vitals revealed a blood pressure of 94/65mmHg, and heart rate of 94 bpm. Skin exam showed a diffuse erythematous rash sparing palms and

soles with punctate pustules on her chest, face, and legs. Laboratory examination revealed a WBC 17.5, an absolute eosinophil count of 1000 after steroids were discontinued, BUN of 78mg/dl and creatinine of 6.57 mg/dL. Urinalysis showed trace blood and protein, negative nitrite and leukocyte esterase, 11-25 WBCs, 3-5 RBCs. Urine microscopy showed many WBC clumps. Urine culture was negative. Spot urine protein: creatinine ratio was 0.4. FeNa was 2.0%. Complements, ANA, ANCA, and ASLO titers were negative. Skin biopsy confirmed AGEP. She was treated with intravenous fluids and topical steroid creams. Her serum creatinine normalized to 0.6 mg/dl on day four.

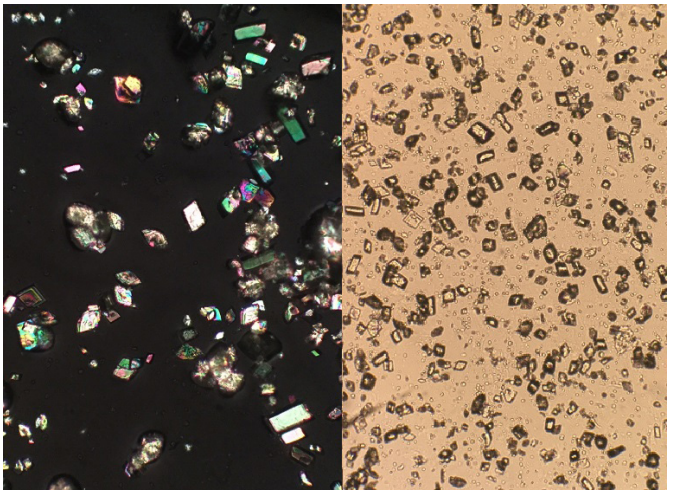
Discussion: AGEP is characterized by T cell mediated inflammatory reaction. Renal involvement is rare. A previously described case of AGEP with AKI was suspected to be of glomerular origin, and other cases have not described the etiology of AKI. We believe the AKI in our patient was primarily an allergic interstitial nephritis, as characterized by rash, fever, peripheral eosinophilia after discontinuation of steroids, sterile pyuria, and its association with a cephalosporin. Clinicians should be aware of this rare dermatological entity and its possible associated renal manifestation.

PUB509

Sulfamethoxazole Crystal-Induced Nephropathy - A Rare Cause of Acute Kidney Injury in an HIV Patient Arani D. Nanavati, Georges Nakhoul. *Nephrology, Cleveland Clinic Foundation.*

Introduction: Drug-induced crystalluria can be a cause of acute kidney injury (AKI). Sulfonamides are known to cause crystallization in the urine. We report a case of AKI due to sulfamethoxazole crystal induced nephropathy in a patient with HIV who was treated with intravenous (IV) Trimethoprim-Sulfamethoxazole (TMP-SMX).

Case Description: 56-year old male with normal baseline serum creatinine(SCr) of 0.7 presented with respiratory failure. He was empirically being treated for community acquired pneumonia. He was diagnosed with HIV with CD4 count of 18. Bronchoalveolar lavage was performed and patient was diagnosed with *Pneumocystis Jirovecii* Pneumonia (PJP). He was started on IV TMP-SMX. Within one day of the treatment initiation, his SCr started to trend up to 1, then to 1.3 and then 2. He also had refractory hyperkalemia with serum potassium of 5.5-6.1 despite medical management. Urine microscopy revealed abundance of polarizing, strongly bi-refringent and polychromatic crystals of various shapes: rhomboid, losangic and hexagonal.



Calculi analysis of urine was performed via Fourier Transform Infrared Spectroscopy and it revealed presence of SMX crystals. Neither cystine nor uric acid were identified. Urine alkalinization was not performed as he had respiratory acidosis with compensatory metabolic alkalosis. Patient received a session of dialysis for refractory hyperkalemia. TMP-SMX was stopped and an alternative antibiotic was started. Patient's renal function recovered and he did not require additional dialysis treatments. Repeat urine microscopy revealed disappearance of the crystals.

Discussion: SMX induced crystal nephropathy is an uncommon cause of AKI. While it is usually considered as a well-known entity, literature describing the appearance SMX crystals is actually scarce. This case provides images of SMX crystals and highlights the importance of urine microscopy in the diagnosis of AKI.

PUB510

It's More Than HIV and HAART in HIV with AKI Deewan Deewan,[1] Matthew J. Diamond,[1] Daniel Kleven.[2] [1]*Dept of Nephrology, Augusta Univ, Augusta, GA;* [2]*Dept of Pathology, Augusta Univ, Augusta, GA.*

Introduction: Immune reconstitution syndrome (IRIS) is a multiorgan inflammatory condition in human immunodeficiency virus (HIV) patients following initiation of antiretroviral (HAART) therapy. Rarely does IRIS cause acute kidney injury (AKI). This case presents a patient who developed AKI thought due to IRIS.

Case Description: A 35-y/o man was hospitalized for uremia (BUN = 146 mg/dL, Cr = 16 mg/dL) and hemodialysis (HD) initiation. He had recently been started on triple therapy for pulmonary MAI (ethambutol, chlarithromycin, and rifabutin), and recently had his HAART modulated to elvitegravir/cobicistat/emtricitabine/tenofovir. He also previosly developed IRIS several months earlier from initiation of HAART. An ultrasound demonstrated normal sized echodense kidneys with with multiple punctate calcific lesions noted in both kidneys and his liver. A kidney biopsy revealed acute tubular necrosis (ATN), mononuclear interstitial infiltrates, and myoglobin cast nephropathy. In addition, one core sample revealed granulomatous material which contained acid-fast bacteria, later identified as MAI. No mitochondrial or glomerular damage was noted. Given the mononuclear infiltrate, sparing of the glomeruli, and disseminated MAI, the AKI was thought to be caused from IRIS. Prednisone was started of IRIS treatment, moxifloxacin replaced ethambutol for MAI treatment, and his HAART was restarted after a brief hiatus. With these changes, the patient recovered renal function, with a new baseline creatinine of 1.73 mg/dL, and no longer required HD.

Discussion: This case demonstrates that IRIS can cause AKI, and is treatable with steroids, as well as continuation of HAART. Although considerably rare, this phenomenon has been reported in the literature over the past 15 years; most are associated with concomitant mycoplasma infection. When appreciated, a mononuclear interstitial infiltrate is demonstrated on the kidney biopsy, with sparing of the glomeruli. Furthermore, this case demonstrates the utilization of kidney biopsy in an HIV patient to accurately define the pathology for proper therapeutic intervention.

PUB511

IgA Vasculitis versus IgA Dominant Post-Infectious Glomerulonephritis? A Case of Severe Oxacillin Resistant *S. aureus* (ORSA) Cellulitis Vivek Ramesh Sanghani, Luanna Yang, Volker Nickeleit, Patrick H. Nachman. *UNC Kidney Center, Univ of North Carolina, Chapel Hill, NC.*

Introduction: IgA dominant post-infectious proliferative glomerulonephritis has been described in association with ORSA. These cases may be difficult to differentiate from primary IgA nephropathy or IgA vasculitis with superimposed infection. We present a case illustrating this differential diagnosis.

59 yo female with a history of Hepatitis C and venous stasis presented with lower extremity ulcerated wounds and acute kidney injury. A large deep ulcer with heaped borders and purulent base extended from the left knee to the ankle. A smaller ulcer affected the R ankle. A non-blanching erythematous macular and petechial rash involved the thighs, forearms and hands. Wound cultures grew ORSA which was treated with vancomycin. Serum Creatinine (Cr) was 1.92 mg/dl (from <1 a month earlier). Her urine was tea colored, the sediment revealing numerous dysmorphic red blood cells. Urine protein/creatinine ratio = 1.6 g/g. Serum C3, C4, rheumatoid factor, ANA, ANCA and Hepatitis B surface Ag were normal. Hepatitis C viral load was 794775 [IU]/ml with normal AST and ALT. ESR: 44mm/hr and CRP: 2.7mg/dL. A renal biopsy demonstrated moderate mesangial matrix expansion and hypercellularity, focal and segmental endocapillary proliferation and cellular crescents in 15% of glomeruli. There was 3+ IgA and C3 granular deposition within the mesangial space and along peripheral glomerular capillary walls. Intratubular red blood cell casts were noted. No large subepithelial deposits were found by electron microscopy. A skin biopsy from the arm showed granular depositions of IgA and fibrinogen in the papillary dermal vessels, thus confirming a diagnosis of IgA vasculitis. Corticosteroids were initiated because of progressive decline in GFR.

Discussion: This case illustrates an acute nephritic exacerbation of IgA vasculitis, precipitated by the ORSA infection. This is supported by the normal serum complements, the absence of large subepithelial immune complex type deposits, and the skin biopsy findings. Differentiating between this and IgA dominant post infectious glomerulonephritis is crucial to direct therapy.

PUB512

Acute Kidney Injury with Polyclonal Lympho-Plasmacytic Interstitial Infiltrate Secondary to Diffuse Infiltrative Lymphocytosis Syndrome (DILS) in an Untreated HIV Patient Gregory R. Varghese, Navneet Kaur, Sandeep Aggarwal, Suganthi Soundararajan. *Nephrology, Drexel Univ College of Medicine, Philadelphia, PA.*

Introduction: Acute kidney injury (AKI) in HIV is multi-factorial and includes toxic, infectious, and autoimmune etiologies. We present a rare case of Diffuse Infiltrative Lymphocytosis Syndrome (DILS) induced AKI in the setting of HAART noncompliance.

Case Description: A 38 year old AAF with known HIV infection (CD4 count 34 cells/microliter) that had been uncontrolled due to HAART noncompliance. She presented to our facility for fever (102.2 F), loss of appetite, and weight loss. On admission, patient noted to have acute kidney injury (AKI) with creatinine at 2.04 mg/dL (baseline creatinine 0.7-1.0 mg/dL 6 months prior). Urinalysis study showed >100 WBC's, 6-10 RBC's, occasional bacteria, 2+ protein, and 3+ leukocyte esterase. For pertinent labs, CD4:CD8 was 0.35, IgA 676 mg/dL, IgG 3401 mg/dL, IgM 1075 mg/dL, HSV-1 & 2 DNA and IgM antibodies were negative as well as acute viral hepatitis panel. ANA titer was 1:40 with speckled pattern but C3 & C4 were normal. Renal ultrasound was unremarkable. Renal function continued to worsen despite fluid resuscitation with medication adjustments, therefore a renal biopsy was performed. Light microscopy was notable for polyclonal-lymphoplasmacytic interstitial infiltration with diffuse moderate to severe tubulo-interstitial inflammation correlating with a predominance of circulating CD-8 positive T lymphocytes and poly hyper-gammaglobulinemia. Special staining for adenovirus, CMV, HSV were all negative. A diagnosis of DILS with renal involvement was made. Patient was treated with short course of steroids and HAART with improvement of renal function to baseline.

Discussion: DILS is a rare etiology of AKI in HIV-infected patients. The diagnosis should be considered in patients that are treatment naïve or non-compliant to HAART therapy. Early biopsy with multi-disciplinary approach may help improve the outcome of this disease.

PUB513

An Unusual Case of Pulmonary Hemorrhage with Acute Renal Failure due to Systemic Lupus Erythematosus and Polyangitis Mohammed Nazmul, Anustup Datta, Marius C. Florescu. *Nephrology, Univ of Nebraska Medical Center, Omaha, NE.*

Introduction: Pulmonary hemorrhage with proliferative glomerulonephritis is a characteristic manifestation of anti-glomerular basement disease or pauci immune vasculitis but unusual in Systemic Lupus Erythematosus (SLE).

Case Description: A 19 years old woman presented to ER with hemoptysis, dyspnea and decreased urine output for 1 week. Physical examination revealed bibasilar lung crepitation,2+ ankle edema but no rash, organomegaly or lymphadenopathy.Laboratory tests significant for severe renal failure with hyperkalemia.Chest X ray showed bilateral consolidation. She was intubated and anuric. Emergent hemodialysis and plasmapheresis initiated. Labs included positive anti-nuclear, anti-double stranded DNA , anti-nuclear cytoplasmic antibodies with perinuclear pattern of distribution , low C3 and C4;negative lupus anticoagulants, anti-GBM, anti-proteinase 3 and anti-myeloperoxidase antibodies. Blood culture showed Escherichia coli and Enterobacteriaceae. Urine microscopy revealed RBC's and WBC clumps.Renal biopsy showed diffuse proliferative glomerulonephritis with cellular crescents and fibrinoid necrosis, "full house staining" on immunofluorescence consistent with Type IV lupus nephritis. Following plasmapheresis, she received 6 months of oral cyclophosphamide, prednisone and hydroxychloroquine. After 6 weeks hemodialysis her renal function improved and hemodialysis stopped.

Discussion: Pulmonary renal syndrome is a rare life threatening complication of SLE. Presence of p-ANCA may indicate an associated acute vasculitis with biopsy showing fibrinoid necrosis.Antecedent infection could trigger wide spread vasculitis reaction with underlying medical illness of lupus. Clinical presentation was concerning of vasculitis but further work up confirmed active lupus.This case highlights that different disease processes can be responsible for the occurrence of pulmonary renal syndrome. Association between small vessels vasculitis and SLE signifies the fact that small group of patient with SLE may also have an underlying polyangitis where biopsy findings provide valuable guidance for appropriate early intervention which is paramount due to the severity of their illness.

PUB514

Incarcerated Inguinal Hernia as a Presenting Complication of Polycystic Kidney Disease Ahmed Daoud,[1] Mostafa Alfishawy.[2] *[1]Nephrology, UAMS, Little Rock, AR; [2]General Medicine, Queens' Hospital, New York, NY.*

Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is a multisystemic disorder with renal and extrarenal complications. End stage renal disease is the most feared complication affecting almost 50% of ADPKD patients by 60 years. We are presenting a case of ADPKD that was diagnosed when the patient presented with incarcerated inguinal hernia. The incarcerated hernia is probably a result of increased intra-abdominal pressure due to polycystic kidneys.

Case Description: Herein we present a 56 year old Male with ADPKD who presented to the emergency room with abdominal and groin pain. He was admitted for possible small bowel obstruction and CT scan performed and showed incarcerated inguinal hernia and bilateral huge cystic kidneys, cystic liver and pancreas. Patient was managed conservatively then he was discharged and scheduled for outpatient bilateral inguinal hernia repair with mesh.

Discussion: ADPKD affects approximately one in 1000 people. The most common presentation is a palpable mass, hypertension (after their third decade of life), abdominal pain, and hematuria. Abdominal wall hernias are up to five times more common in ADPKD patients with prevalence estimated to be 45%. The increased prevalence is thought to be due to a combination of increased intraabdominal pressure from enlarged kidneys and weak abdominal musculature due to the connective tissue pathology. Our patient was discovered to have Polycystic Kidneys after presenting with incarcerated hernia. Up to our knowledge, this is the second case of ADPKD presenting with incarcerated hernia. Our point is that incarcerated hernia may be a rare presentation of ADPKD.

PUB515

A Case of Plasmapheresis in Treatment of Myeloma Kidney Shehryar H. Ashraf, Niralee Patel, Ruchir D. Trivedi. *UCONN Health Center, Farmington, CT.*

Introduction: Myeloma kidney, also called light chain cast nephropathy, is caused by monoclonal immunoglobulin infiltration and light chain deposition many times requiring renal replacement therapy. Treatment includes chemotherapy, but the use of plasmapheresis has been used for removal of light chains in acute disease.

Case Description: We present a 69-year-old male patient diagnosed with multiple myeloma with associated acute kidney failure requiring hemodialysis. Due to significantly elevated lambda SFLC and renal disease, plasmapheresis was initiated. He received plasmapheresis for three days, subsequently, began chemotherapy. SFLC levels were obtained daily, prior to any interventions of the day. Lambda SFLC decreased by 19% from two sessions of plasmapheresis prior to starting chemotherapy and a tremendous 60% after 11 days (figure 1).

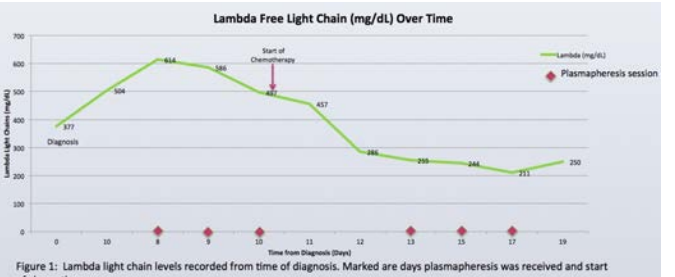


Figure 1: Lambda light chain levels recorded from time of diagnosis. Marked are days plasmapheresis was received and start of chemotherapy.

Discussion: Chemotherapy decreases SFLC production, thus affecting the underlying myeloma kidney disease. However, after initial diagnosis, plasmapheresis can be utilized to physically remove the SFLC and directly decrease the damage to the kidney. Based on a study by Zucchelli et al., there was an observed increased survival with the use of plasmapheresis in addition to chemotherapy. However, Clark et al. reached no statistically significant difference with plasmapheresis with chemotherapy. Hutchinson et al. found that decreasing SFLC by 60% in 21 days resulted with renal recovery. Our patient was treated successfully by reducing SFLC by 60%. We hope for renal recovery in the future, by becoming independent of dialysis.

PUB516

BRAF Inhibitors- Induced Renal Injury and Electrolyte Disturbances Ahmed Daoud, Gerren Hobby, Umbar Ghaffar. *Nephrology, UAMS, Little Rock, AR.*

Introduction: Agents that inhibit the BRAF kinase pathway showed promise in treating malignant melanoma.Two specific agents, vemurafenib and dabrafenib, and the MEK inhibitor, trametinib, have been licensed since 2011 for treatment of patients with unresectable or metastatic melanoma with BRAF mutation. While these drugs have greatly improved the prognosis of this disease, they have been associated with nephrotoxicity & electrolyte disturbances.

Case Description: 74 year old male with recently diagnosed metastatic malignant melanoma, was admitted to our facility with confusion and found to have AKI & hypercalcemia. AKI was initially thought to be due to hypercalcemia but did not improve with volume repletion. Based on urine sediment findings, diagnosis of acute interstitial nephritis was made and patient started on steroids. During admission, patient was continued on BRAF inhibitor therapy with Dabrafenib and trametinib. Renal function continued to deteriorate & patient required hemodialysis for few weeks followed by recovery of renal function. He was readmitted a month later following a syncopal episode with another episode of AKI. At this time his urine showed presence of persistent white blood cells and protein indicating likely chronic interstitial nephritis related to his chemotherapy agents which were stopped. Renal function slowly recovered .He also had persistent hypokalemia with a normal anion gap acidosis that has been described with BRAF inhibitors.

Discussion: BRAF inhibitors vemurafenib and dabrafenib have significantly improved survival in patients with *BRAF* V600–mutant metastatic melanoma, when compared with standard therapy. However, both of these drugs appear to be associated with an increased risk for acute kidney injury. Data from the US Food and Drug Administration Adverse Event Reporting System (FAERS) revealed that from July 2011 through June 2014, 132 cases of acute kidney injury were reported in patients receiving vemurafenib therapy. In addition, 13 cases of renal injury were reported in those receiving dabrafenib. BRAF inhibitors cause tubulointerstitial damage and electrolyte disturbances. Careful monitoring of renal function and electrolytes is strongly recommended for patients on BRAF inhibitors.

PUB517

Successful Outcome Using Belatacept in a Recipient with Systemic Thrombotic Microangiopathy after Receiving a Donor Kidney with Fibrin Thrombi Amit K. Rajput, Beatrice P. Concepcion, Paisit Paueksakon, Derek E. Moore, Manish Anand. *Vanderbilt Univ Medical Center.*

Introduction: Deceased donor kidneys with diffuse fibrin thrombi due to disseminated intravascular coagulation in the donor have a high rate of delayed graft function or primary non-function. Traditionally, this has been in the setting of calcineurin inhibitor (CNI) maintenance immunosuppression. In this case, we describe a patient who received a kidney with known fibrin thrombi resulting in subsequent slow graft function, severe thrombocytopenia, and microangiopathic hemolytic anemia immediately post-transplant. Tacrolimus was switched to belatacept with immediate clinical improvement.

Case Description: A 71 year-old female with end stage renal disease secondary to polycystic kidney disease received a deceased donor kidney transplant from a 22 year-old donor who died of a gunshot wound to the head. The donor's terminal creatinine was 1.9mg/dL and the procurement biopsy showed glomeruli with scattered fibrin thrombi. The recipient had a panel reactive antibody of 98%, was induced with alemtuzumab/methylprednisolone, and started on mycophenolate mofetil on post-operative day (POD) 0 with tacrolimus on POD 1. The post-operative course was complicated by worsening thrombocytopenia (POD 3: Platelets 28,000/mcL) and hemolytic anemia (Hct 19%, LDH 924units/L, Haptoglobin<8mg/dL and shistocytes on peripheral smear). A biopsy was performed, which showed diffuse thrombotic microangiopathy (TMA) and extensive acute tubular injury, but no evidence of acute rejection. Tacrolimus was discontinued and belatacept was initiated. The patient had immediate improvement in both thrombocytopenia and serum creatinine (0.8mg/dL three months post-transplant).

Discussion: Belatacept should be considered as an alternative to CNIs for maintenance immunosuppresion in patients who receive deceased donor kidneys with fibrin thrombi and subsequently have slow/delayed graft function, or in those who develop systemic signs of TMA. CNIs are known to cause drug-induced TMA via endothelial injury and in this setting, may augment ongoing injury in the donor kidney. Avoidance of CNIs may lead to a more rapid resolution of the TMA and improvement in allograft function.

PUB518

Hypokalemic Tetraparesis as the First Manifestation of Autoimmune Disorder: A Case Report Nicola Lepori,[1] Matteo Floris,[1] Andrea Angioi,[1] Riccardo Cao,[1] Maura Conti,[1] Anna Maria Asunis,[2] Alice Atzeni,[1] Valentina Loi,[1] Patrizia Melis,[1] Stefania Aresu,[1] Giulia Dessì,[1] Doloretta Piras,[1] Antonello Pani.[1] *[1]Nephrology, G. Brotzu Hospital, Cagliari, Italy; [2]Pathology, G. Brotzu Hospital, Cagliari, Italy.*

Introduction: We report an unusual case of life-threatening potassium wasting due to selective damage of the distal tubule, hypothesized as being related to circulating ENA-SSA Ab.

Case Description: A 50 y/o woman was admitted to our hospital because of severe hypokalemic tetraparesis (K+: 1.6 mEq/L) with no obvious underlying causes. Further laboratory tests showed normal renal function, hyperchloremic metabolic acidosis, urinary potassium wasting (88 mmol/24h) and alkaline urine, suggesting type 1 renal tubular acidosis (RTA). Supporting therapy with i.v. NaHC03 and KCl led to temporary recovery. Meanwhile, SPEP showed an IgGK monoclonal spike, ANA (1:640), elevated ENA-SSA (689 U/ml), while anti-dsDNA were normal. We recommended a renal biopsy, but the patient refused. Two months later she was admitted to our Division complaining of blood hypertension and ankle swelling. At that time, renal function was normal, K+ 2.7 mEq/L, CRP 0.7 mg/dl. Urinalysis revealed microhematuria and 24h proteinuria of 3.6 g. IgGK monoclonal spike was confirmed by immunofixation. Serology revealed low C3 and C4, ANA (1:320), elevated ENA-SSA (314 U/ml) and rheumatoid factor (258 U/ml); viral serology was negative. A renal biopsy was then performed, revealing MPGN with focal pseudothrombi (with IgG and C3 deposits) and severe tubulointerstitial nephritis (TIN) with preponderant lympho-plasmacytic infiltrate. Finally, mixed cryglobulinemia was confirmed by serology. Sjogren syndrome was suspected, but exocrine glands were unremarkable.

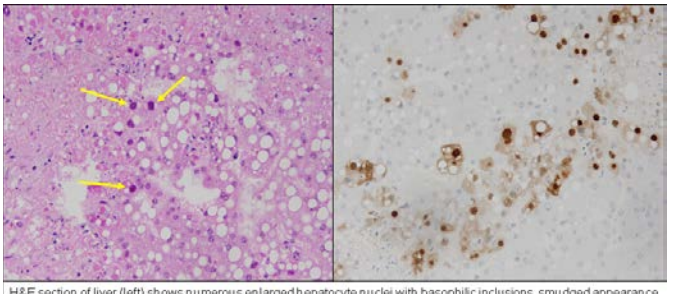
Discussion: Occasionally, type 1 RTA is part of puzzling autoimmune disorders. This case highlights life-threatening hypokalemic tetraparesis as the first manifestation of a systemic autoimmune process, albeit with no evident extra-renal involvement. Hopefully, follow-up and response to treatment will reveal more about it.

PUB519

Fatal Disseminated Adenovirus Infection in Renal Transplant Recipient Darpan Gandhi,[1] Olorunkemi O. Oluwole,[1] Alisa Caudell,[2] Maria N. Salazar,[1] Prince Mohan.[1] *[1]Div of Nephrology, Medical Univ of South Carolina, Charleston, SC; [2]Dept of Pathology, Medical Univ of South Carolina.*

Introduction: Adenoviruses are increasingly recognized as contributors to morbidity and mortality among solid-organ transplant recipients. Mortality from disseminated adenovirus disease is as high as 75% in immunocompromised host.

Case Description: 61 year old white female with ADPKD received cadaveric renal transplant from 8 year old female who died in motor vehicle accident. She received of basiliximab (induction) with maintenance immunosuppression of tacrolimus, prednisone, and MMF. 49 days post-transplant she presented with cough and diarrhea. She had neutropenia (ANC 0.77 K/CUMM); acute kidney injury, serum creatinine (sCr) of 1.4 mg/dl (baseline sCr 0.9 mg/dl), elevated AST 549 U/L, and ALT 228 U/L. Chest CT showed diffuse bronchiectasis. MMF and tacrolimus were stopped. Colonoscopy showed active colitis with biopsy negative for CMV. Serum adenovirus PCR was 1.3 billion copies, and was also detected in stool and respiratory panel. AST and ALT peaked to 3515 U/L and 555 U/L respectively. She was treated with antibiotics, IVIG and cidofovir. She required hemodialysis, developed respiratory failure and after 7 days, she expired from septic shock despite aggressive resuscitation with vasopressors. Autopsy showed isometric vacuolization of tubular epithelium of transplant kidney without viral inclusions and extensive necrosis of liver.



H&E section of liver (left) shows numerous enlarged hepatocyte nuclei with basophilic inclusions, smudged appearance (arrows), characteristic of adenovirus cytophathic effect. The background liver parenchyma displays patches of necrosis and macrovesicular steatosis. Immunohistochemical stain for adenovirus (right) reveals strong positivity within many hepatocytes confirming diagnosis of adenoviral hepatitis.

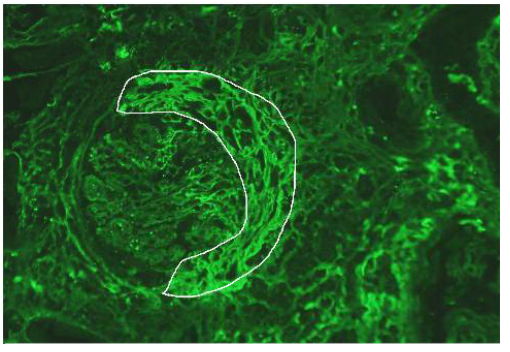
Discussion: Adenovirus should be included in differential diagnosis of post kidney transplant hepatitis, hepatic failure and colitis. Infection occurred within first two months of transplant and donor kidney did not show viral inclusion suggesting novel infection or reactivation of latent infection in recipient. Prognosis is poor and therapy remains challenging despite reducing immunosuppression, use of IVIG, and cidofovir.

PUB520

No Smoke but Raging Fire- Urinalysis Is an Imperfect Clue Melissa L. Swee, Lama A. Noureddine. *Div of Nephrology, Univ of Iowa, Iowa City, IA.*

Introduction: The urine dipstick has long been considered a "liquid biopsy of the kidneys," providing valuable diagnostic information. However, the absence of proteinuria or hematuria does not rule out pathology. We present a case illustrating this cautionary principle.

Case Description: A 59 year-old female presented with a two-month history of nightly fevers (up to 101.3*F), decreased appetite and 20-pound weight loss. She denied urinary frequency, hematuria, edema, dyspnea, cough, or rash. Vital signs were notable for fever (100.6*F), tachycardia (109bpm), and hypertension (147/70mmHg); the rest were within normal limits. Cardiopulmonary, dermatologic and musculoskeletal examinations were unremarkable. There was no pedal edema or costovertebral angle tenderness. Comprehensive metabolic panel revealed increased serum creatinine (2.8mg/dL) and blood urea nitrogen (21mg/dL), which, 3 months ago, were 1.1mg/dL and 14mg/dL, respectively. C-reactive protein and erythrocyte sedimentation rate were also elevated (17.3mg/dL and 120mm/hr). Urine dipstick repeated thrice did not reveal any proteinuria, hematuria, leukocyte esterase, or nitrite. ANA, complement levels, and ASO were negative but ANCA titers were elevated at 1:320. MPO was also high (>8 AI) but not PR3. This was confirmed on renal biopsy, which demonstrated pauci-immune, necrotizing glomerulonephritis, with crescents as seen on immunofluorescence staining for fibrin .



Discussion: ANCA-associated vasculitis is a set of systemic vasculitides that frequently leads to pauci-immune crescentic glomerulonephritis. As such, proteinuria and hematuria are the most common renal manifestations of the disease, but this is not strictly required. This case emphasizes that nephrologists should have a high index of clinical suspicion for ANCA-associated vasculitis in patients with deterioration of kidney function even in the absence of proteinuria or hematuria.

PUB521

Case Report: A Case of Anti-Neutrophil Cytoplasmic Antibody Glomerulonephritis, Drug Induced Lupus and Sweet Syndrome Ahmed Daoud,[1] Gerren Hobby,[1] Neriman Gokden,[2] John M. Arthur,[1] Manisha Singh.[1] *[1]Nephrology, UAMS, Little Rock, AR; [2]Pathology, UAMS, Little Rock, AR.*

Introduction: We report a case of ANCA vasculitis with co-existing Sweet syndrome & drug induced lupus. Sweet syndrome is a hypersensitivity reaction that occurs in response to systemic factors, such as hematologic disease, infection, or drug exposure. All three disease processes ANCA GN, drug induced lupus & Sweet syndrome in this patient appear to be secondary to use of Hydralazine.

Case Description: A 73 year old Caucasian man, hypertensive on Hydralazine was referred to Haematology-Oncology for suspected Waldenstrom's Macroglobulinemia (WM). He developed A-fib for which he was admitted. WM was ruled out with bone marrow biopsy. He developed a maculopapular rash after admission on the face, scalp, and upper torso. Dermatology diagnosed the rash to be Sweet syndrome after skin biopsy. Following this he developed acute kidney injury (AKI). Creatinine during hospitalization was initially 2.5 - 2.7mg/dl, but rose to 3.1mg/dl. Urine sediment showed dysmorphic RBCs, and urinalysis had hematuria with nephrotic range proteinuria. Serology showed low complements, with elevated titers of ANA, Anti-chromatin, anti-cardiolipin, anti-histones, leading to diagnosis of drug-induced Lupus. ANCA titers (both MPO & PR3) were also elevated. The patient developed cough with bloody sputum. Kidney biopsy showed Crescentic GN consistent with ANCA vasculitis. He was treated with steroids, plasma exchanges & rituximab, with resolution of hemoptysis and creatinine returned to 2.8 before discharge.

Discussion: Our patient had ANCA vasculitis, drug induced lupus and also Sweet syndrome, as proven by serologies and biopsy. The titers of both ANCA-MPO & ANCA-PR3 were elevated, together with anti-histone titers, as well as lupus panel. All these are known to be associated with hydralazine use. Drug-induced Sweet syndrome has been reported with furosemide, hydralazine, minocycline and Bactrim. There are three reported cases of ANCA vasculitis with sweet syndrome; two of them were on Hydralazine. Up to our knowledge this is the second reported case with the concurrent three hydralazine-induced diagnoses that our patient carries.

PUB522

A Case of Granulomatous Interstitial Nephritis in a Patient with History of Crohn Disease without Evidence of Active Flare or Current Use of Salicylates

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Introduction: Granulomatous interstitial nephritis (GIN) is a condition associated with Crohn disease and characterized by interstitial inflammation and granuloma formation in the renal parenchyma, most cases of which are reported with an active flare or use of 5-amino salicylate (5-ASA) derivatives. We present a case of GIN in the absence of a clinical flare of Crohn disease or recent 5-ASA exposure, and while taking a TNF-alfa inhibitor, which is used in treatment of granulomatous disorders.

Case Description: A 43 year old lady was admitted with an elevated creatinine. Her history included Crohn disease for 4 years, treated with mesalamine and budesonide for only a few months. Twenty months before admission, she developed jejunal perforation and underwent partial small bowel resection after which she was started on infliximab and achieved complete remission. One month before admission, her plasma creatinine concentration rose from 0.75 mg/dl to 2.30 mg/dl. Her UA revealed WBC casts; the urine protein creatinine ratio was 0.2 g/g. Serological evaluation including ANA, ANCA, Hepatitis Panel, HbA1c was negative or normal. Anti-infliximab antibodies were negative. Serum infliximab concentration was 1.3 mcg/ml (target > 0.5 mcg/ml). Renal biopsy revealed severe GIN. She received no more infliximab. Oral prednisone was started and on follow up 2 weeks later her creatinine had decreased to 1.58 mg/dl.

Discussion: Our patient had not received 5-ASA therapy for over 2 years before evidence of decline in renal function, making 5-ASA an implausible cause of her GIN. Her CD was clinically quiet, thus eliminating the two most common causes of GIN with CD. Her serum infliximab level was in the low end of the target range and may have failed to treat subclinical CD, leading to GIN. Alternatively, TNF-alfa inhibitors are reported to have a paradoxical effect and may have precipitated the granulomatous nephritis in our patient.

PUB523

Lactic Acidosis as the Presenting Sign of a Signet-Ring Cancer

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Introduction: Lactic acidosis that is not associated with severe sepsis or shock could be due to a variety of causes (type B lactic acidosis). Solid tumors can cause sustained lactic acidosis due to normoxic glycolysis (Warburg effect).

Case Description: A 56 y/o man with ADPKD and cyst-related pain presented to the ED with worsening frank and abdominal pain for a week. He was hemodynamically stable. His abdomen was soft but diffusely tender. His blood HCO3 was 20 mmol/L, Cr 1.9 mg/dL (baseline 1.5) and lactate 3.9 mmol/L (reference range: 0.6-2.3). He was not on medications that may cause lactic acidosis. Abdominal CT scan showed ADKPD and new retroperitoneal lymphadenopathy (not seen 6 months ago). Overnight, the pain subsided; lactate was 2.8. He was discharged with a plan for a repeat CT in 3 months. A week later, he was admitted with severe abdominal pain and shock (BP 70/p). Serum Cr 3.0 mg/dL and lactate 6.5. He was treated for presumed infection, stabilized hemodynamically and HD initiated. The lactate elevation persisted in the next 4 days (ranging 4-8 mmol/L). A contrast-enhanced CT showed metastatic cancer with lesions in bilateral lunch fields in addition to the lymphadenopathy. Percutaneous lymph node biopsy showed poorly differentiated adenocarcinoma with signet-ring presentation, consistent with metastatic cancer of gastric primary. The patient expired 2 weeks after the cancer diagnosis.

Discussion: Cancer contains oxidative and glycolytic cells. Oxidative cancer cells show a lactate preference, saving glucose for glycolytic cells to generate lactic acids. Lactate, in turn, feeds oxidative cells for energy generation. Such a perfect metabolic symbiosis has been observed in cancers of multiple origins. Lactic acidosis through activating HIF-1 and degrading extracellular matrix promotes rapid cancer growth, angiogenesis and metastasis, leading to a high mortality. New lymphadenopathy in the setting of sustained lactic acidosis should be investigated promptly as most of cancers with lactic acidosis tend to rapidly progress and be fatal.

PUB524

Masquerading ANCA-Associated Vasculitis: A Strange Case of Inflammatory Polyneuropathy

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Introduction: A rare case of sensory and motor polyneuropathy as the presenting symptom of Microscopic Polyangiitis (MPA).

Case Description: A 69 year-old woman was admitted to the neurology unit with 5-days of progressive right lower extremity (LE) weakness, and 'flu-like symptoms' for several weeks, including fatigue, anorexia and night sweats. PMHx notable only for hypothyroidism. Physical exam demonstrated a right foot drop with sensory deficits below the knee, loss of proprioception along with paresthesias of right upper extremity (UE), and motor deficit of left UE, including left wrist drop. EMG consistent with sensory plus motor axonal neuropathy involving LE>UE, concerning for AIDP vs. mononeuritis multiplex. Laboratory data: Hb 9.7 g/L, WBC 24,000, Platelet 492,000, serum Cr 0.7 mg/dL. UA: +1 Protein, +2 Hb, 3-5 RBC/Hpf. Chest x-ray was unremarkable. CTA and MRI brain revealed a basilar tip aneurysm (11.5 x 9 mm), which did not explain the patient's neurological presentation per neurosurgery. Workup for polyneuropathy included negative lumbar puncture (hence more consistent with mononeuritis multiplex than AIDP), CRP 28.8 mg/dL, ESR 67 mm/HR, EBV Ag and Ab negative, Lyme Ab negative, albumin 1.9 gm/dL, and positive C-ANCA 160 (ref<20), prompting nephrology consultation. Treatment for inflammatory polyneuropathy was initiated with IVIG and steroids. Further pertinent positives included: MPO 489.6 (ref<20), RF 99 IU/mL, ANA Ab 320 (ref <20) with normal complements. Urine (Ur) microscopy negative for active sediment, spot Ur protein 164 mg/dL, spot Ur Cr 105 mg/dL (ratio 1.56), and renal biopsy was performed.

Renal biopsy demonstrated focal segmental necrotizing and pauci immune crescentic glomerulonephritis affecting 10% glomeruli, consistent with ANCA associated vasculitis. Treatment of C-ANCA MPO vasculitis was initiated.

Discussion: Polyneuropathy is a rare primary manifestation of MPA; motor-sensory neuropathies are reported in 7 to 15% of patients with MPO ANCA vasculitis, mostly accompanying RPGN/ renal involvement, but rarely as an initial presentation. Cranial and peroneal nerve involvements are the most frequent neurological manifestations.

PUB525

A Different Kind of Renal Crisis

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Introduction: Systemic sclerosis (SSc) is an autoimmune disorder characterized by skin thickening with variable systemic organ involvement. Renal involvement often takes the form of scleroderma renal crisis (SRC) and is typically characterized by abrupt onset of severe hypertension and acute kidney injury. Additional findings on presentation include congestive heart failure, encephalopathy and thrombotic microangiopathy (TMA). SRC is sometimes difficult to distinguish from other forms of TMA as the presentations may be similar. We present a patient with an established diagnosis of scleroderma who presented with symptoms consistent with SRC but biopsy revealed TMA not related to SRC.

Case Description: A 47-year-old female with known SSc with positive anti-RNA polymerase III autoantibodies presented to the hospital with shortness of breath and lower extremity edema. She had undergone hematopoietic cell transplantation (HCT) for SSc 15 days prior to admission for which she had received large doses of glucocorticoids. On admission she was found to have an elevated creatinine and a systolic blood pressure 40mmHg above her baseline. ACE inhibitor therapy was initiated for presumed SRC. Kidney function continued to deteriorate. A renal biopsy was performed and showed changes consistent with TMA confined to the glomerular compartment, and none of the classic vascular changes seen in SRC. Her respiratory status worsened necessitating ICU admission where she was found to have H1N1 pulmonary infection. As her infection was treated, her renal function stabilized and her TMA resolved.

Discussion: Due to its significant mortality, SRC should always be empirically treated when patients with SSc present with acute hypertension and AKI. While SRC is typically a clinical diagnosis, renal biopsy can help confirm diagnosis. Our patient's biopsy confirmed the presence of TMA however she had no pathologic features of SSc. Our patient's diagnosis of H1N1 introduces the possibility that her TMA could have been related to H1N1. A literature search revealed two cases of patients with H1N1 associated TMA, however to our knowledge this is the first case in a patient with SSc.

PUB526

Acute Kidney Injury in End Stage Renal Disease Patients on Hemodialysis and Renal Function Recovery

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Introduction: Chronic kidney disease (CKD) patients are at risk for developing acute kidney injury (AKI) and once labeled as ESRD, emphasis on renal function recovery becomes a lower priority. We report two chronic hemodialysis (HD) patients as AKI-D (dialysis) managed with coordinated care among various health care providers and were successfully taken off HD with return of renal function.

Case Description: Case 1: A 77 year old woman with CKD stage 4 who underwent cardiac and renal artery catheterization for recurrent flash pulmonary edema and hypertension which showed 99% stenosis of the left renal artery with successful stent placement and 80% stenosis of the right renal artery with no stent. Afterward, she became anuric with a serum creatinine 9.63 mg/dL. HD was initiated with left radiocephalic AV fistula. Her intradialytic weight gain and blood pressure control were monitored with improvement in urine output. Her HD frequency decreased twice to once a week. She recovered kidney function (S Cr 2.02 mg/dL) and was taken off HD one year later. She remained off HD for 9 months so far. Case 2: A 70 year old woman with CKD stage 4 and left atrophic kidney who underwent cardiac catheterization due to ST elevation myocardial infarction. She developed AKI with uremic symptoms and creatinine 5.25 mg/dL. She was started on HD with left brachial-axillary Acuseal AV graft. Three months post HD initiation; she was decreased to twice a week HD then once a week six months later. Ten months later, she was taken off HD with current S Cr of 2.14 mg/dL. She has been off HD for 4 months so far.

Discussion: CKD patients who develop AKI needs individualized care, focused on renal function recovery. This type of directed care is important as AKI patients in future can receive HD at ESRD facilities as of Jan 1, 2017. Creation of an arteriovenous access may slow decline in GFR. Both were successfully taken off HD through careful management of their dry weights, blood pressures, medications leading to progressive tapering of their HD schedules.

PUB527

Non-Uremic Calciphylaxis Treated with Intralesional Sodium Thiosulfate

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Introduction: Calciphylaxis is characterized by systemic medial calcification of the arterioles that leads to ischemia and subcutaneous necrosis. It is rarely reported in ESRD patients but even more rarely seen in non-ESRD patients. Treatment strategies are also less defined in non-uremic calciphylaxis with only three cases reporting the use of IV sodium thiosulfate (STS) and no cases reporting treatment with intralesional STS.

Case Description: Case: A 61-year-old female with a history of rheumatoid arthritis, chronic corticosteroids, TNFα inhibitors, Tociluzumab, Abatacept, Tofacitinib, Anakinra and recently started on denosumab developed a left lower extremity lesion that started as papular erythema and progressed to have a necrotic center. Laboratory examination revealed GFR ranging 55 to 77 mL/min and normal serum calcium and phosphorus. Vitamin D was elevated at 111 ng/ml. PTH was elevated at 320 pg/ml. Fibroblast Growth Factor 23 level was only mildly elevated. Anticardiolipin antibody was normal. Other negative work up included, negative PR3 and MPO. Biopsy was consistent with calciphylaxis. The leg wounds continued to worsen until intralesional STS was instituted. Her initial lesion improved significantly, however, further lesions developed on her opposite leg and as such plans to institute IV STS are underway.

Discussion: Intralesional sodium thiosulfate may be a useful strategy for treatment of non-uremic calciphylaxis but based on the appearance of new lesions may not be adequate in all cases if systemic calciphylaxis is present.

PUB528

Aggressive IgA Nephritis Presenting with Microangiopathic Hemolytic Anemia

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Introduction: Microangiopathic anemia (MAHA) is not a classical feature in IgA vasculitis; though, recent case reports have suggested aberrations in the alternative complement cascade may contribute to this phenotype. Here, we describe an aggressive case of IgA vasculitis presenting with acute on chronic nephritis and MAHA without any detectable abnormalities in the alternative complement cascade.

Case Description: A previously healthy 19 year old Caucasian female presented with a six week history of headache, nausea, and abdominal pain. Three weeks after the initial onset of symptoms, she developed arthralgias and decreased urination without hematuria. At presentation, she complained of edema. On exam, she appeared pale with 1+ lower extremity edema but had no rash. Her initial laboratory tests revealed BUN 65 mg/dl, creatinine 14 mg/dL, hemoglobin 7.8 mg/dL, and platelets 70 k/UL. Haptoglobin was undetectable and peripheral smear had rare schistocytes. Serologic testing including ASO, ANA, dsDNA, complements, ANCA, anti-GBM, ADAMTS-13 as well as stool studies were negative. She was started on renal replacement therapy and plasmapheresis. She had a renal biopsy which showed acute on chronic crescentic and necrotizing glomerulonephritis as well as a thrombotic and necrotizing arteriolitis with IgA deposits in the vascular wall in addition to the glomeruli. She had extensive interstitial fibrosis and tubular atrophy. Though her renal function was not thought to be salvageable, the severe vasculitis and MAHA were treated with high dose Solumedrol and Rituximab. Her hemoglobin stabilized, her thrombocytopenia resolved, and haptoglobin remained low but was now detectable. Genetic analysis for complement abnormalities detected no known mutations and complement activation panel was normal, making atypical hemolytic uremic syndrome less likely.

Discussion: This case was confounded by the aggressive IgA vasculitis leading to MAHA. Recent studies have suggested that adding immunosuppressive therapy to intensive supportive care in IgA vasculitis and advanced nephropathy yields no significant outcome benefit. In this unique case, despite the poor renal prognosis, the severe vasculitis prompted use of immunosuppression to curb ongoing MAHA.

PUB529

Isolated Hyperphosphatemia with Suppressed Urinary Phosphate Excretion in a Patient with Undifferentiated Leukemia

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Introduction: Chemotherapy is mainstay treatment of malignant diseases, providing improved survival for patients, but have adverse effects including electrolyte abnormalities.

Case Description: A 27-year-old female presented with thrombocytopenia and leukopenia which prompted hematology consult. A bone marrow biopsy was performed and revealed acute myeloid leukemia with dysplastic changes. She was admitted for induction therapy with cytarabine and idarubicin. . Her serum phosphate which was 3.9 mg/dL two months earlier had increased to 5.2 despite normal kidney function (Table 1). Post-induction , phosphate level continued to rise to a peak of 7.1 mg/dL, requiring initiation of sevelamer. In addition to labs in Table 1,Serum potassium and alkaline phosphate (AlkP)were normal. She had no evidence of glucosuria or aminoaciduria.One month later, she was re-induced with mitoxantrone, etoposide, and cytarabine. She continued to have isolated hyperphosphatemia. FGF-23 levels were measured at 101 Ru/ml when serum phosphorous was at 6 mg/dL.

	phosphate on admission (mg/dL)	serum creatinine (mg/dL)	FePo4	Ca (mg/dL)	Mg (mg/dL)	PTH (pg/ml)	1.25 Vitamin D (pg/ml)	24 Hr urine calcium (mg/TV)
1st admission	5.2	0.5	<1%	9-9.5	2-2.1	53	16	
2nd admission	5.0	0.5	2.2%	8.9-10.2	1.8-2.1	21	10	75.7

She remains on phosphate binders to maintain normal serum phosphorous levels.

We report a case of hyperphosphatemia in a patient with normal kidney function but markedly suppressed urinary phosphate excretion. Normal AlkP and potassium argue against rapid release of phosphate from cellular or bone stores. There was no history to suggest chronic ingestion of high amounts of phosphate. Serum PTH was normal and 1,25 Vit D was appropriately suppressed.In this case, suppressed urine phosphate excretion with normal kidney function suggests an isolated proximal tubule defect for phosphate excretion. FGF-23 levels were appropriate for the serum phosphate indicating that she has a normal feedback.

Discussion: We suspect the patient may have renal resistance to FGF-23, perhaps mediated by Klotho and associated either with her malignancy or cytarabine.

PUB530

Idiopathic Granulomatous Interstitial Nephritis: A Diagnosis Dilemma

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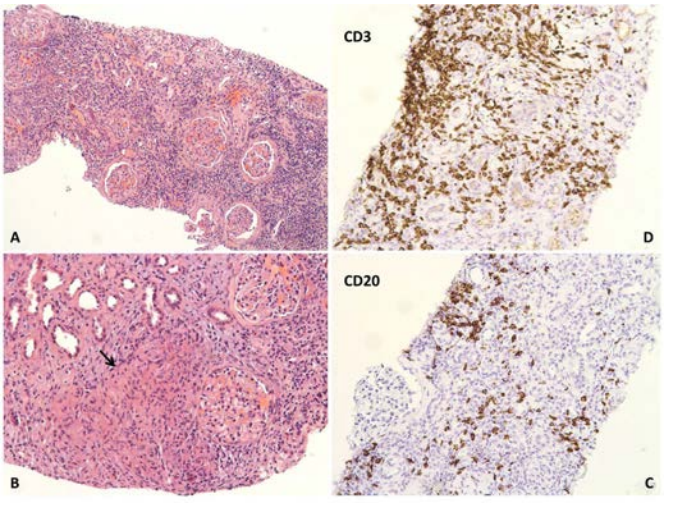
Introduction: Granulomatous interstitial nephritis (GIN) is a rare histologic diagnosis found in 0.5% to 0.9% of native renal biopsies. The causes of GIN include medications, sarcoidosis, tubulointerstitial nephritis and uveitis, paraproteinemias and fungal infections. Herein we describe a case of idiopathic GIN and review the workup necessary to exclude secondary causes.

Case Description: A 45 year-old man with a history of positive hepatitis C antibody presents with a serum creatinine (SCr) level of 4.93mg/dl. It was 3.69mg/dl 2 weeks prior, 2.7mg/dl 6 months prior and 0.8mg/dl 2 years earlier. His BP was 138/84; he denied: dysuria, skin rashes, arthralgia, and taking any medications. The urinalysis showed 20mg/dl of protein, 9WBCs, 2RBCs, no cellular casts. Spot urine protein/creatinine ratio was 0.4mg/mg. The following labs were either normal or negative: C3/C4, hepatitis C viral load, Hepatitis B antibodies, anti MPO, anti PR3, ANCA, ANA, ACE level, quantiferon TB gold, cryoglobulins, aspergillus, histoplasma, blastomyces and coccidioides antibodies. A kidney biopsy revealed GIN. Staining for bacteria, mycobacteria, IgG4 was negative. It showed T lymphocytes without monoclonality.



B: Nonnecrotizing granuloma, black arrow. A chest and abdomen CT were unremarkable. Given the progressive rising SCr, that peaked at 6.37, he received 1 gram of solumedrol intravenously for 3 days, followed by 60mg of prednisone. The SCr improved to 4.3mg/dl seven days after treatment. He never required dialysis. Thirty days after initial presentation, the SCr level was 3.7 mg/dl.

Discussion: The workup was negative for secondary causes of GIN. Ruling out infectious etiologies is a priority. Timely initiation of steroid therapy proved beneficial. Further response to the current therapy will determine the need for steroid-sparing agents namely azathioprine or mycophenolate mofetil.

PUB531

Recurrent Thromboembolic Phenomenon: An Unusual Complication in Immunoglobulin A Nephropathy

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Introduction: Thromboembolic phenomenon (TEP) is a rare extrarenal manifestation of immunoglobulin A nephropathy (IgAN). We report a case of man with IgAN complicated by early recurrent unprovoked TEP.

Case Description: A 68-year-old man with IgAN presented with sudden onset of dyspnea 6 months after he was diagnosed with IgAN. He was treated with antibiotics for pneumonia without improvement. Further work-up revealed an acute right popliteal deep venous thrombosis (DVT) and V/Q scan showed high probability for pulmonary embolism. Serum creatinine (SCr) was at baseline of 2.2 mg/dL and urinary total protein to creatinine ratio (UPCR) was 1 g/g of Cr. Serum albumin was 3.1 g/dL. All hypercoagulable work-up were negative. He was treated with heparin and prolonged warfarin given unprovoked TEP. He presented with purpuric rashes with central necrosis on both shins 1 year later. He also had recurrent acute DVT at the same area. Since warfarin-induced skin necrosis was a possibility, warfarin was switched to enoxaparin. He also developed RPGN-type picture with an elevated SCr up to 3.19 mg/dL and UPCR was up to 3.3 g/g of Cr. Renal biopsy was performed and showed IgAN without crescent. He was treated with high dose steroids without improvement of renal function. Nine months later, SCr trended up to 4.16 mg/dL and UPCR was in nephrotic range of 4.4 g/g of Cr (Figure 1). He was referred for pre-kidney transplant evaluation. All routine age-appropriate cancer screening was negative.

Discussion: Our patient presented with an early onset of TEP and slightly hypoalbuminemia; however, he had nephrotic range proteinuria with normal serum albumin at the second episode of DVT. Although IgAN complicated by TEP is not as common as membranous glomerulonephritis, TEP could occur even without a known risk factor such hypoalbuminemia.

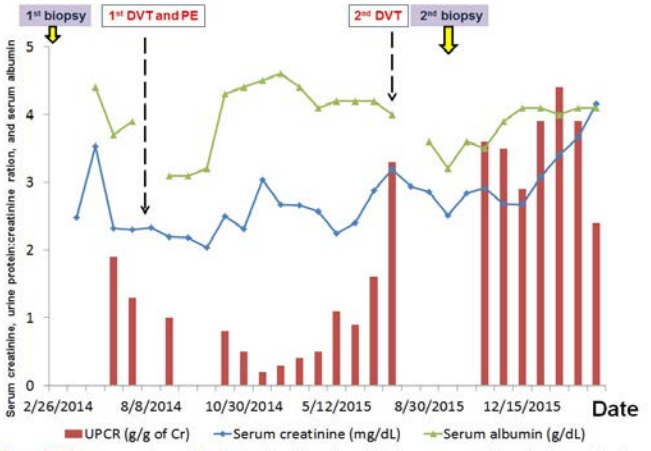

Figure 1: Clinical course demonstrates 2 episodes of thromboembolic phenomenon and the patient's renal function, degree of proteinuria, and serum albumin. *Cr, creatinine; DVT, deep venous thrombosis; PE, pulmonary embolism*

PUB532

Bevacizumab Induced Nephrotic Range Proteinuria Managed with Dual RAAS Blockade Haritha Karuparti, Jason Prosek. *Nephrology, Ohio State Univ, Columbus, OH.*

Introduction: Nephrotic range proteinuria (NRP) caused by vascular endothelial growth factor (VEGF)inhibitors like bevacizumab is a known entity. Patients who develop NRP are at risk for renal and cardiovascular adverse events. While guidelines recommend discontinuing bevacizumab (BZ) in NRP, there is no evidence-based protocol for management of proteinuria. We report a case of a BZ induced NRP managed with dual renin-angiotensin-aldosterone system (RAAS) blockade.

Case Description: 35-year-old Caucasian man underwent resection of glioblastoma followed by chemo-radiation. He began BZ (10mg/kg) every 2 weeks with temozolomide for progression of disease. After 6 cycles, he developed hypertension (HTN) and was started on amlodipine. After 9 cycles 6gm proteinuria developed. BZ was held and he was referred to Nephrology. Amlodipine was replaced by Lisinopril. After 4 weeks, proteinuria decreased to 3 g/day. BZ was resumed at 21 day- cycles. Since BP remained elevated, losartan was added. After 8 weeks of maximal-RAAS blockade, proteinuria declined to 1 g/day. BZ was then resumed at 14 day-cycle. Given dry cough, lisinopril was replaced with eplerenone . After 14 cycles of BZ, proteinuria remains 0.5-1.0 g/day. No adverse effects were noted, with normal renal function and potassium.

Discussion: Renal adverse outcomes from VEGF-inhibitors are NRP and HTN. Etiology of VEGF-inhibitor induced NRP include loss of endothelial fenestration podocyte dysfunction and in rare instances thrombotic microangiopathy. Implications of asymptomatic proteinuria are unknown. However, overt proteinuria is a known risk factor for chronic kidney disease and cardiovascular adverse events. Our case is unique for several reasons. First, it demonstrates the beneficial effects of dual RAAS blockade for NRP. While dual RAAS blockade is not tolerated in patients with vascular disease it may be a viable option in young patients when monitored closely. Second, when BZ was resumed, NRP did not recur while on dual RAAS blockade. This suggests that RAAS inhibitors may provide a direct protective effect on podocytes and endothelial cells. In the appropriate population, dual RAAS blockade is an effective longterm strategy to enable extended use of anti-VEGF targeted therapies.

PUB533

A Case of Azygos Vein Embolism Associated with Transient Antiphospholipid Syndrome in Urinary Tract Infection with *Escherichia coli* Sang Jo Han, Hong Joo Lee. *Dept of Nephrology, Seoul Red Cross Hospital, Seoul, Korea.*

Introduction: The classical antiphospholipid syndrome (APS) is characterized by the presence of antiphospholipid antibodies (aPL)-that is, lupus anticoagulant or anticardiolipin antibodies- which bind target phospholipid molecules and are associated with recurrent fetal loss and thromboembolic phenomena. Many infections may be accompanied by increases in aPL and, in some, these increases may be accompanied by clinical manifestations of APS.

Case Description: A 73-year-old woman with diabetes admitted for treatment of an intertrochanter fracture of the femur and a urinary tract infection (UTI) with *Escherichia coli* developed thrombosis in her right azygos vein, which was thought to be associated with antiphospholipid and IgM anticardiolipin antibodies. After antibiotic therapy, antiphospholipid antibody was undetectable, and a repeat chest computed tomography revealed complete resolution of the azygos vein thrombosis.

Discussion: A wide variety of infections can be associated with thrombotic events in patients with transient antiphospholipid syndrome (APS), and this case serves as a reminder that we should consider the possibility of transient APS in patients who have venous thrombosis in the setting of a UTI.

PUB534

Calciphylaxis in Myeloma Multiple and Chronic Kidney Disease Fernanda Paula Feres Rios Da Costa, Alicia Imada, Luiz Fernando Christiani, Maria Izabel Neves de Holanda. *Nephrology, Hospital Federal de Bonsucesso, Rio de Janeiro, Brazil.*

Introduction: Calciphylaxis is a rare and serious complication observed mainly in secondary hyperparathyroidism to chronic Kidney Disease(CKD). Others diseases also can complicate with it: HIV, primary hyperparathyroidism and hematologic diseases such as multiple myeloma(MM). It is characterized by cutaneous ischemic necrosis, acute and progressive installation, secondary calcification of blood vessels of small or medium caliber. Diagnosis is done throughhistopathological analysis of the injuries. The pathogenesis is unclear. The treatment is prevention, maintenance of adequate levels of calcium and phosphorus.

Case Description: We report a case of a patient presented CKD and Myeloma multiple(MM) that evolved with Calciphilaxis secondary lesions one year after diagnoses.

G.C.S, 70 y/o,female, diagnosed in june/2015 MM after headache, dizziness, back pain and diarrhea. She denied comorbidities and medications use. The exams showedanemia, renal dysfunction, hyperkalemia, hypercalcemia, lytic lesions in skull and reduced sizes of kidneys. She started hemodialysis and the MM treatment using burtezomib and dexamethasone. During this period, she was admitted several times for infectious episodes and presenting refractory hypercalcemia. She didn't present a good response for the MM. In 02/2016 she was readmitted with pneumonia and evolved ulcerations in the lower limbs. The lesions started as erythematous areas, progressing to ulcerations of necrotic center and intense pain refractory to common analgesia. The venous/arterial doppler excluded thrombosis and skin biopsyshowed calciphylaxis. We started alendronate, low calcium in hemodialysis, phosphate binder(renagel) and dexamethasone as therapy for the underlying disease. Patient died few days after with sepsis and worse in lesions. There are few reports in the literature relating MM and calciphylaxis.

Discussion: This case demonstrated an aggressive calciphylaxis manifestations inone year of Chronic kidney disease. The lack of response of the underlying disease influenced the severity. Calciphylaxisis a rare complication and has high morbidity and mortality, our knowledge is important to prevent its appearance.

PUB535

Leaky Pipes: A Case Report of Pseudo-Azotemia Secondary to Intraperitoneal Extravasation of Urine following a Urological Procedure Payam Pourhassani, Christopher Richard Kern, Sandeep Aggarwal. *Internal Medicine, Drexel Univ College of Medicine, Philadelphia, PA.*

Introduction: Azotemia is a marker of net nitrogen balance that depends on both production and excretion. Consequently, BUN and creatinine may rise in the absence of kidney injury or reduction of GFR if either process is impaired, leading to "pseudo-azotemia." We report a case of a post-operative increase in serum creatinine secondary to a urinoma (pararenal pseudocyst), initially labeled as acute kidney injury.

Case Description: A 50-year-old male with history of prostate cancer underwent robot-assisted laparoscopic prostatectomy with bilateral pelvic lymph node resection. On post-operative day 1, he became oligoanuric and had a sudden rise in serum creatinine which peaked at 8.74 mg/dL. However, he was without uremic signs/symptoms, dyselectrolytemia, or severe acidosis. He subsequently had a retrograde urogram with Cystografin that showed extravasation at the ureterovesical interface. He had an IR drain placed, followed by surgical placement of bilateral ureteral stents with complex foley placement, to ensure that the ureteral orifices were not draining outside of the ureterovesical anastomosis. On the following day his creatinine decreased from 8.74 to 3.31 mg/dL; his discharge creatinine was 2.22 mg/dL.

Discussion: The elevation of serum biomarkers of renal failure (i.e. BUN and creatinine) following bladder rupture is well elucidated and occurs from diffusion of solutes from the extravasated urine through the peritoneal membrane. Patients can develop uremic symptoms requiring hemodialysis if the diagnosis is delayed. Where available, kidney injury biomarkers like NGAL/KIM1 may be helpful in determining true renal tissue injury.

Fortunately, with timely diagnosis and removal of the source of urinary leakage, serum biomarkers often return to normal very quickly as long as there is no concomitant renal injury from another cause.

PUB536

Rare Case of Histiocytic Glomerulopathy with Spontaneous Resolution of Nephrotic Syndrome Tarek Rashid,[1] Kamaldeep Singh,[2] Belinda Jim,[1] Glen S. Markowitz,[3] Kisra Anis.[1] *[1]Dept of Medicine, Jacobi Medical Center, Bronx, NY; [2]Dept of Medicine, North Central Bronx Hospital, Bronx, NY; [3]Dept of Pathology&Cell Biology, Columbia Univ Medical Center, New York, NY.*

Introduction: Histiocytic glomerulopathy (HGP), a recently described glomerular pathology, is characterized by prominent glomerular histiocytic infiltrates. Clinically, it can present with the onset of acute kidney injury (AKI) and nephrotic syndrome and has mainly been reported in association with hemophagocytic syndrome (HPS). **CASE PRESENTATION:** A 33-year-old Female, from Bangladesh, with a past medical history of hypothyroidism, migraines, and occasional NSAID use, presented with a non-specific febrile illness associated with low grade fever, myalgia, arthralgia and dysuria, suspected to be urinary tract infection and treated with NSAIDs and nitrofurantoin.She returned a week later with nausea, vomiting, AKI (creatinine 1.6 mg/dl), and new onset of nephrotic syndrome. Patient was normotensive and physical exam was remarkable for 3+ edema. Urinalysis showed small blood with 0-6 RBC,>300mg/dl protein. Urine protein to creatinine ratio was 14 g/g with a bland urine sediment on microscopy. She had hypoalbuminema, mildly elevated AST/ALT, LDH, triglycerides and ferritin, positive ANA, and depressed C3 and C4 levels. All Other serologies were normal. She had a decreas in her Hgb and platelets during the course of illness. Renal ultrasound was unremarkable. Kidney biopsy showed glomeruli with prominent infiltrating monocytes/histiocytes, endothelial swelling, and foot process effacement, most consistent with histiocytic glomerulopathy. Over the course of 2 weeks, in the absence of immunosuppressive therapy, we witnessed spontaneous resolution of her symptoms and nephrotic syndrome. **DISCUSSION:** HGP is typically associated with (HPS) which can occur in the setting of acute viral infection, autoimmune disease, or malignancy. Our patient did not meet the current diagnostic criteria for HPS on presentation. This is the first reported case of HGP with nephrotic syndrome, occurring without definitive evidence of HPS, with an extremely short self-limiting clinical course.

PUB537

An Interesting Case and Treatment Dilemma Involving a Progressive Immune Complex Mediated Membranoproliferative Glomerulonephritis Abdul Hameed Zaid, Robert D. Zenenberg. *Internal Medicine, Saint Barnabas Medical Center, Livingston, NJ.*

Introduction: Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury with mesangial and endocapillary proliferation, and glomerular basement membrane thickening. Recently, greater understanding of the pathophysiology has led to subsequent reclassification based on immunoflourescence. Immunoglobulin staining with complement suggests an immune complex mechanism from certain infections, autoimmune diseases or a monoclonal gammopathy. Isolated complement staining suggests disorders of alternate complement pathway. We present an interesting case and treatment dilemma of an immune complex mediated MPGN.

Case Description: A 61 year old Chinese man presented with progressive renal insufficiency and proteinuria. He had chronic Hepatitis B (HBV) leading to end-stage liver disease undergoing an orthotopic liver transplant 4 years earlier, and was on Mycophenolate and Entecavir®. History included a CNS lymphoma and subsequent systemic lymphoma, both treated successfully years earlier. At presentation, creatinine had worsened (1.3 mg/dL to 4 mg/dL over 1 year) with edema and nephrotic range proteinuria. He had undetectable HBV viral loads, negative hepatitis C and ANA as well as negative immunofixation and free light chain assay. CT scan of the abdomen showed no evidence of lymphoma. Further studies showed mildly reduced serum C3, normal C4 and mildly elevated Type III cryoglobulin. Renal biopsy showed immune complex MPGN with cryoglobulin deposits found on closer scrutiny. Corticosteroid therapy led to dramatic improvement in creatinine (to 1.8mg/dL) and proteinuria over several months.

Discussion: This patient presented with a polyclonal immune complex mediated MPGN and had a history of both HBV and lymphoproliferative disease. Steroids should generally be avoided in HBV mediated MPGN, but this patient had persistently undetectable viral loads. The possibility of recurrent lymphoproliferative disease or an infectious process causing the Type III cryoglobulinemia was certainly possible, but was not evident. Considering the progressive nature of the glomerular disease, more aggressive immunosuppression to target the cryoglobulins was warranted.

PUB538

Bile Cast Nephropathy Complicating Primary Sclerosing Cholangitis Sang Jo Han, Hong Joo Lee. *Dept of Nephrology, Seoul Red Cross Hospital, Seoul, Republic of Korea.*

Introduction: Bile cast nephropathy(BCN), a condition of renal dysfunction in the context of cholestatic liver dysfunction is not uncommon. While the exact etiology remains unknown, BCN is presumed to be secondary to multiple concurrent insults to the kidney including direct toxicity from bile acids, obstructive physiology from bile casts, and systemic hypoperfusion from vasodilation. Primary sclerosing cholangitis(PSC) is a chronic cholestatic liver disease of unknown cause and long-standing, progressive course, leading to cirrhosis and requiring orthotropic liver transplant. The association with PSC and BCN has been reported previously in very limited number of cases.

Case Description: A 27-year-old male was admitted with jaundice and dark-colored urine. Laboratory tests showed progressive obstructive jaundice including high bilirubin levels and anuric renal failure requiring prolonged hemodialysis. Computed tomography of the hepatobiliary system revealed normal intrahepatic and extrahepatic duct size with normal common bile duct without any sign of hepatobiliary duct obstruction. Liver biopsy showed primary sclerosing cholangitis. A kidney biopsy, performed a few days after the initiation of dialysis, demonstrated the presence of bile casts along with acute tubular injury. The patient is continuing to be hemodialysis and waiting for liver transplantation.

Discussion: We present here an unusual case of kidney injury secondary to BCN occurring in a context of PSC.

PUB539

Treatment of Recurrent Focal Segmental Glomerulosclerosis (FSGS) in a Post Kidney Transplant Recipient with Adrenocorticotropic Hormone (ACTH) Gel Jose F. Ramirez-Porres,[1] Amr El-Husseini Mohamed,[1] Virgilius Cornea,[2] Nada Alachkar.[3] *[1]Medicine, Univ of Kentucky, Lexington, KY; [2]Pathology, Univ of Kentucky, Lexington, KY; [3]Transplant, johns Hopkins, Baltimore, MD.*

Introduction: ACTH has shown efficacy in idiopathic FSGS and other glomerulopathies. The data on using ACTH to treat recurrent FSGS post renal transplantation is limited. This case report describes our experience using ACTH in treating recurrent FSGS in a live donor kidney transplant.

Case Description: A 38 year old male who underwent live-related kidney transplant secondary to primary FSGS, presented with elevated creatinine, microscopic hematuria and nephrotic range proteinuria approximately two months after transplant. Serum creatinine increased to 1.8 mg/dl from a baseline of 1.3 mg/dl. Spot urine protein creatinine ratio (UP/C) was 2.5 mg/mg.

Graft biopsy revealed findings suggestive of vasculitis and early recurrent FSGS. P-ANCA and C-ANCA serologies were negative. Patient received 3 days high dose pulse intravenous steroids, 3 months of oral cyclophosphamide then switched to Rituximab therapy due to lack of response. Serum creatinine went up to 3.34 mg/dl and UP/C to 6.1 mg/mg. A second graft biopsy revealed only recurrent FSGS. ACTH 40 units subcutaneous twice a week was started and then increased to 80 units subcutaneous twice a week. Four weeks after initiating a repeat serum creatinine was 2.25 mg/dl and UP/C decreased to 4.2 mg/mg. Three months later serum creatinine increased again to 3.5 mg/dl and UP/C increased to 6.2 mg/mg. A third graft biopsy revealed more advanced recurrent FSGS so every other day plasma exchange was started and Achtar gel was continued along with mycophenolate mofetil and prograf. Kidney function continued to decline slowly with progressive rise of serum creatinine to 4.5 mg/dl and UP/C persisted around 6 gm.

Discussion: The response to ACTH treatment in this case with post-transplant recurrent FSGS was not satisfactory. Early initiation of plasma exchange is necessary to remove circulating permeability factors. Further research is necessary to determine if ACTH may be a useful therapy in patients with recurrent FSGS.

PUB540

Diet and the Domino Effect in Oxalate Nephropathy Rungwasee Rattanavich, Laura J. Maursetter, Tripti Singh, Gauri Bhutani. *Nephrology, Univ of Wisconsin, Madison.*

Introduction: Oxalate nephropathy (ON) is an under-recognized entity, important to consider in individuals at risk for fat malabsorption since timely intervention may preserve renal function.

Case Description: 65 year-old male, baseline serum (S.) creatinine (Cr) 1.0 mg/dL, was admitted after incidental discovery of elevated Cr (4.6 mg/dl). He was non-oliguric and denied any acute events/symptoms other than incarceration 1 year back. He had known history of alcoholism, diabetes, hypertension, extrahepatic biliary excision and Roux-en-Y hepaticojejunostomy (2003) for cholangiocarcinoma. His only medication was triamterene-hydrochlorothiazide. Physical exam: BP-154/81mmHg, no edema. Urinalysis: Sp. gravity 1.008, occasional WBCs and renal epithelial cells. A renal biopsy revealed massive calcium oxalate (ox) crystal deposits, interstitial nephritis, and severe chronicity. Daily hemodialysis (HD; Pre-HD Cr 5.37 mg/dl), dietary changes (low ox/fat diet), oral citrate, oxalate binders and pancreatic enzymes were initiated. Diuretics were changed to calcium channel blocker. 24-hr urine revealed severe hyperoxaluria (HO), hypocitraturia and hypocalciuria- 90, <27, 53 mg/day, respectively. Fecal fat level was very high (26.3 g/day) but Pre-HD S. ox only mildly elevated at 11.0 umol/L. HD was halted due to low likelihood of benefit at this ox level. On further review, patient continued to deny diarrhea but prior CT scans disclosed chronic pancreatitis. Dietary history revealed ample peanut butter intake following incarceration. He was discharged on above dietary/pharmacologic measures with a stable Cr of 5.2 mg/dl. Follow up 4 weeks later was notable for improved Cr of 4.34 mg/dL.

Discussion: Our case highlights several known and novel aspects of OH: (a) the domino effect of fat malabsorption, diuretic use and ox/fat rich diet (peanut butter) in OH;(b) Biliary diversion may be a risk factor for OH; (c) severe ON/HO may occur even in setting of only mild S. ox elevation; (d) HD, dietary/pharmacologic measures may result in preservation of renal function although the exact role of these interventions remains poorly defined in literature. Continued incarceration and resultant restricted dietary choices, unfortunately, remain a limiting factor for our patient.

PUB541

Rapidly Progressive Glomerulonephritis: Cause or Consequence of Developing Posterior Reversible Encephalopathy Syndrome

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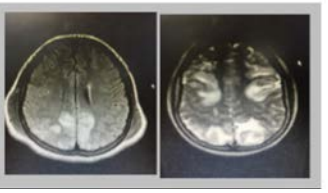
Introduction: Rapidly progressive glomerulonephritis it is characterized by quick deterioration of renal function. Early diagnosis and immunosupressive therapy plays a key role in kidney survival. More than half of these cases advance into end stage renal disease, this group of diseases are at risk of developing posterior reversible encephalopathy syndrome (PRES). PRES consists of acute neurological symptoms caused by endothelial disfunction, which results in vasogenic cerebral edema mainly in white matter, generated in most cases by severe changes of hypertension, but 15-20% of patients have normal or low blood pressure, so it has been attributed to direct endothelial damage caused by immunosupressant drugs, preeclamsia, and autoimmune disease. Diagnosis is based on clinical symptoms, radiological findings in posterior brain and the pattern of the frontal superior sulcus as well as their reversibility.

Case Description:

Etiology of Rapidly Progressive GMN	Good Pasture syndrome (anti glomerular basement membrane disease)	Pauci-immune GMN (granulomatosis with poliangitis)
Age	22	24
Gender	Female	Female
Neurological symptoms	Headache, encephalopathy, epileptic status	Headache, encephalopathy, epileptic status
Blood pressure at time of evaluation	180/100 mmHg	140/90 mmHg
Systemic involvement of base disease	Lung hemorrhage	Nasal involvement
Treatment for base disease	Metilprednisolone/prednisone/ Cyclophosphamide, Plasmapheresis 10 sessions	Metilprednisolone/prednisone/ Cyclophosphamide Plasmapheresis 4 sessions
Kidney function at time of PRES developement	Patient in chronic hemodialysis 3 months after diagnosis	Patient in chronic hemodialysis 3 months after diagnosis
MRI findings Hyperintense areas in T2		

Discussion: Kidney injury is present in at least 55% of PRES cases. Its association is affected by accompanying presence of hypertension or autoimmune disease, as we can see in case 1 which presented with severe hypertension. Of the established risk factors for PRES both cases present autoimmune disease, kidney injury and the use of immunosupressive therapy. It is important to define if rapidly progressive kidney dysfunction, systemic involvement of base illness, age and gender could be considered independent risk factors for developing PRES. Prospective studies that determine associations, manifestations and prognosis must be continued so that a risk scale can be established which can determine if the sum of these factors increase the risk of developing PRES.

PUB542

Air Embolism: A Rare Complication of Tunneled Dialysis Catheters

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Introduction: Air embolism is a feared complication of hemodialysis, typically associated with the dialysis procedure itself. Here we report a case of air embolism associated with tunneled dialysis catheter placement.

Case Description: A 60 year old male with ESRD frompolycystic kidney disease (PKD) presented to the hospital with a bleeding left upper extremity AVF and found to have MSSA bacteremia. A temporary dialysis catheter was inserted without complication. The patient was found to have MSSA endocarditis by echocardiogram, with a large vegetation on the mitral valve. The patient underwent ligation of the brachiocephalic fistula due to friable vessel tissue. He subsequently underwent placement of a tunneled dialysis catheter. In the recovery unit, the patient had an acute onset of right sided weakness and slurring of speech. A head CT revealed air in the left frontal and parietal lobes. Echocardiogram with agitated saline contrast demonstrated a late left to right shunt that did not augment with Valsalva maneuver, which is suggestive of an intrapulmonary shunt. The patient was started on high flow oxygen. It was determined that he was a poor candidate for hyperbaric therapy due to his history of COPD and metastatic squamous cell lung cancer. The family then decided to withdraw aggressive medical care and patient died a few hours later.

Discussion: Air emboli can occur at various stages of dialysis catheter use: insertion, manipulation, use or removal. Complications of air emboli depend on the vascular source of the embolization. Typically, use of veno-venous dialysis catheters will result in pulmonary manifestations of air embolization, characterized by dyspnea, tachypnea, wheezing, rales or respiratory failure. In the presented case, the patient exhibited signs of arterial embolization with neurologic compromise. This venous to arterial shunting can be due to a patent foramen ovale, ventricular septal defect, or presence of a pulmonary arteriovenous malformation (AVM). In this patient, he was suspected of having an AVM as a consequence of untreated lung cancer. Although rare, air emboli can cause sudden symptoms of decompensation and the risk of air embolization should be considered when using dialysis catheters.

PUB543

Seronegative Renal Limited Lupus Nephritis

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Introduction: Lupus Nephritis (LN) is a common manifestation of systemic lupus erythematosus (SLE) that often presents early in the disease process. However, previous case reports discuss a specific patient population (typically females, childhood to middle aged) that demonstrate LN without meeting American College of Rheumatology (ACR) criteria and have negative serologic markers. Here, we discuss a unique presentation of seronegative LN in an elderly Caucasian male.

Case Description: A 69 year-old male with chronic kidney disease stage 3 from long-standing hypertension was referred to Nephrology for a persistent acute kidney injury (AKI) and new onset hematuria. The patient was admitted three months prior to presentation for altered mental status, attributed to severe sepsis from *S. pneumoniae* pneumonia. The hospital course was complicated by oliguric AKI (Cr 3.0mg/dL from baseline 1.2mg/dL), hypertensive urgency, and hematuria that was attributed to traumatic foley insertion. Despite clinical improvement, the patient had unremitting AKI and hematuria along with newly discovered 7.96g proteinuria. Serologic work up, including ANA, Anti-DNAse B, ASO titers, Anti-Smith, Anti-dsDNA, SPEP/UPEP, ANCA, RF, HIV, Hepatitis Panel, and cryoglobulins were negative. However, the patient was found to be hypocomplementemic (C3: 48mg/dL, C4: <8.0mg/dL), prompting a renal biopsy. Pathology demonstrated classic full house immunofluorescence staining with Focal Proliferative Immune Complex Glomerulonephritis and mild-to-moderate arterionephrosclerosis. The patient was treated with cyclophosphamide IV once monthly for six months along with a prednisone taper. Six months after initiation of treatment, the patient is showing full recovery to baseline (Cr 1.2mg/dL and 0.2g proteinuria).

Discussion: LN is a serious complication of SLE with rapid progression to end-stage renal disease (ESRD) if not diagnosed and treated in a timely manner. Prompt recognition and initiation of treatment are essential for reducing morbidity and mortality. As evident by our patient, relying on ACR classification criteria or serologies alone to diagnose LN can lead to delays in treatment, with an increased risk to ESRD progression.

PUB544

A Venous Anonime Stenosis at Costo-Clavicular Junction (CCJ)

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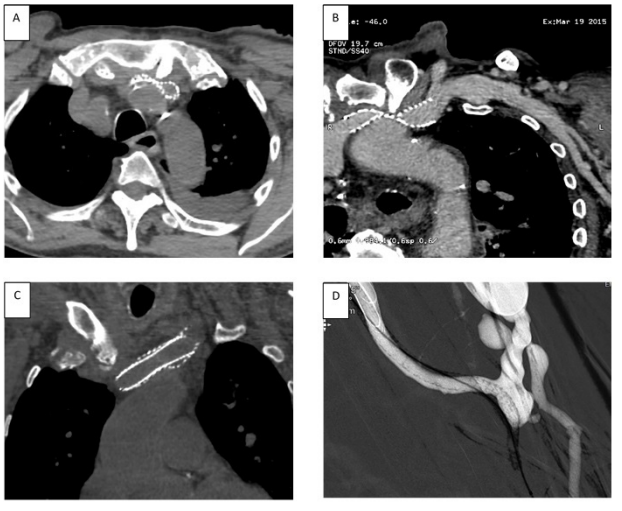
Introduction: Central venous stenosis (CVS) is a frequent complication in hemodialysis (HD) patients. Venous obstruction at the costoclavicular junction (CCJ) requires a different approach beyond PTA and stenting.

Case Description: A 82ys-old man on HD with left radio-cephalic arterovenous fistula (AVF) presented severe edema of AVF arm. Ultrasounds (US) did not show significant venous stenosis. TC showed a severe stenosis of the left brachiocephalic vein so we performed multiple PTA and placing of a 16x60-mm stent. Unfortunately, edema recurred and MS-TC showed an instent-stenosis by left clavicle bony hypertrophy. Vascular surgery performed one third anterior claviculectomy. After surgery for persistent intra-stent stenosis of left brachiocephalic vein we placed 16x40-mm intra-stent Wall Stent Boston stent successfully. After 5 months patient was referred from peripheral dialysis unit for edema and distal ischemic lesions. US showed a decreased flow rate, significant stenosis of cephalic vein, thrombosis of basilic vein and ischemic steal syndrome. We performed endovascular closure of AVF with endoprothesis 6mmViabhan in radial artery.



Discussion: PTA and stenting are the primary option for treating stenosis surrounded by soft tissue. Vein stenosis adjacent to the CCJ poorly respond to PTA/stenting, and, generally, require bony decompression for long-term patency. On our experience, the surgical decompression allowed secondary stent placing intra-stent successfully**.** The long time duration of venous hypertension may cause irreversible arterial microcirculatory stasis and ischemic steal syndrome. Our experience highlights the importance of early diagnosis of CCJ venous stenosis and a multidisciplinary approach for its treatment.

PUB545

IgA Dominant Methicillin-Sensitive *Staphylococcus aureus*-Associated Rapidly Progressive Glomerulonephritis

Amit K. Rajput, Agnes B. Fogo, Paul Persad, Raymond C. Harris. *Vanderbilt Univ Medical Center.*

Introduction: Post-infectious glomerulonephritis (GN) typically refers to poststreptococcal GN, often seen after the infection has resolved. However, an uncommon entity has been demonstrated in the middle aged and elderly patient populations, in which active staphylococcal infections are associated with progressive renal failure. We present a case of rapidly progressive glomerulonephritis (RPGN) from an active Methicillin-sensitive staphylococcus aureus (MSSA) infection.

Case Description: A 72 year-old male with chronic kidney disease stage 3 from long-standing diabetes mellitus type 2 (DM2) was receiving nafcillin IV for a left foot diabetic ulcer with superimposed cellulitis (no osteomyelitis), which was complicated by oliguric acute kidney injury (AKI) with a serum creatinine 5.7mg/dL (from baseline 1.0mg/dL) and new onset hematuria. Investigation revealed MSSA septicemia, with the left foot wound as the infection source. During evaluation, the patient's renal function declined precipitously, warranting an urgent renal biopsy and initiation of renal replacement therapy (RRT). Pathology demonstrated endocapillary proliferation and exudative proliferative glomerulonephritis with IgA and C3 dominant deposits, characteristic of an infection-associated GN, in addition to mild-to-moderate diabetic nephropathy. The patient underwent urgent left below-the-knee amputation for infection source control, but despite intervention, renal function did not recover. The patient was declared end-stage renal disease (ESRD) and passed two months later from a non-renal related illness.

Discussion: As opposed to poststreptococcal GN, staphylococcal-associated GN presents with concurrent infection. Although the mechanism remains unclear, it is postulated that the infection provides an antigen to which an immune complex is formed and deposited in the glomerulus. Staphylococcal infections seem to be associated with IgA dominance on immunofluorescence, compared to IgG dominance in poststreptococcal GN, with skin wounds as the most common infection source. Furthermore, previous analysis suggests a correlation with underlying diabetic nephropathy and worse renal prognosis, as evident with our patient.

PUB546

Severe, Refractory Hypokalemia in a Patient with Systemic Lupus Erythematous Receiving Cyclophosphamide

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Case Description: We describe a 42-year-old female patient with a history of systemic lupus erythematous who presented with severe, refractory hypokalemia following cyclophosphamide therapy. She was diagnosed with lupus at age 14 and previously had class III lupus nephritis treated with cyclophosphamide years prior to this admission. She was then maintained on mycophenolate and hydroxycholoquine with a normal eGFR and minimal proteinuria over next few years. She then developed steroid refractory musculoskeletal and cutaneous manifestations, eventually leading to the initiation of cyclophosphamide. Following her fifth infusion of cyclophosphamide, she presented to her community hospital with weakness, nausea and hypokalemia ranging from 1.5 to 2.5 mmol/L. Her relevant home medications included furosemide, metolazone, dexamethasone, and hydroxychloroquine. During her hospitalization, she required transfer to the intensive care unit for an episode of torsades de pointes due to hypokalemia. Her diuretics were held and she was started on parenteral and enteral potassium supplementation. 24 hour urine collection demonstrated urinary potassium of 147 mmol (25-125 mmol), normal urine calcium, magnesium, sodium, and total volume of 6.1 L. Serum bicarbonate was 30 mmol/L (22-29 mmol/L), with elevated supine serum renin and normal aldosterone levels. She was placed on indomethacin, amiloride, spironolactone and ramipril in an attempt to reduce urinary potassium wasting. She remained in hospital with persistent hypokalemia for over six months and was seen in consultation by nephrology, rheumatology, and endocrinology. She was eventually diagnosed with an acquired Bartter like syndrome either secondary to cyclophosphamide or due to an antibody mediated channelopathy. Given the possibility of an antibody-mediated etiology, a trial of IVIG was initiated followed by a trial of plasma exchange consisting of 7 sessions over a two-week period. Her potassium did seem to improve and stabilize following plasma exchange. She eventually was discharged home about a month later on about 100 mEq per day of potassium supplementation, amiloride, ramipril, as well as spironolactone.

PUB547

A Case of Antithyroid Drug-Induced Double ANCA-Positive Vasculitis

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Introduction: Antithyroid drugs are shown to induce antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). While both methimazole (MMI) and propylthiouracil (PTU) are potential causes of AAV, the incidence of PTU-induced AAV is 40-fold higher than that of MMI-induced AAV.

Case Description: A 68-year-old woman was admitted to our hospital because of acute kidney injury. She was diagnosed with Graves' disease and had been treated with MMI for 18 years. On admission, she presented proteinuria and microscopic hematuria, and both MPO- and PR3-ANCA were positive. Since MMI-induced AAV was suspected, MMI was discontinued right after the admission. Kidney biopsy revealed pauci-immune crescentic glomerulonephritis. Although intravenous methylprednisolone pulse therapy (1000mg/day for 3 days) followed by oral prednisolone 40mg daily was initiated, her renal failure was exacerbated and hemodialysis was started. Thereafter, urine volume was gradually increased and her renal function was recovered. Following the discontinuation of MMI, serum levels of PR3-ANCA were rapidly normalized and those of MPO-ANCA were decreased before the initiation of steroid therapy.

Discussion: We report a case of MMI-induced double ANCA positive vasculitis with acute kidney injury that was successfully treated with immunosuppressive agent. PTU has been demonstrated to produce multiple antigens including MPO-ANCA and PR3-ANCA. Antithyroid drug-induced AAV usually occurs in patients with Graves' disease who are resistant to drug treatment. Previous reports suggested the possibility that repeated administration of PTU alters the MPO structure surrounding the heme iron and the changes in MPO configuration induces the antigenicity. In our current case, prolonged administration of MMI could alter the MPO structure and induced AAV.

PUB548

A Rare Case of Hodgkin Lymphoma Complicated with Membranous Nephropathy in a Young Male Patient

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Introduction: The most common glomerulopathy associated with Hodgkin lymphoma (HL) is minimal change nephrotic syndrome, but other types of glomerulopathy including membranous nephropathy (MN) have rarely been reported. We here report a case of HL complicated with MN, who responded well to the treatment with chemotherapy and radiotherapy.

Case Description: A 16-year-old man was admitted to our hospital due to proteinuria and hematuria. His serum creatinine level was 0.63 mg/dL and urinary protein excretion was 2.18 g/g creatinine. Renal biopsy revealed MN (stage I-II). In the immunofluorescence study, IgG4 was most strongly stained for IgG subclass analysis; there was no evidence of glomerulopathy associated with amyloidosis or paraproteinemia. Only partial remission of proteinuria was obtained despite the treatment with 40 mg/d of oral prednisolone. Four months after starting oral corticosteroid therapy, slightly enlarged lymph nodes were noticed above the collarbone. Lymph node biopsy showed lymphocyte-depleted classical HL (stage II). He was treated with four cycles of ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) chemotherapy along with radiotherapy, and a complete hematologic response was achieved. Then, the patient showed drastic reduction in proteinuria after an effective treatment of HL.

Discussion: The association between MN and malignancy has well been documented, but HL-associated MN has rarely been reported. Remission in glomerular disease was achieved in accordance with hematologic remission by chemotherapy and radiotherapy, suggesting a causal relationship between the two diseases.

PUB549

Drug Induced Antineutrophil Cytoplasmic Autoantibody Vasculitis Secondary to Propylthiouracil

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Introduction: We describe a case of a 72-year-old male who developed antineutrophil cytoplasmic autoantibody (ANCA) vasculitis after treatment with propylthiouracil (PTU) for hyperthyroidism.

Case Description: A 72-year-old male with a ten-year history of hyperthyroidism treated with PTU presented for evaluation of acute renal failure. On routine labs, he was noted to have renal insufficiency with creatinine 2.5 mg/dL rising to 4.4 mg/dL on recheck from a baseline of 1.1-1.3 mg/dL. Urine microscopy revealed dysmorphic red blood cells and RBC casts. ANA, C3, and C4 complements were normal. MPO-ANCA titer was 118.4 U/mL. Renal biopsy revealed pauci-immune focal crescentic glomerulonephritis with 10% cellular to focal fibrocellular crescent formation, associated diffuse severe tubulointerstitial nephritis, marked peritubular capillaritis, and interstitial hemorrhage, suggesting drug associated ANCA vasculitis in the setting of PTU. Treatment was initiated with pulse dose steroids, 7 treatments of plasma exchange, cyclophosphamide 500 mg/m^2, and rituximab 1000 mg. One month later, he received an additional dose of cyclophosphamide 0.75 mg/m^2 and rituximab 1000 mg. Two months after treatment, creatinine was 1.2 mg/dL and MPO-ANCA titer was 11.3 U/mL.

Discussion: ANCA vasculitis is an autoimmune disorder affecting small vessels caused when autoantibodies to myeloperoxidase or proteinase 3 induce a systemic inflammatory response. Minocycline, hydralazine, levamisole-contaminated cocaine, and PTU are the most common drug culprits. PTU induced ANCA vasculitis typically manifests as a pauci-immune and crescentic necrotizing glomerulonephritis associated with high titer MPO-ANCA positivity. PTU or one of its metabolites may bind to MPO in neutrophils, creating a systemic immunogenic response. Permanent cessation of the offending agent is essential to treatment. Pulse dose steroids, plasma exchange, and immunotherapy are also indicated. Further studies are needed to elucidate the mechanism of autoimmunity in all forms of drug-induced ANCA vasculitis in order to more effectively develop targeted therapies.

PUB550

Recurrent Dense Deposit Disease: A Report of Two Cases with Varying Presentations, Pathologic Findings and Patient Outcomes
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Introduction: Dense Deposit Disease (DDD), previously classified as a subgroup of primary membranoproliferative glomerulonephritis (MPGN) is currently regarded as a type of C3 glomerulopathy due to developments in the understanding of complement-mediated glomerular disease. We report two cases of recurrent DDD with clinical presentations, pathologic findings and patient outcomes on divergent ends of a spectrum.

Case Description: The cause of end stage renal disease (ESRD) in both patients (male = 1 and female = 2) was MPGN, diagnosed in adolescence. Further similarities include an average of 5 years to renal replacement therapy (RRT), and an average of 3 years to (initial) recurrence. At recurrence, both displayed no evidence of cell/antibody mediated rejection. Both also displayed C3 predominant staining by immunofluorescence with linear and intramembranous dense deposits noted ultrastructurally. Patient 1 was retransplanted 4 years after initial failure secondary to recurrence and developed a second recurrence 8 years later. Proteinuria and serum creatinine at the second recurrence were 3.73 g/day and 1.89 mg/dL respectively. Patient 2 presented with acute pain over the allograft, 12.4 g/day of proteinuria and serum creatinine of 3.33 mg/dL. Recurrent DDD was noted, as well as 6/18 glomeruli (33%) showing crescentic proliferation. Patient 1 is being initiated with Rituximab therapy, however continues to have increasing proteinuria and worsening renal function. Rituximab therapy was attempted on the patient 2, however due to recurrent infections; she was unable to complete therapy and subsequently progressed to require RRT. Serum complement was not measured on either patient.

Discussion: Recurrent DDD can have varying clinical and pathologic presentations. Evaluation of serum complement levels is recommended in patients with a history of, or suspected recurrence of MPGN/C3 glomerulopathy. Our cases also support the accepted theory that regardless of etiology, crescentic glomerulitis is typically associated with an acute presentation and a more rapid progression to ESRD.

PUB551

Rhabdomyolysis and Acute Kidney Injury in Mycoplasma Pneumoniae: A Case Report
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Introduction: Mycoplasma pneumoniae is a common cause of atypical pneumonia. Rare complications such as hemolysis, encephalitis, aseptic meningitis, cardiac conduction abnormalities, and rheumatological symptoms have been reported. We report a case of mycoplasma pneumonia leading to rhabdomyolysis and acute kidney injury requiring renal replacement therapy.

Case Description: A 46 year old African American man presented to an emergency room with malaise. Three weeks prior to his presentation, he had dry cough and had been prescribed a course of Bactrim. He had no joint pain. He was found to have a serum creatinine of 8.7 mg/dl. Urinalysis was significant for hematuria, proteinuria and the presence of myoglobin. His serum CPK was greater than 42,670. He became anuric. One day after admission, he was initiated on dialysis for uremic symptoms. He underwent a renal biopsy that showed acute tubular necrosis with granular eosinophilic casts consistent with the diagnosis of rhabdomyolysis. Work up was remarkable for *Mycoplasma pneumoniae* by nucleic acid amplification.

Discussion: Rhabdomyolysis is a common cause of acute kidney injury, but is rarely due to mycoplasma pneumonia. Myalgias are often described in patients with mycoplasma, but rhabdomyolysis is a rare complication and has only been sparingly reported. (Minami 2003) Patients with rhabdomyolysis of unknown cause should be screened for infections such as HIV, legionella and mycoplasma as treatment could potentially decrease muscle breakdown.

PUB552

Patient with an Urgent Need for Initiation of Peritoneal Dialysis
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Introduction: Patients who require emergent dialysis are not considered suitable for urgent-start peritoneal dialysis in general. Most of them are treated with hemodialysis or continuous renal replacement therapy utilizing a temporary vascular catheter.

Case Description: A 43-year-old man with terminal kidney injury and with obvious signs of uremia, hyperkalemia, volume overload and resistent hypertension refused hemodialysis. The reason for rejection was his father's bad experience with this modality of dialysis in the past. Peritoneal dialysis (PD) catheter was introduced to this patient urgently using a laparoscopically assisted puncture implantation (LAPI) technique. The first three days the patient started with low-volume exchanges and remained in a recumbent position. After this period we have observed regressed uremic symptoms, but uremic catabolities decreased slowly and signs of volume overload and hypertension persisted. Ten days after PD catheter placement the patient went home from the hospital and continued with PD exchanges in our outpatient dialysis center. The procedure was without any complications. Continuously routine education in PD was initiated and 3 weeks after PD catheter placement the patient started with regular chronic PD. Then we initiated adjustement before kidney transplantation. The patient needed cholecystectomy because of cholelithiasis and he refused periprocedural hemodialysis again. One day after laparoscopically cholecystectomy the patient started with peritoneal protocol such as at the beginning. Minor leek was managed conservatively. Fourtheen month after newly discovered end-stage renal disease (ESRD) the patient successfully recieved renal graft. We have fulfilled the wishes of the patient. Since the acute initiation of PD, through abdominal surgery without interruption peritoneal dialysis, we have led him to the desired kidney transplant.

Discussion: Urgent-start peritoneal dialysis appears to be as safe as routine peritoneal dialysis, although there may be an increase in the incidence of peritoneal leaks. We believe, based on our experience, that some patients with urgent need of dialysis may benefit from initiation of renal replacement therapy, using peritoneal dialysis.

PUB553

Case Report Sustained Low Efficiency Dialysis in a Patient with Severe Acute Kidney Injury Caused by Dengue Shock Syndrome
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Introduction: Dengue infection is a growing problem in Indonesia, where acute kidney injury could be one of the rare and lethal complication of it. The incidence of Dengue Associated Acute Kidney Injury itself was around 13.3%, where two-thirds had mild AKI and one-third had moderate-severe AKI. The incidence of AKI with Dengue Shock Syndrome was around 0.9-3.3%. Mortality was more than 10% for dengue patients with AKI. Renal Replacement Therapy is one option of treatment, but could be very challenging in a low thrombocyte level, shock and severe plasma leakage.

Case Description: A 24-year-old female was referred in a shock condition, decreased of consciousness and restless. Fever was at day 5, no nausea, and had periods with usual volume and schedule. Physicalexamination: restless, dyspnea with BP 93/53, PR 107, RR 40-45X/min and temperature 36°C. She had rhales at both lungs, epigastric pain, ascites,edema was occurred. Urine production was decreased to 150 cc/24 hour. Her BUN was 70 mg/dL and SC was 3.2 mg/dL. Pre admission chest x ray was without pleural effusion which worsened to minimal pleural effusion on the right costo-phrenic angle. She was diagnosed with Dengue Shock Syndrome complicated by massive plasma leakage, hyponatremia (117) and AKI RIFLE Failure. She was treated in ICU, colloid and 2 inotropic agents were administered. Other treatment was levofloxacin iv, cefotaxim, calcium gluconas. She was inserted cvp monitor and temporary double lumen catheter. Thrombocyte concentrate was given before first SLED to raise thrombocyte level from 9 to 26. USG was with normal kidney echogenicities, both sides pleural effusion, ascites, suspected pancreatitis and hepatitis. IgG and IgM dengue were positive. She was treated for 15 days and discharge with urine production of 2.5 liters after 6.05 liters of polyuria phase at day 14. She was discharged with BUN 28 mg/dL, SC 0.86 mg/dl, thrombocyte 159.

Discussion: This case illustrated a severe dengue case with complication of severe kidney failure. Although she had a very low thrombocyte, SLED were done both to ultra-filtrate massive fluid leakage and to dialyze. The balance of anticoagulation is necessary; as long dialysis would decrease thrombocyte level.

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PUB554

Hyponatremia due to Unrelenting Renal Salt Wasting in a Patient with Malignancy
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Introduction: Cisplatin therapy is well known for its nephrotoxic side effects including renal tubular epithelial cell toxicity. The effects on tubular transport processes can result in urinary magnesium loss and in very rare instances, marked sodium loss leading to the development of a Renal Salt Wasting Syndrome (RSWS).

Case Description: A 72-year-old man with history of head and neck squamous cell carcinoma treated with resection and post-operative radiation, hypothyroidism, and history of tobacco smoking presented with recurrence of his head and neck cancer. Palliative chemotherapy with Cisplatin and Cetuximab was initiated. Physical examination showed a cachectic man with stable vital signs and no orthostatic blood pressure changes. He was alert and oriented, without focal neurologic deficits. A summary of clinical and laboratory data follows:

Days after Chemotherapy	Serum [Na^+] (meq/L)	Urinary [Na^+] (meq/L)	Serum [Mg^{2+}] (mg/dl)	Serum Creatinine (mg/dl)	Free T4 (ng/dl)	Fluid balance(L/day)
0	134		2.08	0.43	0.44	
6	124	118	1.89	0.43	0.47	-1.2
9	120	118	1.85		0.57	+0.15
22	124	137		0.30		+3.0
26	119	134	1.49	0.33	0.99	-2.6

Discussion: The patient developed hyponatremia even after administration of isotonic saline before the first dose of cisplatin, in an attempt to prevent nephrotoxicity. A significant diuresis leading to negative fluid balance ensued on day 6. The patient

persisted with hyponatremia with markedly elevated urinary sodium levels despite volume expansion, thyroid and mineralocorticoid hormone replacements (day 9). The development of signs of volume overload on day 22 prompted the discontinuation of saline infusion but the hyponatremia and the natriuresis worsened (day 26). This clinical presentation is compatible with the RSWS, rarely diagnosed after cisplatin therapy. Our patient seemed to have developed a sodium tubular reabsorptive defect that persisted after a month of a single dose of cisplatin. This syndrome should be included in the differential diagnoses of hyponatremia associated with cisplatin-based chemotherapy.

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PUB555

Tacrolimus Induced Thrombotic Microangiopathy: Everolimus Is Not the Answer Reem Daloul, Tarek Alhamad, Rowena B. Delos Santos, Daniel C. Brennan, Thin Thin Maw. *Div of Renal Transplant, Washington Univ School of Medicine, Saint Louis, MO.*

Introduction: Post-transplant calcineurin inhibitor (CNI) induced thrombotic microangiopathy (TMA) is a reported complication associated with poor graft outcomes. Management is based on reduction of CNI or use of alternative agent including mammalian target of rapammune inhibitors (mTORi).

Case Description: Clinical case: A 35-year-old Caucasian female with end stage renal disease presumed secondary to congenital nephrotic syndrome underwent a deceased donor kidney transplant with thymoglobulin induction. Maintenance therapy consisted of tacrolimus, Mycophenolic acid, and prednisone. On post-operative day three she developed acute kidney injury associated with hemolytic anemia and thrombocytopenia in the context of an acute rise in tacrolimus level. Kidney biopsy showed acute tubular injury and one glomerulus with fibrin thrombi. C4d staining was negative and no donor specific antibodies (DSA) were identified. Renal function, hemoglobin, platelets, and lactate dehydrogenase recovered gradually mirroring the decrease in CNI which was changed to everolimus. Two weeks after discharge, patient presented with wound dehiscence, infection, acute renal failure, and recurrence of hemolytic anemia and thrombocytopenia. Repeat graft biopsy showed diffuse TMA, interstitial hemorrhage, and negative C4d staining. DSA remained negative. Everolimus was switched to belatacept along with weekly eculizumab. Patient remained anuric and repeat graft ultrasound was concerning for renal vein thrombosis. Surgical exploration showed a non-viable ischemic graft that was resected without evidence of clotting in renal artery or vein. Genetic testing for complement mutation was negative.

Discussion: CNI induced TMA might reflect an endogenous predisposition to TMA even with a negative testing for genetic mutations. Bearing this in mind, it is advised to avoid mTORi which carries a similar propensity to induce TMA. Belatacept appears to be a reasonable alternative in such situations.

PUB556

Case Report: Collapsing Glomerulopathy Associated with Systemic Lupus Erythematous Sergio A. Trevino Manllo, Daphne Harrington Knicely. *Div of Nephrology, Johns Hopkins Univ School of Medicine, Baltimore, MD.*

Introduction: Collapsing glomerulopathy (CG) is most often associated with HIV. Most cases of CG not associated with HIV are idiopathic. Other secondary causes include infections, autoimmune, malignancies, genetic, drug exposures and post-transplantation. Given a wide variety of disorders, no definable pathogenic trigger factor has been identified.

Case Description: This is a case of CG associated with Systemic Lupus Erythematous (SLE) in a 61 years old African American female who presented with malaise, fever and arthralgias. During the admission, she was found to have an acute kidney injury with a creatinine of 1.9 mg/dL from a baseline of 1 mg/dL. A urine protein-to-creatinine ratio showed 12.07 grams of protein and a follow-up 24-hour urine showed 7,045 mg of proteinuria. During the hospital stay, she was diagnosed with SLE based on a positive ANA, positive ds-DNA, hypocomplementemia, positive direct Coombs, leukopenia, arthritis, and mucosal ulcers. HIV, hepatitis B and C were negative. A kidney biopsy showed collapsing glomerulopathy with extensive podocyte injury associated with scattered immune complex deposits and acute tubular necrosis. She was started on methylprednisolone then transitioned to prednisone 60 mg daily along with hydroxychloroquine 400 mg daily. A prednisone taper was done over 4-months. She had complete remission with a creatinine around 1.2 mg/dL and her a urine protein-to-creatinine ratio is 0.06 grams.

Discussion: CG associated with SLE with or without lupus nephritis is a rare disease. There is an association between collapsing glomerulopathy and SLE specifically in the setting of a lupus flare, massive proteinuria, and renal failure. In the majority of cases, treatment is initiated with high-dose steroids for prolonged periods. Partial and complete responders had fewer collapsing lesions, less global glomerulosclerosis, and less interstitial fibrosis.

PUB557

Reduction of Serum Free Light Chains Not Apheresis Use May Be the Major Determinant of Improved Renal Function in Light Chain Nephropathy Dawson Dean, Richard N. Hellman. *Dept of Medicine, Div of Nephrology, Indiana Univ, Indianapolis, IN.*

Introduction: Acute renal injury (AKI) due to light chain nephropathy (LCN) is common in multiple myeloma (MM) and its presence a major prognostic factor as is recovery from AKI. The role of Apheresis in the management of AKI due to LCN is uncertain with some studies showing no effect and some showing improvement of renal function and less need for renal replacement therapy if free serum light chains (SLC) are reduced by more than 50%.

Case Description: We describe a 78 year old MWF with IgG K MM and cast nephropathy presenting 10/13 as AKI with a presumptive diagnosis of RPGN who was initially treated with solumedrol empirically prior to renal biopsy showing LCN. Subsequent SPEP showed a monoclonal spike. She responded to corticosteroids, with serum creatinine dropping from initial 4.39 mg/dL to 2.85 mg/dL. Due to initial fall of K light chains and drop in Creatinine, Apheresis was held. She was subsequently treated with 7 courses of bortizomab and dexamethasone and is now on q 3 month Zoledronate. At last outpatient visit she was doing well clinically, CBC was normal, serum creatinine fell further to 1.18 mg.dL, serum free K light chains fell from an initial 1082.5 mg/dL to 16.20 mg/dL, and urine protein from 1,310 mg/24hr to 117mg/24hr since initial presentation October 2013 to December 2015.

Discussion: Reduction of serum Free Light Chains, not the method by which it is done such as chemotherapy and/or Apheresis, may be the major determinant of improved renal function in LCN. We propose that Apheresis may not be necessary in the treatment of LCN if SLCs are falling with chemotherapy and renal function is improving. In this case, serum creatinine and serum light chains were used to measure response to initial treatment and defer Apheresis. Additional consideration for Apheresis use may be failure of SLCs to fall with chemotherapy alone, very high SLC levels or inability to promptly initiate chemotherapy.

PUB558

Unusual Presentation of Cocaine-Associated Systemic Vasculitis without Skin Findings Muhammad Farooq, Joe Ghata, Usman Z. Bhutta. *Renal, Univ of Oklahoma HSC/VA Medical Center, Oklahoma City, OK.*

Introduction: ANCA-associated vasculitis (AAV) is a cause of crescentic glomerulonephritis and diffuse alveolar hemorrhage (DAH). Both cocaine and levimasole, an adulterant in cocaine, have been described in cases of cutaneous AAV. We describe a severe instance of cocaine associated microscopic polyangitis (MPA) without skin findings.

Case Description: 61 yo male with Hepatitis C and HTN, who abused cocaine in 12/2015, was admitted in 1/2016 for elevated creatinine, (peak 5 mg/dL; baseline 1 mg/dL in 12/2015) and productive sputum. He received antimicrobials for pneumonia and required 2 dialysis sessions. He left AMA with persistent productive cough in 2/2016, and was readmitted in 3/2016 for worsening renal failure and hemoptysis, with DAH seen on bronchoscopy, requiring intubation/mechanical ventilation. Labs were significant for anemia without schistocytes, no eosinophilia, nephritic range proteinuria, and low C3/C4. ANA, SPEP, UPEP, anti-GBM antibodies and cryoglobulins were negative. P-ANCA and anti-myeloperoxidase (anti-MPO) serologies were elevated in high titers. A kidney biopsy showed necrotizing, crescentic pauci-immune glomerulonephritis consistent with MPA. He received steroids, plasmapharesis, hemodialysis and Rituximab. His DAH responded to treatment, and he was extubated. He unfortunately remains dialysis dependent. He was discharged on a slow prednisone taper. Three months later, his p-ANCA and MPO serologies remain positive.

Discussion: About 70% of illicit cocaine consumed in the United States is contaminated with levamisole, a known immunomodulator. Prolonged cocaine use in humans has been linked to cutaneous vasculitis and production of drug-induced auto-antibodies. In the literature, cocaine-associated ANCA antibodies are mostly high-titer anti-MPO, similar to our patient. Our case highlights not only an association of cocaine and severe ANCA-associated systemic vasculitis but also a diagnostic challenge due to absence of typical skin manifestations. Moreover, this patient's serologies persisted despite cocaine cessation and aggressive treatment, suggesting a potential life-long complication of cocaine-induced vasculitis.

Funding: VA Support

PUB559

Rapidly Growing Mycobacteria Causing Subcutaneous Abscess in a Case of Renal Allograft: A Case Report Abhishek Goel, Tushar A. Dighe, Atul Sajgure, Atul Mulay, Charan Bhadrappa Bale, Ashwini Sharma, Jayraj Korpe, Nilesh Shinde. *Nephrology, Dr. D Y Patil Medical College, Pune, Maharashtra, India.*

Case Description: A 38-year-old male, milk vendor by occupation was admitted at our hospital, as end stage renal disease of unknown etiology on maintenance hemodialysis from past one year. Patient underwent live donor transplant in January 2016, mother as donor. He was started with corticosteroids, Tacrolimus and Mycophenolate sodium. He had stable renal functions with range of serum creatinine between 0.9 to 1.2 mg/dl and adequate serum tacrolimus levels. Five months post transplant patient presented with local redness without pain, tenderness and without local rise of temperature, three to five centimeters from pubic symphysis. His serum creatinine was 1.2 mg/dl and his tacrolimus level at current presentation was 4.7 ug/l. Ultrasonography and non contrast CT abdomen showed a subcutaneous abscess 3.0x2.0x4.2 cm (25cc) below the suture scar. Evaluation of aspirate showed acid fast bacilli on Ziehl Neelsen stain and culture grew rapidly growing atypical mycobacteria (species identification pending).Patient was initiated on anti tubercular medications- Isoniazid, Pyrazinamide, Ethambutol and Levofloxacin. As per the AFB culture report, linezolid and clarithromycin were added in addition to previously mentioned anti tubercular treatment. Currently patient is doing well, with resolution of local signs and serum creatinine of 1.2 mg/dl.

PUB560

Dapsone Induced Vertigo, a Forgotten Side Effect Valerie Suzanne Barta, Mala Sachdeva. *Nephrology, Northwell Health, Great Neck, NY.*

Introduction: Solid organ transplant patients, particularly liver and kidney, frequently engage with multiple disciplines within a health care system. Their medications include immunosuppressants as well as the prophylactic regimens necessary to keep them free from opportunistic infections. Dapsone is a known alternative to PCP prophylaxis in patients intolerant to Bactrim whether it be secondary to allergy, rise in creatinine, or hyperkalemia. Dapsone is not a first line treatment for PCP prophylaxis, and there seems to be a void of knowledge with respect to a labeled side effect, vertigo.

Case Description: We report a 67 year old male with CKD stage 3, non-alcoholic fatty liver disease status post liver transplant 3 months prior, hospitalized for acute kidney injury and bleeding from lovenox injection sites. He complained of 7 weeks of dizziness described as positional vertigo. Medications included prednisone, tacrolimus and mycophenolate mofetil immunosuppression. Prophylaxis included nystatin, valgangcyclovir, and dapsone. Dapsone replaced Bactrim shortly after transplant secondary to increased creatinine. He was admitted to hospitalist service, and seen by neurology, transplant hepatology, and nephrology during his stay. Work up for vertigo included a negative head CT scan. Vertigo was attributed to orthostatic hypotension secondary to blood loss anemia, however symptoms did not resolve with volume resuscitation. No cause for his vertigo was established and the patient was discharged home. His symptoms persisted, impairing his ability to ambulate. He consulted an outpatient ENT several weeks after discharge who immediately recognized dapsone-induced labyrinthitis. Dapsone was stopped and he was treated with intra-tympanic triamcinolone, leading to complete resolution of symptoms.

Discussion: Transplant medication side effects need to be widely known in the nephrology, gastroenterology, and medicine community, who will inevitably treat these patients. Vertigo is a rare side effect of many antibiotics including dapsone. This case illustrates the importance of improved awareness of dapsone associated vertigo in order to recognize, treat and improve quality of life of affected patients.

PUB561

A Perfect Storm from Ecstasy Associated Multi-Organ Failure Rungwasee Rattanavich, Ali I. Gardezi, Didier A. Mandelbrot. *Nephrology, Univ of Wisconsin, Madison.*

Introduction: Ecstasy or 3,4 methylenedioxymethamphetamine(MDMA) has both stimulant and hallucinogen effects. It is commonly abused, including 39% of college students in the United States, causes euphoria and increased energy. The minor adverse effects of Ecstasy are dry mouth or sweating. Rare but lethal side effects include serotonin syndrome, hyperpyrexia, severe rhabdomyolysis, symptomatic hyponatremia, acute kidney injury and multi-organ failure.

Case Description: 18 y/o man presented after a seizure. He had used Ecstasy 4 hrs prior. Physical exam revealed high grade fever, hypotension, tachypnea and tachycardia, dilated reactive pupils, no response to noxious stimuli. Labs revealed AKI, lactic acidosis, hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia and severe rhabdomyolysis. He was treated with cooling blankets and aggressive IV fluids. He was later started on CRRT. He developed fulminant hepatic failure within 24 hrs of presentation. He had severe hypocalcemia which was treated with aggressive calcium replacement. He underwent orthotopic liver transplantation. He later developed persistent hypercalcemia with evidence of calcium deposition in muscles on imaging studies. It did not respond to IV fluids, furosemide and pamidronate initially and required intermittent hemodialysis. He had full renal recovery by week 12 of hospitalization. He required daily normal saline and furosemide for 4 more weeks before serum calcium normalized.

Discussion: Ecstasy causes release of serotonin, dopamine and norepinephrine into the central nervous system and inhibit serotonin re-uptake which could cause serotonin syndrome. MDMA toxicity, unlike other drugs abuse, is not dose dependent. Direct toxicity on the kidneys is unclear. MDMA associated AKI is reported to be secondary to rhabdomyolysis due to seizures, hyperthermia and serotonin syndrome. There is no specific antidote. The mainstay of treatment is aggressive management of these complications. The persistent hypercalcemia in our case could have been due to sustained release of the calcium deposited in the soft tissues. The likely reason was initial movement of calcium into the injured muscles in rhabdomyolysis resulting in hypocalcemia which was treated with aggressive calcium replacement.

PUB562

A Challenging Diagnosis of Atypical Hemolytic Uremic Syndrome Victoria Chung, Shubha Ananthakrishnan. *Nephrology, UC Davis Medical Center, Sacramento, CA.*

Introduction: Hemolytic uremic syndrome is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. HUS is further classified into typical or atypical HUS. aHUS is a rare disease of complement dysregulation and carries a poorer prognosis and often requires ongoing renal replacement therapy. It is often difficult to differentiate aHUS from other TMAs. We present a case here with diagnostic challenges.

Case Description: A 68-year-old woman with hyperlipidemia presented with recent complaint of progressive fatigue found to have transfusion dependent hemolytic anemia, thrombocytopenia, and acute kidney injury requiring dialysis. She was initially treated with plasmapharesis prior to transfer to our medical center for further evaluation of and management of TMA. Patient was not taking any medication except for statin. Review of history revealed a vague viral prodrome without diarrhea. Work up for infection and malignancy were negative. ADAMTS13 returned with normal levels, arguing against TTP. Interestingly, patient was found to have new onset hypertension requiring antihypertensive medications, dry eyes, and significant thickened facial skin finding concerning for scleromyxedema. These findings raised concern for scleroderma-type renal crisis that has been associated with cutaneous scleromyxedema. Her extensive workup at our medical center showed evidence of ongoing TMA, normal C3, low C4, weakly positive ANA (1:40), negative anti-DNA, anti-RNP70 Ab, anti-scleroderma, anti-SSA Ab, and RF. Repeated skin biopsies showed evidence of fibrosis and couldn't exclude scleromyxedema. Renal biopsy performed confirmed sub-acute TMA. Complement panel revealed a mutation in exon 6 of CFHR-5 which could explain aHUS. Given her overall diagnostic workup was more consistent with aHUS, the decision was made to proceed with eculizumab, a complement C5 inhibitor. Treatment result is pending at this time.

Discussion: We present a case of aHUS with interesting clinical findings of scleromyxedema, which is a cutaneous process sometimes associated with renal manifestations, similar to scleroderma renal crisis, which made the diagnosis of aHUS challenging. Renal biopsy in such cases can be useful to help identify the disease process.

PUB563

Kidney Transplant after Bench Resection of a Renal Cell Carcinoma in the Donor Organ Jeremy F. Wright, Sara J. Fine, Jahan Montague, Marie A. Sosa. *Dept of Nephrology, Univ of Massachusetts, Worcester, MA.*

Introduction: Ex vivo resection of small renal tumors from live-donor kidneys supports the inclusion of donors with resectable tumors for transplant. Previous reports document the success of this technique with low risk of tumor recurrence in the recipient. The earliest report from Stubenbord in 1982 describes a functioning recipient graft without recurrence at 8 years. The largest case series to date reports transplant of 43 kidneys with tumors up to 3 cm into patients who were elderly, had multiple comorbidities, or were considered high risk for rejection. Among 97 total reported cases of kidney transplantation following resection of small renal cancer, no tumor recurrence has been definitively identified.

Case Description: A 30-year-old woman volunteered to be a living kidney donor to her father with end-stage renal disease. During routine donor evaluation abdominal imaging revealed a small cystic lesion in her right kidney, subsequently characterized by MRI as an 8 mm Bosniak grade IIF lesion in the posterior cortex of the interpolar region. After a review of various management approaches and risks of continuing donation, both patients elected to proceed with the surgery. Right-sided donor nephrectomy was followed by ex vivo excision of a 1cm exophytic tumor with negative margins and successful transplant into the recipient. RCC chromophobe type (chRCC) was identified on pathology. At 1 year follow up, there was no evidence of tumor recurrence in the donor or recipient and both patients have good renal function.

Discussion: This case adds to growing but limited experience with ex vivo tumor resection in a live-donor kidney prior to transplantation. In this case, the tumor was identified as a Bosniak IIF lesion on imaging, which correlates with a 25% risk of malignancy. Although previously published reports have not specified radiologic classification, many of the reported cases were "presumed RCC" and most were shown to be RCC on pathology, suggesting possible Bosniak IIF or higher classification. This case reports chRCC, a rare subtype with reportedly low malignant potential, which has been reported in only one previous living kidney donation.

PUB564

Hypersensitivity Reaction to Magnesium Sulfate Infusion in Gitelman Syndrome Ndidiamaka O. Obadan, Roberto Pisoni, Ruth C. Campbell. *Dept of Medicine, Div of Nephrology, Medical Univ of South Carolina, Charleston, SC.*

Introduction: We report a rare case of a suspected type I hypersensitivity reaction to IV magnesium sulfate used in the treatment of severe hypomagnesaemia in Giltelman syndrome.

Case Description: A 33 year old Caucasian woman with Gitelman Syndrome maintained on oral magnesium sulfate supplementation and daily magnesium sulfate intravenous infusions for repeated episodes of severe hypomagnesaemia was admitted for evaluation of suspected hypersensitivity reaction. She was referred to the ED after reporting an erythematous, pruritic rash that developed after her daily intravenous infusion of magnesium sulfate 5 gm. She had been receiving daily home magnesium sulfate infusions for 5 years. She denied facial/throat swelling or difficulty breathing. She denied illicit substance use or recent medication, lotion, soap or dietary changes. On presentation, BP was 106/66 and she had a pink wheal in the right axilla. Laboratory testing included magnesium=1.2 mg/dL, potassium= 2.9 mmol/L, HCO3=30 mmol/L and creatinine of 0.8 mg/dL. There was concern for latex allergy and she was given magnesium sulfate 1 gm IV in the ED in a latex free preparation under close supervision. An urticarial rash developed during the infusion, which was stopped. There was no hypotension or respiratory compromise. She was transferred to the ICU for observation. She received IV Methyl prednisone and antihistamines with resolution of the rash. A possible reaction to a preservative or salt of the magnesium sulfate solution was suspected. She tolerated IV magnesium chloride for magnesium levels of 1 mg/dL while hospitalized and was eventually discharged on oral magnesium chloride tablets, in addition to amiloride, spironolactone and potassium chloride. At 3 months follow up visit she had not required intravenous magnesium supplementation and the rash did not recur.

Discussion: Anaphylactoid reactions due to magnesium sulfate are rare. This is the sixth case in the literature of clinically diagnosed cutaenous reaction to IV magnesium sulfate. In this case, the patient tolerated IV magnesium chloride, suggesting that the sulfate component was responsible for the reaction.

PUB565

A Case of Acute Interstitial Nephritis Secondary to Novel HCV Treatment Paritaprevir/Ritonavir/Ombitasvirf/Dasabuvir (PrOD)

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Introduction: A 66 year old AA male with history of CKD Stage IV (presumed secondary to DM and HTN) and HCV, diagnosed at pre-Transplant evaluation, developed Acute Kidney Injury. Admission creatinine [Cr] was 5.57 mg/dL with baseline 3.28 mg/dL He presented with symptoms of generalized weakness, fatigue, and edema. PrOD was started approximately five days before admission. He denied any symptoms of rash, fevers, chills, nausea, vomiting, or diarrhea, and initially was treated for pre-renal azotemia with intravenous fluid hydration (IVF).

Case Description: Point of care urinalysis was bland, with minimal proteinuria and negative for blood, leukocyte esterase or nitrites. His fractional excretion of sodium (FE_{Na}) was 0.53%, suggestive of pre-renal azotemia. Despite 24 hours of hydration with 1.5 liters NSS, there was no improvement in Cr. He was noted to have peripheral eosinophilia as high as 11% prior to the initiation of treatment, however with an elevated urine eosinophil level of 5% and persistent peripheral eosinophilia of 6%, AIN remained high on the differential. Complements (C3 and C4) and cryoglobulin levels were negative. He received two more liters of IVF over the next 24 hours and the Cr gradually returned to baseline over the next four days.

Discussion: AIN is classically seen with drugs such as Proton Pump Inhibitors, antibiotics, and NSAIDs[1]. This is likely one of the first cases of AIN seen with PrOD. Although his urine was bland, the elevated urine and peripheral eosinophils combined with temporal relationship of therapy makes AIN the most likely diagnosis[2]. With renal improvement to baseline after stopping PrOD a biopsy was not performed nor was he treated with steroids. After renal recovery, he was successfully treated with ledipasvir/sofosbuvir without complications.

[1]Perazalla M , Markowitz G. Drug Induced Acute Interstitial Nephritis. Nature Reviews Nephrology (2010) 6(8), 461-470

[2]Praga M, Gonzalez E. Acute Interstitial Nephritis. Kidney International 2010;77(11):956–61.

PUB566

Symptomatic Hypermagnesemia in Normal Kidney Function with Colonic Cleansing Agent

Yoo Jin Lee, Yang Wook Kim, Bongsoo Park, Sihyung Park. *Internal Medicine, Haeundae Paik Hospital, Busan, Republic of Korea.*

Introduction: Hypermagnesemia is an uncommon clinical situation if the iatrogenic magnesium administration and decreased renal function do not exist. Most of reported cases of hypermagnesemia were related with laxative abuse and impaired renal function. Magnesium containing bowel cleansing agents are widely used before colonoscopy without specific complications. However, we experienced a symptomatic hypermagnesemia with normal renal function after using bowel cleansing agent.

Case Description: A 74-year-old man with normal renal function complained about lethargy and motor weakness after taking bowel cleansing agent containing 14 gram of magnesium before colonoscopy due to hematochezia. His magnesium level was 12 mg/dL and electrocardiogram reveals fisrt-degree atrioventricular block and ventricular premature beat. Fluid stasis in the gut due to colonic obstruction might be the plausible cause of hypermagnesemia. He was treated with bowel enema and intravenous calcium. As magnesium levels declined, his general medical condition improved and his electrocardiogram changes were normalized.

Discussion: The present case suggests that severe hypermagnesemia can occur in the absence of pre-existing renal dysfunction with gastrointestinal diseases. We should be cautious in prescribing drug for colonoscopy if the colonic obstruction is suspected.

PUB567

Bile Cast Nephropathy: A Potential Cause of Acute Kidney Injury in Hyperbilirubinemia

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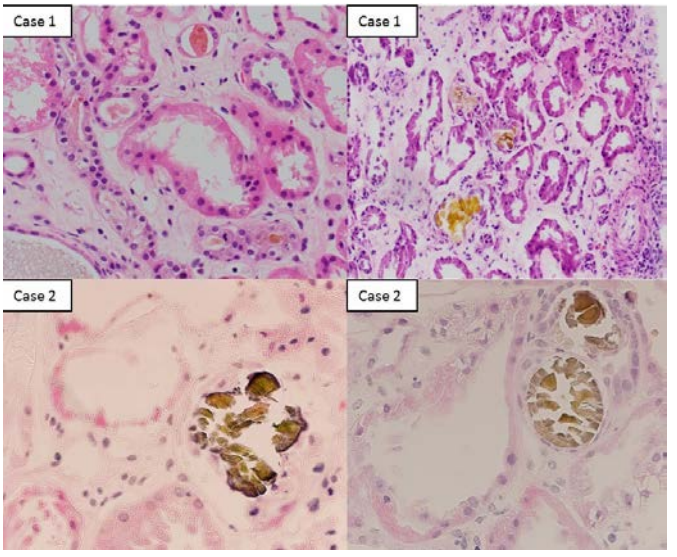
Introduction: Acute kidney injury (AKI) in the setting of liver disease is frequently a functional, hemodynamically mediated injury. However, studies have proposed that bile casts can cause tubular injury through obstructive and direct toxic effects, a pathologic entity recently referred to as bile cast nephropathy. We present two cases of patients who developed AKI in the setting of hyperbilirubinemia, both of whom showed bile casts on kidney biopsy.

Case Description: Case 1: 37 y/o male admitted to the hospital with altered mental status and diffuse jaundice. Labs: BUN 38 mg/dL, creatinine 3.8 mg/dL, total bilirubin 27.9 mg/dL, AST 377 U/L, ALT 166 U/L, GGT 1094 U/L. U/A: 2+ bilirubin, urobilinogen, and granular casts. Aggressive treatment for alcoholic hepatitis was started with prednisolone. His creatinine peaked at 11.1 mg/dL on day 9. Kidney biopsy showed orange-brown casts in proximal tubules. He required transient dialysis. His creatinine and bilirubin trended down. He was discharged on day 34. Case 2: 87 y/o male admitted to the hospital with progressive jaundice and pruritus, on Augmentin for an ear infection. Labs: BUN 29 mg/dL, creatinine 0.9 mg/dL, total bilirubin 37.6 mg/dL, direct bilirubin 27.1 mg/dL, AST 36 U/L, ALT 37 U/L, ALP 349 U/L . He was treated supportively for drug-induced liver injury. Creatinine peaked at 3.2 mg/dL on day 14. U/A: 2+ bilirubin, urobilinogen, and granular casts. Kidney biopsy showed yellow-green casts in proximal tubules. His creatinine and bilirubin trended down without aggressive therapy or dialysis. He was discharged on day 18.



Discussion: Bile cast nephropathy is an important pathologic entity that may account for reversible renal dysfunction in some patients with liver disease. As reported in some cases this is associated with severe elevations in bilirubin, as in our cases, and improving renal function with improvement in the cholestasis.

PUB568

Salicylate Toxicity Can Cause Rhabdomyolysis and Sepsis Like Syndrome-A Case Report

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Introduction: Rhabdomyolysis is characterized by myocyte membrane rupture with release of intracellular contents which includes creatine phosphokinase,lactate dehydrog enase,aldolase,myoglobin,purines,potassium and phosphates.We describe a case where patient had rhabdomyolysis and sepsis like syndrome from salicylate.

Case Description: A 41 years old female with unknown past medical history was brought to emergency room because of altered mental status.She was febrile of 102 F,tachycardic of 121,tachypneic at 32 and hypotensive with blood pressure of 70/50.She was intubated for airway protection and started on pressors and antibiotics.Laboratory on presentation**.**

WBC - 25.8 cells/microL	Neutrophils -88%	Hemoglobin-15.4 g/dl	Lactic acid –11 mmol/L	Na–142 mEq/L
K -5.2 mEq/L	Hco3-8 mEq/L	Phosphorus 14.2 mg/dl	Creatine phosphokinase(CPK) -532 U/L on Day 1	Salicylate -78.6 mg/dl on D1
CPK on Day 2(D2)-32,000 maxed to 73,000 U/L	Alcohol Panel-Negative	Drug screen – Negative except Salicylate		

Patient was started on hemodialysis within few hours of admission for salicylate toxicity.After 1 hour of completion of hemodialysis,salicylate level decreased to 13 and then to 8.4 on D2 of hospitalization.Patient developed oliguric acute kidney injury on D2 with elevated CPK.She was started on hemodialysis three times/week and CPK decreased to below 5,000 on D6.Patient was off pressors on D2 and all cultures were negative.Patient was discharged with twice weekly hemodialysis as outpatient.Her kidney function recovered in about 4 weeks with no further need of hemodialysis.

Discussion: The exact mechanisms by which salicylates cause muscle necrosis is unknown.But,it is thought that uncoupling of oxidative phosphorylation by salicylates leads to increase heat production which enhance permeability of muscle enzymes into circulation. Also Salicylates suppress cyclooxygenase pathway and lead to breakdown of arachidonic acid via lipoxygenase pathway,leading to formation of leukotrienes,which has muscle damaging effects.Salicylate toxicity should be considered as cause of rhabdomyolysis and differential diagnosis of septic shock especially in patients who have no obvious source of infection.

PUB569

Polyomavirus Nephropathy in Native Kidneys of an Immunocompetent Patient

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Introduction: Polyomavirus nephropathy has emerged as an important cause of graft loss in kidney transplant recipients. Polyomavirus rarely affects the native kidneys of an immunocompetent individual.Until now, polyomavirus nephropathy in native kidneys of an immunocompetent individual has not been reported, as far as we know.

Case Description: A 34-year-old man was transferred from a local clinic to be evaluated for the cause of azotemia. He was a hepatitis B carrier and had not been treated for hepatitis B. Serum creatinine was 2.85 mg/dL. His urinalysis revealed red blood cells, 0–2/high-

power field (HPF), and white blood cells, 0–2/HPF. The protein-to-creatinine ratio in spot urine was 69.6 mg/g. Kidney ultrasonography showed increased renal cortical echogenicity and decreased kidney size. Renal biopsy was performed. In the hematoxylin eosin stain and the periodicacid-Schiff stain, tubular epithelial cells frequently showed intranuclear inclusion bodies. The Masson trichrome stain showed interstitial fibrosis. There were localized small electron-dense materials in the mesangium. Epithelial cell foot processes remained relatively patent. The immunofluorescence microscopy showed a strong simian virus 40 large tumor antigen staining mainly in the tubular epithelial cells, confirming the diagnosis of polyomavirus nephropathy.

Discussion: Polyomavirus nephropathy may also be considered a cause of renal dysfunction in the native kidneys of immunocompetent patients.

PUB570

Hypercalcemia due to Calcitriol Secondary to Silicon Injection Butt Augmentation Rahul N. Pawar, Savneek S. Chugh, Venkata Buddharaju. *Nephrology, New York Medical College, Valhalla, NY.*

Introduction: Buttock augmentation and implants are the fastest growing type of cosmetic surgery in 2015, according to American Society of Plastic Surgery with close to 15,000 procedure performed in U.S. only. While the incidence of this is rising, more and more complications are now been uncovered secondary to this type of procedure. One of the rare but lethal complication is severe hypercalcemia mediated by excessive calcitriol (1, 25 Vitamin D) production from the granulomatous inflammation. We are reporting a very rare and interesting case of such entity.

Case Description: A 36 year old lady with history of hypertension, systemic lupus erythematosus, class IV and V lupus nephritis, CKD stage 3, who had multiple hospitalizations due to dehydration and hypercalcemia over the past few months. She has been followed in our renal clinic for few years and currently in remission for lupus nephritis. But over the past few months, she started to develop hypercalcemia with calcium increasing from 8.2mg/dl to 10.5mg/dl. She presented once with lethargy and creatinine of 2.5 when her serum calcium was 14. Work up for the hypercalcemia showed that I, 25 Vitamin D was 90. Of note, she had silicone injection to her buttocks 1.5 years ago. On imaging, her subcutaneous fat of the buttocks and hips demonstrate extensive abnormality including calcifications and nodular soft tissue densities. She was then started on a higher dose prednisone 20 mg to 40 mg per day. Since being on a higher dose of prednisone, her serum calcium levels subsequently improved to 9.4mg/dl and she is been in this for more than 1 year now.

Discussion: While the social media highlights this cosmetic effect, it encourages more and more young females to opt for this procedure. What are not depicted are the underlying dangers to this kind of procedure. We think this is important information for not only the nephrology but entire medical community as more and more of these procedures are desirably performed.

PUB571

Monoclonal Gammopathy of Renal Significance in Light Chain Deposition Disease Gheorghe Ciprian Cazan,[1] Ketki K. Tendulkar.[1] *[1]Nephrology, UNMC, Omaha, NE; [2]Nephrology, UNMC, Omaha, NE.*

Introduction: Light chain deposition disease may have an indolent presentation and a high clinical suspicion is needed for an early diagnosis. We present the case with worsening kidney disease in the setting of a normal UA, SPEP, UPEPand a modestly abnormal K:L ratio.

Case Description: 55-old Caucasian male with HTN and a baseline creatinine of 1.1 mg/dL was referred due to an increase in serum creatinine level to 2.84 mg/dl within 8 months from his last documented baseline creatinine. He was started on lisinopril 10 mg daily 2 weeks earlier and was taking meloxicam 15 mg daily for C6 radiculopathy. UA was negative for proteinuria or hematuria and further investigations revealed normal urinary Pr/Cr ratio, Alb/Cr ratio and renal ultrasound. After discontinuing lisinopril and meloxicam and with better control of his blood pressure, his renal function slightly improved with creatinine nadir of 2.2 mg/dL within 6 weeks. He had a kidney biopsy that was significant for focal global glomerulosclerosis, tubular atrophy and interstitial fibrosis 70%, weak linear staining for Kappa light chain. SPEP and UPEP were normal but Serum free light chains were remarkable for Kappa 530 mg/L, Lambda 19 mg/L (ratio-27.89). Bone marrow biopsy - mild hypocellularity 30%, 5 % plasma cells and 1.69 % cytoplasmic kappa expression. It was considered as a Monoclonal Gammopathy of Renal Significance but no definite criteria for further treatment. He underwent active surveillance with persistent normal UA, SPEP and stable kappa lambda chain ratio for 5 months. When his GFR started to decline. repeat bone marrow biopsy - unchanged, renal biopsy - brighter staining for kappa light chain.

Discussion: Light chain deposition disease can occur in any organbut renal involvement is present in 93-100% of the cases, a high suspicion is needed if a normal UA and no other explanation. There is a strong association between hematologic response to chemotherapy and renal outcome.

PUB572

Delayed Renal Graft Dysfunction following Renal Transplant Pyelonephritis Essa Abuhelaiqa,[1] Jeffrey I. Silberzweig.[1,2] *[1]Nephrology & Hypertension and Medicine, Weill Cornell Medicine, New York, NY; [2]The Rogosin Inst, New York, NY.*

Introduction: Patients presenting with pyelonephritis often present with acute kidney injury due to insteristitial nephritis and/or prerenal azotemia especially in those with renal allografts. We present a case of acute kidney injury, which developed after the patient's pyelonephritis had been treated for four days.

Case Description: A 62 year old male with history of type 1 diabetes mellitus treated by an insulin pump and end stage kidney disease secondary to diabetic nephropathy for which he received a kidney transplant from a deceased donor eight years prior to admission. On admission, he complained of urinary frequency, hesitancy and dysuria accompanied by fever and chills for four days. His admission serum creatinine was 2.6mg/dL, which is at his baseline. Urinalysis was notable for leukocyte esterase and pyuria (> 50 WBC/hpf) and urine culture grew *Klebsiella Pneumoniae*. His blood pressure was controlled throughout his hospitalization. He was treated piperacillin/tazobactam and intravenous fluids, but his creatinine increased to 4.1mg/dL over the subsequent 6 day period, and he developed new tenderness at the renal allograft site. His cyclosporine level was subtherapeutic (59.3ng/mL) so concern arose for transplant rejection and a renal biopsy was performed. Pathology demonstrated global glomerulosclerosis (13 out of 17 glomeruli) with patchy infiltration of neutrophils and mononuclear cells; minimal plasma cells were present. There was only focal tubulitis and tubular injury, staining was negative for C4d, and there was no evidence of glomerulitis or vasculitis. Based on clinical and pathologic data, we diagnosed our patient with acute kidney injury due to interstitial nephritis resulting from pyelonephritis. With continued treatment of his infection, his clinical symptoms improved and he was discharged with improved serum creatinine.

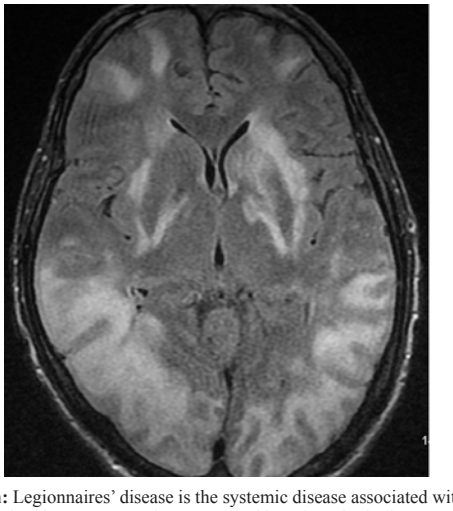
Discussion: Acute interstitial nephritis due to pyelonephritis can cause delayed onset acute kidney injury; biopsy is warranted to differentiate this entity from acute rejection in patients with renal allografts.

PUB573

Therapeutic Plasma Exchange for Acute Disseminating Encephalomyelitis following Legionnaires' Disease Latoya L. Brathwaite,[1] Paras Dedhia,[1] Charuhas V. Thakar.[1,2] *[1]Dept of Nephrology and Hypertension, Univ of Cincinnati, Cincinnati, OH; [2]Renal Section, Cincinnati VA, Cincinnati, OH.*

Introduction: Acute disseminating encephalomyelitis (ADEM) is an immune-mediated demyelinating disorder of the brain and usually occurs within 2 to 30 days after an antigenic challenge. Neurological symptoms of Legionnaires' disease range from headache and lethargy to encephalopathy.

Case Description: A 50-year-old male transferred to ICU from other institute with hypoxic respiratory failure secondary to legionella pneumonia. He was diagnosed with legionella pneumonia based on urine antigen and was treated with Azithromycin for 14 days. His hospital course was complicated by oliguric AKI to septic acute tubular necrosis and rhabdomyolysis and required renal replacement therapy. His creatinine increased from 1.1 mg/dl on admission to peak Cr of 4.5 mg/dl. On hospital day 16, noted to be less responsive with significant change in mental status. Exam was significant for increased tone and clonus in all 4 extremities with no response to verbal or tactile stimuli. MRI brain was notable for mixed pattern of diffusion signal involving both cerebral hemispheres and extending into basal ganglia and internal capsules. Also EEG showed an evidence of status epilepticus and was started on Levetiracetam and Fosphenytoin. In view of concern for hemorrhagic variant of ADEM, he was started on therapeutic plasma exchange (TPE) with 5% albumin. He received 5 sessions of TPE and noted to have significant improvement in neurological signs. After TPE, he was alert, awake and following commands and was moving all 4 extremities.



Discussion: Legionnaires' disease is the systemic disease associated with Legionella infection with significant extra pulmonary manifestations including renal failure and neurological abnormalities. This case highlights successful use of TPE in management of hemorrhagic variant of ADEM.

PUB574

Diagnostic Challenges in the Setting of Acute Kidney Injury and Thrombotic Microangiopathy Ian Logan, John Andrew Sayer. *Renal Services, Freeman Hospital, Newcastle upon Tyne, United Kingdom.*

Introduction: Thrombotic Microangiopathy can present in numerous ways, including Acute Renal Failure, and has several causes including Thrombotic Thrombocytopenia Purpura, Malignant Hypertension, Diarrhoeal Haemolytic Uraemic Syndrome and the ultra-rare atypical Haemolytic Uraemic Syndrome (aHUS). An underlying diagnosis of aHUS allows the opportunity to treat with Eculizumab but it can be a difficult diagnosis to make, owing to a lack of tests.

Case Description: We report a 38 year old male presenting with headache, nausea and mild diarrhoea. Past medical history included poorly controlled hypertension for 5 years and obesity. No family history was forthcoming and there were no regular medications. Blood pressure at presentation was 220/110 mmHg. Biochemical tests showed a plasma creatinine of 813 µmol/l, and raised bilirubin / LDH. Haematological tests demonstrated a platelet count of 65, haemoglobin of 11.9, and a blood film with red cell fragments. ECG suggested left ventricular hypertrophy. Percutaneous renal biopsy demonstrated features consistent with a thrombotic microangiopathy, although a lack of vascular intimal thickening that would be expected with hypertensive disease. Case Description: Haemodialysis was started within 48 hours for fluid overload, whilst antihypertensive medications were introduced, resulting in an improvement in platelet count but no renal recovery. The presumed diagnosis was Thrombotic Microangiopathy resulting from Malignant Hypertension. Diarrhoeal Haemolytic Uraemic Syndrome (HUS) was also considered, whereas ADAMTS13 testing excluded Thrombotic Thrombocytopenia Purpura. Genetic testing for aHUS was requested to exclude an underlying complement defect. This revealed a heterozygous deletion encompassing the CFH locus, extending to CHFR1, hereby producing a hybrid regulatory gene. This variant causes complement dysregulation and aHUS, the final diagnosis in this patient.

Discussion: Our case highlights difficulties in the diagnosis and management of Thrombotic Microangiopathy, with the need to consider aHUS. This allows treatment with Eculizumab and the opportunity for genetic screening of family members.

PUB575

Rapid and Progressive Glomerulonephritis Associated with Sweet Syndrome Rahul N. Pawar, Savneek S. Chugh, Rameen Hashemiyoon. *Nephrology, New York Medical College, Valhalla, NY.*

Introduction: Sweet Syndrome Manifesting as Rapidly Proliferative Glomerulonephritis.

Case Description: A 42 year female presented with an erythematous lesion on the leg associated with edema and fevers since her return from Africa, few days ago. This was followed by ulceration and inability to ambulate requiring debridement and empiric antibiotics for necrotizing fasciitis. Her clinical course was complicated by non-oliguric acute kidney injury (AKI) and respiratory failure. Laboratory investigation revealed leukocytosis (24.9), anemia (Hgb 6.7), and AKI (SCr. 0.62 à 1.44). She had ANA positive, in addition to decreased complement levels with negative ds-DNA or anti-smith antibodies. Skin biopsy exhibited acute inflammatory infiltrate involving the epidermis, dermo-epidermal junction, extending to the hair follicles. Direct immunofluorescence presented fibrillary staining with antisera to fibrin-related antigens in the superficial dermis, findings compatible with Sweet Syndrome. Her urinalysis was significant for hematuria with red blood cell casts and proteinuria of around 1gm/day. Patient was hypotensive and unstable for renal biopsy. In addition to antibiotics, patient also received pulse dose of steroids along with intravenous cyclophosphamide infusion and prednisone 60 mg. After two weeks, the patient experienced normalization of her creatinine and resolution of proteinuria.

Discussion: Sweet Syndrome, also referred to as acute febrile neutrophilic dermatosis, is a rare disease process affecting predominantly females aged 30-50 years of age. Sweet syndrome can manifest as kidney disease, specifically mesangiocapillary glomerulonephritis including urinalysis abnormalities (hematuria and proteinuria). Systemic corticosteroids remain the gold standard of treatment. In our patient, constitutional symptoms resolved within 72 hours, followed by clearance of skin lesions in 3-9 days. Corticosteroids were gradually tapered over the course of 2-6 weeks. Clinical and diagnostic acuity along with rapid implementation of treatment remain the mainstay of approaching a patient with Sweet Syndrome for favorable results.

PUB576

Ischemic Monomelic Neuropathy: Rare Complication of Dialysis Access Presenting as a Foot-Drop Like Ravi K. Thimmisetty, Noreen F. Rossi. *Nephrology, Wayne State Univ, Detroit, MI.*

Introduction: Ischemic monomelic neuropathy (IMN) is a rare complication developed after acute arterial occlusion or reduced blood flow to a peripheral nerve. In the review of our literature, we could not find any IMN cases that are reported in lower extremities following vascular access surgery for hemodialysis.

Case Description: A 59-year-old man was admitted for a creation of vascular access at the left femoral site for dialysis. He does have multiple deep venous thrombosis in upper extremities at AV fistula sites. He underwent left superficial femoral artery to vein fistula loop graft without any complications. Post-operatively patient was complaining of pain and weakness at the surgical site. Neurological examination revealed left foot dorsiflexion 1/5, left foot plantar flexion is 3/5. Left hip flexion is 3/5 on laying. Foot invertors are 0/5, foot evertors 0/5. Sensation to light touch, cold, pinprick and temperature are decreased on left from lower 1/3rd of the leg to foot and normal on the right side. Lower extremities pulses are not palpable due to chronic edema. All the imaging (CT scan of abdomen and pelvis, ultrasound of left thigh, MRI of lumbar spine) tests didn't show any acute pathology. Ultrasound of left thigh shows patent AV graft, no hematoma. Pre and post AV Graft Ankle-Brachial Index were 0.93 and 0.67 suggestive of the tibial obstructive disease. Foot drop and weakness after surgery without lumbar radiculopathy pointed to the IMN, which is a diagnosis of exclusion. As patient doesn't have any other sites to create another access, decided wisely to preserve the current graft and managed the complication conservatively by physical therapy and ankle-foot arthrosis.

Discussion: IMN is a difficult clinical diagnosis because of the inconsistency of clinical signs and occurrence in the immediate postoperative period. Owing to the low incidence and under-reporting of these cases, experiences regarding management are insufficient. A more global awareness among the multidisciplinary team is necessary to diagnose early and prompt treatment of IMN to prevent both short and long term disabilities.

PUB577

Rare Case of Lupus Nephritis with Positive Cytoplasmic Anti-Neutrophil Cytoplasmic Antibodies (C-ANCA) Venkata Buddharaju, Savneek S. Chugh, Rahul N. Pawar, Renee E. Garrick. *Nephrology, New York Medical College, Valhalla, NY.*

Introduction: Renal involvement in Systemic lupus erythematosus (SLE) is common with urine abnormalities present in up to 75% patients. Lupus can cause a wide range of renal manifestation including glomerular disease, Tubulointerstitial nephritis, Thrombotic microangiopathy, collapsing glomerulosclerosis and RPGN. ANCA positivity can be seen of lupus patients with predominantly perinuclear pattern (P-ANCA) and atypical pattern. We present to you a rare case Lupus nephritis with C-ANCA positivity.

Case Description: This is a case of a 23 y/o woman with a past medical history of childhood MPGN type 1 (15 years) who was recently diagnosed with lupus nephritis and was sent from her nephrologist's office for induction therapy. She was past treated with prednisone therapy from 15-17 years of age followed by a taper and then subsequently went into remission. However, last month she has been complaining of progressively increased swelling of her lower extremities with normal renal function. Urinalysis showed 3+ protein and 1+ blood with nephrotic range (9 gm) proteinuria in 24 hour collection. Further work up, showed low complements, positive ANA, C-ANCA and negative P-ANCA and ds-DNA. Patient underwent renal biopsy, which on Immunofluorescence staining revealed granular diffuse glomerular capillary wall and focal mesangial staining. There was no extra glomerular staining in the tubular basement membranes or in the blood vessels with any of the immunoreactants. Glomerular capillary wall staining is suggestive of both subendothelial and subepithelial deposits consistent with class IV/V lupus nephritis as seen on histology. She was subsequently started on pulse dose steroids for followed by induction dose of mycophenolate. Since then patient went into complete renal remission with negative C-ANCA titers.

Discussion: SLE is a multisystem disorder with multiple antibody production including ANCA. The prevalence of ANCA is reported to be as high as 31% of patients in lupus patients with predominantly P-ANCA but C- ANCA is rarely associated with Lupus. The pathogenesis of Lupus nephritis associated with C-ANCA and its significance is still unclear and will need further studies.

PUB578

Impact of Hypotonic Fluid on Prevalence of Sodium Disturbances in Children Hospitalized for Treatment of Surgical Conditions Marie Fouad, Poonam Thakore, Zachary Sartor, Janet Meller, Tetyana L. Vasylyeva. *Pediatrics, Texas Tech Univ Health Sciences Center, Amarillo, TX.*

Background: Pediatric surgical patients are at risk of developing hyponatremia, which can lead to cerebral edema, seizures and death, making fluid management in pediatric surgical patients an important topic. The aim of this study is to evaluate the differences between hyponatremic (HN) and normonatremic (NN) pediatric surgical patients.

Methods: This is a retrospective chart review of pediatric patients hospitalized between January 2012 and December 2012. A subset of 133 surgical patients was obtained for analysis. Only patients with serum sodium level documentation who received hypotonic (HT) fluid were included. Hyponatremia was defined by; mild if Na 130-135 mEq/L, moderate if Na 125-129 mEq/L and severe if <125 mEq/L. Age, sex, length of HT fluid administration and length of hospital stay (LOS) for HN and NN patients was studied. Comparisons were made using a two-tailed unpaired t-test ($p<0.05$).

Results: 16 of 68 patients (23.5%) with an average age of 6.0±0.6 yo had mild hyponatremia. Average sodium level for the HN group was 132±0.4 mEq/L, and the NN group had an average of 138±0.3 mEq/L. No cases of moderate or severe hyponatremia were found, and no cases of hypernatremia occurred. Out of 16 HN patients, 5 were female (3.1%) and 11 were male (68.8%) with no statistical significance ($p=0.5$). The HN group had a lower average age (6±0.6 years) than the NN group (8.7±0.7 years), with no statistical difference in average age ($p=0.09$). The LOS for the HN group was longer (5.3±0.6 days) than the NN group (4.6±0.6 days), with no statistical difference ($p=0.4$). The length of HT fluid administration for the HN group was longer (3.6±0.5 days) than the NN group (2.5±0.2 days), with statistical significance ($p=0.01$).

Conclusions: In our study, mild hyponatremia was prevalent at an overall rate of 23.5% in pediatric surgical patients. The prevalence of hyponatremia was higher in males compared to females. The HN group also had a lower average age than the NN group. Hyponatremia was associated with an increased length of HT fluid administration and longer LOS.

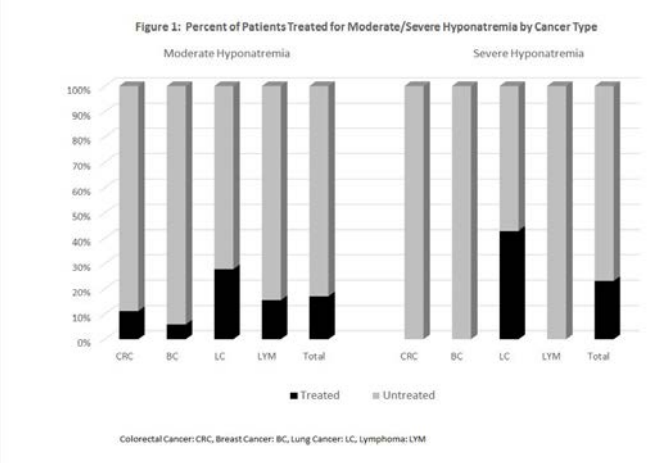
PUB579

Moderate to Severe Hypervolemic or Euvolemic Hyponatremia in Cancer Patients Is Largely Untreated Ilya Glezerman,[1] Jorge Castillo,[2] Holly Krasa,[3] Lois Lamerato,[5] Joseph Chiodo,[3] Kathy Schulman.[4] *[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Dana-Farber Cancer Inst, Boston, MA; [3]Otsuka PDC, Inc., Princeton, NJ; [4]OR Solutions, Inc., Waltham, MA; [5]Henry Ford Health System, Detroit, MI.*

Background: Hyponatremia (HN) is a negative prognostic indicator in cancer. It's unclear if it's a marker of severe disease or if correction improves quality of life. We characterized treatment/survival in cancer patients with moderate/severe (M/S) HN.

Methods: Tumor registry and medical record data were abstracted from the Henry Ford Health System for 125 adults with incident lymphoma, breast, lung or colorectal cancer having ≥1 episode of moderate (125–130 mEq/L) or severe (<125 mEq/L) hypervolemic or euvolemic HN. Patients were followed until death, clinical trial entry, onset of a new primary cancer or Health Alliance Plan disenrollment.

Results: Most patients (90%) had moderate HN (55% female, mean age 60 yrs, 61% stage 4); 41% were symptomatic. The most common symptoms were fatigue, nausea/vomiting, and headache. Few cases (18%) were treated. Mean (SD) duration of M/S HN was 29 (71.0) days. Thirty-five percent of patients experienced another episode of M/S HN. In the 30 days prior to index, 47% were hospitalized, 46% (14%) received chemotherapy (radiation), 10% were designated a fall risk and 6% experienced a fall. In the 30 days post index, 21% of patients were hospitalized, 44% (28%) received chemotherapy (radiation), 14% received comfort care, 20% were designated a fall risk and 3% experienced a fall. A total of 50 (40%) patients died. Median (95% CI) survival time was 275 (221-432) days; 16% died in the first 30 days.



Conclusions: M/S HN in cancer patients is largely untreated. While some form of end of life or comfort care frequently accompanies M/S HN, the majority of patients in our study lived in excess of three months. The potential exists to improve patient care and outcomes by actively treating HN.

Funding: Pharmaceutical Company Support - Otsuka PDC, Inc., Princeton, NJ

PUB580

Cost Analysis of Treatment of Hyperkalemia with Standard Therapy Compared to the Cation Exchanger Patiromer Maria T. Story,[1] Prakash M. Nadkarni,[1,2] Bradley S. Dixon,[1,3,4] Lama A. Noureddine.[1,3] *[1]Internal Medicine, Univ of Iowa Hospitals and Clinics, Iowa City, IA; [2]Inst for Clinical and Translational Science, Univ of Iowa Hospitals and Clinics, Iowa City, IA; [3]Nephrology, Univ of Iowa Hospitals and Clinics, Iowa City, IA; [4]VAMC, Iowa City, IA.*

Background: Current treatment (tx) of hyperkalemia (HK) is time consuming and costly. Here, we analyzed how the cost for treating HK might change with the use of patiromer.

Methods: We performed a single center, retrospective analysis of current tx costs for HK versus projected costs of tx with patiromer. Adult patients with a serum potassium (K) ≥6.0-6.4 mEq/L (a range used in published studies of patiromer) between 8/1/14-11/30/15 (15 mo) were identified from the electronic medical record. The cost for medications, emergency department (ED) visits, hospitalizations, dialysis, and physician charges were obtained from hospital pharmacy and accounting. All costs for outpatient encounters for HK (K≥6.0-6.4) during the study period were summed and compared to the cost of a prescription for patiromer for the 15 mos (pricing provided by Relypsa, Inc).

Results: 125 outpatients were identified; 53.6% were on an ACE inhibitor or angiotensin receptor blocker. The major etiologies of HK were renin-angiotensin-aldosterone (RAAS) blockade and acute/chronic renal failure. Within 24 hrs of HK, there were 13 ED visits and 18 hospitalizations incurring 109 patient-days (average length of stay 4.9 days). The total cost for tx HK was $183,232; 95% of which was for inpatient services. If all patients on RAAS blockers (53.6%) were tx with patiromer for 15 months, the prescription cost would be $597,975. Hospitalization for RAAS-induced HK might be eliminated ($32,838) but overall costs for tx HK using patiromer would be $748,369.

Conclusions: The current cost for tx acute HK is significantly less than the projected cost of long-term tx with patiromer. However, use of patiromer may allow more patients to be treated with RAAS blockade and possibly reduce costs related to inadequate RAAS blockade. Use of patiromer may also shift more cost of treating HK from insurance to patients, potentially increasing their financial burden.

PUB581

Value of Fractional Uric Acid Excretion in Differential Diagnosis of Hyponatremia Saubhik Sural. *Nephrology, Peerless Hospital & B K Roy Reseach Centre, Kolkata, West Bengal, India.*

Background: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is an important cause of hyponatremia. The purpose of the study is to compare serum uric acid (UA) and and Fractional Excretion of Uric Acid(FE- UA) between hyponatremic patients with and without SIADH.

Methods: The cases(n= 102) included all patients admitted to our institute with hyponatremia, who met the inclusion and exclusion criteria. The diagnosis of SIADH was confirmed by the existing consensus criteria available. Serum and urinary UA was assayed on an Olympus 480 platform. Fifty three patients were diagnosed to suffer from SIADH. Forty nine hospitalized patients had other types of hyponatremia . The study duration was 3 years and the data obtained was treated statistically using the MedCalc Software for descriptive values and diagnostic performance. Significance was considered at p less than 0.05.

Results: Results showed the mean(SD) serum uric acid(mg/dl) to be significantly lower in SIADH group as compared to other non SIADH Hyponatremia 2.4(0.88) vs 4.6(1.31). FE-UA (%) was significantly higher in SIADH as compared to other non SIADH patients 15.3 (2.97) vs 7.86 (2.6). Receiver Operating Curve (ROC)showed an area under curve (AUC) of 0.88 and 0.98 for Serum UA and FE-UA respectively for SIADH patients. At a cut off less than 3.1 mg/dl for Serum UA in SIADH showed a diagnostic sensitivity of 86 % and specificity of 81 %. Whereas at cut off greater than 13 % for FE-UA the sensitivity was 86% and specificity of 98%.

Conclusions: SIADH patients have significantly lower Serum Uric Acid levels and increased renal excretion (higher FE-UA) as compared with hyponatremic patients with other causes. Combining Fractional Excretion of UA along with Serum UA gives excellent sensitivity as well as specificity in the differential diagnosis of hyponatremia. Particularly in a resource constrained healthcare set ups where very few clinical labs have Osmometers, FE –UA is a very important diagnostic tool in SIADH.

PUB582

Development and Testing of Prediction Models for Fluid Overload Related Hospitalizations in Hemodialysis Patients Yue Jiao,[1] Sheetal Chaudhuri,[1] Terry L. Ketchersid,[1] Dugan Maddux,[1] Brian Scott Ash,[1] John W. Larkin,[1] Len A. Usvyat,[1] Peter Kotanko,[2,3] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Renal Research Inst, New York, NY; [3]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Hospitalizations due to fluid overload are common in hemodialysis (HD) patients. We aimed to utilize clinical data sources to develop and test predictive models (PMs) that can identify HD patients with a high probability of multiple fluid overload related hospitalizations in the next 12 months.

Methods: We analyzed patient data from the Fresenius Medical Care Data Warehouse from Apr 2013 to Mar 2015. Various PMs were developed for prediction of ≥3 fluid overload related hospital admissions in the next 12 months, and included the generalized linear model, partitioning and regression trees, artificial neural networks, and generalized additive model (GAM). In all, 11,062 of cleaned clinical records on 33 variables was utilized for development of the PMs. Variables included data on patients' history of fluid overload related hospital admissions, demographics, morbidities, laboratories, and other parameters. Of the entire study dataset, 70% was randomly selected for PM development and prediction accuracy of the PMs was tested with the remaining 30%. The area under the receiver operating characteristic curve (AUC), sensitivities and specificities were investigated to determine the PMs' performance. The sensitivities and specificities were derived by taking the maximum of the Youden index to determine the optimal cutoff value.

Results: The GAM had the highest performance, with an AUC of 0.86 (95% CIs 0.83-0.90), sensitivity of 73% (95% CIs 65-81%), and specificity of 83% (95% CIs 82-84%) for the PM utilizing a 30% test dataset.

Conclusions: Testing of the developed PMs demonstrates that predictive analytics utilizing clinical data can assist in identifying patients with a high probability for being admitted to the hospital for fluid overload related complications.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB583

Can Urine pH Predict Plasma pH in ICU Patients with Abnormal Plasma Bicarbonate Levels? Navneet Kaur, Jesse M. Goldman. *Internal Medicine, Div of Nephrology, Drexel Univ College of Medicine, Philadelphia, PA.*

Background: Physicians are often called upon to interpret the acid-base status of critically ill patients demonstrating abnormal venous plasma bicarbonate values. It is longstanding dogma that when plasma bicarbonate concentration is either above or below normal, an arterial blood gas is absolutely necessary to obtain a plasma pH and calculate the acid-base condition of an individual patient. Since the kidney is a major sensor and

regulator in maintaining acid-base balance, we wondered whether urine pH might reliably predict arterial pH and thereby (in the right circumstances) correlate with arterial pH, avoiding need for an arterial blood gas specimen.

Methods: We performed retrospective chart review on 181 patients admitted to intensive care units at our institution from September 2013 to September 2014 to identify patients with a urinalysis and an arterial blood gas performed within 24 hours of each other. Of the 181 patients screened, 41 patients met this criteria. We reviewed serum chemistries, urinalyses and blood gases to assess for correlation between urine and plasma pH. We excluded patients with normal serum bicarbonate and patients receiving renal replacement therapy.

Results: Among the 41 patients, only 10 patients (24%) showed successful correlation between urine and serum pH. No correlation was noted in the remaining 31 patients. Within our cohort of 41 patients, 10 had cirrhosis, 5 had urinary infections, 4 with gastrointestinal bleeding, and 7 were ventilator dependent.

Conclusions: On our retrospective chart review of 41 critically ill patients, only 11 patients showed correlation between the urine and blood pH and 31 patients did not demonstrate a useful correlation. Among patients admitted in the intensive care units at our institution, there is a high frequency of sepsis and acute renal failure. In the setting of acute renal failure, there is poor function of renal tubules, not allowing appropriate compensation by the kidney and inability to maintain the acid base status as predicted. Our research supports the need for obtaining a blood pH specimen to interpret the acid-base status in critically ill patients with abnormal plasma bicarbonate values.

PUB584

Not Serum Potassium Level, but Serum Creatinine Level Has More Impact on Clinical Judgement for Emergent Dialysis for Severe Hyperkalemia Takamasa Miyauchi, Masahiko Nagahama, Taisuke Ishii, Sawako Kobayashi, Hiroyuki Yamamoto, Fumika Taki, Yasuhiro Komatsu. *Nephrology, St. Luke's International Hospital, Akashi-cho chuo-ku, Tokyo-to, Japan.*

Background: Hyperkalemia is a relatively common problem in hospitalized patients. However, management of hyperkalemia has been traditionally based on the physician's judgement, or institutional protocols, and treatment practice pattern for hyperkalemia is not well studied. The aim of the present study is to determine overall practice pattern of treatments for severe hyperkalemia, and clarify the most influenced factor for emergent HD in hospitalizes patients.

Methods: We analyzed clinical and biochemical parameters of all hyperkalemic patients admitted to St.Luke's Int Hosp in Tokyo over a 10-year period (2006-2016). Hyperkalemia is defined as serum $K^+ \geq 6.5$mEq/L anytime in hospitalization. Dialysis patients and pediatric patients were excluded.

Results: There were 883 patients who met the criteria for this study. Serum K^+ ranged from 6.5 to 17 mEq/L. The mean serum K^+ was 7.1±0.9 (mean±S.D.) mEq/L. The mean age was 69.1±15.6 yr, the male ratio was 56.3%, the mean serum creatinine level was 2.8±3.1 mg/dl, and the average urine output per day was 820±1034 ml. Insulin plus dextrose was the most commonly used emergent therapy (41.3%), followed by calcium gluconate (29.8%), sodium bicarbonate (22.7%), loop diuretics (12%), albuterol (1.8%), and sodium polystyrene sulfate (1.5%) on the day the hyperkalemia was recorded. 8.9% of patients underwent emergent HD. On univariate analysis, patients treated with emergent HD had significantly higher serum creatinine than patients without emergent HD (8.0±4.9 vs 2.8±3.1 , HD vs. non HD, $p<0.01$). Multivariate logistic regression analysis identified high serum creatinine to be independently associated with emergent HD (odds ratio=1.31, $p<0.01$). Neither higher serum K^+ nor higher urine output was associated with emergent HD.

Conclusions: Emergent treatment for severe hyperkalemia in hospitalized patients was performed successfully. Of interest, emergent HD is prescribed more frequently for the patients with worse kidney function. This implies that not serum K^+ level, but serum creatinine level has more impact on clinical judgement for emergent HD.

PUB585

Evidence-Based Management of Hyperkalemia: A Systematic Review Eirini Palaka,[1] Saoirse A. Leonard,[2] Amy M. Buchanan-Hughes,[2] Anna Bobrowska,[2] Susan Grandy.[3] *[1]AstraZeneca Ltd, Cambridge, United Kingdom; [2]Costello Medical Consulting Ltd, Cambridge, United Kingdom; [3]AstraZeneca, Gaithersburg.*

Background: Hyperkalemia (HK; defined as elevated serum potassium levels of >5.0 mmol/L) is a potentially life-threatening condition that can occur in patients with impaired renal function. To support evidence-based treatment, we conducted a systematic literature review (SLR) to identify studies on the efficacy or safety of interventions for managing HK.

Methods: MEDLINE, MEDLINE In-Process, Embase, CDSR, CENTRAL and DARE were searched from database inception to 27 April 2016 using terms for HK combined with terms for interventional and observational study designs. Abstract books from key congresses and bibliographies of previous SLRs were hand-searched for additional studies. Eligible publications, screened by 2 independent reviewers, reported randomized controlled trials (RCTs), interventional non-RCTs or observational studies investigating the efficacy or safety of pharmacological or non-pharmacological interventions for the treatment or prevention of HK.

Results: Database searches identified 848 unique records of which 151 were selected for full-text review. 126 publications from database searches and 30 additional publications from hand-searches were included for a total of 21 RCTs, 26 interventional non-RCTs and 34 observational studies. Of these, 16 RCTs, 20 interventional non-RCTs and 10 observational studies reported results in patients with renal dysfunction. Key interventions investigated in the RCTs across all patient populations included the newer treatments sodium zirconium cyclosilicate (ZS) and patiromer (3 RCTs each), as well as sodium and calcium polystyrene sulfonate (SPS/CPS; 2 RCTs) and combinations of temporizing agents (eg. insulin, salbutamol; 6 RCTs). RCTs of key interventions on renal dysfunction patients included ZS and patiromer (2 RCTs each), SPS/CPS (2 RCTs) and temporizing agents (5 RCTs).

Conclusions: Despite the mortality risk associated with HK, only a small number of robust published RCTs were identified, especially in high-risk patients with renal dysfunction. This lack of evidence is associated with unclear treatment recommendations for renal patients with HK.

Funding: Pharmaceutical Company Support - AstraZeneca Ltd

PUB586

Identification of Potential Pediatric Hyponatremia Cases in Three Large United States Patient Databases Siddhesh Kamat, Holly Krasa, Suzanne Watkin, Robert A. Stellhorn, Ann Dandurand, Kimberly D. Sikes. *Otsuka Pharmaceutical Development & Commercialization, Inc.*

Background: Hyponatremia (HN), defined as a plasma sodium concentration less than 135 mmol/L, is one of the most commonly encountered electrolyte disorders; however clinically relevant hyponatremia requiring medical intervention is less common. Clinical trials are ongoing to evaluate pharmaceutical treatments for sodium correction among pediatric patients and large retrospective patient databases may be useful in evaluating the feasibility of conducting such trials. Our objective was to estimate the occurrence of pediatric HN patients using retrospective patient databases.

Methods: Three large US databases (Optum Clinformatics and Truven Marketscan Commercial claims data from 2010-2014, and the Humedica Electronic Health Records database from 2010-2013 covering approximately 12, 43, and 12 million members, respectively) were used to identify potential pediatric HN patients. Patients receiving medical claims with International Classification of Disease – 9th Revision (ICD-9) code of 276.1 (hyponatremia, hypo-osmolality) in primary or secondary diagnosis fields were identified as potential HN cases. Among patients in the Humedica database, serum sodium values of <130 mmol/L in the inpatient or outpatient setting were used in addition to ICD-9 codes to identify potential cases with HN.

Results: Based on occurrence of ICD-9 codes, 22,373 out of approximately 12.3 million members in the Optum database were coded for HN of which 1,004 were <=17 years of age resulting in a rate of 1 in 12,334 members covered in the data. Similarly, analysis of the Truven database resulted in a rate of 1 in 15,374 members. In the Humedica electronic health records data, after applying the criteria of ICD-9 codes for HN and the presence of at least two lab values of <130 mmol/L on separate dates, 1 in 318 patients with HN codes were <=17 years of age.

Conclusions: This retrospective database analysis suggests an infrequent occurrence of potential cases of HN with age <=17 years. From the standpoint of feasibility of clinical trials, results suggest that trial recruitment may be challenging given the low occurrence of potential cases.

Funding: Pharmaceutical Company Support - Otsuka Pharmaceutical Development & Commercialization, Inc.

PUB587

Utilization of Tolvaptan and Associated Budget Impact among Hospitalized Heart Failure Patients with Hyponatremia Siddhesh Kamat, Robert A. Stellhorn, Shirin Sundar, Holly Krasa. *Otsuka Pharmaceutical Development & Commercialization.*

Background: Hyponatremia (HN), defined as plasma sodium concentration less than 135 mmol/L, is a commonly encountered electrolyte disorders in hospitals. Given the increasing pressures for cost containment, hospitals are likely to consider the budget impact of treatments used in the inpatient setting during formulary policy-making. Fluid restriction and treatments such as tolvaptan (a vasopressin V2-receptor antagonist) are used for correction of clinically significant hypervolemic and euvolemic HN. Our objective was to describe utilization patterns of tolvaptan and evaluate the budget impact among hospitalized heart failure (HF) patients with HN in the real-world inpatient setting.

Methods: A retrospective database analysis was conducted using the Premier Inpatient database representing 700 US hospitals from 1/1/2011 through 12/31/2014 to identify patients with a discharge diagnosis of HF (ICD-9 428.xx) and a secondary diagnosis of HN (ICD-9 276.1x). Utilization patterns of tolvaptan and costs incurred were analyzed using descriptive statistics. Budget impact of tolvaptan use was presented per HF-related inpatient visit with codes for HN.

Results: A total of 23,842 inpatient visits were identified with a discharge diagnosis of HF and codes for HN. Among these visits, 935 or 3.9% visits had evidence of tolvaptan use. Inpatient visits with tolvaptan use had a mean length of stay of 11.5 days (median 9) and 297 (or 31.8 %) of visits included intensive care unit (ICU) services over the duration of the entire hospitalization. Inpatient stays with HF and HN and with evidence of tolvaptan use cost an average of $26,955 (median $14,075) whereas mean costs related to tolvaptan use were $981 (median $480). The budget impact associated with tolvaptan use was $38.4 per HF-related inpatient visit with secondary diagnosis codes for HN (Mean cost of tolvaptan treatment per visit*Number of visits with tolvaptan use/number of HF-related inpatient visits with codes for HN).

Conclusions: Tolvaptan utilization in the inpatient setting is associated with a marginal budget impact in terms of all HF-related hospital visits with codes for HN.

Funding: Pharmaceutical Company Support - Otsuka PDC

PUB588

Descriptive Analysis of Patients Receiving Tolvaptan in the Inpatient Setting Siddhesh Kamat, Robert A. Stellhorn, Shirin Sundar, Holly Krasa. *Otsuka Pharmaceutical Development & Commercialization.*

Background: Hyponatremia (HN), defined as a plasma sodium concentration less than 135 mmol/L, is one of the most commonly encountered electrolyte disorders in hospitals. Fluid restriction and treatments such as tolvaptan (a vasopressin V2-receptor antagonist) are used for correction of clinically significant hypervolemic and euvolemic HN. Lack of consistent guidelines for the management of HN result in high variability in treatment patterns. Our objective was to conduct a descriptive analysis of patients receiving tolvaptan in the inpatient setting.

Methods: Analysis was conducted using the Premier Inpatient database representing 700 United States hospitals from 1/1/2011 through 12/31/2014. Inpatient visits with use of tolvaptan were described in terms of patient demographic and clinical characteristics, length of inpatient stay, occurrence of HN (ICD-9 276.1x), heart failure (ICD-9 428.x, HF), syndrome of inappropriate antidiuretic hormone secretion (ICD-9 253.6x, SIADH), and other commonly occurring discharge diagnoses.

Results: A total of 11,744 inpatient stays were identified with evidence of tolvaptan use – patients had a mean age of 68 years (median 69 years) and 45.7% male. Among these inpatient visits, 6,647 (56.5%) had ICD-9 codes for HN, 4,063 (34.5%) had codes for HF, and 4,704 (40.0%) had codes for SIADH in any diagnosis field. In terms of discharge diagnosis, the most commonly codes were for SIADH (15.4%), 9.9% for HN and 9.8% of patients had HF. Septicimia (2.5%), pneumonia (2.4%), and rehabilitation procedures- non-specific (2.3%) were other commonly occurring discharge diagnosis in patients prescribed tolvaptan. Average length of stay for patients receiving tolvaptan was 10.6 (median 8) days.

Conclusions: Tolvaptan use was associated with varying diagnosis codes with the majority relating to HN, SIADH, and HF. Discharge diagnosis for those prescribed tolvaptan varied widely potentially reflecting the variability in the use of treatment in the inpatient setting or low rates of coding HN at discharge.

Funding: Pharmaceutical Company Support - Otsuka PDC

PUB589

Hyponatremia Rarely Associated with Preeclampsia Tokameh Entezari. *Internal Medicine, 1, Reno, NV.*

Background: Introduction:Severe hyponatremia is a rare complication of preeclampsia and only handful cases have been reported in the literature.Early diagnosis and treatment are vitals to reduce maternal and fetal morbidity and mortality.

Case:A 25 years old primiparous woman 27/5 weeks pregnant admitted with new onset of dyspnea on exertion,lower extremity edema and labile hypertension. No prior diagnosis of preelcampsia and no know medical history.

Initial serum sodium was 127 with normal TSH and cortisol level. Total urine protein was up to 6 grams in 24 hours and urine Na was 23. BP was 160/80 and improved with escalating doses of labetalol and nifedipine. Fluid restriction was attempted with limited success initially improving sodium to 130 and later dropped down to 125. At this time, she was 28 weeks and received betamethasone for accelerating fetal lung maturation and baby delivered on hospital day#6. Post partum,her serum sodium started to normalize and BP also improved. Mother and baby were discharged home on day#14 in good health.

DISCUSSION: Pregnancy involves changes in physiology that affect water and sodium homeostasis. The release of hCG during pregnancy may be responsible for a mild resetting of the osmostat downward that is responsible for a fall in the serum sodium concentration of about 5 meq/L. Developement of severe hyponatremia with preeclampsia is rare and only few cases have been reported in the literature. Its exact etiology is not well understood. A non-osmotic stimulation of vasopressin release in the setting of a hypervolemic state with low effective circulating plasma volume is thought to be the main mechanism.

Advanced maternal age and nephrotic range proteinuria have been postulated as risk factors, but their casual role remains unclear. Fluid restriction is a reasonable treatment, and maternal outcomes are favorable. This condition is a rare indication for urgent delivery and often normalizes post-partum.

CONCLUSION: Severe hyponatremia in pregnancy poses diagnostic and therapeutic challenges. Knowledge of these complex physiologic alterations during pregnancy is critical to managing dysnatremias in pregnancy.

PUB590

Clinical Features and Extracorporeal Management of Reported Acetylsalicylic Acid Exposures in the United States Sara Tavernier Burgardt,[1] Meghan A. Jobson,[1,2] Michael Emmett,[3] William Franklin Pendergraft.[1] *[1]UNC Kidney Center, Univ of North Carolina, Chapel Hill, NC; [2]UNC School of Medicine, Chapel Hill, NC; [3]Nephrology, Baylor Univ Medical Center, Dallas, TX.*

Background: Acetylsalicylic acid (ASA, aspirin) is a common analgesic ingredient found in most household medicine cabinets in the US. It has been an important cause of intentional and unintentional poisonings since its discovery. Toxicity can result in severe dyselectrolytemias and cardiac, kidney and central nervous system dysfunction. The objectives of this study were to identify differences in intentional and unintentional poisonings, to identify features unique to cases resulting in death, and to review trends in extracorporeal management of poisonings.

Methods: We used the National Poison Data System to perform a retrospective analysis of reported cases of ASA exposures alone from January 2006 to December 2014. Outcomes were assessed by case intentionality and severity.

Results: There were 85,470 cases of ASA ingestions resulting in 165 deaths. Individuals more likely to experience major effects or death were older and male, and presented with more severe symptoms requiring higher levels of care. Patients who were intubated and mechanically ventilated were more likely to die.

Conclusions: Deaths due to ASA exposure are rare. Of 165 patients who died, only 27% received hemodialysis which continues to be underutilized in management of severe overdoses resulting in major effects or death. Analysis of geographical differences revealed a paucity of dialytic intervention in west south central region of the United States 21% as compared to other regions 27-43% in those with major effects or who died. The decreased utilization of dialysis did not correlate with fewer nephrologists. Standardized management recommendations are made through state or regional poison control centers, thus differences in hemodialysis utilization are unlikely due to differences in management but may be due to underrecognition of severe acetylsalicylic acid poisoning. These data suggest that these regions might benefit from increased public health efforts to limit poisonings and education about prompt management of severe poisoning.

Funding: NIDDK Support

PUB591

Fabry Disease Screening. Report of a Mexican Hemodialysis Center Raul Emanuel Zamora Hernandez, Leonardo Pazarin, Renato Parra, Javier Soto, Mario A. García, Ángel García Vásquez, Victor Hugo Luquin, Oscar César Martinez Garcia. *Nephrology, Inst Mexican of Security Social, Guadalajara, Jalisco, Mexico.*

Background: Fabry disease (FD) is secondary to a mutation of the gene encoding the enzyme acid α-galactosidase (α-GAL A) located on the chromosome X. This genetic disorder is cause of chronic kidney disease. The purpose of the study was to determine the prevalence of FD patients of a hemodialysis center in Mexico.

Methods: Men and women over 16 years diagnosed with CKD in hemodialysis (HD) were included. FD patients with previously diagnosed discarded. December 2015 to March 2016 after the patients signed consent on information, determination of enzyme activity of α-GAL A was performed using fluorescence in dried blood filter for men; for cases with α-GAL activity was decreased to levels determined GB3 molecular analysis also search for mutations in the gene encoding FD. For women only we made the search for gene mutations. Descriptive statistics were performed with absolute frequencies and inferential; SPSS version 22 was used.

Results: 324 patients were evaluated. A mutation in any woman diagnosed. 98 males had levels of enzyme activity of α-GAL A decreased, all GB3 with normal levels. 3 patients positive for gene sequencing GAL were detected. The median age of patients was positive 36 years with a median time of diagnosis of CKD 5 years. Prior to the diagnosis of FD in this study, recorded the cause of CKD was unknown in 2 patients, 1 secondary to diabetic nephropathy. The average level of α-GAL A and Lyso-Gb3 was 0.93 ± 1.01 mmol/l/h and 1.43 ± 0.19 ng/ml, respectively in patients with FD mutation. There were differences between patients with normal α-GAL A levels when compared with patients who had diminished α-GAL A with and without mutation levels.

Conclusions: This is the first report of the prevalence of FD in HD patients in Mexico. We found a prevalence of 0.9%, being higher than that reported in published studies (0.2-0.3%). Regarding the decline in activity levels of α-GAL A mutation found in patients without this series unrelated to any factor was found. These cutoff levels may not be standardized in our population, so it requires validation of this methodology in Mexican population.

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

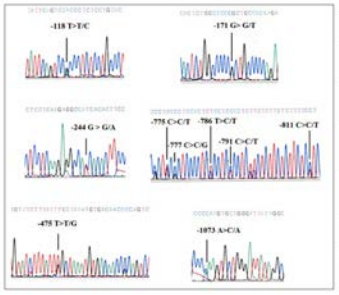
PUB592

Association between the Regulatory Polymorphisms of Organic Anion Transporter 1 (OAT1) and Chronic Kidney Disease Chiao-Yin Sun. *NTU, NTU, Taipei, Taiwan.*

Background: Organic anion transporter 1 (OAT1, SLC22A6) was a prototype of OATs, and played central roles in the renal secretion of organic anions. Accumulated evidences indicated that OAT1 had critical roles in kidney injury by mediating organic anionic toxins accumulation in kidney. This study aimed to analyze the 5' regulatory region polymorphisms (rSNP) in human OAT1, and possible associations with chronic kidney disease (CKD) clinically.

Methods: A case-control study including normal subjects and CKD patients with age and sex match was designed (n=162 for each group). *In vitro* studies were performed to define the possible mechanisms of rSNP of OAT1 on the OAT1 expression.

Results: Results of direct sequencing (-1 to -1196 region) showed that CKD patients had higher frequency of -475 rSNP (T>T/G) than normal subjects (14/162 *vs.* 2/162).



SNP Location	SNP	Normal control (n=162)	CKD (n=162)
-118	T>T/C	0	1
-171	G>G/T	0	1
-244	G>G/A	1	1
-475	T>T/G	2	14 *
-775	C>C/T	1	2
-777	C>C/G	0	2
-786	T>C/T	1	2
-791	C>C/T	1	2
-811	C>C/T	0	1
-1073	A>C/A	2	0

*: P= 0.0034, Fisher's exact test.

Luciferase activity assay resulted showed that OAT1 promoter with -475 rSNP had higher promoter efficiency than wild type significantly. ChIP and LC/MS/MS analysis results showed that therewere 26 proteins up-regulated and 74 proteins down-regulated by -475 mutant. Hepatoma-derived growth factor (HDGF), a transcription repressor, was noted among these down-regulated protein targets. The Southern-Western blot assay also revealed that -475 mutant had decreased HDGF binding than wild type. HDGF over expression significantly attenuated OAT1 expression in renal tubular cells.

Conclusions: Our study results suggested that OAT1 rSNP might associate with chronic kidney disease clinically. The renal tubular cells with -475 rSNP had increased OAT1 expression, which resulted in increasing organic anion toxin transportation into cells. Cellular accumulation of organic anion toxins caused cytotoxicity, and resulted in chronic kidney injury.

Funding: Government Support - Non-U.S.

PUB593

Serum LncRNA Expression Profile of Type IV Lupus Nephritis Patients

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Background: To evaluate the specificity of expression patterns of circulating long noncoding RNAs(LncRNAs) in class IV lupus nephritis (LN).

Methods: Total RNAs were purified from plasma of 3 different LN patients, 3 SLE patients, and 3 healthy controls. We screened lncRNAs expression profiles though the Arraystar Human lncRNA Microarray version 3.0.

Results: 8822 lncRNAs, 9886 mRNA were statistically significantly differentially expressed in LN plasma(fold-change>2),compared with the healthy control patients, 6403 lncRNAs , 4581 mRNAs were increased, 8407 lncRNAs , 6403 mRNAs were decreased in LN; 593 lncRNAs, 375 mRNAs were increased, 462lncRNAs, 200 mRNAs were decreased in SLE; compared with SLE, 6462 lncRNAs, 4523 mRNAs in LN were increased, 8969 lncRNAs, 6766 mRNAs were decreased in LN.Among healthy control, SLE and LN , 69 lncRNA, 73mRNAs were increased by degrees, 96 lncRNAs, 56 mRNAs were progressively reduced.

Conclusions: Gene ontology results suggested that the primary biological processes of these genes were involved in regulation of immune responses, cytokine production, cell differentiation, proliferation , apoptosis, cell cycle, cell adhesion, and metabolic process. lncRNA TCONS_00019182 locate in chr11p15.5, have significantly differentially expressed in LN vs N and SLE vs N, may play a role in development of SLE. lncRNA BDNF-AS1,lncRNA RP1-32B1.4 MYB were progressively increased in healthy control, SLE and LN group, and these abnormal expression of lncRNAs may be crucial in LN development and progression.

PUB594

Is It Time to Re-Visit Aluminum Binders in Our Elderly Patients?

Jack Rubin. *Los Alamitos, CA.*

Background: Patients ingest phosphate binders to mitigate metabolic bone and atherosclerotic disease. In the U.S. the most potent and least expensive agents (1) (Daugirdas JT et al, Semin Dial 2011 24(1):41-49) were marginalized due to concerns of aluminum toxicity. All the products substituted were more expensive. Was this a mistake? In patients with limited life expectancy, aggressive phosphorus control may lead to increased costs and pill burden without improvement in survival.

Methods: We identified our hemodialysis patients 65 and older treated at 7 units - 5 DaVita, 1 Fresenius and an independent. Daily phosphate binder pill burden was counted using their April 2016 medication list. Costs of medications were calculated using prices listed in the Medical Letter# 1483. We assumed phosphate binder potency to be as elaborated in ref 1. We estimated survival in "years to live" for each patient by age cohort as described in the USRDS 2013 report (Vol2, table 6.4). The potential decrease in pill burden using an aluminum binder was estimated by dividing the total number of pills standardized to the potency to calcium acetate by 1.5.

Results: There were 47 patients made up of 27 male and 20 female patients. The mean age (yrs) ± standard deviation (SD) was 75.7 ± 8.1, median 74. The mean calcium was 9.2 mg % ± SD 0.8, median 9.3. The mean phosphorus was 5.7 mg % ± (SD) 5.9, median 4.9. The mean albumin was 3.6 g % ± (SD) 0.5, median 3.7. The estimated survival was 3.6 years ± (SD) 0.9, median 3.8. There were 6 patients not using a phosphate binder. There were 18 patients exclusively using Phoslo (Calcium Acetate), 5 using Phoslo plus Renvela (Sevelamer), 15 exclusively Renvela, 1 exclusively using Fosrenol (Lanthanum carbonate), 2 exclusively Auryxa (Ferric citrate) and 1 using 3 agents including Auryxia. The mean pill burden among those taking binders was 7 ± (SD) 4, median 6 and the estimated cost/ day $31 ± (SD) 30, median 17. Aluminum hydroxide substitution was calculated to yield a pill burden of 5 ± (SD) 4, median 5, with the cost under $2 a day.

Conclusions: When treating patients with limited life expectancy wherein development of aluminum toxicity is a non issue, if phosphate control is deemed helpful, using aluminum -binders to decrease pill burden and costs seems reasonable.

PUB595

Hyperparathyroidism in Elderly Patients with Chronic Kidney Disease

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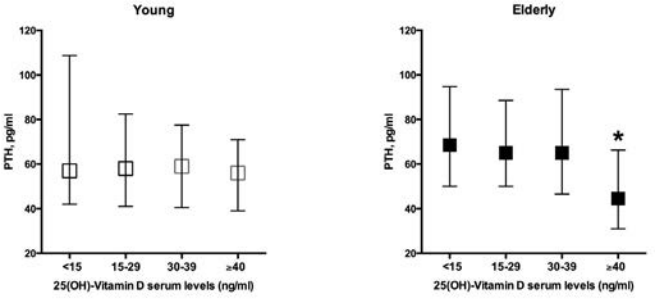
Background: As the world'spopulation ages, the incidence of chronic kidney disease (CKD) is growing. Since older patients mostly present decreased renal function, there is ongoing debate regarding whether high levels of PTH would be related to age or to renal function. Here, we have tested the hypothesis that secondary hyperparathyroidism is frequent among CKD elderly patients and that this population require higher levels of vitamin D than young patients.

Methods: This is across-sectional analysis of stage 3 CKD patients, in ambulatory patients from a Tertiary Academic Hospital. Elderly patients (age ≥ 65 years, N=518) were compared to a 1:1 sex- and eGFR-matched sample of young patients (age < 65 years), to assess demographic and biochemical differences collected from electronic charts.

Results: Elderly patients presented lower phosphate, and higher levels of serum calcium and parathyroid hormone (PTH). Elderly patients with hyperparathyroidism presented low levels of 25(OH)-Vitamin D.



Hyperparathyroidism (PTH > 65pg/ml) was 1.6 fold more common in elderly patients, which was dependent on age, eGFR, calcium, phosphate, low levels of 25(OH)-Vitamin D and furosemide use.

Conclusions: Elderly patients with CKD are at high risk of hyperparathyroidism, and low levels of vitamin D seem to contribute to this finding. This pattern is independent of renal function, which decreases with age. Further investigation is needed to establish an ideal cut-off value of vitamin D in elderly patients with CKD, and also to test if the supplementation of said vitamin can reduce the incidence of secondary hyperparathyroidism in this population.

PUB596

Longitudinal Association between Kidney Function and Mortality in the Very Old

Paula Ferreira Orlandi,[1] Clineu Mello Almada-Filho,[2] Maysa Seabra Cendoroglo,[2] Ricardo Sesso.[1] *[1]Nephrology Div, Univ Federal de São Paulo, São Paulo, São Paulo, Brazil; [2]Geriatrics and Gerontology Div, Univ Federal de São Paulo, São Paulo, São Paulo, Brazil.*

Background: The association of CKD, older age and mortality among individuals older than 80 years is not well defined. This study evaluates the association between kidney function and mortality in a prospective cohort of community-dwelling very old individuals according to different levels of eGFR and albuminuria.

Methods: A total of 231 independent individuals aged ≥80 yr from São Paulo, Brazil were recruited and followed by an average of 3.1 years. All underwent a hand-grip test, the 'mini-mental' cognitive test and laboratorial assessments, including standardized serum creatinine and urinary albumin to creatinine ratio (ACR). Main outcomes were ESRD and death. Creatinine based CKD-EPI equation was used to estimate eGFR.

Results: Participants were predominantly white (67%), female (70%), with median age of 84 years. At baseline, 45% had eGFR<60ml/min/1.73 m2, 12.9% had eGFR<45ml/ min/1.73m2 and 19.5% had ACR >30mg/g. None developed ESRD. Participants with eGFR<45ml/min/1.73m2 or ACR>30mg/g (n= 61) presented higher rates of death (8.5 deaths per 100 persons-year (p-yr), 95%CI: 5.2 to 13.9) comparing to those with eGFR higher than 45ml/min/1.73m2 and ACR lower than 30mg/g (4.2 deaths/100 p-yr, 95% CI: 2.8 to 6.4) (p=0.033). The eGFR threshold of 60ml/min/1.73m2 combined with ACR lower or greater than 30mg/g was not associated with different mortality rates: 4.6 deaths/100 p-yr

(95%CI: 2.7 to 7.8) in the higher eGFR/no albumin group vs. 5.9 deaths/100 pyr (95% CI: 3.9 to 8.7) (p=0.467). Adjusting for age, sex, dyslipidemia, handgrip and mini-mental test, the hazard ratio of death associated with a eGFR <45 ml/min/1.73m2 or ACR >30 mg/g was 2.16 (95% CI: 1.08 to 4.30, p=0.028).

Conclusions: For independent individuals older than 80 yr, a eGFR lower than 45 ml/min/1.73m2 or the presence of albuminuria (ACR>30 mg/g) yields a higher risk of death adjusting for demographic and functional parameters. In the very old, a lower eGFR threshold combined with albuminuria seems necessary to determine a higher risk of death compared to the younger population.

PUB597

Initiation of Dialysis in the Elderly Patient: A Survey of Nephrology Trainee Perceptions and Practices Emily Lu,[1] Manney Carrington Reid,[2] Ronald D. Adelman,[2] Mark S. Lachs,[2] Brian M. Eiss,[2] Clara Oromendia,[3] Phyllis August,[1] Jeffrey I. Silberzweig,[1] Nathaniel E. Berman.[1] *[1]Nephrology & Hypertension, Weill Cornell Medicine/New York Presbyterian Hospital (WC/NYPH); [2]Geriatrics & Palliative Medicine, WC/NYPH; [3]Biostatistics, Healthcare Policy & Research, WC/NYPH.*

Background: Delaying or not initiating dialysis may not impact mortality in elderly chronic kidney disease (CKD) patients, but Nephrologists have not reached consensus on key factors in making this decision. We assessed Nephrology fellows' perceptions and practices about dialysis initiation in CKD age >75 (ELD) versus general CKD (GEN) patients.

Methods: We surveyed New York City Nephrology fellows via a 30-item questionnaire. Responses were collected anonymously. Data were analyzed using paired T, Cohen's Kappa(K) and Chi-square tests (significant if <0.05).

Results: Respondents (n=40) were mostly female (65%), 1st year trainees (70%). 52% had prior geriatrics/palliative care training. Fellows cited functional status (85%) and patient preference (75%) as key factors in ELD. Many felt after dialysis initiation, functional status would decrease in ELD (63%) but increase in GEN (57%) (K=0.212, p<0.01), while mortality risk would not change in either group (45%) or increase more in GEN (30%) than ELD (15%) (K=0.471, p<0.01). Over half said quality of life in ELD would "sometimes" improve. Fellows would initiate dialysis at lower GFR values in ELD (12.7+/-4.2) versus GEN (14.2+/-5.3) (p=0.02), but their threshold serum creatinine (~7mg/dL) and albumin (~2.5mg/dL) levels were similar in ELD and GEN (p=0.27; p=0.08). 67% felt equally prepared to discuss initiating dialysis in ELD and GEN; only 39% were equally comfortable making the decision. 95% said dialysis initiation in ELD with severe, permanent dementia was likely indicated, but disagreed in ELD with good cognitive function and poor mobility/wheelchair-bound (51% "probably indicated," 26% "probably not indicated," 13% "do not know").

Conclusions: Nephrology fellows are aware that prognosis/outcomes may differ in ELD initiated on dialysis versus GEN, but these distinctions did not translate into shared practice patterns, suggesting need for further study of key criteria/factors affecting this decision.

PUB598

Factors Predicting Mortality in Hemodialysis Patients over 65 Years Old Sofia Correia, Josefina Lascasas, Jorge Malheiro, Isabel Fonseca, Andreia Campos, António Cabrita. *Nephrology, CHP, Porto.*

Background: Patients starting dialysis are increasingly elderly and with high morbidity and mortality. Knowledge of prognostic factors in end-stage renal disease patients has improved dialysis management and should be considered when starting renal replacement therapy(RRT).

Methods: The aim of this retrospective study was to analyze the outcomes of 208 incident dialysis patients over 65 years old. Possible predictors of mortality, included in multivariable Cox analysis were:age, sex, ischemic heart disease (IHD), congestive heart failure(CHF), cancer, chronic pulmonary disease, urgent dialysis, catheter as vascular access (CVC), serum albumin, peripheral vascular disease, smoking, dementia and performance status.

Results: Cohort mean age was 75 years.Survival rate at 6 and 36 months was 88 and 61%, the main cause of death was infection (46 and 55%), followed by cardiovascular(CV) disease (35 and 29%) and cancer. Kaplan-Meier analysis showed that age was significantly associated with mortality at the 36 (p=0.007) but not at 6 (p=0.3) months. Independent predictors of mortality detected by multivariable cox regression model considering all causes, infection or CV are represented below.

6-month mortality (all causes)			
	Hazard ratio	**95% Confidence interval**	**p Value**
CVC	2.67	1.09-6.53	0.031
Albumin<3.5	4.78	1.86-12.28	0.001
36-month (all causes)			
Age>75	2.40	1.36-4.26	0.003
CVC	2.41	1.32-4.40	0.004
IHD	2.07	1.16-3.68	0.013
CHF	2.69	1.46-4.95	0.002
Cancer	2.35	1.12-4.94	0.023
Albumin<3.5	2.41	1.39-4.19	0.002
6-month (infection)			
Age>75	6.7	1.23-36.6	0.028
Albumin<3.5	5.15	1.25-21.29	0.024
36-month (infection)			
Age>75	2.35	1.07-5.18	0.034
CVC	2.43	1.08-5.45	0.032
6-month (CV)			
IHD	6.83	1.08-43.13	0.041
Albumin<3.5	6.81	1.19-39.12	0.032
36-month (CV)			
Age>75	4.10	1.35-12.40	0.013
IHD	4.31	1.36-13.64	0.013

Conclusions: Predictors of mortality varied with time on RRT. Early mortality was associated with hypoalbuminemia and CVC, with age only being predictor of infection related early death. Our data may contribute in the decision making process about RRT indication and timing in the elderly.

PUB599

Anemia Is an Independent Risk for Reduced Physical Function in Elderly Patients with Chronic Kidney Disease Kaori Kohatsu, Masahiko Yazawa, Yasuhiro Taki, Yugo Shibagaki. *Dept of Internal Medicine, Div of Nephrology and Hypertension, St. Marianna Univ Hospital, Kawasaki, Japan.*

Background: Recently the prevalence of sarcopenia defined as reduced muscle strength and function has been increasing and considered as a risk for poor prognosis in elderly patients with chronic kidney disease (CKD). In this study, we investigated the risk factor of physical function in predialysis CKD.

Methods: We conducted a cross-sectional study based on data of 134 outpatients of our hospital who are older than 60 years and estimated glomerular filtration rate (eGFR) is under 60 ml/min/1.73m^2. Besides baseline laboratory data and muscle mass, physical and cognitive function were examined. We used skeletal mass index [SMI:muscle mass (kg) / Height (m^2)] using bioelectrical impedance analysis (BIA)to assess the muscle mass and 4-meter walking speed (4mWS) to assess physical function. We compared the variables in those with 4mWS than 0.8m/sec and in those with slower. Similarly, we compared the variables in those with high SMI(> 7.0kg/m^2 in male, > 5.8 kg/m^2 in female)and in those with lower. Student t or chi-squared test were used for comparison and logistic regression were used to conduct multivariate analysis.

Results: Mean age was 77±7.12 years old, 100 out of 134 patients were male. The average eGFR was 28 ±12 ml/min/1.73m^2, and 57 (42.5%) patients have diabetes mellitus. CKD stage G3 accounted for 44.7 %, G4 41.7 %, G5 12.6 %. Slower 4mWS was associated with older age, lower hemoglobin (Hb; 12.0 vs 10.35 g/dl), higher blood urea nitrogen, higher inorganic phosphorus, lower activated vitamin D, higher urinary albumin and protein. On the other hand, urinary albumin, inorganic phosphorus was correlated with SMI. Multivariate logistic regression analysis identified that Hb was the only independent risk factor for slower 4mWS (RR: 2.905, 95%CI: 1.177-7.170). When stratified by CKD stage, only age was associated with 4mWS in CKD stage G3, but in CKD stage 4-5, Hb was the only significant factor (RR:4.634, 95%CI:1.396-16.437).

Conclusions: Our study suggests that reduced physical function is associated with anemia. In elderly CKD patients. This association is especially strong in advanced CKD.

PUB600

The Clinicopathologic Characteristics of the Very Elderly Chinese Patients with Kidney Disease Dong Liu,[1,2] Xiyan Liao,[1,2] Yanna Dou,[1,2] Zhanzheng Zhao.[1,2] *[1]The Nephrology Center, The First Affiliated Hospital of Zhengzhou Univ; [2]Zhengzhou Univ Inst of Nephrology.*

Background: Data regarding renal disease with pathology in the very elderly(age≥80 years older) Chinese is extremely limited. The aim of this study was to examine clinicopathologic presentations in the very elderly patients who underwent renal biopsy and the complications.

Methods: From May 2012 to March 2016, the patients who underwent renal biopsy from our hospital were screened. The very elderly patients(age≥80 years old) were enrolled in the observed group. Their data were compared with the control group (patients aged 65-70 years old). over the same period. The clinical and pathological classifications of the two groups were analyzed.

Results: 33 patients (24 males, 82.7±1.9 years) were in the observed group and 100 patients (71 males, 67.0±1.5 years) were in the control group. Compared with the control group, the observed group showed lower eGFR (48.8±27.7 vs. 67.4±44.8 (mL/(min*1.73m^2), p<0.05). And there was no significant difference in blood pressure, serum albumin, proteinuria of 24 hours, hemoglobin, creatinine and lipids. Primary glomerulopathy was the most frequent pathologic diagnosis(63.64%),followed by secondary glomerulopathy(21.21%).In the patients of primary glomerulopathy with kidney disease, membranous nephropathy was the most frequent histological type (38.1%) and the ratio is lower than the control group (66.7%, p<0.05); followed by glomerular minimal change(33.33% vs. 16.7%, NS), focal segmental glomerulosclerosis(9.5% vs. 1.5%, NS), IgA nephropathy(9.5% vs. 3.0%, NS). Compared to the control group, the ratio of Secondary glomerulopathy was higher than the control group(21.2% vs. 9.1%, p<0.05), and the ratio of amyloid nephropathy was also higher (57.1% vs. 33.3%, p<0.05). And for the very elderly patients with nephrotic syndrome, minimal change disease was the most common histological type(33.33%),followed by membranous nephropathy(28.57%). And there was no side effects of perinephric hematoma, gross hematuria, arteriovenous fistula or other complications.

Conclusions: The pathology type of the very elderly patients with kidney disease is different with the elderly patients.

Funding: Government Support - Non-U.S.

PUB601

Prevalence, Predictors and Clinical Outcome of Frailty in an Elderly Pre-Dialysis Cohort Hatem Ali, Fatima Abdelaal, Jyoti B. Baharani. *Renal Dept, Heartlands Hospital, Heart of England NHS Trust, United Kingdom.*

Background: The relationship between frailty and CKD in elderly population has been recognised and some studies have demonstrated frailty as a predictor of adverse outcome especially among haemodialysis patients. However studies concentrating on frailty in pre-dialysis patients are limited. The aim of this study was to assess prevalence and predictors of frailty in an elderly pre-dialysis population.

Methods: A cross-observational study was conducted in which 108 patients aged 65 years or above with an eGFR of 25ml or less were included. Data including age, sex, FBC, CRP, ferritin, renal function, calcium, albumin, PTH and co-morbidities were collected at baseline and at 3 months interval for one year. Functional performance was assessed using Karnofsky scale. Frailty was assessed using combination of PRISMA questionnaire and Timed up and Go test (TUGT).Endpoints were death or start of dialysis at 1 year follow up.

Results: A frail group (n=61; male =31, female=30) and a non-frail group (n=47; male=20, female=27) were identified. Frailty was prevalent in 53.6% of selected population. Multiple regression analysis was used to compare different variables to frailty and chi squared test was used to compare the endpoints between the 2 groups. Functional performance was significantly lower in the frail group compared to non-frail (P=0.0001). No significant differences between the 2 groups in terms of age(P=0.8), sex(P=0.6), haemoglobin (P=0.2), white blood cells(P=0.4),CRP(P=0.9), Ferritin(P=0.4), Calcium(P=0.2), Albumin(P=0.3), change in creatinine (P=0.9), PTH(P=0.3) or number of co-morbidities(P=0.8)were seen. 6 patients chose conservative management in the frail group and 2 in non-frail group .Rate of death and start of dialysis were significantly higher in the frail group (death =10, dialysis =21) compared to non-frail group (death =2, dialysis =10) with P= 0.007.

Conclusions: Prevalence of frailty is high amongst elderly pre-dialysis patients. These patients have lower functional performance. Anemia, Calcium homeostasis and inflammatory markers do not predict frailty. Rate of death and start of dialysis is significantly higher in the frail group compared to non-frail group.

PUB602

Intrarenal Renin-Angiotensin System Activity Is Augmented after Initiation of Dialysis Naro Ohashi,[1] Shinsuke Isobe,[1] Sayaka Ishigaki,[1] Takayuki Tsuji,[1] Akihiko Kato,[2] Hideo Yasuda.[1] *[1]Internal Medicine 1, Hamamatsu Univ School of Medicine, Hamamatsu, Shizoka, Japan; [2]Blood Purification Unit, Hamamatsu Univ School of Medicine, Hamamatsu, Shizoka, Japan.*

Background: Circulating renin-angiotensin system (RAS) activation is maintained after renal function has deteriorated. The activation of the intrarenal RAS plays a critical role in the pathophysiology of chronic kidney disease (CKD), independent of the circulating RAS. However, it has not been clarified as to whether the intrarenal RAS is activated after renal function has declined.

Methods: We recruited 19 CKD patients (10 without dialysis and 9 with dialysis) who underwent a heminephrectomy. Circulating RAS was investigated before nephrectomy. The levels of intrarenal RAS components were investigated using radioimmunoassay and immunoblot analysis on samples from the removed kidney. Renal damage was evaluated by the extent of tubulointerstitial fibrosis.

Results: No significant differences in circulating RAS between non-dialysis and dialysis patients were found. However, intrarenal angiotensin II (AngII) and tubulointerstitial fibrosis in dialysis patients were significantly increased compared with non-dialysis patients (AngII (pg/g): non-dialysis; 1.84±0.23 vs. dialysis; 2.26±0.43; p=0.013 and tubulointerstitial fibrosis (%): non-dialysis; 32.1±20.5 vs. dialysis; 96.9±6.2; p<0.01). Prorenin and angiotensin converting enzyme (ACE) levels were dramatically decreased in accordance with renal dysfunction (prorenin: non-dialysis; 1.00±0.71 vs. dialysis; 0.18±0.13; p<0.01 and ACE: non-dialysis; 1.00±0.83 vs. dialysis; 0.013±0.035; p<0.01). AngII type 1 receptor (AT1R) expression was significantly increased in dialysis patients compared with non-dialysis patients (non-dialysis; 1.00±0.29 vs. dialysis; 1.50±0.22; p<0.01). In multiple linear regression analyses, there were significant positive and negative relationships between interstitial fibrosis and angiotensinogen (AGT) (β=0.45, p=0.042) and prorenin levels (β=-0.85, p=<0.01), respectively.

Conclusions: A decrease in prorenin and ACE levels and an increase in AGT, AngII and AT1R levels in the kidney occur in dialysis patients and these changes may be associated with intrarenal RAS activation and renal damage.

Funding: Government Support - Non-U.S.

PUB603

Platelet-Activating Factor Induces Transcription of Heparin-Binding Epidermal Growth Factor-Like Growth Factor through κB-binding Activity in MDCK Cells Keisuke Sugimoto,[1] Tomoki Miyazawa,[1] Kohei Miyazaki,[1] Takuji Enya,[1] Hidehiko Yanagida,[2] Mitsuru Okada,[1] Raymond C. Harris,[3] Tsukasa Takemura.[1] *[1]Pediatrics, Kindai Univ Faculty of Medicine, Osakasayama, Osaka, Japan; [2]Pediatrics, Kindai Sakai Hospital, Sakai, Osaka, Japan; [3]Nephrology & Hypertension, Vanderbilt Univ School of Medicine, Nashville, TN.*

Background: Various cytokines and growth factors promote cell proliferation and vascularization in glomerulonephritis. Platelet-activating factor (PAF) is a phospholipid activator/mediator which promotes cell growth as well as secretion of inflammatory cytokines and growth factors, stimulates secretion of heparin-binding epidermal growth factor-like growth factor (HB-EGF), which fosters tissue recovery from renal tubular disorder and some types of glomerulonephritis. Since the nuclear factor involved in HB-EGF production and secretion is unclear, we investigated involvement of PAF stimulation in HB-EGF gene expression and details concerning nuclear factors using MDCK II cells.

Methods: After cells were treated with PAF plus inhibitors and cell extracts were obtained, Northern blotting and electrophoretic mobility shift assays (EMSA) were performed.

Results: PAF enhanced HB-EGF mRNA expression in a dose- and stimulation-duration-dependent manner. PAF-induced NF-kB DNA-binding by NF-kB and HB-EGF mRNA expression were inhibited in the presence of PAF receptor antagonists (L-659989 or WEB 2086). HB-EGF-inducing DNA-binding activity of NF-kB was inhibited by L-659989 and WEB 2086, while mRNA expression and DNA-binding activity of NF-kB were inhibited dose-dependently by PDTC, an NF-kB inhibitor.

Conclusions: PAF is involved in gene control in MDCK cells, activating NF-kB binding, and strongly inducing HB-EGF gene expression.

PUB604

Evaluation of Factors Associated with Central Venous Catheter and Immature Arteriovenous Fistula Use at Initial Dialysis Ken J. Park,[1] Micah L. Thorp,[1] Eric S. Johnson,[2] Ning Smith.[2] *[1]Kaiser Permanente Northwest, Milwaukie, OR; [2]Kaiser Permanente Center for Health Research Northwest, Portland, OR.*

Background: Patients with end stage renal disease (ESRD) have high mortality rate thought related to use of central venous catheters (CVC) for initial dialysis. We sought to examine factors associated with CVC use and presence of immature fistula (AVF) at initial dialysis.

Methods: Retrospective cohort of incident hemodialysis patients from large HMO who started dialysis between 1/1/04 to 1/1/14 (n=918). Variables recorded included age, gender, race, diabetes, peripheral vascular disease, congestive heart failure, grade of proteinuria (divided into <0.2 gm, 0.2-0.5 gm, 0.5-3.5 gm, and >3.5 gm), length of predialysis nephrology care, number of hospitalizations predialysis over 2 year period, early start, history of acute kidney injury, and timing of AVF placement. Primary outcome was presence of CVC at initial dialysis. Secondary outcome was presence of immature AVF at initial dialysis. Multivariable logistic regression model was used to evaluate factors associated with outcome.

Results: At initial dialysis, AVF was used in 36% and CVC was used in 64% of the cohort. Higher odds of CVC use was associated with increased hospitalizations (OR 1.07) while increased length of predialysis care was associated with lower odds of CVC use (OR 0.98). Female gender was associated with higher odds (OR 1.7) of immature AVF at initial dialysis as was shorter time of AVF placement pre dialysis. Grade of proteinuria was associated with both CVC use and presence of immature AVF at initial dialysis. Patients with proteinuria between 0.5-3.5 gm had the lowest odds for starting dialysis with CVC or immature AVF.

Conclusions: Grade of proteinuria was associated with both use of CVC and presence of immature AVF at initial dialysis. Increased predialysis hospitalizations and shorter predialysis nephrology care was associated with increased odds of CVC use but not with presence of immature AVF. Female gender and delayed timing of AVF placement was associated with increased odds of immature AVF use.

PUB605

Haemodialysis Vascular Access: Current Practices amongst Indian Nephrologists Dinesh Bansal,[3] Eric S. Chemla,[2] Vijay K. Kher,[3] Vivekanand Jha,[1] Debasish Banerjee.[2] *[1]PGIMER Chandigarh; [2]St. Georges Hospital London; [3]MEDICITY Delhi.*

Background: Despite the growing number of patients receiving haemodialysis (HD) in India, little is known about vascular access practice. We document use and cost of different vascular accesses as reported by practicing Indian Nephrologists.

Methods: A web-link for a national online survey was emailed to 920 Indian nephrologists in Jan-Feb 2016. A total of 388 (42.1%) completed the survey; 98.5% of whom were responsible for managing dialysis patients, and 98% in hospitals.

Results: At start of RRT, 65% of the patients had HD, 8% PD, 10% kidney transplantation and 20% conservative care. 48% patients were self-paying, 26% had employee reimbursement and 23% had private insurance. According to 59% responders, >75% of patients started dialysis with uncuffed catheter. Less than a quarter patients started dialysis with fistula [82% nephrologists], graft [99% nephrologists] or tunnelled catheters [90% nephrologists]. Among the prevalent haemodialysis patients, over half of the patients were dialysing with fistula [79% nephrologists], rather than uncuffed catheters [15% nephrologists] or grafts [<1% nephrologists]. 16% reported at least one catheter related sepsis in more than ½ of patients. Placement of uncuffed catheters cost <US$150 in 92% facilities, whereas the cost of placing a tunnelled catheter was estimated at >$300 by about 46%. An AVF could be created for <$150 in the practice of 40% nephrologists, and <$300 in 90% centres. 35% of nephrologists reported grafts were not placed at their institute and the cost, where available, was >$500. 46% nephrologists had access to pre-dialysis clinics, <30% to vascular access program, <17% conducted regular audits of vascular access audits. Over 98% responders were willing to participate in projects related to vascular access or dialysis audits.

Conclusions: The survey demonstrates that most patients are self-paid, start HD with uncuffed temporary catheters, with poor access to predialysis care and vascular access team. There are more fistulae in prevalent patients. The survey highlights the suboptimal vascular access care in haemodialysis patients and the need for pre-dialysis clinics, vascular access services and registry audits.

PUB606

Cross-Sectional Study Demonstrating Arteriovenous Fistula Failure Is Not Associated with Age, Comorbidity, Previous Access or Anatomical Location Viyaasan Mahalingasivam, Amrita Ramnarine, Veronica Smith, Pamela Ayling, Abdelgalil Abdelrahman Ali. *Dept of Nephrology, Broomfield Hospital, Chelmsford, United Kingdom.*

Background: Arteriovenous fistula is the preferred form of vascular access for haemodialysis. However, it is associated with failure rates of up to 49% at two years. Several factors are considered to be responsible for this which may influence surgical access planning. The UK Renal Association published a guideline encouraging best-practice access formation.

Methods: We retrospectively audited 107 fistulae formed at our centre between April 2014 and October 2015. Data was collected for variables including age, sex and comorbidity, as well the anatomical location of the fistula and previous access. Data was analyzed to assess whether variables were associated with an increased risk of fistula failure.

Results: Our audit demonstrated a fistula failure rate of 17.7% with 14 out of 71 (19.7%) failed radiocephalic fistulae and 5 out of 35 (14.3%) failed brachiocephalic fistulae. There was no statistically significant correlation between sex, comorbidity, anatomical location, the use of dominant arm or previous access with an increase in fistula failure. Further subgroup analysis was performed after separating radiocephalic and brachiocephalic fistulae. Neither age nor comorbidity were shown to be associated to significantly increase the risk of failure in either of these groups.

Conclusions: Fistula failure rate at our centre is in keeping with rates documented in the literature. We demonstrated that factors such as sex, comorbidity and anatomical location are not associated with increased rate of fistula failure. We would therefore advocate that all patients destined for haemodialysis undergo fistula formation and unless there is contraindication on the basis of ultrasound evaluation, radiocephalic fistula formation should be attempted in the first instance. Prospective studies with longer follow-up are required to confirm these findings.

PUB607

Patency of Translumbar Percutaneous Catheter for Hemodialysis, Experience of Our Center: Instituto Mexicano del Seguro Social, Specialty Hospital "La Raza" Mexico City, Mexico Juan Carlos Garcia Yanez, Guillermo Jimenez. *Nefrologia, Inst Mexicano del Seguro social, Ciudad de Mexico, Mexico.*

Background: In Mexico we do not have reliable statistics which is the first access of patients starting renal replacement therapy. Over 80% of patients in the United States started hemodialysis therapy with a tunneled catheter (CT). (1) The renal replacement therapy based on Hemodialysis requires placement and maintenance of vascular access that allows adequate blood flow. It is ideal using an arteriovenous fistula (AVF) due to the low rate of complications that offers handling. However, many patients start (23-63%) or continue their treatment (23-41%) through tunneled central venous catheters and non-tunneled. Chronic use of these central catheters cause, as an inevitable consequence, vascular stenosis generation exhaustion, intraluminal thrombosis or associated infection. (3-4). In the following complication of superior vena cava stenosis. When the availability of vascular access for hemodialysis fistulas and vascular prostheses, catheters for hemodialysis, jugular, femoral and subclavian is exhausted, it is mandatory to find alternative vascular approach more complex, requiring more technical and advanced technological tools. the experience of our center in placing Translumbar vascular access (AVT) guided by fluoroscopy to a year in which the first catheter is reported.

Methods: A retrospective study on an electronic database of AVT placed in our hospital was performed survival analysis catheters placed one year of the first catheter was used. The procedure to patients with evidence angiography was performed by bilateral central venous obstruction.

Results: The total number of patients undergoing the procedure were 12, of which 8 were men and 4 were women, the average age is 41 years. The median survival of vascular access is 168.5 days. One patient died from causes attributable to the placement of vascular access.

Conclusions: According to these results the placement of percutaneous vascular access for hemodialysis guided by fluoroscopy through Translumbar approach has proven to be a good alternative for patients with depletion of common vascular access before any surgical intervention.

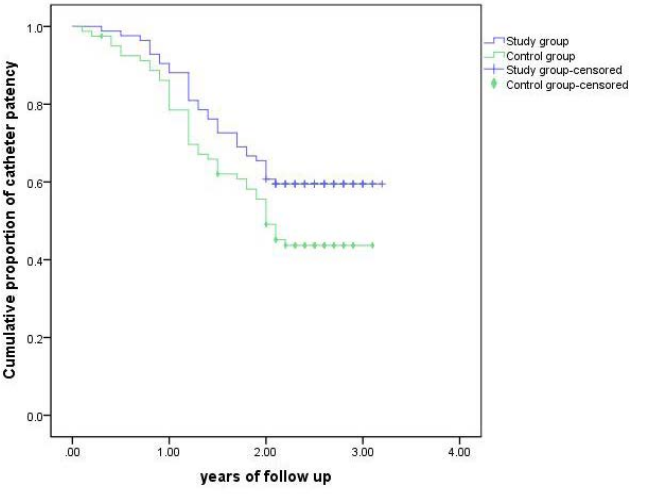
PUB608

A Modified De Novo Insertion Technique for Catheter Replacement in Elderly Hemodialysis Patients: A Single Clinic Retrospective Analysis Li Hua Wang,[1] Fang Wei,[2] Ai Li Jiang.[3] *[1]Dept of Kidney Disease and Blood Purification Centre, Inst of Urology & Key Laboratory of Tianjin, Tianjin, China; [2]Dept of Kidney Disease and Blood Purification Centre, Inst of Urology & Key Laboratory of Tianjin, Tianjin, China; [3]Dept of Kidney Disease and Blood Purification Centre, Inst of Urology & Key Laboratory of Tianjin, Tianjin, China.*

Background: For patients who rely on a Tunneled cuffed catheter, replacement or retrieval is typically necessary. We recently performed a novel de novo insertion technique for catheter replacement in our practice. As the technique has not yet been studied comprehensively, we performed a retrospective study to evaluate the safety and efficacy of de novo placed catheter without delay for catheter replacement in elderly hemodialysis patients.

Methods: A retrospective review of 164 elderly patients was conducted during a period of three years. There were 84 patients in study group, as well as an 80 patient control group, who had catheter replacement by guidewire exchange technique. Clinical follow-up data was collected.

Results: All catheters were placed successfully. The mean survival time per catheter was 641 catheter days (study group) and 485 catheter days (control group).



The primary patency rates of 30 days were 97.7% (study group) and 82.5% (control group), respectively. The episode of catheter infection was similar in both groups (p=0.586), but the case of catheter dysfunction was significantly lower in study group compared to control group (p=0.003).

Conclusions: The de novo placed catheter without delay technique for catheter replacement near the pre-existing venotomy site is safe, and boasts similar infectin rates with lower dysfunction rates compared to tunneled catheter insertion by guidewire exchange technique.

Funding: Private Foundation Support

PUB609

Effects of Vascular Access Care on Hospitalization Rates in Hemodialysis Patients Sheetal Chaudhuri,[1] Hao Han,[1] Marta Reviriego-Mendoza,[1] Sophia Rosen,[1] Karen G. Butler,[1] Jane Brzozowski,[1] John W. Larkin,[1] Elsie Koh,[2] Walead Latif,[2] Gregg Miller,[2] Melvin Rosenblatt,[2] Murat Sor,[2] Len A. Usvyat,[1] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Fresenius Vascular Care, Berwyn, PA.*

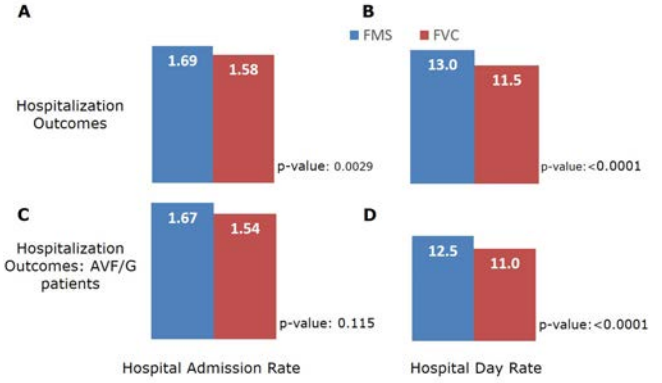
Background: Hemodialysis (HD) patients at Fresenius Medical Care North America (FMCNA) can choose to receive outpatient vascular access (VA) care from Fresenius Vascular Care facilities (FVC). We investigated if hospitalization rates in HD patients receiving VA care from FVC differ from those receiving VA care from other providers that were primarily hospital based or receiving no VA care at all.

Methods: We analyzed data from 4,691 HD patients treated by FVC during entire calendar year 2014. We matched 4,691 control patients exactly by concurrent year of FVC care, state of residence, gender, race, and access type. Also, propensity score matching was performed using the following variables: age, dialysis vintage, albumin, body mass index,

and Kt/v. We repeated the analysis for 4,376 FVC patients with a preexisting arteriovenous fistula/graft (AVF/AVG). Six month hospital admission and day rates per patient year were compared between study groups starting with 1/1/2015.

Results: As compared to controls, we found FVC patients exhibited: 1) 7% and 12% lower rates for hospital admissions and days after ≥1 FVC visit(s) respectively ($p<0.01$ both; Figure 1: A & B); 2) in FVC patients with a preexisting AVF/AVG, there was a nonsignificant reduction of 8% in the admission rate ($p=0.1$; Figure 1: C) 3) hospital days were 12% lower for FVC patients with an AVF/AVG ($p<0.001$; Figure 1: D).

Figure 1



Conclusions: The study results suggest that outpatient VA care at FVC is associated with lower hospitalization rates in HD patients, compared to controls. Further studies are needed to confirm these results.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB610

Outpatient Vascular Access Care Is Associated with Improved Access Sustainability in Hemodialysis Patients Marta Reviriego-Mendoza,[1] Sheetal Chaudhuri,[1] Hao Han,[1] Sophia Rosen,[1] Jane Brzozowski,[1] Karen G. Butler,[1] John W. Larkin,[1] Len A. Usvyat,[1] Walead Latif,[2] Elsie Koh,[2] Gregg Miller,[2] Melvin Rosenblatt,[2] Murat Sor,[2] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Fresenius Vascular Care, Berwyn, PA.*

Background: In hemodialysis (HD) patients, arteriovenous fistula/graft (AVF/AVG) complications are common, life threatening, and can require intermittent catheter exposure. Fresenius Medical Care North America (FMCNA) patients can choose to receive outpatient vascular access (VA) care with Fresenius Vascular Care (FVC). We investigated if FVC VA care is associated with improvements in AVF/AVG sustainability, as compared to matched patients receiving care mainly through hospital VA providers or no care at all.

Methods: Data from 4,691 FVC HD patients during 2014 was analyzed. Control patients (n=4,691) were matched exactly by year of FVC care, state, gender, race, and access type, and nearest neighbor propensity score matching for age, dialysis vintage, albumin, body mass index, and Kt/v. A sub-analysis was performed on 4,376 FVC patients with preexisting AVF/AVG. Duration of AVF/AVG use was calculated by percent of AVFs/AVGs with a stop date in 2015, as well as, via estimating average days from Jan 1, 2015 to the AVF/AVG stop date; an imposed stop date of Jan 14, 2016 was used if none was recorded.

Results: We observed that there were 3% fewer patients requiring AVF/AVG removal/abandonment when enrolled in FVC ($p<0.001$), and on average FVC patients used their AVF/AVG 2.33 days longer than controls ($p<0.001$).

Conclusions: Our analysis suggests that outpatient VA care at FVC is associated with improvements in AVF/AVG sustainability and decrease the need for removal/abandonment, as compared to patients receiving VA care from primarily hospital providers (or no access care). Long term investigations are warranted to confirm the findings.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB611

The Transluminal Interventional Therapy on Heterotopia of Internal Jugular Vein Cuffed Tunneled Catheter Xinxin Jiang,[1] Juan Jin.[2] *[1]Zhejiang Provincial People's Hospital, Dept of Nephrology, Hangzhou, China; [2]Zhejiang Provincial People's Hospital, Dept of Nephrology, Hangzhou, China.*

Background: To summarize the transluminal interventional therapy on heterotopia of internal jugular vein cuffed tunneled catheter.

Methods: We retrospectively analyzed the clinical data, transluminal interventional therapy and results of 11 patients who had heterotopia of internal jugular vein cuffed tunneled catheter.

Results: In 11 patients, 9 patients had no central vein stenosis. Two patients whose right internal jugular vein cuffed tunneled catheter in azygos vein were adjusted without smooth guide wire. Seven patients whose left internal jugular vein cuffed tunneled catheter in right brachiocephalic vein were adjusted by help of smooth guide wire. Two patients whose right internal jugular vein cuffed tunneled catheter pulled back to right internal jugular vein had right brachiocephalic vein stenosis. They had right internal jugular vein catheterization before. The cuffed tunneled catheter was placed after pertaneous transluminal angioplasty of right brachiocephalic vein stenosis. There were no severe complications in 11 patients.

Conclusions: The transluminal interventional therapy on heterotopia of internal jugular vein cuffed tunneled catheter was effective and safe.

PUB612

Analysis of the Effects on Two-Locus Puncture Thrombolytic Therapy for Artificial Vascular Thrombosis by Using Urokinase Hua Liu, Hongli Jiang, Kehui Shi, Quan He, Meng Wang, Jinhong Xue. *Blood Purification, The First Affiliated Hospital of Medical College of Xi'an Jiaotong Univ, Xi'an, Shaanxi, China.*

Background: To analyze the effect of two-locus puncture thrombolytic therapy for the treatment of arteriovenous graft (AVG) thrombosis by using urokinase.

Methods: Two positioning near arteriovenous anastomosis were selected as the centripenal puncture points, then the AVG was treated with 5000 U/ml urokinase, which was repeatedly pumped through the scalp needle, meanwhile the low molecular weight heparin could be used as an auxiliary drug. After treatment, the result of the patients with AVG ultrasound, blood routine examination, coagulation indicator, biochemical criterion were compared with that before treatment, and the adverse reactions were observed at the same time.

Results: Observation of AVG thrombosis (n = 30), AVG usage time was 6 months to 5 years, and thrombus formation time was 3 h to 48 h. Among 30 cases of patients with thrombolytic therapy by two-locus puncture, 26 cases obtained successful thrombolysis (86.7%), with average time of thrombolysis (4.74±2.31) h and average urokinase thrombolytic dosage (35.5±5.5 million)U. There was no significant difference in age, dialysis age and AVG usage time between success group and failure group. The success of the treatment was related to the thrombus formation time and the status of venous terminal flow ($P<0.05$). Before and after thrombolytic therapy, there was no significant difference in hemoglobin, platelet, prothrombin time (PT), thrombin time, activated partial thromboplastin time (APTT), fibrous protein, glutamic-pyruvic transaminase, serum albumin and total bilirubin. The slight rise of APTT and PT was considered as the application of low molecular weight heparin.

Conclusions: The two-locus puncture thrombolytic therapy using urokinase discontinuously and repeatedly has a high success rate, which can reduce the temporary catheter and surgical reconstruction as well as their associated complications. It has a high clinical value, as the ideal choice for the thrombolytic treatment of AVG thrombus formation, especially for basic-level hospitals.

PUB613

Financial Impact of Catheter Malfunction in Dialysis Anjali Acharya,[1,2] Samuel Mon-Wei Yu.[2] *[1]Nephrology, Jacobi Medical Center, Bronx, NY; [2]Medicine, Jacobi Medical Center, Bronx, NY.*

Background: Catheter malfunction and infection are major causes of morbidity and mortality in dialysis patients. It also is a financial burden on the health care system and adds to the costs of providing dialysis. Kidney Dialysis Outcomes Quality Initiative (KDOQI) guidelines, defines catheter malfunction as blood flow less than 300mL/min during the first 60 minutes of hemodialysis. Intrinsic thrombus and biofilm formation or fibrin sheath formation are major contributors to catheter malfunction. Mechanical disruption of the fibrin sheath is commonly used to tackle the problem, with variable success. If catheter malfunction cannot be successfully resolved by this method, exchange of catheter is commonly used with attendant cost and potential risk to the patient.

Methods: We describe 2 patients with ESRD on maintenance hemodialysis, in whom catheter dysfunction required catheter exchange (CEX) every 3-4 weeks over a 6 month period. A decision was made for weekly instillation of thrombolysitc (tPA) into each port which resolved the issue.

Results: Since the initiation of tPA use, neither of the two patients has required catheter exchange as opposed to every 3-4 week exchange earlier in their course. In addition to the obvious clinical benefit to the patients, the economic impact of this intervention with weekly instillation of tPA is huge. Considering a conservative estimate of $1,900 per CEX, the cost difference between the two options is tremendous. Please see table 1 below.

Patient	Number of Exchanges	Time period	Number of CEX-Post weekly tPA installation	Additional cost in the time period($)
#1	11	April 2015-Feb 2016	0	20,900
#2	6	Feb 2015 -Jan 2016	0	11,400

In addition, there is the disadvantage of loss of productivity secondary to time lost due to the procedures, which was not assessed in our evaluation.

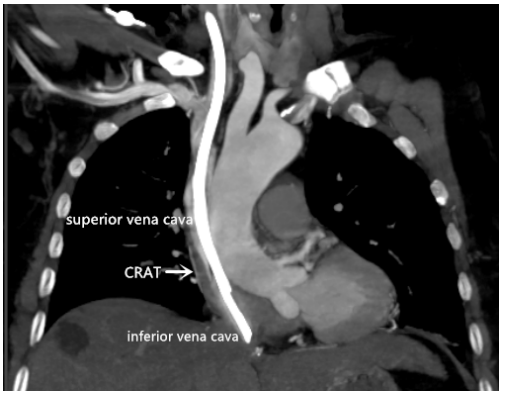
Conclusions: We recommend using weekly tPA protocol in patients with catheter dysfunction before proceeding with catheter exchange, especially in those individuals requiring frequent exchanges. This needs to be explored by further randomized controlled studies and more characterization of the patient population.

PUB614

Management of Right Atrial Thrombi Complicating Use of Tunneled-Cuffed Catheter in Hemodialysis Hongliu Yang,[1] Tianlei Cui,[2] Ping Fu.[3] *[1]Nephrology, West China Hospital, Sichuan Univ, Chengdu, China; [2]Nephrology, West China Hospital, Sichuan Univ, Chengdu, China; [3]Nephrology, West China Hospital, Sichuan Univ, Chengdu, China.*

Background: Catheter-related right atrial thrombosis (CRAT) is a rare as well as underreported but potentially life threating complication of tunneled-cuffed catheter (TCC) in hemodialysis (HD) patients. There is no current guideline for the management of this complication. Thus, we aimed to explore the optimal treatment of HD patients with CRAT and evaluate their outcomes.

Methods: We reviewed hospital records of 20 HD patients dialysed through TCC with diagnosis of CRAT from March 2013 to August 2015 and followed through 31 May 2016. Once CRAT was diagnosed, TCCs were exchanged over a guide-wire in situ with reposition of the catheter tip.



Immediately after insertion and at the end of each HD session, both ports of the catheters were locked with unfractioned heparin solution. Patients younger than 70 were administered with warfarin [target international normalized ratio (INR) 1.5-1.9]. Patients beyond the age of 70 were administered with dual antiplatelet therapy. All the patients maintained regular dialysis without thrombolysis or thrombectomy.

Results: During the follow up, 3 patients died: 2 of gastrointestinal massive hemorrhage and 1 of acute myocardial infarction. 4 patients suffered from pulmonary embolism but none of them died. There was no death directly attributed to CRAT. Resolution of CRAT was observed in 8 patients and size of thrombi decreased in 12 patients.

Conclusions: Regular maintenance HD through replaced catheter with reposition of catheter tip and oral anticoagulation may be a successful management in HD patients suffered from CRAT. Nevertheless, prospective studies are needed to identify risk factors of development and to determine the optimal management of CRAT in HD patients.

Funding: Government Support - Non-U.S.

PUB615

Superior Cava Vein Syndrome due to Catheter-Related Thrombosis Treated with Angiojet Rheolytic Thrombectomy Michele Ferrannini,[1] Alessia Centi,[1] Paola Tatangelo,[1] Eleonora Bernabei,[1] Gianluca Smedile,[3] Roberto Cancellieri,[2] Marco Guazzaroni,[2] Roberto Palumbo.[1] *[1]Nephrology and Dialysis Dept, St. Eugenio Hosp., Rome, Italy; [2]Radiology Dept, St. Eugenio Hosp., Rome, Italy; [3]Vascular Surgery Dept, St. Eugenio Hosp., Rome, Italy.*

Background: The rescue of the vascular access is mandatory in hemodialysis. In literature it is know the efficacy of mechanical thrombectomy devices for arteriovenous (AV) fistula thrombosis, but few data about the superior caval or brachiocefalic veins percutaneous declotting. We report 9 cases of superior cava vein syndrome (SCVS) due to central venous catheter-related central vein thrombosis, 8 of which treated with AngioJet™ rheolytic thrombectomy (RT).

Methods: 9 dialyzed patients (3 male) were admitted with SCVS. All of them had long term central venous catheter (lt-CVC), 7 in right and 2 in left Internal Jugular Vein (IGV). Angio-TC scan showed SCV complete obstruction in 1 case and subocclusions in 3 cases, 8 occlusions or subocclusions of brachiocefalic veins. In all cases the lt-CVCs were enveloped into the clot. In one case we desisted to treat because of the complete occlusion of SCV and brachiocefalic veins, the presence of efficient collateral circulations and the dangerous comorbidity of patient. In the others, we performed a double jugular and femoral vein approach: in the first we inserted a guide into lt-CVC just before its removal, in the second we inserted an other guide; this second one was captured by a goose-neck catheter introduced in jugular vein and then dragged out of jugular vein own, to obtaining a unique guide from femoral to jugular vein. From femoral approach, the RT was performed with Angiojet system.

Results: The initial technical success to recanalize cava and brachiocefalic vein was 100%. In all cases adjunctive procedures were performed: balloon angioplasty (8 patients, 12 vessels), and stent placement (3 patients, 6 stents). No pulmonary embolism occurred; in one case a hemotransfusion was performed for haemolysis; bradyarrhythmias and thoracic pain occurred in two cases. The patency at 6 months was 87.5% (7/8 patients).

Conclusions: In our experience AngioJet RT is an useful tool in cases of SCVS due to lt-CVC complications.

PUB616

A Timely Catheter Removal Program Decreases the Time to Hemodialysis Access Appointments and Catheter Exposure Time Michele Inglese,[1] Dugan Maddux,[1] Karen G. Butler,[1] Walead Latif,[2] Yue Jiao,[1] Sheetal Chaudhuri,[1] Hao Han,[1] Jerry Damon Jasperson,[1] Marta Reviriego-Mendoza,[1] John W. Larkin,[1] Len A. Usvyat,[1] Sandra Bodin,[1] Margaret Milfort,[1] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America; [2]Fresenius Vascular Care.*

Background: In hemodialysis (HD) patients (Pts), the transition from a central venous catheter (CVC) to a permanent dialysis vascular access (VA) reduces the risk of negative outcomes. We implemented a pilot Timely CVC Removal Program (TCRP) and analyzed its impacts on the time to VA appointments, VA surgery, CVC removal, and the total CVC exposure time.

Methods: We deployed the TCRP in 8 Fresenius Medical Care North America clinics, and analyzed VA-related data from HD Pts for the months of August 2015 and May 2016. TCRP includes care coordination between HD clinic staff, vascular access experts (VAEs), interventionalists, and surgeons. Weekly clinic reports were generated and included metrics for all CVC Pts regarding dates of VA appointments, VA surgery, and CVC removal, as well as, total CVC exposure time for each clinic and the Pt population. The "time to" metrics denoted in Figure 1 were utilized to investigate the areas of performance associated with the TCRP.

Results: Overall, we studied data from 144 Pts. After 10 months of the TCRP, we observed notably lower median time from the CVC insertion to the VAE appointment. Despite this, there was an increased time from the VAE appointment to the VA surgeon appointment. The median total CVC exposure time for the clinic and Pt population was found to be lower 10 months after implementation of the TCRP (Figure 1).

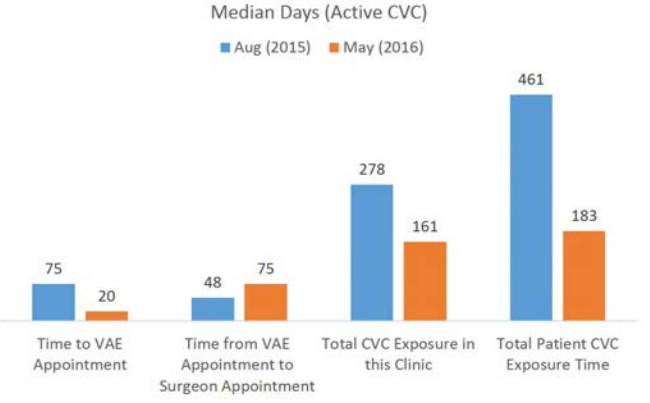


Figure 1

Conclusions: Our findings suggest the TCRP hastens placement of a permanent VA in HD Pts and reduces total CVC exposure. Tracking "time to" metrics was beneficial in identifying areas for improvement, which further enhancements of TCRP might be able to address.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB617

Health Economics of Arteriovenous Fistulas (AVFs) among U.S. Hemodialysis Patients Mae Thamer,[1] Timmy C. Lee,[2] Monnie Wasse,[3] Marc H. Glickman,[4] Qian Zhang,[1] Daniel Gottlieb,[5] Scott Toner,[5] Timothy A. Pflederer.[6] *[1]MTPPI; [2]Univ of Alabama; [3][lrm]Northwestern Univ; [4]RenalCare Associates; [5]Proteon Therapeutics Inc; [6]Sentara CarePlex Hospital.*

Background: Despite the importance of vascular access (VA) for adequate hemodialysis, few studies have examined real world costs related to long-term VA management. To address these gaps, we use national claims data to examine per patient VA costs over a 2.5 year period for different clinical outcomes of AVF use, patency and abandonment.

Methods: Observational *intention-to-treat* principle guides this retrospective study using Medicare claims to identify all incident elderly HD patients from 2010-2011 who underwent AVF creation. Using a multidisciplinary expert panel, we identified VA-related diagnostic, imaging, endovascular, surgical, infection, hospitalization and anesthesia codes to calculate total VA costs. The impact on costs of timing of AVF placement was also examined. Total per patient VA costs were calculated for all patients and for subsets based on AVF outcomes prior to use or during the 1st year after AVF creation: 1) no interventions; 2) any intervention to achieve or maintain patency; and 3) AVF abandonment. Patency loss and AVF use were defined using procedure, diagnosis and V (vascular) codes which indicate VA type in use each month. **Results:** Preliminary results suggest total Medicare costs for VA management were substantial and account for a significant portion of reported ESRD expenditures. Results also suggest that AVF patients with no loss of patency in year 1 have significantly lower 2.5 year VA costs compared to patients with loss of primary or secondary patency in year 1 (*final results will be presented at ASN for **Table 1***).

Table 1. VA-related per patient per year (PPPY) costs for incident Medicare HD patients in 2.5 years following AVF creation.

AVF cohorts	*No Intervention*		*Intervention*		*Abandonment*
	Unassisted use	**Primary unassisted patency**	**Assisted Use**	**Loss of primary patency**	**Loss of secondary patency**
	mean, median, 25th and 75th percentile costs				

Conclusions: Improvements in processes of care and technologies to enhance AVF use and patency should result in less morbidity with the potential for significant cost-savings.

Funding: Pharmaceutical Company Support - Proteon Therapeutics Inc

PUB618

The Effect of Extended Antibiotic Prophylaxis on Infection in Vascular Access Intervention Therapy Mariko Ichijo,[1] Namiko Kobayashi,[1] Yohei Kono,[1] Ayumu Nomizu,[1] Yoshitatsu Ohara,[1] Yutaro Mori,[1] Shotaro Naito,[2] Takayuki Toda,[1] Noriaki Matsui.[1] *[1]Nephrology, Tsuchiura Kyodo General Hospital, Tuchiura, Ibaraki, Japan; [2]Nephrology, Tokyo Medical and Dental Univ, Tokyo, Japan.*

Background: Vascular access is the lifeline for hemodialysis patients, and Vascular Access Intervention Therapy (VAIVT) has improved the quality of life of such patients. However, the efficacy of extended antibiotic prophylaxis of bloodstream infection among patients treated with VAIVT remains unknown.

Methods: We performed a retrospective study. To clarify whether antibiotic prophylaxis is effective or not, we reviewed the records of 487 procedures of VAIVT between 2011 and 2015 performed in our hospital. Selection of patient who required VAIVT received prophylaxis was at discretion of the doctor attending the case. We evaluated the association between prophylaxis and incidence of infection by logistic regression analysis.

Results: The 487 procedures of VAIVT (419 stenosis cases, 68 thrombosis cases) involved 260 men (53.5%) and 227 women (46.5%), with a mean (SD) age of 70.2 (11.0) years. 220 patients received prophylaxis, and 267 patients did not. The duration of the VAIVT procedure (34 vs. 31, p = 0.28), the types of VA (arteriovenous fistula 211 vs. 258, p = 0.675), complication of diabetes (81 vs. 109, p = 0.367), between the two groups were not significantly different. In logistic regression analysis, the incidence of infection after VAIVT, defined as hyperthermia (greater than 101 degrees F), was not significantly different between both groups (1 case in prophylaxis group, none in non-prophylaxis groups, odds ratio 1.005 [95% CI 0.996 – 1.014]).

Conclusions: In VAIVT, antibiotic prophylaxis does not influence rates of infection. Future prospective, randomized studies with a larger number of catheters are needed to confirm or refute these results.

PUB619

Gender Differences in Catheter Use over Hemodialysis Vintage: Results from the Monitoring Dialysis Outcomes Initiative (MONDO) Alice Topping,[1] Xiaoling Ye,[1] Jochen G. Raimann,[1] Frank van der Sande,[4] Adrian M. Guinsburg,[2] Bernard Canaud,[2] Xiaoqi Xu,[6] Albert J. Power,[3] Neill D. Duncan,[3] Jeroen Kooman,[4] Len A. Usvyat,[5] Peter Kotanko,[1,8] Maria E. Ferris.[7] *[1]Renal Research Inst, New York, NY; [2]Fresenius Medical Care EMEALA, Bad Homburg, Germany; [3]Imperial College, London, United Kingdom; [4]Maastricht Univ, Netherlands; [5]Fresenius Medical Care North America, Waltham, MA; [6]Fresenius Medical Care Asia Pacific, Hong Kong; [7]Univ of North Carolina Chapel Hill; [8]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Vascular access (VA) is an essential component to successful and efficient hemodialysis (HD). Catheter use is associated with higher mortality rates in HD patients (Xue et al, 2003). Previous research has highlighted differences in VA type by gender (Marcus et al, 2007), but have not compared catheter use over HD vintage across regions (rgs).

Methods: Prevalent patients(pts) in MONDO from 2006-2010 were analyzed for differences in catheter use by gender at HD initiation, and at one yr and three yr vintage. For pts beginning HD with a catheter, time to arteriovenous fistula (AVF) use was compared by gender overall and for each rg using the Wilcoxon-Mann-Whitney (WMW) test.

Results: There were 62,431 pts at baseline, 48,618 at one yr and 9,098 at three yr vintage eligible for analysis. Overall 59.2% of males (M) and 63% of females (F) initiated HD with a catheter ($p<0.0001$). At one yr, 28.3% of M and 34.6% of F ($p<0.0001$) and at three yrs, 21.3% of M and 28.5% of F ($p<0.0001$) had catheters. Statistically significant differences were found in all rgs at baseline and at one yr vintage; Europe and Asia Pacific rgs had the largest gender gaps in catheter use. The median time to AVF use for incident pts with catheter was 104 days for F and 91 days for M. Results from the WMW test show differences in time to AVF use for M compared to F overall ($p<0.0001$), and in all rgs except South America where data were scarce.

Conclusions: We found gender differences in catheter use in all rgs, with F having higher catheter rates. While we observe some variation in size of effect, efforts to reduce catheter rates should take gender inequalities into consideration.

Funding: Pharmaceutical Company Support - Fresenius Medical Care

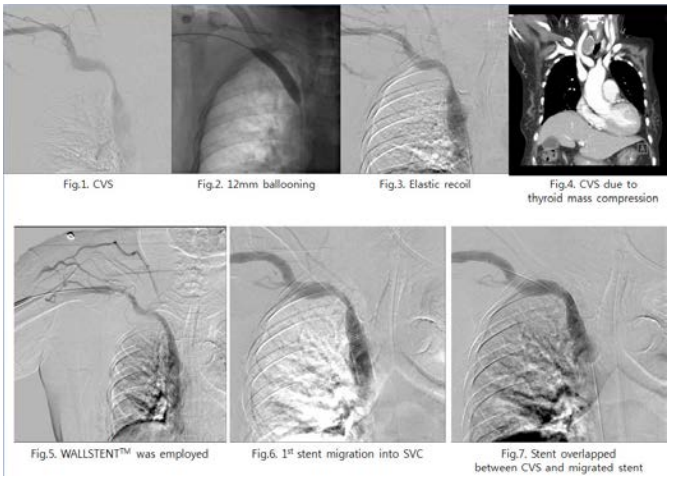
PUB620

Overlapping of Second Stent Placement between Previous Migrated Stent and Elastic Recoil of Rt. Brachiocephalic Vein Stenosis due to Rt. Thyroid Mass: Case Report Jin Ho Lee, Heeryong Lee, Joon Seok Oh, Dongyeol Lee, Yong Ki Park, Yong Hun Sin, Seong Min Kim, Joong Kyung Kim. *Internal Medicine, Bongseng Memorial Hospital, Busan, Dong-Gu, Korea.*

Background: Central vein stenosis(CVS) is commonly associated with arteriovenous fistula for hemodialysis. CVS associated with morbidity, hospitalization and morbidity. Endovascular intervention should be considered to management of CVS, such as balloon angioplasty, stent deployment. Especially, stenting at refractory CVS was choice of treatment. We announced a case that overlapping another stent between previous migrated stent and refractory CVS compressed by thyroid mass.

Methods: 75-year-old woman with advanced DM nephropathy on hemodialysis. Rt. Brachiocephalic AVF op was done at Jan, 2016. Rt. arm swelling and delayed hemostasis was occurred at POD 60days. We decided percutaneous transluminal angioplasty(PTA). Significant Rt. brachiocephalic vein(>80%) stenosis was presented. Despite of 12mm balloon angioplasty(MUSTANG™), stenosis(70~80%) was remained(Fig.1, Fig.2, Fig.3). To find reason of elastic recoil, enhanced chest CT was performed. CT shows Rt. brachiocephalic vein was compressed by thyroid mass(3.4 X 2.7mm), Rt. brachiocephalic artery and 1st rib(Fig.4). Then, stent(WALLSTENT™, 14mm X 4cm) was placed at stenotic lesion because of high radial resistive strength(Fig.5). Immediate technical success was achieved. But, ipsilateral arm edema was recurred 3days after intervention. In central venography, stent was migrated into SVC and Rt. brachiocephalic vein stenosis was remained(Fig.6). Stent(EPIC™, 14mm X 4cm) was overlapped between CVS and migrated stent(Fig.7). Arm swelling was disappeared.

Results:



Conclusions: Stent deployment was one of treatment choice of CVS. But, stent migration often occurred and could be a risk to patient. Our patient was treated by overlapping 2nd stent placement between primary CVS and migrated 1st stent tip.

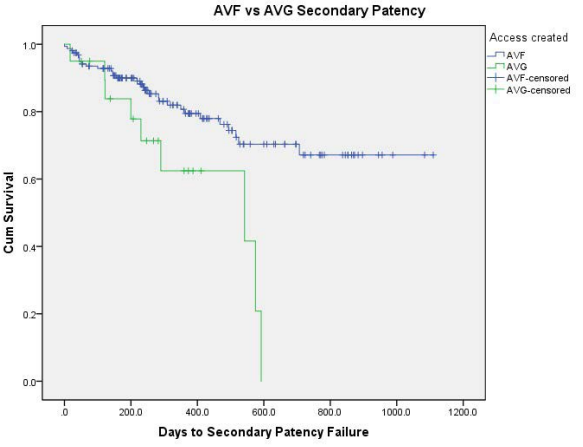
PUB621

Arteriovenous Fistulae Provides Superior Patency and Survival over Arteriovenous Graft Hareeshan Nandakoban, Ananthakrishnapuram N. Aravindan, Govind Surya Narayanan, Stephen T. Spicer, Imelda De Guzman, Jeffrey Wong. *Renal Unit, Liverpool Hospital, Sydney, NSW, Australia.*

Background: Review of permanent hemodialysis (HD) access creation in our institution and their outcomes. Arteriovenous fistulae (AVF) and arteriovenous graft (AVG) primary and secondary patency as well as overall vascular access survival was analysed over the study period.

Methods: A retrospective review of vascular access database over a 3 year period with additional data obtained from the electronic medical record (*e*MR). Student's T-test, Chi-square test, ANOVA and Kaplan-Meier survival analyses were used and significance for $p<0.05$.

Results: From 1st April 2013- 31st March 2016, 177 permanent vascular accesses were created in 159 unique patients: 157 AVFs and 20 AVGs. Patient characteristics: average age 58 yrs; males 67%; diabetes 63%; coronary disease 34%; pre-op tunnelled catheter (TVC) use (52%); and seen in pre-dialysis clinic 58%. Pre-dialysis review was associated with reduced TVC use 8% vs. 45%. 60% of all access worked, 14% failed to work despite intervention with no difference between AVF & AVG, and 26% were not used by study end. Primary patency of AVF was superior to AVG with a median period of 279 vs. 135 days *($p<0.05$)*. Gender, surgeon or access location had no influence. Overall secondary patency at 2 years was 68%. AVFs had superior mean survival to AVGs of 849 vs. 422 days *($p<0.05$)*. The presence of: diabetes, coronary disease, access location or side, or operating surgeon did affect secondary patency rates. Assisted access use within 3 months was 14%, and 41% at 6 months.



Conclusions: AVF were the predominant vascular access created. AVF have a superior primary and secondary patency rate to AVG that is not affected by the patient comorbidities, location of access placement or surgeon. Pre-dialysis clinic has a positive impact in reducing patient TVC exposure. There were low rates of early use of vascular access.

PUB622

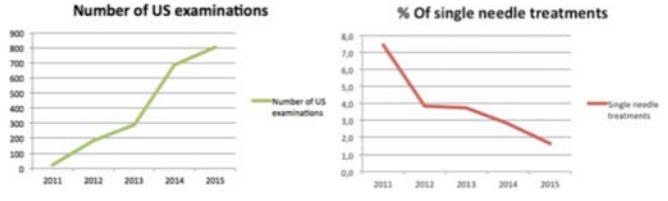
Ultrasound and ColorDoppler in Hemodialysis Patients for the best Management of Vascular Access Federico Nalesso, Sara Samoni, Alessandra Brendolan, Claudio Ronco. *IRRIV - International Renal Research Inst Vicenza, IRRIV - San Bortolo Hospital, Vicenza, Italy.*

Background: Vascular access is a key determinant in adeguate extracorporeal purification in CKD patients. Artero-Venous Fistula and Graft are subject to complications such as ematoma, blood effusions and other injuries during the cannulation procedures. These complications may be avoided by the use of Ultrasound and Color Doppler during the cannulations and the pre-cannulation mapping of the access. In case of complications in the vascular access a single needle is frequently required to obtain the extracorporeal circulation despite of reducing the KT/V and the total ultrafiltration.

Methods: We performed a complete Ultrasound and Color Doppler evaluation in all hemodialysis patients before the first access use. In case of difficult procedures of vascular access cannulation and after the report of abnormalities at the physical examination the ultrasound guide cannulation was performed. In our center we started to use this protocol of US analysis from the second part of 2012. (Figure 1)

Results: During our period of observation the total amount of complications drastically decreased progressively as attested by the total percentage of single needle use compared to the total amount of treatments performed

YEAR	SINGLE NEEDLE TREATMENTS % OF TOTAL HD TREATMENTS	TOTAL US-CD EXAMINATIONS
2011	7,5	20
2012	3,9	186
2013	3,7	290
2014	2,8	686
2015	1,6	802



Conclusions: Ultrasound and Color Doppler is a useful technique that can be performed at bedside reducing the complication related to the cannulations of vascular access. The vascular mapping before the first cannulation allow to determine the best sites to put the needles avoiding injuries and complications that can require the single needle use.

PUB623

Hemodialysis's Catheter Blood Stream Infection: A Great Challenge and Feasible Preventive Strategy in a Public General Hospital Katia V. Carvalho,[1] Augusto C. Haddad,[2] Thais Nemoto Matsui,[1] Fabiana Dias Carneiro,[1] Bento C. Santos,[1] Reginete C. Costa.[2] *[1]Centro de Diálise Einstein, Hospital Israelita Albert Einstein, São Paulo, São Paulo, Brazil; [2]Nefrologia, Hospital Municipa Moysés Deutsch, São Paulo, São Paulo, Brazil; [3]Centro de Diálise Einstein, Hospital Israelita Albert Einstein, São Paulo, São Paulo, Brazil; [4]Centro de Diálise Einstein, Hospital Israelita Albert Einstein, São Paulo, São Paulo, Brazil.*

Background: Blood stream infection catheter related (BSIRC) leads to an increased morbimortality in hemodialysis (HD) patients, associated with sepsis, cardiovascular complications, prolonged hospitalization, high cost, overload in health system and worse survival.The aim was to evaluate a program to prevent BSIRC(PP-BSIRS) in the Intensive Care Unit (ICU) and wards(WD)in a general public hospital at a low income area of São Paulo, where a high rate of ICU nursing staff turnover (45% in 2015) is a constant challenge.

Methods: A cross-sectional study with patients treated with HD between 2014 and 2015 was evaluated. Data from 2014 before and 2015 after PP-BSIRC implementation in January 2015 was analyzed. PP-BSIRC included: Daily patient bath with chlorhexidine 2%, double lumen and best site of catheter insertion, continuing education of nurses, 5 moments of hand hygine protocol, quality and safety audit of curative and interaction with hospital Infection Control Service. BSIRC diagnosis was defined according to CDC 2015 criteria.

Results: In 2014, 1099 HD were performed and 1245 in 2015.The mean age was 58.8 ± 15.4 yo, 62% men, 46% diabetes and 20% with previous diagnosis of CKD V. Patients in both periods did not differ according to gender, age, prevalence of diabetes or vascular access. Of note, in 2015, HD were significantly more incident in ICU patients, therefore with a higher frequency of vascular access manipulation. HD Patients after the PP-ICS had longer time duration of catheter (11.9 ±18.5 *vs* 10.2± 12.5 days**; p <0.001**) and lower frequency of BSIRC (0% vs.14%; **p <0.001**).

Conclusions: Albeit structural difficulties at public hospital in a low income area, target protocols, continuing education and multidisciplinary approach improved catheter survival and decreased incidence of BSIRC.

PUB624

Characteristics of High-Dose Hemodialysis Patients: A Systematic Review Dilip Makhija, Aseel Hatim Bin Sawad, J. Ken Leypoldt, Angelito A. Bernardo. *Baxter Healthcare Corporation, Deerfield, IL.*

Background: Conventional hemodialysis (CHD) (i.e., 4-hour session 3 times/week) is the most common dialysis regimen. High-dose hemodialysis (high-dose HD) (i.e., more frequent and/or longer sessions), has been associated with a 30-45% improved survival rate vs. CHD in large observational studies. Patients on high-dose HD have better blood pressure control, improved quality of life and decreased left ventricular mass. However, the characteristics of patients who may benefit from high-dose HD have not been identified. This systematic review aims to summarize high-dose HD patient characteristics.

Methods: Medline and Embase were used to identify randomized controlled and observational clinical studies evaluating the high-dose HD regimen (i.e., no 2-day gap without dialysis; short-daily: ≥5 sessions of ≥2 hours/week, nocturnal: ≥3.5 sessions of ≥6 hours/week; standard Kt/V ≥3.0). To be included, a study had to have at least 20 patients and published in English language between January 2000 and March 2016. Two independent reviewers selected studies and data extraction was performed.

Results: After screening 91 full text articles (total 3,652 citations), only 13 met the eligibility criteria (2,907 hemodialysis patients - 1,088 on high-dose HD: 509 at home; 579 in-center). High-dose HD patients were generally young (mean age range: 43±2 to 58±18.9 years), mostly men (60%-72%), Caucasian (34%-88%), and mean BMI ranging from 21.5±2.9 to 29.9±14.85 kg/m^2. The most commonly reported causes of ESRD were diabetes (6%-77%), diabetic neuropathy (27%-36%), glomerulonephritis (12%-41%), and polycystic kidney disease (4%-22%). Only 1 study reported a Charlson Comorbidity Index Score (CCI) of 3.2 ± 0.4 for high-dose HD patients. When a short daily regimen was used, patients performed 6-7 sessions/week of 1.5-3 hours/session. For nocturnal dialysis regimen, patients performed 5-6 sessions/week of 6-8 hours/session. The standard Kt/V ranged from 3.24 to 5.86 per week.

Conclusions: Based on the literature, the target patients for a high-dose HD regimen are generally young Caucasian males. In addition, underlying causes for ESRD like polycystic kidney disease are more frequent in high-dose HD patients compared to CHD.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corporation

PUB625

Hypertension (HTN) in High School Students (stu): Genetic and Environmental Factors: The Empowerment of Dietary Salt Intake Roberto Bigazzi,[1] Stefano Bianchi,[1] Salvatore Lenti,[3] Roberto Burano,[3] Giada Santini,[1] Francesca Nistri,[1] Chiara Bilanceri,[1] Elisa Poderelli,[1] Silvia Campatelli,[1] Vito M. Campese.[2] *[1]Nephrology, ASLNORDOVEST Toscana, Livorno, Italy; [2]Medici per San Ciro, Grottagie, Italy; [3]Nephrology, USC, Los Angeles.*

Background: Due to the epidemic of obesity, the prevalence of HTN is increasing among children. Identification of pre-HNT at this age is important to implement lifestyle interventions. The aim of this study is to evaluate 3,000 high school stu in 3 regions of Italy (IT); in the north, in the center and in the south to: 1. Determine the prevalence of obesity

and HTN; 2. Perform genetic analyses to determine a link between specific polymorphisms and/or mutations of the Adducin genes and HTN; 3. Explore whether urine Na/K excretion and markers of inflammation and oxidative stress are linked to HTN and CV risk in stu with selected genotypes.

Methods: So far, we have enrolled 753 stu (394 in central and 359 in south IT). Here we present preliminary data referred to the first year of the study focousing on the relationship of dietary Na and K intake with HTN.

Results: The average age was 16.4±1.4 yr;42.7% M and 49.7% F. In central IT, the average BMI was 21.8±0.5; waist circumference 75.5±9.6; 8,2% of stu were overweight and 2.3% obese. Average urinary sodium (UNa) excretion was 83.4±2.5 and potassium (UK) was 36.6±10mEq/g creatinine. In southern IT, the average BMI was 22.5±0.6;19% of stu were overweight and 6 % obese (P<0.01 compared with central IT). The average UNa was 144±5.5 and UK excretion 44±8,3mEq/g creatinine. (P< 0.01 compared with central IT). Among parents of overweight or obese stu, 85.4 % were obese or overweight. Of interest, UNa of stu from hypertensive parents was lower (p<0.02) than those from normotensive patents.

Conclusions: Our data indicate that: 1) overweight and obesity are more common among children from south than central IT; 2) salt intake is higher in south than central IT; 3) UK is low both in central and south IT suggesting that adherence to a Mediterranean diet is currently not applied. 4) The surprising reduced dietary salt intake among children from hypertensive parents may reflect a tendency of families with an hypertensive patients to reduce salt intake.

Funding: Government Support - Non-U.S.

PUB626

Renal-Artery Stenosis and Renal Impairment after Renal Denervation

Birgit Doris Bader,[1] Stephan H. Duda,[2] Beata Lux,[2] Christiane M. Erley.[1] *[1]Dept of Medicine 2, St. Joseph Hospital Berlin-Tempelhof, Berlin, Germany; [2]Ihre Radiologen, Center for Diagnostic and Minimally Invasive Therapy, Berlin, Germany.*

Background: Descriptions of renovascular complications after renal denervation (RDN) are rare. We report the case of a 70 yr. old female patient who has developed a significant renal-artery stenosis 3.5 yr. after RDN.

Methods: Our patient had several clinical admissions because of treatment-resistant hypertension between 2009 and 2012. So she was selected for RDN according to the guidelines in September 2012. Blood pressure could not be controlled (RR 160-220/95-115 mmHg) under antihypertensive therapy including beta blocker, AT2 receptor antagonist, calcium channel blocker, moxonidine and loop diuretic. The CT- and conventional angiography showed no stenosis of the renal arteries. The renal function was normal (S-creatinine 0.99 mg/dL). in October 2012 RDN was performed. Blood pressure before intervention was measured to be 220/115, after intervention 130/70 mmHg. In the following time the antihypertensives could be reduced. There were no more clinical admissions due to hypertension.

Results: In January 2016 the patient was admitted to our hospital with a decline of renal function (S-creatinine 2.18 mg/dL) and hypertensive blood pressure levels (RR 170/80 mmHg). Over the last two years a raise in blood pressure was observed and her family doctor has increased the antihypertensives again. We performed a MR-angiograpy of the renal arteries and detected a 90% stenosis of the left renal artery with reduced perfusion of the renal cortex. Due to these findings a percutaneous angioplasty was performed. After sequential dilatations of both lobar arteries there was a rapid development of clot or possibly clot dislodgement that needed arterial thrombolysis with 10 mg of rtPA. Afterwards blood pressure was easier to control but the patients still needs up to seven antihypertensives. The renal function of the patient didn't changed (S-creatinine 2.16 mg/dL).

Conclusions: The complication rate associated with RDN is still considered to be rare. However, we recommend imaging follow-up after RDN, especially in patients showing rising blood pressure levels or worsening of renal function after initially successful RDN.

PUB627

Race, Obesity, and the Renin-Angiotensin System Predict Treatment Response in Pediatric Essential Hypertension

Andrew M. South,[1,2] Lester M. Arguelles,[4] Gal Finer,[3] Craig B. Langman.[3] *[1]Pediatric Nephrology, Wake Forest School of Medicine, Winston Salem, NC; [2]Hypertension and Vascular Research Center, Wake Forest School of Medicine, Winston Salem, NC; [3]Pediatric Kidney Diseases, Feinberg School of Medicine, Northwestern Univ, Chicago, IL; [4]Public Health, Univ of Illinois at Chicago, Chicago, IL.*

Background: Pediatric essential hypertension (peHTN) is increasingly recognized but the effect of patient characteristics on outcomes is not well described. We hypothesized patient parameters such as race, body habitus, first-line medication choice, and the renin-angiotensin system (RAS) influence blood pressure (BP) response in peHTN.

Methods: Retrospective cohort of 102 consecutive patients with peHTN. Primary outcomes were the changes per year in systolic and diastolic BP (SBP, DBP). Secondary outcomes included the change per year in left ventricular mass index (LVMI) and the number of antihypertensive medications. We evaluated whether plasma renin activity (PRA), aldosterone, renin-to-aldosterone ratio (RAR), obesity, race, initial drug choice, and multidrug therapy were associated with the outcomes using linear and logistic regression.

Results: Racially diverse (28% black, 43% Hispanic, 25% white) and predominantly overweight/obese (75%) patients were studied. Median length of follow-up was 14.5 months. Lower baseline aldosterone and obesity were each associated with increased SBP (+1.1 and +21.7 mm Hg/year) and DBP (+8.9 and +17.7 mm Hg/year) during follow up. Lower PRA and obesity were each associated with increased SBP z score (+0.53 and +1.38/year) and increased LVMI (+5.8 and +18.2 $g/m^{2.7}$/year). Higher RAR was associated with increased DBP z score (+0.14/year). Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARB) lowered the likelihood of polytherapy (OR 0.15, p <0.001), particularly in blacks (OR 0.07, p = 0.04), while obesity increased it (OR 4.91, p = 0.03).

Conclusions: The pre-treatment RAS profile predicted follow-up BP and LVMI. Obese patients were at risk for inadequate treatment response. Treatment with an ACEi or an ARB was associated with monotherapy, especially in black patients.

PUB628

Augmentation Pressure, Augmentation Index and Pulse Wave Velocity in Chronic Kidney Disease Patients

Jafar Al-Said. *Internal Medicine and Nephrology, Bahrain Specialist Hospital, Bahrain.*

Background: CKD patients have an elevated Augmentation Pressure (AUP), Augmentation Index (AUI) and Pulse Wave Velocity (PWV). The association with other Cardiovascular (CV) risk factors among CKD patients is not yet clear. The aim of this study is to test the correlation between AUP, AUI and PWV with major CV risk factors among CKD as compared to non CKD patients.

Methods: This is a retrospective cross sectional study of outpatients visiting the Nephrology clinic with a central pressure checked. Demographic features, CV risk factors as well as AUP, AUI and PWV were obtained from the files. The central BP is measured with a Mobil-O-graph monitor from the Lt. arm. Peripheral and central BP measured from the Lt Brachial artery with an external arm cuff. All measurements were standardized with two readings in a comfortable sitting position over 3 minutes. Forty-seven CKD patients were matched for age, gender and BMI with 47 normal kidney function individuals. Central BP parameters association with CV risk factors were compared between both subgroups.

Results: The total number of patients was 281. Mean age was 49 years (SE 0.9). Males were 59%. Mean BMI was 29 kg/m^2 (SE 0.39). The CKD subgroup were 54. Mean age was 61 years (SE 1.9). Males form 69%. Mean BMI was 31.5kg/m^2 (SE 0.8). Mean eGFR was 26ml/min. AUP, AUI and PWV were significantly associated with CKD in univariate correlations. However, with multivariate regression including demographic and other CV risk factors, AUP was the only central pressure parameter associated with CKD. (RR 0.35), Correlation Coefficient 0.23 (P<0.0001). AUP, AUI and PWV were associated with most of the major CV risk factors among non-CKD patients but not in CKD patients. PWV was the only central BP parameter in CKD subgroup associated significantly with age, DM and Hyperuricemia.

Conclusions: Although AUP, AUI and PWV were significantly associated with CKD, but when considering age, gender, BMI and other major CV risk factors only AUP remained significant. PWV was associated in CKD subgroup with age, DM and Hyperuricemia. The raised central pressure parameters among CKD patients in our cohort was not translated into a significant association with major CV risk factors.

PUB629

Psychological Impact of a Diagnosis of Hypertension in Pediatric Patients

Howard Trachtman, Laura Jane Pehrson, Suzanne M. Vento, Laura Malaga-Dieguez, Nigel Madden. *Pediarics, NYU Langone Medical Center, New York, NY.*

Background: The prevalence of hypertension (HT) in children and adolescents has increased markedly over the last 20 years, primarily as a result of the obesity epidemic. Because high blood pressure (BP) tracks into adulthood and possibly causes increased cardiovascular morbidity, it is considered standard of care to measure BP in pediatric practice. However in 2013, the US Preventive Services Task Force (USPSTF) concluded that there are inadequate data to support routine BP screening in asymptomatic children. The potential adverse consequences of screening for high BP in pediatric patients have not been addressed. The objective of this study was to assess the psychological impact of a diagnosis of HT in children and adolescents.

Methods: Patients, age 10-21 yr old, with a diagnosis of HT and their parents were eligible for inclusion. They were recruited in the Fink Ambulatory Care Center or the Bellevue Nephrology Clinic. A 9-question Hypertension Quality of Life Questionnaire was developed to evaluate emotional, performance, and interpersonal aspects of well-being. The primary outcome measure was the total and three subdomain scores in the child version of the survey, based on a 5-point Likert scale. Child and parent scores were compared for internal consistency in rating the psychosocial burden of a diagnosis of HT.

Results: There were 20 participants, 14M:6F, mean age 16.5±2.1 yr, 11 White, 3 Black, 4 Hispanic and 2 Other. 16 subjects were in middle or high school and 4 attended college. The parents were married in 14, divorced in 2, or single in 4 cases and in 17 families at least 1 parent attended college. 9 participants were receiving antihypertensive drugs. The survey was completed 2.6±2.8 yr after the diagnosis of HT was made. The mean total score was +0.40 units (P=0.75). The mean emotional subscore was -0.95 units (P=0.10) and 15 (75%) had a negative score. There were no significant differences between the participant or parent responses.

Conclusions: Our findings suggest that there may be adverse psychological consequences of being given a diagnosis of high BP, especially in emotional status, in adolescents and young adults. Further work is needed to address this issue.

Funding: Clinical Revenue Support

PUB630

Ankle Brachial Index and Glomerular Filtration Rate as Predictors for Independent Mortality All Causes in Patients with Hypertension Arterial Systemic Franklin Correa Barcellos,[1,2] Annelise Reges,[1] Gabriela Araujo Duarte,[1] Alexia Schuch,[1] Mateus De Mamann Vargas,[1] Jamile Gardin Dos Santos,[1] Luiza Morrone Gastaud,[1] Maristela Bohlke.[1] *[1]Medicine School, Univ Catolic of Pelotas, Brazil; [2]Medicine Faculty, Univ Federal of Pelotas, Pelotas, Brazil.*

Background: High blood pressure, chronic kidney disease(CKD), and peripheral arterial disease (PAD) are predictors of mortality in the general population. It has been suggested that patients with arterial hypertension, glomerular filtration rate (GFR) <60 ml/min/173m2 and PAD diagnosed by the ankle brachial index (ABI) <0.9 also suffer increased mortality rate.

Objective

Identification of predictors of mortality from all causes in a sample of patients with hypertension.

METHODOLOGY

Cohort study that followed nondiabetic patients with hypertension, include variables gender, skin color, age, blood glucose, lipid profile, ABI and GFR calculated from serum creatinine(CKD-Epi-formule) The association between potential predictors and mortality were evaluated using logistic regression.

RESULTS

The sample of 150 subjects had age (mean / SD) of 65.05 (10.88) years, 36.7% male, 67.9% white and 43.0% patients with chronic kidney disease, were accompanied by an average of 2.82 (0.73) years.

There were a total of 13 (10.16%) deaths in the follow-up period. Presence of CKD (OR 5.38; 95% CI 1.07 to 27.08, P = 0.04) or decreased GFR (OR 0.95 95% CI 0.91 to 0.99; p = 0.01) and ITB reduced (OR 0.02 95% CI 0.001 to 0.57, p = 0.02) were independent predictors of death during follow-up. Ten of the 13 deaths occurred in patients with CKD.

CONCLUSIONS: Reduction in GFR, as the lowest ITB has been associated with increased mortality in the general population. This study confirms the prognostic impact of these variables also among non-diabetic elderly patients with hypertension.

PUB631

Single-Pill Irbesartan/Amlodipine Combination Therapy Improves Clinic and Home Blood Pressure Profiles in Hypertensive Patients with Chronic Kidney Disease Kouichi Tamura, Ryu Kobayashi, Hiromichi Wakui, Masato Ohsawa, Kengo Azushima, Kazushi Uneda, Sona Haku, Kotaro Haruhara, Kohji Ohki, Sho Kinguchi. *Dept of Medical Science and Cardiorenal Medicine, Yokohama City Univ Graduate School of Medicine, Yokohama, Kanagawa, Japan.*

Background: Accumulating evidence indicates that appropriate blood pressure (BP) control is essential to inhibit renal deterioration and to prevent cardiovascular complication in hypertensive patients with chronic kidney disease (CKD).In this study we examined the efficacy and safety of single-pill irbesartan/amlodipine combination therapy for 12 weeks in hypertensive CKD patients, by evaluating self-measured home BP profile.

Methods: Hypertensive patients with CKD who have already been treated with antihypertensive therapy comprised of renin-angiotensin system inhibitors or calcium channel blockers were eligible for this study if they could not achieve the target BP (clinic systolic BP≥ 130 mmHg and/or diastolic BP≥ 80 mmHg). After the run-in period, eligible patients were given a single pill of irbesartan/amlodipine tablet for 12 weeks. Clinic BP and home BP profiles as well as parameters of vascular function were evaluated at baseline and after the protocol therapy. Self-measured home BP values were obtained upper arm cuff oscillometric device with a memory-equipped system (HEM-7080IC, Omron, Kyoto, Japan).

Results: 20 patients were enrolled and assigned to the single-pill irbesartan/amlodipine combination therapy for 12 weeks. Combination therapy for 12 weeks significantly decreased clinic BP and home BP (home morning BP; baseline vs 12 weeks, 150±16/85±10 mmHg vs 133± 12/76±9, *P*<0.01). In addition, the combination therapy significantly decreased within-visit variability of clinic BP and day-by-day variability of home BP after 12 weeks treatment. Concerning parameters of vascular function, the combination therapy significantly improved central systolic BP, AI, baPWV and CAVI.

Conclusions: The results of present study suggest that the single-pill irbesartan/amlodipine combination therapy may exerts beneficial effects on clinic and home BP profiles including BP variability and vascular function, in addition to BP lowering, in hypertensive CKD patients.

PUB632

Variability of Circadian Blood Pressure Differentiates Hypertensive Kidney Damage from Chronic Glomerulopathy Arkadiusz Lubas, Grzegorz Kade, Stanislaw Niemczyk. *Internal Diseases Nephrology and Dialysis, Military Inst of Medicine, Warsaw, Poland.*

Background: Unknown medical history, well-controlled hypertension and clinically latent stable chronic kidney disease (CKD) make it difficult to recognize the initial etiology of kidney damage. The aim of the study was to investigate whether echocardiography or blood pressure profile could help in differentiating between hypertensive nephropathy (HN) and glomerulonephitis (GN) related CKD.

Methods: Sixty nine patients (9 F; 60 M; age 54,3 ±14,1) with stable CKD (CKD-EPI 53,2 ±26,9 ml/min/1,73m^2) and a history of hypertension (44 with HN) were enrolled in the study. Serum Creatinine (Cre), Cystatin C (Cys), echocardiography and ABPM were tested. Renal function was estimated according to Cre and Cys based on CKD-EPI formula.

Results: Groups with HN and GN did not differ in renal function, systolic, diastolic and mean blood pressure (BP), pulse pressure, left and right ventricles dimensions, as well as left ventricular hemodynamic parameters (E/E', ejection fraction, stroke volume). Patients in HN group were older (age 57,5 ±13,2 vs 48,6 ±14,1 years; p=0,01) but had lower day to night drop of mean BP (D/N) (11,2 ±8,5 vs 16,0 ±5,8 %; p=0,01) and preawakening morning surge (PMS) (12,8 ±10,1 vs 18,5 ±7,6 mmHg; p=0,02). Diagnosis of HN correlated with age (r=0,31), PMS (r=-0,30), D/N (r=-0,27) and stroke volume (r=0,25). After adjusting to the age, in logistic regression, only D/N was significantly connected with likelihood of HN (r=-0,084; OR 0,919; 95% CI: 0,847- 0,997; p=0,04). In ROC analysis D/N ≤ 10 % recognized HN with specificity of 88%, and sensitivity of 40 % (p=0.01).

Conclusions: Nondipping pattern of blood pressure promotes recognition of hypertensive nephropathy rather than glomerulonephritis as the etiology of chronic kidney disease.

Funding: Government Support - Non-U.S.

PUB633

The Effect of Cyclooxygenase-2 Inhibition on Sodium Handling in the Proximal Tubule in Healthy Men and Women Ann A. Zalucky, Shahbal Bill Kangarloo, Sofia B. Ahmed. *Medicine, Univ of Calgary, Calgary, AB, Canada.*

Background: Cyclooxygenase-2 (COX-2) inhibitors are associated with increased cardio- and renovascular risk, with altered renal sodium handling suggested in animal studies as a contributing factor. We examined the effect of COX-2 inhibition on the fractional excretion of lithium, a marker of proximal tubular function in healthy humans.

Methods: Twelve healthy subjects (42% female, 37±10 years) were studied in high-salt balance pre- and post-14d daily ingestion of the COX-2 inhibitor celecoxib 200mg. The set-point of proximal renal tubular sodium excretion was estimated by fractional excretion of lithium (FELi, calculated as $lithium_{urine}$ x $creatinine_{serum}$/ $lithium_{serum}$ x $creatinine_{urine}$), which is not altered by changes in diet. Endogenous serum and urine lithium was measured by graphite furnace atomic absorption spectroscopy. In addition, fractional excretion of sodium (FENa, calculated as $sodium_{urine}$ x $creatinine_{serum}$/ $sodium_{serum}$ x $creatinine_{urine}$) was calculated for comparison.

Results: No significant changes in blood pressure, salt balance, or renal hemodynamics were observed pre- vs post-COX-inhibition. Similarly, COX-2 inhibition was not associated with any significant change in FELi (6.97±2.94 vs 6.48±2.94, p=0.4; pre- vs post-celecoxib). There were no sex differences in FELi at baseline (7.17±2.67 vs 6.83±3.33; p=0.8) or in response to COX-2-inhibition (ΔFELi: 0.01±2.54 vs 0.84±1.97; p=0.6; all values women vs men). FENa did not change in response to COX-2 inhibition (0.72±0.28 vs 0.66±0.47; p=0.7, pre- vs post-celecoxib).

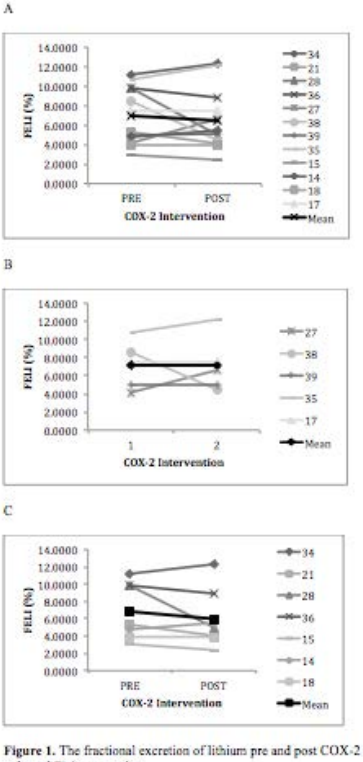


Figure 1. The fractional excretion of lithium pre and post COX-2 inhibition in **A)** all participants **B)** in women only and **B)** in men only.

Conclusions: In healthy humans, short-term COX-2 inhibition is not associated with changes in proximal tubular function. Whether these same findings apply to the CKD population is unknown.

PUB634

Finger Arterial Pressure as Index of Impaired Vessel Wave Reflection and Peripheral Vascular Disease in Hemodialysis Patients Gaetano Alfano, Francesco Fontana, Gianni Cappelli. *Dept of Surgery, Medical and Dentistry, Univ Hospital of Modena, Modena, Italy.*

Background: Nexfin monitor evaluates continuous and non-invasive measurement of arterial blood pressure (BP) through finger-cuff technology; it reconstructs brachial arterial pressure (BAP) analyzing peripherally changes of systolic and diastolic wave reflections. It was validated against the auscultatory method using sphygmomanometer but aim of our study is to evaluate Nexfin in maintenance hemodialysis patients(HD).

Methods: Forty hemodynamically stable HD underwent serial measurement of Nexfix arterial pressure (NAP) and BAP before HD-session. BAP was taken in the upper arm by oscillometric sphygmomanometer.

Results: Patients mean age was 68.9±14.9 years, being 65% > 65 yrs and 29% > 75 yrs; 27% of pts were diabetic. Bland-Altman analysis comparing NAP measurements with BAP revealed: a mean bias±LA of 15.3±34.8 mmHg (29% error) for systolic BP, a mean bias±LA of -0.9±20.34 mmHg (32% error) for diastolic BP and a mean bias of 4.5±21.34 mmHg (26% error) for MAP. Nexfin had poor accuracy in the reconstruction of diastolic and mean BP and extremely inaccurate for systolic BP.

Table 1. Comparison of BAP versus NAP

		Systolic	Diastolic	MAP
No. of patients: 40				
Mean BAP	mmHg	122,3	62,9	82,7
R^2		0,3	0,44	0,44
P value		0,0002	< 0,0001	< 0,0001
Bias	mmHg	15,3	-0,9250	4,575
SD of bias	mmHg	17,8	10,38	10,89
Lower LA	mmHg	-19,6	-21,27	-16,77
Upper LA	mmHg	50,2	19,42	25,92
Percentage error	%	29	33	26

R^2: squared multiple correlation
BAP: brachial arterial pressure; MAP: mean arterial pressure.

Multivariate analysis showed diabetes, neuropathy and increasing systolic BAP as significant predictors of disagreement in systolic BP values between NAP and MAP, F (3.34) = 10.787, p<0.005, R^2 = 0.488. Neuropathy was unrelated to diabetes as correlation analysis showed no significant correlation.

Conclusions: The Nexfin does not meet the criteria of interchangeability with standard oscillometric method in HD. The negative influence of diabetes, neuropathy and increase of systolic BAP limit the feasibility of Nexfin to perform a correct evaluation of BAP in presence of peripheral vasculopathy. On the other hand the unreliability of BAP reconstruction by NAP could be considered as indirect sign of peripheral vascular disease in these patients.

PUB635

Cardiovascular Risk in Healthly Subjects Evaluated with Genetic Test Francisco Javier Lavilla, Pedro Errasti, Maria Jose Molina Higueras, Pelayo Moiron Fdez-Felechosa, Christian Israel Alfaro Sanchez, Paloma L. Martin Moreno, Nuria Garcia-Fernandez. *Nephrology, Clínica Univ de Navarra, Pamplona, Navarra, Spain.*

Background: Evaluate cardiovascular risk (CVR) in healthy subjects.

Methods: Include 94 subjects (médium age 53 years 0.911, male 73.5%) Study CVR genetic test (evaluated cardiovascular age, global cardiovascular risk using validated genetic and clinical score), with carotid echography (intima-media thickness in left –IMTLC- and right -IMTRC- carotid) and ecocardiography (E/A and E/E´ index). We evaluate levels of Glucose, Triglycerides, cholesterol, uric acid, creatinine (mg/dL) and creatinine clearance (ml/min) (MDRD-4 and CKD-EPI).

Results: Mean biological age 53 years (SE 0.911),cardiovascular age 60 years (SE 0.81). Differential age was 6.2 years (SE 0.64) (0-26). Increase in cardiovascular age was >10 years in 21.3%. with more IMTLC (p=0.007), IMTRC (p=0.145) and lower E/E'(p=0.171). CVR measure with genetic test are associated with intima media thickness. CKD-EPI are better associated with genetic test than MDRD. Metabolic parameters (except cholesterol) are associated with genetic test and intima media thickness. Intima media thickness left carotid is better than right to evaluate CVR.

	AGE	CVA	GCVR	IMTLC	IMTRC
IMTLC r p	0.499 0.001	0.588 0.001	0.492 0.001		
IMTRCr p	0.493 0.001	0.511 0.001	0.398 0.001		
EA r p	-0.299 0.011	-0.252 0.033	ns	-0.255 0.040	-0.253 0.042
CR r p	ns	0.269 0.009	ns	ns	ns
CKD-EPI r p	-0.364 0.001	-0.361 0.001	ns	ns	ns
MDRD-4 r p	ns	ns	ns	ns	ns
GLUCOSE r p	ns	0.272 0.008	0.224 0.031	0.254 0.020	0.214 0.051
TRIGLIC. r p	ns	0.360 0.001	0.453 0.001	0.400 0.001	0.241 0.027
URIC A. r p	ns	0.376 0.001	0.353 0.001	0.242 0.027	ns

Conclusions: In healthy subjects can evaluated CVR with genetic test, carotid echography and ecocardiography. This CVR is associated with metabolic parameters (especially glucose, triglicerides and uric acid). Intima media thickness measure in left carotid and renal function with CKD-EPI, is better associated with genetic test CVR calculated.

PUB636

Denosumab Induced Severe Symptomatic Hypocalcemia in a Patient with Normal Renal Function Ashwin Reddy Ganta. *Dept of Nephrology, Archbold Memorial Hospital, Thomasville, GA.*

Background: A 69 y/o Caucasian female was referred to our clinic for resistant hypocalcemia with panic attacks over the past 18 months. She complained of severe anxiety symptoms with significant impairment of QOL and was on Buspirone and Aplrazolam with some relief. Her PMH was significant for HTN and Osteoporosis. Her medications included OTC Vitamin D and Calcium Supplements. Her physical examination was significant for Osteoporotic signs and a positive Trousseau sign. Her lab work done a few months ago prior to this presentation was significant for Low Calcium (5.6 mg/dl), Low Ionized Calcium (3.5 mg/dl) with normal albumin and Serum Creatinine (0.7 mg/dl and Cr Clearance 92 ml/min). Her 25(OH) Vit-D level was low (23 ng/ml) with elevated 1,25 (OH)2 Vit-D levels (144 ng/ml) and PTH elevated at 399 pg/ml (Normal 15-65 pg/ml). Her magnesium level was normal. On further questioning, patient admitted that received 4 doses of Prolia (Denosumab) for Osteopenia over the last 2 years. Her hypocalcemia was attributed to Denosumab and her elevated PTH level was most likely compensatory. She has been initiated on high dose Vitamin D analog and elemental Calcium therapy and is doing better. Discussion : Denosumab is a fully human monoclonal antibody that inhibits bone resorption by binding to receptor activator of Nuclear Factor kB Ligand (RANKL). CKD stage IV/V, Male sex and Malignancy have been found to be risk factors for Denosumab induced symptomatic hypocalcemia and mild non symptomatic hypocalcemia has been reported as a side-effect as well. Based on Pubmed review, to our knowledge this is the first case report of Denosumab induced hypocalcemia in a patient with normal renal function and no known malignancy. With Denosumab use increasing due to the side effects with Bisphosphonate use, physicians need to be aware of the potential severe side-effects with Prolia.

PUB637

The Incidence and Prevalence of Hypomagnesemia in the Intensive Care Units Satyam Patel, Maria V. DeVita, David Selzer, Michael F. Michelis. *Nephrology, Lenox Hill Hospital, New York, NY.*

Background: The incidence and prevalence of hypomagnesemia in the critical care setting have both been reported as high as 65%. However, a substantial amount of data is from outside the United States and more than 10 years old. This present study evaluates the incidence and prevalence of hypomagnesemia in the intensive care setting.

Methods: A prospective, observational study was done on consecutive patients admitted to medical and surgical intensive care units at a tertiary hospital. Each patient's chart was reviewed for magnesium (Mg) level and medications in the ICU for up to 7 days. Hypomagnesemia was defined as <1.6 meq/L.

Results: To date, of the 157 patients reviewed, 108 patients had Mg measured on Day 1. In this cohort, the prevalance of hypomagnesemia was 18/108 = 16.7% (95% CI: 10.2-25.1). Among the 90 patients had a normal Mg the 1st day, 6 patients did not have Mg level measured during the remainder of their ICU stay, while 84 patients had Mg measured on at least one occasion from day 2 to day 7. Among these 84 patients, 2 patients developed hypomagnesemia at day 2 and no patient developed hypomagnesemia at day 3 or later. Therefore, the estimated incidence of hypomagnesemia is 2/84 = 2.4% (95% CI: 0.3-8.3). Interestingly, 77 patients had at least one Mg supplementation, for a total of 114 supplements administered; the average Mg level at which supplementation occurred was 1.7 mg/dL, indicating that most patients are supplemented prior to actually reaching a low Mg level. There was not enough evidence to conclude that other selected factors, such as diuretics, PPIs, and antibiotics were associated with hypomagnesemia. The only comorbidity associated with hypomagnesemia was a history of DVT/PE (62.5%) compared to patients without DVT/PE (15.0%) (p=0.005).

Conclusions: These results suggest that the while the prevalence of hypomagnesemia is within the previously reported range, the incidence is significantly lower that previously reported studies. The finding that critical care areas are more readily identifying and treating Mg level even at concentrations deemed to be acceptable shows a change in the standard of care and an awareness of the importance of this electrolyte.

PUB638

Hip Structure Analysis Reflects the Bone Strength Changes after Eldecalcitol Administration Better Than the Bone Mineral Density by DEXA Megumi Sato,[1] Katsuyuki Funato,[2] Junichi Takada.[3] *[1]Jinzo Naika Megumi Clinic, Nephrology, Sapporo, Japan; [2]Jinzo Naika Megumi Clinic, Clinical Laboratory, Sapporo, Japan; [3]Kitago Orthopedics Clinic, Orthopedics, Sapporo, Japan.*

Background: Bone strength has been usually assessed by bone mineral density(BMD) but it is well known that BMD is not directry related to the bone strength.Hip Structure Analysis(HSA) is a new method the bone strength which is calculated by reconstructing 3-dimentional bone structures with BMD by DEXA.We compared the HSA parameters with the BMD after Eldecalcitol administration.

Methods: Eighteen chronic dialysis patients were enrolled to the study;10 males and 8 females, the average of age are 73.7 years old in male, 69.3 years old in female. HSA consists of 4 indices for assessing several bone strength;Cross Sectional Area(CSA),Cross Sectional Moment of Inertia(CSMI), Section Modulus(SM) and Buckling Ratio(BR). These parameters were calculated in following 3 parts of femur; Narrow Neck(NN), Intertrochanteric part(IT) and femoral shaft(FS). BMD were measured both Neck and Total parts of femur.

Results: BMD in male were significantly increased in both Neck and Total at before/12-mo.; Neck, 0.604/0.615, p=0.1406 ; Total, 0.780/0.797, p=0.042. However, BMD in female did not changed; Neck, 0.586/0.592, p=0.515 ; Total, 0.704/0.709, p=0.5452. The HSA parameters were preserved or increased in male but most of them were decreased in female after Eldecalcitol administration.

HSA index	pre.	12 mo.after	p-value
CSA in male			
NN	2.41±0.36	2.43±0.33	*0.0584*
IT	3.90±0.46	3.98±0.50	*0.0411*
CSA in female			
NN	2.11±0.42	1.98±0.61	n.s.
IT	3.36±0.89	3.34±0.80	*0.0460*

Conclusions: In the current study we admitted the increase of BMD after Eldecalcitol; however, the HSA parameters in male were improved but deteriorated in female. It suggests that BMD is not a reliable parameters for monitoring the bone structural changes and strength after some treatment. Bone fracture is one of the serious prognostic factors in dialysis patients and it has been reported that the risk of fractures were closely related to the bone strength rather than BMD. We should assess the bone strength and fracture risk not only by BMD but by HSA.

PUB639

Smoking Is Associated with Decreased Osteocalcin (BGP) Levels in Dialysis Patients (VIKI Study) Maria Fusaro,[1] Maurizio Gallieni,[2] Mario Plebani,[3] Andrea Aghi,[3] Enrico Schileo,[4] Piergiorgio Messa,[5] Carlo M. Alfieri,[5] Nicola Veronese,[3] Marina Foramitti,[6] Laura Cosmai,[6] Stefania Sella,[3] Maria Cristina Mc Mereu,[7] Giovanni Tripepi,[8] Sandro Giannini.[3] *[1]National Council of Research, Pisa, Italy; [2]Univ of Milano, Italy; [3]Univ of Padova, Italy; [4]Istituto Ortopedico Rizzoli, Bologna, Italy; [5]IRCCS Fondazione Ca' Granda, Milano, Italy; [6]Istituti Ospitalieri di Cremona, Italy; [7]Ospedale San Gavino Monreale, Italy; [8]IFC-CNR, Reggio Calabria, Italy.*

Background: BGP is a vitamin K-dependent protein involved in the regulation of bone mineralization and in vascular calcification (VC). In a secondary analysis of the VIKI study, we analyzed the association of osteocalcin and smoking among CKD patients, including the possible consequences on bone metabolism and mineral bone disorders.

Methods: We determined BGP and MGP levels, and verified the presence of any vertebral fractures (VF) and vascular calcification (VC) by spine radiographs. Among patients (36% female), 35% was smoker or former smoker, age 65.4 ± 13.5 years, dialysis duration 61.9±49.4 months, BMI 25.3±4.3 Kg/m^2. Comorbidities among smokers were: 26% diabetes, 82% arterial hypertension, 51% coronary artery disease, 13% cerebrovascular disease, 38% peripheral vascular disease, and 54% of patients had a vertebral fractures.

Results: Smoker patients had significantly lower phosphate levels than non smokers (4.53 ± 1.26, 4.86 ± 1.22 mg/dL, ***p*= 0.013**). Smokers also showed lower albumin (3.73 ± 0.45 vs 3.89 ± 0.40 g/dL, ***p*= 0.001**), and total BGP levels: 152 (92-251), 204.5 (111-362) ng/mL, ***p*= 0.003.** Most of the smoking patients (85%, compared to 77% in the control group, p=0.09) also showed presence of abdominal aortic calcification. We found lower BGP levels in patients with high prevalence of VF levels: 151 (91-276), 213 (107-369) ***p*=0.009** and VC levels: 164 (87-276), 262 (134-436), ***p*<0.001.** Smoking was associated to a reduction of total BGP levels of about 20% in the average values of BGP (Stepwise Table 1, R^2= 0.53).

Variable	Parameter estimate	p-value
Age	-0.01087	< 0.001
BMI	-0.03240	< 0.001
Smoke	-0.22452	< 0.001
R^2= 0.53		

Conclusions: This is the first clinical study in a dialysis population identifying smoke as a factor negatively affecting osteocalcin levels.

PUB640

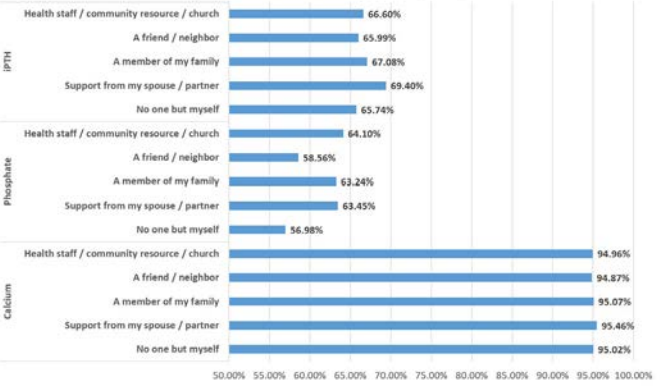
Impact of Social Support on Dialysis Patients Achieving Mineral Bone Disorder Laboratory Goals Felicia N. Speed,[1] Yue Jiao,[1] John W. Larkin,[1] Marta Reviriego-Mendoza,[1] Dugan Maddux,[1] Jessica Demaline,[1] Savannah Roberts,[2] Terry L. Ketchersid,[1] Stephanie Johnstone,[1] Len A. Usvyat,[1] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]FreseniusRx, Franklin, TN.*

Background: The type of social support dialysis patients (Pts) receive from family, friends, or caregivers has the potential to affect outcomes, but has not been widely investigated. We studied if the social support type is associated with dialysis Pts achieving mineral bone disorder (MBD) laboratory goals.

Methods: We analyzed data from Jan 2014 to Dec 2015 on 185,131 Pts at Fresenius Medical Care North America who completed the social work assessment questionnaire. We studied responses to the question "when you have a big problem, can you usually rely on?", which has choices for support types including: "no one but myself", "support from my spouse/partner", "a member of my family", "a friend/neighbor", or "health staff/community resource/church". We compared support types to the proportion of Pts meeting mean 6 month laboratory goals for calcium (Ca) [≤10.0mg/dL], phosphate (P04) [=3.0-5.5mg/dL], and intact parathyroid hormone (iPTH) [=150-600pg/mL] prior to completing the questionnaire.

Results: We observed Pts that received social support from a friend/neighbor or nobody had a distinguishably lower proportion of Pts meeting PO4 goals, as compared to other support types. Pts who received support from a spouse/partner had slightly more Pts meeting goals for iPTH versus other support types. Almost all Pts achieved Ca targets with no remarkable differences between types of support (Figure 1).

Figure 1: Percent of MBD Laboratories in Target Range



Conclusions: Our study indicates that social support from a spouse/partner, family member, or health staff/community resource/church may result in better control of PO4 levels, as compared to support from a friend/neighbor or no one. This may be indicative of improved adherence to PO4 binders with improved social support.

Funding: Pharmaceutical Company Support - Fresenius Medical Care North America

PUB641

Tailoring Phosphate Binders to Patients' Needs: Outcomes of a Short Term Pilot Study of a New Web-Based Tele-Medical Device for Smartphones and Tablets (P-MED) Guseppe Rombolà,[1] Luca Neri,[2] Alice Fattori,[2] Elisa Ottonello.[1] *[1]Unit of Nephrology, Ospedale Di Varese, Varese, Italy; [2]Univ of Milan, Milan, Italy.*

Background: Non-adherence to phosphate binders hampers clinical outcomes and increases costs. We assessed the suitability of a new tele-medical device (P-MED) designed to help nurses personalize clinical decisions and improve patient's adherence. We assessed outcomes of P-MED usage in clinical practice over a 2-month follow up.

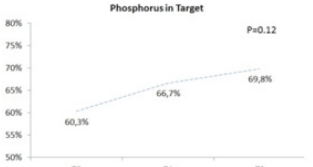
Methods: P-MED allows to record, view and integrate data on phosphorus lab values, medical prescriptions, p-binders dose, dietary habits, and the 8-item Morisky's adherence scale. The dietary interview is administered via a computer assisted system selecting the most informative question based on previous patients responses. Based on p-binders dose equivalence charts and nutritional charts, P-MED calculates and display the binding needs and the "calcium carbonate 1000 mg" equivalent dose (CC1000-ED) taken by the patients in the day preceding each interview. The pilot study took place in a single center in Italy from April to June 2016. Nurses were allowed to take as many interviews as deemed appropriate,

and encouraged to negotiate adjustments to medication dose based on phosphorus dietary intake with patients. Key clinical trajectories have been evaluated with random intercept generalized models.

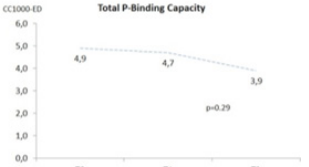
Results: Ten nurses voluntary elected to participate in the study and 63 patients took part to the study. During the 2-month follow up 84 adherence interviews and 380 dietary interviews occurred. Baseline charcteristics and clinical outcomes are reported in figure 1.

Baseline Characteristics	Mean (Std) or n (%)
Age	71.2 ± 5.8 years
Phosphorus	5.2 ± 1.5 mg/dL
Phosphorus in Target	37 (60%)
Estimated Dietary Pi Intake	932 ± 474.8 mg
CC1000-ED	4.9± 2.9
Phosphorus Gap *	9.0 ± 270.3
Morisky's Score=0	18 (29%)

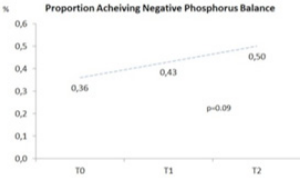
Table 1. Baseline Characteristics. * Phosphorus Gap represents the estimated amount of un-binded ditary intake based on dietary consumption and p-binder dosage



Panel A: Proportion of patients acheiving normal phosphorus levels (3.5<p<5.5 mg/dL)



Panel B: Estimated Total Binding Capacity from Phosphate Binders assumed by patients. 1 equivalent unit represent the binding capacity of 1000 mg of Calcium Carbonate.



Panel C: Proportion of patients who achevied a negative balance between dietary phosphorus intake and phosphorus binding (including phosphorus removal obtained with HD).

Conclusions: The application was well accepted by nurses and patients as showed by the high usage frequency. Despite non statistically significant the improvement in clinical outcomes and the reduction in medication usage is sizeable and merits further investigation in longer term and larger clinical studies.

PUB642

Quality of Mineral Bone Disease Care in Non-Dialysis Chronic Kidney Disease: Results of a Multi-Centre Audit and Survey Questionnaire in the Irish Health System Muhammad Umair Sharif,[1,2] Mohamed Elsayed,[1,2] Ahmed Alghali,[1,2] Mohammed A. Kaballo,[1,2] John P. Ferguson,[4] Xia Li,[2,3] Austin G. Stack.[1,2,3] *[1]Graduate Entry Medical School (GEMS), Univ of Limerick, Limerick, Ireland; [2]Dept of Nephrology, Univ Hospital Limerick, Limerick, Ireland; [3]Health Research Inst (HRI), Univ of Limerick, Limerick, Ireland; [4]Health Research Board (HRB) Clinical Research Facility, National Univ of Ireland, Galway, Ireland.*

Background: Mineral Bone Disease (MBD) is the most prevalent complication of Chronic Kidney Disease (CKD) and contributes to multiple adverse clinical outcomes. We sought to describe the prevalence, disease characteristics and quality of care of CKD-MBD in non-dialysis Irish CKD population. Parallel to this audit we explored the opinions and attitudes of Irish nephrologists, and their adherence to guidelines.

Methods: Data were captured on several aspects of outpatient MBD care in 530 non-dialysis CKD patients from nephrology clinics across 6 Irish health regions. Correspondingly, the survey questionnaire captured the attitudes of nephrologists on use of clinical guidelines and thresholds for intervention. Descriptive statistics and comparisons across groups were made using chi-square, ANOVA and logistic regression.

Results: The overall prevalence of CKD-MBD was 48%. The rate of MBD testing increased from 41% in Stage 3 to 88% in Stage 5. Overall 91% of patients' in Stage 3-5 had optimal phosphate control (Phosphorus <4.6 mg/dL). Among 9% patients with hyperphosphataemia, calcium-based binders were the preferred first-line treatment. The opinion of nephrologists varied widely on the threshold for binder initiation, choice of second line binder as well as the desired target for optimal control. The most frequently used guidelines were from UK Renal Association (41%).

Conclusions: Although control of MBD is generally good in the Irish Health system, residual deficits exist. Low treatment and testing rates didn't correspond to nephrologists' opinions, which varied widely. Variability in clinical practice may in part be due to these differences and may contribute to differential outcomes. Knowledge of these differences will serve as a useful starting point in seeking consensus for the production of national standards.

PUB643

Is There Really an Correlation between Serum Soluble Klotho Levels and Survival in Maintenance Hemodialysis Patients Jie Ma, Xuemei Li, Yang Yu. *Nephrology Dept, Peking Union Medical College Hospital.*

Background: Transmembrane α-Klotho (TM-Klotho) expressed in renal tubules, is a cofactor for FGF23-receptor. Circulating soluble-α-Klotho(**sαKl**) results from TM-Klotho, the extracellular domain of α-Klotho can be cleaved and released into various extracellular fluids, such as blood. Decreased TM-Klotho, prevents actions of FGF23 and lessens circulating sαKl. Thus, levels of sαKl could represent a marker of CKD-MBD, also possibly plays a role in determining the risk of mortality in some populations. The relationship between the level of serum soluble α-Klotho and overall mortality in hemodialysis patients is unclear yet.

Methods: We prospectively followed a cohort of 119 maintenance hemodialysis patients for 30 months in Peking Union Medical College Hospital dialysis center. We assessed the level of the soluble α-Klotho -and FGF23 of these patiens . Cox regression models were used to analyze the relationships between the primary outcomes(death) and the serums soluble α-Klotho and FGF23 levels.

Results: A total of 119 cases were enrolled this study, male 59, female 60, age 19-90years, mean age 59.3years, with duration of dialysis for10-95 months. The mean serum sαKl level and FGF23 level were no significance different between two groups of HD patients.

	Dead HD Patients	Survival HD Patients	*P*
Klotho	285.07±156.56	339.22±201.93	0.397
FGF23	435.05±690.46	1090±848.64	0.234

Also we did not find any correlation between soluble-α-Klotho and FGF23 and all-cause mortality.

Conclusions: We suspect that there may not be an correlation between serum soluble Klotho levels and all-cause mortality in maintenance hemodialysis patients.

PUB644

High-Resolution Magnetic Resonance Imaging to Assess Bone Microarchitecture in Patients with Chronic Kidney Disease Ashish K. Sharma,[1,2] Nigel David Toussaint,[1,2] Grahame J. Elder,[3,4] Stephen G. Holt,[1,2] Patricia L. Robertson,[1,2] Peter Robert Ebeling,[5] Paul A. Baldock,[4] Chamith S. Rajapakse,[6] Rosemary Masterson.[1,2] *[1]Royal Melbourne Hospital, Parkville, VIC, Australia; [2]Univ of Melbourne, Parkville, VIC, Australia; [3]Westmead Hospital, Westmead, NSW, Australia; [4]Garvan Inst of Medical Research, Sydney, NSW, Australia; [5]Monash Health, Clayton, VIC, Australia; [6]Univ of Pennsylvania, Philadelphia, PA.*

Background: Renal osteodystrophy (ROD) affects bone quantity and quality and is associated with increased fracture risk. Screening for ROD is hindered by inadequacy of current diagnostic methods. Bone biopsy is invasive and infrequently performed routinely. High-resolution magnetic resonance imaging (HR-MRI) is a new technique to assess trabecular and cortical microarchitecture. We aimed to validate HR-MRI assessment of bone structure compared to histomorphometry and micro-CT of bone biopsies from kidney transplant recipients.

Methods: Distal tibia HR-MRI scans and iliac crest bone biopsies were performed in 10 transplant recipients at transplantation. Structural parameters of biopsies were analyzed by histomorphometry and 3D micro-CT. Measurements included trabecular bone volume (TV/BV), thickness (TbTh), number (TbN), separation (TbS), mean cortical thickness (CtTh) and porosity (Po.%). Bone mineral density (BMD) was measured by peripheral quantitative computed tomography (pQCT, radius) and dual energy x-ray absorptiometry (DXA, hip). Associations were determined by analysis with Spearman's rank correlation coefficients.

Results: HR-MRI (tibia) and micro-CT (iliac crest biopsy) indices correlated positively for TbN and TbS (r=0.52 and r=0.56 respectively) and TV/BV, with no significant correlation for CtTh at these differing sites. HR-MRI (tibia) CtTh correlated to CtTh and BMD measured by pQCT (radius) (r=0.65 and 0.78 respectively). Micro-CT (iliac biopsy) CtTh correlated to BMD by DXA (hip), and cortical porosity by micro-CT correlated negatively to BMD by DXA (r=-0.65).

Conclusions: Micro-CT histomorphometry correlates to tibial HR-MRI for trabecular indices and to hip DXA for cortical indices. HR-MRI and DXA combined with biochemical turnover markers may provide rapid, accessible information to guide management of ROD.

PUB645

Does Potassium Citrate Have Equivalent Therapeutic Effect in Patients with Diabetes? Kimberly Maciolek, Kristina L. Penniston, Leema M. John, Sara Best. *Dept of Urology, Univ of Wisconsin School of Medicine & Public Health.*

Background: Diabetes (DM) increases the risk of stone formation. Patients with and without DM may have both acidic urine and low citrate but with different etiologies. Potassium citrate therapy (KCit) is used to alkalinize urine and raise citrate, but its efficacy in patients with DM, whose urinary derangements may be more significant, has not been assessed. We compared changes in 24hr urine parameters after KCit in stone formers with and without DM.

Methods: We identified 32 patients (16 with DM) who had 24hr urine results pre- and post-KCit. Changes in urinary risk factors between patients with and without DM were evaluated.

Results: Age and BMI were similar between groups (58 vs 55 y, p=0.39; 35.3 vs 31.5 kg/m2, p=0.25). Median time between starting KCit and the follow-up urine collection was 173 and 300 days (DM vs non-DM, p=0.13). 24hr urinary parameters were similar between groups before KCit. All patients were deemed to be compliant with KCit. Changes in group means for 24hr urine parameters are shown in the table.

Table 1 : Mean change in urinary risk factors after initiating KCit		
	Patients with DM	Patients without DM
Cit (mg/d)	95	126
pH	0.50*	0.40
K (mEq/d)	20*	13
SS Br	0.09	0.66*
SS UA	-0.68*	-0.21
*Statistically significant change (p<0.05) pre- vs post-KCit		

Neither group achieved a statistically significant rise in citrate after initiating KCit. Those with DM experienced a significant rise in pH. A significant proportion of patients without DM achieved therapeutic levels of citrate (>320mg/d) with KCit (81%, p=0.028). Brushite supersaturation (SS) rose significantly only in patients without DM after initiating KCi. Uric acid SS decreased in both groups but was significant only in patients with DM. Other changes in 24hr urine were statistically similar regardless of DM status.

Conclusions: The effect of KCit on 24hr urine risk factors for stone formation is similar in patients with and without DM. Patients with DM may experience a greater improvement in urine pH than patients who do not have DM and may do so without risking a rise in brushite SS.

PUB646

Addressing an Unmet Need in Patients with Secondary Hyperoxaluria Sagar U. Nigwekar,[1] James E. Lingeman,[2] Louis Brenner,[3] Danica Grujic,[3] Annamaria T. Kausz.[3] *[1]Div of Nephrology, Massachusetts General Hospital, Boston, MA; [2]Dept of Urology, Indiana Univ, Indianapolis, IN; [3]Allena Pharmaceuticals, Newton, MA.*

Background: Kidney stones are common, and secondary hyperoxaluria (2^0HOx) is a known risk factor. However, randomized controlled trials (RCT) of 2^0HOx are rare, and little is known about dietary oxalate intake and its correlation to 24h urinary oxalate (UOx) excretion. Here we present characteristics of patients with 2^0HOx enrolled in two Phase 2 double blind, placebo-controlled RCTs of ALLN-177, a novel oral, crystalline enzyme therapy that specifically degrades oxalate in the GI tract, decreasing the amount available for absorption. Our prior trials demonstrated that ALLN-177 reduced 24h UOx in both healthy volunteers and patients with 2^0HOx.

Methods: In Study 649, 42-60 subjects are being randomized to receive 1500, 3000 or 7500 units of ALLN-177 or placebo TID with meals x 7d, then cross over to an alternate arm for 7d. In Study 713, 44 subjects are being randomized to receive 7500 units of ALLN-177 or placebo TID with meals x 28d. Subjects remain on their usual diet, monitored with dietary recalls throughout the study. The primary efficacy assessment is based on mean change in 24h UOx.

Results: To date, 30 and 13 subjects have enrolled in Study 649 and 713, respectively. Across both studies, mean age is 60 years, 74% are male and 26% have 2^0HOx from bariatric surgery or inflammatory bowel disease. Subjects report on average ~6 stones in the past 5 yrs. Nearly 75% of subjects received some guidance to modify dietary intake. Entering the study, mean (SD) dietary intake of oxalate was 351 (435) mg/d, calcium 981 (578) mg/d, and fluids 3.9 (1.3) L/d. Mean (SD) excretion of UOx was 77 (32) mg/d, calcium 248 (178) mg/d and citrate 738 (576) mg/d; urine volume was 2.4 (0.76) L/d.

Conclusions: The characteristics of subjects enrolled in ALLN-177 clinical trials highlight the need for an effective therapy for 2^0HOx. Despite adequate fluid intake and dietary guidance, patients have excess oxalate in their diet, remain hyperoxaluric, and have recurrent kidney stones. Results of these Phase 2 studies will provide further confirmation of the efficacy and tolerability of ALLN-177 for treating 2^0HOx.

Funding: Pharmaceutical Company Support - Allena Pharmaceuticals

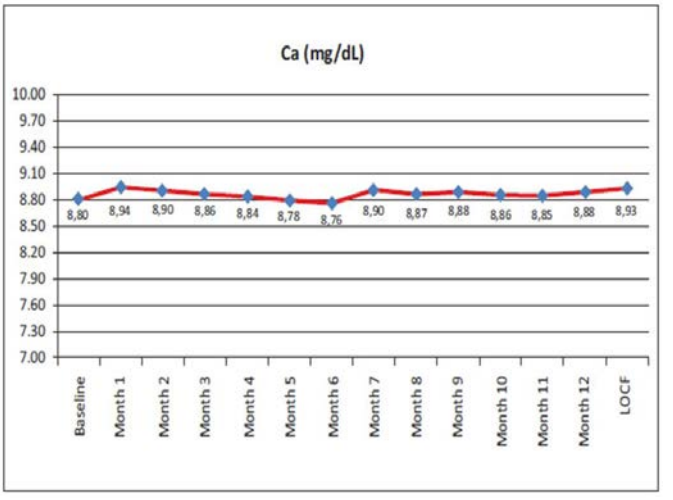
PUB647

Follow-Up of HD Patients Receiving sVDRA for Prevention and Treatment of SHPT: An Observational Study (P12-314) Fevzi F. Ersoy,[1] Hasan Koc,[2] Hasan Hoser,[3] Yalcin Akdag,[4] Cemaliye Kendir.[5] *[1]Akdeniz Univ Medical School, Antalya, Turkey; [2]Hayat Dialysis Center, Istanbul, Turkey; [3]Cinar Dialysis Center, Kutahya, Turkey; [4]Larende Dialysis Center, Karaman, Turkey; [5]Besyuzevler Safak Hospital, Istanbul, Turkey.*

Background: Secondary hyperparathyroidism (SHPT) is caused by decreased calcitriol synthesis, phosphate (P) accumulation and hypocalcemia during chronic kidney disease (CKD). The aim of this study was to evaluate monthly changes of iPTH and other major mineral/bone marker levels in hemodialysis (HD) patients with SHPT receiving paricalcitol.

Methods: 493 (F/M 244/249) adult hemodialysis (HD) patients, who were selected from 22 HD units in Turkey; receiving sVDRA treatment; with iPTH>300 mg/mL; Ca<10.2 mg/dL and P<6 mg/dL were included in this multi-center, national, prospective, observational study. Efficacy, safety and adverse events information on sVDRA treatment were collected by monthly visits along with iPTH, Ca, P and hsCRP values for 12 months. Mortality data was collected 6 months after the end of study.

Results: The mean age and duration of CKD Stage 5 were 58.3±15.8 years and 6.2±5.5 years, respectively. HD duration was ≤1 year in 14.4%, whereas longer than 3 years in 59.2% of subjects. Dialysate Ca concentrations were 125 mmol/L in 77.1% of patients. As of 12th month, no statistically significant changes have been observed in Ca and hsCRP levels (p>0.05) (Figure 1) and iPTH values were decreased from 646±424 pg/mL to 473±387 pg/mL (p<0.001). There were clinically insignificant increases in P and albumine levels at 12th month compared with the baseline (p= 0.017 and p<0.003 respectively).



Conclusions: Our study has shown that, paricalcitol, in addition to successful iPTH control, had favorable effects on serum Ca and P, which are consistent with previous studies. Increased serum albumin levels at Month 12, may be related to nutritional factors.

Funding: Pharmaceutical Company Support - AbbVie Tibbi Ilaçlar San. Tic. Ltd. Sti, Istanbul

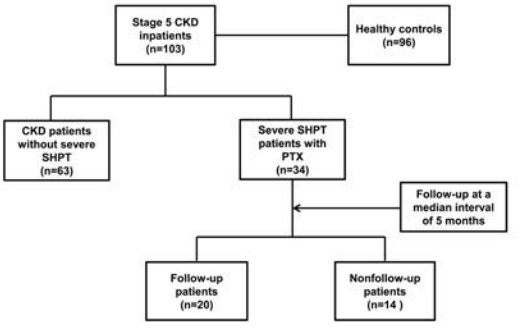
PUB648

Effects of Parathyroidectomy on Blood Bone Markers and Heart Rate Variability in Stage 5 Chronic Kidney Disease Patients Ningning Wang, Huimin Chen. *Dept of Nephrology, First Affiliated Hospital with Nanjing Medical Univ, Nanjing, China.*

Background: Attenuated heart rate variability(HRV) is associated with cardiovascular autonomic nerve disorders. No study has investigated the correlations between blood bone markers and HRV in chronic kidney disease(CKD), especially in secondary hyperparathyroidism(SHPT) patients.

Methods: We performed cross-sectional and prospective studies.

Figure 1. Study population flow diagram.



Bone parameters included (1)intact parathyroid hormone(iPTH), whole PTH(wPTH), and (7-84)PTH as bone remodeling regulators;(2)bone-specific alkaline phosphatase(BAP), representing bone formation;(3) tartrate-resistant acid phosphatase(TRACP-5b), indicating bone resorption;(4) bone-derived hormone, fibroblast growth factor 23(FGF23) and its cofactor Klotho.

Results: Compared with controls, baseline circulating levels of phosphorus, iPTH, wPTH, (7-84)PTH, BAP, TRACP-5b, and FGF23 were increased, while Klotho and wPTH/iPTH were decreased in CKD patients. Baseline plasma wPTH, (7-84)PTH, TRACP-5b, and FGF23 levels were associated with HRV in CKD. In parathyroidectomy(PTX) group, baseline and postoperative changes of bone markers which predicting the normalization of HRV were shown in table 1.

Dependent Improved HRV variables	Independent bone markers variables
Δmean 24h heart rate	Δ(7-84)PTH
Δmean normal-to-normal R–R intervals	(7-84)PTH
Δstandard deviation of the normal-to-normal R–R intervals	TRACP-5b
Δroot mean square of differences between adjacent normal R–R intervals	ΔiPTH
Δproportion of adjacent R–R intervals differing by >50 ms over 24 h	ΔiPTH
Δvery-low frequency	TRACP-5b
Δlow frequency	TRACP-5b
Δhigh frequency	TRACP-5b

Conclusions: In CKD, (7-84)PTH, TRACP-5b, wPTH, and FGF23 predict imbalances of cardiovascular autonomic nervous system. We offer novel insights into the relationship between bone resorption and cardiovascular disease in CKD.

Funding: Government Support - Non-U.S.

PUB649

Does Combination of Cinacalcet with Paricalcitol in Secondary Hyperparathyroidism Treatment Make Sense? Jacek P. Zawierucha,[1] Wojciech Marcinkowski,[4] Jolanta Malyszko,[2] Jacek S. Malyszko,[3] Teresa Dryl-Rydzynska,[1] Tomasz R. Prystacki.[4] *[1]Fresenius Medical Care Polska S.A., Poznan, Poland; [2]Second Dept of Nephrology and Hypertension with Dialysis Unit, Medical Univ of Bialystok, Bialystok, Poland; [3]Depatment of Nephrology with Dialysis Unit, Medical Univ of Bialystok, Bialystok, Poland; [4]Fresenius Nephrocare Polska sp. z o.o., Poznan, Poland.*

Background: Prospective 6 month observation study of the sHPT paricalcitol treatment effectiveness with and without association with cinacalcet in hemodialysis patients.

Methods: The study included 64 hemodialysis patients aged 19-90, average PTH 930pg/mL±440pg/mL (2718;516pg/mL, median 784pg/mL). Paricalcitol included in an initial dose of approximately 48mcg/month (5-180mcg/month depending on the initial iPTH level). 16 patients were additionally administered with cinacalcet (0,6mg/kg/day initially).

Results: Paricalcitol impact on the concentration of iPTH, corrected calcium and alkaline phosphatase activity is shown in table 1.

	PAR(n=48)	PAR+CIN(N=16)	all(n=64)
baseline iPTH(pg/mL)	888	1055	930
week 24 iPTH(pg/mL)	356	516	396
p	<0.05	<0.05	<0.05
baseline corrected Ca(mg/dL)	9.5	7.4	8.9
week 24 corrected Ca(mg/dL)	9.7	10.5	9.9
p	>0.05	<0,05	<0.05
baseline ALP(U/L)	159	295	193
week 24 ALP(U/L)	116	158	127
p	<0.05	>0.05	<0,05

Paricalcitol significant effected significalnly on the corrected calcium concentration. Cinacalcet had also a similar effect on PTH level. In both groups effect on serum calcium and phosphate was observed. In both groups baseline iPTH was similar (888pg/mL (2718;516pg/mL) in paricalcitol group vs 1055pg/mL (2224;523pg/mL) in paricalcitol and cinacalcet group, NS). No significant hypercalcemia during the 6 months treatment with paricalcitol was observed.

Conclusions: Treatment of sHPT with paricalcitol in hemodialysis patients is effective and has a good safety profile. The combination of paricalcitol and cinacalcet does not improve the results of the treatment. The combination of paricalcitol and cinacalcet does not improve the results of the treatment. However, possible combination of two drugs may be considered in case of hypocalcemia, but cost-effectiveness should be taken into account.

Funding: Pharmaceutical Company Support - Fresenius Medical Care

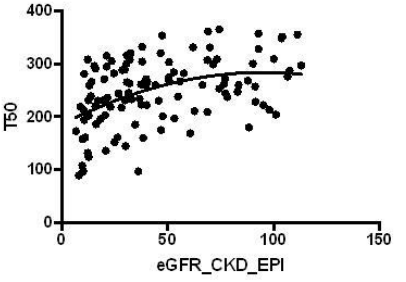
PUB650

Effect of eGFR on a Novel Assay of Calcification Propensity in Chronic Kidney Disease Bernhard O. Bielesz,[1] Thomas Johannes Reiter,[1] Rodrig Marculescu,[2] Andreas Gleiss,[4] Marija Bojic,[1] Daniel Cejka.[3] *[1]Medical Univ of Vienna, Div of Nephrology and Dialysis, Vienna, Austria; [2]Medical Univ of Vienna, Dept of Laboratory Medicine, Vienna, Austria; [3]Elisabethinen Hospital, Div of Nephrology, Transplantation, and Rheumatology, Linz, Austria; [4]Medical Univ of Vienna, Center for Medical Statistics, Informatics, and Intelligent Systems, Vienna, Austria.*

Background: Calcification propensity (CP) of human serum,which can be measured by a novel assay,associates with declining renal function and adverse outcomes such as mortality and cardiovascular events in chronic kidney disease (CKD) 3-4.We assessed which biochemical and bone-mineral metabolism markers modify increasing CP with declining kidney function.

Methods: Propensity of serum for calcification was determined by measuring the half-maximal transition time (T50) from primary to secondary calciprotein particles in serum (Pasch et al.,JASN 2012).Parameters were grouped into six mediator classes (cl1-6). T50,[calcium (Ca),phosphate (Pi),parathyroid hormone (PTH),fibroblast growth factor 23 (FGF23)] cl1;[25OH-Vitamin D;1,25OH-Vitamin D] cl2;[fetuin A (total and free fraction)] cl3;[Osteocalcin (carboxylated and uncarbox.),C-telopeptide,Osteoprotegerin,n-terminal type 1 procollagen] cl4;[sclerostin] cl5;[bicarbonate] cl6;magnesium,albumin were measured in 120 non-dialysis CKD patients.The difference between direct and total (direct and mediated by respective class) effect of eGFR was calculated in linear regression models including 95% bias-corrected and accelerated bootstrap confidence intervals.

Results: Ca,Pi,PTH,and FGF23 significantly alter the effect of eGFR on T50.



Effect eGFR doubling	95%CI	Effect
22.1375	11.7483-32.5266	Total
4.5777	-10.9753-20.1307	Direct
17.5598	3.8403-30.3569	Difference

Conclusions: Mineral-bone metabolism markers modify increased calcification propensity in renal function impairment.

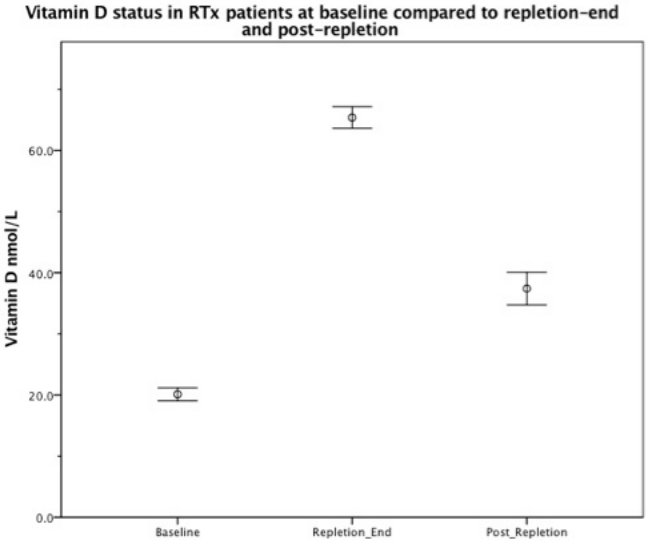
PUB651

Dynamics of Short-Term Native Vitamin D Repletion in Long-Term Renal Transplant Patients Oliver J. Ziff,[1] David Goldsmith.[2] *[1]Inst of Cardiovascular Science, Univ College London, London, United Kingdom; [2]Dept of Nephrology and Transplantation, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom.*

Background: Renal Transplant patients (RTx) are often Vitamin D (VD) depleted by CKD and repletion is warranted for multiple health issues, but how, and for how long, this should be achieved is unknown.

Methods: Bone biochemistry parameters were analysed from 102 repletion courses in 98 RTx patients (>10yr post-engraftment). 6month repletion was either 240,000IU colecalciferol (if 25(OH)D between 20-50), and 360,000IU (if <20nmol/L). 12months post-repletion data were available for 40 patients. All studied patients had stable, functional with PTH > 60ng/L and 25(OH)D <50nmol/L prior to supplementation.

Results: At baseline, 25(OH)D was 20.1±1.0nmol/L (mean±SEM), increasing to 65.4±1.8nmol/L following repletion (median 6months, p<0.0001). Following repletion and no further VD administration, 25(OH)D fell to 37.4±2.7nmol/L (median interval 12 months, p<0.0001).



PTH followed the opposite trend with baseline, repletion-end and post-repletion values being 144.22±12.0ng/L, 109.6±7.5ng/L (p<0.0001), and 122.4±17.0ng/L (p=0.08).

	Baseline (n = 102)	Repletion end (n = 102)	Rate of Change per year	Post repletion (n = 40)	Rate of Change per year
Vitamin D nmol/L	20.1 ± 10.3	65.4 ± 17.2 p<0.0001	+90.6	37.9 ± 16.7 p<0.0001	-27.5
PTH ng/L	144.2 ± 119.2	109.6 ± 72.6 p<0.0001	-69.2	119.5 ± 106.3 p=0.08	+9.9

There was no hypercalcemia (>2.65mmol/L), and renal function remained stable (eGFR change -2.98±10.2 mls/min/yr).

Conclusions: VD repletion can safely and effectively be achieved in chronic stable RTx recipients using a 6months intermediate-dose schedule, while significantly reducing raised PTH. Following repletion, 25(OH)D fell significantly, though at a 3-fold slower rate than seen with the impact of supplementation.

PUB652

Vitamin D: A New Marker for Acute Kidney Injury Progression

Jeanne Kamal,[1] Christine Boumitri,[2] Patricia Nasr,[1] Joseph Saabiye,[1] Lara El Khoury,[1] Firas Safa,[1] Julie Zaidan,[1] Rania El Mais,[1] Suzanne E. El Sayegh,[3] Elie El-Charabaty.[3] *[1]Internal Medicine Dept, Staten Island Univ Hospital, Staten Island, NY; [2]Gatroenterology Dept, Univ of Missouri, Columbis, MO; [3]Nephrology Dept, Staten Island Univ Hospital, Staten Island, NY.*

Background: Acute Kidney Injury (AKI) is a common and serious complication occurring in 5-7% of hospitalized patients. Markers helping in the early recognition of patients at risk are still lacking. Low levels of vitamin D and its metabolites occur in AKI. This raises the interest of studying vitamin D as a predictor of AKI outcome.

Methods: Patients admitted to SIUH with AKI with a normal baseline GFR (>60) were enrolled. All patients had their serum creatinine (SCr) checked within 24 hours of admission (D0) and 3 days after (D3) and Vitamin D levels (25 hydroxyvitamin D; 1,25 hydroxyvitamin D) at D0. Vitamin D was collected at D3 for the patients who remained in AKI and not for those who recovered (50% decrease in SCr or return to baseline).

Results: 56 patients in AKI were enrolled. 37 were men, mean age of 64.6, and BMI of 31.1. 22 (39.3%) were diabetic and 34 (60.7%) were hypertensive. 35 (56.4%) patients recovered from AKI and 21 (43.6%) remained in AKI at D 3. 1,25 DihydroxyVitamin D levels was significantly higher in patients whom kidney function improved (43.63 vs 30.1; p=0.036). There were no significant findings with respect to 25-hydroxyvitamin D (19.51 vs 18.86; p=0.77).

Conclusions: 1,25 DihydroxyVitamin D is the active metabolite of vitamin D. High levels of Calcitriol were associated with clinical improvement of AKI. A possible explanation of the low levels in kidney disease is probably due to the suppressed renal 1α-hydroxylase activity in contrast to 25-hydroxyvitamin D which levels reflect the total body stores of Vitamin D. Higher Calcitriol level is a marker of better outcome in AKI. Could supplementing patients in AKI with Clacitriol be an intervention helping in their recovery?

PUB653

Serum 1, 25-Dihydroxyvitamin D and Clinical Characteristics of End Stage Renal Disease Patients: A Cross-Sectional Study

Jing Luo, Junwei Yang. *Center for Kidney Disease, Second Affiliatted Hospital, Nanjing Medical Univ, Nanjing, Jiangsu, China.*

Background: Most patients with end stage renal disease (ESRD) have vitamin D deficiency, including deficiencies in both active (1, 25-dihydroxyvitamin D, 1, 25(OH)2D) and inactive vitamin D (25-hydroxyvitamin D, 25(OH)D). Most of the previous studies examined the inactivated form; however, the serum level of activated form and its role in ESRD patients were largely unknown. In this study we tested the levels of 1, 25(OH)2D in serum and evaluate their relations with clinical characteristics of ESRD patients.

Methods: This cross-sectional study enrolled a cohort of 709 ESRD patients on maintenance hemodialysis for at least 6 month, who came from two different hospitals. The serum concentration of 1, 25(OH)2D was measured by liquid chromatography mass spectrometer. Clinical covariates, including sex, age, dialysis duration were recorded. Serum concentrations of intact PTH (iPTH), calcium, phosphate, fibroblast growth factor 23 (FGF23) and alkaline phosphatase (ALP) were examined. Coronary artery calcification score (CACS), left ventricular ejection fractions (LVEF) and bone density were also measured.

Results: The serum levels of 1, 25(OH)2D were markedly decreased in hemodialysis patients (105.28 ± 65.74 pg/ml) compared with health control (110.70 ± 28.04, P<0.05). According to the quartile of serum 1, 25(OH)2D levels, the hemodialysis patients were divided into three groups. The serum FGF23, LVEF and blood flow rate were significant different among these three groups. However, no statistical differences were found in age, dialysis duration, serum iPTH, ALP and CACS. Nevertheless, no significant difference in serum 1, 25(OH)2D levels was found in patients with or without active vitamin D supplementation (66.24±5.48 pg/ml vs. 65.23±4.85 pg/ml, P>0.05). Moreover, lower serum 1, 25(OH)2D was significantly associated with incidence of osteodynia and skin itching (P<0.05).

Conclusions: ESRD patients have active vitamin D deficiency. It seemed that supplement with active vitamin D could not restore serum active vitamin D level. Lower serum 1, 25(OH)2D levels was associated with the incidences of osteodynia and pruritus.

Funding: Government Support - Non-U.S.

PUB654

Does the Treatment for Secondary Hyperparathyroidism in End-Stage Kidney Disease (ESKD) Benefit Phosphorus Metabolism?

Jose Maria Bautista, Fernando Tornero, Serena Gatius, Jose A. Herrero, Marisol Poma Tapia, Amir Shabaka, Virginia López de la Manzanara Pérez, Fabio Procaccini, Mauricio Alejandro Miranda Cam, Ana Sanchez Fructuoso. *Nephrology, Hospital Clinico San Carlos, Madrid, Spain.*

Background: The rationale for increased PTH observed in patients with end-stage kidney disease is probably the increase in urinary phosphorus excretion. For the treatment of secondary hyperparathyroidism (SHP), most of the current clinical practice guidelines recommend lowering PTH levels. However, control of PTH could be accompanied by a decrease in the urinary phosphorus excretion and an increase in its serum concentration. Our goal was to evaluate the influence of PTH reduction on urinary phosphorus excretion in patients with ESKD.

Methods: We analized 64 patients with ESKD, 33 males, mean age 69.3±12.9 years, diagnosed with SHP with PTH-lowering treatment (59 with paricalcitol, 5 with cinacalcet). We evaluated epidemiological factors, renal function, calcium and phosphorus metabolism parameters before and after treatment. Patients with other therapeutic modifications that could have influenced calcium and phosphorus metabolism were not included.

Results: After treatment, we observed a significant decrease in PTH levels (from 385±35.1 pg/ml to 311±36.2 pg/ml; p=0.001), an increase in serum phosphorus levels (from 4.35±0.1 to 4.65±0.1; p=0.003). There was also a significant decrease in phosphorus excretion, measured both as 24-hour phosphaturia (from 582.5±29.2 mg/24 h to 528±28.1 mg/24 h; p=0.024), and as fractional excretion of phosphorus (from 47.9±1.8% to 44.2±2.2%; p=0.029), and parallel to this, an increase in tubular reabsorption of phosphorus (from 52.3±1.9% to 55.3±2.1 %; p=0.029). Regarding renal function, we observed an increase in serum creatinine (from 3.7±0.14 mg/dl to 4.03±0.17 mg/dl; p=0.005), associated to a decrease in the glomerular filtration rate measured by CKD-EPI (from 16.3±0.7 ml/min to 14.6±0.6 ml/min; p=0.002). No significant differences were found in terms of levels of serum calcium and vitamin D.

Conclusions: The treatment for SHP in patients with ESKD can have a detrimental effect on serum phosphorus levels, increasing them by reducing its urinary excretion.

PUB655

Response of Serum 25-Hydroxyvitamin D Levels to Ergocalciferol Administration: Comparison of ESKD Patients and Healthy Volunteers

Ornatcha Sirimongkolchaiyakul, Katherine Wesseling-Perry, Georgina Chow, Barbara Gales, Isidro B. Salusky. *Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA.*

Background: Vitamin D deficiency is common in CKD patients and oral ergocalciferol supplementation is often used in this population. However, current studies are inconsistent as to the efficacy of ergocalciferol in ESKD patients as compared to healthy individuals. Thus, we compared changes in serum 25(OH)D between hemodialysis patients and healthy volunteers after the administration of oral ergocalciferol.

Methods: 16 hemodialysis patients (age 53.76 ± 26.1 years) and 7 healthy volunteers (age 44.71 ± 13.77 years) ingested a single dose of 50,000 IU of oral ergocalciferol. Biochemical levels were measured at baseline and 3 days after ergocalciferol ingestion. Changes of the 25(OH)D levels were compared between two groups.

Results: Patient age, sex and race were similar between groups. Baseline 25(OH) D levels were higher and a greater increase in levels was observed with ergocalciferol ingestion in healthy volunteers.

Results

	Healthy controls (N=7)	ESKD (N = 16)	p-value
Sex : female (N)	3 :42.86%	5 :31.25%	
Age (yr)	44.71 ± 13.77	53.76 ± 26.1	0.21
Race (N)			
-white	5 :71.43%	6 :37.50%	
-hispanic	1 :14.29%	4 (25%)	
-asian	1 :14.29%	3 (18.75%)	
-black		3 (18.75%)	
Cause of ESKD (N)			
-DM		5	
-unknown		4	
-interstitial nephritis		2	
-reflux nephropathy		1	
-complication after KT		1	
-hepatorenal syndrome		1	
-tubular necrosis		1	
S-25 -OH- vitamin D (ng/ml)			
-Baseline	26 ± 15.31	19.43 ± 6.70	0.32
-Post-therapy	43.57 ± 19.79	22.61 ± 6.29	0.24
-Change in 25D concentration	17.57 ± 6.43*	3.55 ± 3.43*	<0.001
S-PO4 (mg/dl)	3.27 ± 0.20	5.17 ± 1.34	<0.001
S-Ca (mg/dl)	9.19 ± 0.29	9.00 ± 0.50	0.21
S-PTH (pg/ml)	58.86 ± 15.75	192 ± 199	0.53

Values expressed as mean ± SD or median (IQ range).
* p<0.01 from baseline

Conclusions: ESKD patients exhibit a decreased response to ergocalciferol therapy as compared to healthy controls. Whether these differences reflect altered absorption or increased metabolism is unknown and warrants further investigation.

Funding: NIDDK Support

PUB656

The Efficacy of Intra-Operative PTH Assay during Parathyroidectomy for Patients with Renal Hyperparathyroidism

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Background: The value of intra-operative parathyroid hormone (ioPTH) during parathyroidectomy (PTX) for renal secondary and tertiary hyperparathyroidism (HPT) remains unclear. The present study aims at evaluating PTX in a single center experience and the ability of ioPTH assay to assist in the proper surgical excision of parathyroid gland (PTG) tissue.

Methods: The ioPTH was determined in 83 consecutive patients (51% males and 49% females) who underwent PTX from 2005 to 2015. Near-total PTX was performed in 74% of patients and total PTX in 26%.Sixty patients were on hemodialysis and 5 on peritoneal dialysis and 18 patients had a functional kidney transplant at the time of PTX. The ioPTH monitoring included 3 samples: pre-intubation (pre-ioPTH), at 10- and 20-minute post PTG excision (10-ioPTH and 20-ioPTH).

Results: Pre-, 10- and 20- ioPTH levels were 1194 pg/ml [403-1892], 123 pg/ml [67-224] and 87 pg/ml [45-149], resp. There was no significant difference in pre-, 10- and 20-ioPTH levels between the 3 PTX procedures (P = 0.60, 0.50 and 0.89, resp.). In patients with a functional kidney transplant, pre-ioPTH levels were lower than those on dialysis, (294 [180-403] vs. 1447 [868-2176] resp., P =0.004). However, the percentages of decrease of PTH at 10 and 20 min normalized with pre-ioPTH were not different in both groups (-83.9% versus -75.7%, P = 0.40 and -10.6% versus -26.5%, P = 0.42, resp.). Thirty-one % of the patients were readmitted to the hospital within 90 days mostly because of hypocalcemia (73.9%). Apart from easily treated hypocalcemia the PTX surgeries were uneventful in most patients (93%), 3 patients had local hematomas, 1 patient had significant local bleeding, 1 had temporary vocal cord palsy and 1 had local wound infection.

Conclusions: PTX is a safe procedure for renal patients with 7.2% surgical morbidities and no surgical related mortalities. As expected, easily correctable hypocalcemia after surgery is common and it accounts for approximately 2/3 of readmissions. Measuring ioPTH is very useful in directing the amount of PTG tissue removed.

PUB657

Abstract Withdrawn

PUB658

The Examination of the Adult Cases with Mild Proteinuria and the Alport-Like GBM Abnormality

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Background: Alport syndrome (AS) and Thin basement nephropathy(TBMN) are related to type IV collagen. About 40% of people of TBMD were reported the carrier of autosomal recessive Alport syndrome. Sometimes it is difficult to distinguish AS and TBMN. The genetic screening is useful, but has an ethical problem. To determine whether initial pathology, we examined pathological type and the renal outcomes.

Methods: This retrospective study population of 35 adult patients with biopsy-proven GBM abnormality who were registered at our hospital between 1985 to 2015 wiht a urinary protein<0.5g/gCre, eGFR>60 ml/min/1.73m2. We divided patients with clinical, pathological characters to three groups, which was AS(n=8), TBMN(n=7),atypical group(20 cases). We compared three groups. The primary endpoint was a 25%,50% reduction of eGFR, and secondary endpoint was the increase of urinary protein.

Results: The kidney biopsy for adaptation of the donors was 9 cases(AS:n=2,TBMN:n=3, atypical:n=4), the eGFR of donors was below 60ml/min/1.73 m^2 after the operation. The 50% reduction in the eGFR was observed with the patients of AS(n=2). A urinary protein>1g/gCre was observed at AS (n=5), atypical group(n=2).

Conclusions: AS and TBMN at adult ages are sometimes not clearly divided. We take care these type IV collagen nephropathy.

PUB659

Macular Holes Occur in Alport Syndrome Regardless of Genotype

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Background: Ocular manifestations occur commonly in patients with Alport syndrome. Most commonly these are diagnostically helpful and do not impair vision, for example retinal flecks and temporal retinal thinning. Less frequently anterior lenticonus can severely affect vision and may require lens extraction and replacement. Macular holes are uncommon, devastating to central vision, appear relatively specific to Alport syndrome, but no molecular genetic information has been published.

Methods: Over decades of studies on Alport syndrome we became aware of 6 patients with macular holes. Mutations in COL4A5 were identified by DGGE, ASOT probe tests, RNAse protection assays, and multiplex genomic PCR-SSCP in 5 families. All were confirmed by direct sequencing.

Results: Molecular characterization showed 5 patients with COL4A5 mutations and one probably autosomal recessive Alport syndrome.

Patient #	Sex	Mutation	Retina	Renal state at diagnosis
5020166	M	COL4A5 L1649R	Macular holes OU	SCr 1.0 mg/dl
2017006	M	COL4A5 Y1597X	Macular holes OU	Transplanted
2224004	M	Likely autosomal recessive	Macular holes OU, retinal flecks	SCr 1.0 mg/dl
2163003	M	COL4A5 G1205S	Macular holes OU, retinal flecks	Hemodialysis
2316001	F	COL4A5 3218+1 g>t	Macular hole OD	Not on dialysis
2158001	M	COL4A5 1981+3 g>t	Macular holes OU	Transplanted

Macular holes developed either early or late in the course of Alport syndrome. Renal phenotypes varied from COL4A5 mutations causing a severe (Y1597X, G1205S, 1981+3 g>t), uncertain (COL4A5 3218+1 g>t), or late onset (COL4A5 L1649R) renal phenotype. One patient comes from a family that appears autosomal recessive by pedigree analysis and by segregation of chromosome 2 haplotypes. Whole exome sequencing of this kindred is currently under way.

Conclusions: Giant macular holes occur occasionally in Alport syndrome, much more commonly than in the general population. They are not confined to a single mode of inheritance nor to COL4A5 mutations that cause a severe renal phenotype.

PUB660

The Novel Arg646Gly SLC4A1 Mutation Is Responsible for Distal Renal Tubular Acidosis

Joaquim T. Calado,[1,2] Sandra Brum,[3] Catarina Sofia Urbano Silveira,[4] Ana Santos,[2] Fernando E.B. Nolasco.[2] *[1]ToxOmics, NOVA Medical School, Lisbon, Portugal; [2]Nephrology, CHLC, Lisbon, Portugal; [3]Nephrology, Hospital de Santo Espírito, Angra, Portugal; [4]GenoMed, IMM, FML, Lisbon, Portugal.*

Background: The Cl^-/HCO_3^- exchanger (AE1), encoded by *SLC4A1*, is differentially expressed in the erythrocyte and kidney. The full transcript (eAE1) has a structural role in the red cell, while the shorter isoform (kAE1) is essential for renal acidification. *SLC4A1* mutations can account for hemolytic anemia or distal renal tubular acidosis (dRTA). Since mutations that give rise to spherocytosis/ovalocytosis are different from those responsible for dRTA, the occurrence of a dual hemolytic and dRTA phenotype is extremely rare. The few cases reported involve mostly a compound heterozygous condition for the Δ400-408 allele, leading to autosomal dominant southeast Asian ovalocytosis (SAO), together with a restricted number of mutations responsible for recessive isolated dRTA.

Methods: We report a 53 years old male of southeast Asian ancestry presenting with severe hypokaliemia (1.7 mmol/L) and a non-anion gap metabolic acidosis, with normal renal function and persistent alkaline urine. Nephrocalcinosis was documented by ultra-sound, recovered calculi were shown to be made of calcium phosphate and a diagnosis of dRTA was established. In spite the lack of anemia, an abdominal ultra-sound revealed cholelithiasis and cavernous transformation of the portal vein. Additional workup characterized a Coombs' negative chronic hemolysis displaying the typical findings of spherocytosis in the blood smear together with hemossiderosis in liver biopsy.

Results: Sanger sequencing of *SLC4A1,* identified 3 heterozygous variations: the c.1199_1225del27 (Δ400-408), the c.166A>G (p.Lys56Glu), known to be in linkage with the former, and the c.1936C>G (p.Arg646Gly) mutation. This latter allele is not found within the 1000 Genomes Project or the Exome Aggregation Consortium and is predicted to be pathogenic by *in silico* analysis.

Conclusions: The current report broadens the spectrum of *SLC4A1* mutations associated with dRTA and suggests this *novel* Arg646Gly mutation, in addition of being a codominant allele for the dual phenotype, may act as a recessive allele for isolated dRTA.

PUB661

Hereditary Transthyretin Amyloidosis and Kidney Injury

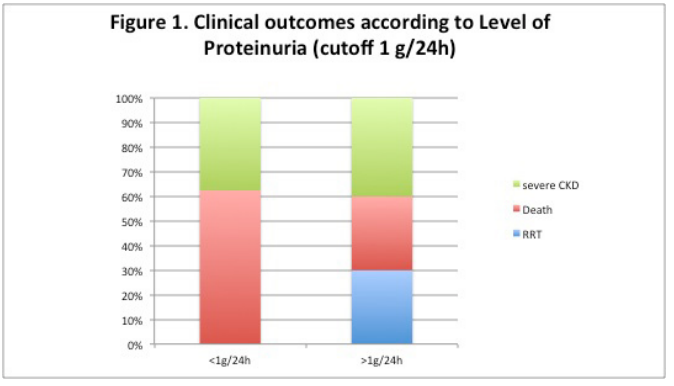
Asuncion Ferrer-Nadal,[1] Cristina Gallego,[2] Manuel Raya,[2] Mercedes Uson,[3] Antoni Figuerola,[3] Carles Montala,[4] Cristina Descals,[4] Tomas Ripoll,[5] Juana Nuñez,[5] Hernan Andreu,[6] Eugenia Cisneros-Barroso,[2] Juan Buades.[2] *[1]Dept of Nephrology, Hospital Son Llàtzer, Palma de Mallorca, Baleares, Spain; [2]D. Internal Medicine, H. S. Llàtzer; [3]D. Neurology, H. S. Llàtzer; [4]Neurophysiology U., H. S. Llàtzer; [5]D. Cardiology, H. S. Llàtzer; [6]D. Gastroenterology, H. S. Llàtzer.*

Background: Transthyretin-associated amyloidosis (ATTR) is a common autosomal-dominant form of amyloidosis frequently associated with the substitution of methionine for valine at position 30. Mallorca represents one of the most important focus of ATTR in the world. Kidney disease has been reported in Portugal as a result of renal deposition. They identified one third of patients with proteinuria and 10% progression to End Stage Renal Disease (ESRD).

Methods: Retrospective and prospective study of renal disease development in ATTR V30M. Renal assessment included clinical and laboratory tests in blood and urine. Chronic kidney Disease (CKD) was considered as a glomerular filtration measured by MDRD formula of 6 variables and Cistatine C.

Results: 155 ATTR V30M carriers were recruited at the Hospital Son LLàtzer among 2002 and 2016. Mean age at the onset was 48,64 years (SD 16,2), median 46,5 (IQR 35,2-62,7). 52% male. 36 cases (23,2%) presented CKD with MDRD < 60 ml/min and 22 (14,2%) with severe CKD (<30 ml/min). Cistatine C formula showed a significant increase

of CKD in this group of patients. 80% of patients developed proteinuria (73% < 500 mg and 27% >1g/24h). Only 4 patients with severe CKD developed nephrotic proteinuria. Liver transplantation was achieved in 53 patients (34,2%). 20 (12,9%) patients died during the study period.



Conclusions: We observed 2 different phenotypes of ESRD, one proteinuric and another not proteinuric, suggesting that the patients develop ESRD by totally different pathophysiologic mechanisms. MRDR formula underestimates CKD in this group of patients.

PUB662

Clinical Utility of Medical Exome Sequenscing/Whole Exome Sequencing in the Diagnosis of Genetic Renal Diseases Tomoko Uehara,[1] Toshiki Takenouchi,[1,2] Midori Awazu,[2] Kenjiro Kosaki.[1] *[1]Center for Medical Genetics, Keio Univ School of Medicine, Shinjuku-ku, Tokyo, Japan; [2]Pediatrics, Keio Univ School of Medicine, Shinjuku-ku, Tokyo, Japan.*

Background: Recently, genetic causes have been identified in various renal diseases thanks to the advent of next generation sequencing (NGS). We evaluated the clinical utility of NGS among patients who presumably have genetic renal diseases on clinical grounds.

Methods: The probands and their parents were recruited through the Japanese nation-wide undiagnosed disease program, Initiative on Rare and Undiagnosed Diseases (IRUD). Whole blood was collected from them after informed consent. Comprehensive genetic diagnosis was performed by whole exome sequencing (WES). Variants detected by the sequencer were filtered on quality, frequency, segregation pattern, previous reports, and genetic function and were confirmed by Sanger sequencing.

Results: 27 families with clinical diagnosis of genetic renal diseases were recruited based on positive family history or co-occurrence of extrarenal abnormalities: Ten were diagnosed as having congenital abnormality kidney and urinary tract (CAKUT), 11 presented with ciliopathy phenotype, 2 had VATER association, and others were chronic kidney disease (CKD) with extrarenal phenotypes. We confirmed 12 types of genetic diagnosis in 13 probands: Compound heterozygous mutations in MKKS, UBE3B, CC2D2A, CSPP1, and BBS10, a homozygous mutation in RPGRIP1L, heterozygous mutations in WAS, AGT, RET, PKD1, and JAG1, and a hemizygous mutation in OFD1.

Conclusions: Comprehensive genetic testing allowed genetic mutations in 13 of the 27 families (48.2%). These detection rate was comparable to that reported in the previous reports. Identification of precise genetic cause could contribute to medical management of the patients. An illustrative case was a patient with clinical diagnosis of CKD and thrombocytopenia. He was demonstrated to have WAS mutation through WES. The WES result made renal biopsy unnecessary. In addition, bone marrows transplantation was suggested to be effective. Further analyses are needed for unresolved families.

PUB663

Targeted Next Generation Sequencing of Alport Syndrome in Japan Tomohiko Yamamura,[1] Kandai Nozu,[1] Shogo Minamikawa,[1] Takeshi Ninchoji,[1] Yuko Shima,[2] Koichi Nakanishi,[2] Kazumoto Iijima.[1] *[1]Pediatrics, Kobe Univ Graduate School of Medicine, Kobe, Japan; [2]Pediatrics, Wakayama Medical Univ, Wakayama, Japan.*

Background: Alport syndrome (AS) is a hereditary disease caused by mutations of *COL4A3/COL4A4/COL4A5* genes. In recent years, comprehensive genetic analyses using next generation sequencer (NGS) are available for diagnosis of many genetic diseases. Comprehensive analyses such as whole genome sequencing or whole exome sequencing are very expensive. In contrast, targeted next generation sequencing using a custom panel is cost-effective and expedient if this method is applied to appropriate patients.

Methods: 40 patients suspected of having AS from their clinical findings and renal pathological findings or family histories were studied. Mutational analyses were performed using the targeted sequencing panel including 44 genes causing AS, other inherited glomerulopathies and X-linked kidney diseases.

Results: 32 patients (80%) were genetically diagnosed with AS by targeted next generation sequencing. 19 patients were diagnosed with X-linked AS (XLAS) caused by mutations of *COL4A5* gene and other 13 patients were autosomal dominant AS caused by mutations of *COL4A3* gene (5 patients) or *COL4A4* gene (8 patients). Of the remaining 8 patients, one patient was diagnosed with XLAS caused by deep intronic mutation using cDNA analysis. One patient was diagnosed with Dent disease caused by mutations of *CLCN5* gene and another patient who showed lamellation of the glomerular basement membrane (GBM) was diagnosed with Pierson syndrome caused by mutations of *LAMB2* gene.

Conclusions: Our results suggest that targeted next generation sequencing is a useful diagnostic tool for patients clinically suspected of having AS. In addition, it was revealed that some other inherited glomeruropathies with GBM changes or X-linked nephropathies can be diagnosed as AS by clinical findings, therefore this method is crucial for the accurate diagnosis of inherited kidney diseases.

PUB664

Development a Method of Estimating Salt Intake by Self-Completed Questionnaire for Japanese Mari Odamaki,[1] Eiko Kawakami,[1] Hiromichi Kumagai,[2] Yoshiko Tsumuraya,[2] Akihiko Kato,[4] Hideo Yasuda,[3] Yoshihide Fujigaki,[3,5] Akira Hishida.[6] *[1]Dept of Health and Nutritional Sciences, Tokoha Univ, Hamamatsu, Japan; [2]Dept of Clinical Nutrition, Univ of Shizuoka, Shizuoka, Japan; [3]First Dept of Medicine, Hamamatsu Univ School of Medicine, Hamamatsu, Japan; [4]Blood Purification Unit, Hamamatsu Univ School of Medicine, Hamamatsu, Japan; [5]Dept of Internal Medicine, Teikyo Univ School of Medicine, Tokyo, Japan; [6]Nephrology, Yaizu City Hospital, Yaizu, Japan.*

Background: It is important to know daily salt intake for hypertension treatment. We developed a method of estimating salt intake by self-completed questionnaire for Japanese.

Methods: We recruited 650 (male: female=237:413) people who agreed to participate in this study. We made a list of food which is eaten by Japanese people in their usual diet. We divided the food into seven groups by salt content per serving. We made a self-completed questionnaire to ask how often they consume each group of food per week. From this questionnaire we estimated daily salt intake in each person. In parallel, we calculated salt intake by measuring salt in the urine collected for 24 hours. Using the result of calculated salt intake, we evaluated the accuracy of the estimation method.

Results: A significant positive correlation was found between estimated salt intake by questionnaire and calculated salt intake by 24 hours urine collection ($r=0.03$, $p<0.0001$, $y=0.382x+5.23$). On eleven people, we made the estimation and calculation of salt intake twice, before and after the instruction of salt restriction. The change of the salt intake in each person estimated agreed well with the calculated one. The average decrease in 1.0g of salt intake estimated by the questionnaire corresponded to the decrease in 1.2 g of salt intake calculated by 24 hours urine collection.

Conclusions: The questionnaire we developed is useful for estimating salt intake in Japanese and for evaluating the effects of salt restriction instruction.

PUB665

Nutritional Assessment of Haemodialysis Patients Muhammad Nauman Hashmi, Wael Said Alshazly, Hammad Raza, Fayez F. Alhejaili. *Haemodialysis, King Abdullah International Foundation for Haemodilaysis, Riyadh, Central, Saudi Arabia.*

Background: Malnutrition is a strong predictor of mortality in Haemodilaysis patients. Several Scoring systems have been used previously but either they were on non-renal patients or include costly investigations or more subjective rather than objective.

Methods: This is prospective analysis of maintenance Hemodilaysis patients over period of 12 months in a single centre.This analysis was carried out from June 2015 till May 2016.It includes 5 objective assessments (Body Mass index,No of years on HD, Serum Albumin, Ferritin & Co-morbidities).1 Subjective assessment of Functional capacity was included in this scoring system. These parameters were evaluated every 3 months. Co-morbidities (Diabetes Mellitus, Ischemic Heart disease, Cerebrovascular disease and Hypertension--Every co-morbidity was given 1 score).

Score	0	1	2	3
Body Mass Index	≥20	18-19.99	16-17.99	<16
Functional capacity	Normal	Occasional difficulty	Difficulty with Independent Activity	Bed/Chair bound
No of years on Hemodilaysis	<1	1-3	3-4	>4
Serum Albumin	≥35 gm/l	32-35 gm/l	28-31 gm/l	<28 gm/l
Ferritin	<700 mcg/l	700-800 mcg/l	800-1000 mcg/l	>1000mcg/l
Co-Morbidities(D.M,HTN,CVA,IHD)	1 Co-morbidity	2 Co-morbidities	3 Co-morbidities	4 Co-morbidities

Maximum score is 18. Patients scoring ≥8 were categorised as high risk &<8 as low risk.Total no of patients present throughout assessment 174.

Results: We identified 12,10,11 &11 no of patients scoring ≥8 score in every quarterly assessment during 12 months.There were 6 patients constantly present in high risk group.In High risk group 3 patients died.Low risk group had 1 mortality during this study.

Conclusions: Nutritional Assessment plays key role in management of Hemodialysis patients.With this scoring system we are able to identify patients as high and low risk groups.This tool helps to identify at risk patients so that timely measures are taken to improve patient survival.This scoring system is cost effective and convenient.Our analysis suggests that it is reliable and we will continue to monitor patients with help of this tool to get more data over coming years.

PUB666

Prevalence of Protein Energy Wasting in Predialysis Patients Anita Saxena, Amit Gupta. *Nephrology, Sanjay Gandhi Post Graduate Inst of Medical Sciences, Lucknow, Uttar Pradesh, Indonesia.*

Background: Evaluating nutritional status is important for prevention of protein energy wasting (PEW). Objective: Prevalence of PEW in predialysis patients on first visit to a nephrologist.

Methods: Three day dietary intake of 484 CKD stage 3 and 4 patients. ISRNM criteria used for diagnosing PEW.

Results: Serum albumin was 3.77±0.83 (males) and 3.68±0.81 g/dL (females). As appetite, BMI and income decreased dietary protein and energy intake decreased significantly

Average Dietary Intake				
Sex	Energy kcal/kg	Energy deficit	Protein	Protein deficit
male	17.22±8.29	17.78±8.29	0.66±0.28	0.09±28
Female	16.88±7.66	18.12±7.66	0.64±0.30	0.11±0.30
Dietary intake based on Appetite				
	Normal 26.4%	Average 18.6%	Poor 26.4%	Anorexic 20.8%
Protein/M	0.79±0.23	0.58±0.17	0.50 ± 0 .20	0.27±0.17
Protein/F	0.79±0.23	0.56±0.16	0.48 ±0.15	0.29 ±.20
Energy/M	21.57±7.85	25±3.70	12.36±4.26	6.92 ±4.36
Energy/F	21.19 ±5.81	14.67±3.09	12.79±3.92	7.25± 3.95
Dietary Intake Based on BMI				
N%	Normal 52.8%	Uderweight 15.0%	Severly Underwt 32.71%	
Energy kcal/ kg	17.2 ±9.0 Deficit18	17.0±10.0 Deficit 18	15.91±11.1 Deficit 19	
Protein g/kg	0.6 ±0.34	0.5±0.4 (0.1 deficit)	0.5±0.44 (deficit 0.04)	
Based on Income groups				
	High Middle(17.2%)	Low Middle (53.9%)	Poor	
Energy Kcal/ kg	17.0(1037.11±331.99)	15.0(918.47±396.15	14.9 (913.15±392.84	
Protein g/kg/	0.63 (38.92±14.17)	0.57 (35.34±15.30)	0.50 (35.48±16.22)	
Serum Albumin	3.26±0.38	3.57±0.97	3.07±0.92	
BMI	23.98±4.98	23.59±4.41	20.84±3.46	

Appetite correlated with energy, protein, BMI with energy and GFR (p 0.000), income with BMI, protein and energy (p.000). Significant difference in appetite groups in energy, protein, GFR (p0.000) and serum albumin (p 0.025). Significant difference between income groups in BMI (P 0.000), energy (p 0.019), protein (p 0.031), albumin (0.001). Prevalence of PEW based on energy was 91%, protein 57%, BMI 56.6%, and appetite69.2%.

Conclusions: Dietary counseling can help preserve nutritional status. Appetite, BMI and income are markers of PEW in CKD.

PUB667

Which Inflammatory Biomarkers Are Associated with Diabetic Kidney Disease? Flaviu Bob,[1] Romulus Timar,[1] Daniel F. Lighezan,[2] Geta Bujor,[3] Mircea Munteanu,[1] Florica Gadalean,[1] Adelina Mihaescu,[1] Bogdan Timar,[4] Diana Lighezan,[1] Sagren Pillay,[1] Adalbert Schiller.[1] *[1]Internal Medicine 2, Univ of Medicine and Pharmacy, Timisoara, Romania; [2]Internal Medicine 1, Univ of Medicine and Pharmacy, Timisoara, Romania; [3]Biochemistry, Univ of Medicine and Pharmacy, Timisoara, Romania; [4]Medical Informatics, Univ of Medicine and Pharmacy, Timisoara, Romania.*

Background: Inflammation is associated in patients with chronic kidney disease (CKD) with an increased mortality. However, there is still uncertain which of the inflammatory biomarkers are prominently involved in CKD. In the present study we tried to compare the role played by two of these markers (interleukin-6 and C-reactive protein- CRP) in patients with diabetic kidney disease (DKD).

Methods: We performed this study on 52 patients with diabetes mellitus (DM) (13 patients with DM without renal involvement and 39 patients with DKD- with eGFR <60ml/ min or urinary albumin/creatinine ratio > 30mg/g), with a mean age of 64.16 +/- 8.35. In all patients we performed, using standard methods the following: serum creatinine, CRP, serum calcium, phosphorus, iPTH, urinary albumin/creatinine ratio; while IL6 was performed using ELISA method.

Results: In our subjects we tried to see if the studied inflammation markers show any correlation with renal function, and we found out that there was a statistically significant correlation between serum creatinine and IL6 levels (r=0.35, p=0.04), but there was no correlation between serum creatinine and CRP (r=-0.187, p=0.27). When we compared the group of patients with DKD with the control group, we found statistically significant higher levels of IL6 in the patients with DKD (10.74+/- 7.43 pg/ml vs. 5.7 +/-6.3 pg/ml, p=0.02), but no difference regarding CRP. We found also no statistically significant correlation between the two markers of inflammation (CRP and IL-6): r=-0.187, p=0.27. There were also no statistically significant correlations found between IL-6 or CRP with albumin/ creatinine ratio, serum calcium, serum phosphorus or iPTH.

Conclusions: In our study we found that the two inflammation markers studied – CRP and IL-6- showed different patterns of evolution, with an increase of IL-6, and not CRP, in patients with DKD.

Funding: Government Support - Non-U.S.

PUB668

Is Plasma Electronegative LDL Associated with Obesity in Chronic Kidney Disease Patients? Denise Mafra,[1] Felipe Rizzetto Santos,[2] Gisella Pires Mello,[2] Ana Beatriz Lesqueves Barra,[2] Maurilo Leite.[3] *[1]Federal Univ Fluminense; [2]Federal Hospital of Lagoa; [3]Federal Univ of Rio de Janeiro.*

Background: The progression of atherosclerosis is associated with the synthesis of different forms of modified LDL, including an electronegatively charged LDL subfraction, called LDL(-). In CKD patients the LDL (-) plasma levels are increased, but it is unknown whether obesity may be associated with these high levels. The aim of this study was to evaluate a possible association between obesity and LDL(-) plasma levels in non-dialysis CKD patients.

Methods: A cross-sectional study was conducted in 32 non-dialysis CKD patients (58.5 ± 12.7 years old, 23 men, 17 diabetics, BMI of 27.9 ± 5.7 Kg/m^2, creatinine clearance of 35.5 ± 19.6mL/min). The biochemical parameters were measured using routine methods and the CrCl was calculated according to the simplified MDRD formula.LDL(-) plasma levels were determined by ELISA using an anti-LDL(-) human monoclonal antibody. Body Mass Index (BMI) was defined as weight in kilograms divided by the square of height.

Results: The biochemical parameters are shown in Table 1.

Parameters	Values
Blood urea nitrogen (mg/dL)	90.4 ± 37.1
Creatinine (mg/dL)	2.4 ± 0.8
Glucose (mg/dL)	114.4 ± 42.9
Potassium (mEq/L)	4.9 ± 0.5
Hemoglobin (g/dL)	12.2 ± 1.6
Hematocrit (%)	37.8 ± 5.1
Uric acid (mg/dL)	7.2 ± 1.7
Cholesterol (mg/dL)	197.6 ± 61.9
Triglycerides (mg/dL)	158.0 ± 76.3
LDL (mg/dL)	136.8 ± 65.1
HDL (mg/dL)	32.8 ± 9.2
Albumin (g/dL)	4.3 ± 0.6

According to BMI, 25.8% were eutrophic, 38.7% overweight and 35.5% were obese. The LDL (-) plasma levels were 2.2 (1.2-6.1)U/L and there was a positive correlation with BMI. The linear regression analysis showed that BMI was an independent predictor for LDL (-) levels (β=0.6, p=0.007) after adjustment on age, gender, urea, glucose, cholesterol LDL and total cholesterol levels.

Conclusions: Obesity in non-dialysis CKD patients seems to have association with high levels of LDL (-), a modified, highly atherogenic LDL fraction.

PUB669

Differences in the Nutritional State of Advanced CKD and Hemodialysis (HD) Patients Using Malnutrition Inflammation Score (MIS) Guillermina Barril, Angel Nogueira, Martin Giorgi, Carmen Sanchez-Gonzalez, Jose-Antonio Sanchez-Tomero. *Nephrology, Hospital U. Princesa, Madrid, Spain.*

Background: To evaluate the nutritional state of CKD patients in stages 3-5 without dialysis and those undergoing hemodialysis by comparing malnutrition-inflammation percentages with the MIS . Thus also comparing nutritional parameters such as visceral proteins, hemoglobin, CRP and body composition by bio-impedance (BIVA) in both cases.

Methods: 350 patients were nutritionally evaluated. 180 (51.42%) with CKD and 170 (48,57%) undergoing HD. 61,14% were males. CKD xage was 71.71± 13,25 years vs xHD 68.94±13.76 years (p0.055). The stratified nutritional state diagnosis was established through the MIS and differences between HD and CKD were also found in other nutritional parameters such as Biochemical and body composition by BIA.

Results:

MIS Stages	well nourished	mil-moderate malnutrition	moderate-severe malnutrition	severe malnutrition	extreme malnutrition	Total
CKD	102 (56,6%)	47 (27.22%)	16 (8.88%)	11 (6.11%)	2 (1.11%)	180
Hemodialysis	22 (12,94%)	64 (37.64%)	35 (20.58%)	21 (12.35%)	28 (16.47%)	170
Total	124 (35,42%)	113 (32.28%)	51 (14.57%)	32 (9.14%)	30 (8.57%)	350

The results for MIS in CKD and HD show a lower percentage of well-nourished for HD than CKD in the studied population with under-nutrition being equally higher for HD than CKD for the different MIS strata. Significant differences between CKD vs HD were also found for : weight 72.81±16.20vs 67.70±15.45(p0.003), BCM% 38.52±10.38%

vs 35.46±11.75(p0.010), TBW 54.42±7.52% vs 52.75±7.18%, (p0.034), Muscle Mass% 35.65±9.56 vs 32.06±9.71(p0.001), BCMI6.84±2.17 vs 5.50±2.22 (p0.000), Hb 12.04±1.39 vs 1.32±1.42 p(0,000), albumin4.15±0.72 vs 3.99±0.50 (p0.019), prealbumin 26.46±7.15 vs 24.02±6.76 (p0.003), CRP 0.96±2.22 vs 1.64±2.52(p0.010).

Conclusions: 1. Monitoring the nutritional state in CKD units favoured the maintenance of a good nutritional state in a high percentage of patients. 2. In comparison with HD patients a greater percentage of normo-nourished patients was observed in CKD patients with differences in biochemical parameters , body composition and MIS scale.

PUB670

Attitudes and Opinions of Canadian Nephrologists Toward Continuous Quality Improvement Options Carina Iskander,[4] Gihad E. Nesrallah,[1] Christian G. Rabbat,[2] Rory F. McQuillan,[3] David C. Mendelssohn.[1] *[1]Nephrology, Humber River Hospital, Toronto, ON, Canada; [2]Medicine, McMaster Univ, Hamilton, ON, Canada; [3]Medicine, Univ of Toronto, Toronto, ON, Canada; [4]Univ of Western Ontario, London, ON, Canada.*

Background: Accountability and public reporting are increasingly prominent in health care. At the present time, quality improvement in Canadian nephrology is based on reporting of facility-wide performance. The objective of the study was to determine the attitudes and opinions of nephrologists towards a potential shift of improvement efforts from facility based to the individual physician level.

Methods: A pilot tested, web-based instrument was used to administer a survey to 330 nephrologists across Canada, through the Canadian Society of Nephrology (CSN).

Results: Out of the initial 320 eligible nephrologists contacted, 137 nephrologists responded (43%). Amongst all respondents, 48% agreed or strongly agreed that "there is significant variation in physician performance in my facility". 79% agreed or strongly agreed that "there are quality metrics that nephrologists should be responsible for". More than 80% agreed or strongly agreed that "there are some appropriate and valid measures that should form a basis for CQI activities". 82% agreed or strongly agreed to "receive a confidential, personalized score card reflecting my individual patient care". Only 30% agreed or strongly agreed that "public reporting of physician performance is likely to improve patient outcomes". Of note, compared to staff nephrologists, medical directors were twice as likely to agree or strongly agree that "shifting from program to physician level measurement and reporting is likely to improve care".

Conclusions: Overall, the majority of nephrologists were not supportive of shifting from program to physician-level measurement and public reporting. Leadership level physicians were more likely to support this shift. As modern medicine evolves towards more accountability and public reporting, the nephrology community must grapple with how to adapt to these trends and apply those methods that are validated and proven to improve patient care and outcomes.

PUB671

Primary Care Providers' (PCPs) Perceptions of Medication Safety in Chronic Kidney Disease (CKD) Clarissa Jonas Diamantidis, John Sperati, Mark A. Perazella, Yang Liu, Khaled Abdel-Kader, Sandeep S. Soman, Kerri L. Cavanaugh, Michelle M. Estrella, Varun Agrawal, Bernard G. Jaar, Michael J. Choi, Raquel C. Greer. *NKF Education Committee, New York, NY.*

Background: Renal clearance and potential nephrotoxicity makes medication safety in CKD a unique challenge, particularly among PCPs managing the complex multi-morbidity of CKD patients.

Methods: We conducted 4 qualitative focus groups of PCPs (n=32) across 4 US metro areas to assess their views of medication management in CKD. Participants were asked: "What aspects of medication safety are the most [and least] challenging for you and why?"; "Please describe resources, tools, or features of your practice that make it easier for you to address medication safety."; "What would you find helpful in addressing medication safety for your patients with CKD?" Focus group content was transcribed, and relevant concepts were identified.

Results: PCPs identified patient-level barriers to medication safety including lack of awareness of nephrotoxins such as NSAIDs and non-disclosure of their over-the-counter use. For example "I think they don't see this [NSAID use] as an issue and I take care of a lot of people who are educated and you would think explaining all this they get it. They don't get it half the time because their kidneys don't bother them." PCPs described inadequate knowledge of recommended dose adjustments in CKD, stating "I always forget like some antibiotics you actually have to adjust and I always forget which ones it is…" Difficulties managing polypharmacy and pain were identified as common challenges: "The guy has severe arthritis taking a lot of pain medicine that affects the kidneys. Then what are your alternatives? That's my problem." PCPs described facilitators of CKD medication safety such as educational materials to increase patient NSAID risk awareness, routine integration of pharmacists in CKD care, and utilization of electronic decision support tools.

Conclusions: Interventions targeting patient awareness of adverse renal effects of medications and enhancement of clinical medication safeguards using pharmacists and decision support tools may improve CKD medication safety in primary care.

Funding: NIDDK Support, Private Foundation Support

PUB672

Inferior Vena Cava Index: A Bedside Method for Dry Body Weight Assessment in Critically Ill Haemodialysis Patients Mostafa Abd-Elsalam Abd-Elkhalek. *Mansoura Nephrology and Dialysis Unit, Mansoura Medical School, Mansoura, Dakhlia, Egypt.*

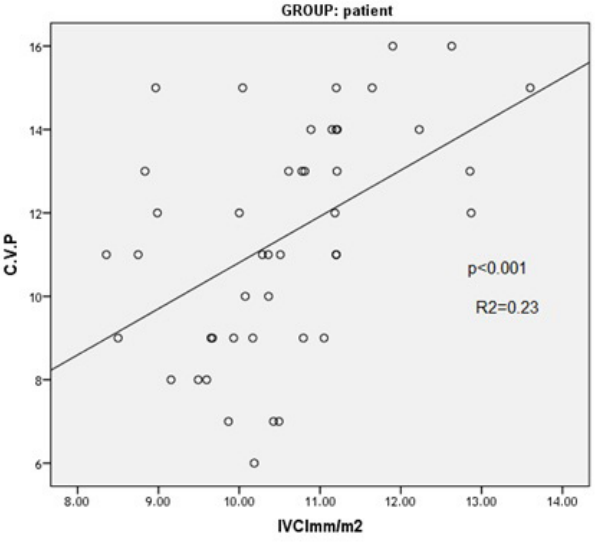
Background: Assessment of dry body weight in emergency conditions is still a matter of mystery. Central venous pressure is accurate but invasive. we try to find a simple non invasive method for assessment of dry weight in critically ill haemodialysis patients.

Methods: This is prospective observational study conducted on 45 haemodialysis patients referred to Mansoura Nephrology and Dialysis Unit from emergency hospital. The candidates for this study were seeking for urgent haemodialysis using temporary central intravascular access. Abdominal ultrasonography for assessment of IVC index was done immediately 30 min after dialysis session with measurement of the CVP through temporary central haemodialysis catheter. Pearson correlation between central venous pressure as an invasive maneuver to assess dry weight in haemodialysis patients, IVC maximum diameter in deep inspiration and IVC index was done.

Results: Pearson correlation between CVP and IVC maximum diameter in deep inspiration and IVC index revealed a statistically significant positive correlation between CVP and IVC maximum diameter (r=.411. P<0.005) and a statistically significant positive correlation between CVP and IVCI (R=.483, P<0.001). Multiple linear regression analysis (table 1) for CVP values as the dependent variable and both the IVC maximum diameter in inspiration and IVC index as independent variables was done using the step wise procedure.

Parameter		C.V.P
IVCI (mm/m2)	r	0.48
	p	<0.001
INSPMax	r	0.41
	p	<0.005

The procedure selected the IVC index as the best independent predictors for CVP value (R2=0.233, p<0.001).



Conclusions: Bedside sonographic measurement of inferior vena cava index which is simple, quick and non invasive method could be used as a reliable and accurate method for assessment of dry weight in critically ill chronic renal failure patients.

PUB673

Concomitant Use of Vancomycin and Contrast Exposure and AKI: Quality Improvement Program Muhammad Muneeb,[1] Farah Dadabhoy,[1] Charuhas V. Thakar.[1] *[1]Div of Nephrology, Univ of Cincinnati Medical Center, Cincinnati, OH; [2]Dept of Nephrology, Cincinnati VA, Cincinnati, OH.*

Background: Supratherapeutic Vancomycin (Vanc) is known to cause tubular toxicity leading to acute kidney injury (AKI). Intensive Vanc dosing and radio-contrast exposure are frequently needed together, for diagnosis and treatment in patients with high morbidity. Thus, a known event that reduces glomerular filtration rate (eGFR) can result in supra-therapeutic Vanc levels, resulting in AKI. In a prior institution wide trainee survey (ASN 2015), 60% providers were uncomfortable with Vanc dosing and depended on pharmacy protocols.

Methods: We describe two case-reports, which led to the development of a Quality Improvement Program (QIP) to reduce kidney adverse events due to exposure to concomitant nephrotoxins.

Results: We noted two cases of AKI to be associated with Vanc dosing protocol and contrast exposure. Patient-1 (33 yo male) and Patient 2 (59 yo male) were admitted for abdominal abscess and diabetic foot ulcer respectively. Figure 1 shows the course of AKI after Vanc and contrast exposure. Both patients were discharged with partial renal recovery (discharge creatinines > 2.0 mg/dl). Current pharmacy protocol utilizes pre-Vanc dosing labs and recent Vanc levels to determine daily dose, and do not consider concomitant nephrotoxin exposure (e.g. contrast), which although reversibly, could temporarily reduce eGFR. This

results in relative overdosing of Vanc for an average daily eGFR. In collaboration with pharmacy service, following recommendations are being adopted when implementing Vanc dosing protocol: 1. Alert to pharmacy of concomitant orders of nephrotoxins; 2. Modify Vanc dose; 3. Use frequent level monitoring.

Conclusions: Cases identified a current gap in drug safety; and multi-disciplinary QI programs in high risk patients could reduce AKI and associated morbidity.

PUB674

Native Kidney Biopsies: Complications and Yield: A Quality Improvement Initiative Mahwash Kamal, Karthikeyan Meganathan, Kotagal Shashi Kant. *Kidney and Hypertension, Univ of Cincinnati, Cincinnati, OH.*

Background: The kidney biopsy is the gold standard in the diagnosis and management of many renal diseases. Sample size is critical for the diagnosis of most renal pathologies. We performed a three year retrospective review to analyse our experience with the complications and diagnostic yield of native kidney biopsies and their impact on patient safety.

Methods: Native kidney biopsies were identified on the basis of pathology coding between January 2013 and December 2015. A biopsy sample was defined as adequate when it had at least 10 glomeruli for light microscopy and sufficient tissue for electron microscopy and immunofluorescence. Complications were defined as minor and major. Minor complications included bleeding requiring monitoring and no intervention. Major complications included, bleeding requiring intervention, nephrectomy and death.

Results: We performed 64 native kidney biopsies in 3 years. 47(73.4%) biopsies were performed by interventional radiologists and 17(26.6%) were performed by nephrologists.6(9.4%) patients had complications; 2 had minor and 4 had major. 33(51.5%) biopsies were adequate and 31(48.5%) were not adequate. There were only 3(4.7%) biopsies in which the pathologist was unable to provide any diagnosis. We found a higher likelihood of inpatient biopsies to be performed by IR. Rising creatinine increases the odds of biopsy to be performed by IR. Rising creatinine also increases odds of complications. Statistically significant difference for complication rates was not found with differences in gender, BMI, clinical setting, operator, age, kidney size, blood pressure and hemoglobin. Statistically significant difference for biopsy adequacy was not found with differences in BMI, operator or kidney size.

Conclusions: Our complication rates were comparable to other centers, however our biopsy sample adequacy was lower. Measures proposed to improve biopsy sample adequacy in our institution include: 1) changing biopsy needle size from 18 gauge to 16 gauge; 2) Visualizing all specimens under direct microscopy for sectioning; 3) identifying operators on the basis of experience and interest and designating them as the preferred operators for native kidney biopsies.

PUB675

Preventing Contrast-Induced Nephropathy in Patients with Renal Disease in a Nephrologic Day Hospital Nuria Rodriguez Mendiola, Maite Rivera, Victor Burguera, Estefania Yerovi, Martha Elizabeth Diaz, Jose L. Teruel, Fernando Liano. *Nephrology, Hospital Ramón y Cajal, Madrid, Spain.*

Background: The best established treatment for the prevention of CIN is intravenous hydration. Traditional regime consist of fluid volume loading before and after intravascular contrast media (CM) administration, which requires the patient to be admitted to hospital. We analyze the efficacy of intravascular hydration with n-acetyl-cysteine (NAC) in only one dose before CM administration, in an ambulatory way.

Methods: From January 2013 to December 2014, 97 patients with preexisting impairment of renal function (GFR<60 ml/min/1, 73 m2) (table 1) received our preventive scheme prior to intravenous radiographic contrast media.

Patients characteristics	
Age (years)	66±13(range 23-89)
Male/female (%)	76/24
Hipertensión (%)	81
Diabetes (%)	36
Peripheral vascular disease (%)	25
Serum creatinine (mg/dl)	3,9±2,9
Charlson index punctuation	5,8±2,7 (range 2-12)
ARB/ACE receivers (%)	58
Chronic kidney disease stages % : 3 4 5	 36 29 35

All the imaging tests were computed tomography (CT) with 100 cc of Iohexol as contrast media (concentration of 350 mg/ml). Imaging tests were programmed in the afternoon. During the morning patients were fluid loaded with 1000 cc isotonic saline solution with intravenous formulation of 2 grams of NAC post CM fluid infusion was not given. This treatment was administrated in the day hospital of Nephrology department, with no need of patient´s admittance. Serum creatinine was measured before and within 10 days of exposure to intravascular CM.

Results: Contrast induced nephropathy was defined as an increase of 25 % in serum creatinine level from baseline (KDIGO definition). With this criteria just 4 patients showed this rise in basal serum creatinine, and three of them recovered later within 1 month.

Conclusions: Intravenous saline solution with NAC precontrast, without infusion postcontrast, is shown to be effective in reducing the risk of CIN in patients with a preexisting renal dysfunction undergoing contrast CT scan. This is administered in ambulatory nephrologic day hospital, what avoids complications associated to hospital admittance and reduces costs.

PUB676

Implementation of an Evidence Based Protocol for Management of Hyperkalemia Jason K. Law,[1] Gaurav Ghosh,[1] Miriam Chung,[1,3] Ezra Gabbay,[1] Jeffrey I. Silberzweig.[1,3] *[1]Medicine, Weill Cornell Medical College, New York, NY; [2]Nephrology, The Rogosin Inst, New York, NY.*

Background: Hyperkalemia (Potassium > 6.0 mmol/L) is a common, potentially life-threatening emergency among hospitalized patients. Most patients at our institution are not routinely evaluated prior to initiation of treatment. Only 85% of patients with a serum potassium value above 6.5 mmol/L had an ECG. Most patients (82.1%) treated with calcium gluconate did not have ECG changes nor did patients treated with insulin and dextrose (68.5%). There is minimal data to guide management of hyperkalemia and common treatments can have serious adverse effects.

Methods: We reviewed the literature to evaluate the safety and efficacy of treatments for hyperkalemia and developed a protocol for management. The protocol incorporates the severity of hyperkalemia, physical examination, ECG findings, renal function as measured by urine output and dialysis status, presence of conditions which could rapidly raise potassium levels and other variables into a stepwise approach. The protocol is currently being piloted among patients admitted to our nephrology service.

Results: Initial results document that since the protocol was implemented, acquisition of ECGs in patients with hyperkalemia improved from 88.4% (61/69) to 100% (11/11). The number of patients unnecessarily receiving calcium gluconate decreased (46.4% (32/69) to 10% (1/10)) as did the utilization of the insulin and dextrose (68.5% (24/35) to 0% (0/9)). There have been no adverse events reported.

Conclusions: Our initial results show that implementing a standardized evidence-based protocol for management of hyperkalemia can improve the treatment of patients by reducing unnecessary treatment and improving monitoring. Our goal is to continue to revise the protocol and eventually distribute it to the rest of the hospital.

PUB677

The Comfort Status after Renal Biopsy Hui-Qun Li,[1] Wenbo Zhao,[1] Geng-Xi Sun,[2] Tan-Qi Lou.[1] *[1]The Third Affiliated Hospital of Sun Yat-sen Univ, Guangzhou, Guangdong, China; [2]Affiliated Hexian Memorial Hospital, Southern Medical Univ, Guangzhou, Guangdong.*

Background: Renal biopsy (RB) is an important auxiliary examination. It is helpful to identify the pathological types, guide treatment and learn prognosis of kidney disease. Because of strictly confined in the bed within 24 hours after RB, patients often have the physiological and psychological discomfort. The purpose of this study was to investigate the comfort status of patients after RB.

Methods: Renal biopsy (RB) is an important auxiliary examination. It is helpful to identify the pathological types, guide treatment and learn prognosis of kidney disease. Because of strictly confined in the bed within 24 hours after RB, patients often have the physiological and psychological discomfort. The purpose of this study was to investigate the comfort status of patients after RB.

Results: The GCQ scale scores increased gradually with the time after RB. The total GCQ score was 68.3±5.42 in the 6 hours and 85.2±6.63 in the 24 hours. The scores of physiological, psychological, social culture and environment dimensions in 24 hours were higher than in 6 hours after puncture. The discomfort which the patients complained mainly included the back pain and dysuria in bed.

Conclusions: Patients after renal biopsy had many uncomfortable aspects, especially in 24 hours. So medical personnel should be as much as possible to help the patients relieve discomfort, promote the patients to recovery and reduce complications.

PUB678

Improving Quality of Care in Acute Kidney Injury and Continuous Renal Replacement Therapy: From Clinical Practice Guidelines to Quality Measures Rhea Bhargava,[1] Saiprasad Narsingam,[1] Himmat Grewal,[3] Reem Mustafa.[2,1] *[1]Dept of Internal Medicine, Univ of Missouri- Kansas City; [2]Dept of Nephrology and Hypertension, Univ of Missouri- Kansas City; [3]Dept of Internal Medicine, Saint Vincent Hospital, Worcester, MA.*

Background: Monitoring quality in health care is of vital significance to avoid preventable medical errors and to improve the quality of health care which is delivered. There is wide variation across the globe in the care of patients with acute kidney injury

(AKI) and who are receiving continuous renal replacement therapy (CRRT). Clinical practice guidelines are available for patients with AKI and for patients who are receiving CRRT. We wish to present potential quality measures and their level of adaptation by health care delivery organizations.

Methods: Databases of Acute Dialysis quality initiative (ADQI) and Kidney Disease Improving Global Outcomes (KDIGO) were reviewed for clinical practice guidelines and potential quality measures prescribed by them for patients with AKI and for those needing CRRT. Then a search was done to determine whether these were endorsed by National quality forum(NQF) and Centers for Medicare and Medicaid services(CMS).

Results: Clinical practice guidelines for the diagnosis and management of AKI and guiding CRRT are available from both ADQI and KDIGO. These include factors affecting CRRT - patient selection, timing for initiation, insertion site of the dialysis catheter, risk of infection, type of anticoagulation, bleeding risk among others and AKI-definition and diagnosis . No clinical practice guidelines were being used as quality measures framed by National quality forum (NQF) or as Centers for Medicare and Medicaid services (CMS) core measures.

Conclusions: Wide scale use of quality measures are needed to monitor and thereby standardize and improve quality of health care delivery to patients with AKI and patients needing CRRT. NQF and CMS core measures do not currently contain measures pertaining to quality for AKI and CRRT populations. Incorporating them could lead to increased adherence to clinical practice guidelines and provide a much needed framework to improve the care for the AKI and CRRT populations in the hospital.

PUB679

Defining the Optimal Method to Monitor Albuminuria over Time in Toddlers Sophie Van den Belt,[1] Valentina Gracchi,[2] Dick de Zeeuw,[1] Hiddo Jan Lambers Heerspink.[1] *[1]Clinical Pharmacy and Pharmacology, UMCG, Groningen, Netherlands; [2]Pediatric Nephrology, UMCG, Groningen, Netherlands.*

Background: Microalbuminuria can also be found in toddlers. This could have important consequences for understanding pathophysiology and guiding possible treatment. In adults, the guideline for establishing and monitoring microalbuminuria over time recommends to use first morning void (FMV) urine samples collected over three consecutive days. Since such a guideline is absent in toddlers, we tested several urine collection strategies for albuminuria measurement in toddlers.

Methods: A FMV urine sample and random daytime urine sample were collected on three consecutive days at week 0 (period 1), week 4 (period 2) and week 8 (period 3) in toddlers aged 12 - 48 months. Urinary albumin (U_{AC}) and albumin:creatinine ratio (U_{ACR}) were assessed. Intra-individual coefficient of variation (CV), calculated as the standard deviation divided by the geometric mean of U_{AC} or U_{ACR}, was determined using only the first U_{AC} or U_{ACR} measurement of each study period and secondly using all three U_{AC} or U_{ACR} measurements per study period.

Results: A total of 38 toddlers (mean age 28.4 months, SD10.6, 64% male) were included. The geometric mean U_{AC} was 5.0 mg/L in the FMV and 5.2 mg/L in the random daytime sample, U_{ACR} was 13.3mg/g and 18.6mg/g, respectively. The lowest intra-individual CV was observed when U_{AC} was measured in FMV over three consecutive days (table).

Table: Within individual Coefficient of Variation in albuminuria

	Single urine sample per period		Three urine samples per period	
	FMV sample	*Daytime sample*	*FMV sample*	*Daytime sample*
U_{AC}	46.3%	72.7%	33.5%*	38.8%**
U_{ACR}	49.4%	69.8%	40.1%†	52.0%††

* p<0.009 single FMV U_{AC}; †p=0.02 vs single FMV U_{ACR}; **p=0.004 vs daytime single U_{AC}; ††p<0.001 vs daytime single U_{ACR}.

Conclusions: These data suggest that U_{AC} should be measured in FMV urine samples over three consecutive days to assess and monitor (micro)albuminuria in toddlers.

PUB680

L-Carnitine Replacement Improves Proximal Tubular Function in Patients with Fanconi Syndrome Kazuya Matsumura, Nariaki Asada, Midori Awazu. *Dept of Pediatrics, Keio Univ School of Medicine, Japan.*

Background: Fanconi syndrome (FS) is known to cause L-carnitine deficiency due to loss in the urine. On the other hand, L-carnitine deficiency causes FS by the impairment of mitochondrial ß-oxidation. We examined whether L-carnitine replacement improves proximal tubular dysfunction in patients with FS.

Methods: Six patients with FS (2 males and 4 females, age 8 to 22 years; 4 chemotherapy-induced, 1 Lowe syndrome, 1 extremely low birth weight) were studied. The median eGFR was 67 ml/min/1.73 m^2 (range 47-98). We assessed the presence or absence of and the severity of hypophosphatemia, phosphaturia, hypouricemia, uricosuria, glucosuria, ß2 microglobulinuria, enzymuria (assessed as N-acetyl-ß-glucosaminidase-to-creatinine ratio), aminoaciduria, and microalbuminuria.

Results: Total (median 30.3, range 23.1-38.8, normal 45-91 µmol/L) and free carnitine (median 30.3, range 23.1-38.8, normal 45-91 µmol/L) were decreased in all patients. Acylcarnitine was normal in 4 patients (median 8.5, range 4.7-11.9, normal 6-23) and decreased in 2 patients (4.7 and 5.6). The median dose and duration of L-carnitine treatment were 1160 mg/m^2/day (range 330-1980) and 25.5 months (range 18-26), respectively. Total and free carnitine were normalized in all 5 patients in whom serum level was measured after treatment. Acylcarnitine was normal in 4 after replacement, and increased in 1 (40) whose initial level was normal and eGFR was 47. Aminoaciduria, ß2 microglobulinuria, and enzymuria were present in all (6/6), glucosuria and microalbuminuria in 5, phosphaturia and hypophosphatemia in 3, and hypouricemia in 2. No patients had renal tubular acidosis. After replacement, at least one tubular dysfunction improved in all patients. Aminoaciduria, hypophosphatemia, and enzymuria resolved in 3 (50%), 2 (67%), and 1 (17%), respectively. The severity of enzymuria improved in 5 patients.

Conclusions: Free and total carnitine were decreased with low to normal acylcarnitine levels in FS. L-carnitine replacement partially improved tubular dysfunction including aminoaciduria, hypophosphatemia, and enzymuria. These results indicate that L-carnitine deficiency causes secondary proximal tubular impairment in patients with FS.

PUB681

Genotypic and Phenotypic Spectrum of Hereditary Nephrotic Syndrome in a Single Saudi Center Majed Aloufi, Naif Fahad Abdulmajed, Abdulmonem Mohammad Alghamdi, Saeed Ali Alghwery, Saeed Ali Alzahrani. *Pediatric Nephrology, Prince Sultan Military Medical City, Riyadh, Saudi Arabia.*

Background: Hereditary nephrotic syndrome (HNS) is a rare renal genetic disorders that present in children early in life and lead to end stage kidney disease (ESKD). We aim to describe their genotypic spectrum.

Methods: We identified 10 children with HNS presented between 2013 and 2015 in a single centre, where genetic testings and clinical courses reviewed.

Results: Three have PLCE1 mutation, three WT1, two NPHS1, one LAMB2, and one has putatively pathogenic variants at DGKE, KANK1 and PAX2.

Patient	Age (months)/ Sex	Histology	Genotype	Clinical course
HNS1	5/M	FSGS	Homozygous *PLCE1* mutation c.3058C>T (p.Gln1020*)	NS ESKD Septicemia Death
HNS2	5/F	FSGS	Homozygous *PLCE1* mutation c.3058C>T (p.Gln1020*)	NS ESKD Septicemia Death
HNS3	12/F	DMS/FSGS	Homozygous *PLCE1* mutation c.3058C>T (p.Gln1020*)	NS ESKD
HNS4	1/F	Not done	Heterozygous WT1 mutation (c.1385G>A p.Arg462Gln)	AKI ESKD Death
HNS5	7/F	MPGN	Heterozygous mutation in exon 9 of the WT1 gene (c.1357T>C p.Cys453Arg).	AKI ESKD
HNS6	18/M	Collapsing FSGS	Heterozygous variant at position c.299 in exon 1 of the *WT1* gene c.299C>G (p.Ala100Gly).	NS CKD IIIb
HNS7	2/F	Not done	Homozygous deletion of a single nucleotide at position c.139 in exon 2 of *NPSH1*(c.139delG), (p.Ala47Profs*81)	CKD II
HNS8	3/F	Not done	homozygous duplication of one nucleotide at position c.3250 in exon 24 of *NPSH1* (c.3250dupG), (p.Val1084Glyfs*12)	CKD II
HNS9	2/M	Not done	Homozygous mutation in exon27 of LAMB2 gene (c.4276dupG), (p.A1426fs)	NS AKI Septicemia Death
HNS10	18/M	MCD	No mutation detected. Putatively pathogenic variants detected in DGKE, KANK1 & PAX2 genes	NS SDNS FRNS

Conclusions: Correlating genotypic and phenotypic diagnoses will help in identifying the involved genes, so preventive measures such as family counseling can be undertaken. Our result is biased by small sample size, therefore a large national multi-center study is needed, as well as going further toward a national registry of those cases of HNS.

PUB682

GFR-Estimation Using Serum Creatinine Is Not Affected by Corticosteroid Therapy Emil Den Bakker,[1] Joanna Van Wijk,[1] Isabelle Hubeek,[2] Arend Bokenkamp,[1] Berend Koene.[1] *[1]Nefrology, VUMC, Amsterdam, Netherlands; [2]Clinical Chemistry, VUMC, Amsterdam, Netherlands.*

Background: Glucocorticosteroids (GCS) are widely used in patients with kidney disease. While the effect of GCS is well characterized for endogenous GFR markers as urea. cystatin C. β -2 microglobulin and β-trace protein. Little is known about their effect on serum creatinine (sCr) the standard endogenous parameter for GFR estimation.

Aims: To study the effect of GCS on the relationship between sCr and GFR measured by single injection inulin clearance (Cin).

Methods: Retrospective analysis of estimated GFR using the pediatric Schwartz equation (eGFR) and simultaneous Cin. Paired analysis of 22 children with and without GCS (median prednisone dose 35.5 mg/m^2/d). Cross-sectional study in 50 nephritis patients with similar characteristics, 31 of which received long-term GCS (median dose 12 mg/m^2/d, median GFR 93.7 ml/min/173m^2). The difference between eGFR and Cin (ΔGFR) was used to assess the interaction between creatinine and GCS using non-parametric tests and linear regression analysis for paired and cross-sectional data respectively.

Results: There was no significant difference in ΔGFR by paired analysis:

	GCS (-)	GCS (+)	P
	Median [IQR]	*Median [IQR]*	
Cin (ml/min/1.73m²)	103.5 [82.5-130.4]	116.3 [92.0-129.3]	0.123
eGFR	113.6 [91.3-166.9]	105.5 [90.6-163.6]	0.823
ΔGFR	-6.7 [-39.0-6.9]	-8.4 [-31.4-14.0]	0.527

Univariate linear regression analysis with ΔGFR as dependent parameter showed a significant relation with age, while prednisone dose and duration of GCS treatment had no significant effect on ΔGFR.

	B [95% CI]	P
Age	2.393 [0.593 to 1.494]	0.010
Gender	-4.451 [-19.130 to10.228]	0.545
Dose (mg/m²/d)	-0.325 [-0.737 to 0.087]	0.120
Dose (mg/kg/d)	-9.771 [-24.421 to 4.879]	0.186

These findings were confirmed by stepwise multivariate regression analysis in which only age was retained in the final model.

Conclusions: Data in dogs and man indicate that GFR increases in glucocorticoid excess. In the present study this was corrected for by using [ΔGFR as indicator of a potential GCS effect on the performance of serum creatinine as marker of GFR.

Conclusion

In the dosage studied, GCS do not interfere with the use of sCr as an endogenous marker of GFR.

Funding: Clinical Revenue Support

PUB683

Lack of Correlation between Changes in Ejection Fraction and Weight in Patients with Heart Failure Treated with Peritoneal Dialysis

Abhilash Koratala, S. Irfan Qadri, Amir Kazory. *Univ of Florida, Gainesville.*

Background: There is mounting evidence on the beneficial effects of peritoneal dialysis (PD) as an alternate therapeutic modality in patients with chronic heart failure (HF) and fluid overload, in the absence of end stage renal disease (ESRD). Improvement in left ventricular ejection fraction (LVEF) is one of the most frequently reported benefits of PD in this patient population. It is unclear whether the observed amelioration in cardiac function is correlated with correction of hypervolemia and lowered end-diastolic left ventricular pressure or due to less well understood mechanisms.

Methods: Available data from clinical trials of PD in HF performed between January 2000 and March 2016 that included more than 10 patients were selected and reviewed. Those studies evaluating the impact of PD on LVEF and volume status (assessed through changes in weight) in non-ESRD patients were included. Pertinent data were extracted and using Pearson product-moment correlation, the degree of linear dependence and correlation between these two variables was determined.

Results: Nine studies with a total of 426 participants were included. The mean age was 71.5 years, and the mean LVEF and weight before PD were 36% and 70.9 Kg respectively. There was substantial variation in the reporting time point for cardiac function and weight. LVEF changes ranged from -1 to +8.2 % (mean 3.6 ± 2.8) and weight changes ranged from -8.3 to +2 Kg (mean -2.56 ± 3.1). There was no correlation observed between changes in LVEF and weight (r=0.08, 95% CI of Correlation -0.62 to 0.70).

Conclusions: Currently available evidence suggests that changes in cardiac function and weight do not correlate in chronic HF patients who undergo PD. Hence, effective fluid removal and optimization of hemodynamic status via a left-shift on the Frank-Starling curve is unlikely to be the sole mechanism underlying improvement in left ventricular systolic function. Future studies are needed to clarify whether other proposed PD-specific factors, such as reduction in neurohormonal activation or removal of inflammatory mediators may play a role in this setting.

PUB684

Early and Late Patient Outcomes in Urgent Start Peritoneal Dialysis: A Matched Case-Control Study

Emily J. See, Yeoung Jee Cho, Carmel M. Hawley, Lauren R. Jaffrey, David W. Johnson. *Dept of Nephrology, Princess Alexandra Hospital, Australia.*

Background: Significant interest in the practice of urgent start peritoneal dialysis (USPD) is mounting internationally. Although several observational studies have supported the safety, efficacy and feasibility of this approach, little is known about the early complication rates and long-term technique and peritonitis-free survival of USPD compared to conventional start peritoneal dialysis (CSPD).

Methods: This single-centre, matched case-control study evaluated patients commencing peritoneal dialysis (PD) between 2010 and 2015. USPD patients, defined as needing to commence PD within 2 weeks of catheter insertion, were matched 1:3 with CSPD controls. The primary outcomes were early complications, both following catheter insertion and PD start (within 4 weeks). Technique and peritonitis-free survival were secondary outcomes.

Results: 104 patients (26 USPD, 78 CSPD) were included (mean age 50.9±14.1yr, 63% male). USPD patients were more likely to be referred late (73 vs 1%, P<0.01), initiate PD in hospital (58 vs 4%, P<0.01), and be prescribed lower initial exchange volumes (1.0L vs 2.0L, p<0.01). USPD patients experienced more frequent leaks post-catheter insertion and catheter migration post-PD start. There were no significant differences in overall or infectious complications, or technique or peritonitis-free survival between the groups.

	Within 4 weeks of insertion			Within 4 weeks of PD start		
	USPD (n=26)	**CSPD (n=78)**	**P value**	**USPD (n=26)**	**CSPD (n=78)**	**P value**
Overall	8 (31%)	16 (21%)	0.28	8 (31%)	14 (18%)	0.17
Leak	3 (12%)	1 (1%)	0.047	3 (12%)	2 (3%)	0.10
Exit site infection	4 (15%)	10 (13%)	0.92	4 (15%)	5 (6%)	0.38
Catheter blockage	1 (4%)	0 (0%)	0.25	1 (4%)	0 (0%)	0.25
Catheter migration	3 (12%)	3 (4%)	0.16	3 (12%)	1 (1%)	0.047
Peritonitis	0 (0%)	3 (4%)	0.57	0 (0%)	7 (9%)	0.19

Conclusions: Compared with CSPD, USPD has acceptably low early complication rates and similar long-term outcomes. USPD appears to be a safe and effective way to initiate urgent renal replacement therapy and has the significant advantage of vascular catheter avoidance. Serious consideration should be given to its future use.

PUB685

Tenckhoff Catheter Removal Is Not Mandatory in Tuberculosis Peritonitis Patients on Continuous Ambulatory Peritoneal Dialysis

Qijun Wan, Yongcheng He. *Dept of Nephrology, The First Affiliated Hospital of Shenzhen Univ, Shenzhen Second People's Hospital, Shenzhen, Guangdong, China.*

Background: The prevalence and prognosis of tuberculosis peritonitis (TBP) among continuous ambulatory peritoneal dialysis (CAPD) patients are not well known in China. Whether the Tenckhoff catheter must be removed or not in TBP patients still remains controversial. Our aim is to report a single-center experience in the management of TBP on CAPD patients.

Methods: This is a single-center case cohort study. 178 CAPD patients followed up in our center from 1997 to 2015 included. IFN-γ, IFN-γ (PB+P8.10), IFN-γ(P8.10)(ELISpot) in blood and peritoneal effluent fluid were examined in the clinical suspicious TBP patients to confirm the diagnosis, respectively. Anti- tuberculosis combined with CAPD treatment were given to the confirmed TBP patients. Clinical and laboratory data were assessed at the 0 month, 3 th month, 6 th month and 12 th month of the follow-up, respectively.

Results: Only one 39-year old woman with severe thalassemia and without extraperitoneal tuberculosis was diagnosed TBP. The prevalence of TBP in the present study was only 0.56%, which accounted for 0.9 % of all peritonitis episodes. The incidence of TBP was 1/806 months. Fever was normal five days after the initiation of anti-tuberculosis treatment. Other clinical and laboratory data were gradually improved during follow-up. The complications such as intestinal obstruction, peritoneal-wall fistula were not found. The Tenkehoff catheter was in perfect function during the whole follow-up.

Conclusions: The incidence and prevalence of TBP among CAPD patients are rare in this single China center. TBP should be considered in CAPD patients with neutrophilic 'sterile' peritonitis with no response to antibacterial medications. The severe anemia may be the risk factor for TBP in this patient. Tenckhoff catheter removal is not mandatory in TBP patients receiving anti-tuberculous therapy.

PUB686

The Evaluation of Balance and Fall Risk in Patients with Peritoneal Dialysis: Cross-Sectional Controlled Study

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Background: This study aimed to compare the balance parameter, and fall risk between in patients on peritoneal dialysis (PD) and healthy subjects. It was also aimed to determine whether there is a correlation between biochemical parameters with fall risk and balance assesments in PD patients.

Methods: We evaluated 58 patients on PD treatment (PD Group) and 75 healthy subjects (Control Group) for this cross-sectional controlled study. Balance parameters and risk of fall were masured by using Tetrax® Interactive Balance System. All participants were also evaluated via Berg Balance Scale (BBS) to determine dynamic and functional balance status. These variables were compared between two groups. Duration of PD, Kt/V_{urea} and serum biochemical parameters were recorded in patients on PD. Correlation analysis between these parameters and balance measurements were made in patients on PD.

Results: The mean age of PD and Control Groups were found 54.21±12.16 and 50.38±12.11 years respectively.No statistically significant difference was found between groups in terms of the sociodemographic features. Fall risk of PD Group was significantly higher than control group (p:0.00005) according to Tetrax measurement, but BBS score were similar (p>0.05) between two groups. Age of PD patients was negative correlated with BBS (r:-0.433). Risk of fall was positive correlated with BMI (r:0.339). Blood glucose, BUN of PD patients were positively correlated with balance parameters. There was no statistically significant correlation between duration of PD and Kt/V_{urea} with balance parameters and the risk of fall.

Conclusions: Balance is impaired in patients undertreatment of PD. Fall risk may be evaluated using Tetrax® Interactive Balance System instead of BBS in those patients. BMI and age affect the balance and fall risk. Biochemical parameters are not correlated of balance and risk of fall except BUN and glucose. Duration of PD and Kt/V_{urea} do not affect balance system.

PUB687

Microparticle Formation in Peritoneal Dialysis Rima Abou Arkoub,[1] Shareef Akbari,[2] Suzy Sun,[2] Mercedes N. Munkonda,[2] Swapnil Hiremath,[1,2] Brendan Mccormick,[1,2] Marcel Ruzicka,[1,2] Dylan Burger.[2] *[1]Div of Nephrology, The Ottawa Hospital; [2]Kidney Research Centre, Ottawa Hospital Research Inst.*

Background: Injury to the mesothelial layer of the peritoneal membrane during peritoneal dialysis (PD) is implicated in loss of ultrafiltration capacity but there are no validated biomarkers for mesothelial cell injury. Microparticles (MPs) are 0.1-1.0 µm vesicles shed from the cell surface following injury. Our laboratory and others have previously reported that MPs are sensitive markers of tissue injury in hypertension, hyperlipidemia, and diabetes however there are no studies examining the formation of MPs in the peritoneal cavity during PD.

Methods: We examined MP levels in peritoneal dialysis effluents by electron microscopy, nanoparticle tracking analysis (NTA), flow cytometry, pro-coagulant activity, and Western blot. PD effluents (Dianeal® 4.25%) were collected during a peritoneal equilibration test at 0 hours, 1 hour, 2 hours, and 4 hours dwell.

Results: NTA identified particles in the size range of 30-900 nm, with a mean of ~240 nm. MP levels increased in a progressive, non-linear manner and there was approximately a 4-fold increase in MP levels at 4 hours ($P<0.01$, $n=6$). Electron microscopy confirmed size and morphology of vesicles consistent with characteristics of MPs as well as the presence of mesothelin on the surface. Western blot analysis of the MP fraction also identified the presence of mesothelin after 4 hours suggesting that MPs found in PD effluents arise, at least in part, from mesothelial cells.

Conclusions: Our results show that MPs are formed and accumulate in the peritoneal cavity during PD, possibly as a stress response. Assessing levels of MPs in PD effluents may be useful as a biomarker for peritoneal membrane damage.

PUB688

The Opinion of Nephrologists Regarding Quality Management in Peritoneal Dialysis – The Network-Based Conjoint Analysis Study Hisako Yoshida,[1] Kazuhiko Tsuruya.[2] *[1]Clinical Research Center, Saga Univ Hospital, Saga, Japan; [2]Dept of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu Univ, Fukuoka, Japan.*

Background: In Japan, peritoneal dialysis (PD) is selected as the mode of renal replacement therapy in less than 10% of incident end-stage kidney disease patients, in spite of some medical and social benefits of PD have been revealed. One of the reason might be that quality management by means of PD is considered too difficult for a number of doctors and health care staffs. In the present study, we conducted a questionnaire study to elucidate the opinion of nephrologists regarding PD management using a network clustering-based conjoint analysis method.

Methods: The 34 simulation cases were created to quantify the relative importance of 9 hypothetical patient attributes, including 1) age and living, 2) sex and self-management, 3) blood pressure, volume status and dialysate types, 4) primary disease and cardio-cerebrovascular disease, 5) PD vintage, 6) peritoneal equilibration test, 7) residual renal function and mineral and bone disorders, 8) peritonitis, and 9) anemia. These attributes were extracted using network clustering method which were significantly associated with outcomes defined transfer to hemodialysis or death, in actual 105 PD patients observed from May 2006 to November 2014. The sample size was calculated according to precedent studies (Whitman CB, et al. Clin J Am Soc Nephrol, 2013). In the present study, participants completed 34 tasks with 5 alternatives and 5 levels, producing a sufficient sample size of 15.

Results: Sixteen nephrologists in Kyushu University Hospital were participated in this study. Attribute of "blood pressure, volume status and dialysate types" was the most important factor for nephrologists' evaluation of management in PD patinens, which accounted for 19.1% of decision making, followed by "peritonitis" (13.0%). According to the utility scores of these clinical factors, sustained volume overload and repeated peritonitis had an impact on the opinion of the nephrologists regarding quality management in PD.

Conclusions: For nephrologists, volume overload and peritonitis might be considered important factors to maintain PD.

PUB689

Bedside Peritoneal Dialysis Catheters for the Management of Refractory Ascites: A Multi-Centre Experience Reid Whitlock,[1,2] Paul Komenda,[1,2,3] Navdeep Tangri,[1,2,3] Claudio Rigatto,[1,2,3] Jay P. Hingwala,[3,4] Sean Armstrong.[1,3] *[1]Chronic Disease Innovation Centre, Seven Oaks General Hospital, Winnipeg, MB, Canada; [2]Community Health Sciences, Univ of Manitoba, Winnipeg, MB, Canada; [3]Medicine, Univ of Manitoba, Winnipeg, MB, Canada; [4]Nephrology, Health Sciences Centre, Winnipeg, MB, Canada; [5]Nephrology, St. Boniface General Hospital, Winnipeg, MB, Canada.*

Background: Refractory ascites is when fluid recurrently accumulates in the peritoneal cavity, and is a common complication of liver cirrhosis. It can result in symptoms of anorexia, early satiety, nausea and vomiting, shortness of breath, and cause limited mobility. The initial management typically involves sodium restriction and diuretic therapy. When ascites no longer can be controlled by these measures, large volume paracentesis (LVP) is the treatment of choice in many patients. We believe that tunneled, peritoneal dialysis catheters placed at the bedside by trained operators is a safe, effective alternative for the palliation of refractory ascites.

Methods: The Manitoba Renal Program interventional nephrology program has offered the service of placing bedside PD catheters in patients with refractory ascites since 2010. We have collected basic demographic and comorbidity data on these patients in addition to complications of the procedure and outcomes such as peritonitis and survival.

Results: We have placed 29 PD catheters for the sole indication of refractory ascites since 2010. We have experienced no complications with the insertion procedure itself. Our patients had a mean age of 64 years and 52% were male. The reasons for ascites in each patient included cirrhosis (14), malignancy (10), heart failure (4) and other (1). The median survival time from the time of insertion was 56 days. In a total person-time at risk of 302 months, only 1 infection of peritonitis was detected. There were no cases of peritonitis among those whose ascites was caused by cirrhosis.

Conclusions: Bedside PD catheter insertion by trained operators appears to be a safe, effective option for the management of refractory ascites. Prospective, randomized trials are needed to assess survival, quality of life and patient satisfaction metrics for this palliative procedure.

PUB690

Factors of the PD Patient That Affect the Period of the First Incidence Peritonitis Won Min Hwang, Se-Hee Yoon, Sung-Ro Yun. *Dept of Nephrology, Konyang Univ Hopital, Daejeon, Republic of Korea.*

Background: PD peritonitis is the most important cause of failure of peritoneal dialysis and the times of first incidence of peritonitis are not the same on all patients. And there are very few studies on the factors that affect the time of manifestation of the first incidence of peritonitis. So, through this Study we will try to examine the clinical and environmental factors that affect the time of manifestation of the first incidence of peritonitis and the effect of the time of manifestation of the first incidence of peritonitis on convalescing patients.

Methods: Retrospective researches have been executed on the basis of the medical records on the occurrence of peritonitis, clinical factors (cause of ESRD, BMI, serum albumin, hemoglobin, accompanying diseases and microbiologic cause) and environmental factors (gender, age, residence, educational level and whether employed or not) of these subjects. Factors that affect the time of the 1st manifestation of peritonitis were analyzed by conducting multivariate analysis on the aforementioned factors. The subjects were divided into the 'early peritonitis group' and the 'late peritonitis group' on the basis of 6 months as the standard time of manifestation of peritonitis since the commencement of dialysis in order to comparatively analyze the prognosis of the patients.

Results: 478 patients over the age of 18 years who continued to undergo peritoneal dialysis for more than 90 days after having commenced peritoneal dialysis during the period from January 2008 to December 2015 were chosen as the subjects of this study. In this study, two environmental factors, namely, the residence and the level of education, affected the time of manifestation of the first incidence of peritonitis on patients. In addition, the early peritonitis group had a higher incidence of manifestation of peritonitis with longer periods of hospitalization.

Conclusions: Therefore, it is anticipated that delaying the manifestation of the 1st incidence of peritonitis through management and provision of education for the peritoneal dialysis patients would be helpful to the patients not only from the perspective of the prognosis but also save them from long pricy hospitalization.

PUB691

Molecular Hydrogen Dissolved Dialysate Suppress Iron Induced Peritoneal Mesothelial Change in Rat Models Wan-Jun Zhu,[1,2] Ayano Gibo,[1] Shigeru Kabayama,[2] Masaaki Nakayama.[1] *[1]Dept Kidney and Hypertension, Fukusihma Medical Univ, Fukushima, Japan; [2]Medical Device, Nihon Trim, Osaka, Japan.*

Background: Free iron induces oxidative stress by Fenton reaction and causes peritoneal mesothelial injury consequently. Molecular hydrogen (H2) has anti-oxidative and inflammatory effects in biological way. This study is to clarify whether H2 could protect peritoneal mesothelial injury by iron.

Methods: SD male rats (n=10, 8wks old) were divided into two groups: Fe and H2-Fe (HFe) group. Rats were subjected to intraperitoneal injection of peritoneal dialysate (20mL/daily) for ten days; dialysate contained 0.05mM Fe2Cl3 in Fe group, and that with 0.8-1.0 ppm H2 in HFe group, respectively. Parietal peritoneal membrane thickness and shedding length (loss of mesothelium) were analyzed with Masson Trichrome staining pictures. Immunohistochemistry staining was performed for determining proliferative changes (Ki67), apoptosis (m30cyto) and EMT (vimentin). Real time PCR were performed in collected surface cells to analyzed wound healing, inflammation related cytokines.

Results: There were significant differences between the two groups, in peritoneal thickness (HFe vs. Fe: 53.3±5.7 vs. 60.9±3.1mm; $p<0.05$), and in shedding cells analysis (2.4±1.5 vs. 28.9±7.1%; $p<0.05$). In regards to surface immunostaining positive cells, there were significant increases in Ki67 (0.010±0.002 vs.0.004±0.001/mm; $p<0.05$), and decreases in m40cyto (0.018±0.004 vs. 0.013±0.002 /mm; $p<0.05$) in HFe as compared to Fe group, respectively, while no differences were found in vimentin. Real time PCR showed that, expressions in HFe were significantly lower as compared with Fe group, in TNFa (0.6±0.2 vs. 6.3±3.1; $p<0.05$), and IL1b (0.2±0.2 vs. 4.2±1.8; $p<0.05$), while they were higher in TGFb (5.5±2.1 vs. 0.6±0.1), Fibronectin (5.5±2.1 vs. 1.4±0.3) and CTGF (4.4±0.9 vs. 2.5±1.3).

Conclusions: Molecular hydrogen could ameliorate oxidative/inflammatory peritoneal injury induced by iron, through the mechanisms such as, suppression of apoptosis, and enhancing regenerative process of mesothelial cells.

Funding: Government Support - Non-U.S.

PUB692

Low Protein Diet in Early Years of PD Initiation Leads to the Preservation of Residual Kidney Function in Peritoneal Dialysis Patients

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Background: In peritoneal dialysis patients, dietary protein restriction is recommended 0.9-1.2g/kg/day in Japan. This recommendation is based on the effect of the protein leakage into the dialysis fluid and nutritional status. However, it is not discussed in terms of residual kidney function and few reports examined the protein restriction effects on residual kidney function. This study aimed to evaluate the protein restriction effects on the residual kidney function in peritoneal dialysis patients.

Methods: A total 29 PD patients (15 males, mean age of 53 years old) who visited our hospital between January 2006 and May 2015 were enrolled. We evaluated the relationships between the residual kidney function and clinical parameters in peritoneal dialysis patients over three years after the initiation of peritoneal dialysis.The study protocol was reviewed and approved by the Ethics Committee of Kansai Medical University.

Results: In multivariate models, decreases in residual Kt/V from first PET to second PET were most associated with nPCR at first PET (r2 = 0.319, P = 0.021). Next, to define the effectiveness of protein-restricted diet in PD patients, we conducted a sub-analysis by dividing the patients into two groups: those with nPCR of < 0.8 and >= 0.8 at first PET or second PET. The group of strict dietary restriction of nPCR of < 0.8 slowed the decline of residual renal function compared with that of nPCR of >= 0.8, without worsening indicators of nutrition and arteriosclerosis, for example albumin and skeletal muscle rate.

Conclusions: Our observations indicated that decreases in residual renal function were most associated with nPCR and strict dietary restriction of less than 0.8 nPCR, which is the predialysis level, may postpone reduction of residual renal function without causing malnutrition, during early years of PD initiation.

PUB693

Markers of Rhabdomyolysis in Peritoneal Dialysis

Sofia H. Marques, Rute Carmo, Luís Mendonça, Ana Teresa Nunes, Ana Beco, Ana Oliveira, Manuel Pestana. *Nephrology, Centro Hospitalar São João, Porto, Portugal.*

Background: Rhabdomyolysis results from injury to skeletal muscle and leakage of intracellular contents such as creatine kinase (CK). It may lead to nephrotoxicity, myalgias, muscular weakness and possible electrolyte abnormalities. Little information is available regarding rhabdomyolysis in peritoneal dialysis (PD) patients. We aimed at analyzing its incidence and possible determinants in this population.

Methods: We performed a retrospective analysis of the 115 patients in our PD program in December 2015, reviewing demographic, clinical and laboratory information dating from the last 4 months. All patients had recent results of CK, myoglobin and aldolase.

Results: Mean age was 53.5 years (±14.0), 54.8% of the patients were men and 71.1% were taking statins. Median values for CK, aldolase and myoglobin were 111 (IQR 78-188) U/L; 5.5 (IQR 4.5-7.7) U/L and 254 (IQR 184-409) ng/mL respectively. Only 7.8% of the patients had all markers within the reference range; 31.3% had 2 and 13% had the 3 markers above the normal range. CK correlated well with the 2 other markers (r=0.497 for aldolase and r=0.771 for myoglobin; p=0.00). CK had a positive correlation with the Adragao vascular calcification score (r=0.24; p=0.01), systolic blood pressure (r=0.21; p=0.03), total body water measured by bioimpedance (r=0.34; p=0.00), body mass index (r=0.22; p=0.04) and negative correlation with serum calcium (r= - 0.29; p=0.00). Men had a higher CK than women (median value 144 vs. 88; p=0.00). No significant relationships were found between CK and age, diabetes, use of statins, vitamin D analogs, cinacalcet, phosphate binders, erythropoiesis-stimulating agent, renin-angiotensin system blockers, serum albumin, phosphate, sodium, B-natriuretic peptide, dialysis efficiency by Kt/V or being on continuous ambulatory peritoneal dialysis vs. automatic peritoneal dialysis.

Conclusions: Higher calcification scores were associated with an increased risk for rhabdomyolysis in PD patients, maybe due to tissue hypoxia. Statins were not associated with rhabdomyolysis in our population and seem to be safe, although this is a cross-sectional analysis.

PUB694

Identifying Urine Microbiome in Patients Receiving Peritoneal Dialysis

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Background: No data exists on urinary microbiome in peritoneal dialysis (PD) patients. The aim of this pilot study is to identify urinary microbiome and correlate with urinary symptoms in patients receiving PD.

Methods: Patients who were 18 years and older and receiving PD at our institute are included. Patients who received antibiotics within 4 weeks or had an episode of peritonitis 8 weeks prior to enrollment were excluded. 10 cc of random mid-stream urine is collected using routine sterile techniques. 16S rRNA gene sequencing is used to identify bacteria that are not routinely cultivated by clinical microbiology laboratories. Demographic and clinical characteristics are collected from electronic medical records.

Results: Of the 25 PD patients, 5 are excluded (3 patients were on antibiotics and 2 refused).9 of the 20 remaining patients with native urine output are included in the study. Baseline characteristics are shown in table 1.

Table 1: Baseline Characteristics of Study Population in Patients who have urine output (n=9)	
Mean age in years	57.5 years
Sex (M:F)	1:1.25 (5:4)
Race	AA: 33.3 % (3) Hispanic: 44.4 % (4) Others: 22.2 % (2)
Diabetes	44.4 % (4)
History of peritonitis (over the last year)	0 % (0)
History of abdominal surgery	77.7 % (7)
Type of transporter	High Average: 44.4 % (4) Low Average: 44.4 % (4) High: 11.1 % (1) Low: 0 % (0)
Mean dialysis vintage time in years	1.39 years

There is wide variation in the urinary microbiome. Streptococcus is the predominant bacteria in 3 patients (2 female and one male), lactobacillus in one female and prevotella in another male patient. 3 patients have no predominant bacteria. Nocturia (waking up more than once in the middle of the night to urinate) is predominant in male PD patients compared to females (80% vs. 25% respectively). The sample size was too small to make any meaningful correlation between urinary microbiome and urinary symptoms.

Conclusions: Urinary microbiome varies in each patient and further research is needed to delineate its role urinary tract symptoms in PD patients with native urine output.

PUB695

Hypoalbuminemia in Peritoneal Dialysis

Sofia H. Marques, Rute Carmo, Luís Mendonça, Ana Teresa Nunes, Ana Beco, Ana Oliveira, Manuel Pestana. *Nephrology, Centro Hospitalar São João, Porto, Portugal.*

Background: Hypoalbuminemia is associated with mortality in peritoneal dialysis (PD) patients and may result from malnourishment, non-nutrition factors or PD-related factors such as protein loss in the effluent. We aimed to study determinants of serum albumin in a PD population.

Methods: 115 patients in our PD program in December 2015 entered this cross-section analysis. Current therapy, PD modality, clinical data, serum markers dating from the last 4 months were recorded.

Results: Mean age was 53.5 (±14.0) years, 54.8% of the patients were men and only 25.4% had normal serum albumin. The remaining had serum albumin < 4g/dL, in 39.8% of cases < 3.5g/dL. Median protein losses were 18.0 (IQR 12.3-24.5)g/day. Serum albumin had a significant negative correlation with age (r= - 0.19; p=0.047), C-reactive protein (r= - 0.19; p=0.04), B-natriuretic peptide (r= - 0.20; p=0.03) and extracellular/intracellular water ratio by bioimpedance (r= - 0.33; p=0.00). A positive correlation was found with urine output (0.27; p=0.00), hemoglobin (r=0.21; p=0.03), serum calcium (r=0.25; p=0.01), potassium (r=0.20; p=0.03) and sodium (r=0.22; p=0.02). Hypoalbuminemia was significantly more frequent among patients on automatic peritoneal dialysis (APD) vs. continuous ambulatory peritoneal dialysis (3.48±0.54 vs. 3.78±0.48 g/dL; p=0.00) diabetics (3.42±0.54 vs 3.77±0.48 g/dL; p=0.00), those who had a weekly Kt/V under the target of 1.7 (3.42±0.69 vs 3.69±0,45 g/dL; p=0.04) or an Adragao vascular calcification index > 2 (3.34±0.47 vs 3.80±0.50 g/dL; p=0.00). Dialysis vintage, use of icodextrin, protein losses in the effluent, body fat measured by bioimpedance and serum phosphate were not significantly associated with hypoalbuminemia.

Conclusions: We found important correlations between hypoalbuminemia and inflammation, markers of volume overload and factors possibly associated with a higher comorbidity burden and worse condition such as diabetes, vascular calcification index, less efficient dialysis and being on APD.

PUB696

A Comparison of Body Composition between Continuous Ambulatory and Continuous Automatic Peritoneal Dialysis

Carlos Alberto Garza, Gabriela Leal, Bernardo Moguel. *Nephrology, Inst Nacional de Cardiologia Ignacio Chavez, Tlalpan, Mexico City, Mexico.*

Background: Body composition in the literature compares hemodialysis and peritoneal dialysis,an uneven comparison.We analyzed differences in body composition after a transition from Continuous ambulatory(CAPD) to continuous automatic peritoneal dialysis(APD).

Methods: We performed multiple frequency bioelectrical impedance analysis (InBodyS10, InBodyCo) and standard laboratories in patients with CAPD at baseline and 1 month after transition to APD.

Results: Twenty subjects are described, 12 men and 8 women, median age 28 years(22.15-40), height 163cm(157.25-165).Median and IQR along with Wilcoxon rank test for related samples were performed. We found statistical significance in EBW/TBW ratio in favor of APD, and increase in albumin and hemoglobin.

Variable	Units	Baseline	1 month	*p*
Weight	Kilogram	62.95(55.27-71.25)	63.75(53.75-69.10)	0.07
Body Mass Index	Kg/m^2	24.75(20.60-27.52)	24.85(20.45-28.07)	0.07
Systolic Blood pressure	mmHg	148(130-168)	137(126-166)	NS
Diastolic Blood pressure	mmHg	91(77.25-104.25)	89(78.50-107.50)	NS
Total body water (TBW)	Liters (L)	34.70(30.62-39.12)	33.85(31.02-37.30)	NS
Extracellular body water (EBW)	L	13.35(11.82-15.15)	13.05(11.95-14.25)	NS
Intracellular body water (IBW)	L	21.05(18.85-23.90)	21.05(18.87-23.15)	NS
EBW/TBW ratio	Ratio	**0.39(0.38-0.40)**	**0.38(0.38-0.40)**	**0.01**
Lean Muscle Mass	K	44.35(39.30-50.12)	43.50(39.72-47.85)	NS
Body Fat	K	17.35(6.77-23.10)	17.65(8.97-23.42)	0.06
Basal Metabolic Rate	Kcal/day	1388.00 (1274.50-1518.75)	1364.50(1286.00-1462.75)	NS
Hemoglobin	g/dL	**9.35(7.40-10.82)**	**10.30(8.47-11.12)**	**0.05**
Albumin	g/dL	**3.98(3.53-4.25)**	**4.04(3.77-4.27)**	**0.03**
Phosphorus	mg/dL	6.71(5.69-8.16)	6.54(5.63-7.93)	NS
Creatinine	mg/dL	11.33(8.76-15.85)	11.05(8.52-17.42)	NS
BUN	Mg/dL	68.50(54.35-91.75)	63.75(55.71-78.62)	NS

Conclusions: Peritoneal dialysis by CAPD or APD maintain, with exception of the EBW/IBW, a similar body composition.

PUB697

Telemedicine in the Provision of Remote Peritoneal Dialysis Care: Preliminary Results Vinay Narasimha Krishna,[1] Russell Griffin,[2] Michael Louis Smith,[3] Eric L. Wallace.[1] *[1]Nephrology, Univ of Alabama, Birmingham, AL; [2]Epidemiology, Univ of Alabama, Birmingham, AL; [3]Alabama Dept of Public Health, Montgomery, AL.*

Background: Geography may pose a significant barrier in delivering peritoneal dialysis (PD) care to remote underserved populations leading to low utilization rates and poor outcomes. Telemedicine as a replacement for a face-to-face visit may serve as a solution to overcome geographic barriers in delivering PD care.

Methods: A telemedicine network was established through collaboration with Alabama Department of Public Health. PD patients living in a county different from the University of Alabama (UAB) Home Dialysis Unit were included in the study. A single cohort cross-over design was adopted. Patients started with 6 standard in-person (SOC) visits followed by 2 quarterly SOC visits, followed by 2 telemedicine visits. Kidney Disease Quality of Life (KDQOL-36) and the Illness Intrusiveness Ratings Scale (IIRS) were administered three times in the SOC and telemedicine arm. Telemedicine visits included interactive videoconferencing, physical exam including auscultatory exam using bluetooth enabled stethoscopes, and exit site examination using a handheld high definition camera. Labs were drawn at county health departments and shipped to a central lab. Dialysis flow sheets were faxed at the time of telemedicine visit.

Results: To date 12 telemedicine visits have been completed in 4 different counties/patients. The average physician encounter time was 8 minutes longer for telemedicine versus SOC visits ($p=0.05$). An average of 162 miles and 142 minutes of driving time was saved per telemedicine visit. Preliminary analysis showed the largest improvement was in SF12 physical component of the KDQOL-36 which increased an average of 5 points. IIRS scoring showed an average improvement (decrease) of 7.6 points when comparing telemedicine to SOC visits. All patient concerns were successfully addressed over telemedicine.

Conclusions: Telemedicine visits, although more time consuming for the physician, saves patients substantial driving time and trends towards improvement in quality of life for PD patients who live in a county different from the UAB Home Dialysis Unit.

Funding: Pharmaceutical Company Support - Baxter Healthcare Corp

PUB698

Cat in the Bag Naseem H. Siddiqi. *Nephrology, Apex Medical Group, Knoxville, TN.*

Background: A.B. is a 33 year old white male, suffering from ESRD secondary to Diabetic Nephropathy and has been on Peritoneal Dialysis. Presented with abdominal pain, nausea, vomiting, elevated temperature and clouded fluid.

Methods: Patient was initially started on IP Vancomycin and Fortaz. His PD fluid showed evidence of Peritonitis with an increased WBC count and the PD culture showed Pasteurella Multocida Infection. After the PD culture results came back, the patient was then switched to Fortaz alone for a period of 14 days. Patient completely recovered from Peritonitis. Pasteurella Multocida Infection comes from cats and dogs. Patient was quizzed about having a cat or dog and confessed that he had acquired a cat therefore his Peritonitis was a result of the cat being handled by him. Therefore he was asked to find another home for the cat.

Results: The patient completely recovered from Pasteurella Multocida Infection.

Conclusions: Pasteurella Multocida Peritonitis is very rare but does occur. We should be screening patients with regard to having pets in the house before starting PD and be vigilant that they do not acquire and handle pets while they are on PD program.

PUB699

Prediction of the Mortality Risk in Peritoneal Dialysis Patients: Machine Learning Approach Using a Prospective Cohort in Korea Kyung Don Yoo,[1] Junhyug Noh,[2] Hajeong Lee,[3] Dong Ki Kim,[3] Chun Soo Lim,[3] Shin-Wook Kang,[4] Chul Woo Yang,[5] Yong-Lim Kim,[6] Gunhee Kim,[2] Jung Pyo Lee,[3] Yon Su Kim.[3] *[1]Dongguk Univ Gyeongju Hospital; [2]College of Engineering, Seoul National Univ; [3]Seoul National Univ College of Medicine; [4]Yonsei Univ; [5]Catholic Univ; [6]Kyungpook National Univ.*

Background: Peritoneal dialysis(PD) has several benefits for ESRD patients compared to hemodialysis in terms of residual renal function, reducing cardiovascular complications, improving quality of life. However, survival benefit was not consistently shown in each subpopulation.

Methods: A total of 1,730 PD patients in the Clinical Research Center for ESRD prospective cohort from Aug 2008 to Dec 2014 were enrolled to this study. Mortality risk model was validated by the individual learning algorithms such as survival decision tree(DT), ridge/lasso/Cox regression, and ensemble learning algorithms such as survival bagging and random forest.

Results: We analyze records of 1,127 prevalent and 603 incident PD patients, among which we use 21 independent attributes to learn our models including. The mean age was 52.7 years, and 57.4% were men. Survival tree algorithm had presented the most accurate prediction model, and it outperforms a conventional method such as Cox regression (Concordance index 0.802 vs. 0.745, respectively). Among various survival DT models, Charlson Comorbidity index(CCI) was selected for the best predictor of mortality. If PD patients with high CCI ($\geq$4) were more than 70 years old, survival hazard ratio (HR) was predicted as 4.61 compared to overall study participants(C-index 0.802). In patient under 70yrs old, if serum uric acid at dialysis initiation is 7.5mg/dl or more, the survival HR is decresed from 0.19 to 1.88. Survival HR is only 0.104, if CCI is 2 or less at the same age. Consequently, low risk patients whose CCI 3 or 4 were depend on serum BUN level and phosphorus level for survival HR (C-index 0.802).

Conclusions: We propose machine learning based models with estimated-death risks for presenting more accurate than conventional models. In our final model, age at dialysis initiation and CCI were interrelated as notable risk factors for mortality in Korean PD patients.

PUB700

Microbiology and Outcomes of Peritoneal Dialysis Peritonitis in a Korean Medical Center Jung-Woo Noh, Eunjung Kim, Dong Ho Shin. *Div of Nephrology, Hallym Univ Medical Center, Seoul, Korea.*

Background: Knowledge on microbiologic profiles and antibiotic resistance patterns are important to guide treatment for peritoneal dialysis (PD) peritonitis. Changes in prevalence of etiologies have been reported. We analyze the incidence of peritonitis, the causative pathogens, antibiotic resistance of commonly isolated pathogens and clinical outcomes.

Methods: We enrolled 321 patients on PD between January 2000 and December 2014. The endpoints analyzed were resolution, catheter loss, death due to peritonitis and shift to hemodialysis.

Results: There were 237 episodes of peritonitis in 138 of 321 patients over a cumulative follow-up period of 1205.5 patient-years. The overall rate was 0.20 episodes/patient-year. Gram+ cocci were identified in 122 (51.5%) episodes, whereas Gram- bacilli were isolated from 67 (28.3%). Methicillin-resistant Coagulase negative staphylococi (CoNS) was the most common isolate. Methicillin susceptibility was observed in 16 of 41 (39%) due to CoNS and 21 of 39 (53.8%) due to S.aureus. The ceftazidime susceptibility rate was 79.1% among Gram- bacilli, 88.5% among E.coli, 88.9% among Klebsiella spp., 33.3% among P. aeruginosa, 74.1% among Acinetobacter spp. The resistance rate was higher among P. aeruginosa than among E.coli (p=0.01). Episodes of Enterococcus spp. (p<0.001) and Pseudomonas spp. (p=0.04) presented lower resolution rates than those caused by CoNS. The death rate was not different among etiological groups (P = 0.6). Antibiotic resistance did not influence outcome. The main empirical antibiotic regimens were i.p. cefazolin plus ceftazidime (210 episodes), and i.p. vancomycin plus ceftazidime (27 episodes). Gram+ coverage with cefazolin was associated with higher resolution rate (91.6% versus 74.1%; p=0.05), lower catheter removal rate (8.4% versus 25.9%; p=0.05).

Conclusions: Although, methicillin susceptibility rate was low in this study, Gram+ coverage with cefazolin did not show negative impact on outcomes. Antibiotic resistance did not influence outcome. These findings suggested empirical antibiotic regimen i.p. cefazolin plus ceftazidime could be acceptable regardless of antibiotic resistance.

PUB701

Predictors of Mortality and Technique Failure in Incident Peritoneal Dialysis Patients in a Larger Center Maria C.C. Andreoli, Marco A. Nadaletto, Cláudia Tótoli, Laurisson A. Costa, Eduardo J.B. Monteiro, Camila Barbosa Silva Barros, Vanessa S. Dutra, Silvia Regina Manfredi, Sergio A. Draibe, Maria Eugenia F. Canziani. *Hospital do Rim - Disciplina de Nefrologia, Univ Federal de São Paulo, Sao Paulo, Brazil.*

Background: Center size has been associated with clinical outcomes in Peritoneal Dialysis (PD), with better results in larger centers. The aim of this study was analyze related factors to the clinical outcomes, death and technique failure, in incident patients in PD in a single larger center, during a period of 13 years.

Methods: All patients admitted in our PD center from January 1, 2003 and December 31, 2015, were evaluated. Technique failure was defined as theswitch from PD to hemodialysis therapy. Kaplan-Meier curves and the log-rank test were used to evaluate mortality and technique failure, and Cox proportional hazards model was used to identify factors associated with outcomes.

Results: A total of 633 patients [58.9 (44.7-68.2) years, 49% male, 33% diabetes] were analyzed.The peritonitis rate in the last 5 years was 1 episode every 34 months. During this period, 213 (34%) patients died: 101 (47%) from cardiovascular events, 64 (30%) from infectious complications not related to therapy and 27 (13%) from infectious complications related to therapy. Technique failure occurred in 204 (32%) patients especially due to peritonitis (51%). One-year and 5-year patient survival were 85% and 42%, respectively, and 1-year and 5-year technique survival were 83% e 51%, respectively. In Cox analysis, age (HR=1.045, CI95% 1.034-1.055; p<0.001) and diabetes (HR=1.636, CI95%1.246-2.149; p<0.001) were associated with mortality, while age was inverse related (HR=0.991, CI95% 0.982-0.999; p=0.037) with technique failure.

Conclusions: Non-modifiable risk factors such as age and diabetes were the important determinants of survival in a larger PD center. The low peritonitis rate observed in this population seem to be not sufficient to avoid transfer to hemodialysis, suggesting that management of this infection should be more effective.

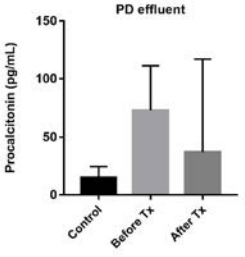
PUB702

Procalcitonin Is Not a Superior Biomarker for Peritoneal Dialysis Peritonitis Jae Seok Kim,[1] Jae Won Yang,[1] Byoung Geun Han,[1] Min Keun Kim,[1] Minseob Eom,[2] Seung-Ok Choi.[1] *[1]Internal Medicine, Yonsei Univ Wonju College of Medicine, Wonju, Republic of Korea; [2]Pathology, Yonsei Univ Wonju College of Medicine, Wonju, Republic of Korea.*

Background: Peritonitis is a common complication in peritoneal dialysis (PD). Procalcitonin is a useful biomarker for bacterial infection. We aim to investigate the utility of procalcitonin in PD peritonitis.

Methods: This study included thirty-three PD peritonitis episodes for the periods of total 450 days and peritosol analysis from seven patients without peritonitis. We investigated clinical characteristics and inflammatory markers including serum and PD effluent levels of procalcitonin at the time of initial visit and discharge.

Results: The mean of dialysis vintage in the patients with peritonitis was 1774.4 days, incidence of total peritonitis during their PD periods; 4.3 times, interval from symptom onset to visit; 13.6 hours, duration of intra-peritoneal antibiotic treatment; 8.2 days, and interval from clinical improvement to recurrence; 80.7 days. Initial serum procalcitonin increased to 402.2±278.4 pg/mL (mean±SEM, <50 pg/mL in healthy people). PD effluent procalcitonin increased compared with in control group, but not significantly (72.6±38.6 vs. 14.7±3.8 pg/mL, p=0.503). The serum procalcitonin decreased to 132.5±63.2 pg/mL with clinical improvement but not significantly (p=0.267), and the PD effluent procalcitonin decreased 37.0±16.3 pg/mL, but not significantly (p=0.378) .



Pearson's correlation analysis showed that the serum and PD effluent procalcitonin did not have relationships with existing inflammatory markers such as ESR, CRP. Procalcitonin could not predict recurrence and mortality of peritonitis.

Conclusions: Procalcitonin showed the tendencies corresponding to clinical course of PD peritonitis, but not statistical significances. We believe that procalcitonin is not a superior biomarker in PD peritonitis compared with other existing markers.

PUB703

Remote Blood Pressure Monitoring in Peritoneal Dialysis: A Comparison of Home Blood Pressure Readings with Readings Retrieved via Cycler-Embedded Remote Monitoring Patrick R. Harnett. *Renal Medicine, Southend Hospital, Westcliff On Sea, Essex, United Kingdom.*

Background: Blood pressure control is important for the reduction of cardiovascular risk. We report results of home blood pressure recordings obtained by patients and entered into a remote, PD cycler-embedded, interactive cloud-based platform (Sharesource) with blood pressures collected at home using validated home BP monitors Sharesource enables retrieval of clinical data on blood pressure and dialysis performance remotely and automatically via the wireless 3G network. The data is collated at a server and is presented to the clinical team via an interactive "dashboard".

Methods: Patients at a single centre were changed from conventional automated peritoneal dialysis (APD) to an APD device with embedded remote monitoring features (Claria- Sharesource) in Oct. 2015. Patients were instructed to record daily blood pressures at home using the Omron M10-IT home bp monitor. Readings were then entered by the patient into the Sharesource at the start of each dialysis session. Omron blood pressure monitor data were retrieved and processed by a bespoke data management system.

Results: 4 patients had recorded and entered daily blood pressure via Sharesource for 4 months total of 487 days of readings. The blood pressure data was retrieved for the same period from the Omron/Proton blood pressure collection system and compared to the corresponding month of sharesource blood pressure results.

fig 1	Home BP			Sharesource			
	No. of readings = 488			No. of readings = 541			p value
Mean systolic mmHg	142.55	sd	16.98	137.98	sd	17.93	<0.005
mean diastolic mmHg	82.53	sd	10.36	82.06	sd	9.85	0.232

Conclusions: Mean retrieved home blood pressure was significantly higher. Inaccuracies were also apparent. Protocols and education are required to maintain data quality. Further development of the technique (eg Bluetooth enabled blood pressure monitors) may minimise input error.

PUB704

Peritoneal Dialysis Associated Peritonitis in the Elderly: Clinical Characteristics, Outcomes and Prognostic Factors Chen Yu, Yue Chen. *Nephrology, Tongji Hospital, Shanghai, China.*

Background: To investigate the clinical characteristics, outcomes and prognostic factors of peritoneal dialysis associated peritonitis (PDAP) in the elderly.

Methods: We conducted a retrospective cohort study including all peritonitis episodes cases in peritoneal dialysis (PD) patients at a single center from January 2012 and December 2015. Demographic data, clinical data at admission, causative organisms and drug resistance were collected. The outcomes of patients were recorded at the time of 4 weeks after the completion of antibiotic therapy. Treatment failure included death or removal of PD catheter for peritonitis episodes.

Results: 129 episodes of peritonitis occurred in 87 PD patients including 61 elderly patients and 26 younger patients. The proportion of elderly patients with diabetes was higher (P=0.001). The incidence of primary glomerular diseases (PGD) was lower in the elderly (P<0.001). The levels of serum albumin (Salb), blood urea nitrogen, serum creatinine and uric acid were lower in the elderly (P<0.005). There was minor difference in spectrums of causative organisms from effluents between the elderly and younger. The proportion of Enterococcus species to gram-positive bacteria was lower in the elderly (P=0.029). The occurrences of outcomes were similar in the elderly and younger. More WBC counts in effluent on d5, lower Salb and fungal or polymicrobial infections were associated with treatment failure.

Conclusions: The elderly PDAP patients were more likely to have diabetes as a comorbid disease and had worse nutritional status. The outcomes of the elderly were comparable to those of the younger. The treatment response for PDAP caused by fungi or polymicrobe was challenging in the elderly.

PUB705

How Far We Can Go: Extremes of Body Mass Index in Peritoneal Dialysis Yougandhar Akula,[1] Sohail Abdul Salim,[1] Betzaida Rodriguez,[2] Lajos Zsom,[3] Tibor Fulop,[3] Mehul P. Dixit.[4] *[1]Div of Nephrology, Univ of Mississippi Medical Center, Jackson, MS; [2]Div of Hospital Medicine, Univ of Mississippi Medical Center, Jackson, MS; [3]Dept of Surgery, Div of Transplantation, Univ of Debrecen, Debrecen, Hungary; [4]Div of Pediatric Nephrology, Univ of Mississippi Medical Center, Jackson, MS.*

Background: The State of Mississippi leads the nation in the epidemics of obesity and, with the rising tide of chronic kidney disease, inevitably the need for renal replacement therapy (RRT) in many overweight subjects. The feasibility of peritoneal dialysis in extremely obese subjects is not well understood.

Methods: We reviewed our peritoneal dialysis (PD) unit for extremely obese subjects (body mass index [BMI] ≥40 kg/m^2) and evaluated their biochemistry and PD adequacy parameters, in comparison with those with normal weight individuals (BMI 20-25). Results were expressed with means (SD) and percent (%); between-group comparison was performed with independent sample t-test.

Results: : We observed six subjects with BMI > 40 kg/m2: mean weight was 134.7 (SD=12.5) kg, body length 174.8 (11.8) cm with mean BMI 44.3 (SD=4.2) kg/m^2 [range: 40.2-51.6]. Age was 39.3 (7.6) years with PD vintage 15.8 (16.2) months; all African-American and using cycler-assisted peritoneal dialysis. Weekly Kt/V measured 1.8 (0.18), creatinine clearance 90.1 (46.4) liter (L)/1.73 m^2 week with total exchanged volume 12.2 (1.35) L. Residual urine output (RUO) measured 708 (561) mL and residual creatinine clearance 48.5 (44.3) L/week/1.73 m^2. The lean (n=20) subjects had mean weight of 66.5 (9.8) kg and BMI 23.3 (1.4) kg/m^2. While both weight and BMI differed significantly (p<0.0001), weekly global and residual creatinine clearance and RUO did not. Exchanges volumes were larger (p=0.04) and Kt/V smaller (p=0.007) in the obese subjects. None of the serum biochemistry parameters were significantly different between the subcohorts.

Conclusions: Successful PD appears feasible even in massively obese subject and provides RRT access when no arteriovenous fistula available.

PUB706

A Simplified Method to Measure GFR in Swine by the Plasma Clearance of Iohexol Consolacion C. García-Contreras,[1] Marta Vazquez,[1] Sergio Luis Lima,[3] Susana Astiz,[1] Antonio Gonzalez-Bulnes,[1] Esteban Porrini.[2] *[1]Comparative Physiology Group (SGIT-INIA), Madrid, Spain; [2]Univ de La Laguna, La Laguna, Spain.*

Background: There is no definitive method to measure GFR in swine.

Methods: We used two groups (testing and validation), of 8 adult iberian pigs each in which 10 mL of iohexol (6.47 g) was injected intravenously (marginal auricular vein) and blood samples were collected at 15, 30, 45, 60, 90, 120, 180, 240, 300, 360 and 420 minutes (orbital sinus). Iohexol plasma clearance was measured by two-compartment model (CL2-reference method) using all the samples and by one-compartment model (CL1) using the last six.

Results: Plasma clearance calculated by CL1 lead to a ±30% overestimation of CL2. A correction formula [CL= -47.909+(1.176xCL1)-(0.00063968xCL1^2)] was created to recalculate CL1. This approach increased the correlation between CL2 and CL1 (R=0.969). The latter (CL1 and the correction formula) was the simplified method (SM). In the validation group, GFR averaged 229±68.6 µl/min (CL2) and 276.9±85.3 µl/min (CL1). The recalculation of GFR with the formula lead to 224.7±71,5 ml/min, comparable to CL2. Similar results were observed in the testing group.

Testing Group					
Pig ID	Weight (kg)	CL2 (ml/min)	CL1 (ml/min)	SM (ml/min)	Diff (%) SM vs CL2
1	113.5	119.6	150.4	114.6	-4.2
2	172.6	172.6	236.3	194.3	12.5
3	225.8	225.8	301.6	248.7	10.1
4	233,8	233.8	255.4	210.8	-9.9
5	175,8	175.8	216.4	176.7	0.5
6	341,8	341.8	433.1	341.4	-0.1
7	266.1	300.5	345.6	282.1	-6.1
8	311,9	392.0	527.4	394.4	0.6
mean±SD	265.8 ± 65.2	243± 92.8	308.3 ± 128.2	245.3 ± 91.4	
Validation Group					
Pig	Weight (kg)	CL2 (ml/min)	CL1 (ml/min)	SM (ml/min)	Diff (%) SM vs CL2
9	173,7	173.7	213.7	174.2	0,3
10	252,2	246.8	275.9	227.9	-7,7
11	112.1	112.1	128.0	92.2	-17,8
12	289.9	289.9	394.6	316.6	9,2
13	202.8	202.8	253.5	209.1	3,1
14	289.6	289.6	331.2	271.4	-6,3
15	202.8	202.8	257.7	212.7	4,9
16	313.9	313.9	360.9	293.2	-6,6
mean±SD	212.9 ± 39.2	229±68.6	276.9 ± 85.3	224.7 ± 71.5	

Conclusions: We offer a simple method to evaluate GFR in conscious swine which does not need urine collection and allows repeating the measurement in the same animal.

Funding: Government Support - Non-U.S.

PUB707

Outcome Measures for Fatigue in Patients on Hemodialysis Angela Ju,[1,2] Jonathan C. Craig,[1,2] Mark L. Unruh,[3] Allison Tong.[1,2] *[1]School of Public Health, The Univ of Sydney, Sydney, NSW, Australia; [2]Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, NSW, Australia; [3]Div of Nephrology, Univ of New Mexico, Albuquerque, Mexico.*

Background: Fatigue is a prevalent and debilitating symptom in patients on hemodialysis but is measured infrequently, inconsistently, and using instruments that may not be valid for this population.

Methods: We searched MEDLINE, Embase, PsycINFO, CINAHL to March 2016 for all studies that measured and reported fatigue in patients on hemodialysis. Content, validity, reliability and feasibility were assessed using criteria developed by adapting the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist and the National Health Service checklist.

Results: The 117 studies included 36 different instruments; 17 (47%) scales were developed for populations other than hemodialysis, 2 (1%) for chronic kidney disease patients regardless of disease stage, and 17 (47%) specifically for haemodialysis (12 were author-developed for their study). Of these, 26 (72%) were specifically designed to measure fatigue. All scales assessed global fatigue, some of which also included emotional (9 [24%]), cognitive (10 [27%]), and physical fatigue (14 [39%]). Within these domains, the severity of fatigue and life impact were assessed. The most frequently used instrument was the vitality sub-scale of 36-Item Short Form Health Survey (SF-36) (19 [16%] studies) but it has not been validated the hemodialysis population, along with the majority of other instruments used to measure fatigue in this population.

Conclusions: Although several scales have been used to measure fatigue in patients on hemodialysis, there is insufficient evidence of validity to ensure an adequate representation of their experience. A well-validated instrument for fatigue is needed to improve the consistency and accuracy of measurement for a better understanding and management of this important patient-centered outcome.

Funding: Government Support - Non-U.S.

PUB708

Comparative Biocompatibility of Polysulfone Hemodialysers Applied in Different Treatment Modalities Stephan Wagner,[1] Ansgar Erlenkoetter,[2] Katharina Brand,[2] Ursula Kreuzberg,[2] Adelheid Gauly.[2] *[1]Praxis für Nieren- und Hochdruckerkrankung, Giessen, Germany; [2]Fresenius Medical Care, Bad Homburg, Germany.*

Background: The biocompatibility profile of two polysulfone hemodialyzers was evaluated based on hemocompatibility markers.

Methods: In a prospective randomized crossover study 24 adult patients on online hemodiafiltration (HDF) were treated one week each with the dialyzers FX100 on hemodialysis (HD), FX CorDiax 100 on HD and HDF (Fresenius Medical Care, Germany). Linear mixed models were used for inferential statistical analysis including fixed effects for treatment, period and a random subject effect. Differences for the estimated means at 10 min. and for the whole treatment (area-under-the-curve, AUC), or relative changes from pre- to post-dialysis were analyzed.

Results: The complement factors C3a and C5a increased early in the treatment, comparable between FX Cordiax and FX in HD, but less with FX Cordiax HDF, likely due to convective elimination. sC5b9 increased in all three phases with the highest level after 60 min., overall (AUC) it was significantly lower with FX Cordiax HDF than in both HD settings. Leukocytes decreased in the first 10 min of the treatment, without significant differences at 10 min. and over the entire treatment in all phases. Thrombocytes decreased slightly in all phases in the first 30 min., with FX Cordiax HDF significantly more than with the two HD settings. TAT increased to a different extent towards treatment end, significantly more with FX Cordiax HDF compared to both HD settings. Elastase increased in the first hour with all dialyser/modality settings, the least with FX Cordiax HDF. Kallikrein as a marker of contact activation showed a slight increase at 10 min, but not significantly different by dialyser/modality at 10 min. or overall. Tryptase decreased significantly more with FX CorDiax HDF than with both dialysers in HD. No difference was observed for IgE and hsCRP. All adverse events occurring during the study were judged as unrelated to dialyser and treatment.

Conclusions: This study confirmed a comparable biocompatibility profile of FX CorDiax and FX. Some differences observed with FXCorDiax HDF are likely due to convective elimination of middle molecules.

Funding: Pharmaceutical Company Support - Fresenius Medical Care

PUB709

Intradialytic Hypotension – Can We Reduce the Incidence? Narayanan Unni Vavullipathy. *Nephrology, Aster Medcity, Kochi, Kerala, India.*

Background: All attempts should be made to avoid Intradialytic hypotension during maintenance haemodialysis **Objectives**:To study the incidence of intradialytic hypotension in patients on maintenance haemodialysis, if the Nephrologist makes an assessment of the patient before each dialysis session and decides on the volume of ultrafitration every time. **Materials & Methods**: Patients with chronic kidney disease stage 5 on maintenance haemodialysis from June 2014 to May 2016 were studied. They were dialysed for 4 hours thrice a week using a Fresenius Polysulfone dialyzer with a surface area equal to 75% of body surface area with Fresenius hemodialysis machine model 4008S. The blood flow was kept at 250 to 300ml per minute , with a dialysate flow of 500ml per minute at 37 degree Celsius. A qualified experienced Nephrologist evaluated the patients before each dialysis session and decided on the volume of ultrafiltration at every session. All patients were asked to have their antihypertensive medications as usual. Pulse rate and blood pressure was monitored every 10 minutes with a Philips multiparameter monitor model Intellivue P5 . Intradialytic hypotension was defined as a fall in systolic blood pressure by 20mmHg or a decrease in mean arterial blood pressure by 10 mmHg , and need for nursing interventions (K/DOQI definition). **Results**: During the study period, 10075 haemodialysis sessions were done in 80 patients (58 males and 22 females). The mean age was 55 years (Range : 24 to 82). Diabetic nephropathy constituted 52% of the cases. Seventy seven patients were hypertensive and the mean BMI was 22.8 (14.1 to 34.6) . Diastolic dysfunction on echocardiogram was seen in 74% of patients. The mean interdialytic weight gain was 1.87 kilograms (0.5 to 3.5Kg.). The incidence of intradialytic hypotension was 1.55%. **Conclusions**: Incidence of hypotension was very low in our patients, compared to published reports. Assessment by the Nephrologist before every dialysis session and determination of the ultrafiltration volume at every session is extremely useful to avoid intradialytic hypotension.

PUB710

Will Flushing of Normal Saline Reduce the Clotting Incidence during Hemodialysis? Jafar Al-Said, Leonor Fontanillia. *Nephrology, Bahrain Specialist Hospital.*

Background: Hemodialysis is the main renal replacement mode for ESRD. Clotting is the major technical problem that could affect the blood flow and the clearance. It carries a significant risk for access loss with all its consequences. Proper Anticoagulation is needed to prevent the clot formation and maintain proper hemodialysis clearance. Adding prefilter saline flush to the regular Anticoagulation might reduce the clotting incidence by diluting the blood and facilitating removal of small clots from the filter.

Methods: Nine patients from our hemodialysis unit were selected. The recruitment was based on stable hemodynamics, no vascular access problems, and those using regular anticoagulant dose. Over two weeks half of their dialysis sessions were performed with hourly flushing of 100ml normal saline in addition to the Heparin boluses. The remaining sessions were performed with only Heparin. Clotting in the filters as well as the arterial

and venous chambers were monitored by the end of each session by two nursing staff. The session was labeled accordingly: **(0)** No clot. **(1)** Clots present in moderate amount. **(2)** Sever clotting required changing of the filter and tubing.

Results: Nine patients had 50 HD sessions over two weeks. Five males and 4 females. Mean Age was 62.5 years (SE 7), Mean BMI 22.3 (SE1.3). The access in 24 sessions were cuffed tunneled catheters, in 16 sessions it was an AVF and 10 sessions were performed via AVG. Aspirin was used on a regular daily dose of 81mg by 5 patients. The mean interdialytic wt. gain was 2.3kg (SE 0.13). The mean Heparin dose used per session was 4313 IU (SE 281). Intradialytic hypotension noticed in 4 sessions during the study period. There were no clots in any of the 25 sessions using saline flush and Heparin. However, among the other 25 sessions, with only Heparin, moderate clotting was identified in one session. The difference was not statistically significant.

Conclusions: Using saline in addition to the regular Heparin anticoagulation during hemodialysis did not make a significant difference in regard to the intradialytic clotting incidence. A Larger study is required to test the effect of saline flushing as a sole method to reduce clotting in dialysis lines.

PUB711

Reusing Dialysis Catheter Caps Jafar Al-Said, Tyrene Joy Sevilla. *Nephrology, Bahrain Specialist Hospital.*

Background: Hemodialysis catheter caps are utilized to secure the venous and arterial ports of the catheter from contamination, prevent blood leak and air embolism. Soaking hemodialysis catheter caps in antiseptic solution to be reused is practiced in our dialysis unit. This procedure was described in KDOQI Vascular Access Guidelines in 2000. It was not included in the 2006 update. Moreover, it is not a CDC recommendation. In the view of possible increased bacterial contamination, the question whether we should use new caps each session or reuse the same caps after sterilization with 10% Betadine was addressed by this study.

Methods: Five patients using cuffed tunneled catheters as their permanent dialysis access were included from our unit. The duration for the catheters use was between 2 - 9 months. The catheter caps were reused after each hemodialysis session from the time the catheters were inserted. The caps were soaked in 10% Betadine during the hemodialysis session. The caps were flushed with 9% saline by the end of the session and then used to cover the arterial and venous ports of the catheter. Personal protective equipment was emphasized and monitored as part of our hemodialysis strict infection control policy. During this study, these caps were sent for culture and replaced with new ones. The caps were transferred to the labs in sterile containers. Each Cap was flushed with 1 ml nutrient broth and incubated at 37°C for 24 hours. The broth was subcultures for another 24 hours in different agar plates. Having a positive bacterial culture within 48 hours would indicate a possible contamination to the catheters and thus to the blood.

Results: Table (1) shows the culture report of the catheter caps as well as the duration of use. All cap cultures were negative with no growth regardless of the duration the catheter caps use.

Patient	Duration of cap reuse in months	Culture result
1	9	Negative
2	8	Negative
3	8	Negqative
4	7	Negative
5	2	Negative

Conclusions: Reuse catheter caps after soaking in Betadine solution does not lead to increased risk of contamination, infection or harm to our dialysis patients. It can be followed with strict aseptic technique and proper infection control procedures.

PUB712

Barriers to Reducing Sodium (Na) Intake among Black ESRD Patients Carla Boutin-Foster,[1] Sania Tahir,[2] Amar V. Patel,[3] Jenna M. George,[3] Subodh J. Saggi.[3] *[1]Div of Internal Medicine, SUNY Downstate Medical Center, Brooklyn, NY; [2]Long Island Univ, Brooklyn, NY; [3]Div of Nephrology, SUNY Downstate Medical Center, Brooklyn, NY.*

Background: Black patients are 3 times more likely to have ESRD, which places them at significant risk of adverse cardiac events. Na intake is an important aspect of reducing fluid retention and subsequent cardiac events. The objective was to examine outcomes of a standard program to reduce Na intake among ESRD patients cared for in a dialysis unit located in a medically underserved community.

Methods: Outcomes for patients who had elevated inter-dialytic weights (IDWs) and who received an educational program by a registered dietician were examined. Na intake was calculated using the formula: $V \times ([Na]_{pre} - [Na]_{post}) + (\Delta IDW \times [Na]_{pre})$, where V= total body water. The standard protocol entailed showing patients their actual Na intake, education on low Na alternatives to traditional meals, and keeping a food log. Final Na intake was calculated at 3-months.

Results: Outcomes were reviewed for 13 patients; all were black; 8 were male; age was 49.6 + 11.98; all were hypertensive; and 6 were diabetic. An increase in Na intake was observed at 3 months (3.7 + 1.3g to 4.2 + 1.3g), (P>.05). Patients revealed physical and socioeconomic barriers to reducing Na intake. Physical barriers included difficulty seeing salt labels and measuring salt due to visual impairment. Ambulation and dexterity problems limited the ability to prepare meals, resulting in a high consumption of fast-foods. Patients described a lack of social support by family members for preparing low Na meals. Socioeconomic barriers limited access to buying low Na foods.

Conclusions: Patients face multiple barriers to Na reduction. In medically underserved communities, standard dietary education may need to be enhanced. Future programs may benefit from a greater focus on the social determinants and sociocultural aspects of adherence.

PUB713

Adult Intradialytic Hypotension: A Systematic Review Mohit Gupta,[1] Allen Reeves,[4] Mustafa Ascha,[2] Ramya Vajapey,[3] Rupesh Raina.[1] *[1]Dept of Internal Medicine, Akron General Medical Center, Akron, OH; [2]Clincal and Translational Science Collaborative, Case Western Reserve Univ, Cleveland, OH; [3]School of Medicine, Northeast Ohio Medical Univ, Rootstown, OH; [4]Cleveland Clinic Akron General, Akron, OH.*

Background: Intradialytic Hypotension is a frequent complication of Hemodialysis and occurs in up to 30% of cases. By a systematic review, we will discuss various therapeutic strategies and review their effect on Intradialytic Hypotension.

Methods: PubMed/MEDLINE was searched for the terms "intradialytic" and "hypotension" with parameters for randomized controlled trials. Inclusion criteria were (1) adult population, (2) hemodialysis, (3a) hypotension frequency or (3b) pre-dialysis and post-dialysis blood pressure measurement or (3c) difference between pre-dialysis and post-dialysis blood pressure measurement, and (4) variable dialysate electrolyte concentrations, dialysate temperature, volume management/ultrafiltration strategies, or pharmacological therapy. Exclusion criteria were hemofiltration or hemodiafiltration.

Results: Of 69 results, 47 articles were selected; 11 focused on dialysate temperature, 17 on dialysate electrolyte composition, 11 on volume control, and 4 on pharmacologic therapy. Variable Temperature Approaches: Of the 11 trials, lower dialysate temperatures were linked to a reduced incidence of hypotension. Maggiore et al reported that isothermic dialysis had a lower incidence of hypotension when compared to thermoneutral dialysis. Dialysate composition: 17 studies evaluated the impact of dialysate electrolyte composition. Calcium Dialysate: Gabutti et al found that higher calcium concentrations were associated with a lower incidence of hypotension. Sodium Dialysate: Oliver et al reported use of a sodium-profiled treatment versus constant-sodium was associated with a reduced risk of hypotension. Volume-based: Santoro et al reported that a volume-based approach based on effective blood volume was associated with a lower incidence of hypotension.

Conclusions: We found that the use of dialysis at (a)lower temperatures, (b)higher concentrations of calcium, (c) with sodium profiling and (d) volume-based strategies was linked to a lower incidence of Intradialytic hypotension.

PUB714

Acquired Cystic Kidney Disease in ESRD Patients on Maintainance Hemodialysis at a Tertiary Care Dialysis Center Syed Rizwan A. Bokhari,[1] Maria Rizwan Bokhari,[2] Hafiz I. Ahmad,[1] Syed A. Khalid,[1] Muhammad Zaman Khan Assir.[1] *[1]Nephrology, AIMC/JHL, Pakistan; [2]Radiology, AIMC/JHL, Pakistan.*

Background: Renal cysts are commonly observed in patients on maintenance hemodialysis (HD). Most of these patients are asymptomatic, while some report hematuria and lumbar pain. Its association with renal cell carcinoma is also well known. Frequency of acquired cystic kidney disease (ACKD) is not known in our End stage renal disease (ESRD) population. We studied the prevalence of ACKD and its correlation with patient's characteristics in our dialysis population.

Methods: Seventy-Four ESRD patients on maintenance hemodialysis at Jinnah Hospital Dialysis center were assessed for the study. Three patients with Autosomal dominant polycystic kidney disease (ADPKD) were excluded. None of the other 71 patients had previously known history of renal cysts. These patients underwent ultrasound examination by consultant radiologist for presence of renal cysts.

Results: Median age of patients was 50 years (range 17-82) and 44 (64%) were male. Median duration on hemodialysis was 4 years (1-12 years). Cause of ESRD was Hypertension (63%) Diabetes mellitus (30%) and obstructive uropathy (7%). Twenty-nine (40%) patients had hepatitis C infection. Sixty (85 %) patients were on thrice weekly and 11 (15%) were on twice weekly HD. Fifty five (77%) patients had 1 renal cyst, 26 patients had 2-5 renal cysts and 12 patients had more than 5 renal cysts bilaterally. Thirty-five (49%) Patients getting HD for less than 3 years had median of 3 cysts (range 0-15), while remaining patients on HD for more than three years had median number of 4.5 cysts (range 0-26). Nine (13%) on HD for less than 1 year had multiple renal cysts (1-4). No significant correlation was found between ACKD and duration of dialysis, frequency of dialysis, age, gender, co morbidities, Hepatitis C status. None of these patients had evidence of extra renal cysts, retroperitoneal or intrarenal hemorrhage.

Conclusions: No significant correlation between ACKD and duration of hemodialysis was observed while a high frequency of renal cysts was seen earlier (within 1 year of HD). The reason may be the late initiation of HD at a much lower GFR which is a routine in the developing countries.

PUB715

Hyperphosphatemia and Its Relation with Carotid Intima Media Thickness in ESRD Patients Farah Rizwan,[1] Hafiz I. Ahmad,[1] Syed Rizwan A. Bokhari,[1] Zumar Sardar,[1] Syed A. Khalid,[1] Arif Asif.[2] *[1]Nephrology, Allama Iqbal Medical College/ Jinnah Hospital Lahore, Pakistan; [2]Internal Medicine, Jersey Shore Univ Medical Center.*

Background: Increased phosphate level is commonly observed in chronic kidney disease patients. While its role in vascular calcification is well established, its effect on arterial wall thickness remains largely unknown in end stage renal disease (ESRD) population. We set out to determine the frequency of hyperphosphatemia in ESRD patients on maintenance hemodialysis and to compare the mean carotid intima media thickness (CIMT) in those with and without hyperphosphatemia.

Methods: All56 ESRD hemodialysis patients in the center were enrolled in the study. Serum phosphate level was measured. Hyperphosphatemia was labelled in accordance with KDOQI guidelines. Carotid intima media thickness was measured by ultrasound using linear transducer by a consultant radiologist.

Results: Mean age of the patients was 47.29±14.7 (ranging: 25- 82 years). Thirty-six (63.4%) patients were male. Eleven (19.6%) patients had ischemic heart disease. Nineteen (33.9%) patients had uncontrolled hypertension. Mean carotid intima thickness in patients with and without ischemic heart disease was 1.13±0.5 mm and 0.80±0.24 mm, respectively. Mean serum phosphate level was 5.62±1.95 (range: 1.4- 10.4 mg/dl). Mean carotid intima media thickness was 0.87±0.34mm in our cohort.Twenty-nine (51.8 %) had hyperphosphatemia. Mean carotid intima media thickness in patients with hyperphosphatemia was 0.85±0.34 mm which was similar to those without hyperphosphatemia0.9±0.34 (p value=0.56).

Conclusions: In our dialysis population hyperphosphatemia, common carotid artery intima media thickness was not observed.

PUB716

Regular Treatment with Haemodiafiltration Results in Fewer Hospital Admissions Than Haemodialysis Hemali Kanji. *Nephrology, Univ Hospital Coventry and Warwickshire NHS Trust, Coventry, United Kingdom.*

Background: There is debate whether haemodiafiltration(HDF) is preferable to haemodialysis(HD) in stable patients, and hence a question whether the expense of HDF machines is necessary.

Methods: We compared the admission rate to hospital of 40 patients at a satellite unit who have outpatient haemodialysis(HD) with 40 patients at another satellite unit who have outpatient haemodiafiltration(HDF) over a twelve months.

Results: The HD group were 18 men and 22 women aged 25-74(mean age 63) of whom 24 were diabetic and the HDF group were 16 men and 24 women aged 22-68 (mean age 57) of whom 17 were diabetic. There were 56 admissions in the HD group and 48 in the HDF group. The reason for admission was more often due to difficulties with access in the HDF group And their length of stay was shorter (2-7 days) compared to the HD group (2-40 days).

Conclusions: Having regular HDF is associated with less inpatient stay than HD. Whilst the initial cost of HDF machines may be greater than for machines which provide HD alone, there may be a cost saving in terms of fewer and shorter hospital admissions, and this needs to be considered when planning dialysis units.

PUB717

Low Calcium (Ca) Baths and Relation to Intact Parathyroid Hormone (iPTH) Niralee Patel, Larissa Kruger Gomes, Ibrahim M. El-Ali, Andre A. Kaplan. *UCONN Health Center, Farmington, CT.*

Background: Patients on dialysis have impaired calcium metabolism and can develop vascular and metastatic calcifications. It has been postulated that net positive Ca balance may promote formation of these calcifications. A kinetic analysis of net Ca balance in hemodialysis patients concluded that low Ca baths are required to avoid net Ca accumulation. Furthermore, in patients taking vitamin D analogues and calcium containing phosphate binders, a dialysate bath of 2.0 Ca would be required in order to avoid ongoing positive Ca balance (Gotch et al. KI 78:343, 2010). Given these conclusions, we have employed several low Ca dialysates in the hope of decreasing the net absorption of calcium.

Methods: As a Quality Assurance project we conducted a retrospective, single center study to determine the iPTH response to a lower calcium bath. Three separate study periods were reviewed, each lasting for 3 months. Ten patients who were dialyzed on a 2.25mEq/L bath were switched to 2.0mEq/L, six patients who were dialyzed on a 2.5mEq/L bath were switched to 2.25mEq/L, and 6 patients who were on a 2.5mEq/L bath were changed to 2.0mEq/L.

Results: As seen on Table 1, we found a tendency for increases in iPTH as the bath concentration was decreased but none of these increases were statistically significant in our small samples. Of interest, is that of 6 patients treated with the most substantial drop in Ca bath (2.5 vs. 2.0), 2 developed a decrease in iPTH.

Table 1: Mean Values at the Beginning and at 3 Months After Lowering Calcium Bath

Calcium Bath	2.25mEq/L	2.0mEq/L	2.5mEq/L	2.25mEq/L	2.5mEq/L	2.0mEq/L
Patients (n)	n=10		n=6		n=6	
P_i (mg/dL)	5.38	5.53	5.07	6.23	5.8	6.3
Ca^{2+} (mEq/L)	9.03	9.28	9.03	9.03	9.2	8.8
Ca^{2+} Pi Product	48.5	51.2	45.6	54	52.99	53.33
IPTH (pg/ml)	411	489	322	351	349	512
Calcium Acetate	n=6		n=1		n=4	
Calcium Carbonate	n=2		n=2		n=0	
No Phosphate Binders	n=4		n=3		n=2	
Sevelamer	n=0		n=1		n=0	
Activated IV Vitamin D Hectorol	n=10		n=6		n=6	
iPTH pre vs. post (p value)	0.23= NS		0.74=NS		0.23=NS	

NS = Non-significant

Conclusions: We conclude that low Ca baths are associated with relatively modest and variable changes in iPTH and may prevent calcifications by reducing net Ca balance.

PUB718

Clinical Significance of Serum Ferritin in Malnourished Dialysis Patients Yoo Jin Lee, Yang Wook Kim, Sihyung Park, Bongsoo Park. *Internal Medicine, Haeundae Paik Hospital, Busan, Republic of Korea.*

Background: Malnutrition is an important clinical threat in dialysis patients. Malnutrition is related to high morbidity and mortality rate. Although nutritional status cannot be judged by single method, we planned this study to assess nutritional status in dialysis patients by easy and convenient biochemical parameters.

Methods: Protein, albumin, albumin/globulin ratio, somatomedin-C, ferritin, transferrin saturation, phosphate, hydration status and body mass index were analyzed in hemodialysis, peritoneal dialysis patients. Body composition monitor (BCM) was used to evaluate lean tissue index (LTI). Malnutrition was defined by below 10 percentile of age-sex matched LTI.

Results: A total 34 patients were enrolled. 20 (58%) patients of malnutrition group showed higher ferritin level (450 ng/mL vs 230 ng/mL, r = -0.367). Other parameters were not different significantly. In subgroup analysis, ferritin (655 ng/mL vs 220 ng/mL, r = -0.518) was higher, however, CRP level was not different significantly in malnourished hemodialysis patients (12/19, 63%). In peritoneal dialysis patients, lower Somatomedin-C (214 ng/mL vs 304 ng/mL, r = 0.495) level was revealed in malnourished peritoneal dialysis patients (8/15, 53%).

Conclusions: The prevalence of malnutrition in dialysis patients was higher than we expected. Serum ferritin is a useful and convenient biochemical parameter for assessing nutritional status in dialysis patients.

PUB719

End-Stage Renal Disease Medication Self-Management: What Are the Effects of Everyday Racial Discrimination? Tamara Savage. *College of Social Work, Univ of South Carolina, Columbia, SC.*

Background: Poor medication self-management leads to increased risk for morbidity and mortality in end-stage renal disease (ESRD) patients. African American ESRD patients have poorer rates of medication self-management when compared to Whites. Studies have not investigated the impact of broader social issues such as everyday discrimination on this disparity. It is critically important to understand how everyday discriminatory acts within the healthcare system contribute to this disparity in medication self-management. Thus, a qualitative study was conducted to ascertain how everyday discrimination impacts medication self-management within this population.

Methods: Primary data were gathered from five in-depth interviews with African American ESRD patients (N = 5) in Greensboro, NC. Each interview was 1.5 to 2 hours in duration. Participants were recruited from attendees at the National Kidney Foundation Patient Empowerment Meeting. The interviews were transcribed verbatim. Grounded theory was used to identify themes that emerged from a line-by-line review of the interview transcripts.

Results: Participants explained that everyday discrimination perpetuated within the healthcare system negatively affected their medication self-management. Themes of racial discrimination that emerged which quashed further questions or engendered misunderstandings regarding their medication include: assumptions that patients could not pay for prescriptions not covered by insurance, assumptions that patients were not intelligent enough to understand medication instructions, patients were ignored by medical staff so they had to "pin the nurse down to ask about medication", and information about their medication and lab results being withheld or given to them without further consultation while white patients received in-depth consultation.

Conclusions: These findings provide the basis for development of future research concerning the impact of everyday discrimination on medication adherence in the African American ESRD population. Such research could lead to antiracist praxis, strategies, and targeted interventions that can address the medication adherence health disparity.

PUB720

Predictive Value of Histological Acute Kidney Injury Parameters in Implantation Biopsies for Delayed Graft Function Anke Keijbeck,[1] Tim C. Van Smaalen,[2] Marielle Gelens,[3] Robert Jan Van Suylen,[4] Floortje Steegh,[1] Maarten H.L. Christiaans,[3] Ernest Van Heurn,[2,5] Carine Peutz-Kootstra.[1] *[1]Pathology, MUMC, Maastricht, Netherlands; [2]Surgery, MUMC, Maastricht, Netherlands; [3]Internal Medicine, MUMC, Maastricht, Netherlands; [4]Pathology, Jeroen Bosch Hospital, 's-Hertogenbosch, Netherlands; [5]Surgery, AMC, Amsterdam, Netherlands.*

Background: Ischemia-reperfusion injury (IRI) in kidney transplantation is an important risk factor for later complications such as delayed graft function (DGF) and reduced graft survival. Clinical parameters such as cold ischemia time (CIT) and donor type are indicative for IRI, however, the additional value of post reperfusion histology is not known. The aim of this study was to investigate the predictive value of histological parameters of acute kidney injury for DGF.

Methods: The biopsy results of 192 consecutive donor kidney recipients transplanted between April 2003 and December 2009 at the Maastricht University Medical Centre (MUMC) with representative renal biopsy taken 30-60 minutes after reperfusion and a functional graft one year after transplantation were analysed. Biopsies were scored for 5 parameters for IRI known from animal studies: tubular cell necrosis, oedema, loss of brush border, neutrophils in glomerular capillaries and neutrophils in peritubular capillaries (PTC), which were scored in a dichotomic manner.

Results: Donor types were equally distributed in the cohort: 32.8% living donors, 35.4% donors after brain death (DBD) and 31.7% donors after cardiac death (DCD). The incidence of DGF in the cohort was 35%. Tubular cell necrosis was a risk factor for DGF (OR=2.6 [1.1-6.0]), while oedema was protective (OR=0.39 [0.160-0.954]). Other histological IRI markers didn't affect the risk of DGF in addition to the known clinical factors CIT and DCD donor type. Area under the curve of the ROC curve (0.88 [0.83-0.93]) shows an excellent discriminant power of the model.

Conclusions: This study shows that IRI is already visible in implantation biopsies. Assessment of histological acute kidney injury parameters in the post reperfusion kidney biopsy has added value to predict DGF.

PUB721

The Change of Fcγ Receptor 1α mRNA in the Graft of Acute Rejection Rat Renal Transplantation Model Yiqiao Li. *Zhejiang Provincial People's Hospital, Dept of Nephrology, Hangzhou, China.*

Background: To study the change of Fcγ receptor 1α mRNA in the graft of the rat renal transplantation model, especially after the acute rejection.

Methods: After at the seventh days and the fourteenth day to collect the samples, 3 rats in each time point. After abdominal aortic blood collection, blood samples is under the 3000rpm centrifugal 10 min to check serum creatinine and renal tissue -80 degree preservation, real-time PCR method was applied to test the change of Fcγ receptor 1α mRNA expression of each group.

Results: In the sham operation group, serum creatinine, maintaining at a normal level, was 27.67mol/L at the 7 days after operation, and 20.33 mol/L at the 14 days after operation, suggestting that renal function was normal. In allograft acute rejection group, the levels of serum creatinine increased gradually, after renal transplantation 7 day was 58 mol/L, 14 day 308 mol/L. The expression level of Fcγ receptor 1α mRNA in renal of sham operation group is relatively stable. In allograft acute rejection group Fcgr-1a mRNA levels were higher than those in the sham operation group, the level of expression of Fcγ receptor 1α mRNA in the kidney was 5.17after operation 7 days, 14 days 4.35, the Fcγ receptor 1α mRNA expression in allograft acute rejection group had significant change (P<0.05). 14 days after operation compared with the the allograft acute rejection group was no significant difference (P>0.05).

Conclusions: Renal Fcγ receptor 1α mRNA expression is up-regulated in the acute rejection, after immune inhibitors to down-regulated, suggesting that Fcγ receptor 1α play a certain role in the acute reaction of renal transplantation, in-depth understanding of its mechanism can provide experimental basis and ideas for clinical prevention.

PUB722

Proteinuria Associated with mTOR Inhibitor Use in Heart Transplant Recipients Negiin Pourafshar, Ashkan Karimi, Seyed Hossein Aalaei Andabili, Amir Kazory. *Univ of Florida, Gainesville, FL.*

Background: The mammalian target of rapamycin inhibitors (mTORi) have been used in patients with orthotopic heart transplant (OHT) to avoid the nephrotoxicity associated with calcineurin inhibitors use as well as prevention of cardiac allograft vasculopthy. Since proteinuria is a known complication of mTORi in renal transplant recipients, we sought to determine whether these agents are associated with increased urinary protein excretion in OHT patients.

Methods: This is a retrospective study of adult patients who received OHT at the University of Florida between January 2000 and December 2015. All patients who received mTORi, whether de novo or following conversion from a calcineurin inhibitor regimen, were included. The patients' clinical and laboratory information were reviewed and relevant data such as renal function and urinary protein excretion were recorded.

Results: There were a total of 411 OHT patients, of which 91 received mTORi (72 sirolimus and 19 everolimus). The mean age of recipients was 47.7 years and 80 % were men. mTORi was started de novo in 35% of the patients. The timing of the measurement of proteinuria was highly variable ranging from 4 weeks to 7 years after starting mTORi (median 15.7 months). mTORi therapy was associated with an increase in the urinary excretion of protein in 31 (34 %) patients. The mean albumin/creatinine and protein/creatinine ratios were as high as 1.11 mg/g and 2.5 g/g respectively, and 17% developed nephrotic-range proteinuria. Interestingly, all these patients had negative or unremarkable proteinuria before initiation of mTORi.

Conclusions: To our knowledge this is the largest study on the impact of mTORi on urinary protein excretion in the setting of OHT. Based on these findings, mTORi use can be associated with development of moderate to severe proteinuria in a significant subset of these patients. Serial assessment of urinary protein excretion should be integrated in the therapeutic protocols that include these agents in OHT. Future studies are needed to determine the risk factors associated with mTORi-related proteinuria and its potential impact on renal and cardiovascular outcomes.

PUB723

Successful Treatment of Severe Antibody Mediated Rejection in Simultaneous Liver Kidney Transplant: A Case Report Aditi Gupta, Abhisekh Sinha Ray, Anjushree Kumar, Sri G. Yarlagadda. *Internal Medicine, Nephrology, Univ of Kansas Medical Center, Kansas City, KS.*

Background: Simultaneous liver-kidney (SLK) transplants are often performed in the presence of donor specific antibodies (DSAs) and/or positive cross match. The presence of DSAs is associated with increased risk of antibody mediated rejection (AMR). We report a case of severe AMR resistant to conventional therapy with steroids, plasmapheresis (PP) and intravenous immunoglobulin (IVIG) respond to Eculizumab, a monoclonal antibody against the terminal complement C5.

Methods: A 64 year-old woman with primary biliary cirrhosis and end stage renal disease received a SLK. She had class I DSA and a positive T cell flow crossmatch. She received induction with anti-thymocyte globulin and solumedrol and was maintained on mycophenolic acid, tacrolimus and prednisone. Since she had DSAs, she received PP and IVIG on post-operative day (POD) 1, 3 and 5, and was discharged on POD 6 with a serum creatinine of 0.9mg/dl. However, on POD 8, she presented with anuria, thrombocytopenia and anemia with laboratory evidence of hemolysis. The renal ultrasound did not show any obstruction or vascular compromise. Intravenous steroids, PP and IVIG were restarted for presumed AMR. She remained anuric after four sessions of PP. She was then treated with eculizumab. Her hemoglobin, platelet count and urine output improved after two doses of eculizumab (POD 12 and POD 19). With improvement in thrombocytopenia, a renal biopsy was performed on POD17 confirming AMR. There was no evidence of thrombotic microangiopathy in the biopsy.

Results: Serum creatinine started to improve and returned to baseline of 0.9mg/dl by POD 25. She received a total of four doses of weekly eculizumab. After 24 months, her renal function continues to remain stable with a serum creatinine of 0.8-0.9mg/dl and without any detectable proteinuria on dipstick.

Conclusions: SLKs are often performed despite presence of pre-transplant DSAs that are associated with early AMR. Treatment with a monoclonal antibody against the terminal complement C5 can prevent early graft loss from severe AMR.

PUB724

Combined Liver and Kidney Transplantation (CLKT) in Children with Autosomal Recessive Polycystic Kidney Disease: Indications, Postoperative Outcomes and Long-Term Results Rainer Büscher, Anja K. Büscher, Peter F. Hoyer. *Pediatric Nephrology, Univ of Duisburg-Essen, Essen, Germany.*

Background: Combined liver and kidney transplantation (CLKT) is a single case decision in children for special indications such as autosomal recessive polycystic kidney disease (ARPKD) or primary hyperoxaluria type 1 (PH1). So far, only limited data on long-term outcomes are available. We report on 8 children and adolescents with ARPKD who underwent CLKT in our hospital between 1999 and 2016.

Methods: Eight children were diagnosed with ARPKD based on clinical and genetic examinations. Children (5 male) were aged 10.0+3.7 years (3.8 to 14 years) at time of transplantation. Average wait time was 1.2±0.5 years (0.6 to 2.1 years); weight was 27.1±11.2 kg (14.0 to 45.4 kg) and length 123.9±23.0 cm (86.0 to 152.0 cm) prior to CLKT. Three patients received dialysis treatment before (1 HD, 2 PD) and preemptive transplantation could be performed in 5 patients.

Results: All 8 ARPKD patients received CKLT. Recurrent episodes of ascending cholangitis (1-2/year) were observed in 3 patients and 2 patients suffered from severe portal hypertension prior to transplantation. Seven patients received a full liver while split liver transplantation (segments 2-3) was performed in one case only. Cumulative time on ICU was 13.8±8.4 days (4 to 41 days). Sufficient renal function was achieved in 5 patients within 48 hours and 3 patients required intermittent HD following CLKT. Surgical complications requiring revision included bleeding in one patient. Cumulative survival of all patients within 5 years was 87.5%. One boy died within 4 weeks of transplantation due to prolonged sepsis, one adolescent died after 10 years. Acute liver rejection after 20 days was observed in one girl only and could be resolved by steroid therapy. So far, four patients could be transferred into adult care and remained on a stable liver and kidney function within an observation period of ten years.

Conclusions: CLKT can be performed in children with good outcomes and long-term survival rates are currently comparable to that of isolated liver or kidney transplantations. However, indications for CLKT must be decided on a case-by-case basis by a multidisciplinary team.

PUB725

Association between Kidney Transplantation and Diabetes Management in Recipients with Kidney Failure due to Diabetic Nephropathy

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Background: It is important to determine if diabetes self-management improves after renal transplant as this impacts post-operative outcomes.

Methods: Glycemic control was retrospectively measured by hemoglobin-a1c (HbA1C), insulin, hypoglycemic agents, and hospitalizations due to diabetes or transplant complications in 79 transplant patients with renal failure due to diabetic nephropathy. Data was analyzed at initial evaluation, pre-, 1-year post-, and 2 years post-transplant using a linear mixed-effects model and 4 by 4 variance-covariance matrix. Comparison involved two years pre- versus post-transplantation mean. Subgroup analyses accounted for sex, race, education, and age.

Results: There was no statistical significance in pre- versus post-operative HbA1c (slope 0.28; 95% CI -0.14 to 0.71), insulin (OR 0.96; 95% CI 0.70 to 1.31), or antiglycemic agents (OR 0.86; 95% CI 0.62 to 1.19). Hospitalizations were significant (OR 2.26; 95% CI 1.55 to 3.30). There was no statistical significance for HbA1c (slope 0.28; 95% CI -0.14 to 0.72), insulin (OR 0.85; 95% CI 0.59 to 1.21), or antiglycemic agents (OR 0.83; 95% CI 0.57 to 1.20) when adjusted for demographic. Hospitalizations were significant (OR 2.20; 95% CI 1.46 to 3.31).

Conclusions: Hba1c, insulin, and antiglycemic agents were expected to significantly decrease post transplant, but they did not. Diabetes management appears to have remained status quo. Hospitalizations were increased pre- to post-transplant. Lack of optimization of HbA1c, insulin, and antiglycemic agents can be correlated with increased hospitalizations. Transplant management also utilizes immunosuppressive agents that are known to cause hyperglycemia, prompting further inquiry into any confounding due to these agents. No significant difference was found when data was adjusted for demographic, showing that post-transplant diabetes management is not an isolated issue. Further studies are needed to assess post-transplant hospitalization and its correlation with diabetes management – a factor that can reduce the risk of post-operative complications and thus reduce morbidity and mortality in these patients.

PUB726

Kidney Transplantation Outcomes among Patients with Different Causes of ESRD: Nephritic Syndrome versus Nephrotic Syndrome versus Primary Diseases of Non-Autoimmune Origin

Sophia Lionaki,[1] Ilias Makropoulos,[1] Nikolaos Altanis,[1] Konstantinos Panagiotellis,[1] Apostolis Pappas,[1] Aliki Iniotaki,[2] Georgios Zavos,[3] John Boletis.[1] *[1]Nephrology & Transplantation, Laiko Hospital, National & Kapodistrian Univ of Athens, Athens, Greece; [2]Pathology, Laiko Hospital, Athens, Greece; [3]Transplantation Unit, Laiko Hospital, Athens, Greece.*

Background: To compare kidney transplantation (KTx) outcomes of patients with different causes of end stage renal disease (ESRD).

Methods: We retrospectively compared the outcomes of KTx recipients with biopsy proven glomerular primary disease (PD), i.e nephritic and nephrotic syndrome, with those of KTx recipients with a PD of non-autoimmune origin. All patients were transplanted during the period 1/1985-1/2015 and had 1 year of follow up post KTx or more.

Results: 180 KTx recipients with biopsy proven glomerular PD were identified, and a control group of 110 patients with PKD, hypoplastic kidneys or obstructive uropathy, as PD was selected. The two groups were similar with respect to baseline characteristics at KTx, but patients with glomerular PD, had received more grafts from living donors than the controls (p=0.02), most of them (75.35%) had been treated with immunosuppressants prior to KTx (p<0.0001) and had donor specific antibodies (DSA) less frequently.

Parameter (mean±sd), %	KTx with glomerular PD N=180	Control group N=110	p-value
DSA pre-KTx	9	27.6	0.001
De novo DSA	15.6	18.4	0.68
Patients with acute rejection	9.6	8.1	0.68
Survival with functioning graft	77.6	95.3	0.0001
Graft survival	75.7	95.3	<0.0001
Graft survival (living donors)	80	100	0.02
Graft survival KTx after 2000	88.2	96.8	0.02
Ser creatinine at end fup (mg/dl)	1.7±0.9	1.39±0.6	0.007
Follow up time (months)	66±52.3	58±.4	0.14

Conclusions: KTx recipients with a glomerular PD had inferior renal function and worst graft survival, compared to those with a PD of non-autoimmune origin. The difference in graft function and survival remained significant when the analysis was contacted per decade of follow up or was limited to living donor KTx. No differences in KTx outcomes were found between patients with nephritic and nephrotic syndrome as PD.

PUB727

Early Recurrence of Diabetic Nephropathy in Kidney Allografts

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Background: Although recurrent diabetic nephropathy (rDN) after kidney transplant (KT) is reported in 70% of cases, most patients are diagnosed after 10 years. Early rDN within 5 years of kidney transplant is extremely uncommon.

Methods: Patients' demographics, clinical data and pathological reports of patients who had KT due to diabetic nephropathy at the University of North Carolina Kidney Center from March 2000 to October 2013 were reviewed. All patients received their allograft from non-diabetic donors. Diagnosis of rDN was made based on pathological classification. The recurrence rate of early DN, defined as pathological lesions present within 5 years post-KT, were reported.

Results: Of 156 patients with native DN, 4 patients (2.5%) had early rDN during median follow-up of 1.78 ± 4.57 years. These patients were described in details. Blood pressure and serum glucose were not well-controlled among these patients. HCV seropositivity was present in one patient. Some patients had rDN without significant proteinuria. In contrast, another patient presented with marked proteinuria. His biopsy revealed co-existing focal segmental glomerulosclerosis (FSGS).

Patient Demographics	Donor Type	Time-to-recurrence	BP (mmHg)	SCr (mg/dL)	UPC	Biopsy Results
55 yo WM	DD	2.5 yr	161/91	1.2	6.3	Moderate mesangial expansion with nodules, FSGS
54 yo WM	ECD	4.5 yr	128/60	1.8	0.2	Mild-to-moderate vaguely nodular mesangial expansion and arteriosclerosis
70 yo WM	DD	2.0 mo	151/69	2.5	1+ (dip-stick)	Segmental scarring, variable mesangial expansion, mild IFTA, mild arteriole hyalinosis
66 yo AAM	DD	1.0 yr	217/99	1.5	4.7	Moderate nodular mesangial expansion, mild IFTA

AA=African-American; BP=blood pressure; DD=deceased donor; ECD=extended criteria donor; IFTA=interstitial fibrosis and tubular atrophy; M=male; SCr=serum creatinine; UPC=urine protein:creatinine ratio; W=white.

Conclusions: To date, it is inconclusive to establish the recurrence rate of early DN after KT. A larger cohort is required to demonstrate the association between clinical characteristics and early recurrent diabetic nephropathy.

Funding: Clinical Revenue Support

PUB728

Effect of Meeting Brain-Dead Donor Management Goals on the Development of Delayed Graft Function in Kidney Transplant Patients

Stéphanie Grondin,[1] Pierre Marsolais,[1] Martin Albert,[1] Anne-Marie Lagacé,[1] Isabelle Houde,[2] Anne Boucher,[1] Dana Baran,[3] Yannick Begin,[4] Melanie Masse,[4] Heloise Cardinal,[1] Josee Bouchard.[1] *[1]Univ of Montreal, Canada; [2]CHUQ, Canada; [3]CUSM, Canada; [4]CHUS, Canada.*

Background: A recent US study suggests that meeting several hemodynamic, respiratory and metabolic goals in organ donors (donor management goals, DMG) could reduce the incidence of delayed graft function (DGF) in kidney transplant recipients (KTR). We determined if DMG goals were met in our kidney donors and how this influenced the incidence of DGF.

Methods: We collected data on consecutive brain-dead donors and corresponding KTR from June 2013 to February 2015. Using guidelines from Transplant-Québec, we evaluated whether DMG were met at donor neurological death (DND), and before organ procurement (OP). We used generalized estimating equations to predict DGF, including DMG parameters and other risk factors for DGF (expanded-criteria donors (ECD), cold ischemia time (CIT), use of Lifeport perfusion, and recipient body mass index).

Results: The 69 consecutive donors had a median age of 50 years (IQR 31.5-62.0), and 36.2% were ECD donors. Mean serum creatinine was 71 (61-91) µmol/L, and Lifeport perfusion was used in 42.2% of cases. The percentages of DMG met increased over time, e.g. central venous pressure (51.2% at DND; 57.9% at OP), urinary output (63.2% at DND; 75.4% at OP) and appropriate use of vasopressors (70.6% at DND; 91.3% at OP). Median CIT was 14.0 hours (8.0-17.8). DGF, defined as dialysis during the first week after transplantation, occurred in 25.0% of 128 KTR. In univariate analysis, no variables significantly predicted DGF, including mean arterial pressure within targets (OR 0.69;95%CI 0.30-1.62). However, the use of Lifeport perfusion was significant in multivariate analysis (OR 0.37; 95%CI 0.15-0.93).

Conclusions: Although DMG were met in the majority of our cases, we were unable to show a significant relationship between this achievement and the occurrence of DGF in KTR. This may be due to small sample size and/or the fact that peri-operative and recipient factors may carry more weight in the context of good donor management.

PUB729

Thrombotic Microangiopathy after Transplant: Which Is the Role for Eculizumab? Ana Avila, Eva Gavela, Mercedes Gonzalez, Marco Montomoli, Asunción Sancho, Julia Kanter, Jose F. Crespo, Luis M. Pallardo. *Nephrology, H. Univ Dr Peset, Valencia, Spain.*

Background: We describe the prevalence and management of thrombotic microangiopathy (TMA) after transplant.

Methods: Retrospective study of the incidence of TMA after kidney transplant from cadaveric donors in our center between Jan-2010 and May-2016. We reviewed the risk factors associated to TMA, management and the evolution after treatment.

Results: 315 kidney transplants were performed. We found 13 TMA cases (4.1%), 8 males. Recipient age was 55 years (r:30-67). Donor age: 42,5 years. Eleven patients presented TMA early after transplant (mean time: 10 days; r:3-33), 2 patients presented late TMA (7 months and 8 years after transplant). Three patients presented TMA in the context of severe intraabdominal bledding, 3 related to AMR, 2 after transplant with a non heart beating donor, 4 to drug induced TMA and one, aHUS relapse. Ten patients presented hematological manifestations and kidney function impairement. A kidney biopsy, performed in 11 patients, showed TMA. ADAMTs13 activity deficiency was ruled-out. The patients were managed controlling TMA risk factors (AMR treatment, drugs withdrawal). Ten required plasma exchange (median 4.5 sessions). In 6/10 patients diagnosed after 2012, after non response to previous measures, eculizumab was started. Mean time to eculizumab treatment was 6 days. A complete hematological response was seen in all of them, but 4 patients loss their grafts. Most of the remaining patients (8/9) improved kidney function (mean Cr 2.45 mg/dl, r:0.9-5.22) at the end of the follow-up (mean follow-up after TMA was 9.3 months (r:1-23). The duration of eculizumab treatment was 133 days (7-240). In 7 patients, a complement system genetic study was performed, showing antiFH antibodies in one case and CFI mutation in another.

Conclusions: TMA is a rare but severe disease that can lead to graft loss or to reduced kidney function. It is associated to several risk factors presented in kidney transplant (AMR, drugs). In patients who do not respond to classic measures (drug withdrawal, plasma exchange) eculizumab can reverse TMA and improve kidney function.

PUB730

Chronic Kidney Disease after Living Kidney Donation: A Single Center Cohort Suthanit Laowalert, Pisut Katavetin, Yingyos Avihingsanon, Kearkiat Praditpornsilpa, Natavudh Townamchai. *Dept of Medicine, Faculty of Medicine, Chulalongkorn Univ, Bangkok, Thailand.*

Background: Post kidney donation outcomes in nonwhite living kidney donors (LKDs) are lacking. This is the first study of Thai population to assess the incidence of chronic kidney disease (CKD) after donor nephrectomy and estimated glomerular filtration rate (eGFR) for donation.

Methods: A retrospectively cohort of all 205 LKDs in King Chulalongkorn Memorial Hospital between 1999-2014 were retrieved to ascertain development of CKD stage 3 or higher. The eGFR was determined by the CKD-EPI.

Results: 143 of 205 records were available, mean age at donation was 37.0 years. 18 of 143 (12.6%) had CKD stage 3 after median follow-up duration of 4 years (range 1-17 years). Predonation eGFR was an independent risk factor in developing CKD stage 3. The risk was significantly increased in donor with eGFRs 85-90 mL/min/1.73m^2 and eGFRs<85 mL/min/1.73m^2 compared with eGFRs>90 mL/min/1.73m^2 (HR 10.3, p<0.05, HR 13.7, p<0.001, respectively).

Table 1 Cox proportional hazard analysis of clinical risk factors for development of CKD in 143 LKDs

Variable	Univariate		Multivariate	
	Hazard ratio (CI)	P-value	Hazard ratio (CI)	P-value
Male gender	0.57 (0.23-1.47)	0.235		
Age	1.087 (1.029-1.148)	0.003	1.037 (0.98-1.1)	0.231
Predonation eGFR <85 ml/min/1.73m2 85-90 ml/ min/1.73m2 >90 ml/min/1.73m2 (reference)	17.49 (5.46-56.06) 13.9 (3.44-56.20) -	<0.001 0.046 -	13.65 (4-46.61) 10.32 (2.39-44.45) -	<0.001 0.002 -
BMI	1.08 (0.962-1.218)	0.189		
UPCR	19.68 (0.539-718.70)	0.105		
SBP	1.036 (0.994-1.08)	0.093		
DBP	1.029 (0.97-1.092)	0.344		

Age at donation was associated with the development of CKD stage 3 only in univariate analysis (HR 1.09, P=0.003). There were 17 (11.9%) and 3 (2.1%) donors developed hypertension and diabetes mellitus. One donor (0.7%) experienced ESRD from secondary FSGS.

Conclusions: Incidence of CKD stage 3 and ESRD of kidney donor were 12.6% and 0.7%, respectively. Predonation eGFRs<90 mL/min/1.73m^2 was a strong determinant of development of CKD, which led to the extended thresholds of eGFR for a donor candidate.

PUB731

Donor Specific Antibodies in Living Related Renal Transplant Recipients Anil Bhalla. *Nephrology, Sir Ganga Ram Hospital, New Delhi, India.*

Background: The clinical impact of anti-HLA antibodies is one of the major areas of research in renal allograft transplantation and a lot of advances have taken place in the methodology of detection of these antibodies. Luminex Platform is presently the favoured technology fordetection of HLA antibodies in addition to the CDC crossmatch (XM) which is considered the gold standard. Pre transplant (Tx) Luminex DSA crossmatch has been recently introduced in India for detecting antibodies that are missed by CDC XM.

Methods: The present study includes patients from January 2012 to December 2013 with one year follow up post kidney transplant. Pre-transplant sera from 46 renal transplant recipients with a negative CDC crossmatch were assessed for donor-specific antibodies (DSA) detection on Luminex Platform using Lifecodes DSA kit (Immucor). The serum samples with DSA (HLA-Class I or II or both) of MFI (mean fluorescent intensity) value more than 500 was considered to be positive. The results were then correlated with the clinical outcomes of the renal allograft.

Results: DSAs were found in 19 out of 54 recipients (35.1%). Of the nineteen DSA positive patients, 5 patients (27.27%) developed acute graft rejection. All these 5 patients had positive C4d staining in their biopsies and the MFI value of the DSA on Luminex platform was found to bemore than 1000. The remaining 14 DSA positive patients showed no rejection and had stable graft function. The MFI value of the DSAs in these patients ranged from 500-1000. All the 35 DSA negative patients (64.8%) were also having stable graft function in one year follow up.

Conclusions: There was a higher incidence of AMR in patients with pre-transplant DSA despite a negative CDC crossmatch. The present study clearly establishes that the Luminex DSA crossmatch is helpful for predicting post transplant graft outcome or rejection. The laboratory cut off value of the MFI for positive DSA was increased from 500 to 1000. However, the clinical impact of the pre-Tx DSAs detected by Luminex techniques has to be fully evaluated in terms of graft survival and more r etrospective studies with larger sample size.

PUB732

Median Arcuate Ligament Syndrome at 1 Year Follow-Up in a Living Kidney Donor Sara J. Fine, Jeremy F. Wright, Jahan Montague, Marie A. Sosa. *Nephrology, Univ of Massachusetts, Worcester, MA.*

Background: Median arcuate ligament syndrome (MALS) is a rare disorder of unknown etiology caused by celiac artery compression from the fibers of a low lying median arcuate ligament (1). Symptoms include postprandial abdominal pain and weight loss that resolve with celiac artery decompression, MAL ligation, and celiac ganglionectomy (2). 1.Dunbar JD, Molnar W, Beman FF, Marable SA. Compression of the celiac trunk and abdominal angina. *Am J Roentgenol Radium Ther Nucl Med.* 1965 Nov;95(3):731–744. 2.Jiminez JC, Hariander-Locke M, Dutson EP. Open and laparoscopic treatment of medican arcuate ligament syndrome. J Vasc Surg 2012;56:869.

Methods: A 30-year-old woman undergoing routine evaluation for live kidney donation to her father with end-stage renal disease was found to have a small right kidney lesion. After extensive discussion of possible risks, both patients elected to proceed. The donor underwent right nephrectomy. A 1cm exophytic chromophobe renal cell carcinoma containing negative margins was excised prior to successful recipient transplantation. The donor had no immediate post-op complications, but appeared notably thin at 1 year follow-up. She reported an unintentional 21lbs weight loss with symptoms of severe right flank pain, worse with meals, that prevented her from maintaining a normal diet. Work-up revealed expected range creatinine, no proteinuria, normal LFTs, AFP, CEA-125 and CA19-9. She was seen by oncology, urology, gastroenterology and endocrinology. Contrast imaging of her chest, abdomen and pelvis showed no evidence of solid masses. However, superior indentation of her proximal celiac artery with 80-90% focal stenosis was noted as a new finding, absent on prior studies. A diagnosis of MALS was posited and subsequently confirmed by elevated celiac artery expiratory flow velocities on ultrasound (1). 1. Erden A, Yurdakul M, Cumhur T. Marked increase in flow velocities during deep expiration: A duplex Doppler sign of celiac artery compression syndrome. Cardiovasc Intervent Radiol. 1999;22(4):331.

Conclusions: This case reports the development of MALS diagnosed one year post kidney donation and reinforces the need for close, thorough follow-up after donation.

PUB733

The Effect of Ureteral Stents Post Kidney Transplant on the Incidence of Pyuria, Bacteriuria, and Hospitalization Niralee Patel,[1] Ibrahim M. El-Ali,[1] John F. D'Avella.[2] *[1]UCONN Health Center, Farmington, CT; [2]Hartford Hospital Transplant Center, Hartford, CT.*

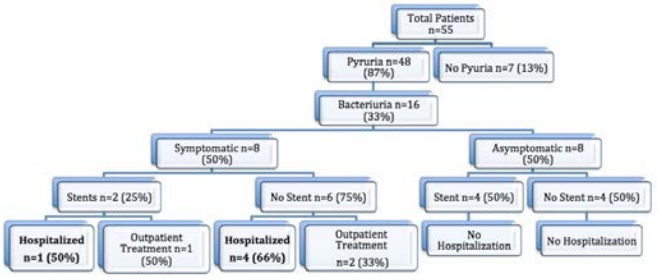
Background: In an effort to decrease the incidence of ureteral complications, many programs place ureteral stents in patients post kidney transplant. Patients are routinely screened for asymptomatic bacteriuria up until three months after transplantation. It is unclear what effect the presence of a stent has on the incidence of pyuria, bacteriuria, and hospital admissions. It is thought that urinary tract infections are more common than the general population in post transplant patients; furthermore, they are also associated with higher mortality.

Methods: As a quality project, we looked at the incidence of pyuria (>10 WBC/HPF), bacteriuria (>100,000 colonies of a single bacteria) in transplanted patients during 2014. All patients had ureteral stents for 4 to 6 weeks post transplant. 60 patients were

transplanted, of which 5 were excluded because of age less than 18 years, acute rejection, or anatomical ureteral problems; thus a total of 55 patients were studied. 45% were female and 55% were male.

Results: We found that pyuria and bacteriuria are unreliable predictors of a true symptomatic urinary infection. 87% of our patient sample had pyuria, of which only 33% developed bacteriuria. We additionally found that in patients with bacteriuria, 50% developed symptoms that require treatment. Among the patients that require treatment, only 25% had a ureteral stent in place (Figure 1).

Conclusions: In summary, our study indicates that ureteral stents post renal transplant do not have a higher incidence of true symptomatic infection or hospitalization compared to patients without a stent. Further studies are useful to confirm these findings.



(Figure 1)

PUB734

Impact of Conversion from Original MMF to Generic MMF in Kidney Transplant Recipients: A Single-Center Experience Hajime Hirano,[1] Haruhito Azuma,[1] Hideki Matsumura,[3] Hideaki Shima,[2] Tatsuhiko Mori,[2] Akira Ashida.[3] *[1]Blood Purification Center, Osaka Medical College, Takatsuki, Osaka, Japan; [2]Dept of Nephrology, Osaka Medical College, Takatsuki, Osaka, Japan; [3]Dept of Pediatrics, Osaka Medical College, Takatsuki, Osaka, Japan.*

Background: Recently, more and more generic drugs have been used for immunosuppressive drugs in the field of organ transplantation. Some reports have indicated that blood concentration of most generic drugs is difficult to maintain stability, and it may cause the difference in graft survival of transplanted organs between original drugs and generic drugs. In this article, we report the cases could not maintain blood concentration of generic drugs of mycophenolate mofetil (MMF).

Results: In 4 cases out of 5 cases that we had to change original MMF to generic MMF, there were cases that blood concentration level was not stabilized. There were possibility that the lowered blood concentration level of MMF caused a rejection, in two cases. Mean MMF trough level wase decreased from 3.6±1.9μg/ml to 0.6±0.4μg/m. Due to the early detection, it did not become severe or failure of graft function, however, we cannot deny the possibilities that side effects were increased and rejection rose. In these cases, we discontinued to use the generic drugs thereafter due to unstable plasma concentration of MMF.

Conclusions: Some reports have indicated that failure to maintain plasma concentration of MMF leads to rejection. Therefore, maintenance of effective plasma concentration and prevention of rejection are essential to long-term graft survival in kidney transplant. Conversion to the generic drug,it may cause differences in effects and absorption. If the generic drug should be used, patients should be closely monitored.

PUB735

Allograft Rejection in the HIV Infected Kidney Transplant Recipient Adriana Dejman, Juan E. Kusnir, Juan Camilo Duque Ballesteros, David Roth. *Nephrology, Univ of Miami, Miami, FL.*

Background: Excellent graft survival outcomes have been reported in HIV patients on anti-retroviral therapy with undetectable viral loads and CD4 count >200 at time of transplant. Prior studies also observed higher incidences of acute rejection with limited data on variables that associate with this outcome.

Methods: Retrospective chart review for patients with HIV who had a kidney transplant between 2001-2014. A multivariate logistic regression model adjusted for demographics, co-morbidities, induction immunosuppression (IS), chronic IS with steroids, presence of drug-drug interaction (DDI) between protease inhibitors (PI) and calcineurin inhibitors (CNI), type of transplant, initial graft function (immediate/IGF, slow/SGF or delayed/DGF), calculated panel reactive antibodies (cPRA), histologic type of rejection and donor specific antibodies (DSA) was used.

Results: 58 consecutive patients were included and divided into Group A, no-rejection (N=41, 70.7%) and Group B, biopsy proven rejection (N=17, 29.3%). Mean age was 52.1 ± 9 in A and 53.3 ±8 in B. Six patients (14.2%) in A had hepatitis C. Induction IS included high dose IV steroids (S), antithymocyte globulin (T) and one of two IL2 receptor blockers: basiliximab (B) or daclizumab (D). STB was used in 65.8% of A and 58.8% of B. Chronic IS with steroids was 82.9% in A and 94.1% of B and 39% in A had a DDI between PI and CNI compared with 47% B. In A, 65.8%, 14.6% and 19.5% had IGF, SGF and DGF respectively versus 58.8%, 17.6% and 23.5% in B. In the Cox model, no variables were statistically different between groups. In B, interval (mean) from transplant to rejection was 808 days; 41.2% had T cell rejection, 23.5% had antibody-mediated rejection and 35% was mixed. cPRA was available for 15/17 of B: 86.6% had 0% and 2 were < 80%. At time of rejection 6/17 had DSA: 5/6 pre-existing and 1/6 *de novo*.

Conclusions: We were unable to identify variables associated with the higher incidence of allograft rejection. However, outcomes are excellent and justify continuing to offer kidney transplants to well-managed HIV infected patients. Intense monitoring of these patients is critical because of the significant DDIs and higher incidence of rejection.

PUB736

Living Donor Kidney Transplantation in Atypical Hemolytic Uremic Syndrome: Favorable Outcome without Prophylactic Therapy Jacobien Verhave,[1] Nicole Van De Kar,[2] Jack F. Wetzels.[1] *[1]Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands; [2]Paediatric Nephrology, Radboud Univ Medical Center, Nijmegen, Netherlands.*

Background: In atypical hemolytic uremic syndrome (aHUS), kidney transplantation has become feasible with the development of the complement inhibitor eculizumab. Many advocate the use of prophylactic therapy to prevent recurrent disease. Living kidney donation may be associated with lower recurrence rate.

Methods: Since 2011, ten aHUS patients were transplanted with a living donor. There was no prophylactic therapy and the protocol emphasized the reduction of triggers for aHUS recurrence (low dose tacrolimus, blood pressure control, statin therapy).

Results: The table shows patient characteristics. Median follow up was 2.6 years. Thus far, only one patient (no 10) had a recurrence of aHUS and is currently treated with eculizumab. One patient (no 6) had BK nephropathy successfully treated by tapering immunosuppression. One patient (no 8) had type 2a rejection without signs of thrombotic microangiopathy on biopsy. Renal function recovered on methylprednisolone and ATG. One patient (no 9) had presumed rejection and was treated with methylprednisolone. At the end of follow-up mean eGFR was 51ml/min/1.73m2, and proteinuria was negligible.

Conclusions: Kidney transplantation in aHUS is safe without eculizumab prophylaxis by using living donors and a protocol that reduces triggers for aHUS recurrence.

patient	gender	age at Tx	genetic mutation	Previous Tx with aHUS recurrence	Current eGFR	Follow-up (months)
1	F	34	C3 p.Arg161Trp, C3 p.Glu1258Ala		46	55
2	F	29	CFH p.Arg1210Cys	Y	78	53
3	F	54	C3 p.Arg161Trp		47	53
4	M	46	C3 p.Lys65Gln	Y	67	50
5	F	40	C3 p.Arg161Trp		60	30
6	M	58	C3 p.Arg161Trp	Y	35	30
7	F	63	C3 p.Arg161Trp		50	18
8	F	24	CFH p.Tyr475His		58	18
9	M	68	C3 p.Arg161Trp		30	13
10	F	40	No known mutation	Y	40	1

PUB737

Hepatitis C Virus in Kidney Transplant Recipients: A Problem on the Path to Extinction Carmen Gonzalez Corvillo, Alejandro Suarez Benjumea, Gabriel Bernal Blanco, Miguel Angel Gentil Govantes. *Nephrology, Hospital Univ Virgen Rocio, Sevilla, Spain.*

Background: HCV still has significant prevalence in kidney transplant(KT)recipients and is related to poor recipient and graft survival.The new antivirals are leading to a radical change in the problem.

Methods: We study HCV prevalence at time of transplant and in follow-up patients,the way RNA+ cases are handled and the results of direct-acting antivirals(DAA).

Results: From 1978 to 2015,2001 transplants had been performed in our center. Serology was present in 1880cases,being + in 13.4%.1195 were still being monitored by our service,60(5%)were HCV+/RNA+ in 45 cases(3.6%).Of these 45 patients:26 were being treated,6 were about to begin treatment,1 was awaiting a new DAA for low GFR,3 were being evaluated to select the ideal DAA,2 excluded due to high comorbidity,2 denied to be treated and 2 needed to return to hemodialysis.Clinical characteristics:4combined liver-kidney transplants;mean age 50.0±9yo;38% were diabetic;average time on replacement renal therapy:255±130months;average time after KT:145±125months;29% showed advanced fibrosis;genotype prevalence:1b(67%);1a(9.5%);3(14%);4(9.5%);The rate of previously failed treatment was 35%.The data were analyzed on May 31st,2016:21 patients had completed treatment(84%).2 patients had to interrupt DAA(8%),one due to hepatotoxicity and another as a result of a liver transplant.In every case graft maintained function and negativization of viral replication occurred in 100% of cases.The rate of side effects has been low,main side effect:anemia related to Ribavirin.It has frequently been necessary to adjust immunosuppression treatment with higher doses of tacrolimus.Renal function has remained stable(pretreatment serum Cr:1.39mg/dl vs at 1st month:1.39mg/dl).

Conclusions: The prevalence of HCV in KT is about to decrease over time as a result of lower incidence and negative selection.DAA lead us to the virtual eradication of this major negative factor that HCV poses for our patients.Otherwise,the treatment of these patients is complicated because of the use of multiple medications and immunosuppression,which is why it requires close collaboration between nephrologists and hepatologists.

PUB738

Cost-Effectiveness of Machine Perfusion Use in a Brazilian Kidney Transplantation Program Ana Carvalho Matos, Daniel Tavares Malheiro, Silvia Regina Morgado, Eduardo J. Tonato, Milton Borrelli, Mario Nogueira Junior, Marcelino Souza Durao, Lucio Roberto Requiao-Moura, Alvaro Pacheco-Silva. *Renal Transplant Unit, Hospital Israelita Albert Einstein, Sao Paulo, Brazil.*

Background: The incidence of DGF is one of most important problem in kidney transplant in Brazil: higher than 60%. Static cold storage (CS) is the standard method of preservation performed by governmental allocation. Our center has used perfusion machine (PM) as preservation method since 02/2013, however we have only used PM after long time in CS. Aim: to determine the relative cost-effectiveness between renal machine perfusion (MP) after long CIT in CS and standard CS preservation.

Methods: Probabilistic decision tree was developed to compare MP versus CS and the results and probabilities of our own center were used to construct this model. The model estimated Economic Impact (EI=MPcost–CScost) and Incremental Cost-Effectiveness Ratio (ICER=EI/[Effectiveness MP – Effectiveness CS]). Direct and indirect medical costs were considered and sensitivity analysis was performed with variations of several parameters. IGF and DGF were considered as outcomes.

Results: MP group had TIF 11 hours higher than CS, despite of this the incidence (79.2% vs. 61.1%, p=0.02) and length of DGF (9 vs. 5 days, p<0.001) were reduced significantly, leading to a reduced length of hospital stay (18 vs. 13 days, p<0.001). The mean cost of each transplant was: MP=U$12,588.15 and CS= U$16,660.83.The budget impact was U$ -4,078.28. ICER for each DGF avoided saved was U$ -226.26. The variables that most impacted the costs were length in hospital and length of DGF.

	Prob-ability	Cost (U$)	Probability* Cost (U$)	Cost (U$)	Cost MP-CS (U$)	Effec-tiveness	ICER (U$)
MP IGF	0.39	10,633.02	4,146.88	12,588.15			
MP DGF	0.61	13,838.15	8,441.27				
CS IGF	0.21	11,090.32	2.328.97	16,660.83	4,072.68	18%	-226.26
CS DGF	0.79	18,141.60	14.331,86				

Conclusions: The use of MP after long CS preservation was cost-effective. This is the first economic study performed in Brazil and will enable other transplant centers to decide on incorporating the renal MP as a strategy to prevent DGF and reduce costs.

PUB739

Association of Childbearing Age with Live Birth after Kidney Transplantation: A Retrospective Single-Center Cohort Study Yasushi Ohashi,[1] Yoshihiro Itabashi,[2] Masaki Muramatsu,[2] Yuko Hamasaki,[2] Seiichirou Shishido.[2] *[1]Nephrology, Sakura Medical Center, School of Medicine, Toho Univ, Chiba, Japan; [2]Nephrology, Omori Medical Center, School of Medicine, Toho Univ, Tokyo, Japan.*

Background: Despite the restoration of fertility after kidney transplantation, the live birth rate after kidney transplantation is markedly lower than that in the general population. Our objective is to determine the reasons for this discrepancy.

Methods: With a total of 315 women who underwent kidney transplantation from 1983 to 2015 (a median of age at kidney transplantation [10th–90th percentile] of 32 years [7–55 years]), we experienced 10 abortions and 21 live births from our 23 recipients and 2 abortions and 7 live births in 7 recipients from other transplant center. Age, date of kidney transplantation, underlying disease, modality of dialysis therapy, donor type, type of fertilization, and pregnancy complication were evaluated at childbearing age, which was defined as those aged between 15 and 49 years old.

Results: The 223 recipients who had undergone kidney transplantation at our hospital were between the ages of 15 to 49 years old as of March, 2016. The live birth rate was 8.9 per 1,000 women transplant recipients-childbearing age year. Seven recipients received either treatments of artificial insemination or in vitro fertilization. Average age at pregnancy was 33.2 ± 3.2 years old, and the periods of childbearing age in post-transplantation were longer in recipients with live births than those with no live births (14.1 ± 7.1 vs. 9.9 ± 7.3 years, $P < 0.05$). In 42.9% of them, pregnancy-induced hypertension was observed in the last trimester of pregnancy. The gestational age and the average birthweight were 32.8 ± 5.0 months and 2,184 ± 632 g, respectively. During a median of 14.5-year follow-up period, one graft of them was lost; that incident rate was 2.5 per 1,000 women transplant recipients-year.

Conclusions: Recipients may be concerned about various aspects of having children. The shorter periods of childbearing age in post-transplantation may disrupt pregnancy,even if fertility is restored. Although the frequency of pregnancy complications should not be overlooked, childbirth do not influence long-graft survival.

PUB740

The Risk Factors of Mammalian Target of Rapamycin Inhibitor Associated Post-Transplant Proteinuria Lee-Moay Lim,[1] Hung-Tien Kuo.[1,2] *[1]Div of Nephrology, Dept of Internal Medicine, Kaohsiung Medical Univ Hospital, Kaohsiung, Taiwan; [2]Faculty of Renal Care, College of Medicine, Kaohsiung Medical Univ, Kaohsiung, Taiwan.*

Background: The Mammalian Target of Rapamycin Inhibitors (mTORI) has been associated with an increased incidence of proteinuria after kidney transplantation as compared to other immunosuppressive agents, yet the precise mechanism remain unclear. The objective of this study was to investigate the risk factor for proteinuria after mTORI treatment in kidney transplant recipients.

Methods: A total of 123 kidney transplant recipients following up in a medical center in Southern Taiwan from January 1999 till April 2016 were included. We examined the risk factor for mTORI associated proteinuria using multivariate logistic regression analysis. P<0.05 was considered as statistically significant.

Results: The mean transplant days before the initiation of mTORI was 638 days. Patients with higher body mass index (BMI) and hyperlipidemia have higher percentage of proteinuria after mTORI use**.**

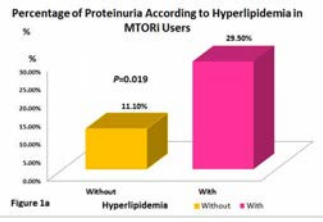


Figure 1a

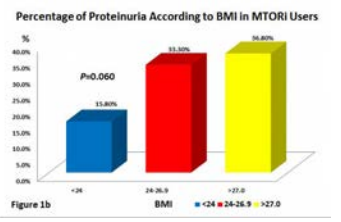


Figure 1b

In univariate analysis, BMI >27 kg/m² (OR=3.111, *P*=0.047) and hyperlipidemia (OR=3.345, *P*=0.024) were associated with proteinuria after mTORI use. After adjusting for confounding factors, hyperlipidemia (adjusted OR=3.740, *P*=0.026) and BMI at 24-26.9 kg/m² (adjusted OR=4.7, *P*=0.021) were significantly associated with risk of proteinuria.

	Adjusted OR (95% CI)	***p* value**
Age at mTORi use	0.957(0.917-0.998)	0.042
Male	1.112(0.415-2.983)	0.833
BMI <24	1	1
24-26.9	4.700(1.265-17.475)	0.021
>27	2.918(0.844-10.088)	0.091
Hyperlipidemia	3.740(1.167-11.983)	0.026

Conclusions: Hyperlipidemia and obesity at the initiation of mTORI treatment were strong predictors for proteinuria. Earlier identification of these risk factors may assist physician to decide the best candidate for mTORI conversion in order to optimize transplantation outcomes.

PUB741

Association of Serum Soluble α-Klotho, Fibroblast Growth Factor 23, and 25 (OH) Vitamin D with Kidney Function in Japanese Kidney Transplant Recipients Makoto Tsujita.[1,2] *[1]Transplant Surgery, Nagoya Daini Red Cross Hospital; [2]Nephrology, Nagoya Univ School of Medicine.*

Background: There are many reasons of deteriorating graft kidney function in kidney transplant recipients. Any marker for predicting kidney function is needed to prevent.

Methods: This was a retrospective cohort study. Forty-seven consecutive patients were enrolled in this study at Nagoya Daini Red Cross Hospital in 2011.Serum intact fibroblast growth factor (FGF) 23, soluble α-Klotho(sαKlotho), 25(OH)Vitamin D[25(OH)D], estimated glomerular filtration (eGFR), and other clinical parameters at 1 year and eGFR at 3 years after kidney transplantation(KTx) were measured to investigate the usefulness of these markers for predicting kidney function. We also evaluated α-Klotho expression in kidney biopsy samples at 1 year after KTx.

Results: The median serum sαKlotho, intact FGF23, 25(OH)D were 516.3 pg/ml, 58.7 pg/ml, and 5.7 ng/ml, respectively. Serum sαKlotho levels were associated with difference between eGFR at 1 year and at 3 years after KTx (ΔeGFR) (*r = 0.37, p= 0.01*). Multivariate regression analysis revealed that serum sαKlotho was the strongest predictor of kidney function. Serum sαKlotho levels were associated with α-Klotho expression in kidney biopsy samples (*r = 039, p= 0.007*) .

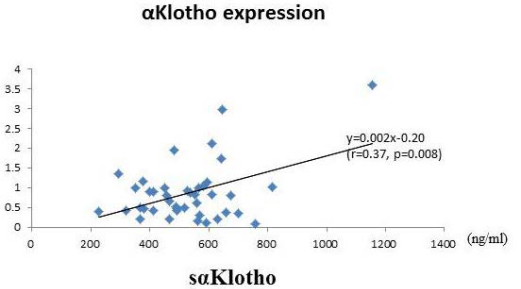


Fig. 1 the relationship between αKlotho in kidney samples and serum sαKlotho levels

Conclusions: Serum sαKlotho may be a good marker for kidney function in Japanese kidney transplant recipients.

PUB742

Collectin Liver 1 and Collectin Kidney 1 of the Lectin Complement Pathway Are Associated with Mortality after Kidney Transplantation
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Background: Kidney recipients have significantly higher mortality compared to the general population. The innate immune system may play an important role during periods with suppression of the adaptive immune system. In the present study, the association of two soluble pattern recognition molecules of the lectin complement pathway, Collectin liver 1 (CL-L1) and Collectin kidney 1 (CL-K1), with long-term graft and recipient survival were investigated.

Methods: The levels of CL-L1 and CL-K1 were measured at the time of transplantation in 382 patients (³17 years) transplanted in 2000-2001. The cohort was subsequently followed until December 31, 2014. Data on patient and graft survival were obtained from the Norwegian Renal Registry.

Results: Both high CL-L1 (≥376 ng/ml) and high CL-K1 (≥304 ng/ml) levels were significantly associated with overall mortality in multivariate COX analyses with HR 1.50, 95 % CI 1.09-2.07, p=0.013 and HR 1.43, 95% CI 1.02-1.99, p=0.038, respectively.

				Multivariable Cox regression analyses			
Variable	HR	95%CI	p	Variable	HR	95%CI	p
High CL-L1	1.50	1.09-2.07	0.013	High CL-K1	1.43	1.02-1.99	0.038
Recipient age, per year	1.07	1.05-1.08	<0.001	Recipient age, per year	1.07	1.05-1.08	<0.001
Diabetic nephropathy	2.17	1.39-3.39	<0.001	Diabetic nephropathy	2.00	1.23-3.15	0.003

Moreover, high CL-K1 levels were significantly associated with cardiovascular mortality. No association between measured biomarkers and death censored graft loss was found. Finally, there was a significant correlation between these two collectins, r=0.83 (95%CI 0.80-0.86).

Conclusions: CL-L1 and CL-K1 were significantly associated with mortality in kidney transplant recipients, when adjusted for other relevant risk factors for mortality. No association with death censored graft loss was found. The levels of those two proteins were significantly correlated.

PUB743

Donor Specific Antibody Kinetics in Patients with Antibody Mediated Rejection Treated with Plasmapheresis and Bortezomib
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Background: The best choice to treat acute antibody mediated rejection (AMR) is not supported by several evidences, and recently the interest in drugs as Bortezomib has improved. Aim: Evaluted the kinetics of donor specific antibody (DSA) in patients with AMR who were treated with Plasmapheresis (PP) or PP and Bortezomib.

Methods: The diagnose of AMR was performed according Banff'07. The treatment consisted of PP added only one dose of Imunoglobulin (0.4g/kg) following the last PP. Bortezomib was used in patients who did not reduce the highest DSA or sum of DSA more than 50% after 6-12 PP. DSA was detected by Luminex and expressed in mfi. The antibodies kinetics were evaluted using three variables: the highest DSA for each patient, all DSA and sum of DSA for each patient.

Results: AMR incidence was 4.2% (N=32), time to diagnose was 14 days and 81.5% patients had diagnose in the first month posttransplant. The changes in biopsies were: ATN-30%, PTC- 58.8%, and C4d was negative in 20%. More than one DSA were indetified in 43.7% of patients. The number of PP was 7.9±6.3 (6[1-24]). Regarding total treatment we observed significant reduction in all variables of kinetics: highest DSA from 6.436 to 1.175 (p<0.001); all DSA (N=56) from 4.872 to 1.087 (P<0.001); sum of DSA from 7.395 to 1.966 (p<0.001). Bortezomib was used in 22% of patients where 57.1% had submitted to desensitization treatment. In these patients PP doesn't change DSA kinetics: all DSA (n=19) from 3,931 to 3,275 and sum of DSA (n=7) from 14,657 to 12,896. After Bortezomib we observed a significant reduction in DSA kinetics to 1,308 P=0.008) and 2,057 (p=0,006), respectivly. One year renal function, graft and patient survival were 1.63±0.80 mg/dl, 81.1% and 100%, respectively.

Conclusions: The AMR treatment using PP was efetive in more than 80% of patients and we observed a good response with Bortezomib in patients who had not a satisfactory response to PP.

PUB744

Renal Sulfate Reabsorption and Long-Term Outcome in Renal Transplant Recipients
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Background: Sulfate is the fourth most abundant anion in human plasma, which is freely filtered by the kidneys. Under normal conditions, tubular sulfate reabsorption works at near maximal rate, with up to 90% of the filtered sulfate being reabsorbed in the proximal tubule. When plasma sulfate levels increase, such as during chronic renal failure, the filtered load quickly exceeds the maximal tubular reabsorption and non-reabsorbed sulfate is excreted at high rate in the urine. We aimed to investigate the rate of renal sulfate reabsorption in RTR and potential long-term consequences of variation therein.

Methods: Plasma sulfate was measured in a well-characterized prospective RTR cohort by a validated ion-exchange chromatography assay and RSR was defined as 1-fractional sulfate excretion. Nutritional intake was assessed by validated food frequency questionnaires.

Results: We included 707 RTR (57% male, age 53±13 y, eGFR 52±20 ml/min/1.73m2, and median plasma sulfate 0.42 [IQR 0.35-0.54] mM) and 330 healthy controls (47% male, age 54±11 y, eGFR 91±14 ml/min/1.73m2, and median plasma sulfate 0.27 [IQR 0.24-0.31] mM). Median RSR was 56% [IQR 48-64%] and 65% [IQR 47-76%] for RTR and controls, resp. (P<0.001). In RTR at baseline, RSR was positively associated with BMI, hs-CRP, heart rate, NT-proBNP, and plasma sulfate (all P<0.05). RSR was inversely associated with intake of cysteine, methionine, water, alcohol, and bread (all P<0.01), but not eGFR (P=0.56). After median follow-up of 38 [32-46] months, 81 (12%) RTR died and 45 (6%) developed graft failure. RSR was associated with all-cause mortality (HR 1.67 [95% CI 1.29-2.14]), but not graft failure (HR 1.14 [0.82-1.59]), independent of potential confounders, including age, sex, BMI, and eGFR (HR 1.60 [1.26-2.04]).

Conclusions: RSR is lower in in RTR than controls. RSR in RTR is related to cardiovascular risk factors and dietary intake of sulfate sources. Higher RSR is associated with increased mortality risk in RTR. Renal sulfate handling seems of considerable pathophysiological interest in RTR.

Funding: Private Foundation Support

PUB745

Outcomes of Renal Transplantation in Alport Syndrome Compared with Other Forms of Renal Disease
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Background: Alport syndrome is an inherited renal disease characterised by haematuria, renal failure and hearing loss. Patients with Alport syndrome who undergo renal transplantation have been shown to have overall survival and graft survival rates similar to or better than those of patients with other renal diseases, though studies have varied in the reporting of this outcome.

Methods: In this national retrospective case series, based in Beaumont Hospital, Ireland, we examine the transplant-related outcomes of all patients with end-stage kidney disease caused by Alport syndrome that were diagnosed there over the past 35 years. These outcomes are compared with those of all other transplant patients with end-stage kidney disease not caused by Alport syndrome, taken from the Irish National Transplant Registry.

Results: 3,918 patients underwent kidney transplantation in Beaumont Hospital between 1982-2014. Of these, 62 patients had end-stage kidney disease due to Alport syndrome. 15-year graft survival was 61% for Alport patients and 42% for non-Alport patients (p = 0.11). Factors that were independently associated with improved graft survival included recipient age, donor age and sex, HLA mismatch, cold ischemia time and the occurrence of acute rejection. 20-year patient survival rate was 70.2% for Alport patients and 44.8% for non-Alport patients (p = 0.01). Factors that were independently associated with improved survival included recipient age and sex, cold ischemia time, donor age and the occurrence of acute rejection. No patients developed *de novo* anti-glomerular basement membrane disease post renal transplantation.

Conclusions: Patients with Alport syndrome have excellent long-term allograft survival, equivalent to that of patients with non-Alport renal disease, and superior overall long-term survival compared to patients with other forms of renal disease.

PUB746

Potential Risk Factors for Resistant BK Viremia in Kidney Transplants
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Background: BK viremia is common post renal transplant, and unchecked BK viremia can lead to allograft dysfunction and loss. The management of BK viremia remains somewhat controversial as no universally agreed upon protocol exists. Immunosuppression (IS) reduction with an option to add leflunomide remains the conservative approach at most centers. Other treatment options for more resistant BK viremia include cidofovir

and IVIG, but these treatments remain controversial and are not usually instituted until the conservative approach fails, increasing risk for allograft injury. We hypothesize that potential risk factors exist which contribute to more resistant BK viremia.

Methods: We performed a retrospective chart review of all patients who underwent renal transplantation at our center between 2003 and 2014. We divided the recipients who developed BK viremia into two groups for analysis: recipients who received only conservative management for BK viremia (IS reduction +/- leflunomide) and recipients who received cidofovir +/- IVIG. Age at transplant, sex, race, body mass index, IS medications (induction and maintenance), type of donor, cytomegalovirus status of donor and recipient, cPRA, HLA mismatch status and cold ischemia time were abstracted. Serum creatinine (sCr) at BK viremia detection and upon resolution were also collected. Parametric statistics were used for data evaluation.

Results: A total of 54 recipients with BK viremia were identified with 42 receiving IS reduction +/- leflunomide and 12 receiving cidofovir +/- IVIG. None of the abstracted parameters were statistically significant between the two groups. The change in sCr between BK detection and resolution within each group also did not statistically differ.

Conclusions: We did not identify any significant risk factors for resistant BK viremia. An interesting finding was that neither management approach contributed to a statistical improvement in sCr. The limitations of our study include a small sample size, single-center experience, and potential for sampling bias. Further studies are needed to better risk stratify patients in order to determine the optimal management strategy for BK viremia.

PUB747

Early Initiation of ACE Inhibitors in the Post Renal Transplant Period: A Study from a State Run Tertiary Care Centre

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Background: Angiotensin converting enzyme inhibitors (ACEI) comprise a drug class that inhibit the effects of angiotensin II. ACEI are well documented to be potent antihypertensives with renoprotective effects but are grossly underutilized in renal transplant recipients. However, these drugs have been reported to cause elevated potassium and creatinine levels in some renal transplant patients. There have been no reports of prospective studies of ACEI in renal transplant patients in the early post-transplant period. The purpose of this study is to assess the safety of an ACEI class, when started in early post-transplant setting.

Methods: We reviewed 84 kidney transplant patients during the period of January 2012 to April 2016 at our Institution. 72 patients were initiated on ACEI therapy. patients who initiated therapy after day 5 and before day 365 of post transplant were included.

Results: Recipients were stratified into two groups according to the time of ACEI into early (within 6 months post-transplantation) and late (after 6 months after transplantation) group. For each patient, haemoglobin, serum creatinine and potassium levels were analyzed at the beginning of ACE inhibitors and at the end of the 1st, 6th and 12th month. In the 57(79.1%%) of the 72 patients ACE inhibitors were initiated within six months post-transplantation and in 15 (20.9%) patients ACE inhibitor were initiated, but after six months post-transplantation. There was no statistically significant difference between the two groups related to age or gender and due to the duration of dialysis treatment before the transplantation. Analyzing the Hb, creatinine and potassium serum levels after initiation of therapy with ACEI trough observed period, we did not found any statistically significant difference in all measured parameters between the two groups of patients and also within the same group of patients.

Conclusions: ACEI can be used successfully post-renal transplant with beneficial long term impact on renal function. There is need for further randomized controlled studies for to see the effect of ACEI on Graft function and its survival.

PUB748

Predicting Outcomes in Pediatric Renal Transplant Recipients

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Background: Pediatric kidney transplant recipients (pKTRs) experience multiple sequelae of their condition, yet an assessment of the cumulative burden and relationship to poor patient outcome is lacking in the literature. Our objective was to develop a composite outcome measure for pKTRs that considers the most common comorbidities and evaluate its ability to predict outcomes 2 years later.

Methods: We retrospectively reviewed all KTRs at our center from 10/2008 through 2/2015. An optimal outcome composite measure was created consisting of 15 criteria in five domains: allograft health (CKD stage <3, urine protein/creatinine ratio < 0.5), histology & immunology (absence of DSAs, no or mild interstitial fibrosis and tubular atrophy, no transplant glomerulopathy, and no history of AMR or ACR), infection (BKV PCR <10,000, CMV PCR ≤0, no history of PTLD or symptomatic EBV), cardiovascular health (triglycerides <500, LDL <130, BP <90th%ile, fasting glucose <126), and growth (BMI <85th%ile, height z-score >-2 SD). We evaluated the ability of these pass/fail criteria to predict poor outcome (patient death, graft failure, and 20% decline in GFR) at years 3 and 5 post-transplant.

Results: A total of 37 patients were evaluated at post-transplant year 3 and 32 patients were evaluated at year 5. Subjects having a low outcome score (lower third quantile) at year 1 and year 3 trended towards poor outcome at years 3 and 5 respectively, although potential prediction was not significant. Of the 15 outcome criteria, presence of proteinuria was the only criteria predictive of poor outcome ($p<0.05$).

Conclusions: The presence of proteinuria is predictive of poor outcome in pKTRs in terms of patient death, decreased allograft function, or failure. The use of a composite score consisting of criteria characterizing allograft health and common comorbid conditions may be predictive of overall outcome, however a larger sample size is needed for validation. Evaluation of risk factors for poor outcomes will allow practitioners to focus clinical outcome improvement efforts.

PUB749

Use of Eculizumab for Atypical Hemolytic Uremic Syndrome in Kidney Transplantation - Single Center Experience in Brazil

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Background: Atypical hemolytic uremic syndrome (aHUS) is associated with a 50% rate of mortality/dialysis dependence at 5 years. Kidney transplantation (KTx) is the best treatment for end stage renal disease (ESRD), but in patient with aHUS recurrence rate >80% has historically discouraged transplantation. Eculizumab has caused a shift in the management of these patients. The drug is not available worldwide.

Methods: Case series on aHUS patients using eculizumab either before or after kidney transplantation.

Results: Between June 2012 and August 2014, eight patients received eculizumab, being three on a prophylactic basis before KTx, three after KTx due to aHUS recurrence and two after kidney allograft loss. They were mainly women (7/8); 27±14 years old presenting past history of thrombotic microangiopathy in kidney biopsy, microangiopathic anemia (MA) and extrarenal organ damage. Prior to eculizumab all patients received ACWY anti-meningococcal vaccine and antibiotic prophylactic were maintained lifelong. They were divided in three groups- clinical characteristics and outcomes are presented in (Figure 1).

	Pre-KTx (n=3)	Post-KTx recurrence (n=3)	After kidney allograft loss (n=2)
Age (years)	25.2±7.8	28.1±22	24.5±9.2
Female gender (n)	3	3	1
Time from diagnostic to eculizumab treatment (months)	-514.0± 712.0	0.9 ± 0.4	16.5±35.0
Clinical manifestation pre-eculizumab	ESRD + MA	Nephritic syndrome, proteinuria, AKI + MA	ESRD + MA
ADAMS 13	➢ 70%	➢ 70%	➢ 70%
Reduced C3 level (n)	2	2	2
Gen mutation (n)	Thrombomodulin (1) C3 (1) Factor H (1)	NA	NA
Plasmapheresis (n)	2	2	1
Dialysis post-dx (n)	3	1	2
Live donor (n)	2	1	1
Panel reactive antibody >0% (n)	2	2	0
Imunosupression therapy (n)			
ATG induction	2	2	1
Tacrolimus	3	2	1
mTOR inhibitor	0	0	0
Outcomes Time under eculizumab (months)	19.6 ±9.3	11.5 ±7.2	7.7 ±0.4
Serum creatinine (mg/dl)	1.2 ± 0.1	0.9 ±0.3	Dialysis
eGFR (ml/min)	54.8 ± 17.2	68.6 ± 17.8	Dialysis
Graft loss (n)	0	0	Not applied
Death with Functioning graft (n)	0	2 (pulmonary infection)	0
Anemia recurrence (n)	0	0	0

NA: Not available

Conclusions: Eculizumab, either used for prophilaxis of aHUS recurrence or early after post-Tx recurrence, allowed good renal function and stable hematological profile. The two patients who did not receive eculizumab in an appropriate time-schedule, lost the allografts. Using eculizumab after renal loss avoided microangiopathyc anemia and extrarenal organ damage in this short term follow–up. Death with functioning graft due to pulmonary infection raises awareness of infection risk of eculizumab on top of the current imunosupression regimen.

PUB750

Attitude of Kidney Transplant Recipients about Influenza Vaccination and Preventive Measures: Comparison of 2009 versus 2016

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Background: An outbreak of influenza A virus H1N1 was identified in Mexico and USA in Apr/09. The government established intensive campaign of diffusion about preventive measures and vaccination. In early 2016, we had another outbreak of influenza but with little diffusion to the population. Aim: to compare the effect of diffusion campaign on kidney transplant recipients' (KTR) attitude about vaccination and preventive measures during the outbreak in 2009 vs 2016.

Methods: During 2009 outbreak, we applied a standardized survey to evaluate: use of flu vaccine the previous winter, during the outbreak and intention to receive it in next winter, prophylactic measures during contingency. In May/2016 we apply the same survey to KTR and compared them.

Results: We included 131 cases of 2009 and 155 of 2016. In table1 we compare demographic characteristics, vaccination frequency previous and after outbreaks, and use of

preventive measures. Only 4 cases have had influenza since 2009. In cases with symptoms or direct contact with influenza patient, an increase of use of facial mask was observed. 53 patients had symptoms but it didn't change the attitude to vaccination.

Variable	2009 n= 131 (%)	2016 n= 155 (%)
Age (years)	39.8 ± 12.5	39.4 ± 15.1
Female	72 (55.0)	84 (54.2)
Vaccinated last Winter*	26 (19.8)	61 (39.4)
Vaccinated during outbreak	2 (1.5)	9 (5.8)
Vaccine next winter (intention)*	83 (63.4)	118 (81.9)
Contact with sick people	7 (5.3)	11 (7.2)
Facial mask use*	122 (93.1)	80 (51.6)
Hand washing	125 (95.4)	137 (88.4)
Avoid crowded situations*	119 (90.8)	84 (54.2)
Avoid shaking hands / kisses*	102 (77.9)	66 (42.6)
Clean workplace*	95 (72.5)	51 (32.9)
*p<0.01		

Conclusions: Despite an intention to received vaccine next winter increased in 2009 (63.4%), the actual percentage that received vaccine last winter (2015) was substantially reduced (39.4%) despite another outbreak of influenza, most probably due to limited publicity.

PUB751

Urinary Liver Type Fatty Acid Binding Protein and Urinary Albumin Excretion Improve Prediction of Graft Failure after Renal Transplantation

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Background: Immunosuppression after renal transplantation has improved but long-term risk of graft failure is still high. Early markers are needed as current monitoring is mainly based on serum creatinine and proteinuria. We tested the added value of urinary liver type fatty acid binding protein (L-FABP) and urinary albumin excretion (UAE) as early prognostic markers for risk of graft failure after renal transplantation.

Methods: A longitudinal cohort of 702 stable renal transplant recipients was included median 5.4 [1.9–12.1] years after transplantation. L-FABP and UAE were measured in 24hr urine samples collected at inclusion. Correlations were assessed by Spearman's rho. Cox regression was used to predict risk of graft failure with hazard ratios (HR) expressed per log2 L-FABP and log UAE. L-FABP and UAE were tested on top of traditional risk factors age, sex, serum creatinine, proteinuria, donor status, and history of previous graft failure. Prediction improvement was assessed with Harrell's C and best model fit by AIC.

Results: Participants (57% male, age 53.0±12.7 years) were followed for median 3.1 [2.6–3.8] years. 45 developed graft failure. At inclusion median L-FABP was 2.1ng/mL [0.9–6.8]. Median UAE was 43.3mg/24hr [11.0–203.4]. L-FABP correlated with UAE (r=0.62), eGFR (r=-0.39), proteinuria (r=0.59) and serum creatinine (r=0.52)(all p<0.01), and UAE with eGFR (r=-0.25), proteinuria (r=0.77) and serum creatinine (r=0.35)(all p<0.01). Higher L-FABP (HR=2.80 (95%CI 1.55–5.04)p<0.01) and higher UAE (HR=1.89 (95%CI 1.23–2.90)p<0.01) were independently associated with graft failure. L-FABP and UAE combined improved prediction of graft failure on top of traditional risk factors (increase in Harrell's C from 0.87 (95%CI 0.81–0.93) to 0.90 (95%CI 0.85–0.94)(p<0.01). A best reduced model included sex, serum creatinine, L-FABP and UAE.

Conclusions: L-FABP and UAE improve prediction of graft failure on top of traditional risk factors. These results are promising for use in routine clinical practice but first require confirmation in an external cohort.

PUB752

Creatinine Clearance Measurement in the Immediate Adult Post Kidney Transplant (KTx) Period with Functioning Allograft: Interim Results

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Background: Several formulae are available to estimate renal function based on serum creatinine values. However these do not take into account of progressive decrease in serum creatinine with functioning renal allograft. Primary objective of the study is to compare the urinary creatinine clearance measured by urinary collection every 12 hours with estimated creatinine clearance by currently available formulae.

Methods: Nine (9) consenting post kidney transplant subjects (5 male, 4 female), mean age 51.8 ± 8.1 years, 7 Caucasian, 1 African American and 1 Hispanic, and with primary allograft function were included in the study. Urine was collected to measure creatinine concentration using Foley catheter every 12 hours starting immediately after kidney transplant for first 5 days post KTx. The creatinine clearance was compared with 1) Cockcroft-Gault (CG) formula, 2) eGFR using Modification of Diet in Renal Disease (MDRD) formula, 3) Jellife adult bedside (formulae where creatinine clearance is estimated with single serum creatinine value) and with 4) Brater and 5) Jellife and Jellife.

Results: Mean value of serum creatinine mg/dL before KTx and every 12 hours after the primary allograft function, calculated creatinine clearance by urinary excretion and estimation by various formulae at the same time points are shown in figure 1.

Figure 1: Actual measured Urinary CrCl in comparison to various formulae in post kidney transplant(KTx)period

Post KTx days	-1	1	1.5	2	2.5	3	3.5	4	4.5
Serum Creatinine (mg/dL) (n=9)	6.3 (±1.9)	5.3 (±1.6)	3.8 (±1.3)	2.7 (±1.3)	2.4 (±1.6)	1.8 (±1.2)	1.6 (±0.7)	1.3 (±0.4)	1.3 (±0.3)
Creatinine Clearance(mL/min)		36.9	48.3	55.6	62.5	82.3	78.3	83.9	71.7
Cockcroft-Gault (mL/min/1.73 m2)		20.3	29.2	42.8	53.8	72.8	71.8	74.8	69.3
MDRD (mL/min/1.73 m2)		12.2	18.8	29.5	38.4	54	52.5	55.2	51.6
Jellifie adult bedside		14.2	20.7	30.5	38.4	51.9	50.8	54.1	51.5
Brater (mL/min/70 kg)		3.3	12	17.3	25.2	37.7	46.7	38.9	51.6
Jellifie and Jellifie (ml/min/1.73 M2)		-9	10.5	9.9	5.1	5.8	3.6	7.2	2.7

Conclusions: Our observations suggest that currently used formulae underestimate the renal function in working allograft. The variability is higher in the first few days with rapidly decreasing serum Creatinine. There is a need to develop a new formula to estimate renal function in functioning allografts with rapidly decreasing creatinine.

Funding: Clinical Revenue Support

PUB753

Comparison of Tacrolimus with Everolimus or Mycophenolate Mofetil or Steroid Regimen and Their Association with Tryptophan Metabolism: A Pilot Study

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Background: Assess graft survival and safety profile at one year. Explore Tryptophan metabolism pathway as a clinical tool to predict graft survival.

Methods: All patients received induction therapy with thymoglobulin(3mg/kg). They recieved Tacrolimus, mycophenolate mofetil, steroid and were randomised into three groups at the end of 3 months. Group 1 (control) patients received Tacrolimus /Mycophenolate/ Steroid. Group 2: Tacrolimus/Mycophenolate Mofetil/Everolimus and group 3: Tacrolimus/ Everolimus/Steroid. Patients were assessed with RFT, Hemogram, Urine R/M, Lipid profile, Blood Sugar levels, Serum Tacrolimus/ Everolimus levels. Adverse events such as anaphylaxis, life threatening infections were noted. Tryptophan metabolite measurement was done using Quantitative real-time RT-PCR.

Results: Graft survival at one year: Control group 1: 7/11 patients had stable graft outcomes, 1 patient had ATN & 3 were lost to follow up. Group 2:4/ 6 patients had stable graft outcomes & 2 had ATN. Group 3: 4/7 patients had stable graft outcome, 1 had ACR+ AMR. **Safety:** No patient had serious adverse events. One patient with Dyslipidemia was reported in each of the Groups 2 & 3. Furunculosis was noted more in group 3. **Tryptophan metabolism enzyme levels:**Control Group**:** No changes were seen in various enzymes levels for the 9 patients available. Group 2 & Group 3**:** Various enzymes showed low expression, but no association was observed with graft survival. Low expression of IDO 1 was observed in 5 patients out of which 4 patients were associated with stable graft outcome & 1 with graft dysfunction. No significant difference was observed in drug levels, Hemoglobin, Creatinine , TLC, Platelets, Triglycerides & Total Cholesterol levels among different groups (*p= NS*).

Conclusions: Larger study is needed to establish the role of Tryptophan metabolizing enzyme as predictive biomarker for graft survival. IDO 1 may possibly show some association. Corticosteroid sparing immunosuppressant regimen(Tac+MMF+EVE) appear to be safe as compared to Steroid containing immunosuppressant regimens (Tac+MMF+Steroid/Tac+EVL+Steroid).

PUB754

Prevalence and Risk Factors for Post-Transplant Anemia in a Reference Center in Mexico

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Background: Anemia is a common complication after kidney transplantation (KT) and has a controversial impact on graft or patient survivals. The aim of the study was to describe the prevalence of anemia before and after KT and to find the characteristics of the patients with anemia.

Methods: All the kidney transplants in adult patients (over 16 yrs of age) performed from December 2012-December 2014 in Hospital de Especialidades Centro Médico Nacional de Occidente in Guadalajara were included. We used data collected in our registration program during one year following transplantation. Anemia was defined according the WHO: hemoglobin (Hb) levels <12 g/dl in women and <13 g/dl in men.

Results: 505 recipients were included in the analysis, 361 male and 144 female had an overall mean age at transplantation of 29±10 years. Most patients were from living donor (86%). Evolution is shown.

Parameter	Baseline	3 mo	6 mo	12 mo
Serum Cr (mg/dl)	1.1±0.5	1.2±0.7	1.2±0.8	1.3±1.2
Serum Hb (g/dl)	10.5±2.1	12.8 ± 2.0	13.6±2.2	14.1±2.3
Anemia (yes/no)	(434/71)	(234/271)	(172/333)	(111/394)

Post-transplant anemia at 1 year			
	Yes (n = 111)	No (n = 394)	p
Female recipient (%)	40	25	0.004
Male donor (%)	54	50	0.475
Recipient age (years)	29 ± 10	29 ± 10	0.62
Donor age (years)	39 ± 12	36 ± 11	<0.01
Donor type (%)			0.879
Living Donor	85	88	
Deceased Donor	15	12	
Induction (%)			0.639
Basiliximab	59	57	
Thymoglobulin	41	43	
Maintenance (%)			
Tacrolimus	97	98	0.28
MMF	100	100	--
Time in dialysis (months)	36 (24-71)	28 (18-58)	0.1
Baseline eGFR (ml/min/1.73)	90 ± 29	95 ± 26	0.04
Baseline hemoglobin (g/dl)	10 ± 1.5	11 ± 1.8	0.001
Creatinine (mg/dl)	1.7 ± 1.9	1.15 ± 0.75	0.001
eGFR (ml/min/1.73)	73 ± 33	89 ± 23	0.001
Hemoglobin (g/dl)	11 ± 2.0	15 ± 1.6	0.001
Graft loss (%)	11	1	0.0001
Patient survival (%)	97	99.5	0.008

Variables that predicted anemia at 12 months (mo) were Hb at 6 mo and eGFR at 6 mo *(RR 1.9 (1.6-2.3) p<.0001 and RR 1.02 (1.01-1.03) p<.002)*. Higher baseline Hb level predicted less graft loss *(RR 0.6 (0.3-0.9) p.001)* and higher Hb level at 1 year predicted better patient survival *(RR 0.6 (0.4-0.8) p.001)*.

Conclusions: In contrast with other studies, we had lower incidence of anemia at 1 year. We found relation between graft function and anemia diagnosis. Baseline Hb and at 1 year does impact in graft and patient survival, respectively.

PUB755

Triglyceride Metabolism before and after Meal in Post Kidney Transplant Recipients

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Background: Many factors cause dyslipidemia after kidney transplantation. Low density lipoprotein cholesterol (LDL-C) has been focused to reduce cardiovascular disease (CVD), but residual risk factors such as triglyceride (TG), remnant-like lipoprotein cholesterol (RLP-C) or small dense LDL-C(sdLDL-C) are also important to reduce CVD.

Methods: TG metabolism could be evaluated by cookie test.(Endcrine Journal 2006,53(2),173-180) We performed the test for sixty three stable kidney transplant recipients at one year after transplantation in 2014. TG, RLP-C, LDL-C/apoB ratio (substitute for small dense LDL-C), Blood sugar (BS) etc. were measured at fasting(f), and at 2 hour (2h) and 4hours (4h) after test.

Results:

Figure 1. Patients' characteristics and the result of this study

Gender(male),n	34
age, years	47.7 ± 13.0
T-CHO, mg/dL	181.0 ± 24.6
HDL, mg/dL	56.2 ± 13.5
non HDL, mg/dL	124.7 ± 21.6
LDL/apoB ratio	1.2 ± 0.2
TG fasting, mg/dL	139.4 ± 62.6
TG 2h, mg/dL	212.2 ± 90.1
TG 4h, mg/dL	206.3 ± 105.2
RLP-C fasting, mg/dL	5.6 ± 3.4
RLP-C 2h, mg/dL	9.7 ± 4.7
RLP-C 4h, mg/dL	9.1 ± 5.6
BS fasting, mg/dL	97.5 ± 34.8
BS 2h, mg/dL	130.7 ± 48.3
BS 4h, mg/dL	135.9 ± 57.8
HbA1c, %	5.9 ± 1.1
eGFR, ml/min/m2	46.6 ± 11.4
CyA+MMF+PSL,n	11
Tac+MMF+PSL,n	34
CyA+EVL+PSL,n	16
Tac+EVL+PSL,n	2
statin use,n	35
DMN,n	10

CyA: Cyclosporine A, Tac: Tacrolimus, EVL: Everolimus
PSL: Prednisolon, DMN: Diabetic nephropathy, BS: Blood sugar

Figure 1 showed the result of this study. TG2h and TG4h levels were higher than TGf levels (r=0.83 p<0.001, r=0.79 p<0.001, respectively). A negative correlation was seen between TGf and eGFR (r=-0.48 p<0.001).TGf had positive correlation with RLP-C, non HDL-C, LDL-C/apoB ratio(r=0.80 p<0.001, r=0.47 p<0.001, r=0.48 p<0.001 respectively). LDL-C levels were under control because of statin use, but LDL-C/apoB ratio levels in 50% of recipients were below 1.2, meaning the rate of sdLDL-C in LDL-C was high. And LDL-C/apoB ratio was associated with TG4h (r=0.30 p=0.009). TG metabolism in non DM group was similar with that in DM group. In EVL group, TGf levels were higher than that in non EVL group (p=0.04).

Conclusions: This study revealed most recipients had some problems with TG metabolism. Any intervention to improve TG metabolism will be needed.

PUB756

Controlled Cardiac Death Donor (cDCD) for Kidney Transplantation: Factors Associated to Best eGF after 2 Years: Spanish Multicentre SENTRA-GEODAS Group

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Background: Controlled donation after cardiac death (cDCD) programs are running in some countries for years. National transplant organization (ONT) has developed a nationwide program in Spain from Jan2012 and 45 centers had started by Dec2015. Eighteen centers out of them have joined our study group. We present our preliminary analysis for best eGF after 2 years.

Methods: ***Study***: Observational prospective multicentre study. ***Intervention***: Kidney transplantation (KTx) from cDCD at joined units. Local centre surgical procedures and IS protocols. ***Main Variable:*** Best eGF along 1st post –TX year as measured by MDRD-4.

Results: ***Cohort description:*** 430 grafts were obtained from 215 cDCD. 13 kidneys were discharged for several reasons and 28 implanted out of our group. 389 recipients: 56.3 years, 69.1% males, 75,6% first KTx, others 2ndor 3rd. Cold ischemia time (CIT): 12,5h; median warm IT 24min, HLA-mismatch: 4 [0-5]. Immunosuppression: 98,8% induction plus prednisone-MMF-Tacrolimus or mTOR. **Graft Function**: Primary graft failure (PGF): 3%, delayed graft function (DGF): 49,7% Nadir Cr: 1.5 mg/dl [0,6-3,1]. **Best eGFR** was 55,3 (24.6) ml/min. For patient with more than 1 year follow-up, best renal function was 55,3 (SD 24.6) ml/min; serum Cr was 2.1 mg/dl at month, 1.8 mg/dl at 3rd month, 1.9 mg/dl at 6th month, 1,6 mg/dl at 1st year and 1.6mg/dl at 2nd year. In the multivariate analysis for the probability to reach 1st year best eGFR>50 ml/min after the first cDCD-KTx was associated to lower donor age (<54years ,OR 2,2 [1.2-3.9]) a shorter CIT (OR 1,04 per hour) and previous treatment (PD vs HD OR 1.9 [1.0-3.6) but not to HLA-missmatch or DGF.

Conclusions: Modifiable risk factor for best eGFR has been stated. KTx with cDCD present higher DGF than historic reference for brain death donor but similar PGF rate and patient or graft survival rates.

PUB757

Effects of Protein A Immunoadsorption in Patients with Sensitized Penal Reactive Antibody Waiting for Kidney Transplantation

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Background: To investigate the effects of protein A immunoadsorption therapy in 4 patients with sensitized penal reactive antibody (PRA) waiting for kidney transplantation.

Methods: 4 patients with sensitized PRA accepted protein A immunoadsorption therapy. Heparin was used for anticoagulation. The PRA, immunoglobulin G (IgG), immunoglobulin M (IgM), immunoglobulin A (IgA), routine blood test, liver function and blood coagulation index were tested before and after each treatment, and adverse reactions were observed, then the PRA was followed up for 3 months after treatment.

Results: There was no obviously adverse reactions occurred in 4 patients. There was significant decline in PRA level after treatment, compared with PRA before treatment (4.375±4.375% vs 25.00±6.847%, $P < 0.05$), and PRA was negative in 3 cases after 2-3 times treatment of protein A immunoadsorption. In the three patients with negative PRA, their antibody isotyping were anti HLA - I type or anti HLA - I + II type, and 1 patient got success renal transplantation after treatment. But there was no change in PRA of another patient, after 2 times consecutive treatment, and we found the PRA genotype of this patient was HLA-DR53, which belonged to HLA - II type. The IgG levels significantly decreased after treatments (7.749±1.097 g/L vs. 2.820±0.447 g/L, $P<0.001$), but there was no obvious change in IgM and IgA levels. Before and after treatment, significant difference was found in the result of activated partial thromboplastin time (APTT) ($P<0.05$), but it was not found in hemoglobin, patelet, fibrinogen, prothrombin time, total bilirubin, albumin and glutamic-pyruvic transaminase. The change of APTT was related to the use of heparin. Follow-up for 3 months after treatment in 3 patients with negative PRA, PRA were rising again on the first month, also include the patient undergoing renal transplantation, but there was no rejection.

Conclusions: Protein A immunoadsorption can reduce serum PRA levels, which can provide opportunity of renal transplantation for patient with sensitized PRA. Its different effect is associated with the types of PRA.

PUB758

The Epstein-Barr Virus DNA Load in the Peripheral Blood of Transplant Recipients Does Not Accurately Reflect the Burden of Infected Cells
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Background: Transplant recipients frequently evince an increased Epstein-Barr virus (EBV) load in the peripheral blood. Predicting post-transplant lymphoproliferative disorders is the rationale behind the quantification of the EBV load in the peripheral blood. However, this assay was shown to have a poor predictive value.

Methods: EBV load was quantified in kidney and stem cell recipients by qPCR. EBV infected cells were determined by in situ hybridisation, lytic antigens by immunostaining. Fluorescence in-situ hybridization (FISH) was used to determine the number of EBV episomes per infected cell. Binding and transformation assays were performed with either plasma or serum.

Results: We quantitated the number of EBV-infected cells in the peripheral blood of 23 transplant recipients and defined the mode of viral infection, latent or lytic. These data indicated that there is no strong correlation between the number of infected cells and the EBV load. This can be explained by a highly variable number of EBV copies per infected cell and by lytic replication in some cells. The plasma of these patients did not contain free infectious viruses. Some of the investigated samples carried a highly variable number of infected cells in active latency. However, a third of the samples expressed neither latent nor lytic proteins.

Conclusions: Patients with an increased EBV load represent a heterogeneous group of patients whose infection cannot be characterized by this method alone. Evaluation of the clinical significance of an increased EBV load, in particular as a predictive marker of PTLD, requires the inclusion of additional investigations, in particular the number of EBER RNA-positive cells.

PUB759

Evaluation of Efficacy and Safety of a Lower Dose of Thymoglobulin as Induction Therapy in Kidney Transplantation
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Background: Thymoglobulin® (rATG), a rabbit antithymocyte globulin is the most common induction therapy used in kidney transplantation. Although its use is essential to reduce acute rejection incidence, it is also associated with many infectious complications, such as cytomegalovirus (CMV) infection. Objective: To evaluate if a 3 mg/Kg single dose of rATG as induction therapy is effective in preventing acute rejection without compromising safety.

Methods: This was a retrospective cohort of 409 patients, whose kidney transplantation was performed from 18-Aug-2014 to 31-May-2015, with a follow-up until 31-May-2016. Before 18-Aug-2014, we used a 6mg/Kg dose of rATG as induction therapy only to sensitized patients (panel reactive antibody-PRA class I or II > 50%) or those with deceased expanded-donor. Since then, we changed the induction protocol to a 3mg/Kg single dose of rATG to all transplanted patients. Outcomes evaluated were acute rejection incidence, renal function, graft and patient survival and CMV infection incidence.

Results: A total of 409 patients receiving the new induction protocol were included. Of these, 58% (n: 238) were under Tacrolimus, Prednisone and Azatioprine as immunossuppression regimen, comprising transplants of living or deceased standard-criteria donors and 42% (n: 171) were under Tacrolimus, Prednisone and Myfortic, comprising transplants of deceased expanded-criteria donors or sensitized patients. Patients had a mean age of 45.8 ± 12.6 years, 82% had deceased donors, 10% had a PRA class I > 50% and 7 % had a PRA class II > 50%. In the Azatioprine group, after one year of follow-up, 8% had biopsy-proven acute rejection and 33% had a CMV infection episode. In the Myfortic group in the same period of follow-up, 6% had biopsy-proven acute rejection and 50% had a CMV infection episode. [table 1] We didn't use a prophylaxis drug for CMV infection. Our strategy was the preemptive treatment for the patients with positive CMV antigenemia.

Conclusions: The 3mg/Kg single dose of rATG as induction therapy was associated with a low incidence of acute rejection after one year of follow-up.

PUB760

On the Significance of Onset of De Novo DSA in Kidney Transplant Recipients after Alemtuzumab Induction
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Background: The presence of de novo DSA (dnDSA) is associated with antibody mediated rejection (ABMR) and reduced graft survival. Despite this, uniform screening and treatment has not been established. One and 5 year incidence of dnDSA post-transplantation varies according to immunosuppression and detection protocols, (~10% and 35% respectively) as does time to appearance, (~2-5 years). Our aim was to evaluate the significance of onset of dnDSA appearance.

Methods: Kidney transplant recipients were screened for dnDSA from 7/1/2014 to 3/31/2016 at 1, 2, 3, 4, 5, 6, 9, 12 and 18 months. Sera were tested with the Luminex assay and levels > 500 mfi considered positive. Induction was with alemtuzumab and maintenance was with tacrolimus and mycophenolate mofetil. DnDSA was treated if mfi was >5,000 or antibody induced injury was seen on biopsy.

Results: In total, 124 consecutive patients were screened for dnDSA appearance. Mean follow-up was 7.2 ± 4.2 months and included 35 patients who completed 1 year. Of these, 42/124 (34%) developed dnDSA. Very early onset (months 1-3) occurred in 32/42 patients, and later onset (month 4+) occurred in 10/42 patients. In the very early group, dnDSA at onset was 14 class I (mean 2,393 mfi), 17 class II (mean 2,093 mfi) and 1 patient with both. In the later onset group, dnDSA at onset was 4 class I (mean 2,090 mfi) and 6 class II (mean 1174 mfi). In all, 9/42 were treated; 7/32 (22%) in the very early group and 2/10 (20%) in the 4+ months group. Of those treated, 4 had evidence of ABMR on biopsy, 3 did not and 2 were not biopsied. The remaining untreated patients (n=33) were serially monitored and of note, 16/33 experienced complete resolution of dnDSA by the end of their first post-transplant year. Interestingly, all patients with dnDSA resolution were from the very early onset group.

Conclusions: Following alemtuzumab induction, dnDSA occurred in 34% of recipients, mostly within the first year post-transplant. Patients with very early dnDSA appearance, both class I and II, were more likely to have resolution of their dnDSA than those who developed dnDSA at 4+ months.

PUB761

The Use of Mammalian Target of Rapamycin Inhibitors (i-mTOR) Could Improve Renal Function in Renal Grafts from Uncontrolled Donation after Cardiac Death Donors (UDCDD)
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Background: Ischemia injury in kidneys grafts from UDCDD could produce a poor renal function. Minimized blood levels of CNI associated with i-mTOR therapy could avoid acute rejection and decreased CNI nephrotoxicity.The aim was to describe evolution of renal function before and after CNI minimization associated with conversion from MMF to i-mTOR in a population with renal transplants (RT) from UDCDD.

Methods: All RT from UDCDD received steroids, tymoglobuline, mycophenolate (MMF) and delayed introduction of CNI(tacrolimus). Blood levels of tacrolimus had to be between 8-10 ng/mL at first months after transplantation. We selected for our study patients in whom the immunosuppression was changed after 3 months of transplantation minimization of tacrolimus blood levels to 5 ng/mL and conversion from MMF to i-mTOR. We evaluated renal function before and after these change.

Results: Our center have performed 207 RT from UDCDD. Minimization of tacrolimus blood levels (10 to 5 ng/mL) and conversion from MMF to i-mTOR was performed in 46 (22%) cases at 11 (6,32) months from transplantation. Causes of immunosuppression change were: 20 (44%) CNI nephrotoxicity, 14 (30%) neoplasm, 6 (13%) clinical trials, 3 (7%) viral infections, 1 (2%) BK nephropathy, 1 (2%) posttransplantation diabetes and 1 (2%) gastrointestinal intolerance to MMF. The evolution of renal function is showed in Table 1.

	1 year before	Basal	3 months	1 year after
Serum Creatinine (mg/dL)	1.4±0.4*	1.6±0.4	1.5±0.4*	1.5±0.5
GFR (mL/min)	57±22	501±9	54±20*	52±17
Proteinuria (g/day)	0.2 (0.1-0.4)	0.2 (0.1-0.3)	0.2 (0.2-0.4)*	0.3 (0.2-0.4)*
Aannual GFR		-4 (-10,5)		9 (-3,8)

*p<0.05

Withdrawn of i-mTOR occurred in 8 (17%) patients: 3 edemas, 2 intolerance to i-MTOR, 1 proteinuria, 1 pneumonitis and 1 neurological symptoms.

Conclusions: Minimization of tacrolimus blood levels and conversion from MMF to i-mTOR in kidney transplant from UDCDD is efficient and safe with low rate of i-MTOR withdrawn and improves renal function.

PUB762

Prevalence of HLA-DR15 in Lupus Kidney Transplant Patients
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Background: Systemic Lupus erithematosus (SLE) is a severe auto imune disease, characterized by envolvement of multiple organ systems. Lupus Nephritis is one of the mainly complications of the disease and is associated with poor survival and high morbidity, particularly for patients who develop end-stage renal disease (ESRD). the cause of the disease is complex and both environmental and genetic factors are involved. recent studies demonstrated that HLA class II genes are consistently associated with SLE susceptibility, especially some alleles of DR-15.

Methods: The aim of this study is to evaluate the association of HLA-DR15 in a Lupus patients that underwent to a kidney transplant between 1981 and 2016 in Bonsucesso Federal Hospital, Rio de Janeiro, Brazil. This is a retrospective study, and the Lupus group was compared with a control group. The control Group was composed with patients from the subsequent transplants in the same year of the lupus patients transplant. The analyses were performed using Chi square test and spss.

Results: Forty eight patients were included in the lupus group, 41 female patients, 23 were caucasian, 25 african-american.The median age was 31 years old. Thirty one patients in this group was Live donor transplant. The control group was composed by 92 patients, 65 female patients, 43 patients were caucasian, 49 african americans. The median age

was 43 years old. The prevalence of undelying diseases were 51 hypertension patients, 5 diabetes,13 glomeruloesclerosis, 12 Polcistic Kidney disease and 10 others diseases. Forty three underwent to a live donor transplant.The HLA DR-15 was present in 16 patients(33%) in the lupus group compared with 15 patients(16%) in the control group (p=0,021).

Conclusions: The association of HLA DR-15in lupus patients was relevent in this study. Further studies are necessary to evaluate this correlation with lupus nephritis and the progression of this patients after kidney transplant and the graft survival.

PUB763

Graft Survival at 5 Years in Living Donor Renal Transplantation: Does Azathioprin versus MMF Based Immuno Suppression Influence the Outcome? Raju Balasubramaniyam,[1] Sivaram Kannan Swaminathan,[2] Hemalatha Anantha Kumar Naidu.[1] *[1]Nephrology, Kauvery Hospital, Chennai, Tamil Nadu, India; [2]Internal Medicine, Madras Medical College, Chennai, Tamil Nadu, India.*

Background: Retrospective evaluation of renal transplant outcome at 5 years post transplantation, in live transplant program was analysed.

Methods: Live renal transplant recipients from 1998 to 2007 were included .Cadaver transplantation ecipients, who did not follow up and who died prior to reaching 5th year were excluded. Mean age, gender distribution, basic disease, degree of HLA matching, immuno suppression and its influence studied.

Results: 123 patients fulfilled the inclusion criteria -99 men (80.5%) 24 women (19.5%), mean age 38.09 years. Basic disease was Glomerulonephritis in 58(47%), interstitial disease 30 (24.3%), hypertensive nephrosclerosis 20 (16.3%), diabetic nephropathy 12 (9.75%) and 3(2.43%) other diseases. First degree relatives donated in 92 (74.8%) and the rest 31 (25.2%).13 were full house, 69 were haplo identical, 35 mismatches, and 6 were single antigen matched. 86 (70%) received cyclosporine, azathioprin and steroids and 34(30%) received cyclosporine, MMF and steroid based immuno suppression. Among those who took Azathioprin 59/86 patients(68.6%) had normal graft function at 5 years and 25 (31.4%) had varying degrees of azotemia (18 patients had creatinine from 1.5-3 mgm%, 7 had creatinine from 3-5 mgm% and 2 had creatinine > 5 mgm%) . Of the MMF patients 23/37 (62.1%) had normal graft function and 14 (37.9%) had azotemia. (12 had creatinine between 1.5 and 3 mgm% and 2 patients had creatinine > 5 mgm%).Comparison between these 2 groups with respect to normal and with graft dysfunction revealed a 'p' value of 0.53(NS).

Conclusions: 71% of our patients had follow up with us at the end of 5 years and 29% were lost for follow up. Glomerulonephritis and Interstitial nephritis constituted 88 (71.3%) ,the common basic diseases in our transplant program. Mother, sister and spouse were the common donors. 70% of our patients received azathioprin based therapy and 30% received MMF, along with cyclosporine and steroids. Graft function at the end of 5 years did not differ significantly between these two groups.

PUB764

Malnutrition at the Moment of Kidney Transplantation Is Associated to Worst Long-Term Renal Function Carlo M. Alfieri,[1] Maria Teresa Gandolfo,[1] Valentina Binda,[1] Donata Cresseri,[1] Mariarosaria Campise,[1] Anna Regalia,[1] Francesco Cosa,[1] Deborah Mattinzoli,[2] Masami Ikehata,[2] Piergiorgio Messa.[1] *[1]Nephrology, Dialyisis and Renal Transplantation Unit, Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico, Milano, Italy; [2]Renal Research Laboratory, Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico, Milano, Italy.*

Background: The relationship between weight anomalies(WA) and kidney transplantation (KTx) dysfunction is debated. Our study performed in KTx patients aims to: calculate the WA in the 1styear of KTx;Evaluate the relations between body mass index(BMI), clinical and biochemical exams;Explore the influence BMI in renal function (RF) variations.

Methods: Routinely evaluations at 1st(T1) and 12th(T12) mths after KTx were performed in 440(M=250;age 48±11 yrs) KTx pts transplanted between 2004 and 2013. Patients were categorized as: malnourished (MN-BMI≤ 20 kg/m2), normal (N-BMI>20 to ≤25 kg/m2), overweight (OW-BMI>25≤30 kg/m2) and obese (OB->30 kg/m2) and by median BMI(23kg/m2) in upper(BMI-up) or under (BMI-un) median. Serum creatinine(sCr–mg/dL), 24h-proteinuria (Prot-U–g/24h) and eGFR (mL/min) were used as RF indicators. RF variation was calculated by T12-T1 values. Delayed graft function(DGF-12% of patients) was defined by the need of dialysis during the week after KTx.

Results: At T1 and T12, 27% and 7% of patients were MN, and 41%, 28% and 4% at T1 and 50%, 39% and 4% at T12 were N, OW and OB resp. (p<0.0001). During the 1styear of KTx, BMI increased (p<0.0001). BMI-T1 correlated with age, systolic blood pressure(SBP), glucose, acid uric, albumin and Hb. No associations with length of hospital stay and DGF were present. At T12 a decline of sCr,stronger in BMI-up (p=0.02)was observed. Of note, only in MN an increase of sCr was observed(p<0.0001) at T12. Prot-U was lower at T12 (p=0.46), with no relation with BMI. BMI-T1 was associated to sCr reduction(p=0.005). In the 1styear of KTx 12 patients (6 OW) restarted dialysis and 2 (OW) died.

Conclusions: In the 1styear of KTx BMI increased, mostly because of a normalization of malnourished patients. BMI is associated to nutritional parameters and to SBP. No effect of BMI in RF recovery was found, whereas malnutrition seems influence negatively the long term trend of RF.

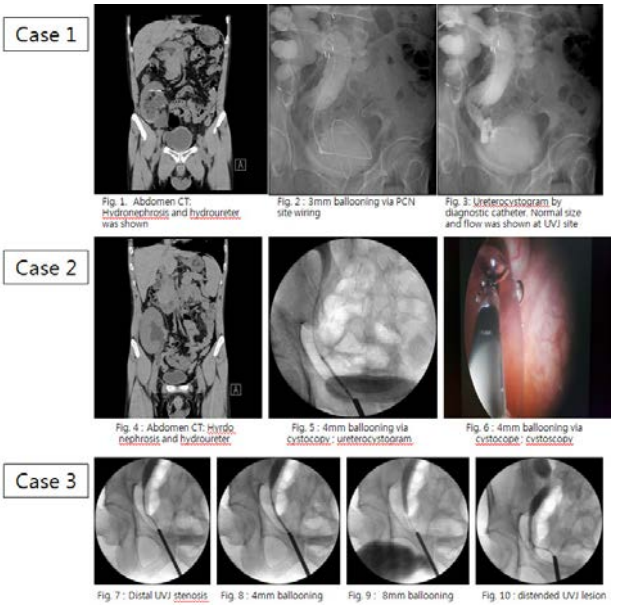
PUB765

Balloon Dilatation at Ureterovesical Junction Stenosis in Kidney Transplantation Patient by Interventional Nephrologist: 3 Cases Jin Ho Lee, Heeryong Lee, Joon Seok Oh, Dongyeol Lee, Seong Min Kim, Yong Ki Park, Yong Hun Sin, Joong Kyung Kim. *Internal Medicine, Bongseng Memorial Hospital, Busan, Dong-Gu, Korea.*

Background: Hydronephrosis is one of the etiology of allograft dysfunction in KTP. Ureter stone, midureter ischemia, surgical technique error, and the other reasons make the hydronephrosis. To eliminate the hydronephrosis due to ureter stenosis, balloon dilatation may be the treatment option. We announced 3 cases of hydronephrosis due to UVJ stenosis causing graft dysfunction was treated balloon dilatation by interventional nephrologist.

Methods: Case 1: 59-year-old man who underwent KTP at Feb, 1989. His serum creatinine was elevated to 3.2mg/dl. Image modalities show hydronephrosis and UVJ stenosis(Fig.1). Then, we underwent percutaneous nephrostomy. We inserted guide wire and ballooning(MUSTANG™, 3.0mm)(Fig.2) was done via PCN site. After that, UVJ stenosis was improved(Fig.3). His serum creatinine was declined to 2.2mg/dl. Case 2: 38-year-old man who underwent KTP with deceased donor at Jan, 2015 was admitted for elevated serum creatinine, from 1.6 to 2.2mg/dl. His CT and abdominal US findings show hydronephrosis and UVJ stenosis(Fig.4). We underwent cystoscopy and ballooning (MUSTANG™, 4.0mm) (Fig.5) was done. After that, diameter was increased at stenotic ureter(Fig.6). His serum creatinine was declined to 1.8mg/dl. Case 3: 28-year-old man who underwent KTP with deceased donor at Sep, 2015. At POD 21, graft kidney CT scan shows hydronephrosis and hydroureter. His serum creatinine level increased slowly. We performed cystoscopy and ballooning at stenotic lesion. Ballooning was done(MUSTANG™, 4.0mm and 8.0mm) (Fig. 7, 8, 9). After that, ureter size was normalized(Fig. 10).

Results:



Conclusions: UVJ stenosis in KTP patient could be treated by balloon dilatation and D-J catheter insertion by interventional nephrologist.

PUB766

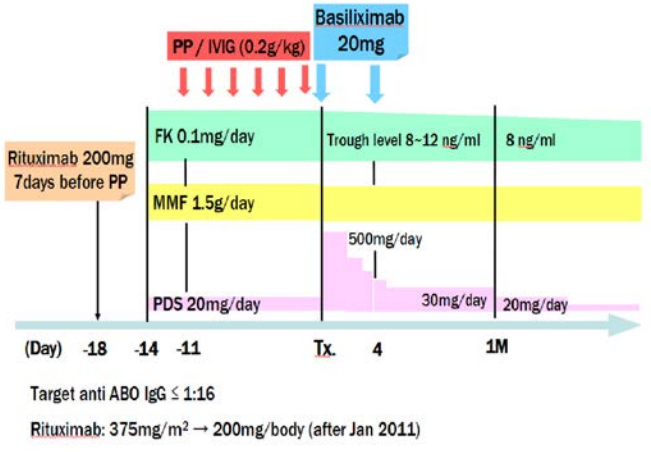
Overcoming of Very High Anti A/B Antibody Titer in ABO Incompatable Kidney Transplantation: Single Center Study Heeryong Lee, Jin Ho Lee, Dongyeol Lee, Joon Seok Oh, Yong Hun Sin, Seong Min Kim, Yong Ki Park, Joong Kyung Kim. *Internal Medicine, Bong Seng Hospital, Busan, Korea.*

Background: ABO incompatable KTP is effective way to reduce the shortage of living donor. In some studies, the presence of high titer of anti A/B Antibody was considered to contraindication for ABOi KTP. With the development of desensitization therapy, 512 or more high titer ABOi KTP could perform.

Methods: Eleven patients with end-stage renal failure underwent ABO-incompatible living kidney transplantation. Baseline anti-A/B antibody titer was 577.16(IgG, range; 512~1024) and 192.72(IgM, range; 8~512), titer was performed by tube method.

Age(year)		55.7±12.2
Sex	Male	4
	Female	7
Causative disease	DM	2
	IgA nephropathy	3
	MGN	1
	MPGN	1
	Unknown	4
Dialysis vitage(month)		17.5 ± 28.6
Initial isoagglutinin titer, IgG(log2)		577.16 ± 207.11(9.18 ± 0.40)
Initial isoagglutinin titer, IgM(log2)		192.72 ± 136.16(6.10 ± 0.98)
ABO incompatibility	A-> O	4
	B-> O	6
	A-> B	1
Donor	Father	1
	Son	1
	Daughter	4
	Brother	1
	Sister	3
	Wife	1
HLA mismatches		2.18 ± 1.72
Plasmapheresis		6.10 ± 0.98

We tried plasmapheresis(PP) and IVIG for removal of the anti A/B antibodies before the kidney transplantation and the number of PP was 6.10 ± 0.98. We used Basiliximab, methylprednisolone for induction immunosuppressant and tacrolimus, mycophenolate mofetil, prednisolone for maintenance IS according to desensitization protocol.



Results: Mean follow-up duration was 41.9 months(range 3~75months). We had one case of biopsy proven acute cellular rejection, and then we loss the graft despite of rescue therapy. There was no antibody mediated rejection episodes and all patients are alive.

Conclusions: Very high Anti A/B antibody titer(≥512, IgG, Isoaggluttinin tube method) in ABOi KTP shows excellent outcomes.

PUB767

The Use of Sirolimus in Patients with Recurrent CMV Infection after Kidney Transplantation: A Retrospective Case Series Analysis Rachel Hung, Ali M. Shendi Mohamed, Ben Caplin, Mark Harber. *Renal, UCL Centre of Nephrology, Royal Free Hospital, London, United Kingdom.*

Background: CMV is the commonest opportunistic infection in kidney transplant recipients (KTRs) and remains a cause of morbidity and mortality. Mammalian target of rapamycin(mTOR) inhibitors have a theoretical antiviral advantage compared to conventional immunosuppression.

Methods: We studied a cohort of 19 consecutive KTRs who were transplanted at the Royal Free Hospital having recurrent(>3) or prolonged(>3 months) CMV viremia before the Sirolimus switch, despite appropriate preemptive anti-viral therapy.CMV titres were analysed for the period from the first positive (>200 copy/ml) test until the commencement of sirolimus and an equal period thereafter. Creatinine levels at discharge,3 months and 1 year were recorded.

Results: 13 males and 6 females with mean age at transplantation of 48 years (20-73) were studied.4 patients had primary CMV infection and 15 patients had CMV reactivation/ reinfection. All patients had standard immunosuppression of basiliximab induction, tacrolimus, MMF and early steroid withdrawal. The first viraemic episode occurred after a mean transplantation period of 28.8±11.8 days.The mean time to starting Sirolimus from transplantation was 125±41 days. Sirolimus was used to replace MMF in all patients. Acute rejection was commoner before starting sirolimus in the context of immunosuppression reduction (4 vs 2 patients after commencement of sirolimus). The mean number of days on anti-viral treatment was reduced after sirolimus conversion (39 ± 31 days vs 74 ± 30 days). 4 patients developed ganciclovir resistance. The area under the curve for Log_{10} CMV viral load was significantly higher before than after the sirolimus switch(p= 0.0034) Mean serum creatinine before conversion to sirolimus was 296.5 (79 – 718), at 3 months after conversion at 159.8 (69-271) and 170.4 (69-287) at 1 year.

Conclusions: Patients with recurrent CMV viraemia who are high immunological risk patients or those with anti-viral resistance risk life-threatening infection or sacrifice of the transplant. In our experience the use of an mTORi is a useful strategy in treating recurrent CMV viraemia without provoking rejection.

PUB768

Validity of Kidney Donor Risk Index for Prediction of Graft Outcome in Deceased Donor Kidney Transplantation; a Singe Center Experience Kyung Sun Park, Jongha Park, Hyun Chul Chung, Jong Soo Lee. *Internal Medicine, Ulsan Univ Hospital, Ulsan, Republic of Korea.*

Background: Donor organ quality is a key determinant of graft outcomes in deceased donor kidney transplantation (DDKT), and several donor quality scoring systems have been proposed.

Methods: To validate the kidney donor risk index (KDRI) for prediction of graft outcome, we screened 134 patients who received DDKTs at Ulsan University Hospital from April 2003 to May 2015. Among them, 91 DDKTs whose KDRIs were available were included this analysis.

Results: Median follow-up was 48 months. Mean age of recipients and donors are 47.3 and 42.5 years, respectively. Mean KDRI was 1.31 ± 0.31 (range from 0.68 to 2.23). During follow up, delayed graft function (DGF) and biopsy-proven acute rejection (BPAR) developed for 6 and 16 patients, respectively. One- and 5-year BPAR-free survival was 88.8% and 79.3%, respectively. BPAR-free survival was tend to be higher for DDKTs from donor with KDRI ≤ 1.0 but not statistically significant (P = 0.073), compared to those with KDRI >1.0. Graft failure occurred to only 2 patients at 5 and 29 months after DDKT, and their KDRIs were 1.28 and 1.98, respectively. In multivariate liniear regression, DGF (standadized beta = -0.273, P = 0.005), BPAR (standardized beta = -0.261, P = 0.012) and KDRI (standardized beta = -0.521, P < 0.001) were significant predictors of last-vistit estimated glomerular filtration rate.

	Coefficient	Standard error	Beta	P
Delayed graft function	-27.549	9.605	-0.273	0.005
Biopsy-proven acute rejection	-17.287	6.671	-0.261	0.012
KDRI	-34.660	6.362	-0.521	< 0.001

Conclusions: KDRI is an easily applicable scoring system and is a good prognostic tool for graft outcomes in DDKTs.

PUB769

Hair Matters: Underrated Side Effect of Immunosuppressive Therapy in Children Antonia Bouts,[1] Maritza A. Middelkamp-Hup.[2] *[1]Pediatric Nephrology, Emma Children's Hospital, Academic Medical Center, Amsterdam, Netherlands; [2]Dermatology, Academic Medical Center, Amsterdam, Netherlands.*

Background: Early steroid withdrawal (ESW) after renal transplantation (rtx) in children improves growth and reduces metabolic risks without increasing the number of acute rejections. Hair loss is reported as a non-frequent side effect of tacrolimus (Tac) and mycophenolate mofetil (MMF). Since we switched to an immunosuppressive regimen of ESW combined with Tac, MMF and basiliximab (ESW protocol) we encountered an increased number of children with hair loss, varying from mild to severe. To assess this observation we compared hair loss in children receiving the ESW protocol with children receiving the previous non-ESW schedule (basiliximab plus steroids; plus MMF or azathioprine; plus cyclosporine which is switched to Tac 6 months after rtx).

Methods: Results are given in median (range). Differences between groups was tested with Fisher exact.

Results: Five of 16 ESW-children (31%) and 3 of 13 non-ESW children (23%; n.s.) developed hair loss, which cannot be put aside as a minor nuisance. As an example, a 12-year old girl received a kidney transplant following the ESW-regimen according to TWIST. One year after rtx she developed near-total hair loss of the scalp, eyebrows and eyelashes. Other causes such as infection, zinc- and iron deficiency and thyroid disorder were excluded. Prednisolone was reintroduced and Tac tapered to a trough level of around 3 ug/L. MMF dosage was maintained at 600 mg/m². Hair growth recovered but remained thin.

	ESW		Non-ESW
patients	16		13
age at rtx (years)	11,5 (1,7-16,4)		10,7 (3,2-16,6)
	ESW maintained ESW	Steroids restarted	
	10	6	
Hairloss (%)	4 (40%)	1 (17%)	3 (23%)
onset after rtx (months)	14,8 (5,3-22,6)	5,3	30 (9-58)

Conclusions: The number of patients in this study is too small to show significant differences, but ESW treatment might give more hair loss than steroid-based therapy. Hair loss after renal transplantation in children is an underrated problem with a significant cosmetic impact, especially for teen-agers. The cause can be multifactorial and needs more exploration.

PUB770

Hemolytic Anemia after Kidney Transplant and Polyclonal Antibodies Alice Lança, Rita Birne, Ivo Laranjinha, Sofia Semedo Coelho, Liliana Maria Goncalves Cunha, Tiago J. Carvalho, Cristina Jorge, Margarida Bruges, Patrícia Matias, Teresa Adragao, Andre L. Weigert, Domingos Machado. *Nephrology, Hospital Santa Cruz, CHLO, Lisbon, Portugal.*

Background: Hemolytic anemia (HA) after renal transplantation (RT) may result from hemolytic-uremic syndrome (HUS), donor-derived antibodies (ab) against recipient's erythrocytes or related to calcineurin inhibitors (CNI). However, an association with polyclonal ab (PAbs) has been poorly described.

Methods: We conducted a single-center cohort study to evaluate the incidence of HA in the first 30 days of RT in patients (pts) who randomly received ATG-Fresenius (ATG-F) or Thymoglobulin-Genzyme (TMG-G) between 01/2009 and 04/2016. HA was defined as decrease of at least 1g/dL hemoglobin (Hb) in 24h and haptogloblin <30mg/dL. Pts with identified causes of HA were excluded.

Results: We enrolled 180 pts; 59% males; mean age 50 ± 11 yrs; Less than 1% was pre-emptive. Six percent obtained a living donor graft and 16% a 2nd RT. Regarding immunossupression, 58.9% received ATG-F (mean cumulative dose (mCD): 17.9/kg) and 41.1% TMG-G (8.4/kg). Out of 180, 11.7% developed HA. Demographic data, RRT modality and vintage, kidney failure etiology, deceased vs. living organ donor, cold ischemic period, anemia, erythropoietin (EPO) use and blood transfusions (BT) before RT were similar in ATG-F and TMG-G group and in HA and non-HA group (NHA). In HA pts, ATG-F was used in 95.2% (p<0,001) in similar doses to NHA pts. HA group had lower Hb at day 1 (9.8 vs 10.6 g/dL; p=0.023), day 3 (8.3 vs 9.3 g/dL; p=0.003), day 7 (8 vs 9.3 g/dL; p <0.001) and day 15 (8.1 vs 9.1 g/dL; p<0.001) after ATG-F/TMG-G use requiring more BT (median 2 vs 0; p=0.006). Higher EPO dose (19238 vs 12952 UI/week; p=0.005) was needed for identical Hb at day 30. No differences were found concerning serum creatinine, maintenance IMS (CNI, mTor inhibitors, anti-proliferative), HLA-mismatches number, donor specific ab and panel reactive ab percentage. HA group had no irregular ab. Overall, 19% of ATG-F pts developed HA compared to TMG-G (0.01%).

Conclusions: In our study, 11.7% pts developed HA in the first month, 95.2% occurring in the ATG-F group. A prospective study on the influence of different PAbs in HA is needed.

PUB771

Monitoring of Serum Fibrinogen in Patients with ESRD Undergoing Plasma Exchange by Single Membrane Separation Technique for ABO Incompatible Kidney Transplantation Joon Seok Oh,[1] Seong Min Kim,[2] Yong Ki Park,[2] Joong Kyung Kim.[1] *[1]Div of Nephrology, Dept of Internal Medicine, Bong Seng Memorial Hospital, Busan, Korea; [2]Div of Nephrology, Internal Medicine, Dongnae Bong Seng Hospital, Busan, Korea.*

Background: Some variations in plasma exchange technique for antibody reduction was reported, the confusion about both efficacy and safety were added. We had compared the serum fibrinogen changes of patients who received plasma exchange by single membrane separation technique and centrifuge technique during the last 2 years.

Methods: All subjects were received ABO incompatible living donor kidney transplantation in our hospital. 68 times of plasma exchange were carried out at every other day in 13 patients before transplantation, using the COBE® Spectra™ apheresis system. 50 times of plasma exchange were perfomed at every other day in 10 patients before transplantation, using the Prisamflex ® system with TPE 2000 filter. The levels of serum fibrinogen were measured at pre-exchange, post-exchange one day. In procedure, 1.0 time the calculated plasma volume was replaced with an electrolyte solution containing 5% salt-free human albumin or fresh frozen plasma (FFP).

Results: The serum fibrinogen levels (mg/dL) were markedly reduced immediately following the plasma exchange in cases of 5% albumin solution replacement but increased in cases of FFP replacement. And there were not a significant difference of serum fibrinogen changes between the two methods for plasma exchange.

			Pre-exchange	Post-exchange 1 day
Single membrane separation technique	5% albumin replace	mean	306.10 ± 97.75	1528.57 ± 42.75
		change from the baseline		-147.53
	FFP replace	mean	232.83 ± 66.57	247.93 ± 38.56
		change from the baseline		+15.10
Centrifuge technique	5% albumin replace	mean	274.83 ± 128.82	177.90 ± 49.86
		change from the baseline		-96.93
	FFP replace	mean	233.31 ± 39.03	237.27 ± 39.03
		change frome the baseline		+13.96

Conclusions: According to our experience in plasma exchange, we could say that it is not different the change of coagulation factor during the plasma exchange by single membrane separation technique with the plasmapheresis by centrifugal technique.

PUB772

Experience with IL-1 Blockade in Renal Transplant Patients with Gout Arthritis Vega Goedecke, Marcus Hiss, Hermann G. Haller, Annette D. Wagner. *Dept of Nephrology, Hannover Medical School, Hannover, Germany.*

Background: Hyperuricemia and gout are common comorbid conditions experienced by up to 28% of kidney transplant recipients. Reasons for this include reduced excretory renal function, intake of diuretic medication as well as side-effects of immunosuppressant drugs such as calcineurin-inhibitors. Use of selective IL-1 Inhibitors shows promising results in the treatment of gout. However, data on the use of IL-1 blockade as treatment for gout in renal transplant patients are limited.

Methods: Here we present our experience with interleukin 1 blockade in 3 patients after renal Transplantation with therapy refractory gout arthritis.

Results: Two patients had no gout symptoms since starting IL-1 blocking therapy. One patient suffered from pneumonia. This patient developed hyperuricemia under IL-1 blockade. He was started on rasburicase therapy.

	Patient 1	Patient 2	Patient 3
Age / sex	28 year-old male	59-year old male	64 year-old female
eGFR	25 ml/min	29 ml/min	21 ml/min
Year of transplantation	1996	2009	1991,1992 and 2005
Immunosuppressant regimens	Everolimus, Mycophenolate mofetil, Steroid	Cyclosporin, Mycophenolate mofetil, Steroid	Tacrolimus, Azathioprin, Steroid
Previous gout medication	Allopurinol, Benzbromaron, Febuxostat and Colchicine	Benzbromaron, Febuxostat, Colchicine	Increased Steroid dose, Colchicine
Reason for starting interleukin-1 blockade	Podagra, lumbar facet joint gout arthritis	Raised liver enzymes under current gout therapy, gout arthritis	Gout arthritis, allopurinol and febuxostat due to azathioprine contraindicated
Dose of Interleukin 1 blockade	Canakinumab 150 mg s.c. every 3 months	Canakinumab 150 mg s.c. single dose	Kineret 100 mg s.c. twice weekly
Clinical course	Symptoms resolved	Gout tophi progressed	Symptoms resolved
Systemic inflammation markers	Markedly imroved	Markedly improved	Variable due to Urinary tract infection
Side effects	Medication induced hypertriglyceridemia	Pneumonia, Hyperuricemia	Urinary tract infection

Conclusions: Treatment of gout in renal transplant patients needs to be individualised.

PUB773

Infections in Kidney Transplant Recipients in the Biggest Transplant Hospital of Mexico (Western National Medical Center, IMSS) Alejandra Elizabeth Ramirez, Moises Marcial, Marco A. Torres-González, Jose Ignacio Cerrillos, Benjamin Gomez, Petra Martínez. *Nephrology, Western National Medical Center, IMSS, Gualajara, Jalisco, Mexico.*

Background: Infections are a major cause of morbidity and mortality in kidney transplant recipients. **Aim. To** describe the frequency, risk factors and major clinical syndromes associated to infections in patients renal post-transplant period.

Methods: Retrospective cohort. Medical records of kidney transplant patients who were hospitalized in the department of Nephrology between January to December 2015 and clinical, biochemical and socio-demographical and level of immunosuppression, cultures, kidney function and kind of infections were recorded. All patients over 18 years old, recipients of renal transplant with an infectious processes were included in the statistics analysis.

Results: A total of 1409 kidney transplant patients who were hospitalized in 2015, of these 325 (23%) had infectious, the average age was 31.5±10.8 years old, 63% men, 56% transplant from live donor related, 32 of brain death, in 92% of cases received induction therapy. Acute rejection was present in 11%. Presentation of post-transplant infections median was at 4 (2-11) months. Urinary tract infections were the most frequent 54%, Cytomegalovirus 4%, Pneumonia 3%, 2.5% parvovirus, 2% polyomavirus, invasive fungal infections 2%, 1% lower respiratory tract infections and 0.6% tuberculosis. Added syndromes whose etiology was infectious origin such as febrile syndrome, diarrhea and febrile neutropenia syndrome which accounted for 3%, 4% and 4% respectively.

TABLE 1: ANALYSIS OF PREDICTION OF INFECTIONS $\chi^2 = 285.5$; $P < 0.0001$

VARIABLE	OR	CI 95%	P- value
AGE	0.86	0.78 - 0.96	0.006
INDUCTION	5.20	0.70 - 38.78	< 0.0001
ALBUMIN	7.42	1.64 - 33.55	0.0009
TACROLIMUS	0.013	0.001 - 0.120	0.0001
controlled by gender, type donor, risk infectologic			

Conclusions: Interaction between immunosuppression-infection is the protagonist in renal transplant recipients, related with drugs immunosuppressants, and give us the information to prevent this kind of infections.

PUB774

Monoclonal Gammopathy of Undetermined Significance in Kidney Transplant Patients Gaetano Alfano, Francesco Fontana, Gianni Cappelli. *Dept of Surgery, Medical and Dentistry, Univ Hospital of Modena, Modena, Italy.*

Background: Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic pre-malignant plasma cell disorder; its prevalence in the general population in Italy was reported to be 2.9% increasing with ageing. MGUS prevalence after kidney transplant (KT) has been reported in few studies, with conflicting results. We assessed MGUS prevalence in KT recipients at our Center, linked to clinical outcomes.

Methods: We retrospectively reviewed medical charts of patients receiving KT between 1998 and 2015 and assessed MGUS prevalence and its characteristics.

Results: Out of 535 screened patients, MGUS was detected in 61 cases. We further analyzed outcomes of patients with postKT stable MGUS compared with a control KT population matched for sex, age and KT date. In 14 patients MGUS spontaneously disappeared during follow-up, while in 47 remained stable. 42 patients developed MGUS after KT (7.8% of total KTpts). Mean time from KT to MGUS appearance was 5.2 year. At diagnosis 26% of patients were younger than 50 years, representing an extremely uncommon feature for general population; in contrast with previous observations, the occurrence of MGUS was not influenced by age and sex. Plasma concentration of monoclonal protein remained stable during a 8 yrs follow-up; only 1 patient (2%) developed MGUS progressing to multiple myeloma. No differences were found between KT patients with MGUS and matched KT controls for mortality, graft failure, development of "de novo" malignancies, incidence of biopsy-proven rejection and replication of lymphotropic viruses (i.e. HCV and EBV). The MGUS group had a significantly higher prevalence, compared to KT controls, of Monoclonal B-cell Lymphocytosis (MBL) developed after MGUS diagnosis (p=0,03).

Conclusions: In conclusion, we report a high incidence of MGUS after KT, with a younger age at diagnosis compared to general population and with no sex difference. KT patients with MGUS had similar rates of mortality, graft failure, malignant neoplasms, rejection and replication of lymphotropic viruses when compared to a matched KT control group. To the best of our knowledge, this is the first report describing an association between MBL and MGUS in KT patients.

PUB775

Familial Mediterranean Fever Is Associated with Increased Mortality after Kidney Trasnaplantation - A 19-Year Single Center Experience Hefziba Green,[1,2] Shelly Lichtenberg,[1] Ruth Rahamimov,[1,2] Avry Chagnac,[1,2] Benaya Rozen-Zvi.[1,2] *[1]Nephrology and Hypertension, Rabin Medical Center, Israel; [2]Sackler Faculty of Medicine, Tel Aviv Univ, Israel.*

Background: Previous small, short-term studies suggested that kidney transplantation offers a good prognosis for patients with familial Mediterranean fever (FMF) who reaches end stage renal disease (ESRD) secondary to reactive amyloidosis A (AA).

Methods: Between 1995 and 2014 we performed 2160 kidney transplantations in 2086 patients. During this time 20 patients (0.9%) with FMF were transplanted. We compared them to 82 control patients (32 with diabetes mellitus (DM), 50 with nondiabetic kidney disease). Major outcome data included overall patients' and grafts' survival.

Results: Mean overall follow-up was 116.6 ±67.5 months. Patients transplanted because of FMF or nondiabetic kidney disease were younger than patients transplanted due to DM; 43.8±14 and 41.7±13 years versus 52.3±10.6 years respectively (p=0.001). Thirty –seven patients (36%) died during the follow-up period: 11 with FMF (55%), 15 with DM (47%) and 11with other diseases (22%) (p=0.028). Median time of death for patients with FMF was 5.8 years (range 1.3-11); 91% of the deaths (10/11) occurred within 6.7 years after transplantation. FMF was associated with a 2-fold increased risk for death after transplantation; HR 2.2 (95% CI 1.1-4.4, p=0.032); and a 3-fold increased risk for hospitalization because of infection in the first year; HR 3.26 (95% CI 1.36-7.88, p=0.008). Five-year, 10-year and actuarial 15-year overall patients survival rates were 73%, 45% and 39% respectively for patients with FMF; 79%, 53% and 43% respectively for patients with DM; 87%, 75% and 75% for patients with nondiabetic kidney disease (p=0.05). Major causes of death were sepsis and CVD. Absence of hypertension before transplantation and delayed-graft function were significantly associated with increased mortality risk for patients with FMF. Overall graft survival was similar between groups.

Conclusions: In this long-term cohort study we have shown that FMF is associated with increased mortality risk after kidney transplantation compared to patients transplanted for other causes.

PUB776

Neutrophil-Lymphocyte Ratio as a Predictor for Cardiovascular Risk in Patients following Kidney Transplantation Carola-Ellen Ruiner, Louisa Werberich, Miranda Leunga Mbouamba, Roxana Werberich, Rainer Woitas. *Nephrology, Bonn Univ Hospital, Bonn, Germany.*

Background: Neutrophil to lymphocyte ratio (NLR) has been proposed as a predictor for outcome among patients with coronary heart disease (CAD). Patients on chronic renal replacement have a particular high risk for cardiovascular disease (CVD). We determined the prognostic value of NLR for cardiovascular risk and major adverse cardiac events (MACE) in patients following kidney transplantation.

Methods: The study cohort consisted of 422 consecutive patients that were kidney transplanted between March 1996 and May 2015. MACE was defined as myocardial infarction, stroke, intervention requiring CAD or death for cardiovascular reason. Blood samples were drawn prior to the kidney transplantation. C-reaktive protein (CRP) and white blood count (WBC) were measured by routine methods and NLR calculated accordingly. Observation period lasted up to 16 years (median 3 years). Mann-Whitney *U* tests, univariate and multivariate Cox regression analyses were performed. Multivariate Cox regression was adjusted for potential clinical confounders: Age, sex, diabetes mellitus, hypertension, smoking, LDL- and HDL-cholesterol and CAD.

Results: Within the first year after kidney transplantation the incidence of MACE was highest at 0.088%. MACE occurred in 16.1% of patients. Univariate analysis revealed NLR as significant predictor for MACE after renal transplantation (HR 1.16, 95%CI 1.089-1.234, p<0.001). NLR was significantly higher in patients suffering of MACE compared to the other recipients (mean ± SE 4.7 ± 0.45 vs 3.45 ± 0.11, p<0.002). After adjustment for conventional cardiovascular risk factors the multivariable Cox regression revealed NLR as independent cardiovascular risk factor (HR 1.85, 95%CI 1.025-1.149, p<0.05) beside age (HR 1.04, 95%CI 1.009-1.061, p< 0.01), CAD (HR 2.22, 95%CI 1.805-2.733, p<0.001) and smoking (HR 1.67, 95%CI 1.216-2.293, p<0.001). Additionally neither WBC nor CRP were significant predictors of MACE.

Conclusions: NLR is a cheap and easy to perform predictor for cardiovascular disease in kidney transplant recipients independent from conventional CVD risk factors. After kidney transplantation NLR is significantly higher in patients with MACE.

PUB777

Gastrointestinal Pathologies in Patients after Successful Renal Transplantation – One Center Prospective Study Anna M. Dobies,[1] Alicja Kubanek,[1] Marcin Renke,[1] Wojciech Wolyniec,[1] Lukas Palenicek,[1] Ewa Krol,[2] Slawomir Lizakowski,[2] Przemyslaw Rutkowski,[2] Boleslaw Rutkowski,[2] Alicja Debska-Slizien.[2] *[1]Dept of Occupational, Metabolic and Internal Medicine, Medical Univ of Gdansk, Gdansk, Poland; [2]Dept of Nephrology, Transplantology and Internal Medicine, Medical Univ of Gdansk, Gdansk, Poland.*

Background: The aim of this study was to evaluate the prevalence of gastrointestinal pathologies in patients after kidney transplantation .

Methods: Adult patients after kidney transplantation being under care of Outpatient Department of Nephrology in Gdansk after giving their consent were given questionnaire regarding alarm symptoms and referral for testing the presence of fecal occult blood. 186 out of approximately 940 pts being under care completed the questionnaire, 105 performed the stool sample testing. After analyzing the questionnaires and stool results 93 patients were qualified for further investigation.

Results: So far the endoscopic examination was performed in 47 patients (31m/16f) at mean age 59 (range 35-83) years. The examination revealed: gastritis and/or duodenitis in 40 patients, stomach polyps in 6 patients, diverticular colon disease in 18 pts, inflammatory bowel disease in 10, colon polyps in 14 and cancers in 3 patients.

Conclusions: The results indicate that gastrointestinal pathologies are very common in patients after the kidney transplantation. It could be taken into consideration to perform colonoscopy in each patient over 40 years old before the kidney transplantation is performed.

Funding: Government Support - Non-U.S.

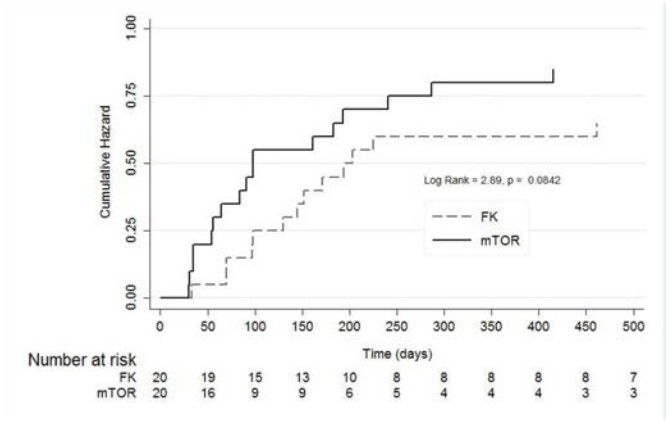
PUB778

mTOR Inhibitors in the Prevention of BK Nephropathy: A Randomized Clinical Pilot Study Sumit Mohan,[1] Mariana C. Chiles,[1] Darshana Dadhania,[3] Samnang Lee,[1] Bekir Tanriover,[2] Russell J. Crew,[1] David J. Cohen.[1] *[1]Columbia Univ; [2]Univ of Texas Southwestern; [3]Weill Cornell.*

Background: BK infection is an early and frequent complication of kidney transplantation that often results in graft loss. BK viremia (BKV) is associated with calcineurin inhibitor (CNI) use while mTOR based immunosuppression (IS) have lower rates of BK viremia. mTOR inhibitors have been associated with low rates of BKV. We compare the impact of CNI based IS reduction compare to mTOR based IS conversion in steroid free transplant recipients.

Methods: The study was a multicenter prospective randomized controlled pilot with 40 patients (Pts) randomized to reduction of CNI and antimetabolite (MPA) IS or conversion to mTOR and reduction of MPA at the time of BKV detection and started on study intervention once BKV PCR >5000 copies/mL. Primary end point was BKV clearance within 12 months of enrollment and groups were compared with an intent to treat analysis.

Results: Pts (56.7±14.0 yrs, 35% female, 23% Black, creatinine 1.41±0.4 mg/dL) were enrolled after BKV was detected 12.3±14.5 months post-transplant. Pts in the FK and mTOR arm were similar with respect to age (61±14.1 v 52.4±12.7,p=0.055), gender (30 v 40%, p=0.51), race (15 v 30%, p=0.45), creatinine (1.49 ±0.46 v 1.34±0.40 mg/dL, p=0.30). The FK and BK groups were similar with respect to complete and partial clearance of viremia (70 and 85%, p=0.58 and 70 and 95%, p=0.092, respectively). Pts exposed to mTOR had a shorter time to complete and partial clearance (134 v 158 and 67 v 109 days, respectively). Pts in the FK arm appeared to be less likely to reach BK clearance (HR=1.87; 95% CI: 0.90– 3.86; p=0.091).



Conclusions: The results from this study indicate that mTOR IS has potential to be an effective treatment option for BKV. Given the observed effect size, a clinical trial with 90 pts is needed to demonstrate a statistically significant benefit.

Funding: Pharmaceutical Company Support - Pfizer

PUB779

Increase in Epicardial Fat Impairs the Regression of Left Ventricular Hypertrophy in Kidney Transplantation Recipients

Daniel Constantino Yazbek,[1] Aluizio B. Carvalho,[1] Cinara Barros de Sá,[1] Jose Medina-Pestana,[3] Carlos Eduardo Rochitte,[2] Raul Santos,[2] Maria Eugenia F. Canziani.[1] *[1]Federal Univ of Sao Paulo; [2]Heart Inst (InCor). Univ of São Paulo; [3]Hospital Rim.*

Background: Epicardial fat (EF) a component of visceral adipose tissue has been related to increased cardiovascular risk in chronic kidney disease (CKD). Left ventricular hypertrophy (LVH) is associated with high morbidity and mortality in this population and tends to decrease after kidney transplant. The aim of the present study was to investigate the association between changes in EF and left ventricular mass index (LVMI) during the first year after kidney transplant.

Methods: Heart images previously obtained by multislice CT from a randomized, controlled and open-labeled study that tested the effects of statins on coronary calcification in incidents kidney transplant recipients (KTRs), were evaluated. EF (milliliters) was measured by VitreaCore® software, at baseline and after 12 months. LVMI was calculated by transthoracic echocardiography at the same periods.

Results: A total of 87 KTRs, 62% men, aged 41.0 ±10.1 years, average of 24 (11 – 49) months on dialysis were evaluated. LVMI was respectively 128.5±46.1 g/m³ and 102.5 ±33.4 g/m³ at baseline and 12 months. A decrease in LVMI was observed in 39 (79%) patients. EF was 318.1 (269.0 – 356.6) and 325.9 (273.0 – 382.3) ml at baseline and 12 months, respectively. In 58 (66%) patients EF progressed during follow-up (EF progressors). These patients, when compared to those in which EF decreased, had a greater increase in body mass index (2.9 ± 2.1 kg/m² vs. 1.3 ±1.7 kg/m², p<0.001), in serum glucose concentration (6 (-3 – 12) mg/dl vs. -1 (-9 – 7) mg/dl, p=0.046) and a trend to smaller decrease of LVMI (-18 (-37 – -2) g/m³ vs. -42 (-51 – -10) g/m³, p=0.09). . The lipid profile at baseline and after 12 months, as well as the use of statins were similar between the groups. The general linear model analysis showed that the progressor group had a smaller decrease in LVMI during follow up (p for group effect <0.001; p for time-effect =0.09; p for interaction =0.03).

Conclusions: The increase of EF impaired the regression of left ventricular mass in CKD patients after kidney transplant.

PUB780

Percutaneous Ultrasound Guided Renal Transplant Biopsies Outcomes as Performed by Two Specialties

Camilo Cortesi,[1] Franco H. Cabeza Rivera,[2] Phillip Ruiz,[3] Giselle Guerra,[2] Adela D. Mattiazzi.[2] *[1]Internal Medicine, Univ of Miami - Jackson Memorial Hospital, Miami, FL; [2]Transplant Nephrology, Miami Transplant Inst - Univ of Miami, Miami, FL; [3]Surgery and Pathology, Univ of Miami, Miami, FL.*

Background: Percutaneous Ultrasound-guided renal transplant biopsy (US-TB) is the preferred method to assess renal allograft dysfunction. Reported complications rates range between 0.06-13%. We aim to analyze moderate to severe complications related to US-TB when performed either by Interventional Radiology (IR) or Transplant Nephrology (TN) specialists in a teaching hospital.

Methods: We retrospectively reviewed the US-TB performed at our center between Jan 1st 2015 and Dec 31st 2015. Demographic data, blood pressure ≥160/90mmHg, BMI, creatinine, BUN, INR, platelets counts, antiplatelet and/or anticoagulant agents held, biopsy core number, and time of complication were analyzed. Moderate complications were defined as hematoma, hydronephrosis, arteriovenous fistula (AVF), hemoglobin drop >2 g/dl, and need for blood transfusion. Severe complications were defined as development of Page kidney or need for nephrectomy, hematoma/hydronephrosis and/or AVF all associated with kidney dysfunction.

Results: 222 US-TB were performed in 204 patients; 165 (74%) by IR and 57 (26%) by TN. There was no statistical significance among demographic, clinical and laboratory data. 19 (8.5%) complications were reported. 15 (6.7%) in the IR group: 11(73%) moderate and 4 (27%) severe. 4 (1.8%) in the TN group, all moderate (NS). The most common moderate complications were hematoma and need for blood transfusion in both groups. IR group had severe complications with hematoma with kidney dysfunction. Moderate complications were diagnosed on day 1 in 33% IR group and 50% in the TN group. All severe complications were diagnosed within the first 5 days after the procedure.

Conclusions: We found no statistical significance after Percutaneous US-TB performed by the two teaching services at our institution. Further analysis is guaranteed to identify and decrease risk factor for complication.

PUB781

The Efficacy and Safety of Plaquenil in Kidney Transplants Patients with Lupus

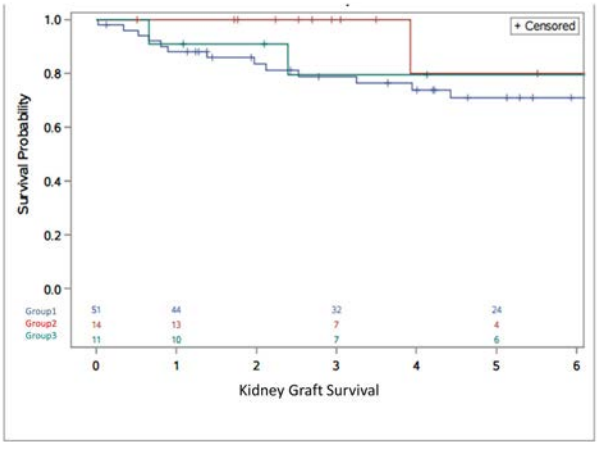
Salwa Rhazouani,[1] Siddiq Anwar,[1] Daniel C. Brennan,[1] Krista L. Lentine,[2] Karthikeyan Venkatachalam,[1] Tarek Alhamad.[1] *[1]Washington Univ; [2]Saint Louis Univ.*

Background: Hydroxychloroquine, also known as Plaquenil (PLQ) is an antimalarial drug with immunomodulatory action. Recent studies have demonstrated a protective effect of PLQ in the management of native renal lupus nephritis. The use of PLQ in kidney transplant recipients has not been examined.

Methods: A retrospective analysis of 76 kidney transplant patients with history of lupus between 1998 and 2014. Patients were categorized into 3 groups according to their PLQ use. Associations between pattern of PLQ use and post-transplant graft failure and patient death over 6 years were examined by Kaplan-Meier analysis and Cox regression.

Results: There were 14 patients who received PLQ as an alternative or adjunctive to standard immunosuppression at the time of discharge (group 2), and the remaining 62 patients were discharged with standard immunosuppression . 11 out of the 62 patients (18%) (group 3) received PLQ at a later time due to lupus nephritis or arthritis. The remaining 51 patients (group 1) never received PLQ after kidney transplantation. Graft survival and Patient Survival at 6 years was similar.

	HR for Graft Survival	HR for Patient Survival
Group 1 (Did not require PLQ)	Reference	Reference
Group 2 (PLQ on Discharge)	0.95, CI 0.27-3.34	1.23, CI 0.25-5.9
Group 3 (PLQ after Discharge)	1.14, CI 0.37-3.49	1.02, CI 0.21-4.9



Acute graft rejection during the study period was similar among the three groups (group 1= 21.5%, group 2= 28.5% and group3=36.3%, p=0.55). Only 4 out of 25 patients discontinued PLQ, mainly for anemia and leukopenia.

Conclusions: Around 20% of kidney transplant recipients with native kidney lupus nephritis require PLQ after transplant discharge for recurrent lupus symptoms or arthritis. In general, the use of PLQ is safe. Larger studies are needed to determine whether PLQ use protects survival of kidney graft.

PUB782

Incidence of Human Parvovirus B19 Infection in Kidney Recipients

Milagros Melissa Flores Fonseca, Pablo Eduardo Nava Diaz, Celina Margarita Rodriguez, Benjamin Gomez. *Nephrology and Organ Transplant Unit, Centro Medico Nacional de Occidente, Guadalajara, Jalisco, Mexico.*

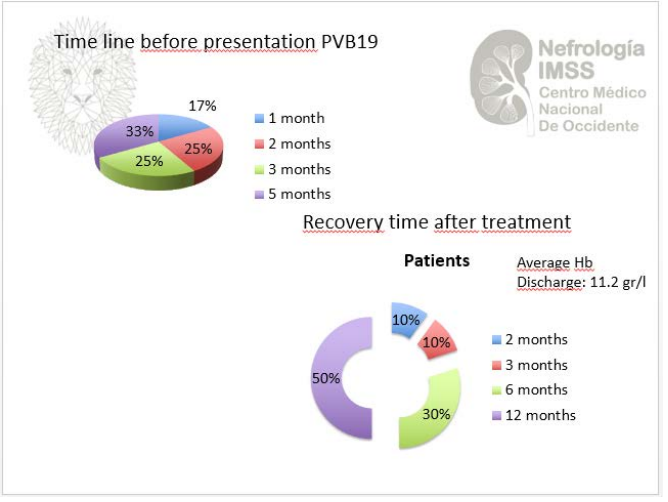
Background: Human parvovirus B19 (PVB19) infection is a rare infectious complication in immunosuppressed patients. The only manifestation is usually evidence of persistent and progressive anemia, occurring during the first year after transplantation, during which immunosuppression reaches its maximum state.

Methods: Retrospective analysis, identifying patients with persistent anemia and confirmed PVB19 in Centro Médico Nacional de Occidente (CMNO) between 2013 -2015.

Results: 12 Patients with confirmed PVB19 were identified, regardless of gender, where the average age was 25.6 years, none recipients of deceased donors, first trimester was the time line of its presentation.

Baseline Characteristics	PVB19: Number/ (%)
Gender -Male -Female	6 (50%) 6 (50%)
Age (years) -0-20 years -21-40 years -41-60 years	 1 (8.33%) 10 (83.3%) 1 (8.33%)
Kidney donor -Living related -Living unrelated	10 (83.3%) 2 (16.67%)
Induction therapy -Basiliximab -Antithymocyte globulin	8 (66.66%) 4 (33.33%)

Finding persistent anemia with hemoglobin (Hb) average 8.14 g/dl, PCR detection of viral DNA 83.3% (10/12) and/or histological evidence in bone marrow 16.67% (2/12).



Recovery evidence during the first six months after treatment 50% with an average Hb 11.2 g/dl. One patient experienced three anemia recurrences, suffering pure red cell aplasia (PRCA) confirmed by bone marrow biopsy.

Conclusions: In this retrospective analysis PVB19 infection agrees with general literature, with an incidence of 2 to 12 %. PCR for PVB19 detection had a rentability 83 %. Initial immunosuppression reduction allows initial diagnostic approach, but does not provide a benefit in the erythrocyte correction. In a patient with high clinical suspicion and PCR viral DNA should not be a criteria for exclusion of it.

PUB783

Histological and Electron Microscopy (EM) Predictors for Progressive Transplant Glomerulopathy Lavanya Kodali, Valerie R. Bloss, Erika R. Bracamonte, Catherine M. Spier, Prabir Roy-Chaudhury. *Univ of Arizona.*

Background: Transplant Glomerulopathy (TG) is an important cause of chronic allograft failure. Despite the magnitude of the clinical problem, there are currently no truly effective *biopsy based* markers of progression in patients with TG. The objective of the current study was to perform a quantitative and descriptive analysis of selected histological and electron microscopy (EM) criteria, in the context of patients with TG.

Methods: Biopsies with a diagnosis of TG and available clinical, histological and EM data were identified. Biopsies were scored for cg and cv using Banff criteria. An EM analysis was used to quantify PTC basement membrane multi lamellation (BML; normal = 0, > 4 layers was scored as 4) and the presence or absence of endothelial swelling (ES). A descriptive analysis of the full dataset for these parameters was performed, followed by a logistic regression analysis (cg 1 vs 2-3; cv 0 vs 1-3; EM changes (present vs not present), to identify predictors for a composite clinical endpoint of ESRD or doubling of serum creatinine at 1 year post biopsy.

Results: Results are shown in Table 1. While there were no statistically significant differences between the ESRD and non ESRD groups, there was a trend towards a higher cg and cv score and the presence of EM changes in patients who progressed to the composite clinical endpoint within a year. There were no differences in the composite end point between patients with lower vs higher cg/cv scores or in those with EM changes (BML and ES).

CRITERIA	TOTAL DATASET	ESRD	NO ESRD
cg Score	2.0+/-0.88	2.0+/-0.89	2.0+/-0.92
cv Score	1.07+/-1.03	1.60+/-1.14	0.75+/-0.88
PTC Multi Lamellation (EM analysis)	2.18+/-1.77	3.0+/-2.0	1.71+/-1.60
Endothelial Swelling present (EM analysis)	27%	33%	25%

Conclusions: These initial data suggest that a more detailed histological and in particular EM analysis of biopsies with TG may be warranted in order to glean the maximum available predictive information from these tissue samples; an important first step towards a more individualized/precision medicine approach to clinical transplantation.

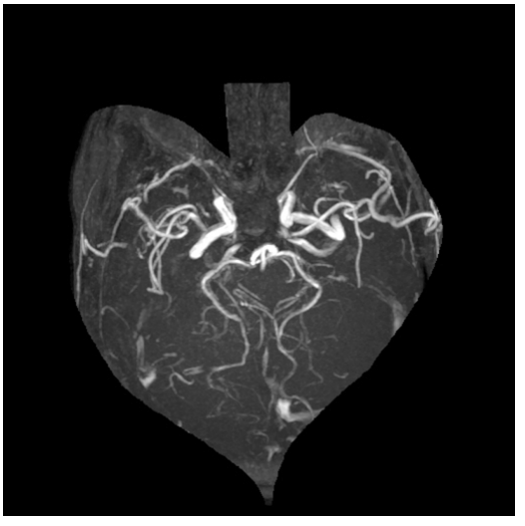
PUB784

Case of Stroke in an Adult Renal Allograft Recipient after Parvovirus B19 Infection Ravindra V. Bhattu,[1] Sonali R. Bhattu.[2] *[1]Nephrology & Renal Transplantation, DHOOT Hospital, Aurangabad, Maharashtra, India; [2]Internal Medicine, MGM's Medical College, Aurangabad, Maharashtra, India.*

Background: Viral infections manifest very differently in renal allograft recipients because of their immunosuppressed status. Parvovirus B19 infection commonly presents as anaemia. Here we present a rare case of stroke secondary to Parvovirus B19 infection in an adult renal allograft recipient.

Methods: A 35-yr old male with stage V CKD underwent pre-emptive renal transplant with his sister as donor. Immunosuppression used was standard Tacrolimus, MMF and steroids, which was started two days prior to transplant. No induction was used in view of low immunological risk. Post transplant course was uneventful with a rapid graft function achievement. Eight weeks post transplant, patient presented with severe anaemia(Hb 4.6gm%). Evaluation revealed confirmed presence of Parvovirus, hence IV Immunoglobulin therapy was started. He developed headache and visual deficit, to start with, and deteriorated within 72 hrs leading to coma and death.

Results: Serum Iron and B12 studies were normal. Bone marrow trephine biopsy revealed severe suppression of erythropoeisis and marrow was remarkable for scattered large erythroid cells (Glycophorin C and CD 117 expressing cells) with prominent large eosinophilic nuclear inclusions suggestive of Parvovirus infection, which was confirmed by Parvovirus B19 DNA demonstration by PCR. MRI brain revealed thrombosis of anterior cerebral arteries bilaterally, along with multiple infarcts in frontal areas, caudate nucleus and thalamus.



Conclusions: Viral infections manifest atypically in renal allograft recipients. Parvovirus B19 commonly presents with severe anaemia. To our knowledge this is the first ever case report of stroke secondary to Parvovirus B19 infection in an adult renal allograft recipient. This has to be kept in mind while evaluating neurological syndromes in post-transplant period.

PUB785

Design of a Real World Program to Transition Kidney Transplant Patients from Pediatric to Adult Care Tamar Y. Springel, Pat Minshall, Beth A. Vogt, Robert J. Cunningham. *Pediatrics, Rainbow Babies and Children's Hospital, Cleveland, OH.*

Background: It is hypothesized that failure of appropriate transition from pediatric to adult care may contribute to the increased risk of graft loss during early adulthood. Few studies have focused on designing a transition program for the non-research, "real world" setting. Most pediatric kidney transplant programs have limited resources to dedicate to a transition program, and may benefit from an easily adaptable program. We set out to design a program to transition kidney transplant patients from pediatric to adult care which will be easily adaptable and require limited resources.

Methods: We performed a thorough literature review of previous studies and guidelines for transitioning patients with chronic disease from pediatric to adult care. We collaborated with adult transplant nephrology physicians and transplant coordinators to ascertain hurdles to patient transition.

Results: We developed a protocol which focuses on helping patients achieve the milestones which are necessary for successful transition. Starting at age 14, readiness for transition is assessed twice yearly through previously published transition questionnaires. Patients complete one survey every 6 months, alternating between two surveys. These questionnaires are used to set patient-centered goals which are reviewed twice yearly

through a transition report card with patients and caregivers. Goals are dependent on patient's individual abilities and the caregiver's future expectations. Patients are reviewed among the pediatric and adult providers on a quarterly basis in preparation for transition in order to align care plans between pediatric and adult care. Following transition, patients are monitored more closely for the first year.

Conclusions: We designed a patient-centered program for transition kidney transplant patients from pediatric to adult care. This program can be easily adapted by most pediatric kidney transplant centers without the need for additional staff. In the future, outcomes, including adherence to appointments, adherence to laboratory testing, graft outcomes, and patient and physician satisfaction may be examined.

PUB786

Rapamycin Induced Minimal Change Disease in a Renal Transplant Recipient: A Case Report

Vasil Peev. *Rush Univ Transplant Program, Rush Univ, Chicago, IL.*

Background: Recurrent or de novo minimal change disease (MCD) in a renal transplant recipient represents a rarity. I report an unusual case of Rapamycin induced MCD in a renal transplant recipient eleven years after transplantation.

Methods: A 42- year old African American male with unknown cause of end stage renal disease (ESRD) received cadaveric renal transplant from donor after cardiac death (DCD). His postoperative course was complicated by slow graft function. He received induction immunosuppression with Campath and Solumedrol followed by maintenance immunosuppression with Prograf (FK) and Prednisone. Renal allograft biopsy preformed two years after transplant for evaluation of elevated serum creatinine revealed mild interstitial fibrosis and borderline cellular rejection. He was treated with high dose steroids. Six years later, due to concern for progressive interstitial fibrosis and persistently elevated serum creatinine he was converted from FK and prednisone to Rapamycin and prednisone. Within nine months of this conversion he developed gradually worsening proteinuria from prior baseline of 0.3g/g, now up to 2.4 g/g with otherwise normal urine sediment. Due to stable renal function and absence of donor specific antibodies (DSA) his renal biopsy was deferred. Eleven years later his proteinuria peaked at 2.5 g/g and he developed mild lower extremity edema prompting repeat renal biopsy. This showed normal glomeruli on light with diffuse foot processes effacement on electron microscopy, consistent with the diagnosis of MCD. Post Transplant Lymphoproliferative Disorder (PTLD) was ruled out based on absence of lymphadenopathy on physical exam and normal thoracic and abdominal computer tomography imaging. Intake of non-steroidal agents was ruled out per history. Conversion of Rapamycin to FK lead to prompt resolution of his near nephrotic range proteinuria.

Conclusions: In conclusion, I report a rare case of Rapamycin induced podocytopathy consistent with MCD.

PUB787

Medium and Long-Term Outcomes following Treatment of Acute Antibody Mediated Rejection Complicating Renal Transplantation- Low Morbidity and Mortality

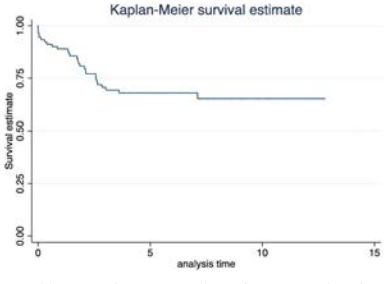
Leny Hidayati,[1] Peter D. Hughes,[2] Michael Lian,[2] Peggy Teh,[2] Marcus B. Tan,[2] Susheel Sharma,[2] Shlomo J. Cohney.[1,2] *[1]Dept of Nephrology, Western Health, Victoria, Australia; [2]Dept of Nephrology, Royal Melbourne Hospital, Victoria, Australia.*

Background: Antibody mediated rejection (AbMR) carries a high risk of graft loss, & significant treatment related morbidity & mortality. Short-term results have improved with intravenous gammaglobulin (IVIG) & plasma exchange (PEx). Little data exists on long-term outcomes, which were examined in this single centre study.

Methods: Outcomes of 87 patients diagnosed with acute AbMR between Jan 2000 & Dec 2011 were reviewed. Standard treatment included PEx, with 1 or 2 doses of intravenous methylprednisolone & no increase in maintenance immunosuppression.

Results: 91 episodes of AbMR occurred in 87 patients, 56 deemed early(<90 days post-transplant) & 35 late (>90 days post-transplant). 68 episodes were treated with PEx and IVIG; in addition, 15 received rituximab & 5 bortezemib. Two had Pex alone, IVIG alone (n=10), rituximab alone (n=1). At median follow-up of 63 months post-AbMR, patient & graft survival at 2 years were 98% & 81% & at 5 years were 93% & 65%.

Figure 1. Graft Survival Curve for All Patients



Graft loss occurred in 28 patients at median of 20.5 months after AbMR began, 12 in early AbMR group and 16 in late AbMR group. Patients with late AbMR had a 2.7-fold increased risk of graft failure (95% CI:1.30, 5.87, p-value = 0.008). There was no difference in outcome in patients receiving rituximab compared to those who did not. Amongst the 6 patients who died, median survival was 4 months after returning to dialysis. No death occurred during or was attributable to treatment of AbMR.

Conclusions: Mortality was low in this cohort of patients with AbMR treated primarily with PEX and without augmented immunosuppression while graft survival was comparable to previously published series using more aggressive therapy.

PUB788

Clinical Outcome of Kidney Re-Transplantation in Comparison with First Kidney Transplantation in Korea: Nationwide Cohort Study

Ji-Yeun Chang,[1,2] Chul Woo Yang,[1,2] Cheol Whee Park,[1] Byung Ha Chung.[1,2] *[1]Div of Nephrology, Dept of Internal Medicine, Seoul St. Mary's Hospital, The Catholic Univ of Korea, Seoul, Korea; [2]Transplant Research Center, Seoul St. Mary's Hospital, The Catholic Univ of Korea, Seoul, Korea.*

Background: Due to the limitation of the survival of kidney allograft, increasing number of patients needs to take re-transplantation (re-KT) after the first allograft failure. In this study, we investigated the clinical characteristics and clinical outcomes of re-KT recipients in comparison with those of first KT using nationwide registry.

Methods: We retrospectively analyzed 4757 adult kidney transplant recipients(KTR) registered in Korean organ transplantation registry database from 2009 to 2012. These cases were divided into 4 groups; first KT (n=2762) and re-KT (n=162) from living donor (LD), first KT (n=1647) and re-KT (n=186) from deceased donor (DD). We compared the clinical outcomes such as early or late biopsy-proven acute rejection and also allograft or patient survival rate across those groups.

Results: Out of total 4,757 KTRs, 348 (7.5%) cases were re-KT. The proportion of DDKT and sensitized patients was significantly higher in re-KT group compared to first KT group (DDKT; 53.4% vs. 37.4%; P<0.05, sensitized patients; 21.6% vs. 3.7%, P<0.05). Especially in LDKT, the proportion of ABO incompatible KT was higher in re-KT group than first KT group as well (18.5 % vs. 12.5%; P<0.05). The incidence of early biopsy-proven acute rejection (BPAR) was significantly higher in re-KT group than first KT group in DDKT (19.4% vs. 11.3%; P<0.05), but not in LDKT (7.4% vs. 9.0%; P>.05). Incidence of late BPAR was not significantly different between re-KT and first KT groups both in DDKT (0.6% vs. 2.4%; P>.05) and LDKT (1.6% vs. 2.6%; P>.05). In multivariate analysis, re-KT was an independent risk factor for development of early BPAR in DDKT (odd ratio, 1.724; 95% confidence interval, 1.10 to 2.67; P<.05). However, allograft and patient survival rate were not significantly different between re-KT and first KT group in DDKT and LDKT (P>.05, for all).

Conclusions: Our study showed that overall clinical outcomes of re-KT was comparable to those of first KT irrespective of donor type.

Funding: Government Support - Non-U.S.

PUB789

Real-World Experience with Astagraf XL™ in the U.S.: A Retrospective, Single-Institution Study to Evaluate Short-Term Clinical Outcomes

Samantha Montag,[1] Christy Houle,[2] Jason J. Schwartz,[2] Lihui Zhao,[1] Edward Lee,[2] Hardik Bhagat,[2] Amna Daud,[1] Asantewaa B. Ture,[1] Bing Ho,[1] Anton I. Skaro,[1] Daniela P. Ladner.[1] *[1]Northwestern Univ Transplant and Outcomes Research Collaborative (NUTORC), Chicago, IL; [2]Astellas Pharma Global Development, Inc., Northbrook, IL.*

Background: Prolonged-release tacrolimus (Astagraf XL™, AXL) is a once daily formulation approved by the FDA in 2013, but data under real-world US practice conditions are lacking. As such, we examined the patient characteristics of kidney transplant (KTx) recipients who received AXL and compared their short-term clinical outcomes [eGFR, acute rejection (AR), and graft loss] with a similar population using twice-daily immediate-release tacrolimus (TAC BID).

Methods: This case-control study was executed using the Northwestern Medicine (NM) Enterprise Data Warehouse, a repository of clinical data capturing electronic health records used at any NM clinical facility. Adult KTx patients with any AXL use through 10/2015 were matched 1:3 to KTx patients using TAC BID. Groups were matched on age, Charlson-comorbidity index (CCI), and propensity score that included gender, ethnicity, insurance status, education, language preference, organ donor type, cold ischemia time, and transplant date.

Results: Overall, 36 AXL patients were matched to 108 TAC BID patients such that there were no significant differences in baseline characteristics between the cohorts. Panel-reactive antibody and time on dialysis were similar between cohorts. AXL patients were mostly male (69.4%), had a mean age of 45.4 years, and a mean CCI of 3.8. Sixty-one percent had received a living donor transplant. After one year, there was no significant difference in eGFR (p=0.629) or graft survival (p=0.997) between the two cohorts. The hazard ratio (HR) for AR at 1 year was not significant (HR=0.317, 95% CI: 0.0395, 2.531), for AXL compared with TAC BID.

Conclusions: Preliminary analyses show that there are no significant differences in relevant short-term clinical outcomes between patients treated with AXL and TAC BID. Long-term outcomes and measures need to be evaluated.

Funding: Pharmaceutical Company Support - Astellas Pharma

PUB790

Does Left Ventricular Mass Decrease after Successful Renal Transplantation? An Updated Metaanalysis of Observational Studies Bernhard M.W. Schmidt,[1] Kai Bergmann,[1] Anette Melk.[2] *[1]Nephrology and Hypertension, Hannover Medical School, Hannover, Germany; [2]Pediatric Nephrology, Hannover Medical School, Hannover, Germany.*

Background: Left ventricular hypertrophy is the hallmark of uremic cardiomyopathy and has been shown to be of prognostic importance in patients after renal transplantation. Several small studies have examined left ventricular mass index (LVMI) in renal transplant recipients with unequivocal results. We therefore performed a metaanalysis of the available evidence to assess the effect of renal transplantation on (LVMI).

Methods: We identified manuscripts using Medline and Scopus databases. The search terms were ("left ventricular mass" OR "left ventricular hypertrophy") AND (renal OR kidney) AND transplantation. For the final analysis we identified 8 manuscripts comparing LVMI in kidney transplanted patients cross-sectional with healthy controls, 6 manuscripts comparing LVMI in kidney transplanted patients cross-sectional with patients on dialysis, 13 manuscripts examining LVMI longitudinally before and at least 12 months after renal transplantation and 2 studies examining LVMI longitudinally for at least 12 months using a control cohort. Standardized means were computed and a random effect model was used for analysis. A p value 0f .05, two-sided was considered significant. heterogeneity was assessed using I2 test for heterogeneity and Cochran Q test. Publication bias was tested using funnel-plots. "Comprehensive Meta Analysis V2", Biostat, Enlewood, USA" was used for analysis.

Results: Compared to healthy controls LVMI was higher in renal transplant recipients (standardized mean difference=0.584±0.270, p= 0.030; I2= 90; Q=102,5, p<0.001), but compared to patients on dialysis LVMI was lower (standardized mean difference=0.444±0.096, p<0.001; I2= 5.2; Q= 6.3, p=0.387). In the studies with longitudinal observation LVMI was decreased after at least 12 months of follow-up (standardized mean difference=0.431±0.069, p<0.001, I2= 42, Q=20.5, p=0.058).

Conclusions: LVM Decreases after renal transplantation, but remains higher than in normal controls, reflecting a cardiovascular risk that is decreased compared to dialysis patients but remains elevated.

PUB791

Alterations in Glucose Metabolism in the Waiting List for Renal Transplatation Armando Torres, Estefanía Pérez-Carreño, Tatiana Collantes, Maria Jose De la Vega, Ana González Rinne, Domingo Marrero, Esteban Porrini. *Hospital Univ de Canarias, La Laguna, Spain.*

Background: Post-transplant diabetes (PTDM) is a severe complication after renal transplantation. Some risk factors for PTDM are present before transplantation, including obesity and insulin resistance. However, the impact of alterations in glucose metabolism (AGM) i.e. prediabetes and diabetes diagnosed by an oral glucose tolerance test (OGTT) is not completely clear.

Methods: We studied 93 patients on the waiting list, without diabetes (diagnosed by baseline hyperglycemia or the use of medications). All underwent an OGTT and were classified as normal, prediabetes (impaired fasting glucose or glucose tolerance) or occult diabetes (glucose > 200 mg/dL at 120 min). 53 patients were transplanted. OGTT was repeated at 3-m after transplantation. Insulin resistance and secretion indexes were calculated (HOMA-R, McAuley, HOMA-sec and insulinogenic index).

Results: OGTTs were abnormal in 29 (31%) patients in the waiting list (22.5% prediabetes, 8.6% DMo). Age was the best predictor of an abnormal OGTT (OR: 1.07, 95% CI 1.01-1.12, p=0.02), age≥ 55 years was the best cut off point to distinguish a pathological OGTT by (ROC curve and Youden index): <55 yr, 16,1% prediabetes and 4.8% DMo hidden; ≥ 55 yr 35.5% and 16.1% respectively). Age(45±12 vs. 55±9 y), BMI (23±3 vs 29±4) and HBA1C (4.9±0.3 vs 5.2±0.5%) on waiting list were higher in patients who developed PTDM (p<0.01). BMI≥29 and age ≥55 at pre-transplant showed the highest values of the Youden test detect the risk for PTDM at 3 months. 20 of 53 (37%) patients who received a renal transplantation developed PTDM. Of them, 4 (20%) had DMo, 6 (30%) had prediabetes and 10 (50%) had normal OGTT at pre-transplant.

Conclusions: The best strategy to detect patients on waiting list with hidden disorders of glucose metabolism and increased risk for PTDM is to perform and OGTT in subjects ≥ 55 years old and a BMI≥ 29. This may help in the design of preventive strategies to reduce the burden of PTDM.

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PUB792

Association of Blood Pressure Levels and Blood Pressure Variability with Left Ventricular Hypertrophy in Pediatric Kidney Transplant Recipients Fatma Lale Sever, Ayse Agbas, Nur Canpolat, Salim Caliskan. *Pediatric Nephrology, Istanbul Univ, Cerrahpasa Medical Faculty, Istanbul, Turkey.*

Background: Recent studies suggest that not only blood pressure (BP) levels but also BP variability (BPV) is important for the development of target organ damage and cardiovascular morbidity. We aimed to evaluate the association of BP levels and BP variability with left ventricular mass index (LVMI) in pediatric kidney transplant recipients.

Methods: 32 patients (20 males, mean age 16.0±3.5 years) with a well-functioning graft (GFR>60 mL/min/1.73 m^2) who had been performed kidney transplantation (Tx) before 18 years of age were evaluated. Demographic data and medications were noted. Ambulatory BP monitoring (ABPM) and echocardiography were carried out. Standard deviation scores (SDS) for 24-h/day/night BP readings were calculated based on normative data. BP dipping and BP loads, BPV parameters [standard deviation (SD) and coefficient of variation (CV) of 24-h/day/night BP readings and average real variability (ARV)]; were recorded from ABPM files. Left ventricular hypertrophy (LVH) was defined as LVMI >95. percentile for age and gender. Hypertension was classified according to American Heart Association criteria.

Results: The median duration of dialysis before Tx was 2.47 (0-16) years and the follow-up period after Tx was 6.5 (0.3-7.5) years. Immunosuppressive protocol included triple therapy (prednisolon, MMF and tacrolimus).16 patients were on antihypertensive therapy (calcium channel blockers and/or renin angiotensin blockers). A total of 18 patients (56%) had ambulatory hypertension and 14 patients (43%) had LVH. Significant correlations were found between ambulatory BP SDS parameters and LVMI whereas BPV parameters were not associated with LVMI. Significant risk factors for LVH are shown in Table 1.

Factors influencing LVMI.

	r	p
Tx Duration	-0.405	0.021
24-h MAP SDS	0.350	0.049
Day SBP SDS	0.518	0.002
Day DBP SDS	0.356	0.045

Conclusions: It is important to note that ambulatory BP levels are strongly associated with LVH in pediatric kidney transplant recipients.

PUB793

Post-Transplantation Graft Function Is Associated with Major Cardiovascular Events in Kidney Transplant Recipients: A Multicenter Cohort Study Jae Yoon Park,[1] Yun Kyu Oh,[2] Chun Soo Lim,[2] Jung Pyo Lee,[2] Yon Su Kim.[3] *[1]Dept of Internal Medicine, Dongguk Univ Ilsan Hospital; [2]Dept of Internal Medicine, Seoul National Univ Boramae Medical Center; [3]Dept of Internal Medicine, Seoul National Univ College of Medicine.*

Background: Reduced kidney function is an independent risk factor for cardiovascular disease in the general population. However, the association between post-transplantation graft function and subsequent cardiovascular disease remains uncertain. Therefore, we investigated the outcomes of transplantation in kidney transplant recipients.

Methods: A total of 2,419 kidney transplant recipients in a multicenter cohort were included to evaluate the effects of post-transplant graft function on major adverse cardiovascular events (MACE: cardiac death, nonfatal myocardial infarction, or coronary revascularization), graft failure, and mortality. Recipients were classified into 3 groups according to their estimated glomerular filtration rate (eGFR): group 1 (eGFR ≥ 60 mL/min/1.73 m^2, n=1,441), group 2 (30 ≤ eGFR < 60 mL/min/1.73 m^2, n=907), and group 3 (eGFR < 30 mL/min/1.73 m^2, n=71). Multivariate Cox hazard model was used to explore the association of eGFR with MACE.

Results: Median age was 42 years and 58.8% were male. Median eGFR was 63.6 mL/min/1.73 m^2. In 2,419 participants, there were 93 cases of MACE, 214 cases of graft failure, and 76 patient deaths over a median of 6.1 years. The cumulative rates of MACE were higher in the group of lower graft function. In multivariate Cox regression, lower graft function was significantly associated with the occurrence of MACE (hazard ratio 1.5, 95% confidence interval 1.0–2.3, *P*[thinsp]=[thinsp]0.04) compared to higher graft function. Additionally, cumulative rates of graft failure and mortality were also significantly higher in recipients with lower graft function.

Conclusions: Post-transplant graft function independently correlates with MACE, graft failure, and mortality, suggesting management of graft function may improve the patient and graft survival and cardiac outcome of kidney transplant recipients.

PUB794

Kidney Transplant Outcomes in Two Adults with Down Syndrome Kammi J. Henriksen,[1] George P. Bayliss.[2] *[1]Pathology, Univ of Chicago, Chicago, IL; [2]Nephrology, Alpert Medical School, Brown Univ, Providence, RI.*

Background: There is little literature about renal transplantation in adults with trisomy 21 (Down syndrome). We present the cases of two adults transplanted at different institutions to describe their post-transplant course and outcomes.

Methods: Electronic medical records (2000-present) were reviewed at two institutions to identify adult patients with Down syndrome who had undergone kidney transplant.

Results: Patient 1 is a 45 year old man with insulin dependent type 2 diabetes initiated on hemodialysis in 2010. He underwent kidney transplant in 2014 from a 52 year-old woman who died of a stroke. Pre-transplant biopsy showed 7% glomerular sclerosis and 1% interstitial fibrosis. He received standard immunosuppression. Post-operative course was marked by delayed graft function (DGF). Initial biopsy showed acute T cell- and antibody-mediated rejection, as well as thrombotic microangiopathy (TMA). Biopsy POD 27 showed acute tubular injury, resolving inflammation, and TMA with acute and chronic features. Final biopsy at 2 months showed TMA with chronic features, despite switching tacrolimus to cyclosporine. Kidney never functioned, and patient 1 remains on dialysis. Patient 2 was a 38 year old man at his time of death in 2014. He had ESRD secondary to type 1 diabetes, and was initiated on hemodialysis in 2000. He underwent kidney transplant in 2006 from a 5 year-old deceased donor who underwent prolonged resuscitation efforts. The postoperative course was notable for DGF, for which the patient received dialysis and thymoglobulin infusion. He was discharged with stable renal function after 2 weeks, and enjoyed excellent renal function for 7.5 years on standard immunosuppression. The patient was admitted from an outside hospital in 2014 with small bowel obstruction and sepsis, and subsequently died.

Conclusions: The cases represent extremes of renal transplantation in an adult. Patient 1 remains inactive on the list, with his mother reluctant to agree to another transplant. Patient 2 enjoyed over seven years of stable renal function prior to his death. Taken together the cases underscore the need to evaluate adults with Down syndrome individually for renal transplantation.

PUB795

Surveillance Biopsy Findings with Different Induction Agents in Kidney Transplant Recipients Hector M. Madariaga,[1] Cinthia Drachenberg,[2] Nadiesda A. Costa,[1] Jonathan Bromberg,[3] Matthew R. Weir,[1] Abdolreza Haririan.[1] *[1]Div of Nephrology, Univ of Maryland Medical Center, Baltimore, MD; [2]Dept of Pathology, Univ of Maryland Medical Center, Baltimore, MD; [3]Dept of Surgery, Univ of Maryland Medical Center, Baltimore, MD.*

Background: Surveillance renal transplant biopsies (SBx) could detect subclinical histological changes that could affect graft outcomes. The impact of the induction agent on SBx findings is not well defined.

Methods: We conducted a retrospective cohort study of 466 patients who underwent SBx from 1/2007 to 12/2012, with stable graft function and no proteinuria, and had received induction with alemtuzumab (ALZ) (60%), anti-thymocyte globulin (rATG) (15%) or basiliximab (BXB) (24%).

Results: 410 patients had SBX at 4.0+-2.1 and 245 at 13.4 +- months post-transplant, 228 had both. Mean creatinine was 1.4 and 1.8 mg/dL, respectively.

First Biopsy Findings

	TCMR					BKV	ABMR			
	Borderline	1A	1B	2A	Total	SV40	Glomerulitis	PTCitis	C4d>10%	DSA
BSX	7	1	1	4	13(13.3%)	3%	9%	8.90%	14%	39.3%
rATG	7	0	0	0	7(10.5%)	4.8%	3%	2.20%	8%	50%
AlZ	9	5	1	1	16(6.5%)	3.3%	4%	2.20%	11%	52%

Second Biopsy Findings

	TCMR					BKV	ABMR			
	Borderline	1A	1B	2A	Total	SV40	Glomerulitis	PTCitis	C4d>10%	DSA
BSX	3	2	1	0	6 (10.7%)	8%	5%	2.90%	9%	39.3%
rATG	3	1	0	1	6 (12.8%)	0	23%	12.0%	13%	58.3%
AlZ	12	4	2	1	19 (11.9%)	3%	13%	5.30%	11%	62.1%

Conclusions: Our study suggests that subclinical histologic changes are not uncommon with modern IS regimens and the prevalence of these findings with ALZ induction was comparable to other induction agents.

PUB796

Incidence of Anti-HLA Antibodies Specific Donor in Kidney Transplant Recipients (KTR) and Its Association with Acute Rejection (AR) on Immunosuppression Schemes with or without Steroids Jorge Andrade-Sierra, Enrique Rojas-Campos, Jose Ignacio Cerrillos, Benjamin Gomez, Luis Alberto Evangelista-Carrillo, Alfonso M. Cueto-Manzano. *Nephrology, IMSS, Guadalajara, Jalisco, Mexico.*

Background: Antigen-specific humoral and cellular immune mechanisms contribute to an increased number and severe episodes of AR, conditioning chronic damage and graft loss. **OBJECTIVE:** To compare the incidence of donor-specific HLA-antibodies (HLA-DSA) and its association with AR in KTR on immunosuppression schemes with and without steroids.

Methods: Prospective Cohort, from March-2013 to March-2014, on participants over 18 years of age, first living donor kidney transplant (LDKT) with maintenance immunosuppression after transplantation without steroids compared to those who remained on steroids. All had negative crossmach (flow cytometry) and anti-HLA antibodies [Lifecodes LifeScreen Deluxe (LMX)] before transplantation.

Results: 77 patients posttransplant were included, 30 without steroids and 47 with steroids. At the end of follow-up the formation of donor-specific HLA-antibodies class I (13% vs 2.1%; p = 0.05) and class II (17% vs 4%; p = 0.06) was higher in the group without steroids and this intervention tended to predict the development of HLA-DSA class II [RR 5.7, CI (0.93 - 34.5). p = 0.06]. A history cellular AR was present in 80% (p = 0.07) in those who formed HLA-DSA class I and 86 % (p = 0.03) among class II and was a predictor for antibody class II formation [RR 7.23, CI (1.2 - 44); p = 0.03] Sixty-two percent of patients with positive HLA-DSA bordering changes for AR corresponded to immunosuppression without steroids.

Conclusions: The HLA-DSA class I and II were present in both groups from the early stages of transplantation, with no significant trend to be higher among those who did not receive steroids. AR predicts production of renal antibody receptors without steroids.

PUB797

Kidney Transplantation in Human Immunodeficiency Virus Positive Recipients - A Single Center Experience Javier Enrique Monserrate, Roberto L. Collazo-Maldonado, Kosunarty Fa. *Nephrology, Methodist Health System Dallas, Dallas, TX.*

Background: HIV-associated nephropathy (HIVAN) is the 3rd cause of ESRD in HIV(+). We report 10 HIV(+) KTx from HIV(-) donors.

Methods: In a 4-year period (2009-2013), data from 10 HIV(+) KTx was reviewed. Transplant criteria were: undetectable HIV RNA levels, CD4+ count ≥ 200/mm^3, stable antiretroviral Rx, and no opportunistic infections. 3 patients had biopsy-proven HIVAN: 1 had IgAN. Of 6 patients presumed to have HIVAN, one had diabetes and one had hepatitis C. Race: Black (9/10), male (7/10), mean age of 49 years. Nine KTx were from a deceased-and 1 from a living related-donor. Immunosuppression: induction with Basiliximab (n=9) or Thymoglobulin (TGB) (n=1) + tacrolimus (FK) + mycophenolic acid + steroids. KTx on Protease Inhibitors (PI) were switched to a non-PI Rx. Demographics, patient (PS) and graft survival (GS), CD4 and HIV RNA counts, renal function, as well as incidence of acute rejection (ACR), opportunistic infections and cancer were evaluated.

Results: KTx were followed for a mean of 45 months (range 19–77). ACR was diagnosed on 4 patients, most of them severe, with a mean time to first ACR of 117 days (range 6-394), and mostly associated with low or undetectable FK levels. Three KTx had opportunistic infections (1 CMV disease, 1 BK viremia and 1 PCP). Two of them had received TGB for previous ACR. One patient developed colon cancer less than 18 months post KTx. Pre-KTx mean CD4 was 574 ± 150 and 321 ± 170, at last follow up. Low CD4+ levels post KTx were attributed to a patient who had received TGB for ACR and another patient receiving chemotherapy for colon cancer. None of the patients showed reactivation of the HIV virus. Among patients with a functioning kidney, the mean serum creatinine was 1.60±0.48 mg/dl with a mean Glofil GFR of 67.2±36.6 cc/min. GS at 1 to 4 years were 90&, 80%, 80% and 80%. PS were, respectively, 100%, 90%, 90% and 90%.

Conclusions: The use of antirejection Rx does not result in the reactivation of the HIV virus. ACR tend to be severe and associated with suboptimal immunosuppression. KTx is a feasible and safe option for renal replacement in HIV(+) patients with equivalent GS and PS to HIV(-) KTx.

PUB798

Low Bioavailability Steroids for Treatment of Diarrhea Associated with Mycophenolate in Renal Transplant Recipents Pooja Budhiraja, Charity Thompson, Amna Ilahe. *Dept of Transplant, Univ of Kansas, Kansas City, MO.*

Background: Mycophenolic acid (MPA) is one of the main immunosuppressant's used in organ transplants. Diarrhea can be seen in 20% of subjects. Mycophenolic acid-acyl glucuronide is a metabolite of MPA, which causes inflammation and cytokine release and plays major role. Corticosteroids due to anti-inflammatory activity are drug of choice for noninfectious inflammatory colitis. Low bioavailability steroids act locally in the intestine and have minimal absorption into systemic circulation.

Methods: We present cases with MPA induced diarrhea who responded to these. They had no history of IBS, IBD, malabsorption and had never experienced diarrhea. Infectious work up and Celiac disease panel were negative. They had colonoscopy which revealed normal appearing terminal ileum and colonic mucosa. Random biopsies taken from the colon revealed acute and chronic inflammation, cryptitis, and focal crypt distortion. Their immunosuppression consisted of Myfortic, Prograf and prednisone. First patient is a 47 year old male with history of kidney transplant in 2014 for PKD. He presented 16 months post-transplant for diarrhea. Patient was having 5-10 episodes of watery diarrhea daily for the 2 months. The patient was started on budesonide 9 mg once a day and had improvement in diarrhea in 2 weeks**.** He continued on 9 mg for a total of 6 weeks and then tapered to 6 mg daily with taper over 12 weeks. He has been on budesonide for 8 weeks and denies diarrhea. Second patient is a 63 year old male with history of kidney transplant in 2014 for MPGN. He complained of chronic diarrhea one year post transplant. His baseline creatinine was 2.5mg/dl and he had low TPMT level. He was started on beclomethasone 2 mg three times a day and reported improvement in symptoms in 2 weeks. It was tapered to 2 mg twice a day at 6 weeks and plan is to taper it over 12 weeks. We will finish the course of oral low bioavailability steroids and observe the patient and repeat colonoscopy in 6 months after they finish treatment.

Conclusions: Oral low bioavailability steroids can improve MPA associated diarrhea and help minimize unnecessary reduction of MPA, help improve compliance and promote long term allograft survival.

PUB799

Crossed Kidney Transplantation from a Multiple-Arteries Living Donor. Arterial Reconstruction and Reimplantation in Gonadal Vein Patch Enrique Broseta, Beatriz Plaza. *Urology, Hospital Univ i Politècnico, Valencia, Spain.*

Background: Multiple arteries exist in almost 30% of these renal grafts,challenging the exvivo repair and implantation.The target of this work is to describe an infrequent arterial reconstruction technique on kidneys with multiple arteries.

Methods: 41 year-old male with chronic renal failure with no-filiated etiology is candidate for renal transplant.Living donor program is accepted.Due to AB0 incompatibility both are included in the crossed living donor program.Multi-centric crossed transplant is initiated,and a compatible left renal graft is received.Remarkably, the graft shows 4 renal arteries(3 short primaries and 1 polar) of 3-4 mm diameter.Due to the complexity

of the vascular surgery, the previous ex vivo repair is performed.During the ex vivo reconstruction,done with continous saline infusion (4ºC)and Celsior solution,the polar artery is linked,due to the endotelial injury during the explant,and the latero-lateral anastomosis of 2 principal superior arteries is done,creating a common ostium.A gonadal vein patch is created and the two joined arteries and the lower artery are anastomosed separately. The implant is made through right para-rectal incision. The arterial anastomosis is made between the right external iliac artery and the gonadal vein patch,acting as a Carrel patch.A terminolateral anastomosis is made from the donor's iliac external vein to the receiver's unic renal vein.Last,a uretheroneocystostomy is done with a Lich-Gregoir technique,including a doubleJcatheter placement.

Results: A good renal parenchyma perfusion was observed as well as positive flow in all arteries with intra-operatory continuous doppler.No intra-operatory complications were observed,and there was no need of hemo-derivates transfusion.The control doppler ultrasounds showed a normal espectral curves and normal resistance index of the renal arteries.The scanner after two months showed permeable renal arteries without signs of tenosis. After two months, the creatinine value is of 1.87mg/dL with a glomerular filtration rate of 43mL/min.

Conclusions: The use of gonadal vein acting as a Carrel patch is a safe surgical alternative in case of donor with multiple-arteries kidney.

PUB800

Oxidative Stress, and Its Association with Vascular Calcification in End Stage Renal Disease Patients Edith Viridiana Alatorre,[1] Enrique Rojas-Campos,[2] Alfonso M. Cueto-Manzano,[2] Benjamin Gomez,[1] Jose Ignacio Cerrillos.[1] *[1]Nfrologia y Trasplantes, Inst Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico; [2]Unidad de Investigacion Medica en Enfermedades Renales, Inst Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico.*

Background: Oxidative stress(OS) is closely associated to uremia, and induce endothelial dysfunction and atherosclerosis. Aim:determine the association between OS and Vascular Calcification(VC) in ESRD patients.

Methods: A cross sectional study performed in 88 patients(HD 50%);VC (Adragao´s score) and OS by means of superoxide dismutase(SOD), catalase and 8 hidroxy-2'-deoxyguanosine(8-OHdG) were evaluated. Other CKD-MBD and metabolic variables were recorded.

Results: Age was 30±11years; males were 52%. Frequency of VC was 48%; of them 56% has ≥3 VC points. Patients with VC had lower 8-OHdG; and higher P, PTH and ALP concentrations compared to non-VC.

Variable	VC	No VC	*P value*
Age (years)	30±11	31±12	0.51
Catalase (U/mg)	16.0±9.0	17.7±9.1	0.54
SOD (UI/ml)	8.2±7.1	8.4±9.4	0.93
8-OHdG (ng/ml)	6.5±5.8	9.2±4.6	***0.03****
25 (OH) Vitamin D (ng/ml)	22±8	23±11	0.55
Paratohormone iPTH (pg/ml)	638 (246-1010)	439 (139-790)	***0.03****
Phosphorus P (mg/dl)	4.1±2.4	2.5±1.4	***<0.0001****
Total cholesterol TC (mg/dl)	163±45	158±32	0.49
Triglycerides TG (mg/dl)	159±100	135±58	0.09
LDL-cholesterol (mg/dl)	89±37	87±29	0.83
Alkaline phosphatase ALP (U/l)	142 (95-314)	97 (77-163)	***0.003****

There was not difference among groups with other variables. Correlations between OS and CKD-MBD markers were: Catalase-Vitamin D (r= -0.39;*p*=0.01), Catalase-ALP(r= -0.35;*p*=0.02); SOD-P(r=0.41;*p*=0.001), SOD-VC(r= 0.25;*p*=0.04); 8-OHdG-P(r= -0.27;*p*=0.03), 8-OHdG-VC(r= -0.41;p=0.0001).

Conclusions: Antioxidant markers were not different between patients with and without VC. DNA damage marker (8-OHdG), was higher in no VC; this finding could represent cellular damage before the VC presence. 25(OH) vitamin D, ALP, and VC were associated with lower antioxidant concentration (catalase). The higher the phosphorus the higgher the SOD(antioxidant).

PUB801

A Time Dependent Analysis of Long-Term Renal Outcome and Mortality among Critical Acute Kidney Injury Patients Receiving Different Dialysis Modality Jian-Jhong Wang,[1] Vincent Wu.[2] *[1]Internal Medicine, Chi Mei Medical Center, Liouying, Tainan, Taiwan; [2]Internal Medicine, National Taiwan Univ Hospital, Taipei, Taiwan.*

Background: Initial dialysis modality could relate to kidney outcome among AKI patients. The aim of this study was to determine the relationship between dialysis modalities and long-term outcome after critical acute kidney injury.

Methods: A retrospective, observational study was conducted to include patients underwent acute dialysis after major operation. All-cause mortality and the renal outcome at the time of hospital discharge, 90 days and 365 days after hospital discharge were assessed. Daily dialysis modalities during critical care units were analyzed using a time-dependent model in regarding to competing risk of mortality.

Results: We identified 1,101 patients (mean age 64.57 years; 66.7% were male). CVVH had the highest mortality rate and was less likely to be dialysis dependence at index time points. However, there was no difference in odds of dialysis withdrawal for patients commencing IHD, SLED versus CVVH, in the time-dependent model analysis taking the competing risk for mortality into account at index times. All cause of mortality and composite outcome also did not different between groups. Daily receipt of CVVH as time dependent modalities, however, had the highest risk of mortality and composite outcomes but was a protective factor for dialysis withdrawal with reference to SLED or IHD (all $p < 0.01$).

Conclusions: We found no significant difference in hazards for long-term dialysis dependence or composite outcomes with initial modalities of dialysis from time dependent approach. However, the subsequently daily receipt of CVVH was a risk for composite outcomes but was a protective factor for dialysis withdrawal.

PUB802

Clinical Significance of Different Carnitine Levels in Improving the Prognosis of Hemodialysis Patients Yumei Zhang,[1] Dapeng Chen,[1] Wenge Li.[1] *[1]Nephrology, China- Japan Friendship Hospital, Beijing, China; [2]Nephrology, China- Japan Friendship Hospital, Beijing, China; [3]Nephrology, China- Japan Friendship Hospital, Beijing, China.*

Background: Carnitine is an amino acid derivative, which produces energy required for muscle and cell metabolism. It has been suggested that disturbed carnitine homeostasis in hemodialysis(HD) patients. The objective of this study was to investigate the clinical significance of different carnitine levels in HD patients.

Methods: HD patients (n=133) were divided into medication group (received carnitine treatment) and non-medication group. According to patients' Fc(free carnitine)level, medication group were further divided into three subgroups: Fc80~199umoL/L group, Fc200~299umoL/L group and Fc≥300umoL/L group. We used non-derivative tandem mass spectrometry to determine carnitine level and observed clinical symptoms, such as weakness, hypotension and muscle cramps during dialysis.

Results: The Fclevel in non-medication group was significantly lower than that in control group, while the Fc, Ac(acyl-carnitine)level in medication group were higher than that in non-medication group (P<0.05). Compared with that in non-medication group, symptoms like weakness, hypotension and muscle cramps during dialysis in medication group is fewer occur (P<0.05). A further intercomparison was made in them and showed the incidence of hypotension and muscle cramps in Fc<80~199umoL/L group was lower than that in Fc≥300umoL/L medication group and non-medication group. The differences were statistical significance.

Conclusions: A general lack of carnitine in patients with hemodialysis. L - carnitine can effectively increase the concentration of Fc. We found that appropriate range of free carnitine can improve complications in dialysis, however, beyond certain range could be counterproductive. The proper range of Fc need to be further studied.

Funding: Private Foundation Support

PUB803

Evaluating CTLA-4-Ig and a CXCR4 Antagonist as Potential Treatment Options for Diabetic Kidney Disease (DKD) Bhaskarjyoti Sarmah, Hana Baker, Courtney Wooden, Tao Wei, Paul J. Ryan, Sheng-Bin Peng, Victor Obungu, Matthew D. Breyer, Josef G. Heuer. *Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN.*

Background: Renal inflammation is a hallmark of DKD pathophysiology. CTLA-4 is a co-inhibitory receptor present on activated T and regulatory T cells that blocks co-stimulatory B7-1 and B7-2 ligands on antigen presenting cells, thereby limiting CD28 receptor mediated T-cell activation. Reportedly, soluble CTLA-4-Ig (abatacept) that acts as a B7 ligand trap was shown to reduce proteinuria in FSGS and nephrotic SLE patients.

Methods: We set out to test if targeting B7 molecules with CTLA-4-Ig constitutes a promising therapeutic avenue for treating DKD.

Results: There is increased mRNA expression of B7-1 in glomeruli and B7-2 and CD28 in both glomeruli and tubules of human DKD patients. B7-1 and B7-2 mRNA expression are also increased in kidneys of the *renin-AAV* uninephrectomized *db/db* mouse model. Interestingly, CTLA-4-Ig treatment retards albuminuria progression in this model compared to the vehicle control, but doesn't reduce albuminuria from baseline or further reduce albuminuria when added to Lisinopril. Among other inflammatory pathways prominently upregulated in human DKD kidney is the CXCL12/CXCR4 chemokine signaling pathway. CXCL12/CXCR4 engagement activates several signaling pathways (e.g. MAPK, PI3K/AKT, NF-κB and JAK/STAT) and is known to play a major role in cell survival, angiogenesis, inflammation, and mobilization/homing of bone marrow stem/immune cells. As both B7/CD28 and CXCL12/CXCR4 pathways are concordantly upregulated in human DKD, targeting both pathways simultaneously may result in better efficacy. The CXCR4 antagonist alone or in combination with Lisinopril doesn't impact albuminuria. However, the CTLA-4-Ig + CXCR4 antagonist + Lisinopril combination shows greater reduction of albuminuria compared to Lisinopril alone and reduces BUN and serum creatinine levels consistent with renal function improvement.

Conclusions: We conclude that CTLA-4-Ig has modest preventative effects on albuminuria in a hypertensive model of DKD and requires additional interventions to confer albuminuria reduction.

PUB804

Increasing Serum Chloride Is Associated with Acute Kydney Injury in Critically Ill Patients David Massicotte-Azarniouch,[1] Thomas Mavrakanas,[1] Sheldon Magder,[2] Peter Goldberg,[2] Ahsan Alam.[1] *[1]Nephrology, McGill Univ Health Center, Montreal, QC, Canada; [2]Critical Care, McGill Univ Health Center, Montreal, QC, Canada.*

Background: Physiologic studies have shown hyperchloremia may negatively affect kidney function. However, few studies have looked at the impact of hyperchloremia on adverse outcomes in critically ill patients. We examined the association between serum chloride levels and the development of acute kidney injury (AKI) and mortality in an intensive care unit (ICU) setting.

Methods: We conducted a retrospective, single-center, cohort study of 1866 adults admitted to an ICU between 2006 and 2011. Serum chloride values during the first 48 hours of ICU admission were collected and analysed for baseline levels, peak levels, and change in the first 48 hours. Adjusted logistic regression analysis was used to examine the association between serum chloride and the incidence of AKI (2012 KDIGO criteria) and ICU mortality.

Results: The incidence of AKI was 56.3% and ICU mortality was 12.8%. The mean (SD) baseline chloride was 106 (7.1) mmol/L and average peak chloride 106 (7.1). The mean change in chloride was -2.2 mmol/L, with 12.8% of patients showing an increase within the first 48 hours of admission. An increase in serum chloride was significantly associated with AKI and ICU mortality. In multivariate analysis adjusting for age, APACHE II score, ventilation status and pH value, the association remained significant between the serum chloride increase and severe AKI (OR 1.756, 95% CI 1.140-2.706, p=0.0107) and ICU mortality (OR 2.260, 95% CI 1.384-3.69, p=0.0011). There was no significant association between baseline or peak chloride and AKI or ICU mortality.

Conclusions: An increase in serum chloride in critically ill patients during the first 48 hours of admission is significantly associated with the development of severe AKI and ICU mortality, independent of disease severity (APACHE II score). Serum chloride increase may have a deleterious effect on kidney function. Whether this justifies the use of chloride-restrictive fluid strategies requires further evaluation.

Funding: Clinical Revenue Support

PUB805

Genetic Ablation or Pharmacologic Inhibition of the Natriuretic Peptide Clearance Receptor NPR-C Delays Chronic Kidney Disease Progression in Mouse Models

Bhaskarjyoti Sarmah,[1] Courtney Wooden,[1] Hana Baker,[1] Derek D. Yang,[1] Marikka Elia,[2] Stephanie M.E. Truhlar,[2] David J. Stokell,[1] Rebecca R. Miles,[1] Rohn Millican,[1] Yiqing Feng,[1] Zhonghua Qi,[1] Josef G. Heuer,[1] Matthew D. Breyer.[1] *[1]BioTechnology Discovery Research, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN; [2]Lilly Biotechnology Center, Lilly Research Laboratories, Eli Lilly and Company, San Diego, CA.*

Background: Natriuretic peptides (NPs, e.g. ANP, BNP, CNP) play a crucial role in cardiorenal homeostasis. NPs signal through NPR-A and NPR-B guanylyl cyclase receptors inducing cGMP signaling cascade, thereby promoting peripheral vasodilation, glomerular filtration, and salt and water excretion, and inhibiting the renin-angiotensin-aldosterone system. The third receptor, NPR-C is primarily involved in NP clearance.

Methods: We hypothesize that NPR-C inhibition will accentuate NP/cGMP signaling locally in the glomerulus, where this clearance receptor is normally expressed alongside the signaling receptors; and could be useful for treating CKD.

Results: In support of this hypothesis albuminuria progression was significantly attenuated in the *NPR-C* loss-of-function mutant mice (*NPR-C*$^{-/-}$) following remnant (3/4th renal ablation) surgery compared to wild-type littermates. No significant change in serum creatinine or BUN but significant decreases in serum renin and urinary cGMP levels are observed in the *NPR-C*$^{-/-}$group. These observations indicate that kidney NP signaling is potentiated in *NPR-C*$^{-/-}$mice which attenuates CKD progression.

To further explore this we generated high affinity NPR-C antagonist mAbs that inhibit ligand binding to the receptor, induce receptor internalization and degradation, and potentiate cGMP signaling in *NPR-A NPR-C* co-expressing cells. Interestingly, one mAb significantly retards albuminuria progression compared to vehicle in the 129*svev* mouse remnant kidney model. This mAb depletes NPR-C protein levels in the kidney confirming target engagement. However, significant changes in urine cGMP levels were not observed.

Conclusions: Overall, the NPR-C blockade was found to retard CKD progression in the hypertensive remnant kidney model.

PUB806

Case Report of Long-Term Recovery from Advanced Chronic Kidney Disease following Alternative Oxidative Therapy and Supplements

Priya Visweswaran Balakrishnan. *Div of Renal Diseases, The Immortality Inst, Houston, TX.*

Background: CKD affects nearly 3-20 million people in the US alone and 20-100 milliom people world-wide. While there are drugs available to slow progression to ESRD, nothing has been shown to absolutely, and consistently, prevent the need for Renal Replacement therapy, when CKD Stage V is attained, or RRT becomes a medical necessity. We hereby report a long-standing diabetic patient with CKD Stage V (who had needed RRT for more than 6 months with an eGFR of 12), who has successfully remained off any modality of RRT, 1 year and 3 months, after receiving thirty of our treatments.

Methods: IV administration of a mixture of oxygen and ozone gases (as described by Drs. Tom Corbett, Howard Robins, Gopal Rabindranath - nephrologist who has described this in human beings, and Sylvia Menendez - who has described this in human beings and animals), was given to the patient through a peripheral IV, at a concentration of 55 mcg/ml, starting with 2.5 ml, and slowly escalating the dose by 5-10 ml each treatment, for a minimum of 3 times a week. Vitamin B12 IM was recommended and administered as well. This is patented.

Results: Patient no longer felt weak, tired, depressed, lethargic; lost around 20 lbs of weight along with copious urination; experienced improvement of peripheral neuropathy and strength and endurance.

Conclusions: We are able to reverse uremia (to a greater or lesser extent), even in long-standing CKD, with a mixture of gaseous substances and other supplements, as needed, delivered carefully, with close observation. This may obviate the need for RRT, in several patients, even in those with long standing CKD, due to diabetes, which is generally considered to be irreversible.

Funding: Pharmaceutical Company Support - The Immortality Institute

PUB807

Mortality and Hospitalization in Patients That Fail to Reach Dry Weight

Suzanne E. El Sayegh, Nabil Zeineddine, Raja Asif Masood, Marco Campitelli, Salim Bou Slaiman, Sandy El Bitar. *Internal Medicine, Staten Island Univ Hospital.*

Methods: Patients with end stage renal disease have an elevated risk for hospitalization, cardiovascular complications and increased mortality compared with the general population. The high rate of mortality and the high burden of cardiovascular events in ESRD patients may be related to a set of complications that occur during hemodialysis, such as intradialytic hypotension with consequent tissue hypoxia which is known to occur in relatively large number of dialyzed patients. This study was conducted to investigate the effect of failing to reach dry weight in a hemodialysis patient on mortality, hospitalization and morbidities, and whether a drop in blood pressure during hemodialysis with or without reaching the dry weight will affect a patient outcome. (intradialytic hypotension defined based on the KDOQI as " a decrease in systolic BP by 20 mmhg from predialysis to nadir intradialytic levels plus 2 or more responsive measures (saline administered, rate of dialysis decreased or dialysis stopped).

Results: 49 hemodialysis patients (49% males, 51% females. Mean age 60.7 years) with ESRD charts were reviewed, and data from 1763 hemodialysis session was collected; 37.2% (644) of the hemodialysis sessions ended with the patient reaching his dry weight. In 16.4 % (283) of hemodialysis sessions hypotension occurred. 69.4% (n=34) of the studied patients were hospitalized in a one year follow up period. 20.5% (7/34) were hospitalized for a cardiovascular complication (myocardial infarction, CHF exacerbation,or a newly diagnosed angina), 20.5% (n=7/34) were hospitalized for hemodialysis access site complications.

Conclusions: The high rate of mortality and the high burden of cardiovascular events and access complications seen in ESRD patients may be related to a set of complications that occur during hemodialysis, such as intradialytic hypotension which is known to occur in relatively large number of dialyzed patients. Analysis will be conducted further to investigate the effect of failing to reach dry weight in a hemodialysis patient on mortality, hospitalization and morbidities, and whether a drop in blood pressure during hemodialysis with or without reaching the dry weight will affect a patient outcome.

Funding: Other NIH Support - Staten Island University Hospital

PUB808

Relaxin Reverses Contrast-Induced Human Kidney Proximal Tubular Epithelial Cell Apoptosis by Activation of Akt Signaling Pathway In Vitro

Ming Wang, Xiangcheng Xie, Xiao Fei. *Nephrology, Hangzhou First People's Hospital, Affiliated Hangzhou Hospital of Nanjing Medical Univ, Hangzhou, Zhejiang, China*.

Background: Contrast-induced acute kidney injury, CI-AKI, is a common acute renal dysfunction, which is the third most common cause of hospital-acquired acute renal failure. However, the treatment strategies remain limited. The present study was designed to investigate the impact of relaxin on the contrast-induced cell injury in order to find an effective way to treat contrast-induced acute kidney injury(CI-AKI).

Methods: In this experiment, renal tubular epithelial cells (HK-2) were exposed to ioversol (100 mg iodine/mL) for 0.5 hours. The Relaxin (10ng/ml) was added 1.5 hours before Ioversol, as well as the PI3K inhibitor LY294002 (50 uM). Then cells were incubated for 24 hours in normal medium. CCK-8 assay was used to measure cell viability. Apoptotic morphologic alterations were observed using Hoechst 33342 stating method. Apoptosis was detected by Annexin V stain. Western blot analysis was employed to measure the expression of pAKTser473, AKT, Cleaved-Caspase3, Bcl-2, Bax, ACTIN protein.

Results: Ioversol reduced cell viability of HK-2 cells. Western blot results revealed that the expression of phosphorylated Akt (p-Akt) in cells decreased after exposure to ioversol. Ioversol increased both the activities of caspase-3, and the expression of the Bax protein, while the expression of Bcl-2 protein decreased. As a result the Bax/Bcl-2 ratio was therefore increased after the treatment with ioversol. These effects were reversed when co-treated with relaxin. However, when pre-administration of Akt inhibitor LY294002, the effect of relaxin was blocked, indicating that relaxin can attenuate contrast-induced cell apoptosis by activating Akt signaling pathway.

Conclusions: Our study demonstrated that relaxin attenuated the Ioversol induced cell apoptotic injury via activation of PI3K/Akt signaling pathway, suggesting that H2 relaxin might play a protective role in the treatment for CI-AKI.

Funding: Government Support - Non-U.S.

AUTHOR INDEX

The number refers to the location of the body of the abstract in the publication section.

KEYWORD INDEX

The number refers to the location of the body of the abstract in the publication section.

HI-OR01

Liraglutide and Renal Outcomes in Type 2 Diabetes: Results of the LEADER Trial Johannes F. Mann, Kristine Brown Frandsen, Gilbert Daniels, Peter Kristensen, Michael Nauck, Steve Nissen, Stuart Pocock, Neil Poulter, Soren Rasmussen, William Steinberg, Mette Stockner, Bernard Zinman, Florian Baeres, Richard Bergenstal, Steve Marso, John Buse. *Nephrology, Friedrich Alexander Univ, Erlangen, Germany.*

Background: The effects of liraglutide, a long-acting glucagon-like peptide-1 (GLP-1) analog, on renal outcomes in type 2 diabetes are unknown. We conducted a randomized, double-blind, placebo-controlled trial comparing liraglutide vs placebo, both on a background of standard of care, in participants with type 2 diabetes and high cardiovascular risk.

Methods: The Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial was initiated in 2010 and completed in 2015. Renal events were key secondary outcomes. The primary renal outcome was a composite of new onset of persistent macroalbuminuria, persistent doubling of serum creatinine, end stage renal disease (ESRD), or death due to renal disease. Risk of renal outcomes was determined using intention-to-treat in time-to-event analyses; competing risk of death was taken into account. Change of eGFR and loss of eGFR by >-30% was also analyzed.

Results: 9340 patients were randomized and median follow-up was 3.84 years. The primary renal outcome occurred in fewer participants treated with liraglutide (268 of 4668) than with placebo (337 of 4672; HR 0.787 [0.670;0.924] p=0.003). The difference was primarily driven by new onset of persistent macroalbuminuria, occurring in fewer participants treated with liraglutide (161 of 4668) than with placebo (215 of 4672; HR 0.74 [0.61;0.91] p=0.004). Doubling of serum creatinine and ESRD tended to be less frequent with liraglutide. eGFR decreased significantly less and albuminuria increased less with liraglutide than placebo. The difference in change of eGFR was driven exclusively by the subgroup with eGFR <60 ml/min at baseline (N=2458). The difference in change of albuminuria was independent of baseline eGFR or albuminuria.

Conclusions: In conclusion, liraglutide in addition to standard of care therapy reduced the progression of diabetic nephropathy.

Funding: Pharmaceutical Company Support - Novo Nordisk

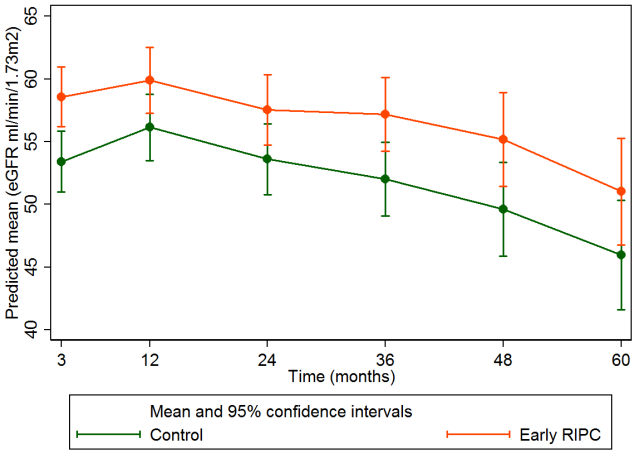
HI-OR02

Remote Ischaemic Preconditioning (RIPC) Leads to Sustained Improvement in Allograft Function Following Live Donor (LD) Kidney Transplantation: 5 Year Follow Up in the REnal Protection Against Ischaemia Reperfusion in Transplantation (REPAIR) Study Kristin Veighey,[1] Jennifer Nicholas,[2] Tim Clayton,[2] Raymond Macallister.[3] *[1]Wessex Kidney Centre; [2]London School of Hygiene & Tropical Medicine; [3]Univ College London.*

Background: Ischaemia reperfusion (IR) injury at transplantation contributes to damage that limits allograft longevity. The REPAIR study demonstrated a trend towards improved iohexol GFR (adjusted mean difference 3.08ml/min/1.73m^2; p=0.13), and a significant improvement in eGFR (4.98ml/min/1.73m^2; p=0.011) at 1 year in patients undergoing early RIPC prior to LD kidney transplantation. We analysed eGFR data up to 5 years.

Methods: 406 adult live donor/recipient pairs were randomised by factorial design to: sham RIPC/early RIPC (immediately pre-surgery)/late RIPC (24 hours pre-surgery)/dual RIPC (early+late RIPC). The primary outcome was iohexol GFR at 12 months. eGFR (CKD-EPI) up to 60 months was an important secondary outcome.

Results: eGFR data demonstrated a sustained benefit of early RIPC - adjusted mean differences between control & early RIPC groups were 3.94 (p=0.052), 5.16 (p=0.015), 5.55 (p=0.039) & 5.05 (p=0.104) ml/min/1.73m^2 at 2,3,4 & 5 years (100% completed 3 years, 4 & 5 year follow up ongoing).



There was no strong evidence for an effect of late RIPC on allograft function. There were no clinically significant/prolonged adverse effects. Lower graft loss & mortality was noted in all preconditioned groups.

Conclusions: RIPC, a safe and virtually cost-free intervention, resulted in sustained improvement in eGFR post LD transplantation, reaching 13% by 5 years. This is expected to translate into increased graft longevity, and with longer follow up, RIPC might also reduce mortality & graft loss. Given the resultant clinical, economic & quality of life implications, we recommend that RIPC is adopted into routine care for these patients.

HI-OR03

Rabbit-ATG or Basiliximab Induction for Rapid Steroid Withdrawal after Renal Transplantation: An Open-Label, Multicentre, Randomized Controlled Trial Christian Hugo,[1] Michael Sean Wiesener,[3] Mirian Opgenoorth,[1] Oliver Thomusch.[2] *[1]Univ Hospital Carl Gustav Carus of the Technische Univ Dresden, Dresden, Germany; [2]Univ Hospital Freiburg, Freiburg, Germany; [3]Univ Hospital Erlangen, Erlangen, Germany.*

Background: In this trial we examine the efficacy and safety parameters of rapid steroid withdrawal after induction therapy either with rabbit antithymocyte globulin (rabbit ATG) or basiliximab during the first year after kidney transplantation.

Methods: We randomly assigned 615 renal transplant recipients to receive either basiliximab induction with low dose tacrolimus, mycophenolate mofetil and steroid maintenance therapy (arm A), or rapid corticosteroid withdrawal on day 8 (arm B), or rapid corticosteroid withdrawal on day 8 following rabbit ATG instead of basiliximab (arm C). The primary end point was the incidence rate of biopsy proven acute rejections at 12 months. Glomerular filtration rate (GFR), cardiovascular risk factors and safety parameters were analyzed as secondary endpoints.

Results: Biopsy proven acute rejection rates were not reduced by rabbit ATG (9·9%) compared to both other treatment arms A (11·2%) or B (10·6%) (A versus C: p=0·75; B versus C: p=0·87). As a secondary endpoint, rapid steroid withdrawal reduced posttransplantation diabetes mellitus in arm B to 23·9% and in arm C to 22·7% compared to standard arm A with 39·2% (Odds Ratio: 0·49, 95% CI: 0·30-0·82, p=0·0070). Patient and censored graft survival after 12 months were excellent and equivalent in all arms with 94·7%, 97·4%, 96·9% and 96·1%, 96·8%, 95·8% respectively. Safety parameters did not differ between the study arms.

Conclusions: Rabbit ATG failed to show superiority over basiliximab induction for the prevention of biopsy proven acute rejections after rapid steroid withdrawal within one year after renal transplantation. Nevertheless, rapid steroid withdrawal after induction therapy for patients with a low immunologic risk profile can be achieved without any loss of efficacy and is highly advantageous in regard to posttransplantation diabetes mellitus incidence. (NCT 00724022)

Funding: Pharmaceutical Company Support - Investigator Initiated Trial, finanical support by Astellas Pharma GmbH, Sanofi, Roche Pharma AG

HI-OR04

The Sodium Lowering in Dialysate (SoLID) Trial: A Randomised Controlled Trial of Low versus Standard Dialysate Sodium Concentration (DNa) during Hemodialysis (HD) for Regression of Left Ventricular (LV) Mass Mark R. Marshall,[1] Alain C. Vandal,[4] Joanna Leigh Dunlop,[1] Janak Rashme de Zoysa,[5] Imad A. Haloob,[2] Christopher J. Hood,[1] John Irvine,[3] Philip J. Matheson,[6] David Mcgregor,[3] Kannaiyan Samuel Rabindranath,[7] David Semple.[2] *[1]Counties-Manukau DHB, Auckland, New Zealand; [2]Auckland DHB, Auckland, New Zealand; [3]Canterbury DHB, Christchurch, New Zealand; [4]Auckland Univ of Technology, Auckland, New Zealand; [5]Waitemata DHB, Auckland, New Zealand; [6]Nephrology, Capital & Coast DHB, Wellington, New Zealand; [7]Waikato DHB, Hamilton, New Zealand.*

Background: LV hypertrophy contributes to premature cardiovascular (CV) mortality in dialysis patients. Reducing sodium exposure through lower DNa during HD may reduce LV mass.

Methods: Single-blind trial in 99 patients on home/selfcare HD from 11 centers in NZ, randomized to dNA 135mM or 140mM for 12 mo, stratified by center and conventional (≤18 h/wk) vs. extended-hour (>18 h/wk) HD. Main efficacy endpoint: LV mass index (LVMI) at 12 mo by cardiac MRI; Main safety endpoint: LV wall motion score index (WMSI) at 12 mo by cardiac MRI. We performed intention-to-treat analyses, for efficacy using a Gamma GLM with identity link function, for WMSI (dichotomising 1 vs. >1) using binomial with logit link, adjusting for baseline LVMI and WMSI. We adjusted for other covariates after blinded review (protocol BMC Nephrol 14:149/15:120/16:120, ACTRN12611000975998).

Results: Baseline data was similar across groups. Overall mean (SD) age 50.6 (13.5) yr, M/F 67/32, median (IQR) vintage 2.7 (1.3-5.9) yr, diabetes 31%, mean LVMI 94.2 (25.1), WMSI 1.1 (0.3). Conventional HD 90%, extended-hour HD 10%.

LVMI	**Est Treatment Effect (g/m^2)**	**95% CIs**	**P Value**
135mM vs. 140mM (covariate unadj)	-2.03	(-7.61,3.52)	0.47
135mM vs. 140mM (covariate adj)	-2.21	(-7.38,2.95)	0.40
WMSI	**Est Odds Ratio**	**95% CIs**	**P Value**
135mM vs. 140mM (covariate unadj)	1.37	(0.4, 5.03)	0.62
135mM vs. 140mM (covariate adj)	2.15	(0.51,10.86)	0.32

Conclusions: Reducing DNa to 135mM for 12 mo does not reduce LVMI or increase WMSI relative to 140mM. Analyses for other endpoints (e.g. BP, IDWG, IDH) will be presented.

Funding: Government Support - Non-U.S.

HI-OR05

AURA-LV: Successful Treatment of Active Lupus Nephritis with Voclosporin William Franklin Pendergraft,[1] James A. Tumlin,[2] Brad H. Rovin,[3] Mary Anne Dooley,[1] David R.W. Jayne,[5] David Wofsy,[6] Frederic A. Houssiau,[7] David Isenberg,[8] Tak mao Chan,[9] Neil Solomons,[10] Robert B. Huizinga.[10] *[1]UNC; [2]UT; [3]OSU; [4]UNC; [5]UCambridge; [6]UCSF; [7]Univ Catholique de Louvain; [8]UCL; [9]HKU; [10]Aurinia.*

Background: In lupus nephritis (LN), complete (CR) or partial remission (PR) is associated with improved renal survival. Voclosporin (VCS) is a novel CNi with improved safety and predictable PK-PD profile.

Methods: The trial primary objective was CR defined as a urine protein/creatinine ratio (UPCR) of ≤0.5 mg/mg using first morning void with an eGFR ≥ 60 mL/min without a decrease of ≥20%. Entry criteria:renal biopsy within 6 months (Class III-V LN, ISN/RPS); UPCR>1.5 (III-IV) or 2.0 mg/mg (V);serologic evidence of active LN; and eGFR >45ml/min. Low (23.7 mg BID) or high dose VCS (39.5 mg BID) was administered with MMF and steroids.

Results: 265 patients were enrolled. Baseline UPCR (mg/mg) was 4.4 (placebo), 5.2 (low dose VCS) and 4.5 (high dose VCS). 24 week CR: **19.3%** (placebo), **32.6%** (low dose) and **27.3%** (high dose) (OR: 2.03, p=0.045 low dose vs. placebo). The results were confirmed by 24 hour urine collections (p=.047). Both the low and high dose VCS were statistically superior to placebo in PR and time to CR and PR. In the VCS groups, eGFR fell by a median of 8-9 ml/min by week 4 and then stabilized. Mean blood pressure between groups was similar. Over 90% of subjects experienced at least one adverse event with the most common being infectious and GI events. More patients experienced serious adverse events in both voclosporin groups (25.8% low, 25.0% high, 15.8% placebo) with the nature of SAEs consistent with those observed in patients with highly active LN. There were 13 deaths (1 placebo, 10 low, 2 high) with 11/13 in Asia. Causes were multi-factorial including sepsis and other lupus-related complications. None were considered related to VCS by investigators.

Conclusions: The AURA study is the first global study to demonstrate the positive effects of VCS in the treatment of active LN. Adverse events were higher in the treated patient group, consistent with increased immunosuppression. There was a higher mortality rate in the low-dose group with heterogenous causation. These favorable data will help plan subsequent studies of voclosporin in LN.

Funding: Pharmaceutical Company Support - Aurinia Pharmaceuticals Inc

HI-OR06

Efficacy and Safety of Sparsentan, a Dual Angiotensin II (Ang II) and Endothelin (ET) Type A Receptor Antagonist, in Patients with Focal Segmental Glomerulosclerosis (FSGS): A Phase 2 Trial (DUET) Howard Trachtman,[1,2] Peter J. Nelson,[3] Radko Komers.[4] *[1]Pediatric Nephrology, NYU School of Medicine, New York, NY; [2]NYU Langone Medical Center, New York, NY; [3]Nephrology, Univ of WA, Seattle, WA; [4]Retrophin, Inc., Cambridge, MA.*

Background: This phase 2, double-blind (DB), controlled trial (NCT01613118) evaluated the efficacy and safety of sparsentan (SPAR) as a treatment for primary FSGS.

Methods: After a 2-week ACEI/ARB washout, 109 patients, aged 8–71 yrs, with biopsy-proven FSGS were randomized to receive SPAR 200, 400, or 800mg/day, or the active control ARB irbesartan (IRB, 300mg/day) for 8 weeks. The primary endpoint was the change in urine protein-to-creatinine ratio (UPC) from baseline. The proportion of patients who achieved UPC ≤1.5g/g with >40% reduction in UPC at Week 8, a modified partial responder analysis, was evaluated as a secondary endpoint.

Results: The analysis included 96 randomized patients who completed 8 weeks of DB treatment with paired urine samples. After pooling all SPAR dose groups per the prespecified analysis plan, SPAR-treated patients demonstrated greater reductions in UPC vs those treated with IRB (45% vs 19%, *P*=.006). A significant reduction in UPC was also observed in pooled 400–800mg groups (47% vs 19%, *P*=.011). The proportion of patients who achieved UPC ≤1.5g/g with >40% reduction was 28% across all SPAR groups and 9% in IRB (*P*=.04). Complete remission (UPC <.3g/g) occurred in 4 SPAR- and 0 IRB-treated patients. In the DB period, the most common treatment emergent adverse event (AE) was hypotension; 2 SPAR patients had serious AEs (anemia, unrelated hospitalization), which did not result in discontinuation of treatment; and 3 patients discontinued due to AEs (AKI and modest LFT elevation in SPAR; hypoalbuminemia in IRB). All patients who completed the DB period were offered to continue on open-label SPAR treatment.

Conclusions: In summary, in patients with FSGS, dual Ang II and ET blockade with SPAR achieved significantly greater antiproteinuric effect compared with blockade of Ang II alone with IRB. In accord with prior studies in essential hypertension, SPAR appears to be safe and well tolerated in patients with FSGS.

Funding: Pharmaceutical Company Support - Retrophin, Inc.

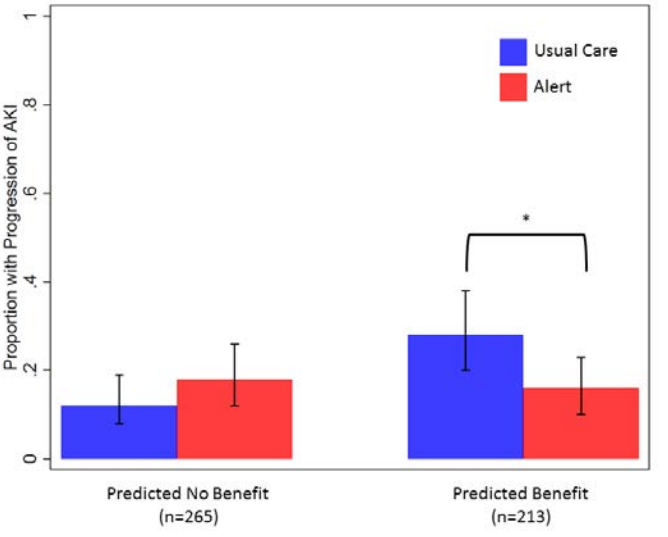
FR-PO1121

Development and Validation of a Model to Improve Targeting of Electronic Alerts for Hospitalized Patients with Acute Kidney Injury Francis Perry Wilson,[1,2] Aditya Biswas,[1] Chirag R. Parikh,[1,2] Harold I. Feldman,[3] Amit X. Garg,[4] Paul M. Palevsky,[5] Stephen R. Latham.[1] *[1]Program of Applied Translational Research, Yale Univ, New Haven, CT; [2]Clinical Epidemiology Research Center, Veterans Affairs Medical Center, West Haven, CT; [3]Dept of Medicine, Perelman School of Medicine at the Univ of Pennsylvania, Philadelphia, PA; [4]Dept of Medicine, Univ of Western Ontario, Ontario, Canada; [5]Dept of Medicine, Univ of Pittsburgh, Pittsburgh, PA.*

Background: The proliferation of alerts in the hospital can lead to alert fatigue. Uplift modeling may allow for personalized targeting of alerts to reduce provider burden and increase effectiveness.

Methods: Using data from our prior randomized trial of electronic alerts for acute kidney injury (AKI), we trained a neural-network based uplift model on the first 4/5ths of study participants. We then tested the model in the last 1/5 of study participants to identify a subgroup of individuals who would particularly benefit from alerts, manifested by a reduction in the risk of progression of AKI at 7 days.

Results: A total of 19.7% of patients had progression of AKI in the training set and 17.8% in the test set (p=0.35). Alerting showed no significant benefit on AKI progression in either the training or test set (p=0.12, p=0.60, respectively). The uplift-model identified 213 individuals in the test set predicted to benefit from alerts, and 265 predicted not to benefit. Among those expected to benefit, alerting significantly reduced progression of AKI (OR 0.48, 0.24-0.93, p=0.03). There was no significant alert effect in those not expected to benefit (p=0.19).



Conclusions: An uplift-modeling approach successfully identified a subset of patients for whom AKI alerts were associated with a clinical benefit, and may be a feasible method to personalize alert targeting.

Funding: NIDDK Support

FR-PO1122

Effect of Oral Curcumin on Markers of Injury and Clinical Acute Kidney Injury from Elective Abdominal Aortic Aneurysm Repair Amit X. Garg. *Western Univ, Canada for Curcumin AAA Investigators.*

Background: Curcumin is a popular herbal supplement from the spice turmeric. It has anti-oxidant, anti-inflammatory and anti-apoptotic properties, and reduces ischemic reperfusion and nephrotoxin injury in animals. We tested whether oral curcumin reduces markers of injury and clinical acute kidney injury (AKI) in patients undergoing elective abdominal aortic aneurysm repair.

Methods: We randomized 606 patients at 10 centres to take oral curcumin or matching placebo for 4 days (2000 mg on 8 occasions) at the time of elective open or endovascular abdominal aortic aneurysm repair. The primary outcomes were 4 makers of injury after the repair. Secondary outcomes included clinical AKI, a composite of adjudicated clinical events, hospital length of stay and safety outcomes (diarrhea, anemia). The methods and analyses were pre-specified (ClinicalTrials.gov NCT01225094).

Results: Oral curcumin was well tolerated with >90% scheduled pills taken. Curcumin (n=304) versus placebo (n=302) had no significant effect on any injury marker, nor any other outcome. Results were consistent in additional analyses.

	Curcumin n=304	Placebo n=302	p-value
_			
post-op urine IL-18 pg/mL	13 (6, 27)	16 (7, 30)	0.12
pre-op - post-op change in serum/plasma			
... NT pro BNP, mesoscale pg/mL	2689 (702, 5642)	2296 (550, 5324)	0.38
... high sensitive C-reactive protein µg/mL	58 (28, 95)	58 (30, 90)	0.46
... creatinine µmol/L	1 (-7, 19)	1 (-6, 12)	0.37
_			
AKI (KDIGO defn)	17%	10%	0.051
Composite (includes death, myocardial infarction, stroke)	9%	9%	0.69
Hospital length of stay, days	2 (5,8)	2 (5, 7)	0.29
Diarrhea	5%	7%	0.38
post-op - pre-op change in hemoglobin g/L	-33 (-46, -23)	- 34 (-43, -24)	0.99
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data presented as median (25th, 75th percentile) or percent			

Conclusions: Oral curcumin did not reduce markers of injury or clinical AKI from abdominal aortic aneurysm repair. Funding: Canadian Institutes of Health Research.

Funding: Government Support - Non-U.S.

FR-PO1123

Randomized Controlled Trial for Renal Denervation in Resistant Hypertensive Patients (SYMPATHY): Relevance of Medication Adherence

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Background: Randomized controlled trials of catheter-based renal denervation (RDN) as therapy for resistant hypertension produced conflicting results. Medication adherence may be important in (partially) explaining that.

Methods: SYMPATHY is a prospective open label multicenter trial in Dutch patients with resistant hypertension (NCT01850901). Primary outcome was change in daytime systolic ambulatory blood pressure (ABPM) at 6 months. Patients were randomly assigned to RDN or not on top of usual care. Secondary outcome included medication adherence, which was qualitatively assessed by liquid chromatography/tandem mass spectrometry with spectra library search, using blood samples collected on the day of blood pressure (BP) measurements. Patients and physicians were unaware of adherence assessment. SYMPATHY was approved by the Ethics Committee.

Results: SYMPATHY enrolled 139 patients (95 RDN; 44 control) from May 2013 to January 2016. Mean differences between control and RDN in changes in daytime systolic ABPM after 6 months was 2.0 mmHg (95% CI -6.1 to 10.2), in 24h systolic ABPM 1.0 mmHg (-7.1 to 9.1) and in office systolic BP -8.2 mmHg (-17.1 to 0.7). In four out of five patients fewer medications were detected than were prescribed. Baseline mean number of prescribed types of BP lowering drugs was 3.8±1.5 and of detected was 1.7±1.4. The better the adherence, the lower daytime systolic ABPM. A significant increase in number of detected drugs at 6 months (increase of 0.6 pills, (0.1 to 1.0), p=0.03) was found in the control, but not in the RDN group (0.3 pills (-0.2 to 0.8)).

Conclusions: This is the second largest trial in the field of RDN and the first that objectively assessed medication use in both the intervention and the control arm. RDN as therapy for resistant hypertension was not superior to usual care. Medication adherence is poor, when patients were unaware of monitoring. Hypertension which seems "resistant" to treatment is (partially) explained by poor medication adherence. Changes over time in adherence differ between RDN and control group. This complicates the interpretation of the results on BP.

Funding: Pharmaceutical Company Support - Medtronic, Government Support - Non-U.S.

FR-PO1124

Phase 2a Clinical Trial of Mitochondrial Protection (Elamipretide) during Stent Revascularization in Patients with Atherosclerotic Renal Artery Stenosis

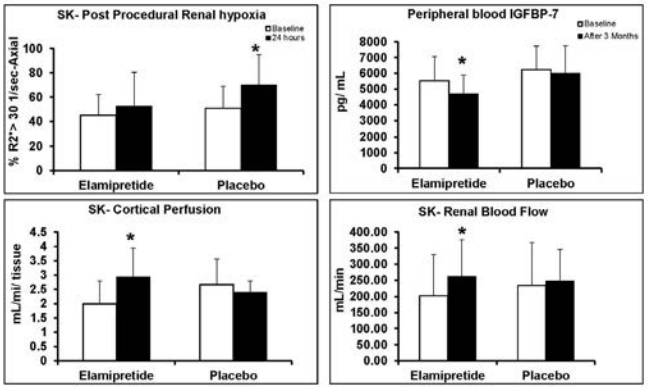
Ahmed Saad, Sandra Herrmann, Lilach O. Lerman, Stephen C. Textor. *Mayo Clinic.*

Background: Atherosclerotic renal artery stenosis (ARAS) reduces renal blood flow (RBF) and GFR and amplifies stenotic kidney (SK) injury.Renal revascularization with percutaneous transluminal renal angioplasty and stenting (PTRA) often fails to recover renal function possibly due to Ischemia reperfusion injury (IRI) developing after PTRA. Elamipretide is a mitochondrial targeted peptide that reduces IRI and improves GFR when infused during PTRA in experimental models. We hypothesized that Elamipretide plus PTRA would improve GFR, oxygenation, RBF and reduce biomarkers of cell cycle arrest (IGFBP-7) in a Phase 2a, randomized, blinded, placebo-controlled pilot study in ARAS patients undergoing PTRA.

Methods: Inpatient studies were performed during 150 mEq Na+ intake and ACE/ARB Rx in patients with severe ARAS scheduled for unilateral or bilateral PTRA. Patients were treated with a 3h IV infusion of Elamipretide (0.05 mg/kg/hour, n=6) or placebo (n=8). We measured plasma levels of IGFBP-7; Tissue oxygenation with BOLD MR before and 24 hours after PTRA. SK cortical perfusion and RBF were measured using contrast-enhanced CT before PTRA and after 3 months.

Results: Age and basal GFR did not differ between the groups. Transient hypoxia developed 24 hours after PTRA only in the placebo group (p< 0.05). IGFBP-7 decreased 3 months after PTRA in the Elamipretide-group only (p<0.05). SK-RBF and cortical perfusion increased 3 months after PTRA (p<0.05 vs. baseline) in the Elamipretide-group. Over 3 months, systolic blood pressure decreased, and eGFR increased in the Elamipretide group only.

	Elamipretide (N=6)		*Placebo (N=8)*	
Age (years)	66.7 ± 6.8		72.5 ± 8.1	
	Baseline	***3 months***	***Baseline***	***3 months***
Creatinine mg/dL	1.58 ± 0.36	1.42 ± 0.34*	1.83 ± 0.52	1.7 ± 0.44
eGFR mL/min	40.7 ± 13.3	46.5 ± 15.1*	35.6 ± 9.5	38.3 ± 10.5
Systolic blood pressure mmHg	154.2 ± 16.3	132.5 ± 16.8 *	154.2 ± 18.5	143.7 ± 26
*P< 0.05 vs baseline. Values are presented as mean ± SD				



Conclusions: Adjunctive Elamipretide during PTRA reduced immediate post-procedure hypoxia and lowered cell-cycle arrest biomarkers. It increased RBF and eGFR at 3 months. These pilot data support a role for targeted mitochondrial protection to improve outcomes of PTRA for human ARAS.

Funding: Pharmaceutical Company Support - STEALTH Biotherapeutics

FR-PO1125

Renal and Vascular Effects of Uric Acid Lowering in Patients with Uncomplicated Type 1 Diabetes Mellitus

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Background: Even within the normal range, higher plasma uric acid (PUA) levels are associated with lower GFR and higher blood pressure (BP) in young adults with type 1 diabetes (T1D). Our aim was to determine the impact of PUA lowering on renal and vascular function in patients with uncomplicated T1D.

Methods: T1D patients (n=49) were studied under eu- and hyperglycemic conditions at baseline and after treatment with the xanthine oxidase inhibitor febuxostat (FBX), for 8 weeks. Healthy controls (HC) were studied under euglycemic conditions (n=24). PUA, GFR (inulin), effective renal plasma flow (ERPF, paraaminohippurate), BP and hemodynamic responses to an infusion of angiotensin II (to assess the intrarenal RAAS) were measured pre- and post-FBX. Arterial stiffness, flow mediated and nitroglycerin mediated dilation (FMD and GMD respectively) were measured pre- and post-FBX. Gomez's equations were used to estimate afferent (R_A) and efferent (R_E) arteriolar resistances and glomerular hydrostatic pressure (P_{GLO}).

Results: FBX decreased PUA in HC (303±71µmol/L to 131±55µmol/L, p<0.0001) and T1D (240±62µmol/L to 124±53µmol/L, p<0.0001). FBX had a modest systolic BP lowering effect in T1D patients (112±10mmHg to 109±9mmHg, p=0.049), but not in HC, which was not accompanied by changes in arterial stiffness, FMD or GMD in either cohort. FBX enhanced the filtration fraction response to hyperglycemia in T1D patients, through larger increases in R_E and P_{GLO}, but without impacting the RAAS.

Conclusions: PUA lowers systolic BP and may modulate the renal R_E responses to hyperglycemia. Ongoing longitudinal outcome trials will determine whether BP and renal hemodynamic effects of PUA lowering modify renal or cardiovascular outcomes in patients with T1D.

Funding: Government Support - Non-U.S.

FR-PO1126

Anti-Albuminuric Effects of Topiroxostat in Hyperuremic Patients with Diabetic Nephropathy: A Multicenter, Open-Label, Randomized Trial

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Background: Proteinuria is an established risk factor for diabetic nephropathy. Recent studies indicate that some xanthine oxidase inhibitors (XOi)s have a renoprotective effect.

Methods: The ETUDE study (Effect of Topiroxostat, a selective XOi, on Urinary albumin in hyperuricemic patients with Diabetic nEphropathy) was a 24-week, multicenter, open-label, randomized (1:1) trial of 80 patients. Hyperuricemic patients with diabetic nephropathy (estimated glomerular filtration rate [eGFR] ≥ 20 mL/min/1.73 m2) and overt proteinuria (0.3 ≤ urine protein to creatinine ratio (UPCR) < 3.5 g/g Cr) were assigned to either high dose (160 mg daily) or low dose (40 mg daily) topiroxostat. The primary endpoint was the change in albuminuria measured by urine albumin-to-creatinine ratio (UACR) after 24 weeks relative to the baseline values.

Results: Baseline characteristics were similar between the groups. In the high dose group after 24 weeks of treatment the UACR significantly decreased by -122 mg/gCr (95% CI: -5.1 to -240.1, P = 0.025), while in the low dose group the decrease in UACR was not significant (-201.4 mg/gCr [95% CI: 14.5 to -417.3, P = 0.066]). In the linear mixed model including baseline albuminuria, eGFR, age, and sex as covariates, the decreases in UACR in patients treated with topiroxostat were still significant from baseline to 12 weeks by 228.7 ± 83.2 mg/gCr (P = 0.0075) in the high dose group and to 24 weeks by 203.9 ± 77.1 mg/gCr (P = 0.001) in the low dose group. There was no significant difference between the groups. Topiroxostat had mild and significant lowering effects on eGFR and systolic and diastolic blood pressure, and it steadily reduced serum uric acid levels. The adverse event profile during this study was not different between the groups.

Conclusions: Topiroxostat 160 mg daily reduced albuminuria in patients with diabetic nephropathy. Trial registeration: UMIN 000015403.

Funding: Pharmaceutical Company Support - Sanwa Kagaku Kenkyusho Co., Ltd.

FR-PO1127

Abstract Withdrawn

FR-PO1128

Effects of Blisibimod, a Selective Inhibitor of B-Cell Activating Factor, in Patients with IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the commonest glomerulonephritis in the world. Elevated serum B-cell-activating factor (BAFF) correlates with IgAN histological severity. We report interim results of a Phase 2, randomized, double-blind, placebo-controlled trial evaluating the effects of blisibimod, a BAFF inhibitor, in patients with IgAN [BRIGHT-SC Study, NCT02062684].

Methods: Subjects with biopsy-proven IgAN, urine protein:creatinine ratio (UPCR) 1-6g/g,eGFR >30mL/min/1.73m² on renin-angiotensin blockade were randomized to subcutaneous blisibimod (100mg 3x/week for 8 weeks, then 200mg weekly) or placebo.57 subjects met the entry criteria, 47 of whom had been followed for ≥6 months at the time of analysis.

Results: B-cell subsets and immunoglobulin levels decreased significantly in the blisibimod group, demonstrating pharmacological inhibition of BAFF. Proteinuria reduction was seen in the blisibimod group, while a steady increase was seen with placebo, this effect persisted to week 96 (% change from baseline -8.7% vs+59.4%, p=0.017). Separation between treatments in time-average UPCR also increased over time. There was, however, no treatment effect on eGFR. Two subjects progressed to end-stage renal disease, one in each arm. Blisibimod was well-tolerated with no safety concerns reported by the safety monitoring board.

Baseline characteristics	Blisibimob	Placebo	Number
Male(%)	45		57
Asian/White/Black(%)	76/22/2		57
UPCR(g/g)	2.0	2.3	57
eGFR(mL/min/1.73m²)	68.8	68.6	57
Blood Pressure(mmHg)	126/80	122/79	57
Treatment Effects			
UPCR Week 8(g/g)	2.0	2.7	52
UPCR Week 24(g/g)	2.2	2.2	49
UPCR Week 96(g/g)	1.8	3.5	12
B cell count Week 24(% of baseline)	73.2	102.1	41
IgA Week 24(% change)	-7.8	-1.3	47

Conclusions: The data support a hypothesis that blisibimod-mediated BAFF inhibition acts to reduce peripheral B cells and immunoglobulins,and may prevent deterioration of UPCR levels in IgAN. The data support longer-term observation of the cohort.

Funding: Pharmaceutical Company Support - Anthera Pharmaceuticals, CA USA

FR-PO1129

Impact of Vitamin D on Cardiac Structure and Function in Chronic Kidney Disease: A Randomised Controlled Trial

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Background: CKD is associated with cardiac hypertrophy. We examined impact of oral cholecalciferol supplementation on cardiac structure and function, in a double-blind, placebo-controlled randomised trial.

Methods: After screening 84 stable, non-diabetes, CKD stage 3-4 patients on ACEi/ARB, with vitamin D concentrations <75 nmol/L, 48 patients with left ventricular [LV] mass in the upper tertile of normal range, were randomised to receive either 6 directly-observed doses of 100,000 units of cholecalciferol or matched placebo over 42 weeks. Cardiac MRI and echocardiography were performed at baseline and 52 weeks.

Results: The clinical characteristics were well matched at baseline between vitamin D and placebo groups as follows: age 52±12 vs 52±11 years (p=0.94); eGFR 35±11 vs. 34±11 ml/min/1.73m² (p=0.75); calcium 2.4±0.1 vs 2.4±0.1 mmol/L (p=0.37); phosphate 1.1±0.2 vs 1.0±0.3 mmol/L (p=0.42). The vitamin D concentrations in the vitamin D and placebo groups; at baseline, 24 weeks and 52 weeks, were 43±18 vs. 43±20 nmol/L [p=0.95], 77±14 vs. 49±27 [p<0.001], 78±24 vs. 43±21 nmol/L [p<0.001] respectively. The left ventricular mass by MRI scan at baseline and 52 weeks, in the vitamin D and placebo groups were 104±39 vs. 100±29 gm [p=0.97] and 108±39 vs. 96±27 gm [p=0.28]. At 52 weeks there were no difference in LV volumes, RV volumes and mass, RA area, LA area, Mitral valve E/A ratio, E/e' ratios at septum and lateral wall, pulmonary artery systolic pressure between the vitamin D and placebo groups [see table 1].

Conclusions: Cholecalciferol supplementation over 52 weeks increased vitamin D levels but did not have an impact on cardiac structure of function in stable, non-diabetic, CKD patients with low vitamin D.

Table 1: The outcome variables at 52 weeks

Outcome measures	Placebo	Vitamin D	p value
LV ED Mass (gm)	96±26	108±39	0.28
LV stroke volume (ml)	96±21	95±23	0.86
LV ED Volume (ml)	149±36	154±36	0.67
LV ES Volume (ml)	108±29	118±46	0.25
RV Stroke Volume (ml)	97±24	98±33	0.74
RV ED volume (ml)	161±43	162±39	0.92
RV ES Volume (ml)	66±26	64±15	0.69
RV ejection fraction (%)	59.9±7.0	59.8±8.6	0.97
RA Area (cm²)	20±5	20±4	0.68
LA Area (cm²)	21±3.7	22±3.7	0.63
MV e/a ratio	1.02±0.22	0.96±0.27	0.41
E/e' lateral wall	9.68±4.50	7.6±2.80	0.93
E/e' septum wall	10.8±3.1	9.9±3.2	0.92
PA systolic pressure (mmHg)	22.5±8.0	22.4±5.3	0.96

Legend: LV=left ventricle, RV=right ventricle, RA=right atrium, LA=left atrium, PA=pulmonary artery, ED=end diastolic, ES=end systolic, MV=mitral valve

Funding: Private Foundation Support

FR-PO1130

Abstract Withdrawn

FR-PO1131

Efficacy of LDL Apheresis in the Treatment of Drug-Resistant Nephrotic Syndrome

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Background: LDL apheresis (LDL-A) is an extracorporeal measure to correct dyslipidemia (DL). In Japan, LDL-A is approved as a treatment of secondary DL associated with refractory nephrotic syndrome (NS) due to focal segmental glomerulosclerosis (FSGS). In addition to correction of DL, LDL-A is thought to enhance responses of immunosuppressants leading to rapid resolution of NS. A frequently encountered dilemma is the management of clinically evident FSGS despite an otherwise established biopsy-proven diagnosis. We investigated the effect of LDL-A on biopsy-proven FSGS (pFSGS) and clinically-diagnosed FSGS (cFSGS).

Methods: 10 cases of LDL-A performed for the first time against drug-resistant NS of FSGS origin (pFSGS=3, cFSGS=7) between 4/2008-8/2016 were enrolled. Clinical parameters before and after LDL-A was compared between pFSGS and cFSGS, and between complete remission (CR) and incomplete remission (ICR) groups. In addition, efficacy of LDL-A and length of hospital stay was evaluated among 3 of the relapsed cases thereafter, where LDL-A was performed for the second time.

Results: All patients received concomitant treatment of immunosuppressants (prednisone=10, cyclosporine=4), and all achieved remission from NS with LDL-A (Up

4.0±2.7 g/day to 0.8±0.8 g/day). Rate of remission did not significantly differ between pFSGS (CR 33%) and cFSGS (CR 42%). There were no clinical parameters that significantly differed between CR and ICR. Of the relapsed cases, length of hospital stay shortened from an average of 59 days to 29 days by early administration of LDL-A.

Patient	Diagnosis	Hospital stay (days)		Up at discharge (g/day)	
		1st time	2nd time	1st time	2nd time
Total		59	29	1.25	1.12
1	pFSGS	53	24	0.13	0.14
2	pFSGS	13	9	3.4	3.1
3	cFSGS	113	54	0.24	0.13

Conclusions: LDL-A was effective in treating drug-resistant NS whether by pFSGS or cFSGS. The high reproducibility of its antiproteinuric effect suggests its potential of shortening hospital stay, especially when initiated early among relapse cases with known efficacy.

FR-PO1132

Abstract Withdrawn

FR-PO1133

Cell-Free DNA to Discriminate Active Rejection in Kidney Allografts Daniel C. Brennan,[1] Roy D. Bloom,[2] Jonathan Bromberg,[3] Emilio D. Poggio.[4] *[1]Washington Univ in St. Louis, St. Louis, MO; [2]Univ of Pennsylvania, Philadelphia, PA; [3]Univ of Maryland, Baltimore, MD; [4]Cleveland Clinic, Cleveland, OH.*

Background: The standard test to differentiate rejection and injury in kidney transplants is the allograft biopsy. Donor-derived cell free DNA (dd-cfDNA) is a noninvasive test of allograft cell injury that may enable more frequent, quantitative, and safer assessment of allograft status.

Methods: We prospectively collected blood specimens from kidney recipients at scheduled post-transplant intervals, as well as concomitantly with clinically indicated or protocol kidney biopsies. Dd-cfDNA levels were measured in blood plasma and correlated with allograft rejection status ascertained by renal biopsy.

Results: Of 384 patients with 1272 blood samples, 219 patients had ≥1 renal biopsy. The dd-cfDNA level discriminated biopsy specimens showing rejection (T cell-mediated (TCMR) and/or antibody-mediated (ABMR)) from those without rejection with a receiver-operating-characteristic (ROC) area under the curve (AUC) of 0.74; 95% CI 0.61- 0.86. The ROC-AUC for discriminating ABMR from no-rejection controls was 0.87 (95% CI 75-97). Median %dd-cfDNA was 2.9 (ABMR), 1.2 (TCMR, Types ≥ IB), 0.2 (TCMR Type IA), and 0.3 in controls (p <0.001, ABMR vs controls; p=0.05, TCMR Type ≥ IB vs controls). In a subset of stable patients, the dd-cfDNA median value was 0.21% (interquartile range 0.12-0.39%), and the 97.5th percentile was 1.20%. The positive and negative predictive values for ABMR at a cutoff of 1.0% dd-cfDNA were 44% and 96%, respectively Mean serum creatinine was 2.5 mg/dl in both the active rejection and control groups (p=0.3), and thus had no discriminatory value for rejection.

Conclusions: The dd-cfDNA level may be used to assess allograft rejection and injury status; a cutoff of ≥1% indicates a risk of active rejection (most likely ABMR or TCMR types ≥IB). Dd-cfDNA levels below threshold reflect absence of moderate or greater active rejection and may be useful to guide immunosuppressive management.

Funding: Pharmaceutical Company Support - CareDx

FR-PO1134

Associations between Functional and Health Status Indices in Elderly Hemodialysis Patients Khin N. Chan, Ralph Rabkin, Yu Chen, Atul A. Nagare, Baruch Vainshelboim, Jenny Kiratli, Jonathan N. Myers. *Research and Development, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA.*

Background: Physical function and health status decline as renal failure progresses. While functional and health status measures have been widely studied in cardiovascular and pulmonary disease, little is known regarding these measures in maintenance hemodialysis (MHD), and which is best associated with measured functional capacity.

Methods: Twenty elderly ESRD patients (mean age: 68 ± 7, Male: 15, Female: 5) with on MHD for 3.5 ± 3 years with Kt/V: 2.1 underwent a battery of functional and health status tests, including peak VO2, six-minute walk (6MWT), strength, and one-minute sit-to-stand test to evaluate function, and body composition by Dual-energy X-ray absorptiometry (DXA). Health status was assessed using the SF-36v2 physical (PCS) and Mental (MCS) components.

Results: Mean peak VO2 was 14.52± 4.9 ml/kg/min, representing 61% ± 14.5 of the age-predicted value. Mean values for % percent predicted six-minute walk and one-minute sit-to-stand tests were 66.0 ± 17.68 and 50.7 ± 27.68, respectively. Peak VO2 was significantly related to 6MWT and lower body strength (r = 0.77, p <0.001 and r = 0.71, p <0.001 respectively); whereas peak VO2 was modestly related to upper body strength and 1-minute sit-to-stand test (r=0.54, p=0.02 and r=0.46 p=0.05, respectively). Among health status measures, peak VO2 was modestly associated with PCS (r=0.41, p=0.09) but inversely related to the MCS component (r=-0.35, p=0.16). 6MWT was strongly related to PCS (r=0.59, p=0.01). Measures of physical function were poorly related to body composition determined by DXA, including total and lower body muscle mass (r=0.03, p=0.91) and %percent of total body fat (r= -0.16, p= 0.52).

Conclusions: Functional capacity is impaired in MHD patients, but surrogate measures of function are only modestly related to peak VO2. These findings suggest that although exercise and non-exercise indices of physical function reflect different facets of health status in MHD, it appears that the 6MWT is a valid, easily performed clinical test for monitoring the physical function of MHD patients.

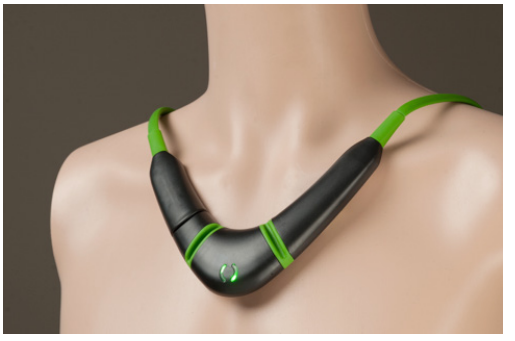
Funding: VA Support

FR-PO1135

Predicting Adverse Events with Non-Invasive Monitoring Mark S. Segal,[1] Robert W. Nappo,[2] Matthew J. Banet,[3] Susan M. Pede.[3] *[1]Nephrology, Univ of Florida, Gainesville, FL; [2]Operations, UFHealth Dialysis, Gainesville, FL; [3]ToSense.*

Background: To investigate if adverse events can be identified prior to occurrence through non-invasive monitoring. Additional objectives' were estimating true 'dry weight' and evaluation of waveforms to identify hypokalemia.

Methods: Prior to start of a dialysis session, research personnel applied toSense's CoVa™ Monitoring System (the 'Sensor') (figure 1) which made frequent measurements of stroke volume, cardiac output, thoracic fluid index, heart rate, respiration rate, and ECG waveforms and wirelessly communicated the data to a cloud based storage system to patients. Additional data captured and analyzed included patients' weight before and after each dialysis session, blood pressure, fluid removed, adverse events during the dialysis session, and lab values.



Results: 28 males and 22 females participated in the study. 48 adverse events from 22 patients were captured including two patients with hypokalemia. Preliminary results indicate that: i) stroke volume decrease systematically during dialysis and precedes adverse events by 10 – 60 minutes; ii) changes in heart rate and heart rate variability precede adverse events; and iii) blood pressure can be measured without a cuff semi-continuously. One patient experienced a 12.5-kilogram weight loss over 8 dialysis sessions. Thoracic fluid measurements indicated a plateau at a dry weight. Waveform data from the hypokalemic patients is still being analyzed.

Conclusions: This study demonstrates that the Sensor's non-invasive measurements of stroke volume and fluid index may be able to predict adverse events during dialysis. Additionally, the ability to cufflessly measure blood pressure will provide earlier notification of hypotensive events during dialysis. In addition, repeated non-invasive measurements of thoracic impedance may provide insight into true dry weight for dialysis patients.

Funding: Pharmaceutical Company Support - ToSense, Inc

FR-PO1136

Predictors of Health Deterioration among Older New Zealanders after Twelve Months of Dialysis Therapy: Provisional Findings Robert J. Walker, Ari Samaranayaka, Bronwen M. McNoe, Mark R. Marshall, John B.W. Schollum, Sarah Derrett. *Univ of Otago, Dunedin, New Zealand.*

Background: The Dialysis Outcomes in those aged ≥65 years old Study (DOS65+) is a prospective longitudinal study examining patient-reported global health outcomes. Baseline characteristics independently predicting Worse health outcomes 12 months later are reported.

Methods: Of all 225 participants in DOS65+, this paper reports 150(88%) who were all dialysing at baseline, and had either completed a 12-month interview or died before the scheduled 12-month interview. The NZ Health and Disability Multi-region Ethics Committee granted ethical approval (MEC/10/084). Trial registration ACTRN 12611000024943. Variables were grouped according to demographic, social, health and functioning, dialysis location ['Home' or 'Clinic' (in-centre dialysis)] and ESKD symptoms. Participants' responses to: "Compared to one year ago, how would you rate your health in general now?" was the outcome of interest; categorised as 'Same or Better' or 'Worse' health. Those who died before their 12-month interview were categorised as Worse health. A modified Poisson regression model estimates relative risks and 95% confidence intervals (95%CI) using robust standard errors.

Results: At 12-month follow-up, 97 (65%) reported Same/Better health compared to one year ago; 53 (35%) reported Worse health. Risk factors for Worse health were: no satisfaction with social relationships at baseline (RR=1.66 95%CI=1.27,2.17); comorbidities (RR=1.19 95%CI=1.09,1.30); EQ-5D anxiety/depression (RR=1.61 95%CI=1.07,2.42) and poor/fair general health (RR=1.60 95%CI=1.37,1.85). Home dialysis had reduced risk of Worse health regardless of modality (HHD RR=0.55 95%CI=0.36,0.83) or (PD RR=0.86 95%CI=0.79, 0.93). Pacific people had reduced risk of Worse health at 12-months compared to European/Other ethnicities (RR=0.63 95%CI=0.52,0.72) and greater ESKD symptoms at baseline were also at reduced risk (RR=0.78 95%CI=0.62, 0.97).

Conclusions: Key findings in this older age group were that those on home dialysis reported better health than those in dialysing in Clinics, social support was important, and Pacific people reported better outcomes than Europeans.

Funding: Government Support - Non-U.S.

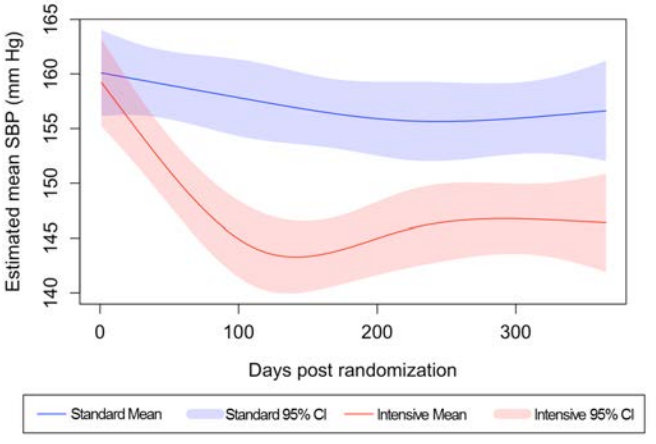
FR-PO1137

Blood Pressure in Dialysis (BID) Trial Philip Zager,[1,4,5] D. Miskulin,[2,4,5] Jennifer J. Gassman.[3,5] *[1]UNM; [2]Tufts; [3]Cleveland Clinic; [4]DCI; [5]On Behalf of the BID Study Group.*

Background: The KDOQI systolic blood pressure (SBP) guidelines for hemodialysis (HD) are based on expert opinion. Trial data are needed to determine if the benefits of intensive control of SBP in high-risk patients shown in SPRINT extend to HD patients. The BID Pilot assessed feasibility and safety of conducting a full-scale trial of intensive vs. standard control of SBP.

Methods: We randomized 126 patients to a predialysis SBP of 110-140 (n=62) or 155-165 (n=64) mm Hg for 1 year. We estimated mean SBP in each arm from a linear mixed model. We assessed the relationship of SBP to interdialytic weight gain (IDWG). We compared adverse events across arms. Change in left ventricular mass (LVM) was assessed by MRI.

Results:



In days 91 to 365 the mean separation in SBP between arms was 12.9 mm Hg. The number of antihypertensive medications at baseline (2.9 vs. 2.4), 6 (3.3 vs. 2.4) and 12 (3.4 vs. 2.5) months was higher in the intensive vs. standard arm. We used Cox models (referent: standard arm) to assess time to first death (HR 4.29), all cause (HR 1.36) and cardiovascular (HR 1.27) hospitalizations (H), all NS. There were 4 deaths in the intensive (not protocol related) and 1 in the standard arm (possibly protocol related). The numbers of H and vascular access thromboses (T) were higher in the intensive (H 85, T 20) vs. standard arm (H 47, T 7), both P<0.05. However, the number of patients with H and T was similar in the intensive (H 29, T 10) and standard arms (H 25, T 7) (NS). Intradialytic hypotension was more frequent in the intensive vs. standard arm. Overall there were no statistically significant relationships between IDWG and SBP. The median change in LVM was similar in the intensive (-0.8 g) vs. standard arm (1.5g) (NS).

Conclusions: It is feasible to conduct a full-scale trial to determine if intensive control of SBP may improve clinical outcomes. However, the possible safety signal merits inclusion of a vanguard phase.

Funding: NIDDK Support, Pharmaceutical Company Support - Dialysis Clinic, Inc. (DCI)

FR-PO1138

Blood Volume Monitoring Guided Ultrafiltration Biofeedback on Reduction of Intradialytic Hypotensive Episodes in Hemodialysis: Results of a Randomized Crossover Trial Kelvin C.W. Leung, Pietro Ravani, Robert R. Quinn, Jennifer M. MacRae. *Medicine, Univ of Calgary, Calgary, AB, Canada.*

Background: Intradialytic hypotension (IDH) is associated with significant patient morbidity. One type of biofeedback technology proposed for the prevention of IDH in hemodialysis (HD) is blood volume monitoring (BVM) guided ultrafiltration (UF) biofeedback which automatically adjusts the fluid removal rate based on blood volume parameters. The effect of BVM biofeedback on the reduction of IDH was tested in a randomized trial.

Methods: We performed a 22-week, single blind, randomized crossover trial in maintenance HD patients who had >30% of HD sessions in the preceding 8-weeks complicated by symptomatic IDH in 5 centres in Calgary, Alberta, Canada. Participants underwent a four-week run-in phase for dialysis prescription and dry weight optimization and those meeting inclusion criteria were randomized to best clinical practice HD (control) or best clinical practice plus BVM-guided UF biofeedback (intervention) for 8-weeks. This was followed by a two-week washout phase prior to crossing over for a second 8-week study phase. The primary outcome was the rate of symptomatic IDH. An intent-to-treat analysis was performed.

Results: Thirty-five participants entered the study, 32 met inclusion criteria for randomization, and 26 completed the study. The rate of symptomatic IDH during the biofeedback intervention was 0.0977/hr (95% confidence interval [CI] (0.0556-0.1398/hr) and 0.0741/hr (95% CI 0.0498-0.0984/hr) during the control dialysis (P>0.05). There was no difference in the rate and proportion of sessions effected by asymptomatic IDH or symptoms alone between the two interventions. Results remained consistent when adjusted for randomization order and study week. There was no difference in interdialytic weight gain, proportion of patients achieving target weight, brain natriuretic peptide, cardiac troponins, body water content, ultrafiltration rate, and patient recovery time between the two interventions.

Conclusions: The use of BVM-guided UF biofeedback in IDH prone patients did not reduce the rate of symptomatic IDH events.

FR-PO1139

Study of the Effect of Dilution Mode of On-Line HDF on the Intra-Dialytic Hemodynamic Stability: EDOIDEA Study Ikuto Masakane,[1] Hideki Kawanishi.[2] *[1]Nephrology, Yabuki Hospital, Yamagata, Japan; [2]Nephrology, Tsuchiya General Hospital, Hiroshima, Japan.*

Background: On-Line hemodiafiltraiton (OL- HDF) is a rapidly developing dialysis modality, however, even in the latest systematic review the advantages of OL-HDF has been still controversial. OL-HDF is generally performed in performed in post-dilution (Post-HDF) in Europe and other many countries but pre-dilution (Pre-HDF) has been the major in Japan. A Randomized control trial evaluating clinical advantages of pre-dilution OL-HDF has been thirsted for to clarify which dilution modality is more effective to solve several issues in chronic dialysis patients. EDOIDEA study was designed and has been performed by Japanese Society for Hemodiafiltration (JSHDF) to answer the question.

Methods: EDOIDEA study is a randomized parallel crossover style for evaluating the influence of dilution method on intra-dialytic hemodynamic stability. The patients with informed consent were randomly divided into the next 2 groups, Group A and Group B. the patients were treated in the conventional therapy, Pre-HDF, Post-HDF, Pre-HDF in Group Aa and in the conventional therapy, Post-HDF, Pre-HDF, Post-HDF in Group B. Primary outcomes were about intra-dialytic hemodynamic stability and secondary outcomes were changes in blood chemistry, dialysis efficacy, albumin loss during dialysis session and patients' subjective symptoms.

Results: Finally 99 patients were divided into 48 patients in Group A and 51 patients in Group B. The average substitution volumes were 54.3 L/session in Pre-HDF and 14.4 L/session in Post-HDF. There were no differences in blood pressure and intra-dialytic hypotension between pre-dilution and post-dilution. Kt/V urea was greater in post-dilution than pre-dilution. The removal rate of beta2 microglobulin was not different between 2 Groups but albumin loss was greater in Post-HDF than Pre-HDF. There were no significant differences in the patients' subjective symptoms.

Conclusions: There were no definitive differences on the hemodynamically stabilities between Pre-HDF and Post-HDF. The risks of albumin loss during dialysis session and hypoalbuminemia were greater in Post-HDF than Pre-HDF.

FR-PO1140

Elevated Tissue Na+ Deposition in Hemodialysis Patients with Insulin Dependent Diabetes Mellitus Detected by 23Na-Magnetic Resonance Imaging Anke Dahlmann,[1] Christoph Kopp,[1] Peter Linz,[2] Matthias Hammon,[2] Daniela Amslinger,[1] Kai-Uwe Eckardt,[1] Friedrich C. Luft,[3] Jens Titze.[4] *[1]Nephrology and Hypertension, Univ Hospital Erlangen-Nürnberg, Erlangen, Germany; [2]Radiology, Univ Hospital Erlangen-Nürnberg, Erlangen, Germany; [3]Max-Delbrück Center for Molecular Medicine and Charité Medical Faculty, Berlin, Germany; [4]Clinical Pharmacology, Vanderbilt Univ, Nashville.*

Background: Long-term elevated blood sugar, as observed in patients with insulin dependent diabetes mellitus (IDDM), results in matrix-compositional changes of skin and muscle tissue. We used ^{23}Na-magnetic resonance imaging (^{23}Na-MRI) to quantify tissue Na^+ storage in skin and muscle of hemodialysis (HD) patients with or without concomitant IDDM. We hypothesized that tissue Na^+ might accumulate to a higher extent in HD+IDDM patients.

Methods: We determined tissue Na^+ content by ^{23}Na-MRI measurements pre- and post HD treatment in 13 HD+IDDM patients and in 46 age-matched control HD patients. Simultaneously, tissue water content was detected by ^{1}H-MRI and blood samples were taken to determine HbA1c values.

Results: ^{23}Na-MRI demonstrated increased Na^+ content in muscle and skin tissue of HD+IDDM patients compared to control HD patients. Simultaneously measured tissue water content detected by ^{1}H-MRI was not significantly different. Ratio of tissue Na^+ to water signal suggested edema-free Na^+ storage. Muscle Na^+ levels correlated with patients' HbA1c values. Na^+ and water mobilization during HD treatment lowered muscle Na^+ and water content to a greater degree in HD+IDDM patients than in HD controls.

Conclusions: ^{23}Na-MRI detected increased Na^+ in muscle and skin tissue of HD+IDDM patients compared to control HD patients. Muscle Na^+ values were directly correlated with HbA1c levels. Our findings provide first evidence that impaired serum glucose metabolism is associated with disturbances in tissue Na^+ and water content in the subpopulation of HD patients co-diagnosed with IDDM.

Funding: Private Foundation Support

FR-PO1141

Intermittent HEMOdialysis Anticoagulation with TINzaparin versus Unfractionated Heparin (HEMO-TIN): A Multicentre Randomized Control Trial Christine M. Ribic,[1] Azim S. Gangji,[1] Louise M. Moist,[2] Michael Walsh,[1] Deborah J. Cook,[1] Mark A. Crowther.[1] *[1]Medicine, McMaster Univ, Hamilton, ON, Canada; [2]Medicine, London Health Sciences Centre, London, ON, Canada.*

Background: The predominant renal elimination of low molecular weight heparins (LMWHs) has raised safety concerns regarding their use as extracorporeal anticoagulants on hemodialysis (HD) due to potential bioaccumulation. Tinzaparin may be less dependent on renal clearance compared to other LMWHs. The safety and efficacy of tinzaparin for HD anticoagulation is unknown.

Methods: We conducted a double-dummy design, crossover RCT to evaluate the safety and efficacy of tinzaparin versus unfractionated heparin (UFH) for anticoagulation in patients maintained on facility-based, thrice weekly HD(NCT01930396). Patients received either UFH and tinzaparin placebo or tinzaparin and UFH placebo for 3 months followed by crossover to the alternate regimen for 3 months. Patients, health care providers and outcome adjudicators were blinded to treatment allocation. Dose titration for clinically apparent clotting of the HD circuit/filter or patient bleeding was protocolized. Primary outcomes were patient and study reported major, clinically important non-major or minor bleeds. Secondary outcomes included: a) anti-Xa and PTT levels pre and post HD; b) dialysis efficacy (Kt/V) and c) sessional HD tubing/membrane clotting using a novel scale which was validated in 205 participating dialysis nurses.

Results: 189 patients from 4 centres were randomized of which 157 crossed over and 125 completed the trial with a total of ~12, 100 HD sessions evaluated. 1238 pre and 1241 post HD anti-Xa values underwent preliminary review by the data safety monitoring board and did not raise concern for bioaccumulation. 26 dose titrations occurred in 18 patients with 13 dose increases (6 UFH; 7 Tinzaprain) for clotting and 13 dose decreases (6 UFH; 7 Tinzaparin) for bleeding events. 139 (88.5 %) patients remained on 2500 units of tinzaparin throughout the trial.

Conclusions: Tinzaparin requires minimal dose titration for bleeding or clotting events in patients requiring HD. Full data with respect to minor and major bleeding, clotting scores, dialysis efficacy and anti-Xa levels will be presented.

Funding: Pharmaceutical Company Support - Leo Pharma

FR-PO1142

Roxadustat for the Treatment of Chronic Kidney Disease-Associated Anemia in Japanese Patients Not on Dialysis Tadao Akizawa,[1] Manabu Iwasaki,[2] Tetsuro Otsuka,[3] Michael Reusch,[4] Toshihiro Misumi.[3] *[1]Showa Univ School of Medicine, Tokyo, Japan; [2]Seikei Univ, Tokyo, Japan; [3]Astellas Pharma Inc., Tokyo, Japan; [4]Astellas Pharma Europe B.V., Leiden, Netherlands.*

Background: Anemia is a complication of CKD. The purpose of this study was to evaluate the efficacy and safety of ASP1517 (roxadustat) in Japanese non-dialysis anemic CKD patients.

Methods: During the 1st 6 weeks of this phase 2, double-blind, 24-week study (NCT01964196), anemic Japanese patients with CKD were randomized to oral placebo (PBO) or roxadustat (50, 70, or 100mg) 3x weekly (TIW). During weeks 6 to 24, dose was adjusted to maintain hemoglobin (Hb) at 10–12 g/dL; patients who met pre-defined criteria were re-randomized to roxadustat TIW or once weekly (QW). The primary end point was rate of rise in Hb (ΔHb, g/dL/week) during the 1st 6 weeks; response rate over the whole study and mean Hb and change in Hb from baseline (BL) at Weeks 18–24 were also evaluated. Safety was assessed by adverse events (AEs). Data are presented as mean (SD).

Results: 107 patients were randomized to PBO (n=27) or roxadustat 50mg (n=27), 70mg (n=26), or 100mg (n=27). Hb (g/dL) at BL was 9.34 (0.66) for PBO, and 9.39 (0.59), 9.39 (0.60), and 9.36 (0.50) for roxadustat 50mg, 70mg, and 100mg, respectively. The primary end point, ΔHb (g/dL/week), was –0.052 (0.142) for PBO and +0.200 (0.160), +0.453 (0.256), and +0.570 (0.240) for roxadustat; differences from PBO for all roxadustat doses were statistically significant (*P*<.0001*)* by the closed testing procedure. Response rate was 14.8% for PBO and 93.8% for pooled roxadustat (n=81). Mean Hb at Weeks 18–24 was 9.42 (0.84) for PBO and 10.48 (0.64), 10.72 (0.56), and 10.88 (0.66) for roxadustat; change from BL in Hb was –0.17 (0.61) for PBO and +1.10 (0.71), +1.33 (0.82), and +1.55 (0.88) for roxadustat. No major adverse cardiac events (ie, myocardial infarction, stroke, death) occurred in roxadustat-treated patients.

Conclusions: These data demonstrate a dose-dependent and significant correction of Hb with roxadustat vs PBO. Roxadustat was well tolerated, which is consistent with previous studies. These results support the phase 3 investigation of roxadustat for the treatment of CKD-associated anemia in patients not on dialysis.

Funding: Pharmaceutical Company Support - Astellas Pharma Inc